A Strategy for Integrative Computational Physiology

Organ function (the heart beat for example) can only be understood through knowledge of molecular and cellular processes within the constraints of structure-function relations at the tissue level. A quantitative modeling framework that can deal with these multiscale issues is described here under the banner of the International Union of Physiological Sciences Physiome Project.

The Need for a Multiscale Modeling Framework

The wealth of data now available from 50 years of research in molecular and cellular biology, coupled with recent developments in computational modeling, presents a wonderful opportunity to understand the physiology of the human body across the relevant $10^9$ (from nanometers to meters) range of spatial scales and $10^{15}$ (from microseconds to a human lifetime) range of temporal scales. The challenge is to develop mathematical models of structure-function relations appropriate to each (limited) spatial and temporal domain and then to link the parameters of a model at one scale to a more detailed description of structure and function at the level below. To span from molecules to organ systems requires databases of models at many spatial and temporal levels and software tools for authoring, visualizing, and running models based on widely adopted modeling standards. It also requires the development of ontologies dealing with anatomy, physiology, and molecular and cellular biology to uniquely identify and link model components. In this review, we outline a framework for computational physiology being developed under the auspices of the Physiome and Bioengineering Committee (co-chaired by P. Hunter and A. Popel) of the International Union of Physiological Sciences (IUPS). We give examples of its application to several organs and organ systems, particularly the heart, and highlight the challenges for this so-called Physiome Project (1, 3, 10, 11, 19, 20). Note that the focus on computational physiology is the distinguishing feature of the Physiome Project but that it also encompasses the area traditionally known as systems biology, which has arisen out of molecular and cellular biology and which typically deals with subcellular signaling cascades, metabolic pathways, and gene-regulation networks.

Lessons from Physics and Engineering: Continuum Fields and Constitutive Laws

One of the most important concepts of mathematical analysis in the physical and engineering sciences is that of a “field,” which, together with appropriate mathematical operations on fields, is used to express the physical conservation laws of nature, such as conservation of mass, momentum, charge, etc. Fields were first introduced by the great 19th-century British scientist Michael Faraday to represent the intensity and direction of the force experienced by a small charged particle in the presence of magnetic dipoles and electric charges throughout a three-dimensional space. The greatest success of 19th- and early 20th-century physics was the discovery that most observable phenomena could be described by differential equations operating on these fields: Maxwell's field equations for electricity and magnetism, Einstein's field equation for gravity, the Yang-Mills field equations for subatomic particles, and the field equations of continuum mechanics were derived from Newton's laws of conservation of mass and conservation of momentum.

There is an interesting analogy with molecular biology here: just as the classical field theory world of physics was overshadowed in the early 20th century by quantum theory and particle physics, the integrative systems-level physiology of the first half of the 20th century gave way to the reductionist molecular biology of the second half. In both cases the challenge now is to reconcile the continuum/systems view with the particle/molecular view. For physicists, this may be achievable by describing their equations in a higher-dimensional space via superstring theory. For mathematical biologists, it is likely to be achieved via multiscale modeling.

Many of the great accomplishments of electrical and mechanical engineering, respectively, in the 20th century were built (for the former), on the sound theoretical basis of Maxwell's field theory and quantum mechanics and (for the latter) on continuum mechanics. In both cases, however, the theoretical field theory models had to be supplemented with empirical descriptions of material behavior that hide molecular or atomic detail behind approximate “constitutive laws.” For elec-
Physiome Project models: just as the leaders of the modeling. Presenting a strategy for integrative multiscale modeling. This journal's space limitations mean that both of these issues are delegated to the references for the models we discuss. Similarly, the physiological insights achieved by these models are not noted, also implies not too simple!, and empirical principles are applied at many levels (see Table 1): at the scale of whole organs, in which the overall geometry and structure is modeled and used to solve the coupled systems of field equations (see FIGURE 1); at the tissue level, typically dealing with millimeter-sized blocks of tissue in which structures are defined at the micrometer level; at the cell level, typically dealing with a resolution of 0.1 μm; and even at the protein level. Good progress is being made on modeling the anatomy and biophysics of the heart (FIGURE 1A), the lungs (FIGURE 1B), the digestive system (FIGURE 1C), and the musculoskeletal system (FIGURE 1D). In each case the field equations are a little different (the lungs, for example, do not require the electrical field equations), and, despite very different anatomy and material properties (expressed via the constitutive laws), the numerical modeling framework required to solve these field equations is the same for all. At the current rate of progress, models of all 12 organ systems should be available within a few years, at least for physiologically normal human anatomy. Linking the organ and organ systems together to yield models that can predict and interpret multiorgan physiological behavior is the focus of systems physiology. To examine the behavior of these systems over long time intervals, the models are often lumped-parameter models in which system-identification techniques are applied to the detailed field-equation models illustrated in FIGURE 1. This approach allows the parameters of the lumped-parameter models to be linked to the more biophysically based organ models (see the cardiac example below).

