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Abstract

We have developed a model of the blood glucose / insulin metabolism of a diabetic patient. The model consists of a combination of a compartment module and a neural network module and was trained with data from a diabetic patient using the dynamic backpropagation algorithm. We demonstrate how our model can be used both to predict blood glucose levels and to optimize the patient's therapy.

1 INTRODUCTION

Modeling physiological systems is considered indispensable for biomedical research. In particular, recent progress in the treatment of cardiovascular disease and diabetes is credited partially to the improvements in mathematical and computer models (FASEB, 1989). There are two principle applications for physiological models: first, in a research context, modeling can suggest new experiments or test new hypotheses. Second, in a therapeutic context, computer models can be used to predict the effects of a treatment and to design improved therapies.

Physiological modeling is typically performed using compartment models in which the link between the model and the underlying physiology is relatively strong. Compartment models can be readily interpreted since model parameters consist of (in principle) measurable quantities for an assumed structure. However, the model structure may rely on (possibly incorrect) prior physiological assumptions (such as linearity). In contrast to compartment models, artificial neural networks have the ability to learn structure from data and, either alone or in combination with compartment models, open up a new dimension for physiological modeling.

As a case study we have considered the glucose / insulin metabolism of a diabetic patient. Although the most important physiological interactions are known qualitatively, a quantitative model which is sufficiently sophisticated for therapeutic use has not yet been developed. Difficulties arise since the interactions are multi-dimensional, highly nonlinear, time variant and patient specific. The goal of this work is the development of a patient-specific model that is accurate enough to form the basis for a system that warns the patient of dangerous metabolic states and makes recommendations to optimize the patient's therapy. Furthermore, a metabolic model is necessary to design a stabilizing control system for blood glucose regulation, a so-called "artificial beta cell".

2 DIABETES MELLITUS

Figure 1 shows a very simplified model of the glucose metabolism. The digestive tract breaks down most of the carbohydrates in the food into glucose and releases it into the blood stream. Glucose is stored in the liver as glycogen and released again if the blood glucose drops too low. The extraction of glucose from the blood stream by the liver requires insulin, which suppresses indirectly the inverse process, the release of glucose by the liver.

Most cells (including muscle cells) need insulin to absorb and utilize glucose. One exception is the central nervous system which relies completely on glucose for its energy, but fortunately does not require insulin to metabolize it. Glucose is lost in urine (renal clearance) if the blood glucose level increases above the renal threshold.

The glucose metabolism and blood glucose level in a healthy person are kept within tight tolerances and are controlled by the secretion of insulin by the beta-cells of the pancreas. In a person with type 1 diabetes mellitus, the insulin production is either largely reduced or ceases completely due to impairment or death of the beta cells. Treatment consists of administering insulin by injection, or more rarely, through an external or implanted insulin pump. In modern "intensive therapy", the patient attempts to lead as normal a life as possible, adjusting his or her daily schedule of meals and exercise by monitoring his or her blood glucose a few times a day. Essentially, the patient has to replace an internal feedback mechanism with an external feedforward control which can be done only imperfectly. Consequently, a patient's blood glucose can often be outside of the desired range.

The goal of this work is the development of a physiological model which can be used as a basis for predictions and therapeutic recommendations. In the design of our system, we have had to take into account that the model must be able to capture variations between patients and parameter drifts for a given patient. Furthermore, the model must be able to adapt using patient data collected under normal every day conditions rather than the controlled conditions typical of a clinic. In a non-clinical setting, only a few blood glucose measurements per day are available. Between measurements, the model must predict the blood glucose level based on the past sequence of measurements, the carbohydrate intake, the times and dosages of insulin injections, and the times and intensities of exercise.

Our data set consists of the protocol of a diabetic over a period of almost 6 months. During that time period, the patient recorded the times and dosages of insulin injections (basal insulin and normal insulin), the times and amounts of food intake (fast, intermediate and slow carbohydrates), the times and durations of exercise (regular or intense) and the blood glucose level (measured a few times a day).

3 MODELING THE GLUCOSE METABOLISM

In this section we describe two models we have developed, a nonlinear compartment model and a combined neural-compartment model.[1] Both models have the structure depicted in figure 2.

