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Bioinformatics, multiscale modeling and the IUPS Physiome Project

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Abstract

Multiscale modeling is required for linking physiological processes operating at the organ and tissue levels to signal transduction networks and other subcellular processes. Several XML markup languages, including CellML, have been developed to encode models and to facilitate the building of model repositories and general purpose software tools. Progress in this area is described and illustrated with reference to the heart Physiome Project which aims to understand cardiac arrhythmias in terms of structure-function relations from proteins up to cells, tissues and organs.

Keywords: *multiscale modeling; Physiome Project; markup languages; CellML; FieldML*

INTRODUCTION

Interpreting the wealth of quantitative data now available on cellular and subcellular processes requires a new level of international collaboration between biological, physical (including engineering), mathematical, computer and computational scientists. Biological processes operate primarily at the molecular scale (ligand/protein/DNA/RNA interactions) but are influenced by, or in turn create an influence on, the physiological systems of cells, tissues, organs and whole body organ systems. This influence therefore encompasses a 10^9 range of spatial scales (from nm at the molecular scale to m at the human organ system level), and a 10^{15} range of temporal scales (from μs for molecular interactions to the 10^9 s of a human life span). Our ability to investigate human disease with the tools of genetics and proteomics as well as physiological tests and diagnostic imaging on an individual patient (MRI, CT, etc.) is a tribute to impressive developments in instrumentation at the two ends of this spectrum of spatial scales. But our current ability to link our knowledge of structure and function across these spatial and temporal scales is, with few exceptions, dismal. Mathematics is the language of quantitative science and the only way to address this challenge is through mathematical modeling. In particular, multiscale modeling based on biophysical principles ('mechanistic' modeling) is needed, along with numerical techniques that can adequately represent the highly complex 3D structures of biological systems from proteins to organs.

The Physiome Project was initiated by Denis Noble and Jim Bassingthwaighte of the International Union of Physiological Sciences (IUPS) to meet this challenge. The IUPS Physiome committee (chaired by the first author together with Aleksander Popel) was established at the 33rd international IUPS congress in St Petersburg in 1997 to lead the project [1]. Significant recent events have been the recognition by NIH of the importance of developing a computational modeling infrastructure for human biology [2], and the funding under the Framework 7 ICT call by the European Commission [3] for a Network of Excellence to co-ordinate the 'EuroPhysiome' contribution to a 'Virtual Physiological Human' (VPH).

In this review, we survey some of the features needed in a computer science infrastructure to facilitate multiscale modeling and then discuss the

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application of the current infrastructure to modeling the heart. The philosophical underpinnings of the Physiome Project have been eloquently expressed in a recent book by Noble [4]. For other recent publications on the Physiome Project, including discussion of applications in healthcare, see [5–7].

AN INFRASTRUCTURE FOR COMPUTATIONAL PHYSIOLOGY

Some of the key requirements for multiscale computational modeling of biological systems are discussed below. Note that all physiome standards are open, all software uses open source licensing, and all model and data repositories are web-accessible and freely available.

(i) Markup languages to encode models and data in an unambiguous fashion. There are currently three markup languages (MLs) under development for the Physiome Project:

CellML Many models of biological processes at the subcellular level ignore the detailed 3D structure of the cell and model the cell excitability, mechanics, calcium (or other second messenger) transients, motility, signaling, metabolism or gene regulation, etc., in a 'lumped parameter' system of ordinary differential equations (ODEs). Sometimes the models also include non-linear algebraic equations or need to solve constrained optimization problems as part of the solution strategy, but they do not require the solution of partial differential equations (PDEs). In some cases the models are 'systems physiology' models at the whole body level, but again without the need for solving PDEs. The markup language CellML (http://www.cellml.org) has been developed to provide an unambiguous definition of these lumped parameter models. The language is designed to support the definition and sharing of models of biological processes by including information about: model structure (how the parts of a model are organizationally related to one another); mathematics (equations describing the underlying biological processes); and metadata (additional information about the model that allows scientists to search for specific models or model components in a database or other repository).

CellML has a simple structure based upon connected components. These components abstract concepts by providing well-defined interfaces to other components, and encapsulate concepts by hiding details from other components. Connections provide the means for sharing information by associating variables visible in the interface of one component with those in the interface of another component. Consistency is enforced by requiring that all variables be assigned appropriate physical units, which must match when variables are connected. Public and private interfaces enable encapsulation hierarchies, providing further mechanisms for information hiding and abstraction. Model reuse is facilitated by the import element, enabling new models to be constructed by combining existing models into model hierarchies. The CellML 1.1 standard is available at http://www.cellml.org/specifications/cellml_1.1. Note that another markup language SBML (http://sbml.org) is also in widespread use for describing biochemical reaction networks.

FieldML To cater for models that do include 3D spatial information, another markup language called FieldML (http://www.fieldml.org) is being developed. FieldML files contain all the parameters needed to mathematically specify spatial fields. The most common form of parameterization is a finite element mesh, where the parameters are nodal parameters, element topology and the element-basis functions that interpolate the nodal parameters over the elements. However, FieldML is intended to handle more general parameterizations than just finite element fields and also includes dense data formats (e.g. for images embedded inside models).