The organ-level models shown in FIGURE 1 are based on finite-element models of the anatomic

“The appropriate name for this application of physical and engineering principles to physiology is computational physiology.”
<table>
<thead>
<tr>
<th>Physiological Level</th>
<th>Types of Model, etc.</th>
<th>Imaging Technologies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organ systems</strong></td>
<td>Systems theory</td>
<td>MRI, CT, PET</td>
</tr>
<tr>
<td>Cardiovascular, respiratory, musculoskeletal, digestive, skin, urinary, nervous, endocrine, lymphatic, male reproductive, female reproductive, special sense organs</td>
<td>Lumped-parameter models</td>
<td>3-D Ultrasound</td>
</tr>
<tr>
<td></td>
<td><strong>Software</strong> JSIM</td>
<td>1 mm or 10⁻³ m</td>
</tr>
<tr>
<td></td>
<td>BioPSE</td>
<td></td>
</tr>
<tr>
<td><strong>Organs</strong></td>
<td>Continuum theory</td>
<td>MicroCT, Optical</td>
</tr>
<tr>
<td>226 bones</td>
<td>Conservation of mass</td>
<td>coherence tomography</td>
</tr>
<tr>
<td>850 muscles</td>
<td>Conservation of momentum</td>
<td>10 μm or 10⁻⁵ m</td>
</tr>
<tr>
<td>2817 arteries, arterioles, and capillary beds</td>
<td>Conservation of charge</td>
<td>Serial sections</td>
</tr>
<tr>
<td></td>
<td><strong>Software</strong> JSIM</td>
<td>1 μm or 10⁻⁶ m</td>
</tr>
<tr>
<td></td>
<td>BioPSE</td>
<td></td>
</tr>
<tr>
<td><strong>Tissues</strong></td>
<td>Conservation equations</td>
<td>Confocal microscopy</td>
</tr>
<tr>
<td>Epithelial</td>
<td>Passive flux equations</td>
<td>1 μm or 10⁻⁶ m</td>
</tr>
<tr>
<td>Connective</td>
<td>Carrier-mediated transport</td>
<td>2-photon microscopy</td>
</tr>
<tr>
<td>Muscle</td>
<td>Electroneutrality constraints</td>
<td>Electron tomography</td>
</tr>
<tr>
<td>Nerve</td>
<td><strong>Software</strong> CMISS, Continuity</td>
<td>1 nm or 10⁻⁹ m</td>
</tr>
<tr>
<td><strong>Cells</strong></td>
<td>Continuum models</td>
<td>MicroCT, Optical</td>
</tr>
<tr>
<td>Approximately 200 cell types</td>
<td>Lattice-Boltzmann equations</td>
<td>coherence tomography</td>
</tr>
<tr>
<td></td>
<td><strong>Software</strong> CMISS, Continuity</td>
<td>10 μm or 10⁻⁵ m</td>
</tr>
<tr>
<td></td>
<td><strong>Software</strong> Continuity</td>
<td>Serial sections</td>
</tr>
<tr>
<td><strong>Organelles</strong></td>
<td>Conservation equations</td>
<td>Confocal microscopy</td>
</tr>
<tr>
<td>Cell membrane, mitochondria, nucleus, endoplasmic reticulum, ribosomes, Golgi apparatus, centrioles, lysosomes, peroxisomes</td>
<td>Passive flux equations</td>
<td>1 μm or 10⁻⁶ m</td>
</tr>
<tr>
<td><strong>Cell function</strong></td>
<td>Continuum models</td>
<td>Confocal microscopy</td>
</tr>
<tr>
<td>Membrane receptors</td>
<td>Lattice-Boltzmann equations</td>
<td>1 μm or 10⁻⁶ m</td>
</tr>
<tr>
<td>Membrane ion channels</td>
<td>Stochastic models</td>
<td>Confocal microscopy</td>
</tr>
<tr>
<td>Signaling pathways</td>
<td>Markov models</td>
<td>Confocal microscopy</td>
</tr>
<tr>
<td>Metabolic pathways</td>
<td>Hodgkin-Huxley models</td>
<td>2-photon microscopy</td>
</tr>
<tr>
<td>Transport</td>
<td>Network models</td>
<td>Electron tomography</td>
</tr>
<tr>
<td>Motility</td>
<td><strong>Software</strong> AMBER, CHARMM</td>
<td>1 nm or 10⁻⁹ m</td>
</tr>
<tr>
<td>Maintenance</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proteins, carbohydrates, and lipids</strong></td>
<td><strong>Software</strong> AMBER, CHARMM</td>
<td>X-ray diffraction, NMR</td>
</tr>
<tr>
<td>Cell cycle</td>
<td></td>
<td>1 Å or 10⁻¹⁰ m</td>
</tr>
<tr>
<td><strong>Posttranslational modifications</strong></td>
<td>Stochastic models</td>
<td>Microarrays</td>
</tr>
<tr>
<td>Protein folding</td>
<td>Boolean network models</td>
<td>2-D gel electrophoresis</td>
</tr>
<tr>
<td>Translation</td>
<td></td>
<td>Mass spectrometry</td>
</tr>
<tr>
<td>Posttranscriptional modifications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene regulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transcription</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Genes</strong></td>
<td></td>
<td>Nucleic acid</td>
</tr>
<tr>
<td>20,000 genes</td>
<td></td>
<td>sequencing</td>
</tr>
</tbody>
</table>