3.1 A NONLINEAR COMPARTMENT MODEL

Most compartment models described in the bioengineering literature are linear. Linearized models of the glucose / insulin metabolism have sometimes been used in the the design of a closed-loop control systems for the artificial beta cell, but due to the inherent system nonlinearities perform purely as predictors. We developed a nonlinear model consisting of an input compartment module followed by a nonlinear glucose dynamics module (see figure 2). The input module $\mathcal{M}_d$ models the time delays associated with external control actions $\mathbf{x}$ which affect the blood glucose level, such as insulin injections, food ingestion, and exercise. The glucose dynamics module $\mathcal{M}_n$ models the nonlinear dynamics of the blood glucose level in response to delayed inputs $\mathbf{y}$ and internal metabolic processes.

[1] For a description of a hierarchical neural/compartment model which we have not included here, see Tresp *et al.* (1993). For a review of more traditional approaches based upon expert systems and linear controllers, see Carson and Deutsch 1992. For a general description of compartment models, see Seber and Wild 1989.

The components of the input vector $\mathbf{x}$ are x_1: fast carbohydrates, x_2: medium fast carbohydrates, x_3: slow carbohydrates, $x_4 = x_{ins}$: normal insulin, x_5: basal insulin, x_6: exercise, and x_7: intensive exercise. $\mathbf{x}$ is equal to zero except if there is an event, such as food intake, insulin injection or exercise. For our data set, inputs $\mathbf{x}$ were recorded with 15 minute time resolution.

The output $\mathbf{y}$ of the compartment model $\mathcal{M}_d$ can be expressed in simplified form as a convolution $\mathbf{F} \circ \mathbf{x}$, where $\mathbf{F}(t-\tau)$ is a diagonal matrix of impulse response functions which capture the delayed response. Each diagonal element of $\mathbf{F}$ has a functional form

$$f_{ii}(t) = a_i t^{p-1} e^{-b_i t} \ ,$$

where p denotes the model order (number of compartments in series) for that input variable. Hence, the components of $\mathbf{y}$ are

$$y_i(t) = \sum_{\tau=-\infty}^{t} f_{ii}(t-\tau)\, x_i(\tau) \ .$$

As an example, the uptake rate of normal insulin after a single injection is determined by the diffusion of the subcutaneously injected insulin into the blood stream. This delayed effect can be modeled by three first order linear compartments in series or equivalently, as we have done, by a third-order response equation $y_{ins}(t) = a(t-\tau)^2 e^{-b(t-\tau)} x_{ins}(\tau)$, with τ being the time of injection.

The impulse response functions $f_{ii}()$ for the digestive tract and for exercise are less well known. In our experiments, we followed Detschew (1990) and used a third order response function as above, but where the coefficients a and b depend nonlinearly on the amplitude of the input (for details, see Detschew (1990)). This refinement complicates the impulse response so that the linear convolution described above is no longer completely accurate. Thus, our $\mathcal{M}_d$ is a nonlinear, rather than linear, compartment model.

Module $\mathcal{M}_n$ captures the dynamics of the blood glucose g by the nonlinear differential equation

$$\begin{aligned} \frac{dg}{dt} &= c_1 \times (y_1 + y_2 + y_3) + c_2 \times (e^{-c_3 \times (y_4 + y_5)} - c_4 \times g) \\ &\quad - c_5 \times (y_4 + y_5) \times (g + c_6) - c_7 \times \sqrt{g} - c_9 \times (y_6 + y_7) - c_8 \times g^3 . \end{aligned} \tag{1}$$

The first term on the right side of the equation describes the increase in blood glucose due to carbohydrates in the food, the second term approximates the insulin dependent glucose production of the liver (if this term becomes negative, it is set to zero), the third term describes insulin dependent usage of blood glucose, the fourth term describes the insulin independent usage of blood glucose, the fifth term describes the blood glucose lowering effect of exercise and finally the last term describes the renal clearance (this term should be set to zero if blood glucose is below the renal threshold). We formulated this equation and chose the initial values for the parameters ($c_1 ... c_9$) with the benefit of published data (Andreassen et al., 1991, Cobelli and Mari, 1983, Detschew, 1990).

The prediction performance of the model was improved considerably after we adapted the parameters of both $\mathcal{M}_d$ and $\mathcal{M}_n$ using the dynamic backpropagation algorithm. A description of dynamic backpropagation and an evaluation of the performance of our nonlinear compartment model is found in Section 4.

