Modeling human physiology: the IUPS/EMBS physiome project

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Invited Paper

The Physiome Project is an international collaboration to provide a framework for understanding human physiology, from proteins and cells to tissues and organs, with multiscale models that use computational techniques derived from engineering and software approaches from computer science. With the increasing interest in modeling living systems from research scientists in many branches of mathematics, physics, and engineering, it is timely to review what has been achieved, what lessons can be learned from the efforts so far, and what needs to be done to facilitate the international collaboration that is essential to the project's success. In particular, we review the development of models at spatial scales from genes and proteins to the whole body, and the development of standards, tools, and databases to facilitate multiscale modeling. Some applications of the physiome models are described, including applications in medical diagnostics, the design of medical devices, virtual surgery, surgical training, and medical education.

Keywords*—Computational biology, computational physiology, mathematical modeling, Physiome Project.*

I. Introduction

As reductionist biomedical science succeeds in elucidating ever more detail at the molecular level, it is increasingly difficult for physiologists to relate integrated whole-organ function to underlying biophysically detailed mechanisms that exploit this molecular knowledge. Organ and whole-organism behavior needs to be understood at both a systems level and in terms of subcellular function and tissue properties. Understanding a reentrant arrhythmia in the heart, for example, depends on knowledge of not only numerous cellular ionic current mechanisms and signal transduction pathways, but also larger scale myocardial tissue structure and the spatial variation in protein expression. The only means of coping with this explosion in complexity is computational modeling—a situation very familiar to engineers and physicists who have long based their design and analysis of mechanical, electrical, and chemical engineering systems on computer models. Biological systems, however, are vastly more complex than human engineered systems and understanding them will require specially designed instrumentation to measure material properties, databases of models, and software for model authoring, visualization, and simulation. Moreover, a quantitative analysis of structure–function relations across the relevant range of spatial scales (nanometers to meters) and temporal scales (microseconds to human lifetime) requires a hierarchy of models in which the parameters of a model at one limited spatial or temporal scale can be linked to a more detailed model of structure–function at the level below [19], [20], [33]. Note that a model-based analysis of human physiology will also facilitate the quantitative assessment of human pathophysiology via changes in model parameters at all spatial and temporal scales [6], [39].

The project will require substantial international and interdisciplinary collaboration. Here we outline a framework for handling the hierarchy of computational models, and associated experimental data and publications, which will help integrate knowledge at the genomic and proteomic levels into an understanding of physiological function for intact organisms. The endeavor is called the "IUPS/EMBS Physiome Project" to emphasize the oversight role of both the International Union of Physiological Sciences (IUPS) and the IEEE Engineering in Medicine and Biology Society (EMBS) in the project.[1] A brief historical background to the Physiome Project is given in Box 1. Note that the focus on computational physiology is the distinguishing feature of the Physiome Project but that it also encompasses the area commonly referred to as systems biology, which includes, for example, subcellular signalling cascades, metabolic pathways, and gene regulation networks [10], [32], [52].

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[1]IUPS: [Online]. Available: http://www.iups.org. EMBS: [Online]. Available: http://www.embs.org. The IUPS Physiome Project is run under the auspices of the IUPS Physiome and Bioengineering Committee and the EMBS Physiome Project Technical Committee.

The fact that we can even contemplate building a "virtual human" based on models of structure–function relations across multiple spatial scales, is the consequence of many developments, including the following.

1) 50 years of research in molecular and cellular biology that has given us an extraordinary knowledge of subcellular processes including the sequence of nucleotides in the human genome.
2) An understanding of nature's physical conservation laws (conservation of mass, momentum, heat, charge, etc.) and how to apply these laws to deformable, conductive, and diffusive materials.
3) The computational power of modern computers, together with 50 years of numerical algorithm development such as the finite-element method and multigrid methods.
4) The development and wide availability of remarkable medical imaging devices such as NMR, MRI, CT, ultrasound, MCG, etc., that can yield detailed information on the structure and function of an individual patient.
5) The internet and the powerful tools (e-mail, Web browsers, etc.) of the existing World Wide Web and the coming semantic Web[2] for rapid access to information and for international collaboration.

Box 1. **Brief History of the Physiome Project**.

The concept of a "Physiome Project" was presented in a report from the Commission on Bioengineering in Physiology to the IUPS Council at the 32nd World Congress in Glasgow, U.K., in 1993. The term "physiome" comes from "physio" (life) + "ome" (as a whole), and is intended to provide a "quantitative description of physiological dynamics and functional behavior of the intact organism" [1]. A satellite workshop "On Designing the Physiome Project," organized and chaired by the Chair of the IUPS Commission on Bioengineering in Physiology (Prof. J. Bassingthwaighte), was held in Petrodvoretz, Russia, following the 33rd World Congress in St. Petersburg, Russia, in 1997. A synthesium on the Physiome Project was held at the 34th World Congress of IUPS in Christchurch, New Zealand, in August 2001 and the Physiome Project was designated by the IUPS executive as a major focus for IUPS during the next decade. The author was appointed Chair of the Physiome Commission of the IUPS in 2000, and is now cochair with Prof. A. Popel of the combined IUPS Physiome and Bioengineering Committee. A Technical Committee of the IEEE-EMBS is currently being established to manage the involvement of EMBS in the Physiome Project.

II. Multiscale Modeling

Engineering techniques are commonly used in the design of medical devices or analysis of biological systems. For example, finite-element stress analysis is used for the design of hip joint prostheses and arterial stents, and computational fluid dynamics (CFD) is used in blood flow analysis of heart valves. Mathematical analysis of subcellular systems, such as metabolic and signal transduction pathways, is similarly widespread among the mathematical biology community. None of these applications, however, deal with the multiscale, multiphysics modeling characteristic of the Physiome Project. To illustrate what the Physiome Project is trying to achieve, consider the multiscale modeling framework shown in Fig. 1. The heart model is used here as an example but we also consider the issues relevant to each spatial scale for other organ systems. The numbered headings below refer to the steps in spatial scale shown in Fig. 1. Note that all models must be validated against experimental data and that the principle of Occam's razor should be applied: models should be as simple as possible consistent with the level of experimental data available but, as Einstein noted, not too simple.

A. Genes: DNA, Mutations, and mRNAs; Gene Regulation Modeling

At the smallest spatial scale a segment [Fig. 1(a)] of one of the 22 (plus sex-linked X and Y) pairs of human chromosomes in the human nucleus contains the DNA code for a particular protein. The full sequence of 3.2 billion A-T and C-G nucleotide base pairs for the human genome has recently been determined,[3] including the approximately 20 000 regions (genes) that code for the amino acids making up a protein—constituting only about 1.5% of the genome [80], [81]. Each amino acid (there are 20 types) is specified by 3 base-pairs (a codon) although with 64 $(4 \times 4 \times 4)$ combinations of A, T, C, and G most amino acids have multiple encodings. About half of the remaining 98.5% of the genome appears to code for RNAs involved in gene regulation (turning gene expression on and off) and the other half is so-called junk DNA. Understanding and modeling this "hidden layer" may be the greatest of all challenges for the Physiome Project (see [4], [7], [8], [25], [26], [29], [44], [76], [82] for references to models of gene regulation and other fascinating aspects of gene transcription).

When activated by proteins called transcription factors that bind to DNA, the enzyme polymerase II unzips the double stranded helix to allow the creation of matching RNAs within the nucleus—a process called transcription. Note that the protein-encoding gene transcript contains noncoding segments called introns that are removed. The coding segments called exons (expressed sequence) are then reconnected to create the messenger or mRNA that moves out of the nucleus into the surrounding cytoplasm. The exons are in fact often combined in more than one way to yield several "splice variants"—hence, the number of proteins is likely to be considerably larger than the number of genes (five splice variants per gene on average would yield

