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Microcirculation and the Physiome Projects

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Abstract

The Physiome projects comprise a loosely knit worldwide effort to define the Physiome through databases and theoretical models, with the goal of better understanding the integrative functions of cells, organs, and organisms. The projects involve developing and archiving models, providing centralized databases, and linking experimental information and models from many laboratories into self-consistent frameworks. Increasingly accurate and complete models that embody quantitative biological hypotheses, adhere to high standards, and are publicly available and reproducible, together with refined and curated data, will enable biological scientists to advance integrative, analytical, and predictive approaches to the study of medicine and physiology. This review discusses the rationale and history of the Physiome projects, the role of theoretical models in the development of the Physiome, and the current status of efforts in this area addressing the microcirculation.

Keywords

Microcirculation; multiscale systems analysis; modeling methods and standards; model databases; model dissemination; model reproducibility

Several efforts worldwide to define the Physiome, the Virtual Human, or the computational integrated organism are based on the principle that integration of information is best accomplished with clarity and precision through building mathematical models. These include the Human Brain Project, several Cardiome Projects, the Lung Physiome, and the Quantitative Kidney Database. The combination of multiple, and relatively simple, components can give rise to unexpected, emergent behavior, so that the whole is greater than the sum of the parts and new insight is obtained. The value of theoretical models for the design and interpretation of experiments, for integration of information, and for creating understanding is now appreciated by scientific leaders and government agencies. The goal of this review is to present the rationale and history of the Physiome projects, to highlight the role of theoretical models in the development of the Physiome, and to indicate the current status of Physiome projects that describe aspects of the microcirculation.

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PHYSIOME: RATIONALE AND HISTORY

“Physiome”: Coining a simple name is useful in spreading a concept. Bernard [10] developed an integrated approach to understanding biological systems. His concept was to regard all the cells of the body as bathed in a supportive nutrient medium, the “milieu interieure”; the concept was later labeled “homeostasis.” Following his concept, I defined the “Physiome” as the quantitative description of the functional behavior of the physiological state of an individual of a species [3,4]. Physiome means “life as a whole.” In its fullest form, it should define relationships from genome to organism. The long-term goal is to develop a comprehensive integrated system in which genomic and proteomic information can be incorporated and interpreted. Physiological studies provide a setting for defining the connectivity and, in the longer term, the kinetics and dynamics of proteomic networks, gene-regulatory networks, and signaling pathways. Knowledge of these areas is, in general, still in its infancy: The components are mainly well identified, but their connectivity is yet to be worked out in a quantitative integrated fashion [9]. The situation is perhaps analogous to the status of biochemistry 60–80 years ago, when the Cori husband-and-wife team [11,12] and Hans Krebs [21,22] were assembling the sequences of reactions we now know as the Krebs cycle. Likewise, it may be another half century before the “interactome” of the proteome and of gene regulation is understood at the kinetic and thermodynamic levels. A wonderfully thought-out study of the gene-physiology relationships is the book by Noble [27], in which he makes clear that environment (i.e., conditions in which the organism lives) and behavior influence expression as well.

The International Union of Physiological Sciences (IUPS) has long supported the Physiome concept. In 1993, the IUPS, led by its President, Masao Ito, and Secretary, Denis Noble, invited me to chair a new Commission on Bioengineering in Physiology, with the goal of developing integrative and quantitative physiology. Led by the next IUPS president, Ewald Weibel, the IUPS Council formed an IUPS Committee on the Physiome in 2001, chaired by Peter Hunter [5,13,17,18]. There is, currently, no overall administrative umbrella for the Physiome Projects and no committed source of long-term funding. However, several intellectual leaders are coming together informally in the spirit of collaboration and a desire to exchange information, data, and approaches to advance the science. Information on the Physiome project can be found via the following Web sites: www.physiome.org and www.physiome.org.nz.

PHYSIOME: ROLE OF THEORETICAL MODELS

Theoretical modeling is central to the Physiome perspective. As increasingly detailed information about a system is assembled, a purely intuitive or qualitative approach does not provide an adequate basis for predicting or understanding the relationships between the component parts and the resulting behaviors. The complexity of biological systems may suggest the need for massive computational models. An explicit model of the human lung, with airways branching through 23 generations to reach the alveoli, is indeed large. In some cases, such a model is needed. An alternative is to use “multiscale” approaches, in which models with differing levels of spatial resolution are integrated. In this way, microscale structures can be modeled in relationship to a whole tissue, without the need to represent the entire system in microscopic detail.