3.2 COMBINED NEURAL-COMPARTMENT MODEL

The response functions $f_{ii}()$ in $\mathcal{M}_d$ describe the delayed effect of the inputs on the blood glucose, and we assume that the functional form of $f_{ii}()$ is sufficient to capture the various delays of the inputs and can be tuned to the physiology of the patient by varying the parameters a, b. The nonlinear dynamical Equation 1, on the other hand, is based on a number of uncertain physiological assumptions, and we cannot necessarily expect that the true interactions can be well approximated by just adapting equation parameters.

To be able to capture more complex interactions, we replace $\mathcal{M}_n$ described above by a neural network. While there are many ways in which we could use a neural network for this problem, utilizing a neural network in this way has two advantages: first, although our model is a feedback system the network itself is purely feedforward and we do not have to incorporate any hidden dynamics in the network and, second, $\mathcal{M}_d$ allows us to incorporate prior knowledge concerning the delayed effects of the inputs.

As for the nonlinear compartment model described above, the four inputs to the network are food: $(y_1 + y_2 + y_3)$, insulin: $(y_4 + y_5)$, exercise: $(y_6 + y_7)$ and the current estimate of the blood glucose g. In the next section we describe the network learning rules and preliminary experimental results.

4 PREDICTION WITH THE COMBINED MODEL

4.1 TRAINING

The neural network $\mathcal{N}$ predicts the rate of change of blood glucose

$$\frac{dg}{dt} = \mathcal{N}(g, \mathbf{y}). \tag{2}$$

The least squares estimate of the weights in the network can be found by minimizing $E = \sum_m (g_m^* - g(t_m))^2$ where g_m^* is the measured blood glucose level at time t_m and $g(t)$ is the model glucose value at time t.

Since target values g_m^* are only available a few times a day, a dynamic learning rule had to be employed (dynamic backpropagation, Narendra and Parthasarathy, 1990). Let u be a generic weight in the neural network and v be a generic parameter in the compartment module and $w = (v, u)$. The adaptation rule for w is gradient descent in the error,

$$\Delta w \propto -\frac{dE}{dw} = \sum_m (g_m^* - g(t_m)) \frac{dg}{dw}.$$

The sensitivities $g_w \equiv \frac{dg}{dw}$ obey differential equations obtained by differentiating Equation 2 with respect to w. For network weights u and for compartment module parameters v we obtain[2]

$$\frac{dg_u}{dt} = \frac{\partial \mathcal{N}}{\partial u} + \frac{\partial \mathcal{N}}{\partial g} g_u \qquad \frac{dg_v}{dt} = \sum_i \frac{\partial \mathcal{N}}{\partial y_i} \frac{dy_i}{dv} + \frac{\partial \mathcal{N}}{\partial g} g_v. \tag{3}$$

In our experiments, we used networks of either sigmoidal response units (MLP) or radial-basis functions (RBF).

4.2 PREDICTION

Figure 3 shows some preliminary experimental results. Although it is too early to give quantitative results, it seems that the combined neural-compartment model can make good qualitative short term predictions. When we trained the models on half of the available data and tested the generalization on the other half, the combined neural-compartment model improved the generalization with respect to the nonlinear compartment model by 30%.

5 CONTROL: OPTIMIZING THE THERAPY

The goal of the therapy is to normalize the metabolic state of a diabetic patient (normoglycemia). The previous sections showed how we can construct predictive models of the metabolism. We can now use such models to optimize the times and dosages of insulin injections (here we consider only normal insulin). Our control objective in this optimization is to achieve normoglycemia, i.e. to keep the blood sugar level within its normal range.

A cost function C penalizes deviations between predicted blood glucose and desired blood glucose. In general, C should be chosen according to physiological knowledge about short term and long term risks. We use $C = \int (g_{desired} - g(t))^2 \, dt$, where g is the blood glucose predicted by the model and $g_{desired} = 30$ mmol is the desired blood glucose.[2] The goal is to optimize the therapy such that C is minimized. Without continuous measurement and control, we cannot expect to reduce C to zero. Assuming that we have obtained a good model, however, we can reduce C dramatically from what is obtained by the traditional outpatient therapy methods.

[2]The desired range is between 3.3 - 5.6 mmol/liter or 19.8 - 33.6 mmol of blood glucose total assuming that our patient has 6 liters of blood. We chose 30 mmol as the desired value since low values are dangerous.

