Using CellML in Computational Models of Multiscale Physiology

David Nickerson* Peter Hunter†

*University of Auckland, d.nickerson@auckland.ac.nz

†University of Auckland, p.hunter@auckland.ac.nz

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David Nickerson and Peter Hunter
Bioengineering Institute
The University of Auckland
Auckland, New Zealand
Email: d.nickerson@auckland.ac.nz

***Abstract*— A computational modeling framework is presented which enables the integration of multiple physics and spatial scales in models of physiological systems. A novel aspect of the framework is the use of CellML to specify all model and simulation specific mathematical equations including cellular models and material constitutive relationships. Models of cardiac electromechanics at cellular, tissue, and organ spatial scales are used to illustrate the developed and implemented framework and other applications are discussed.**

I. Introduction

The goal of the IUPS Physiome Project is to develop the technology and methods required to simulate the behavior of biological organisms from the cellular spatial scale up to the whole organism scale (Fig. 1). To achieve this multiple different physics needs to be integrated over this extreme range of spatial scales. For example, electrical activation in the heart is coupled to mechanical contraction and production of the energy required to drive this contraction which results in the application of pressure to the systemic circulation system propelling blood, rich in oxygen due to gas exchange in the lungs, around the human body.

A significant outcome of the Physiome Project has been the development of XML-based standards for the storage and exchange of biological models. With the development of these languages comes the ability to create and populate repositories of models that are freely available for use by the scientific community. The most advanced language is CellML, which was initially designed for application to models of cellular electrophysiology and reaction pathway models but has since been used in a wide range of mathematical models.

In this work we have developed a computational modeling framework that begins to allow scientists to perform numerical simulations using models of integrative physiological function across the cellular, tissue, and organ spatial scales. The framework was initially developed with a focus on overcoming the problem of modeling tightly coupled electromechanics in the heart (Section III) but the implementation is sufficiently general that application to other areas of modeling have begun to be investigated (Section IV).

The framework we have developed allows the use of CellML for the specification of all model and simulation specific mathematical equations, for example cellular electrophysiology models and passive material constitutive relationships.

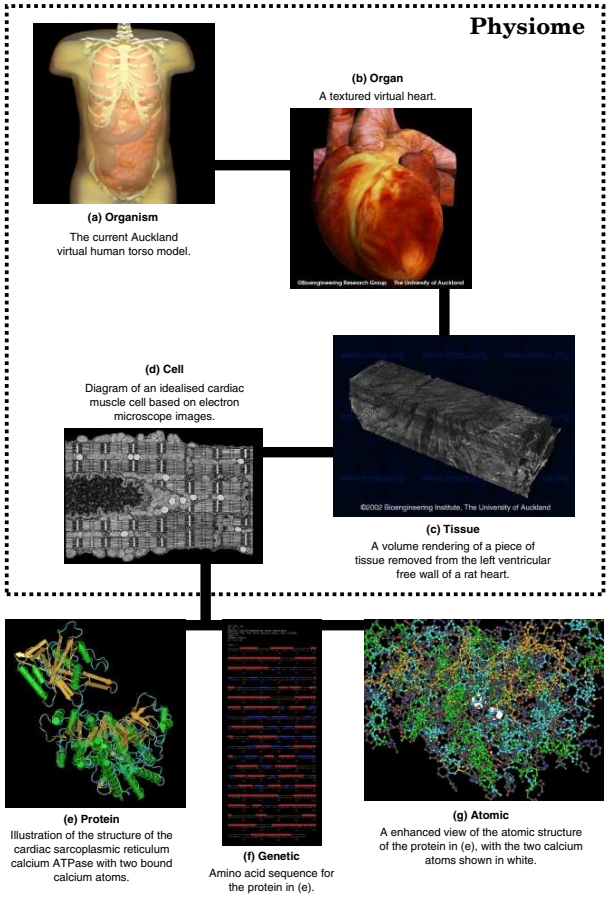


Fig. 1. The hierarchy of spatial scales used in the IUPS Physiome Project (dashed box). Below the dashed box shows the link downwards in scale to the protein and molecular levels.

The simulation framework developed here is built upon the extensive base provided by the CMISS software package developed in-house at the Bioengineering Institute at The University of Auckland.

A. CellML

CellML (`www.cellml.org`) is an XML based language developed by the Bioengineering Institute at the University of Auckland, New Zealand, in collaboration with Physiome Sciences Inc., USA. CellML is a language designed to store

and exchange computer based biological models and, where appropriate, the language builds upon existing XML standards – such as MathML (www.w3.org/Math) for the specification of mathematical equations and the resource description framework (www.w3.org/RDF) for the encapsulation of metadata.

