Impact of exercise on sleep and glycemic outcomes in adults with type 1 diabetes: towards predictive models and decision support systems

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CERTIFICATE OF APPROVAL

This is to certify that the PhD dissertation of
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Abstract

Type 1 diabetes (T1D) is an autoimmune disease characterized by the destruction of pancreatic β cells and culminating with absolute insulin deficiency. Intensive insulin therapy is the standard of care for individuals with T1D, but attaining optimal glycemic control is extremely onerous and requires multiple daily insulin injections or continuous subcutaneous insulin infusion by an insulin pump, complemented by frequent monitoring of blood glucose (BG). When compared with endogenous insulin secretion, subcutaneously injected insulin has both delayed action and clearance, this leads to large and dangerous fluctuations in BG values. These fluctuations can often lead to hypoglycemia and hyperglycemia. Chronic hyperglycemia leads to long term complications such as retinopathy, neuropathy and cardiovascular disease while, acute episodes of hypoglycemia have been associated with coma and death. Both hypoglycemia and hyperglycemia can often be traced back insulin bolus mistiming, imbalance of the basal or bolus doses, meal related challenges and physical activity (PA). People with T1D make recurring insulin dosing decisions many times during the course of the day. Implementation and adherence to this complex and demanding self-treatment insulin regime is quite challenging. Encumbered by the complexity of managing this condition, majority of this population fails to reach or maintain target glycosylated hemoglobin values, putting them at increased risk for vascular complications. There is a clear need to provide these individuals with modern decision support tools to improve chronic disease management. This project is focussed on addressing the challenges around PA and contributing towards providing the tools needed to support PA in these individuals.

Clinical practice guidelines strongly recommend PA to individuals with T1D, as regular exercise is associated with greater life expectancy and a lower frequency of diabetes related vascular complications. Despite this, majority fail to achieve the recommended levels of PA. Besides the usual barriers (i.e. lack of time/space, low energy, work etc.) individuals with T1D list fear of hypoglycemia as an important barrier to engage in PA. During PA there is an increased risk of hypoglycemia and pronounced glycemic imbalance. Moreover, exercise mediated hypoglycemic risk is amplified not only during the bout of exercise but also for many

hours after. The objective of this dissertation is to both understand the glycemic challenges associated with physical activity and develop model based decision support systems to assist these individuals during and after PA . The first step in attempting to create these model based systems is to understand the challenges faced by these individuals in real world conditions. We designed and conducted a comprehensive pilot study to understand that effects of PA (resistance training or aerobic exercise) on sleep and nocturnal hypoglycemia.

- The data from the study indicated that individuals with T1D on average lost 70 minutes of sleep following aerobic exercise and only lost 27 minutes of sleep following resistance exercise. We also showed that the odds of experiencing a nocturnal hypoglycemic event after any type of exercise was much higher than when compared with days with no exercise activity.

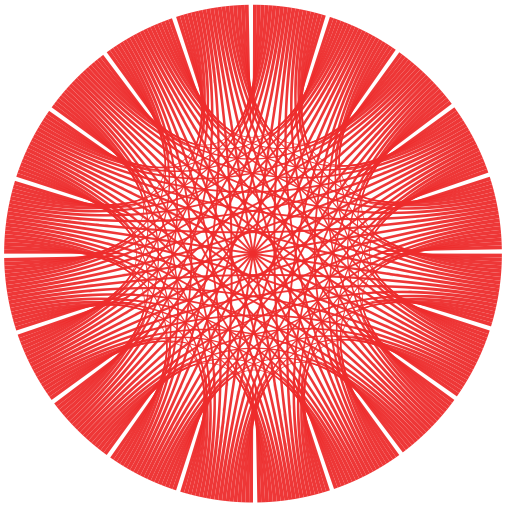
- Results from the study also indicated that the participants experienced improved glycemic control in the 24 hours after resistance training even though they increased overall energy consumption during the same period.

- Building on the observations of the challenges with glycemic control during the PA bouts, a prediction algorithm was developed to identify the risk of hypoglycemia due to aerobic exercise. This machine learning algorithm achieved an accuracy of 87% at predicting exercise induced hypoglycemia.

- In an effort to reduce nocturnal hypoglycemia, using the data collected during this study, an approach was developed to predict the risk of a nocturnal hypoglycemic episode during sleep. The machine learning algorithm designed to identify this risk at the start of bed time was able to achieve an accuracy of 85%.

To my grandfather,

whose legacy includes my love of knowledge, and the power of perseverance.



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Listing of figures

Listing of tables

It is in the nature of a hypothesis when once a man has conceived it, that it assimilates everything to itself, as proper nourishment, and from the first moment of your begetting it, it generally grows stronger by everything you see, hear or understand

Laurence Sterne,

The Life and Opinions of Tristram Shandy, Gentleman

1

Introduction

Type 1 diabetes accounts for less than 10% of all the cases of diabetes in the world [American Diabetes Association, 2017]. Type 1 diabetes (T1D) is a heterogeneous disorder characterized by an immune-mediated destruction of β—cells resulting in the need of a lifetime of exogenous insulin treatment [Skyler et al., 2016]. Type 2 diabetes is a progressive disorder with underlying insulin resistance coupled with the loss of β—cell functionality [Skyler et al., 2016]. As the healthcare system is overwhelmed by the epidemic of obesity and type 2 diabetes, it tends to conceal the chronic health care challenges and complications associated

with T1D [Insel et al., 2015, The International Expert Committee*, 2009]. Although it has been long considered "juvenile diabetes" a disorder in children and adolescents, this opinion has considerably morphed over the last decade [The International Expert Committee*, 2009, Nowicka et al., 2011]. Many individuals are also diagnosed in adulthood with T1D, left untreated this condition leads to chronic hyperglycemia [Skyler et al., 2016]. To avoid long term complications, individuals with T1D need exogenous insulin treatments. In this thesis, the daily challenges faced with these treatments are discussed and in particular, the struggle with engaging in physical activity is considered and strategies are proposed to support these individuals.

1.1 Epidemiology

The incidence and prevalence of T1D varies widely around the globe with highest prevalence in nordic countries such as Finland, while it is very uncommon in India and China [Atkinson et al., 2014]. It has been noted that the difference between the incidences among the various populations worldwide is greater than 350-fold. As the rates of incidence of T1D continue to increase, the global incidence could double over the next decade [De Beaufort, 2006]. A plethora of geographical and environmental influences have been attributed to the increases in incidence but no clear underlying mechanisms have been established [Dane-

man, 2006]. With low mortality rates among youth with T1D, an increase in incidence has translated into high prevalence of the disease in the adult populations. In the United States, the SEARCH for Diabetes in Youth Study identified the prevalence of T1D was 2.28/1000 in youth less than age 20 years[Chiang et al., 2014, Dabelea et al., 2014]. Currently it is estimated that approximately 3 million individuals (youth and adults) in the U.S. have T1D, and it is estimated that the prevalence over last few years has increased by 21% [Dabelea et al., 2014]. As the clinical onset of T1D follows an acute course in most cases, requiring the lifelong administration of exogenous insulin, along with the monitoring of blood glucose, the challenge is in both achieving and maintaining tight glycemic control safely as early as possible after disease onset [Chiang et al., 2014]. Individuals with T1D with poor glycemic control experience acute hypoglycemia and long term hyperglycemia [Skyler, 2012]. Severe hypoglycemia is debilitating and rarely, associated with death. Prolonged hyperglycemia has been associated with a higher risk cardiovascular complications, dyslipidemia, renal disease and diabetic ketoacidosis [Rawshani et al., 2017, Livingstone et al., 2015]. Faced with the difficult task of managing this chronic condition and the prevalence of acute and longer term complications, individuals with T1D experience a sharp reduction in life expectancy of 11.1 years when compared with normal healthy individuals [Livingstone et al., 2015]. The foundational goal of ther disease management using exogenous insulin therapies is to achieve optimal glycemic control which could lead to reductions in both long term and short term complications.

1.2 Disease Pathogenesis

T1D has long been recognized as an autoimmune disorder resulting from the destruction of pancreatic β cells by T cells of the immune system [Skyler et al., 2016]. The progressive loss of the β-cell mass is driven by various genetic and environmental factors [Campbell-Thompson et al., 2015, Ferrannini et al., 2005], that manifests clinically as hyperglycemia. The disease is most often diagnosed in individuals, usually presenting with a classic trio of symptoms (i.e., polydypsia, polyphagia, polyuria) alongside of overt hyperglycemia [Skyler et al., 2016]. T1D is a polygenic disease, with disease heritability risk among family members [Noble et al., 2010]. Recent research into the genetic influences on the triggering of islet autoimmunity and disease progression has contributed to the increased understanding of the disease heritability risk among family members [Törn et al., 2014, Stankov et al., 2013]. The Human Leukocyte Antigen (HLA) complex, provides the greatest contribution (i.e., 50-60%) to the overall genetic susceptibility of T1D [Cooper et al., 2008, Törn et al., 2014]. Approximately 50 additional genes individually contribute smaller effects on various aspects of the disease pathogenesis [Cooper et al., 2008, Törn et al., 2014] including immune regulation[Aly et al., 2006], modified viral responses[Colli et al., 2009] and environmental responses [Sosinowski & Eisenbarth, 2013].

Destruction of β cells as a result of the autoimmune response has been associated with insulitis but the effect on α cells is still being defined [Burrack et al., 2017]. Development of severe hypoglycemia in a minority of people with T1D has led to speculation that autoimmune reaction could be responsible [Farhy & McCall, 2015, Mukherjee et al., 2015] for the destruction of the α cells. This remains an active area of research to both identify the reasons for severe hypoglycemia and understanding the impact of the possible regulation breakdown due to the destruction of the β cell mass [Farhy & McCall, 2015].

1.3 Normal Glucose Homeostasis

Evolutionary hunter-gatherer lifestyle determined the mechanisms regulating glucose homeostasis in healthy humans [Drucker, 2007]. Physiological systems developed to store energy when food was in abundance and provide the requisite amount of glucose during periods of scarcity. With the goal of maintaining a relatively narrow range of circulating glucose concentrations, insulin and glucagon are the key hormones that facilitate the proper functioning of these mechanisms [Maggs et al., 2008]. Glucose fluxes are a result of the following primary mechanisms through which these hormones maintain near uniform glucose concentration:

- *Glycogen Synthesis* —Synthesis of the most readily available source of energy in both the liver and skeletal muscle tissue
- *Glycogenolysis* — Breakdown of glycogen to provide glucose to the body
- *Gluconeogenesis* — Non-carbohydrate based glucose production from the liver
- *Glucose Uptake* — Uptake of glucose by skeletal muscle during high periods of glucose utilization
- *Glycolysis* — Metabolism of glucose by adipose and muscle tissues

To understand the interplay between insulin and glucagon, three specific daily situations are considered:

- Fasting state
- Fed state/ Post-prandial state
- Exercise state

The metabolic effects of each of these states help elucidate the complexity in managing near normal glucose levels in individuals with T1D and lay the foundations of the objectives and goals of this thesis.

Fasting State

Near uniform glucose levels are maintained during the fasting state by reducing insulin concentrations while increasing glucagon concentrations. This insulin:glucagon ratio favors increased hepatic glucose production through both glycogenolysis and gluconeogensis [Heijboer et al., 2006, Drucker, 2007]. The glucose utilization across the body is reduced and the

dependency on the non-glucose sources of energy is increased. During short overnight fasts, the brain accounts for a majority of the glucose utilization. Glucagon increases the release of glycogen from the liver to maintain glucose levels, while also promoting the catabolic state resulting in increased fat metabolism (gluconeogenesis). These metabolic adaptions optimally maintain brain functions while limiting glucose utilization.

Fed state/Postprandial state

Postprandially, rising glucose levels result in an increase of the insulin concentrations while limiting glucagon secretion. In the fed state, surplus food is converted into glycogen, fat and protein. The increased insulin:glucagon ratio contributes to the disposal of enteral or orally consumed glucose surplus by increasing the rate of glycogen synthesis and suppressing hepatic glucose output. Insulin is an anabolic hormone and in the fed state, it increases uptake of glucose by skeletal muscle and adipose tissue (increasing peripheral uptake) while also increasing both protein and fat formation [Maggs et al., 2008, Drucker, 2007, Heijboer et al., 2006].

Post prandial glucose excursions in healthy humans is primarily determined by two factors —the rate of insulin release from the pancreatic islets of Langerhans (β—cells) in response to circulating glucose, and the sensitivity of the target tissues to insulin. The interplay between these two components determines the overall physiological tolerance of the body to glucose and its ability to maintain glucose homeostasis within the normal physiological range.

Insulin secretion from the β —cells responds, without delay, to any changes in glucose concentration within the physiologic range. This maintains the glucose levels within the range of 70–150 mg/dL —euglycemia in healthy individuals [Skyler, 2012]. β —cells have the unique ability to sense the glucose levels and control the release of insulin. There is a close correlation between the rate of insulin secretion and glucose metabolism [Skyler, 2012]. Though insulin and glucagon are the key players in the fed state, there are various other glucoregulatory hormones such as ghrelin, glucagon like peptide-1 (GLP-1), etc., that are released in the fed state in response to an oral glucose load [Skyler, 2012].

Exercise State

Exercise instigates both increased glucose utilization and hepatic glucose production [Coker & Kjaer, 2005]. Glycogen stores in the muscle are the primary sources of fuel during the early stages of exercise, while hepatic glycogenolysis supplies glucose during prolonged exercise. The neuro-endocrine systems maintain relatively constant circulating glucose levels during exercise [Camacho et al., 2005]. Hepatic glucose production is increased by the elevated secretion of glucagon and the down-regulation of insulin [Ploug et al., 1984]. Outside of the exercise state, insulin regulates glucose uptake in muscles, but during exercise, due to the down regulation of insulin, this glucose uptake is up-regulated by increased translocation of the glucose transporter isoform 4 (GLUT-4) [Camacho et al., 2005, Ploug et al., 1984].

Different modalities of exercise tend to produce different physiological responses [Loon

et al., 2001]. In normal physiology, during aerobic exercise, carbohydrate is the preferred fuel source, while short bursts of high intensity exercises, such as weightlifting or sprinting, elicit release of muscle and hepatic glycogen stores through greater catecholamine response [Fahey et al., 2012, Davey et al., 2013a]. Endogenous insulin secretion is also different during these two types of exercise modalities, with a marked reduction during aerobic activities but no significant change during high intensity interval training[Loon et al., 2001]. With all forms of physical exercise, once activity is discontinued, the secretion of glucagon and catecholamines rapidly decline, the levels of plasma insulin increases and euglycemia is maintained [Coker & Kjaer, 2005].

In healthy individuals glucose homeostasis is maintained through a complex hormonal network involving the liver, gut, pancreas, kidneys and the brain. Near-normal glucose levels are maintained following food intake, intense physical activity and long periods of fasting (overnight) [Skyler, 2012]. In normal physiology insulin secretion tends to lower glucose levels, and glucagon in contrast increases glucose levels.Taking a systems perspective, near-normal glucose levels are the natural steady state of the system and they are achieved rapidly post any perturbations such as meals, physical activity or long fasting periods. In individuals with T1D, this system is disrupted due to the destruction of the β—cells leading to impaired glucose homeostasis.

1.4 T1D - Glucose Control

T1D is the result of autoimmune destruction of the β—cells leading to complete insulin deficiency resulting in hyperglycemia and ketoacidosis. Though the rest of the pancreas is relatively preserved, the glucagon secretion from the α—cells is excessive, which accounts for some of the hyperglycemia of the disease state[Skyler, 2012]. Type 2 diabetes (T2D), on the other hand, is primarily due to insulin resistance or decreased insulin sensitivity and reduced compensatory insulin secretion resulting in abnormally high fasting glucose values. Resistance of insulin by many of the large organ bodies and tissues results in increased glucose production and underutilization[Skyler, 2012, Groop et al., 1993].

1.4.1 Exogenous Insulin Replacement Therapy

Ever since the Nobel prize winning discovery of insulin in 1921, T1D went from being a death sentence to a chronic condition[Bliss & Purkis, 1982], however, exogenous insulin replacement therapy does not provide optimal glycemic control. The findings of the Diabetes Control and Complications Trial (DCCT), and the following Epidemiology of Diabetes Interventions and Complications (EDIC) recommended intensive insulin therapy as the stan-

dard of care for this population[Control & Group, 1993, Nathan, 2005]. These seminal trials provided unquestionable evidence of the importance of achieving optimal glycemic control, critical for reducing the risk of long-term complications associated with T1D, particularly retinopathy and nephropathy [Nathan, 2005]. Any improvement in glycemic control, as measured by the decrease in the hemoglobin Ac (HbA_{1c}) to the concentration below 7%, was associated with similar declines in the relative risk of long-term complications. HbA_{1c}, which is an estimated measure of the mean plasma glucose concentration over a 120 day period [for Drugs & in Health, 2015]. Studies in individuals with type 2 diabetes have demonstrated that achieving near normal HbA_{1c} as soon as the disease is diagnosed has a protective influence against the development or progression of complications[Holman et al., 2008]. Taking in aggregate early and optimal glycemic control is necessary to maintain a complication free life in these individuals. These long term studies also showed that the major limitation of intensive insulin therapy is hypoglycemia. Hypoglycemia still remains the main side-effect of insulin therapy and a barrier to reaching optimal glycemic control [Cryer, 2014].

People with T1D require insulin therapy for survival. The goal of insulin therapy is to match the normal pattern of insulin secretion as closely as possible to optimize glycemic control while limiting hypoglycemia [Levy, 2017]. There are two main approaches that are available to simulate the normal healthy insulin secretion.

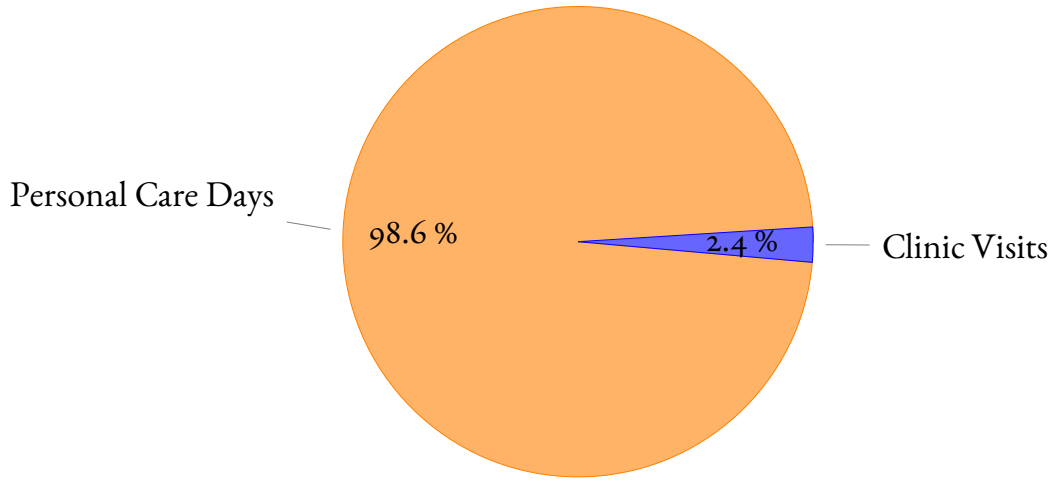

Figure 1.1: T1D is a self managed condition. T1D requires intensive self-management to avoid acute and long-term health complications. Day to day care is managed by the individual with T1D and not by the physician. In the above graphic the amount of time diabetes care that is managed by the individual versus the time spent receiving the care from the physician are shown.

The first approach is continuous subcutaneous insulin infusion (CSII) via an electro-mechanical insulin pump which constantly infuses fast-acting insulin to mimic basal secretion, along with self-selected insulin boluses for meals, pre-meal glucose values and anticipated activity. Basal insulin delivery through insulin pump can be modified in short time intervals for varying insulin needs through the course of day or night [Levy, 2017].

The alternative therapeutic option available for individuals with T1D is using multiple daily injections (MDI). A combination of long-acting insulin is delivered to provide basal insulin with separate injections of rapid-acting insulin for meals (prandial doses). This method relies on ≥ 4 injections daily to provide the necessary insulin therapy. These injections are

currently available in many pre-filled injectable pens, as this form of intensive insulin therapy —MDI —is widely used across the world [Levy, 2017].

Basal-bolus therapy is the broad term under which these two approaches of insulin delivery approaches are placed. Basal-bolus therapy, along with frequent monitoring of glucose is termed, open loop control or self-management of T1D. Open loop control involves frequent insulin dose adjustments, monitoring glucose levels regularly and hypoglycemia management. These tasks are challenging, leading to poor overall compliance with many people with T1D struggling to achieve glycemic target of HbA_{1c} <7% [Levy, 2017]. T1D is a predominantly self-managed condition with individuals taking dosage decisions throughout the day. Figure 1.1 shows how much of the time an average person with T1D visits the physician taking care of his disease relative the time spent self-managing the condition.

Glycemic outcomes have significantly improved, but achievement of normal glucose levels is still an elusive goal for a majority of people with T1D[Cryer, 2014]. Striving to achieve euglycemia is associated with an increased risk of hypoglycemia. Despite many advances in insulin therapies and devices, hypoglycemia still remains the main side-effect of insulin therapy and barrier to achieving glycemic targets [Cryer, 2014]. In the past decade, with the goal of limiting hypoglycemia while maintaining euglycemia, automated insulin delivery systems

have been under development and will be discussed in section 1.4.3.

1.4.2 Altered Glucose Homeostasis

Here we explore the same specific daily situations considered above, to understand the counter-regulatory deficiencies observed in this disease state with the current self-managed care.

Fasting State

As individuals with T1D rely on exogenous insulin delivery, during overnight, when there is a long period between meals, there could be a situation of either hyperinsulinemia or hypoinsulinemia. If the prevailing insulin levels are higher, a sustained stimulus for glucose uptake by various tissues in the body is in effect while suppressing both gluconeogenesis and glucagon secretion, resulting in nocturnal hypoglycemia. Independent of hyperinsulinemia, long standing duration of T1D diminishes the counter-regulatory response to hypoglycemia. In the case of low levels of circulating insulin concentration, hepatic glucose production continues unabated while also lowering glucose uptake by skeletal muscles, resulting in hyperglycemia.

Fed State

Rising glucose concentrations after a meal are not ideally matched by the subcutaneous

delivery of insulin, due to delay of both insulin absorption and insulin action. This mismatch creates delayed glucose utilization in the individuals with T1D and results in hyperglycemia immediately following large meals. The carbohydrate content of the meals is the main determinant of the post-prandial glycemic excursion. If the prevailing insulin levels continue to be higher after meals, this could precipitate into hypoglycemia.

Exercise State

During exercise, circulating insulin levels could potentially increase due to increased blood flow and absorption of the injected insulin residing in subcutaneous depots. As the ratio of the circulating insulin:glucagon levels are not responsive to changes in glucose in individuals with T1D at the start of exercise, the increase in glucose utilization is not adequately supported by the hepatic glucose production. During prolonged ($\approx$ 30-45 min) sub-maximal exercise, the combination of inadequate counter-regulatory response to exercise and elevated plasma insulin levels may lead to hypoglycemia. The rapidity of the glucose flux during aerobic exercise causes many individuals with T1D to experience hypoglycemia. Short periods of intense exercise tend to produce a greater counter-regulatory response through the catecholamine (adrenaline and noradrenaline) secretion. This tends to result in either a sharp hyperglycemic excursion or limited change in glucose levels. Thus, exercise state shows the functional limitations of the current insulin therapies in individuals with T1D.

1.4.3 Advances in Glycemic control

Self-treatment behavior amplifies the imperfect altered glucose homeostasis. Self-treatment behaviors such as infrequent monitoring of blood glucose, mistiming of boluses or missing of meals could lead to large fluctuations in glucose levels. The daily situations listed above can lead to dangerous situations if there are repeated instances of insulin mistiming or an imbalance of basal or bolus doses, missing meals or inappropriate meal doses, and exercise. Taking a systems perspective, the risk of hypoglycemia or hyperglycemia is the culmination of an altered complex metabolic system, that is constantly perturbed, while being regulated using a flawed external methodology [Cryer, 2016, Monnier et al., 2016]. This causes an asymmetric risk in people with T1D, a function representing this risk is shown in Figure 1.2. Optimization of glycemic control without increasing the risk of hypoglycemia is goal of clinical care[Monnier et al., 2016]. Higher frequency of hypoglycemia leads to impaired hypoglycemia unawareness and further reduced counter-regulatory response [Cryer, 2016].

SCYLLA AND CHARYBDIS are two fabled sea monsters in Greek mythology described by Homer in *The Odyssey*. They were located close enough to each other that they posed an inescapable threat to passing sailors, including Odysseus. Avoiding Charybdis meant passing too close to Scylla and vice versa. Substitute Scylla for hypoglycemia and Charybdis for hyper-

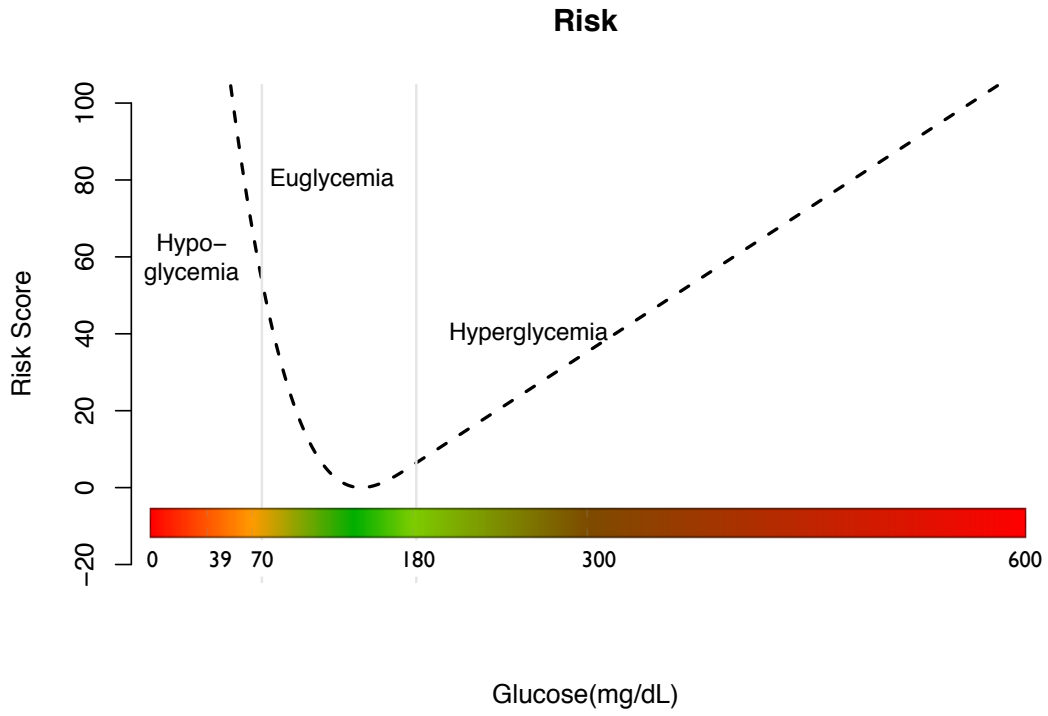

Figure 1.2: The asymmetric risk function that is associated with poor glucose regulation; the risk sharply increases with lower blood glucose levels in hypoglycemia, while only increasing gradually with higher levels of glucose in hyperglycemia with a zero risk point set at 140 mg/dL. The green zone on the glucose color bar indicates euglycemia. Adapted [Kovatchev et al., 1998, 2000].

glycemia. Individuals with T1D experience a constant roller coaster between hypoglycemia and hyperglycemia. The storms (constant fluctuations of glucose) require the strength of Odysseus to sail safely toward a complication free life. There are two distinct ways to support individuals with glycemic control. One of those strategies relies on having a mathematical algorithm take control of dosing choices of insulin while continuously monitoring plasma glucose values. The alternative is providing a decision support system that would alleviate some of the routine challenges faced by these individuals who are experienced with self-managing this condition. The goal of this thesis is to contribute various models that would form the backbone of this decision support framework. As discussed earlier in section: section 1.4.2, there are three scenarios (fed, fasting and exercise state) in which these models would have enormous impact, the two states addressed in this thesis are the *fasting state* and *exercise state*.

Glucose Monitoring- only in the last ten years have continuous glucose monitoring systems (CGM) become available to people with T1D [Garg et al., 2006]. Current CGM systems use a thin wire that is inserted into the subcutaneous space to measure interstitial glucose levels via the glucose-oxidase reaction. These devices need very few calibrations and accurately report glucose levels within the same error levels as expected from self-monitoring using a blood glucose meter (SMBG). The CGM systems provide a readout every five minutes, with an inherent delay from the plasma glucose concentration ranging between $\approx$ 5 to 15 minutes

[Keenan et al., 2009]. CGM data provides a complete picture of the current glucose values within the context of the previous few hours of data. Augmenting the sensor data with an insulin pump dramatically reduced the HbA_{1c} levels when compared with then standard of care -multiple daily injection therapy, but wearing the sensor, calibrating the sensor and servicing the alarms was an additional burden on the participants[Bergenstal et al., 2011]. Sensor glucose data provides an added benefit to warn the wearer of impending hypoglycemia or hyperglycemia. The glucose data alone tends to be overwhelming to many individuals with T1D. However, this data coupled with action is what is beneficial to these individuals. A decision support system would use the data from the CGM and suggest the appropriate action as needed for the given situation. Providing a clear and decisive action to a glucose level is one of the objectives of this dissertation.

Artificial Pancreas (AP) is the current embodiment of many years of research and incremental improvements in the components to provide a true replacement of the endocrine functionality lost in individuals with T1D [Thabit & Hovorka, 2016, Kowalski, 2015]. AP systems combine sensor glucose data from CGMs, with mathematical algorithms, to command drug delivery pumps to make automated adjustments to insulin/glucagon delivery in people with T1D. AP systems tend to come in many flavors; some provide partly (hybrid close loop) or fully automated delivery of insulin (AID systems) alone (single hormone) and

some systems provide automated delivery of glucagon (dual hormone) to prevent or treat hypoglycemia when decreasing or suspending insulin delivery alone is insufficient. These systems provide the synergy required to improve glycemic control while reducing the burden of self-management. U.S. Food and Drug Administration's (FDA) decision to make the development of closed-loop systems a priority have resulted in rapid advances in this field resulting in the first commercial closed-loop device recently being approved by the FDA in September 2016 [Voelker, 2016b].

Based on the outcomes of a recently published meta-analysis [Weisman et al., 2017], current hybrid control systems should achieve at least 70% of sensor glucose values between 70 and 180 mg/dL with <4% of values <70 mg/dL and a mean glucose of ≈155 mg/dL, equivalent to an estimated HbA_{1c} of 7.0%. These hybrid AP systems cannot completely eliminate hypoglycemia. Dual hormone AP systems provide the only alternative currently in research that could lead to the complete elimination of hypoglycemia [Jacobs et al., 2016, 2014, El Youssef et al., 2011]. A schematic of one such system is displayed in Figure 1.3.

1.5 Hypoglycemia

Definition of hypoglycemia American Diabetes Association (ADA) proposed a biochemical definition of hypoglycemia as a plasma glucose of ≤70mg/dL, with this level de-

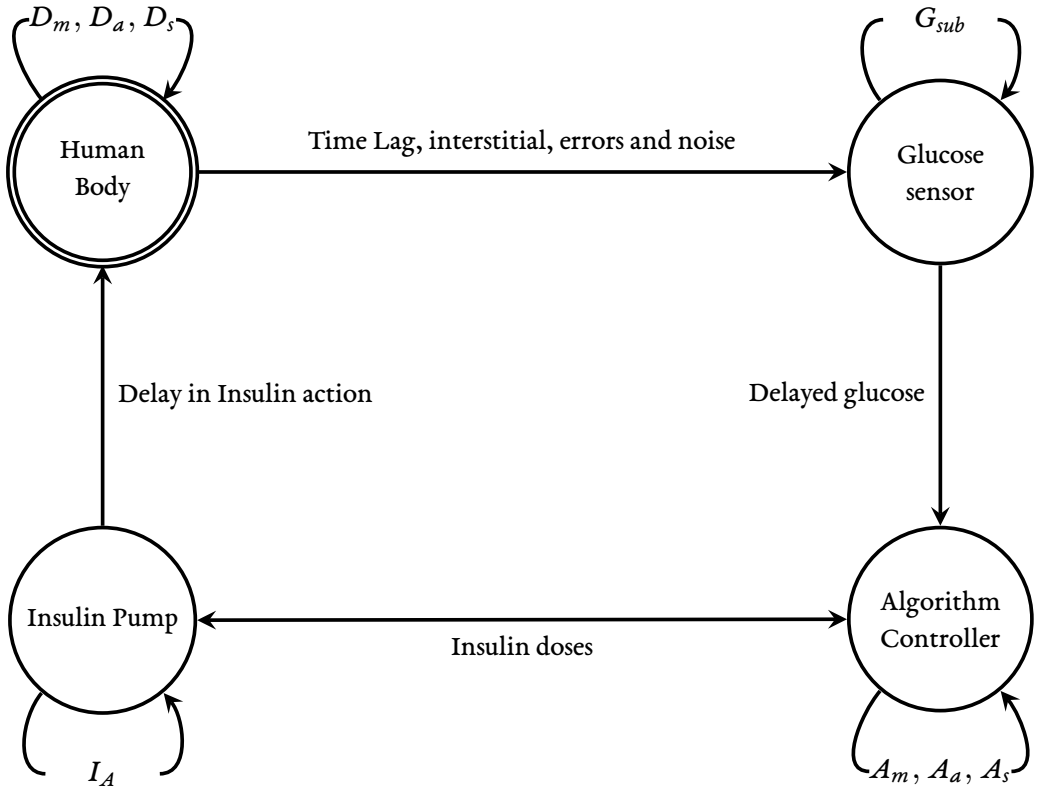

Figure 1.3: New direction of glycemic control: Closed loop control system or Artificial pancreas. Components of the artificial pancreas (AP) are shown above. Here the challenges associated with AP systems are shown in the arrows: glucose sensing in the interstitial fluid reflects a delay in the circulating glucose levels, another limitation that the AP systems have to take into account is the delay in both insulin absorption and insulin action. D_m-meal, D_a-physical activity and D_s-sleep duration represent the various disturbances/perturbations that could affect the human body; G_{sub} is the subcutaneous/interstitial glucose measurement. Attributes or controller settings that could be modified to better account for each of these different disturbances: A_m-meal, A_a-physical activity, A_s-sleep and I_A - insulin action.

termined based on the secretion of glucagon and adrenaline that occurs around a plasma glucose level of 70mg/dL in healthy individuals [Association et al., 2005]. There are *three broad categories* of hypoglycemia based on the severity of the event.

Severe hypoglycemia is defined as an event requiring assistance from another person to treat the hypoglycemic episode. This situation implies that the individual's plasma glucose has fallen too low and has impaired cognitive functionality. Sometimes these severe hypoglycemic episodes could cause loss of consciousness, seizures or coma and often require glucagon rescue treatment from the assistant. In people with T1D, severe hypoglycemic episodes are thought to occur at rates between $\approx$ 115 —320 per 100 person years [Cryer, 2016, 2014] .

Mild hypoglycemia is defined as an episode where the individual with T1D experiences symptoms suggestive of hypoglycemia and is able to successfully self-treat the episode. Additionally a sub category of this condition exists known as *moderate hypoglycemia* in which the individual is aware of the condition and can self-treat but experiences severe disruption to the current activity. Both these types of episodes can also be categorized as *Symptomatic hypoglycemia*. The rates of mild hypoglycemia vary widely in this population with episodes being recorded at the rate of one or two a week

[Diabetes Research in Children Network (DirecNet) Study Group, 2007].

Asymptomatic hypoglycemia is defined as an episode in which the individual with T1D measures a low blood glucose value but does not experience any of the associated symptoms. These are situations when the individual coincidentally checked the blood glucose values and they were lower than anticipated. Repeated such episodes could be described as *hypoglycemia unawareness*.

Causes of hypoglycemia. As described earlier in section 1.4.1, the current insulin therapies are an imprecise way to manage people with T1D. Pharmacokinetic/pharmacodynamic (PK/PD) rates of the current formulations of insulins do not mimic that of human insulin or insulin that is already injected in the body does not adequately respond to the changes in plasma blood glucose levels [Cryer, 2016]. Hypoglycemia is the imbalance between glucose utilization and the amount of glucose generated through digestion and hepatic glucose production [Cryer, 2016].

Causes of hypoglycemia in T1D

- Inappropriate insulin injection —e.g. excessive insulin dose, timing issue, wrong insulin formulation.
- Inadequate carbohydrate intake —e.g. missed meal, bed time snack, long fasting periods such as overnight fast.
- Increased glucose utilization —e.g. exercise.
- Diminished endogenous glucose production —e.g. inappropriate or excessive alcohol consumption.
- Altered insulin sensitivity —e.g. post exercise periods, weight loss, diet modifications.
- Decrease in insulin clearance —e.g. inadequate renal function.

People with long standing T1D tend to lose to the ability to release glucagon in response to hypoglycemia and also inevitably lose their ability to respond with adrenaline, leading to increased risk of more protracted hypoglycemic episodes [Cryer, 2016]. Repeated exposure to hypoglycemic episodes attenuates the responses and is often associated with impaired awareness, culminating in Hypoglycemia-Associated Autonomic Failure (HAAF) [Cryer, 2016]. Hypoglycemia unawareness occurs in roughly 25% of patients with longstanding T1D and they have an increased risk of severe hypoglycemia (25 fold increase) [Gold et al., 1994, Frier et al., 1988]. Antecedent hypoglycemia, sleep and exercise cause defective glucose counter-

regulation by the attenuation of epinephrine responses to hypoglycemia. Every hypoglycemic episode induces a response by the body to restore normal blood glucose responses to the brain. This response creates a pre-conditioning response by the neurons for future hypoglycemic episodes and elicits preparation of these cells to utilize alternative fuel sources to respond to low blood glucose levels. In individuals with T1D, as the hypoglycemia occurs due to "non-physiological" situations, higher insulin levels, and limited glucagon response, the counter-regulatory responses are impaired and the access to alternative fuels is also suppressed. After each subsequent hypoglycemic episode, the counter-regulatory responses are further depleted and the reaction occurs at a lower glucose level. As antecedent hypoglycemia has an important role in the pathogenesis of HAAF, rigorous avoidance of hypoglycemia is crucial to avoid the vicious recurrent iatrogenic hypoglycemia cycle.

1.5.1 Nocturnal Hypoglycemia

Nocturnal hypoglycemia is very common in people with T1D [Allen & Frier, 2003a, Group et al., 2010]. Many people with T1D experience nocturnal hypoglycemia once or twice weekly [Group et al., 2010]. Even in the DCCT study, 43% of episodes of severe hypoglycemia occurred between midnight and 08:00h [Bode et al., 1996, Group et al., 1991], and 55% of episodes occurred when individuals were asleep [Group et al., 1991]. Many asymptomatic episodes of nocturnal hypoglycemia are not reported. Deep sleep tends to attenuate the

counter-regulatory responses to hypoglycemia resulting in long protracted hypoglycemic episodes [Group et al., 2010]. The potential for nocturnal hypoglycemia creates a sense of anxiety and fear among many of the individuals with T1D [Fidler et al., 2011]. To combat the risk of nocturnal hypoglycemia many maintain higher blood glucose concentrations at bedtime and tend to consume bed time snacks. During sleep there is attenuation of the sympathoadrenal response to hypoglycemia and as a result people with T1D are not able to wake up to a hypoglycemic event without the aid of an alert system. Furthermore, the *dead-in-bed* syndrome accounts for approximately 6% of all deaths in people with T1D under the age of 40 years, which is probably related to severe nocturnal hypoglycemia [Sovik & Thordarson, 1999].

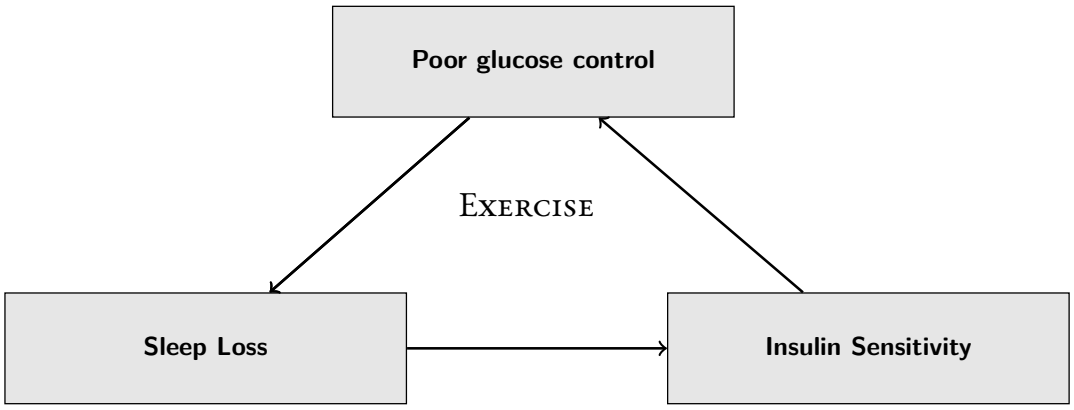

Figure 1.4: Schematic representation of the putative mechanisms underlying sleep curtailment and T1D.

Prevailing characteristics that lead to the development of nocturnal hypoglycemia [Cryer, 2016, Chow & Heller, 2014]

- Insulin stacking, imprudent insulin dosage or incorrect type of insulin
- Inadequate carbohydrate consumption during dinner or long duration between meals
- Excessive alcohol consumption before sleep leading to diminished hepatic glucose production
- Increased exercise activity during the day leading to increased glucose utilization to replenish depleted glycogen stores
- Diminished counter-regulatory responses due to antecedent hypoglycemic episodes or sleep

As nocturnal hypoglycemia has been associated with poor quality of life, and one of the

objectives of this thesis was to understand how much sleep is lost during the night as a result of nocturnal hypoglycemia, identify the risk of nocturnal hypoglycemia and subsequent sleep loss due to different types of exercise.

Interaction of sleep and T1D. Poor sleep is endemic in our society with more than 30% of the population not sleeping adequately[Larcher et al., 2015]. Specifically, people with T1D have an unique relationship with both poor sleep the disease burden could alter sleep duration, and short sleep duration, in turn, could impact disease outcomes. In small controlled studies, adults with T1D were shown to have an altered neuroendocrine sleep architecture [Jauch-Chara et al., 2008] and moderate sleep deprivation was shown to affect insulin sensitivity [Donga et al., 2010a]. People with T1D with poor glycemic control, represented by a higher HbA_{1c}, were objectively determined to have short sleep duration (<6.5 hr per night) compared with patients who slept >6.5 hr a night; poor glycemic control leads to frequent nocturnal hypoglycemia, which in turn leads to sleep disturbances [Borel et al., 2013a]. Schematic in Figure 1.4 shows the complicated underlying mechanisms that exacerbate T1D due to sleep quality. Little is known about how the variations in daily sleep quality patterns affect insulin sensitivity or glycemic control in people with T1D. An exploratory research objective of this thesis was to demonstrate that day to day variations in sleep can lead to changes in glycemic control.

1.5.2 Exercise Related Hypoglycemia

Exercise related hypoglycemia is mainly due to the inability of the individuals with T1D to adequately modulate the exogenous insulin concentrations prior to, and during exercise. As described earlier, in the section 1.4.2, exercise hypoglycemia also occurs due to the increased circulation of the subcutaneous insulin depot and the lack of adequate counter-regulatory response to attenuate the drop in glucose. The imbalance between the glucose utilization and the glucose production result in either a symptomatic or asymptomatic hypoglycemic episode. In the Table 1.1, factors that influence hypoglycemia are listed.

Physical exercise protects against a number of disease risks, across all ages in the general healthy population [Colberg et al., 2016]. Though exercise is highly recommended to individuals with T1D, the altered metabolic state of exercise and the lack of endogenous counter-regulatory response put the longer term cardiovascular benefits at odds with the short term hypoglycemic risk[Colberg et al., 2016, Chu et al., 2011a]. Majority of the individuals with T1D fail to adhere to exercise recommendations and remain less active than their peers without diabetes [Riddell et al., 2017]. Besides the usual barriers to exercise, people with T1D list fear of hypoglycemia, and the difficulty in maintaining normal glucose levels after exercise, as additional hurdles preventing them from engaging in exercise activities [Yardley & Colberg, 2017, Colberg et al., 2016].

Table 1.1: Factors that can influence the changes in glycemic control during exercise[a]

Hypoglycemia	Euglycemia	Hyperglycemia
No prior alterations to insulin dosage	Adequate adjustment to insulin dosage before the last meal and hours before the start of exercise	Complete reduction or elimination of insulin leading to ketoacidosis
Extended aerobic activity without carbohydrate supplementation or insulin reduction	Requisite carbohydrate intake prior to and during activity	Long durations of insulin dose elimination
New activity regiment or inadequate training	Mild and moderate activity ($\leq$ 55-60% maximal oxygen consumption)	Vigorous activity ($\geq$ 80% maximal oxygen consumption)
Defective counter-regulatory response (HAAF)	No HAAF	Repeated intermittent bouts of high intensity exercise
Symptoms of hypoglycemia reduced due to exercise	Early detection of symptoms	Excessive carbohydrate consumption during or after the exercise

[a] Adapted from [Riddell et al., 2017]

Table 1.2: Benefits and Risk associated with Exercise in individuals with T1D[a]

	Active	Sedentary
Body Composition	$\uparrow$	$\downarrow$
Glycemic Control	$\uparrow$ / $\downarrow$	$\downarrow$
Hypoglycemic events	$\downarrow$	$\simeq$
Hyperglycemic episodes	$\uparrow$	$\simeq \downarrow$
Total daily insulin usage	$\uparrow$	$\downarrow$
Insulin sensitivity	$\uparrow$	$\downarrow$
Blood lipid profile	$\uparrow$	$\downarrow$
Cardiovascular fitness	$\uparrow$	$\downarrow$
Inflammation	$\uparrow$	$\simeq$ / $\downarrow$

$^{\simeq}$ No variation

$^{\uparrow}$ Improvement

$^{\downarrow}$ Deterioration

[a] Adapted from [Colberg et al., 2016]

Individuals with T1D who engage in regular exercise experience lower frequencies of diabetic complications and a lower cardiovascular risk profile [Riddell et al., 2017]. In Table 1.2, the benefits and risks associated with exercise in this population are listed. There are a number of unique challenges faced by individuals with T1D at various stages around exercise: they need to prepare for exercise by modifying insulin levels well in advance, taking additional carbohydrates at the start of exercise, and/or during while closely monitoring the glucose levels to prevent any hypoglycemia; and after each session of exercise, they need to be vigilant to the amplified exercise mediated hypoglycemic risk. Post-exercise related hypoglycemia could also lead to HAAF.

Although clinical guidelines for reducing this hypoglycemic risk exist, they are quite generic in nature and not personalized to the individual. General recommendations only considered a single aspect of exercise such as type of exercise, duration, carbohydrate intake, insulin dosage, glucose levels, and intensity. Carbohydrate intake recommendations during exercise are 30 - 60 g of carbohydrates per hour of exercise [Francescato et al., 2015a] but this carbohydrate intake does not take the prevailing glucose levels neither exercise intensity nor suggest an appropriate insulin dosage. Although, guidelines have been improved to include suggested carbohydrate intake suggestions before, during and after exercise, these suggestions are not individualized [MacKnight et al., 2009, Gallen et al., 2011]. Tailoring advice to an individual should be provided on each of following dimensions

- Mode and Type of insulin delivery

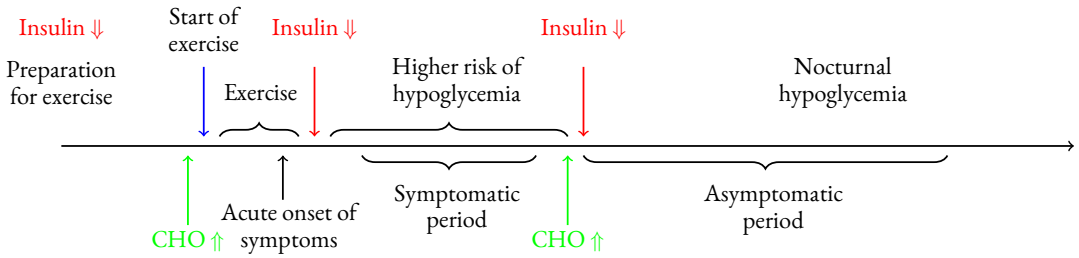

Figure 1.5: Where can decision support be provided. Each arrow indicates, the location where the individual with T1D has to make a decision about their care. Decision support system could provide dosage suggestions or the amount of carbohydrates to be consumed at different points along the day/night. CHO - Carbohydrates, here refers to the suggestion of carbohydrate/snack ingestion.

- Timing of exercise relative to the meal intake
- Timing of exercise relative to insulin bolus
- Current glucose levels at the start of exercise
- Antecedent Hypoglycemia
- Duration and type of exercise
- Intensity of exercise

With these limitation of the guidelines in mind, we approach to solve this challenge by creating a holistic mathematical model based approach. A research objective of this thesis is to provide a model based system that is able to predict hypoglycemia prior to the start of the exercise event.

1.6 Objectives

In this section the research objective and goals are listed, along with how those goals were achieved, within the context of the clinical study conducted. One of the focus of this dissertation is to understand the impact of exercise on sleep and glycemic control in this population. Firstly, to determine the impact sleep duration during the night following different modalities of exercise bouts. Secondly, to evaluate the impact of different modalities of exercise on glycemic control during the 24 hr. after each exercise bout. One of the goals of this dissertation is to provide individuals with T1D tools that would support various dosing decisions and improve long term blood glucose control. As described earlier, the altered glucose homeostasis in the fasted state (overnight) and exercise states is exacerbated by inappropriate insulin dosage choices. To achieve this goal, we conducted a clinical study to identify the challenges with exercise and nocturnal hypoglycemia. Data collected during the study enabled in the design and development of machine learning algorithms to provide the necessary decision support to these unique challenges. In the schematic Figure 1.5 an example of how a decision support system could function is shown.

- Decision support could be provided in the time before exercise to help the individual ascertain the appropriate insulin dosage.
- At the start of exercise, the risks associated with the bout could be assessed and evaluated based on the intensity of upcoming exercise, amount of insulin present in the body and various anthropometric features. This risk and the associated action is per-

sonalized to the individual and the context in which the bout of exercise is being undertaken.

- Based on the glycemic outcome during the exercise, insulin dosing suggestions could be made by the decision support system.
- Due to the elevated risk of nocturnal hypoglycemia after an exercise bout, both insulin and carbohydrate recommendations could be made to limit of this undesirable outcome.

The objectives of this dissertation include the following:

1. Determine the effect of different modalities of exercise on sleep duration in adults with type 1 diabetes
2. Determine the effect of different modalities of exercise (Aerobic exercise and Resistance training) on glycemic control in adults with type 1 diabetes
3. Develop a new algorithm that can be used to predict hypoglycemia during aerobic exercise in adults with type 1 Diabetes
4. Develop a new algorithm that can be used to predict nocturnal hypoglycemia prediction in adults with type 1 diabetes

1.7 Chapter Outline

To accomplish the objective of creating a model based decision support system, a comprehensive pilot clinical study was conducted. The study protocol is provided in the chapter 9. The pilot study was named: *A randomized, three-way, cross-over study to assess the impact*

of nocturnal hypoglycemia on sleep in adults with Type 1 diabetes. After 1 week of run-in, 10 adults with T1D, who self-managed their glucose levels with their own insulin pump, were followed for 3 additional weeks, and each of those weeks were randomized to aerobic, resistance or no exercise (control). During each exercise week, participants completed two monitored 45 minute exercise sessions at OHSU. To accomplish the goal of comprehensive data collection, participants were given a continuous glucose monitor, an activity monitor and a custom smart-phone app to capture all the meals consumed during the study. The data from this study forms the basis of the models developed to provide decision support.

Chapter 2: We describe the challenges associated with exercise. On the night following exercise, we show that subjects in the study experienced significant amount of sleep loss after aerobic exercise, but not after resistance training. We also quantified the increased odds of experiencing nocturnal hypoglycemia after a bout of either resistance or aerobic exercise.

Chapter 3: Prevailing epidemiological & experimental evidence has shown that physical exercise is beneficial in reducing long term complications in adults with T1D. Here we strengthen this premise by showing that resistance training, as opposed to aerobic exercise, also provides favorable glycemic outcomes.

Chapter 4: Detecting aerobic exercise as early as possible is crucial in the context of AP systems to prevent exercise related hypoglycemia. In this chapter, we describe how an exercise detection system was created, tested and validated in a clinical study.

Chapter 5: Wrist-based consumer wearable devices have the ability to measure heart rate and intensity of activity. In this chapter we describe the accuracy of these devices and the challenges associated with using these devices in the context of AP systems.

Chapter 6: In this chapter, multiple classification models are presented to predict exercise related hypoglycemia. A simple heuristic model, that could be used by individuals with T1D, and a complicated machine model, that could be used by both AP systems and decision support systems, is validated using clinical data.

Chapter 7: In this chapter, we present a data-driven approach to predict nocturnal hypoglycemia at bed time. Using a machine learning approach we develop and test multiple classification models. The goal of this approach was to *proactively* prevent nocturnal hypoglycemia.

Chapter 8: In this concluding chapter, exploratory outcomes from the clinical study and the future directions of this research are presented.

1.8 Dissertation Contributions

This thesis presents several contributions to the area of research that are at the intersection of T1D, exercise, sleep and disease management. These contributions include two basic science contributions, one device validation and three engineering contributions. These contributions are discussed in more detail below.

1.8.1 Basic Science Contributions:

In Chapter 2, we present the novel outcomes from the clinical study on the impact of exercise on sleep in adults with T1D. We showed that on the nights after aerobic exercise individuals with T1D experienced significant sleep disruption leading to an average sleep loss of 70 minutes. The average sleep loss after resistance training was more variable with an average sleep loss of only 27 minutes. The findings from this study clearly demonstrated the increased likelihood of nocturnal hypoglycemia after exercise. This work has been published in the journal —Diabetes, Obesity & Metabolism -*Diabetes, Obesity & Metabolism, Volume 20, Issue 2, pp. 443-447*.

In Chapter 3, we show that exercise interventions in adults with T1D could have a posi-

tive effect on the glycemic control. We show that there is a significant improvement in the time in range after resistance training but not after aerobic exercise. The improvement in the time in range was 14% higher during the 24 hr. after resistance training when compared with days following no exercise. We also showed that the overall energy consumption after either type of exercise is significantly higher than when there is no explicit exercise done by the subjects. We also demonstrated using a random-effects model that even after adjusting for the increased energy consumption the benefits of resistance training on glycemic control are maintained. In the past other groups, have speculated that the reason for the lack of improvement in glycemic control after aerobic exercise interventions could be the glycemic variability associated with increased carbohydrate consumption. In this work, we showed that due to increased carbohydrate ingestion after exercise and relative imbalance in the insulin dosage patterns after exercise, the benefits to glycemic control are diminished. This work has been published in the journal —Canadian Journal of Diabetes. - *Canadian Journal of Diabetes, August, 2018. https://doi.org/10.1016/j.jcjd.2018.08.193.*

1.8.2 Device Validation Contributions:

In Chapter 5, we measured in a multi-site clinical study the accuracy of both heart rate and energy expenditure for two common wrist-worn devices during dynamic activities. We

showed that both the Fitbit device and the Garmin device were reasonably accurate at measuring heart rate with an overall negative bias. The energy expenditure estimates were found to correlate poorly with indirect calorimetry. This work extended the knowledge in the area by validating these devices in non-steady state activities such as e.g., resistance exercises and high intensity interval training. We demonstrated that these devices perform poorly when there is a lack of repetitive wrist motions. We also showed the importance of indicating the onset of activity. This work has been published in the journal —Journal of Medical Internet Research (JMIR mHealth and uHealth). *JMIR mHealth and uHealth, March,2018. https://doi.org/10.2196/10338*.

1.8.3 Engineering Contributions:

In Chapter 4, we present an extension of a validated energy expenditure algorithm to be applied for exercise detection in the context of an artificial pancreas system. Early detection of exercise and appropriate control system response is an ongoing area of research. We extended the energy estimation algorithm developed and validated in adolescents using older sensors to adults using the current generation of sensors. We identified the threshold for detection of exercise and validated that this identified threshold is appropriate for use with the context of artificial pancreas systems. In a recently concluded clinical study, the implementation of this

adapted algorithm successfully detected 95% of the exercise events[Castle et al., 2018a].

In Chapter 6, we present two separate models that could be used to predict hypoglycemia at start of exercise. While, other groups have identified the risk of hypoglycemia during exercise, here we present an approach that identifies the risk of hypoglycemia at the start of exercise using a combination of glucose and activity inputs. This combined with the early detection of exercise presented in Chapter 4, could used to prevent exercise induced hypoglycemia in adults with T1D. We also present a simple heuristic based approach to predict hypoglycemia related to aerobic exercise. This simple model was able to achieve an accuracy of 80% at identifying hypoglycemia. The complex machine learning model-random forest model that was developed using multiple inputs can be used in both artificial pancreas systems and automated decision support tools. This model was developed and validated using clinical data collected from multiple studies. This model achieved an accuracy of 87% in the validation data set. This tool has the potential for reducing the risk of hypoglycemia due to exercise and could lead to increased adoption of an active lifestyle by many people living with T1D. This work has been prepared for publication in Diabetes Technology & Therapeutics.

In Chapter 7, a classifier to detect if an individual with T1D would experience nocturnal hypoglycemia during sleep is presented. Multiple classification models were built to ascertain

the risk associated with experiencing a nocturnal hypoglycemic event. The best performing machine learning algorithm- gradient boosted machine was developed and validated using the data collected as part of this thesis. Nocturnal hypoglycemia can be detected using current continuous glucose monitoring technology, however the alert happens at the time of hypoglycemia, and the person is oftentimes not awakened by the alert. The work presented here advances the detection of the hypoglycemic event to before the individual is asleep. This approach could be used potentially in the context of decision support systems to advise individuals with T1D about the appropriate course of action at bed time.

To trace something unknown back to something known is alleviating, soothing, gratifying and gives moreover a feeling of power. Danger, disquiet, anxiety attend the unknown—the first instinct is to eliminate these distressing states. First principle: any explanation is better than none... The cause-creating drive is thus conditioned and excited by the feeling of fear...

Friedrich Nietzsche,

Twilight of the Idols and The Anti-Christ

2

The effect of exercise on sleep in adults with type 1 diabetes

HIGHLIGHTED in this paper is one the significant challenges associated with exercise in adults with Type 1 diabetes. Post exercise nocturnal hypoglycemia tends to occur during the night after exercise and in this paper we showed that on average 70 minutes of sleep loss is associated with aerobic exercise. We also show that the odds of nocturnal hypoglycemia occurring on

nights after either aerobic or resistance exercise are much higher than previously reported.

Chapter summary

- Adults with T1D on average experience 70 minutes of sleep loss after aerobic exercise
- Sleep loss after resistance exercise is more variable with an average sleep loss of only 27 minutes
- Odds of nocturnal hypoglycemia after aerobic exercise is 5.4 times than on nights following no structured exercise.
- Resistance exercise is associated with 7 times higher odds of experiencing nocturnal hypoglycemia

This work was originally published in 2018 by

Diabetes, Obesity & Metabolism, Volume 20, Issue 2, pp. 443-447

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2.1 Abstract

The aim of this pilot study was to investigate the effect of exercise on sleep and nocturnal hypoglycaemia in adults with type 1 diabetes (T1D). In a 3-week crossover trial, 10 adults with T1D were randomized to perform aerobic, resistance or no exercise. During each exercise

week, participants completed 2 separate 45-minutes exercise sessions at an academic medical center. Participants returned home and wore a continuous glucose monitor and a wrist-based activity monitor to estimate sleep duration. Participants on average lost 70(±49) minutes of sleep (P= .0015) on nights following aerobic exercise and 27(±78) minutes (P=.3) following resistance exercise relative to control nights. The odds ratio with confidence intervals of nocturnal hypoglycaemia occurring on nights following aerobic and resistance exercise was 5.4 (1.3, 27.2) and 7.0 (1.7, 37.3), respectively. Aerobic exercise can cause sleep loss in T1D possibly from increased hypoglycaemia.

2.2 Introduction

Regular structured physical activity (PA) in adults with type 1 diabetes (T1D) provides physiological and psychological benefits including reduction in macrovascular complications, improvement in lipid profiles, increased lean body mass, and enhanced self-esteem[Chu et al., 2011b]. However, PA is associated with an increased risk of hypoglycaemia that may occur during, shortly after or even many hours after PA, and the risk of nocturnal hypoglycaemia can persist for several days[Diabetes Research in Children Network (DirecNet) Study Group, 2007, McMahon et al., 2007, Wilson et al., 2015]. The risk of nocturnal hypoglycaemia ranges from 14% to as high as 56% in children and adults[Allen & Frier, 2003b]. Nocturnal hypoglycaemia increases anxiety levels and is associated with a negative effect on the quality of life due

to its effect on sleep quality and quantity[Allen & Frier, 2003b, Brod et al., 2013a]. While prior groups have related PA to increased nocturnal hypoglycaemia, no-one has yet quantified the amount of sleep loss either due to nocturnal hypoglycaemia or due to the increased risk of nocturnal hypoglycaemia on nights following different types of exercise. While exercise has been shown to increase sleep duration in people without type 1 diabetes[Youngstedt, 2005], the effect of exercise in people with T1D is unknown. The purpose of the current study was to examine the effect of late afternoon PA on nocturnal hypoglycaemia and sleep duration. We hypothesized that there would be increased nocturnal hypoglycaemia and related sleep loss after aerobic exercise and also after resistance exercise relative to nights following control days of no structured PA.

2.3 Methods

In this study, participants carried wearable glucose sensors, actigraphy sensors, their own insulin pump, and a custom-built food-tracking Android smart-phone application that measured their glucose, PA, insulin, food, and sleep continuously for 4 consecutive weeks. The first week of the study was a run-in week in which participants became accustomed to the wearable sensors. After the run-in week, participants performed 1 week of in-clinic aerobic exercise twice that week, 1 week of in-clinic resistance exercise done twice that week, and 1 control week when no structured exercise was done by the participants. The order of the aerobic,

resistance, and control weeks were randomized for each subject.

The Institutional Review Board at the Oregon Health and Science University (OHSU) approved the study protocol and consent form. Eligibility criteria were age 21 to 45 years, a duration of type 1 diabetes >1 year, current insulin pump use, an absence of diabetes-related complications and participating in PA at least 30 minutes 3 or more times per week. Ten adults (6F) were recruited (mean± standard deviation (SD): age 33±6 years, BMI 24.4±2.1 kg/m^2, duration of diabetes 18±10 years, HbA_{1c} 7.4%±1%(57±11 mmol/mL), VO_2peak 46.8±11.55 mL/kg/min). All participants completed a screening visit, training visit, and 4 structured exercise sessions.

After providing informed consent, enrolled participants were given a VO_2max x test according to the standard Bruce Protocol on a MedTrack ST 55 treadmill. Participants returned on a separate day to be trained in how to use a DexCom G4 or G4 Share CGM (continuous glucose monitor) system (DexCom, San Diego, CA) and how to use the activity monitor (ActiGraph wGT3X-BT; ActiGraph, Pensacola, FL). Participants replaced the CGM each week (at least a day before the exercise visit) and calibrated the sensor at least twice daily using a Contour Next glucose meter (Ascensia Diabetes Care, NJ). Although participants were blinded to CGM values, for safety, glucose alerts were set at 55 mg/dL (3.0 mmol/L) and 300 mg/dL (16.7 mmol/L). Hypoglycaemia was defined as CGM values less than 70 mg/dL (3.9 mmol/L). A 1-repetition maximum (1-RM) test for bench press, leg press and seated row

was performed to set the exercise intensity (ie, weight lifted) for resistance training sessions. Participants completed 3 validated sleep questionnaires, the Pittsburgh Sleep Quality Index (PSQI)[Buysse et al., 1989], the Epworth Sleepiness Scale (ESS) [Johns, 1991] and the Berlin Questionnaire (BQ) [Netzer et al., 1999]. These were used to assess sleep quality, excessive daytime sleepiness, sleep apnea risk. Computer randomization was used to determine the sequence of the exercise and control weeks.

Participants wore ActiGraph wGT3X-BT - a small, lightweight (19 g), triaxial accelerometer with a light sensor on their nondominant wrist for the entire duration of the study. Sleep was measured using this activity monitor and data were analyzed using the ActiLife software (ActiGraph) with the Cole-Kripke algorithm [Cole et al., 1992].

2.3.1 Experimental Visits

Subjects participated in 2 sessions of aerobic training during the aerobic exercise week and 2 sessions of resistance training during the resistance week. Participants arrived at the laboratory at 4:00 PM for each of the exercise sessions. For both the aerobic and resistance exercise weeks, the same exercises were performed on 2 separate days with 1 day in between (eg, resistance training session on a Tuesday and Thursday). The days on which exercise sessions were conducted were identical for each participant across weeks. All exercise sessions were conducted on weekdays excluding Friday. Control nights were selected to be on the same nights

as the exercise nights. Resistance exercise sessions included 3 sets of 8 to 12 repetitions($\approx$ 60-80% of 1-RM) of 5 different exercises (leg press, bench press, leg extension, leg flexion and seated row) with a 90-second rest period between exercises and sets (duration $\approx$45min). The Borg perceived exertion scale was used to estimate fatigue by the participant and with the goal to not exceed the moderate intensity rating of 12 to 14 for each exercise performed. Aerobic exercise consisted of 45 minutes of treadmill exercise (60% of VO_2max). The duration of the exercise intervention was kept consistent for the 2 types of exercise; but the energy expenditure for these 2 types of exercises was not controlled for in this study. Capillary glucose was checked before the start of the exercise period and immediately after exercise. If the subject was below 70 mg/dL or above 300 mg/dL, exercise was delayed until glucose returned to within range. Glucose tablets or juice was provided to treat hypoglycaemia. Each exercise session was followed by 60 minutes of monitored resting recovery. Participants selected one of 2 meals to eat during the recovery period and the identical meal was consumed during subsequent study visits.