ModelML A third markup language, called ModelML, is being developed to encode the workflows needed to set up the governing physical equations, boundary conditions and initial conditions for a modeling problem in computational physiology. Currently this is done with Perl or Python scripts, but a marked up form of workflow will facilitate dealing with the solutions of complex problems involving many different types of physical equation systems.

In each case, the markup language is made available through a formal specification and with an 'application programming interface' (API) that provides code for software programmers to access model or data repositories.

(ii) *Bio-ontologies and metadata standards* for the markup languages that give biological meaning to the components of the models. CellML is designed to represent the essential entities and relationships relevant to biological interactions. While it is descriptive from a modeling perspective, it makes no attempt to directly represent the biological (and other) information associated with model constituents. It does, however, provide standard methods that enable metadata to be linked to CellML entities. These methods are defined in the CellML specification and discussed more fully in a CellML metadata specification (http://www.cellml.org/specifications/metadata).
Metadata are associated with entities in a CellML model by labeling each entity with a unique cmeta:id identifier then linking appropriate information, in the form of RDF to those identifiers (RDF, http://www.w3.org/RDF), is a metadata format for making statements about resources in the form of subject-predicate-object expressions, called triples. The subject denotes the resource, and the predicate denotes properties of the resource and expresses a relationship between the subject and the object). This mechanism provides a very powerful method for annotating CellML models with information not directly covered by the CellML specification. Metadata are commonly associated with appropriate ontologies or controlled vocabularies. For example, document and author information may be described in a form consistent with the Dublin Core (http://dublincore.org/documents/dces) and vCard (http://www.w3.org/TR/vcard-rdf) specifications, respectively. Similarly, entities in CellML models may be annotated with biological information by linking them to appropriate biological ontologies such as the Systems Biology Ontology (http://www.ebi.ac.uk/sbo) and BioPax (http://www.biopax.org).

(iii) *Processes for graphically rendering models* and their components in a biologically interpretable form. CellML models are usually structured in order to accurately represent the biophysical information associated with biological processes. In general, this biophysical information is more detailed than is necessary for representing biological information at a more abstract user-dependent level—it is not useful to graphically render every entity associated with a biological model. Furthermore, there is generally not a one-to-one mapping between biophysically- and biologically-relevant entities. It is thus difficult to provide an automatic translation between the biophysical and biological representation of biological processes. There are ways, however, to facilitate this translation by linking entities in CellML models to biophysical, biological and other ontologies. We have been tackling this issue by automatically translating CellML models from their XML representation to an OWL (http://www.w3.org/TR/owl-features/) representation that captures all of the semantics of the original model. In this form the CellML model and its metadata may be expressed in the same OWL language enabling the application of rules within an OWL reasoner. In particular, the biophysical and biological metadata can provide sufficient information to enable graph reduction rules to be applied to the OWL representation of the model within the reasoner. Coupling the results of this process with an appropriate biological (or biophysical) glyph library results in a biological (or biophysical) graphical rendering of the CellML model.

(iv) *Repositories of models and data* based on the markup languages. The CellML model repository, available at (http://www.cellml.org/models), contains mathematical models of biological processes. Some key features of this repository are that it allows the user to search the repository, display bibliographic information about a particular model (authors, publication reference, etc.), give a brief synopsis of the model, render the equations encoded in the model and display the code generated automatically by the code generation service in various languages. It also provides information on the level to which the model has been curated and, if it is a working model, provides a link to run the model directly from the website using a browser with the solver plugin (such as PCEnv, http://www.cellml.org/tools/pcenv). Note that nearly all models published in referred journals contain mistakes, typographical errors or missing parameters. The process of curating

a model to the point where running the CellML model gives results, consistent with those given in the publication, usually requires help from the authors of the original paper. In our experience this help is almost always forthcoming.

MULTISCALE MODELING OF THE HEART

To illustrate the use of these markup languages in multiscale modeling, we briefly describe the approach being taken in the cardiac Physiome Project (http://www.heart.physiomeproject.org) to link ion-channel mutations to whole heart arrhythmias and ECG patterns on the chest. The markup languages CellML and FieldML are used to encode models at a number of spatial scales (Figure 1), and we comment here on the processes used to link across spatial and temporal scales. Further comments on multiscale modeling are given in the Discussion.

The hierarchy of models is further explained in Figure 2. At the cell level a lumped parameter model incorporates the relevant various cellular processes. The Hodgkin–Huxley type ion channel models sometimes incorporate Markov processes. In future these will be linked to more detailed models based on coarse-grained molecular dynamics (MD) models that are in turn derived from MD and quantum mechanical models. At the tissue level, models that incorporate detailed structure-function relations are used to derive simpler continuum models appropriate for the organ level. The organ level model incorporates the electrical activation of the myocardium, the mechanical deformation of the ventricular wall, the blood flow and heart valve mechanics within the ventricles and the coronary blood flow. Models of neural activation by the autonomic nervous system are currently being developed.

