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The role of theoretical modeling in microcirculation research

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Abstract

Theoretical modeling approaches have made important contributions to research in the biological sciences including the microcirculation, and their value is increasingly recognized. However, misconceptions about the nature and role of theoretical models persist, and such work is often presented in a way that does not maximize its value, especially for scientists who are not themselves using such models. In this review, a categorization of models as phenomenological, qualitative conceptual, quantitative conceptual or predictive is proposed, and the characteristics of each type are discussed. Recommendations are made for the presentation of models and for the future development of modeling approaches. The concepts discussed are generally applicable to the theoretical modeling of biological systems, and are illustrated using examples of modeling in microcirculation research.

Introduction

Theoretical modeling of blood flow, solute transport, and other phenomena in the microcirculation dates back at least ninety years, to the Krogh cylinder model [10]. Microcirculatory modeling entered a period of increasing activity in the late 1960s and 1970s [1, 7]. Since that time, theoretical approaches have been an accepted and valued aspect of research into microcirculation. Microcirculatory research is an inherently interdisciplinary field and many investigators with engineering or physical sciences backgrounds were among the pioneers of the field. This may be a reason for the relatively early acceptance of theoretical approaches by microcirculation researchers.

In the last decade or so, the need for development of mathematical and computational approaches has become more apparent throughout biomedical science (Figure 1), as exemplified by the increasing interest in ‘systems biology’ and ‘multi-scale modeling’. Integration of knowledge across multiple levels of biological organization, which has long been central theme in physiology, is now receiving more emphasis in other branches of biological science. In a sense, modelers of microcirculation have been leaders of this development. However, it is timely to reexamine the status of modeling in the field of microcirculation. In particular, it is worthwhile to consider how theoretical modeling should be carried out to maximize its value, and how different types of modeling should be presented to the scientific community to ensure that they are properly understood in terms of their approaches, capabilities and limitations. Achieving this represents a significant challenge. Theoretical models are often presented using mathematical terminology that is unfamiliar to many biologists. Also, conventions for the description of the aims and methods

of theoretical models are not as well established as they are for experimental studies. As a result, such work is often viewed with a degree of skepticism by experimental biologists. The introduction of generally accepted schemes for the description and classification of modeling studies might help a broad scientific audience to assess the relevance and reliability of such studies and to appreciate the insights that they provide into complex biological systems.

Types of theoretical models

Theoretical models can serve a number of different functions in research, including integration of disparate information within a consistent system, identification of key elements, testing of hypotheses, prediction of function and simulation and optimization of experimental methods [5]. Thus, models can contribute at different stages in the understanding of biological phenomena. The following classification represents an attempt to define the types of models, although the categories are not necessarily complete or mutually exclusive (Table 1):

I. Phenomenological models

In this case, observed properties are described by fitted equations or other relationships that are not based on mechanistic descriptions of the underlying processes. Such a description can provide a mathematically compact representation of a complex set of experimental data (e.g., [17]), and can be used as a building block in constructing higher-level models. In general, each fitted parameter in such a model does not correspond directly to a specific physical or biological property of the system being modeled. Such a model cannot be reliably extrapolated to predict behavior outside the envelope of the underlying experimental data, and may be difficult to extend in order incorporate new information. While a model of this type is unlikely to lead to new insights or predictions relevant to the process being modeled, it can be useful in revealing statistical relationships in the fitted data.

II. Qualitative conceptual models

A conceptual model is typically based on a hypothesis about the mechanism underlying an experimentally observed phenomenon. The proposed mechanism is expressed in mathematical terms, and the range of possible predicted behaviors is explored and compared with the observed behavior. Model parameters are not necessarily evaluated, and the comparison with observations may be qualitative rather than quantitative. For example, Rodbard [20] (see [18]) used a qualitative conceptual model to test (and disprove) the hypothesis that structural adaptation in response to wall shear stress alone provides a basis for controlling vessel diameters in networks.

