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Mathematical modelling of the heart: cell to organ

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Abstract

Single cell and whole organ mathematical models of cardiac electrophysiology, mechanics and metabolism are presented. The important elements of each model are outlined and, in particular, the methods, techniques and considerations for coupling each element together to create an integrated cardiac model are discussed. Results for both individual tissue and whole organ simulations are presented along with preliminary results from coupled models. © 2002 Published by Elsevier Science Ltd.

1. Introduction

The recent advances in high performance computing together with mathematical modelling now provide a framework for the coupling of previously separate areas of cardiac physiology. Increased computational power means that detailed biophysically based models of single cell systems of electrophysiology, contraction and metabolism can begin to be incorporated into two and three-dimensional, and ultimately whole organ representations of cardiac tissue. Furthermore, the goal of whole organ research via modelling provides motivation for coupling each of these systems together, so that their complex interactions can be investigated at a macroscopic level. The ultimate goal for this work is the ability to accurately predict whole organ behaviour under normal and pathological conditions, such as during myocardial ischaemia or re-entrant arrhythmias. Outlined in this manuscript is the modelling framework within which the physiological components, being developed in our respective groups, are coupled together. Preliminary results are presented and the future goals of such large-scale integrative modelling are discussed.

2. Methods

With each of the three cardiac cellular components (electrophysiology, mechanics and metabolism) comes a differing modelling proposition. The cellular and whole organ techniques used to represent these systems are summarised below.

2.1. Modelling cardiac electrophysiology and activation

2.1.1. Electrophysiological cellular models

Mathematical description of inter-cellular and intra-cellular ion transport in cardiac cells have become increasingly complex since the initial work of Noble [19]. The relative sophistication of these models provides an ideal foundation on which to build models of mechanics and metabolism. The most recent cellular models have included representations of

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many of the sub-cellular organelles [8,12,13,20], such as the diadic space, sarcoplasmic reticulum (SR) and mitochondria, and/or have been focused specifically on individual ion transporters [21,26]. Typical of complete ventricular cell models are the equations developed by Noble et al. [20], consisting of a system of 26 ordinary differential equations, specifying the rates of change of key cellular ion concentrations, which are themselves dependent on a number of diffusive and energy dependent exchange processes. Much of the cellular modelling work in our groups is based around the electrophysiological model of Noble et al., which describes biophysically based currents that are coupled to the model of cardiac contraction of Hunter et al. [7], via the changes in cytosolic calcium concentration induced by release from the SR. Since Ca^{2+} kinetics are critical to this coupling, work has recently begun to integrate the specific calcium kinetics model of Snyder et al. [26], to refine the framework provided by the Noble model.

The transient changes in ion concentrations are solved by integrating the system of equations that define the rate of each cellular reaction through time. This integration is performed using an Adams–Moulton numerical integration method which uses both adaptive step size and order. This scheme is chosen to provide increased efficiency over fixed schemes such as Runge–Kutta methods as it is able to accommodate the widely varying time-scales of the individual currents over the duration of an action potential (e.g., the rapidly varying sodium current up-stroke compared with the relatively slow changing potassium currents). An efficient integration method is less important when solving single cell models where computational expense is small. However, computational efficiency becomes essential when simulating the combined effect of large numbers of cells in multi-dimensional models of cardiac tissue as presented in Section 2.1.2.

2.1.2. Whole heart activation

The effect of inhomogeneities on the function of cardiac tissue is clearly beyond the scope of the single cell models presented in Section 2.1.1. For example, regional ischaemia produces disturbances such as ectopic beating and re-entrant arrhythmias. However, by using these cell model equations to provide current sources embedded in a continuum model, many of the spatio-temporal effects of activation wave propagation can be investigated.

Each numerical approximation point in a tissue model is treated as a "black box", whose source/sink characteristics are determined by the complex ion kinetics of the underlying cellular model. The spread of current is then modelled by numerically solving an advection–diffusion equation over this domain of points. Within the tissue model, conductivity and capacitance determine the electrical coupling between approximation points and ultimately the spread of activation throughout the tissue.The anisotropic nature of cardiac tissue means this conductive coupling is represented by a tensor with values that are determined from the tissue microstructure that has its local axes aligned with the fibre, sheet and sheet-normal directions in the tissue.