Cell level modeling

The process of modeling myocardial activation (and hence cardiac arrhythmias) starts with models of the excitability of cardiomyocytes—the cardiac muscle cells that both support electrical propagation in heart muscle and generate force to cause heart contraction. The ion channels—primarily sodium (for generating the rapid upstroke of the action potential), calcium (for generating the internal rise in calcium concentration that initiates contraction) and

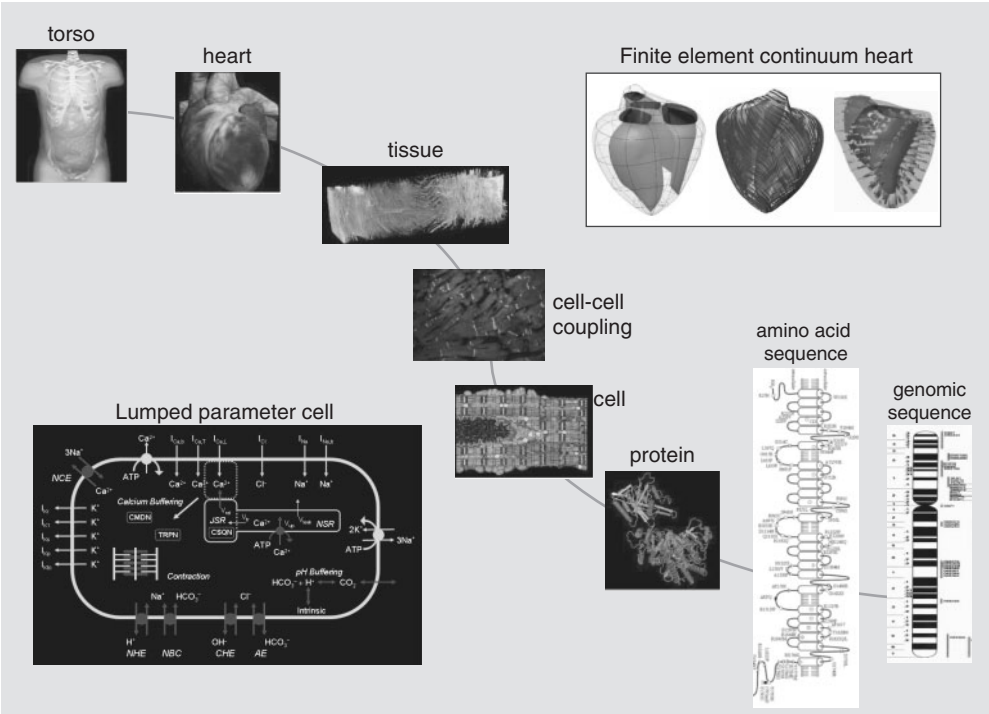

Figure 1: The multiscale modeling hierarchy from genes to the whole organism. Structure-function relationships are used if the relevant data exists and, if not, lumped parameter models are needed (see Figure 2). Parameters used in a model at one scale can often be derived from a more detailed model at a lower spatial scale.

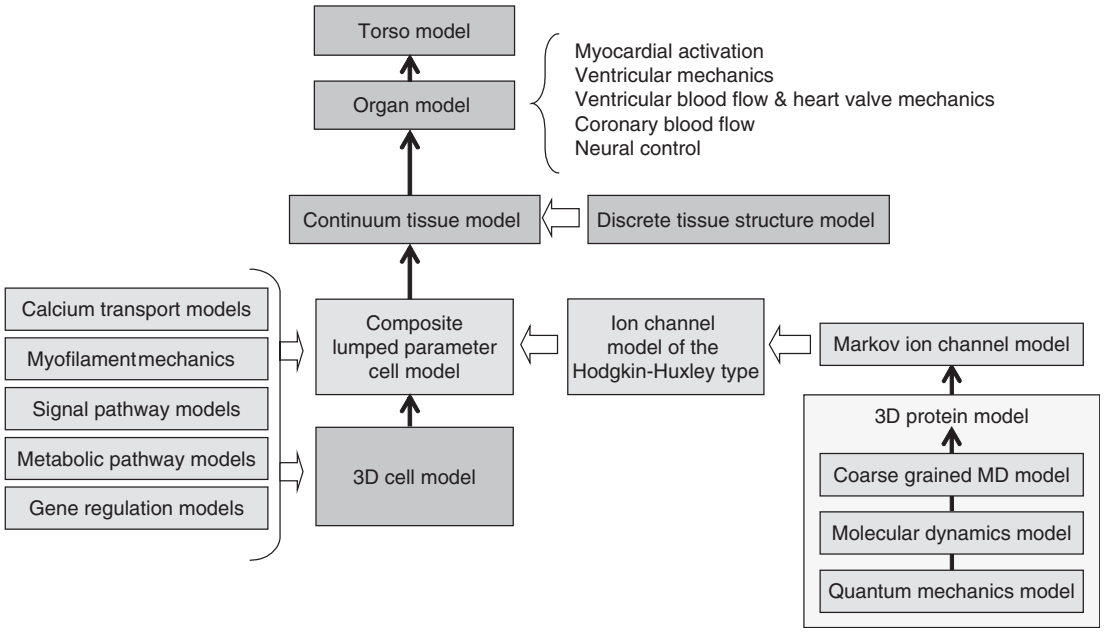

Figure 2: Types of model used in the multiscale modeling hierarchy. Some models are based on systems of ODEs and algebraic equations (so called 'lumped parameter' models) and these are coded in CellML. The higher level models that require the solution of PDEs are encoded in FieldML. The FieldML models link to CellML models at material points in the tissue. The arrows above are shown as unidirectional but, in fact, information flows both ways. The 3D protein models shown on the bottom right will be linked into the cardiac modeling hierarchy in the future.

