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Models of ventricular arrhythmia mechanisms

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Abstract— **The mechanisms that initiate and sustain ventricular arrhythmias in the human heart are clinically important, but hard to study experimentally. In this study, a monodomain model of electrical activation was used to examine how dynamics of electrophysiology at the cell scale influence the surface activation patterns of VF at the tissue scale. Cellular electrophysiology was described with two variants of a phenomenological model of the human ventricular epicardial action potential. The tissue geometry was an 8.0×8.0×1.2 cm 3D tissue slab with axially symmetric anisotropy. In both cases an initial re-entrant wave fragmented into multiple wavelets of activation. The model variant with steep action potential duration restitution produced much more complex activation, with a greater average number of filaments (13.79) than the variant with less steep restitution (3.08). More complex activation was associated with proportionally fewer transmural filaments, and so the average number of epicardial wavefronts and phase singularities per filament was lower. The average number of epicardial phase singularities and wavefronts for the model variant with less steep restitution were consistent with experimental observations in the human heart. This study shows that small changes in cell scale dynamics can have a large influence on the complexity of re-entrant activation in simulated 3D tissue, as well as on the features observed on the epicardial surface.**

I. Introduction

Despite recent developments such as the widespread use of implantable defibrillators, sudden cardiac death resulting from cardiac ventricular arrhythmias remains an important problem in the industrialized world. Over the last 20 years, our understanding of the mechanisms that initiate and sustain ventricular arrhythmias in the heart have benefited from novel experimental techniques such as optical mapping of electrical activation combined with computational models of cardiac electrophysiology. The key advantage of models is that they can provide detailed information that may be difficult or impossible to obtain experimentally.

During a normal heartbeat, electrical activation initiates in the sino-atrial node, and propagates throughout the heart. In contrast, during ventricular tachycardia (VT) and ventricular fibrillation (VF) rapid and self-sustained electrical activation arising in the ventricles overthrows the sino-atrial node. During VF rapid and incoherent electrical activation results in circulatory collapse and death unless a normal rhythm can be restored by defibrillation. The main focus of efforts to understand the mechanisms of VT and VF has been on animal hearts. However, a recent trend has been towards developing models of arrhythmias in the human heart, and these studies combined with experimental work have shown that activation patterns during VF in the human heart may be less complex than in animal hearts because of differences in the dynamic behavior of cells and tissue [1].

The aims of this study were to simulate VF in 3D human ventricular tissue using models with different dynamical behavior, to examine the behavior of surface 2D features in each model, and to compare these with experimental data from the human heart [2, 3].

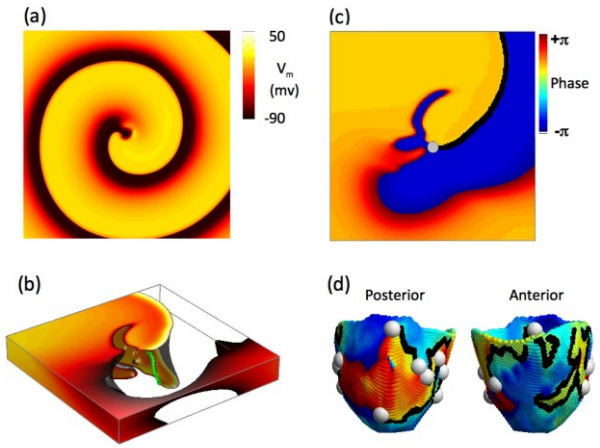

Figure 1. Snapshots of simulated re-entry in (a) 2D sheet, and (b) 3D slab. Color encodes voltage, and in (b) the filament is shown in green. (c) surface view of (b), with color encoding phase, grey disk showing PS, and black line wavefront. (d) snapshot of activation pattern during VF in human heart, data shown are from [3].

II. Background

A. Ventricular Arrhythmia Mechanisms

In the ventricles, arrhythmias may arise from focal activity, where spontaneous electrical activation occurs, or re-entry, where a circulating wave of electrical activation continually propagates into recovering tissue, giving rise to rotating spiral shaped patterns of activation on the tissue surface. VT frequently results from a single re-entrant circuit, which may orbit an anatomical obstacle such as scar. The mechanism of VF in the human heart is consistent with interacting re-entrant waves [2]. The spatiotemporal complexity of electrical activation patterns during VF can be quantified by tracking both the phase singularities (PS) around which re-entrant waves rotate [4], and wavefronts (WF) of activation [5].