Due to the completely generic specification of the language, CellML has a much broader range of applicability than the name suggests. For the purposes of this work CellML is considered a language for the description of annotated mathematics, *i.e.,* the specification of mathematical equations and the connections between equations and between variables contained in equations.

B. CMISS

CMISS (www.cmiss.org) is a computational package for modeling the structure and function of biological systems. It is designed to model the anatomy and material properties of organ systems (*e.g.,* cardiovascular, respiratory, and special sense organs) from the component organs (*e.g.,* heart, lungs, and eyes) down to the cellular and subcellular levels, including the coupling that occurs between and within all these levels. Equations derived from physical laws of conservation are solved to predict the integrative behavior of an organ from knowledge of the anatomical structure and tissue properties. The tissue properties used in these organ simulations can incorporate tissue structure and cellular processes, together with spatial variation of the parameters characterizing these processes. CMISS has facilities for fitting models to geometric data from various imaging modalities (*e.g.,* MRI, CT, and ultrasound) and has a rich set of tools for graphical interaction with the models and the display of simulation results. Control of CMISS is via graphical user interfaces, an interactive console based interpreter, or batch-mode scripting.

The origins of CMISS are based in the PhD work of Peter Hunter [1] as a finite element program for stress analysis of large deformations in the heart. It has since evolved into a general purpose biological systems modeling tool in the areas of **C**ontinuum **M**echanics, **I**mage analysis, **S**ignal processing, and **S**ystem identification. Recently, work has begun to modularize CMISS to enable the development of specialized and focused tools for various medical and other applications. The main academic goal of CMISS is to support the IUPS Physiome Project. See reference [2] for a detailed review of the abilities of CMISS in relation to the heart.

II. Incorporation of CellML into CMISS

The goal of this work was to implement a process of enabling the specification of model specific mathematical equations in CMISS through CellML. For example, prior to this work the standard way of implementing a new cellular model in CMISS was to write the equations in Fortran and add this to the CMISS code base. This method has two main disadvantages: the author of the Fortran code is normally translating a published piece of work, which leads to errors in the translation and typographical errors; and the generated code is very specific to CMISS and thus not easily transferred to another modeling or simulation package. This also assumes that the published model itself is free from error. Similar to cellular models, the hard-coding of other mathematical equations into the CMISS code base has disadvantages.

To avoid these problems CMISS has been made capable of importing mathematical models from CellML (Fig. 2). This provides the ability to store and simulate models in an open standard, where the models could conceivably originate from various sources.

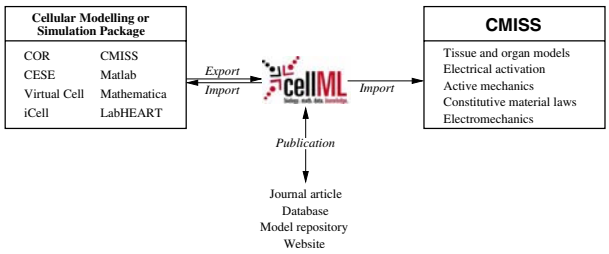


Fig. 2. Here we illustrate how CellML can be used to allow the development of mathematical models using domain-specific software, while allowing the models to be easily incorporated into tissue and organ level models. The cellular modeling and simulation packages listed are examples of software that can already understand CellML or are working on gaining that understanding.

The first step in implementing this ability in CMISS was to develop a standard Application Program Interface (API) for use when accessing a CellML model description. The API developed builds on top of the W3C DOM standard (www.w3.org/DOM) and the W3C MathML DOM (www.w3.org/Math/DOM). At this stage the API works with a subset of CellML 1.0 relevant to models of cellular electrophysiology and mechanics, but will be extended to cover the full CellML 1.1 specification. The most recent API developments are freely available from the CellML SourceForge.net site (cellml.sourceforge.net).

With an API defined the ability to import CellML could be added to CMISS, allowing the definition of mathematical models via CellML. This also requires the capability of translating the mathematical expressions from the CellML model (stored as MathML 2.0) into a dynamically loadable object that can be utilized by CMISS during a given simulation. Given the structure of the content elements of MathML 2.0, the translation to such an object is reasonably straightforward (Fig. 3).