[2][Online]. Available: http://www.w3.org/2001/sw

[3][Online]. Available: http://www.ncbi.nlm.nih.gov/genome/guide/human/

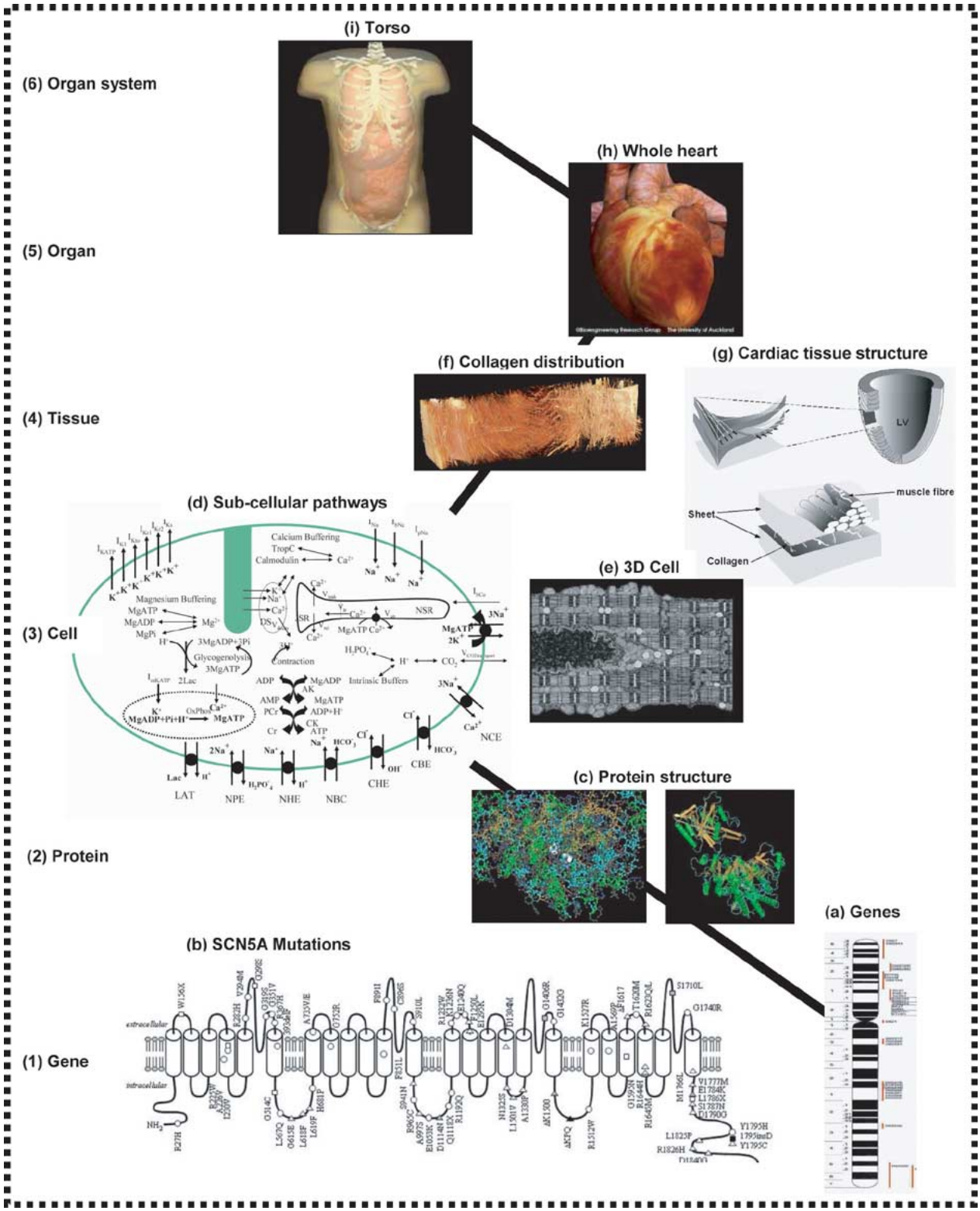


Fig. 1. An illustration of the hierarchy of spatial scales used in the Heart Physiome Project. Fig. 1(b) was kindly provided by Dr. Charles Antzelovitch (*from: The Brugada Syndrome: From Bench to Bedside,* C. Antzelevitch and P. Brugada, eds. Oxford, U.K.: Blackwell Futura, 2005, Ch. 1, p. 8, with permission); all other figures are from the Auckland Bioengineering Institute.

100 000 proteins). The mRNAs are interpreted by ribosomes (large protein complexes outside the nucleus) to assemble the chain of amino acids that constitute proteins—a process called translation. A further sequence of posttranslational modifications (such as adding sugar groups) is carried out in other cellular organelles.

The variations in nucleotide sequence, such as single nucleotide polymorphisms (SNPs), that yield the inherited differences between individuals are currently being elucidated[4] and the particular genetic defects that are associated with some human diseases are also being characterized.[5] For example, the genetic mutations associated with the SCN5A gene that codes for the sodium channel protein (that is responsible for the abrupt voltage change in activated cardiac cells) are shown in Fig. 1(b). Understanding how some of these mutations can lead to cardiac arrhythmias is one of the goals of the Heart Physiome Project [5], [16], [17]. The important point here is that the mutations are only part of the explanation for arrhythmias (or any phenotype for that matter). Tissue structure and the environmental influence of, for example, exercise are equally important.

B. Proteins: Molecular Dynamics and Coarse-Grained Modeling

A protein on average contains 800 amino acids (1.5% of 3.2 billion base-pairs divided by 20 000 genes at 3 base-pairs per codon) folded into a 3-D structure that achieves a particular function such as voltage-gated ion transport in the case of an ion channel or ligand binding, in the case of a membrane receptor. The 3-D structures of about 30 000 proteins have been determined, primarily by X-ray crystallography and NMR spectroscopy, and deposited in the Protein Data Bank (PDB)[6] [3]. Another great challenge in computational biology is to be able to predict the folded shape of the protein from the sequence of residues and many efforts are underway to achieve this, not least the IBM Blue Gene project.[7] Massive efforts are also just beginning to accelerate the determination of protein structures and it is the long-range goal of the Protein Structure Initiative (PSI) is to make the three-dimensional (3-D) atomic-level structures of most proteins obtainable from knowledge of their corresponding DNA sequences.[8] The other major components of cells—lipids and carbohydrates—are also being characterized in a comprehensive fashion.[9] These large-scale projects—genome, proteome, lipidome, etc.—provide a parts list for human biology. A logical next step in this bottom-up approach is characterizing the interactions between components. For example, the "reactome" project is developing a curated resource of core pathways and reactions for protein interactions.[10]

Fig. 1(c) shows the atomic coordinates for the sarcoplasmic calcium ATPase (SERCA) from the PDB database (note the two bound calcium atoms in white) and also a coarser grained model of structure for the same protein. Molecular dynamics (MD) models of the atomic structure of ion channels, pumps and exchangers, etc., are being developed 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 (QM) calculations. Water is usually included in discrete molecular form or, for greater distances, as a bipolar continuum field. These models require knowledge of the protein's atomic structure, but there are few membrane proteins in the PDB. Structures are currently known for a few bacterial potassium channels such as KcsA, KirBac, and KvAP which have close homology (sequence similarity) in the pore region to mammalian K^+ channels [58]. MD calculations, based on about 100 000 atoms in current models, are very computationally expensive and on current computers are typically run for periods of only 10 ns [14]. Sometimes homology modeling is used in combination with MD simulation to generate, test, and refine models of mammalian K channels based on bacterial templates [15]. Note that the function of a protein is determined primarily by its shape (there can be many alternative amino acid sequences for the same shape) and the surface distribution of electrostatic charge, together with the capacity to occasionally form covalent disulphide bonds (the amino acids cysteine and methionine contain sulphur groups). Another key aspect of function is the "binding motif" for a specific interaction site.

A major challenge now is to develop "coarse-grained" (less detailed) models of these ion channels and other proteins with parameters calculated from the MD models. Coarse-grained models should include transient gating behavior for time intervals up to about 100 ms. Models of channel kinetics based on whole cell voltage clamp data—the now-classical Hodgkin–Huxley (HH) equations, which use ordinary differential equations to describe the time- and voltage-dependent gating behavior of ion channels, were developed over 50 years ago for Na^+, K^+, and Cl^- channels in giant squid axons [28] and over 40 years ago for cardiac ion channels [51]. The subsequent development of the single-channel patch clamp led to refinement of these models with Markov state variable models [70] which assign a number of open and closed states for the gates and the probability of transitions between the states. One of the challenges now for the Heart Physiome Project is to derive the parameters of the HH or Markov models from the MD models via coarse-grained intermediate models as the molecular structures of these proteins become available. This multiscale linkage will benefit the understanding of structure/function relations at both levels.

C. Cells: Subcellular Pathways and 3-D Cell Models

The human body has about 200 cell types often divided into the following major categories: blood, bone and cartilage, cardiac, central nervous system (CNS), epidermal, gas-

[4][Online]. Available: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=handbook.chapter.1143

[5][Online]. Available: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM

[6][Online]. Available: http://www.pdb.org

[7][Online]. Available: http://www.research.ibm.com/bluegene/

[8][Online]. Available: http://www.nigms.nih.gov/psi

[9][Online]. Available: http://www.lipidmaps.org

[10][Online]. Available: http://www.reactome.org

trointestinal, immune, neural, liver, pancreatic, respiratory, sensory system, skeletal muscle, male reproductive, and female reproductive cells. The eukaryotic (nucleus containing) cell is the result of evolutionary development from the beginning of life on earth ~4 billion years ago (the earth formed about 4.8 billion years ago) up to the 10 million year period called the Cambrian explosion that occurred about 500 million years ago. The subsequent evolution of multicellular life forms, including mammals, has occurred since then, but the basic cellular machinery appears not to have changed very much. The primary functions of cells of transport, metabolism, signaling, motility, organizing the cyto-skeletal structure, and performing the cell cycle are common to almost all cells across all animal species, a remarkable fact that makes experiments on yeast cells, drosophila, or mice relevant to human physiology.

A repository of cell models dealing with many of these cell functions and derived from refereed journal publications and encoded in an eXtensible Markup Language (XML) standard called CellML (discussed later) has been established.[11] The CellML standard includes import mechanisms for building composite models from submodels using standard ontologies for naming and linking model components [27]. The repository has mechanisms for version tracking and model curation. It contains about 300 models in the following categories:

1) signal transduction pathway models;
2) metabolic pathway models;
3) cardiac electrophysiological models;
4) calcium dynamics models;
5) immunology models;
6) cell cycle models;
7) simplified electrophysiological models;
8) other cell type electrophysiological models;
9) smooth and skeletal muscle models;
10) mechanical models and constitutive laws.

For the heart physiome, lumped parameter models (i.e., without diffusion modeling) of various processes within cardiac myocytes are now well advanced [Fig. 1(d)]. The composite cell models encompass all the ion channels, ATPase pumps, and exchangers known to support the cardiac action potential [49], together with equations governing calcium transport [62], proton exchange [78], [79], myofilament mechanics [34], metabolic pathways [2], and signal transduction pathways that modulate the phosphorylation state of intracellular proteins [59]–[61]. All of these models are available in the CellML repository.

Cells are, of course, not homogeneous bags of proteins, lipids, and carbohydrates, but rather are highly organized structures with compartments (called organelles) such as the nucleus (contains the genetic material), mitochondria (site of oxidative metabolism) and the Golgi apparatus (posttranslational processing of proteins), dedicated to specialist functions. Even within the cytoplasm (the space within the cell that lies outside the organelles) there is a high degree of organization. For example, in the cardiac cell shown in Fig. 1(e) the proteins governing mechanical contraction are arranged to slide past one another and are tethered laterally all the way out to the outer membrane (the sarcolemma). The invaginations of this membrane (the T-tubules) are aligned to communicate the membrane voltage changes which trigger the release of calcium to initiate contraction. Many of the intracellular signalling systems that modulate the activity of contractile proteins and membrane ion channels and pumps are confined to 3-D paths through the cytoplasm by the organized distribution of enzymes (phosphodiesterases) that break down the "second" (intracellular) messenger cAMP.