fields (geometry and tissue structure) encoded in a markup language called FieldML (http://www.physiome.org.nz/fieldml/pages). In all of these models, the anatomic description is designed to facilitate the efficient solution of the field equations representing organ function. The dependent variables used in these field equations (such as the deformed geometry, membrane potential, oxygen concentration, etc.) can also be exported from computational codes in FieldML-formatted files. The use of FieldML as a standard for encoding field information allows the models and their solution fields to be read by a range of simulation and visualization codes (see Table 1). The spatially varying physical properties of the tissues are also described with FieldML files. Note that an important difference between engineering materials and biological tissues is that the latter are almost always anisotropic (e.g., material properties are different in orthogonal material directions), inhomogeneous (properties vary with position in the material), and nonlinear. This makes the characterization of biological tissue properties much more difficult than it is for engineering materials and also reinforces the need to derive the material parameters of the constitutive laws used in organ models from more detailed models of the underlying tissue structure (13).

Cell-Level Models: CellML, Associated Tools, and Databases

A framework for modeling cell function has been developed over the past five years by the Bioengineering Institute at the University of Auckland. The key elements are: 1) the development of a markup language called CellML to standardize the mathematical description and metadata (information about the model) of cell models (12, 15, 30); 2) application programming interfaces (APIs) to define the way that information is passed between the CellML model files and computer pro-

FIGURE 1. Organ-level models
A: geometry and microstructure of ventricular myocardium shown in a 3-D finite-element model of the heart. Left: finite-element surfaces fitted to measurements from the left and right ventricles of the pig heart. Middle: 2 layers of streamlines (one on the epicardial surface and one midway through the wall) are used to visualize the epicardial and midwall fiber directions. Right: coronary arteries modeled from pig heart data (52). B: models of the lung (6, 54). Left: airways. Right: pulmonary arteries. C: models of the digestive system, including the esophagus, stomach, intestines, and colon (4). Middle: diaphragm. Right: stomach and large intestines. D: models of the musculoskeletal system (14). Left: human skeleton with all bones modeled and also showing muscles in the left leg as well as heart, lungs, and digestive system. Right: muscles of the left arm.
at http://www.cellml.org/examples/repository includes ~300 models in the following categories:

- Signal transduction pathway models
- Metabolic pathway models
- Cardiac electrophysiological models
- Calcium dynamics models
- Immunology models
- Cell cycle models
- Simplified electrophysiological models
- Other cell type electrophysiological models
- Smooth and skeletal muscle models
- Mechanical models and constitutive laws

For each model, the information on the website describes which biological processes are represented, references the associated publication, and links to the CellML model file itself. Although the use of CellML can never replace the need for a peer-reviewed publication of a model, it can enhance the availability of the model and ease the burden of implementation validity checking by the model users. A model-publishing workflow is being developed to allow reviewers of submitted papers to access and test the models and also to allow updating of models if errors or omissions are found after publication. Note that another XML-based standard called systems biology markup language (SBML; see http://www.sbml.org) has been developed for describing models of biochemical reaction networks (18).

Multiscale User Interfaces and Ontologies

To facilitate access to the anatomically based
organ-level models and their links downward to tissue properties and cell-level processes, we are developing browser-based graphical user interfaces that exploit the open-source software framework provided by the Mozilla community (http://www.mozilla.org). These use an XML-based description of the user interfaces, called XUL, which allows problem-specific interfaces to be easily created, as illustrated in FIGURE 3.

Providing a set of unique names for the components of a biological model (a “controlled vocabulary”), together with the relationships between the components, allows the application of reasoning algorithms and access to the growing number of protein databases that give, for example, data on protein-protein interactions. We are working with a number of groups who are developing domain-specific ontologies such as the Gene Ontology project (http://www.geneontology.org) and the Foundational Model of Anatomy (http://sig.biostr.washington.edu/projects/fm/AboutFM.htm l) (41). A web interface based on these ontologies is being developed for accessing models (http://n2.bioeng5.bioeng.auckland.ac.nz/ontology). The specific biological information that is relevant to each model in the CellML model repository is represented in the metadata associated with a model and is bound directly to parts of the ontology. The CellML metadata editor will be extended to use the ontologies, supplying modelers with a system of biological entities and relations that they can associate with their modeling structures.

An Example: Computational Physiology of the Heart

The development of the Auckland-Oxford-UCSD heart model is used here as an example of multiscale physiome modeling. The long-term goal is to be able to predict the effect of a channel mutation or drug-binding event on arrhythmogenesis at the whole-heart level, together with its clinically observable effect on the body surface. Although there are still many gaps, this example will serve to illustrate what has been achieved with the physiome approach and where further research is needed. All models described here are encoded in CellML and FieldML and are available from the IUPS Physiome Project databases. The various levels referred to here are illustrated in FIGURE 4.

Atomistic models

Molecular dynamics (MD) models of the atomic structure of ion channels, pumps, exchangers, etc. are needed that can predict the open-channel permeation of the channels, the voltage dependence of the channel permeability, and the time- and voltage-dependent gating behavior. These models describe the atomic mass and bonded (covalent) and nonbonded (electrostatic, van der Waals) forces operating on all (or a sizable subset of) atoms in the protein and then solve Newton’s laws of motion. The covalent forces can be computed as a function of bond length, bond angle, and dihedral angle from quantum-mechanical calculations. Water is usually included in discrete molecular form or, for greater distances, as a bipolar continuum field. These models require the protein’s atomic structure to be known from X-ray diffraction or NMR, and this has proved very difficult for membrane-bound proteins. Ideally of course this structure would come from protein-folding computations, but this is some way off. Structures are currently known for a few bacterial potassium chan-
Models of channel kinetics based on whole-cell voltage-clamp data—the now classic Hodgkin-Huxley equations (16)—were developed over 50 years ago for sodium, potassium, and chloride channels in giant squid axons and over 40 years ago by Denis Noble for cardiac ion channels (36). The subsequent development of the single-channel patch clamp led to refinement of these models with Markov-state variable models (53). One of the challenges now for the Heart Physiome Project is to derive the parameters of the Hodgkin-Huxley or Markov models from the MD models via coarse-grained intermediate models as the molecular structures of these proteins become available.