The high mesh density required to accurately represent the large changes in spatial ion gradients at the front of a propagating wave in cardiac tissue lends itself to a finite difference solution technique. The relative efficiency of finite difference grid point calculations compensates for the large number of grid points required. Despite this, the calculation of activation wave spread in the heart is currently not computationally tractable, since it requires an estimated 1.02 TB of disk storage and the solution to 281 billion equations for a single beat. Two potential solutions to this problem are (i) combining the finite difference scheme with multi-grid methods and (ii) applying parallelisation techniques.

The use of multi-grid methods [3,23] introduces several levels of increasing grid density, which are recruited based on the need to represent the spatial gradients in each region. A relatively small number of computational points would be used in regions of inactive or refractory tissue. Higher densities, obtained from interpolating currently active points, would be used in regions at, or just ahead of, the wave front. We estimate that this could result in a 95% reduction in the number of active grid points needed at any stage in time, and thus a large computational saving.

The parallelisation of grid point calculations is relevant for tissue simulations for two reasons. Firstly, the ionic current calculations at each grid point can be performed independently of those at all other grid points. Second, integrating these complex systems of cellular equations is a major contributor to computational load in comparison to the tissue-based differencing scheme. Thus, in theory, large problems should remain linearly scalable for relatively high numbers of processors.

Results demonstrating how spatial inhomogeneities in a continuum model can disturb excitation propagation are shown in Figs. 1 and 2. In these models, a two-dimensional tissue network was constructed with 7225 grid points. Using the cell model discussed in Section 2.1.1, the rate of Ca^{2+} release from the SR was increased from 0.25 to 1.0 mmol l^{-1} ms^{-1} and the rate of uptake by the SR was decreased from 0.006 to 0.0004 mmol l^{-1} ms^{-1} in a small region of tissue. Fig. 1 shows the geometry of this region, which produced a single ectopic beat. The characteristics of this region could probably be concluded from single cell results. However, Fig. 2 shows how by altering the geometry of the ischaemic region, a sustained sequence of ectopic beats was produced. These two simulations show the importance of the interaction between tissue geometry and cellular physiology and the importance of using continuum models to understand tissue phenomenon.

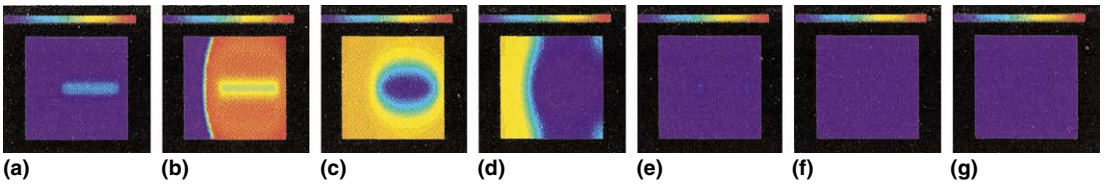

Fig. 1. The two-dimensional simulation of an 11 mm^2 membrane showing propagation from an ectopic beat. This was produced by increasing the rate of Ca^{2+} release and decreasing the uptake of the SR within the cell. The region of altered cellular properties can be seen in (a) as the bar of raised membrane potential.

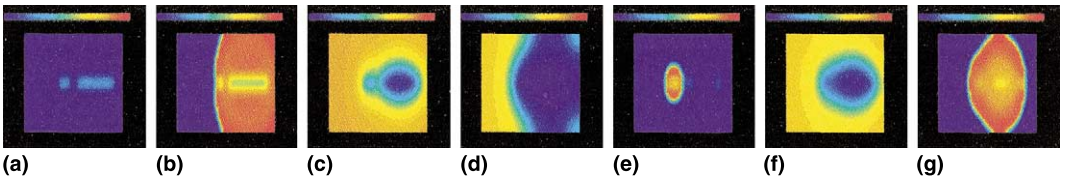

Fig. 2. Similar model to the simulation shown in Fig. 1 with a different geometry of the ionically altered region. These geometric differences resulted in a sustained sequence of ectopic beating compared to the previous model.

Using techniques validated in two dimensions, the goal is to investigate why often fatal, re-entrant arrhythmias develop in the whole organ. Each computational point for the whole heart simulations is located within the local material coordinates of the anatomically accurate high-order finite element mesh of the cardiac ventricles, developed at the University of Auckland [11,18]. Registration of the finite difference grid points from local or material points within the mesh becomes important once deformation of the mesh due to active contraction or passive mechanics are introduced. Examples of this type of coupled problem are illustrated in Section 2.2.2.