5.1 SENSITIVITY ANALYSIS

According to our model, the response to an insulin injection can be described as

$$y_{ins}(t) = \sum_j U_j \; f_{ins}(t - T_j).$$

Here, $U_j \; f_{ins}(t - T_j)$ is the insulin response to an injection of U_j units injected at time T_j. In other words, T_j are the instants in time for which x_{ins} is unequal to zero and has amplitudes (dosages) U_j. U_j and T_j can be optimized by gradient descent

$$\begin{aligned} U_j^{new} &= U_j + \Delta \int (g_{desired} - g(t)) \frac{dg}{dU_j} dt \\ T_j^{new} &= T_j + \Delta \int (g_{desired} - g(t)) \frac{dg}{dT_j} dt \; . \end{aligned}$$

The sensitivities $g_{U_j} = \frac{dg}{dU_j}$ and $g_{T_j} = \frac{dg}{dT_j}$ can be found by integrating the dynamic equations

$$\frac{dg_{U_j}}{dt} = \frac{\partial \mathcal{N}}{\partial y_{ins}} \frac{dy_{ins}}{dU_j} + \frac{\partial \mathcal{N}}{\partial g} g_{U_j} \qquad \frac{dg_{T_j}}{dt} = \frac{\partial \mathcal{N}}{\partial y_{ins}} \frac{dy_{ins}}{dT_j} + \frac{\partial \mathcal{N}}{\partial g} g_{T_j}$$

where the compartment model sensitivities to therapy are

$$\frac{dy_{ins}}{dU_j} = f_{ins}(t - T_j) \qquad \frac{dy_{ins}}{dT_j} = -U_j \; f'_{ins}(t - T_j).$$

Here, the prime denotes the derivative with respect to the argument. Figure 4 shows the improvement of the blood glucose achieved by optimizing the therapy.

6 CONCLUSIONS

Our initial results are very encouraging. Our system's ability to both predict blood glucose levels and to suggest therapy modification (control) makes it unique. The adaptive nature of our system allows it to be fine-tuned to individual patients and to respond to nonstationarity in the patients' metabolism.

However, the problem of predicting and controlling the glucose metabolism remains difficult due to the complexity and nonstationarity of the physiological processes. A great deal of further development and testing will be required before a system like ours could be widely used by diabetic patients or by their physicians.

Encouraged by our initial success, however, we are convinced that neural networks will find a large number of applications for modeling complex dynamical systems in medicine, biology, and chemistry.

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Figures

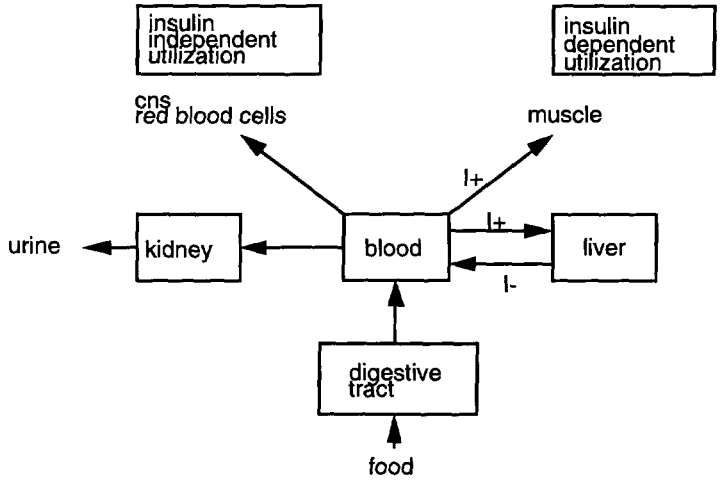

Figure 1: Simplified model of the glucose metabolism. I^+ and I^- indicate insulin-activated and insulin-suppressed pathways, respectively. The liver stores glucose as glycogen. See section 2 for further details.