B. Models of Arrhythmia Mechanisms

One of the earliest computer models of electrical excitation in cardiac tissue was used to examine possible mechanisms of atrial fibrillation [6], and the level of detail included in cardiac cell and tissue models continues to

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increase [7]. These models have been used to investigate re-entry in idealized 2D and 3D representations of cardiac tissue, as well as anatomically detailed models (Fig. 1 a,b). Experimental observation of arrhythmia mechanisms is usually limited to surface measurements, so an important role for models is to generate 3D patterns that are consistent with 2D experimental observations (Fig. 1 c,d). However, it is important to recognize 2D observations may not be uniquely generated by a single 3D pattern, and so ways of quantifying surface complexity, such as PS, are valuable tools.

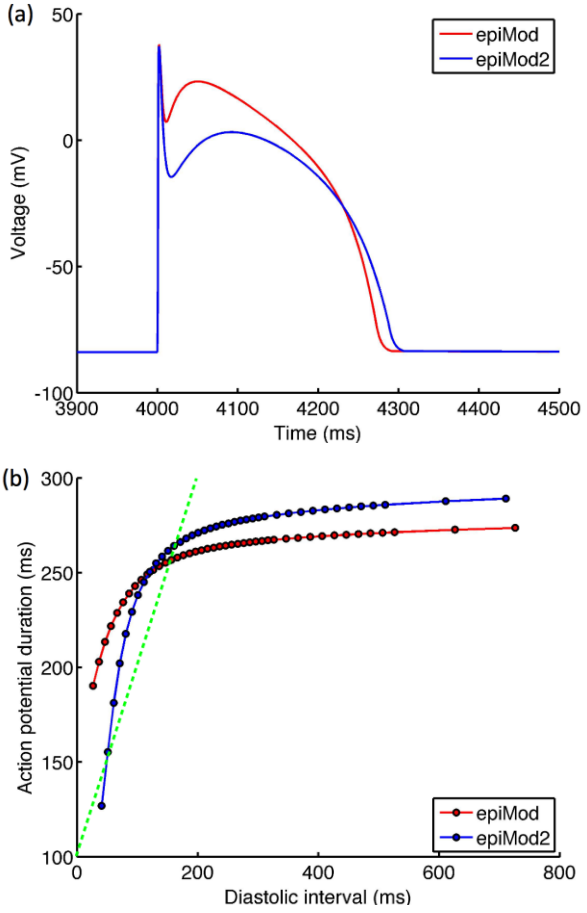

Figure 2 Action potential shape (a) and APD restitution (b) for epiMod (red) and epiMod2 (blue) variants of the 4-variable model. In (b), restitution was measured with S1S2 protocol, with S1 interval of 1000 ms. Green line indicates slope of 1.

III. Methods

A. Human Ventricular Cell and Tissue Model

Electrical activation was simulated using a monodomain model of cardiac tissue [7], with cellular electrophysiology described by a phenomenological 4-variable model that reproduces the action potential shape and restitution properties of human cardiac cells without the computational overhead of more detailed models [8]. Two variants of the phenomenological model were implemented. In each, some parameter values were changed to modify action potential duration (APD) restitution, while all other parameters were exactly as described in the model paper [8] for epicardial cells. In variant *epiMod* τ_{v1}^- was changed from 60.0 to 10.0, and τ_{v2}^- was changed from 1150.0 to 20.0. In variant *epiMod2* τ_{v1}^- and τ_{v2}^- were changed as for *epiMod*, and in addition τ_{so1} was changed from 30.0181 to 28.0, and τ_{s2} from 16.0 to 40.0. Fig. 2 shows action potential and APD restitution for each variant, measured in a 2D tissue strip.

Unstable re-entry is promoted by a restitution curve that is steeper than 1 [9], although other mechanisms can also contribute to instability [10]. Fig. 2b shows that the *epiMod* variant had an APD restitution curve with a slope of 1 at short diastolic interval. However the *epiMod2* variant had both a steeper slope, and a slope > 1 over a greater range of diastolic interval.

B. Numerical and Computational Approach

The model was solved with a space step of 0.02 cm and a time step of 0.05 ms using an explicit finite difference simulation framework evaluated in [11]. The tissue geometry was an 8.0×8.0×1.2 cm 3D slab, with axially symmetric anisotropy and 120° clockwise fibre rotation from endocardial to epicardial surface [12]. Diffusion coefficients were 0.001 cm^2 ms^{-1} parallel to fibres, and 0.00025 cm^2 ms^{-1} transverse to fibres, resulting in plane wave conduction velocities of 0.59 and 0.23 ms^{-1} respectively. No-flux boundary conditions were imposed, and the initial conditions were an Archimedian spiral corresponding to a single re-entrant wave with a single transmural filament.