The conductivity tensors are based on fitted fields of fibre-sheet architecture [11]. Sands [22] incorporated a simple cellular model into the three-dimensional myocardial framework to simulate ventricular excitation, as illustration in Fig. 3.

With advances in computational power and the implementation of the techniques discussed above, work is currently underway to extend this research to investigate clinically relevant disruptions of activation wave propagation in the whole heart.

2.2. Mechanics

2.2.1. Myocyte mechanics models

Deformation of cardiac tissue is central to the function of heart. Similar to the electrophysiological modelling, active myocardial mechanics have been modelled using a cellular model, which relates transient ionic concentrations to actively developed tension. This cell model is then integrated into a continuum framework and used in combination with

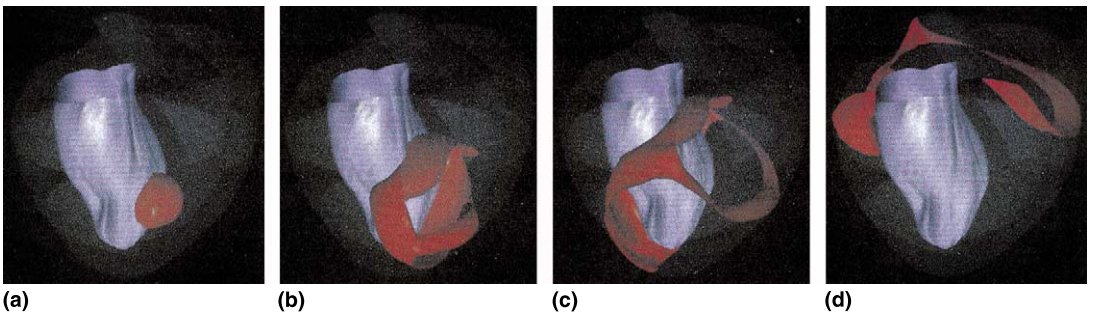

Fig. 3. Simulation of activation wave propagation in the anatomically accurate ventricular model from Sands [22].

the finite element method to predict whole organ deformation throughout the cardiac cycle. This deformation is governed by active and passive mechanical properties of the tissue. The passive mechanical properties are modelled using a constitutive law based on the non-linear and anisotropic nature of cardiac tissue. The active properties are tightly coupled to cardiac activation and metabolism, also discussed in this paper. It is the electrophysiology of the action potential, or more specifically the associated calcium transient that underlies myocyte contraction on a relatively fast time-scale. Generated tension is also dependent on the metabolic processes of energy production within the cell. Thus an ionic model of contraction is essential in the development of a fully integrated cardiac model.

Hunter et al. [7] have recently developed such a model. Like the electrophysiological models, the key rates of ionic (calcium) transport and binding are represented via a system of differential and integral equations.

Key elements to this model are the binding and release of Ca^{2+} to troponin-C, tropomyosin kinetics and cross-bridge kinetics. The equation parameters are fitted to steady-state tension–length–Ca^{2+} relations and to transient tension responses to rapid length steps for a variety of experimental preparations. The model is then shown to predict results from a range of other tests including the length response to step changes in load, mechanical frequency response tests. The mechanical state of the cell is clearly affected by the Ca^{2+} transient supplied (primarily) from the SR release channels but the electromechanical coupling also works the other way as well: mechanical perturbations which alter the release of Ca^{2+} from troponin-C also thereby influence the electrophysiological state of the cell.

Fig. 4 demonstrates this interaction with results from a two-dimensional coupled electromechanics model. The tissue is stimulated at one edge, with the resulting propagating wave travelling from left to right inducing contraction within the underlying finite element mesh. In the third element from the left along the bottom edge, the extracellular potassium concentration has been raised and the pH lowered, simulating ischaemia and inhibiting contraction. These alterations in ionic concentrations at the cellular level resulted in slowed conduction through this region, a shortened action potential and the lack of active contraction. At the tissue level, these cellular changes in turn disrupted the wave-front and altered the repolarisation pattern. The lack of contraction resulted in this element being stretched as the normal tissue contracted around it. Furthermore, stimulation of currents via stretch activate channels [10] in the ionic membrane can cause disruptions in conduction and repolarisation sequences, which are potentially arrhythmogenic. Investigations