All statistical analyses were performed using R-Software [R Core Team, 2017]. A paired means power analysis was used to carry out sample size power analysis. A total sample size of 10 achieved 90% power to detect a mean of paired differences of 30 minutes in sleep loss. This is with an estimated standard deviation of differences of 25 and with a significance level (alpha) of .05 using a 2-sided paired t-test comparing sleep loss during the weeks of exercise

interventions with the week without any explicit exercise. Two analyses were done: the first to assess effect of exercise on sleep duration and the second to assess effect of exercise on occurrence of a single hypoglycaemia event in a night. For the first analysis, duration of sleep after the exercise sessions (resistance and aerobic) was analyzed and compared with the duration of sleep on nights when no explicit exercise was done (control). As each subject had 2 aerobic exercise sessions, 2 resistance sessions, and 2 corresponding control days, we averaged sleep duration, carbohydrate intake, insulin dosed, and time in severe hypoglycaemia across both nights and compared the average between weeks of exercise interventions with the week without any explicit exercise. Paired sample t-tests were used to perform pairwise post hoc comparisons for average of nights between resistance and aerobic interventions relative to the control. As 2 interventions were compared against a single control, significance was adjusted to .025. For the second analysis, a randomized mixed effects logistic regression model with subject as random effect was used to estimate the odds ratio of a single hypoglycaemia episode occurring on nights (9:00 PM to 9:00 AM) following aerobic and resistance exercise compared with control nights. For this analysis, each night was used as a binary variable indicating whether a single hypoglycaemia event occurred during that night (9 PM to 9 AM). We further considered the order of the nights as a repeated measure and evaluated the significance of the order.

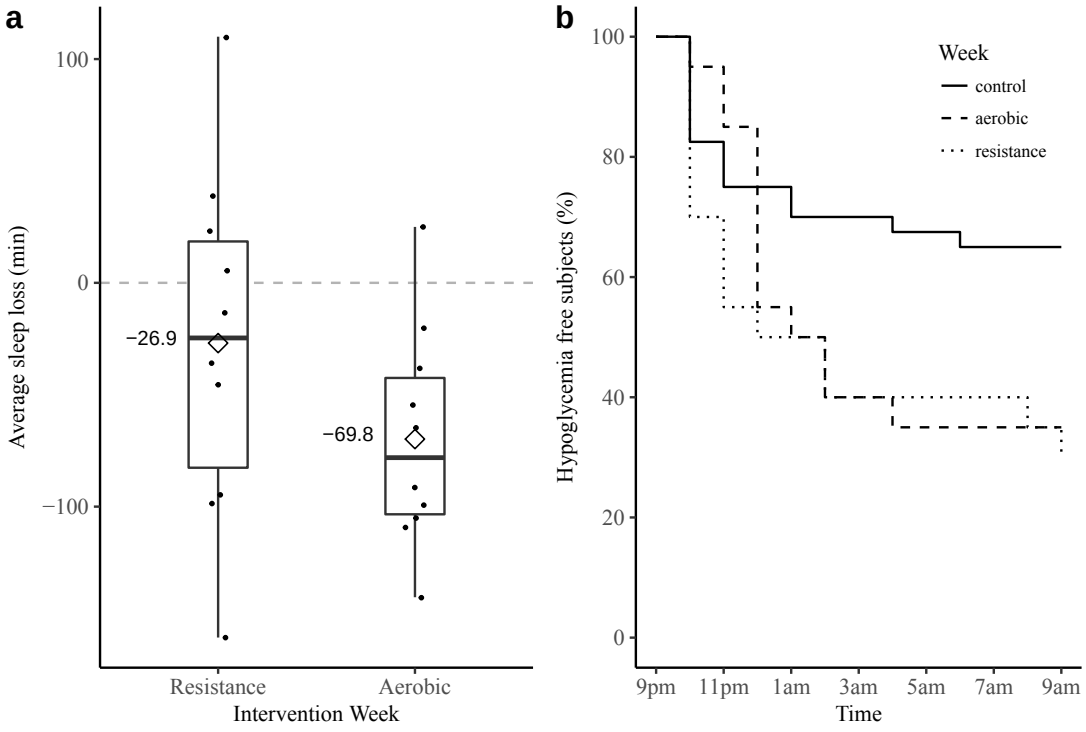

Figure 2.1: A, Average sleep loss (minutes) for each of the intervention weeks as compared with the control week. The dashed line (- - -) indicates the no change in sleep during the night of observation relative to the control night. The ◊ and the number next to it, indicate the mean value of the sleep loss. All but one participant experienced sleep loss on nights following aerobic exercise. B, Kaplan–Meier plot for hypoglycaemia-free subjects and the incidences of hypoglycaemia events. The solid line (—) indicates the control nights, the dashed line (- - -) and the dotted line (...) indicates resistance nights.

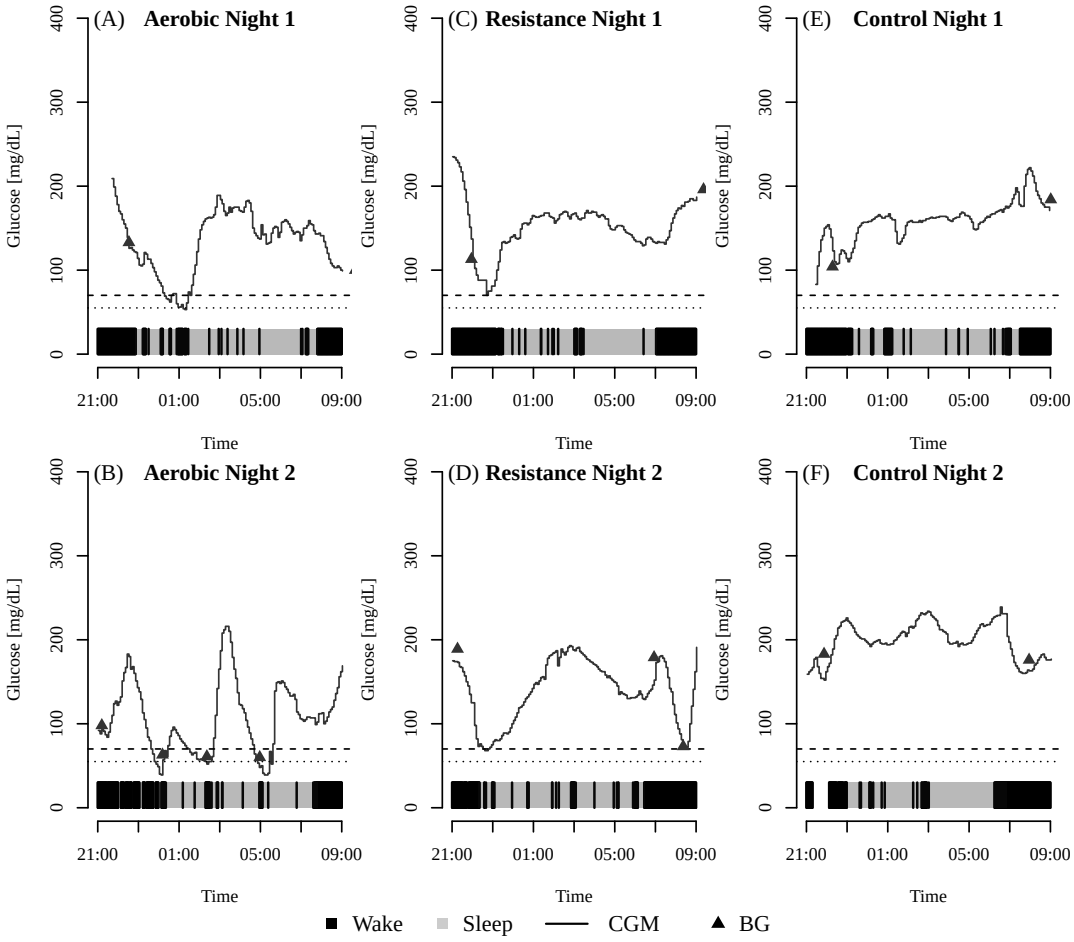

Figure 2.2: Here we show the CGM sensor and the actigraphy data overlaid. The CGM sensor data are shown as a solid black line and the actigraphy data are shown below the sensor data, as indicated by the gray squares for sleep and black squares for being awake. Capillary blood glucose (BG) checks performed by the subject are indicated with a black triangle. Panels A-B show the aerobic nights, panels C-D show the resistance nights and panels E-F show the control nights. The dashed line indicates hypoglycaemia at 70 mg/dL (3.9 mmol/L) and the dotted line indicates severe hypoglycaemia at 54 mg/dL (3.0 mmol/L). Hypoglycaemia events during the nights following aerobic exercise are associated with sleep loss and can be observed by the change in the actigraphy state. Hypoglycaemia events during the nights following resistance exercise occur early in the night and were not associated with sleep loss. And hypoglycaemia did not occur during control nights

2.4 Results

All participants completed the full protocol. In this active participant cohort none of the participants reported sleep issues at baseline with no excessive daytime sleepiness (ESS score <7), with 2 subjects reporting habitual snoring but no other symptoms of sleep apnea based on the BQ. Participants had good overall sleep quality (PSQI score <3). The mean (±SD) sleep duration was 6.8(±0.8) h/night during the control week (weeknights only), 5.6(±1.1) h/night during nights following aerobic exercise, and 6.4(±1.5) h/night during the nights following resistance exercise. The 70 minutes of sleep loss on the nights following aerobic exercise compared with control nights was statistically significant (P = .0015) but the sleep loss on the nights following resistance exercise compared with control nights was not (P = .3). Figure 2.1 A shows how all but one participant experienced less sleep on nights following aerobic exercise compared with the control week. The average sleep onset latency was 0.5(±1.4) min/night and the average bedtime was 11:30 PM (±65 minutes) and there was no difference in either sleep latency or bed time between the different weeks. The percentage of nights in which at least one hypoglycaemia event occurred (CGM <70 mg/dL) was 30%, 65%, and 70% for nights following control, aerobic, and resistance days. Average insulin on board concentration at bed time was lower following both aerobic and resistance exercise days as compared with the control and the reported carbohydrate intake was higher following aerobic and re-

sistance exercise days as compared with the control (See 2.1). Subjects were more likely to consume a pre-exercise snack when doing aerobic exercise compared with resistance exercise (See 2.2). And subjects were more likely to reduce or suspend insulin following aerobic exercise compared with resistance exercise (See 2.3). Figure 2.1B shows the Kaplan–Meier plot for the percentage of subjects who remained hypoglycaemia-free on nights following exercise and control nights. Severe hypoglycaemia (CGM < 54 mg/dL [3.0 mmol/L]) occurred on 8 nights following aerobic exercise as compared with 3 nights on nights following resistance and 3 nights for control nights. The average percent of time spent in severe hypoglycaemia was 3.7%($\pm$8.4%), 1.8%($\pm$7.3%), 2.4%($\pm$6.1%) during the nights following aerobic, resistance and control, respectively. A majority of the hypoglycaemia events for the nights following the resistance exercise occurred earlier in the night. The odds of hypoglycaemia occurring increased by 5.4 (1.3, 27.2) on nights after aerobic exercise compared with nights after nonexercise control days and by 7.0 (1.7, 37.3) on the nights following resistance exercise. We did not observe an order effect on hypoglycaemia in day 1 and day 2 of exercise for either intervention. While nocturnal hypoglycaemia was related to PA (chi-squared = 7.4, P = .025, R^2 = 0.30), nocturnal hypoglycaemia was not found to relate with sleep duration in this small sample size. This may have been due to the substantial variability in the response of the participants to hypoglycaemia. For example, some subjects slept through hypoglycaemia while others treated their hypoglycaemia at night and experienced sleep loss. Figure 2 2.2 shows the

sensor glucose and the sleep data overlaid for a single subject across the different nights of the study. This subject experienced multiple hypoglycaemia events during the nights following aerobic exercise and each hypoglycaemia event caused sleep loss.

2.5 Discussion

This study assessed the effect of structured exercise on sleep duration related to nocturnal hypoglycaemia in physically active individuals with T1D. Results here also confirm higher hypoglycaemia after structured PA. These results indicated that aerobic activity can negatively affect sleep by reducing total sleep duration on the night following exercise by an average of 70 minutes. While resistance exercise also led to sleep loss, the effect was less and not statistically significant in this small sample size. This study may have been strengthened if we had included a healthy cohort to observe whether stress from PA was a potential confounding factor that may have influenced sleep. However, prior research has shown that in people without T1D, sleep duration is increased with PA, even in people who do not exercise regularly [Youngstedt, 2005]. All participants in the current study were required to be physically active and to do regular exercise (minimum of 30 minutes 3 times per week). Aerobic and resistance exercise are known to impact glycaemic control in different ways, and prior findings indicate that aerobic exercise can lead to sharper drops in glucose levels in people with T1D [Yardley et al., 2013]. It is currently not known whether this change is because less en-

ergy is expended during resistance exercise compared with aerobic exercise or if there is some other mechanism. It has been reported that the increase in catecholamine levels during resistance activities could contribute to increased hepatic glucose production and inhibit insulin-mediated glucose uptake [Yardley et al., 2013]. While people with T1D may be aware of the increased risk of hypoglycaemia during PA, immediately after PA and overnight up to 7 to 11 hours later [Pinsker et al., 2016], they may not be aware of the effect on sleep loss. Given that the interaction between sleep disturbance and T1D is complex and that the loss of sleep could result in decreased insulin sensitivity on the day after a poor night's sleep [Donga et al., 2010b] increased vigilance and improved recommendations for post-exercise insulin delivery are needed to help overcome nocturnal hypoglycaemia and the associated sleep loss.

2.6 Supplementary Data

2.6.1 Insulin and Carbohydrate Intake

Week	IOB @ start of exercise (U)	IOB @ end of exercise (U)	IOB @ start of start of bedtime (U)	Carbohydrate Intake (g)
Control	4.90	4.66	6.17	84.40
Aerobic	4.56	3.75	5.74	121.72 *
Resistance	4.68	4.62	4.38*	108.83 *

Table 2.1: The table details the average on board insulin concentrations (IOB) at different points of time and the reported carbohydrate intake after the exercise bout and before bed time. Paired sample t tests were used to perform pairwise post hoc comparisons for nights between resistance and aerobic interventions relative to the control. Since two interventions were compared against a single control, significance was adjusted to 0.025. (*p<0.025)

2.6.2 Preparation for Exercise

Week	Percentage of participants who consumed a pre-exercise snack (%)	Percentage of participants who reduced/suspended basal Insulin (%)
Aerobic Exercise	55	85
Resistance Training	25	40

Table 2.2: The table details how participants prepared for the exercise visit. All participants were aware of the current insulin and carbohydrate recommendations prior to exercise.

2.6.3 Preparation post Exercise

Week	Percentage of participants who who reduced/suspended basal insulin (%)	Percentage of participants who reduced meal bolus (%)
Aerobic Exercise	55	65
Resistance Training	25	30

Table 2.3: The table details how many participants changed insulin basal rate post exercise bout and the meal bolus for the post exercise meal that was provided.

Thus the discovery of the barometer transformed physics, just as the discovery of the telescope transformed astronomy...The history of science has its own revolutions, just like the history of nations ...with this significant difference, that revolutions in science...successfully achieve what they set out to do.

Vincenzo Antinori, Notizie istoriche,1841

3

Effect of aerobic and resistance exercise on glycemic control in adults with type 1 diabetes

Physical Exercise interventions in adults with type 1 diabetes (T1D) have not been shown to have a positive effect on the glycemic control. This has been attributed to excessive carbo-

hydrate treatments after exercise and relative imbalance in the insulin dosage patterns after exercise. In this study we show that there is a significant improvement in the time in range after resistance training but not after aerobic exercise. We also show that the overall energy consumption after either type of exercise is significantly higher than when there is no explicit exercise done by the subjects. We also demonstrate using a random-effects model that even after adjusting for the increased energy consumption the benefits of resistance training on glycemic control are maintained.

Chapter Summary

- The mean time in range in the 24 hr. following resistance training is 70% vs only 56% in 24 hr. following no explicit exercise. The mean time in range in the 24 hr. following aerobic exercise is only 60%.
- The time spent in the hypoglycemic range was not different between either interventions (Resistance or Aerobic)
- Participants reported consuming higher amount of energy after either bouts of exercise.
- Resistance training may improve glycemic control in adults with type 1 diabetes.
- Glucose levels tend to decline less during resistance exercise compared with during aerobic exercise.

This work has been accepted for publication in the

Canadian Journal of Diabetes

3.1 Abstract

Aims: Physical exercise is recommended to individuals with type 1 diabetes (T1D) yet the effects of exercise on glycemic control have not been well-established. We evaluated the impact of different modes of exercise on glycemic control in people with T1D.

Methods: In a 3-week randomized crossover trial, 10 adults with T1D who self-managed their glucose levels with their own insulin pump (4 M, 6 F; age 33 $\pm$ 6 yrs, duration of diabetes 18 $\pm$ 10 yrs, HbA_{1c} 7.4 $\pm$ 1%) were assigned to three weeks of intervention: aerobic (treadmill at 60% of VO_2max), resistance (8-12 repetitions of 5 upper and lower body exercises at 60-80% of 1-RM) or no exercise (control). During each exercise week, participants completed two monitored 45—minute exercise sessions at an academic medical center. For each week of the study we analyzed participant's insulin pump data were downloaded, glucose sensor data was recorded using a continuous glucose monitor (Dexcom G4) and energy intake was recorded using a custom smart-phone app including photographs of the meals which were analyzed post-hoc by a dietitian. The primary outcome was percentage of time in range (glucose >3.9 mmol/L and <=10 mmol/L) for the 24 hours after each bout of exercise or rest during the control week. The study was registered on ClinicalTrials.gov (NCT:02687893).

Results: Aerobic exercise caused a mean glucose reduction during exercise of 3.94 ± 2.67 mmol/L while the reduction during resistance was 1.33 ± 1.78 mmol/L (p=0.007). Mean percentage time in range for the 24 hours fThe mean percentage of time in range following resistance exercise was significantly greater than during the control period (70% vs. 56%, respectively, $P = 0.013$) but not following aerobic (60%).

Conclusions: Results from this pilot study indicate that while considering various confounders, resistance training could have improvements on glycemic control in this population. □

3.2 Introduction

□ In the coming decades the number of patients with type 1 diabetes (T1D) is expected to triple [Imperatore et al., 2012]. Less than a third of the adults with T1D achieve the target glycated hemoglobin level of lower than 7.0% [Miller et al., 2015b] and a majority are overweight or obese [Weinstock et al., 2016b, McKnight et al., 2015]. Bohn et al, have recently shown that less than a fifth of adults with T1D manage to meet physical activity recommendations [Bohn et al., 2015]. Overweight and obese weight status in individuals with T1D is higher than the general population and prevalence is rising; this appears to be unrelated to aging and instead related to lack of physical activity and other clinical factors [Conway et al., 2010]. Currently,

adults living with T1D are recommended to perform 150 minutes of moderate aerobic, 75 minutes of vigorous aerobic, or a combination thereof, along with resistance training on two days each week with no more than two consecutive days of no activity [Colberg et al., 2016]. Regular physical activity in individuals with T1D provides many physiological and psychological benefits including improving body composition, increased cardiorespiratory fitness, improved endothelial function, and improved blood lipid profile [Quirk et al., 2014, Miller et al., 2016, Katz et al., 2015]. In addition, exercise also reduces total daily insulin requirements, stress and depression while improving the overall sense of well-being and quality of life [Kennedy et al., 2013, Chimen et al., 2012, Zoppini et al., 2003].

Physical activity has long been associated with improvements in glycemic control in adults with type 2 diabetes (T2D) [Umpierre et al., 2011]. These improvements have been shown to be modest when the physical activity was either aerobic or resistance training, but a combination of both modalities has demonstrated the greatest improvements to glycemic control in adults with T2D [Sigal et al., 2007]. However, in individuals with T1D, the effects of physical activity on glycemic control are not clear [Kennedy et al., 2013, Chimen et al., 2012, Yardley et al., 2014]. Aerobic exercise (endurance-based) is associated with higher frequency (high-repetition) in the muscular contractions under low to medium loads, whereas resistance exercise (strength-based) imposes a low-frequency, high-load demand on the mus-

culature [Zierath & Wallberg-Henriksson, 2015]. The consequence of the distinction in these two modalities, duration and intensity of the type of exercise determines the a wide range of metabolic responses [MacInnis & Gibala, 2017, Hawley et al., 2014]. During acute exercise bouts, increased glucose uptake is a combination of both insulin-independent metabolic pathways and increased insulin sensitivity [MacInnis & Gibala, 2017, Hawley et al., 2014]. In people with T1D, this increased glucose disposal, along with the absence of systemic reduction of insulin and concurrent increase in glucagon production leads to hypoglycemia [Yardley et al., 2013, Chimen et al., 2012, Riddell et al., 2017, Jacobs et al., 2016].

Without advanced planning, these glucose changes are rather challenging to manage. Nocturnal hypoglycemia is common on nights after engaging in physical activity [Reddy et al., 2017]. Optimizing insulin dosage prior to exercise is challenging for many people with T1D engaging in physical activity. Insulin dosage changes have to be made up to 90 min before the start of the exercise [Riddell et al., 2017, Zaharieva et al., 2017] and depending on the modality (aerobic/resistance training) and intensity of exercise (level of exertion), altering insulin dosing may not result in achieving appropriate glycemic control [Riddell et al., 2017, Zaharieva et al., 2017]. Another strategy adopted by many individuals to prevent hypoglycemia, is to maintain blood glucose levels higher during and after exercise by increasing the consumption of carbohydrates [Francescato et al., 2015b, Ryninks et al., 2015]. While many groups have highlighted the acute challenges faced by people with T1D during various types of exercise,

there has not yet been a study showing how exercise impacts glycemic control during longer periods after exercise is performed [Yardley et al., 2012, 2013, Iscoe & Riddell, 2011]. In this paper we examine the impact of aerobic exercise and resistance training and related energy expenditure on glycemic control. We further examine how exercise impacts both insulin dosing requirements along with the amount of dietary intake in a period of 24 hours after a bout of exercise. We hypothesized that compared with days with no exercise, aerobic exercise and resistance training would be associated with increased dietary intake and improved glycemic control. We hypothesized that glycemic control during a period of 24 hours post-exercise would be improved.

3.3 Methods

3.3.1 Study participants

Ten adults with T1D were recruited to participate in this randomized, three treatment, unblinded, single-center crossover study. The inclusion criteria for this study were: adults with T1D (diagnosis of condition >1 year); age 21—45 years; body mass index <30 kg/m^2; physically active (≈150 min of moderate physical activity per week or ≈60 min of vigorous physical activity per week or active at least 3 days a week); currently on an insulin pump; and willing to perform 45 min of exercise. Sufficiently active was defined as participating in at least 150

min of aerobic activity at moderate intensity per week for the last six months based on the guideline by ACSM [American College of Sports Medicine, 2013]. Participants in this study were active at moderate intensity for 7.3± 4 hr/week. The exclusion criteria included the following: cardiovascular disease, renal dysfunction or any condition that would preclude exercise.

The Institutional Review Board at the Oregon Health and Science University (OHSU) approved the study protocol and consent form. This current paper is a secondary analysis using the data collected during the study to examine the effect of exercise on sleep in adults with type 1 diabetes [Reddy et al., 2017]. The study was registered on ClinicalTrials.gov (*NCT:02687893*). Informed consent was obtained from every individual.

Characteristic	Number =10
Age (years)	34±6
Gender (M/F)	4/6
Duration of diabetes (years)	18±10
Body Mass Index (kg/m^2)	25±5
HbA_{1c} (%)	7.4±1.0
HbA_{1c} (mmol/mol)	57±11
VO_2max	46.8±11.5
Fat (%)	30±7

Table 3.1: Baseline characteristics of the participants. Continuous data represented as mean±standard deviation.

3.3.2 Study design

In this pilot study, we performed a secondary analysis on data that was previously published in Reddy et al. [Reddy et al., 2017], a study which found that exercise impacted sleep on nights following exercise. A paired means power analysis was used to carry out sample size power analysis. A total sample size of 10 achieved 90% power to detect a mean of paired differences of 30 minutes in sleep loss. This is with an estimated standard deviation of differences of 25 and with a significance level (alpha) of .05 using a 2-sided paired t-test comparing sleep loss during the weeks of exercise interventions with the week without any explicit exercise. In the current analysis, we hypothesized that glycemic control during a period of 24 hours post-exercise would be improved. The primary outcome was the percent time in a target glucose range of between 3.9 and 10 mmol/L during the 24 hours after exercise. Glucose levels were tracked using a continuous glucose monitor (CGM; Dexcom G4 or G4 Share, Dexcom, San Diego, CA, USA). Participants were blinded to the sensor glucose readings. Physical activity and sleep were monitored using an activity monitor (ActiGraph wGT3X-BT; ActiGraph, Pensacola, FL, USA). Participants managed their own insulin dosage using their personal insulin pump and a capillary blood glucose meter (CBG meter, Contour Next glucose meter; Ascensia Diabetes Care, NJ, USA). Food intake was measured using a custom built food-tracking Android smart-phone app. A smart-phone (Galaxy S4; Samsung, CA, USA) loaded with this app was distributed to the participants. The first week of the study

was a run-in week where participants became accustomed to the wearable sensors. After the run-in, participants performed in-clinic aerobic exercise twice weekly for one week, in-clinic resistance training twice weekly for one week, and no structured exercise for one control week. The order of the aerobic, resistance, and control weeks were randomized for each subject. Block randomization (size of six) with a 1:1:1 ratio was computer generated for the sequence of the interventions. One of the study coordinators carried out the randomization and the allocations were revealed at the start of the admission visit.

3.3.3 Study protocol

All participants completed a screening visit, training visit, and four structured exercise sessions. During the screening visit, baseline examinations included assessment of anthropometric data and physical status, determination of basal metabolic rate as well as an incremental cardiopulmonary exercise test in order to determine VO2max. After providing informed consent, enrolled participants were given a VO2max test according to the standard Bruce Protocol on a Medtrack ST 55 treadmill (Quinton, WA, USA). Oxygen consumption was measured during the VO2max test. The participants wore an air-tight mask (Hans Rudolph Inc., MO, USA), which had a gas sensor (Cosmed, Rome, Italy) attached to it, while heart rate was monitored using a Polar Electro T61 chest heart rate monitor (Polar Inc., Lake Success, NY, USA). Bruce protocol was used to determine VO_2max. Body composition was estimated by

a dual X-ray absorptiometry (DEXA) scan using a Hologic Discovery Wi (Hologic, Bedford, USA, Apex 4.0 software).

Participants returned on a separate day for the training visit, to learn how to use the CGM, how to use the activity monitor and how to accurately record the food intake. Participants performed a one-repetition maximum (1-RM) test for bench press, leg press and seated row during this visit. This was performed to set the exercise intensity (i.e. weight lifted) for resistance training sessions. We chose not to conduct 1RM tests on leg extension and flexion exercises because they are single joint movements and according to recommended guidelines should be avoided in favor of multi-joint movements to minimize injury risk during maximal testing. Rather we estimated training loads for single joint exercises using the multiple RM approach to determine each participant's 8RM workload [Haff & Triplett, 2015]. Participants replaced the CGM each week (at least a day before the exercise visit) and calibrated the sensor at least twice daily using the CBG meter. Although participants were blinded to CGM values, for safety, glucose alerts were set at 3.1 mmol/L and 16.7 mmol/L.

3.3.4 In—clinic exercise sessions

Each participant did 2 sessions of monitored aerobic exercise (AE) during the aerobic exercise week and 2 sessions of monitored resistance training (RT) during the resistance week. Par-

ticipants arrived at the laboratory at 4:00 pm for each of the exercise sessions. For both the aerobic and resistance exercise weeks, the same exercises were performed on two separate days with one day in between (e.g. RT sessions on Tuesday and Thursday). There were at least 48 hours between the exercise visits. Participants were instructed to refrain from formal exercise 24 hours prior to and 24 hours after their scheduled exercise. Actigraph data collected during this time was used to confirm that participants complied with this instruction. A study coordinator also contacted participants on the day following the in-clinic exercise session and asked questions about compliance during this phone call. The days of the week on which exercise sessions were conducted were identical for each participant across weeks. Between each intervention week there was at least 4 days. All exercise sessions were conducted on weekdays excluding Friday. During each exercise session, participants were outfitted with a Zephyr Biopatch (Zephyr Technology, Annapolis, VA, USA) that included a 2 lead ECG based heart rate monitor and 3—axis accelerometer to continuously monitor heart rate. Resistance exercise sessions, following a brief warm up period, included three sets of 8—12 repetitions at 60—80% of 1—RM of five different exercises (leg press, bench press, leg extension, leg flexion and seated row) with a 90 second rest period between exercises and sets (total duration of 45min). The exercises were chosen to recruit similar volumes of upper and lower body muscle mass, using machine based exercises to control movement and for safety, rather than equal numbers of exercises per group. While we allowed participants some flexibility in

doing 8 to12 reps to enable a tolerable workout, participants generally did not change their weight load or number of reps during a session. The Borg perceived exertion scale was used to estimate fatigue and to maintain a moderate intensity rating of 12—14 for each exercise performed. The duration of each set of exercise and the duration of the rest was closely tracked using an electronic data capture tool: Research Electronic Data Capture (REDCap), a secure web-based data capture application hosted at Oregon Health and Science University [Harris et al., 2009]. AE consisted of 45 min of treadmill exercise (60% of VO_2max as determined by heart rate).Based on the VO2max value obtained during the first visit, the heart rate value at the 60% VO_2max value was calculated and used during the aerobic training visits. During each exercise training visit, the heart rate was closely monitored and treadmill speed and grade were adjusted to keep the participants workrate at 60% VO_2max. The duration of the exercise intervention was kept consistent between both types of exercise; but the energy expenditure between these two types of exercises was not controlled in this study. Capillary glucose was checked before the start of the exercise period and immediately after exercise or if the subject experienced any symptoms of hypoglycemia. Each exercise session was followed by 60 minutes of monitored recovery period. Participants were provided with a pre—selected standardized meal of approximately 540 calories (23% protein, 47% carbohydrate, and 30% fat) to eat during the recovery period, the identical meal was provided during all in-clinic exercise sessions.

3.3.5 Exercise Energy Expenditure

Energy expenditure (EE) during the exercise period was estimated to understand the differences between the two types of exercise interventions. Using the data collected during the VO_2max test, a relationship (ordinary least squares linear regression) between the oxygen uptake and the heart rate data was created. We used this equation to estimate the amount of oxygen uptake based on the heart rate data measured during each in —clinic session. EE during the continuous aerobic exercise was estimated by the cumulative oxygen uptake during the exercise period and converting the oxygen uptake to kcal using the standard 1L of O_2 to 5.0 kcal [Vianna et al., 2014, di Prampero & Ferretti, 1999] . To estimate EE during the resistance training, we used the non—steady state model proposed by Scott et al. [Scott et al., 2014] and Vezina et al. [Vezina et al., 2014] by considering the oxygen uptake not only during each bout of exercise($\backsim$ 30 secs) but also during the recovery periods ($\backsim$ 90 secs) in between each bout of resistance training. Both the recorded exercise EE and recovery EE were converted to kcal. The EE values during exercise were calculated using the standard conversion of 1L of O_2 to 5.0 kcal, whereas the EE values during recovery were calculated using the non—steady state conversion of 1L of O_2 to 4.7 kcal.

3.3.6 Nutritional Assessment

All participants were verified to be experienced at carbohydrate counting prior to this study, by asking if they used carbohydrate counting techniques and had recently been educated about it. Each participant was provided with an Android study phone preloaded with a custom food meal photography application. All participants were trained on the usage of the application and were instructed to take pictures of all of the meals consumed during the study. Participants were provided with a ruler to be included in the photograph to provide an approximate size measure for the meal. The custom app provided the ability for the participant to enter the estimated carbohydrate amount, their CBG value at the time of the meal, the type of meal (breakfast, lunch, dinner, snack or hypoglycemic treatment) and an optional text description of the meal. Each entry was uploaded to the study database with the date and time recorded. A trained dietitian analyzed all the meals for each subject on the day of the in-clinic exercise visit and the day after the exercise visits to estimate the meal contents and quantity of each meal. The dietitian also analyzed meal data during matched days of the control week. Energy and macronutrient composition of meals was analyzed with ESHA Food Processor SQL Software (ESHA Research, Salem, UT, USA [Ahuja et al., 2013].

3.3.7 Statistical Analysis

Meal intake, exogenous insulin delivery and glycemic control metrics were calculated over the 24 hr. period from the end of the exercise to the same time next day. One subject failed to report any meal intake on multiple study days and as such, dietary records were only analyzed for 9 subjects and they were included in all of the food analyses. We analyzed the relationship between each outcome and the intervention using a randomized mixed effects regression model with a random intercept to account for correlation between observations on the same participant, since two interventions were compared against a single control, significance was adjusted to 0.025. We included an effect for the day to control for possible carryover effects. Data are presented as mean ± SD or mean (95% CI). All statistical analyses were conducted in R (version 3.4.2) [R Core Team, 2017]

3.4 Results

Results below are described in two sections with regards to two endpoints: first during the in-clinic exercise period and second for the 24 hr. post exercise period.

Ten adults (6 Females / 4 Males) with T1D had the following baseline characteristics, data is represented as mean ± SD: age 33 ± 6 yrs, BMI 24.4 ± 2.1 kg/², duration of diabetes 18 ± 10 yrs, HbA_{1c} 7.4 ± 1%, VO_2max = 46.8 ± 11.6 $ml.kg^{-1}.min^{-1}$, Fat 30 ± 7%, total daily insulin

dose 40.99 ± 7.26 units, resting heart rate 62.8 ± 7 beats/min, daily time in moderate to vigorous physical activity 1.1 ± 0.7 hours/day.

3.4.1 In—clinic exercise visits

At the start of the exercise bouts there was no difference between the glucose levels (aerobic exercise (AE): 8.78 ± 3.22 mmol/L vs resistance training (RT) 8.72 ± 3.5 mmol/L) but the decrease in glucose levels during exercise was significantly different between the two exercise types. AE caused a precipitous reduction in sensor glucose value over the exercise period with mean glucose reduction of 3.94 ± 2.67 mmol/L while the reduction in sensor glucose was smaller during RT with the mean glucose reduction of 1.33 ± 1.78 mmol/L (p=0.007). By the end of the recovery period (60 min post exercise), the sensor glucose levels were not statistically different. CGM glucose values during the exercise and recovery periods are shown in Figure 3.1A. The mean heart rate during the AE bout was 144.6 ± 8 beats/min and the mean heart rate during the RT bouts was 112.3 ± 11 beats/min. Additional RT information is provided in Supplementary Table 1. The EE during the AE visits was significantly higher than during the RT visits, with the EE during the AE visits being 429 ±111 kcal and the EE during the RT visits being 252 ± 65 kcal (p<0.001). The EE values during the in-clinic visits are shown in Figure 3.1B. On average the participants had similar glucose and insulin on board at the start of the exercise interventions. The average insulin on board at the start of the

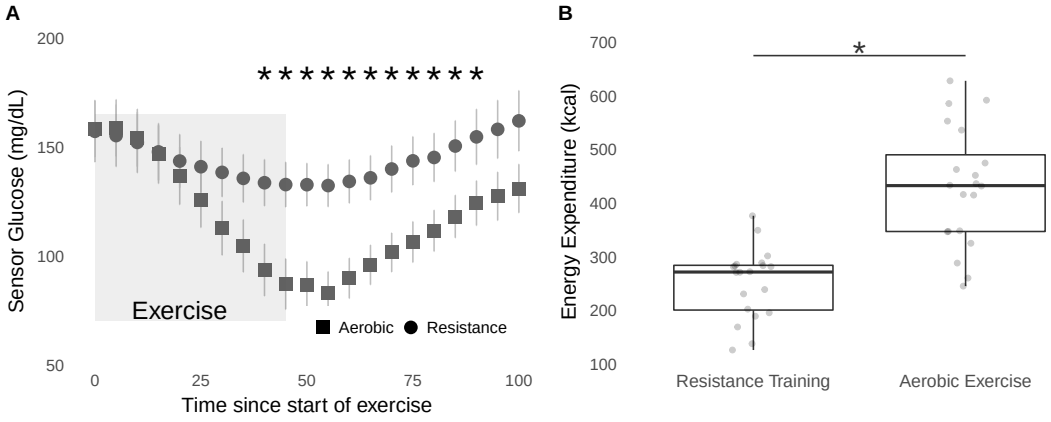

Figure 3.1: A: Glycemic response during the in-clinic exercise visits. Sensor glucose data is represented as Mean ± SE during the exercise (represented by box) and 60 min of recovery: ■ resistance training, ● , aerobic exercise. ⋆ indicate the statistically significant difference between the two interventions based on the paired sample t-tests ($p < 0.05$). B: Box plots with individual points indicating the estimated energy expenditure in kcal during the in-clinic exercise sessions. EE between the visits was significantly different between the interventions. ⋆ indicates the statistically significant difference between the energy expenditure during the two types of interventions based on the paired sample t-test ($p < 0.05$)

aerobic exercise intervention was 4.56 ±1 U and the average insulin on board at the start of the resistance training bout was 4.68 ±1 U.

3.4.2 24 HR. POST EXERCISE IN HOME GLYCEMIC CONTROL

Mean glucose value for the 24 hr. period was the lowest after RT visits (8.01 ± 1.94 mmol/L) as compared with AE visits (8.80 ± 2.17 mmol/L) and during the control week was 9.5 ± 2.7 mmol/L. Mean glucose for the 24 hours post RT visit was 1.39 mmol/L lower than the mean glucose for the 24 hours matched control week (95% CI -2.25 – 0.55, $p = 0.002$, $Z = -3.29$). However, the mean glucose for the 24 hours post AE visits was only 0.66 mmol/L lower than the 24 hour matched control week and the difference was not significant (95% CI -1.51 – -0.19,

p = 0.134, Z = -1.53). Adjusting for the total insulin dosage within the random-effects model, we observed a mean glucose during the 24 hr. period post RT exercise that was 1.03 mmol/L lower compared with the control week (95% CI –1.90 – -0.17, p = 0.024). But making the same adjustment for total insulin dosage, the mean glucose during the 24 hr. period post AE visits was lower than the control week by only 0.40 mmol/L, and the difference was again not significant (95% CI -1.24 – 0.45, p = 0.39). When Controlling for meal intake on mean glucose during this period after the RT visits, we observed a lower mean glucose during the 24 hr. period post RT that was less than during the control week by 0.06 mmol/L (95% CI -0.98 – -1.67, p = 0.036). But making the same adjustment for meal intake, the mean glucose was slightly lower during the 24 hr. period post AE, but the 1.03 mmol/L decrease post RT and not significant (95% CI -17.61 – 15.54, p = 0.903). After adjusting for either insulin dosage or meal intake, the mean glucose was significantly lower after RT but there was no difference from control after AE visits.

Time in range (% of time with sensor glucose between 3.9 mmol/L and 10 mmol/L) over the 24hr. period after the RT visits was 70.3 $\pm$ 15% while the time in range over the 24 hr. period after the AE visits was 60.5 $\pm$ 22%. During the control week, the time in range was 55.7 $\pm$ 27%. We observed a statistically significant improvement in time in range of 14.61% (95% CI 3.50-25.71, p = 0.013, Z = 2.6) for the RT visit compared with the control week, while the increased time in range after the AE visits was only 4.72% compared with the control week

and the change was not significant (95% CI -6.38-15.83, p = 0.41, Z = 0.8).

During the 24 hr. period after the RT visits the time in hyperglycemia (% of time with sensor glucose >10 mmol/L) was 23.1 $\pm$ 17% and after the AE visits was 32.9 $\pm$ 25%. Participants spent 39.1 $\pm$ 28% in hyperglycemia during the same period in the control week of the study. We observed significant reduction in the time in hyperglycemia by -16% (95% CI -26.69 – -5.32, p = 0.005, Z = -2.94) for the 24 hr. period following RT visits compared with the control week. The reduced time in hyperglycemia after the AE visits was only -6.25% (95% CI -16.94 – 4.43, p = 0.258, Z = -1.15) compared with the control week.

The time in hypoglycemia (% of time with sensor glucose $\leq$ 3.9 mmol/L) over the 24 hr. period after the AE visits was 6.7 $\pm$ 8% and was 6.5 $\pm$ 10% after the RT visits, while during the control week this duration was 5.1 $\pm$ 7%. Subjects did not experience statistically significant differences in time in hypoglycemia after either AE or RT visits as compared with the control week of the study.

Table 3.2 shows the summary measures of the 24 hr. glycemic data. Individual markers of 24 hr. glycemic control are shown in Figure 3.2.

3.4.3 Energy and carbohydrate intake

A total of 112 week days of meal data were analyzed for this study. Participant recorded meal data was corroborated with both the insulin pump bolus data and the corresponding glucose

Table 3.2:]

Summary of the average glycemic control, insulin dosage and energy intake for the 24 hr. period after the exercise visit. Randomized mixed effects regression model with a random intercept to account for correlation between observations on the same participant was used to determine the significance of each outcome relative to the intervention. Continuous data represented as mean±standard deviation, Time in hypoglycemia is shown as median [IQR]

Measures	Control	Aerobic Exercise	Resistance Training
Time in range (%)	55.7 ± 25	60.5 ± 22	70.3 ± 15*
Time in hypoglycemia (%)	1.86 [7.15]	3.71 [9.83]	3.63 [6.07]
Time in hyperglycemia (%)	39.1 ± 28	32.9 ± 25	23.1 ± 17*
Glucose Mean(mmol/L)	9.5± 2.7	8.80 ± 2.17	8.01 ± 1.94*
Energy Intake (kcal/day)	1347± 606	1970 ± 630*	1816 ± 362*
24 hr. Insulin dosage (U)	43.6± 9	40.8 ± 9	39.8 ± 9*
24 hr. Bolus Insulin dosage (U)	19.2± 10	18.3 ± 8	15.7 ± 8*
24 hr. Basal Insulin dosage (U)	24.4± 6	22.5 ± 5*	24.1 ± 5

* Since two interventions were compared against a single control, significance was adjusted to 0.025. ($p < 0.025$)

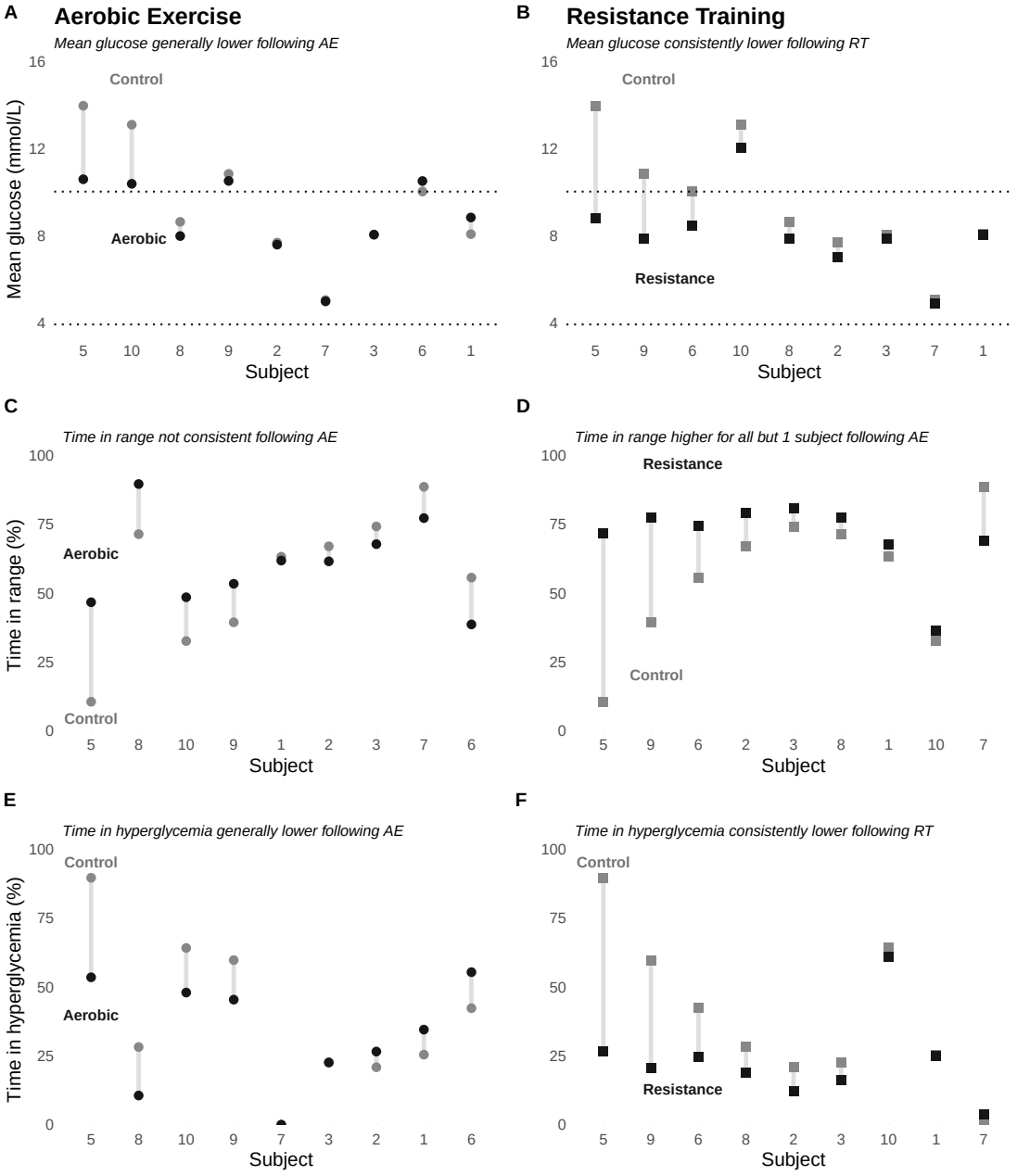

Figure 3.2: Improvements in glycemic outcomes for each study participant are shown in this figure. In the 24 hr. period following RT, all subjects experience positive reductions in mean glucose value and all but one subject experienced reductions in time in hyperglycemia and improvement in time in range range compared with the control week. But the same outcomes after AE are not as consistent. In each panel data for each individual subject is shown with ■ indicating resistance training and ● indicating aerobic exercise. Inset in each panel is the numerical difference in the outcome measured for the intervention represented in the panel.

sensor data. To account for missing meal data we removed that day's data from the analysis if either the participant had not reported more than one main meal for the day or if the total daily estimated consumption was less than 1000 kcals. Nine underreported days from 4 different subjects met the criteria to be deleted from the analysis leaving 103 days of nutrient intake. Participants had a significantly higher amount of energy intake during the 24 hr. duration after both types of in clinic exercise visits relative to the control days. The average energy intake was higher after the AE visits and RT visits compared with the control days by 623 ± 158 kcal ($p < 0.001$) and 468 ± 145 kcal ($p = 0.003$), respectively. There was a higher need for hypoglycemic treatments during the 24 hr. period after the AE and RT visits compared with control days whereby the total carbohydrate intake was higher than the control week by 77 ± 17 g ($p < 0.001$) for AE and 42 ± 19g ($p = 0.02$) for RT. Figure 3.3 A shows the differences in the energy intake during the different weeks of the study.

3.4.4 Twenty-four hour post exercise activity levels

Participants were instructed to refrain from any structured and formal activity during the 24 hr. prior to and 24 hr. after their scheduled exercise or control period. There were no significant differences in time spent in the moderate to vigorous physical activity (MVPA) between the three periods. Participants spent 302 ± 118 minutes in MVPA during the control period, 305 ± 92 minutes in MVPA during the 24 hr. period after AE and 275 ± 96 minutes

in MVPA after RT (p=NS).

3.4.5 Insulin administration

Insulin dosage data is shown in Table 3.2. Despite an increase in both energy and carbohydrate intake, the total insulin dosage during the 24 hr. period, was not significantly higher for days following either types of exercise visits as compared with the control days. Rather, basal insulin dosage was significantly lower by 2 $\pm$ 0.4U of insulin after the AE visits (p <0.001) as compared with control days. Insulin usage was lowered by only 0.4 $\pm$ 0.5U of insulin after RT visits compared with the control week (P=0.3). Participants injected significantly less bolus insulin after the RT visits, a reduction of 3.5 $\pm$ 1.5U of insulin (p=0.01) as compared with control days as opposed to a reduction of only 0.9 $\pm$ 2.7U of insulin (p=0.5) after the AE visits. Figure 3.3 B shows the differences in the total insulin dosage during the different weeks of the study.

3.5 Discussion

Physical exercise is a cornerstone of diabetes management, but recent reviews have shown no clear evidence of glycemic benefit due to physical activity in adults with type 1 diabetes [Kennedy et al., 2013, Yardley et al., 2014, Jewiss et al., 2017] but a potential improvement in HbA1c in children and adolescents [Quirk et al., 2014]. The present study highlights that

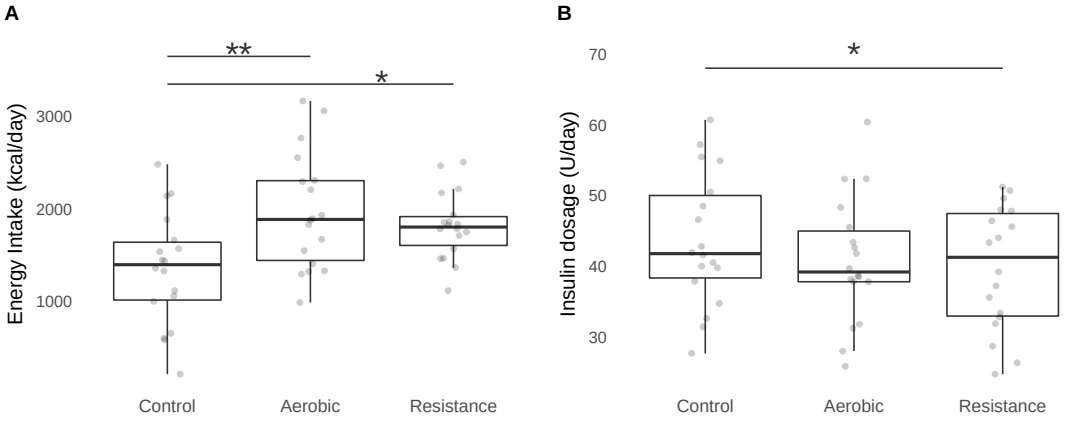

Figure 3.3: A: Box plots with individual data points indicating the nutritionist estimated energy intake from the meal pictures collected during the 24 hr. period after the in-clinic exercise visit during each intervention week. The energy intake was significantly higher during the 24 hr. after the aerobic and resistance training in-clinic sessions, as indicated by the * based on the randomized mixed effects regression model with a random intercept to account for correlation between observations on the same participant ($p<0.025$) B: Box plots with individual data points indicating the insulin dosage downloaded from the insulin pump during the 24 hr. period after the in-clinic exercise visit during each intervention week. The total insulin dosage was significantly lower during the 24 hr. after the resistance training in-clinic sessions, as indicated by the * based on the randomized mixed effects regression model with a random intercept to account for correlation between observations on the same participant ($p<0.025$)

RT is a promising strategy that can lead to improved glycemic control, but for AE the results are not as significant. In this study we demonstrate that during the 24 hr. period after either intervention, subjects increased meal intake both to manage hypoglycemic episodes and increased consumption of post dinner snacks to prevent nocturnal hypoglycemia as was speculated in Kennedy et al [Kennedy et al., 2013]. We also show that the participants used less insulin following both AE and RT exercise interventions, with significantly less bolus insulin after the RT visits and significant reduction in basal insulin after the AE visits. The decrease in bolus after RT could be due to either less correction boluses or reduced meal related insulin boluses. We also showed that the drop in glucose during RT is less compared with AE, which

confirms prior reports [Yardley et al., 2013]. But we also found that the time spent in hypoglycemia during the 24 hr. period after either bout of exercise was no different as compared with the control week. Another insight generated by this study was that EE during AE and RT are significantly different, with participants during the RT bout expending less energy compared with AE and then subsequently consuming less food after the exercise compared with AE.

People with T1D find it challenging to dose insulin appropriately for meals and this becomes more challenging when exercise must also be considered as exercise is known to affect insulin sensitivity for many hours after exercise [Brazeau et al., 2013]. This study further expands on the published literature by investigating the effects of physical activity (RT and AE) on glycemic control during the 24 hr. period after the intervention while controlling for total insulin dosed and/or meal intake. These data highlight that individualized physical activity regimes could augment current insulin therapies to achieve optimal glycemic control. The responses to exercise are heterogonous in our subjects but most improvement in time in range was experienced by individuals who spent higher duration of time in the hyperglycemic range during the control weeks. Engaging in specific strategies to adjust insulin doses and minimize excessive carbohydrate consumption before, during and after exercise could help improve glycemic control and prevent dysglycemia.

Three prior studies on people with T1D have demonstrated that RT could provide improvements in HbA1c [Durak et al., 1990, Mosher et al., 1998, Ramalho et al., 2006]. But a recent non-randomized long term study conducted in 8 adults with T1D who participated in unsupervised recreational training comprised of both AE and RT showed no improvement in HbA1c [Rissanen et al., 2017]. This inconsistency may have been due to the fact that both AE and RT exercises were performed during this study. As we show in the current study, RT showed significant improvement in glycemic outcomes while AE did not. The inconsistencies may also be explained by the fact that these studies have not accounted for varying meal and insulin intake during the monitoring period, and that metrics beyond HbA1C are important to consider [Wright & Hirsch, 2017, Agiostratidou et al., 2017]. A regular exercise regime of RT has been demonstrated to elicit beneficial metabolic responses (reductions in HbA1c and increased insulin sensitivity) in individuals with T2D due to gains in muscle mass and improved mitochondrial oxidative capacity [Pesta et al., 2017, Mann et al., 2014].

Limited stores of muscle and liver glycogen stores are used as energy substrates during aerobic and resistance exercise, with the source and relative rate of glycogen depletion dependent upon the type and intensity of training [Egan & Zierath, 2013] . The effects of either type of modality on glycemic levels can often last for several hours after exercise completion. As observed in this study, increased energy consumption after both exercise modalities, could be a result of needing to replenish glycogen stores. Other studies have shown that glucose up-

take by the exercising muscles may be enhanced for many hours and often overnight [Iscoe & Riddell, 2011]. While we strove to have participants performing both aerobic and resistance training at moderate intensities, it is possible that the relative rates of glycogen depletion and other sources of depletion (e.g., liver vs. muscle) differed between the two modalities and could account for some of the variation in glucose dynamics between AE and RT.

This pilot study had a few limitations including a small sample size. We have plans to replicate this study in a larger number of subjects. Another limitation is that we did not test other exercise modalities such as intermittent high-intensity interval training or a combination of both AE and RT, thus our findings here should be interpreted accordingly. We plan to investigate alternative exercise modalities in future projects to continue to understand how exercise impacts glycemic control. Another limitation of the current study is that while we controlled for the duration and intensity of exercise, we did not control for the energy expenditure between the two exercise modalities. It is not possible to simultaneously control for duration, intensity, and energy expenditure, and we chose in this study to control for the first two. In the future, it would be important to study whether these results hold when energy expenditure is maintained constant between the exercise modalities. A further limitation was that while more than half of the participants were female, we did not collect information on the female participants' menstrual cycle, which is known to impact glucose levels.

3.6 Conclusion

Resistance training may improve glycemic control in adults with T1D, even when adjusting for changes in meal intake and changes in insulin dosage after the exercise event. The benefit of aerobic exercise on glycemic control may be tempered by increased amounts of food consumed during the day following exercise to balance increased energy expenditure.

3.7 Supplementary Data

Table 3.3: Summary of the resistance exercises during the resistance training visits. Continuous data represented as mean±standard deviation

Resistance Exercise	Weight lifted (Kg)	Perceived Exertion (RPE)	Repetitions (reps)	Sets	% 1-RM
Leg Press	134 ± 43	13 ± 1	12 ± 1	3	68 ± 10
Bench Press	49 ± 17	15 ± 1	12 ± 1	3	67 ± 10
Leg Extension	23 ± 7	13 ± 2	12 ± 0	3	NA
Leg Flexion	11 ± 2	13 ± 1	12 ± 0	3	NA
Seated Row	38 ± 10	15 ± 1	12 ± 1	3	70 ± 10

The whole of science is nothing more than a refinement of everyday thinking.

Albert Einstein, A Dictionary of Scientific Quotations.

4

Validation of an exercise detection algorithm for use in artificial pancreas systems

Exercise is a cornerstone in the management of type 1 diabetes (T1D). However, exercise leads to glycemic imbalance that could precipitate hypoglycemia. Fear of hypoglycemia can

dissuade many individuals from engaging in regular exercise. Artificial pancreas (AP) systems have been developed to improve glycemic control, however exercise presents a significant challenge to these systems. Detecting exercise early, and responding appropriately is an ongoing area of research. In this chapter, a description of the integration of both heart rate and activity data from a chest worn sensor to estimate energy expenditure in adults is presented. Using an algorithm, that had been previously developed in a youth cohort, we adapt this algorithm to a T1D adult cohort. The accuracy of this adapted algorithm is presented here. We also show the methodology for detecting aerobic exercise and validate the accuracy of this detection algorithm.

Chapter summary

- Early detection of aerobic exercise is critical in the context of AP systems to appropriately respond to the rapid imbalance of glucose dynamics
- We identify the appropriate energy expenditure detection threshold for AP systems to detect the onset of exercise
- We validate both the energy estimation algorithm and the intensity threshold detection for use in a dual hormone AP system

4.1 Introduction

Clinical practice guidelines strongly recommend regular physical activity for individuals with type 1 diabetes (T1D) [Colberg et al., 2016]. Regular physical activity is known to enhance cardiovascular fitness [Tikkanen-Dolenc et al., 2017a], reduce the risk of long term diabetes related complications [Tikkanen-Dolenc et al., 2017b] and improve blood lipid profile [Riddell et al., 2017], yet many fail to engage in the recommended amount of exercise due to the fear of exercise related hypoglycemia[Colberg et al., 2016, Ryninks et al., 2015, Brazeau et al., 2008, Mann et al., 2014]. Individuals with long standing T1D suffer from absolute insulin deficiency necessitating the need for exogenous insulin delivery [Atkinson et al., 2014]. The imbalance between the insulin dosage reduction and altered counter-regulatory hormonal response leads to dysglycemia [Riddell et al., 2017, Cryer, 2014]. Artificial pancreas (AP) systems are the current state of the art in glucose control [Jacobs et al., 2014, Breton et al., 2017, Huyett et al., 2017, Turksoy et al., 2013]. In healthy individuals, exercise increases rates of glucose uptake by skeletal muscles while halting the secretion of insulin from the pancreas. In response to the increased glucose utilization, hepatic glucose production is increased through glycogenolysis and gluconeogenesis, assisted by the increase in glucagon secretion. This prevents healthy individuals from experiencing hypoglycemia related to exercise [Skyler, 2012, Coker & Kjaer, 2005]. Dual hormone AP systems, equipped with both insulin and glucagon

can effectively regulate the reduction in insulin delivery and increase glucagon delivery to provide the necessary synergy needed to appropriately respond to the challenges of exercise [Jacobs et al., 2015]. In recent work, we showed that announcing exercise to the dual hormone AP is necessary to reduce exercise induced hypoglycemia [Jacobs et al., 2016].

To enjoy the benefits of exercise, individuals with T1D have to plan for exercise as many as 4 hours in advance by modifying insulin dosage at the prior meal and altering the basal insulin levels just before, during and after [Riddell et al., 2017]. Many situations before exercise demand additional carbohydrate consumption to prevent hypoglycemia during exercise [Riddell et al., 2015, Colberg et al., 2016, Riddell et al., 2017, McCarthy et al., 2016b]. Excessive weight gain is one of the common side effects of exogenous insulin delivery in people with T1D [Mottalib et al., 2017] and many engage in exercise to combat this weight gain. The fear of hypoglycemia during exercise and the challenge of maintaining suitable insulin dosage to manage eulgycemia is quite cumbersome [Mottalib et al., 2017, McCarthy et al., 2016a]. In individuals managing glycemic control with an AP system, exercise could be an unforeseen event encountered by the system. Steady state glycemic control in this situation is hampered by the slow insulin pharmacokinetics and pharmacodynamics. This inherently places the single hormone (insulin only) AP systems at a distinct disadvantage when exercise is encountered. Dual hormone AP systems have the promise to solve this problem by improving the closed loop control.

In insulin only AP systems, hypoglycemic events need to be treated with additional carbohydrate treatments; glucagon dosage in dual hormone AP systems rely on the release of stored glycogen stores, from the liver to address the increased glucose utilization need during exercise. Another challenge faced by AP systems with exercise is that exercise causes increased vascular blood flow to the subcutaneous depot of insulin in the body causing increased circulating levels of insulin at the start of exercise. This coupled with the increased sensitivity of insulin during exercise makes hypoglycemia quite common [McCarthy et al., 2016b].

Riddell et. al laid out the challenges associated with creating an AP system that is capable of detecting physical activity (PA) and responding appropriately to the different types of exercise to mimic a normally functioning pancreas [Riddell et al., 2015]. In this chapter, two of those challenges are addressed:

1. Identifying the appropriate intensity of exercise that would require the AP system to enter exercise mode.
2. Early detection of exercise using body worn sensors.

4.1.1 Objectives

To overcome the challenges presented by aerobic exercise to individuals with T1D, we identified the following approaches:

1. Identify the appropriate intensity threshold of exercise at which an AP system needs to enter exercise mode or activity mode

2. Create an algorithm using body-worn sensors to detect activity/exercise with high accuracy while maximizing specificity. False detection of exercise is acceptable in an AP system, as the user could cancel exercise mode if the mode were triggered accidentally or inadvertently.

In this chapter, we describe how we adapted the Zakeri model [Zakeri et al., 2008] to be used in a dual hormone AP system to identify the start of an exercise window. This algorithm was originally created and validated in adolescents. We adapted this algorithm to be used in a dual hormone AP system for adults. Here we describe the way in which both heart rate data and activity data from a single body worn sensor are incorporated into an equation to estimate energy expenditure. We also identify the appropriate intensity of exercise at which an AP system needs to enter exercise mode. A block diagram version of the algorithm is shown in Figure 4.1. Finally, we validate this approach in adults comparing the estimated energy expenditure with the measured energy expenditure from a portable VO_2 indirect calorimeter. The work shown here is mainly related to the adaption of the Zakeri algorithm and validation of the same to indicate if the intensity of the energy expenditure has crossed a pre-determined threshold.

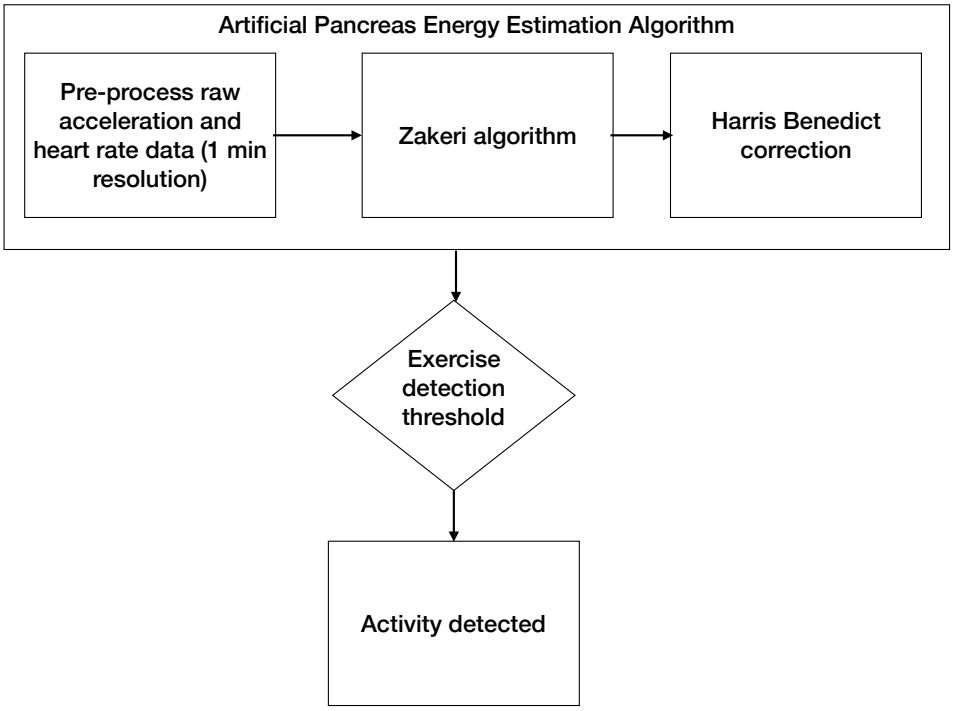

Figure 4.1: A block diagram describing how the Zakeri algorithm was adapted to be used in the Artificial pancreas system.

4.2 Methods

4.2.1 Devices

Criterion measure - Metamax 3B (Cortex, Leipzig, Germany and Viasys Healthcare Inc., Yorba Linda, CA) portable metabolic system was used as a criterion measurement in this study. EE was estimated from a direct measurement of oxygen consumption and carbon dioxide production. This portable metabolic analyzer is widely used as a criterion reference in validation studies examining EE from wearable monitors [Stahl et al., 2016]. The portable metabolic system's volume and gas measurements were calibrated before each study visit.

Measurement device - Heart rate and 3-axis accelerometer data streams are obtained from a body worn Zephyr Biopatch (Zephyr Technology, Annapolis). The Zephyr Biopatch was attached across the sternum using ECG leads.