C. Quantification of Complexity in Simulations

In 3D tissue, filaments are lines of phase singularity, around which re-entrant waves rotate. A surface PS occurs where a filament intersects with the surface. Simulated trans-membrane voltage was transformed into phase using time delay embedding of 2 ms, and filaments were identified as voxels of phase singularity using convolution kernels [13]. Surface PS were identified from phase on the top surface of the slab, and WF were identified as lines of zero phase using an active edge technique [2].

IV. Results

Fig. 3 shows snapshots of electrical activation in models with *epiMod* and *epiMod2* dynamics. With *epiMod* dynamics, the initial re-entrant wave was preserved, with breakup of the initial filament close to the core.

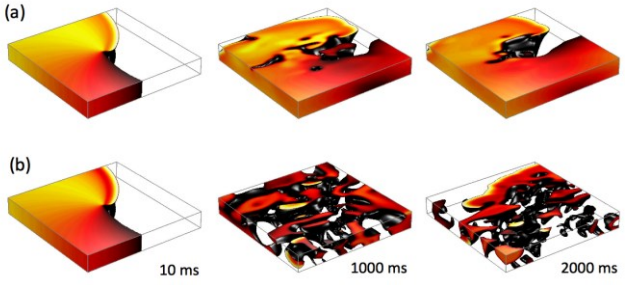

Figure 3. Snapshots of voltage in models with (a) *epiMod* dynamics, and (b) *epiMod2* dynamics, 10, 1000, and 2000 ms after initiation. The regions enclosed by each isosurface are those with voltage > -20 mV, and brighter colors indicate higher levels of depolarization.

With *epiMod2* dynamics, steeper APD restitution resulted in fragmentation of the initial re-entrant wave into multiple interacting wavelets of activation. Fig. 4 shows the filaments and surface WF corresponding to the snapshots shown in Fig. 3. It is clear from these figures that the complex activation patterns shown in Fig. 3b can be reduced by this approach to a relatively small number of features. Both the intersections of filaments with the epicardial surface and the number of WF can be compared with experimental data recorded from the heart surface, such as those shown in Fig. 1d.

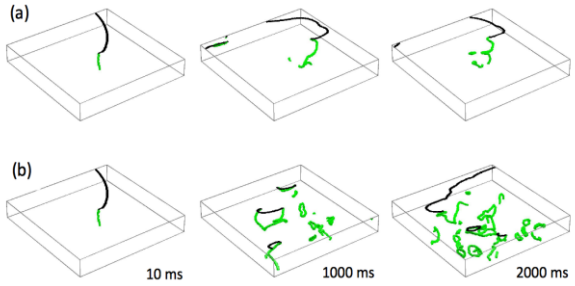

Figure 4. Snapshots showing filaments (green) and surface WF (black) corresponding to the snaphsots of voltage shown in Fig. 3.

Fig. 5 shows the number of filaments throughout each simulation, and how these relate to surface measures of PS and WF. Overall, the number of filaments, PS, and WF increased, reaching a quasi-stable state after about 1000 ms. Between 1000 and 2000 ms, the average numbers of filaments, PS, and WF were 3.08, 2.70, and 2.11, respectively for *epiMod* dynamics, and 13.79, 8.01, and 4.44, respectively for *epiMod2* dynamics. The average number of PS per filament was 0.93 for *epiMod* dynamics, and 0.57 for epiMod2 dynamics, indicating that with epiMod2 dynamics a lower proportion of filaments intersected the epicardial surface. The average number of transmural filaments linking top and bottom faces of the slab was 1.05 for *epiMod* dynamics and 1.15 for *epiMod2* dynamics, however the number of transmural filaments as a proportion of the total number of filaments for *epiMod* dynamics was 0.39, much larger than the proportion for *epiMod2* dynamics, which was 0.08. This trend did not have a big effect on the average number of epicardial PS per WF, which was 1.28 for *epiMod* dynamics and 1.83 for *epiMod2* dynamics.

V. Discussion and Conclusion

Models of ventricular cardiac electrophysiology can reconstruct 3D mechanisms of arrhythmias that are important for understanding the often incomplete information that can be obtained from experimental studies. This problem is especially acute for studies in the human heart.

"*All models are wrong, but some models are useful*" is a statement attributed to the statistician George Box, and it is important to remember that all models embed assumptions and uncertainties. Models of cardiac electrophysiology that are used to investigate the mechanisms of ventricular arrhythmias usually ignore the mechanical behavior of the heart, but there is evidence from modeling studies that the interaction of mechanical and electrical activity can destabilize re-entry [14]. Different detailed models of human cellular electrophysiology include different models of transmembrane currents, even when based on data from human cardiac cells, and these different representations can have important effects on the shape and duration of the action potential [15]. There are regional differences in action potential shape and duration within the human ventricle [16], and these have the potential to influence the stability of re-entry [17].