potassium (for repolarizing the cell to its resting membrane potential)—have been studied for over 40 years using voltage clamp and patch clamp techniques to define their current/voltage/time characteristics. Models of the whole cell are built from the individual ion channel models [8], and incorporated into tissue scale models as illustrated in Figure 3 [9]. Other membrane proteins acting as ion exchangers (such as the Na–Ca exchanger that uses the Na gradient to remove Ca from the cell), and ATP-dependent pumps (such as the Na–K pump [10]) that maintain ion concentrations, are also included in these models. But note that these are 'lumped parameter' cell models that do not incorporate the 3D structure of the myocyte.

Along with cardiac excitability (included here via the Pandit *et al*. model [11]), several other cell level processes need to be modeled since they influence the electrical behavior of the cardiomyocyte. Most importantly, cardiac cells contract. The wave of electrical propagation passing over the cell membrane and down into the invaginations of this membrane, called 'transverse-'or 'T-tubules', releases Ca from internal stores located at points where the internal reticular network called the 'sarcoplasmic' reticulum (responsible for soaking up Ca from the cytoplasm) is adjacent to the T-tubules. Release of Ca from these stores through ryanodine receptors is initiated by voltage-activated Ca channels in the external membrane (included here via the Hinch *et al*. model [12]). The released Ca diffuses to troponin-C binding sites on the contractile myofilaments and initiates force production (included here via the Niederer *et al*. model [13]). It is necessary to consider Ca transients and mechanical contraction along with the excitability of cardiac cells because the action potential is heavily influenced by Ca movements across the membrane, and these in turn are influenced by the mechanical shortening of the cell. Further coupling occurs through stretch-dependent ion channels [14].

The CellML versions of each of these models are available as follows: Pandit electrophysiology model [11] (http://www.cellml.org/models/pandit_clark_giles_demir_2001_version07), Hinch calcium dynamics model [12] (http://www.cellml.org/models/hinch_greenstein_tanskanen_xu_winslow_2004_version01), and Niederer active contraction model [13] (http://www.cellml.org/models/niederer_hunter_smith_2006_version01).

The process of coupling these models in an integrated cell model using the CellML 1.1 import