4.2.2 Estimating energy expenditure

Exercise detection is accomplished using a cross-sectional time series modeling approach to predict the energy expenditure (EE) from both heart rate (HR) and physical activity (PA). Cross-sectional time series (CSTS) models are used in applications where there is a structure of correlation between the repeated observations from the same individual. Using a validated

CSTS model [Zakeri et al., 2008], EE is predicted every minute. The CSTS model selected involves lag and lead values of HR (beats per min) and PA (counts per min) along with the various time-invariant covariates such as age (year), sex (M/F), weight (in kg), height (in cm), minimum HR (beats per min), sitting HR (beats per min) and interactions between the different terms. See equation below for calculating the EE for the current minute.

$$
\begin{aligned}
EE = &-0.0527 * HR + 0.0000935 * PA + \\
&0.000072 * (HR^2) - 5.3e^7 * PA^2 + \\
&0.00430 * HR(lag1) + 0.0074 * HR(lag2) + 0.00514 * HR(lead1) + \\
&0.0146 * HR(lead2) + 0.000343 * PA(lag1) + 0.000486 * PA(lag2) + \\
&0.00720 * age + 0.00105 * age^2 - 0.123 * sex - 0.0101 * weight - \\
&0.00761 * height - 0.0140 * minimalHR - 0.00683 * sittingHR + \\
&0.0000412 * (PA * weight) + 0.000205 * (HR * weight) + \\
&0.000243 * (HR * height) - 0.000452 * (PA * sex) - \\
&0.000672 * (HR * age) + 2.573
\end{aligned}
\tag{4.1}
$$

The output of this equation is EE in kcal/min. Sex is coded 0 for Male and 1 for Female. Lag1 and lag2 refer to 1 and 2-min lagged values and lead1 and lead2 refer to 1 and 2-min lead values.

4.2.3 Pre-processing Zephyr Biopatch data

HR and PA values are obtained from a body worn Zephyr Biopatch (ZB) and are incorporated in the above equation to obtain the EE. The values for the HR and PA are obtained from the ZB every second. The values are averaged over a minute to obtain the HR in beats per min and PA in counts per min. To incorporate the PA values from a higher frequency and higher resolution 3 axis accelerometer into an equation designed for a single axis, lower resolution and lower frequency device, the following translations are performed on each one second measure of activity:

1. The activity value per second is divided by a value - 0.001663871 to the value of count [Umukoro et al., 2013].

$$count = activity/0.001663871 \tag{4.2}$$

2. This value of count is scaled from a higher resolution to lower resolution by multiplying by 0.064
3. The count value is scaled from a higher frequency of collection (100Hz) to a lower frequency of collection (32Hz) by multiplying by 3.125 and to covert from a 3-axis device to a 1-axis device the count value is multiplied by 0.6401 [Kelly et al., 2013].
4. This count value is summed over the duration of a minute to obtain the PA in the required unit- counts per min.

This minute level processed data is passed to the unmodified Zakeri algorithm listed above Equation 4.1.

4.2.4 Harris-Benedict Correction

Harris-Benedict correction is intended to correct the EE value from the Zakeri algorithm to provide an estimation that is applicable for use among an adult cohort. The following steps were taken to the convert this output from Zakeri to the EE value applicable in the current implementation.

1. The EE value is converted from kcal/min to a value of metabolic equivalents (METs), energy measure is often reported as METs. A MET is an estimate of intensity based on the ratio of working metabolic rate to resting metabolic rate. One MET is equivalent to an oxygen update of 3.5 ml. kg^{-1}. min^{-1}, which represents energy expended at rest for a reference human. Recently, there has been concern about the accuracy of using 1 MET =3.5 ml. kg^{-1}. min^{-1} as a proxy value for the resting metabolic rate (RMR) because of its potential to overestimate measured RMR values that are less than 3.5 ml. kg^{-1}. min^{-1} [Kozey et al., 2010, Byrne et al., 2005]. Critics argue that the use of 3.5 ml. kg^{-1}. min^{-1} as the RMR reference value to compute METs underestimates the true energy cost of physical activities obtained when using a measured RMR. To provide more accurate estimate of the RMR which is considered a measure of an individual's level of physical activity, it is necessary to account for personal variation in sex, body mass, height, and age by dividing the standard MET 3.5 ml. kg^{-1}. min^{-1} by a predicted RMR, obtained from the Harris-Benedict equation [Harris & Benedict, 1918] using age, height, body mass, and sex. The resulting MET value is referred to as a *corrected MET* value.

2. Harris Benedict resting metabolic rate (kcal/day) for Males = 66.4730 + 5.0033 * (Height in cm) + 13.7516 * (Weight in kg) – 6.7550 * (Age in yr)
   Harris Benedict resting metabolic rate (kcal/day) for Females = 655.0955 + 1.8496 * (Height in cm) + 9.5634 * (Weight in kg) – 4.6756 * (Age in yr)

3.

$$Corrected\ MET = \frac{Estimated\ MET * 3.5(\ ml\ /\ kg\ /min)}{Personalize\ Harris\ Benedict\ RMR(\ ml\ /kg\ /min)} \tag{4.3}$$

4.2.5 Exercise detection threshold

Using the personalized equation described above, we determined the EE threshold of 4 METs for the AP to enter exercise mode. This determination was based on the analysis of participant data collected during an in-clinic study [Jacobs et al., 2016]. In-clinic aerobic exercise data was collected as part of a randomized cross-over study to assess the efficacy of an automated bi-hormonal (insulin and glucagon) delivery system (ABD) to reduce exercise related hypoglycemia [Jacobs et al., 2016]. In this 3 arm crossover trial, 21 adults with T1D were randomly assigned to ABD with exercise dosing adjustment, ABD with no exercise dosing adjustment and sensor-augmented pump (SAP) therapy. Each visit lasted 22 hours, after an overnight stay and 2 hours after breakfast, participants performed mild exercise for 45 minutes at 60% of their maximum heart rate on a treadmill, with no pre-exercise snack. Data acquired during these 22 hours was used to determine the threshold. A subset of the resulting data is shown in Figure 4.6. During rest or non-exercise periods, EE values were below 4 METs and during the exercise period EE values were above 4 METs. Using this 4 METs cut-off, we were able to achieve a 97% sensitivity and 98% specificity to detect the exercise periods. This performance data is shown in Figure 4.3. Five consecutive minutes of EE values above 4 METs were

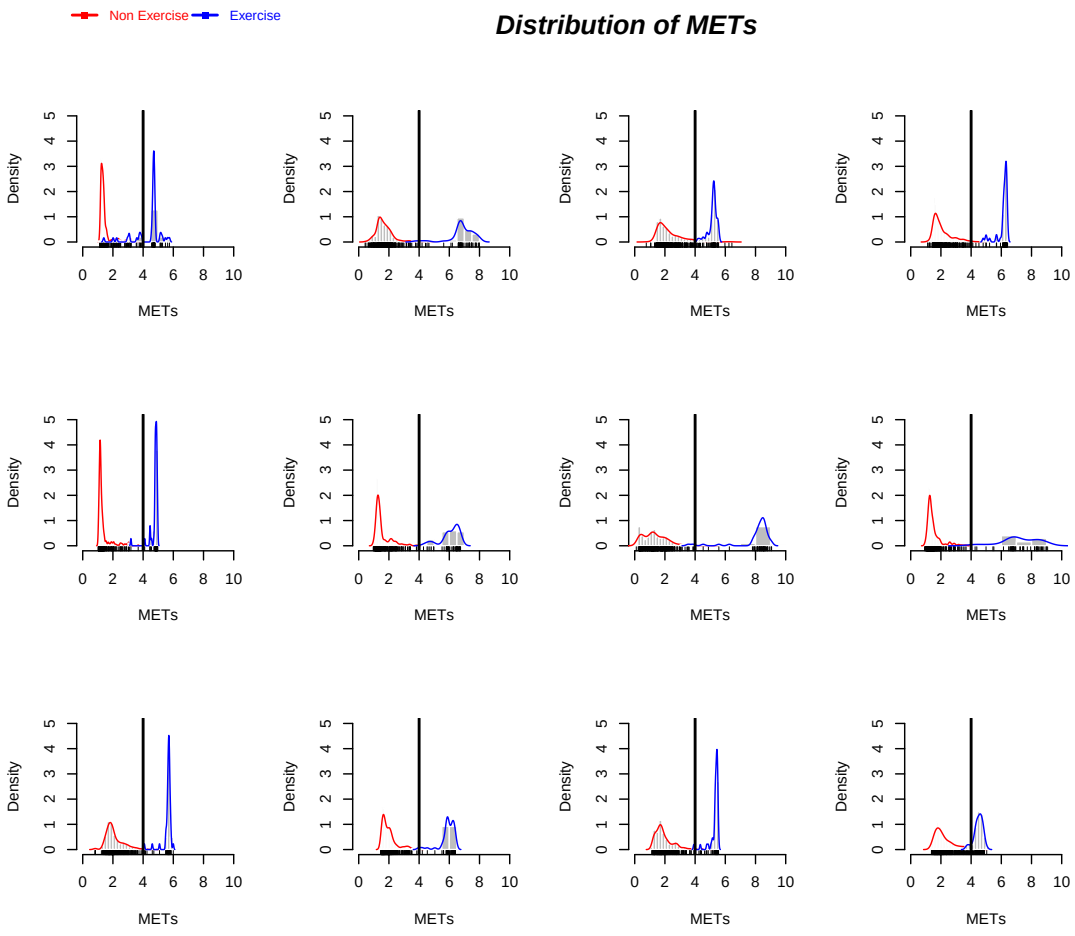

Figure 4.2: A random subset of 12 subjects EE data from the 22 hour in-clinic stay in the hospital is shown here. Exercise periods show an increased energy expenditure with EE values above 4 METs while during the non—exercise periods, these EE values were well below 4 METs.

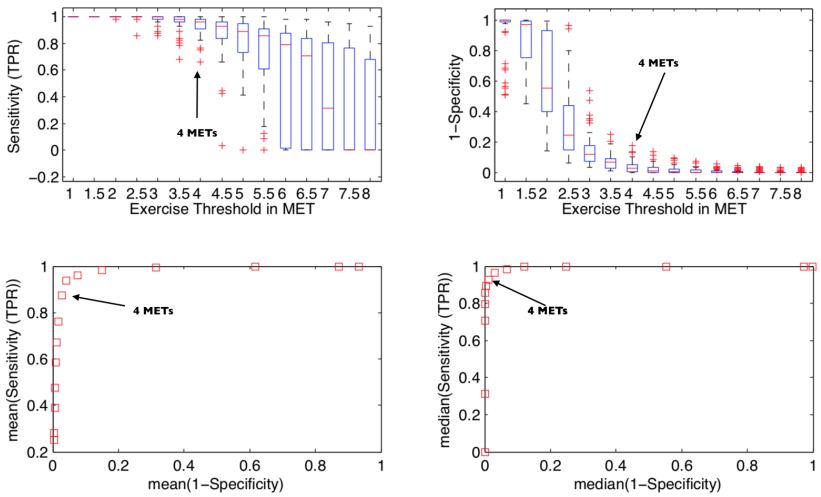

Figure 4.3: Sensitivity and specificity plots of the chosen 4 METs threshold. This threshold was arrived using the data collected during a 22 hour in-clinic study.

required by the AP system to enter exercise mode and change insulin and glucagon dosage. The adaptions to exercise are described in [Jacobs et al., 2015].

4.2.6 Participants in the validation study

Healthy adults and adults with T1D were recruited to participate in the validation of the exercise detection algorithm. Only adults between the ages of 21—45 were recruited. Participant's characteristics are described in Table 4.1. The experimental protocol conformed to the standards set by the Declaration of Helsinki and was approved by the Institutional Review Board at the Oregon Health and Science University (OHSU, Portland Oregon). Participants were

screened for any cardiovascular complications using a resting ECG test and using a Physical Activity Readiness Questionnaire http://eparmedx.com/. This study recruited 10 adults (6 females) who all provided informed consent before taking part in the study. Although adults with T1D participated in this study and glucose levels were monitored, glucose data, insulin data and hypoglycemic events were not analyzed and are not part of this analysis. After obtaining consent, subjects were fitted with a portable VO_2 indirect calorimeter and baseline resting metabolic rate (RMR) data was collected.

Characteristic	Number = 10
Age (years)	30±6
Gender (M/F)	6/4
Healthy/T1D	5/5
Body Weight (kg)	75±7
Height (cm)	174±9
Body Mass Index (kg/m^2)	24.5±2
Resting metabolic rate ($ml.\ kg^{-1}.\ min^{-1}$)	3.63±0.4

Table 4.1: TTEA Participant characteristics. Continuous data represented as mean±standard deviation; Resting metabolic rate (RMR) was measured during the screening visit.

4.2.7 Data collection for the validation study

Participants attended the research laboratory to engage in three blocks of activity, namely: aerobic, resistance and activities of daily living. Activities of daily living were performed first

during the visit and the aerobic and resistance blocks were randomized. Subjects were outfitted with a portable metabolic unit and a two-lead ECG device —ZB on the chest. ZB records both HR data and Activity data. This recorded data was transmitted to a Nexus 5 smart phone master controller via Bluetooth. The smart phone was running the algorithm described in the section 4.2.2 to estimate the EE and if the EE during 5 consecutive minutes exceed the pre-established threshold, an exercise detection announcement was made. As the algorithm estimating EE requires both 2 min lead and 2 min lag values, the algorithm is inherently delayed by >2 min and the exercise detection is only populated every 5 min.

4.2.8 Activities in the validation study

Each study visit began with activities of daily living (ADLs). Six ADL were performed to simulate daily chores, each activity was performed for 5-15 minutes of duration. These included sitting on a chair or lying on a bed; washing of dishes and simulated loading and unloading of a dishwasher; sweeping or vacuuming of a small room; organizing a room or adjusting furniture in the room; scrubbing of walls and carpet/floor; and self-paced ascending and descending of a flight of stairs. Five minutes of rest was given before and after these activities. Subjects then transitioned to do aerobic or resistance activities. Aerobic exercises were performed on a treadmill. Subjects walked/ran on the treadmill at three different speeds: 2.0 miles/hour, 3.0 miles/hour and 4.0 miles/hour. Each of these speeds were maintained for

15 minutes of duration with 10 minutes of rest between each speed. Body weight resistance training was performed for 20 minutes. Two exercises : straight-leg raises and wall sits were conducted for 5 minutes each. There was a period of 5 minutes of rest in between each type of resistance exercise.

A schematic representation of the exercise protocol and data from one of the participants showing the data from the criterion measure and the algorithm being tested is shown in Figure 4.4.

4.3 Results

The results from the validation study are divided into two section, accuracy of the EE estimation algorithm (Modified Zakeri algorithm) and the accuracy of the threshold detection algorithm (5 consecutive minutes of EE $\geq$ 4 METs).

4.3.1 EE estimation algorithm

The EE estimated by the algorithm was biased higher by a mean of 0.5$\pm$ 1.8 METs and mean absolute difference between the estimation and the criterion measure was 1.4$\pm$ 1.2 METs. The errors in estimation were primarily observed during the transition periods, the estimation algorithm was inherently delayed by 2 min due to the equation requirement. During the steady state activities, the errors in the estimation, though biased higher toward the algorithm

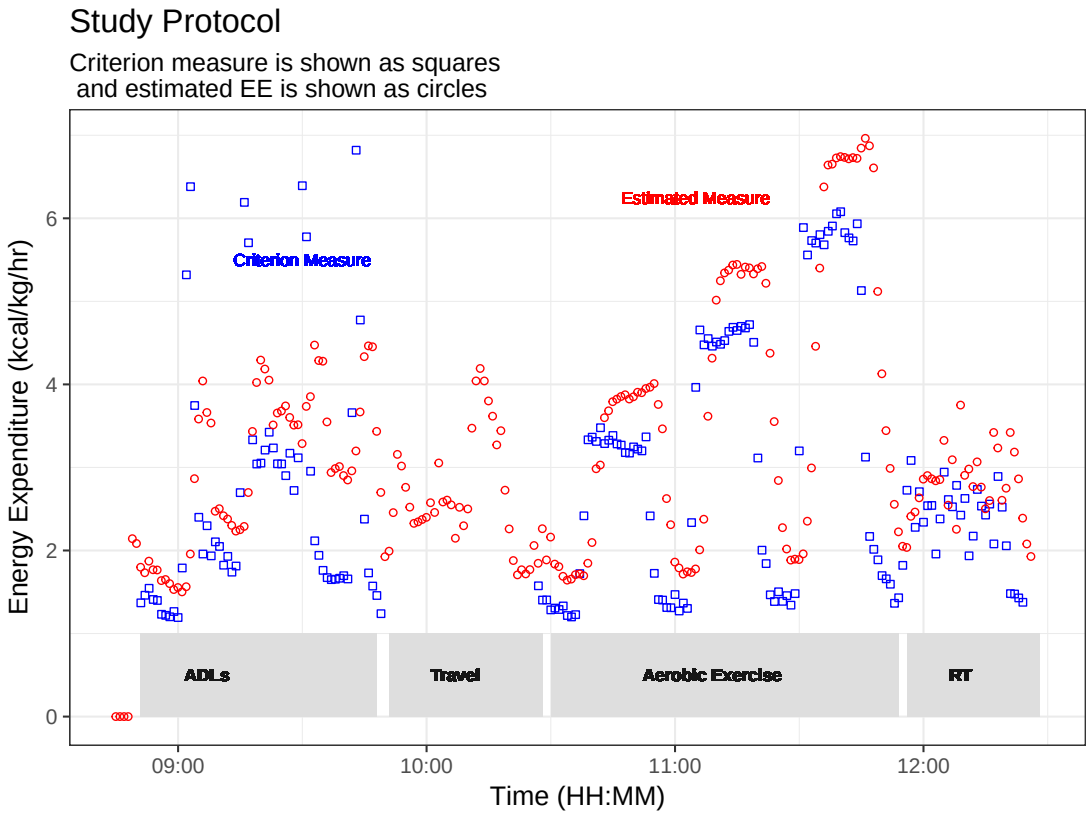

Figure 4.4: EE data is shown here for one study participant. Notice the sharp increases in the criterion measured data during the ADLs, these were situations when the subject was asked to climb stairs. These sharp increases are not evident in the algorithm estimation.

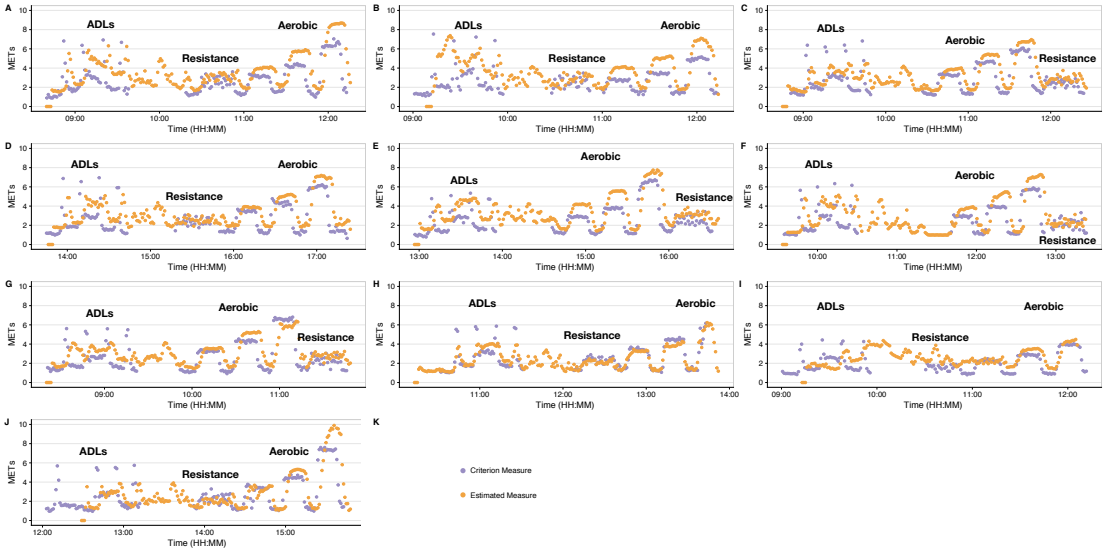

Figure 4.5: EE data for each subject participated in the study is shown. There is a bias in the EE estimation by the algorithm compared with criterion device in many of the subjects, but the bias is not similar in each of the participants. In 8 of the 10 subjects, the estimate EE (orange dots) is higher during the steady state exercises as compared with the criterion measure (gray dots).

were consistent for each participant. In Figure 4.5, each subject's data is shown. EE estimation by the algorithm is higher in the majority of subjects.

Bland Altman plot showing the EE data during the various activity blocks is show in Figure 4.7. The error associated with the estimation of the EE across all the subjects is shown in Figure 4.6.

4.3.2 Accuracy of the threshold detection algorithm

To determine the accuracy of the threshold detection algorithm EE data from each subject was divided into 5 unique subsets based on the activity namely: ADLs, Resistance exercise,

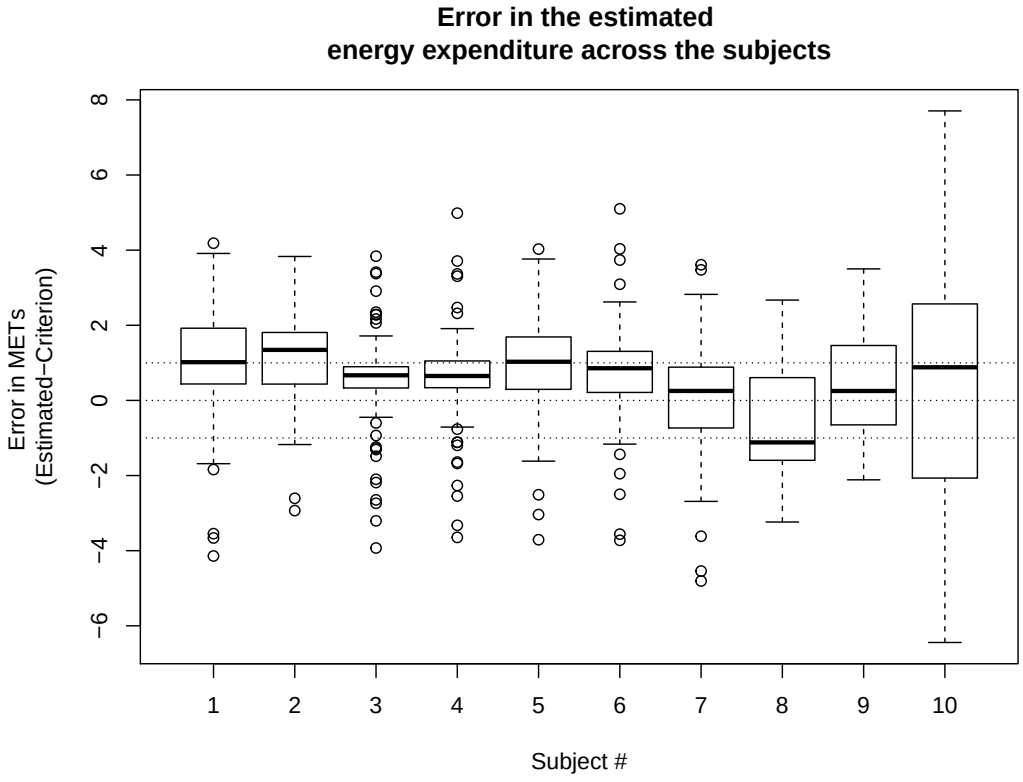

Figure 4.6: Box plot showing the difference between the energy expenditure estimated and the energy expenditure measured by the indirect calorimeter for each subject. The bias is clear between the estimation in the majority of the subjects, but the error is not consistent. The dotted lines represent the $\pm$ 1 MET around zero.

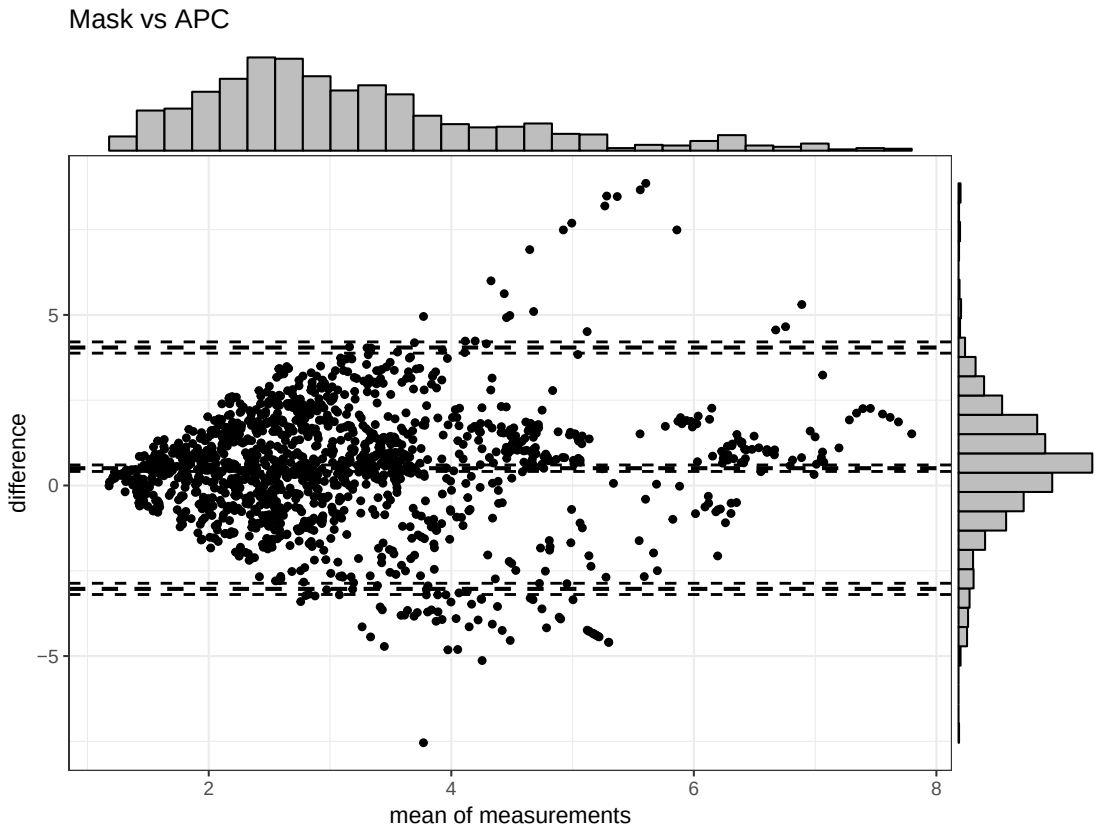

Figure 4.7: Bland Altman plot comparing the EE data collected from both criterion-portable indirect calorimeter and estimated using the algorithm. The mean error and 95%CI between these two measurements is 0.56 (-3.0 – 4.0) METs with a critical difference of 3.53. The histogram plots on the margins of the Bland Altman plot indicate the distribution of the errors and the mean of the measurements. Majority of the error between the two measurements (70% of the error) is between the range of 2.31 and -1.3 METs.

and 3 speeds of aerobic exercise: 2.0 miles/hour, 3.0 miles/hour and 4.0 miles/hour. The threshold detection algorithm was applied to each of these unique subsets, there were a total of 50 subsets from 10 subjects.

- For each subset to be considered a true positive (TP) both the criterion measured EE and the algorithm estimated EE must be above 4 METs for 5 consecutive minutes.
- A subset of data was considered a true negative (TN) if both the criterion measured EE and the algorithm estimated EE were not greater than or equal to 4 METs for 5 consecutive minutes.
- A data subset was considered a false positive (FP) when the criterion measured EE was less than 4 METs but the algorithm estimated EE was above 4 METs for 5 consecutive minutes.
- A data subset was considered a false negative (FN) when the criterion measured EE was greater than 4 METs for 5 consecutive minutes but the algorithm estimated EE was less than 4 METs for 5 consecutive minutes.

The performance of the detection algorithm for each subject across the different types of activities is shown in Table 4.2. Activities of daily living and slow steady state walking were falsely detected as exercise events. In the case of slow walking activity, the bias reported earlier from the EE estimation algorithm could be responsible for the false detections. The confusion matrix describing the performance of the EE estimation algorithm is presented in Table 4.3. The total accuracy of detection was 78%.

Subject #	ADLs	Resistance	2mph	3mph	4mph
1	FP	TN	FP	TP	TP
2	FP	TN	FP	FP	TP
3	TN	TN	FP	TP	TP
4	FP	TN	FP	TP	TP
5	FP	TN	FP	TP	TP
6	FP	TN	TN	TP	TP
7	TN	TN	TN	TP	TP
8	TN	TN	TN	TP	TP
9	TN	TN	TN	TN	TP
10	TN	TN	TN	TP	TP

Table 4.2: Accuracy of the threshold detection algorithm in each of the subsets of data is presented. There was 50% false detection during the activities of daily living and during the slow walking steady state activities.

4.4 Discussion

In this chapter we have shown that an algorithm validated in adolescents and developed with older sensors (1-axis accelerometer) was successfully adapted (with 3-axis accelerometers, described in section 4.2.3) to be used in a dual hormone AP system for adults. However, we observed that the EE estimation algorithm was prone to higher estimation of EE. We also validated that the selected EE intensity threshold was successful at detecting the aerobic exercises. As indicated before, the objectives of this chapter were to identify the appropriate threshold that would qualify as exercise and present an higher sensitivity approach to detect exercise at

		Criterion EE $\geq$ 4 METs		
		Positive	Negative	Total
EE Estimation $\geq$ 4 METs	Positive	21	11	32
	Negative	0	18	18
	Total	21	29	50

Table 4.3: Confusion matrix describing the detection of the different type activities by the EE estimation algorithm combined with the detection algorithm.

the expense of specificity. These two objectives were achieved.

Aerobic exercise can lead to rapid changes in glucose concentrations and by allowing the subject to acknowledge the exercise detection is a conservative approach to overcome the bias in the energy estimation. Energy estimation and exercise detection is a challenging field and providing a form of human input is helpful as there are a myriad other activities that were not tested in this validation protocol.

Exercise naive AP systems were not able to prevent hypoglycemia during exercise [Breton et al., 2012] but were able to reduce the risk of hypoglycemia many hours after the exercise bout. This was followed by many groups attempting to include sensors to enable early detection of exercise in the context of AP systems. Breton et al [Breton et al., 2014a] showed that using only change in HR to detect exercise was beneficial in reducing hypoglycemia during exercise. In that study they adopted a relative change in HR as a marker for detecting exercise, though HR is an good marker for detecting exercise levels, HR alone could have some inherent disadvantages for individuals with T1D. It has been shown that many people with T1D

suffer from autonomic dysfunction [Pop-Busui, 2010], this leads to tachycardia and could lead to unreliable HR data. Turksoy et al showed that a multivariable adaptive model with multiple inputs to adjust insulin delivery could improve glucose control in a small sample size [Turksoy et al., 2013, 2014a], they used a Bodymedia armband sensor that is no longer in production, leading to limited application potential by other groups.

Stenerson et al undertook a study to identify if adding HR data to accelerometer data to detect physical activity was necessary and concluded that HR data is not needed to detect exercise [Stenerson et al., 2014]. They found that in a simulated setting using an accelerometer augmented insulin pump suspension algorithm decreased the incidence of exercise induced hypoglycemia.

Detection of exercise while relying on accelerometers is very dependent on the location of the sensors and activities such as horse riding or four-wheeling could produce signals that are not correlated with exercise. Using a combination of both HR and accelerometer, Dasanayake et. al, showed that early detection could be accomplished before rapid changes in glucose were observed [Dasanayake et al., 2015b], but detection combined with intensity of exercise has not been shown so far. In this work we show a system that is dependent of various anthropometric features along with HR and PA data could be successfully used to detect activities from body worn sensor.

Delayed absorption and clearance of insulin action along with lag and error associated

subcutaneous glucose sensor data during exercise presents a challenge to the current AP systems using only insulin to manage exercise [Doyle et al., 2014, Cinar, 2017]. As mentioned earlier AP systems that are only insulin based are at an inherent disadvantage as shut off of insulin alone in response to detected aerobic exercise has been shown not to prevent hypoglycemia [Zaharieva et al., 2017]. The synergy of early detection of exercise with the turn off of insulin along with the dosing of glucagon in response to rapid drops in glucose is the panacea needed. This approach mimics the response of a person with healthy functioning pancreas.

4.5 Conclusions

In this chapter we have shown, that energy expenditure could be estimated using both HR and PA data obtained from a body worn sensor. We also show that the exercise intensity threshold that was determined to be safe and could accurately detect 78% of the exercise events in this validation study.

Basic research is like shooting an arrow into the air and,

where it lands, painting a target.

Homer Adkins, Nature 312, p.212, 1984

5

Accuracy of wrist-worn activity monitors during different forms of physical activities

Wrist worn wearable devices are ubiquitous. Currently they are only being used recreationally to track health and fitness. Individuals with type 1 diabetes are at a constant risk of hypoglycemia and this risk is elevated during and for many hours after exercise. As artificial pancreas systems become available to control glucose levels in individuals with type 1

diabetes, adding a wrist worn wearable device is a logical next step to improve detection of exercise and prevent exercise related hypoglycemia. In this chapter we discuss the accuracy of these wrist worn wearable devices and highlight some of the challenges that are associated with these devices.

Chapter summary

- Comprehensive testing of two popular wrist worn devices in a variety of dynamic, non steady state and structured activities of daily living was conducted
- During these tests the overall accuracy of heart rate measurement from these devices was acceptable when compared with the reference standard chest strap
- Per activity energy expenditure measurements were found to be inaccurate when compared against the gold standard indirect calorimeter.
- We also observed that indicating to the device the type of activity performed vastly improved the accuracy of heart rate measurements.

This work has been accepted for publication in the

Journal of Medical Internet Research

5.1 Abstract

Background: Wrist-worn activity monitors are often used to monitor heart rate (HR) and energy expenditure (EE) in a variety of settings, including more recently in medical applications. The use of real time physiological signals to inform medical systems including drug delivery systems and decision support systems will depend on the accuracy of the signals being measured including accuracy of HR and EE. Prior studies assessed accuracy of wearables only during steady state aerobic exercise.

Objective: To validate the accuracy of both HR and EE for two common wrist-worn devices during a variety of dynamic, non steady state activities that represent a variety of physical activities associated with daily living including structured exercise.

Methods: We assessed the accuracy of both HR and EE for two common wrist-worn devices (Fitbit Charge 2®, Garmin vívosmart®HR+) during dynamic activities. Over a two-day period, 20 healthy adults (age: 27.5±6.0 yrs; BMI: 22.5±2.3 kg/m^2; 11 females) performed a maximal oxygen uptake test, free-weight resistance circuit, interval training session, and activities of daily living. Validity was assessed using a HR chest strap (Polar®) and portable indirect

calorimetry (COSMED). Accuracy of the commercial wearables vs. research-grade standards was determined using Bland-Altman analysis, correlational analysis, and error bias.

Results: Fitbit and Garmin were reasonably accurate at measuring HR but with an overall negative bias. There was more error observed during high intensity activities, when there was a lack of repetitive wrist motion, and when the exercise mode indicator was not used. The Garmin estimated HR with a mean relative error (MRE) of -3.3% ±16.7 while Fitbit estimated HR with a MRE of -4.7% ±19.6 across all activities. The highest error was observed during high intensity intervals on bike (Fitbit: -11.4% ±35.7; Garmin: -14.3% ±20.5) and lowest error during high intensity intervals on treadmill (Fitbit: -1.7% ±11.5; Garmin: -0.5%±9.4). Fitbit and Garmin EE estimates differed significantly with Garmin having less negative bias (Fitbit: -19.3% ±29.9, Garmin: -1.6%±30.6, P <0.001)) across all activities, with both correlating poorly with indirect calorimetry measures.

Conclusions Two common wrist-worn devices show good HR accuracy, with a small negative bias, and reasonable EE estimates during low to moderate intensity exercise and during a variety of common daily activities and exercise. Accuracy was compromised markedly when the activity indicator was not used on the watch or when activities involving less wrist motion such as cycle ergometry were done.

5.2 Introduction

Consumer-based wrist-worn multi-sensor activity monitors (AMs) have emerged as an increasingly popular way to track various physiological metrics such as heart rate (HR) and physical activity levels, with the latter being typically expressed in the form of step counts and/or energy (caloric) expenditure (EE). Sales of AM devices have doubled from 30 million units in 2014 to 70 million units in 2017 [Haselton, 2017]. The growth in activity tracking wearables has been largely driven by consumer interest in monitoring, and sometimes sharing, their own physical activity levels, workouts and total daily EE. In the scientific community, there is increasing interest in whether AMs may also be used within a healthcare setting to collect these same data and help patients and healthcare providers better manage weight control and/or chronic illnesses. For example, in patients with type 1 diabetes, aerobic exercise is known to cause steep drops in blood glucose levels while anaerobic exercise can cause glucose levels to rise[Riddell et al., 2017] . Monitoring of patient physical activity levels may be helpful in implementing insulin and or nutritional strategies to help preserve glucose control [Zaharieva et al., 2017]. In theory, AMs could help individuals with diabetes better manage their glucose levels if they could be used in conjunction with implanted continuous glucose monitors, an insulin pump and a control algorithm to adjust insulin delivery, and perhaps glucagon delivery, in real time [Jacobs et al., 2015, 2016]. AMs can also can be used within

algorithm-driven decision support systems to help avert exercise-induced hypoglycemia or late onset hypoglycemia. Automated insulin delivery systems can potentially modify insulin dosing in response to AMs to reduce the risk (or severity) of exercise-induced hypoglycemia in people living with type 1 diabetes [Huyett et al., 2017, Breton et al., 2014b, Turksoy et al., 2014b, Breton et al., 2017]. For any medical system utilizing an AM, the accuracy of the HR and EE estimates by the AM is critical as it can influence medical dosing decisions and patient outcomes. There are three distinct challenges with using the AMs within medical systems, namely detecting the onset of the activity, distinguishing the type of the detected activity and estimating the intensity and duration of the activity, as each of these functions can determine how medical system may behave. In this paper, we explore the accuracy of HR and EE estimates from two popular AMs to determine if the accuracy of these wearables is sufficient for use within medical applications such as automated insulin delivery systems for use within type 1 diabetes glucose management.

In the earlier models of AMs, only accelerometers were used to estimate EE [Lee et al., 2014] but in more recent multi-sensor models, photoplethysmography (PPG) is being used to estimate HR [Bai et al., 2017] and potentially to improve the accuracy in estimating EE [Chowdhury et al., 2017]. With the inclusion of HR as measured by the PPG sensor and acceleration as measured by the accelerometers, the accuracy of the estimated EE is expected to be improved in newer models. For example, Zakeri et al. [Zakeri et al., 2008] showed that

EE can be estimated using both accelerometry and HR along with several additional patient-specific parameters such as age, weight and height. The Zakeri et al. algorithm utilizing accelerometry and HR to estimate EE, and metabolic equivalents (METs) has been used in the past to inform an AP during physical exercise [Jacobs et al., 2015]. In recent studies involving predominantly aerobic activities, wrist-worn AMs have been shown to have reasonable accuracy in HR estimation (≈5% error) but a poor estimate of EE where the error was found to be closer to ≈30% [Shcherbina et al., 2017]. In free-living conditions, however, AMs are worn, typically on the non-dominate wrist, during multiple forms of exercise in non-steady states, not just aerobic exercise performed at a constant workload or intensity. For example, in free-living conditions, some people frequently perform resistance exercise, involving free weights or their own body weight, while others may perform high intensity interval training (HIIT), within the same session. In fact, in the diabetes population, patients are encouraged to perform both resistance and aerobic training and HIIT has recently been recommended by numerous authors to rapidly improve fitness, body composition and overall glycemic control [Helal et al., 2017, Wormgoor et al., 2017, Rooijackers et al., 2017, García-García et al., 2015, Jelleyman et al., 2015].

Presently, there are at least four studies [Boudreaux et al., 2018, Bai et al., 2016, Horton et al., 2017, Jo et al., 2016] that have investigated the accuracy of wearable devices during resistance exercises and none during HIIT training. Bai et al. [Bai et al., 2016] reported that EE

measured during an unstructured resistance exercise protocol in which participants selected exercises and loads was inaccurate across numerous devices. The devices included five wrist-worn devices (Fitbit Flex, Jawbone Up24, Misfit Shine, Nike+ Fuelband SE, and Polar Loop) and two research monitors (Actigraph GT3X+ on the waist and the BodyMedia Core on the arm). In this study 52 participants tested seven different devices and the wearable devices had lower accuracy for EE when compared with a metabolic analysis system. None of the devices in this study reported HR measures. Horton et al. [Horton et al., 2017] assessed the validity of HR only using the Polar M600 when compared with a three-lead ECG during both aerobic and resistance exercises. The accuracy of the wearable device was reported to be better during aerobic exercise (92%) as compared with only 35% accurate during the resistance exercises. In this study, participants completed squats, shoulder shrugs, bicep curls, and lunges with dumbbells at a self-selected weight. Jo E et al. [Jo et al., 2016] reported poor correlation and HR accuracy in the Fitbit Charge HR device. In this study, subjects completed a short resistance exercise bout involving resisted arm raises, resisted lunges, and isometric plank. In a large cohort study, Bourdreaux et al. [Boudreaux et al., 2018] standardized the selection of the weights utilized during the resistance exercises: two upper body exercises (chest press, latissimus dorsi pulldown) and two lower body exercises (leg extension and leg curl) among the subjects using a standardized 10-rep max protocol. Results from this study demonstrated that HR measured by non-wrist worn devices were relatively accurate while, wrist-worn de-

vices showed poor correlations ('R' < 0.8) and higher error during resistance exercises (MAPE > 9%). They also showed that the EE measured by the devices was poor with MAPE values ranging between 43% and 57%.

The primary aim of this study was to examine the accuracy of both HR and EE across a wide range of dynamic activities including resistance training, HIIT and aerobic training. A secondary aim was to examine the accuracy when the optional *activity mode* is not selected on the wearable. There may be times when people exercise, but they do not indicate that they are exercising; we wanted to determine the accuracy both when they do and do not indicate that they are exercising.

5.3 Methods

5.3.1 Participants

The experimental protocol conformed to the standards set by the Declaration of Helsinki and was approved by the Institutional Review Board at the Oregon Health and Science University (OHSU, Portland Oregon) and by the Research Ethics Board at York University (Toronto, Canada). This study recruited 20 healthy adults (11 females; 10 subjects at OHSU; 10 at York University) who all provided informed consent before taking part in the study. Participants were screened for any cardiovascular complications using a Physical Activity Readiness Ques-

tionnaire http://eparmedx.com/.

5.3.2 Study Protocol

Participants attended the research laboratory on two separate occasions, separated by 24 hours. Each visit involved simultaneous recordings of HR (beats per minute) and EE (kcals and METs) from the respective criterion measures during a series of physical activities and structured exercises. On the first visit, a stadiometer (Seca, model220, Hamburg, Germany) was used to measure the height to the 0.25 cm (without shoes) and body mass was measured to the nearest 0.1 kg using a scale (Seca, model 707, Hamburg, Germany) with the participant dressed in workout clothes. As per the manufacturer's instructions, age, gender, height and weight were used to initialize the wearable devices and associated applications. These same data we also entered to a portable metabolic unit (Cosmed, Rome, Italy). Two wearable devices (one of each brand) were tested at the same time on all participants (one on each forearm as per manufacturer's instructions), using a randomized and counterbalanced method. On each visit, participants undertook two activity blocks (see below for further details) following setup of the devices and synchronization of all the devices to a single clock before the exercise protocol commenced.

5.3.3 Activities

In Visit 1, participants performed two blocks of activity separated by a 30 minute rest period. In the first block, participants performed a graded maximal aerobic exercise test (treadmill or cycle ergometer, 10 subjects per mode) to volitional exhaustion (i.e. progressive to peak oxygen consumption [VO_2peak]). These will be referred to as MAX-T (treadmill) and MAX-C (cycle ergometer) tests. During MAX-T, each participant began with a 5 min standing rest, followed by 4 min of walking as a warm up (3.0 mph, 0% grade for 2 min then at 5% grade for 2 min). After the warm up, participants self-selected a comfortable running speed between 4-6 mph and subsequently the treadmill incline was increased by 2% every 2 minutes until the participant reached volitional exhaustion. At each workload stage, participants were asked to assess their level of physical exertion using the Borg Rating of Perceived Exertion (RPE) 10 point scale[Borg, 1982]. For the participants performing the MAX-C test, each participant began with a 5 min seated rest followed by 4 minutes of warm up cycling at a moderate cadence (≈50—60 revolutions per minute—rpm) at zero load. After this, cycling cadence was maintained at 60 RPM and the power output was increased every 2 min by 30 Watts until the participant reached volitional exhaustion. Borg RPE was assessed at the end of each 2 min stage. For both MAX-T and MAX-C protocols, the wearables were placed in the appropriate exercise setting (i.e. running or cycling) and worn on the wrist as per manufacturer's specifications. Following the exercise test, the participants rested for 30 minutes. In the second

block of activity on the same day, a resistance circuit workout was performed (2 sets of 8 repetition max of all the major muscle groups). Subjects selected a suitable dumbbell weight that they could maintain a proper from for 8 repetitions before muscular fatigue. The following 6 exercises were performed: dumbbell bicep curls, Romanian deadlifts, Bulgarian split squat, dumbbell bench press, dumbbell shoulder press and dumbbell step ups. After a 20 minute cool down, participants then left the laboratory.

In Visit 2, performed the next day, participants undertook two new activity blocks. The first activity block consisted of 28 min of routine activities of daily living (ADL) while the second block included high intensity interval training (HIIT) for 27 min (including warmup and cool down). Six ADLs were performed to simulate daily chores, each of 3 minutes of duration. These included sitting on a chair or lying on a bed; washing dishes and simulated loading and unloading of a dishwasher; sweeping or vacuuming of a small room; organizing a room or adjusting furniture in the room; scrubbing walls and carpet/floor; and self-paced ascending and descending of a flight of stairs. These activities were bookended by two 5 minute periods of seated rest. In the second activity block, participants choose the same exercise mode (i.e. treadmill, cycle ergometer) as with the peak exercise test. The high intensity activities will be referred to as HIIT-T (treadmill) and HIIT-C (cycle ergometer). For HIIT-C, participants were asked to cycle at ≈60 rpms for 2 min at a low intensity with low resistance, corresponding to ≈30% of their peak power output in watts (as measured during MAX-C), and then at

a high intensity (60 rpms), at a power output corresponding to ≈80% of their peak power output for 2 min, for a total of 5 cycles. For the treadmill intervals, participants were asked to walk for 2 min at a treadmill speed and slope corresponding to ≈30% heart rate reserve (as measured during MAX-T), and then run/jog at a speed and slope corresponding to ≈80% of their heart rate reserve for 2 min, for a total of 5 cycles. This session was completed by a cool down period of 5 min.

5.3.4 Wearables Devices

Although multiple devices were available to that could provide the relevant exercise metrics, we chose the following two devices after considerable consideration to the cost of the devices and ability to integrate with a control system running on an Android platform. Henriksen et al. provided a detailed review of the many devices that are available and have been tested over the last few years [Henriksen et al., 2018].

Garmin vívosmart®HR+

The Garmin vívosmart ®HR+ (2016 version, Garmin International Inc, Kansas, USA) is a multi-sensor activity monitor that has an accelerometer, global positioning system (GPS) and built-in PPG sensor which uses the "Elevate" wrist heart rate technology to measure heart rate at the wrist. The frequency at which HR is measured is normally once every 15 seconds but triggering the 'device key' button and setting the wearable to an activity mode (e.g. run)

increases the frequency at which HR is measured to once per second. EE values are reported per activity bout in calories, also when the device key is pressed. Garmin provided a special interface to export data from the device when the 'device key' button was not indicated. This provided a reliable method to download data. The firmware version of the device was 3.20. Data was exported via bluetooth low energy (BTLE) to the Garmin-Connect App Version 3.17.

Fitbit Charge 2®

The Fitbit Charge 2®(2017 version, Fitbit Inc, California, USA) is a multi-sensor activity monitor which has an accelerometer and built-in PPG sensor which uses the "PurePulse" wrist heart rate technology to measure heart rate at the wrist . The frequency at which heart rate is measured varies and depends on the level of activity, the Charge 2 uses SmartTrackTM to automatically detect and record select exercises, but the manufacturer recommends using the exercise menu to improve the 'precision' of HR and EE measurements. EE values are reported per exercise bout in calories. Data were exported via bluetooth low energy (BTLE) to the Fitbit App Version 2.35. The firmware version of the device was 22.54.6. Data was downloaded at the highest resolution through Fitabase (Small Steps Labs, California, USA), a third party research platform designed to collect data from Fitbit using the developer API. The use of Fitbit with Fitabase also allows for estimates of metabolic equivalents (METS) for an additional assessment of the relative energy costs of a given activity, compared to rest, and for the

determination of estimated oxygen consumption (VO_2) expressed in ml $O_2 \cdot kg^{-1} \cdot min^{-1}$.

Criterion Measures Heart Rate Criterion Measure Participants wore the Polar H7 (BTLE version, Polar Electro, Kempele, Finland) chest strap HR monitor, which was secured tightly to ensure skin contact. The data from the Polar H7 was transmitted to the Polar A300 (Polar Electro, Kempele, Finland) and the second level data from this device was downloaded using the Polar Flow App. Although some studies have shown the limitation of these devices as compared with the gold-standard electrocardiogram (ECG) measure of heart rate [Henriksen et al., 2018, Horton et al., 2017], these chest based HR monitors have been used to inform glucose control systems of exercise [Breton et al., 2014b, 2017, Dasanayake et al., 2015a].

Energy Expenditure Criterion Measure Cosmed K4b2/ Cosmed K5: Participants wore a portable indirect calorimeter: Cosmed K4b2 or Cosmed K5 (Rome, Italy), which collected breath by breath data on the ventilatory parameters (i.e. oxygen consumption [VO_2]), EE was estimated from the direct measurement of oxygen consumption and carbon dioxide production. The units were calibrated prior to each session according to the manufacturer's instructions. EE data was downloaded from the cardiopulmonary exercise testing (CPET) Suite.

5.3.5 Statistical Analysis

Statistical analysis was performed separately for HR and EE. Data from the indirect calorimetry (VO_2 and VCO_2) served as the reference standard measurement for calculations of EE

(kcal/min). Data from the Polar HR monitor served as the as the reference standard for HR (beats-per-minute; bpm). In this analysis for both EE and HR, we analyzed all the data collected from each device and error was calculated as $error = device\ measurement - reference\ standard$ and % relative error (%RE) was calculated as

$$\%RE = \frac{(device\ measurement - reference\ standard) * 100}{reference\ standard} \tag{5.1}$$

We also report mean absolute percent error (MAPE) as absolute value of

$$\%MAPE = \frac{abs(device\ measurement - reference\ standard) * 100}{reference\ standard} \tag{5.2}$$

Error in HR was calculated at each measurement of the device and matched in time with the closest data collected from the reference standard. The frequency of measurement of the devices varied, with the reference standard measuring the HR at every second as opposed to the Fitbit (variable from 1 sec to 15 sec) and Garmin (variable ranged from 5 sec to 60 sec). Pearson (ϱ) correlation coefficients, Concordance correlation and Bland-Altman analysis were used to assess the mean bias and agreement between the devices and the reference standard. Error in EE was only calculated for each activity for the summed data for the entire activity. Higher resolution data for the EE values could not be obtained. All statistical analyses were conducted in R (version 3.4.2) [R Core Team, 2017] and GraphPad Prism 7 (version 7.0c).

5.4 Results

All 20 participants recruited for the study completed the procedures. Table 5.1 describes the participant characteristics.

Characteristic	Number = 20
Age (years)	28±6
Gender (M/F)	9/11
Body Weight (kg)	68±11
Height (cm)	173±10
Body Mass Index (kg/m^2)	22.5±2
VO_2max	48±9
Wrist (cm)	16±2
Race - White	85%
Race - Asian	10%
Race - Native American/Canadian	5%

Table 5.1: Participant characteristics, Continuous data represented as mean±standard deviation. VO2 max (maximal oxygen uptake) was measured at the incremental test to exhaustion.

5.4.1 Heart Rate Accuracy

We analyzed a total of 83,349 simultaneous heart rate pairs of data, whereby a pair is either a Garmin or a Fitbit measurement compared with the reference standard (Polar chest strap).

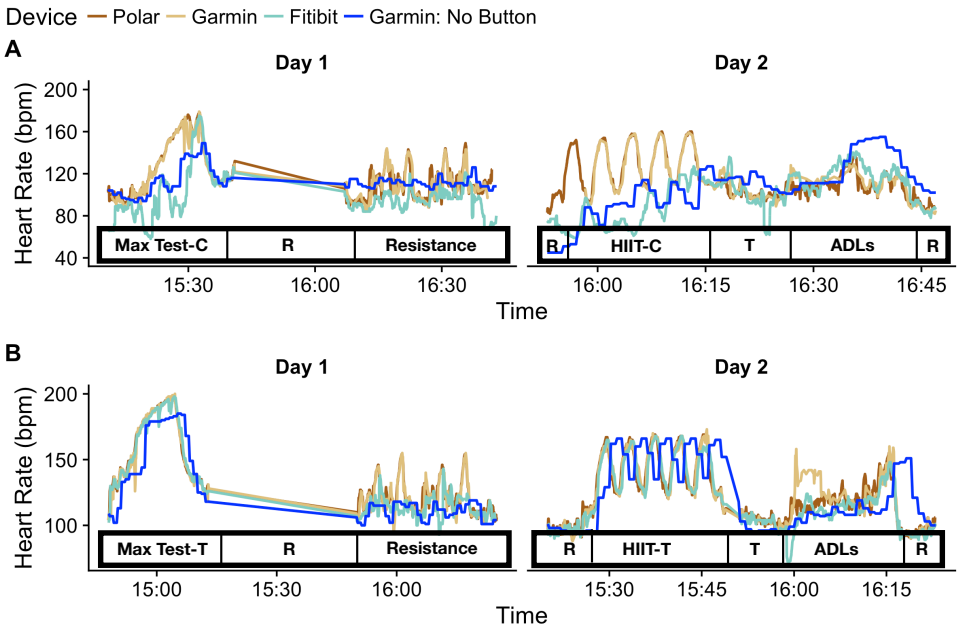

Figure 5.1: Two-day study protocol with *R* indicating the rest periods, and *T* indicating the transition period between the different types of activities. Data is shown from 2 different participants wearing all devices in panels A and B. Note, Garmin devices were worn by the participants here in two different modes, one with the activity mode indicated (Garmin) and the other without (Garmin: No Button). Panel A shows the data during the cycle ergometer tests and Panel B shows the data from the treadmill tests. Data in panel-A highlights the error observed during higher intensity exercises where wrist movement was less pronounced during cycle ergometer testing. Panel B shows treadmill results when the Garmin, Fitbit and Polar data are very closely matched across the exercise types.

There were a total of 61,499 pairs for the Fitbit heart rate data, 18,317 pairs of heart rate data from Garmin (with the activity mode indicated) and 3,533 pairs of heart rate data from Garmin with no button press (activity mode not indicated). We analyzed data collapsed across all activities and also looked at accuracy during each individual activity. There was no difference in accuracy between the two devices when the activity mode was indicated (Garmin and Fitbit). The overall performance was significantly worse if the activity mode was not indicated on the Garmin device compared to when activity mode was indicated (P <0.001). Figure 5.1 shows results of the HR data across both sessions for two subjects. Both panels show that when the activity mode is not indicated, there is less accuracy and also a distinct phase shift whereby the Garmin: No Button trace appears to be shifted in time relative to the Polar. This shift in time is a minor contributor to the inaccuracy within the HIIT activities. The majority of error was from devices failing to track during dynamic activities.

For HR data collected with the activity mode indicated, a systematic negative bias was observed across all three devices, the mean relative error (%RE)$\pm$SD for the Fitbit device on the pooled data was -4.71%$\pm$19.63, the mean %RE$\pm$SD for the Garmin (with activity mode initiated) was -3.33%$\pm$16.67 and the mean %RE$\pm$SD for the Garmin (with activity mode not initiated) was -5.47%*pm*22.79 (comparing the Garmin devices with activity mode indicated vs not indicated. P <0.001) MAPE$\pm$SD for the Garmin and Fitbit was 10.79% $\pm$13.14 and 11.33%$\pm$16.71 respectively. Mean HR measures for each activity were pooled and compared

with the reference standard, this data is shown in Table 5.2.

The lowest mean error in measuring HR was observed during the HIIT-T (Fitbit: -1.7%±11.5, Garmin: -0.5%±9.4), while the highest error was observed on both HIIT-C (Fitbit: -11.4% ±35.7, Garmin: -14.3%±20.5) and during MAX-C (Fitbit: -16.4%±21.6, Garmin: -9.3%±17.0). Figure 5.2 shows the variability between and within activities. When the activity mode of the wearables are activated (panels A and B), median % relative errors are within the 5% error threshold for both devices. When the activity mode is not activated, as observed in panel C, the median % relative error significantly exceeds the 5% threshold across many of the activities.

The correlation between the HR values on the wearables and our reference standard was best during MAX-T (Fitbit 0.94, Garmin : 0.94), while poor correlation between the HR values was observed during the HIIT-C (Fitbit: 0.46, Garmin: 0.71). The relative error across the collapsed data for the activities with repetitive motion (Treadmill Tests) was observed to be significantly lower at -1.6%± 9.6 when compared with activities with no repetitive motion (Ergometer tests) at -12.25%±19.3 ($P < 0.001$). Scatterplots between the simultaneous measures across all the activities are shown in Figure 5.3.

Bland-Altman plots indicated that all three devices underestimate the HR when compared with the reference standard as indicated in Figure 5.4 . The variability between these devices was comparable. However, the wearable devices tended to have significantly higher

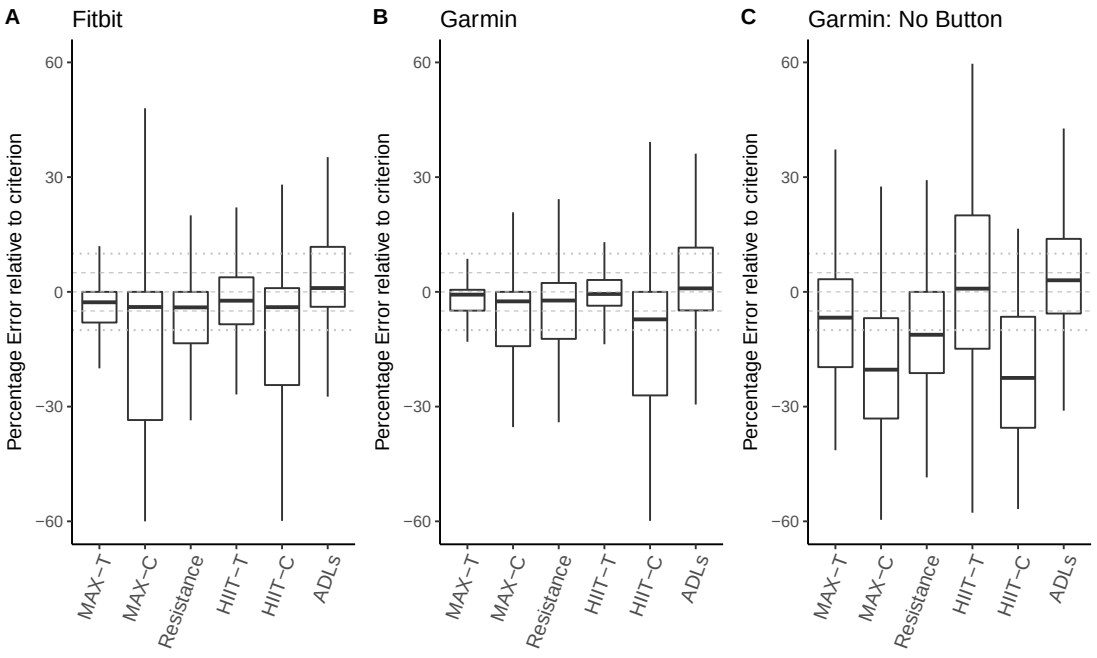

Figure 5.2: : Percent relative error (% RE) in HR across all the activities in this protocol from all the devices tested. Percent Error is calculated as $\%error = device\ measurement - reference\ standard * 100/reference\ standard$. The box-whisker plots indicate the error along with the 25% quantile, median -50% quantile, 75% quantile marked in each box plot Gray horizontal dashed lines indicated the 5% error threshold and the dotted lines indicate the 10% error threshold. When the activity is indicated both Garmin and Fitbit devices, median % relative errors were within the 5% error threshold. When the activity is not indicated as observed in panel: C, the median % relative error significantly exceed the 5% threshold across many of the activities.

error when the HR signal transitioned quickly and at higher intensity.

There was a generally small but significant impact of the wrist side worn (i.e. left vs right) on the percent absolute relative error. Using a t-test, the error was higher on the right hand vs. the left hand for the MAX-T (6.6% vs. 5.1%, P <0.001), HIIT-T (6.72% vs. 5.85%, P = .002), and ADLs (13.33% vs. 11.17%, P <0.001). While the error was higher on the left hand vs. the right hand for resistance (15.0% vs. 13.5%, P <0.001) and MAX-C (9.53 vs. 2.97%, P <0.001).

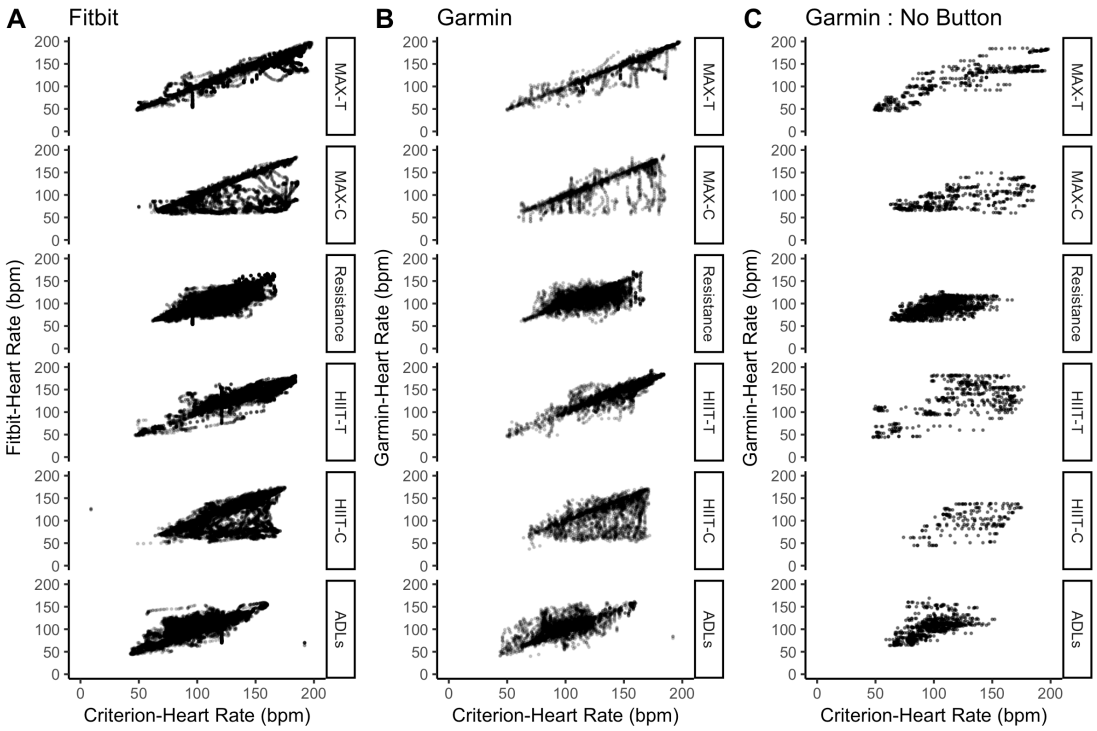

Figure 5.3: Scatter plots showing simultaneous heart rate measurements from the reference standard criterion device: Polar chest strap compared with the AMs, across all the activities that were tested in this study. Panel: A shows the correlation plot comparing the Fitbit and the Polar, Panel: B shows the correlation plot comparing the Garmin (with activity indication) and the Polar and Panel: C shows the correlation plot comparing the Garmin (with no activity indication) and the Polar.

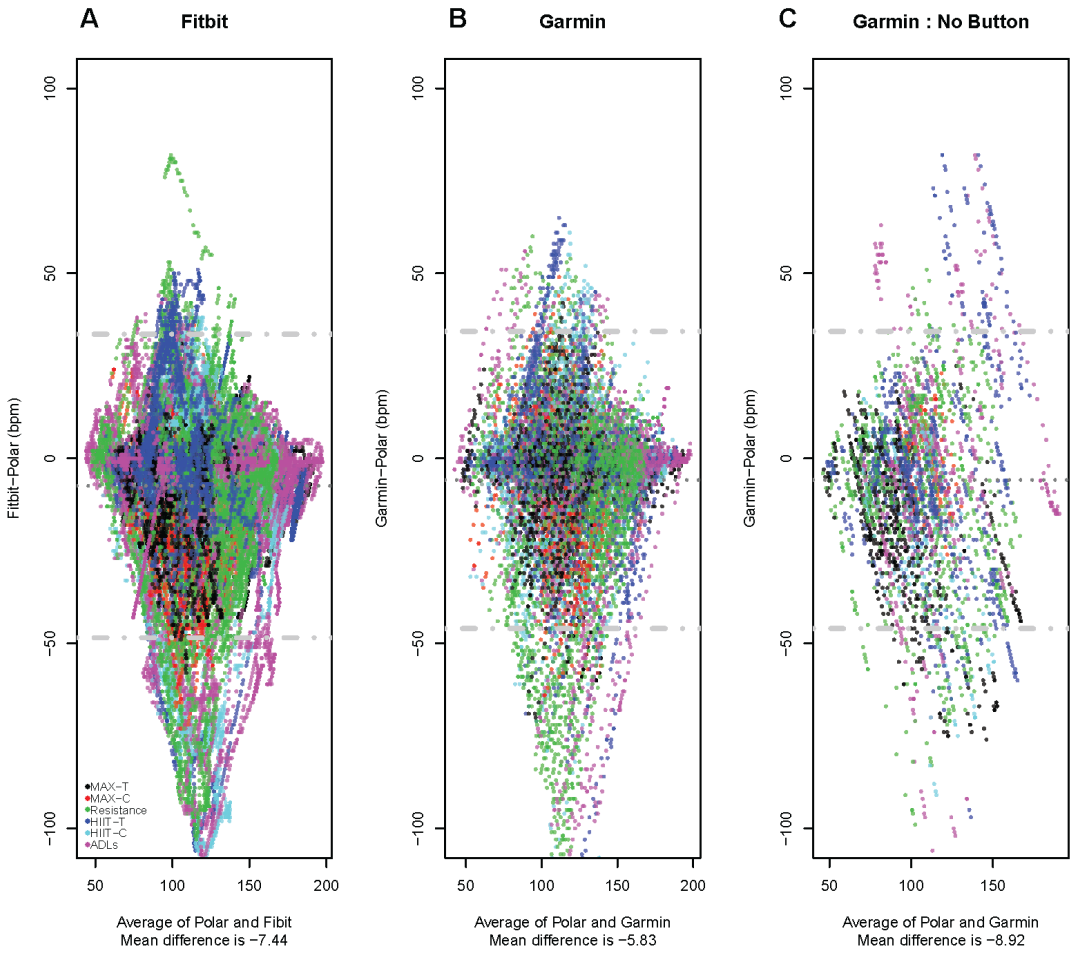

Figure 5.4: Bland-Altman plots showing simultaneous heart rate measurements from the reference standard criterion device: Polar chest strap compared with the AMs, across all the activities that were tested in this study. Different colors in this figure indicate each of the activity that was tested. Mean heart rate is shown on the x-axis and the difference between the simultaneously measured heart rate is on the y-axis. The gray dotted line indicates the mean difference (bias) between the measurement and the gray dashed lines indicate the limits of agreement (mean $\pm$ 2*SD). Panel: A shows the Bland-Altman plot comparing the Fitbit and the Polar, Panel: B shows the Bland-Altman plot comparing the Garmin (with activity indication) and the Polar and Panel: C shows the Bland-Altman plot comparing the Garmin (with no activity indication) and the Polar.