A fundamental challenge in physiological modeling is the lack of a “gold standard”: there is no perfect and complete description of the biology. All models are evolutionary transients in the advance of the science, yielding or falling aside when better data and ideas on how the system works become available. Progress is driven by a growing body of experimental data, which allows increasing discrimination between competing hypothetical models, often leading to “The great tragedy of science: the slaying of a beautiful hypothesis by an ugly fact” as T.H.

Huxley put it. The current “best” model may be the one that best aids in the design of the experiment that leads to its own destruction. Platt’s [28] admonition was, given that science advances by disproof, to devise not just one hypothesis, but also a second, realistic yet feasible, alternative hypothesis and then to devise the experiment that distinguishes between the two hypotheses; if both are truly viable hypotheses, then the experiment must disprove one and so advance knowledge. As models of physiological systems include increasing biological detail, their complexity hampers our ability to understand and contradict them. Therefore, it is important to provide not only functioning models, but also sufficient metadata and structural information to allow examination of particular aspects of their behavior. In this way, they can be more thoroughly tested for consistency with experimental reality.

Theoretical models have been categorized elsewhere in this volume as *phenomenological*, *qualitative conceptual*, *quantitative conceptual*, and *predictive* [33], although the categories are not necessarily complete or mutually exclusive. The conceptual models (i.e., qualitative or quantitative) emphasize the development and testing of hypotheses, as discussed above. Predictive models represent systems in which the underlying mechanisms and properties are well established, and so the governing equations and parameters can be confidently established. Models that have reached this relatively advanced level of maturity are ready to be used as building blocks for analyzing higher level systems and are thus most suited to inclusion in the Physiome framework. Below, we define goals and standards for such models.

We begin with the characteristics of biophysically based models that make them suitable for archiving in a Physiome database. Models should ideally satisfy all applicable conservation principles, although this is not always feasible. However, all models should have unitary balance, otherwise the equations are probably incorrect. Similarly, mass balance provides a fundamental test of all models involving chemical species. Balances of charge, osmolarity, and energy provide important constraints that should be recognized and addressed. Assumptions are made in every model construction; these should be listed explicitly, so that potential users are alerted to make their own judgment as to the validity of each.

“Verification” demonstrates that the mathematical expressions defining the model are complete, and that the method of computation provides correct solutions. Having unitary balance, with initial and boundary conditions defined, and having explicit definitions for each parameter and variable, units, and reference sources for each parameter, gives a good start. An important aspect of verification is achieved by providing the running code, supplied in some reasonably commonly used form, to reviewers and users. The code should: 1) run correctly with little dependence on step size; 2) run from varied initial or external driving conditions to appropriate steady states; 3) run on more than one computer operating system; and 4) exhibit numerical solutions matching appropriate reduced cases having analytical solutions, as demonstrations of numerical fidelity. Verification precedes validation testing in order not to waste time on a computationally inadequate model construct.

“Validation” provides evidence that the model is applicable to biological data. This starts with the provision of initial and boundary conditions consistent with physiological conditions. Provision of experimental data to be fitted by the model, and from which sets of parameters can be defined through good fits of model to data, is often part of this process.

Documentation is critical. A publication providing a full description of the model, and the verification and validation steps taken is desirable. Peer-reviewed publication is a criterion for inclusion in the CellML (www.cellml.org), SBML (sbml.org), and Biomodels (www.ebi.ac.uk/Biomodels) databases, though it is not required for the Physiome Wiki site (www.physiome.org/Models). Descriptions of the lineage of the model, its historical antecedents, and its contemporary setting create perspective. Explicit description of model

components or submodels and their sources is most helpful to understand the construction. For complex models, an operations manual and a tutorial are needed.