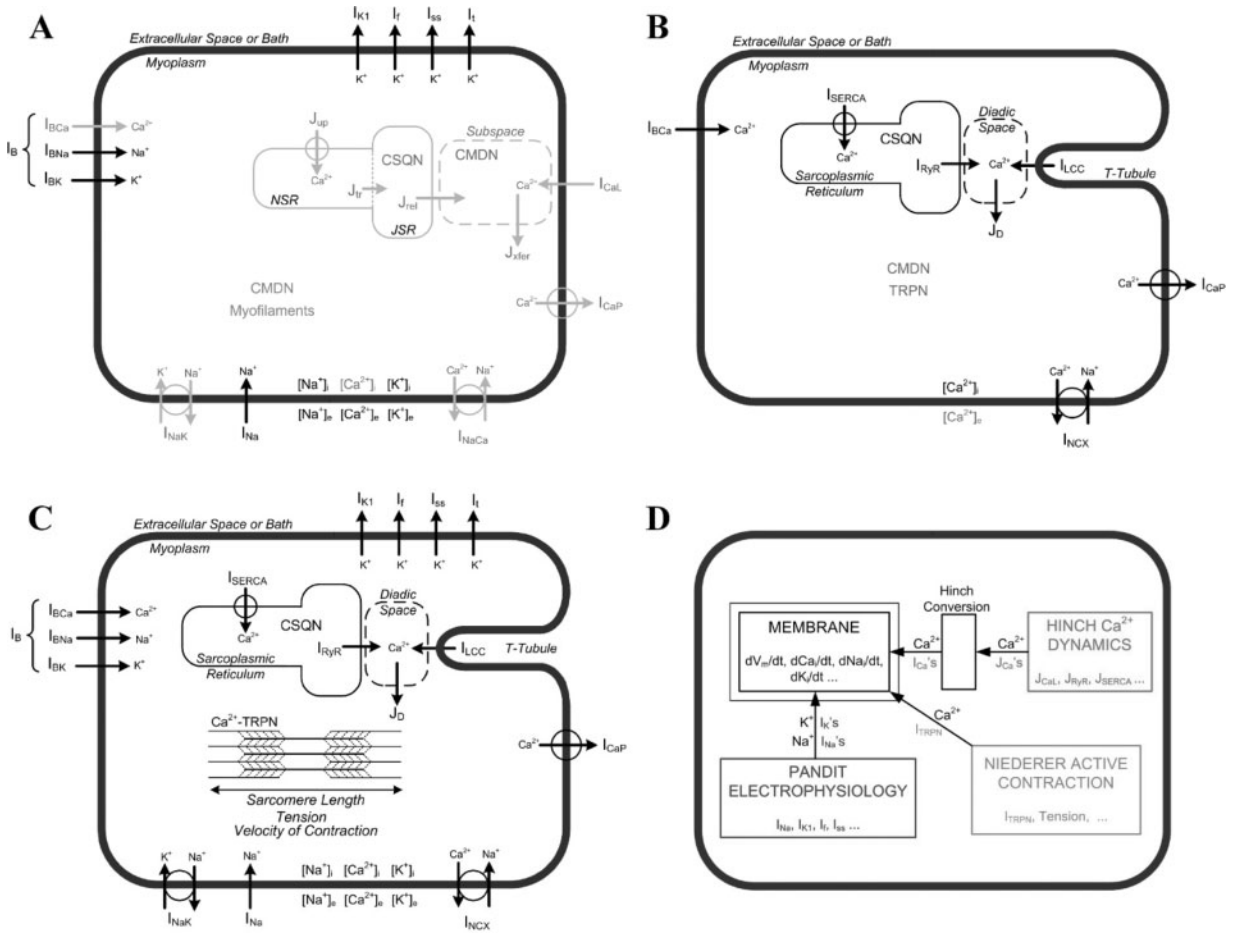

Figure 3: Coupling models of cellular processes with CellML. The Pandit ion-channel model (**A**) is coupled with the Hinch calcium dynamics model (**B**) and the Niederer active contraction model (**C**) to form the composite model (**D**). Note that the lightly greyed areas shown in some models represent components contributed by other models. From [15].

mechanism is shown in Figure 3, where A includes only the Pandit electrophysiology model, B includes the Hinch calcium dynamics and C includes the Niederer active contraction model. Figure 3(D) is the resulting composite model [15]. The mathematical components of these separately developed models are identified with standard biological terms from an ontology such as GO (http://www.geneontology.org).

The composite model shown in Figure 3 includes the basic cellular processes needed to support coupled electro-mechanics in the heart. There are, however, many other cellular processes that influence these ones and are needed in more comprehensive studies of whole heart function. For example, the aerobic metabolic pathway that controls ATP production has been modeled [16] and is available in the CellML model repository. The control of key proteins involved in excitatory, calcium and mechanical function in cardiac cells via β-adrenergic [17], CaM-kinase [18] and IP_3 [19] pathways have also been modeled and are available in CellML. The CellML models for these processes are: metabolic pathways [16] (http://www.cellml.org/models/beard_2005_version01), β-adrenergic signaling [17] (http://www.cellml.org/models/saucerman_mcculloch_2004_version01), CaM-kinase [18] (http://www.cellml.org/models/livshitz_rudy_2007_version01), and IP_3 signalling [19] (http://www.cellml.org/models/cooling_hunter_crampin_2007_version01).

Tissue level modeling

The equations governing behavior at the tissue level are usually PDEs that treat the myocardium as a continuum [9]. This means that the detailed

3D structure is replaced, for modeling purposes, by a continuous field approximation. A similar approach is used in electrical engineering where electromagnetic fields, governed by Maxwell's equations, represent an average behavior of physical phenomena that, on a smaller spatial scale, obey the laws of quantum mechanics. For example, reaction-diffusion equations representing conservation of current flow in tissue, coupled with the ion channel electrophysiological cell models, are solved to determine the spread of electrical current through the myocardium. The tissue conductivity used in solving these equations needs to be derived from the underlying tissue structure and material properties. Similarly, mechanical contraction at the tissue level, governed by the equations of large deformation finite elasticity theory (derived from physical laws representing conservation of mass and conservation of momentum), uses mechanical material properties that represent the spatially averaged tissue behavior.

The 3D structure of tissue that gives rise to continuum properties (conductivity, elasticity, etc.) is shown in Figure 4. Note that there are characteristic material directions in the tissue that define structural features, such as the fiber direction or sheet orientation, and that the continuum properties are different in each direction (the tissue is said to be 'anisotropic'). Note also that these characteristic material directions and the values of the continuum properties vary throughout the tissue (the tissue properties are said to be 'inhomogeneous'). Thus the electrical and mechanical properties along the fiber direction in cardiac muscle are different from those properties measured transversely to the fibers and these properties are different in different material locations. In fact cardiac muscle is usually regarded as being 'orthotropic', meaning that the properties are different in three orthogonal material directions ('fiber', 'sheet' and 'sheet-normal' [20]), as well as being inhomogeneous.