Thus the model and simulation specific mathematical equations no longer need to be hard-coded in Fortran in the CMISS code base, but a scientist can develop, for example, their cellular model using software that is perhaps better suited to single cell modeling or is used in their experimental work. Then as long as the software is capable of exporting CellML, it is possible to take the cell model and perform tissue and whole heart simulations that are based on the model.

Another important requirement in the importation of CellML models into tissue modeling is the ability to specify spatial variation of whole models and parameters within a model. For example, when modeling the spread of excitation from

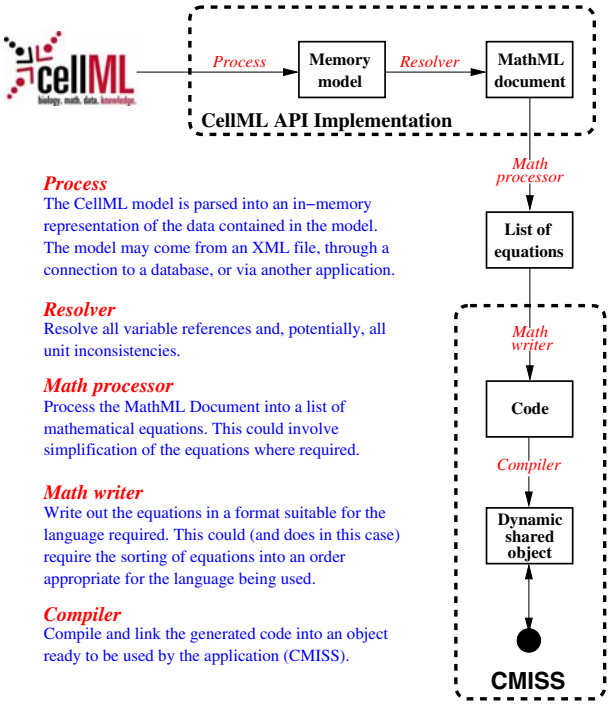
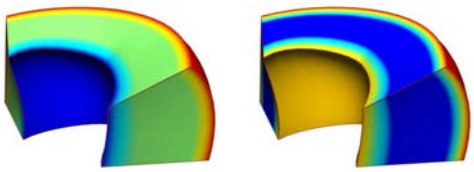


Fig. 3. An illustration of the work flow involved in the generation of code suitable for use in CMISS from a CellML source. The upper dashed box encapsulates the processes that are internal to the CellML API Implementation, and the lower encapsulates those internal to CMISS. The math processor is independent and external to both of these.

the pacemaker cells in the sinus node into the atria a modeler would typically want to use different cellular electrophysiological models for each of two regions of tissue. Another example is the variation of ion channel distributions through the ventricular wall (Fig. 4), where the modeler might want the same model represented at all points in the ventricles but need to specify a spatial distribution of channel densities.



(a) G_{to} (b) G_{Ks}/G_{Kr}

Fig. 4. Examples showing the variation of the G_{to} and G_{Ks}/G_{Kr} parameters through the ventricular wall. In (a), G_{to} is $0.0005\ \mathrm{mS \cdot mm^{-2}}$ at the endocardial surface (blue), $0.005\ \mathrm{mS \cdot mm^{-2}}$ in the midmyocardium, and $0.011\ \mathrm{mS \cdot mm^{-2}}$ at the epicardial surface (red). In (b), G_{Ks}/G_{Kr} is 19 at the endocardial surface (yellow), 7 in the midmyocardium, and 23 at the epicardial surface (red). The geometry is a wedge taken from the LV free wall of the porcine ventricular model and the parameter variation is described in reference [3].

III. Multiscale Modeling of Cardiac Electromechanics

Previous work has developed a comprehensive finite element model of the canine heart [4], including geometry and the fibrous structure of the heart. This heart model, in CMISS, has been further developed to enable the simulation of the finite elastic deformation of the heart [5] and the propagation of the wave of electrical excitation [6], [7]. A similar model has also been developed for the porcine heart [8].

When modeling the coupled electromechanics of cardiac tissue, the model can be broken into two distinct sub-models – the electrical activation and mechanical contraction. Each of which is the combination of two levels in the physiome hierarchy – the cellular and the tissue levels. The approach taken in this work is to treat this as a coupled problem while attempting to keep each of the submodels as independent as possible.

With this approach it is relatively simple to swap any of the sub-models without requiring any modification to the remainder of the model. For example, the scientist may wish to perform a set of simulations on the same piece of tissue but with a different cellular model for each simulation. Or a scientist might want to test the effect of various electrical propagation models on a single mechanical model.

