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Arrhythmogenesis Research: A Perspective from Computational Electrophysiology Viewpoint

Natalia Trayanova and Gernot Plank*

Johns Hopkins University, Baltimore, MD, USA

Abstract

The mechanisms by which arrhythmias are generated in the heart remains a field of intensive research. Recent advances in computational biology and electrophysiology have enabled researchers to use an alternative tool in the study of arrhythmia mechanisms, the multi-scale modeling and simulation of cardiac arrhythmogenesis at the organ level. This article reviews the recent advances and achievements using this approach.

Keywords

Arrhythmias; modeling; bidomain model

Understanding how electric current delivered to the heart to terminate lethal arrhythmias traverses myocardial structures and interacts with wavefronts of fibrillation has been challenging researchers for many years. Of particular importance is insight into the mechanisms by which the shock fails – re-initiation of fibrillation is related not only to the effect of the shock on the electrical state of the myocardium, but also to the intrinsic properties of the tissue that lead to destabilization of post-shock activations and their degradation into electric turbulence. The complexity of the relationships and dependencies to be teased out and dissected in this quest has been staggering. Historically, overwhelming electrical artifacts had prevented researchers from recording during as well as shortly after the shock. A breakthrough in mapping cardiac activity associated with defibrillation occurred during the last decade of the 20th century with the introduction of potentiometric dyes, which allowed continuous recording of activity before, during, and after the shock.

At the same time, the theoretical electrophysiology community adopted a novel modeling methodology, termed the bidomain model. The bidomain model [1] is a continuum representation of the myocardium that takes into consideration current distribution resulting from a particular characteristic of cardiac tissue: the fact that the two spaces comprising the myocardium, the intra- and extracellular, are both anisotropic but to a different degree; the myocardium is thus characterized with ‘unequal anisotropy ratios’. Since the bidomain model accounts for the current flow in the interstitium, it became instantly a powerful modeling tool in the study of stimulation of cardiac tissue (with an eye on defibrillation), where current delivered in the extracellular space finds its way across the membranes of cardiac cells. The first significant achievement of this new approach was the study of the passive (i.e. the ionic currents are not accounted for) shock-induced change in

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*also with University of Graz, Austria

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transmembrane potential following a strong unipolar stimulus. Bidomain simulations by Sepulveda et al. [2] demonstrated that the tissue response in the vicinity of a strong unipolar stimulus involved simultaneous occurrence of positive (depolarizing) and negative (hyperpolarizing) effects in close proximity. This finding of “virtual electrodes” was in stark contrast with the established view that tissue responses should only be depolarizing (hyperpolarizing) if the stimulus was cathodal (anodal). Optical mapping studies that followed convincingly confirmed these theoretical predictions [3]. Since, virtual electrode polarization (VEP) has been documented in experiments and simulations involving various stimulus configurations.

The next big contribution of passive bidomain modeling was the detailed analysis of VEP etiology and its dependence on cardiac tissue structure and the configuration of the applied field; both were shown to be major determinants of the shape, location, polarity, and intensity of the shock-induced polarization [4]. In particular, theoretical considerations led to the recognition of two types of VEP: (1) ‘surface VEP’, which penetrates the ventricular wall over a few cell layers, due to current re-distribution near the boundaries separating myocardium from blood cavity or surrounding bath, and (2) ‘bulk VEP’ throughout the ventricular wall [5]. Analysis of the bidomain equations revealed that a necessary condition for the existence of the bulk VEP is the unequal anisotropy in the myocardium. Sufficient conditions include either spatial non-uniformity in applied electric field, or non-uniformity in tissue architecture, such as fiber curvature, fiber rotation, fiber branching and anastomosis, and local changes in tissue conductivity due to resistive heterogeneities.