The relationship between tissue structure and the fiber, sheet and sheet-normal material axes for defining continuum properties is illustrated in Figure 5. A tissue segment is shown removed from the left ventricular (LV) wall and then expanded to show the myocytes forming the sheet. The long axis of the myocyte defines the fiber direction, the direction of strong cell–cell coupling in the plane of the sheet orthogonal to the fiber direction defines the sheet axis, and the direction orthogonal to these two axes defines the sheet-normal axis.

The process of linking CellML models of cellular behavior into FieldML models of tissue properties is illustrated in Figure 6. The mechanics equations are usually solved using finite element techniques [21], and the electrical activation equations are solved using finite volume or similar techniques [9] based on grid points defined as material points of the deforming mechanics grid. Note that the resolution required to achieve a spatially converged solution for the wave front propagation is much higher than that needed for the mechanics (see Figure 6 legend).

An example of a strategy for linking behavior at the microstructural level in tissue to the equivalent continuum properties that can be used at the whole organ level is shown in Figure 7. Reaction-diffusion equations are solved on a microstructurally detailed finite element model, using tissue conductivities. The material conductivity tensor links the voltage gradients generated by cell excitability to a current vector that describes current flow in the tissue (a 3D version of Ohm's law)—a relationship that is called a 'constitutive law'. The resulting wave fronts at various times after point stimulation are compared with the solution of a continuum model in which the microstructure is ignored, and the material conductivity properties are defined with a conductivity tensor based on the fiber-sheet axes described above. Values in this conductivity tensor are chosen to ensure that the tissue continuum model closely

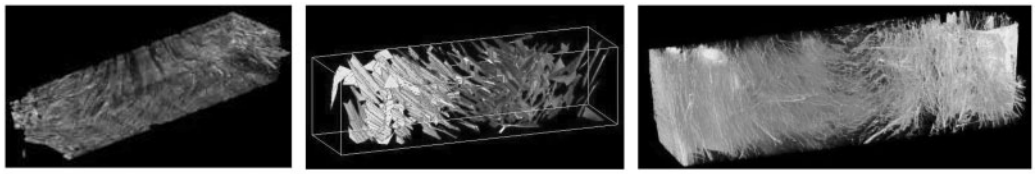

Figure 4: The anisotropic and inhomogeneous structure of myocardial tissue. (**A**) A transmural block of tissue showing the fibrous-sheet structure of cardiac muscle. (**B**) The segmented 'cleavage planes' showing the discontinuities in structure. (**C**) The changing density and orientation of collagen fibers in the transmural block of tissue.

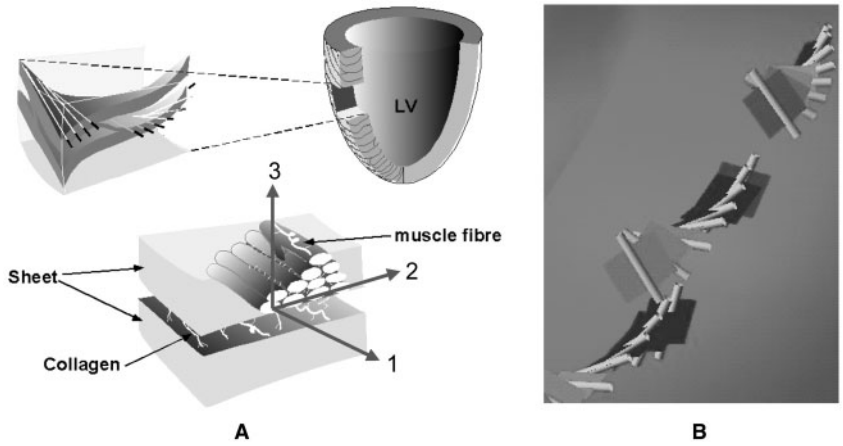

Figure 5: Fibrous-sheet structure of myocardium. (**A**) Schematic showing how the muscle fibers (cardiac myocytes) are bound tightly by endomysial collagen into layers or 'sheets' 4–5 cells thick. The longitudinal axis of the myocyte defines the *fiber direction* (shown as '1'); the direction of tight coupling defines a second *sheet axis* '2' and together these define the sheet plane. A third *sheet-normal* '3' is defined orthogonal to this plane. (**B**) The spatially varying fiber direction (cylinders) and sheet plane (squares) are shown at a number of material points in the myocardium.

