Whole-Heart Modeling
Applications to Cardiac Electrophysiology and Electromechanics

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Abstract: Recent developments in cardiac simulation have rendered the heart the most highly integrated example of a virtual organ. We are on the brink of a revolution in cardiac research, one in which computational modeling of proteins, cells, tissues, and the organ permit linking genomic and proteomic information to the integrated organ behavior, in the quest for a quantitative understanding of the functioning of the heart in health and disease. The goal of this review is to assess the existing state-of-the-art in whole-heart modeling and the plethora of its applications in cardiac research. General whole-heart modeling approaches are presented, and the applications of whole-heart models in cardiac electrophysiology and electromechanics research are reviewed. The article showcases the contributions that whole-heart modeling and simulation have made to our understanding of the functioning of the heart. A summary of the future developments envisioned for the field of cardiac simulation and modeling is also presented. Biophysically based computational modeling of the heart, applied to human heart physiology and the diagnosis and treatment of cardiac disease, has the potential to dramatically change 21st century cardiac research and the field of cardiology. (Circ Res. 2011;108:113-128.)

Key Words: whole-heart model ■ electrophysiological modeling ■ electromechanical modeling ■ simulation ■ cardiac disease

Modeling and simulation has long been intertwined with the biological sciences, including cardiac research. The review articles in this issue of Circulation Research provide vivid examples of this relationship and underscore the newly found power of cardiac simulation. Modern cardiac research has increasingly recognized that appropriate models and simulation can help interpret an array of experimental data and dissect important mechanisms and interrelationships. Paraphrasing Cohen,1 modeling and simulation are becoming cardiac-research community’s “next microscope, only better.” As advances in computer modeling are transforming many traditional areas of physics and engineering, they are also transforming the understanding of cardiac function in health and disease and the clinical practice of cardiology.

Recent developments in cardiac simulation have rendered the heart the most highly integrated example of a virtual organ. These developments are firmly anchored in the long history of cardiac cell modeling (this year marks the 50th anniversary of the first ion current–based myocyte model2) and are rooted in the iterative interaction between modeling and experimentation. Importantly, modeling the function of the heart has benefitted significantly from the revolution in medical imaging and from the systematic incorporation of validated biophysical relationships, resulting in a dramatic

Original received August 13, 2010; revision received November 8, 2010; accepted November 9, 2010. In October 2010, the average time from submission to first decision for all original research papers submitted to Circulation Research was 13.9 days.

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Circulation Research is available at http://circres.ahajournals.org DOI: 10.1161/CIRCRESAHA.110.223610
The latter forms the basis for contractile protein movement and initiation of release of calcium from its intracellular stores, followed by binding of calcium to Troponin C and cross-bridge cycling. The reaction—diffusion PDE describes current flow through myocardial tissue, governed by a set of ordinary differential (ODE) and algebraic equations; ionic models of different complexity are currently in use. Simultaneous solution of the PDE(s) with the set of ionic model equations represents simulation of electrical wave propagation in the heart. The intracellular calcium released during electrical activation couples the electrical and mechanical components of the model (Figure 1A). It serves as an input to the "cellular model," representing the generation of active tension within each myocyte, where sets of ODEs and algebraic equations describe, to a varying degree, calcium binding to troponin C, cooperativity between regulatory proteins, and cross-bridge cycling. Contraction of the ventricles arises from the active tension generated by the myocytes. Deformation of the organ is described by the equations of continuum mechanics, with the myocardium being an orthotropic, hyperelastic, and nearly incompressible material, with passive properties defined by an exponential strain energy function. Simultaneous solution of the myofilament model equations with those representing passive cardiac mechanics over the volume of the heart (Figure 1A) constitutes simulation of cardiac contraction. During contraction, the stretch ratio (ratio of myocyte length before and after deformation) and its time derivative influence, in turn, cellular myofilament dynamics, including length-dependent calcium sensitivity. Finally, to simulate the cardiac cycle and the corresponding pressure–volume loop, conditions on chamber volume and pressure are imposed by a lumped-parameter models of the systemic and pulmonary circulatory systems (Figure 1A). Note that currently fully coupled electromechanical modeling is still the exception rather than the rule in the cardiac modeling community (see below for details).

### General Approach to Whole-Heart Modeling

#### Model Components

A schematic of the general approach to modeling cardiac electromechanical function is shown in Figure 1A. It consists of 2 coupled parts, which simulate the electrical and the mechanical functions of the heart, respectively. As an electrical wave propagates through the heart, the depolarization of each myocyte initiates release of calcium from its intracellular stores, followed by binding of calcium to Troponin C and cross-bridge cycling. The latter forms the basis for contractile protein movement and the development of active tension in the myocyte, leading to deformation of the ventricles. The electromechanical model of the heart represents these processes.

The electrical component of the model in Figure 1 simulates the propagation of a wave of transmembrane potential by solving the monodomain reaction–diffusion partial differential equation, PDE (or a system of coupled PDEs if the extracellular current flow is explicitly accounted for, ie, the bidomain problem), over the volume of the heart. The reaction–diffusion PDE describes current flow through myocytes that are electrically connected via low-resistance gap junctions. Cardiac tissue has orthotropic passive electrical conductivities that arise from the cellular organization of the heart into fibers and laminar sheets. Global conductivity values are obtained by combining fiber and sheet organization with myocyte-specific local conductivity values. Current flow in the tissue is driven by active processes of ionic exchanges across myocyte membranes. These processes are represented by the "cellular model" (Figure 1A), where current flow through ion channels, pumps, and exchangers, as well as subcellular calcium cycling, are governed by a set of ordinary differential (ODE) and algebraic equations; ionic models of different complexity are currently in use. Simultaneous solution of the PDE(s) with the set of ionic model equations represents simulation of electrical wave propagation in the heart. The intracellular calcium released during electrical activation couples the electrical and mechanical components of the model (Figure 1A). It serves as an input to the "cellular model," representing the generation of active tension within each myocyte, where sets of ODEs and algebraic equations describe, to a varying degree, calcium binding to troponin C, cooperativity between regulatory proteins, and cross-bridge cycling. Contraction of the ventricles arises from the active tension generated by the myocytes. Deformation of the organ is described by the equations of continuum mechanics, with the myocardium being an orthotropic, hyperelastic, and nearly incompressible material, with passive properties defined by an exponential strain energy function. Simultaneous solution of the myofilament model equations with those representing passive cardiac mechanics over the volume of the heart (Figure 1A) constitutes simulation of cardiac contraction. During contraction, the stretch ratio (ratio of myocyte length before and after deformation) and its time derivative influence, in turn, cellular myofilament dynamics, including length-dependent calcium sensitivity. Finally, to simulate the cardiac cycle and the corresponding pressure–volume loop, conditions on chamber volume and pressure are imposed by a lumped-parameter models of the systemic and pulmonary circulatory systems (Figure 1A). Note that currently fully coupled electromechanical modeling is still the exception rather than the rule in the cardiac modeling community (see below for details).