An area of current interest is how the structure of ventricular tissue influences activation patterns in ventricular arrhythmias. The continuing development of high resolution imaging techniques has enabled very detailed anatomical models of rabbit ventricles to be constructed, and initial studies indicate that anatomical detail has only a small influence on arrhythmia mechanism [18].

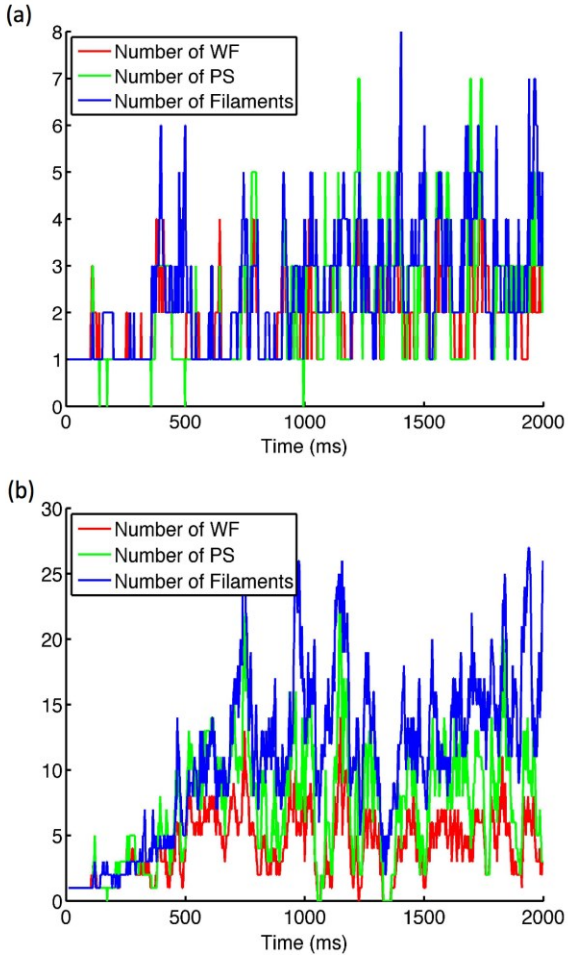

Figure 5. Number of filaments (blue), PS (green), and WF (red) in simulations with (a) epiMod and (b) epiMod2 dynamics.

In the present study, a deliberately simplified representation of the ventricular wall was used, so that the dynamics of filaments and surface features could be tracked without the additional complication of anatomical structure, topology and boundary conditions. An earlier study [1] showed that a good fit to experimental data on VF in the human heart could be obtained in a model with detailed

ventricular anatomy and an ionic model of human ventricular myocytes, which produced an average number of 9.5 filaments and 7.0 epicardial PS.

The epicardial surface of the slab geometry used in the present study was 6400 mm^2. If the human heart is considered to be an ellipsoid with a diameter at the base of 80 mm, and a base to apex distance of 100 mm, then the surface area is approximately 21000 mm^2, i.e. about 3.3 times the surface of the slab used in this study. During VF in the perfused human heart, experimental data indicate that on average there are around 8 epicardial PS, and 6 WF [1]. If these values are corrected for the estimated difference in surface area of the human heart and 3D slab geometry, assuming that conduction velocities are comparable, and neglecting the differences in topology and boundary conditions between a slab and the ventricles, then these experimental observations would correspond to an average value of 2.4 epicardial PS in the slab, which is close to the value found for *epiMod* dynamics. The ratio of PS to WF in experimental data is 1.3, which again is close to the value observed in the present study with *epiMod* dynamics.

Experimental measurements of VF complexity are therefore broadly consistent with simulations having *epiMod* dynamics. This conclusion is supported by earlier work with a more detailed model, which showed that VF with steep APD restitution (as in the *epiMod2* variant in the present study) results in a higher density of epicardial PS than are observed experimentally [1].

However, these conclusions must be tentative, because comparisons have been made between average numbers of filaments, PS, and WF, and Fig. 5 indicates that actual numbers of these features fluctuate throughout a simulation. Experimental data are often collected over a period of minutes, and as well as showing similar fluctuations there are clear trends in complexity occurring over timescales of several minutes. Even with simplified models, simulations of VF longer than a few seconds are computationally demanding.

While the simplified models described in this study offer valuable insight into the mechanisms of VF in the human heart, further work is needed to assess the contribution of anatomically detailed geometry and electrophysiological heterogeneity. Further, VF is most likely to occur in diseased hearts, and it is very likely that the structural and electrophysiological heterogeneity resulting from disease will also influence the complexity of VF activation patterns.

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