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# Computational modeling of physiological systems

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IN RECENT YEARS, THE DEVELOPMENT of information-gathering technologies such as high-throughput technology in genomics and proteomics, and the introduction of related techniques for managing and mining large-scale data, have facilitated a dramatic increase in the degree of quantification applied to modern biological research. In the coming years, computational modeling and analysis will play a critical role in deciphering meaningful systems descriptions from large sets of noisy and incomplete data and developing an engineering understanding of biological systems. See, for example, the National Institutes of Health “Roadmap for Medical Research in the 21st Century” (<http://nihroadmap.nih.gov/>), which outlines the need for a mechanistic systems approach to biological sciences. Thus, in analyzing and interpreting physiological data, we must seek to develop mechanistic biophysical models that not only explain our data in statistical terms, but also are constructed within a unifying framework obedient to fundamental mechanical and physicochemical principles.

A physical engineering-based approach to physiological research would mark a return to the science as practiced by pioneering physiologists such as Fick, Poiseuille, and Krogh. Early scientific investigations of the workings of physiological systems were, in the most basic terms, studies of how chemical, electrical, and mechanical forces are transmitted, transduced, and processed in and around living organisms. As physical scientists, pioneering physiologists made critical contributions to the development of fluid dynamics (13), physical chemistry (3), optics (6), and electrochemistry (4). Looking back even further into history, William Harvey’s elucidation of the circulation in the early 1600s demonstrated understanding of mass conservation, a concept that was not appreciated by the alchemists of Harvey’s day, but which through logical, deductive reasoning succeeded in persuading the scientists of the day that blood really did circulate, not oscillate back and forth. In the current era of informatics-based and computational biology, practicing physiologists will do well to remember physiology’s origins as a physical science. As Lamarck wrote, “La vie. . . n’est autre chose qu’un phenomén physique” (10), or, to paraphrase, “physiology is physics.”

Although quantitative physiology has never really been abandoned, it has been neglected in many physiology departments in recent decades. In the century since Stewart (17) first measured cardiac output in intact animals, more or less affirming Harvey’s calculations, and Krogh and Erlang (9) presented what one might argue was the first paper on mathematical modeling in biomedical science, and Wiggers (18) used Fourier analysis to describe pressure waveforms, computationally oriented research in physiology, biophysics, and biochemistry

has been pursued with vigor. While great advances have been made through molecular biology as a qualitative endeavor, now attention is shifting toward integrative computational modeling in biomedical research to link the magnificent body of new knowledge to an understanding of how intact organisms function. In the hope that this attention and any resources that come with it bear as much fruit as possible, we outline in this essay a set of recommendations for the practice of and training for computational modeling in physiological science.

## GOALS FOR COMPUTATIONAL MODELING IN PHYSIOLOGICAL SYSTEMS

An obvious first step is to define a goal or coherent set of goals to be achieved in any modeling study. J. E. Bailey (1) provides valuable guidance by discussing a set of answers to a simple question. Why make models? In brief, Bailey’s answers are as follows: 1) “to organize disparate information into a coherent whole;” 2) “to think (and calculate) logically about what components and interactions are important in a complex system;” 3) “to discover new strategies;” 4) “to make important corrections to the conventional wisdom;” and 5) “to understand the essential qualitative features.”

Bailey (1) provides an excellent discussion on these topics. We have taken the liberty of rephrasing *goals 3 and 4* as follows, respectively: 3) “to simulate, predict, and optimize procedures, experiments, and therapies” and 4) “to disprove hypotheses and to define improved hypotheses.” Computational models help in these efforts by providing a quantitative framework for the scientific method. While models may be merely descriptive, providing quantifiable bases for comparisons, the most useful ones are quantitative mechanistic hypotheses. Disproof of hypotheses that are formalized as computational models, or components of computational models, is based on comparison of model-predicted and experimentally measured variables. Thus working toward *goal 4* requires developing models and designing experiments in tandem, ensuring that sets of modeled and measured variables can be matched to each other and that experiments are optimally designed to identify model unknowns.

These goals reveal modeling as a useful tool in the working physiologist’s toolbox, helping in designing experiments, analyzing the data collected, and testing and generating hypotheses. However, *goals 2 and 5* suggest a deeper (and perhaps alarming) incursion of computational modeling into a physiologist’s intellectual territory. A working physiologist who has developed a deep understanding and intuition of how particular systems operate through years of education, experience, and experimental observation may be dubious of the expectation that a computer model, which is putatively constructed based on the essential features of a given system, could reveal previously unknown essential features of that system. To those readers sympathetic to this view of computer modeling, we suggest, don’t knock it until you try it. After all, mathematical

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and computer modeling represent undisputed intellectual cornerstones of modern research in the other physical sciences.