Previous computational models of cardiac electromechanics (*e.g.,* [9]–[12]) have consisted of loosely coupled electromechanics, they have typically solved for electrical activation times and used these times to trigger local active contraction of the cardiac tissue. The activation times can be computed either from a simulation of electrical activation (generally using fairly simple cellular electrophysiology models) or through the use of an eikonal model to solve for activation times directly [13].

In this work we have developed a computational modeling framework which allows simulation of cardiac electromechanics with tightly integrated electrophysiology and mechanics within and across the cellular, tissue, and organ spatial scales. The addition of this tight coupling allows the investigation of a much wider range of physiological phenomena, especially in areas of pathophysiology.

Fig. 5 presents the results of a simulation of the active portion of the cardiac cycle in a simple left ventricular geometry. At the cellular level this model consists of the Fenton and Karma electrical activation model [14] coupled to the Hunter-McCulloch-ter Keurs mechanics model [15] via the calcium dynamics described by Beeler and Reuter [16]. The pole-zero material constitutive law [17] is used to describe the mechanical behavior of the tissue microstructure and a simple constant volume cavity model provides the pressure boundary condition applied to the endocardial surface of the LV model during the isovolumic contraction and ejection phases of the cycle.

IV. Further Applications

Further application of the work described above has also begun in other organ systems which involve electromechanics.

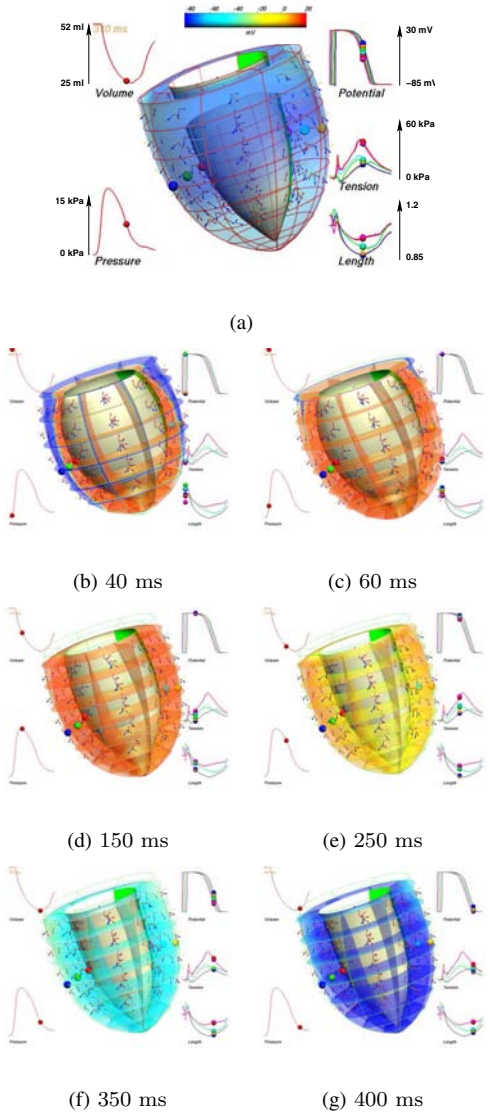


Fig. 5. Results of the active contraction and ejection of blood using a simple left ventricular geometry. (a) provides the key to describe the simulation results. The color bar above (a) provides the spectrum used for the transmembrane potential values drawn as colored surfaces within the LV model and the arrows within the wall indicate the microstructural fiber (red), sheet (yellow), and sheet-normal (blue) axes. (b)–(g) provide the simulation results at the indicated times.

A large system in which modeling of electromechanics is becoming more important is the musculo-skeletal system. While the detail of the skeletal muscle electromechanics differs from cardiac muscle, the underlying methods we have developed for the cardiac models is equally applicable to skeletal muscle [18]. With CellML it is trivial to replace the cardiac cellular models with skeletal and simulations of, for example, knee flexion can be made [19].

Similar to skeletal muscle, smooth muscle also undergoes active contraction in response to stimuli. While skeletal and cardiac muscle are quite similar, smooth muscle is significantly different. Once again, however, the underlying modeling framework developed in this work is capable of representing models of contracting smooth muscle. Initial investigation of this has recently begun in the area of modeling an active bronchial airway [20].