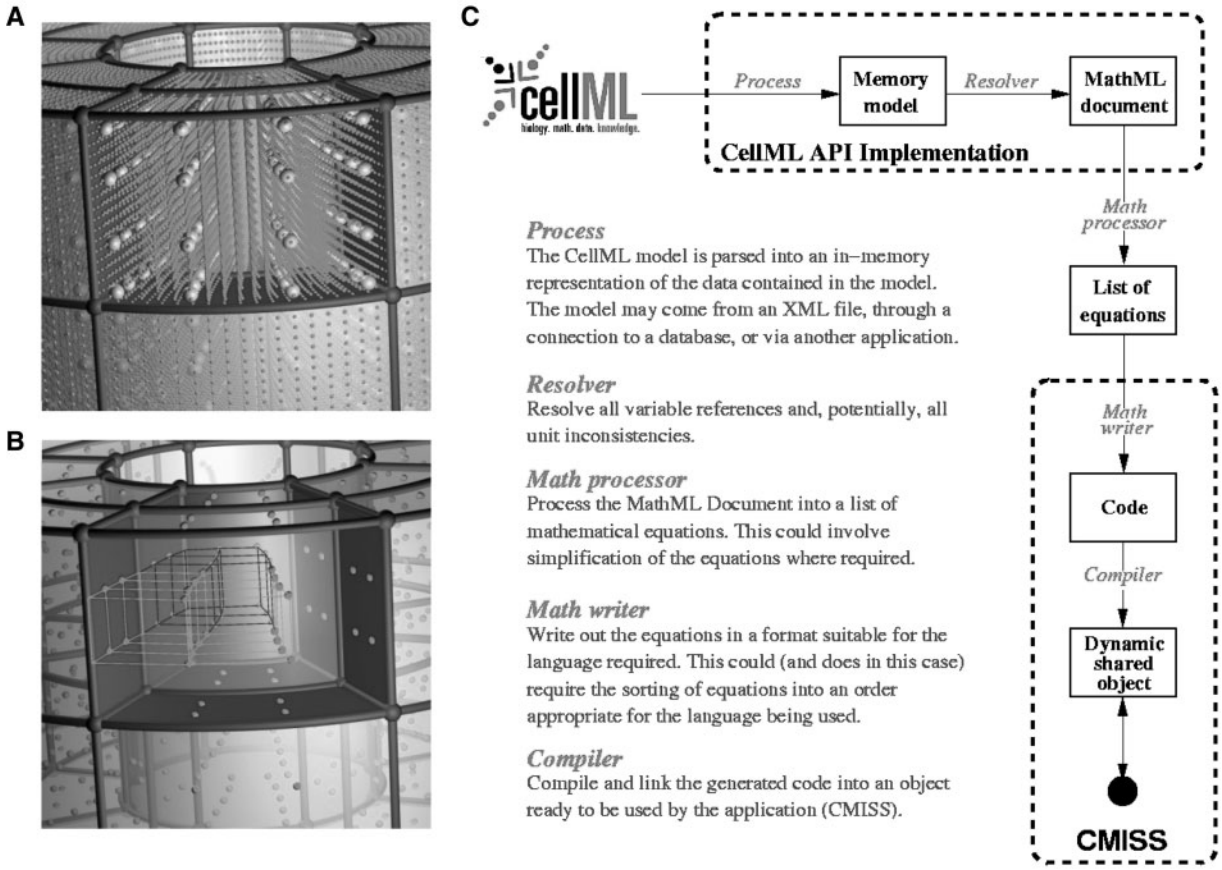

Figure 6: Coupling cell equations (defined with CellML) to tissue equations (defined with FieldML). (**A**) Finite element model (thick lines) used for solution of the equations governing deformation of the tissue during heart contraction and Gaussian quadrature points (spheres) of compare the grid spacing in A shown by the small dots with the finite element mechanics mesh shown by the thick lines. (**B**) Lower resolution grid. (**C**) Workflow for linking CellML models into the solution of tissue or organ level FieldML models.

matches the simulations with the microstructurally detailed model [22].

The concept of a 'constitutive relation' is a crucial step in multiscale modeling because it summarizes the mechanical behavior of a complex 3D network of muscle cells and extracellular matrix. Constitutive relations can be measured experimentally or, as shown here, can be derived from microstructurally detailed models in order to establish a better understanding of the multiscale relationships.

Organ level modeling

Here, we consider the anatomical features and physiological processes that need to be considered at the whole heart level in order to examine the influence of ion-channel mutations or drug-binding events on ventricular arrhythmias. The starting point for modeling the physiology of the intact heart is the geometry and fibrous-sheet structure of the heart. Finite element methods provide a convenient and computationally efficient means of modeling the anatomy of the heart. Figure 8(A) shows a finite element model of the left and right ventricles, and Figure 8(B) shows the muscle fiber distributions on the epicardial surface of the heart, based on pig heart measurements [23]. Figure 8(C) shows the coronary circulation [24]. At each point in the myocardium a set of three orthogonal axes is defined, aligned with the local fiber-sheet tissue structure as described in the tissue modeling section above. These axes are defined to be orthogonal in unloaded reference state but become non-orthogonal as the muscle stretches and shears during the cardiac cycle.

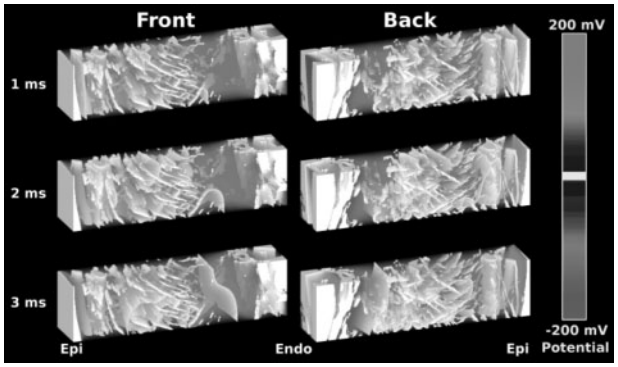

Figure 7: Propagation of the wave of electrical excitation in cardiac tissue using a microstructurally detailed model. Solutions of this model are compared with solutions from a continuum model in order to calculate the coefficients of the tissue conductivity tensor. See [22].