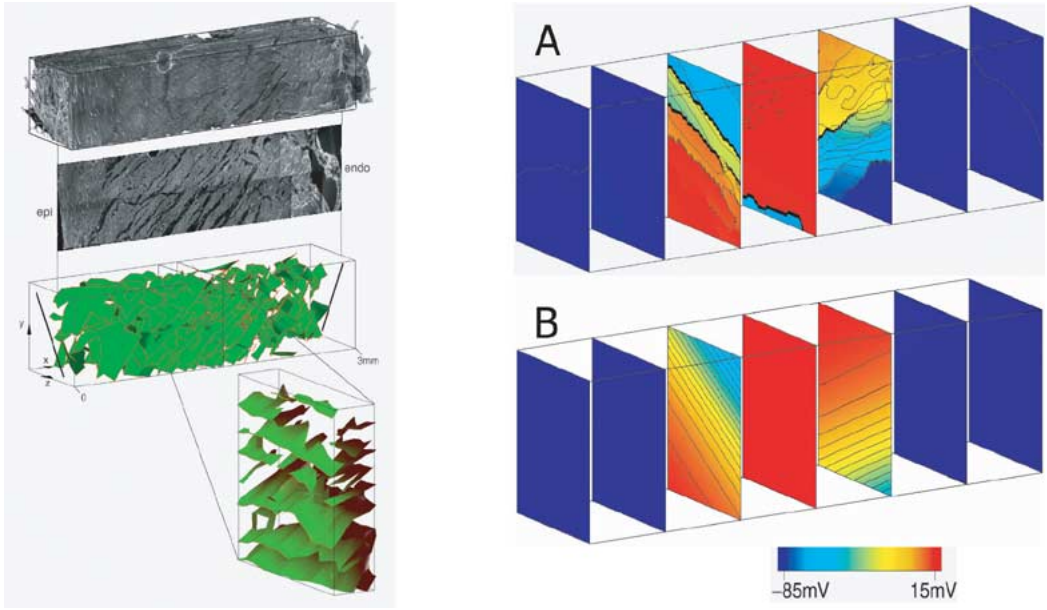
The next stage of development of cell models will therefore need to take account of the spatial distribution of proteins within a cell and subcellular compartments, where second messengers (Ca^{2+}, IP_3, cAMP, etc.) are localized [62]. The spatial distribution of the transverse tubular system in cardiac myocytes has been measured with two-photon microscopy [66] and the spatial modeling of proton transport and buffering in the myocyte is also well advanced [78]. Developing 3-D models at the cellular level will help to fill the large gap in spatial scales between proteins and intact cells.

D. Tissues: Fields and Continuum Models

There are four basic tissue types (epithelial tissue, connective tissue, muscle tissue, and nervous tissue) and each has a highly organized arrangement of cells. In the case of cardiac tissue the dominant (by volume) cell type is the cardiac myocyte [shown in Fig. 1(e)] although fibroblasts, which produce the protein collagen that binds the cells together, are more numerous. The distribution of collagen through the free wall of the left ventricle is shown in Fig. 1(f). The organization of myocytes and collagen is shown diagrammatically in Fig. 1(g). The myocytes (muscle fibers) are bound into sheets about three or four cells thick that can slide relative to one another to facilitate the shearing action that supports wall thickening in the intact beating heart [42].

The concept of a "field" (the mathematical representation of a spatially and temporally continuous and varying quantity) and the idea of expressing nature's physical laws via partial differential operators on these fields has been taken for granted by electrical engineers since Faraday's pioneering work on magnetic dipoles and electric charges and Maxwell's discovery of the field equations for electricity and magnetism in the 19th century. Much 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 which hide molecular or atomic detail behind approximate "constitutive laws." For electrical engineering, for example, Ohm's law gives a linear relationship between voltage gradient and current flow. The proportionality constant (electrical "resistance") can be measured directly and used in the solution of the governing Maxwell's

[11][Online]. Available: http://www.cellml.org



(a) (b)

Fig. 2. (a) *Upper*: reconstructed volume of rat left ventricular free-wall myocardium. *Middle*: transmural slice from the reconstructed volume showing a complex network of cleavage planes which course between myocyte laminae. *Lower*: the bilinear finite-element geometrical description of the cleavage planes through the entire rat tissue block, and a smaller midwall subsection. Myofiber orientation is shown on the epi- *(epi)*, and endo- *(endo)* cardial surfaces. (b) Potential maps for discontinuous model (A), in which current flow is computed around the discretely modeled sheets, and continuous model (B), in which the spatially varying fiber and sheet axes are included and a continuum representation is used with a conductivity tensor defined relative to these axes. Transmembrane potentials are mapped on seven equi-spaced surfaces through the reconstructed rat tissue volume, at 8 ms following midwall stimulation. Isopotential lines at 5 mV intervals are shown in black. Site of stimulation is shown with black dot at center of volume. The cleavage plane obstacles in (A) lead to a highly discontinuous form of propagation, which is, however, well approximated by the continuous model. Figures from Hooks *et al.* [30].

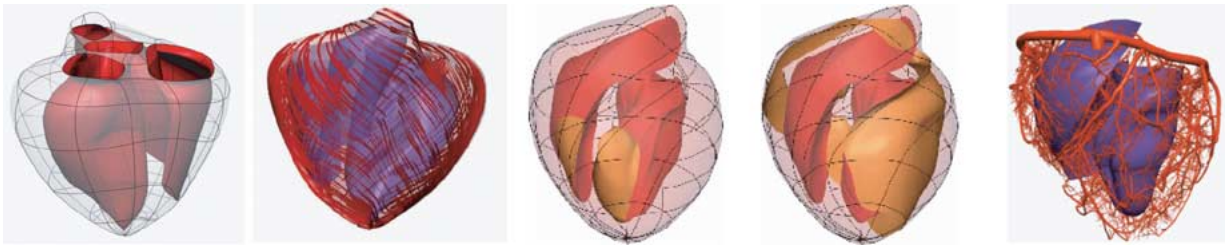
field equation (which reduces to Kirchoff's current law in this simple example) without dealing with the underlying structure of the material. For mechanical engineering the equivalent is the empirically derived relationship between stress and strain (or strain *rate* for a fluid), although in this case these two measures of force and deformation, respectively, require the use of tensors each with six components (three components represent forces or deformations acting normal to the three orthogonal faces of a cube and three represent the shearing forces or deformations). Field ideas are of course also highly relevant to continuum models in biology. An implementation of biological multiscale modeling would be to derive the constitutive relation (Ohm's law or stress/strain relation) from field equations applied to the detailed material structure.

The challenge of tissue modeling is therefore to derive the mechanical, electrical, etc., material properties of tissue from a parameterized description of structure that includes the density and spatial orientation of the constituent cells and proteins. An example of this is shown in Fig. 2, where the fibrous-sheet structure of myocardial tissue is represented in a continuum model [Fig. 2(a)]. Solution of field equations in this model yields suitable approximations for anisotropic tissue conductivities in a coarse-grained model [30] that can be used to solve electrical propagation in the whole heart (see below).

This example illustrates an important feature of physiome modeling—the use of a detailed model of structure at one spatial scale (in this case solving reaction-diffusion processes with a model containing the detailed anatomy of the fibrous-sheet structure of cardiac tissue) to derive appropriate parameters for use in the continuum model at a larger spatial scale (in this case, the conductivity tensor used in solving reaction-diffusion for the whole heart). The model at the whole-heart level (see next section) needs to include a representation of the orientation of the fibrous-sheet structure in order to express the constitutive laws (e.g., conductivity tensor) relative to those axes, but it does not need to include the detailed architecture of the myocardial sheets. In this example, the molecular ion channels are represented at both scales (at considerable computational cost) because we have not yet discovered how to simplify the cellular electrophysiology for use at the whole-heart level. Ideally, use of nonlinear system identification techniques would allow the detailed cellular models to be replaced at the whole-heart level by a computationally more efficient "black-box" systems model that behaved equivalently. The use of material constitutive laws, whose parameters are derived from microstructurally based models, to represent the stress–strain behavior at the whole-organ level is another example of multiscale modeling.

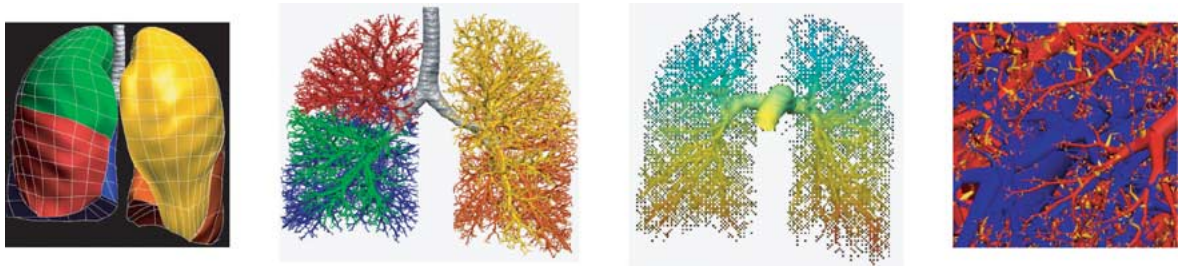
E. Organs: Whole-Heart Structure and Function

Models at the whole-heart level now incorporate the anatomy of the right and left ventricles [Fig. 3(a)] and the fibrous-sheet architecture of the myocardium [Fig. 3(b)] [40], [41]. Computational methods are used to solve for the activation wavefront propagation computed from bidomain



(a) (b) (c) (d) (e)

Fig. 3. The organ-level heart model. (a) The geometry of ventricular myocardium shown in a 3-D finite-element model of the heart [67]. The inner surfaces (endocardium) of the left and right ventricles are shown in red through the translucent outer surface (epicardium) of the heart model. (b) Fiber orientations on the epicardial surface of the heart [50]. (c) The wave of electrical depolarization (orange) shown at an early stage of myocardial activation and (d) at a later stage [77]. (e) The coronary arteries modeled from pig heart data [64]. The physiome heart model couples these various physical processes together and links the tissue level properties to subcellular processes such as ion channel current flow and mechanical force generation.