#### Whole-Heart Model Geometry and Anatomic Structure

Whole-heart electromechanical models are modular in the sense that they can provide solutions to electrophysiological or electromechanical problems on user-specified whole-heart areas, using diverse computational tools such as finite element simulations, coupled with subcellular models. The anatomic structure is divided into regions, each with a specific geometry and material properties, which determine the propagation of electrical and mechanical waves. The model components are integrated through boundary conditions and material properties, allowing for the simulation of atrial, ventricular, and coronary artery function.
geometries, which can be idealized (such as cylindrical and elliptical shapes\textsuperscript{12,13} or anatomically accurate, the latter either representing averaged geometries obtained from histological sectioning\textsuperscript{14–16} or the geometry and structure of individual heart\textsuperscript{11,17,18} such as obtained from MR images\textsuperscript{19,20}). The modular structure of the model also allows the use of any cellular ionic and myofilament models, of different species, and with different levels of biophysical detail.

Figure 1B presents different whole-heart geometries used in electrophysiological and electromechanical modeling. The first 2 hearts (rabbit [University of California, San Diego data\textsuperscript{14}] and swine [Auckland data\textsuperscript{15}]) are examples of averaged geometries obtained from histological sectioning, whereas the other 3 are examples of image-based individual geometries\textsuperscript{17}. Using MRI data for model geometry also permits representation of the structural remodeling of the individual heart, such as infarction (Figure 1C; see elsewhere\textsuperscript{17} for details on infarct segmentation).

Solutions to electrophysiological or electromechanical whole-heart models nowadays involve the use of the finite element method. The governing equations are thus solved on a spatially discretized version of the heart volume, i.e., on the computational mesh. The electrical and mechanics parts of the model have different requirements regarding the degree of discretization (i.e., element size), as well as the element type, thus the 2 parts of the model require 2 different computational meshes. The electrical mesh requirements are based on spatiotemporal characteristics of wave propagation; a spatial resolution of approximately 250 to 300 µm is appropriate for electrophysiological finite element models.\textsuperscript{4} A novel approach was recently published\textsuperscript{21} for electrical mesh generation directly from segmented MRI images. The meshing technique is automatic and produces boundary-fitted and locally refined meshes (Figure 1D). The mechanical mesh, on the other hand, typically consists of hexahedral elements with Hermite basis. This choice of finite elements increases the degree of strain continuity and is appropriate for maintaining incompressibility constraints.\textsuperscript{22} The mechanical mesh of the heart can also be generated directly from segmented MR images (Figure 1C).\textsuperscript{11}
Fiber and laminar sheet organization underlie the orthotropic electrical conductivities of the tissue and its mechanical properties. In the electrical mesh, local fiber and sheet directions are typically mapped at the centroids of the finite elements, whereas in the mechanics mesh, fiber and sheet orientations and their derivatives are defined at mesh nodes and then interpolated over the elements. This is typically done based on histological sectioning information of diffusion tensor (DT) MR data (the primary, secondary, and tertiary eigenvectors of the water diffusion tensors are aligned with the fiber direction, with the direction transverse to the fiber direction and in the plane of the laminar sheet, and with that normal to the laminar sheet, respectively). The same procedure is used for fiber mapping in hearts with structural remodeling such as infarction; DTs are mapped on every finite element centroid, followed by the delineation of the infarct scar and border zone (BZ). Figure 1D presents fiber orientation, as reconstructed from DTMRI images, in the electrical mesh of a slice of the canine heart and in the whole canine heart, and the sheet orientations in the ventricular mechanics mesh. In cases where neither histological nor DTMRI imaging information is available, rule-based approaches have been used to assign fiber orientation consistent with measurements.

Numerical Solutions
Simulations of whole-heart electromechanical function are typically executed on parallel high performance computing hardware. The electrical problem is significantly more computationally demanding than the mechanical; notable packages used in simulations include MEMFEM and CARP. A review of the various numerical approaches used in solving the electrical problem is included in the Online Data Supplement, available at http://circres.ahajournals.org.

Cardiac Electrophysiology Applications
This section reviews the application of whole-heart models in cardiac electrophysiology and, specifically, in the study of normal propagation in the heart, as well as of the mechanisms that give rise and maintain cardiac arrhythmias under normal and pathological conditions. Modeling in all the studies reviewed here involved the use of electrical ventricular models of different species (left component in Figure 1A).

As the different sections below describe, whole-heart modeling has often been used to test hypotheses regarding phenomena, the existence of which cannot be proven directly with experimental methods, such as behavior within the depth of the ventricular walls. In testing such hypotheses, whole-heart models constrained and subsequently validated with available experimental data have been used. The predicative capabilities of whole-heart electrophysiological models have been ascertained most frequently with optical or electrical mapping recordings of normal or reentrant propagation on the epicardial surfaces, or with global experimental variables such as, for instance, defibrillation thresholds. With the advent of image-based individual heart models, the expectation is that experiments will be conducted with the same heart from which the model is generated, ensuring an unprecedented match between experimental and simulation results.

Models of Ventricular Propagation
Although the majority of electrophysiological whole-heart applications pertain to the mechanisms of cardiac arrhythmias, there are a handful of studies that have focused on the properties of normal wave propagation in the ventricles, providing insight, which cannot be obtained by experimentation, into the role of organ structure in the patterns of wave propagation and repolarization. Two studies are particularly notable. The study by Samson and Henriquez investigated how heart size (by comparing an MRI-based mouse ventricular model to the University of California, San Diego rabbit model), myocardial properties, and spatial distribution of cell types affect functional action potential duration (APD) dispersion within the ventricular volume. The authors concluded that a larger heart size decreases global electrotonic effects and unmasks intrinsic APD differences between cell types, thus increasing APD dispersion. The second is the recent study by Bishop and coworkers, which used the high-resolution MRI-based Oxford rabbit heart model (Figure 1B, 25 µm raw data resolution). Because the model included blood vessels and endocardial trabeculations, it was used to ascertain the role of these structural heterogeneities in ventricular propagation. Figure 2A illustrates the propagation of a wave front elicited at the apex in this model compared to that in a simplified whole-heart model based on the same imaging data but excluding vessels and trabeculations. The results underscore the regional differences in activation attributable to shortcut pathways and indicate the important role cardiac microstructure could play in impulse propagation.

Models of Ventricular Arrhythmia Mechanisms
Most of the whole-heart models used in the study of arrhythmia mechanisms have focused on the self-sustained reentrant propagation of complex 3D waves. Historically, these were the first applications of whole-heart modeling. Whole-heart modeling studies have revealed important aspects of reentrant arrhythmias that could not have been established via experimentation alone, among which the dynamic characteristics of ventricular fibrillation (VF) and the role of alternans and restitution in arrhythmogenesis.

The first demonstrations that whole-heart modeling of arrhythmias is feasible and tractable came from the Winslow team at Johns Hopkins University (in a series of public presentations approximately 10 years ago) and from the work of Panfilov and Keener at the University of Utah. In the latter, the authors developed a 3D model of scroll-wave activation using the Auckland canine geometry and the 2-variable FitzHugh–Nagumo model of cellular kinetics. The study demonstrated that the organizing centers (filaments) of reentrant activity in the structurally normal heart could be maintained entirely within the myocardial wall, manifesting themselves as focal sources on the surfaces. The same model was subsequently used to propose that whereas in small hearts (mice, rabbits), a single rapidly drifting and meandering rotor could underlie VF, in large hearts, including those of humans, VF could be sustained by numerous coexisting rotors. Panfilov extended this concept by demonstrating, in the same model, that not only the presence of scroll waves but...
also their breakup (dynamical instability) was relevant to VF sustenance. Winslow and coworkers were the first to use models reconstructed from MRI scans\(^3\), using a rabbit heart model, the authors demonstrated that early afterdepolarizations (EADs) can lead to reentrant arrhythmias. The role of the complex ventricular geometry in wave fragmentation and spiral wave breakup was explored by Xie et al.\(^3\). The presence of cardiac microstructure was also found to impact the reentrant wave (Figure 2B),\(^3\) in a manner similar to the way it alters normal propagation.