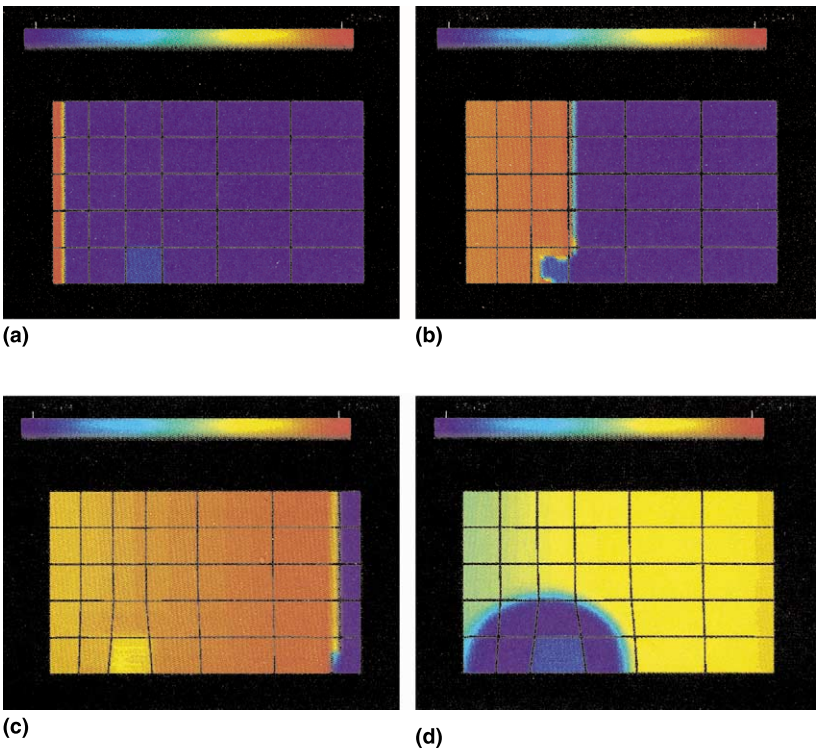

Fig. 4. A two-dimensional electromechanical simulation of a 68 mm by 40 mm myocardial membrane sheet with 16,685 grid points and an ischaemic region.

using these coupled models and anatomically accurate deformation models introduced in Section 2.2.2 will provide further insight into many of these phenomena.

2.2.2. Whole organ finite deformation mechanics

The same anatomically accurate heart model used for whole organ activation simulations in Section 2.1.2 has been developed by Nash [17] to provide a mathematical framework for global ventricular mechanics.

The non-homogeneous laminar micro-structure of cardiac muscle has been characterised using a fully three-dimensional orthotropic pole-zero constitutive law [7]. This is used to account for the strain limiting behaviour of resting myocardial tissue locally about the three axes defined by the tissue organisation (fibre, sheet, and sheet-normal). As the tissue is stretched along each axis, there is a very steep rise in stress as the limiting strain or "pole" is approached. The parameters of this constitutive law have been estimated from in vitro biaxial tension, compression and shear tests on small samples of ventricular tissue.

The myocardial contractile properties are modelled using a simplified steady-state version of the cellular based cardiac mechanics model presented in Section 2.2.1 that defines the relationship between fibre extension ratio, intracellular calcium concentration and active myocardial stress. Using these material properties, whole organ deformation was determined using the finite element method to solve the governing equations of finite deformation elasticity for the ventricular model. Deformations were induced by alternations in intra-cellular calcium concentration and in the left and right ventricular cavity pressures, which were incremented throughout the cardiac cycle starting at a residually stressed unloaded resting state. Each subsequent state was solved as a quasi-static problem using the solution from the previous state as the initial condition. The non-linear system of finite element equations was solved at each step using Newton's method.

The mechanics model of ventricular contraction is split into four distinct phases, diastole (or inflation), isovolumic contraction, ejection and isovolumic relaxation. Each phase consists of a number of individual mechanics steps. The deformation at the end of each phase is shown in Fig. 5.

At the beginning of the diastolic inflation phase, the ventricular model had zero transmural pressure and intracellular calcium was set to 0 mM. The left ventricular pressure (LVP) was then incremented by 0.1 kPa and the right ventricular pressure (RVP) by 0.02 kPa over 10 steps so that by the end of diastolic loading $LVP = 1.0$ kPa and $RVP = 0.2$ kPa. Isovolumic contraction was then induced by steadily incrementing intracellular calcium over 24 steps while maintaining constant ventricular cavity volumes. The ejection phase was spread over 26 mechanics steps. A cavity impedance parameter was used to model the resistance of the blood flow out of the ventricles (see [17] for details). Deformation during ejection was determined by incremental reductions in the impedance parameter until a physiological realistic left ventricular ejection fraction (44% [1]) was reached, which defined end-systole. Intermediate deformation states were determined for each step in cavity impedance. The final isovolumic relaxation phase was modelled by reducing the intra-cellular calcium to its diastolic value (zero).