(a) (b) (c) (d)

Fig. 4. Finite-element lung models. (a) The outer surfaces of the five lobes of the left and right lungs. (b) A model of the conducting airways constructed from CT data to fit airways down to branch generations 6–9, and an airway generation algorithm to fill a CT-based volume mesh from the CT airways out to the terminal bronchioles. The right upper lobe airways are green, right middle lobe are red, right lower lobe are blue, left upper lobe are yellow, and left lower lobe are orange. (c) A model of the pulmonary arteries showing the calculated pressure distribution. (d) Small arteries (red) and veins (blue). This project has now integrated air flow, blood flow, and tissue mechanics and is currently embedding the lung model in a model of the thoracic cavity, which includes the rib cage, intercostal muscles, and diaphragm [13], [71]–[74]. Models of gas exchange in the alveoli have also been developed. The lung models are being used for research on COPD and asthma (see also paper by Clough *et al.* in this issue).

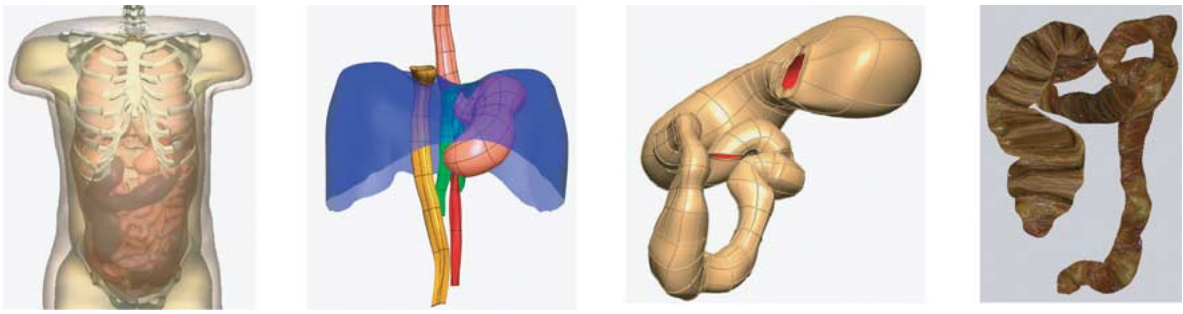
field equations [36], using a conductivity tensor based on the fiber-sheet orientations and the ion channel cell models referred to above [Fig. 3(c) and (d)], and the large deformation mechanics of the ventricles, using "orthotropic" constitutive properties (i.e., properties different in three orthogonal material directions) based on the fiber-sheet orientations [42], [50]. These models have shown how the shearing properties of myocardial tissue are crucial to its mechanical function [23], [48]. The coupling between the mechanical and electrical models is also achieved with calcium, released from internal stores, binding to a protein called troponin-C to initiate cross-bridge interaction [34] and mechanoelectric feedback mechanisms such as "stretch-activated" channels (membrane channels that change their conductive properties in response to stretch) [38]. A model of the coronary tree [Fig. 3(e)] has also been developed [64], [65] and coupled with the ventricular mechanics model in order to examine regional energy demand/supply relations [63]. Current work is linking myocardial mechanics to the fluid mechanics of blood flow in the ventricles and to the function of the heart valves, and will soon include models of the Purkinje network and the autonomic nervous system [54]. (See also paper by Kerckhoffs *et al.* in this issue.)

F. Organ Systems

The 12 organ systems in the human body are cardiovascular, respiratory, musculoskeletal, digestive, skin, urinary, nervous, endocrine, lymphatic, male reproductive, female reproductive, and special sense organs. The top level of the multiscale modeling hierarchy in Fig. 1 is the torso [Fig. 1(i)]. Models have now been developed to compute the distribution of body surface potentials generated by the activation wavefronts described above [55]. These and similar models are being used in inverse electrocardiography to compute cardiac electrical dysfunction from body surface potential maps [57]—see also Fig. 9(a). Another clinical application of the heart model is shown in Fig. 9(b) where the model is fitted to patient MRI data in order to obtain the distribution of strain around the heart throughout the cardiac cycle.

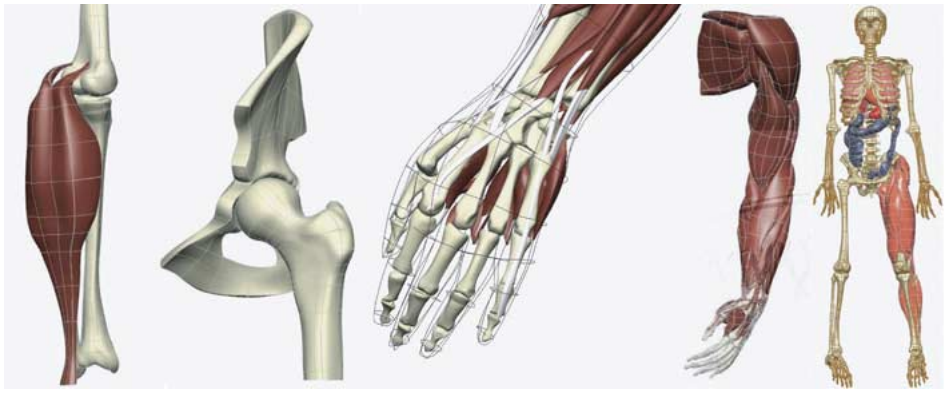
As well as the heart and circulation, multiscale and multiphysics physiome models are being developed for the lungs (Fig. 4), the digestive system (Fig. 5) and the musculoskeletal system (Fig. 6). A kidney physiome model is also being developed (see paper by Thomas *et al.* in this issue).

Note that in all of these organ level models the representation of the large scale anatomy (the geometry and tissue



(a) (b) (c) (d)

Fig. 5. Finite-element models of the digestive system. (a) The digestive system models shown within the thoracic and abdominal cavities. (b) The esophagus and stomach shown in relation to the diaphragm. (c) The stomach and duodenum. (d) The colon. The models are being used to study contractile wave propagation in the stomach and intestines [11] and are being developed in conjunction with SQUID magnetic field detectors for clinical diagnostic purposes.



(a) (b) (c) (d) (e)

Fig. 6. Finite-element models of the human musculoskeletal system. (a) Gastrocnemius muscle [24]. (b) Hip joint. (c) Muscle bones and ligaments in the hand. (d) Muscles of the left arm. (e) Human skeleton with all bones modeled and also showing muscles in the left leg and also heart, lungs, and digestive system [24]. The models are being used in a number of biomechanics applications including gait analysis.

structure) together with the material properties of tissues that link down to models of cellular function, means that the environmental influences operating on the body (e.g., the loads supported by the muscles and bones in the musculoskeletal system) can be transferred in a spatially distributed fashion down to the cells. Cells are highly regulated by the environment in which they operate, as evidenced by the large numbers of receptors on their surface and the many signal transduction pathways operating within them. It is clearly very important that the flow of information in physiome models moves both upwards from the genes and downwards from environmental influences.

III. Markup Languages and Ontologies

One of the primary goals of the Physiome Project is to promote the development of standards for the exchange of information between models. A number of standards have previously been developed for handling biological and medical data [22]. The best known example is the DICOM standard,[12] developed in 1993 by the American National Standards Institute and the National Electrical Manufacturers Association to facilitate the exchange of medical images. This allows all of the major medical image modalities (MR, CT, ultrasound, X-ray, ECG, pathology images, angiograms, and nuclear images) to be treated in a uniform and consistent manner [69]. Every medical equipment manufacturer supports the standard, which continues to evolve under the guidance of standing committees dealing with each type of medical imaging device. Standards are being developed in microscopy by the Open Microscopy Environment (OME)[13] and standards for the encoding of microarray and gene expression (MAGE) data are also being developed by the Microarray Gene Expression Data (MGED) Society[14] (see [9], [43], [68], [75]).

A similar requirement exists for Physiome Project models. The process of coding up differential equations from mathematical descriptions of complex cellular processes published in journals is fraught with potential error. Invariably there are typographical errors in published papers and even in the subsequent errata published either in the same journal or on an author's Web site. The constitutive laws for tissue properties, such as stress/strain for mechanics, current/Grad(voltage) for

