Statistical Biophysics Blog: Statistical mechanics in biology and biocomputation
http://statisticalbiophysicsblog.org/

[Note: Some posts were originally written at the University of Pittsburgh. Corrections and updates are included in this Digital Commons version.]

Keywords: biology, bioenergetics, book review, physics, chemistry

Title: So you want to learn biology? Required reading, Part 1.
http://statisticalbiophysicsblog.org/?p=134
Original publication date: June 23, 2016

You're a quantitative person and you want to learn biology. My friend, you are in a difficult situation. If you really want to learn how biology works in a big-picture sense, as opposed to cutting yourself a very narrow slice of the great biological pie, then you have a challenging road ahead of you. Fortunately, many have walked it before you, and I want to give you some advice based on my own experiences. I should say at the outset that my own learning has focused mostly on the cell-biology part of the pie - not physiology, zoology, ecology, … and so my comments here refer to learning cell biology.

The scary thing is that I have been at this for almost 20 years (very part-time admittedly) and I would never dare to call myself a cell biologist. But I think it's fair to say that by now I have a decent sense of what I know and what I don't know. I will never be able to draw out the Krebs cycle, but I have a qualitative sense of its purpose and importance, as well as of general principles of cycles and catalyzed reactions in biochemistry. Not that impressive, I know, but I'm proud of it anyway.

If you're looking at this post, you've probably already tried to read a general, molecular or cell biology book and suffered the usual fate of the quantitative scientist: the sense of being overwhelmed by so many special cases … and wondering whether there are basic principles at play beyond the quantum mechanics of chemical reactions. My advice is to hold onto that 1,500 page book - it will be a great reference, I promise. (My own favorite is Alberts et al., *Molecular Biology of the Cell,* which actually has a solid physical grounding.) But there are much better places to start.

Required text #1: *The Way of the Cell,* by Franklin Harold, Oxford, 2001.

Call (or go to) your favorite local bookstore and order Franklin Harold's *The Way of the Cell.* This is the introductory book you've been waiting for. It's 15 years old now, and a lot of new things have been discovered in biology, but Harold's book sticks close to the fundamentals and so little of it is out of date. I would say his book is fairly prescient in many ways, foreseeing the importance of a "systems" view of the cell, for example.

The first thing you should know about Franklin Harold is that he is a bioenergeticist. His job has been to understand the physics of metabolism, roughly speaking, and he wrote a famous textbook on the subject. He can discuss the tension between physical and biological worldviews in a profound way. He was inspired to pursue biology partly because of Erwin Schrodinger's *What is Life?* He is also a beautiful writer who sets the context for cell biology in the stream of evolution and the origin of life.

Harold does discuss textbook subjects like the tree of life and cell shape variation, but he does so in ways that will make you understand and remember. The archaea, for example, while still single-celled, are as divergent from bacteria as they are from eukaryotes, which was first recognized from ribosomal RNA. And why ribosomal RNA? You'd better read the book.

Most importantly for quantitative and physical scientists, Harold clarifies the energetic nature of molecular processes - and how energy makes it way from the sun's photons to our ATP. Pictures, examples, and layman's descriptions of key experiments are given. As a bioenergeticist, Harold is very much at home discussing free energy and the importance of (non-equilibrium) energy flows.

An overarching theme is why the cell is more than sum of its parts. "How do lifeless chemicals come together to produce those exquisitely ordered structures we call organisms?" In physical terms, this can be framed as a self-assembly problem. We know that (many) proteins fold spontaneously, that lipid bilayers assemble spontaneously. So why can't a cell be made by mixing up all the constituent molecules? Part of the answer comes from the 'historical' nature of a cell: each cell was produced from an earlier cell. Harold offers a simple counter-example to answer the self-assembly thought experiment: most membrane-spanning proteins are directional, not symmetric and must face a certain way to function properly; spontaneous self-assembly would not distinguish the two orientations, however.

Harold accomplishes the key task of tempering the traditional biological world view (i.e., that the sum is more than its parts - and so understanding parts alone fails to capture biology) with recognition of the important contributions from quantitative and physical perspectives. Unlike some more conservative biologists, Harold welcomes the input of a wide diversity of scientists concentrating on biological questions, and you will learn about contributions from a range of quantitative scientists besides Schrodinger - Morrow, Prigogine, Turing, to name just a few.

The book follows Harold's own research focus on single-celled organisms. The cell, after all, is the essential unit of life. Beautiful plants and animals are just extensions and generalizations of that unit. Harold's deep knowledge of the microbiological world frames most of the discussion and offers openings to discusses cell division, shape variation, and much more.

The Way of the Cell is great science writing by an author who knows the big picture and the details - and who balances them just right in a clear, beautiful book. I consider it truly required reading for anyone who wants to get a comprehensible overview of cell biology. In the 250 pages of Harold's book, you will absorb much more than you ever could from a cell biology textbook five times the length.