5.4.2 Energy Expenditure

Because of the limitation on the Garmin Connect application, EE data could only be compared at a very low resolution, namely at each activity block (e.g. ADL, HIIT-C or HIIT-T). Both Fitbit and Garmin performed reasonably well in estimating task-specific EE, when looking at the group as a whole, but considerable error was noted for some of the activity blocks.

Fitbit and Garmin EE estimates differed significantly with Garmin having less negative bias (Fitbit: -19.3% ±29.9, Garmin: -1.6% ±30.6, P <0.001). Table 5.3 shows the activity block (task) level data for both devices while Figure 5.6 shows the boxplot errors when compared with the Cosmed indirect calorimeter.

MAPE±SD for Garmin and Fitbit was 27.0% ± 21.8 and 25.1% ± 17.3, respectively. The lowest mean error in measuring EE was observed during ADL (-8.8% ± 29.2) for Fitbit and MAX-C (-4.5% ± 25.3) and HIIT-T (-4.7% ± 29.3) for Garmin. The highest error was observed during MAX-C (-39.1% ± 30.6) and HIIT-C (-41.9% ± 31.3) for Fitbit and resistance (21.0% ± 35.7) for Garmin. Figure 5.6 shows the %RE in EE for Fitbit and Garmin during all pooled treadmill and pooled cycle ergometer activities as scattered dot plots.

Both Fitbit and Garmin demonstrated negative bias when activities were performed on

the treadmill (Fitbit: -15.1% ± 13.5, Garmin: -7.4% ± 30.1, P = 0.18). For activities performed on the ergometer, both devices displayed a negative bias, but there was significantly higher mean error on Fitbit compared to Garmin (Fitbit: -40.5% ± 30.2, Garmin: -7.9% ± 27.6, P <0.001).

Figure 5.7 shows the absolute percent error in EE during each activity as box-whisker plots for Fitbit and Garmin, compared to Cosmed- derived EE. Garmin was significantly more accurate than Fitbit at estimating EE during MAX (Fitbit: 31.5% ± 21.5, Garmin: 22.9% ± 16.8, P = 0.047) and all ergometer activities (Fitbit: 42.7% ± 26.8, Garmin: 22.8% ± 16.6, P = 0.03). Fitbit was significantly more accurate than Garmin at estimating EE during ADL (ADL: 20.9% ± 21.8, Ergometer: 42.7% ± 26.8, P = 0.02) and all treadmill activities (Treadmill: 16.9% ± 10.9, Ergometer: 42.7% ± 26.8, P = 0.003) compared to all activities performed on the cycle ergometer.

□

5.4.3 Spurious Heart Rate measurements

During the early phase testing of these devices, it was discovered that these devices would produce spurious HR measurements during periods of non-wrist use, such as when devices were stored in a backpack during commute. PPG sensors use a light source, commonly a

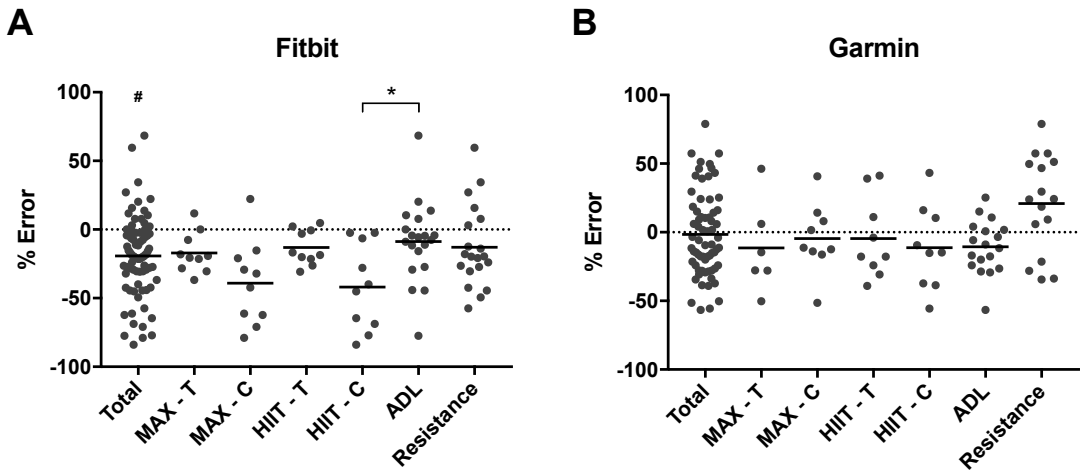

Figure 5.5: Percent relative error (%RE) in energy expenditure (EE) across different exercise modalities for Fitbit (A) and Garmin (B). Negative bias in estimating EE is apparent across exercise modalities. The horizontal lines represent the mean. ⋆P<0.05. #P<0.0001 compared to Garmin.

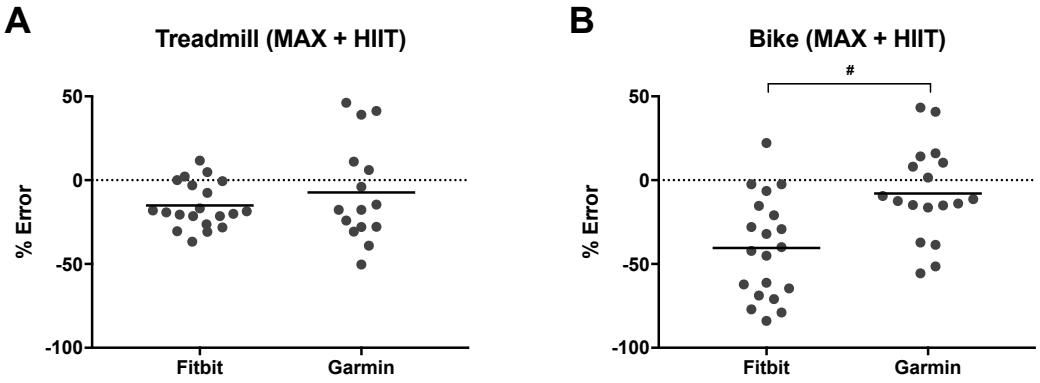

Figure 5.6: Percent relative error (%RE) in energy expenditure (EE) during the VO_2peak test (MAX) and high intensity interval training (HIIT) on the treadmill (A) and cycle ergometer (B) for Fitbit and Garmin. Negative bias in estimating EE is demonstrated by both devices during both modes of exercise, with the greatest mean error displayed by Fitbit during MAX and HIIT performed on the cycle ergometer. The horizontal lines represent the mean. #P<0.0001

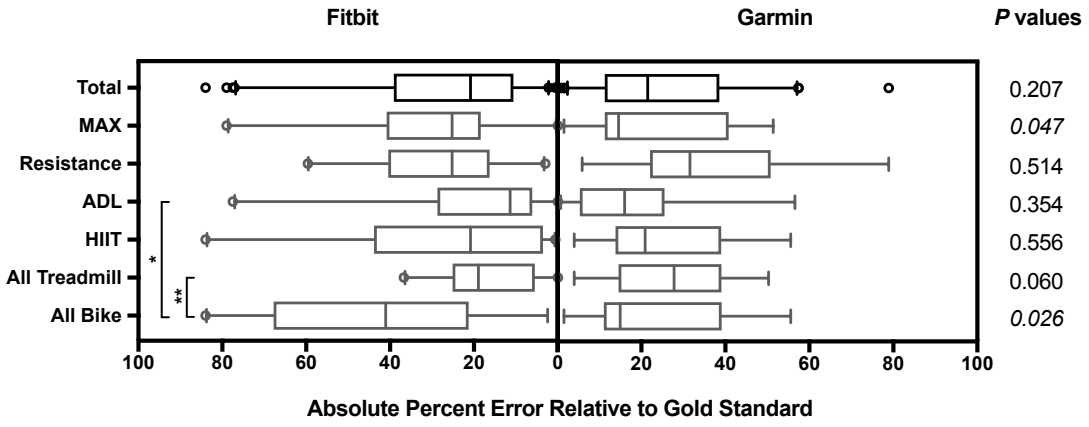

Figure 5.7: Absolute percent error in energy expenditure (EE) across different exercise modalities for Fitbit and Garmin. Each box-whisker plot consists of a box that extends from the 25% to the 75% quantile, with a line in the middle of the box representing the median (50% quantile). Each box has error bars that extend to the 5% and 95% quantiles, with outliers displayed with open circles. The P values listed on the right side display the difference in absolute percent error for EE between Fitbit and Garmin during each activity. ⋆P<0.05. ⋆⋆P<0.01.

group of light emitting diodes to illuminate the tissue of the wrist, and the HR measurement is based on the differential reflection of the light as measured by the photodetector in response to the pulsatile nature of the blood perfusion in the superficial vessels. Under these working principles, if there is no light reflection from the surface, we suspected that the devises reports HR measurements even if they are not "on body" (i.e. spurious results). We performed a simple laboratory experiment to confirm this. Using a standard bench top variable speed laboratory nutator (Fisher Sci # S06622) we simulated 3D wrist rotating motion at a fixed speed (22 rpm) and we recorded spurious HR results from both of the test devices. The data and the experimental picture are shown in Figure 5.8.

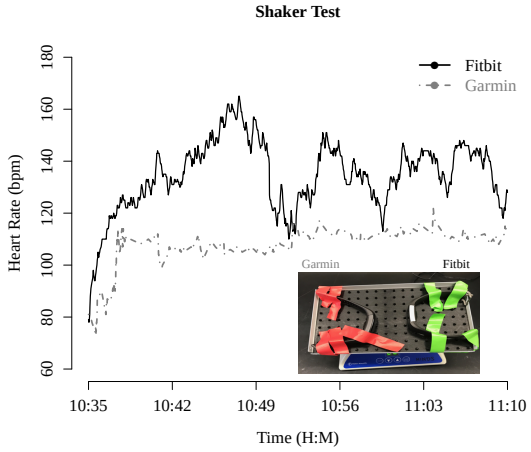

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Figure 5.8: Spurious heart rate as reported by the devices, when not being worn by an individual. The experimental setup is provided in the inset.

5.5 Discussion

This study examined the accuracy of two common wrist-worn, consumer-grade activity monitors for estimating HR and EE during a variety of non-steady state activities. Similar to previous studies [Chowdhury et al., 2017, Wang et al., 2017, Dooley et al., 2017, Stahl et al., 2016, Wallen et al., 2016], we found reasonable accuracy in HR and EE estimations for these two devices under certain exercise conditions. Our findings are also in agreement with prior work looking at HR and EE estimates across many different devices [Shcherbina et al., 2017, Abt et al., 2018], however these two prior studies took measurements only at steady state conditions once heart rate had stabilized. recent review by Bunn et al. [Bunn et al., 2018] showed that energy expenditure was generally underestimated by PA devices and that heart rate mea-

surements were generally more accurate at rest or on a cycle ergometer as compared with treadmill. Dondzila et al. [Dondzila et al., 2018] also looked at the Fitbit Charge HR and found that with aerobic exercise under laboratory conditions, the Fitbit Charge HR underestimated the HR compared with a Polar chest strap, with higher error at slower speeds. Jo et al. [Jo et al., 2016] compared the Basis Peak and the Fitbit Charge HR with ECG and also found a negative bias of HR with respect to ECG measurements (-4.9 bpm for the Basis and -12.7 bpm for the Fitbit). In results presented in the current paper, HR and EE measured by both the Garmin and Fitbit devices during the resistance exercise were similar to the measurements reported by Boudreaux et al. [Boudreaux et al., 2018]. Although, the resistance exercises were different, the intensity of the exercises was similar.

There are three novel contributions from this study. First, we report HR accuracy in these AMs in modes not tested previously (e.g., activities of daily living, and high intensity interval training). Second, we show that HR accuracy measured by these AMs is acceptable during low intensity activities and high intensity activities with repetitive wrist motion but that HR accuracy is poorer when there is no repetitive wrist motion and when any activity is at a high intensity (i.e. $\geq 70\%$ of maximal aerobic capacity). Prior research has suggested that PPG sensors used to measure the HR is liable to poor accuracy during activities with increased physical exertion or activities involving repetitive contractions of forearm skeletal muscles [Rafolt & Gallasch, 2004, Allen, 2007, Spierer et al., 2015]. It has been suggested that during activities

involving sustained muscle contractions or higher intensity exercises, the contact between the device's PPG sensor and skin is increased leading to a disruption in the signal quality and causing poor quality data [Allen, 2007, Spierer et al., 2015]. Third, we show that HR, as measured by the Garmin, is significantly improved when the device is in the activity mode setting. Since the HR measurement algorithm is proprietary to Garmin, we do not know why the accuracy is worse when activity mode is not indicated. It appears that the watch uses different HR measurement algorithms depending on the activity mode selected. It may be that the activity mode algorithms implement less smoothing than the non-activity mode algorithm and are thereby designed to respond faster to rapid heart rate changes.

While both AMs showed reasonable accuracy in HR, we did see differences between the two AMs in EE estimates across all activities and both AM devices correlated poorly with indirect calorimetry measures of EE. It is unclear why we found poor estimation of the EE. EE values are dependent on many anthropometric characteristics of the subject as well as the HR measurements [Zakeri et al., 2008]. We assume that the EE estimations provided by these devices are also utilizing this information but these calculations are proprietary. According to the manufacturers, Fitbit's EE estimate includes both active calories and the basal metabolic rate (BMR), whereas Garmin only reports active calories without BMR. Even with the inclusion of BMR in EE estimates, Fitbit still displayed a greater negative bias during most activities compared to Garmin. If EE estimates by Garmin included BMR, there would likely

be greater accuracy in the EE values reported by these devices. At the time of testing, these AMs provide different ways to indicate the various types of activity, such as running, stationary bike, strength training and "other" but there is not a clear indication for activities such as HIIT. Perhaps this is the reason for the high error rate recorded during these types of activities. As these consumer devices are constantly improved by the respective companies, the algorithms estimating EE should be improved or personalized to provide more accurate estimates. As these wearables transition from consumer reporting tools to clinical monitoring devices, a higher level of accuracy and precision is required. Clearly, the algorithms running on these wearables that estimate HR and EE are proprietary and can change without warning from the manufacturers, which poses further challenges for those wanting to integrate these devices into medical products. The onus of integrating these devices and assessing the level of accuracy and precision needed to make drug dosage decisions rests in the hands of those designing and evaluating medical algorithms.

Integrating these AMs into medical systems such as type 1 diabetes decision support systems or automated drug delivery systems in the future will require high fidelity data both from the HR signal and the EE estimates. The findings from this study point to shortcomings that could arise in both detecting activity and distinguishing the type of activity based on the HR signal. While the mean error of the HR measurement was within the acceptable range for both devices, the range of the error was wider than anticipated. This issue and

the inaccuracies associated with the EE data could lead to issues with estimating the intensity of the activity accurately. Additionally, short non-steady state exercises such as a 10 second maximal sprint have been shown to limit the rapid change in glucose response [Davey et al., 2013b], but findings from this study indicate that detecting these quick non-steady exercises might be challenging for AMs to capture. WWe found spurious HR measurements when the AM device is not worn on the wrist. Integration of these devices into a life supporting drug delivery system must account for an on- wrist / off-wrist detection algorithm, which are currently not a part of the AMs evaluated. Another feature that could be integrated with further evaluation into a medical system is the exercise detection that is available on these devices. The Garmin device performed better when the exercise type was indicated through a button press on the watch. Future versions of these wearables are integrating automated exercise detection and this is an area that should be further researched in terms of accuracy Lastly, if physical activity data are to be properly incorporated into medical systems including real-time drug delivery systems, access to the data in near real time (e.g. every 5 minutes) would be important. In the automated insulin dosing scenario, decisions would need to be made at the onset of exercise to prevent exercise-induced hypoglycemia. Currently, neither of these watches provide real-time access to their data streams. An approach to overcome some of the challenges associated with exercise detection and accuracy of detection would be to alert the individual before exercise dosing decisions are made. Effective integration of AMs is an active

area of research in the medical community, and the findings from this study point to both the abilities and challenges associated with real-time monitoring and integrating into medical systems.

5.6 Limitations

Our study has a limitation in that we only tested two popular consumer grade devices. The choice was based on the ubiquity of these sensors in the market, affordability, and potential to be easily integrated into existing medical system architectures through, for example, an API. Our current data and interpretations may be limited as we did not account for the skin color in our study. It has been reported that skin color could influence the accuracy of the HR measurement [Shcherbina et al., 2017] and future studies should report the Fitzpatrick skin tone scale to account for this limitation. Another limitation of our study is that exercise was conducted in a laboratory setting as opposed to the real world. However, we attempted to capture several real-world activities of daily living to minimize this limitation, though these activities were also recorded within a lab. It would be important to do further investigations in real world settings to corroborate our results. Another limitation was that heart rate measurements from the wearable devices were not compared against a true gold standard such as ECG.

5.7 Conclusions

We conducted a thorough assessment of two of the most popular low-cost consumer wrist-worn activity monitors during multiple exercise modalities and during daily activities. We found that in steady state activities and during low intensity activities the HR measurements were within acceptable error range (5%) but less accurate during higher intensity more dynamic activities that do not involve wrist motion. The EE estimates provided by these devices were inaccurate during all activities.

5.8 Acknowledgements

We would like to acknowledge the generous support from the Leona M. and Harry B. Helmsley Charitable Trust which funded the project through the grant *Exercise in Diabetes Initiative: The Effect of Exercise on Glycemic Control in Type 1 Diabetes (Pilot Study)*.

Table 5.2: Pooled Heart Rate data from all the tested devices for each of the different blocks of activities performed by the subjects in the study. Various metrics of interest are reported in the table.

Measures	Fitbit	Garmin	Garmin+No Button
Max Test (Treadmill): Progressive exercise to volitional fatigue			
No of pairs #	7127	2037	476
Device mean± SD	129.6±38	139.6±37.3	112.2±38.2
Criterion mean± SD	137.2±40.9	144.7±36.5	122.3±45.5
Mean difference± SD	-7.6±13.6	-5.1±13.0	-10.1±21.5
% Mean Relative Error± SD	-4.8±10.3	-3.3±9.6	-5.9±16.6
% Mean Absolute Error± SD	7.3±11.8	5.8±8.4	14.5±10.1
Concordance correlation (95 %CI)	0.92 (0.92-0.93)	0.93 (0.92-0.93)	0.84 (0.82-0.87)
Pearson's correlation (ϱ)	0.94	0.94	0.88
Max Test (Ergometer): Progressive exercise to volitional fatigue			
No of pairs #	6375	1705	444
Device mean± SD	101.4±31.2	115.5±34	91.5±21.3
Criterion mean± SD	125.3±32.7	128.9±33.3	120.3±34.1
Mean difference± SD	-23.8±33.4	-13.4±25.6	-28.8±27.8
% Mean Relative Error± SD	-16.4±21.6	-9.3±17.0	-20.6±18.2
% Mean Absolute Error± SD	17.9±32.3	11.8±15.3	22.9±15.2
Concordance correlation (95 %CI)	0.36 (0.34-0.37)	0.66 (0.62-0.68)	0.34 (0.29-0.39)
Pearson's correlation (ϱ)	0.46	0.71	0.58
Resistance Exercise			
No of pairs #	17420	5215	1200
Device mean± SD	105.9±21.2	112.9±17.7	91.8±15.6
Criterion mean± SD	114.4±21.4	119.5±20.1	104.6±19.4
Mean difference± SD	-8.5±14.4	-6.5±17.5	-12.8±17.4
% Mean Relative Error± SD	-6.9±12.0	-4.2±14.2	-10.7±14.9
% Mean Absolute Error± SD	9.8±12.1	10.6±10.4	15.0±10.7
Concordance correlation (95 %CI)	0.72 (0.71-0.72)	0.54 (0.52-0.56)	0.40 (0.37-0.45)
Pearson's correlation (ϱ)	0.88	0.9	0.53
Daily chores and activities of daily living			
No of pairs #	14883	3605	738
Device mean± SD	101.8±20.5	104.0±22.0	104.5±20.8
Criterion mean± SD	98.6±20.8	100.2±21.8	98.2±17.0
Mean difference± SD	3.3±15.2	3.9±17.4	6.3±18.0
% Mean Relative Error± SD	3.3±16.5	5.6±19.5	7.4±19.4
% Mean Absolute Error± SD	11.4±11.2	13.0±13.2	14.0±15.4
Concordance correlation (95 %CI)	0.72 (0.71-0.73)	0.68 (0.66-0.69)	0.52 (0.47-0.57)
Pearson's correlation (ϱ)	0.73	0.69	0.56
Treadmill: Intermittent high intensity exercise			
No of pairs #	8105	3315	482
Device mean± SD	129.7±28.0	138.8±26.9	125.7±38.1
Criterion mean± SD	133.2±30.6	139.9±26.3	120.0±35.4
Mean difference± SD	-3.5±14.4	-1.2±11.9	5.7±33.5
% Mean Relative Error± SD	-1.7±11.5	-0.5±9.4	8.9±33
% Mean Absolute Error± SD	8.5±10.0	9.0±6.0	25.0±23.3
Concordance correlation (95 %CI)	0.87 (0.87-0.88)	0.90 (0.89-0.91)	0.58 (0.52-0.63)
Pearson's correlation (ϱ)	0.88	0.9	0.59
Ergometer: Intermittent high intensity exercise			
No of pairs #	7589	2440	193
Device mean± SD	110.6±31.2	110.9±30.3	100.4±26.6
Criterion mean± SD	127.0±25.7	131.2±25.3	131.2±24.2
Mean difference± SD	-16.4±27.2	-20.3±28.9	-30.8±27.4
% Mean Relative Error± SD	-11.4±35.7	-14.3±20.5	-22.5±19.8
% Mean Absolute Error± SD	16.0±24.4	26.0±17.6	25.0±13.4
Concordance correlation (95 %CI)	0.47 (0.45-0.48)	0.37 (0.34-0.39)	0.24 (0.16-0.32
Pearson's correlation (ϱ)	0.56	0.47	0.42

Table 5.3: Pooled Energy Expenditure data for the different blocks of activities undertaken during the study. Data is shown for each activity type. Sample size, mean± sd of each of the measured device, mean ± sd of the difference between the device measurement and the reference standard, the mean relative difference ± sd (%), the mean absolute difference ± sd (%) and the correlation between the measures.

Measures	Fitbit	Garmin
Max Test (Treadmill): Progressive exercise to volitional fatigue		
N #	10	6
Device mean± SD	192.1±47.2	216.5±55.3
Criterion mean± SD	237.3±72.5	260.5±77.2
Mean difference± SD	45.2±44.4	-44.0±90.1
% Mean Relative Error± SD	-17.0±14.6	-11.4±33.7
% Mean Absolute Error± SD	19.4±11.0	28.8±17.2
Pearson's correlation (ϱ)	0.81	0.11
Max Test (Ergometer): Progressive exercise to volitional fatigue		
N #	10	6
Device mean± SD	133.6±77.6	207.0±48.7
Criterion mean± SD	225.3±74.7	231.4±76.5
Mean difference± SD	-91.7±87.2	-24.4±63.9
% Mean Relative Error± SD	-39.1±30.6	-4.5±25.3
% Mean Absolute Error± SD	43.5±23.0	18.9±16.2
Pearson's correlation (ϱ)	0.35	0.56
Resistance Exercise		
N #	20	16
Device mean± SD	130.2±46.2	179.8±56.8
Criterion mean± SD	153.1±45.5	155.2±47.8
Mean difference± SD	-22.9±44.0	24.6±56.6
% Mean Relative Error± SD	-12.9±29.7	21.0±35.7
% Mean Absolute Error± SD	27.7±15.9	35.7±19.7
Pearson's correlation (ϱ)	0.54	0.43
Daily chores and activities of daily living		
N #	20	18
Device mean± SD	103.5±38.2	100.6±23.4
Criterion mean± SD	114.4±25.7	114.8±27.0
Mean difference± SD	-10.9±39.4	-14.3±28.2
% Mean Relative Error± SD	-8.8±29.2	-10.6±19.3
% Mean Absolute Error± SD	20.9±21.8	17.0±13.7
Pearson's correlation (ϱ)	0.29	0.38
Treadmill: Intermittent high intensity exercise		
N #	10	9
Device mean± SD	211.1±57.0	226.9±58.1
Criterion mean± SD	246.6±71.9	249.7±75.6
Mean difference± SD	-35.5±34.6	-22.8±61.7
% Mean Relative Error± SD	-13.1±12.7	-4.7±29.3
% Mean Absolute Error± SD	14.5±10.9	25.0±13.4
Pearson's correlation (ϱ)	0.88	0.60
Ergometer: Intermittent high intensity exercise		
N #	10	9
Device mean± SD	128.2±60.4	205.8±76.4
Criterion mean± SD	232.8±44.2	234.9±46.4
Mean difference± SD	-104.6±83.8	-29.1±80.2
% Mean Relative Error± SD	-41.9±31.3	-11.2±30.8
% Mean Absolute Error± SD	41.9±31.3	26.7±17.0
Pearson's correlation (ϱ)	-0.26	0.22

[a] Energy expenditure was aggregated from each device and compared with the criterion measure for each individual activity block

The purpose of models is not to fit the data, but to sharpen the questions

Samuel Karlin, R. A. Fisher Memorial Lecture, Royal Society, 1983

6

Prediction of Hypoglycemia during Aerobic Exercise in adults with Type 1 Diabetes

Fear of hypoglycemia is one of the main barriers to physical activity for individuals with type 1 diabetes. In this chapter we develop a simple heuristic based approach to predict hypoglycemia related to aerobic exercise. We also developed a complex machine learning model that could be used in automated systems. Reducing the risk of hypoglycemia due to exer-

cise could potentially increase the adoption of an active lifestyle by people living with Type 1 Diabetes.

Chapter summary

- This study is the first one to propose a simple heuristic based tool that could predict and prevent exercise related hypoglycemia
- The validated simple heuristic based approach using current glucose value and the expected exercise heart rate could be used to predict hypoglycemia with an accuracy of $\approx 80\%$
- For an automated control system, we provide a validated machine learning approach that uses many of the different anthropometric features along with the insulin on board data to predict hypoglycemia with an accuracy of $\approx 87\%$

This work has been prepared for submission to the

Journal of Diabetes Science and Technology

6.1 Abstract

Background

Fear of exercise related hypoglycemia is a major reason why people with type 1 diabetes (T1D) do not exercise. There is no validated prediction algorithm that can predict hypoglycemia at

the start of aerobic exercise.

Methods

We have developed and evaluated two separate algorithms to predict hypoglycemia at the start of exercise. Model 1 is a decision tree and Model 2 is a random forest model. Both models were trained using a meta-data set based on 154 observations of in-clinic aerobic exercise in 43 adults with T1D from 3 different studies that included participants using sensor augmented pump therapy, automated insulin delivery therapy, and automated insulin and glucagon therapy. Both models were validated using an entirely new validation data set with 90 exercise observations collected from 12 new adults with T1D.

Results

Model 1 identified two critical features predictive of hypoglycemia during exercise: heart rate and glucose at the start of exercise. If heart rate was greater than 121 bpm during exercise and glucose at the start of exercise was less than 182 mg/dL, it predicted hypoglycemia with 79.55% accuracy. Model 2 achieved a higher accuracy of 86.7% using additional features and higher complexity.

Conclusions

Models presented here can assist people with T1D to avoid exercise related hypoglycemia. The simple Model 1 heuristic can be easily remembered (*the 180/120 rule*) and Model 2 is more complex requiring computational resources making it suitable for automated artificial pancreas or decision support systems.

6.2 Introduction

American Diabetes Association guidelines strongly recommend physical activity (PA) to individuals with type 1 diabetes (T1D) [noa, 2017]. Regular PA in these individuals is associated with increased cardiorespiratory fitness[McCarthy et al., 2016a] leading to improved blood lipid profiles[Lumb, 2014] and reduction in long term cardiovascular disease risk [Pierre-Louis et al., 2014]. During PA individuals with T1D have an increased peripheral insulin sensitivity due to the upregulation of the expression of glucose transporter type 4 [Dohm, 2002, Younk et al., 2011, Goodyear & Kahn, 1998] and an impaired counter-regulatory hormonal response [McMahon et al., 2007] creating an imbalance of hepatic glucose production and glucose utilization often resulting in exercise-induced hypoglycemia [Riddell et al., 2017]. The increased likelihood and fear of hypoglycemia during exercise and for many hours afterward[Reddy et al., 2017, Chimen et al., 2012] discourages a majority of people with T1D

from engaging in regular PA. In individuals with T1D, early hypoglycemic symptoms tend to be masked during PA, resulting in cases of more severe hypoglycemic episodes [Younk et al., 2011]. A recent consensus statement [Riddell et al., 2017] provides guidelines and recommendations on adjusting insulin and consuming carbohydrates prior to exercise to avoid hypoglycemia. However, many people with T1D have difficulty following these recommendations and still report exercise-induced hypoglycemia [Pinsker et al., 2016]. Many people with T1D do not understand the complex interplay between insulin kinetics and dynamics and exercise intensity and so they tend to consume extra carbohydrates either before or during exercise, which can result in worse glucose control [Pinsker et al., 2016, Yardley & Sigal, 2015, Cryer, 2016].

There are multiple options for people with T1D to manage their glucose under normal every-day conditions and also during exercise. These therapies can be divided into two categories, open loop and closed loop therapies. Open loop therapies require the person with T1D to measure their glucose either through finger-stick measurements or through continuous glucose monitors (CGM) and dose insulin themselves. Many of people with T1D use multiple daily injection (MDI) therapy to control their glucose levels [Pickup, 2012]. Approximately 40% of people with T1D use insulin pumps that deliver a constant insulin level throughout the day [Pickup, 2012]. Closed-loop systems that automate the delivery of insulin have recently become commercially available to help people with T1D better manage

their glucose [Voelker, 2016a]. These so-called artificial pancreas (AP) systems are comprised of a CGM, an insulin pump and a control algorithm that automates the delivery of insulin in response to the sensed glucose [Thabit et al., 2015].Glucagon can also be included as an additional hormone to help avoid hypoglycemia [Russell et al., 2014, Jacobs et al., 2014].

More recently, various research groups including our group have reported success at integrating PA into the AP [Jacobs et al., 2016, Breton et al., 2014b, Jacobs et al., 2015, Turksoy et al., 2014b, Stenerson et al., 2014]. Within the context of AP systems, there are two distinctive challenges with incorporating PA characteristics into the control algorithm. The system must accurately detect that exercise has occurred. And second, the AP system must respond to the exercise event by either adjusting dosing of insulin and optionally glucagon in response to the exercise event or recommend a behavior change such as consumption of a carbohydrate. With the advent of accurate, wearable physical activity sensors [Shcherbina et al., 2017], incorporating activity data from accelerometers and heart rate data have enabled detection of PA and incorporation of exercise metrics into AP systems to better enable the avoidance of exercise-induced hypoglycemia [Jacobs et al., 2016, Breton et al., 2014b, Jacobs et al., 2015, Turksoy et al., 2014b, Stenerson et al., 2014, Dasanayake et al., 2015a]. Once exercise is detected, AP system can reduce or shut-off insulin [Turksoy et al., 2014b, Breton et al., 2014b]. Second, the system can recommend consumption of carbohydrates to avoid hypoglycemia during or after exercise [Stenerson et al., 2014, Taleb et al., 2016]. And lastly,

the system can suggest increased glucagon dosing [Jacobs et al., 2016]. AP systems have been shown to reduce time in hypoglycemia, but they not have been effective at preventing hypoglycemia altogether. In this paper, we present two new prediction algorithms with different levels of complexity to identify the risk of hypoglycemia at the start of exercise.

6.3 Materials and Methods

6.3.1 Participants

Data was compiled from 3 separate randomized clinical studies into 244 exercise observations from 55 adults with T1D (22 men, 33 women; weight:76±15 kg; age:33±6 years). Demographic information is listed in table 6.1. The clinical trial information for each of these three clinical studies can be accessed at, Study 1: NCT02241889, Study 2: NCT02687893, and Study 3: NCT02862730. Each of these studies were conducted at the clinical research centre at Oregon Health and Science University (Portland, Oregon). Each study was approved by the Institutional Review Board and informed consent was obtained from each subject before any data was collected.

Characteristic	Number =55
Age (years)	33±6
Gender (M/F)	22/33
Duration of diabetes (years)	18±9
HbA_{1c} (%)	7.5±0.9
Body Weight (kg)	76±15
Height (cm)	173±9
Body Mass Index (kg/m²)	25±5
VO_2max	41±11

Table 6.1: Clinical and Demographic characteristics of the subjects in the clinical studies. Continuous data represented as mean±standard deviation.

6.3.2 Data collection protocols

Study 1

In-clinic aerobic exercise data were collected as part of a randomized cross-over study to assess the efficacy of an automated dual-hormonal (insulin and glucagon) AP system to reduce exercise related hypoglycemia [Jacobs et al., 2016]. In this 3 arm crossover trial, 21 adults with T1D were randomly assigned to AP with exercise dosing adjustment, AP with no exercise dosing adjustment and sensor-augmented pump (SAP) therapy.Participants performed mild exercise for 45 minutes at 60% of their maximum heart rate (30%-50%VO_2max)on a treadmill, with no pre-exercise snack. A total of 63 exercise observations were used from this study.

Study 2

In-clinic aerobic exercise data was collected as part of a study designed to assess the impact of nocturnal hypoglycemia on sleep in patients with T1D [Reddy et al., 2017]. In this 3-week crossover trial, 10 adults with T1D were randomized to perform aerobic, resistance or no exercise. During each exercise week, participants completed two separate 45-minute exercise sessions. Participants managed their glucose levels using a BG meter and insulin pump therapy and performed moderate aerobic exercise for 45 minutes at 60% of their VO_2max at 4pm. Twenty exercise session observations were used from this study.

Study 3

In-clinic aerobic exercise data were collected as part of a study designed to assess the efficacy of a dual hormone AP with exercise detection vs. either single hormone AP with exercise detection, a predictive low glucose suspend system (PLGS) form of therapy or SAP therapy [Castle et al., 2018b]. In this 4 arm crossover trial, 20 adults with T1D were randomly assigned to each of the study arms. Each study arm lasted 4 days, with 2 in-clinic exercise visits on the first and last day of the study. Participants performed moderate exercise for 45 minutes at 60% of their VO_2max on a treadmill. A total of 161 exercise session observations were used from this study.

6.3.3 Data processing and feature extraction

The algorithms that we developed detect the likelihood of hypoglycemia (<70 mg/dl) at the start of exercise. The algorithms were designed to notify a person with T1D immediately at the beginning of exercise if there is a high likelihood that they will become hypoglycemic without a change in their behavior (e.g. consumption of a rescue carbohydrate). In this way, we used the time point at the start of exercise of each exercise observation to make a prediction of hypoglycemia during the exercise event. If the algorithm predicted subsequent hypoglycemia and if the person subsequently became hypoglycemic during exercise, this was counted as a true positive, whereas if they did not experience hypoglycemia during exercise, it was counted as a false positive. The feature vector for the prediction algorithms utilized anthropometric data, physiologic data at the start of exercise, glucose data at the start of exercise, and insulin data at the start of exercise. All of the features can be obtained within the first five minutes of exercise. The exercise features included a heart rate estimate and an estimate of metabolic energy expenditure (MET) during the first five minutes of exercise. The energy expenditure was estimated using a validated linear regression model [Zakeri et al., 2008] that was personalized based on characteristics of an individual (weight, height, sex, and age) [Harris & Benedict, 1918]. The insulin features include the insulin on board at the start of exercise in units [Toffanin et al., 2013, Jacobs et al., 2014] and the total daily insulin dosage (TDI) in units/day. The glucose feature included the capillary blood glucose (CBG) or sub-cutaneous sensor glucose

(SG) at the start of exercise. In addition, there was a feature for whether glucagon was used within the therapy and expressed as a 1 for usage of glucagon, and a 0 if it was not used. All the features can be found in Table 6.2.

Anthropometric features	Exercise Intensity features	Insulin features	Glucose features
Sex (encoded as 0 for male and 1 for female)	Exercise heart rate (bpm)	Insulin on board at start of exercise (Units)	Blood glucose (CBG) value at start of exercise (mg/dL)
Weight (kg)	Energy Expenditure (METs)	Average daily dosage (Units/day)	Glucagon (encoded as 0 for insulin only and 1 for dual hormone)
Height (cm)			
Body mass index (kg/m^2)			

Table 6.2: Features computed from each observation. Features included anthropometric, exercise, glucose and insulin features.

6.3.4 Predictive Models

We developed two predictive models: one decision tree classification models and one random forest (RF) classifier. We undertook a supervised machine learning approach to *learn* the structure of the trees and the RF from the data.

Model 1:

Decision trees are one of the most popular machine learning approaches for the task of classification [Wu et al., 2008]. One of the main reasons for this popularity is the visual repre-

sentation of the model in a simple decision tree format with the underlying ability to track and evaluate every part of the decision making process. A second reason for their success is that they are capable of determining nonlinear relationships between the predictors [Christopher, 2016]. Decision Tree Models are predictive models that consist of a root node, chance nodes and terminal nodes. Root node represents the highest node. The root node splits the data into two mutually exclusive sets; the chance nodes represent descriptive attributes and the terminal nodes represent the final classification. The structure of a decision tree is a hierarchy of branches. Each decision rule is a path traversed from the root node through the chance nodes ending at a terminal node. These pathways are represented as 'if-then' rules. A decision tree is grown in a recursive fashion, by selecting a conjunction over one feature that results in purer subset. A pure node is one which has all the data correctly classified. Purity is measured according to the Gini's diversity index. A pure node has a Gini index of 0, if there are any misclassifications, the Gini index is positive, minimization of the Gini index is the criterion to minimize the probability of misclassification. Many elegant algorithms for building decision tree models have been introduced and applied to real life problems. CART [Breiman et al., 1984] is one of the best known programs for constructing decision trees. An implementation of CART called the rpart package in the R environment was used to build this type of model [Therneau et al., 2015].

Model 2

A random forest classifier (RF) is an ensemble of randomized decision trees. RF is highly adaptive to the data and is able to account for correlation and interactions among features. Each decision tree is grown nondeterministically using a two-stage randomization process. Each tree is learned from a random sample of training observations and a second layer of randomization is introduced at the node level when growing the tree. Rather than splitting a node using all variables, at each node of a tree, the RF selects a random subset of variables, and only those variables are used as candidates to find the best split for the node. This two-step randomization is designed to decorrelate trees so that the ensemble will have low variance. RF was chosen amongst the many machine learning classification algorithms because it has a number of advantages namely: (i) feature selection is greedy (the greedy optimization is a tree building recursive approach that splits the data at each node, while optimizing the desired result) and encompassed during the training phase, and noninformative features are reliably ignored; (ii) it can represent both nonlinear and multimodal functions ; (iii) it is a type of ensemble learning, which makes it more robust to noise than an individual tree. The importance of each feature to the RF classifier can be calculated by iteratively holding out each feature and calculating the change in accuracy of the resulting classifier [Breiman, 2001]. Predictions generated by each tree in the forest are aggregated and the final model prediction (i.e., hypoglycemia or not) is based on the majority vote. An implementation of this

approach called the *randomForest* [Liaw et al., 2002] and *caret*[Kuhn et al., 2014, Kuhn & Johnson, 2013] packages within the R environment were used to build this model.

6.3.5 Training and validation data sets

- Model training: A total of 154 observations were used to develop two predictive models
- Model validation: A total of 90 observations (independent) were used to validate these two models.

6.3.6 Model 1 data set

	Data collection protocol	Training set (Hypoglycemia/ Avoidance of hypoglycemia)	Validation set (Hypoglycemia/ Avoidance of hypoglycemia)
SAP	Study 1, Study 2 & Study 3	58 (21/37)	22 (13/9)
PLGS	Study 3	–	22(14/8)
Total		58 (21/37)	44(27/17)

Table 6.3: The source of the observations used to develop and validate the simple decision tree model is shown in the table. The number of observations that were determined to be hypoglycemic are indicated in the table.SAP: Sensor Augmented Pump therapy, PLGS: Predictive Low Glucose Suspend therapy.

6.3.7 Model 1:

This model was developed with the intention of creating a simple rule of thumb algorithm that could be easily remembered and used by individuals with T1D at the start of PA. To

train the appropriate model for this scenario, we used the observations that were collected from studies 1-3 when these individuals were administering their own care otherwise known as open loop care (OLC) or SAP. Table 6.3 shows a breakdown of the datasets used for development and validation of the model. A total of 58 observations were used to train and test this model. To learn this model, 10 different models were fit on a randomly selected set of 90% of the observations and tested on the remaining 10%. This 10 fold cross-validation was conducted during the training phase. To minimize the complexity, a grid search was performed while tuning the complexity measure (cp). The best model with the highest accuracy and with minimum complexity was selected from this process.

6.3.8 Model 2 data set

	Data collection protocol	Training set (Hypoglycemia/ Avoidance of hypoglycemia)	Validation set (Hypoglycemia/ Avoidance of hypoglycemia)
SAP	Study 1, Study 2 & Study 3	58(21/37)	22 (9/13)
PLGS	Study 3	18 (10/8)	22 (8/14)
SH	Study 3	18 (11/7)	22 (8/14)
DH	Study 1 & Study 3	60 (18/24)	24 (4/24)
Total		154 (60/94)	90 (29/61)

Table 6.4: The source of the observations used to develop and validate the RF model. SAP: Sensor Augmented Pump therapy, PLGS: Predictive Low Glucose Suspend therapy, SH: Single Hormone, DH: Dual Hormone.

6.3.9 Model 2:

An RF model was developed to be used by AP systems to prevent exercise-induced hypoglycemia. To train the appropriate model for this scenario, we used all the available 154 observations that were collected from studies 1-3. The RF model was also trained and tested using the 10-fold cross validation generating 10 different models. The model with the highest accuracy was determined to be the best model. selected from this process. The complexity of the RF model is controlled by four hyper-parameters. These hyper-parameters are number of trees (ntree), number of variables included in each tree (mtry), depth of the tree (interactions between the independent variables) and row sample (number of samples used to train each tree). These four hyper-parameters were optimized using a grid search. We investigated ntree = 25, 50, and 100; mtry from 2 up to the maximum number of variables in increments of 2; max depth = 2, 4, 6, 8, and 10; row sample of 30%, 50% and 90%. The chosen optimal RF model had the hyper parameters: ntree = 25, mtry = 8, max depth = 6 and row sample fraction of 0.90 (90% of the data points were used to train each tree).

The performance of the models were assessed using the prediction accuracy, area under the 'receiver operating curve' (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and balanced accuracy. PPV represents the probability of hypoglycemia when the model output predicts to be hypoglycemia while NPV is the probability of not having a hypoglycemic episode when euglycemia is predicted by the model. The

training and validation datasets were imbalanced in nature, that is the number of events of hypoglycemia are not equal to the number of events of euglycemia after exercise. Considering the prediction accuracy could be misleading about the generalization of the performance of the model. The balanced accuracy metric is defined as the average accuracy obtained on either class. If the model performs equally well on either class, balanced accuracy reduces to the conventional accuracy but in cases of poor model performance on an imbalanced set, the balanced accuracy could be lower. All these statistical analyses, including the preprocessing to compute the inputs and specific implementation of the statistical learning methods, were performed using R-software (www.r-project.org) [R Core Team, 2017]. Models were trained, tuned, cross-validated and validated using the *"party"*[Strobl et al., 2007], *"randomForest"* [Liaw et al., 2002] and *"caret"* [Kuhn & Johnson, 2013, Kuhn et al., 2014] packages within R. This trained model is available from the author.

6.4 Results

The RF model (Model 2) performs better than the decision tree (Model 1) across all accuracy metrics . The performance of the individual models on the training data set are in Table 6.5. Table Table 6.5 shows that on the training data set the RF model with higher complexity performs better on all the metrics accuracy, sensitivity, specificity, PPV also known as precision, NPV and balanced accuracy. The simple heuristic model is shown in Figure 6.1. In

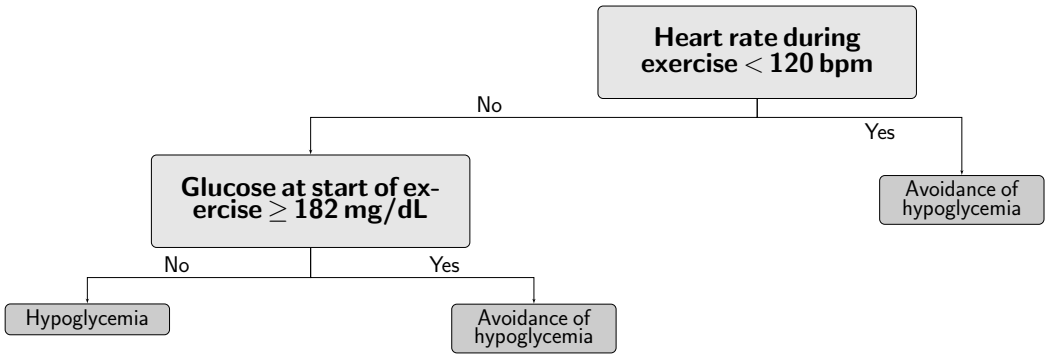

Figure 6.1: Simple decision tree with only 2 branches. This heuristic approach could be used by individuals with type 1 diabetes in conjunction with current exercise recommendations to prevent hypoglycemia. CBG: Capillary blood glucose value.

Figure 6.2 a sub selection of 4 critical features are depicted and also shows how the data separates between these classes.

Classifier	Number of features	Accuracy (%)	Sensitivity (%)	Specificity (%)	Positive Predictive value	Negative Predictive value	Balanced Accuracy (%)	Area Under the curve
Simple model	2	79.31	66.67	86.49	0.74	0.82	76.58	0.78
RF Model	8	97.40	95.00	98.94	0.98	0.97	96.97	0.99

Table 6.5: Performance of the different classifiers, results are shown for the 10 fold cross-validation on the development data set of 154 observations.

The performance of the models on the validation data set is in Table 6.6. Table 6.6 shows that the performance of the simple heuristic model, has an accuracy of 80% using only 2 features, while the more complex RF model achieved an accuracy of 87% on the validation data set. The simple model was validated on 44 observations of the OLC data from study 3 whereas the RF model was validated on 90 observations from study 3.

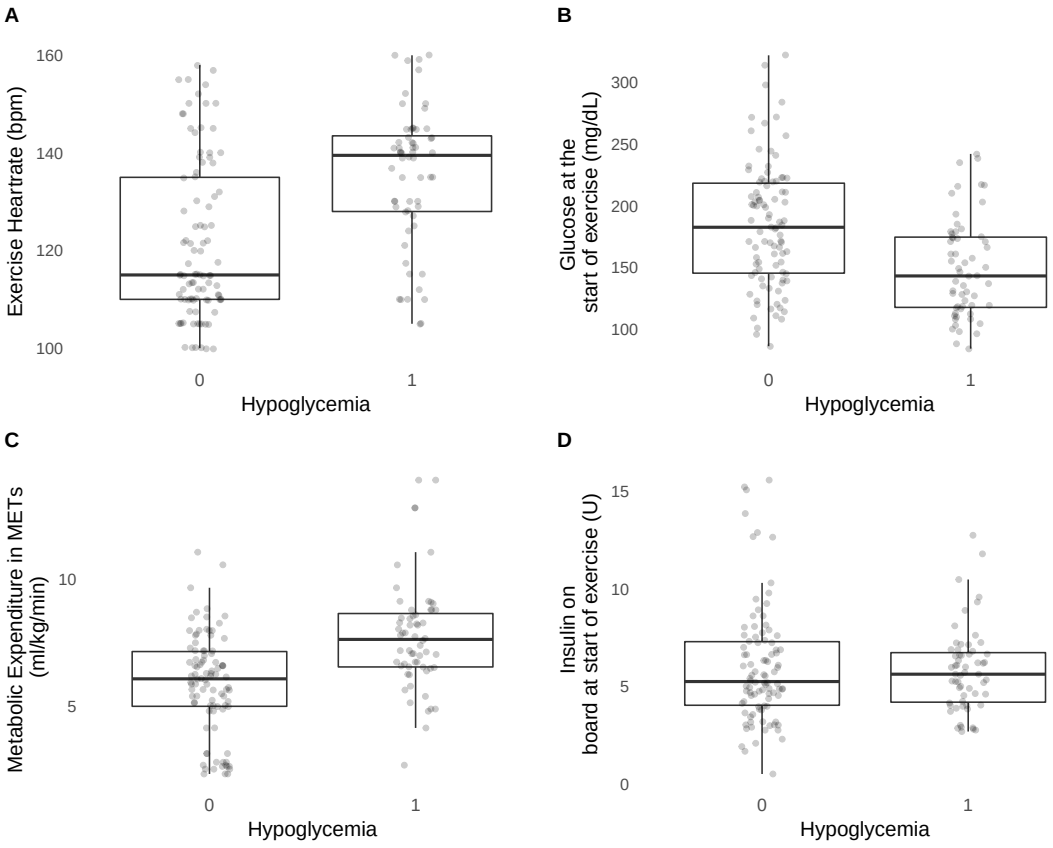

Figure 6.2: A: The relationship between exercise heart rate in beats per min and the observed hypoglycemia in the training set shows a clear separation between the two classes. B: The relationship between glucose at the start of exercise and the observed hypoglycemia in the training set shows lower glucose values at the start of exercise increases likelihood of hypoglycemia during the exercise bout. C: The relationship between energy expenditure in METs and the observed hypoglycemia in the training set shows higher intensity of exercise as measured by the increase in energy expenditure leads to more hypoglycemia. D: The relationship between insulin on board at the start of exercise and the observed hypoglycemia in the training set shows there is no clear distinction in this feature.

Classifier	Number of features	Accuracy (%)	Sensitivity (%)	Specificity (%)	Positive Predictive value	Negative Predictive value	Balanced Accuracy (%)	Area Under the curve
Simple Model	2	79.55	82.35	77.78	0.70	0.88	80.07	0.79
RF Model	8	86.67	82.76	88.52	0.77	0.92	85.64	0.94

Table 6.6: Performance of both classifiers, results here are for the validation data set.

Classifier	Number of features	Accuracy (%)	Sensitivity (%)	Specificity (%)	Positive Predictive value	Negative Predictive value	Balanced Accuracy (%)	Area Under the curve
SH	22	90.91	87.5	92.86	0.88	0.93	90.18	0.91
DH	24	79.17	25.00	90.00	0.33	0.86	57.50	0.93
PLGS	22	81.82	87.50	78.57	0.70	0.92	83.04	0.81
SAP	22	94.45	88.89	100	1.0	0.93	94.44	0.87

Table 6.7: Performance of the RF model across the different therapies in the validation set. SAP: Sensor Augmented Pump therapy, PLGS: Predictive Low Glucose Suspend therapy, SH: Single Hormone, DH: Dual Hormone.

6.5 Discussion

The hypoglycemia prediction algorithms performed well across a large and diverse data set from people with T1D undergoing a variety of glycemic management therapies during exercise. The exercise events used for training and evaluation took place at different times throughout the day (morning, afternoon and late afternoon), under different pre-exercise carbohydrate ingestion scenarios (breakfast, lunch and before dinner), and under early postprandial and late postprandial conditions. The performance of the models during training indicated that the time of day did not impact the accuracy of the models. We provide both a simple rule based decision tree model for individuals with T1D to use as a rule of thumb (the 180/120 rule) and also a more complex RF model that automated AP and decision support systems may use.

As recently been suggested in the exercise consensus statement [Riddell et al., 2017], only under cases of unexplained hypoglycemia and ketone levels are 1.5 mmol/L is exercise contraindicated. Figure 2 shows that exercise intensity, exercise heart rate and blood glucose at the start of exercise are the most important variables that can be used for the prediction of hypoglycemia. We also tried other features such as resting heart rate and heart rate reserve but the performance of the models did not improve with these additional features. early postprandial and late postprandial conditions. The performance of the models in training set, indicated that the time of day did not impact the accuracy of the models. We provide both a simple rule based decision tree model for individuals with T1D to use as a rule of thumb and also a more complex RF model that AP systems could use. Figure 6.2 shows that exercise intensity, exercise heart rate and blood glucose levels at the start of exercise are the most important variables that can be used for the prediction of hypoglycemia. We also tried other features such as resting heart rate and heart rate reserve but the performance of the models did not improve with these additional features.

People with T1D are advised to consume approximately 10 g of carbohydrate if their glucose at the start of exercise was less than 124 mg/dL [Riddell et al., 2017]. We compared the performance of this consensus statement guideline on our validation data set in the OLC data set (same data set used to validate the simple heuristic model), we found that this guideline had an accuracy of 72% at predicting hypoglycemia and only prevented 6 cases of hy-

poglycemia while 11 cases of hypoglycemia were missed. DeBoer et al. [DeBoer et al., 2017] recently showed that adding a HR signal can be used inform of physical activity, in their approach, when the HR exceeds 125% of the resting heart rate and they employ a hypoglycemia predictive algorithm to indicate the risk of hypoglycemia at the start of exercise. Their control to range AP controller [Breton et al., 2014b], this controller indicates the risk of hypoglycemia if in the next 30 minutes after the detection of exercise the forecasted glucose value is less 140 mg/dL, they predict hypoglycemia would occur. We compared the performance of this control to range prediction algorithm in our RF model validation data set, the accuracy of this model was 69% on our data set. Using this predictive threshold approach, out of 90 total observations evaluated, there were 7 false negatives and 20 false positives. Turksoy et al. [Turksoy et al., 2014b] described a method for predicting hypoglycemia using a multivariable ARMAX model that included exercise metrics as an input. Their real-time prediction algorithm was able to achieve a sensitivity of 81.5% and a specificity of 65.7% while predicting 30 minutes in advance on 14 people with T1D under free-living conditions. In comparison, our random forest algorithm achieved a sensitivity of 82% and a specificity of 78%. However, it's difficult to compare the two algorithms as the test scenarios were quite different.

Our work had some limitations. All exercise sessions were conducted in a controlled inpatient environment; therefore, future trials in real-life settings will be needed to confirm our results. All bouts of exercise were limited to aerobic exercise at varying intensities (30-60%

of VO2max) and the duration of exercise is between 30 and 45 minutes. Another limitation is that the algorithm requires HR data 5 minutes into the start of the activity and if hypoglycemia is predicted, the individual will have to stop exercise and treat the predicted hypoglycemia. A variant of this approach is being explored whereby we use past HR data as the input to the algorithm to anticipate future HR during exercise. Additional scenarios such as longer or higher intensity exercise will need to be tested to further evaluate our results. As shown in Table 6.7, the performance of the RF model is good across all forms of AP therapy; this could be further improved with a therapy specific model in the future.

In conclusion, the validated models shown here provide evidence that exercise-induced hypoglycemia can be accurately identified and possibly prevented in a majority of the cases. This work represents a promising step forward to encourage individuals with T1D to engage in PA with reduced fear of exercise-induced hypoglycemia.

6.6 Supplementary Data

6.6.1 RF model

The RF model with all its component trees is shown. All trees traversed at the same time till an end node is reached.

```
Tree [[1]]
  "Weight..kg. > 68.8  &  CBGExStart < 98  &  CBGExStart < 129.5  =>  0"

Tree [[2]]
 "Weight..kg. < 58.45  &  CBGExStart > 98  &  CBGExStart < 129.5  =>  0"

Tree [[3]]
"exerciseStartIOB < 5.385  &  HR..bpm. > 123  &  CBGExStart > 129.5  =>  0"

Tree [[4]]
 "HR..bpm. < 149.5  &  Weight..kg. < 68.8
&  CBGExStart < 98  &  CBGExStart < 129.5  =>  1"

Tree [[5]]
 "HR..bpm. > 149.5  &  Weight..kg. < 68.8  &
CBGExStart < 98  &  CBGExStart < 129.5  =>  0"

Tree [[6]]
 "Weight..kg. > 96.3  &  Weight..kg. > 58.45  &
CBGExStart > 98  &  CBGExStart < 129.5  =>  0"

Tree [[7]]
  "HR..bpm. < 113  &  Height.cm. < 185.9  &
HR..bpm. < 123  &  CBGExStart > 129.5  =>  0"

Tree [[8]]
 "exerciseStartIOB < 5.545  &  Height.cm. > 185.9  &
```

```
 HR..bpm. < 123  &  CBGExStart > 129.5  =>  0"

Tree [[9]]
 "exerciseStartIOB > 5.545  &  Height.cm. > 185.9  &
HR..bpm. < 123  &  CBGExStart > 129.5  =>  1"

Tree [[10]]
 "correctedMETs > 9.405  &  Weight..kg. < 96.3  &  Weight..kg. > 58.45  &
CBGExStart > 98  &  CBGExStart < 129.5  =>  0"

Tree [[11]]
 "Sex1 > 0.5  &  HR..bpm. > 113  &  Height.cm. < 185.9  &
 HR..bpm. < 123  &  CBGExStart > 129.5  =>  0"

 Tree [[12]]
 "correctedMETs < 6.4  &  exerciseStartIOB < 7.4276  &
exerciseStartIOB > 5.385  &  HR..bpm. > 123  &  CBGExStart > 129.5  =>  0"

Tree [[13]]
 "HR..bpm. > 143  &  exerciseStartIOB > 7.4276  &
exerciseStartIOB > 5.385  &  HR..bpm. > 123  &  CBGExStart > 129.5  =>  0"

Tree [[14]]
 "Height.cm. < 160.45  &  correctedMETs < 9.405  &
Weight..kg. < 96.3  &  Weight..kg. > 58.45  &
CBGExStart > 98  &  CBGExStart < 129.5  =>  0"

Tree [[15]]
 "CBGExStart < 164.5  &  Sex1 < 0.5  &  HR..bpm. > 113  &
Height.cm. < 185.9  &  HR..bpm. < 123  &  CBGExStart > 129.5  =>  0"

Tree [[16]]
 "CBGExStart > 164.5  &  Sex1 < 0.5  &  HR..bpm. > 113  &
 Height.cm. < 185.9  &  HR..bpm. < 123  &  CBGExStart > 129.5  =>  1"

Tree [[17]]
 "exerciseStartIOB < 6.946  &  correctedMETs > 6.4  &
 exerciseStartIOB < 7.4276  &  exerciseStartIOB > 5.385  &
```

```
 HR..bpm. > 123  &  CBGExStart > 129.5  =>  1"

Tree [[18]]
 "Sex1 < 0.5  &  HR..bpm. < 143  &  exerciseStartIOB > 7.4276  &
  exerciseStartIOB > 5.385  &  HR..bpm. > 123  &  CBGExStart > 129.5  =>  0"

Tree [[19]]
 "Sex1 > 0.5  &  HR..bpm. < 143  &  exerciseStartIOB > 7.4276  &
exerciseStartIOB > 5.385  &  HR..bpm. > 123  &  CBGExStart > 129.5  =>  1"

Tree [[20]]
  "exerciseStartIOB < 5.11  &  Height.cm. > 160.45  &
 correctedMETs < 9.405  &  Weight..kg. < 96.3  &  Weight..kg. > 58.45  &
 CBGExStart > 98  &  CBGExStart < 129.5  =>  1"

Tree [[21]]
 "HR..bpm. < 137.5  &  exerciseStartIOB > 6.946  &
correctedMETs > 6.4  &  exerciseStartIOB < 7.4276  &  exerciseStartIOB > 5.385  &
HR..bpm. > 123  &  CBGExStart > 129.5  =>  1"

Tree [[22]]
 "HR..bpm. > 137.5  &  exerciseStartIOB > 6.946  &
correctedMETs > 6.4  &  exerciseStartIOB < 7.4276  &  exerciseStartIOB > 5.385  &
HR..bpm. > 123  &  CBGExStart > 129.5  =>  0"

Tree [[23]]
  "Sex1 < 0.5  &  exerciseStartIOB > 5.11  &  Height.cm. > 160.45  &
 correctedMETs < 9.405  &  Weight..kg. < 96.3  &  Weight..kg. > 58.45  &
 CBGExStart > 98  &  CBGExStart < 129.5  =>  0"

Tree [[24]]
  "CBGExStart < 115  &  Sex1 > 0.5  &  exerciseStartIOB > 5.11  &
 Height.cm. > 160.45  &  correctedMETs < 9.405  &  Weight..kg. < 96.3  &
 Weight..kg. > 58.45  &  CBGExStart > 98  &  CBGExStart < 129.5  =>  1"

Tree [[25]]
 "CBGExStart > 115  &  Sex1 > 0.5  &  exerciseStartIOB > 5.11  &
Height.cm. > 160.45  &  correctedMETs < 9.405  &  Weight..kg. < 96.3  &
```

```
Weight..kg. > 58.45  &  CBGExStart > 98  &  CBGExStart < 129.5  =>  1"
```

Figure 6.3: Kernel density representation of post exercise hypoglycemia and euglycemia as function of both exercise heart rate and glucose values at the start of exercise. The data represented here is from a free living study - data set 2, individuals were very accustomed to aerobic exercise and prepared for the activity according to the best available recommendations, yet experienced hypoglycemia.

6.6.2 Contour plot

To gain some intuition about the relationship between the exercise heart rate and the glucose at the start of the exercise, the following contour plot was created. The plot in Figure 6.3 shows the relationship that higher exercise heart rates and low glucose levels could lead to hypoglycemia due to aerobic exercise. Higher heart rates during exercise and higher glucose

levels might have additional variables that could be responsible for hypoglycemia during exercise.

History cannot create laws with predictive power. An understanding of the past might help in the present insofar as it broadens our knowledge of human nature, provides us with inspiration or a waring, or suggests plausible, though always fallible arguments about the likely possibilities of certain things happening under certain conditions. None of this, however, comes anywhere near the immutable predictive certainty of a scientific law.

Richard Evans, In Defense of History

7

Nocturnal hypoglycemia prediction in adults with type 1 diabetes

Nocturnal Hypoglycemia is one of the most serious adverse effects of current exogenous insulin based diabetes therapy and the factor that limits achieving optimal glycemic control in people with type 1 diabetes (T1D). Overnight is the longest interval between meals, blood glucose checks and also the time of increased insulin sensitivity. Sleep attenuates many

of the counter-regulatory responses to hypoglycemia leading to many of these episodes being undetected and often leading to extended duration of hypoglycemia at night. Many of the available solutions are *reactive* to the event of hypoglycemia. In a decision support system the solution needs to be *proactive*. Based on the premise that nocturnal hypoglycemia could be predicted, we propose a machine learning approach to predict nocturnal hypoglycemia before the individual retires to bed for the night.

Chapter summary

- Nocturnal hypoglycemia is commonplace in self-managed individuals with T1D on intensive insulin therapies.
- The risk of overnight hypoglycemia is greater in individuals who exercise regularly. In this chapter using data collected in active individuals managing their own glucose levels under normal living conditions, we propose a machine learning approach to predict if they will experience nocturnal hypoglycemia.
- The balanced error associated with accurate prediction of nocturnal hypoglycemia or not was $\approx$ 15% using the best machine learning approach.
- The variables of highest importance as indicated by the machine learning approaches such as mean glucose in the past 24 hours and insulin on board at the time of bedtime closely reflect the findings of both clinical recommendations and finding from observational studies.

7.1 Introduction

Diabetes self-management in people with T1D is challenging. Maintaining optimal glycemic control requires precise adjustment of insulin dosing while frequently monitoring glucose values [Atkinson et al., 2014]. Insulin dosage modifications have to be made for varying levels of food intake, exercise, sleep, illness and other variables, while countering the slow pharmacokinetics and pharmacodynamics of insulin therapy [Atkinson et al., 2014]. One of the severe side-effects of inadequate adjustments to the insulin dosing is iatrogenic nocturnal hypoglycemia [Cryer, 2016](iatrogenic nocturnal hypoglycemia is the side effect of the treatment associated with dynamic nature of the insulin pharmacokinetics). Nocturnal hypoglycemia is defined as an episode of hypoglycemia (measured glucose <70mg/dL) that occurred while the person was asleep. The Majority of the recorded severe hypoglycemic (requiring external assistance) episodes occur during sleep [Cryer, 2014, 2016, Group et al., 1991]. Nocturnal hypoglycemia tends to be asymptomatic and under reported with <30% episodes being detected by individuals with T1D [Woodward et al., 2009]; due to the attenuation of the counter-regulatory responses during sleep. Nocturnal hypoglycemic episodes are widespread in this population, with only 3% of the participants in a large observational cohort study having hypoglycemia free nights [Group et al., 2010]. Nocturnal severe hypoglycemic episodes have been associated with seizures, coma, and morbidity [Dahlquist & Källén, 2005]. Nocturnal

hypoglycemic episodes adversely impact quality of life, leading to poor cognitive functionality, poor sleep quality, and fatigue the following day [Jauch-Chara et al., 2007, Brod et al., 2013b].