As with the finite difference scheme used to stimulate whole organ activation wave propagation, sections of the finite element method algorithm can be divided into blocks on which computations can be performed in parallel. Parallelisation of the assembly phase of the global stiffness matrix produced near linear speed up with additional processors, which contributes greatly to reducing overall computation time.

Extensions to this model will include the energy production mechanisms on which cardiac contraction is dependent. The modelling of these metabolic processes is presented in the following section.

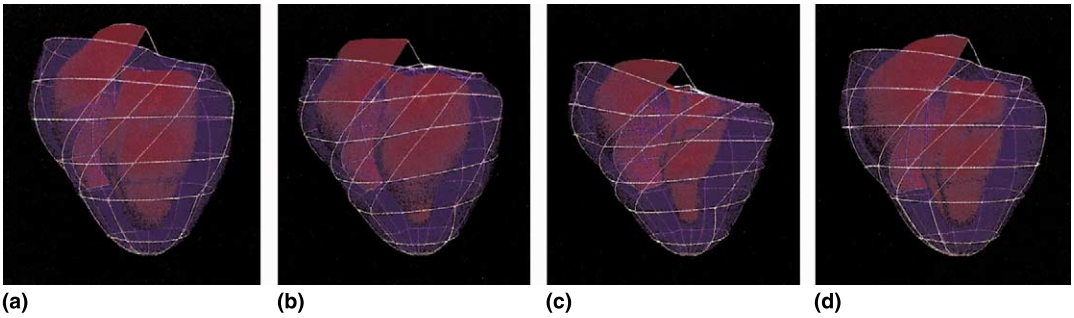

Fig. 5. The four phases of ventricular mechanics. White lines show the epicardial boundaries of ventricular wall elements, while shaded epicardial surfaces show how the right ventricle wraps around the left ventricle.

2.3. Cardiac energy production

2.3.1. Cellular metabolism

The mechanical and electrophysiological processes of the heart are dependent on a constant supply of energy in the form of ATP. The cell supplies ATP by oxidising fuel molecules via a number of metabolic pathways. As has been outlined in the previous sections, detailed and biophysically realistic cellular models have been developed that integrate cardiac electrophysiology and mechanical processes; however, to date, metabolism has been largely ignored in these models. One reason for this is that most electrophysiological and mechanical processes occur on a much faster time-scale than metabolic processes. For example, while a human heartbeat takes about 1 s, it can take over 10 min for ATP to fully deplete once the supply of oxygen to a cell has been stopped [4]. Hence, ATP and other metabolite concentrations can often be assumed to be constant during the time-scale of interest. However, if we are to use these models to better understand clinical pathologies such as ischaemia, it will be important to understand the relationships between electrophysiology, contraction, and metabolism on minute time-scales (and longer).

The main difficulties in modelling metabolism tend to relate to the physiological aspect of the modelling process rather than the mathematics. Mathematically, the task of modelling a metabolic system is relatively simple. As a first approximation, it is usually assumed that metabolite concentrations are spatially homogeneous within each organelle or compartment. Thus, the rate of change of metabolites can be described by a system of ordinary linear differential equations for which the right-hand side consists of linear combinations of the rate equations that describe each reaction. Each linear combination is determined by the stoichiometry of the metabolic system. Linear dependencies between the rows of the stoichiometry matrix allow the identification of the so-called conservation sums, which then allow the elimination of some of the concentration variables from the model. Further simplification can be obtained by a consideration of the time hierarchy of the system. For example, modal analysis can be used to identify the various time-scales of the model. This may then allow the use of further approximation methods to again reduce the number of metabolite or state variables (see [6] for a comprehensive review of these concepts).