[12][Online]. Available: http://medical.nema.org/

[13][Online]. Available: http://www.openmicroscopy.org

[14][Online]. Available: http://www.mged.org/Workgroups/MAGE/mage.html

[15][Online]. Available: http://www.cellml.org

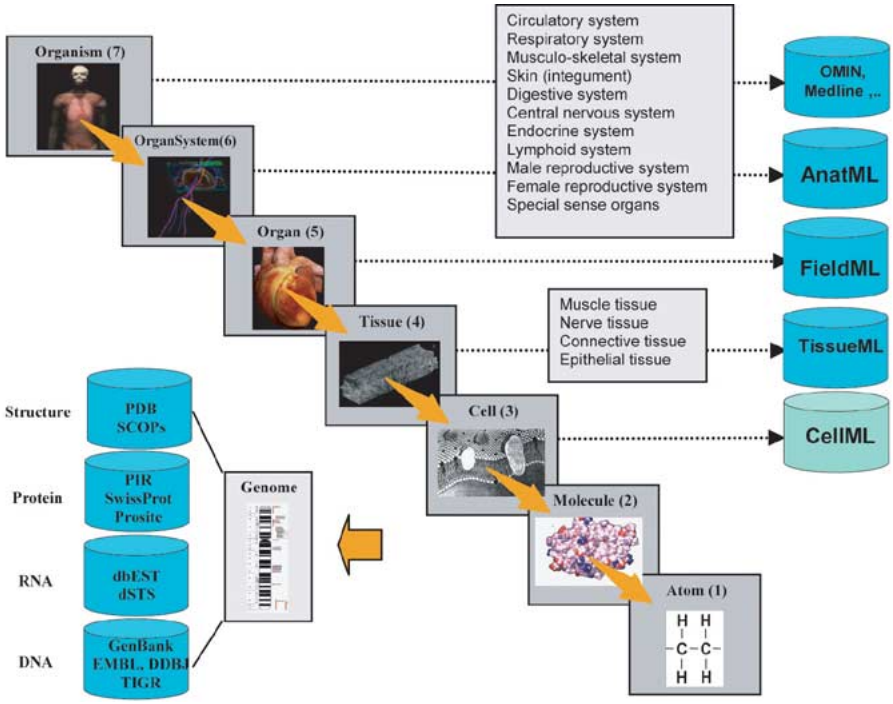


Fig. 7. Accessing information at the various spatial scales using ontologies and Web databases containing models encoded in the markup languages. The markup languages ensure that models are encoded in a consistent form and allow simulation packages to import the models in a standard format. Information on CellML can be found at http://www.cellml.org. The database will allow models at, for example, the tissue level to be obtained from the TissueML database with parameters that are appropriate to the relevant organ (and to the spatial location within the organ). This is indicated here by the orange arrow that illustrates the tissue structure at a particular location in the heart. From Hunter *et al.* [37]].

current, heat flux/Grad(temperature) for heat flow, etc., can involve complex mathematical expressions and the same requirement for a more robust process of encapsulating their expression is also needed. An XML-based standard called CellML[15] has therefore been developed for the Physiome Project using the MathML standard for mathematics, developed by the World Wide Web Consortium (W3C) body, and Resource Description Framework (RDF), a W3C standard for representing information about resources in the World Wide Web.[16]

Another requirement for the Physiome Project is to use a standard nomenclature for model components. This requires formal ontologies both to uniquely name all the biological components of the models (a controlled vocabulary) and to specify the relationships between components. An ontology of genes and gene products called Gene Ontology (GO) has been developed[17] and also an ontology for human anatomy called the Foundation Model of Anatomy (FMA)[18] [18], [56]. An organization called Open Biological Ontologies (OBO) has been formed to coordinate the development of families of ontologies[19] and a new Web ontology language called OWL has recently been developed by the W3C.[20] These ontologies are incorporated into the next release of the CellML standard [45]. Another markup language standard, targeted particularly at pathway models, is the Systems Biology Markup Language (SBML) [31].

The XML-encoded physiome models, together with the parameter variations for various diseases, need to be accessible via the Web from databases with user-friendly interfaces, as has been done by the bioinformatics community. The hierarchy of user interfaces and Web databases of XML-encoded models being developed for the Physiome Project is illustrated in Fig. 7.

Note that the use of markup languages and Web-accessible model repositories addresses problems with typographical errors in journals but does not address a failure by a model to adequately represent the real physiology. To be included in the model repository, models must be published in peer-reviewed journals so the presumption is that the normal reviewing process is providing critical evaluation of model validity. There may be a case for an additional layer of critical commentary on published models contained within the physiome model repositories, particularly where more than one model is available for a given biological function, but this needs to be done via peer-reviewed review papers.

IV. Software Tools

Another important goal of the Physiome Project is the development of open source tools for creating and visualizing models and running model simulations. User interfaces for two of these packages are shown in Fig. 8 (Protégé and MozCellML). The tools being developed by various groups listed in Table 1 divide into the following categories:

1) tools for creating and editing ontologies (Protégé);

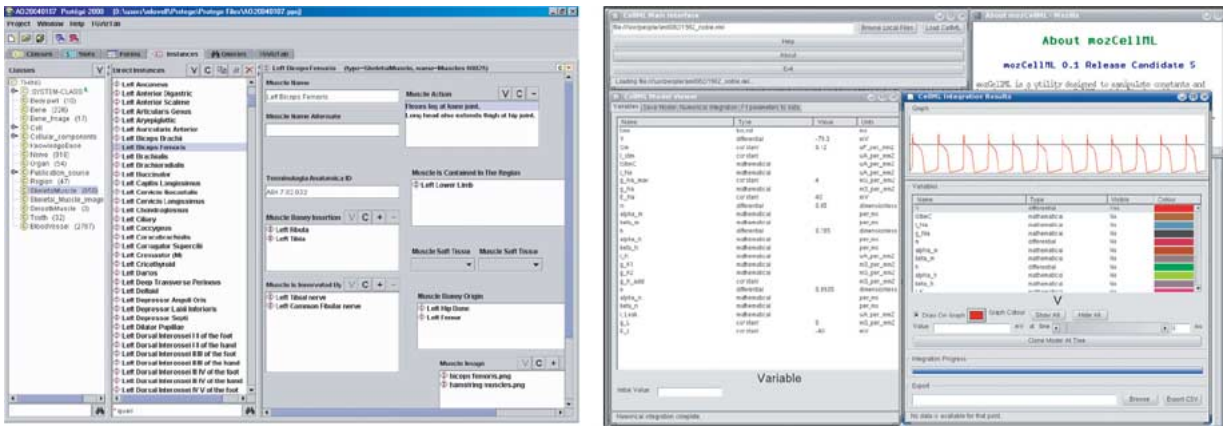
[16]See http://www.w3.org/RDF for the metadata associated with a model [21].

[17][Online]. Available: http://www.geneontology.org

[18][Online]. Available: sig.biostr.washington.edu/projects/fm/

[19][Online]. Available: http://www.obo.org

[20][Online]. Available: http://www.w3.org/2004/OWL



(a) (b)

Fig. 8. (a) Protégé window used for editing the biological ontologies. (b) MozCellML simulation tool for models from the CellML database. The CellML file, in this case describing the cardiac cell ion channels that generate the membrane action potential, is read and transformed to code which is complied and linked on the fly. The resulting executable program integrates the differential equations to yield the time course of the (typically 10–50) dependent variables in the model. The computed action potential is seen in the graphical output window. Another set of windows (not shown here) is designed for creating CellML models.

Table 1
Tools Being Developed for the Physiome Project

Tool Name	Group	Function	Read ML	URL
COR	Oxford	Cardiac Electrophysiology Simulator	CellML	http://cor.physiol.ox.ac.uk
iCell	Memphis	Cardiac Electrophysiology Simulator	No	http://ssd1.bme.memphis.edu/icell
JSIM	Seattle	Systems physiology	CellML	http://chief.cs.uga.edu/~jam/jsim
CellMLeditor	Auckland	CellML editor	CellML	http://cellml.sourceforge.net
MozCellML	Auckland	Cell simulator	CellML	http://cellml.sourceforge.net
CMGUI	Auckland	Visualization	FieldML	http://www.cmiss.org
CMISS	Auckland	PDE Simulator	CellML, FieldML	http://www.cmiss.org
Continuity	San Diego	PDE Simulator	No	http://cmrg.ucsd.edu/modelling/cont6
Gepasi	Virginia	Biochemical Simulator	SBML	http://www.gepasi.org
Systems Biology Workbench (SBW)	Caltech	A framework to facilitate application intercommunication	SBML	http://sbw.sourceforge.net
Virtual Cell	Connecticut	Biological Simulator	CellML, SBML	http://www.nrcam.uchc.edu
SCIRun	Utah	Visualization	No	http://software.sci.utah.edu
BioPSE	Utah	Electrical Field Simulator	No	http://software.sci.utah.edu
CESE	Canada	Cardiac Electrophysiology Simulation environment	CellML	http://cese.sourceforge.net

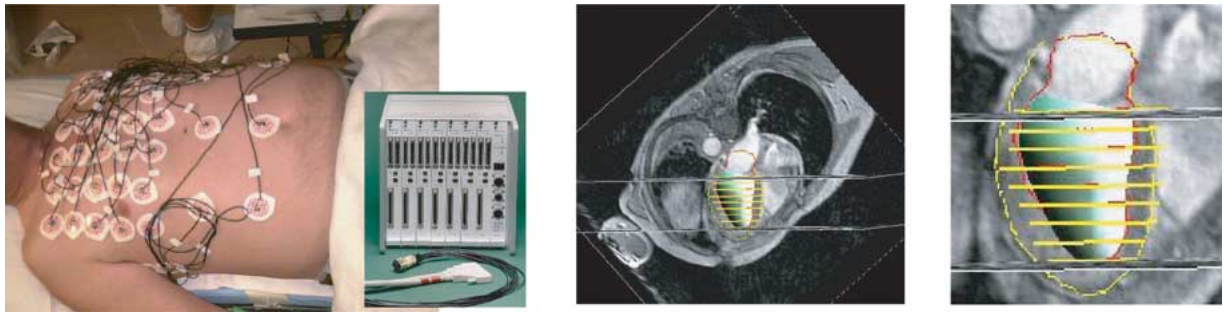
2) tools for creating and running electrophysiological models (CESE, iCell, MozCellML);
3) tools for creating and running pathway models (CellMLeditor/MozCellML, Gepasi, SBW);
4) tools for creating, visualizing, and running anatomical models—e.g., finite-element models (BioPSE, cmgui/CMISS, Continuity, SCIRun, Virtual Cell);
5) tools for systems physiology (JSIM);
6) tools for facilitating communication between models (SBW).

V. Application Areas

The range of practical applications of the Physiome Project models and software infrastructure are enormous but certainly include medical diagnostics, the design of medical devices, virtual surgery and surgical training, medical education, and, ultimately, drug discovery. Some examples are given in Figs. 9 (medical diagnostics), 10 (surgical training), and 11 (medical education).