Recurring episodes of hypoglycemia lead to reduced recognition of the symptoms, and this leads to the reduced counter-regulatory response to protect against hypoglycemia, and this in-turn leads to impaired awareness, and culminates in hypoglycemia-associated autonomic failure (HAAF) [Cryer, 2016]. It is therefore paramount for people with T1D to avoid hypoglycemia. Continuous glucose monitoring (CGM) can be used to help people with T1D avoid hypoglycemia by sounding an audible alert if hypoglycemia is detected [Bode et al., 2004]. CGM can also be used in conjunction with sensor augmented pump (SAP) therapy by turning down or shutting off insulin if a hypoglycemic episode is detected. Both these approaches have successfully helped people with T1D reduce time spent in hypoglycemia [Choudhary et al., 2016, Beck et al., 2017, Bergenstal et al., 2013]. There are some challenges associated with both of these approaches. Hypoglycemia alerts using the CGM requires the user to respond to these alarms and to take appropriate action. The onus of the response falls on the user of the system [Wong et al., 2014]. Many CGM users complain of *alarm fatigue* and many do not wake up to respond to these alarms [Raccah et al., 2009, Buckingham et al., 2005, Wong et al., 2014]. On the other hand, some users respond to the predictive alerts from SAP therapy by taking in additional carbohydrates resulting in hyperglycemia. Consuming addi-

tional carbohydrates coupled with insulin shut-off can lead to hyperglycemia. In both these cases, users experience disturbed sleep resulting in poor sleep quality. Both these approaches require the user to *react* to the situation. In this chapter we propose an approach that is more *proactive* in nature. This approach involves predicting the nocturnal hypoglycemia episode at bedtime and suggesting either an ingestion of a complex carbohydrate snack or an appropriate reduction of the overnight insulin dosage. Another approach that uses a similar *proactive* approach is the closed loop control system, or artificial pancreas system using, either a single hormone predictive model to reduce hypoglycemia [Weisman et al., 2017] or with the use of a dual hormonal system [Jacobs et al., 2016].

Based on prior studies and prevailing knowledge, the following characteristics have been associated with nocturnal hypoglycemia [Cryer, 2016, Chow & Heller, 2014]. These include incorrect insulin dosing leading to insulin stacking or use of an incorrect type of insulin, inadequate carbohydrate intake or long duration between meals, excessive alcohol consumption before bed leading to diminished hepatic glucose production, exercise during the day leading to increased glucose utilization to replenish depleted glycogen stores, and diminished counter-regulatory responses due to antecedent hypoglycemic episodes or sleep.

We hypothesized that using machine learning approaches we could created a nocturnal hypoglycemia prediction algorithm that could be applied before the bedtime.

7.2 Methods

7.2.1 Data acquisition

Ten adults with T1D were recruited to participate in this randomized, three treatment, open, single-center crossover study. The inclusion criteria for this study were: adults with T1D (diagnosis of condition >1 year); age 21—45 years; body mass index <30 kg/m^2; physically active (≈150 min of moderate physical activity per week or ≈60 min of vigorous physical activity per week or active at least 3 days a week); currently on an insulin pump; and willing to perform 45 min of exercise. The exclusion criteria included : cardiovascular disease, renal or hepatic dysfunction, hypertension, congenital heart disease, use of adrenergic blocking agents, ongoing acetaminophen use, history of severe hypoglycemia during the past 12 months, or a condition that would preclude exercise. Participant's anthropometric and performance characteristics, as well as diabetes-specific data, are shown in Table 7.1. Subjects were recreationally active and physically fit (VO_2max = 46.8 $\pm$ 11.6 ml.kg^{-1}.min^{-1}) and had no electrocardiogram or blood pressure abnormalities.

The Institutional Review Board at the Oregon Health and Science University (OHSU) approved the study protocol and consent form. This current paper is a secondary analysis using the data collected during a study that examined the effect of exercise on sleep in

adults with type 1 diabetes [Reddy et al., 2017]. The study was registered on ClinicalTrials.gov (*NCT:02687893*). Informed consent was obtained from every individual.

Characteristic	Number = 10
Age (years)	34±6
Gender (M/F)	4/6
Duration of diabetes (years)	18±10
Body Mass Index (kg/m^2)	25±5
HbA_{1c} (%)	7.4±1.0
HbA_{1c} (mmol/mol)	57±11
VO_2max	46.8±11.5
Fat (%)	30±7

Table 7.1: Baseline characteristics of the participants. Continuous data represented as mean±standard deviation.

During this study, we collected participants' glucose levels every 5 min, physical activity using a wrist mounted actigraph, insulin dosage, food intake and sleep duration were continuously measured over the course of four consecutive weeks. Glucose levels were tracked using a continuous glucose monitor (CGM; Dexcom G4 or G4 Share, Dexcom, San Diego, CA, USA). Physical activity and sleep were monitored using an activity monitor (ActiGraph wGT3X-BT; ActiGraph, Pensacola, FL, USA), movement data were acquired at the rate of 80Hz. Participants managed their own insulin dosage using their personal insulin pump and a capillary blood glucose meter (CBG meter, Contour Next glucose meter; Ascensia Diabetes Care, NJ, USA). Food intake was measured using a custom built food-tracking Android smart-phone app. A smart-phone (Galaxy S4; Samsung, CA, USA) loaded with this app was distributed to the participants. The first week of the study was a run-in week where participants became accustomed to the wearable sensors. After the run-in, participants performed

in-clinic aerobic exercise twice weekly for one week, in-clinic resistance training twice weekly for one week, and no structured exercise for one control week. The order of the aerobic, resistance, and control weeks were randomized for each subject. Block randomization (size of six) with a 1:1:1 ratio was computer generated for the sequence of the interventions. A total of 249 nights of glucose data were collected for this analysis. In this data set 29.3% of the nights the subjects experienced nocturnal hypoglycemia.

7.2.2 Feature extraction

We designed a machine learning algorithm to classify in advance whether a person with T1D would become hypoglycemic at night while they slept. The hypothesis was that we could predict the nocturnal hypoglycemia at the time the participant retired to bed based on the features from this data set described in section 7.2.1. The features are broadly classified into 4 types

- Glucose features
- Insulin features
- Meal features
- Activity features

Glucose features were calculated for four different time windows namely, 2hr before bedtime, 6hr before bedtime, 12hr before bedtime and 24hr before bedtime. The features

Glucose features	Insulin features	Meal features	Acitivity features
Mean glucose[a]	Insulin on board	Type of meal eaten	Total number of steps[b]
Standard deviation[a]	Time since the last bolus	Carbohydrate amount	Time spent in MVPA[b]
Coefficient of variation[a]	Last Bolus amount	Time since the last meal	
Time in range[a]	Overnight basal rate		
Time in hypoglycemia[a]			
Time in hyperglycemia[a]			
Glucose value at bedtime			
Glucose value 15 min before bedtime			
Slope of glucose at bedtime			

Table 7.2: Features computed from each observation.
[a] These metrics were calculated for four different time windows, 2hr before bedtime, 6hr before bedtime, 12hr before bedtime and 24hr before bedtime.
[b] These metrics were calculated for three different time windows, 2hr before bedtime, 6hr before bedtime and 12hr before bedtime.

that were calculated were mean, standard deviation, coefficient of variation, % of time spent in range (glucose value >70 mg/dL and $\leq$180 mg/dL), % of time spent in hypoglycemia (glucose value $\leq$ 70 mg/dL) and % time in hyperglycemia (glucose value >180 mg/dL). Additional features were calculated just before bedtime, these were glucose value at bedtime, trend in glucose as indicated the average slope over the past 15 minutes before bedtime and glucose value 15 minutes before bedtime. In total there were 27 glucose features. These are shown in Table 7.2. In Figure 7.1 a subset of these features are shown. Conventional wisdom dictates that antecedent hypoglycemia results in future hypoglycemia and lower glucose mean values result in more episodes of hypoglycemia [Cryer, 2016]. The data shown in Figure 7.1 supports this expectation.

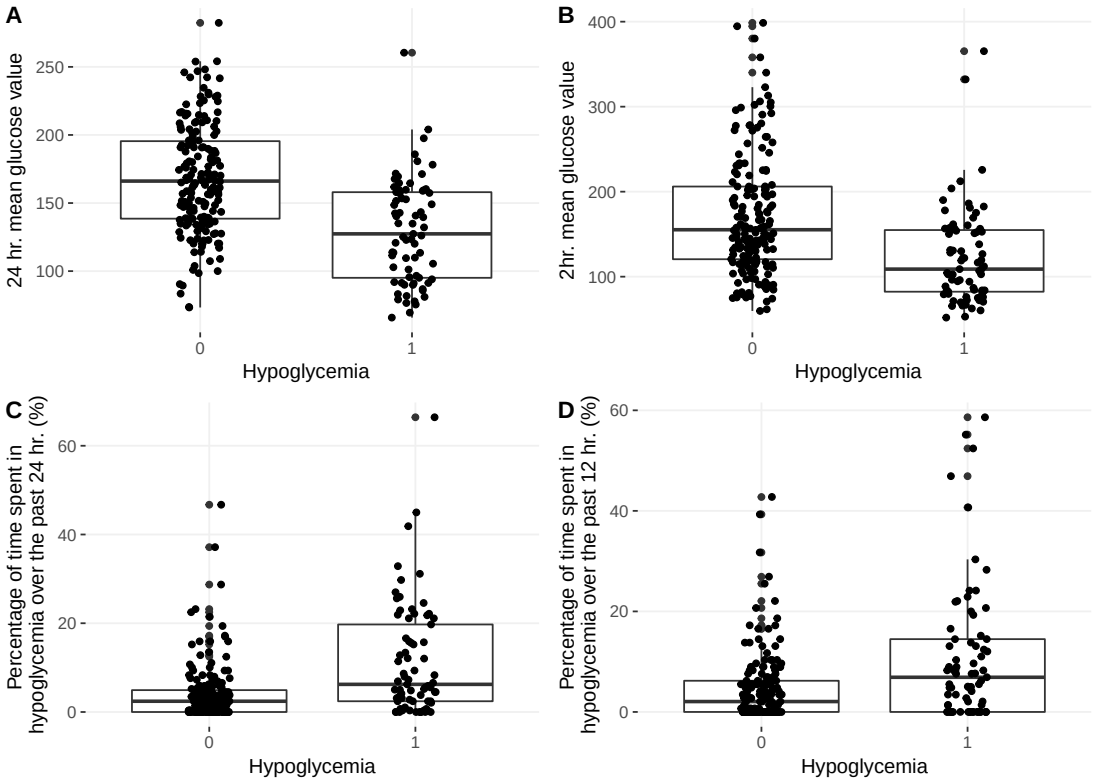

Figure 7.1: A subset of the glucose features are shown here. Nocturnal hypoglycemia episode was coded as *1* and if there was no nocturnal hypoglycemia the night was coded as *0*.

Insulin features were extracted from the data set are shown in Table 7.2. In Figure 7.2 a subset of these features are illustrated. Included is insulin on board (IOB) at bedtime, which serves to indicate insulin stacking, due to the slow rate of absorption and the variable rate of action, some individuals could experience nocturnal hypoglycemia. Both time since the last bolus and amount of the last bolus were included in the feature set, but were only considered if the last bolus was within the last 6hr before bedtime. The last insulin feature was the overnight insulin basal rate. There were a total of 4 insulin features in the data set.

Meal features collected using the smartphone app were included in the data set, shown in Table 7.2. These features were self-reported features by the subjects in the study. Subjects indicated the type of the meal at each meal entry, before bedtime these entries were either, dinner, snack or hypoglycemic treatment. The carbohydrate amount and the time when the last reported meal were consumed were included in the data set but only for meals consumed within the last 6hr before bedtime. In Figure 7.2 a subset of these features are shown.

Activity features measured using the actigraph were extracted for 3 different time periods: 2hr before bedtime, 6hr before bedtime and 12hr before bedtime. The metrics included the number of total steps as counted by the actigraph and % of time spent in moderate to vigorous physical activity (MVPA). MVPA is defined as the activity where the estimated MET

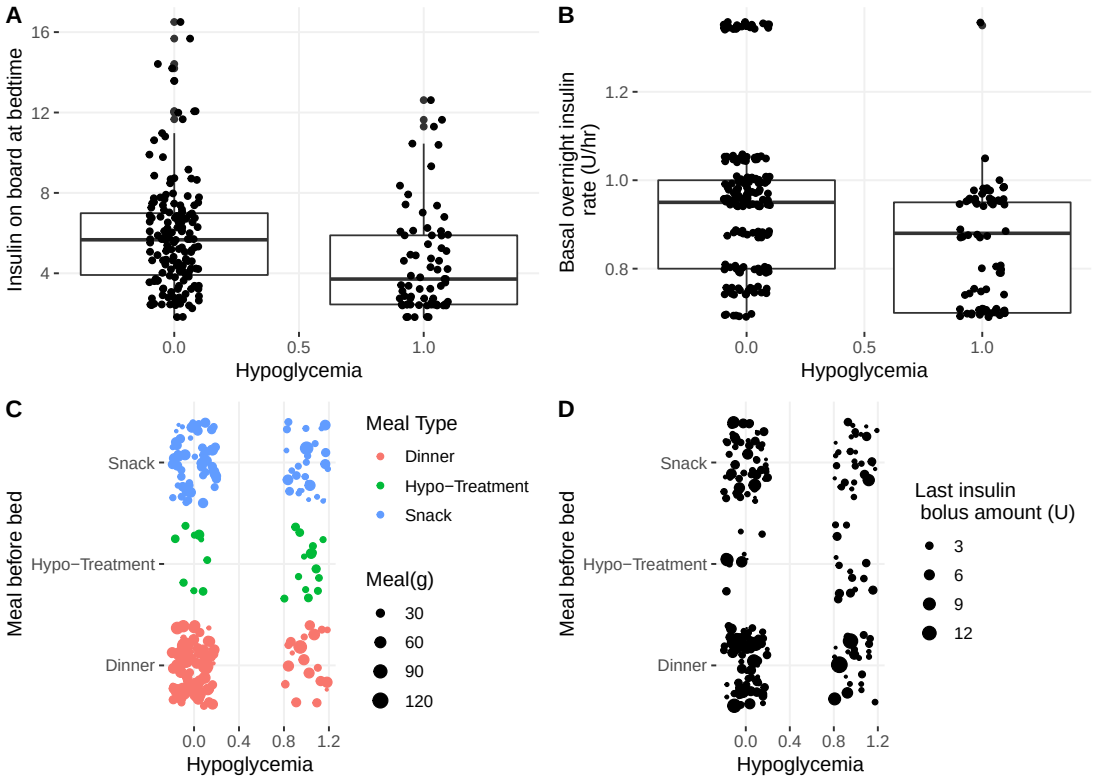

Figure 7.2: A subset of the insulin & meal features are shown here. The size of the meal is indicated by the size of the dot in panels C an D. These features were created to take into account the variability associated with the amount and type of meals eaten and the amount of insulin dosed before bedtime. Nocturnal hypoglycemia episode was coded as *1* and if there was no nocturnal hypoglycemia the night was coded as *0*.

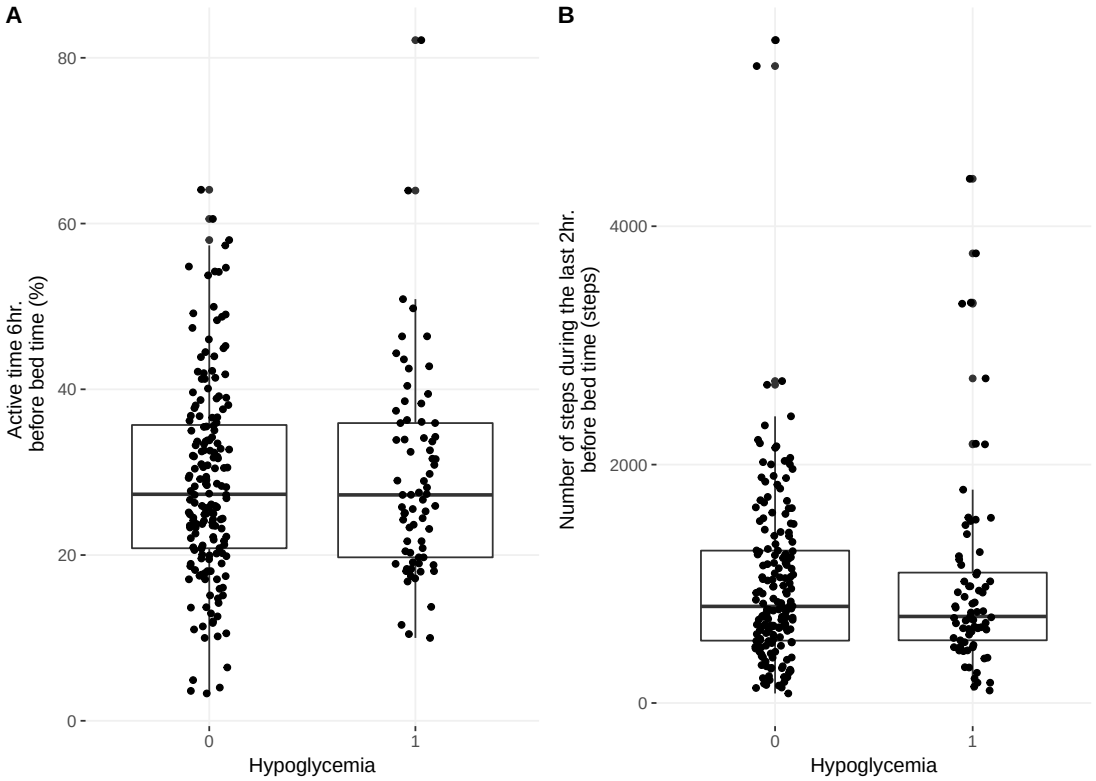

Figure 7.3: A subset of the activity features are shown here. As activity during the day is associated with increased insulin sensitivity and increased risk of nocturnal hypoglycemia, these features were created to understand their impact. These features were created to be used within a machine learning algorithm. Although, they do not appear to be discriminating between these features the combination of these features with other features could be used to distinguish between the outcome of interest. Nocturnal hypoglycemia episode was coded as *1* and if there was no nocturnal hypoglycemia the night was coded as *0*.

value is greater than 3 METs. Any activity involving substantial movement like walking, running etc. are considered as MVPA. MVPA is a surrogate for identifying active individuals. A subset of the activity features are shown in Figure 7.3.

7.2.3 Machine learning models

With the objective to determine if a nocturnal hypoglycemia event would occur during sleep, we designed 4 unique machine learning classifiers. Many machine learning approaches exist to solve a classification problem. Each algorithm uses a different approach to accomplish this objective. Here we selected approaches that had an advantage when the predictors to the algorithm were mixed in nature (continuous numerical variables and categorial variables) [Friedman et al., 2001, Nasrabadi, 2007]. We split the 249 observations into 3 datasets: 80% for model development (60% for training and 20% for testing) and 20% for model validation. Each model was trained using a 10-fold cross validation process. We used a nested cross validation approach, with the outer cross validation loop splitting the 60% of the training data into training and testing folds, and the inner loop was used to identify the model. The training results are based on the cross validated data. The average performance of this model is reported below.

We selected the following 4 machine learning algorithms.

- Logistic Regression: This is a common technique used for binary outcomes. It models the log odds ratio of the outcome class as a linear combination of the predictors. As many of the predictors are co-linear we employed a penalized regression approach to minimize this.
- Naïve Bayes: Naïve Bayes is a supervised learning approach for classification which is based on the Bayes' theorem [Friedman et al., 2001]. Naïve Bayes assumes that for a class of the outcome, all incoming variables are independent of each other (naïve

assumption). Naïve Bayes have been shown to outperform many more complicated algorithms in smaller data sets but performance diminishes in larger data sets.

- Random Forest (RF) : Random Forests use an ensemble classification approach. The underlying principle of a random forest is to build multiple decision trees and use a majority wins approach to arrive at the final classification. To build multiple trees, the predictors are randomly selected and partitioned, this approach is known as bagging. Random Forest approaches are fast to train, can find underlying non-linear connection and are very robust to overfitting [James et al., 2013, Breiman, 2001].

- Gradient Boosted Machine (GBM) : Gradient boosted machine is also based on decision trees, but uses different approach to build multiple decision trees known as boosting. Unlike bagging, where multiple independent models are built (in random forests), boosting adds on the existing model while minimizing the error. This approach can limit both error and bias [James et al., 2013].

Development of these algorithms and the validation was completed using the R framework [R Core Team, 2017] with the help of the following library packages caret [Kuhn et al., 2015] and h2o [Aiello et al., 2016]. Each model's hyper parameters were determined by using a grid search. To evaluate the models we used the area under the receiver operator curve (ROC) metric (AUC) and the % error predicted by the models. The ROC curve plots the true positives against false positives, by selecting different thresholds, the model could be designed to produce more false positives (less specific) or conversely more true positives (more sensitive). We chose an optimal threshold based on the F1—Optimal threshold, defined as

$$F1 = \frac{2 * true\ positive}{2 * true\ positive + false\ positive + false\ negative} \tag{7.1}$$

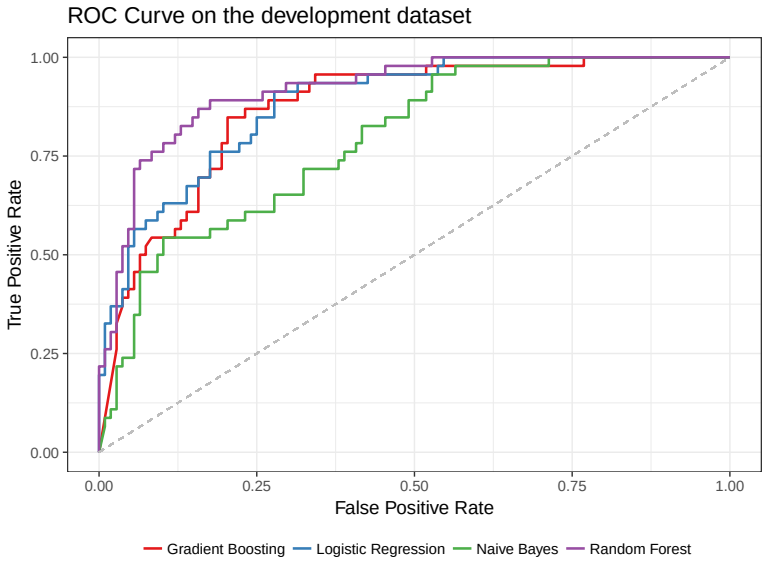

Figure 7.4: Receiver operating characteristic curves (ROC) curves showing the performance of the logistic regression model, naïve bayes model, the random forest model and the gradient boosted machine model in predicting nocturnal hypoglycemia on the development dataset. The curves indicate that other than the naïve bayes model, all the other models perform similarly on the development set.

This threshold gives equal importance to both precision and recall, its harmonic mean of both, using this threshold optimizes both sensitivity and specificity culminating in the highest area under the curve (AUC) [Lipton et al., 2013].

7.3 Results

7.3.1 Training results

Table 7.3 shows the receiver operating characteristic analysis of the different models on the training data set. Both GBM and RF outperform the other algorithms in the development

dataset. Figure 7.4 shows the ROC curves for all the algorithms.

Model	AUC (SD)	Accuracy (SD) (%)
Random Forest	0.75 (0.07)	0.77 (0.06)
Gradient Boosted Machine	0.74 (0.07)	0.76 (0.09)
Naïve Bayes	0.74 (0.09)	0.77(0.08)
Logistic Regression	0.65 (0.11)	0.68(0.14)

Table 7.3: The cross validation results on the training dataset are shown here for each of the classifiers. Area under the ROC curve and the accuracy of the models on the cross validated data set are shown for each model as the mean (standard deviation)

7.3.2 Validation results

Table 7.4 shows the receiver operating characteristic analysis of the different models on the validation data set. RF model, GBM and the naïve bayes had the best performance in the validation dataset based on the area under the ROC curve. Figure 7.6 shows the ROC curves for all the algorithms on the validation dataset. While all the models had similar AUC value, the GBM model is considered the best model based on the sensitivity, specificity and error metrics.

Model	AUC	Sensitivity	Specificity	Error (%)	Accuracy (%)
Random Forest	0.85	0.67	0.88	0.19	0.81
Gradient Boosted Machine	0.88	0.89	0.79	0.15	0.85
Naïve Bayes	0.85	0.67	0.91	0.18	0.81
Logistic Regression	0.81	1	0.55	0.30	0.7

Table 7.4: Comparison of model performances on the development dataset. Logistic regression is very sensitive at identifying the hypoglycemic episodes but is also increases the false positives, GBM and naïve bayes have identical error rates but the GBM model is more sensitive towards the identification of the nocturnal hypoglycemic episodes without many false positives.

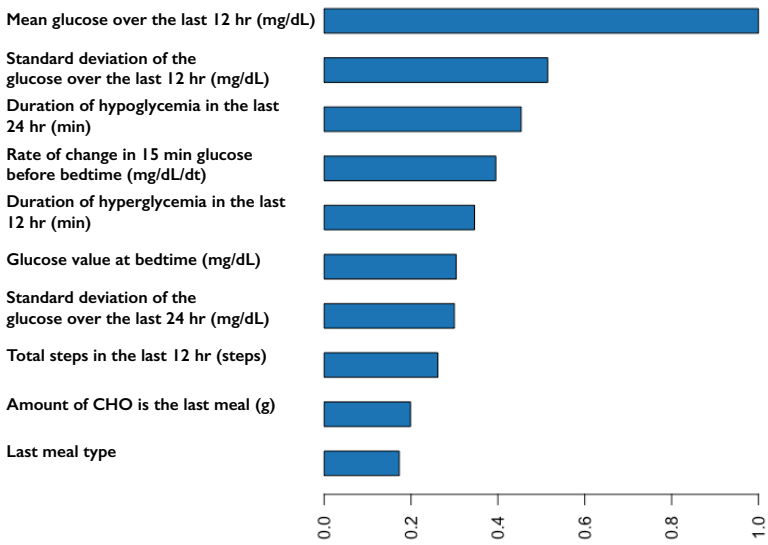

Figure 7.5: The top 10 risk factor variables for the algorithms are listed in descending order of effect size based on the selection frequency in both the random forest model and the gradient boosting machine models.

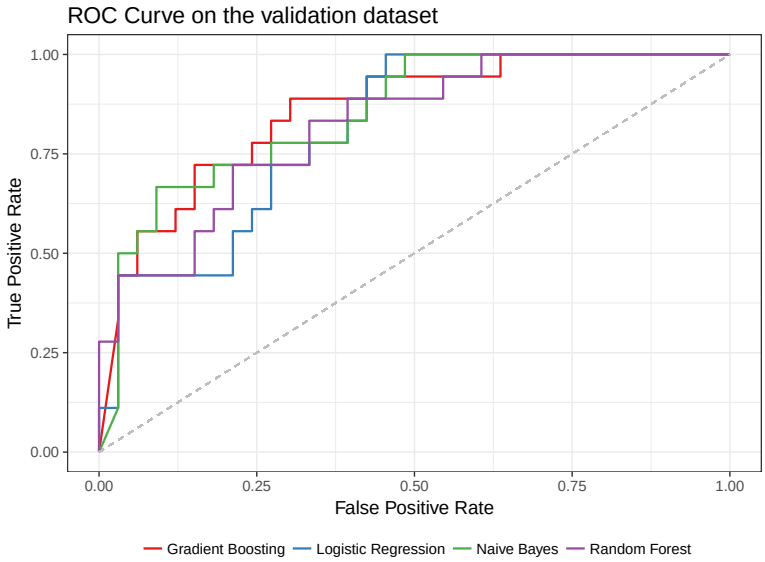

Figure 7.6: Receiver operating characteristic curves showing the performance of the logistic regression model, naïve bayes model, the random forest model and the gradient boosted machine model in predicting nocturnal hypoglycemia on the validation dataset.

7.4 Discussion

We have developed a *proactive* approach to predicting nocturnal hypoglycemia in adults with T1D. In the past, various approaches have been taken to predict hypoglycemia using statistical approaches [Cameron et al., 2008, Dassau et al., 2010, Daskalaki et al., 2012] and time series based approaches [Eren-Oruklu et al., 2010, 2012, Turksoy et al., 2014a]. Both of these approaches were designed to predict the hypoglycemic event in the near future such as <1 hr These approaches are *reactive* in nature and they require the the individual to act on the alarm. Due to the diminished sympathetic drive during sleep in individuals with T1D, the

compliance to treatment or the response to alarms is poor [Buckingham et al., 2005]. In a recent study Wilson et al. [Wilson et al., 2015] found that HbA_{1c}%, exercise, bedtime glucose level and antecedent hypoglycemia were the factors associated with nocturnal hypoglycemia. They were not able to determine any clear guidelines based on their findings. In the analysis presented here, we come to similar conclusions, the average glucose level indicating the level of glycemic control is the most important variable to predict nocturnal hypoglycemia. We also, show that glucose at bedtime along with IOB at bedtime and activity during the day that is closer to bedtime could provide an indication that nocturnal hypoglycemia could occur. A variable importance showing the top 10 important features is show in Figure 7.5

The results from our analysis show that there are some potentially modifiable characteristics the individual could perform to prevent hypoglycemia such as decrease overnight basal dosage or consume additional balanced snack with reduced insulin bolus. These approaches can alleviate the fear of hypoglycemia in people with T1D and reduce disruptions to sleep [Brod et al., 2013a]. Another benefit of these models is they could prevent excessive snacking at bedtime [Desjardins et al., 2012, Matejko et al., 2015]

The limitation of this analysis is the small number of participants in the study. This led to the problem of data leakage between the development dataset and the validation dataset. A large diverse dataset from future studies are needed to further validate these models.

7.5 Conclusion

We developed nocturnal hypoglycemia prediction models using the latest machine learning methods. These models performed reasonably well given our small dataset. We demonstrate that several modeling approaches good prediction of nocturnal hypoglycemia. However, a large diverse dataset and additional validation studies are needed before successfully deploying these models in clinical care. Results from these modeling approaches could be critical for people self managing T1D.

7.6 Supplementary

In this section, the models that have been designed and built will be clearly presented. Each model presented here is shown in java language. The models and the coefficients shown here illustrate the complexity of the models.