Cellular metabolism has received extensive experimental study over the last 50 years and much has been learnt about the kinetics of the individual metabolic reactions. However, there has been limited success in developing models of metabolism that relate the kinetics of the individual components of the metabolic system to its overall behaviour. The only metabolic system for which a detailed and realistic model exists is the human erythrocyte; a cell with a relatively simple metabolism (e.g., [14–16]). Part of the reason for this is the immense complexity of metabolic systems; metabolism in the heart consists of a number of highly interrelated pathways that exhibit multi-site regulation by a large number of state variables in a highly non-linear manner. Only in the last decade or so has the computing power been available to deal with such complicated modelling problems. One early attempt at modelling cardiac metabolism which, to date, remains the most detailed model developed, was the model developed by David Garfinkel and co-workers (e.g., see [5]) and we are currently using this as a basis for a detailed model of cellular metabolism.

In the task of incorporating metabolism into the current cellular models, it has been necessary to modify many of the electrophysiological and mechanics rate equations to account for the interactions of ATP, as well as a number of other metabolites. To do this in a consistent manner, new rate equations have been derived for many processes that are based on a detailed consideration of each reaction mechanism. Many of the existing rate equations were based on equations containing "apparent" constants, which were only valid for a limited set of conditions. In many pathological conditions, the concentrations of ions and metabolites vary greatly and the use of apparent constants is no longer valid.

2.3.2. Whole organ oxygen delivery

The metabolic cellular models in Section 2.3.1 are now ready to be integrated into the whole organ framework in the same way as the cellular electrophysiological and mechanics models outlined in Sections 2.1.1–2.2.2. However, to study pathologies such as ischaemia, knowledge of the regional distribution of metabolites and the delivery of oxygen within cardiac tissue becomes important. Central to this role are the specialised channels for the advection of oxygenated blood throughout the myocardium known as the coronary network. The anatomically realistic finite element model of the coronary network of Smith et al. [25] provides the geometric foundation for development of a mathematical model of coronary blood flow.

This network was generated from measured epicardial vessels and the topological data of Kassab et al. [9]. The largest six of 11 generations of arterial vessels were generated discretely with pairs of veins assumed to be parallel to each arterial vessel. The network geometry was coupled to material points within the anatomically accurate model of the ventricles used for the whole organ activation and mechanics simulations in Sections 2.1.2 and 2.2.2, respectively.

By assuming a radial axi-symmetric velocity profile, the Navier–Stokes equations governing coronary blood flow reduce to one dimension. These flow equations were combined with a pressure–area relationship for the compliant coronary vessel walls, which has been fitted from experimental data. Blood flow through the coronary network model

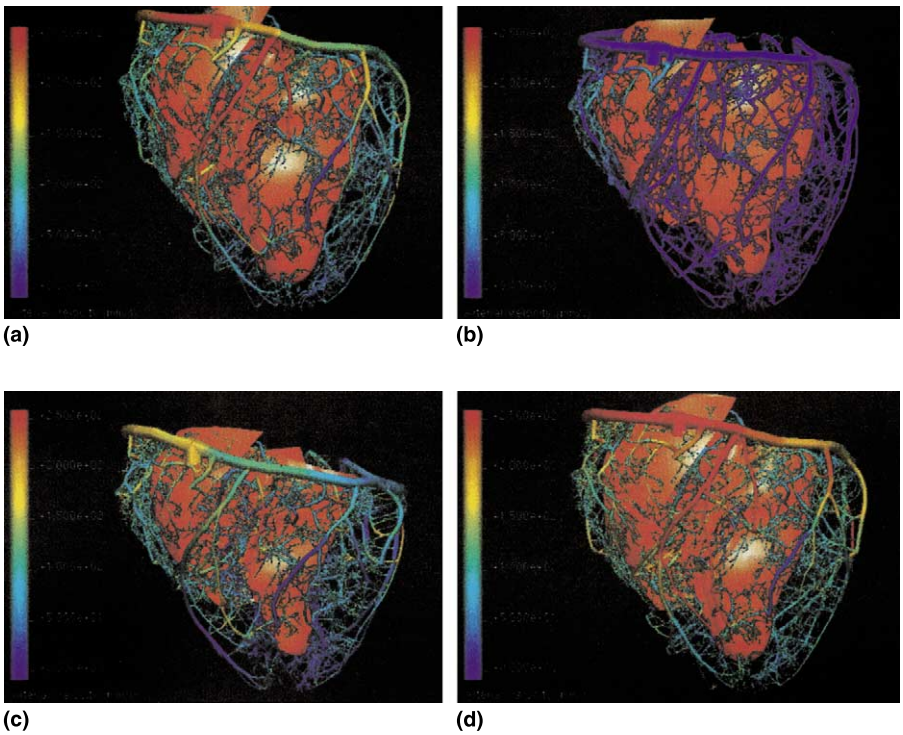

Fig. 6. Calculated coronary arterial blood flow velocities at the end of the four phases of the cardiac cycle.

was calculated using the two-step Lax–Wendroff finite difference representation and the coupled lumped parameter model of Smith et al. [24].