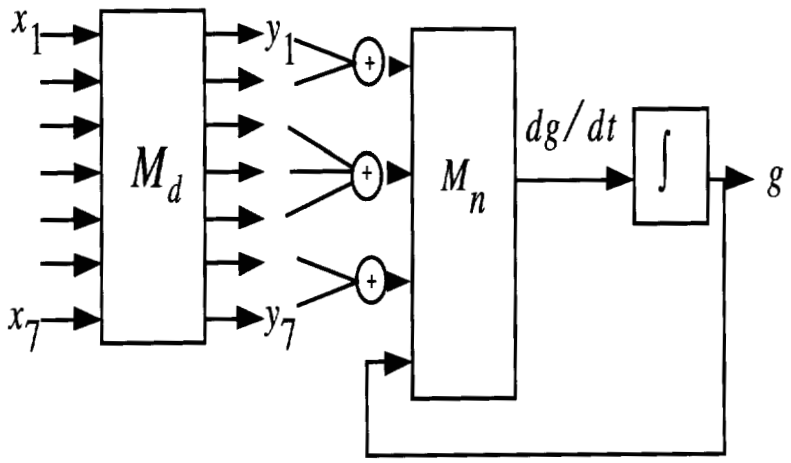

Figure 2: The systems presented in this paper contain two modules, a input compartment module $\mathcal{M}_d$ followed by a nonlinear dynamics module $\mathcal{M}_n$. In one of our models, the functional form of $\mathcal{M}_n$ is hand-designed based on physiological knowledge. In the second, $\mathcal{M}_n$ contains a neural network. In both models, all parameters are determined by dynamic backpropagation.

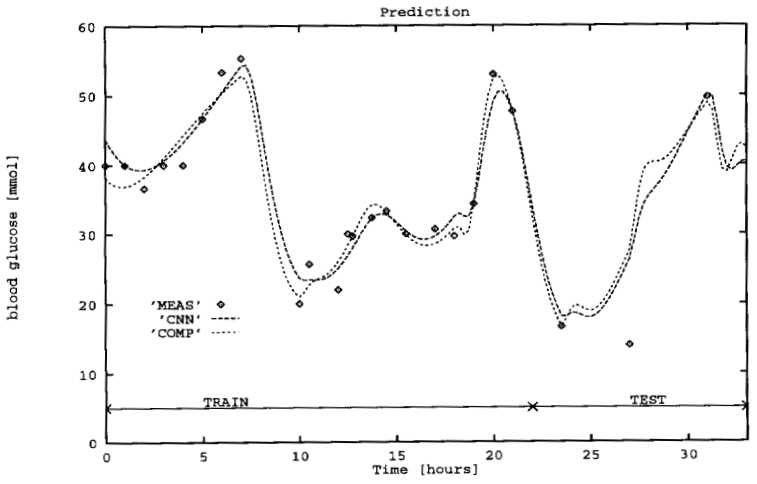

Figure 3: Prediction of the blood glucose by the model and actual measurements. The line labeled "CNN" shows the prediction by the combined neural-compartment model and the line labeled "COMP" shows the prediction by the nonlinear compartment model. Training set and test set are as indicated.

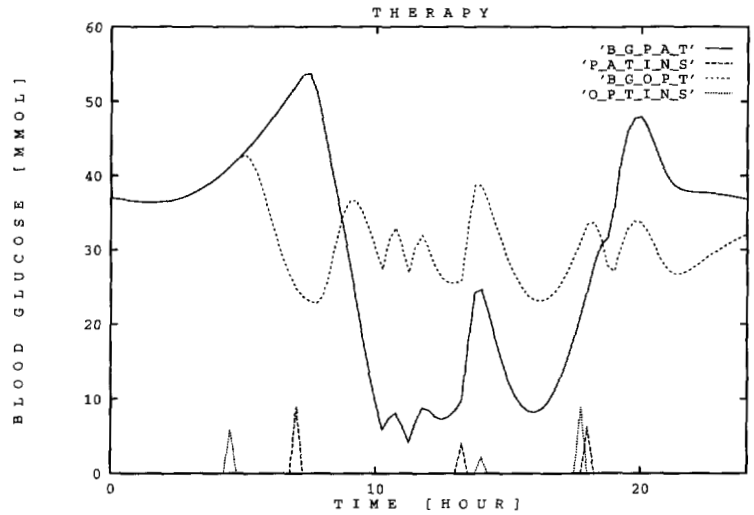

Figure 4: Control of the therapy. Using the combined neural-compartment model, the continuous line (labeled "BG-PAT") shows the predicted blood glucose with the therapy used by the patient. Note the dangerously low blood glucose at around 11 am. The solid line (labeled "BG-OPT") shows the predicted blood glucose if the optimized therapy is employed. The peaks at the bottom indicated the time and amount of insulin injected following initial and optimized therapy.