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REFERENCES

[1] P. J. Hunter, "Finite element analysis of cardiac muscle mechanics." Ph.D. dissertation, University of Oxford, Oxford, UK, 1975.
[2] G. R. Christie, D. Bullivant, S. Blackett, and P. J. Hunter, "Modelling and visualising the heart," *Comput. Visual. Sci.*, vol. 4, pp. 227–235, 2002.
[3] C. E. Clancy and Y. Rudy, "Cellular consequences of HERG mutations in the long QT syndrome: Precursors to sudden cardiac death," *Cardiovasc. Res.*, vol. 50, no. 2, pp. 301–313, May 2001.
[4] P. Nielsen, I. LeGrice, B. H. Smaill, and P. J. Hunter, "Mathematical model of geometry and fibrous structure of the heart," *Am. J. Physiol. Heart Circ. Physiol.*, vol. 260, no. 29, pp. H1365–H1378, 1991.
[5] M. P. Nash, "Mechanics and material properties of the heart using an anatomically accurate mathematical model," Ph.D. dissertation, The University of Auckland, Auckland, New Zealand, 1998.
[6] G. B. Sands, "Mathematical model of ventricular activation in an anatomically accurate deforming heart," Ph.D. dissertation, The University of Auckland, Auckland, New Zealand, 1997.
[7] M. L. Buist and A. J. Pullan, "From cell to body surface: A fully coupled approach," *J. Electrocardiol.*, vol. 34, no. Suppl., pp. 191–195, 2001.
[8] C. Stevens, "An anatomically-based computational study of cardiac mechanics and myocardial infarction," Ph.D. dissertation, The University of Auckland, Auckland, New Zealand, 2002.
[9] P. J. Hunter, M. P. Nash, and G. B. Sands, "Computational electromechanics of the heart," in *Computational Biology of the Heart*, A. V. Panfilov and A. V. Holden, Eds. West Sussex, England: John Wiley & Sons Ltd, 1997, ch. 12, pp. 345–407.
[10] T. P. Usyk, I. J. LeGrice, and A. D. McCulloch, "Computational model of three-dimensional cardiac electromechanics," *Comput. Visual Sci.*, vol. 4, pp. 249–257, 2002.
[11] R. C. P. Kerckhoffs, P. H. M. Bovendeerd, J. C. S. Kotte, F. W. Prinzen, K. Smits, and T. Arts, "Homogeneity of cardiac contraction despite physiological asynchrony of depolarization: a model study," *Ann. Biomed. Eng.*, vol. 31, pp. 536–547, 2003.
[12] R. C. P. Kerckhoffs, O. P. Faris, P. H. M. Bovendeerd, F. W. Prinzen, K. Smits, E. R. McVeigh, and T. Arts, "Timing of depolarization and contraction in the paced canine left ventricle: model and experiment," *J. Cardiovasc. Electrophysiol.*, vol. 14, no. Suppl., pp. S188–S195, Oct. 2003.
[13] K. Tomlinson, A. J. Pullan, and P. J. Hunter, "A finite element method for an eikonal equation model of mycardial excitation wavefront propagation," *SIAM J. Appl. Math.*, vol. 63, no. 1, pp. 324–350, 2002.
[14] F. Fenton and A. Karma, "Vortex dynamics in three-dimensional continuous myocardium with fiber rotation: Filament instability and fibrillation," *Chaos*, vol. 8, pp. 20–47, 1998.
[15] P. J. Hunter, A. McCulloch, and H. E. D. J. ter Keurs, "Modelling the mechanical properties of cardiac muscle," *Prog. Biophys. Molec. Biol.*, vol. 69, pp. 289–331, 1998.
[16] G. W. Beeler and H. Reuter, "Reconstruction of the action potential of ventricular myocardial fibres," *J. Physiol.*, vol. 268, pp. 177–210, 1977.
[17] M. P. Nash and P. J. Hunter, "Computational mechanics of the heart," *J. Elasticity*, vol. 61, pp. 112–141, 2000.
[18] J. W. Fernandez and P. J. Hunter, "An anatomically based finite element model of patella articulation: Towards a diagnostic tool," *Biomechan. Model. Mechanobiol.*, vol. in press, 2004.
[19] J. W. Fernandez, M. L. Buist, D. P. Nickerson, and P. J. Hunter, "Modelling the passive and nerve activated response of the rectus femoris muscle to a flexion loading: A finite element framework," *Med. Eng. Phys.*, vol. in press, 2004.
[20] S. Muttaiyah, M. Tawhai, and W. Thorpe, "Modelling an active bronchial airway," Bioengineering Institute, The University of Auckland, Auckland, New Zealand, Part IV Biomedical Engineering Project, 2004.