The compressive force produced by contraction of the ventricles on the embedded coronary vessels has a major effect on coronary blood flow. This force was calculated from finite element solutions to the finite elasticity equations [17], outlined in Section 2.2.2. For a stress state calculated at a point in the contraction cycle, the stress tensor can be rotated into a vessel coordinate system for each segment in order to calculate the average pressure normal to the vessel wall. This pressure is then incorporated into the pressure–area relationship of the blood flow equations.

Fig. 6 demonstrates a central behaviour of this modelling study showing calculated arterial coronary blood flow at different stages during the contraction cycle. Despite the rise in arterial inflow pressure during systole, contraction significantly impeded total flow over the whole cycle with flow time integrals less than the steady-state values calculated independent of contraction. Along with a number of other key experimental results, this model has been verified using the work of Bassingthwaight et al. [2] on the fractal nature of the regional distribution of blood flow in the heart. What remains is to use this distribution together with metabolic models such that the supply of oxygen determines the nature of energy production and the resulting effects on myocyte and whole heart functions.

3. Discussion and future developments

The foundation components of a fully integrated and functional model of the heart have been presented. Further work developing and refining elements of the cardiac system remains. On the cellular level, this includes adding further cell types, species models and characterising responses to pathologies such as ischaemia. At the whole organ level, work to add the anatomical structures of the arterial conduction network is underway along with a model of the ventricular fluid dynamics.

Coupling of these individual models is now much of the focus of work in our respective laboratories. Critical to this work is the further development of techniques that span the variety of spatial and, particularly, temporal scales of the many different processes we are attempting to model. For example, the time-scale of the sodium current that initiates an action potential is 1–2 ms. In contrast, the stores of ATP fuelling metabolism and contraction take up to 10 min to

completely deplete from the initial onset of total ischaemia [4]. The solution is a hierarchy of models dependent on the processes involved. Fast reactions may need to be reduced to algebraic expressions when modelling the slower metabolic reactions in order to efficiently integrate the system of equations. Conversely, the concentrations of metabolites may be assumed constant for the time-scale, over which individual electrophysiological currents are studied.

Levels of model complexity are also required to fully exploit the wealth of data available from the rapidly expanding fields of molecular-biology and genomics within a currently available computational framework. Using this data, there is real potential to develop cellular models using continuum principles by spatially representing the mechanics of cellular contractile apparatus, ionic diffusion and transport processes. Such models may provide a valuable way to link protein and gene information to cell function. They would, however, in the medium term prove too computationally expensive to be replicated millions of times in a tissue model. Thus, one solution is to provide computationally simple models within the tissue framework, which are based on the more detailed models but still maintain the essential elements of each process.

Critical to any modelling project where different aspects of function are being incorporated together, is constant and systematic experimental verification. As with model development, verification is essential at all levels from protein ion channel characteristics to whole organ function. Such an integrated approach will require input from a wide variety of groups around the world. The development of the Cardiome, as a subset of the Physiome Project initiated by Dr. Jim Bassingthwaighte in 1997, will provide a framework for this cooperative effort. The database developed though this initiative of experimental data and mathematical models will prove invaluable in expediting this process. It is with this focussed effort that the goal of bio-physically based and clinically relevant integrated cardiac modelling will become a reality.