Subcellular pathways

Lumped-parameter models (i.e., without diffusion modeling) of various processes within cardiac myocytes are now well advanced. The composite channels such as KcsA, KirBac, and KvAP, which have close homology (at least in the pore region) to mammalian potassium channels (43). MD calculations, based on ~100,000 atoms in current models, are very expensive and are typically run for periods of only 10 ns (7). Sometimes homology modeling is used in combination with MD simulation to generate, test, and refine models of mammalian potassium channels based on bacterial templates (8). The structures of sodium and calcium channels are also on the horizon, as well as those of key pumps and exchangers.

Protein models

A major challenge now is to develop coarse-grained models of these ion channels and other proteins with parameters calculated from the MD models. This will allow the models to include transient gating behavior for time intervals up to ~100 ms. Models of channel kinetics based on whole-cell voltage-clamp data—the now classic Hodgkin-Huxley equations (16)—were developed over 50 years ago for sodium, potassium, and chloride channels in giant squid axons and over 40 years ago by Denis Noble for cardiac ion channels (36). The subsequent development of the single-channel patch clamp led to refinement of these models with Markov-state variable models (53). One of the challenges now for the Heart Physiome Project is to derive the parameters of the Hodgkin-Huxley or Markov models from the MD models via coarse-grained intermediate models as the molecular structures of these proteins become available.

Subcellular pathways

Lumped-parameter models (i.e., without diffusion modeling) of various processes within cardiac myocytes are now well advanced. The composite...
cell models encompass all of the ion channels, ATPase pumps, and exchangers known to support the cardiac action potential (34), together with equations governing calcium transport (47), proton exchange (55, 56), myofilament mechanics (21), metabolic pathways (2), and signal-transduction pathways that modulate the phosphorylation state of intracellular proteins (44, 45, 46). All of these models are available in the CellML repository.

**3-D cell models**

The next stage of development of cell models will need to take account of the spatial distribution of proteins within a cell and subcellular compartments, where second messengers (Ca²⁺, IP₃, cAMP, etc.) are localized (47). The spatial distribution of the transverse-tubular system in cardiac myocytes has been measured with two-photon microscopy (51), and the spatial modeling of proton transport and buffering in the myocyte is also well advanced (55). Developing 3-D models at the cellular level will help to fill the large gap in spatial scales between proteins and intact cells.

**Tissue models**

Cardiac cells (myocytes and fibroblasts) are organized into layers three or four cells thick (27, 28, 29) that ensure high-conductivity gap-junction-mediated connections within sheets to ensure rapid activation of the myocardium but allow mechanical shearing to occur between sheets to allow the wall thickening that ensures a high ejection fraction for the ventricles. This tissue structure has been modeled mechanically and electrically to bridge the gap between cell-level and tissue-level models (23, 31, 33). For example, computing the propagation of an activation wavefront through a tissue block with a detailed model of tissue structure allows the continuum orthotropic conductivity parameters, which are then used in the whole-heart models, to be evaluated in different regions of the myocardium (17).

**Whole-heart models**

Models at the whole-heart level can now deal with the large deformation mechanics of the ventricles by using orthotropic constitutive properties based on the fiber-sheet orientations (29, 35) and with the activation wavefront propagation computed from bidomain field equations (23) by using a conductivity tensor based on the fiber-sheet orientations and the ion-channel cell models referred to above. The coupling between the mechanical and electrical models is also achieved with calcium released from ryanodine receptors binding to troponin-C to initiate cross-bridge interaction (21) and mechano-electric feedback mechanisms such as stretch-activated channels (25). A model of the coronary tree has also been developed (49, 50) and coupled with the ventricular mechanics model to examine regional energy demand/supply relations (48). Current work is linking myocardial mechanics to the fluid mechanics of blood flow in the ventricles and to the function of the heart valves. Future work will need to include models of the Purkinje network and the autonomic nervous system (39).