The SBML group is attempting to improve model quality by setting up a listing of expectations for reproducing models, minimal information requested in the annotation of biochemical models (MIRIAM) [25]. A more extensive set of standard requirements is defined by a consortium of multiscale modeling groups (http://www.imagwiki.org/mediawiki/index.php?title_Working_Group_10). The approximately 200 models available at www.physio.me.org/Models include elementary teaching modules as well as published models. These models all have units balanced on every equation and can be run over the Web or downloaded for free, along with the modeling system, JSim. The European Bioinformatics EBI group at Cambridge (www.ebi.ac.uk/Biomodels) has partially curated 180 models from the markup model libraries, SBML (sbml.org) and CellML (www.cellml.org); these databases unfortunately use different notations. The curation [24] is incomplete, as not all the models pass checks for unit balance.

PHYSIOME: MICROCIRCULATORY MODELING

The Microcirculation Physiome Project was initiated in 1998, with a meeting of a group of life scientists, including physiologists, biomedical engineers, and bioinformatics specialists. The goal was “to create a World Wide Web accessible database of the microcirculation that encompasses anatomical and functional data, spanning levels from the gene to the tissue, with mathematical models, computational engines, and tools for integration” [29]. The intervening decade has not seen the formation of a central integrated database for microcirculation data of the type envisaged, but the Physiome philosophy has guided a number of research projects on aspects of microcirculation [19,26,34].

At present, one online database (www.physiology.arizona.edu/people/secomb/network.html) is devoted primarily to microcirculatory phenomena. It is a resource for anatomic data on microvascular networks and provides computer methods for simulation of mass transport, especially oxygen transport, by such networks. Some other Web-based resources include substantial components relating to microcirculation. The goal of the Quantitative Kidney DataBase (physiome.ibisc.fr/qkdb) is to make kidney-related physiological data easily available to the scientific community [35]. QKDB includes detailed models for tubular countercurrent exchange [16]. Our University of Washington site (www.physio.me.org) focuses on the blood-tissue exchange processes and the role of the endothelium in the kinetics of imaging agents for positron emission tomography and magnetic resonance imaging.

As an example of the Physiome approach to studies of microcirculation, one may take the theme of characterizing the functions of endothelial cells and the parenchymal or other cells of an organ in the *in vivo* state. Transport across the endothelial barrier of the capillary wall occurs by the passive diffusive exchange of small hydrophilic solutes through the interendothelial cellular clefts and through transendothelial solute permeation (for lipid soluble substances) or via facilitating integral protein transporters in the endothelial cell membranes, some of which facilitate water transport: aquaporin channels [1]. Experimental approaches combine studies of the anatomy, direct observation of capillary volumes or fluid shifts, tracer studies of input-output relationships for multisolute probes of the system, and induced changes in perfusate osmolarity with various sizes of solute molecules [20].

To study the physiology of an organ *in vivo*, one must model the whole system between input and output. For whole-organ studies, we used a multi-faceted and generalized blood-tissue exchange model, GENTEX [7,31], that includes a branching network for arterial inflow and venous outflow in order to account for intraorgan flow heterogeneity. It is based upon a long succession of earlier models [2,6,8,14,15,23,30,36] and is the first one that accounts for three

cell types: RBC, endothelium, and parenchymal cells and for nonlinear competitive processes for transport, binding, and reaction. It was used for the analysis of endothelial-cardiomyocytes exchanges and reactions among purine nucleosides [31,32]. The model accounts for two reference tracers (e.g., vascular and extracellular) and five reacting tracer and nontracer solute fluxes and reactions in the different cell types, for a total of 12 solutes. The model program is coded for computational efficiency; in its minimum configuration, it is a one-compartment, stirred-tank model; at its maximum, using multiple finite elements within each capillary-tissue region, it uses 110,000 differential equations, so it can be called a large multi-scale model.

This type of analysis illustrates the idea of the Physiome, a quantitative approach to characterizing the biology of a functioning physiological system. The targeted molecule is convected, diffuses, is facilitated in its transmembrane passage, and is enzymatically metabolized. The analysis integrates information from multiple sources. The model is multiscale, characterizes subcellular reactions, transmembrane and intratissue transport, and transorgan transport by flow, and the analysis is at the whole-organ level. Microcirculation research has the potential to contribute in crucial ways to the improved understanding of physiological processes. Approaches based on the Physiome philosophy will be central to the process of realizing this potential.

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