Whole-heart models have been used extensively in characterizing VF. Clayton and coworkers\(^3\) examined the evolution of VF within the 3D volume of the rabbit and canine ventricles by quantifying the dynamics of the scroll-wave filaments. These studies determined the number of filaments and their lifetimes, and classified their shapes, which depend on the location of the filaments within the ventricles. Furthermore, the number of the scroll-wave filaments in the rabbit ventricles was found to increase in the presence of APD heterogeneity caused by the inward rectifier K\(^+\) current gradient. Although such heterogeneity has been reported to result in mother rotor fibrillation, where VF is driven by a single rapid and stationary rotor in the region of shortest refractory period,\(^3\) it remained unclear how an initial rotor could migrate to this region.\(^3\) This question was answered by the simulation study of Baher et al\(^3\); results from this rabbit whole-heart model demonstrated that the inclusion of short-term memory (effect of pacing history on APD) resulted in spontaneous conversion of multiple-wavelet to mother-rotor fibrillation. Finally, in recent years, advances have been made to characterize VF in the human heart.\(^4\) The geometric data for the model were obtained from histological slices of an ex vivo normal human heart, with fiber architecture mapped from the canine. Intriguingly, modeling results\(^4\) demonstrated that human VF is driven by a small number of reentrant sources (\(\approx 10\)) and is thus much more organized than VF in animal hearts of comparable size (\(\approx 50\) sources). Among the numerous factors examined in this study as contributing to human VF organization, the minimum APD had the largest effect on the number of rotors, a property that differs significantly between the human and large animal hearts.

Electrical alternans, which are beat-to-beat changes in APD, have long been recognized as a precursor to the development of VF. Alternans can be concordant with the entire tissue experiencing the same phase of oscillation, or discordant, with opposite-phase regions distributed throughout the tissue. Over the last decade, much emphasis has been placed on the restitution curve slope as a major factor in both the onset of arrhythmias following the development of discordant alternans, and the dynamic destabilization of reentrant waves, leading to the transition of ventricular tachycardia (VT) into VF. In what has become known as the restitution hypothesis, flattening the APD restitution curve is postulated to inhibit alternans development and subsequent conduction block and prevent the onset of fibrillation.\(^5\) Simulation studies using whole-heart models\(^6\)–\(^10\) have made important contributions to ascertaining the intricate set of mechanisms by and the conditions under which steep APD restitution could lead to VF onset. Using the rabbit ventricular model, Echebarria and Karma\(^11\) demonstrated that in homogenous tissue with steep APD restitution, the transition from concordant to discordant alternans is dynamic, with contributing mechanisms being either a broad conduction velocity restitution or a localized change in pacing period. Furthermore, the study found that a sudden change in pacing rate could initiate discordant alternans in the presence of a spatial gradient in APD restitution without the involvement of conduction velocity restitution. Cherry and Fenton\(^12\) found, using the same model, that electrotropic and memory effects can suppress alternans, prevent conduction block, and stabilize reentrant waves even when APD restitution is steep. Using the human whole-heart model,\(^13\) Keldermann et al.\(^14\) investigated the effect of heterogeneous restitution properties in human VF by incorporating clinically measured APD restitution. The study found that the number of filaments and the excitation periods depended on the extent of restitution heterogeneity. Thus, restitution heterogeneity was found to contribute to VF dynamics complexity. In a follow-up study,\(^15\) the authors found that under heterogeneous APD restitution, both mother-rotor and multiple-wavelet VF could occur in the same heart, indicating that mother-rotor is a possible mechanism of human VF.
Models of Arrhythmias in the Diseased Heart

Whole-heart computational research into arrhythmia mechanisms in the setting of cardiac disease remains in its infancy, and is one of the potential avenues for growth in whole-heart modeling applications. Simulation research into regional ischemia and infarction in the ventricles has charted the initial path in this direction, by providing insights into the role of electrophysiological and structural heterogeneities associated with cardiac disease in arrhythmia generation. The recent study by Jie and Trayanova characterized the substrate for ischemia phase 1B arrhythmias in the rabbit heart (Figure 3A) by examining how the interplay between different degrees of hyperkalemia in the surviving layers, and the level of cellular uncoupling between these layers and the midmyocardium combine with the specific geometry of the ischemic zone in the ventricles to result in reentrant arrhythmias. The study implemented a realistic representation of the ischemic insult (hyperkalemia, acidosis, hypoxia), including its spatial distribution (a central ischemic zone [CIZ] and BZs). It demonstrated a biphasic change in arrhythmia vulnerability with the increase in extracellular potassium concentration. Figure 3A shows the model, as well as the generation of reentry in the subepicardium following the slow propagation of a premature stimulus. Although the surviving subepicardium and subendocardium exhibited the same changes in electrophysiological properties for varying degrees of hyperkalemia, conduction block occurred preferentially in the subendocardium during both pacing and premature stimulation because of geometric factors (Figure 3A), resulting in reentry being formed only in the subepicardium. Furthermore, the simulation results found that a wide BZ reduced the inducibility of reentry by causing a propagation block in CIZ. Finally, the degree of uncoupling between the surviving (epi- and endocardial) layers and the inexcitable midmyocardium was found to profoundly affect reentry initiation: stronger coupling led to shortened APD and lengthened postrepolarization refractory period of the paced propagation, which in turn reduced inducibility of reentry by blocking propagation of the premature wave front.

An example of simulations of infarct-related VT using an MRI-based canine heart model (see Figure 1C) is presented in Figure 3B. The model incorporated experimental data on electrophysiological remodeling in BZ, including altered ionic channel expression and connexin 43 downregulation. Programmed stimulation from the endocardial surface in this model revealed conduction slowing in the BZ giving rise to VT inducibility and reentrant circuit morphology consistent with experimental data. Figure 3B illustrates epicardial and intramural views of the activation patterns during ventricular tachycardia induction from an endocardial pacing site near the apex. The simulation results demonstrated that the organizing center of infarct-related VT is located within the BZ, regardless of the pacing site from which VT is induced. This result has important implications for ablation of infarct-related VT; further simulation studies on the subject are expected to provide simulation guidance of VT ablation in patients.