7.6.1 GBM model

```
import java.util.Map;
import hex.genmodel.GenModel;
import hex.genmodel.annotations.ModelPojo;

@ModelPojo(name="GBM_grid_0_AutoML_20180903_125524_model_6", algorithm="gbm")
public class GBM_grid_0_AutoML_20180903_125524_model_6 extends GenModel {
  public hex.ModelCategory getModelCategory() { return hex.ModelCategory.Binomial; }

  public boolean isSupervised() { return true; }
  public int nfeatures() { return 40; }
  public int nclasses() { return 2; }

  // Names of columns used by model.
  public static final String[] NAMES = NamesHolder_GBM_grid_0_AutoML_20180903_125524_model_6.VALUES;
  // Number of output classes included in training data response column.
  public static final int NCLASSES = 2;

  // Column domains. The last array contains domain of response column.
  public static final String[][] DOMAINS = new String[][] {
    /* glucosevalue_mean_12h */ null,
    /* glucosevalue_sd_12h */ null,
    /* glucosevalue_cv_12h */ null,
    /* glucosevalue_euglycemia_12h */ null,
    /* glucosevalue_hypoduration_12h */ null,
    /* glucosevalue_hyperduration_12h */ null,
    /* glucosevalue_mean_24h */ null,
    /* glucosevalue_sd_24h */ null,
    /* glucosevalue_cv_24h */ null,
    /* glucosevalue_euglycemia_24h */ null,
    /* glucosevalue_hypoduration_24h */ null,
    /* glucosevalue_hyperduration_24h */ null,
    /* glucosevalue_mean_2h */ null,
    /* glucosevalue_sd_2h */ null,
    /* glucosevalue_cv_2h */ null,
    /* glucosevalue_euglycemia_2h */ null,
    /* glucosevalue_hypoduration_2h */ null,
    /* glucosevalue_hyperduration_2h */ null,
    /* glucosevalue_mean_6h */ null,
    /* glucosevalue_sd_6h */ null,
    /* glucosevalue_cv_6h */ null,
    /* glucosevalue_euglycemia_6h */ null,
    /* glucosevalue_hypoduration_6h */ null,
    /* glucosevalue_hyperduration_6h */ null,
    /* activity_max_2h */ null,
    /* activity_max_6h */ null,
    /* activity_max_12h */ null,
    /* steps_max_2h */ null,
    /* steps_max_6h */ null,
    /* steps_max_12h */ null,
```

```
    /* meal_g */ null,
    /* meal_type */ GBM_grid_0_AutoML_20180903_125524_model_6_ColInfo_31.VALUES,
    /* durationtime */ null,
    /* lastbolus */ null,
    /* durationtime_bolus */ null,
    /* iobBed */ null,
    /* overnightiir */ null,
    /* glucose_at_bed */ null,
    /* glucose_15min */ null,
    /* slope_at_bed */ null,
    /* hypoglycemiayn */ GBM_grid_0_AutoML_20180903_125524_model_6_ColInfo_40.VALUES
  };
  // Prior class distribution
  public static final double[] PRIOR_CLASS_DISTRIB = {0.6987179487179487,0.30128205128205127};
  // Class distribution used for model building
  public static final double[] MODEL_CLASS_DISTRIB = {0.6987179487179487,0.30128205128205127};

  public GBM_grid_0_AutoML_20180903_125524_model_6() { super(NAMES,DOMAINS,"hypoglycemiayn"); }
  public String getUUID() { return Long.toString(-573084366268239344L); }

  // Pass in data in a double[], pre-aligned to the Model's requirements.
  // Jam predictions into the preds[] array; preds[0] is reserved for the
  // main prediction (class for classifiers or value for regression),
  // and remaining columns hold a probability distribution for classifiers.
  public final double[] score0( double[] data, double[] preds ) {
    java.util.Arrays.fill(preds,0);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_0.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_1.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_2.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_3.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_4.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_5.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_6.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_7.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_8.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_9.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_10.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_11.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_12.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_13.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_14.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_15.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_16.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_17.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_18.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_19.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_20.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_21.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_22.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_23.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_24.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_25.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_26.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_27.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_28.score0(data,preds);
    GBM_grid_0_AutoML_20180903_125524_model_6_Forest_29.score0(data,preds);
    preds[2] = preds[1] + -0.841200280519085;
    preds[2] = 1./(1. + Math.min(1e19, Math.exp(-(preds[2]))));
    preds[1] = 1.0-preds[2];
    preds[0] = hex.genmodel.GenModel.getPrediction(preds, PRIOR_CLASS_DISTRIB, data, 0.04004928118629542);
    return preds;
  }
}
// The class representing training column names
class NamesHolder_GBM_grid_0_AutoML_20180903_125524_model_6 implements java.io.Serializable {
  public static final String[] VALUES = new String[40];
  static {
    NamesHolder_GBM_grid_0_AutoML_20180903_125524_model_6_0.fill(VALUES);
  }
  static final class NamesHolder_GBM_grid_0_AutoML_20180903_125524_model_6_0 implements java.io.Serializable {
    static final void fill(String[] sa) {
      sa[0] = "glucosevalue_mean_12h";
      sa[1] = "glucosevalue_sd_12h";
      sa[2] = "glucosevalue_cv_12h";
      sa[3] = "glucosevalue_euglycemia_12h";
      sa[4] = "glucosevalue_hypoduration_12h";
      sa[5] = "glucosevalue_hyperduration_12h";
      sa[6] = "glucosevalue_mean_24h";
```

```
      sa[7] = "glucosevalue_sd_24h";
      sa[8] = "glucosevalue_cv_24h";
      sa[9] = "glucosevalue_euglycemia_24h";
      sa[10] = "glucosevalue_hypoduration_24h";
      sa[11] = "glucosevalue_hyperduration_24h";
      sa[12] = "glucosevalue_mean_2h";
      sa[13] = "glucosevalue_sd_2h";
      sa[14] = "glucosevalue_cv_2h";
      sa[15] = "glucosevalue_euglycemia_2h";
      sa[16] = "glucosevalue_hypoduration_2h";
      sa[17] = "glucosevalue_hyperduration_2h";
      sa[18] = "glucosevalue_mean_6h";
      sa[19] = "glucosevalue_sd_6h";
      sa[20] = "glucosevalue_cv_6h";
      sa[21] = "glucosevalue_euglycemia_6h";
      sa[22] = "glucosevalue_hypoduration_6h";
      sa[23] = "glucosevalue_hyperduration_6h";
      sa[24] = "activity_max_2h";
      sa[25] = "activity_max_6h";
      sa[26] = "activity_max_12h";
      sa[27] = "steps_max_2h";
      sa[28] = "steps_max_6h";
      sa[29] = "steps_max_12h";
      sa[30] = "meal_g";
      sa[31] = "meal_type";
      sa[32] = "durationtime";
      sa[33] = "lastbolus";
      sa[34] = "durationtime_bolus";
      sa[35] = "iobBed";
      sa[36] = "overnightiir";
      sa[37] = "glucose_at_bed";
      sa[38] = "glucose_15min";
      sa[39] = "slope_at_bed";
    }
  }
}
// The class representing column meal_type
class GBM_grid_0_AutoML_20180903_125524_model_6_ColInfo_31 implements java.io.Serializable {
  public static final String[] VALUES = new String[5];
  static {
    GBM_grid_0_AutoML_20180903_125524_model_6_ColInfo_31_0.fill(VALUES);
  }
  static final class GBM_grid_0_AutoML_20180903_125524_model_6_ColInfo_31_0 implements java.io.Serializable {
    static final void fill(String[] sa) {
      sa[0] = "Breakfast";
      sa[1] = "Dinner";
      sa[2] = "Hypo-Treatment";
      sa[3] = "Lunch";
      sa[4] = "Snack";
    }
  }
}
// The class representing column hypoglycemiayn
class GBM_grid_0_AutoML_20180903_125524_model_6_ColInfo_40 implements java.io.Serializable {
  public static final String[] VALUES = new String[2];
  static {
    GBM_grid_0_AutoML_20180903_125524_model_6_ColInfo_40_0.fill(VALUES);
  }
  static final class GBM_grid_0_AutoML_20180903_125524_model_6_ColInfo_40_0 implements java.io.Serializable {
    static final void fill(String[] sa) {
      sa[0] = "0";
      sa[1] = "1";
    }
  }
}

class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_0 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_0_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_0_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[0 /* glucosevalue_mean_12h */] <113.74505f ?
         (data[29 /* steps_max_12h */] <6516.5f ?
             (Double.isNaN(data[39]) || data[39 /* slope_at_bed */] <-0.103125f ?
                1.0657818f :
                -0.7155963f) :
```

```
           1.6595745f) :
         (Double.isNaN(data[5]) || data[5 /* glucosevalue_hyperduration_12h */] <42.773438f ?
             (Double.isNaN(data[10]) || data[10 /* glucosevalue_hypoduration_24h */] <4.9402575f ?
                 (data[13 /* glucosevalue_sd_2h */] <8.285334f ?
                    1.1845403f :
                     (data[30 /* meal_g */] <14.5f ?
                        0.47198907f :
                         (Double.isNaN(data[35]) || data[35 /* iobBed */] <6.8186946f ?
                            -0.7155963f :
                             (Double.isNaN(data[3]) || data[3 /* glucosevalue_euglycemia_12h */] <72.75862f ?
                                -0.7155963f :
                                0.23447199f)))) :
                 (Double.isNaN(data[7]) || data[7 /* glucosevalue_sd_24h */] <50.531685f ?
                     (data[39 /* slope_at_bed */] <0.0052083335f ?
                        1.1845403f :
                        -0.45168847f) :
                    1.6595745f)) :
             (data[19 /* glucosevalue_sd_6h */] <34.161568f ?
                 (Double.isNaN(data[1]) || data[1 /* glucosevalue_sd_12h */] <47.170982f ?
                    -0.7155963f :
                    0.23447199f) :
                -0.7155963f)));
    return pred;
  } // constant pool size = 54B, number of visited nodes = 13, static init size = 0B
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_1 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_1_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_1_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[37 /* glucose_at_bed */] <102.0f ?
         (Double.isNaN(data[0]) || data[0 /* glucosevalue_mean_12h */] <166.3868f ?
             (Double.isNaN(data[18]) || data[18 /* glucosevalue_mean_6h */] <120.54174f ?
                 (data[32 /* durationtime */] <-38.983074f ?
                     (Double.isNaN(data[39]) || data[39 /* slope_at_bed */] <0.016666668f ?
                         (Double.isNaN(data[29]) || data[29 /* steps_max_12h */] <7626.5f ?
                            0.8157593f :
                            0.56614226f) :
                        0.1400794f) :
                    -0.31659308f) :
                0.9158068f) :
            -0.6456969f) :
         (data[33 /* lastbolus */] <1.1762695f ?
             (data[13 /* glucosevalue_sd_2h */] <16.790081f ?
                 (Double.isNaN(data[34]) || data[34 /* durationtime_bolus */] <-42.466408f ?
                    1.0762519f :
                    0.2117871f) :
                 (!Double.isNaN(data[31 /* meal_type */]) && (GenModel.bitSetIsInRange(32, 0, data[31]) && !GenModel.bitSetContains(GRPSPLIT0, 32, 0, data[31])) ?
                    -0.68074274f :
                    -0.60540515f)) :
             (Double.isNaN(data[31 /* meal_type */]) || !GenModel.bitSetIsInRange(32, 0, data[31])
             || (GenModel.bitSetIsInRange(32, 0, data[31]) && !GenModel.bitSetContains(GRPSPLIT1, 32, 0, data[31])) ?
                 (Double.isNaN(data[38]) || data[38 /* glucose_15min */] <228.5f ?
                     (data[0 /* glucosevalue_mean_12h */] <150.53966f ?
                         (data[30 /* meal_g */] <30.5f ?
                            -0.9089511f :
                             (data[20 /* glucosevalue_cv_6h */] <25.930895f ?
                                -0.78588736f :
                                -0.6099812f)) :
                         (Double.isNaN(data[16]) || data[16 /* glucosevalue_hypoduration_2h */] <2.375f ?
                             (data[34 /* durationtime_bolus */] <-179.97f ?
                                -0.6974717f :
                                 (data[19 /* glucosevalue_sd_6h */] <31.02986f ?
                                    -0.6126338f :
                                    -0.60540515f)) :
                            -0.24779576f)) :
                     (data[36 /* overnightiir */] <0.98945314f ?
                        0.38137528f :
                         (data[9 /* glucosevalue_euglycemia_24h */] <41.01968f ?
                            -0.6529074f :
                            -0.60540515f))) :
                0.8148489f)));
    return pred;
  } // constant pool size = 92B, number of visited nodes = 20, static init size = 60B
```

```
  // {00101000 00000000 00000000 00000000}
  public static final byte[] GRPSPLIT0 = new byte[] {20, 0, 0, 0};
  // {00100000 00000000 00000000 00000000}
  public static final byte[] GRPSPLIT1 = new byte[] {4, 0, 0, 0};
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_2 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_2_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_2_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[6 /* glucosevalue_mean_24h */] <113.64919f ?
         (Double.isNaN(data[26]) || data[26 /* activity_max_12h */] <23.135271f ?
             (data[7 /* glucosevalue_sd_24h */] <14.9841175f ?
                -0.33325255f :
                0.5354709f) :
             (Double.isNaN(data[39]) || data[39 /* slope_at_bed */] <-0.06523438f ?
                0.62976676f :
                0.8458738f)) :
         (data[37 /* glucose_at_bed */] <108.0f ?
             (data[14 /* glucosevalue_cv_2h */] <17.34687f ?
                 (data[14 /* glucosevalue_cv_2h */] <9.047145f ?
                    0.14126037f :
                    -0.6252244f) :
                 (data[24 /* activity_max_2h */] <18.44293f ?
                    -0.23338082f :
                     (data[8 /* glucosevalue_cv_24h */] <39.43888f ?
                        0.74289095f :
                        0.6142552f))) :
             (data[8 /* glucosevalue_cv_24h */] <21.71203f ?
                0.27949747f :
                 (Double.isNaN(data[16]) || data[16 /* glucosevalue_hypoduration_2h */] <17.8125f ?
                     (data[23 /* glucosevalue_hyperduration_6h */] <1.5625f ?
                        0.036838926f :
                         (data[1 /* glucosevalue_sd_12h */] <31.899368f ?
                            -0.7043954f :
                             (data[20 /* glucosevalue_cv_6h */] <21.238947f ?
                                 (data[18 /* glucosevalue_mean_6h */] <200.00275f ?
                                    0.30034876f :
                                     (Double.isNaN(data[26]) || data[26 /* activity_max_12h */] <33.828667f ?
                                        -0.55622643f :
                                        -0.621461f)) :
                                 (Double.isNaN(data[1]) || data[1 /* glucosevalue_sd_12h */] <103.69445f ?
                                     (data[30 /* meal_g */] <20.5f ?
                                         (Double.isNaN(data[33]) || data[33 /* lastbolus */] <2.68f ?
                                             (Double.isNaN(data[20]) || data[20 /* glucosevalue_cv_6h */] <28.831259f ?
                                                -0.5551157f :
                                                -0.62474704f) :
                                            -0.6987715f) :
                                         (data[12 /* glucosevalue_mean_2h */] <140.552f ?
                                            -0.58523655f :
                                             (Double.isNaN(data[14]) || data[14 /* glucosevalue_cv_2h */] <23.805737f ?
                                                 (Double.isNaN(data[8]) || data[8 /* glucosevalue_cv_24h */] <38.361675f ?
                                                     (data[13 /* glucosevalue_sd_2h */] <17.108839f ?
                                                        -0.5574834f :
                                                        -0.55753577f) :
                                                    -0.5554328f) :
                                                -0.5659506f))) :
                                     -0.1550865f)))) :
                     0.1783242f))));
    return pred;
  } // constant pool size = 98B, number of visited nodes = 24, static init size = 0B
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_3 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_3_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_3_class_0 {
  static final double score0(double[] data) {
    double pred =      (Double.isNaN(data[6]) || data[6 /* glucosevalue_mean_24h */] <164.89093f ?
         (data[27 /* steps_max_2h */] <636.5f ?
             (Double.isNaN(data[38]) || data[38 /* glucose_15min */] <191.5f ?
```

```
                (data[24 /* activity_max_2h */] <11.54625f ?
                    (data[39 /* slope_at_bed */] <-0.575f ?
                       0.083931476f :
                       -0.5577079f) :
                    (data[21 /* glucosevalue_euglycemia_6h */] <58.219177f ?
                       -0.31454435f :
                        (Double.isNaN(data[5]) || data[5 /* glucosevalue_hyperduration_12h */] <2.1982758f ?
                           0.502395f :
                           0.7135911f))) :
                0.75036967f) :
            (data[19 /* glucosevalue_sd_6h */] <24.879976f ?
                (data[10 /* glucosevalue_hypoduration_24h */] <2.0544982f ?
                   -0.40199775f :
                    (data[32 /* durationtime */] <-133.96875f ?
                       0.67938834f :
                        (data[14 /* glucosevalue_cv_2h */] <11.475167f ?
                           0.2957871f :
                           0.5844513f))) :
                (Double.isNaN(data[20]) || data[20 /* glucosevalue_cv_6h */] <31.588776f ?
                    (data[19 /* glucosevalue_sd_6h */] <30.327747f ?
                        (data[27 /* steps_max_2h */] <971.5f ?
                           -0.61140585f :
                           -0.59488136f) :
                        (data[33 /* lastbolus */] <1.4609375f ?
                           -0.53964883f :
                           -0.5634821f)) :
                    (data[37 /* glucose_at_bed */] <103.5f ?
                       0.60004956f :
                       -0.33767956f)))) :
        (data[19 /* glucosevalue_sd_6h */] <28.379675f ?
           -0.60782653f :
            (data[19 /* glucosevalue_sd_6h */] <36.15081f ?
               0.4765615f :
                (data[28 /* steps_max_6h */] <2840.5f ?
                    (Double.isNaN(data[12]) || data[12 /* glucosevalue_mean_2h */] <198.53f ?
                       -0.5368019f :
                       -0.25056273f) :
                    (Double.isNaN(data[33]) || data[33 /* lastbolus */] <2.9601562f ?
                        (data[11 /* glucosevalue_hyperduration_24h */] <42.906574f ?
                           -0.5661104f :
                            (Double.isNaN(data[11]) || data[11 /* glucosevalue_hyperduration_24h */] <63.728374f ?
                                (data[23 /* glucosevalue_hyperduration_6h */] <28.219177f ?
                                   -0.53611445f :
                                   -0.531684f) :
                               -0.5431898f)) :
                        (data[17 /* glucosevalue_hyperduration_2h */] <70.5f ?
                           -0.58706844f :
                           -0.5478326f))))));
    return pred;
  } // constant pool size = 102B, number of visited nodes = 25, static init size = 0B
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_4 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_4_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_4_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[37 /* glucose_at_bed */] <102.0f ?
         (Double.isNaN(data[0]) || data[0 /* glucosevalue_mean_12h */] <166.3868f ?
             (data[28 /* steps_max_6h */] <2004.0f ?
                0.5923866f :
                 (Double.isNaN(data[32]) || data[32 /* durationtime */] <-151.00885f ?
                    -0.28919107f :
                     (data[32 /* durationtime */] <-63.949345f ?
                         (Double.isNaN(data[28]) || data[28 /* steps_max_6h */] <3329.5f ?
                            0.56960225f :
                            0.5585489f) :
                         (data[33 /* lastbolus */] <1.6046875f ?
                            -0.18572918f :
                            0.47388846f)))) :
           -0.5357479f) :
         (data[30 /* meal_g */] <38.5f ?
             (data[20 /* glucosevalue_cv_6h */] <12.123333f ?
                -0.58184946f :
                 (data[13 /* glucosevalue_sd_2h */] <18.453413f ?
```

```
                    (Double.isNaN(data[25]) || data[25 /* activity_max_6h */] <31.951979f ?
                        (data[10 /* glucosevalue_hypoduration_24h */] <5.0605536f ?
                           0.6389321f :
                            (data[13 /* glucosevalue_sd_2h */] <14.514651f ?
                               -0.17540412f :
                               0.5969708f)) :
                        (data[5 /* glucosevalue_hyperduration_12h */] <19.008621f ?
                           0.40421215f :
                           -0.5445896f)) :
                    (Double.isNaN(data[37]) || data[37 /* glucose_at_bed */] <219.5f ?
                        (data[26 /* activity_max_12h */] <21.776667f ?
                           -0.5746998f :
                            (Double.isNaN(data[33]) || data[33 /* lastbolus */] <2.73f ?
                                (data[12 /* glucosevalue_mean_2h */] <130.249f ?
                                   -0.5301737f :
                                    (data[39 /* slope_at_bed */] <0.2f ?
                                       -0.5183239f :
                                       -0.5224585f)) :
                                -0.54130894f)) :
                        (data[37 /* glucose_at_bed */] <265.0f ?
                           0.59103966f :
                           -0.5608653f)))) :
            (data[19 /* glucosevalue_sd_6h */] <35.99534f ?
                (data[13 /* glucosevalue_sd_2h */] <15.626877f ?
                   -0.5347398f :
                   -0.5628806f) :
                (Double.isNaN(data[8]) || data[8 /* glucosevalue_cv_24h */] <39.931435f ?
                    (data[34 /* durationtime_bolus */] <-100.29896f ?
                       -0.52346605f :
                        (Double.isNaN(data[33]) || data[33 /* lastbolus */] <1.796875f ?
                           -0.52198184f :
                           -0.51904154f)) :
                   -0.53590864f))));
    return pred;
  } // constant pool size = 102B, number of visited nodes = 25, static init size = 0B
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_5 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_5_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_5_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[6 /* glucosevalue_mean_24h */] <113.64919f ?
          (Double.isNaN(data[34]) || data[34 /* durationtime_bolus */] <-30.277637f ?
              (Double.isNaN(data[24]) || data[24 /* activity_max_2h */] <18.586592f ?
                  (data[33 /* lastbolus */] <1.199961f ?
                     0.54220986f :
                     0.56689763f) :
                 0.29462606f) :
             -0.06221227f) :
          (data[2 /* glucosevalue_cv_12h */] <25.17628f ?
              (data[24 /* activity_max_2h */] <21.074629f ?
                  (data[5 /* glucosevalue_hyperduration_12h */] <32.421875f ?
                     0.39202836f :
                     -0.52965945f) :
                  (data[26 /* activity_max_12h */] <21.677896f ?
                     -0.5541437f :
                      (Double.isNaN(data[12]) || data[12 /* glucosevalue_mean_2h */] <150.84032f ?
                         -0.53240126f :
                         -0.5213022f))) :
              (data[2 /* glucosevalue_cv_12h */] <25.920105f ?
                 0.47346082f :
                  (data[37 /* glucose_at_bed */] <105.5f ?
                      (data[11 /* glucosevalue_hyperduration_24h */] <10.304931f ?
                         -0.35792717f :
                          (data[29 /* steps_max_12h */] <10094.0f ?
                             0.55139965f :
                              (data[32 /* durationtime */] <-110.855f ?
                                 -0.09552748f :
                                 0.35670495f))) :
                      (Double.isNaN(data[16]) || data[16 /* glucosevalue_hypoduration_2h */] <17.8125f ?
                          (data[34 /* durationtime_bolus */] <295.5224f ?
                              (data[26 /* activity_max_12h */] <20.765f ?
                                  (data[15 /* glucosevalue_euglycemia_2h */] <12.5f ?
                                     -0.16156901f :
```

```
                                    0.39632577f) :
                                (Double.isNaN(data[31 /* meal_type */]) || !GenModel.bitSetIsInRange(32, 0, data[31])
                                || (GenModel.bitSetIsInRange(32, 0, data[31]) && !GenModel.bitSetContains(GRPSPLIT0, 32, 0, data[31])) ?
                                    (Double.isNaN(data[3]) || data[3 /* glucosevalue_euglycemia_12h */] <66.40536f ?
                                        (data[20 /* glucosevalue_cv_6h */] <21.238947f ?
                                           -0.52949804f :
                                            (Double.isNaN(data[14]) || data[14 /* glucosevalue_cv_2h */] <20.197895f ?
                                                (Double.isNaN(data[4]) || data[4 /* glucosevalue_hypoduration_12h */] <5.586207f ?
                                                    (Double.isNaN(data[13]) || data[13 /* glucosevalue_sd_2h */] <26.180922f ?
                                                       -0.51095706f :
                                                       -0.5119032f) :
                                                   -0.51472175f) :
                                               -0.517296f)) :
                                        (data[21 /* glucosevalue_euglycemia_6h */] <75.0f ?
                                           -0.53089523f :
                                           -0.52027416f)) :
                                    0.11359749f)) :
                            -0.5587279f) :
                        0.22317293f)))));
    return pred;
  } // constant pool size = 107B, number of visited nodes = 25, static init size = 30B
  // {00110000 00000000 00000000 00000000}
  public static final byte[] GRPSPLIT0 = new byte[] {12, 0, 0, 0};
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_6 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_6_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_6_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[0 /* glucosevalue_mean_12h */] <113.74505f ?
         (data[29 /* steps_max_12h */] <6516.5f ?
             (Double.isNaN(data[39]) || data[39 /* slope_at_bed */] <-0.103125f ?
                0.21177642f :
                -0.5307201f) :
             (Double.isNaN(data[29]) || data[29 /* steps_max_12h */] <8580.0f ?
                0.52210087f :
                0.5346764f)) :
         (Double.isNaN(data[3]) || data[3 /* glucosevalue_euglycemia_12h */] <86.52344f ?
             (data[3 /* glucosevalue_euglycemia_12h */] <37.00905f ?
                 (data[6 /* glucosevalue_mean_24h */] <188.37563f ?
                    -0.5290477f :
                     (Double.isNaN(data[0]) || data[0 /* glucosevalue_mean_12h */] <233.33104f ?
                         (data[19 /* glucosevalue_sd_6h */] <42.432934f ?
                            -0.5131825f :
                             (Double.isNaN(data[4]) || data[4 /* glucosevalue_hypoduration_12h */] <5.586207f ?
                                -0.50694424f :
                                -0.50908685f)) :
                            -0.5198914f)) :
                 (Double.isNaN(data[38]) || data[38 /* glucose_15min */] <227.0f ?
                     (data[6 /* glucosevalue_mean_24h */] <126.14403f ?
                        0.40302724f :
                         (Double.isNaN(data[33]) || data[33 /* lastbolus */] <1.03125f ?
                             (data[14 /* glucosevalue_cv_2h */] <12.737163f ?
                                0.4511684f :
                                 (data[33 /* lastbolus */] <0.6f ?
                                    -0.52535444f :
                                    -0.1372657f)) :
                             (Double.isNaN(data[14]) || data[14 /* glucosevalue_cv_2h */] <17.573294f ?
                                 (data[0 /* glucosevalue_mean_12h */] <145.14621f ?
                                    -0.5287336f :
                                     (data[1 /* glucosevalue_sd_12h */] <44.390923f ?
                                        -0.517955f :
                                         (data[18 /* glucosevalue_mean_6h */] <164.75342f ?
                                            -0.50881356f :
                                            -0.51434183f))) :
                                (Double.isNaN(data[32]) || data[32 /* durationtime */] <-137.565f ?
                                    -0.5217726f :
                                    0.35680598f)))) :
                     (data[19 /* glucosevalue_sd_6h */] <50.841522f ?
                        0.5221545f :
                        0.08766776f))) :
             (data[14 /* glucosevalue_cv_2h */] <14.545072f ?
                -0.51973224f :
                -0.5314539f)));
```

```
    return pred;
  } // constant pool size = 90B, number of visited nodes = 22, static init size = 0B
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_7 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_7_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_7_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[37 /* glucose_at_bed */] <102.0f ?
         (data[38 /* glucose_15min */] <77.5f ?
             (data[16 /* glucosevalue_hypoduration_2h */] <17.96875f ?
                -0.51914024f :
                0.27616876f) :
             (data[35 /* iobBed */] <7.8719025f ?
                 (Double.isNaN(data[32]) || data[32 /* durationtime */] <-214.32669f ?
                    -0.2806206f :
                    (data[22 /* glucosevalue_hypoduration_6h */] <3.4246576f ?
                       0.5258473f :
                       0.27251917f)) :
                0.52777755f)) :
         (data[20 /* glucosevalue_cv_6h */] <12.112848f ?
            -0.54491615f :
             (data[13 /* glucosevalue_sd_2h */] <18.464144f ?
                 (data[33 /* lastbolus */] <1.1876953f ?
                    (data[10 /* glucosevalue_hypoduration_24h */] <0.42171282f ?
                       0.5340834f :
                       0.2715803f) :
                    (Double.isNaN(data[13]) || data[13 /* glucosevalue_sd_2h */] <17.24606f ?
                        (data[18 /* glucosevalue_mean_6h */] <110.36087f ?
                           0.2379495f :
                           (data[0 /* glucosevalue_mean_12h */] <155.80931f ?
                              -0.515047f :
                              (Double.isNaN(data[10]) || data[10 /* glucosevalue_hypoduration_24h */] <2.4913495f ?
                                 -0.50849915f :
                                 -0.50584775f))) :
                        0.46354914f)) :
                 (data[9 /* glucosevalue_euglycemia_24h */] <51.02725f ?
                     (data[6 /* glucosevalue_mean_24h */] <188.15817f ?
                        0.303746f :
                        (Double.isNaN(data[33]) || data[33 /* lastbolus */] <2.8710938f ?
                            (data[32 /* durationtime */] <-117.1125f ?
                               -0.50629574f :
                               -0.50448656f) :
                           -0.5108274f)) :
                     (data[33 /* lastbolus */] <2.9171875f ?
                         (Double.isNaN(data[8]) || data[8 /* glucosevalue_cv_24h */] <41.204285f ?
                             (!Double.isNaN(data[31 /* meal_type */]) && (GenModel.bitSetIsInRange(32, 0, data[31])
                             && !GenModel.bitSetContains(GRPSPLIT0, 32, 0, data[31])) ?
                                -0.51748323f :
                                (data[20 /* glucosevalue_cv_6h */] <26.74035f ?
                                   -0.5105624f :
                                   -0.50689995f)) :
                           -0.16264087f) :
                         (data[8 /* glucosevalue_cv_24h */] <30.095692f ?
                            -0.51521724f :
                            -0.52227485f))))));
    return pred;
  } // constant pool size = 99B, number of visited nodes = 23, static init size = 30B
  // {00111000 00000000 00000000 00000000}
  public static final byte[] GRPSPLIT0 = new byte[] {28, 0, 0, 0};
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_8 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_8_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_8_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[6 /* glucosevalue_mean_24h */] <113.64919f ?
         (Double.isNaN(data[26]) || data[26 /* activity_max_12h */] <23.135271f ?
             (Double.isNaN(data[33]) || data[33 /* lastbolus */] <1.2144922f ?
                0.37909308f :
```

```
                -0.34291226f) :
              (data[29 /* steps_max_12h */] <7925.0f ?
                 0.510291f :
                 0.5169041f)) :
         (data[11 /* glucosevalue_hyperduration_24h */] <5.859375f ?
            -0.52035385f :
            (Double.isNaN(data[16]) || data[16 /* glucosevalue_hypoduration_2h */] <33.992188f ?
                (data[39 /* slope_at_bed */] <-0.15625f ?
                    (data[18 /* glucosevalue_mean_6h */] <114.50407f ?
                       0.3656158f :
                       (data[10 /* glucosevalue_hypoduration_24h */] <0.9299308f ?
                           (data[28 /* steps_max_6h */] <3003.5f ?
                              -0.50726223f :
                              0.40606532f) :
                           (data[33 /* lastbolus */] <5.37f ?
                               (data[0 /* glucosevalue_mean_12h */] <150.4f ?
                                  -0.51268756f :
                                  (data[27 /* steps_max_2h */] <941.5f ?
                                     -0.50810975f :
                                     -0.503588f)) :
                               (data[22 /* glucosevalue_hypoduration_6h */] <6.849315f ?
                                  0.13735494f :
                                  0.39097974f)))) :
                    (data[0 /* glucosevalue_mean_12h */] <130.82198f ?
                       -0.51562643f :
                       (Double.isNaN(data[21]) || data[21 /* glucosevalue_euglycemia_6h */] <87.5f ?
                           (Double.isNaN(data[3]) || data[3 /* glucosevalue_euglycemia_12h */] <76.89655f ?
                               (data[7 /* glucosevalue_sd_24h */] <40.020557f ?
                                  -0.5172812f :
                                  (data[21 /* glucosevalue_euglycemia_6h */] <25.479452f ?
                                     -0.50967073f :
                                     (data[35 /* iobBed */] <3.1207273f ?
                                        -0.062239874f :
                                        (Double.isNaN(data[6]) || data[6 /* glucosevalue_mean_24h */] <172.10173f ?
                                            (Double.isNaN(data[13]) || data[13 /* glucosevalue_sd_2h */] <33.31586f ?
                                                (data[34 /* durationtime_bolus */] <-79.36f ?
                                                   -0.50724006f :
                                                   -0.50582546f) :
                                               -0.50451344f) :
                                            (data[39 /* slope_at_bed */] <0.31f ?
                                               -0.5058638f :
                                               -0.5033274f))))) :
                                  0.17163533f) :
                              0.3395154f))) :
              0.4074096f)));
    return pred;
  } // constant pool size = 98B, number of visited nodes = 24, static init size = 0B
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_9 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_9_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_9_class_0 {
  static final double score0(double[] data) {
    double pred =      (Double.isNaN(data[10]) || data[10 /* glucosevalue_hypoduration_24h */] <4.6815867f ?
         (data[5 /* glucosevalue_hyperduration_12h */] <17.578125f ?
             (data[34 /* durationtime_bolus */] <-18.061785f ?
                 (data[26 /* activity_max_12h */] <21.160051f ?
                    -0.52100617f :
                    (Double.isNaN(data[39]) || data[39 /* slope_at_bed */] <-0.428125f ?
                       -0.3666991f :
                       -0.51071304f)) :
                 0.068348005f) :
             (data[6 /* glucosevalue_mean_24h */] <138.12387f ?
                0.43082637f :
                (data[7 /* glucosevalue_sd_24h */] <53.577633f ?
                    (Double.isNaN(data[1]) || data[1 /* glucosevalue_sd_12h */] <50.231842f ?
                        (data[35 /* iobBed */] <3.9995463f ?
                           0.20392895f :
                           (data[14 /* glucosevalue_cv_2h */] <9.765392f ?
                              -0.5108957f :
                              (data[37 /* glucose_at_bed */] <162.0f ?
                                 0.03321405f :
                                 -0.50487024f))) :
                        (data[11 /* glucosevalue_hyperduration_24h */] <36.25649f ?
```

```
                           -0.11462482f :
                           0.48704466f)) :
                    (data[30 /* meal_g */] <19.5f ?
                       -0.5080096f :
                        (data[37 /* glucose_at_bed */] <177.5f ?
                            (data[29 /* steps_max_12h */] <7553.5f ?
                               -0.5026296f :
                               -0.50672907f) :
                            (data[35 /* iobBed */] <4.6476936f ?
                               -0.5019801f :
                                (data[19 /* glucosevalue_sd_6h */] <51.580303f ?
                                   -0.50328696f :
                                   -0.5024925f))))))) :
        (Double.isNaN(data[33]) || data[33 /* lastbolus */] <0.19335938f ?
           -0.36333466f :
            (Double.isNaN(data[5]) || data[5 /* glucosevalue_hyperduration_12h */] <43.448277f ?
                (Double.isNaN(data[37]) || data[37 /* glucose_at_bed */] <206.5f ?
                    (Double.isNaN(data[37]) || data[37 /* glucose_at_bed */] <144.0f ?
                        (Double.isNaN(data[39]) || data[39 /* slope_at_bed */] <-0.05f ?
                            (Double.isNaN(data[9]) || data[9 /* glucosevalue_euglycemia_24h */] <81.48789f ?
                                (data[27 /* steps_max_2h */] <778.5f ?
                                   0.50550276f :
                                   0.5112307f) :
                               0.5176105f) :
                            (data[21 /* glucosevalue_euglycemia_6h */] <75.34247f ?
                               0.3727385f :
                               -0.12277547f)) :
                        -0.50730026f) :
                    0.51704824f) :
                (data[12 /* glucosevalue_mean_2h */] <190.41672f ?
                   -0.509889f :
                   -0.5030017f))));
    return pred;
  } // constant pool size = 106B, number of visited nodes = 26, static init size = 0B
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_10 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_10_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_10_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[37 /* glucose_at_bed */] <102.0f ?
         (data[27 /* steps_max_2h */] <417.5f ?
            -0.33801267f :
            (data[25 /* activity_max_6h */] <20.268984f ?
               0.5133793f :
                (Double.isNaN(data[20]) || data[20 /* glucosevalue_cv_6h */] <31.587234f ?
                    (Double.isNaN(data[19]) || data[19 /* glucosevalue_sd_6h */] <24.265097f ?
                        (Double.isNaN(data[34]) || data[34 /* durationtime_bolus */] <-55.48828f ?
                           0.50617164f :
                           0.11036229f) :
                        -0.37535813f) :
                   0.50784403f))) :
         (Double.isNaN(data[34]) || data[34 /* durationtime_bolus */] <-419.0885f ?
            (data[14 /* glucosevalue_cv_2h */] <14.545072f ?
               -0.50424004f :
               -0.5094721f) :
            (data[20 /* glucosevalue_cv_6h */] <12.123333f ?
               -0.51078564f :
                (data[13 /* glucosevalue_sd_2h */] <18.464144f ?
                    (Double.isNaN(data[9]) || data[9 /* glucosevalue_euglycemia_24h */] <80.47145f ?
                        (data[26 /* activity_max_12h */] <23.407421f ?
                           0.40232572f :
                            (Double.isNaN(data[28]) || data[28 /* steps_max_6h */] <5327.5f ?
                                (data[11 /* glucosevalue_hyperduration_24h */] <28.99654f ?
                                   0.27239665f :
                                    (data[1 /* glucosevalue_sd_12h */] <46.153202f ?
                                       -0.5037858f :
                                       -0.5023832f)) :
                               -0.50526285f)) :
                       0.47248113f) :
                    (Double.isNaN(data[4]) || data[4 /* glucosevalue_hypoduration_12h */] <9.137931f ?
                        (data[0 /* glucosevalue_mean_12h */] <148.30043f ?
                           -0.50650114f :
                            (data[20 /* glucosevalue_cv_6h */] <16.601404f ?
```

```
                                0.19805045f :
                                 (Double.isNaN(data[36]) || data[36 /* overnightiir */] <0.99f ?
                                     (data[14 /* glucosevalue_cv_2h */] <16.22754f ?
                                        -0.5018931f :
                                         (data[23 /* glucosevalue_hyperduration_6h */] <32.876713f ?
                                            -0.5050437f :
                                            -0.5031584f)) :
                                     (Double.isNaN(data[3]) || data[3 /* glucosevalue_euglycemia_12h */] <49.37931f ?
                                         (data[1 /* glucosevalue_sd_12h */] <75.29912f ?
                                            -0.5009402f :
                                            -0.5013269f) :
                                        -0.50210977f)))) :
                            0.25758022f)))));
    return pred;
  } // constant pool size = 94B, number of visited nodes = 23, static init size = 0B
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_11 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_11_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_11_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[37 /* glucose_at_bed */] <102.0f ?
         (data[38 /* glucose_15min */] <77.5f ?
             (Double.isNaN(data[33]) || data[33 /* lastbolus */] <0.90234375f ?
                -0.43832564f :
                 (data[16 /* glucosevalue_hypoduration_2h */] <17.96875f ?
                    -0.5038577f :
                    0.50378907f)) :
             (data[29 /* steps_max_12h */] <5031.0f ?
                0.5088338f :
                 (Double.isNaN(data[2]) || data[2 /* glucosevalue_cv_12h */] <28.1719f ?
                     (Double.isNaN(data[8]) || data[8 /* glucosevalue_cv_24h */] <24.464357f ?
                        0.23308995f :
                        -0.5048436f) :
                    0.5060716f))) :
         (data[34 /* durationtime_bolus */] <310.6796f ?
             (data[20 /* glucosevalue_cv_6h */] <12.123333f ?
                -0.50651497f :
                 (data[13 /* glucosevalue_sd_2h */] <18.464144f ?
                     (Double.isNaN(data[36]) || data[36 /* overnightiir */] <0.9640625f ?
                         (Double.isNaN(data[37]) || data[37 /* glucose_at_bed */] <180.0f ?
                             (Double.isNaN(data[3]) || data[3 /* glucosevalue_euglycemia_12h */] <78.75862f ?
                                 (Double.isNaN(data[36]) || data[36 /* overnightiir */] <0.84375f ?
                                    -0.50321996f :
                                    0.15410532f) :
                                0.5056014f) :
                            0.5078157f) :
                         (data[0 /* glucosevalue_mean_12h */] <159.6041f ?
                            -0.5028116f :
                            -0.09871907f)) :
                     (Double.isNaN(data[37]) || data[37 /* glucose_at_bed */] <216.5f ?
                         (data[23 /* glucosevalue_hyperduration_6h */] <9.375f ?
                            -0.5054513f :
                             (data[24 /* activity_max_2h */] <14.16775f ?
                                -0.5026066f :
                                 (Double.isNaN(data[14]) || data[14 /* glucosevalue_cv_2h */] <26.214544f ?
                                     (Double.isNaN(data[7]) || data[7 /* glucosevalue_sd_24h */] <59.83394f ?
                                         (data[26 /* activity_max_12h */] <33.081f ?
                                            -0.5018574f :
                                            -0.5013168f) :
                                        -0.5008081f) :
                                    -0.502567f))) :
                         (data[37 /* glucose_at_bed */] <259.0f ?
                            0.38718647f :
                             (data[36 /* overnightiir */] <0.99f ?
                                -0.5038568f :
                                -0.5016001f))))) :
            -0.506269f));
    return pred;
  } // constant pool size = 94B, number of visited nodes = 23, static init size = 0B
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_12 {
```

```
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_12_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_12_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[39 /* slope_at_bed */] <-1.0958658f ?
         (Double.isNaN(data[26]) || data[26 /* activity_max_12h */] <36.9641f ?
             (data[34 /* durationtime_bolus */] <-62.004166f ?
                0.41754833f :
                0.5054537f) :
            -0.4137485f) :
         (data[32 /* durationtime */] <-16.498241f ?
             (data[6 /* glucosevalue_mean_24h */] <97.32963f ?
                 (data[15 /* glucosevalue_euglycemia_2h */] <93.75f ?
                    0.23599428f :
                    0.5041961f) :
                 (Double.isNaN(data[3]) || data[3 /* glucosevalue_euglycemia_12h */] <84.940735f ?
                     (data[5 /* glucosevalue_hyperduration_12h */] <11.206897f ?
                        0.50351435f :
                         (Double.isNaN(data[30]) || data[30 /* meal_g */] <33.5f ?
                             (Double.isNaN(data[13]) || data[13 /* glucosevalue_sd_2h */] <27.117758f ?
                                 (Double.isNaN(data[19]) || data[19 /* glucosevalue_sd_6h */] <40.236973f ?
                                     (Double.isNaN(data[13]) || data[13 /* glucosevalue_sd_2h */] <14.9433155f ?
                                         (data[34 /* durationtime_bolus */] <-81.575f ?
                                            0.46300372f :
                                            -0.32900077f) :
                                        0.4934058f) :
                                     (Double.isNaN(data[24]) || data[24 /* activity_max_2h */] <31.852375f ?
                                        -0.5030661f :
                                        0.27940875f)) :
                                 (!Double.isNaN(data[31 /* meal_type */])

                                    && (GenModel.bitSetIsInRange(32, 0, data[31]) && !GenModel.bitSetContains(GRPSPLIT0, 32, 0, data[31])) ?
                                        -0.5022787f :
                                         (data[21 /* glucosevalue_euglycemia_6h */] <45.0f ?
                                            0.2849713f :
                                            -0.50105613f))) :
                             (Double.isNaN(data[13]) || data[13 /* glucosevalue_sd_2h */] <41.952526f ?
                                 (data[37 /* glucose_at_bed */] <143.5f ?
                                     (Double.isNaN(data[2]) || data[2 /* glucosevalue_cv_12h */] <33.05269f ?
                                        -0.50115216f :
                                        -0.503363f) :
                                     (data[28 /* steps_max_6h */] <2656.5f ?
                                        -0.50167495f :
                                         (data[11 /* glucosevalue_hyperduration_24h */] <42.448097f ?
                                            -0.50116426f :
                                             (data[27 /* steps_max_2h */] <959.5f ?
                                                -0.50075907f :
                                                -0.50051785f)))) :
                                 0.09169875f))) :
                     (data[29 /* steps_max_12h */] <9879.5f ?
                        -0.5047404f :
                        -0.28416017f))) :
         (Double.isNaN(data[4]) || data[4 /* glucosevalue_hypoduration_12h */] <9.38847f ?
             (data[29 /* steps_max_12h */] <7757.5f ?
                -0.50226486f :
                -0.07584474f) :
            -0.5074863f)));
    return pred;
  } // constant pool size = 107B, number of visited nodes = 25, static init size = 30B
  // {00001000 00000000 00000000 00000000}
  public static final byte[] GRPSPLIT0 = new byte[] {16, 0, 0, 0};
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_13 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_13_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_13_class_0 {
  static final double score0(double[] data) {
    double pred =      (Double.isNaN(data[10]) || data[10 /* glucosevalue_hypoduration_24h */] <11.243985f ?
         (Double.isNaN(data[4]) || data[4 /* glucosevalue_hypoduration_12h */] <14.139952f ?
             (data[30 /* meal_g */] <16.5f ?
                 (data[33 /* lastbolus */] <1.1601562f ?
                     (data[20 /* glucosevalue_cv_6h */] <18.233637f ?
```

```
                        0.50390965f :
                        0.2089639f) :
                    (Double.isNaN(data[30]) || data[30 /* meal_g */] <11.0f ?
                       -0.50229466f :
                       0.27613866f)) :
                (data[39 /* slope_at_bed */] <-1.3328125f ?
                   0.34300637f :
                   (Double.isNaN(data[35]) || data[35 /* iobBed */] <9.239983f ?
                       (Double.isNaN(data[8]) || data[8 /* glucosevalue_cv_24h */] <31.796003f ?
                           (data[18 /* glucosevalue_mean_6h */] <129.07603f ?
                               (!Double.isNaN(data[30]) ?
                                  -0.50318974f :
                                  -0.5014265f) :
                               (Double.isNaN(data[25]) || data[25 /* activity_max_6h */] <32.406666f ?
                                   (data[14 /* glucosevalue_cv_2h */] <10.012941f ?
                                      -0.5018256f :
                                      -0.5009772f) :
                                   (Double.isNaN(data[29]) || data[29 /* steps_max_12h */] <10584.0f ?
                                      -0.50088054f :
                                      0.15291734f))) :
                           (Double.isNaN(data[10]) || data[10 /* glucosevalue_hypoduration_24h */] <5.017301f ?
                               (Double.isNaN(data[8]) || data[8 /* glucosevalue_cv_24h */] <40.83285f ?
                                   (Double.isNaN(data[20]) || data[20 /* glucosevalue_cv_6h */] <34.70456f ?
                                       (data[19 /* glucosevalue_sd_6h */] <54.181156f ?
                                          -0.5009861f :
                                          -0.5005251f) :
                                       -0.01571241f) :
                                   -0.50141436f) :
                               (data[9 /* glucosevalue_euglycemia_24h */] <62.906574f ?
                                  -0.18611601f :
                                  0.453796f))) :
                       (data[29 /* steps_max_12h */] <7208.0f ?
                          -0.50080794f :
                          0.35469738f)))) :
          -0.50415033f) :
        (data[26 /* activity_max_12h */] <21.036253f ?
            (data[39 /* slope_at_bed */] <-0.23489584f ?
               0.19200046f :
               -0.41774845f) :
            (Double.isNaN(data[12]) || data[12 /* glucosevalue_mean_2h */] <125.00571f ?
                (Double.isNaN(data[22]) || data[22 /* glucosevalue_hypoduration_6h */] <25.428082f ?
                   0.5030569f :
                   0.50145227f) :
               -0.13209057f)));
    return pred;
  } // constant pool size = 96B, number of visited nodes = 24, static init size = 0B
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_14 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_14_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_14_class_0 {
  static final double score0(double[] data) {
    double pred =      (Double.isNaN(data[5]) || data[5 /* glucosevalue_hyperduration_12h */] <42.72461f ?
         (Double.isNaN(data[20]) || data[20 /* glucosevalue_cv_6h */] <35.734814f ?
             (data[30 /* meal_g */] <14.5f ?
                 (data[24 /* activity_max_2h */] <14.211679f ?
                    -0.31434932f :
                     (Double.isNaN(data[33]) || data[33 /* lastbolus */] <1.2159375f ?
                         (data[10 /* glucosevalue_hypoduration_24h */] <4.622621f ?
                            0.5027038f :
                            0.50143373f) :
                        0.12533747f)) :
                 (data[37 /* glucose_at_bed */] <100.5f ?
                     (data[6 /* glucosevalue_mean_24h */] <125.66477f ?
                        0.50215113f :
                        -0.16334455f) :
                     (Double.isNaN(data[31 /* meal_type */]) || !GenModel.bitSetIsInRange(32, 0, data[31])
                      || (GenModel.bitSetIsInRange(32, 0, data[31]) && !GenModel.bitSetContains(GRPSPLIT0, 32, 0, data[31])) ?
                         (data[39 /* slope_at_bed */] <-0.93541664f ?
                            -0.5024322f :
                             (Double.isNaN(data[34]) || data[34 /* durationtime_bolus */] <-256.195f ?
                                 (data[24 /* activity_max_2h */] <25.6805f ?
                                    -0.50070196f :
                                    -0.50135756f) :
```

```
                                (data[12 /* glucosevalue_mean_2h */] <143.788f ?
                                    (data[11 /* glucosevalue_hyperduration_24h */] <34.99135f ?
                                       0.33878052f :
                                       -0.5007494f) :
                                    (Double.isNaN(data[7]) || data[7 /* glucosevalue_sd_24h */] <44.31475f ?
                                       -0.50091094f :
                                       -0.5004211f)))) :
                            0.21570161f))) :
                (Double.isNaN(data[32]) || data[32 /* durationtime */] <-256.23358f ?
                   -0.11571656f :
                    (Double.isNaN(data[29]) || data[29 /* steps_max_12h */] <10429.0f ?
                       0.502357f :
                       0.4625998f))) :
            (Double.isNaN(data[35]) || data[35 /* iobBed */] <10.065324f ?
                (data[7 /* glucosevalue_sd_24h */] <53.25983f ?
                    (Double.isNaN(data[1]) || data[1 /* glucosevalue_sd_12h */] <47.170982f ?
                       -0.5006058f :
                       0.32201195f) :
                    (Double.isNaN(data[3]) || data[3 /* glucosevalue_euglycemia_12h */] <49.752155f ?
                        (data[36 /* overnightiir */] <0.984375f ?
                            (Double.isNaN(data[4]) || data[4 /* glucosevalue_hypoduration_12h */] <2.3275862f ?
                               -0.50052375f :
                               -0.5009212f) :
                            (Double.isNaN(data[30]) || data[30 /* meal_g */] <25.5f ?
                                (data[8 /* glucosevalue_cv_24h */] <38.272873f ?
                                   -0.5005811f :
                                   -0.5004282f) :
                               -0.5003069f)) :
                       -0.5012537f)) :
              -0.5015246f));
    return pred;
  } // constant pool size = 107B, number of visited nodes = 25, static init size = 30B
  // {00110000 00000000 00000000 00000000}
  public static final byte[] GRPSPLIT0 = new byte[] {12, 0, 0, 0};
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_15 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_15_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_15_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[37 /* glucose_at_bed */] <102.0f ?
         (data[39 /* slope_at_bed */] <-0.49941406f ?
             (Double.isNaN(data[10]) || data[10 /* glucosevalue_hypoduration_24h */] <11.366647f ?
                0.5017337f :
                0.40434512f) :
             (data[27 /* steps_max_2h */] <431.5f ?
                -0.5018612f :
                 (data[4 /* glucosevalue_hypoduration_12h */] <2.2898707f ?
                    0.50180304f :
                     (Double.isNaN(data[15]) || data[15 /* glucosevalue_euglycemia_2h */] <78.125f ?
                         (data[2 /* glucosevalue_cv_12h */] <31.878674f ?
                            0.5011606f :
                            -0.0319303f) :
                        -0.41597083f)))) :
         (data[33 /* lastbolus */] <1.1762695f ?
             (data[13 /* glucosevalue_sd_2h */] <16.790081f ?
                 (Double.isNaN(data[5]) || data[5 /* glucosevalue_hyperduration_12h */] <32.88793f ?
                    0.5015976f :
                    0.12286387f) :
                 (data[0 /* glucosevalue_mean_12h */] <156.13103f ?
                    -0.5009873f :
                    -0.5003481f)) :
             (Double.isNaN(data[31 /* meal_type */]) || !GenModel.bitSetIsInRange(32, 0, data[31])
             || (GenModel.bitSetIsInRange(32, 0, data[31]) && !GenModel.bitSetContains(GRPSPLIT0, 32, 0, data[31])) ?
                 (data[7 /* glucosevalue_sd_24h */] <50.79935f ?
                     (data[18 /* glucosevalue_mean_6h */] <127.16952f ?
                        -0.5018174f :
                         (data[14 /* glucosevalue_cv_2h */] <5.999349f ?
                            -0.50096095f :
                             (Double.isNaN(data[7]) || data[7 /* glucosevalue_sd_24h */] <47.933933f ?
                                 (Double.isNaN(data[28]) || data[28 /* steps_max_6h */] <4457.5f ?
                                     (data[21 /* glucosevalue_euglycemia_6h */] <69.863014f ?
                                        -0.5003241f :
                                        -0.500428f) :
```

```
                                   -0.5004679f) :
                               -0.50069314f))) :
                     (data[7 /* glucosevalue_sd_24h */] <53.342255f ?
                        0.38913694f :
                         (Double.isNaN(data[10]) || data[10 /* glucosevalue_hypoduration_24h */] <5.827068f ?
                             (Double.isNaN(data[7]) || data[7 /* glucosevalue_sd_24h */] <85.96978f ?
                                 (data[6 /* glucosevalue_mean_24h */] <179.61453f ?
                                    -0.500826f :
                                     (Double.isNaN(data[37]) || data[37 /* glucose_at_bed */] <270.5f ?
                                         (Double.isNaN(data[1]) || data[1 /* glucosevalue_sd_12h */] <76.59628f ?
                                             (data[32 /* durationtime */] <-156.49417f ?
                                                -0.5004207f :
                                                -0.5002997f) :
                                            -0.50056887f) :
                                        -0.50024503f)) :
                                -0.10843132f) :
                            0.3602407f))) :
                0.45662224f)));
    return pred;
  } // constant pool size = 107B, number of visited nodes = 25, static init size = 30B
  // {00100000 00000000 00000000 00000000}
  public static final byte[] GRPSPLIT0 = new byte[] {4, 0, 0, 0};
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_16 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_16_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_16_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[37 /* glucose_at_bed */] <102.0f ?
         (Double.isNaN(data[38]) || data[38 /* glucose_15min */] <83.5f ?
             (Double.isNaN(data[32]) || data[32 /* durationtime */] <-63.257065f ?
                 (Double.isNaN(data[3]) || data[3 /* glucosevalue_euglycemia_12h */] <77.95258f ?
                     (data[29 /* steps_max_12h */] <7473.5f ?
                        0.19970343f :
                        -0.41053632f) :
                    0.5009977f) :
                -0.29474983f) :
             (Double.isNaN(data[15]) || data[15 /* glucosevalue_euglycemia_2h */] <95.89844f ?
                 (data[22 /* glucosevalue_hypoduration_6h */] <9.631849f ?
                    0.5012241f :
                    0.5005711f) :
                0.05182803f)) :
         (data[33 /* lastbolus */] <1.1762695f ?
             (data[13 /* glucosevalue_sd_2h */] <16.790081f ?
                 (Double.isNaN(data[34]) || data[34 /* durationtime_bolus */] <-42.466408f ?
                    0.5010863f :
                    -0.0041915313f) :
                 (data[0 /* glucosevalue_mean_12h */] <156.13103f ?
                    -0.5005983f :
                    -0.50021106f)) :
             (Double.isNaN(data[31 /* meal_type */]) || !GenModel.bitSetIsInRange(32, 0, data[31])
             || (GenModel.bitSetIsInRange(32, 0, data[31]) && !GenModel.bitSetContains(GRPSPLIT0, 32, 0, data[31])) ?
                 (data[0 /* glucosevalue_mean_12h */] <115.47829f ?
                    -0.5012445f :
                     (data[7 /* glucosevalue_sd_24h */] <50.70252f ?
                         (data[18 /* glucosevalue_mean_6h */] <123.06421f ?
                            -0.5007923f :
                             (data[14 /* glucosevalue_cv_2h */] <6.149991f ?
                                -0.5005523f :
                                 (Double.isNaN(data[7]) || data[7 /* glucosevalue_sd_24h */] <47.933933f ?
                                     (Double.isNaN(data[36]) || data[36 /* overnightiir */] <0.965f ?
                                        -0.500273f :
                                        -0.5001939f) :
                                    -0.50042015f))) :
                         (data[7 /* glucosevalue_sd_24h */] <54.09911f ?
                            0.28478476f :
                             (data[6 /* glucosevalue_mean_24h */] <162.81142f ?
                                0.31072497f :
                                 (data[26 /* activity_max_12h */] <23.727f ?
                                    0.018775383f :
                                     (data[6 /* glucosevalue_mean_24h */] <178.5711f ?
                                        -0.5005408f :
                                         (data[30 /* meal_g */] <44.5f ?
                                             (data[21 /* glucosevalue_euglycemia_6h */] <30.0f ?
```

```
                                            -0.5003489f :
                                            -0.5002136f) :
                                         (data[13 /* glucosevalue_sd_2h */] <19.566267f ?
                                            -0.5002484f :
                                            -0.5001605f))))))) :
                0.39697757f)));
    return pred;
  } // constant pool size = 107B, number of visited nodes = 25, static init size = 30B
  // {00100000 00000000 00000000 00000000}
  public static final byte[] GRPSPLIT0 = new byte[] {4, 0, 0, 0};
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_17 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_17_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_17_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[0 /* glucosevalue_mean_12h */] <113.74505f ?
         (data[29 /* steps_max_12h */] <6516.5f ?
             (Double.isNaN(data[34]) || data[34 /* durationtime_bolus */] <-37.128548f ?
                0.17187291f :
                -0.4377197f) :
             (data[39 /* slope_at_bed */] <-0.103125f ?
                0.50040054f :
                0.500883f)) :
         (data[5 /* glucosevalue_hyperduration_12h */] <5.1757812f ?
            -0.50088394f :
             (data[6 /* glucosevalue_mean_24h */] <133.38052f ?
                 (Double.isNaN(data[4]) || data[4 /* glucosevalue_hypoduration_12h */] <11.072198f ?
                    0.47584075f :
                    -0.13083652f) :
                 (Double.isNaN(data[32]) || data[32 /* durationtime */] <-252.4888f ?
                     (data[37 /* glucose_at_bed */] <139.5f ?
                        -0.5007931f :
                         (data[7 /* glucosevalue_sd_24h */] <41.595966f ?
                            0.222872f :
                             (data[36 /* overnightiir */] <0.915f ?
                                -0.50043786f :
                                 (data[35 /* iobBed */] <3.6218734f ?
                                    -0.045792703f :
                                     (data[11 /* glucosevalue_hyperduration_24h */] <46.53979f ?
                                        -0.5002866f :
                                         (data[11 /* glucosevalue_hyperduration_24h */] <63.75f ?
                                            -0.50008976f :
                                            -0.5001829f)))))) :
                     (Double.isNaN(data[5]) || data[5 /* glucosevalue_hyperduration_12h */] <43.900864f ?
                         (Double.isNaN(data[38]) || data[38 /* glucose_15min */] <195.5f ?
                             (data[37 /* glucose_at_bed */] <107.5f ?
                                0.3101877f :
                                 (data[20 /* glucosevalue_cv_6h */] <23.381826f ?
                                    0.342494f :
                                     (Double.isNaN(data[22]) || data[22 /* glucosevalue_hypoduration_6h */] <1.9178082f ?
                                        -0.5001779f :
                                        -0.5004893f))) :
                            0.42564583f) :
                         (Double.isNaN(data[36]) || data[36 /* overnightiir */] <0.95625f ?
                             (Double.isNaN(data[15]) || data[15 /* glucosevalue_euglycemia_2h */] <42.5f ?
                                -0.5004048f :
                                -0.5002096f) :
                             (data[12 /* glucosevalue_mean_2h */] <211.472f ?
                                -0.50021905f :
                                0.27759248f)))))));
    return pred;
  } // constant pool size = 90B, number of visited nodes = 22, static init size = 0B
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_18 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_18_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_18_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[30 /* meal_g */] <16.0f ?
```

```
        (Double.isNaN(data[33]) || data[33 /* lastbolus */] <1.2890625f ?
            (data[21 /* glucosevalue_euglycemia_6h */] <56.054688f ?
                (data[32 /* durationtime */] <-112.358986f ?
                   0.32659617f :
                   -0.500492f) :
                (data[3 /* glucosevalue_euglycemia_12h */] <76.5625f ?
                   0.5006823f :
                   0.4449142f)) :
            (Double.isNaN(data[34]) || data[34 /* durationtime_bolus */] <-65.259865f ?
                (data[37 /* glucose_at_bed */] <111.0f ?
                   0.5005321f :
                   -0.50019586f) :
               -0.46636355f)) :
        (data[39 /* slope_at_bed */] <-1.0876954f ?
            (data[26 /* activity_max_12h */] <30.111422f ?
               0.5005594f :
               -0.16391927f) :
            (data[26 /* activity_max_12h */] <29.24712f ?
                (Double.isNaN(data[1]) || data[1 /* glucosevalue_sd_12h */] <59.00655f ?
                    (Double.isNaN(data[4]) || data[4 /* glucosevalue_hypoduration_12h */] <3.6206896f ?
                        (data[15 /* glucosevalue_euglycemia_2h */] <50.0f ?
                           -0.5003994f :
                            (Double.isNaN(data[34]) || data[34 /* durationtime_bolus */] <-190.37083f ?
                               -0.500125f :
                               -0.5002122f)) :
                        (data[27 /* steps_max_2h */] <735.5f ?
                           -0.41361624f :
                           -0.50068325f)) :
                    (Double.isNaN(data[21]) || data[21 /* glucosevalue_euglycemia_6h */] <36.71875f ?
                       -0.50011975f :
                       0.33016035f)) :
                (Double.isNaN(data[10]) || data[10 /* glucosevalue_hypoduration_24h */] <10.994269f ?
                    (data[20 /* glucosevalue_cv_6h */] <23.691334f ?
                        (data[30 /* meal_g */] <34.5f ?
                           0.41280687f :
                            (data[18 /* glucosevalue_mean_6h */] <169.46233f ?
                               0.019507648f :
                               -0.5001569f)) :
                        (data[38 /* glucose_15min */] <92.5f ?
                           -0.50064677f :
                            (data[37 /* glucose_at_bed */] <116.5f ?
                               0.39335033f :
                                (Double.isNaN(data[30]) || data[30 /* meal_g */] <36.5f ?
                                    (data[27 /* steps_max_2h */] <1500.5f ?
                                       -0.50029784f :
                                       -0.5001469f) :
                                    (Double.isNaN(data[20]) || data[20 /* glucosevalue_cv_6h */] <36.873104f ?
                                       -0.5000626f :
                                       -0.500126f))))) :
                    0.39902276f))));
    return pred;
  } // constant pool size = 102B, number of visited nodes = 25, static init size = 0B
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_19 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_19_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_19_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[37 /* glucose_at_bed */] <102.0f ?
         (data[27 /* steps_max_2h */] <417.5f ?
            -0.27280065f :
             (Double.isNaN(data[0]) || data[0 /* glucosevalue_mean_12h */] <120.573044f ?
                 (Double.isNaN(data[34]) || data[34 /* durationtime_bolus */] <-150.75111f ?
                    0.5004074f :
                     (Double.isNaN(data[6]) || data[6 /* glucosevalue_mean_24h */] <90.77287f ?
                        0.20263265f :
                        0.5002763f)) :
                 (data[1 /* glucosevalue_sd_12h */] <46.147953f ?
                    -0.25389126f :
                    0.40756106f))) :
         (data[28 /* steps_max_6h */] <1943.5f ?
             (data[37 /* glucose_at_bed */] <168.0f ?
                -0.5004006f :
                -0.5001287f) :
```

```
            (data[33 /* lastbolus */] <1.1876953f ?
                (Double.isNaN(data[13]) || data[13 /* glucosevalue_sd_2h */] <16.918856f ?
                    (data[26 /* activity_max_12h */] <20.99052f ?
                       0.16624887f :
                       0.50035447f) :
                    (data[19 /* glucosevalue_sd_6h */] <47.0994f ?
                       -0.5001918f :
                       -0.50005794f)) :
                (Double.isNaN(data[8]) || data[8 /* glucosevalue_cv_24h */] <44.822983f ?
                    (data[1 /* glucosevalue_sd_12h */] <35.84552f ?
                        (data[30 /* meal_g */] <36.5f ?
                           -0.50029f :
                           -0.500107f) :
                        (data[12 /* glucosevalue_mean_2h */] <123.2275f ?
                           0.17733435f :
                            (Double.isNaN(data[38]) || data[38 /* glucose_15min */] <229.5f ?
                                (data[6 /* glucosevalue_mean_24h */] <160.05121f ?
                                    (data[30 /* meal_g */] <40.5f ?
                                       -0.50023735f :
                                       -0.5001241f) :
                                    (Double.isNaN(data[24]) || data[24 /* activity_max_2h */] <42.5725f ?
                                        (!Double.isNaN(data[31 /* meal_type */])
                                        && (GenModel.bitSetIsInRange(32, 0, data[31]) && !GenModel.bitSetContains(GRPSPLIT0, 32, 0, data[31])) ?
                                           -0.5000713f :
                                            (data[32 /* durationtime */] <-85.4f ?
                                               -0.5000609f :
                                               -0.50004077f)) :
                                       -0.50013435f)) :
                                (Double.isNaN(data[28]) || data[28 /* steps_max_6h */] <3973.5f ?
                                   -0.5001229f :
                                   0.3288608f)))) :
                    0.31000453f))));
    return pred;
  } // constant pool size = 99B, number of visited nodes = 23, static init size = 30B
  // {00111000 00000000 00000000 00000000}
  public static final byte[] GRPSPLIT0 = new byte[] {28, 0, 0, 0};
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_20 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_20_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_20_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[37 /* glucose_at_bed */] <65.5f ?
        0.4111263f :
         (Double.isNaN(data[33]) || data[33 /* lastbolus */] <0.19335938f ?
             (data[21 /* glucosevalue_euglycemia_6h */] <83.39844f ?
                -0.5004082f :
                -0.19519041f) :
             (Double.isNaN(data[16]) || data[16 /* glucosevalue_hypoduration_2h */] <34.0625f ?
                 (data[6 /* glucosevalue_mean_24h */] <126.41735f ?
                     (data[8 /* glucosevalue_cv_24h */] <16.801165f ?
                        -0.18278933f :
                         (Double.isNaN(data[4]) || data[4 /* glucosevalue_hypoduration_12h */] <10.506466f ?
                             (data[27 /* steps_max_2h */] <670.0f ?
                                0.50015885f :
                                0.5002071f) :
                            0.24329509f)) :
                     (Double.isNaN(data[38]) || data[38 /* glucose_15min */] <230.0f ?
                         (data[19 /* glucosevalue_sd_6h */] <33.610146f ?
                             (data[37 /* glucose_at_bed */] <121.5f ?
                                -0.5002894f :
                                 (Double.isNaN(data[21]) || data[21 /* glucosevalue_euglycemia_6h */] <72.5f ?
                                    -0.50014246f :
                                    0.20298213f)) :
                             (data[19 /* glucosevalue_sd_6h */] <36.84132f ?
                                0.25350875f :
                                 (data[37 /* glucose_at_bed */] <100.5f ?
                                    0.22005932f :
                                     (data[0 /* glucosevalue_mean_12h */] <148.12965f ?
                                        -0.5001401f :
                                         (data[38 /* glucose_15min */] <138.0f ?
                                            -0.5001271f :
                                             (Double.isNaN(data[28]) || data[28 /* steps_max_6h */] <4473.5f ?
                                                 (data[12 /* glucosevalue_mean_2h */] <152.264f ?
```

```
                                                -0.500103f :
                                                 (data[14 /* glucosevalue_cv_2h */] <7.655429f ?
                                                    -0.5000591f :
                                                    -0.5000391f)) :
                                              (Double.isNaN(data[37]) || data[37 /* glucose_at_bed */] <200.5f ?
                                                 -0.50003123f :
                                                 -0.50004405f))))))) :
                           (data[38 /* glucose_15min */] <264.5f ?
                              0.3930645f :
                               (data[24 /* activity_max_2h */] <21.914f ?
                                  0.175668f :
                                  -0.50013113f)))) :
                  0.4296529f)));
    return pred;
  } // constant pool size = 90B, number of visited nodes = 22, static init size = 0B
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_21 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_21_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_21_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[37 /* glucose_at_bed */] <65.5f ?
        0.3179808f :
         (data[38 /* glucose_15min */] <77.5f ?
             (Double.isNaN(data[16]) || data[16 /* glucosevalue_hypoduration_2h */] <22.03125f ?
                -0.5002594f :
                0.070987366f) :
             (data[37 /* glucose_at_bed */] <100.5f ?
                 (Double.isNaN(data[33]) || data[33 /* lastbolus */] <1.2357422f ?
                    0.5002034f :
                     (data[27 /* steps_max_2h */] <821.0f ?
                        -0.2828984f :
                        0.3505293f)) :
                 (data[26 /* activity_max_12h */] <17.184687f ?
                    -0.5002606f :
                     (data[33 /* lastbolus */] <1.1382812f ?
                         (data[14 /* glucosevalue_cv_2h */] <12.677206f ?
                             (Double.isNaN(data[10]) || data[10 /* glucosevalue_hypoduration_24h */] <4.723183f ?
                                0.50021267f :
                                0.13083415f) :
                             (data[0 /* glucosevalue_mean_12h */] <157.60103f ?
                                -0.5000916f :
                                -0.5000468f)) :
                         (Double.isNaN(data[31 /* meal_type */]) || !GenModel.bitSetIsInRange(32, 0, data[31])
                         || (GenModel.bitSetIsInRange(32, 0, data[31]) && !GenModel.bitSetContains(GRPSPLIT0, 32, 0, data[31])) ?
                             (data[0 /* glucosevalue_mean_12h */] <141.98103f ?
                                 (data[33 /* lastbolus */] <3.84875f ?
                                    -0.5001486f :
                                    -0.5000468f) :
                                 (data[29 /* steps_max_12h */] <5485.5f ?
                                    0.3435047f :
                                     (Double.isNaN(data[9]) || data[9 /* glucosevalue_euglycemia_24h */] <48.615917f ?
                                         (data[6 /* glucosevalue_mean_24h */] <190.8166f ?
                                            0.29052603f :
                                             (!Double.isNaN(data[31 /* meal_type */]) && (GenModel.bitSetIsInRange(32, 0, data[31])
                                             && !GenModel.bitSetContains(GRPSPLIT1, 32, 0, data[31])) ?
                                                -0.5000565f :
                                                 (data[32 /* durationtime */] <-48.179165f ?
                                                     (data[0 /* glucosevalue_mean_12h */] <211.38448f ?
                                                        -0.50002396f :
                                                        -0.5000181f) :
                                                    -0.50003797f))) :
                                         (Double.isNaN(data[2]) || data[2 /* glucosevalue_cv_12h */] <37.82503f ?
                                             (data[27 /* steps_max_2h */] <818.0f ?
                                                -0.032995407f :
                                                 (Double.isNaN(data[0]) || data[0 /* glucosevalue_mean_12h */] <159.80276f ?
                                                    -0.500087f :
                                                    -0.50004333f)) :
                                            -0.50012815f)))) :
                            0.4018596f))))));
    return pred;
  } // constant pool size = 104B, number of visited nodes = 23, static init size = 60B
  // {00100000 00000000 00000000 00000000}
  public static final byte[] GRPSPLIT0 = new byte[] {4, 0, 0, 0};
```

```
  // {00011000 00000000 00000000 00000000}
  public static final byte[] GRPSPLIT1 = new byte[] {24, 0, 0, 0};
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_22 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_22_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_22_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[0 /* glucosevalue_mean_12h */] <113.74505f ?
         (data[29 /* steps_max_12h */] <6516.5f ?
             (Double.isNaN(data[39]) || data[39 /* slope_at_bed */] <-0.103125f ?
                0.17343776f :
                -0.5002079f) :
             (data[34 /* durationtime_bolus */] <-127.59261f ?
                0.5001443f :
                 (data[32 /* durationtime */] <-71.3776f ?
                    0.5000714f :
                    0.5001156f))) :
         (data[38 /* glucose_15min */] <77.5f ?
            -0.33240512f :
             (data[2 /* glucosevalue_cv_12h */] <25.223671f ?
                 (data[7 /* glucosevalue_sd_24h */] <35.132504f ?
                    0.031106627f :
                     (data[1 /* glucosevalue_sd_12h */] <33.389736f ?
                        -0.50015426f :
                         (!Double.isNaN(data[31 /* meal_type */]) && (GenModel.bitSetIsInRange(32, 0, data[31])
                         && !GenModel.bitSetContains(GRPSPLIT0, 32, 0, data[31])) ?
                            -0.5001058f :
                            -0.5000321f))) :
                 (data[37 /* glucose_at_bed */] <106.0f ?
                     (Double.isNaN(data[3]) || data[3 /* glucosevalue_euglycemia_12h */] <74.07327f ?
                        0.5001747f :
                        0.08432197f) :
                     (Double.isNaN(data[27]) || data[27 /* steps_max_2h */] <1193.5f ?
                         (Double.isNaN(data[38]) || data[38 /* glucose_15min */] <229.5f ?
                             (Double.isNaN(data[10]) || data[10 /* glucosevalue_hypoduration_24h */] <9.33391f ?
                                 (data[10 /* glucosevalue_hypoduration_24h */] <0.4666955f ?
                                    0.24483794f :
                                     (data[6 /* glucosevalue_mean_24h */] <171.66904f ?
                                         (data[35 /* iobBed */] <9.812287f ?
                                            -0.50005543f :
                                            -0.50002974f) :
                                         (data[28 /* steps_max_6h */] <3003.5f ?
                                            -0.50002223f :
                                            -0.5000151f))) :
                                    0.3214088f) :
                                 (data[30 /* meal_g */] <34.5f ?
                                    0.47647592f :
                                    0.09825668f)) :
                             (Double.isNaN(data[33]) || data[33 /* lastbolus */] <2.9171875f ?
                                 (Double.isNaN(data[10]) || data[10 /* glucosevalue_hypoduration_24h */] <5.813149f ?
                                     (Double.isNaN(data[33]) || data[33 /* lastbolus */] <2.35f ?
                                         (Double.isNaN(data[32]) || data[32 /* durationtime */] <-103.73333f ?
                                            -0.50003016f :
                                            -0.50001186f) :
                                        0.050189827f) :
                                    -0.500086f) :
                                -0.5000832f))))));
    return pred;
  } // constant pool size = 103B, number of visited nodes = 24, static init size = 30B
  // {10011000 00000000 00000000 00000000}
  public static final byte[] GRPSPLIT0 = new byte[] {25, 0, 0, 0};
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_23 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_23_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_23_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[37 /* glucose_at_bed */] <65.5f ?
        0.2432203f :
```

```
        (data[30 /* meal_g */] <16.5f ?
            (data[13 /* glucosevalue_sd_2h */] <5.0741577f ?
                (data[34 /* durationtime_bolus */] <-35.55078f ?
                   0.16064617f :
                   -0.32155356f) :
                (Double.isNaN(data[13]) || data[13 /* glucosevalue_sd_2h */] <24.583225f ?
                    (Double.isNaN(data[36]) || data[36 /* overnightiir */] <0.9640625f ?
                        (Double.isNaN(data[6]) || data[6 /* glucosevalue_mean_24h */] <131.44928f ?
                            (data[35 /* iobBed */] <2.6521332f ?
                               0.50004965f :
                               0.5000755f) :
                           0.5001127f) :
                       0.15648788f) :
                    (data[11 /* glucosevalue_hyperduration_24h */] <48.4375f ?
                       -0.5000441f :
                       -0.5000091f))) :
            (data[38 /* glucose_15min */] <95.5f ?
                (Double.isNaN(data[29]) || data[29 /* steps_max_12h */] <10553.5f ?
                   -0.15019262f :
                   -0.50015f) :
                (data[37 /* glucose_at_bed */] <105.5f ?
                   0.4444485f :
                    (Double.isNaN(data[37]) || data[37 /* glucose_at_bed */] <218.5f ?
                        (data[29 /* steps_max_12h */] <6993.5f ?
                            (data[19 /* glucosevalue_sd_6h */] <30.105078f ?
                               -0.5001452f :
                                (data[4 /* glucosevalue_hypoduration_12h */] <1.1034483f ?
                                   -0.5000484f :
                                   -0.500025f)) :
                            (data[18 /* glucosevalue_mean_6h */] <120.11233f ?
                               0.38388357f :
                                (Double.isNaN(data[25]) || data[25 /* activity_max_6h */] <39.0975f ?
                                    (Double.isNaN(data[25]) || data[25 /* activity_max_6h */] <34.74277f ?
                                        (data[30 /* meal_g */] <37.0f ?
                                           -0.5000331f :
                                            (data[3 /* glucosevalue_euglycemia_12h */] <48.689655f ?
                                               -0.5000083f :
                                               -0.5000178f)) :
                                       0.0844022f) :
                                    (data[27 /* steps_max_2h */] <1771.5f ?
                                       -0.5000997f :
                                       -0.5000238f)))) :
                        (data[36 /* overnightiir */] <0.984375f ?
                            (data[37 /* glucose_at_bed */] <249.0f ?
                               0.50012f :
                               0.19148846f) :
                            (data[11 /* glucosevalue_hyperduration_24h */] <49.13495f ?
                               -0.50004834f :
                               -0.50002027f)))))));
    return pred;
  } // constant pool size = 102B, number of visited nodes = 25, static init size = 0B
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_24 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_24_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_24_class_0 {
  static final double score0(double[] data) {
    double pred =      (Double.isNaN(data[23]) || data[23 /* glucosevalue_hyperduration_6h */] <89.01367f ?
          (data[37 /* glucose_at_bed */] <66.0f ?
             0.500175f :
              (data[18 /* glucosevalue_mean_6h */] <80.22916f ?
                 0.3179499f :
                  (data[38 /* glucose_15min */] <79.5f ?
                      (data[24 /* activity_max_2h */] <18.354765f ?
                         -0.500096f :
                         0.059064325f) :
                      (Double.isNaN(data[10]) || data[10 /* glucosevalue_hypoduration_24h */] <4.642857f ?
                          (data[30 /* meal_g */] <16.5f ?
                              (data[30 /* meal_g */] <9.0f ?
                                 (data[25 /* activity_max_6h */] <28.044584f ?
                                    0.28559756f :
                                    -0.5000762f) :
                                 (data[7 /* glucosevalue_sd_24h */] <47.75769f ?
                                    0.50006527f :
```

```
                                    0.068949f)) :
                                (data[23 /* glucosevalue_hyperduration_6h */] <8.630137f ?
                                    (data[38 /* glucose_15min */] <112.5f ?
                                       -0.5000742f :
                                       -0.50002897f) :
                                    (data[23 /* glucosevalue_hyperduration_6h */] <16.39726f ?
                                       0.20948823f :
                                        (data[8 /* glucosevalue_cv_24h */] <22.904896f ?
                                           -0.5000616f :
                                            (Double.isNaN(data[35]) || data[35 /* iobBed */] <8.755725f ?
                                                (data[5 /* glucosevalue_hyperduration_12h */] <36.172413f ?
                                                    (Double.isNaN(data[32]) || data[32 /* durationtime */] <-112.05f ?
                                                       -0.5000286f :
                                                       -0.50001544f) :
                                                    (data[33 /* lastbolus */] <1.775f ?
                                                       -0.50000596f :
                                                        (Double.isNaN(data[30]) || data[30 /* meal_g */] <36.0f ?
                                                           -0.50001687f :
                                                           -0.50001097f))) :
                                                0.13385212f))))) :
                            (data[37 /* glucose_at_bed */] <100.5f ?
                                (data[35 /* iobBed */] <4.819405f ?
                                   0.5000327f :
                                   0.5000886f) :
                                (Double.isNaN(data[37]) || data[37 /* glucose_at_bed */] <221.5f ?
                                    (Double.isNaN(data[14]) || data[14 /* glucosevalue_cv_2h */] <18.026133f ?
                                        (data[6 /* glucosevalue_mean_24h */] <123.39377f ?
                                           0.50004196f :
                                           -0.500026f) :
                                       -0.50008214f) :
                                   0.41154367f))))) :
        -0.5001979f);
    return pred;
  } // constant pool size = 98B, number of visited nodes = 24, static init size = 0B
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_25 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_25_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_25_class_0 {
  static final double score0(double[] data) {
    double pred =      (Double.isNaN(data[5]) || data[5 /* glucosevalue_hyperduration_12h */] <42.72461f ?
         (data[37 /* glucose_at_bed */] <66.0f ?
            0.50010616f :
             (Double.isNaN(data[8]) || data[8 /* glucosevalue_cv_24h */] <46.909264f ?
                 (data[2 /* glucosevalue_cv_12h */] <18.533737f ?
                     (Double.isNaN(data[32]) || data[32 /* durationtime */] <-79.3625f ?
                        0.02855975f :
                        0.50007975f) :
                     (data[38 /* glucose_15min */] <80.5f ?
                        -0.5000735f :
                         (Double.isNaN(data[31 /* meal_type */]) || !GenModel.bitSetIsInRange(32, 0, data[31])
                         || (GenModel.bitSetIsInRange(32, 0, data[31]) && !GenModel.bitSetContains(GRPSPLIT0, 32, 0, data[31])) ?
                             (data[33 /* lastbolus */] <1.65f ?
                                 (Double.isNaN(data[14]) || data[14 /* glucosevalue_cv_2h */] <12.365022f ?
                                     (data[15 /* glucosevalue_euglycemia_2h */] <87.5f ?
                                        0.18046528f :
                                        0.5000456f) :
                                     (Double.isNaN(data[32]) || data[32 /* durationtime */] <-216.635f ?
                                        -0.5000352f :
                                        0.30616432f)) :
                                 (Double.isNaN(data[14]) || data[14 /* glucosevalue_cv_2h */] <29.61562f ?
                                     (data[27 /* steps_max_2h */] <598.5f ?
                                         (data[20 /* glucosevalue_cv_6h */] <28.052368f ?
                                            0.38048625f :
                                            -0.50001734f) :
                                         (data[38 /* glucose_15min */] <139.5f ?
                                            -0.50005615f :
                                             (data[19 /* glucosevalue_sd_6h */] <31.470278f ?
                                                 (data[27 /* steps_max_2h */] <1017.5f ?
                                                    -0.50003076f :
                                                    -0.5000161f) :
                                                 (data[26 /* activity_max_12h */] <28.003f ?
                                                    -0.5000141f :
                                                    -0.22711767f)))) :
```

```
                                    0.423052f)) :
                            0.4607132f))) :
                0.50005704f)) :
        (Double.isNaN(data[30]) || data[30 /* meal_g */] <52.5f ?
            (data[1 /* glucosevalue_sd_12h */] <41.049263f ?
               -0.5000401f :
                (data[19 /* glucosevalue_sd_6h */] <34.545635f ?
                   0.3819203f :
                    (data[11 /* glucosevalue_hyperduration_24h */] <46.172146f ?
                       -0.5000319f :
                        (Double.isNaN(data[6]) || data[6 /* glucosevalue_mean_24h */] <226.8942f ?
                            (Double.isNaN(data[7]) || data[7 /* glucosevalue_sd_24h */] <77.11449f ?
                                (data[30 /* meal_g */] <28.0f ?
                                   -0.5000103f :
                                   -0.5000055f) :
                               -0.5000029f) :
                           -0.50001603f)))) :
           -0.50011057f));
    return pred;
  } // constant pool size = 107B, number of visited nodes = 25, static init size = 30B
  // {00100000 00000000 00000000 00000000}
  public static final byte[] GRPSPLIT0 = new byte[] {4, 0, 0, 0};
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_26 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_26_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_26_class_0 {
  static final double score0(double[] data) {
    double pred =      (Double.isNaN(data[16]) || data[16 /* glucosevalue_hypoduration_2h */] <17.96875f ?
        (data[38 /* glucose_15min */] <77.5f ?
           -0.5000667f :
            (data[37 /* glucose_at_bed */] <100.5f ?
                (Double.isNaN(data[33]) || data[33 /* lastbolus */] <1.9382813f ?
                   0.50005573f :
                   -6.479969E-4f) :
                (data[20 /* glucosevalue_cv_6h */] <12.123333f ?
                   -0.5000445f :
                    (Double.isNaN(data[14]) || data[14 /* glucosevalue_cv_2h */] <13.585295f ?
                        (data[30 /* meal_g */] <39.5f ?
                            (data[33 /* lastbolus */] <1.13f ?
                                (Double.isNaN(data[10]) || data[10 /* glucosevalue_hypoduration_24h */] <4.048443f ?
                                   0.5000322f :
                                   0.27799582f) :
                                (Double.isNaN(data[37]) || data[37 /* glucose_at_bed */] <211.5f ?
                                    (!Double.isNaN(data[31 /* meal_type */]) && (GenModel.bitSetIsInRange(32, 0, data[31])
                                     && !GenModel.bitSetContains(GRPSPLIT0, 32, 0, data[31])) ?
                                       -0.5000201f :
                                       -0.1762604f) :
                                   0.34096798f)) :
                            (data[29 /* steps_max_12h */] <7532.5f ?
                               -0.50002176f :
                                (Double.isNaN(data[35]) || data[35 /* iobBed */] <5.2883754f ?
                                   -0.5000027f :
                                   -0.50000805f))) :
                        (Double.isNaN(data[9]) || data[9 /* glucosevalue_euglycemia_24h */] <67.701126f ?
                            (data[13 /* glucosevalue_sd_2h */] <24.281105f ?
                               0.21486251f :
                                (data[10 /* glucosevalue_hypoduration_24h */] <2.283737f ?
                                   -0.5000115f :
                                    (data[3 /* glucosevalue_euglycemia_12h */] <35.724136f ?
                                       -0.50000393f :
                                       -0.5000073f))) :
                            (Double.isNaN(data[8]) || data[8 /* glucosevalue_cv_24h */] <36.97244f ?
                                (data[14 /* glucosevalue_cv_2h */] <16.811161f ?
                                   -0.5000168f :
                                    (Double.isNaN(data[30]) || data[30 /* meal_g */] <22.5f ?
                                       -0.50001293f :
                                       -0.0687599f)) :
                               -0.5000326f))))) :
        (Double.isNaN(data[3]) || data[3 /* glucosevalue_euglycemia_12h */] <84.08203f ?
            (data[35 /* iobBed */] <7.3915796f ?
                (data[39 /* slope_at_bed */] <-0.098958336f ?
                   0.5000243f :
                   0.50006056f) :
```

```
              -0.15781838f) :
           -0.1406575f));
    return pred;
  } // constant pool size = 99B, number of visited nodes = 23, static init size = 30B
  // {00111000 00000000 00000000 00000000}
  public static final byte[] GRPSPLIT0 = new byte[] {28, 0, 0, 0};
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_27 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_27_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_27_class_0 {
  static final double score0(double[] data) {
    double pred =      (Double.isNaN(data[16]) || data[16 /* glucosevalue_hypoduration_2h */] <17.96875f ?
         (data[38 /* glucose_15min */] <77.5f ?
            -0.5000404f :
            (data[37 /* glucose_at_bed */] <76.5f ?
               0.39260137f :
               (data[13 /* glucosevalue_sd_2h */] <5.062178f ?
                  -0.50003016f :
                  (Double.isNaN(data[10]) || data[10 /* glucosevalue_hypoduration_24h */] <4.8659167f ?
                      (Double.isNaN(data[4]) || data[4 /* glucosevalue_hypoduration_12h */] <1.875f ?
                          (data[30 /* meal_g */] <19.5f ?
                              (Double.isNaN(data[19]) || data[19 /* glucosevalue_sd_6h */] <38.23486f ?
                                 0.46223572f :
                                 -0.5000058f) :
                              (Double.isNaN(data[24]) || data[24 /* activity_max_2h */] <29.306f ?
                                  (Double.isNaN(data[29]) || data[29 /* steps_max_12h */] <11285.5f ?
                                      (data[7 /* glucosevalue_sd_24h */] <42.50865f ?
                                         -0.5000183f :
                                          (Double.isNaN(data[28]) || data[28 /* steps_max_6h */] <3567.5f ?
                                             -0.50000834f :
                                             -0.50000376f)) :
                                         0.042911448f) :
                                      (!Double.isNaN(data[31 /* meal_type */]) && (GenModel.bitSetIsInRange(32, 0, data[31])
                                      && !GenModel.bitSetContains(GRPSPLIT0, 32, 0, data[31])) ?
                                         -0.5000051f :
                                         0.4041722f))) :
                          (data[37 /* glucose_at_bed */] <110.5f ?
                             -0.5000286f :
                              (Double.isNaN(data[6]) || data[6 /* glucosevalue_mean_24h */] <176.51765f ?
                                  (Double.isNaN(data[6]) || data[6 /* glucosevalue_mean_24h */] <145.56793f ?
                                     -0.5000068f :
                                     -0.5000125f) :
                                  (data[30 /* meal_g */] <36.0f ?
                                     -0.5000041f :
                                     -0.5000019f)))) :
                      (Double.isNaN(data[4]) || data[4 /* glucosevalue_hypoduration_12h */] <9.6875f ?
                          (data[22 /* glucosevalue_hypoduration_6h */] <2.7739725f ?
                             0.28707802f :
                             0.46854356f) :
                          (data[27 /* steps_max_2h */] <699.0f ?
                             0.22613588f :
                             -0.5000191f))))) :
         (Double.isNaN(data[9]) || data[9 /* glucosevalue_euglycemia_24h */] <81.93359f ?
             (Double.isNaN(data[6]) || data[6 /* glucosevalue_mean_24h */] <162.19724f ?
                 (data[34 /* durationtime_bolus */] <-139.56302f ?
                    0.50003767f :
                    0.5000151f) :
                -0.17547119f) :
            -0.18121824f));
    return pred;
  } // constant pool size = 99B, number of visited nodes = 23, static init size = 30B
  // {11110000 00000000 00000000 00000000}
  public static final byte[] GRPSPLIT0 = new byte[] {15, 0, 0, 0};
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_28 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_28_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_28_class_0 {
  static final double score0(double[] data) {
```

```
    double pred =      (Double.isNaN(data[5]) || data[5 /* glucosevalue_hyperduration_12h */] <42.72461f ?
         (data[37 /* glucose_at_bed */] <66.0f ?
            0.500024f :
             (data[3 /* glucosevalue_euglycemia_12h */] <53.515625f ?
                0.4713258f :
                 (Double.isNaN(data[8]) || data[8 /* glucosevalue_cv_24h */] <46.909264f ?
                     (data[2 /* glucosevalue_cv_12h */] <18.533737f ?
                         (Double.isNaN(data[8]) || data[8 /* glucosevalue_cv_24h */] <16.984798f ?
                            -0.04051298f :
                            0.5000211f) :
                         (data[38 /* glucose_15min */] <83.5f ?
                            -0.5000235f :
                             (data[37 /* glucose_at_bed */] <108.5f ?
                                 (data[8 /* glucosevalue_cv_24h */] <26.75983f ?
                                    -0.22898614f :
                                    0.50001806f) :
                                 (Double.isNaN(data[9]) || data[9 /* glucosevalue_euglycemia_24h */] <81.55709f ?
                                     (data[35 /* iobBed */] <3.8463848f ?
                                         (data[22 /* glucosevalue_hypoduration_6h */] <3.4246576f ?
                                            0.40595567f :
                                            -0.33621907f) :
                                         (data[20 /* glucosevalue_cv_6h */] <22.740105f ?
                                             (data[28 /* steps_max_6h */] <3429.5f ?
                                                -0.50001585f :
                                                -0.50000596f) :
                                             (data[9 /* glucosevalue_euglycemia_24h */] <58.78893f ?
                                                -0.18944043f :
                                                 (Double.isNaN(data[19]) || data[19 /* glucosevalue_sd_6h */] <46.786995f ?
                                                    -0.5000065f :
                                                    -0.5000032f)))) :
                                     (Double.isNaN(data[31 /* meal_type */]) || !GenModel.bitSetIsInRange(32, 0, data[31])
                                     || (GenModel.bitSetIsInRange(32, 0, data[31]) && !GenModel.bitSetContains(GRPSPLIT0, 32, 0, data[31])) ?
                                        -0.2593573f :
                                        0.5000149f))))) :
                     0.5000139f))) :
         (data[37 /* glucose_at_bed */] <110.0f ?
            -0.5000293f :
             (data[1 /* glucosevalue_sd_12h */] <41.049263f ?
                -0.5000102f :
                 (data[7 /* glucosevalue_sd_24h */] <53.25983f ?
                    0.27649784f :
                     (data[11 /* glucosevalue_hyperduration_24h */] <48.194202f ?
                        -0.50000805f :
                         (data[1 /* glucosevalue_sd_12h */] <59.831177f ?
                            -0.5000052f :
                             (data[20 /* glucosevalue_cv_6h */] <25.93867f ?
                                -0.5000026f :
                                 (data[1 /* glucosevalue_sd_12h */] <78.011375f ?
                                    -0.5000014f :
                                    -0.50000066f))))))));
    return pred;
  } // constant pool size = 103B, number of visited nodes = 24, static init size = 30B
  // {10111000 00000000 00000000 00000000}
  public static final byte[] GRPSPLIT0 = new byte[] {29, 0, 0, 0};
}


class GBM_grid_0_AutoML_20180903_125524_model_6_Forest_29 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += GBM_grid_0_AutoML_20180903_125524_model_6_Tree_29_class_0.score0(fdata);
  }
}
class GBM_grid_0_AutoML_20180903_125524_model_6_Tree_29_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[26 /* activity_max_12h */] <15.480027f ?
        0.35618952f :
         (data[20 /* glucosevalue_cv_6h */] <11.512289f ?
             (Double.isNaN(data[20]) || data[20 /* glucosevalue_cv_6h */] <8.909869f ?
                -0.091129825f :
                -0.5000198f) :
             (data[19 /* glucosevalue_sd_6h */] <17.288477f ?
                0.5000112f :
                 (data[18 /* glucosevalue_mean_6h */] <98.16781f ?
                    -0.37089744f :
                     (data[18 /* glucosevalue_mean_6h */] <105.80982f ?
                        0.49520588f :
                         (data[6 /* glucosevalue_mean_24h */] <116.73014f ?
                            0.5000081f :
```

```java
                                (Double.isNaN(data[32]) || data[32 /* durationtime */] <-239.0f ?
                                    (data[37 /* glucose_at_bed */] <100.5f ?
                                       -0.5000147f :
                                        (data[23 /* glucosevalue_hyperduration_6h */] <34.52055f ?
                                            (data[2 /* glucosevalue_cv_12h */] <25.575167f ?
                                               -0.5000085f :
                                                (Double.isNaN(data[13]) || data[13 /* glucosevalue_sd_2h */] <40.07081f ?
                                                    (data[26 /* activity_max_12h */] <29.69875f ?
                                                       -0.50000286f :
                                                       -0.50000143f) :
                                                   -0.50000477f)) :
                                            (data[19 /* glucosevalue_sd_6h */] <42.939747f ?
                                               0.24208917f :
                                                (data[6 /* glucosevalue_mean_24h */] <195.96211f ?
                                                   -0.5000043f :
                                                   -0.5000019f)))) :
                                    (Double.isNaN(data[32]) || data[32 /* durationtime */] <-39.545f ?
                                        (data[37 /* glucose_at_bed */] <100.5f ?
                                           0.35308588f :
                                            (data[30 /* meal_g */] <33.5f ?
                                                (data[39 /* slope_at_bed */] <-0.64666665f ?
                                                   -0.5000059f :
                                                    (data[13 /* glucosevalue_sd_2h */] <26.948784f ?
                                                       0.45413077f :
                                                       -0.106991306f)) :
                                                (Double.isNaN(data[23]) || data[23 /* glucosevalue_hyperduration_6h */] <62.671234f ?
                                                    (Double.isNaN(data[22]) || data[22 /* glucosevalue_hypoduration_6h */] <2.7739725f ?
                                                        (data[37 /* glucose_at_bed */] <147.5f ?
                                                           -0.50000215f :
                                                           -0.5000029f) :
                                                       -0.5000052f) :
                                                   0.14990143f))) :
                                       -0.5000073f)))))))));
    return pred;
  } // constant pool size = 94B, number of visited nodes = 23, static init size = 0B
}
```