How do cells respond to externally-imposed changes in their transmembrane potential, such as those predicted by the bidomain model? The cellular response to shock-induced VEP depends on its magnitude and polarity, as well as on the electrophysiological state of the cell at the time of shock delivery. Action potential duration can be either extended (by positive VEP) or shortened (by negative VEP) to a degree that depends on VEP magnitude and shock timing, with strong negative VEP completely abolishing (de-exciting) the action potential thus creating post-shock excitable areas in the virtual anode regions. Two-dimensional (myocardial sheet) simulations with the bidomain model that incorporated for the first time ionic fluxes through cell membranes (active bidomain modeling) resulted in the recognition of the importance of the distribution of transmembrane potential established by the shock to the origin of the post-shock activations. Roth [6] demonstrated that the close proximity of a deexcited region and a virtual cathode could result in an excitation at shock end (termed “break” excitation, i.e., at the break of the shock); the virtual cathode serves as an electrical stimulus eliciting a regenerative depolarization and a propagating wave in the newly created excitable area. Break excitations arise at the borders between oppositely polarized regions provided that the transmembrane potential gradient across the border spans the threshold for regenerative depolarization. The finding of break excitations, combined with the fact that positive VEP can result in regenerative depolarization in regions where tissue is at or near diastole (“make” excitation; takes place at the onset of the shock), provided the necessary framework for understanding how a defibrillation shock results in the development of new post-shock activations. Additional insight that arose from bidomain considerations and VEP concepts was the recognition that some post-shock activations could originate much later than the end of the shock. These activations were termed VEP-induced propagated graded responses [7] and were shown to occur in regions of intermediate VEP magnitude. While the spatial gradient in transmembrane potential at the borders between oppositely polarized regions is again the stimulus that elicits the post-shock activation, this occurs at an instant much later than shock-end, when the mildly negatively-polarized region repolarizes enough to “pick up” the stimulus. Such delayed activations have been proposed as a mechanism for the isoelectric window, the electrically-quiescent period observed sometimes after a not-so-strong shock.

The outcome of a defibrillation shock (a success or a failure in terminating the wavefronts of fibrillation) depends crucially on the propagation of the newly-formed post-shock excitations through the shock-induced excitable areas. The shock succeeds in extinguishing fibrillatory wavefronts and not initiating new reentry if the excitations manage to traverse the excitable areas before the rest of the myocardium recovers from shock-induced depolarization. Active bidomain simulations in 2D [8] demonstrated that the latency in the onset of these excitations, their propagation velocity through the excitable gaps, and shock-induced extension of refractoriness in the depolarized areas determine how quickly post-shock activity subsides following successful shocks. Vulnerability and defibrillation failure can also stem from the shock-induced VEP. The onset of a break excitation is associated with the formation of a (VEP-induced) phase singularity [9]; it forms at a point along the boundary between shock-induced depolarization and de-excitation and is independent of the pre-shock state of the myocardium. If these phase singularities survive allowing a spiraling wavefront to develop, the shock results in the (re)initiation of reentrant arrhythmia. The establishment of a reentrant arrhythmia in the ventricles thus strongly depends on the anatomical features and geometrical asymmetries of the cardiac chambers, which significantly affect 3D global post-shock propagation.

The further inquiry into the 3D mechanisms governing the failure of defibrillation has been hampered by the inability of current experimental techniques to resolve, with sufficient accuracy, electrical behavior confined to the depth of the ventricles during and after the shock. Mapping the entire epicardial surface of the ventricles, the current state-of-the-art in optical imaging, does not reveal the global 3D activity that follows the shock since activations could propagate intramurally, without a signature on the epicardial surface. Most importantly, as discussed above, there is a dramatic difference between the magnitude and pattern of shock-induced VEP in the surface layers and in the depth of the myocardium. Such differences in VEP could result in different electrophysiological behavior on the surfaces and in depth, with mid-myocardial post-shock activity remaining confined to the depth of the ventricular wall and detached from surface post-shock behavior for stretches of time. A major breakthrough in understanding of these mechanisms came again from bidomain simulations, this time in 3D.

The quest to unravel how shocks could succeed in terminating fibrillation or how they could re-instate arrhythmia has also driven the technological aspects of computer simulations of 3D bidomain activity. In order to be able to simulate post-shock arrhythmogenesis in the ventricles, computational research has managed to overcome tremendous difficulties associated with obtaining solutions of very large systems of unknowns, involving stiff equations and computational meshes of irregular geometry. The results are fascinating [10]. First, active bidomain simulations of activity in the 3D ventricles demonstrated that understanding of shock-induced phenomena acquired in earlier, simpler bidomain studies, such as the causes of the specific pattern of VEP and how the post-shock activations originate, remain valid in the 3D ventricles. Furthermore, these simulations revealed the importance of accounting for the geometry of the ventricular chambers in the quest to understand generation of post-shock arrhythmias (Fig. 1). The difference in the thickness of the ventricular walls is ultimately manifested as a preferential location of the post-shock excitable area; the post-shock excitable areas were shown by these simulations to be always located in the thick left ventricle and septum, but never in the thin right ventricle (Fig. 1A). In addition, the location of the post-shock excitable area determines the types of post-shock reentrant circuits (Fig. 1B). One can speculate that identifying the location of the main post-shock excitable area could be very important for improving clinical defibrillation efficacy since its eradication can be specifically targeted by auxiliary small-magnitude shocks, resulting in a dramatic decrease in defibrillation threshold.