Ventricular Models of Arrhythmia Initiation With Electrical Shocks and Defibrillation

Ventricular models incorporating realistic geometry have also been used to examine the mechanisms by which a defibrilla-

Figure 3. Arrhythmias in ischemia and infarction. A, Arrhythmogenic substrate in ischemia phase 1B. Left, Model of ischemia phase 1B following left anterior descending arterial occlusion in the rabbit heart, with CIZ and BZ. Colors distinguish the regions. White dashes outline BZ. Asterisk indicates the stimulus site. BZs for different ischemic parameters are also shown. Right, Generation of reentry in the subepicardium following propagation of premature stimulus in myocardium uncoupled from the surviving endo- and epicardium. Activation maps on the anterior epicardial surface and in a cross-section across the LV are shown. S2 and R refer to activation maps for the premature and the first reentrant beats, respectively. Black asterisk indicates reentry exit site. Figure modified from Jie and Trayanova. B, Infarct-related VT in the canine heart. Left, MRI-based model of the infarcted canine heart with scar and BZ. Other panels, Activation maps of VT following programmed stimulation. Arrows indicate direction of propagation.
tation shock induces arrhythmia and defibrillates (terminates VF) in the heart. Whole-heart modeling research has proven particularly indispensable in uncovering these mechanisms because the electrical shock induces virtual electrode polarization in the heart that is a function of organ structure, a relationship which is difficult to tease out by experimentation. These models are accompanied by further complexities, because they require the use of the bidomain representation of cardiac tissue (see section on model components above). Research devoted to the numerical aspects of bidomain modeling is reviewed in the Online Data Supplement.

A series of studies from the Trayanova group was devoted to determining the mechanisms by which a defibrillation shock fails or succeeds in terminating VF. The bidomain model of the rabbit ventricles with monophasic shocks in the same model, Rodriguez et al.57,58 demonstrated that shock outcome and the type of postshock arrhythmia induced by the shock depend on the location of the intramural postshock excitable area formed by shock-induced deexcitation of previously refractory myocardium.

The article by Ashihara et al59 extended these findings in the rabbit ventricles to propose a new theory of postshock propagation and shock-induced arrhythmogenesis. The authors suggested that the mechanism that underlies the quiescent period (this period is termed the isoelectric window) following strong shocks, of strength near the upper limit of vulnerability or the defibrillation threshold (DFT), is attributable to “tunnel propagation” of postshock activations through intramural excitable areas. Figure 4A demonstrates this concept for biphasic shocks delivered by external electrodes. Formation of virtual electrode polarization, quick reexcitation, and synchronous repolarization took place sequentially. However, a wave front that originated deep within the wall remained submerged, giving rise to an isoelectric window, until it broke through onto the epicardium and propagated, resulting in intramural reentry.

This new theory was extended to explain the mechanisms responsible for the existence of isoelectric window following ICD (implantable cardioverter–defibrillator) shocks delivered to the fibrillating heart in a recent article by Constantino et al.60 The simulation results demonstrated that the nonuniform field created by ICD electrodes, combined with the fiber orientation and complex geometry of the ventricles, resulted in a postshock excitable region located always in the left ventricular (LV) free wall, regardless of preshock state. For near-DFT shocks, this excitable region was converted into an intramural tunnel (Figure 4B), through which either preexisting fibrillatory or shock-induced wave fronts propagated during the isoelectric window, emerging as breakthroughs on the LV epicardium. Interestingly, failed defibrillation for near-DFT shocks was found to not always be associated with termination of existing wave fronts and generation of new wave fronts by the shock, as previously believed; instead, wave fronts remained “alive” in the intramural postshock tunnel. Preshock activity within the LV played a significant role in shock outcome: a large number of preshock filaments resulted in an isoelectric window associated with tunnel propagation of preexisting rather than shock-induced wave fronts. Furthermore, shocks were more likely to succeed if the LV excitable area was smaller. Obtaining such insights into the mechanisms of defibrillation would have been impossible with the use of experimentation alone.

The mechanisms underlying initiation of postshock arrhythmias with electrical shocks under the conditions of global ischemia have also been studied using the same rabbit ventricular bidomain model.61

Ventricular Models Incorporating the Purkinje System

The ability to combine a model representation of the Purkinje system with the complex structure of the ventricles provided new opportunities to understand arrhythmogenesis, and specifically, the contribution of Purkinje to the initiation and maintenance of reentry. The first simulation study to incorporate the Purkinje system in a whole-heart model was by...
Berenfeld and Jalife.\textsuperscript{62} The authors converted the Auckland canine model into an isotropic finite-difference mesh; the His bundle branches and the Purkinje system were digitized from anatomic data and superimposed over the endocardium. The end points of the Purkinje system in each ventricle were assigned as Purkinje–ventricular junctions. The model was used to test the hypothesis that Purkinje–ventricular junctions might be responsible for focal subendocardial activations during complex tachyarrhythmias. Reentrant activity involving muscle and the Purkinje was simulated, demonstrating that the reentry pattern evolved with drifting epicardial breakthroughs and transformed on the endocardium from focal activity to figure-of-eight reentry. The reentry terminated if the Purkinje system was disconnected from the muscle before it reached a relative steady state. Thus, the study concluded that the Purkinje system may have a double role in the evolution of reentry: first, it is essential at the initial stages of reentry; and second, it may lead to intramural reentry, which, once formed, is no longer dependent on the Purkinje system.

The Vigmond laboratory recently developed a new sophisticated model of the His-Purkinje system\textsuperscript{63} and incorporated it in the University of California, San Diego rabbit ventricular model. The Purkinje system was modeled as free-running, consisting of 1D fibers (cubic Hermite elements), separated by gap junctions. This representation allows the study not only the role of the network in arrhythmogenesis, but also of its possible involvement in defibrillation and postshock reentry. Defibrillation studies using this model demonstrated that shocks induced focal activations in the His-Purkinje system\textsuperscript{64}; Purkinje fibers were found responsible for reentry initiation at low shock strengths.\textsuperscript{55,65} A recent study by Deo et al\textsuperscript{66} using this model focused on examining the conditions for arrhythmogenesis attributable to EADs originating in Purkinje cells; the latter are known to be are more vulnerable to EADs than ventricular myocytes. The authors demonstrated that a single ectopic beat arising from EAD in the distal Purkinje network can give rise to reentrant arrhythmia; in contrast, EADs in the proximal network were unable to initiate reentry. The contribution of the Purkinje system during arrhythmias\textsuperscript{67} in a heart where the Purkinje fibers penetrate the ventricular wall and reach the subendocardium, such as in the pig, is illustrated in Figure 5. The transient local refractoriness created at these sites is sufficient to split propagating waves and provide epicardial anchor points for the transmural scroll waves (40 ms) (arrow). Successful breakthroughs from excited Purkinje terminals act as secondary sources, accelerating wave fronts and providing escape routes for activity within the Purkinje system (140 ms) (dashed circles).

\section*{Whole-Heart Models of Fluorescent Recording in the Heart}

An interesting application of whole-heart modeling examined the role of photon scattering in signal distortion during optical mapping of cardiac electrical activity. Understanding the sources of this distortion is important for the correct interpretation of fluorescent mapping results and provides a common ground for comparison between experiment and simulation regarding the distribution of transmembrane potential during arrhythmias and defibrillation. Simulation studies\textsuperscript{68–71} combined the rabbit ventricular model with a 3D model of photon scattering. Model results demonstrated that that distortion in the optical signal as a result of photon scattering is truly a 3D phenomenon and depends critically on the geometry of the ventricles, the direction of wave front propagation, and the specifics of the experimental setup. Figure 6A presents results from these simulation experiments. The studies found that photon scattering was responsible for optical signal characteristics such as dual-humps, elevated
resting potentials and reduced action potential amplitudes near the reentrant core (Figure 6A, left), and for underestimation of both the number of surface phase singularities (Figure 6A, right) and the virtual electrode polarization magnitude on the epicardium.