7.6.2 Random Forest Model

```
import java.util.Map;
import hex.genmodel.GenModel;
import hex.genmodel.annotations.ModelPojo;

@ModelPojo(name="rf_covType2", algorithm="drf")
public class rf_covType2 extends GenModel {
  public hex.ModelCategory getModelCategory() { return hex.ModelCategory.Binomial; }

  public boolean isSupervised() { return true; }
  public int nfeatures() { return 27; }
  public int nclasses() { return 2; }

  // Names of columns used by model.
  public static final String[] NAMES = NamesHolder_rf_covType2.VALUES;
  // Number of output classes included in training data response column.
  public static final int NCLASSES = 2;

  // Column domains. The last array contains domain of response column.
  public static final String[][] DOMAINS = new String[][] {
    /* glucosevalue_mean_12h */ null,
    /* glucosevalue_sd_12h */ null,
    /* glucosevalue_cv_12h */ null,
    /* glucosevalue_euglycemia_12h */ null,
    /* glucosevalue_hypoduration_12h */ null,
    /* glucosevalue_hyperduration_12h */ null,
    /* glucosevalue_mean_24h */ null,
    /* glucosevalue_sd_24h */ null,
    /* glucosevalue_cv_24h */ null,
    /* glucosevalue_euglycemia_24h */ null,
    /* glucosevalue_hypoduration_24h */ null,
    /* glucosevalue_hyperduration_24h */ null,
    /* glucosevalue_mean_2h */ null,
    /* glucosevalue_sd_2h */ null,
    /* glucosevalue_cv_2h */ null,
    /* glucosevalue_euglycemia_2h */ null,
    /* glucosevalue_hypoduration_2h */ null,
    /* glucosevalue_hyperduration_2h */ null,
    /* glucosevalue_mean_6h */ null,
    /* glucosevalue_sd_6h */ null,
    /* glucosevalue_cv_6h */ null,
    /* glucosevalue_euglycemia_6h */ null,
    /* glucosevalue_hypoduration_6h */ null,
    /* glucosevalue_hyperduration_6h */ null,
    /* glucose_at_bed */ null,
    /* glucose_15min */ null,
    /* slope_at_bed */ null,
    /* hypoglycemiayn */ rf_covType2_ColInfo_27.VALUES
  };
  // Prior class distribution
  public static final double[] PRIOR_CLASS_DISTRIB = {0.6987179487179487,0.30128205128205127};
  // Class distribution used for model building
  public static final double[] MODEL_CLASS_DISTRIB = {0.6987179487179487,0.30128205128205127};

  public rf_covType2() { super(NAMES,DOMAINS,"hypoglycemiayn"); }
  public String getUUID() { return Long.toString(8136500264882979517L); }

  // Pass in data in a double[], pre-aligned to the Model's requirements.
  // Jam predictions into the preds[] array; preds[0] is reserved for the
  // main prediction (class for classifiers or value for regression),
  // and remaining columns hold a probability distribution for classifiers.
  public final double[] score0( double[] data, double[] preds ) {
    java.util.Arrays.fill(preds,0);
    rf_covType2_Forest_0.score0(data,preds);
    rf_covType2_Forest_1.score0(data,preds);
    rf_covType2_Forest_2.score0(data,preds);
    rf_covType2_Forest_3.score0(data,preds);
    rf_covType2_Forest_4.score0(data,preds);
    rf_covType2_Forest_5.score0(data,preds);
    rf_covType2_Forest_6.score0(data,preds);
    rf_covType2_Forest_7.score0(data,preds);
    rf_covType2_Forest_8.score0(data,preds);
```

```
    preds[1] /= 9;
    preds[2] = 1.0 - preds[1];
    preds[0] = hex.genmodel.GenModel.getPrediction(preds, PRIOR_CLASS_DISTRIB, data, 0.4444444444444444);
    return preds;
  }
}
// The class representing training column names
class NamesHolder_rf_covType2 implements java.io.Serializable {
  public static final String[] VALUES = new String[27];
  static {
    NamesHolder_rf_covType2_0.fill(VALUES);
  }
  static final class NamesHolder_rf_covType2_0 implements java.io.Serializable {
    static final void fill(String[] sa) {
      sa[0] = "glucosevalue_mean_12h";
      sa[1] = "glucosevalue_sd_12h";
      sa[2] = "glucosevalue_cv_12h";
      sa[3] = "glucosevalue_euglycemia_12h";
      sa[4] = "glucosevalue_hypoduration_12h";
      sa[5] = "glucosevalue_hyperduration_12h";
      sa[6] = "glucosevalue_mean_24h";
      sa[7] = "glucosevalue_sd_24h";
      sa[8] = "glucosevalue_cv_24h";
      sa[9] = "glucosevalue_euglycemia_24h";
      sa[10] = "glucosevalue_hypoduration_24h";
      sa[11] = "glucosevalue_hyperduration_24h";
      sa[12] = "glucosevalue_mean_2h";
      sa[13] = "glucosevalue_sd_2h";
      sa[14] = "glucosevalue_cv_2h";
      sa[15] = "glucosevalue_euglycemia_2h";
      sa[16] = "glucosevalue_hypoduration_2h";
      sa[17] = "glucosevalue_hyperduration_2h";
      sa[18] = "glucosevalue_mean_6h";
      sa[19] = "glucosevalue_sd_6h";
      sa[20] = "glucosevalue_cv_6h";
      sa[21] = "glucosevalue_euglycemia_6h";
      sa[22] = "glucosevalue_hypoduration_6h";
      sa[23] = "glucosevalue_hyperduration_6h";
      sa[24] = "glucose_at_bed";
      sa[25] = "glucose_15min";
      sa[26] = "slope_at_bed";
    }
  }
}
// The class representing column hypoglycemiayn
class rf_covType2_ColInfo_27 implements java.io.Serializable {
  public static final String[] VALUES = new String[2];
  static {
    rf_covType2_ColInfo_27_0.fill(VALUES);
  }
  static final class rf_covType2_ColInfo_27_0 implements java.io.Serializable {
    static final void fill(String[] sa) {
      sa[0] = "0";
      sa[1] = "1";
    }
  }
}

class rf_covType2_Forest_0 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += rf_covType2_Tree_0_class_0.score0(fdata);
  }
}
class rf_covType2_Tree_0_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[24 /* glucose_at_bed */] <102.0f ?
         (data[5 /* glucosevalue_hyperduration_12h */] <4.1015625f ?
             (data[13 /* glucosevalue_sd_2h */] <4.7859807f ?
                 (data[26 /* slope_at_bed */] <-0.025520833f ?
                    0.0f :
                     (data[1 /* glucosevalue_sd_12h */] <11.957706f ?
                        0.0f :
                        1.0f)) :
                0.0f) :
             (data[25 /* glucose_15min */] <71.5f ?
                1.0f :
                 (data[9 /* glucosevalue_euglycemia_24h */] <37.890625f ?
                    1.0f :
```

```
                    (Double.isNaN(data[3]) || data[3 /* glucosevalue_euglycemia_12h */] <76.98276f ?
                       0.0f :
                        (data[3 /* glucosevalue_euglycemia_12h */] <80.280174f ?
                           1.0f :
                           0.0f))))) :
        (Double.isNaN(data[14]) || data[14 /* glucosevalue_cv_2h */] <47.93317f ?
            (data[6 /* glucosevalue_mean_24h */] <135.54955f ?
                (data[19 /* glucosevalue_sd_6h */] <24.293444f ?
                    (Double.isNaN(data[3]) || data[3 /* glucosevalue_euglycemia_12h */] <99.11099f ?
                       0.0f :
                       1.0f) :
                    (Double.isNaN(data[6]) || data[6 /* glucosevalue_mean_24h */] <131.1784f ?
                       1.0f :
                       0.0f)) :
                (Double.isNaN(data[10]) || data[10 /* glucosevalue_hypoduration_24h */] <7.686797f ?
                    (data[0 /* glucosevalue_mean_12h */] <155.98965f ?
                       1.0f :
                        (data[11 /* glucosevalue_hyperduration_24h */] <17.1875f ?
                           0.0f :
                            (data[19 /* glucosevalue_sd_6h */] <34.925198f ?
                                (Double.isNaN(data[19]) || data[19 /* glucosevalue_sd_6h */] <27.913588f ?
                                   1.0f :
                                    (data[24 /* glucose_at_bed */] <245.0f ?
                                       0.0f :
                                       1.0f)) :
                                1.0f))) :
                    (data[5 /* glucosevalue_hyperduration_12h */] <43.782326f ?
                       0.0f :
                       1.0f))) :
            0.0f));
    return pred;
  } // constant pool size = 86B, number of visited nodes = 21, static init size = 0B
}


class rf_covType2_Forest_1 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += rf_covType2_Tree_1_class_0.score0(fdata);
  }
}
class rf_covType2_Tree_1_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[12 /* glucosevalue_mean_2h */] <109.666565f ?
         (data[0 /* glucosevalue_mean_12h */] <114.34782f ?
             (data[8 /* glucosevalue_cv_24h */] <16.680094f ?
                 (Double.isNaN(data[2]) || data[2 /* glucosevalue_cv_12h */] <17.869484f ?
                    0.0f :
                    1.0f) :
                0.0f) :
             (data[2 /* glucosevalue_cv_12h */] <28.38684f ?
                1.0f :
                 (data[15 /* glucosevalue_euglycemia_2h */] <64.0625f ?
                    1.0f :
                    0.0f))) :
         (data[0 /* glucosevalue_mean_12h */] <160.56003f ?
             (Double.isNaN(data[13]) || data[13 /* glucosevalue_sd_2h */] <58.536533f ?
                 (data[24 /* glucose_at_bed */] <100.5f ?
                     (data[26 /* slope_at_bed */] <-0.7375f ?
                        0.0f :
                         (Double.isNaN(data[5]) || data[5 /* glucosevalue_hyperduration_12h */] <23.706896f ?
                            1.0f :
                            0.0f)) :
                     (data[14 /* glucosevalue_cv_2h */] <13.611138f ?
                         (data[6 /* glucosevalue_mean_24h */] <114.24109f ?
                            0.0f :
                             (Double.isNaN(data[25]) || data[25 /* glucose_15min */] <225.5f ?
                                 (Double.isNaN(data[7]) || data[7 /* glucosevalue_sd_24h */] <40.5938f ?
                                     (Double.isNaN(data[1]) || data[1 /* glucosevalue_sd_12h */] <34.139248f ?
                                         (data[3 /* glucosevalue_euglycemia_12h */] <83.74138f ?
                                             (data[12 /* glucosevalue_mean_2h */] <130.364f ?
                                                0.0f :
                                                1.0f) :
                                            1.0f) :
                                        0.0f) :
                                    1.0f) :
                                0.0f)) :
                         1.0f)) :
                0.0f) :
```

```
            (Double.isNaN(data[21]) || data[21 /* glucosevalue_euglycemia_6h */] <89.0625f ?
                (data[19 /* glucosevalue_sd_6h */] <34.80089f ?
                    (Double.isNaN(data[7]) || data[7 /* glucosevalue_sd_24h */] <53.872135f ?
                        (Double.isNaN(data[1]) || data[1 /* glucosevalue_sd_12h */] <49.4957f ?
                           1.0f :
                           0.0f) :
                        1.0f) :
                    1.0f) :
                0.0f)));
    return pred;
  } // constant pool size = 90B, number of visited nodes = 22, static init size = 0B
}


class rf_covType2_Forest_2 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += rf_covType2_Tree_2_class_0.score0(fdata);
  }
}
class rf_covType2_Tree_2_class_0 {
  static final double score0(double[] data) {
    double pred =      (Double.isNaN(data[5]) || data[5 /* glucosevalue_hyperduration_12h */] <40.283203f ?
         (data[26 /* slope_at_bed */] <-1.267448f ?
            0.0f :
            (data[12 /* glucosevalue_mean_2h */] <87.388985f ?
                (Double.isNaN(data[22]) || data[22 /* glucosevalue_hypoduration_6h */] <33.518837f ?
                    (data[12 /* glucosevalue_mean_2h */] <75.69926f ?
                        (Double.isNaN(data[0]) || data[0 /* glucosevalue_mean_12h */] <111.936745f ?
                            (data[13 /* glucosevalue_sd_2h */] <2.9456162f ?
                               0.0f :
                               1.0f) :
                            0.0f) :
                        0.0f) :
                    (data[20 /* glucosevalue_cv_6h */] <8.843141f ?
                       0.0f :
                        (Double.isNaN(data[26]) || data[26 /* slope_at_bed */] <1.4385417f ?
                           1.0f :
                           0.0f))) :
                (Double.isNaN(data[13]) || data[13 /* glucosevalue_sd_2h */] <54.04567f ?
                    (Double.isNaN(data[10]) || data[10 /* glucosevalue_hypoduration_24h */] <4.5793686f ?
                        (data[8 /* glucosevalue_cv_24h */] <20.973873f ?
                            (data[25 /* glucose_15min */] <118.0f ?
                               1.0f :
                               0.0f) :
                            (Double.isNaN(data[21]) || data[21 /* glucosevalue_euglycemia_6h */] <86.84931f ?
                               1.0f :
                                (data[14 /* glucosevalue_cv_2h */] <8.825355f ?
                                    (Double.isNaN(data[7]) || data[7 /* glucosevalue_sd_24h */] <55.903435f ?
                                       0.0f :
                                       1.0f) :
                                    (Double.isNaN(data[11]) || data[11 /* glucosevalue_hyperduration_24h */] <51.45329f ?
                                       1.0f :
                                       0.0f)))) :
                        (Double.isNaN(data[24]) || data[24 /* glucose_at_bed */] <209.0f ?
                            (data[12 /* glucosevalue_mean_2h */] <108.538086f ?
                               0.0f :
                                (Double.isNaN(data[14]) || data[14 /* glucosevalue_cv_2h */] <21.191038f ?
                                   1.0f :
                                    (data[9 /* glucosevalue_euglycemia_24h */] <65.0f ?
                                       0.0f :
                                       1.0f))) :
                           0.0f)) :
                    0.0f))) :
         (data[0 /* glucosevalue_mean_12h */] <186.67998f ?
            (data[7 /* glucosevalue_sd_24h */] <39.223354f ?
                (data[24 /* glucose_at_bed */] <141.5f ?
                   1.0f :
                   0.0f) :
               1.0f) :
           1.0f));
    return pred;
  } // constant pool size = 98B, number of visited nodes = 24, static init size = 0B
}


class rf_covType2_Forest_3 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += rf_covType2_Tree_3_class_0.score0(fdata);
```

```
  }
}
class rf_covType2_Tree_3_class_0 {
  static final double score0(double[] data) {
    double pred =      (Double.isNaN(data[16]) || data[16 /* glucosevalue_hypoduration_2h */] <17.96875f ?
         (data[24 /* glucose_at_bed */] <146.0f ?
             (data[6 /* glucosevalue_mean_24h */] <112.54994f ?
                 (data[6 /* glucosevalue_mean_24h */] <77.45204f ?
                    1.0f :
                    0.0f) :
                 (data[1 /* glucosevalue_sd_12h */] <37.551792f ?
                    1.0f :
                     (data[23 /* glucosevalue_hyperduration_6h */] <12.5f ?
                         (Double.isNaN(data[3]) || data[3 /* glucosevalue_euglycemia_12h */] <81.25f ?
                             (data[9 /* glucosevalue_euglycemia_24h */] <56.47059f ?
                                0.0f :
                                1.0f) :
                            0.0f) :
                         (data[6 /* glucosevalue_mean_24h */] <136.88281f ?
                            0.0f :
                             (Double.isNaN(data[22]) || data[22 /* glucosevalue_hypoduration_6h */] <14.79452f ?
                                 (data[14 /* glucosevalue_cv_2h */] <5.295242f ?
                                     (data[12 /* glucosevalue_mean_2h */] <215.09f ?
                                        0.0f :
                                        1.0f) :
                                    1.0f) :
                                0.0f))))) :
             (data[19 /* glucosevalue_sd_6h */] <35.092766f ?
                 (Double.isNaN(data[19]) || data[19 /* glucosevalue_sd_6h */] <28.84006f ?
                    1.0f :
                     (data[26 /* slope_at_bed */] <-0.025520833f ?
                        0.0f :
                         (data[13 /* glucosevalue_sd_2h */] <23.16093f ?
                            0.0f :
                            1.0f))) :
                 (Double.isNaN(data[8]) || data[8 /* glucosevalue_cv_24h */] <56.8229f ?
                    1.0f :
                    0.0f))) :
        (Double.isNaN(data[11]) || data[11 /* glucosevalue_hyperduration_24h */] <44.140625f ?
             (data[16 /* glucosevalue_hypoduration_2h */] <25.9375f ?
                0.0f :
                 (data[22 /* glucosevalue_hypoduration_6h */] <11.943493f ?
                    1.0f :
                     (Double.isNaN(data[2]) || data[2 /* glucosevalue_cv_12h */] <35.804344f ?
                         (data[26 /* slope_at_bed */] <-0.0875f ?
                            0.0f :
                            1.0f) :
                        0.0f))) :
           1.0f));
    return pred;
  } // constant pool size = 90B, number of visited nodes = 22, static init size = 0B
}


class rf_covType2_Forest_4 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += rf_covType2_Tree_4_class_0.score0(fdata);
  }
}
class rf_covType2_Tree_4_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[19 /* glucosevalue_sd_6h */] <24.804222f ?
         (Double.isNaN(data[6]) || data[6 /* glucosevalue_mean_24h */] <163.11523f ?
             (Double.isNaN(data[26]) || data[26 /* slope_at_bed */] <-0.025520833f ?
                 (data[8 /* glucosevalue_cv_24h */] <14.156527f ?
                     (data[6 /* glucosevalue_mean_24h */] <96.86535f ?
                        0.0f :
                        1.0f) :
                    0.0f) :
                 (Double.isNaN(data[25]) || data[25 /* glucose_15min */] <114.5f ?
                     (Double.isNaN(data[0]) || data[0 /* glucosevalue_mean_12h */] <123.188416f ?
                        1.0f :
                        0.0f) :
                    0.0f)) :
            1.0f) :
         (Double.isNaN(data[16]) || data[16 /* glucosevalue_hypoduration_2h */] <2.0507812f ?
             (Double.isNaN(data[3]) || data[3 /* glucosevalue_euglycemia_12h */] <70.703125f ?
                 (Double.isNaN(data[14]) || data[14 /* glucosevalue_cv_2h */] <27.620132f ?
```

```
                    (data[20 /* glucosevalue_cv_6h */] <20.053566f ?
                        (Double.isNaN(data[23]) || data[23 /* glucosevalue_hyperduration_6h */] <82.8125f ?
                            (Double.isNaN(data[14]) || data[14 /* glucosevalue_cv_2h */] <15.198825f ?
                                (Double.isNaN(data[6]) || data[6 /* glucosevalue_mean_24h */] <172.05675f ?
                                    (data[12 /* glucosevalue_mean_2h */] <164.616f ?
                                       0.0f :
                                       1.0f) :
                                    0.0f) :
                                1.0f) :
                            1.0f) :
                        (data[3 /* glucosevalue_euglycemia_12h */] <52.784256f ?
                           1.0f :
                           0.0f)) :
                    (data[12 /* glucosevalue_mean_2h */] <147.05782f ?
                        (Double.isNaN(data[21]) || data[21 /* glucosevalue_euglycemia_6h */] <93.75f ?
                           1.0f :
                           (data[9 /* glucosevalue_euglycemia_24h */] <73.4375f ?
                              0.0f :
                              1.0f)) :
                        (Double.isNaN(data[5]) || data[5 /* glucosevalue_hyperduration_12h */] <20.3125f ?
                            (Double.isNaN(data[13]) || data[13 /* glucosevalue_sd_2h */] <33.13635f ?
                                (Double.isNaN(data[12]) || data[12 /* glucosevalue_mean_2h */] <158.88f ?
                                    (Double.isNaN(data[12]) || data[12 /* glucosevalue_mean_2h */] <154.005f ?
                                       0.5f :
                                       0.0f) :
                                    1.0f) :
                                0.0f) :
                           0.0f))) :
                (data[1 /* glucosevalue_sd_12h */] <42.24404f ?
                   1.0f :
                    (Double.isNaN(data[0]) || data[0 /* glucosevalue_mean_12h */] <171.40987f ?
                       0.0f :
                       1.0f))));
    return pred;
  } // constant pool size = 102B, number of visited nodes = 25, static init size = 0B
}


class rf_covType2_Forest_5 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += rf_covType2_Tree_5_class_0.score0(fdata);
  }
}
class rf_covType2_Tree_5_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[0 /* glucosevalue_mean_12h */] <113.74505f ?
         (data[18 /* glucosevalue_mean_6h */] <83.70256f ?
             (data[1 /* glucosevalue_sd_12h */] <16.223387f ?
                0.0f :
                (data[10 /* glucosevalue_hypoduration_24h */] <16.02779f ?
                   1.0f :
                    (data[13 /* glucosevalue_sd_2h */] <12.521653f ?
                       1.0f :
                       0.0f))) :
           0.0f) :
         (data[24 /* glucose_at_bed */] <109.0f ?
             (data[14 /* glucosevalue_cv_2h */] <17.463612f ?
                 (data[19 /* glucosevalue_sd_6h */] <23.105293f ?
                    0.0f :
                    1.0f) :
                 (data[1 /* glucosevalue_sd_12h */] <45.656586f ?
                     (Double.isNaN(data[1]) || data[1 /* glucosevalue_sd_12h */] <41.542072f ?
                        0.0f :
                        1.0f) :
                    0.0f)) :
             (data[12 /* glucosevalue_mean_2h */] <102.91578f ?
                 (Double.isNaN(data[6]) || data[6 /* glucosevalue_mean_24h */] <167.00487f ?
                    0.0f :
                    1.0f) :
                 (Double.isNaN(data[9]) || data[9 /* glucosevalue_euglycemia_24h */] <82.03125f ?
                     (Double.isNaN(data[5]) || data[5 /* glucosevalue_hyperduration_12h */] <64.0625f ?
                         (data[19 /* glucosevalue_sd_6h */] <34.30703f ?
                             (data[3 /* glucosevalue_euglycemia_12h */] <45.0f ?
                                0.0f :
                                 (Double.isNaN(data[3]) || data[3 /* glucosevalue_euglycemia_12h */] <67.32758f ?
                                     (data[11 /* glucosevalue_hyperduration_24h */] <25.916956f ?
                                        0.0f :
```

```
                                    1.0f) :
                                1.0f)) :
                            (Double.isNaN(data[14]) || data[14 /* glucosevalue_cv_2h */] <41.81591f ?
                               1.0f :
                                (data[14 /* glucosevalue_cv_2h */] <55.89962f ?
                                   0.0f :
                                   1.0f))) :
                        1.0f) :
                    (Double.isNaN(data[13]) || data[13 /* glucosevalue_sd_2h */] <15.17529f ?
                        (data[1 /* glucosevalue_sd_12h */] <35.305485f ?
                           1.0f :
                           0.0f) :
                        1.0f)))));
    return pred;
  } // constant pool size = 90B, number of visited nodes = 22, static init size = 0B
}


class rf_covType2_Forest_6 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += rf_covType2_Tree_6_class_0.score0(fdata);
  }
}
class rf_covType2_Tree_6_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[0 /* glucosevalue_mean_12h */] <113.74505f ?
         (data[14 /* glucosevalue_cv_2h */] <4.622035f ?
             (data[18 /* glucosevalue_mean_6h */] <64.87045f ?
                0.0f :
                1.0f) :
             (Double.isNaN(data[24]) || data[24 /* glucose_at_bed */] <295.5f ?
                 (Double.isNaN(data[25]) || data[25 /* glucose_15min */] <127.5f ?
                    0.0f :
                    (data[25 /* glucose_15min */] <134.5f ?
                       1.0f :
                       0.0f)) :
                1.0f)) :
         (data[25 /* glucose_15min */] <131.5f ?
             (Double.isNaN(data[3]) || data[3 /* glucosevalue_euglycemia_12h */] <84.765625f ?
                 (Double.isNaN(data[23]) || data[23 /* glucosevalue_hyperduration_6h */] <39.511986f ?
                     (Double.isNaN(data[26]) || data[26 /* slope_at_bed */] <0.10520833f ?
                         (data[20 /* glucosevalue_cv_6h */] <28.797375f ?
                             (Double.isNaN(data[19]) || data[19 /* glucosevalue_sd_6h */] <25.694437f ?
                                 (data[25 /* glucose_15min */] <84.0f ?
                                     (data[11 /* glucosevalue_hyperduration_24h */] <26.314878f ?
                                        0.0f :
                                        1.0f) :
                                    0.0f) :
                                1.0f) :
                            0.0f) :
                         (data[8 /* glucosevalue_cv_24h */] <20.378706f ?
                            0.0f :
                             (Double.isNaN(data[21]) || data[21 /* glucosevalue_euglycemia_6h */] <85.0f ?
                                1.0f :
                                0.0f))) :
                    1.0f) :
                1.0f) :
             (data[3 /* glucosevalue_euglycemia_12h */] <36.328125f ?
                1.0f :
                 (Double.isNaN(data[5]) || data[5 /* glucosevalue_hyperduration_12h */] <55.078125f ?
                     (Double.isNaN(data[16]) || data[16 /* glucosevalue_hypoduration_2h */] <11.71875f ?
                         (data[20 /* glucosevalue_cv_6h */] <13.647609f ?
                             (data[8 /* glucosevalue_cv_24h */] <27.845322f ?
                                1.0f :
                                0.0f) :
                             (Double.isNaN(data[1]) || data[1 /* glucosevalue_sd_12h */] <103.79689f ?
                                 (Double.isNaN(data[17]) || data[17 /* glucosevalue_hyperduration_2h */] <60.5f ?
                                    1.0f :
                                     (Double.isNaN(data[21]) || data[21 /* glucosevalue_euglycemia_6h */] <70.0f ?
                                        1.0f :
                                        0.0f)) :
                                 (data[24 /* glucose_at_bed */] <247.0f ?
                                    1.0f :
                                    0.0f))) :
                        0.0f) :
                     (data[24 /* glucose_at_bed */] <160.5f ?
                        1.0f :
                        0.0f)))));
```

```
    return pred;
  } // constant pool size = 106B, number of visited nodes = 26, static init size = 0B
}


class rf_covType2_Forest_7 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += rf_covType2_Tree_7_class_0.score0(fdata);
  }
}
class rf_covType2_Tree_7_class_0 {
  static final double score0(double[] data) {
    double pred =      (Double.isNaN(data[5]) || data[5 /* glucosevalue_hyperduration_12h */] <40.283203f ?
         (data[19 /* glucosevalue_sd_6h */] <16.996605f ?
             (data[20 /* glucosevalue_cv_6h */] <11.378832f ?
                 (data[14 /* glucosevalue_cv_2h */] <3.337877f ?
                    0.0f :
                     (data[25 /* glucose_15min */] <81.5f ?
                        1.0f :
                         (data[12 /* glucosevalue_mean_2h */] <97.055f ?
                            0.0f :
                            1.0f))) :
               0.0f) :
             (Double.isNaN(data[8]) || data[8 /* glucosevalue_cv_24h */] <44.711872f ?
                 (data[14 /* glucosevalue_cv_2h */] <5.205743f ?
                     (Double.isNaN(data[24]) || data[24 /* glucose_at_bed */] <185.5f ?
                        0.0f :
                        1.0f) :
                     (data[26 /* slope_at_bed */] <-1.3166667f ?
                         (Double.isNaN(data[1]) || data[1 /* glucosevalue_sd_12h */] <34.139248f ?
                            0.0f :
                            1.0f) :
                         (Double.isNaN(data[5]) || data[5 /* glucosevalue_hyperduration_12h */] <24.89224f ?
                             (Double.isNaN(data[22]) || data[22 /* glucosevalue_hypoduration_6h */] <5.7534246f ?
                                1.0f :
                                 (data[9 /* glucosevalue_euglycemia_24h */] <84.34256f ?
                                     (data[20 /* glucosevalue_cv_6h */] <25.452454f ?
                                        0.0f :
                                        1.0f) :
                                    1.0f)) :
                             (data[25 /* glucose_15min */] <100.5f ?
                                 (data[20 /* glucosevalue_cv_6h */] <23.053308f ?
                                    1.0f :
                                    0.0f) :
                                 (data[1 /* glucosevalue_sd_12h */] <37.7562f ?
                                    0.0f :
                                    1.0f))))) :
                 (data[10 /* glucosevalue_hypoduration_24h */] <3.2709775f ?
                    1.0f :
                    0.0f))) :
         (Double.isNaN(data[9]) || data[9 /* glucosevalue_euglycemia_24h */] <53.808594f ?
            1.0f :
             (data[2 /* glucosevalue_cv_12h */] <30.711731f ?
                 (Double.isNaN(data[23]) || data[23 /* glucosevalue_hyperduration_6h */] <58.984375f ?
                    1.0f :
                    0.0f) :
                1.0f)));
    return pred;
  } // constant pool size = 90B, number of visited nodes = 22, static init size = 0B
}


class rf_covType2_Forest_8 {
  public static void score0(double[] fdata, double[] preds) {
    preds[1] += rf_covType2_Tree_8_class_0.score0(fdata);
  }
}
class rf_covType2_Tree_8_class_0 {
  static final double score0(double[] data) {
    double pred =      (data[23 /* glucosevalue_hyperduration_6h */] <0.7324219f ?
         (data[10 /* glucosevalue_hypoduration_24h */] <2.248797f ?
            1.0f :
             (Double.isNaN(data[22]) || data[22 /* glucosevalue_hypoduration_6h */] <17.78949f ?
                 (Double.isNaN(data[10]) || data[10 /* glucosevalue_hypoduration_24h */] <34.130287f ?
                    0.0f :
                    1.0f) :
                 (data[4 /* glucosevalue_hypoduration_12h */] <13.510237f ?
                    1.0f :
```

```
                    (Double.isNaN(data[25]) || data[25 /* glucose_15min */] <127.5f ?
                        (Double.isNaN(data[12]) || data[12 /* glucosevalue_mean_2h */] <74.5625f ?
                           0.0f :
                           1.0f) :
                         1.0f)))) :
        (data[18 /* glucosevalue_mean_6h */] <168.03767f ?
            (Double.isNaN(data[10]) || data[10 /* glucosevalue_hypoduration_24h */] <14.55585f ?
                (data[13 /* glucosevalue_sd_2h */] <7.733978f ?
                   0.0f :
                    (data[24 /* glucose_at_bed */] <102.0f ?
                        (data[0 /* glucosevalue_mean_12h */] <124.7958f ?
                           1.0f :
                           0.0f) :
                        (data[6 /* glucosevalue_mean_24h */] <108.82942f ?
                           0.0f :
                            (Double.isNaN(data[18]) || data[18 /* glucosevalue_mean_6h */] <159.77911f ?
                               1.0f :
                                (data[19 /* glucosevalue_sd_6h */] <39.46657f ?
                                   0.0f :
                                   1.0f))))) :
             0.0f) :
            (data[8 /* glucosevalue_cv_24h */] <21.71203f ?
                (Double.isNaN(data[1]) || data[1 /* glucosevalue_sd_12h */] <43.950314f ?
                   1.0f :
                   0.0f) :
                (data[20 /* glucosevalue_cv_6h */] <15.249098f ?
                    (Double.isNaN(data[20]) || data[20 /* glucosevalue_cv_6h */] <14.807876f ?
                       1.0f :
                       0.0f) :
                   1.0f))));
    return pred;
  } // constant pool size = 78B, number of visited nodes = 19, static init size = 0B
}
```

7.6.3 Logistic Model

```
import java.util.Map;
import hex.genmodel.GenModel;
import hex.genmodel.annotations.ModelPojo;

@ModelPojo(name="GLM_model_R_1535384470614_26844", algorithm="glm")
public class GLM_model_R_1535384470614_26844 extends GenModel {
  public hex.ModelCategory getModelCategory() { return hex.ModelCategory.Binomial; }

  public boolean isSupervised() { return true; }
  public int nfeatures() { return 27; }
  public int nclasses() { return 2; }

  // Names of columns used by model.
  public static final String[] NAMES = NamesHolder_GLM_model_R_1535384470614_26844.VALUES;
  // Number of output classes included in training data response column.
  public static final int NCLASSES = 2;

  // Column domains. The last array contains domain of response column.
  public static final String[][] DOMAINS = new String[][] {
    /* glucosevalue_mean_12h */ null,
    /* glucosevalue_sd_12h */ null,
    /* glucosevalue_cv_12h */ null,
    /* glucosevalue_euglycemia_12h */ null,
    /* glucosevalue_hypoduration_12h */ null,
    /* glucosevalue_hyperduration_12h */ null,
    /* glucosevalue_mean_24h */ null,
    /* glucosevalue_sd_24h */ null,
    /* glucosevalue_cv_24h */ null,
    /* glucosevalue_euglycemia_24h */ null,
    /* glucosevalue_hypoduration_24h */ null,
    /* glucosevalue_hyperduration_24h */ null,
    /* glucosevalue_mean_2h */ null,
    /* glucosevalue_sd_2h */ null,
    /* glucosevalue_cv_2h */ null,
    /* glucosevalue_euglycemia_2h */ null,
    /* glucosevalue_hypoduration_2h */ null,
    /* glucosevalue_hyperduration_2h */ null,
    /* glucosevalue_mean_6h */ null,
    /* glucosevalue_sd_6h */ null,
    /* glucosevalue_cv_6h */ null,
    /* glucosevalue_euglycemia_6h */ null,
    /* glucosevalue_hypoduration_6h */ null,
    /* glucosevalue_hyperduration_6h */ null,
    /* glucose_at_bed */ null,
    /* glucose_15min */ null,
    /* slope_at_bed */ null,
    /* hypoglycemiayn */ GLM_model_R_1535384470614_26844_ColInfo_27.VALUES
  };
  // Prior class distribution
  public static final double[] PRIOR_CLASS_DISTRIB = null;
  // Class distribution used for model building
  public static final double[] MODEL_CLASS_DISTRIB = null;

  public GLM_model_R_1535384470614_26844() { super(NAMES,DOMAINS,"hypoglycemiayn"); }
  public String getUUID() { return Long.toString(8410346840176237949L); }

  // Pass in data in a double[], pre-aligned to the Model's requirements.
  // Jam predictions into the preds[] array; preds[0] is reserved for the
  // main prediction (class for classifiers or value for regression),
  // and remaining columns hold a probability distribution for classifiers.
  public final double[] score0( double[] data, double[] preds ) {
    final double [] b = BETA.VALUES;
    for(int i = 0; i < 0; ++i) if(Double.isNaN(data[i])) data[i] = CAT_MODES.VALUES[i];
    for(int i = 0; i < 27; ++i) if(Double.isNaN(data[i + 0])) data[i+0] = NUM_MEANS.VALUES[i];
    double eta = 0.0;
    for(int i = 0; i < CATOFFS.length-1; ++i) if(data[i] != 0) {
      int ival = (int)data[i] - 1;
      if(ival != data[i] - 1) throw new IllegalArgumentException("categorical value out of range");
      ival += CATOFFS[i];
      if(ival < CATOFFS[i + 1])
        eta += b[ival];
```

```
    }
    for(int i = 0; i < b.length-1-0; ++i)
    eta += b[0+i]*data[i];
    eta += b[b.length-1]; // reduce intercept
    double mu = hex.genmodel.GenModel.GLM_logitInv(eta);
    preds[0] = (mu >= 0.052591955044923075) ? 1 : 0; // threshold given by ROC
    preds[1] = 1.0 - mu; // class 0
    preds[2] =       mu; // class 1
    return preds;
  }
    public static class BETA implements java.io.Serializable {
      public static final double[] VALUES = new double[28];
      static {
        BETA_0.fill(VALUES);
      }
      static final class BETA_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = -0.013707173131013849;
          sa[1] = -0.03798041080396817;
          sa[2] = 0.13794737336523416;
          sa[3] = -0.009491023547385008;
          sa[4] = -0.16988214245841735;
          sa[5] = 0.0;
          sa[6] = -0.03172014134222759;
          sa[7] = -0.014302257168059773;
          sa[8] = 0.020597557831554154;
          sa[9] = -0.03447810954346673;
          sa[10] = 0.05356434938373296;
          sa[11] = 0.0;
          sa[12] = -3.4611092284985405E-4;
          sa[13] = 0.024571748213283517;
          sa[14] = -0.03423947636608629;
          sa[15] = 0.010393352783109025;
          sa[16] = 0.048970806900177355;
          sa[17] = 0.0;
          sa[18] = -0.008744644096987601;
          sa[19] = 0.033987459448643766;
          sa[20] = -0.09847440525161656;
          sa[21] = -0.002483989662090961;
          sa[22] = 0.031142290432524724;
          sa[23] = 0.0;
          sa[24] = -0.01754157164782352;
          sa[25] = 0.01894412396804537;
          sa[26] = 0.0;
          sa[27] = 8.296256441250145;
        }
      }
}
// Imputed numeric values
    static class NUM_MEANS implements java.io.Serializable {
      public static final double[] VALUES = new double[27];
      static {
        NUM_MEANS_0.fill(VALUES);
      }
      static final class NUM_MEANS_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 155.72773223217942;
          sa[1] = 49.83066948234612;
          sa[2] = 31.115098496192296;
          sa[3] = 62.30163862365385;
          sa[4] = 6.425943177224359;
          sa[5] = 31.272418199512824;
          sa[6] = 156.81807960961544;
          sa[7] = 51.78002922948719;
          sa[8] = 32.28791512861539;
          sa[9] = 62.07524673239744;
          sa[10] = 6.259626447032053;
          sa[11] = 31.665126820730777;
          sa[12] = 158.6970726495513;
          sa[13] = 22.283216435788464;
          sa[14] = 15.396368267826924;
          sa[15] = 60.86217948717951;
          sa[16] = 7.0865384615384635;
          sa[17] = 32.05128205128205;
          sa[18] = 155.19373834666652;
          sa[19] = 41.61468235509615;
          sa[20] = 26.56044911215385;
          sa[21] = 60.99874023953207;
```

```
          sa[22] = 7.798779416871797;
          sa[23] = 31.20248034362179;
          sa[24] = 158.35897435897428;
          sa[25] = 158.14743589743583;
          sa[26] = 0.014102564108974354;
        }
      }
}
// Imputed categorical values.
    static class CAT_MODES implements java.io.Serializable {
      public static final int[] VALUES = new int[0];
      static {
      }
}
    // Categorical Offsets
    public static final int[] CATOFFS = {0};
}
// The class representing training column names
class NamesHolder_GLM_model_R_1535384470614_26844 implements java.io.Serializable {
  public static final String[] VALUES = new String[27];
  static {
    NamesHolder_GLM_model_R_1535384470614_26844_0.fill(VALUES);
  }
  static final class NamesHolder_GLM_model_R_1535384470614_26844_0 implements java.io.Serializable {
    static final void fill(String[] sa) {
      sa[0] = "glucosevalue_mean_12h";
      sa[1] = "glucosevalue_sd_12h";
      sa[2] = "glucosevalue_cv_12h";
      sa[3] = "glucosevalue_euglycemia_12h";
      sa[4] = "glucosevalue_hypoduration_12h";
      sa[5] = "glucosevalue_hyperduration_12h";
      sa[6] = "glucosevalue_mean_24h";
      sa[7] = "glucosevalue_sd_24h";
      sa[8] = "glucosevalue_cv_24h";
      sa[9] = "glucosevalue_euglycemia_24h";
      sa[10] = "glucosevalue_hypoduration_24h";
      sa[11] = "glucosevalue_hyperduration_24h";
      sa[12] = "glucosevalue_mean_2h";
      sa[13] = "glucosevalue_sd_2h";
      sa[14] = "glucosevalue_cv_2h";
      sa[15] = "glucosevalue_euglycemia_2h";
      sa[16] = "glucosevalue_hypoduration_2h";
      sa[17] = "glucosevalue_hyperduration_2h";
      sa[18] = "glucosevalue_mean_6h";
      sa[19] = "glucosevalue_sd_6h";
      sa[20] = "glucosevalue_cv_6h";
      sa[21] = "glucosevalue_euglycemia_6h";
      sa[22] = "glucosevalue_hypoduration_6h";
      sa[23] = "glucosevalue_hyperduration_6h";
      sa[24] = "glucose_at_bed";
      sa[25] = "glucose_15min";
      sa[26] = "slope_at_bed";
    }
  }
}
// The class representing column hypoglycemiayn
class GLM_model_R_1535384470614_26844_ColInfo_27 implements java.io.Serializable {
  public static final String[] VALUES = new String[2];
  static {
    GLM_model_R_1535384470614_26844_ColInfo_27_0.fill(VALUES);
  }
  static final class GLM_model_R_1535384470614_26844_ColInfo_27_0 implements java.io.Serializable {
    static final void fill(String[] sa) {
      sa[0] = "0";
      sa[1] = "1";
    }
  }
}
```

7.6.4 Naïve Bayes

```
import java.util.Map;
import hex.genmodel.GenModel;
import hex.genmodel.annotations.ModelPojo;

@ModelPojo(name="NaiveBayes_model_R_1535384470614_26879", algorithm="naivebayes")
public class NaiveBayes_model_R_1535384470614_26879 extends GenModel {
  public hex.ModelCategory getModelCategory() { return hex.ModelCategory.Binomial; }
  public boolean isSupervised() { return true; }
  public int nfeatures() { return 27; }
  public int nclasses() { return 2; }

  // Names of columns used by model.
  public static final String[] NAMES = NamesHolder_NaiveBayes_model_R_1535384470614_26879.VALUES;
  // Number of output classes included in training data response column.
  public static final int NCLASSES = 2;

  // Column domains. The last array contains domain of response column.
  public static final String[][] DOMAINS = new String[][] {
    /* glucosevalue_mean_12h */ null,
    /* glucosevalue_sd_12h */ null,
    /* glucosevalue_cv_12h */ null,
    /* glucosevalue_euglycemia_12h */ null,
    /* glucosevalue_hypoduration_12h */ null,
    /* glucosevalue_hyperduration_12h */ null,
    /* glucosevalue_mean_24h */ null,
    /* glucosevalue_sd_24h */ null,
    /* glucosevalue_cv_24h */ null,
    /* glucosevalue_euglycemia_24h */ null,
    /* glucosevalue_hypoduration_24h */ null,
    /* glucosevalue_hyperduration_24h */ null,
    /* glucosevalue_mean_2h */ null,
    /* glucosevalue_sd_2h */ null,
    /* glucosevalue_cv_2h */ null,
    /* glucosevalue_euglycemia_2h */ null,
    /* glucosevalue_hypoduration_2h */ null,
    /* glucosevalue_hyperduration_2h */ null,
    /* glucosevalue_mean_6h */ null,
    /* glucosevalue_sd_6h */ null,
    /* glucosevalue_cv_6h */ null,
    /* glucosevalue_euglycemia_6h */ null,
    /* glucosevalue_hypoduration_6h */ null,
    /* glucosevalue_hyperduration_6h */ null,
    /* glucose_at_bed */ null,
    /* glucose_15min */ null,
    /* slope_at_bed */ null,
    /* hypoglycemiayn */ NaiveBayes_model_R_1535384470614_26879_ColInfo_27.VALUES
  };
  // Prior class distribution
  public static final double[] PRIOR_CLASS_DISTRIB = {0.6987179487179487,0.30128205128205127};
  // Class distribution used for model building
  public static final double[] MODEL_CLASS_DISTRIB = null;

  public NaiveBayes_model_R_1535384470614_26879() { super(NAMES,DOMAINS,"hypoglycemiayn"); }
  public String getUUID() { return Long.toString(3427226973201094506L); }

  // Pass in data in a double[], pre-aligned to the Model's requirements.
  // Jam predictions into the preds[] array; preds[0] is reserved for the
  // main prediction (class for classifiers or value for regression),
  // and remaining columns hold a probability distribution for classifiers.
  public final double[] score0( double[] data, double[] preds ) {
    java.util.Arrays.fill(preds,0);
    double mean, sdev, prob;
    double[] nums = new double[2];
    for(int i = 0; i < 2; i++) {
      nums[i] = Math.log(NaiveBayes_model_R_1535384470614_26879_APRIORI.VALUES[i]);
      for(int j = 0; j < 0; j++) {
        if(Double.isNaN(data[j])) continue;
        int level = (int)data[j];
        prob = level < 27 ?
        NaiveBayes_model_R_1535384470614_26879_PCOND.VALUES[j][i][level] : 2.0/(NaiveBayes_model_R_1535384470614_26879_RESCNT.VALUES[i] + 2.0*NaiveBayes_model_R_153538
        nums[i] += Math.log(prob <= 0.0 ? 0.001 : prob);
```

```
      }
      for(int j = 0; j < data.length; j++) {
        if(Double.isNaN(data[j])) continue;
        mean = Double.isNaN(NaiveBayes_model_R_1535384470614_26879_PCOND.VALUES[j][i][0]) ? 0 :
         NaiveBayes_model_R_1535384470614_26879_PCOND.VALUES[j][i][0];
        sdev = Double.isNaN(NaiveBayes_model_R_1535384470614_26879_PCOND.VALUES[j][i][1]) ? 1 :
         (NaiveBayes_model_R_1535384470614_26879_PCOND.VALUES[j][i][1] <= 0.0 ? 0.001 : NaiveBayes_model_R_1535384470614_26879_PCOND.VALUES[j][i][1]);
        prob = Math.exp(-((data[j]-mean)*(data[j]-mean))/(2.*sdev*sdev)) / (sdev*Math.sqrt(2.*Math.PI));
        nums[i] += Math.log(prob <= 0.0 ? 0.001 : prob);
      }
    }
    double sum;
    for(int i = 0; i < nums.length; i++) {
      sum = 0;
      for(int j = 0; j < nums.length; j++) {
        sum += Math.exp(nums[j]-nums[i]);
      }
      preds[i+1] = 1/sum;
    }
    preds[0] = hex.genmodel.GenModel.getPrediction(preds, PRIOR_CLASS_DISTRIB, data, 0.9876869799180799);
    return preds;
  }
}
// Count of categorical levels in response.
class NaiveBayes_model_R_1535384470614_26879_RESCNT implements java.io.Serializable {
  public static final int[] VALUES = new int[2];
  static {
    NaiveBayes_model_R_1535384470614_26879_RESCNT_0.fill(VALUES);
  }
  static final class NaiveBayes_model_R_1535384470614_26879_RESCNT_0 implements java.io.Serializable {
    static final void fill(int[] sa) {
      sa[0] = 109;
      sa[1] = 47;
    }
  }
}
// Apriori class distribution of the response.
class NaiveBayes_model_R_1535384470614_26879_APRIORI implements java.io.Serializable {
  public static final double[] VALUES = new double[2];
  static {
    NaiveBayes_model_R_1535384470614_26879_APRIORI_0.fill(VALUES);
  }
  static final class NaiveBayes_model_R_1535384470614_26879_APRIORI_0 implements java.io.Serializable {
    static final void fill(double[] sa) {
      sa[0] = 0.69375;
      sa[1] = 0.30625;
    }
  }
}
// Conditional probability of predictors.
class NaiveBayes_model_R_1535384470614_26879_PCOND implements java.io.Serializable {
  public static final double[][][] VALUES = new double[27][][];
  static {
    NaiveBayes_model_R_1535384470614_26879_PCOND_0.fill(VALUES);
  }
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_0 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_0_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_0_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_0_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_0_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 168.47963169550462;
          sa[1] = 40.51991584016765;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_0_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_0_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_0_0_1_0 implements java.io.Serializable {
```

```
        static final void fill(double[] sa) {
          sa[0] = 126.15417815765956;
          sa[1] = 33.58755934170002;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_0_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_0_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_0_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_1 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_1_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_1_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_1_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_1_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 54.14583358666971;
          sa[1] = 24.032112960554976;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_1_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_1_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_1_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 39.823161240404254;
          sa[1] = 23.190642579547514;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_1_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_1_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_1_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_2 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_2_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_2_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_2_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_2_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 31.691636749119258;
          sa[1] = 10.670449924549747;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_2_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_2_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_2_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 29.778020420255313;
          sa[1] = 12.827708310833376;
        }
      }
}
```

```
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_2_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_2_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_2_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_3 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_3_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_3_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_3_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_3_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 57.38690287908257;
          sa[1] = 24.27239928556295;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_3_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_3_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_3_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 73.69964279723403;
          sa[1] = 17.088352575587127;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_3_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_3_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_3_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_4 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_4_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_4_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_4_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_4_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 4.7959506487339425;
          sa[1] = 6.731345203481973;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_4_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_4_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_4_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 10.206138615638299;
          sa[1] = 13.35192337292417;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_4_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_4_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_4_0_1.VALUES;
      }
    }
```

```
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_5 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_5_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_5_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_5_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_5_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 37.817146472550476;
          sa[1] = 25.311119757248058;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_5_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_5_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_5_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 16.094218587574463;
          sa[1] = 16.660988706082364;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_5_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_5_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_5_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_6 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_6_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_6_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_6_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_6_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 169.50366681926607;
          sa[1] = 37.413918241567345;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_6_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_6_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_6_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 127.39831352765957;
          sa[1] = 32.54470783938334;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_6_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_6_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_6_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_7 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_7_0.fill(VALUES);
    }
```

```
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_7_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_7_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_7_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 55.62921211302751;
          sa[1] = 20.88777749416829;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_7_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_7_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_7_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 42.85320084000001;
          sa[1] = 23.178317173841112;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_7_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_7_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_7_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_8 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_8_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_8_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_8_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_8_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 32.410689866000006;
          sa[1] = 8.840510235745544;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_8_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_8_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_8_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 32.00318222702127;
          sa[1] = 12.949858108707815;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_8_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_8_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_8_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_9 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_9_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_9_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_9_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_9_0_0_0 implements java.io.Serializable {
```

```
        static final void fill(double[] sa) {
          sa[0] = 58.13674849343121;
          sa[1] = 21.790215449433035;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_9_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_9_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_9_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 71.20921073340423;
          sa[1] = 15.92911242145302;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_9_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_9_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_9_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_10 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_10_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_10_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_10_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_10_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 4.086672985293578;
          sa[1] = 5.972348481340193;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_10_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_10_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_10_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 11.299029156170215;
          sa[1] = 10.695138789576683;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_10_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_10_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_10_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_11 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_11_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_11_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_11_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_11_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 37.77657852140367;
          sa[1] = 23.26472503372256;
        }
      }
}
```

```
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_11_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_11_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_11_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 17.491760110659573;
          sa[1] = 16.68994222221169;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_11_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_11_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_11_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_12 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_12_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_12_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_12_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_12_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 174.26385321100912;
          sa[1] = 71.25187729701327;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_12_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_12_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_12_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 122.5953900708511;
          sa[1] = 55.28828726743979;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_12_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_12_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_12_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_13 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_13_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_13_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_13_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_13_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 23.85911254347706;
          sa[1] = 14.742848108629635;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_13_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_13_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_13_0_1_0 implements java.io.Serializable {
```

```
        static final void fill(double[] sa) {
          sa[0] = 18.62847865412766;
          sa[1] = 15.518783833412;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_13_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_13_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_13_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_14 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_14_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_14_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_14_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_14_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 15.266200285000005;
          sa[1] = 10.689880086431565;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_14_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_14_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_14_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 15.698247206723408;
          sa[1] = 12.668521891311176;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_14_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_14_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_14_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_15 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_15_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_15_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_15_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_15_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 57.357798165137616;
          sa[1] = 38.95760348354487;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_15_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_15_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_15_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 68.98936170212765;
          sa[1] = 32.70960658013482;
        }
      }
}
```

```
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_15_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_15_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_15_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_16 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_16_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_16_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_16_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_16_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 3.376146788990826;
          sa[1] = 11.510694697658257;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_16_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_16_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_16_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 15.691489361702128;
          sa[1] = 26.425356974161026;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_16_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_16_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_16_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_17 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_17_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_17_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_17_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_17_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 39.26605504587156;
          sa[1] = 40.27007026680284;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_17_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_17_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_17_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 15.319148936170214;
          sa[1] = 27.941792279338195;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_17_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_17_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_17_0_1.VALUES;
      }
    }
```

```
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_18 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_18_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_18_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_18_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_18_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 169.195299733211;
          sa[1] = 54.13374289562525;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_18_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_18_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_18_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 122.72203215234046;
          sa[1] = 41.832735572103935;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_18_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_18_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_18_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_19 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_19_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_19_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_19_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_19_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 46.11852364892661;
          sa[1] = 24.182091004071207;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_19_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_19_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_19_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 31.16960360982978;
          sa[1] = 21.93602005082283;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_19_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_19_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_19_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_20 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_20_0.fill(VALUES);
    }
```

```
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_20_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_20_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_20_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 27.7891805263578;
          sa[1] = 12.459358726974067;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_20_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_20_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_20_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 23.71083796006383;
          sa[1] = 11.338592404328056;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_20_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_20_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_20_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_21 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_21_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_21_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_21_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_21_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 56.541410079477075;
          sa[1] = 29.13673283631885;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_21_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_21_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_21_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 71.33595273838296;
          sa[1] = 27.081913620483416;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_21_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_21_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_21_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_22 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_22_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_22_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_22_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_22_0_0_0 implements java.io.Serializable {
```

```
        static final void fill(double[] sa) {
          sa[0] = 5.2532361442477065;
          sa[1] = 10.33133615700786;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_22_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_22_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_22_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 13.702273389553191;
          sa[1] = 21.835541422397;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_22_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_22_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_22_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_23 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_23_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_23_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_23_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_23_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 38.205353776412835;
          sa[1] = 31.0117831255226;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_23_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_23_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_23_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 14.96177387182979;
          sa[1] = 21.55427233876713;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_23_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_23_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_23_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_24 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_24_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_24_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_24_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_24_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 172.78899082568807;
          sa[1] = 74.95851610681142;
        }
      }
}
```

```
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_24_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_24_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_24_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 124.8936170212766;
          sa[1] = 68.01669681282971;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_24_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_24_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_24_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_25 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_25_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_25_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_25_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_25_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 169.77981651376146;
          sa[1] = 73.71483565919632;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_25_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_25_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_25_0_1_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 131.17021276595744;
          sa[1] = 66.92835856636954;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_25_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_25_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_25_0_1.VALUES;
      }
    }
}
  static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_26 implements java.io.Serializable {
    public static final double[][] VALUES = new double[2][];
    static {
      NaiveBayes_model_R_1535384470614_26879_PCOND_0_26_0.fill(VALUES);
    }
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_26_0_0 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_26_0_0_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_26_0_0_0 implements java.io.Serializable {
        static final void fill(double[] sa) {
          sa[0] = 0.2006116207798165;
          sa[1] = 1.6603211403835296;
        }
      }
}
    static class NaiveBayes_model_R_1535384470614_26879_PCOND_0_26_0_1 implements java.io.Serializable {
      public static final double[] VALUES = new double[2];
      static {
        NaiveBayes_model_R_1535384470614_26879_PCOND_0_26_0_1_0.fill(VALUES);
      }
      static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_26_0_1_0 implements java.io.Serializable {
```

```
        static final void fill(double[] sa) {
          sa[0] = -0.4184397162553191;
          sa[1] = 1.8304299607369323;
        }
      }
}
    static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0_26_0 implements java.io.Serializable {
      static final void fill(double[][] sa) {
        sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_26_0_0.VALUES;
        sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_26_0_1.VALUES;
      }
    }
}
  static final class NaiveBayes_model_R_1535384470614_26879_PCOND_0 implements java.io.Serializable {
    static final void fill(double[][][] sa) {
      sa[0] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_0.VALUES;
      sa[1] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_1.VALUES;
      sa[2] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_2.VALUES;
      sa[3] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_3.VALUES;
      sa[4] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_4.VALUES;
      sa[5] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_5.VALUES;
      sa[6] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_6.VALUES;
      sa[7] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_7.VALUES;
      sa[8] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_8.VALUES;
      sa[9] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_9.VALUES;
      sa[10] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_10.VALUES;
      sa[11] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_11.VALUES;
      sa[12] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_12.VALUES;
      sa[13] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_13.VALUES;
      sa[14] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_14.VALUES;
      sa[15] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_15.VALUES;
      sa[16] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_16.VALUES;
      sa[17] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_17.VALUES;
      sa[18] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_18.VALUES;
      sa[19] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_19.VALUES;
      sa[20] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_20.VALUES;
      sa[21] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_21.VALUES;
      sa[22] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_22.VALUES;
      sa[23] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_23.VALUES;
      sa[24] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_24.VALUES;
      sa[25] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_25.VALUES;
      sa[26] = NaiveBayes_model_R_1535384470614_26879_PCOND_0_26.VALUES;
    }
  }
}
// Number of unique levels for each categorical predictor.
class NaiveBayes_model_R_1535384470614_26879_DOMLEN implements java.io.Serializable {
  public static final double[] VALUES = null;
}
// The class representing training column names
class NamesHolder_NaiveBayes_model_R_1535384470614_26879 implements java.io.Serializable {
  public static final String[] VALUES = new String[27];
  static {
    NamesHolder_NaiveBayes_model_R_1535384470614_26879_0.fill(VALUES);
  }
  static final class NamesHolder_NaiveBayes_model_R_1535384470614_26879_0 implements java.io.Serializable {
    static final void fill(String[] sa) {
      sa[0] = "glucosevalue_mean_12h";
      sa[1] = "glucosevalue_sd_12h";
      sa[2] = "glucosevalue_cv_12h";
      sa[3] = "glucosevalue_euglycemia_12h";
      sa[4] = "glucosevalue_hypoduration_12h";
      sa[5] = "glucosevalue_hyperduration_12h";
      sa[6] = "glucosevalue_mean_24h";
      sa[7] = "glucosevalue_sd_24h";
      sa[8] = "glucosevalue_cv_24h";
      sa[9] = "glucosevalue_euglycemia_24h";
      sa[10] = "glucosevalue_hypoduration_24h";
      sa[11] = "glucosevalue_hyperduration_24h";
      sa[12] = "glucosevalue_mean_2h";
      sa[13] = "glucosevalue_sd_2h";
      sa[14] = "glucosevalue_cv_2h";
      sa[15] = "glucosevalue_euglycemia_2h";
      sa[16] = "glucosevalue_hypoduration_2h";
      sa[17] = "glucosevalue_hyperduration_2h";
      sa[18] = "glucosevalue_mean_6h";
      sa[19] = "glucosevalue_sd_6h";
      sa[20] = "glucosevalue_cv_6h";
```

```
      sa[21] = "glucosevalue_euglycemia_6h";
      sa[22] = "glucosevalue_hypoduration_6h";
      sa[23] = "glucosevalue_hyperduration_6h";
      sa[24] = "glucose_at_bed";
      sa[25] = "glucose_15min";
      sa[26] = "slope_at_bed";
    }
  }
}
// The class representing column hypoglycemiayn
class NaiveBayes_model_R_1535384470614_26879_ColInfo_27 implements java.io.Serializable {
  public static final String[] VALUES = new String[2];
  static {
    NaiveBayes_model_R_1535384470614_26879_ColInfo_27_0.fill(VALUES);
  }
  static final class NaiveBayes_model_R_1535384470614_26879_ColInfo_27_0 implements java.io.Serializable {
    static final void fill(String[] sa) {
      sa[0] = "0";
      sa[1] = "1";
    }
  }
}
```

Todo es comenzar á ser venturoso

(To be lucky at the beginning is everything)

Miguel De Cervantes, Don Quixote

8

Future Directions

From this dissertation three important conclusions can be drawn. The first is that physical activity produces mixed outcomes in people with type 1 diabetes (T1D). During a bout of activity, they could experience hypoglycemia. The impact of this bout of activity is not limited to the duration of exercise but extends for many hours afterward. In the medium term 4-8 hr period, these individuals may experience both symptomatic and asymptomatic hypoglycemia. We quantified the odds of experiencing nocturnal hypoglycemia and found it to be greatly elevated in this cohort. Exercise in the late afternoon has been shown to cause

over an hour of sleep loss in the case of aerobic exercise and less than half hour of sleep loss in the case of resistance training.

The second broad conclusion is that in the longer term—24 hr, the outcomes on glycemic control improve significantly after resistance training, an increased time in range of $\approxeq$ 14% was experienced. We can also conclude that the energy intake after exercise is different after each type of exercise and could be related to the energy expended during the bout of activity. Due to the complexity involved in dosing for the meals after exercise and the increased amounts of hypoglycemic-treatments that have to be consumed, the benefits of aerobic exercise are diminished. This was clearly presented for the first time and showed the complexity of managing T1D after physical exercise.

The third broad conclusion is that real life data could be used to develop machine learning approaches to prevent exercise induced hypoglycemia and nocturnal hypoglycemia in people with T1D. Using a personalized machine learning approach to predict exercise-induced hypoglycemia, we developed and validated a machine learning models that can achieve a prediction accuracy >87%. We also presented a simple heuristic model that individuals with T1D will find very easy to remember to help mitigate the fear of hypoglycemia around exercise. We also present a *proactive* approach to prevent the common side-effect of nocturnal hypoglycemia by demonstrating the use of various clinically acknowledged risks factors can estimate the risk of nocturnal hypoglycemia in free living conditions.

All the above conclusions along with the underlying dataset provide a rich data structure that can be used to further build and develop decision support systems to widely benefit people with T1D.

In the following sections future directions of this work are presented.

The impact of sleep and glycemic control is an area that needs to be explored further. Sleep duration has been associated as a determinant of insulin sensitivity, in people with type 2 diabetes. In addition, various aspects of diabetes could be linked to increased prevalence of sleep disturbances. Impaired sleep and T1D might potentiate each other in some patients, thereby creating a negative vicious circle. Optimizing sleep duration and sleep quality could therefore be considered as a potential therapeutic target to improve metabolic control in people with T1D. In section 8.1 this is further explored.

Current population-based methods for assessing dietary intake, including food frequency questionnaires, food diaries, and 24-h dietary recall, are limited in their ability to objectively measure food intake. Digital photography has been identified as a promising addition to these techniques. We explored this approach in people with T1D. In section 8.2 the meal intake data collected from the study conducted as part of this dissertation is shown. Preliminary analysis of this data is shown here. Implementing modern computer vision approaches to identify the meals and provide an appropriate insulin dosage would provide a much needed technological approach to the challenge of meal time insulin dosage.

An example of an early version of a decision support tool is presented in section 8.3. In this early version of a tool that is currently under development, we provide an example of how insulin dosage can be modified based on past experiences. If an individual experienced nocturnal hypoglycemia after a previous exercise bout a reasonable therapeutic approach would be to reduce the insulin dosage for the next time, this tool optimizes the amount by which insulin dosage could be reduced. This approach of reinforcement learning could provide foundation for robust decision support tool.

Chapter summary

- Based on the study data collected, we show a promising relationship between day to day variations in sleep and glycemic control. Days after subjects slept longer (>6.5 hr), they spent more time in range. This relationship is of particular importance to people with T1D, sleep duration could potentially impact insulin dosage choices.
- We also show used a novel approach to acquire meal intake data from the cohort in this study. Collecting detailed meal data in form of images and type of meals consumed by the participants could be used to provide automated meal insulin bolus recommendations in the context of a decision support system. Analyzing past meal glycemic performance could be used to detect problem meals and respond with the appropriate meal dose for the next occasion.
- An early version of a decision support tool is shown here, this tool is designed to help with estimating adequate reductions in the insulin dosage to improve glycemic outcomes after an individual with T1D has engaged in aerobic exercise.

8.1 Sleep duration and glycemic outcomes

More than a third of the adult population reports habitual short sleep of less than 7 hours a night[Liu, 2016]. Disrupted sleep patterns have been attributed to obesity, insulin resistance and hyperglycemia in adults with type 2 diabetes[Panel et al., 2015]. These disruptions in sleep are a result of either sleep restriction, sleep loss or sleep fragmentation. However, the impact of sleep disruptions or sleep loss in adults with type 1 diabetes (T1D) is not well

understood. Subjective analysis has reported that people with T1D report poor sleep quality when compared with a healthy cohort [Van Dijk et al., 2011]. Nocturnal hypoglycemia and/or glycemic variability are common during sleep and could cause regular sleep fragmentation resulting in poor sleep quality [Jauch-Chara et al., 2008, Brod et al., 2013b]. Less than a third of adults with type 1 diabetes (T1D) achieve the prescribed target glycated hemoglobin level lower than 7.0% and many are overweight or obese [Weinstock et al., 2016a, Miller et al., 2015a]. Partial sleep restriction in healthy adults and adults with T1D has been shown to have negative impact on the insulin sensitivity [Donga et al., 2010a]. These findings suggest that sleep loss could result in poor glycemic control. Since, sleep is a potentially modifiable risk factor for glycemic control, as part of a secondary analysis we evaluated the impact that sleep duration had on the daily glycemic control in adults with T1D in a pilot study [Reddy et al., 2017].

8.1.1 Analysis

We studied 10 adults with T1D who self-managed their glucose levels with their own insulin pump (4 M, 6 F; age 33 ± 6 yrs, duration of diabetes 18 ± 10 yrs, HbA_{1c} 7.4 ± 1%). We assessed a total of 235 nights while participants lived under normal conditions. Sleep was estimated using wrist-worn actigraphy (Actigraph). None of the participants reported clinical sleep issues at baseline and participants had good overall sleep quality (Pittsburgh Sleep Quality

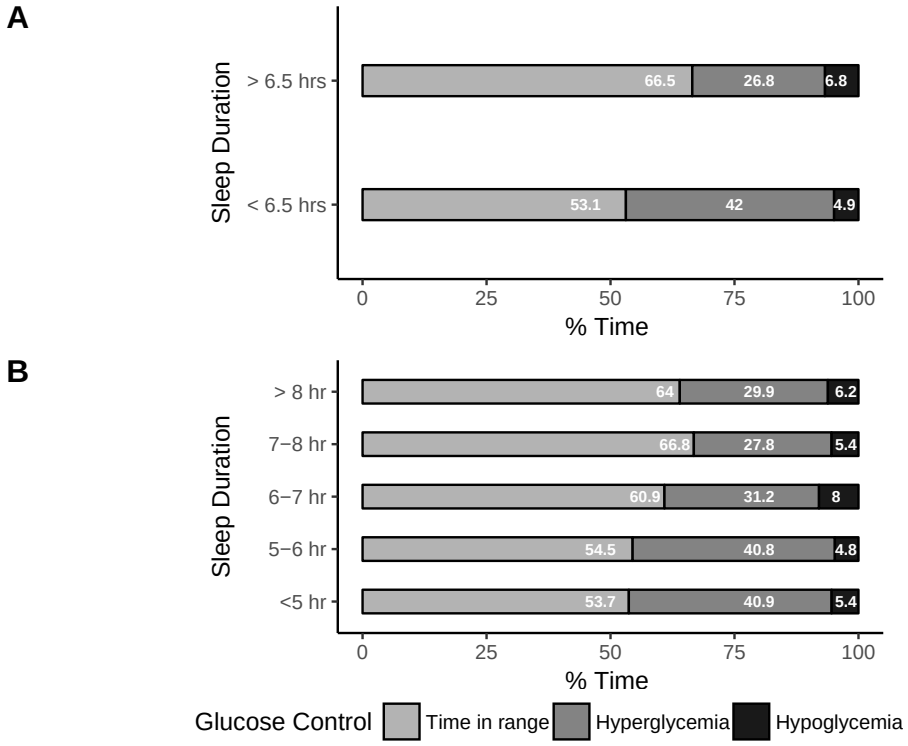

Figure 8.1: A: The relationship between glycemic control and sleep duration. Mean glycemic metrics across the nights of short/long sleep duration are shown here. B: Incremental changes in sleep duration and its impact on the glycemic control metrics is shown here. Glycemic control on the days following longer sleep duration is better but really long duration >8 hr showed a decrease in the time in range, suggesting an inverted-U shaped relationship.

Index score <3; score range 0-21). The primary outcome for this analysis was percentage of time in range (glucose >=70mg/dL and <=180 mg/dL) for the 24 hours after each night of sleep, as measured using a continuous glucose monitor (Dexcom G4). We divided the data in half based on sleep duration using a 6.5 hour cut-off to define short vs. longer sleep periods.

8.1.2 Results

Under the premise, that each night of sleep restriction could have an impact on the glycemic control the next day, we considered each night as an independent unit without considering the subject interaction. The mean percent of time in range following *short sleep* was significantly less than after *long sleep* nights (53.1% vs. 66.5%, respectively, two sample t-test, P<0.001). The mean percent of time in hyperglycemia (sensor glucose >180 mg/dL) following nights of short sleep was higher than after the nights with longer sleep (42% vs. 26.8%, respectively, P <0.001). The mean percent of time in hypoglycemia (sensor glucose <70 mg/dL) following nights of *short sleep* was not significantly different from the nights with *longer sleep* (4.9% vs. 6.8%, Figure 8.1 A). We also observed an inverted-U shaped relationship between sleep duration and the percentage time in euglycemia Figure 8.1 B. The results observed while considering each night of sleep independent of the subject leads to the same conclusions that were drawn by other in the field that poor sleep can be associated with poor glycemic control[Reutrakul et al., 2016].