The theory of large deformation mechanics implemented with the finite element model of Figure 8(A), is used to predict these shape changes. The equations, derived from physical conservation laws (conservation of mass and conservation of momentum), require a relationship to be defined between the six independent components of the strain tensor (which characterize the kinematics or strained state of the tissue) and six independent components of the stress tensor [21]. The functional form and parameter values used in the constitutive relation can be derived from detailed microstructural models of the tissue, in order to link the parameters back to the organization and mechanical properties of the collagen, elastin and proteoglycan components of the tissue. Alternatively, the parameters of the constitutive law can be measured experimentally on a tissue preparation [25].

Another aspect of cardiac anatomy and physiology that is relevant to the study of arrhythmia is the coronary circulation. Arrhythmias are often initiated by the thrombus blockage of a coronary artery that causes local ischaemia, leading to extracellular potassium ion accumulation and a drop in intracellular pH. To understand this sequence of events and under what circumstances it gives rise to

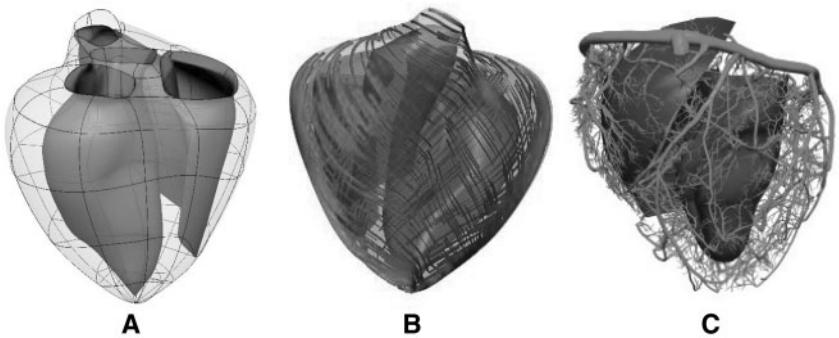

Figure 8: Components of an organ level model of the heart: (**A**) The geometry of the right and left ventricles, (**B**) the epicardial fibre directions and (**C**) the coronary vessels.

arrhythmias, requires a model of the coronary circulation, as shown in Figure 8C, and solution of the Navier–Stokes equations that govern blood flow in arteries and veins. A further important influence on the mechanical function of the heart is the fluid mechanics and its coupling with the ventricular wall [26]. Autonomic neural innervation, both sympathetic and parasympathetic, is another important aspect of cardiac function, providing central control over the rate and force of contraction. The spatial distribution of cardiac nerves is currently being incorporated into the whole heart models.

DISCUSSION

Multiscale modeling requires that information be hidden between the descriptions of physiology which are relevant at different spatial and temporal scales. There are many ways in which this can be done. For example, when modeling the integrated function of a cell it is usually neither necessary nor desirable to represent the molecular dynamics of individual proteins. Rather, the kinetics describing the function performed by each particular type of protein is determined, and these kinetic descriptions combined in order to build a lumped parameter model for the cell. This represents an averaging of the properties of a population of protein molecules over timescales that are rapid compared to the properties of the cell that are of interest. Similarly, microscopic details of tissue structure can be averaged over short spatial scales in order to produce a description of tissue properties at the larger, supracellular level for inclusion in models at the organ level.

To facilitate model reuse among researchers in computational physiology, two XML markup languages for encoding biological models, CellML (http://www.cellml.org) and FieldML (http://www.fieldml.org), are being developed. CellML deals with models of so-called 'lumped parameter' systems, where spatial effects are averaged, and typically involves systems of ODEs and algebraic equations. FieldML addresses the spatial variations in cell or tissue properties where the models typically rely on PDEs. The two standards can be used together. These languages, which define the structure of a model, the mathematical equations and the associated metadata, enable (i) automated checking to ensure consistency of physical units used in the model equations, (ii) models developed by different groups to be combined using commonly agreed ontological terms within the metadata, and (iii) models to be modularized and used in libraries to make it easier to create complex models by importing simpler ones. Model repositories based on these standards and implementing a wide variety of models from peer-reviewed publications have been developed (http://www.cellml.org/models), and open source software tools for creating, visualizing and executing these models are currently available (http://www.cellml.org/tools) and under continuous development.

We have given an example of how this Physiome Project framework is used in modeling the heart. Similar projects are underway on a number of other organ systems [1]. The MLs and models described here are only a very small step toward building a framework for computational physiology. Clearly, much remains to be done, especially in connecting the cell models described here to the protein, lipid and carbohydrates databases being developed by the bioinformatics community.

Key Points

- Multiscale modeling is needed to interpret molecular data in a physiological context.
- Markup language standards provide a robust environment for multiscale modeling.
- Model repositories and open source tools based on these markup languages are being developed.

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