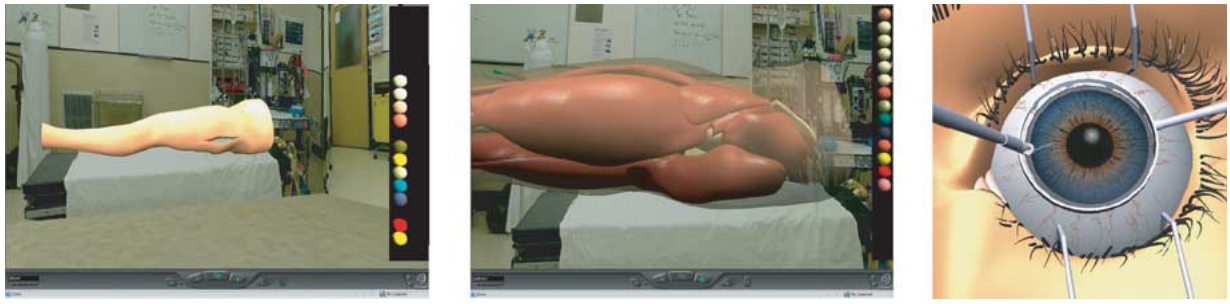
VI. Other Virtual Human Modeling Projects

A list of the projects which deal with some aspects of human anatomy and physiology in a comprehensive and integrated sense are given in Table 2. Some of these have educational and training goals only—rather than as research tools.



(a) (b)

Fig. 9. ***Medical diagnostics***. (a) Use of the heart and torso models for body surface mapping and inverse electrocardiology. Patient-specific model parameters can be obtained by running the model repeatedly in the forward direction under the control of an optimization algorithm that matches the predicted body surface plots to those observed in the clinic [12], [55]. (b) Use of the heart models for fitting tagged MRI data for cardiac strain calculations. The figure on the left shows the heart model superimposed on a patient MRI slice and the one on the right is an enlarged version, both provided by Dr. A. Young of the Auckland Bioengineering Institute. By fitting the models to kinematic data from MRI, the models yield the regional length changes occurring during the cardiac cycle in the patient's heart [83].



(a) (b) (c)

Fig. 10. ***Virtual surgery and surgical training***. (a) Leg skin surface. (b) Leg muscles. An example of physiome models being used in a training tools for orthopaedic surgeons. The model used here includes the bones and muscles of the leg and is designed to allow the trainee surgeon to practice a femoral head screw placement operation. Images provided by Dr. P. Blyth of the Auckland Bioengineering Institute. (c) A virtual environment for surgical training on the cornea (also from the Auckland Bioengineering Institute).

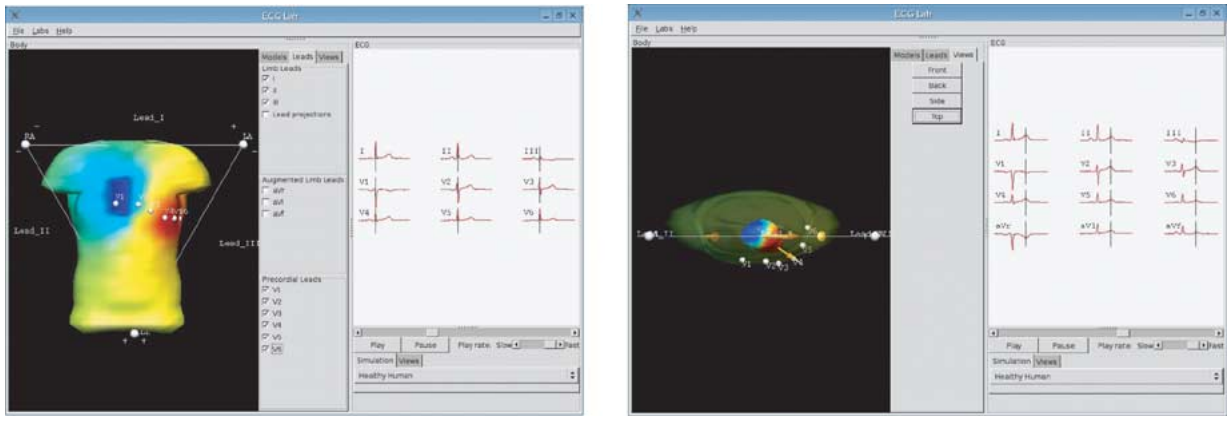


Fig. 11. ***Medical education***. A user interface designed to teach the principles of EKG to medical students. The window on the left of the interface includes 3-D anatomically based models of the heart and torso which can be rotated and zoomed. EKG leads are shown at the standard positions on the torso but these can be moved. An activation sequence is shown on the heart (seen in the right-hand figure) and torso (left-hand figure). Moving current dipole vectors are also computed and displayed. Potential maps are shown on the torso surface as a color map and the time course of EKG leads is shown on the right. Provided by C. Stevens of the Auckland Bioengineering Institute. Note that another freely available program called ECGSIM can be downloaded from http://www.ecgsim.org.

VII. Discussion

Biomedical research and development is currently driven by two separate communities. One operates at the spatial scale of genes and proteins, is informed by chemistry and molecular biology, has an abundance of data, and is generally associated with the discipline called bioinformatics. The other deals with organs and organ systems, is closely allied with medical physics and engineering, and draws on the power of continuum field equations based on nature's physical conservation laws. The two communities deal with the opposite ends of a continuous spectrum of biological length scales from genes, proteins, and subcellular pathways

Table 2
Virtual Human Modeling Projects

Project	Funding source	Purpose	URL
Visible Human	NLM	Human anatomy	http://www.nlm.nih.gov/research/visible/visible_human.html
IUPS Physiome	Various	Multi-scale modeling	http://www.physiome.org.nz/
US Physiome	Various	Links to models	http://www.physiome.org/
Virtual Soldier	DARPA	Wound simulation	http://www.virtualsoldier.net/
Virtual Astronaut	NASA	Medical education	http://virtualastronaut.jsc.nasa.gov/
EU BioSim	European FW 6	Pharmacogenetics	http://chaos.fys.dtu.dk/biosim/
Living Human	European FW 6	Biomechanics	http://www.tecno.ior.it/VRLAB/LHP/
AIMS	TATRC	Education & training	http://www.medsim.org
SIMS	various	Education & training	http://www.socmedsim.org
SESAM	various	Education & training	http://www.sesam.ws
SIMDOT	various	Education & training	http://www.simdot.org

Acronyms: NLM is the U.S. National Library of Medicine, DARPA is the U.S. Defense Advanced Research Projects Agency, NASA is the U.S. National Aeronautics and Space Administration, TATRC is the U.S. Army's Telemedicine and Advanced Research Center, SIMS is the Society for Medical Simulation, SESAM is the Society in Europe for Simulation Applied to Medicine. Some of these projects are described in detail in the accompanying papers in these PROCEEDINGS. Note that the Visible Human Project was the first project to create a comprehensive database of human anatomy (but not function). It has been an extremely valuable resource for many researchers around the world and established a precedent for Web-accessible anatomical data

to cells, tissues, organs, and organ systems—yet the two communities hardly talk to one another. Moreover, from a medical point of view two revolutions have occurred over the past 50 years. One is molecular biology and the sequencing of the human genome; the other is the development and widespread deployment of medical imaging devices that yield extraordinary insights into the structure and function of an individual patient. The challenge for the Physiome Project is to bring these communities together with a multiscale modeling hierarchy in which the parameters of a model at one spatial (or temporal) scale can be interpreted in terms of a more detailed model at the scale below, and to connect the revolution in molecular biology with the revolution in clinical imaging.

This paper has attempted to explain the modeling challenges at the various spatial scales by using the Heart Physiome Project as an example and emphasized the need for modeling standards, open source software tools and Web-accessible databases. The heart physiome has been developed in an international collaboration between research groups at the Universities of Auckland, Oxford, and San Diego (UCSD) [35], [46], [47], [53]. The other organ-based physiome projects are also international collaborations facilitated by the model repositories and open source software tools. Another aspect to the Physiome Project, and one that is particularly relevant to the community of biomedical engineers and medical physicists, is the relationship between the hierarchy of models and the range of clinical measurements of structure and function for an individual patient. The interpretation of clinical measurements within the rational multiscale and multiphysics framework of the Physiome Project has the potential to improve the diagnosis and treatment of a patient and to reduce healthcare costs.

One aim in writing this paper has been to suggest how the Physiome Project should evolve and how other groups could contribute to this communal effort. The underlying premise here is that a multiphysics, multiscale organ modeling project is too large an undertaking for any one academic group and must be done as a collaboration between two or more groups to be successful. Some of the projects described above have been underway for much longer periods than others and so have, of course, made much more progress. It is noteworthy, however, that the more recently initiated projects are able to build on the infrastructure created by the earlier ones and reach a high level of sophistication in a much shorter time. The fact that all cell types make use, to a greater or lesser extent, of common signal transduction pathways and other cellular processes, gives some reassurance that models developed for one organ system can be reused at least to some extent in other organ systems. It is not unreasonable to expect that the anatomy, including tissue structure, and at least normal (nonpathological) physiology of all 12 organ systems of the human body could be modeled within the next 5–10 years. At some point in the not-too-distant future, the level of detail encompassed by the physiome models will be sufficient for their use in drug discovery and toxicity testing.

The Physiome Project is currently a "grass-roots" effort with very little infrastructural funding but with the encouragement of the International Union of Physiological Societies and the IEEE Engineering in Medicine and Biology Society. With its focus on common standards for encapsulating models and importing model components, the development of open source software tools, and the building of freely accessible model databases, the project has provided a vehicle for significant international collaboration on a number of organ system models (particularly the heart and lungs). Much more input, however, is needed from other research groups and professional societies interested in integrative physiology. In relation to the challenges ahead, the project is still in its infancy.

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REFERENCES

[1] J. B. Bassingthwaighte, "Strategies for the Physiome Project," *Ann. Biomed. Eng.,* vol. 28, no. 8, pp. 1043–1058, 2000.