As subject and sleep duration cannot be considered independent, we considered a randomized mixed effects model treating each subject as a random effect. *Longer sleep* duration resulted in an increase of $3.23 \pm 2.9\%$ of increase in the time in range. This effect was not significant in this small cohort. Each subject's relationship between sleep duration and the time in range are shown in Figure 8.2. The mean total daily insulin use (U/day) following

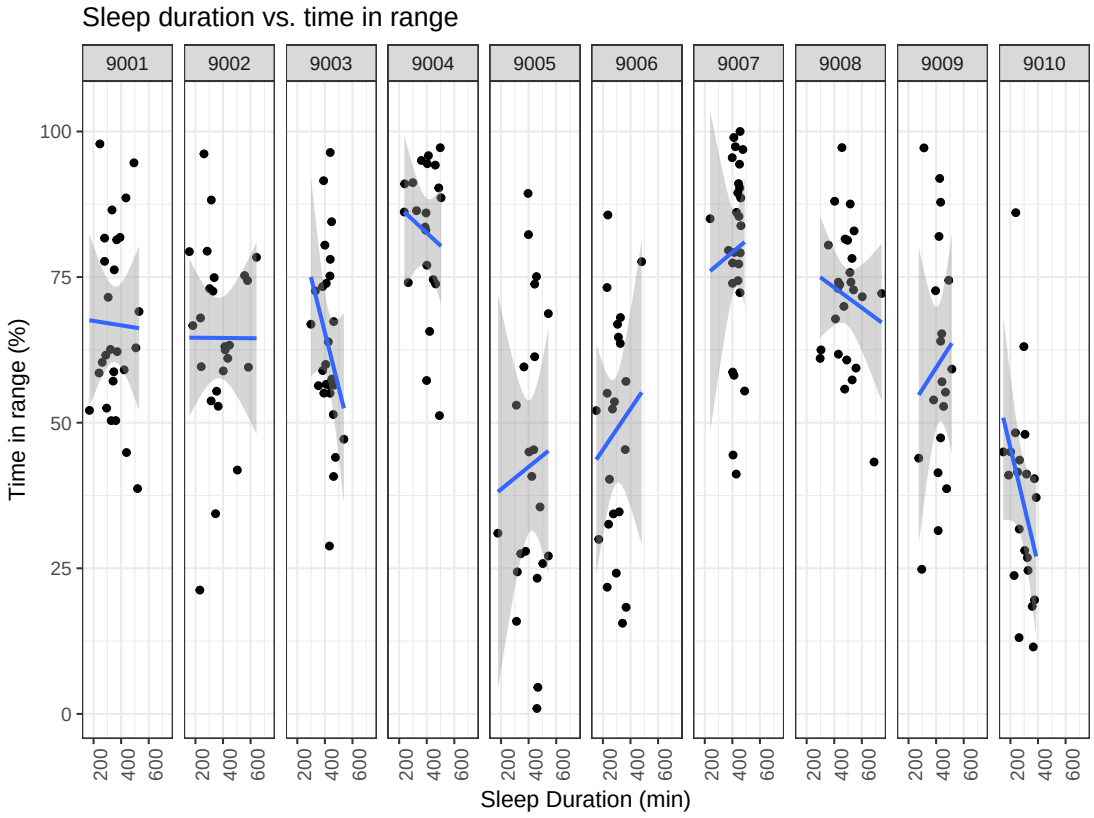

Figure 8.2: Subject level relationship between duration of sleep and the variability in glycemic control. The heterogeneity among the subjects and their respective sleep duration versus time in range is shown here. We observed that four subjects show the pattern that increased sleep duration is related to better glycemic control, while four others showed the opposite relationship and with no relationship between sleep and next-day glycemic control apparent for two subjects.

short sleep was significantly higher than after *long sleep* nights (42.5 vs. 38.6, respectively, two sample t-test, p=0.002). In studies looking at people with T1D and judging glucose control as measured by the HbA_{1c} short sleep was associated with poor glycemic control [Chontong et al., 2016, Borel et al., 2013b], but here we show that under normal living conditions, day to day variations in sleep duration could have an impact on daily glycemic control as well. However, the relationship is variable among the subjects studied Figure 8.2.

8.1.3 Conclusions

The day to day variations in sleep and glycemic control relationship has clinical importance for these individuals, as the amount of exogenous insulin dosage may need to be modified to improve glycemic control on a daily basis. The results presented here need to be considered within the context of the growing evidence [Chontong et al., 2016, Borel et al., 2013b, Larcher et al., 2016, Denic-Roberts et al., 2016, Reutrakul et al., 2016] that indicates that poor sleep is associated with poor glycemic control and poor control may be mediated by the physiological impact of sleep loss [Donga et al., 2010b] leading to changes in insulin sensitivity. The diurnal pattern of insulin sensitivity has been shown to be different and specific to each individual with T1D [Hinshaw et al., 2013]. Our results provide an opportunity for future studies to determine the feasibility for optimization of sleep as a novel behavioral intervention to improve glycemic control or incorporate the duration of sleep as a modality to determine

insulin dosage recommendations.

8.2 Digital Photography for Meal Tracking

The Quantity of carbohydrates (CHO) in a meal is the major nutritional determinant of postprandial glucose levels [Bell et al., 2015]. Accurate estimation of CHO at every meal is critical to limit postprandial glucose excursions in individuals with T1D. Estimates of CHO are necessary to calculate pre-meal insulin bolus amounts [Elleri et al., 2013, Grant & Kirkman, 2015]. Inaccuracies in the estimation of CHO content of the meal leads to increased glycemic variability [Brazeau et al., 2013]. Many people with T1D find this task very challenging [Brazeau et al., 2013] but the precision of CHO counting has been associated with improved glycemic control [Mehta et al., 2009]. The first step to understanding the daily fluctuations in the glycemic control is to understand the variations in the meal data.

Reliability associated with self-reporting of meal intake information is quite imperfect. Current self-reporting techniques involve either filling daily intake forms or using a 24 hr recall method, both of these approaches have been shown to have serious under-reporting issues associated with them. Some recent approaches have involved using digital photography to assist with self-reporting with mixed success [Park et al., 2018]. Individuals with T1D in our study were trained in carbohydrate counting and employed carbohydrate counting to admin-

ister insulin boluses for meals. The quantity of carbohydrates cause the biggest fluctuation in the postprandial glucose levels [Brazeau et al., 2013, Bell et al., 2015]. As part of this dister-ation work, we created a research tool with the ability to track meals with a smartphone app. This application was distributed to the study participants. For each meal that was tracked, a photograph of the meal was taken along with a short description of the meal, the estimated carbohydrate amount, the glucose values from the glucose meter, the location where the meal was consumed, the type of the meal and how the subject was feeling at the time of the meal. Each of these entries were collected and transmitted securely from the phone to a server for storage. A registered dietician estimated the macro nutrient value of these pictures post-hoc. The app screen is shown in Figure 8.3. Subjects were also provided with a ruler to be placed in the photograph to help with size estimation.

8.2.1 Observations

Here we show the observations from 1220 meals that were collected during the course of this study. The data presented here is raw data collected from each of the meal data recorded from the app. The meal intake data revealed some interesting details. We observed that the medium amount of carbohydrate reported per meal by the subjects in the study was only 24 grams of carbohydrate. The distribution of the carbohydrate amount in the meal intake data is shown in Figure 8.4. We also analyzed the average daily carbohydrate intake among the

Figure 8.3: Main screen for the data collection of the meal.

Subject# ID	Mean daily carbohydrate (g) ± SD
9001	113.79 ± 37.64
9002	162.20 ± 68.70
9003	159.14 ± 58.88
9004	75.80 ± 35.52
9005	94.32 ± 81.92
9006	157.00 ± 73.25
9007	57.12 ± 17.69
9008	152.26 ± 50.70
9009	134.18 ± 45.12
9010	171.72 ± 104.02

Table 8.1: Mean daily reported carbohydrate intake

participants of the study, this data is shown in Figure 8.5 and Table 8.1. The average daily intake of carbohydrate across all the subjects with standard deviation (SD) was 127.75 ± 40.3 g. As participants provided additional details for each meal consumed during the study, we were able to analyze the content and descriptions of the meals consumed by the subjects in the study. A word cloud showing the most common descriptions of the meals is shown in Figure 8.6.

We were the first to deploy this type of data collection in this cohort and the quality of data collected during the study was high. Using the knowledge gained from this app development, deployment, ease of data collection, and the type of data we collected, an improved version of this app is being deployed in a large scale study to understand the impact of exercise in glycemic outcomes. The data from this meal analysis is being used to develop a machine learning approach to create an image recognition system that would predict the glycemic response to the meal to suggest an appropriate insulin dosage. To identify the type of food or carbohydrate amount in the picture, the subject provided descriptions are also being used.

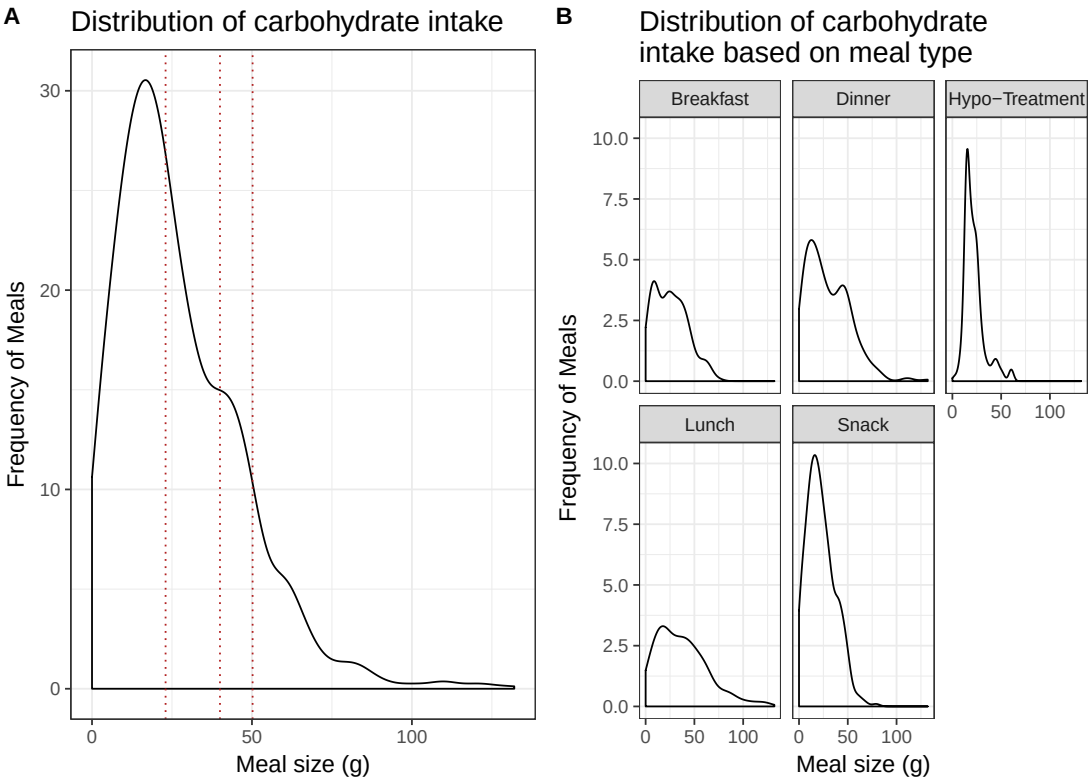

Figure 8.4: Distribution of the meal intake data. B:Distribution of each type of the meal recorded during the study.

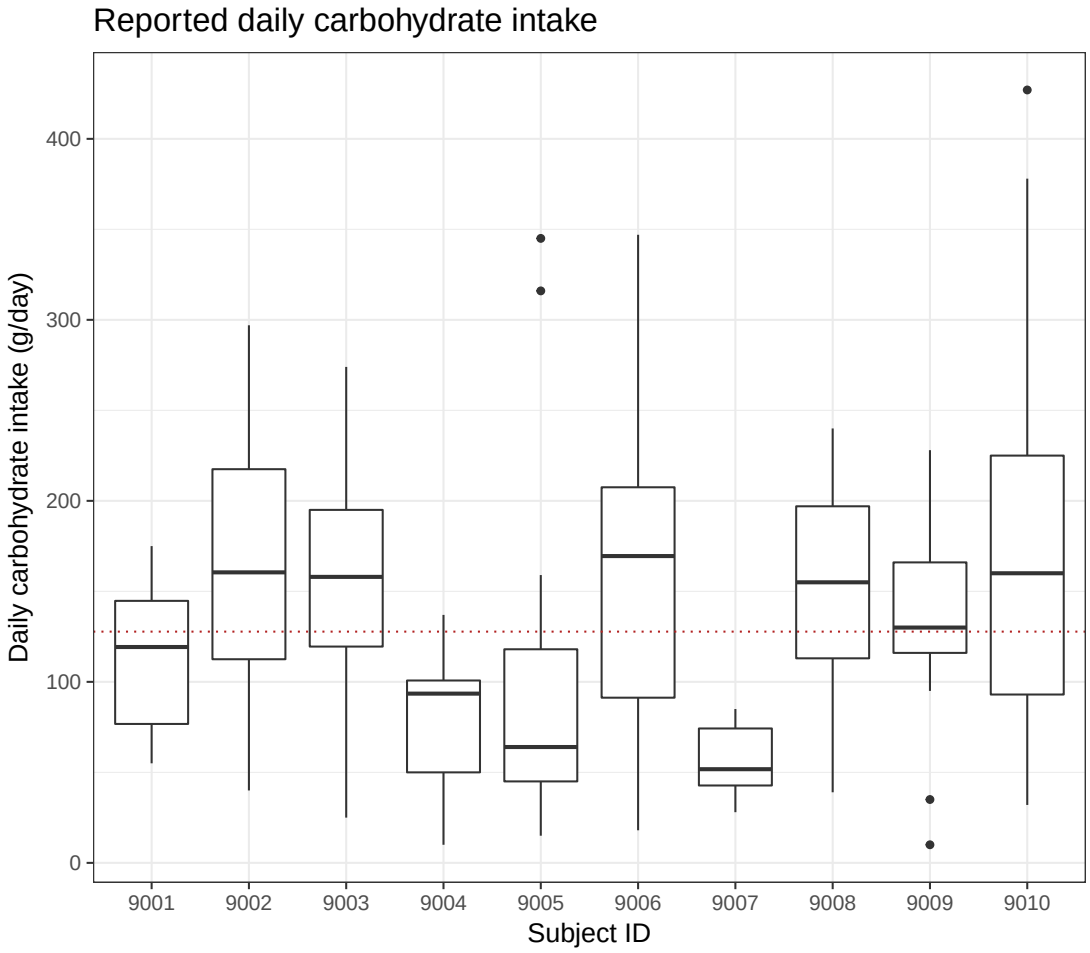

Figure 8.5: Reported daily carbohydrate intake from the clinical study conducted. The heterogeneity among the subjects is evident in amount daily carbohydrate that was reported. The meal data was reported by the individuals and not estimated by the dietitian.

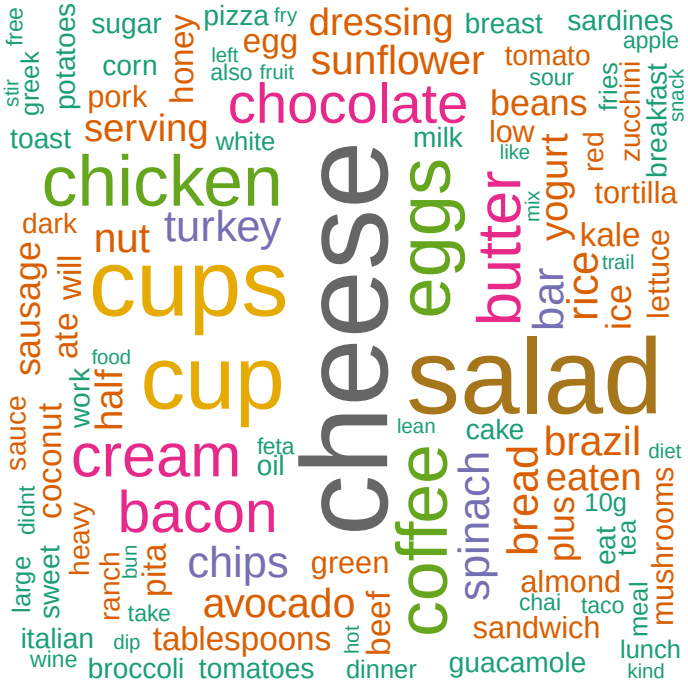

Figure 8.6: Word cloud of the text descriptions of reported meal intake.

8.3 Decision support tools to help people with T1D

The ultimate goal of this dissertation was to be able to provide individuals with T1D a tool they could consult with to guide them to achieve improved glycemic control. The daily self-management of T1D is exhausting to many people with T1D. Many people with T1D fail to achieve the target glycemic control. Hybrid closed loop systems that have recently been approved provide an alternative to managing this disease with improved glycemic outcomes. Artificial pancreas systems with dual hormones that are currently in development offer another alternative to improve glucose control. Decision support systems to aid in the appropriate choices of insulin dosing and carbohydrate intake provide a necessary alternative to aid these individuals with their dosage decisions.

Decision support system-Daily dose, currently in development at OHSU is being designed using the data collected as part of this dissertation. The machine learning tools that were developed as part of this dissertation to identify the risk of hypoglycemia due to exercise and the risk of nocturnal hypoglycemia before bed time are being implemented in the decision support system. Also in development is an approach to "replay" retrospective data from an individual while modifying the insulin dosage choices. Using an approach espoused by Patek et al. [Patek et al., 2016] glucose data from a sensor, insulin dosage data and meal

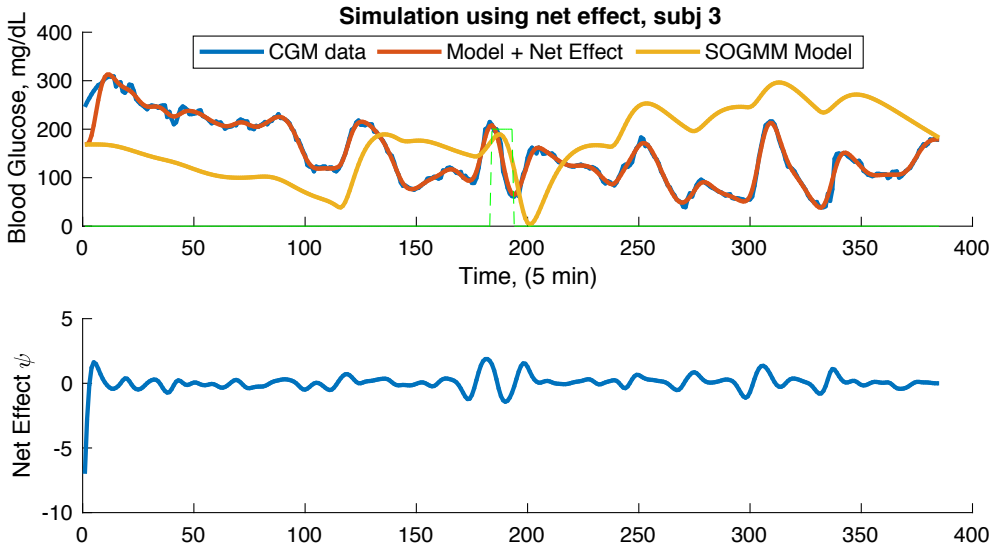

Figure 8.7: Simulation of the individual's glucose trace using the simple oral glucose minimal model (SOGMM) and representing the error between the model and the empirical data.

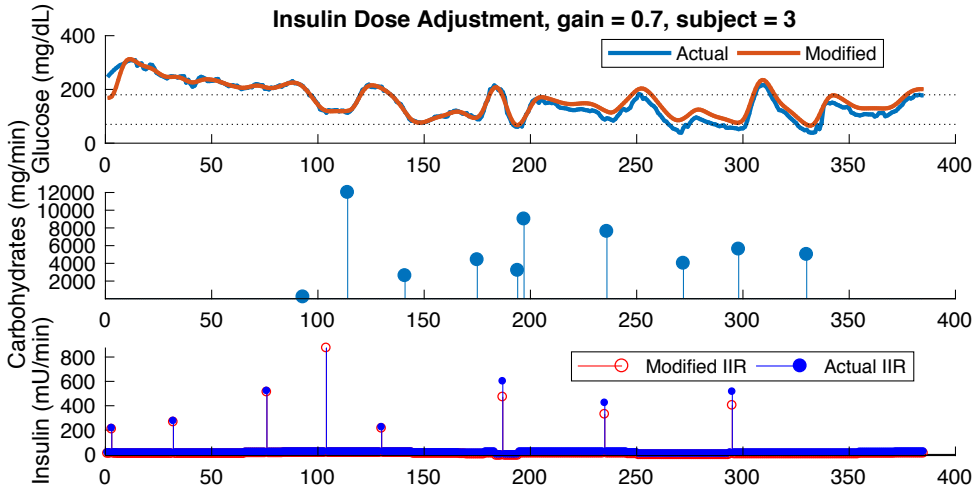

Figure 8.8: Simulating the response of the individual to a reduced dose of insulin. The hypoglycemic events could be prevented if the individual reduced the post exercise dosage by 30%.

intake information is ”fed” back into a mathematical representation of the glucose insulin dynamic system to calculate the error between the model and the true empirical glucose data. This error, termed ”net effect”, represents the mismatch between the physiological model and the true data. This approach allows for the reproduction of the true glucose data collected from the participant. Using this approach the insulin dosage could be adjusted to ”replay” the response of the individual as described by the mathematical equations. In Figure 8.7 an example of this approach using the mathematical model with the addition of the error associated with the model is shown. With the data represented in a mathematical form, a variety of insulin dosage modifications could be applied to simulate the individual's response to these modifications. In Figure 8.8 an example of this approach is shown. In this example, an individual with T1D after exercise experiences nocturnal hypoglycemia due to increased insulin sensitivity. Adjusting the dose of insulin by 30% before bed time could prevent these nocturnal hypoglycemic events. In the example, the glucose data is fit to the model up to the point when the exercise is completed (200 min) and the model is estimated for the period after that. The insulin dosage is modified for the period after the exercise, to ascertain the appropriate dosage that would provide the maximum benefit as determined by the dose that would prevent nocturnal hypoglycemia.

In this dissertaion we demonstrate the challenges associated with exercise in individuals

with T1D. We showed that these individuals could have hypoglycemic events due to exercise and also experience nocturnal hypoglycemia during the night following exercise. We demonstrate the aerobic exercise could cause significant sleep loss in these individuals. We showed that resistance training could improve glycemic control in the 24 hr. following exercise. With the goal towards providing decision support systems, we developed machine learning tools that could be used to estimate the risk of both exercise induced hypoglycemia and nocturnal hypoglycemia. We hope this work contributes in the reduction of hypoglycemic episodes experienced by in these individuals and encourages more individuals with T1D to engage in an active lifestyle.

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Study Protocol

PROTOCOL TITLE: A randomized, three-way, cross-over study to assess the impact of nocturnal hypoglycemia on sleep in patients with Type 1 diabetes.

STUDY SITE: Oregon Health Science University
3181 SW Sam Jackson Park Rd
Portland, OR 97239

FUNDING: M.J. Murdock Charitable Trust

PRINCIPAL INVESTIGATORS: Peter Jacobs PhD

CO-INVESTIGATORS: Jessica R. Castle MD
Joseph El Youssef MBBS

Background:
Growing evidence provided by many observational studies has established a strong link between decreased sleep duration and poor glucoregulation. Sleep deprivation and poor sleep quality induce insulin resistance and decrease glucose tolerance in healthy individuals. However, the influence of poor sleep quality on glycemic control of patients with Type 1 diabetes mellitus (T1DM) is unknown. Persistent sleep deprivation among patients with T1DM has been reported, and this sleep loss can be attributed in part to nocturnal hypoglycemia. Nocturnal iatrogenic hypoglycemia is a limitation of current intensive insulin therapies. Although severe hypoglycemia is associated with adverse events such as seizures and death, less severe nocturnal hypoglycemia has been linked to broad range of adverse consequences [1], both acutely [2,3] and long term [4]. Hypoglycemia stimulates the sympathetic nervous system as a stress response, leading to the stimulation of the hypothalamic–pituitary–adrenal axis (HPA). This results in a counter regulatory hormone cascade, which elicits an excessive cortisol secretion, which is known to cause sleep disturbance and could impair glucose homeostasis after the hypoglycemic event [5]. The hyperinsulinemia in T1DM patients promotes HPA hyperactivity as well [6], which is also associated with impaired sleep quality by leading to sleep fragmentation, decreased slow wave sleep and shortened sleep duration [7]. Sleep disturbances due to nocturnal hypoglycemia can exacerbate HPA axis dysfunction, adversely affecting the sleep–wake cycle. Another impact of poor sleep is the deterioration on insulin sensitivity the following day, it has been shown that reduction in sleep can reduce insulin sensitivity by as much as 20% [8,9] and this further exacerbates the cycle of poor glycemic control. Brod et al.[10,11] reported on a multinational survey of the consequences of non-severe nocturnal hypoglycemia, and found that among the participants who awoke to treat a hypoglycemic event, the average time to return to sleep was over an hour, and some did not return to sleep at all that night.

Regular exercise has been shown to improve glycemic control, reduce cardiovascular risk factors, lower insulin requirements, improve lipid profiles, decrease cardiovascular disease risk, improve endothelial function, delay onset and/or progression of peripheral neuropathy and increase self-reported quality of life in patients with T1DM [12]. However, the risk of hypoglycemia increases considerably during and after exercise [13]. Increased glucose utilization occurs during exercise and increased insulin sensitivity occurs both during and after exercise [14,15]. As a result, many patients with T1DM avoid physical activity, in order to avoid the unpleasant symptoms associated with hypoglycemia. A handful of recent short exercise studies indicated that anaerobic forms of exercise (weight lifting, sprinting and so forth) may reduce this risk [16, 17].

A better understanding of the antecedents of nocturnal hypoglycemia (iatrogenic, exercise, diet, etc.), its impact on sleep and the effect on glycemic control the following day could both improve routine clinical diabetes management and help inform the ongoing development of closed-loop insulin delivery systems.

The pilot study described within this protocol is designed to obtain and analyze data listed below:

- Subcutaneous blood glucose data from the continuous glucose monitor (CGM)
- Capillary blood glucose data from the blood glucose meter
- Daily insulin dosage data from the insulin pump
- Daily activity and sleep data from the activity monitor containing a 3-axis accelerometer and an ambient light sensor. The daily activity patterns will be analyzed in the context of location using the location data from the phone.
- Daily food intake using a photographic diet diary using an app on the phone.

The goal of the study is to understand the impact of nocturnal hypoglycemia on sleep.

Specific Objectives:
Primary Objectives:

- To measure the sleep patterns of patients with T1DM during weeks that include exercise events as compared to a week without exercise.
- To measure the changes in insulin requirements in patients with T1DM during weeks that include exercise events as compared to a week without exercise.

Secondary Objective:

- To measure the changes to insulin sensitivity during the nights with sleep loss compared with insulin sensitivity during nights with undisturbed sleep.

Study Hypothesis:
We propose that the nocturnal hypoglycemia causes loss of sleep in patients with T1DM after moderate exercise as opposed to days with no explicit exercise.

Endpoints
Primary Endpoints: (Time duration: From start of exercise till morning - 7am)

- Percent of time with sensed glucose <70 mg/dl
- Percent of time with sensed glucose between 70 – 180 mg/dl
- Loss of sleep as measured by time spent awake after sleep onset (WASO)

Secondary Endpoints: (Time duration: Entire study duration)

- Glycemic variability during the different treatment weeks
- Duration of sleep in patients with T1DM
- Sleep quality metrics such as time in bed (TIB), sleep start, sleep duration, sleep onset latency (SOL), total sleep time (TST), sleep efficiency (SE), number of wake bouts (# WB), mean wake bout time (MWBT), number of sleep bouts (# SB) and mean sleep bout time (MSBT).
- Number of carbohydrate treatments to treat hypoglycemia
- Daily carbohydrate intake
- Daily insulin intake
- Daily activity level
- Percent of time with sensed glucose <50 mg/dl
- Percent of time with sensed glucose >180 mg/dl

- Percent of time of capillary blood glucose (CBG) <70 mg/dl. Time with CBG <70 mg/dl defined as from the time the CBG is <70 mg/dl until the next CBG that is ≥70 mg/dl. Each time interval is summed and divided by the total time interval and expressed as a percentage.
- Percent of time of CBG between 70 – 180 mg/dl.
- Percent of time of CBG <50 mg/dl
- Percent of time of CBG>180 mg/dl

Study Type
This is a single center, randomized, three treatment, open, crossover trial designed to compare the sleep loss resulting from hypoglycemia during the weeks with days of aerobic exercise, resistance training and no explicit activity.

Study Population
Study population will be adults with type 1 diabetes, ages 21 – 45 years of age. Older subjects are excluded due to higher risk of unrecognized coronary artery disease. Younger subjects are excluded as it is appropriate to assess safety first in the adult population. 14 subjects will be recruited to participate in studies.

Power Analysis
A Paired Means Power Analysis was used to carry out a sample size power analysis. A total sample size of 14 achieves 95% power to detect a mean of paired differences of 30 minutes in sleep loss. This is with an estimated standard deviation of differences of 25 and with a significance level (alpha) of 0.05 using a two-sided paired t-test comparing sleep loss during the weeks of exercise interventions with the week without any explicit exercise.

Protocol Summary:

The study duration is 4 weeks long, during which subjects will undergo a 1 week run-in period followed by 3 randomized weeks of observational study. During the 1 week run-in period, subjects will familiarize themselves with the CGM and the other data collection procedures. Following the run-in week, the subject will be randomized to a specific order of observation weeks. The three observation weeks are a resistance training week, an aerobic exercise week and a control week with no explicit exercise. During the observation weeks, there will be 4 interventions planned, two during both the aerobic exercise and the resistance training week. See Schematic below for details. During both the aerobic exercise week intervention visits, subjects will exercise for ~45 minutes on a treadmill and during the resistance training week, subjects will perform strength training exercises for 1-3 sets per exercise at a weight that can be lifted for 8–12 repetitions (~60-80% of 1-repetition max). The duration of the resistance training period is expected to be ~45min. Subjects will continue to perform daily activities during each of the weeks.

Schematic of Study

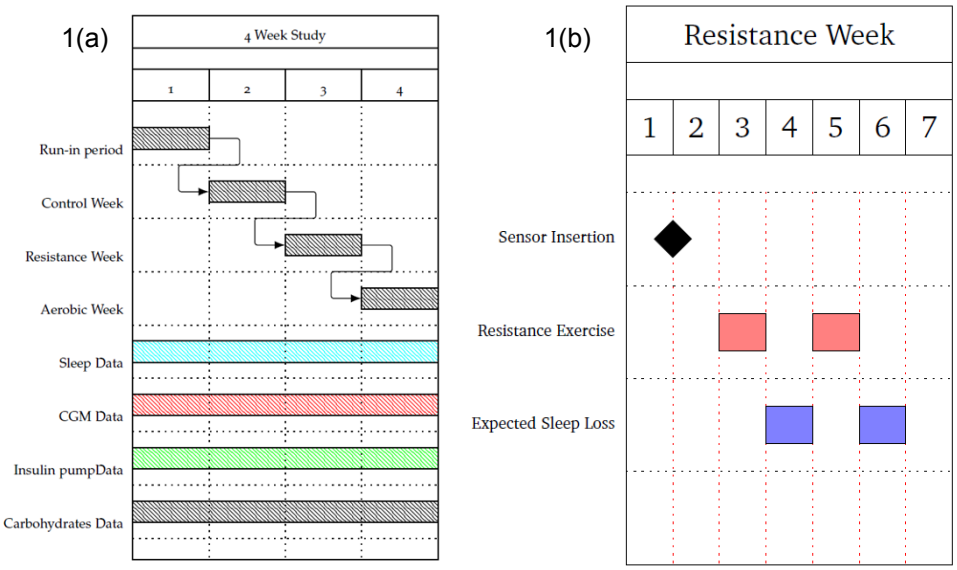

Figure 1(a) is an example of the proposed timeline for the study in which the control week with no exercise is followed by a week during which monitored resistance training is performed for 2 days of the week as shown in figure 1(b). Both the resistance training and aerobic exercise weeks follow a similar time course, the subject performs the exercise visits on the 3rd and 5th day of the week, with at least 5 days between the next set of exercise visits.

During each week, the subject will wear one subcutaneous Dexcom™ G4 or Dexcom™ G4 Share continuous glucose monitoring (CGM) system, one activity monitor- ActiGraph wGT3X-BT or ActiGraph GT9X, one insulin pump (subject's own pump) and one Samsung Galaxy S4 phone loaded with two applications- meal memory and moves. We also plan to include an optional innovative non-contact load cell system for detecting movements, breathing rates and heart rates of the subjects during sleep. The CGM system will provide sensed glucose data every 5 minutes. The CGM data will be blinded to the patient to prevent any abrupt changes in behavior. The accuracy of the sensed data will be obtained by reference measurements of capillary blood glucose. The activity monitor will be secured on the dominant wrist and uses an accelerometer to collect movement data at a high frequency (80Hz). The activity monitor measures both motion and ambient light, this data would be used to determine the various sleep quality measures. A non-contact load cell system may also be utilized to determine sleep quality pertaining to the subjects' vital signs such as breath rate and heart rate. This system consists of an aluminum plate with four load cells (or pressure sensors) on one side attached to a small computer hub. If used, this system will be placed under the mattress of the subject's bed and will be left there for the duration of the study. The load cells employ a subjects' change in pressure and weight distribution during sleep to detect breathing and heart rate. De-identified data from the load cells will be aggregated in the connected computer hub, which then wirelessly transmits the data to a password protected cloud server (Google). All data gathered would then be organized and transferred to OHSU's secure storage space: Box by research staff included in this study. The subject's insulin dosage information from the pump will be downloaded for data analysis purposes. The subject's daily meal intake (photographic log and note diary) and daily movement pattern information will be downloaded from the phone. During the 4 exercise intervention visits, subject's heart rate, accelerometry information from the torso and oxygen consumption measured breath by breath may be collected for data analysis purposes.

In order to try to minimize risks, all exercise interventions will be conducted by trained research study personnel. An on-call investigator will be available at all times during the intervention visits. The study investigators also retain the authority to modify any aspects of the protocol at his/her discretion if he/she believes the subject's safety is a concern.

Subject Criteria

Inclusion Criteria:

1. Diagnosis of type 1 diabetes mellitus for at least 1 year.
2. Male or female subjects 21 to 45 years of age.
3. Physically active on a regular basis, i.e. at least 3 days of physical activity per week.
4. Physically willing and able to perform 45 min of exercise (as determined by the investigator after reviewing the subjects activity level)
5. Current use of an insulin pump.
6. Willingness to follow all study procedures, including attending all clinic visits.
7. Willingness to sign informed consent and HIPAA documents.

Exclusion Criteria:

1. Female of childbearing potential who is pregnant or intending to become pregnant or breast-feeding, or is not using adequate contraceptive methods. Acceptable contraception includes birth control pill / patch / vaginal ring, Depo-Provera, Norplant, an IUD, the double barrier method (the woman uses a diaphragm and spermicide and the man uses a condom), or abstinence.
2. Any cardiovascular disease, defined as a clinically significant EKG abnormality at the time of screening or any history of: stroke, heart failure, myocardial infarction, angina pectoris, or coronary arterial bypass graft or angioplasty. Diagnosis of 2nd or 3rd degree heart block or any non-physiological arrhythmia judged by the investigator to be exclusionary.
3. Renal insufficiency (GFR < 60 ml/min, using the MDRD equation as report by the OHSU laboratory).
4. Impaired liver function, defined as AST or ALT ≥2.5 times upper limit of normal, according to OHSU laboratory reference ranges.
5. Hematocrit of less than or equal to 34%.
6. History of severe hypoglycemia during the past 12 months prior to screening visit or hypoglycemia unawareness as judged by the investigator.
7. Adrenal insufficiency.
8. Any active infection.
9. Known or suspected abuse of alcohol, narcotics, or illicit drugs (except marijuana use).
10. Seizure disorder.
11. Active foot ulceration.
12. Severe peripheral arterial disease characterized by ischemic rest pain or severe claudication.
13. Major surgical operation within 30 days prior to screening.
14. Use of an investigational drug within 30 days prior to screening.
15. Chronic usage of any immunosuppressive medication (such as cyclosporine, azathioprine, sirolimus, or tacrolimus).
16. Bleeding disorder, treatment with warfarin, or platelet count below 50,000.
17. Insulin resistance requiring more than 200 units per day.
18. Need for uninterrupted treatment with acetaminophen.
19. Current administration of oral or parenteral corticosteroids.
20. Any life threatening disease, including malignant neoplasms and medical history of malignant neoplasms within the past 5 years prior to screening (except basal and squamous cell skin cancer).
21. C peptide level of ≥0.5 ng/ml

22. Any concurrent illness, other than diabetes, that is not controlled by a stable therapeutic regimen.
23. Beta blockers or non-dihydropyridine calcium channel blockers.
24. A positive response to any of the questions from the Physical Activity Readiness Questionnaire.
25. Any chest discomfort with physical activity, including pain or pressure, or other types of discomfort.
26. Any clinically significant disease or disorder which in the opinion of the Investigator may jeopardize the subject's safety or compliance with the protocol.

Subject Recruiting:
Subjects will be recruited from OHSU clinics, from flyers to be posted in approved places at OHSU, or from the OHSU Subject Recruitment website. Records from OHSU Harold Schnitzer Diabetes Clinic patients may be screened to find potential subjects. Subjects will also be recruited from a list of subjects who participated in past OHSU studies, past studies involving Drs. Castle or El Youssef and from the OHSU diabetes research registry.

Non-English speaking subjects will not be recruited since this protocol will require use of devices and mobile software (Dexcom G4 Share, moves and meal memory) that do not have non-english versions available yet for users.

Up to 50 subjects may be screened in this study. Goal enrollment is 14 subjects, two blocks of seven patients. Up to four subjects will be replaced if needed, with a total enrollment of up to 18 subjects.

Withdrawal Criteria
The subject may withdraw at will at any time or at the discretion of the Investigator.

A subject must be withdrawn if the following applies:
1. Hypoglycemia during the treatment period posing a safety problem as judged by the investigator.
2. Hyperglycemia during the treatment period posing a safety problem as judged by the investigator.
3. Protocol deviation having influence on efficacy or safety data as judged by the Investigator.
4. Substantial and repeated non-compliance with trial procedures.
5. Pregnancy.
6. Intention of becoming pregnant.

Visit Procedures
Screening (Visit 1)
Screening will take place within 12 weeks prior to the first sensor insertion and training visit (Visit 2). All screening visits, will take place at OHSU's Oregon Clinical Translational Research Institute (OCTRI) or at the Harold Schnitzer Diabetes Health Center. Upon arrival and prior to any procedures, the consent form will be signed. A copy of the consent/authorization form will be given to the subject. The original will be kept for the source document.

Study personnel will review medical history, and medications. Height, weight, pulse, waist and hip circumference will be measured (mean of 3 measures) in a standing position to the nearest 0.1 cm using a non-stretchable tape over the unclothed abdomen at the top of the iliac crest and over the underwear at the largest circumference around buttocks, respectively and blood pressure will also be obtained. A study investigator will perform a physical examination, excluding breast and pelvic exams. Females of childbearing potential will take a urine pregnancy test, which must be negative to participate. A venous

blood sample will be taken for the following tests: hemoglobin A1C, complete blood count, complete metabolic set (including creatinine, liver set, and electrolytes), and c-peptide. An EKG will be performed. A study investigator will assess inclusion/exclusion criteria and review the subject's medical record for clarification as needed. A three-digit subject ID number will be assigned to the subject.

Subjects may undergo VO2max testing for cardiorespiratory fitness and the DEXA scan at the end of this screening visit if all inclusion criteria are met, and no exclusion criteria are met, with the exception of blood test results, which may not be immediately available. Research study personnel will be present during the VO2max testing for cardiorespiratory fitness. Research study personnel will assist the subject in locating the different labs where the tests are being performed. Additional CBG samples will be taken immediately before and after completion of the VO2max test. Subjects will be given 15-20 grams of carbohydrates for CBG values of <70 mg/dL at any point during the screening visit. CBG values will be reviewed by an investigator and subjects will be given juice and the VO2max test will be delayed by approximately 1 hour for CBG values of <80 mg/dL. Heart rate and accelerometry data may be optionally collected from the subject during the screening visit.

Subjects living within the Portland, who agree to sleeping alone on their bed at home may be offered the option of being monitored with the no-contact sleep monitoring system described above. Research staff will help with the in-home installation and dismantling of the system near the start and end dates of the study respectively.

Also, participants who have completed the study or already started the study will not be asked to consent to the addition of this device. Only participants who have not yet started the study or who have been screened but not yet started will be re-consented or given the option of this device being added to their study.

VO2max testing for cardiorespiratory fitness
VO2max testing will take place at the Human Performance Lab, which is located within OHSU and is attached to the main hospital. A code cart is on site within the Human Performance Lab and a code team is available by page at all times. Subjects will be asked to fast before the screening visit for 3 hours. A capillary blood glucose (CBG) will be obtained and measured by a Contour Next glucose meter and recorded after consenting. Prior to measurement of any blood samples, the meter will undergo quality control testing with two different glucose levels, one high and one low, and both values must fall within the accepted range for a meter to be used. After the CBG is obtained, the study investigator may adjust the subject's basal insulin rate as necessary in preparation for VO2max testing to avoid hypoglycemia. This testing is expected to last about 30 min.

DEXA for Bone Mineral Density, Body Composition and Body Fat Distribution:
Whole body and regional skeletal bone mineral density/content, whole body composition (total lean and fat mass and skeletal mineral content) and body fat distribution will be measured using Dual Energy X-ray Absorptiometry (DEXA) scans. A trained technician in OHSU's Body Energy and Composition Core or OHSU School of Nursing Health and Human Performance Lab will perform DEXA scans. Measurements will be made using a Lunar/GE iDXA Densitometer (GE Healthcare, Wauwatosa, WI) or Hologic Discovery WI and are expected to take 15-30 minutes. Actual scan time is less than 10 minutes.

Study procedures training visit and sensor insertion visit (Visit 2)
After arrival at the OHSU School of nursing or OHSU OCTRI or Harold Schnitzer Diabetes Health Center clinic, women of childbearing potential will receive a urine pregnancy test. This test must be negative before further participation is allowed.

Subjects will undergo the one repetition maximum (1-RM) to accurately assess the maximal muscle strength during this visit.

Muscle strength (1-RM):
Muscle strength testing will take place at the Human Performance Lab, which is located within OHSU School of Nursing building. Three distinct exercises, leg press, bench press and seated row will be evaluated to ascertain the maximal muscle strength of the subject. Lower extremity muscle strength will be measured with the 1-repetition maximum (1-RM) for leg press and isokinetic dynamometry of the lower extremity. Upper body chest muscle strength will be measured with 1-RM, for the bench press. Back and shoulder muscle strength including the erector spinae, middle and lower trapezius, rhomboids, latissimus dorsi, teres major and minor, posterior deltoid and the infraspinatus will be measured with 1-RM for the seated row. The 1-RM test is a safe and effective means of evaluating strength, even in populations that have never lifted weights before. The 1-RM is the most commonly used technique for measuring maximal strength in adult populations. The 1-RM test will be conducted according to the American College of Sports Medicine protocols by trained personnel. After the CBG is obtained, the study investigator may adjust the subject's basal insulin rate as necessary in preparation for 1-RM testing to avoid hypoglycemia or hyperglycemia. If CBG value is > 300 mg/dl, the subject may be managed at the discretion of the investigator. Serum ketones will also be checked. If serum ketones are ≥ 0.6 mM, the test may be halted and insulin therapy will be guided by the onsite investigator. Subjects will be given 15-20 grams of carbohydrates for CBG values of <70 mg/dL at any point during the visit.

Each subject will be fitted with one Dexcom™ G4 or Dexcom™ G4 Share CGM system. The wire glucose sensor is sterile and commercially available from Dexcom™ and will be used for single use only as directed by the manufacturer. The sensor will be inserted into the subcutaneous tissue of the abdomen or flank by study personnel after appropriate preparation of the abdominal skin as per the manufacturer's directions. The sensor expires after 7 days of use, the subject will be trained by the study personnel on how to the use the sensor insertion device and also how to insert the wire glucose sensor. The subject will be trained on how to use and calibrate the CGM system. The CGM system will be calibrated at home according to the manufacturer's directions. Subjects will be clearly instructed to use capillary glucose levels, not sensed glucose values, for the purpose of managing their diabetes at home. The sensed glucose values will be blinded to the subject, the subject will not know these values to manage their diabetes at home. The CGM alarms will be activated: 55mg/dL for hypoglycemia and 300mg/dL for hyperglycemia. Subjects will be given a Contour Next meter for measuring their capillary blood glucose in order to calibrate the Dexcom sensor prior to the study. Subjects will be instructed to change the wire glucose sensor in a sterile fashion weekly and follow the instructions available from the manufacturer Dexcom™ on the proper insertion of the wire glucose sensor. Subject may be given the documentation provided by the manufacturer Dexcom™ on the proper use of the glucose sensor and the sensor insertion device. Subjects will be instructed to discontinue the use of acetaminophen for the duration of the study.

The subject will also be asked to check his/her CBG before driving to the clinic and to bring a snack in the car in case hypoglycemia does occur (in which case, the subject must park and treat the hypoglycemia).

During this visit, the subject will also complete a training course on how to photographically record the diet diary, how to use the activity device, how the keep the devices charged and understand the proper use of the devices for the duration of the study. The first week of the study will be a run in period, to acclimatize the subject with the various devices and the procedures the subject is expected to perform. The subject will need to demonstrate competency in operating the devices before beginning the research study. During this visit, the subject may be asked to fill the questionnaires located in the appendix A of this protocol. The duration of this study visit is expected to be approximately 2 hours.

Study procedures follow-up (Visit 3)
The study procedures follow-up visit will be conducted by phone call to the subject at the phone number obtained during screening, to determine the general status of the subject after the study procedures. The subject will be contacted 48 hours (+/- 24 hours) after visit 2 of the study takes place.

2 Hour Intervention Visits (Visits 4, 6, 8 & 10)
These study visits will occur approximately 1 week after the sensor insertion visit (Visit 2). There are 2 visits during both the resistance training week and aerobic exercise weeks. After the last 2 hour intervention visit (either week), a washout period will be 5 days from the day of admission to the research center until the start of the next admission. Subjects will be asked to avoid vigorous activity within the 24 hours prior to all intervention visits. The subject will arrive at the exercise facilities at approximately 4pm. A capillary blood glucose (CBG) will be obtained and measured by a Contour Next glucose meter and recorded. Prior to measurement of any blood samples, each meter will undergo quality control testing with two different glucose levels, one high and one low, and both values must fall within the accepted range for a meter to be used. A new meter will be used for each subject and all CBG testing will be done on a Contour Next glucose meter. When they arrive, subjects will be given 15-20 grams of oral carbohydrate if the CBG reading is less than 70 mg/dl. CBG values > 300 mg/dl will be managed at the discretion of the investigator with a correction bolus. Serum ketones will also be checked. If serum ketones are ≥ 0.6 mM, the study will be halted and insulin therapy will be guided by the on-call investigator. At the start of each intervention visit, subjects may be fitted with an accelerometer, heart rate monitor and a mobile indirect calorimetry system.

Aerobic Exercise Week visits
Subjects will exercise at a fixed intensity level to a target heart rate (±10%) based on the heart rate achieved at 60% of their VO_{2max} determined at screening. This protocol will allow the exercise to be graded according to each participant's relative capacity. The speed and grade of the treadmill will be adjusted by trained research personnel with a goal of keeping participants within their target heart rate range for the entire 45 minutes. Study personnel will monitor the heart rate and the sensed glucose of the subject during the exercise. Each exercise session will be followed by 60 min of monitored resting recovery.

Resistance Training Week Visits:
Subjects will perform multiple-joint exercises with slow to moderate lifting velocity, for 1-3 sets per exercise at a weight that can be lifted for 8–12 repetitions (~60-80% of 1-repetition max). The exercises may include leg press, bench press, leg extension, leg flexion and seated row. Subjects will perform the exercises through the full range of motion. Between each set of repetitions, there would be a 2 minute rest period. The duration of the exercise testing would be approximately 45 minutes.
Study personnel will monitor the heart rate and the sensed glucose of the subject during the exercise. Each exercise session will be followed by 60 min of monitored resting recovery.

During the exercise period, there will be defined rules for stopping exercise, including:

1. If the subject feels unwell,
2. If the subject develops hypoglycemic symptoms, such as excessive sweating, shaking/tremors, palpitations, feelings of dread or panic, light-headedness, nausea, difficulty concentrating or the like.
3. If the subject develops chest pain/pressure,
4. If the subject develops undue shortness of breath (SOB),
5. Signs of poor perfusion: light-headedness, confusion, ataxia, pallor, cyanosis, nausea, or cold and clammy skin

6. If the maximum heart rate of the subject (MHR) is exceeded,
7. For patient preference.

If the exercise is stopped prematurely, the duration of exercise will be noted by the study personnel and if the subject is deemed safe to participate in future visits, the exercise will be stopped after that same time duration for subsequent visits. If capillary blood glucose is < 70 mg/dl at any point during the exercise period, the subject will treat with carbohydrates and delay completion of exercise until blood glucose rises above this level.

Discharge Procedures
The accelerometer, heart rate monitor and the indirect calorimetry device will be removed from the subject. A capillary blood glucose value will be taken immediately prior to discharging the subject. Subjects will be given oral carbohydrate for values below 85 mg/dl, and will be given an insulin bolus if deemed appropriate by the investigator for values above 300 mg/dl. The research on-call physician may consult with the subject regarding appropriate insulin dosing for the remainder of the day. Subjects may also be given a predetermined chosen meal after each exercise visit.

If installed the non-contact load cell equipment will be dismantled from the participants home at the end of the study.

Study intervention follow-up (Visits 5, 7, 9 &11)
The study intervention follow-up visit will be conducted by phone call to the subject at the phone number obtained during screening, to determine the general status of the subject. The subject will be contacted the next day after each exercise intervention of the study takes place. If necessary, an on-call investigator will be notified and will consult with the subject via phone or in person.

Study completion visit (Visit 12)
Subjects will return to OHSU OCTRI or Harold Schnitzer Diabetes Health Center clinic after the completion of the 3 week study period. Subjects will return all the sensors, the smartphone and may complete a questionnaire about the experience. Subject's insulin pump data will be downloaded at this visit.

Cleaning and Disinfecting
All devices will be cleaned and disinfected between subjects. If the heart rate monitor is a chest strap, it will be disinfected through OHSU Sterile Processing where they hand wash the straps and use CIDEX OPA to sterilize. The belt/carrier, smartphone, Dexcom G4 or G4 Share receiver and transmitter, the heart rate device, and activity monitor device watch bands are cleaned by study personnel. Study personnel who are disinfecting units will wash hands thoroughly and wear gloves. All items will undergo intermediate-level disinfection using SANI-CLOTH AF3 Germicidal disposable wipes. The disinfectant will be applied and allowed to air dry. Study personnel will dispose of gloves as biohazard waste and wash their hands immediately after completing disinfection. After disinfection, when the units are completely dry, they will be placed in a sealed bag labeled with the cleaning method, date and initials of study personnel that performed the disinfection.

Confidentiality and Protection of Human Subjects
RISKS and BENEFITS
Risks: The risks of the protocol procedures are considered minor. It should be noted that an investigator skilled in the treatment of diabetes mellitus will be immediately available during intervention visits.

Risks from exercise include falls, sprains, bruises, very low risk of bone fractures and head trauma. The likelihood of significant harm is quite low. In order to try to minimize risks, all testing will be conducted by trained personnel. Precautions to make the exercises as safe as possible have been taken. There is a minimal risk that the participant may feel a change in the firmness under the mattress when utilizing the non-contact load system for sleep analysis as this device will be placed under the subject's mattress.

Benefits: The subject may not directly benefit from being in this study; however, their participation may help to advance automated insulin and glucagon delivery technology.

Monitoring Entity:
Monitoring is described in a separate Data Safety Monitoring Plan uploaded as part of this submission.

Data Collection:
Subject privacy will be protected by using a three digit identifying number to code study documents. Study staff will record data required by the protocol onto the Case Report Forms (CRF). Case report forms (CRF) for this study will be entered into REDCAP, a clinical research electronic data repository housed at Oregon Health Science University and administered by the Oregon Clinical and Translational Research Institute (OCTRI). Investigators and research coordinator will verify that the procedures are conducted according to the approved protocol. All paper source documents will be kept in a locked cabinet for a minimum of five years. Original, completed CRF's will be kept with the PI in a designated repository. All data from CRF's will subsequently be entered into the authorized electronic REDCAP database.

Non-contact load cell data collected during overnight periods, will be aggregated by a computer hub (Odroid) that will be mounted underneath the bed. The Odroid computer will relay the de-identified data over a secure link to a password protected cloud server (Google Drive and Amazon Web Server) and then saved to Box. Only research staff will have access to this data server.

Recording of Data:
Investigators and staff will record data collected during the clinical trial on the CRF's. Case report forms (CRF) for this study will be entered into REDCAP, a clinical research electronic data repository housed at Oregon Health Science University and administered by the Oregon Clinical and Translational Research Institute (OCTRI). The REDCAP CRFs will include:

1. Screening form
2. Sensor Insertion Visit form
3. 2 hour intervention visit
4. Follow up Telephone Update form
5. Adverse Event form
6. Serious Adverse form
7. Concomitant Medications
8. Note to File

The Principal Investigator may authorize other personnel to make entries in the CRF.

Monitoring Procedures:
This protocol is written in accordance with the principles established by the 18th World Medical Assembly General Assembly (Helsinki, 1964) and amendments and clarifications adopted by the 29th (Tokyo, 1975), 35th (Venice, 1983), 41st (Hong Kong, 1989), 48th (Somerset West, South Africa, 1996), 52nd (Edinburgh, 2000), 53rd (Washington, 2002), 55th (Tokyo, 2004), and 59th (Seoul, 2008) General

Assemblies. The investigator will ensure that the study described in this protocol is conducted in full conformance with those principles, the protocol, current FDA regulations, ICH Good Clinical Practices (GCP) guidelines, Good Laboratory Practices (GLP) guidelines, local ethical and regulatory requirements, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), any IEC requirements relative to clinical studies. Should a conflict arise, the investigator will follow whichever law or guideline affords the greater protection to the individual subject. Unanticipated problems will be detected by reviewing descriptions of known or foreseeable adverse events and risks in the IRB-approved research protocol and the current IRB approved consent form, any underlying disease or conditions of the subject experiencing the adverse event, and a careful assessment of whether the adverse event is related or possibly related to the subject's participation in the study.

Triggers for reporting unanticipated problems are seizure, hospitalization, death or any other occurrence considered serious by the PI. If studies in two subjects are stopped for severe hypoglycemia or severe hyperglycemia, then the entire study will be halted. In addition, if there is any unexpected event such as death or patient hospitalization, the studies will be stopped until the root cause is evaluated.

Any adverse event and/or unanticipated problem (UP) will be reported to the PI and medical monitor immediately by one of the investigators. One of the investigators will always be on-call during the studies and will write up a description of the adverse event/unanticipated problem. All unanticipated problems will be reported to the IRB within five calendar days. A summary of all UP's and adverse events will be submitted with the continuing review.

Confidentiality Procedures:

To protect confidentiality, standard institutional practices will be followed as described in the OHSU Information Security and Research Data Resource Guide (http://ozone.ohsu.edu/cc/sec/isg/res_sec.pdf) to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures. Upon enrollment, subjects will be assigned with a three-digit code that will be used instead of their name, medical record number or other personally identifying information. The key associating the code and the subjects personnal identifying information will be restricted to the PI and study staff. The key will be kept secure on a restricted OHSU network drive in a limited access folder.

Electronic files for data analysis will contain only the subject code. Access to data/specimens is restricted to study personnel and requires OHSU ID/password authentication. Paper files will be stored in locked filing cabinets in restricted access offices at OHSU. Electronic data is stored on restricted drives on the OHSU network or stored on encrypted computers as well as on the web-accessible REDCap database housed on an OHSU secure server. User passwords will be changed every 3 months and a firewall will be enabled at all times. After the study, source documents will be maintained at the participating clinical center (or offsite record storage facilities) 2 years after a marketing application is approved for our group's artificial pancreas/decision support device since the data from this study will be included in future software revisions or discontinuance of pursuit of marketing approval. At the end of the study, an electronic copy of the database will be provided on a CD for long-term storage under lock.

Physical Activity Readiness Questionnaire (PAR-Q) and You

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly:

YES	NO		
☐	☐	1.	Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?
☐	☐	2.	Do you feel pain in your chest when you do physical activity?
☐	☐	3.	In the past month, have you had chest pain when you were not doing physical activity?
☐	☐	4.	Do you lose your balance because of dizziness or do you ever lose consciousness?
☐	☐	5.	Do you have a bone or joint problem that could be made worse by a change in your physical activity?
☐	☐	6.	Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?
☐	☐	7.	Do you know of any other reason why you should not do physical activity?

If you answered:	YES to one or more questions
	Talk to your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES. • You may be able to do any activity you want – as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice. • Find out which community programs are safe and helpful for you.

NO to all questions	Delay becoming much more active:
If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can: • Start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go. • Take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively.	• If you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or • If you are or may be pregnant – talk to your doctor before you start becoming more active. Please note: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed use of the PAR-Q: Reprinted from ACSM's Health/Fitness Facility Standards and Guidelines, 1997 by American College of Sports Medicine

Devices

ActiGraph wGT3X-BT

Dexcom Continuous Glucose Monitoring System which includes Sensor, Sensor Receiver and Sensor Transmitter

Samsung Galaxy S4 Smart phone

Contour Next EZ Blood Glucose Meter

Abbott Precision Xtra Meter

Appendix A : Questionnaires

Table 1—*Survey items used to categorize aware or having reduced awareness of hypoglycemia in subjects*

1) Check the category that best describes you: (check one only)
_____ I always have symptoms when my blood sugar is low (A)
_____ I sometimes have symptoms when my blood sugar is low (R)
_____ I no longer have symptoms when my blood sugar is low (R)

2) Have you lost some of the symptoms that used to occur when your blood sugar was low?
_____ yes (R) _____ no (A)

3) In the past six months how often have you had moderate hypoglycemia episodes? (Episodes where you might feel confused, disoriented, or lethargic and were unable to treat yourself)
_____ Never (A) _____ Once or twice (R) _____ Every other month (R)
_____ Once a month (R) _____ More than once a month (R)

4) In the past year how often have you had severe hypoglycemic episodes? (Episodes where you were unconscious or had a seizure and needed glucagon or intravenous glucose)
_____ Never (A) _____ 1 time (R) _____ 2 times (R) _____ 3 times (R)
_____ 5 times (R) _____ 6 times (R) _____ 7 times (R) _____ 8 times (R)
_____ 9 times (R) _____ 10 times (R) _____ 11 times (R)
_____ 12 or more times (U)

5) How often in the last month have you had readings <70 mg/dl with symptoms?
___ Never ___ 1 to 3 times ___ 1 time/week ___ 2 to 3 times/week ___ 4 to 5 times/week
___ Almost daily

6) How often in the last month have you had readings <70 mg/dl without any symptoms?
_____ Never _____ 1 to 3 times _____ 1 time/week _____ 2 to 3 times/week
_____ 4 to 5 times/week _____ Almost daily

(R = answer to 5 < answer to 6, A = answer to 6 > answer to 5)

7) How low does your blood sugar need to go before you feel symptoms?
_____ 60–69 mg/dl (A) _____ 50–59 mg/dl (A) _____ 40–49 mg/dl (R)
_____ <40 mg/dl (R)

8) To what extent can you tell by your symptoms that your blood sugar is low?
_____ Never (R) _____ Rarely (R) _____ Sometimes (R) _____ Often (A)
_____ Always (A)

Four or more R responses = reduced awareness; 2 or fewer R responses = aware.

Berlin questionnaire [1]

Ravi Reddy

September 30, 2015

Height (m)——Weight (kg)——Age——Male/Female

Please choose the correct response to each question

CATEGORY 1

1. **Do you snore?**
   (a) Yes
   (b) No
   (c) May be

If you snore:

2. Your snoring is:
   (a) Slightly louder than breathing
   (b) As loud as talking
   (c) Louder than talking
   (d) Very loud - can be heard in adjacent rooms
3. **How often do you snore**
   (a) Nearly every day
   (b) 3-4 times a week
   (c) 1-2 times a week
   (d) 1-2 times a month
   (e) Never or nearly never
4. **Has your snoring ever bothered other people?**
   (a) Yes
   (b) No
   (c) Don't know
5. **Has anyone notices that you quit breathing during your sleep?**
   (a) Nearly everyday
   (b) 3-4 times a week
   (c) 1-2 times a week
   (d) 1-2 times a month
   (e) Never or nearly never

CATEGORY 2

6. **How often do you feel tired or fatigued after you sleep?**
   (a) Nearly everyday
   (b) 3-4 times a week
   (c) 1-2 times a week
   (d) 1-2 times a month
   (e) Never or nearly never
7. **During your waking time, do you feel tired, fatigued or not up to par?**
   (a) Nearly everyday
   (b) 3-4 times a week
   (c) 1-2 times a week
   (d) 1-2 times a month
   (e) Never or nearly never
8. **Have you ever nodded off or fallen asleep while driving a vehicle?**
   (a) Yes
   (b) No

If yes:

9. **How often does this occur?**
   (a) Nearly everyday
   (b) 3-4 times a week
   (c) 1-2 times a week
   (d) 1-2 times a month
   (e) Never or nearly never

CATEGORY 3

10. **Do you have high blood pressure?**
    (a) Yes
    (b) No
    (c) Don't know

[1] Adapted from : Netzer, N. C., R. A. Stoohs, C. M. Netzer, K. Clark, and K. P. Strohl. 1999. *Using the Berlin Questionnaire to Identify Patients at Risk for the Sleep Apnea Syndrome.* Annals of Internal Medicine 131 (7), 485-91.

Epworth Sleepiness Scale [1]

Ravi Reddy

October 6, 2015

[1] Adapted from : Johns, M. W. 1991. *A New Method for Measuring Daytime Sleepiness: The Epworth Sleepiness Scale.* Sleep 14 (6) : 540—45.

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in recent past. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation :

- 0 = no chance of dozing
- 1 = slight chance of dozing
- 2 = moderate chance of dozing
- 3 = high chance of dozing

Height (m)——Weight (kg)——Age——Male/Female

Please choose the correct response to each question

Situation	Chance of dozing
Sitting and reading	
Watching TV	
Sitting inactive in a public place (e.g a theater or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in traffic	

Name_____ Date_____

Sleep Quality Assessment (PSQI)

What is PSQI, and what is it measuring?

The Pittsburgh Sleep Quality Index (PSQI) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month.

INSTRUCTIONS:

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. What time have you usually gotten up in the morning? _____
4. A. How many hours of actual sleep did you get at night? _____
   B. How many hours were you in bed? _____

5. During the past month, how often have you had trouble sleeping because you	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
A. Cannot get to sleep within 30 minutes				
B. Wake up in the middle of the night or early morning				
C. Have to get up to use the bathroom				
D. Cannot breathe comfortably				
E. Cough or snore loudly				
F. Feel too cold				
G. Feel too hot				
H. Have bad dreams				
I. Have pain				
J. Other reason (s), please describe, including how often you have had trouble sleeping because of this reason (s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
9. During the past month, how would you rate your sleep quality overall?	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)

International physical activity questionnaire [1]

Ravi Reddy

October 2, 2015

[1] Adapted from : Craig, Cora L., Alison L. Marshall, Michael Sjöström, Adrian E. Bauman, Michael L. Booth, Barbara E. Ainsworth, Michael Pratt, et al. 2003. "International Physical Activity Questionnaire: 12-Country Reliability and Validity." Medicine and Science in Sports and Exercise 35 (8): 1381—95.

This document will used to understand the time you spent being physically active in the last 7 days. Please answer each question even if you do not consider yourself to be an active person. Think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the *vigorous activities* which take *hard physical effort* that you did in the last 7 days. *Vigorous activities* make you breathe much harder than normal and may include heavy lifting, digging, aerobics, or fast bicycling. Think about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities? Please consider only those physical activities that were at least 10 minutes at a time.
   (a) _____ Days per week
   (b) Don't know or Not sure
   (c) Refuse to answer
2. How much time did you usually spend doing **vigorous** physical activities on one of those days? Please consider only those physical activities that were at least 10 minutes at a time.
   (a) _____ Hours per day
   (b) _____ Minutes per day
   (c) Don't know or Not sure
   (d) Refuse to answer

Now think about activities which take *moderate physical effort* that you did in the last 7 days. Moderate physical activities make you breathe somewhat harder than normal and may include carrying light loads, bicycling at a regular pace or doubles tennis. Do not include walking. Please consider only those physical activities that were at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do moderate physical activities?
   (a) _____ Days per week
   (b) Don't know or Not sure
   (c) Refuse to answer
4. How much time did you usually spend doing **moderate** physical activities on one of those days? Please consider only those physical activities that were at least 10 minutes at a time.

4. How much time did you usually spend doing **moderate** physical activities on one of those days? Please consider only those physical activities that were at least 10 minutes at a time.

   (a) _____ Hours per day

   (b) _____ Minutes per day

   (c) Don't know or Not sure

   (d) Refuse to answer

Now think about the time you spent walking in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

   (a) _____ Days per week

   (b) Don't know or Not sure

   (c) Refuse to answer

6. How much time did you usually spend **walking** on one of those days?

   (a) _____ Hours per day

   (b) _____ Minutes per day

   (c) Don't know or Not sure

   (d) Refuse to answer

Now think about the time you spent sitting on the week days during the last 7 days. Please include time spent at work, at home while doing course work, and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television.

7. During the *last 7 days*, how much time did you spend **sitting** on a week day?

   (a) _____ Hours per day

   (b) _____ Minutes per day

   (c) Don't know or Not sure

   (d) Refuse to answer

Subject post study survey:
Please circle your answer below.
5 = extremely helpful, 4 = very helpful, 3 = somewhat helpful, 2 = slightly helpful, 1 = not at all helpful

- How satisfied were you with the study?

  Not helpful at all 1 2 3 4 5 (extremely helpful)

- How do you rate the usability of the app?

  Not helpful at all 1 2 3 4 5 (extremely helpful)

- Do you think you would like more training on carb estimation?

  Yes No

- Would you like an application that would suggest changes to basal and bolus dosing based on the photos taken of past and current meals?
  Yes No

- Would you like an application that would suggest changes to basal and bolus dosing based on your past or anticipated exercise?
  Yes No
- Would you like an application that would suggest changes to basal and bolus dosing based on your past or anticipated sleep?
  Yes No

- Would you like an application that would suggest changes to lifestyle decisions such as exercise, sleep, and nutrition based on your past glycemic control?
  Yes No

5 = extremely satisfied, 4 = very satisfied, 3 = somewhat satisfied, 2 = slightly satisfied, 1 = not at all satisfied

- How satisfied are you with your current diabetes therapy?

  Not satisfied at all 1 2 3 4 5 (extremely satisfied)

Please include any additional comments regarding the areas of you would like more decision support on:

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