Results from bidomain simulations have also provided important insights into how the 3D post-shock reentrant circuits established soon after a failed shock can further degrade into ventricular fibrillation [11]. The location and type of post-shock scroll-wave filaments (Fig. 1C) play important roles in this process. As demonstrated by the simulations, transitions between the various types of filaments, I, U, and O, are very frequent at the early stages of post-shock activity (first 200–250ms). U-type filaments (a U-type filament is a filament both ends of which are in contact with the same, endo- or epicardial, surface), such as the one shown in Fig. 1C, often dominate post-shock reentrant activity in the left ventricle.

This short expose on the achievements of bidomain modeling clearly demonstrates the importance of using simulation tools as we attempt 1) to unravel the mechanisms by which lethal arrhythmias arise and 2) to learn how to best terminate them. Given the fact that we are now capable of simulating the 3D activity in the ventricles, as shown in Fig. 1, where do we go from here? What will be the new frontier in defibrillation and shock-induced arrhythmogenesis that will be tackled by simulations in the near future? We believe that the set of questions remaining to be addressed in this field include issues regarding the involvement of features of cardiac structure that have been ignored in the “one heart fits all” approach taken in the studies leading to the present state of knowledge. Fig. 2 illustrates our view of the future through an example of a paced activation in a left ventricular wedge from the rabbit heart [12–14]. Cardiac geometry could be acquired from high-resolution MRI data or histological sectioning; the computational mesh is then generated by gray-level thresholding followed by an octree-based meshing technique. In Fig. 2, a cut through the mesh exposes the presence of structural (micro)heterogeneities, such as blood vessels and collagen septa. A paced propagation through the wedge model, in which the myocardium is represented as a bidomain, is also shown; it demonstrates the feasibility of this approach for studying the role of cardiac (micro)structure in arrhythmogenesis and defibrillation. This approach allows us to also focus on the structural remodeling brought on by cardiac disease, such as infarction. Figs. 3 and 4 present the first steps in the reconstruction of the geometry as well as fiber orientation and infarct structure from diffusion tensor MRI. Simulations in cardiac electrophysiology are clearly on the way to an exciting future.

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Figure 1.

Post-shock transmembrane potentials in the rabbit ventricles. Time is counted from the end of the shock. A: VEP at shock-end and activity at 3 and 10 ms post-shock, demonstrating break excitations (small arrows) and propagation through the post-shock excitable areas (encircled region). B: Shock-induced arrhythmia in the rabbit ventricles. White arrows indicate the direction of propagation of the reentrant waves. C: Post-shock scroll-wave filaments (shown in black). The endings of the filaments are colored in white and are in touch with the same surface, the epicardium (U-type filaments). See inset for schematic of filament location.

Figure 2. Reconstruction of a left ventricular wedge from the rabbit heart. A: Segmented MRI stack. B: Computational mesh (inset shows mesh detail). C: Presence of structural heterogeneities, such as blood vessels and collagen septa. D: Propagation of a paced activation in the bidomain wedge. The location of the pacing stimulus is on the top surface of the wedge.

Figure 3.

MRI data for an apical slice of the infarcted rabbit heart. A: T-2-weighted image showing scar tissue in black (yellow arrow) and viable myocardium in gray (red arrow) in the infarct zone. B: Myofiber helix angle map. C: Map of the mean dot-product of local fiber orientation.

Figure 4.

A. Myocardium delineated from the surrounding volume by a logical masking operation derived from the DTMRI stack. B. Segmented tissue: infarct scar is marked in orange, cleft spaces are red, and the myocardium is in the original gray color. C. Segmentation of the volumes surrounding the heart.