III. Quantitative conceptual models

Such models are based on hypotheses regarding the mechanisms underlying system behavior. In this case, however, the theoretical description of the mechanisms is fully parameterized. Some of the parameters values may be known *a priori*. The question then being addressed is whether model predictions are quantitatively consistent with observed behavior, for suitable values of the unknown parameters. If this is not possible, then the hypothesized mechanisms must be rejected as being inadequate or at least inadequately represented in the model. If, on the other hand, model results are potentially consistent with observations, then a process of optimization is typically required to estimate the unknown parameters for best agreement between prediction and experimental data. The resulting parameter values can be interpreted in terms of the characteristics of the underlying mechanisms. The Hodgkin-Huxley model of nerve impulse propagation [8] is a classic example of this type of model. Theoretical investigations of complex biological processes,

where the key underlying processes are not necessarily known in advance, often utilize this type of approach. Examples include regulation of blood flow [21], angiogenesis [15], and structural adaptation of blood vessels [18].

A common misconception is that the success of a modeling effort should be judged by the closeness of fit between model predictions and experimental observations. However, a failure to achieve such agreement in a model may be an even more useful result. By examining the discrepancies, it may be possible to identify the inadequate aspects of the originally assumptions, and thereby to determine what additional factors should be included. In this way, an increasing level of insight in the system can be developed [19]. Conversely, while close agreement between model predictions and experimental data may increase confidence in the model, such agreement does not prove that the model is correct.

IV. Predictive (application) models

In some systems, the underlying mechanisms and/or constitutive properties are known with a reasonable degree of confidence. A theoretical model can then be constructed to predict system behavior, in which the governing equations and parameters are prescribed *a priori*. For example, the biophysical mechanisms of oxygen transport in tissues are mainly well understood, and this provides a basis for predictive models of the distribution of oxygen levels in tissue [4, 6, 10, 16, 22]. In recent years, diffusive transport of nitric oxide in tissue has received much attention, leading to the development of predictive models [24]. The same trend can be seen in recent work modeling microcirculatory transport of other metabolites and growth factors involved in cellular processes [3, 12]. Similarly, fluid mechanical principles combined with known constitutive properties of blood and blood cells provide a basis for predicting microcirculatory hemodynamics [11]. This type of model is often associated with an engineering approach to biological systems. Model predictions can then be compared quantitatively with observations of system behavior, without the need for any parameter fitting or optimization. However, if significant disagreements are found, it may be inferred that the original assumptions were not correct or adequate. In such cases, the model may revert to the category of quantitative conceptual models.

The ultimate goal of many modeling efforts is the development of a predictive model whose results have been extensively compared with experimental data and found to be consistent. Such a model may be described as being ‘validated’ although such a description is always provisional. The strength of such models is that they can be used to predict system behavior in conditions that may not have been studied experimentally, and they can form major building blocks in the development of multi-scale models for complex systems. Predictive models are needed for the development of integrated quantitative models for physiological systems, as in the Physiome Project [2, 9]. Here, a challenge is that model components may be inherited through multiple generations of a given class of models [23]. Links between original experimental data sources and resulting parameter values may become obscure, making it difficult to update inherited parameters in the light of new or improved measurements.

Presentation of theoretical models

The full value of theoretical models is not realized unless the results are presented in a way that is comprehensible and usable to the relevant scientific community, including both experimentalists and theoreticians. Here, several aspects of model presentation are discussed.

Description of model scope

As described above, theoretical models do not follow a single accepted paradigm. The reader of modeling papers often has trouble discerning key aspects of the approach. This situation could be improved if authors were to ensure that the following pieces of information are clearly stated in their work:

- the type of model, according to the above classification;
- the scale(s) to which the model applies, for example analysis of cellular-level mechanisms to predict organ-level behavior (see Figure 1);
- the number of parameters and whether they are known *a priori* (and if so from what data sources) or fitted to data (again with explicit reference to data sources);
- the types of experimental data used and whether they are incorporated in the model or used for testing model predictions.

A flow diagram can be used to indicate the relationship between experimental data, concepts, assumptions, procedures and results in a non-mathematical way (Figure 2). Inclusion of such flow diagrams may help to make modeling studies accessible to a broader audience.

Reproducibility and interoperability of models

As in any area of research, reproducibility should be an objective of modeling work, but this may be difficult to achieve in practice. A basic requirement, not always observed, is that the assumptions of the model should be clearly stated and that their relation to established concepts or data and their impact on the model results should be discussed. Where practical, underlying governing equations should be specifically listed and assumed parameter values should be stated, with justifications or sources listed. If such information is too lengthy to be included in a publication, it should be included in online supplements to the journal or made available online by the authors.