**Cardiac Electromechanics Applications**

The coupling between electrical and mechanical events in the heart is an active area of research. Experimental and clinical research has demonstrated that the mechanical activity of the heart, in health and disease, affects cardiac electrophysiology. For instance, disturbances in heart rhythm are often attributable to mechanolectric coupling mechanisms in combination with those associated with remodeling in heart disease. Below, is a review of the applications of whole-heart models in cardiac electromechanics, with emphasis on simulations of arrhythmogenesis originating from mechanical stimuli and mechanolectric coupling, as well as those focusing on electromechanical dyssynchrony and cardiac resynchronization therapy. Simulation research reviewed here involved the use of the electromechanical models of the type shown in Figure 1A, with cellular ionic and myofilament models of varying complexity and of different species, where the models have been constrained and validated with experimental measurements, typically strain and hemodynamic data. Studies of cardiac biomechanics only in health and disease, a rich and important field in itself, where whole-heart modeling has been broadly used, are outside of the scope of this review.

**Models of Stretch-Related Ventricular Arrhythmias**

One of the most important mechanism of mechanolectric coupling is the existence of sarcolemmal channels that are activated by mechanical stimuli. A variety of ionic channels activated by changes in cell volume or cell stretch have been identified in cardiac tissue. Of these, stretch-activated channels (SACs), either nonselective or potassium-selective, have long been implicated as important contributors to the proarrhythmic substrate in the heart. The nonuniform distribution of positive myofiber strain (stretching) during mechanical contraction under a variety of pathological conditions could produce, via SAC, a proarrhythmic dispersion in electrophysiological properties. SACs have been shown to shorten or lengthen APD of a single myocyte or produce ectopic beats depending on the timing of the mechanical stimulus application relative to the phase of the action potential. However, uncovering the mechanisms by which SACs contribute to ventricular arrhythmogenesis under a variety of pathological conditions is hampered by the lack of experimental methodologies that can record the 3D electrical and mechanical activity simultaneously and with high spatiotemporal resolution. Thus, computer simulations have emerged as a valuable tool to dissect the mechanisms by which SAC contribute to the ventricular arrhythmogenic substrate.

The first modeling attempts to address the role of SAC in arrhythmogenesis in the whole heart used pseudoelectromechanical models, in which mechanical activity (and, specifically, mechanical impact) was not represented, but its effect on ventricular electrophysiology was, through the recruitment of SAC. The study by Li et al examined the mechanisms by which mechanical impact to the precordial region of the chest (commotio cordis) can lead to arrhythmias. The study used the rabbit ventricular model, in which the mechanical impact was “delivered” to (ie, SAC were assumed open in) a predefined (nearly semispherical) region of the ventricles during repolarization; the dimension of impact was scaled from baseball impacts in man or in pig experimental models to that of rabbit. Despite the simplified representations, this study explained how SAC recruitment in commotio cordis leads to the establishment of ventricular arrhythmias in a narrow time interval during the T-wave.

Because ventricular arrhythmia can be initiated by a mechanical impact, it can also be terminated by it. A similar pseudoelectromechanical model was used to elucidate the mechanisms for termination of arrhythmia by precordial thump under normal and globally ischemic conditions and to determine the reasons for the decreased efficacy of precordial thump in global ischemia. The study demonstrated that increased mechanosenstivity of the K<sub>ATP</sub> channels in ische-
Decoupled mechanical and electrophysiological ventricular rabbit models were used by Li et al.\textsuperscript{79} to uncover the mechanisms for the experimentally observed increase in postshock arrhythmogenesis and elevated DFT in hearts with ventricular dilation.\textsuperscript{80} The study involved a 2-step approach: acute dilation was simulated in a model of ventricular mechanics\textsuperscript{44}; the output of the mechanics model (dilated ventricular geometry with corresponding fiber orientation and strain distributions) was used in the electrophysiological model of defibrillation. The research tested the hypothesis that SAC recruitment and deformations in organ shape and fiber architecture lead to increased arrhythmogenesis following electrical shocks. Results showed that dilation-induced deformation alone did not increase vulnerability to arrhythmia induction by shocks, whereas SAC recruitment increased vulnerability by 37%. The heterogeneous activation of SAC was found to be the main reason for increased vulnerability to electrical shocks because it caused dispersion of electrophysiological properties in the tissue.

True electromechanical models aimed at examining the mechanisms for mechanically mediated arrhythmogenesis are only very recent; in fact, the only 2 ventricular studies in existence were published in 2010. The first is by Keldermann,\textsuperscript{81} who used an electromechanical model of the human LV to investigate the effect of mechanoelectric coupling via SAC on reentrant wave stability. The simulation results revealed that mechanoelectric coupling results in the deterioration of stable reentrant waves into turbulent patterns characteristic of VF (Figure 6B, left). Although the initial scroll wave was found to remain intact, other filaments existed for a short period only (Figure 6B, right). Filament breakup was attributable to SAC recruitment in regions of high fiber stretch (away from the spiral core), resulting in voltage-dependent inactivation of sodium channels there, a mechanism for breakup that is different from other known mechanisms for wave break such as restitution.\textsuperscript{42–47} The simulations results thus provided an alternative explanation for the degeneration of VT into VF.

The mechanisms of spontaneous induction of arrhythmias in the diseased heart was the subject of the second electromechanical study, by Jie et al.\textsuperscript{82} It used a model of the beating rabbit ventricles to gain insight into the role of electromechanical dysfunction in arrhythmogenesis during acute regional ischemia, both in the induction of ventricular premature beats (VPBs) and in their subsequent degeneration into ventricular arrhythmia. The model had CIZ and BZ and represented the electrophysiological and mechanical milieu in the heart at several stages postocclusion. Dynamic mechanoelectric feedback was represented via spatially and temporally nonuniform membrane currents through SACs, the conductances of which depended on local fiber strain rate, $\text{d}E_{\text{f}}/\text{dt}$. Figure 7 presents the essential findings in the study. Figure 7A illustrates the spatial distribution of strain in the fiber direction in the normal and ischemic ventricles (4 minutes postocclusion) during systole. Large myofiber strain developed in the ischemic region. Figure 7B depicts VPB induction in the ischemic heart. VPB originated from 2 locations around the endocardial LV BZ (arrows in 191-ms inset), propagated intramurally in the apical region (195 ms), with the wave front enclosed by the ellipse making the first breakthrough onto the epicardium, followed by the other wave front (enclosed by the square), because the latter propagated across a thicker wall portion. Both epicardial breakthrough sites were located close to the anterior ischemic border, consistent with experimental findings.\textsuperscript{83} Figure 7C presents action potentials recorded at sites 1 (in BZ) and 2 (in CIZ) in the 191-ms inset. At both sites, cells underwent mechanically induced delayed afterdepolarization–like events following the paced beat. At site 1 (BZ), the depolarization (solid arrow) evoked spontaneous firing. At site 2, despite the fact that the peak magnitude of subthreshold depolarization (dashed circle) was larger, no action potential was triggered because of decreased excitability in CIZ. The VPB wave front blocked within CIZ (Figure 7D, top), resulting in reentry. The study also dissected the contribution of the electro-
physiological factors (the ischemic changes) and mechanical factors (SAC recruitment) to the generation of proarrhythmic substrate (Figure 7D, middle and bottom), demonstrating that VPB cannot degrade into reentrant arrhythmia under the conditions of either electrophysiologically (No_SAC) or mechanically (No_Ischemia) induced proarrhythmic substrate alone. The results of this study clearly demonstrate that stretch of ischemic tissue, which loses its ability to contract, by the surrounding normal tissue during contraction leads to mechanically induced depolarizations, via SAC, in the ischemic region. Mechanically induced VPBs originated from the ischemic border in the LV endocardium, initiating reentry. The study by Jie et al82 thus provided the first direct evidence that mechanically induced depolarizations and their spatial distribution within the ischemic region are a possible mechanism by which mechanical activity contributes to the origin of spontaneous arrhythmias.