**Torso models**

A model of the torso has been developed that includes the heart and lungs within the thoracic cavity and the layers of skin, fat, and muscles on the chest to compute the current flow out of the heart that gives rise to the measured EKG or more detailed body surface maps of skin potentials (5). One goal of this work is to solve the inverse problem of electrocardiology: how to compute activation patterns in the heart from measured potential maps on the body surface (40).

**Summary, Goals, and Future Directions**

Anatomically and biophysically based models of 4 of the 12 organ systems in the human body are now quite well developed at the organ and tissue levels (the cardiovascular, respiratory, digestive, and musculoskeletal systems). Others (the lymphatic system, the kidney and urinary system, the skin, the female reproductive system, and the special sense organs) are at an early stage of development, and the remainder (the endocrine, male reproductive, and brain and nervous systems) will be addressed over the next few years. Software to visualize anatomically based models and solve the coupled biophysical field equations on these models is available (see Table 1). All of the models can be readily adapted to an individual patient if appropriate clinical imaging data are available (14, 57).

Many of the tools required to author, visualize, and run models at the cell level are either available now or soon will be (22, 24, 26, 32). In the near future these tools will become more integrated and more easily able to link through ontologies to bioinformatic databases (19, 20, 37). This will facilitate international collaboration between groups working in complementary areas—with the multiscale models acting as the glue to connect and integrate information (38, 42).

Much of the framework for dealing with cell function is in place, and a substantial repository from published models has been created (http://www.cellml.org). An important future development of the CellML framework is to use the importing feature to assemble models from their individually described components. For example, a cardiac cell model may contain mathematical...
descriptions of 30 different ion channels, receptors, transporters, pumps, exchangers, etc. The author of a new cell model will typically “tune” the parameters of these protein models to match measurements of the action potential profile and ion current responses to membrane voltage perturbations. The result is a plethora of models for different species and different parts of the heart (sinoatrial node, atrioventricular node, atria, Purkinje fiber, endothelial cell, mid-myocardial cell, epicardial cell, etc.); there are currently 37 such models in the CellML database. It would be highly preferable to define CellML models of the individual proteins based on patch-clamp data (with allowance for isoform variation) and to automatically import these models into a given cell type using the ontologies and a knowledge of the expression levels for each protein within a specified tissue. There is also an urgent requirement at the cell level for models that capture the 3-D structure of organelles and cytoplasm in the ~200 different human cell types.

An important goal for the Physiome Project is also to use this modeling framework to help interpret clinical images for diagnostic purposes and to aid in the development of new medical devices. Another goal is to apply the anatomically and physiologically based models to virtual surgery, surgical training, and education. A longer-term goal is to help lower the cost of drug discovery by providing a rational multiscale and multiphysics modeling-based framework for dealing with the enormous complexity of physiological systems in the human body. The approach to computational physiology described here is at a very early stage of development but has the potential to help make physiological sense of the vast amount of cellular and molecular detail generated by biomedical scientists over the past 50 years.

We are grateful to many of our colleagues in the Bioengineering Institute at the University of Auckland, whose research work we have drawn on, and in particular to Shane Blackett, Matt Halstead, Catherine Lloyd, Andrew Miller, David Nickerson, Greg Sands, and Carey Stevens for contributions to the cmgui graphics library, ontologies, CellML model database, MozCellML code, CellML APIs, tissue image processing, and Mozilla/XUL user interfaces, respectively. We also gratefully acknowledge Professors Denis Noble, David Paterson, and Peter Kohl at Oxford University, and Professor Andrew McCulloch at the University of California, San Diego, all of whom are contributing to the Wellcome Trust Heart Physiome Project.

Some of the work reported here has been funded by the New Zealand Government Tertiary Education Commission (TEC) through a Centre of Research Excellence grant to the Centre of Molecular Biodiscovery; the Wellcome Trust, through a grant on the Heart Physiome Project; the Health Research Council of New Zealand and the Royal Society (New Zealand) Marsden fund.

References


53. Tanskanen AJ, Greenstein JL, O’Rourke B, and Winslow RL. The role of stochastic and modal gating of cardiac L-type Ca2+ channels on early afterdepolarizations. *Biophys J* 88: 85–95, 2005.