Still, the analogy between mathematical modeling in physics and in physiology is neither perfect nor complete. Approaches to mathematical and computational modeling in biology can be thought of as falling into one of two philosophical categories. The first includes large-scale integrative modeling approaches, for which it is assumed that important biological features emerge from models that strive to estimate the size and complexity of real biological systems. Complementary to this approach is the more traditional approach in applied mathematics and physics of developing the simplest possible model that captures the key features of a system while being accessible to analysis. These philosophies are complementary rather than mutually exclusive. In fact, while realistic large-scale complex models are being widely pursued, simplified models designed to capture the essential biophysics of a given system may prove at least as valuable in terms of understanding the essential and/or qualitative features of biological systems. For example, Goldbeter and Koshland's (5) classic work on signal amplification in protein phosphorylation revealed essential features of complex cellular signaling systems by analyzing a single isolated phosphorylation-dephosphorylation cycle that represented a grossly unrealistic system compared with a real signaling pathway. In a more recent analysis, Sachs et al. (15) revealed much about the structure and interaction in cellular signaling networks using an alternative approach that abandoned detailed biophysical models in favor of statistical and informatic techniques for data analysis. We believe that there will be a tremendous payoff in terms of quantitative analysis and prediction of biological function from integrating biological information databases and biophysical models, a goal currently being coordinated under the auspices of the International Union of Physiological Sciences (IUPS) Physiome Project (7) and defined in much detail as the IUPS Physiome Roadmap ([http://www.bioeng.auckland.ac.nz/physiome/physiome\\_project/roadmap.php](http://www.bioeng.auckland.ac.nz/physiome/physiome_project/roadmap.php)).

#### GUIDELINES FOR COMPUTATIONAL MODELING

Given the widely acknowledged potential for computational modeling to impact our understanding of physiological systems, it is worthwhile to introduce a few guidelines to keep in mind when considering the role of computational modeling in physiological research. We have generated the following list with the aim of providing a useful set of guiding principles.

1) Physiology is more than information science. Even in the "omics age," the disciplines of biology and physiology cannot be thought of as subdisciplines of information science or informatics. The techniques of genomics, proteomics, metabolomics, and so forth, help us to gather information, while the tools of bioinformatics and database management help us to manage and mine that information. Computational modeling should be aimed at understanding and predicting biological information.

2) Statistical inference is not sufficient to build a mechanistic understanding of physiology. To be self-consistent and predictive, models must be built from underlying biophysical principles. The credibility of a model is enhanced by its ability to predict data that was not used to construct (identify) the model. As a corollary, we assert that the term "model identification" should not be used as a synonym for "parameter estimation."

Parameter estimation involves using observed data to estimate values of parameters based on statistical procedures. Model identification is an exercise in assimilating data and physical, chemical, and biological principles into a coherent mechanistic understanding of physiology.

3) Models should be integrateable. That is, we should be able to link models of subsystems together to build models of integrated systems. Only models that are built on a common set of physical/chemical principles can be successfully integrated together. Thus models must simultaneously be consistent with the available experimental data and be constrained by the relevant physics/biophysics. Physics-based models, that is, models built on principles including the laws of mechanics and thermodynamics, in which assumptions and approximations are made explicit, operate with a common currency of mass, charge, energy, and momentum and naturally integrate across disparate scales.

4) Collaborating working groups must be established. Biological systems models inevitably enlarge as more components become integrated, demanding ever broader ranges of expertise and knowledge and requiring the formation of multi-institutional groups focusing on particular targets. This spring saw the gatherings of four separate working physiome groups at the IUPS Congress: in metabolism, cardiac mechanics, electrophysiology, and renal physiology. Such efforts are outlined in working-group publications of Sideman and Beyar (16), Bassingthwaite et al. (2), McCulloch et al. (11), and Hunter et al. (8), all of which represent stages of continuing efforts.

In addition, we invite readers to revisit Platt's "Strong Inference" (12), in which the formal procedure for productive scientific research is laid out as follows:

- (1.) Devising alternative hypotheses; (2.) Devising a crucial experiment (or several of them), with alternative possible outcomes, each of which will, as nearly is possible, exclude one or more of the hypotheses; (3.) Carrying out the experiment so as to get a clean result; (4.) Recycling the procedure. . .

When hypotheses are formalized as computational models, Platt's procedure cycles between model and experiment as progress is made toward models that are decreasingly wrong and increasingly complete and useful.

Progress in this area requires that we continue to train ourselves, our colleagues, and our students and postdoctorates in quantitative concepts. An important recent trend is the expansion of interdisciplinary undergraduate, graduate, and postgraduate programs in Bioengineering, Computational Biology, Bioinformatics, and related fields. Much activity and energy has been invested in such programs nationwide over the last decade and dividends are being paid in terms of students and fellows ready to implement and invent computational tools for physiological modeling. For teaching and learning material, many excellent introductory books are available. For physiologists, one of the most useful resources is the American Physiological Society's *Handbook of Physiology* series, which presents the concepts of physiology in quantitative mechanistic terms. For example, much of the material in the microcirculation volume edited by Renkin et al. (14) is presented in terms of the concepts and language of chemical physics and chemical engineering. Ideally, while no individual researcher is likely to obtain expertise across all relevant disciplines, graduate students (and faculty) in physiology and related fields should have

basic fluency in the biological, physical, and engineering concepts employed in these books.

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