Modeling the Electromechanical Activation Sequence and Electromechanical Feedback Mechanisms in the Normal Heart

The mechanical effect of altered cardiac activation sequence has been the subject of intense discussion because asynchronous electrical activation can cause abnormalities in perfusion and pump function. Whole-heart simulations have played an important role in understanding the relationship between the spatiotemporal pattern of electrical activation and the local sequence of mechanical strain, which is of paramount importance in optimizing the sequence of electrical activation in the diseased heart aimed at achieving maximum pump performance. The study by Usyk and McCulloch84 was the first attempt to examine, using a canine heart electromechanical model, the delay between the onsets of electrical activation and fiber shortening (electromechanical delay [EMD]) in sinus rhythm and LV pacing, assuming homogeneous excitation–contraction latency throughout the ventricles. This early biophysically simplified model (the first whole-heart electromechanical model) found EMD to vary throughout the ventricles, with both positive and negative values, indicating the possibility of fiber shortening before depolarization. Following this first effort, electromechanical models have been adjusted and enriched with experimental data.85,86 The recent study by Gurev et al87 conducted a thorough analysis of the 3D EMD distribution in the rabbit ventricles and its dependence on the loading conditions. To isolate the effect of the pattern of electrical activation on EMD, simulations were executed for sinus rhythm and LV epicardial pacing with homogeneous distribution of excitation–contraction latency; this whole-heart model incorporated the biophysical representation of myofilament dynamics by Rice et al.7 The results revealed that under both activation scenarios, EMD distribution is nonuniform (Figure 8A). Consistent with experimental results,88 in sinus rhythm, EMD is longer at epi- than at endocardium and is greater near the base than at the apex. Following epicardial pacing, EMD distribution is markedly different and changes with pacing rate. Analysis of the mechanisms revealed that for both electrical activation sequences, late-depolarized regions were characterized with significant myofiber prestretch caused by the contraction of the early-depolarized regions (Figure 8B and 8C). This prestretch delays myofiber-shortening onset and results in longer EMD, giving rise to heterogeneous EMD distributions. This study revealed that the loading conditions of the ventricles play an important role in the relationship between electrical and mechanical activation. Understanding the latter relationship is of paramount importance to therapies that use pacing of the heart and particularly cardiac resynchronization therapy (CRT).

The effects of transmural heterogeneity of electrophysiological properties and excitation–contraction coupling in determining LV function was the subject of 2 simulation studies, which concluded that inclusion of transmural heterogeneity in APD 1) had a profound effect on reducing
sarcomere length transmural dispersion during repolarization and impacted predominantly local deformation, particularly during early systole. These studies illustrate the importance of accounting for physiological complexity in the heart in the modeling efforts to establish the mechanisms governing the normal heart functioning.

The heart achieves an efficient coordinated contraction via a complex network of feedback mechanisms that span the hierarchy of biological complexity. The study by Niederer and Smith used a rat LV electromechanical model to explore how feedback loops regulate normal contraction. The relative roles of 4 tension and deformation feedback mechanisms were examined: length-dependent change in calcium sensitivity, filament overlap, tension-dependent binding of calcium to troponin C, and velocity-dependent cross bridge kinetics. Length-dependent changes in calcium sensitivity and filament overlap, which constitute the Frank–Starling law, were found to be the 2 dominant regulators of the efficient transduction of work. The absence of either mechanism not only altered the spatial distribution of stress and strain but also determined the transmural variation in work. These results showed that feedback from muscle length to tension generation at the cellular level is an important control mechanism of pumping efficiency.

**Electromechanical Models of Cardiac Resynchronization Therapy in the Failing Heart**

Heart failure patients often exhibit dyssynchrony in contraction, which diminishes the systolic function of the heart. CRT, the treatment modality that uses biventricular pacing to resynchronize the contraction of the heart, is a valuable therapeutic option for such patients. CRT has been shown to improve heart failure symptoms and reduce hospitalization, yet approximately 35% of patients fail to respond to the therapy. The poor predictive capability of existing approaches to identify potential responders to CRT reflects the incomplete understanding of the complex pathophysiological and electromechanical factors that underlie mechanical dyssynchrony in failing hearts. Simulations of whole-heart electromechanical behavior offer an opportunity to dissect these mechanisms and suggest strategies for optimizing the therapy. Usyk and McCulloch expanded their model to incorporate dilation characteristic of heart failure and demonstrated that it could be used to model CRT under the conditions of left bundle branch block (LBBB). Because a large portion of CRT nonresponders are heart failure patients with chronic myocardial infarction, ascertaining the impact of the infarct on cardiac dyssynchrony and resynchronization is an important aspect of optimizing CRT. The simulation study by Kerckhoffs et al demonstrated, as anticipated, that increased infarct scar size diminishes the improvement of ventricular function following biventricular CRT in the LBBB failing heart. Further simulation efforts are well poised to determine the mechanisms by which infarct location and scar transmurality each contribute to diminished CRT efficacy and the insights could be used to predict an optimal placement of the LV pacing electrode in patients with myocardial infarction.

A recent study by Kerckhoffs et al focused the CRT modeling effort toward assessing the sensitivity, to cardiac dysfunction, of various indices of mechanical dyssynchrony used to quantify contractile dysfunction in patients, such as circumferential uniformity ratio estimate (CURE), internal stretch fraction (ISF), and the percentile range of time to peak shortening (percentile range of time to peak shortening). CURE and ISF are indices that measure distribution of strain magnitudes, whereas percentile range of time to peak shortening measures distribution of strain timing. The basic model was the same as in the study by Usyk and McCulloch but additionally represented heart failure via dilation, dyssynchronous activation (ie, LBBB), decreased inotropy, and prolonged relaxation. All indices were found sensitive to the activation sequence, but only CURE and ISF were sensitive to the combination of dilation and LBBB, a condition typically present in patients receiving CRT, whereas percentile range of time to peak shortening was not. Thus, CURE and ISF, which measure systolic strain nonuniformity, are better predictors of mechanical dyssynchrony because systolic strain nonuniformity, as this modeling study demonstrated, is the dominant determinant of variability in regional work. The results obtained by Kerckhoffs et al have also important implications for the emerging field of patient-specific modeling and, in particular, for patient-specific optimization of the LV pacing location for CRT. With geometry and electrical activation sequence, which can be established by a clinical evaluation, being the major determinants of regional cardiac function, and the hard-to-measure material properties playing a minor role, patient-specific simulations could be performed to suggest optimal CRT tailored to the individual. Work in this direction has begun with the development of MRI-based models of cardiac electromechanical function.

