Balancing Scales in the Use of Biological Models

ADAM PAUL ARKIN
Howard Hughes Medical Institute
Department of Bioengineering, University of California, Berkeley
Physical Biosciences Division, E.O. Lawrence Berkeley National Laboratory
Berkeley, California

"I cannot doubt but that these things, which now seem to us so mysterious, will be no mysteries at all; that the scales will fall from our eyes; that we shall learn to look on things in a different way—when that which is now a difficulty will be the only commonsense and intelligible way of looking at the subject." Lord Kelvin ["Presidential Address to the Institution of Electrical Engineers", 1889]

ABSTRACT [*]

Almost all biology is about evolution. On short time-scales biologists study kinetics of single enzymes and the temporal evolution of product from substrate. At longer time scales, they study the evolution of cellular behaviors that result from the integrated dynamics of the network of nonlinear and possibly stochastic chemical reactions that link genome to physiology and respond to environmental signals. At still longer times, cells develop—changing their overall functions in response to the genetic program and organizing groups of cell into functional units such as spore stalks, organs, and sometimes human beings. Scaling up yet again, these organisms operate as populations that spread across niches in the world and compete with other organisms for resources to survive. This leads to the final scale of biology, the true genetic evolutionary time scale, in which life emerges from the proverbial primordial soup and, over times that defy intuition or complete conception, rewrites itself over and over with mistakes enough that new forms are born and old die during the faster time scale processes just described. To reconstruct the tree of life from the first bacterium, currently dated at something like 3.5

[*] Adam Arkin's full paper will be available at the meeting.

billion years ago, to the modern metazoans like you and me, we peer as "though a glass, darkly" at the striking similarities among phylogenies of fossils and genetic sequences and infer the historical dynamics that created them and us.

From fossil evidence to functional genomics, biological models have always been built to make sense of these complex data and to follow the implications of conceptual theories. There are perhaps three main roles that models generally play in biology: to demonstrate or explain a physical effect or elucidate a principle (such as the Mendelian sorting of traits via the gene theory or the Hodgkins-Huxley model of signal propagation in neurons); to demonstrate consistency as when a number of assertions in the form of a set of biochemical reactions in a cell are combined into an integrated model of a process such as bacterial chemotaxis to show that these reactions are sufficient to explain a cellular behavior such as exact adaptation to a step of chemoattractant; and to explore teleology where models are used to demonstrate why something is the way it is. For example, models may be used to answer why an integral feedback is necessary if small, free swimming cells such as flagellated bacteria are to sense and follow a chemical gradient.

In this talk I will discuss biological models at each of the timescales above and, due to the convergence of improved measurement technology and increased abundance of genetic sequence, how they are becoming linked together. I will then demonstrate the theoretical and computational challenges presented by all of these inherently multi-scaled models that arise due to timescale separations, high-dimensionality, and differing levels of detailed knowledge about different parts of the system. The effects of choosing different physical pictures such as macroscopic versus mesoscopic kinetics on both the computational feasibility of asking certain questions of the model or on predicting correct behavior will be demonstrated. The particular

challenges in the analysis (rather than simulation) of these systems, the comparison of these models to data, and the visualizations of the results will also be discussed. The examples to be followed in this presentation include a model of the control and evolution of stress response in *Bacillus subtilis* and models of spatial signaling in immune cell chemotaxis.