[2] J. B. Bassingthwaighte and K. C. Vinnakota, "The computational integrated myocyte: A view into the heart," *Ann. NY Acad. Sci.,* vol. 1015, no. 1, pp. 391–404, 2004.

[3] H. M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T. N. Bhat, H. Weissig, I. N. Shindyalov, and P. E. Bourne, "The protein data bank," *Nucl. Acids Res.,* vol. 28, pp. 235–242, 2000.

[4] U. S. Bhalla, "Understanding complex signaling networks through models and metaphors," *Prog. Biophys. Mol. Biol.,* vol. 81, pp. 45–65, 2003.

[5] M. Bober, K. Wiehe, C. Yung, T. O. Suzek, M. Lin, W. Baum-Gartner, Jr., and R. L. Winslow, "Cage: Cardiac gene expression knowledgebase," *Bioinformatics,* vol. 18, pp. 1013–1014, 2002.

[6] G. Bock and J. A. Goode*, Integrative Biological Modeling in Silico: In "In Silico" Simulation of Biological Processes*, G. Bock and J. Goode, Eds. New York: Wiley, 2002.

[7] H. Bolouri and E. H. Davidson, "Modeling transcriptional regulatory networks," *Bioessays,* vol. 24, pp. 1118–1129, 2002.

[8] P. Brazhnik, A. de la Fuente, and P. Mendes, "Gene networks: How to put the function in genomics," *Trends Biotechnol.,* vol. 20, pp. 467–472, 2002.

[9] A. Brazma *et al.*, "Minimum information about a microarray experiment (MIAME)—toward standards for microarray data," *Nature Genetics,* vol. 29, pp. 365–371, 2001.

[10] S. Brenner, "Biological computation," in *The Limits of Reductionism in Biology*. London, U.K.: Wiley, 1998, vol. 213, pp. 106–116.

[11] M. Buist, L. Cheng, R. Yassi, L. Bradshaw, W. Richards, and A. Pullan, "An anatomical model of the gastric system for producing bioelectric and biomagnetic fields," *Physiol. Meas.,* vol. 25, no. 4, pp. 849–861, 2004.

[12] M. Buist and A. J. Pullan, "Torso coupling techniques for the forward problem of electrocardiology," *Ann. Biomed. Eng.,* vol. 30, no. 10, pp. 1299–1312, 2002.

[13] K. S. Burrowes, M. H. Tawhai, and P. J. Hunter, "Modeling RBC and neutrophil distribution through an anatomically based pulmonary capillary network," *Ann. Biomed. Eng.,* vol. 32, no. 4, pp. 585–595, 2004.

[14] C. E. Capener and M. S. P. Sansom, "MD simulations of a K channel model—sensitivity to changes in ions, waters and membrane environment," *J. Phys. Chem. B.,* vol. 106, pp. 4543–4551, 2002.

[15] C. E. Capener, I. H. K. Shrivastava, M. L. Ranatunga, R. Forrest, G. R. Smith, and M. S. P. Sansom, "Homology modeling and molecular dynamics simulation studies of an inward rectifier potassium channel," *Biophys. J.,* vol. 78, pp. 2929–2942, 2000.

[16] C. E. Clancy and Y. Rudy, "Linking a genetic defect to its cellular phenotype in a cardiac arrhythmia," *Nature,* vol. 400, pp. 566–569, 1999.

[17] ——, "Na^+ channel mutation that causes both Brugada and long-QT syndrome phenotypes: A simulation study of mechanism," *Circulation,* vol. 105, no. 10, pp. 1208–1213, 2002, 12.

[18] D. L. Cook, J. V. L. Mejino, and C. Rosse, "Evolution of a foundational model of physiology: Symbolic representation for functional bioinformatics," in *Proc. MEDINFO 2004* vol. 11, pp. 336–340.

[19] E. J. Crampin, M. Halstead, P. J. Hunter, P. M. F. Nielsen, D. Noble, N. P. Smith, and M. Tawhai, "Computational physiology and the Physiome Project," *J. Exp. Physiol.,* vol. 89, no. 1, pp. 1–26, 2004.

[20] E. Crampin, N. Smith, and P. Hunter, "Multi-scale modeling and the IUPS Physiome Project," *J. Mol. Histol.,* vol. 35, no. 7, pp. 707–714, 2004.

[21] A. A. Cuellar, C. M. Lloyd, P. M. F. Nielsen, D. P. Bullivant, D. P. Nickerson, and P. J. Hunter, "An overview of CellML 1.1, a biological model description language," *Simulation,* vol. 79, no. 12, pp. 740–747, 2003.

[22] F. C. Dewey, Jr, A. Downes, H. Chou, and S. Zhang, "ExperiBase—An object model implementation for biology," in *8th Annu. Bio-Ontologies Meeting (Program Booklet)* 2005, pp. 31–32 [Online]. Available: http://bio-ontologies.man.ac.uk/download/bio-ontologies-2005-programme-booklet.pdf

[23] S. Dokos, B. H. Smaill, A. A. Young, and I. J. LeGrice, "Shear properties of passive ventricular myocardium," *Amer. J. Physiol.,* vol. 283, pp. H2650–H2659, 2002.

[24] J. Fernandez, P. Mithraratne, S. Thrupp, M. H. Tawhai, and P. J. Hunter, "Anatomically based geometric modeling of the musculo-skeletal system and other organs," *Biomechan. Model Mechanobiol.,* vol. 2, no. 3, pp. 139–155, 2004.

[25] T. S. Gardner, C. R. Cantor, and J. J. Collins, "Construction of a genetic toggle switch in Escherichia coli," *Nature,* vol. 403, pp. 339–342, 2000.

[26] J. Hasty, D. McMillan, and J. J. Collins, "Engineered gene circuits," *Nature,* vol. 420, pp. 224–230, 2002.

[27] W. Hedley, M. R. Nelson, D. Bullivant, and P. Nielsen, "A short introduction to CellML," *Phil. Trans. R. Soc. Lond. A,* vol. 359, no. 1783, pp. 1073–1089, 2001.

[28] A. L. Hodgkin and A. F. Huxley, "A quantitative description of membrane current and its application to conductance and excitation in nerve," *J. Physiol.,* vol. 117, pp. 500–544, 1952.

[29] N. S. Holter, M. Mitra, A. Maritan, M. Cieplak, J. B. Banavar, and N. V. Fedoroff, "Fundamental patterns underlying gene expression profiles: Simplicity from complexity," *Proc. Nat. Acad. Sci.,* vol. 97, pp. 8409–8414, 2000.

[30] D. A. Hooks, K. A. Tomlinson, S. G. Marsden, I. J. LeGrice, B. H. Smaill, A. J. Pullan, and P. J. Hunter, "Cardiac microstructure: Implications for electrical propagation and defibrillation in the heart," *Circulat. Res.,* vol. 91, pp. 331–338, 2002.

[31] M. Hucka, H. Bolouri, A. Finney, H. M. Sauro, J. C. Doyle, H. Kitano, A. P. Arkin, B. J. Bornstein, D. Bray, A. Cuellar, S. Dronov, M. Ginkel, V. Gor, I. I. Goryanin, W. Hedley, T. C. Hodgman, P. J. Hunter, N. S. Juty, J. L. Kasberger, A. Kremling, U. Kummer, N. LeNovere, L. M. Loew, D. Lucio, P. Mendes, E. D. Mjolsness, Y. Nakayama, M. R. Nelson, P. Nielsen, T. Sakurada, J. C. Schaff, B. E. Shapiro, T. S. Shimizu, H. D. Spence, J. Stelling, K. Takahashi, M. Tomita, J. Wagner, and J. Wang, "The Systems Biology Markup Language (SBML): A medium for representation and exchange of biochemical network models," *Bioinformatics,* vol. 19, pp. 524–531, 2003.

[32] P. J. Hunter, "The IUPS Physiome Project: A framework for computational physiology," *Prog. Biophys. Mol. Biol,* vol. 85, no. 2-3, pp. 551–569, 2004.

[33] P. J. Hunter and T. K. Borg, "Integration from proteins to organs: The Physiome Project," *Nature Rev. Mol. Cell Biol.,* vol. 4, pp. 237–243, 2003.

[34] P. J. Hunter, A. McCulloch, and H. E. D. J. ter Keurs, "Modeling the mechanical properties of cardiac muscle," *Prog. Biophys. Mol. Biol.,* vol. 69, pp. 289–331, 1998.

[35] P. J. Hunter, P. Kohl, and D. Noble, "Integrative models of the heart: Achievements and limitations," *Phil. Trans R. Soc. Lond. A,* vol. 359, pp. 1049–1054, 2001.

[36] P. J. Hunter, A. J. Pullan, and B. H. Smaill, "Modeling total heart function," *Ann. Rev. Biomed. Eng.,* vol. 5, pp. 147–177, 2003.

[37] P. J. Hunter, P. Robbins, and D. Noble, "The IUPS human Physiome Project," *Eur. J. Physiol.,* vol. 445, no. 1, pp. 1–9, 2002.

[38] P. Kohl and F. Sachs, "Mechanoelectric feedback in cardiac cells," *Phil. Trans. R. Soc. Lond. A,* vol. 359, no. 1783, pp. 1173–1185, 2001.

[39] P. Kohl, D. Noble, R. L. Winslow, and P. J. Hunter, "Computational modeling of biological system: Tools and visions," *Phil. Trans. R. Soc. Lond. A,* vol. 358, no. 1766, pp. 579–610, 2000.

[40] I. J. LeGrice, P. J. Hunter, and B. H. Smaill, "Laminar structure of the heart: A mathematical model," *Amer. J. Physiol.,* vol. 272, pp. H2466–H2476, 1997.

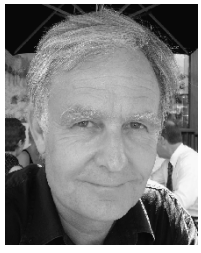
[41] I. J. LeGrice, P. J. Hunter, A. A. Young, and B. H. Smaill, "The architecture of the heart: A data-based model," in *Proc. R. Soc. Lond. A* 2001, vol. 359, pp. 1217–1232.