Ideally, computer code used to generate the results should also be made available to reviewers and publicly upon appearance of the work. However, this is a more complex issue. If proprietary licensed software is used, this cannot generally be published. Software developed by the authors may be usable by them, but require major efforts to make it user-friendly and robust enough to make it of practical use to others. The resources needed to do this are often unavailable. Similar concerns relate to the process of making different models interoperable, such that they can be combined in larger scale models. The development of the markup language CellML [13] is an example of a systematic effort to overcome these difficulties.

Structure of journal articles

Most publications in biology follow the standard format of *Introduction; Methods; Results; Discussion*. This format is not generally followed in mathematics, theoretical physics and (to a variable extent) engineering fields, because it does not fit the expository nature of a theoretical development. Even so, use of the standard format in modeling papers may be advantageous because it makes the work more accessible to a biological readership, and is indeed required by many biological journals. One feasible approach is to describe the steps and logic of model development in a relatively extended *Methods* section, with the *Results* section containing predictions of the fully developed model. The *Discussion* section can advantageously be used to highlight the insights that the model provides into the biological system of interest, and to consider the implications of the results for system behavior as viewed at smaller and/or larger scales.

Future directions

The microcirculation represents an important ‘mesoscale’ in physiological systems, functionally bridging higher and lower scales. Microvascular function is determined by processes occurring at the cellular and molecular levels. The functional status of the microcirculation strongly influences tissue and organ behavior. Conversely, systemic parameters such as blood pressure and fluid balance affect the function of the microcirculation, which in turn determines the environment in which cellular and molecular processes operate. Microcirculatory research naturally adopts Sydney Brenner’s ‘middle out’ [14] rather than ‘top down’ or ‘bottom up’ approach to study cardiovascular function. Theoretical models are needed not only to understand the processes occurring in the microcirculation but to establish quantitative relationships with phenomena occurring on these larger and smaller scales.

Close collaboration between experimental and theoretical investigators continues to be of vital importance in this field. Some individual investigators combine both types of work and expertise. Such work should be motivated by the need to solve biological problems. Mathematically or computationally novel aspects may arise but should not be the main objective. Theoreticians should be willing to learn relevant biological concepts. Conversely, experimentalists must become more conversant with the capabilities and responsive to the needs of modelers. For example, a single detailed set of data regarding a given system with many variables measured in a single instance is generally much more valuable for model development than measurements of few parameters in multiple instances.

It can be expected that theoretical approaches will maintain their important role in microvascular research, and will develop according to emerging trends in biological sciences as a whole, with increasing capabilities to treat multi-scale problems and large and complex sets of data. Overcoming the challenges described above is not easy and requires close communication between theoreticians and experimentalists. Development of widely used conventions for reporting, classifying and assessing theoretical models could help to make modeling approaches more acceptable and useful to the field of microcirculation research.

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Figure 1.

Schematic illustration of the need for theoretical modeling in biology. Reductionist approaches have shown the molecular and cellular basis of life. Although the hope for a direct one-to-one link between molecular information and functions or diseases is realized in some cases, interactions between multiple biological processes and mechanisms at a given level of scale or organization generally influence events occurring on smaller or larger scales. The complexity of these processes is such that intuitive or qualitative approaches are often inadequate. Theoretical models provide a framework for integrating information within and across biological scales.

Figure 2.

Example of flow diagram to indicate the relationship between experimental data, concepts, assumptions, procedures and results in a theoretical model. The text refers to models for solute transport and reaction in a region of tissue with experimentally determined microvascular geometry. Other boxes and arrows could be added to represent comparisons of model predictions with independent experimental data, iterative procedures to refine unknown parameter values, interfaces with models on other scales, etc.

Table 1

Classification of theoretical model types

Type	Mechanisms/ Equations	Parameters	System properties
I Phenomenological models	Fitted	Fitted	Described
II Qualitative conceptual models	Deduced	Free	Used for testing
III Quantitative conceptual models	Assumed	Optimized	Used for validation
IV Predictive (application) models	Known	Known	Predicted