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References

[1] Azhari H, Weiss JL, Rogers WJ, Siu CO, Zerhouni EA, Shapiro EP. Non-invasive quantification of principal strains in normal cannine hearts using tagged MRI images in 3-D. Am J Physiol 1993;264:H205–16.
[2] Bassingthwaighte JB, King RB, Roger SA. Fractal nature of regional myocardial blood flow heterogeneity. Circ Res 1989;65:578–90.
[3] Briggs WL. A multigrid tutorial. Philadelphia, PA: Society for Industrial and Applied Mathematics; 1987.
[4] Ch'en FFT, Vaughan-Jones RD, Clark K, Noble D. Modelling myocardial ischaemia and reperfusion. Prog Biophys Mol Biol 1998;69:497–515.
[5] Garfinkel D, Kohn MC, Achs MJ. Computer simulation of metabolism in pyruvate-purfused rat heart. V. Physiological implications. Am J Physiol 1979;237:R181–6.
[6] Heinrich R, Schuster S. The regulation of cellular systems. 9th ed. New York: Chapman & Hall; 1996.
[7] Hunter PJ, McCulloch AD, ter Keurs HEDJ. Modelling the mechanical properties of cardiac muscle. Prog Biophys Mol Biol 1998;69:289–331.
[8] Jafri S, Rice J, Winslow R. Cardiac Ca^{2+} dynamics: the role of ryanodine receptor adaptation and sarcoplasmic reticulum load. Biophys J 1998;74:1149–68.
[9] Kassab GS, Rider CA, Tang NJ, Fung YC. Topology and dimensions of pig coronary capillary network. Am J Physiol 1994;267:H319–25.
[10] Kohl P, Hunter P, Noble D. Stretch-induced changes in heart rate and rhythm: clinical observations experiments and mathematical models. Prog Biophys Mol Biol 1999;71:91–138.
[11] Le Grice IJ, Smaill BH, Chai LZ, Edgar SG, Gavin JB, Hunter PJ. Laminar structure of the heart I: Cellular organisation and connective tissue architecture in ventricular myocardium. Am J Physiol 1995.
[12] Luo C-H, Rudy Y. A dynamic model of the cardiac ventricular action potential: I. Simulations of ionic currents and concentration changes. Circ Res 1994;74(6):1071–96.
[13] Luo C-H, Rudy Y. A dynamic model of the cardiac ventricular action potential: II. After depolarizations triggered activity and potentiation. Circ Res 1994;74(6):1097–113.
[14] Mulquiney PJ, Bubb WA, Kuchel PW. Model of 2,3-bisphosphoglycerate metabolism in the human erthrocyte based on detailed enzyme kinetic equations: in vivo kinetic characterisation of 2,3-bisphosphoglycerate synthase/phosphatase using 13C and 31P NMR. Biochem J 1999;342:567–80.

[15] Mulquiney PJ, Kuchel PW. Model of 2,3-bisphosphoglycerate metabolism in the human erythrocyte based on detailed enzyme kinetic equations: computer simulation and metabolic control analysis. Biochem J 1999;342:597–604.
[16] Mulquiney PJ, Kuchel PW. Model of 2,3-bisphosphoglycerate metabolism in the human erythrocyte based on detailed enzyme kinetic equations: equations and parameter refinement. Biochem J 1999;342:581–96.
[17] Nash MP. Mechanics and material properties of the heart using an anatomically accurate mathematical model. Ph.D. thesis. The University of Auckland, New Zealand; 1998.
[18] Nielsen PMF, Le Grice IJ, Smaill BH, Hunter PJ. Mathematical model of geometry and fibrous structure of the heart. Am J Physiol 1991;260(Heart Circ. Physiol 29):H1365–78.
[19] Noble D. A modification of the Hodgkin–Huxley equation applicable to Purkinje fibre action and pacemaker potentials. J Physiol 1962;160:317–52.
[20] Noble D, Varghese A, Kohl P, Noble P. Improved guinea-pig ventricular model incorporating diadic space i_{kr} and i_{ks} length and tension-dependent processes. Can J Cardiol 1998;14:123–34.
[21] Rice J, Winslow R, Dekanski J, Mc Veigh E. Model studies of the role of mechano-sensitive currents in the generation of cardiac arrhythmias. J Theoret Biol 1998;190:295–312.
[22] Sands GB. Mathematical model of ventricular activation in an anatomically accurate deforming heart. Ph.D. thesis, The University of Auckland; 1999.
[23] Sands GB, Hunter PJ. A collocation-multigrid model of bidomain activation as a component of a complete electrocardiology model. In: 23rd International Conference on Electrocardiography. 1996.
[24] Smith NP, Pullan AJ, Hunter PJ. An efficient finite difference model of transient coronary blood flow in the heart. SIAM J Appl Math 2002 [in press].
[25] Smith NP, Pullan AJ, Hunter PJ. The generation of an anatomically accurate geometric coronary model. Ann Biomed Eng 2000;28:14–25.
[26] Snyder S, Palmer B, Moore R. A mathematical model of cardiocyte Ca^{2+} dynamics with a novel representation of sarcoplasmic reticular Ca^{2+} control. Biophys J 2000;79:94–115.