[42] I. J. LeGrice, B. H. Smaill, L. Z. Chai, S. G. Edgar, J. B. Gavin, and P. J. Hunter, "Laminar structure of the heart: Ventricular myocyte arrangement and connective tissue architecture in the dog," *Amer. J. Physiol.,* vol. 269, pp. H571–H582, 1995.

[43] R. C. Leif, S. H. Leif, and S. B. Leif, "CytometryML, an XML format based on DICOM for analytic cytology data," *Cytometry,* vol. 54, pp. 56–65, 2003.

[44] S. Liang, S. Fuhrman, and R. Somogyi, "REVEAL, a general reverse engineering algorithm for inference of genetic network architectures," in *Proc. Pacific Symp. Biocomputing* 1998, vol. 3, pp. 18–29.

[45] C. M. Lloyd, M. D. B. Halstead, and P. M. F. Nielsen, "CellML: Its future, present and past," *Prog. Biophys. Mol. Biol.,* vol. 85, no. 2–3, pp. 433–450, Jun.–Jul. 2004.
[46] A. McCulloch, "Modeling the human cardiome in silico," *J. Nucl. Cardiol.,* vol. 7, no. 5, pp. 496–499, 2000.
[47] A. McCulloch, J. B. Bassingthwaighte, P. J. Hunter, and D. Noble, "Computational biology of the heart: From structure to function," *Prog. Biophys. Mol. Biol.,* vol. 69, no. 2–3, pp. 151–572, 1998.
[48] M. P. Nash and P. J. Hunter, "Computational mechanics of the heart. From tissue structure to ventricular function," *J. Elasticity,* vol. 61, pp. 113–141, 2000.
[49] D. P. Nickerson, N. P. Smith, and P. J. Hunter, "A model of cardiac cellular electromechanics," *Phil. Trans. R. Soc. Lond. A,* vol. 359, pp. 1159–1172, 2001.
[50] P. M. F. Nielsen, I. J. LeGrice, B. H. Smaill, and P. J. Hunter, "Mathematical model of geometry and fibrous structure of the heart," *Amer. J. Physiol.,* vol. 260, pp. H1365–H1378, 1991.
[51] D. A. Noble, "Modification of the Hodgkin–Huxley equations applicable to Purkinje fiber action and pace-maker potentials," *J. Physiol.,* vol. 160, pp. 317–352, 1962.
[52] D. Noble, "The rise of computational biology," *Nature Rev. Mol. Cell Biol.,* vol. 3, pp. 460–463, 2002.
[53] ——, "Modeling the heart: From genes to cells to the whole organ," *Science,* vol. 295, pp. 1678–1682, 2002.
[54] D. J. Paterson, "The G.L. Brown prize lecture. Nitric oxide and the autonomic regulation of cardiac excitability," *Exp. Physiol.,* vol. 86, no. 1, pp. 1–12, 2001.
[55] A. J. Pullan, L. K. Cheng, M. P. Nash, C. P. Bradley, and D. J. Paterson, "Noninvasive electrical imaging of the heart: Theory and model development," *Ann. Biomed. Eng.,* vol. 29, no. 10, pp. 817–836, 2001.
[56] C. Rosse and J. V. L. Mejino, "A reference ontology for biomedical informatics: The foundational model of anatomy," *J. Biomed. Inf.,* vol. 36, no. 6, pp. 478–500, 2003.
[57] Y. Rudy, "From genome to physiome: Integrative models of cardiac excitation," *Ann. Biomed. Eng.,* vol. 28, no. 8, pp. 945–950, 2000.
[58] M. S. P. Sansom, I. H. Shrivastava, J. N. Bright, J. Tate, C. E. Capener, and P. C. Biggin, "Potassium channels: Structures, models, simulations," *Biochim. Biophys. Acta.,* vol. 1565, pp. 294–307, 2002.
[59] J. J. Saucerman, L. L. Brunton, A. P. Michailova, and A. D. McCulloch, "Modeling beta-adrenergic control of cardiac myocyte contractility in silico," *J. Biol. Chem.,* vol. 278, no. 48, pp. 47 997–48 003, 2003.
[60] J. J. Saucerman and A. D. McCulloch, "Mechanistic systems models of cell signaling networks: A case study of myocyte adrenergic regulation," *Prog. Biophys. Mol. Biol.,* vol. 85, no. 2–3, pp. 261–278, 2004.
[61] J. J. Saucerman, S. N. Healy, M. E. Belik, J. L. Puglisi, and A. D. McCulloch, "Proarrhythmic consequences of a KCNQ1 AKAP-binding domain mutation: Computational models of whole cells and heterogeneous tissue," *Circulat. Res.,* vol. 95, no. 12, pp. 1216–1224, 2004.
[62] T. R. Shannon and D. M. Bers, "Integrated Ca^{2+} management in cardiac myocytes," *Ann. NY Acad. Sci.,* vol. 1015, no. 1, pp. 28–38, 2004.
[63] N. P. Smith, D. P. Nickerson, E. J. Crampin, and P. J. Hunter, "Multi-scale computational modeling of the heart," *Acta Numerica,* vol. 13, pp. 371–431, 2004.
[64] N. P. Smith, A. J. Pullan, and P. J. Hunter, "The generation of an anatomically accurate geometric coronary model," *Ann. Biomed. Eng.,* vol. 28, pp. 14–25, 2000.
[65] ——, "An anatomically based model of transient coronary blood flow in the heart," *SIAM J. Appl. Math.,* vol. 62, pp. 990–1018, 2002.
[66] C. Soeller and M. B. Cannell, "Examination of the transverse tubular system in living cardiac rat myocytes by 2-photon microscopy and digital image-processing techniques," *Circulat. Res.,* vol. 84, pp. 266–275, 1999.
[67] C. Stevens and P. J. Hunter, "Sarcomere length changes in a 3-D mathematical model of the pig ventricles," *Prog. Biophys. Mol. Biol.,* vol. 82, no. 1–3, pp. 229–241, 2003.
[68] C. J. Stoeckert, Jr., H. C. Causton, and C. A. Ball, "Microarray databases: Standards and ontologies," *Nature Genetics, Suppl.,* vol. 32, pp. 469–473, 2002.
[69] J. R. Swedlow, I. Goldberg, E. Brauner, and P. K. Sorger, "Informatics and quantitative analysis in biological imaging," *Science,* vol. 300, pp. 100–102, 2003.
[70] A. J. Tanskanen, J. L. Greenstein, B. O'Rourke, and R. L. Winslow, "The role of stochastic and modal gating of cardiac L-type Ca^{2+} channels on early after-depolarizations," *Biophys J.,* vol. 88, no. 1, pp. 85–95, 2005.
[71] M. H. Tawhai and P. J. Hunter, "Characterising respiratory airway gas mixing using a lumped parameter model of the pulmonary acinus," *Respirat. Physiol.,* vol. 127, pp. 241–248, 2001a.
[72] ——, "Multibreath washout analysis: Modeling the influence of conducting airway asymmetry," *Respirat. Physiol.,* vol. 127, pp. 249–258, 2001b.
[73] M. H. Tawhai, P. J. Hunter, J. Tschirren, J. M. Reinhardt, G. McLennan, and E. A. Hoffman, "CT-based geometry analysis and finite element models of the human and ovine bronchial tree," *J. Appl. Physiol.,* vol. 97, no. 6, pp. 2310–2321, 2004.
[74] M. H. Tawhai, A. J. Pullan, and P. J. Hunter, "Generation of an anatomically based three-dimensional model of the conducting airways," *Ann. Biomed. Eng.,* vol. 28, pp. 793–802, 2000.
[75] C. F. Taylor *et al.*, "A systematic approach to modeling, capturing and disseminating proteomics experimental data," *Nature Biotechnol.,* vol. 21, pp. 247–254, 2003.
[76] J. Tegner, M. K. S. Yeung, J. Hasty, and J. J. Collins, "Reverse engineering gene networks: Integrating genetic perturbations with dynamic modeling," *Proc. Nat. Acad. Sci.,* vol. 100, pp. 5944–5949, 2003.
[77] K. A. Tomlinson, P. J. Hunter, and A. P. Pullan, "A finite element method for an eikonal equation model of myocardial excitation wavefront propagation," *SIAM J. Appl. Math.,* vol. 63, no. 1, pp. 324–350, 2002.
[78] R. D. Vaughan-Jones, B. E. Percy, J. P. Keener, and K. W. Spitzer, "Intrinsic H^+ ion mobility in the mammalian ventricular myocyte," *J. Physiol.,* vol. 541.1, pp. 139–158, 2002.
[79] R. D. Vaughan-Jones and K. W. Spitzer, "Role of bicarbonate in the regulation of intracellular pH in the mammalian ventricular myocyte," *Biochem. Cell Biol.,* vol. 80, no. 5, pp. 579–596, 2002.
[80] C. Venter *et al.*, "The sequence of the human genome," *Science,* vol. 291, pp. 1304–1351, 2001.
[81] R. L. Winslow and M. S. Boguski, "Genome informatics—current status and future prospects," *Circulat. Res.,* vol. 92, pp. 953–961, 2003.
[82] M. K. S. Yeung, J. Tegner, and J. J. Collins, "Reverse engineering gene networks using singular value decomposition and robust regression," *Proc. Nat. Acad. Sci.,* vol. 99, pp. 6163–6168, 2002.
[83] A. A. Young, S. Dokos, K. A. Powell, B. Sturm, A. D. McCulloch, R. C. Starling, P. M. McCarthy, and R. D. White, "Regional heterogeneity of function in nonischemic dilated cardiomyopathy," *Cardiovasc. Res.,* vol. 49, no. 2, pp. 308–318, 2001.



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