**Directions for Future Whole-Heart Modeling Research**

The whole-heart modeling research efforts reviewed above demonstrate the enormous progress that has been made over the last decade in using whole-heart computational approaches to address both the mechanisms of cardiac dysfunction, as well as issues related to the clinical application of therapies for cardiac disease. In the years to come, this role of whole-heart modeling will be broadened and enriched. The advancement of whole-heart modeling will be strongly dependent on concomitant developments in experimental methodologies, which can provide data to constrain, enrich, and validate the models. Of particular importance to whole-heart modeling will be the capability to better resolve the structural features of the intact heart, by developing methods to characterize complex tissue geometries and specifically, structural remodeling in disease, eg, ischemic cardiomyopathy and fibrosis. The development of unique and sensitive probes for the architecture of cardiac tissues, including tractography and connectivity mapping techniques, will provide a significant impetus to the whole-heart modeling efforts. It will enhance their ability to make significant contributions to the field of cardiac electrophysiology and electromechanics and to the clinical practice of cardiology.

Below is a summary of the future developments that could be envisioned for the field of whole-heart simulation and modeling.
Integration of the Understanding of Cardiac Function in Health and Disease Across the Physical Scales of Increasing Complexity, From Molecule to Cell, Tissue, the Whole Heart, and Ultimately the Patient

The essential role of whole-heart modeling and simulation will be broadened to include not only assisting hypothesis-driven research but also providing the framework for the unification of diverse experimental findings. The goal is to provide a quantitative understanding of the mechanisms of cardiac rhythm and pump dysfunctions, with the heart as a global dynamic system, and at all levels, from the genes to the patient. This involves bridging the spatial and temporal scales, from nanometer to meter, and from nanoseconds to minutes or hours. Furthermore, to address the contribution of various factors to the origin of cardiac dysfunction, simulations will increasingly become multiphysics. For instance, in examining the mechanisms for arrhythmogenesis in cardiac disease, factors stemming from soft tissue mechanics and fluid dynamics will need to be accounted for. Finally, the relationship between structure and function at the various levels of structural complexity in the heart will have to be incorporated in a comprehensive manner.

Providing the Formal and Quantitative Means of Extrapolating Mechanisms From Animal Models of Cardiac Dysfunction to the Human Heart

Although this role of whole-heart simulations and computational approaches is strongly linked to the one described above, it also has its own unique challenge: the lack of availability of human data, at any level of structural complexity, that can inform and constrain the models of human cardiac arrhythmia mechanisms or contractile dysfunction. Future simulations and whole-heart modeling approaches will thus have to play a major role in integrating knowledge, albeit scarce, about the human heart with insights obtained from animal studies, to be able to extrapolate mechanisms that could be at work in the human heart, in both health and disease.

Serving as a Test Bed for New Therapies and a Vehicle for the Development of New Diagnostic Modalities

The augmented role of cardiac modeling in the development of new therapies for cardiac dysfunction and diagnostic modalities arises from its function as the framework that unifies diverse cardiac electrophysiology and electromechanics insight. Multiscale, multiphysics models that incorporate electromechanical and structural remodeling in cardiac disease will serve as the first line of screening of new therapies and approaches, including pharmacological interventions. Furthermore, riding on the heels of diagnostic developments in examining the mechanisms for arrhythmogenesis in cardiac disease, factors stemming from soft tissue mechanics and fluid dynamics will need to be accounted for. Finally, the relationship between structure and function at the various levels of structural complexity in the heart will have to be incorporated in a comprehensive manner.

Patient-Specific Approaches to Analysis and Treatment of Heart Rhythm Disturbances and Contractile Dysfunction

As imaging modalities are becoming more prevalent in patient evaluation, a wealth of patient-specific cardiac structural and functional data are rapidly becoming available. Today, we stand at the threshold of a new era in cardiac modeling and simulation: anatomically detailed, tomographically reconstructed models of patient hearts are beginning to be developed that have the potential to integrate patient-specific information from the ion channel to the electromechanical interactions in the intact heart. The use of models in tailor-made diagnosis, treatment planning, and prevention of sudden cardiac death will slowly become a reality. Currently, researchers face numerous obstacles in the development of patient-specific heart models, among which the low resolution of the in vivo heart scans, the present impossibility of acquiring patient-specific fiber orientation, issues with segmenting out structural remodeling in the patient heart such as the infarct, and, finally, difficulties in validating these models with ECGs and patient electrophysiological data. Furthermore, the advancement of algorithms and approaches for high-speed simulations (see below) is of critical importance in order for these approaches to become clinical reality.

New Emphasis on the Development of Modeling Tools and Techniques

Such emphasis will result in the ability to incorporate fine-grained cardiac structural and functional data and will enable models to run in a period of time appropriate for clinical applications. As described in the Online Data Supplement, research efforts are being invested in dramatically improving the parallel scalability of biophysically detailed whole-heart models; new data demonstrate that a single human heartbeat in such a model can be simulated in only 4 minutes. Furthermore, the best approaches to modularize and interface multiple model levels, as well as to preserve and curate model and data in easy-access repositories, need to be determined.

Development of Interfaces That Allow Model Utilization by Nonexperts

The development and use of electrophysiological and electromechanics models of the heart currently requires a great amount of expertise in a number of different fields such as numerical analysis, computer science, cardiac electrophysiology and mechanics, medicine, and, lately, image processing. Taking advantage, by the broader community, of the new developments in whole-heart modeling and the ability of the latter to integrate data from different scales remains, however, a challenge. Despite some efforts to open source models to the community by the original developers, the process has been hampered by lack of adequate training of the research community in using currently available computational tools, models, and visualization; by time-consuming and cumbersome infrastructures; and by interfaces, if any, that are outright unfriendly. Efforts must be supported to develop user-friendly web-based computing infrastructure for research in heart electrophysiology and electromechanics that could serve as a virtual research environment for the entire community. This infrastructure should allow the direct input of cardiac structural imaging data and the ability to easily assemble models with the click of the mouse.

Biophysically based computational modeling of the heart, applied to human heart physiology and the diagnosis and treatment of cardiac disease, will revolutionize 21st century cardiac research and the field of cardiology. The future that awaits us is exciting.
Acknowledgments

N.A.T. gratefully acknowledges the help of her doctoral students Jason Constantino, Hermenegild Arevalo, and Jason Bayer in the preparation of the manuscript and the significant contribution of Dr Gernot Plank, Medical University of Graz, Austria, to the Online Data Supplement.

Sources of Funding

Supported by NIH grant R01-HLO82729 and National Science Foundation grant CBET-0933029.

Disclosures

N.A.T. is a cofounder of CardioSolv LLC. CardioSolv was not involved in this research.

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Circ Res. 2011;108:113-128
doi: 10.1161/CIRCRESAHA.110.223610
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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Numerical Solutions of the Electrical Problem in the Heart

The Bidomain Equations

The bidomain equations represent the most general description of electrical behavior in the cardiac syncytium. In the elliptic-parabolic form they are given by

$$
\begin{bmatrix}
-\nabla \cdot (\sigma_i + \sigma_e) \nabla \phi_e \\
-\nabla \cdot \sigma_b \nabla \phi_e
\end{bmatrix} =
\begin{bmatrix}
\nabla \cdot \sigma_i \nabla V_m + I_{ei} \\
I_{eb}
\end{bmatrix}
$$

(1)

$$
\beta C_m \frac{dV_m}{dt} = (\nabla \cdot \sigma_i \nabla \phi_i) - \beta (I_{ion}(V_m, \eta) - I_r)
$$

(2)

$$
\frac{d\eta}{dt} = g(V_m, \eta)
$$

(3)

where $\phi_i$ and $\phi_e$ are the intracellular and interstitial/extracellular potentials, respectively, $V_m = \phi_i - \phi_e$ is the transmembrane voltage, $\sigma_i$ and $\sigma_e$ are the intracellular and interstitial conductivity tensors, respectively, and $\sigma_b$ the conductivity of a fluid surrounding the tissue, $\beta$ is the membrane surface to volume ratio, $I_{ei}$ and $I_{eb}$ are extracellular stimuli applied in the interstitial space or the bath, respectively, $I_r$ is a transmembrane stimulus, $C_m$ is the membrane capacitance per unit area, and $I_{ion}$ is the membrane ionic current density which depends on $V_m$ and a set of state variables $\eta$ through a non-linear function $g$. At tissue boundaries, no flux boundary conditions are imposed on $\phi_i$, with $\phi_e$ being continuous. At the boundaries of the conductive bath, no flux boundary conditions are imposed on $\phi_e$. Assuming that the extracellular space is grounded (i.e. $\phi_e = 0$) reduces the bidomain equations to a monodomain.

Numerical Solution

The nature of cardiac bioelectric activity necessitates very fine spatio-temporal resolutions and long observation periods, which renders in-silico experimentation based on the bidomain equations a computationally expensive endeavor. Typically, organ level simulations involve 1 to 50 million grid points, and the solution has to be evolved over tens of thousands of time steps. Such high computational demands can be dealt with in an efficient manner only when using advanced numerical techniques and parallel computing approaches. However, even with current supercomputing facilities, execution times are significant, lagging real-time by roughly a factor of $10^3$ to $10^4$, respectively.\(^1\)

The bidomain equations can be solved either directly as a coupled system\(^2, 3\) or in a decoupled form, where operator splitting techniques are applied to break up the solution scheme into a set of smaller systems solved sequentially. Among the splitting techniques the Strang approach is popular due to the smaller splitting error, which renders the overall scheme second order accurate.\(^4, 5\) When applied to the bidomain equations in the elliptic-parabolic form as in Eqs.(1)-(2), the solver scheme decouples into three major blocks, two linear systems corresponding to the solution of the elliptic (1) and parabolic (2) PDEs, and the solution of the set of ODEs describing cellular dynamics (3).
All major spatial discretization techniques, the finite difference method (FDM), the finite volume method (FVM) and the finite element method (FEM), have been applied to the bidomain problem. Where in earlier studies the FDM was preferred, owing to its ease of use, recent studies have implemented the more advanced FEM,\textsuperscript{2, 6} or FVM,\textsuperscript{7, 8} since they are better suited to handle complex geometries and boundary conditions. The choice of temporal discretization method is governed by stability and accuracy considerations where, in general, accuracy constraints are the limiting factor. Fully implicit schemes have been suggested, but are too expensive with biophysically realistic ionic models.\textsuperscript{9} Implicit-explicit (IMEX) methods,\textsuperscript{2, 4, 5, 10} where diffusion terms are treated implicitly and reaction terms explicitly, are a popular choice for finer grids, whereas explicit schemes are advantageous on coarser grids, since computational cost is less, scalability is better as compared to IMEX or fully implicit methods, and no time stepping penalties incur.

When solving the bidomain equations with IMEX schemes, the solution of the elliptic PDE and the set of ODEs tend to dominate computations, with the solution of the parabolic PDE being of lesser concern. For solving the linear systems either direct or iterative solvers are employed, with matrix factorization costs, iteration costs, speed of convergence, memory costs, and parallel scalability being the key metrics. For smaller, 1D or 2D problems, direct methods have been popular, but for 3D problems they are not competitive due to excessive memory usage and inferior parallel scalability. Among the iterative methods, Krylov subspace methods, such as the Conjugate Gradient (CG) method, with various preconditioners have been established as the standard technique. The utility of CG depends, to a large extent, on performance and scalability of the preconditioner. Using an incomplete LU (ILU) or incomplete Cholesky (ICC) preconditioner for CG has been a standard choice for solving (1),\textsuperscript{2} although a fairly large number (hundreds) of iterations is required to achieve convergence of the solution. The reason for the slow convergence stems from the general weakness of many iterative methods in smoothing the low-frequency error components. Multigrid techniques were specifically designed to overcome this weakness by projecting residuals onto a coarser space, where low frequency components of the error can be dealt with more efficiently. It was demonstrated, in the context of the bidomain equations,\textsuperscript{9-12} that multigrid and multilevel techniques indeed lead to significant performance gains. For instance, when solving (1), a generally applicable algebraic multigrid preconditioner with CG (AMG-CG) reduces the number of iterations per solver step by almost two orders of magnitude compared to ILU-CG. Although a single iteration with AMG is significantly more expensive than with ILU, the dramatic reduction in the number of iterations yields an overall performance gain with a speedup of ~6.\textsuperscript{10} Solving the parabolic PDE (2) is typically less costly. On coarser meshes, where time steps are limited by accuracy constraints, computationally-cheap forward Euler steps can be employed. On finer grids, where stability constraints start to limit time stepping with explicit schemes, IMEX schemes tend to perform better. In this case, the linear system is solved efficiently with fairly cheap preconditioners, at a fraction of the costs of the elliptic PDE, owing to the diagonal dominance of the parabolic system. Nowadays, research efforts are invested in improving the parallel scalability, the main candidate to benefit from the next generation supercomputers. Depending on the problem size, currently used ILU-CG and AMG-CG solvers scale well only up to a moderate number of cores, between 64 and 512,\textsuperscript{1} although with careful domain decomposition and load balancing this limit can be pushed further up to 2000 cores.\textsuperscript{13} A recent study demonstrated strong scalability, of up to 16000 cores, with explicit solvers,\textsuperscript{14} allowing to simulate electrical activity in a human heart while lagging real-time only by a factor of 240, i.e. the simulation of a single heartbeat last only about 4 minutes. Finally, the computational workload of solving the set of ODEs has become negligible in the context of current and, even more so, next generation supercomputers, independently of the complexity of a chosen model of cellular dynamics.\textsuperscript{15} The reason is that state variables in ionic models do not diffuse, which qualifies the ODE solve as an embarrassingly parallel problem. No communication between
processors incurs and thus the parallel scaling is linear. Even when using current biophysically-detailed cellular models, the solution of the ODEs in whole heart simulations is achieved with real-time performance or very close to it.\textsuperscript{16}

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