

Role of cardiac microstructure variability on ventricular arrhythmogenesis

Dominic G Whittaker, Alan P Benson, Irvin Teh, Jürgen E Schneider, Michael A Colman

University of Leeds, Leeds, UK

Abstract

The propagation of cardiac electrical excitation is influenced by tissue microstructure. Quantitatively understanding this relationship presents a significant research challenge, especially during arrhythmias where excitation patterns become complex. Reaction-diffusion computational models of cardiac electrophysiology incorporating both dynamic action potential (AP) behaviour and image-based myocardial architecture provide an approach to study the complex organisation of excitation waves within variable myocardial structures.

The role of tissue microstructure (cardiomyocyte and sheetlet orientations) on organ-scale normal and arrhythmic excitations was investigated. Five healthy rat ventricle datasets were obtained at 100 μm isotropic resolution using diffusion tensor MRI (DTI), from which the primary, secondary, and tertiary eigenvectors were determined. The Fenton-Karma cellular activation model was modified to reproduce the rat AP duration and restitution. Re-entrant scroll waves were initiated in the five anatomical models at ten prescribed locations for three different microstructure scenarios: (i) isotropic (i.e. no microstructure); (ii) anisotropic (i.e. myocyte but no sheetlet microstructure); and (iii) orthotropic (i.e. myocyte and sheetlet microstructure).

Inclusion of anisotropic and orthotropic DTI-based microstructure increased scroll wave filament length, a measure of the complexity of re-entrant activity, to differing extents between the five hearts. Furthermore, variability in anatomy and microstructure accounted for whether simulated scroll waves self-terminated, remained tachycardia-like, or degenerated into fibrillatory activity.

This study shows that anatomy and microstructure influence both specific dynamics of arrhythmias as well as properties such as lifespan and filament length, highlighting the important role of structural variability.

1. Introduction

Cardiac arrhythmias, including ventricular tachycardia (VT) and ventricular fibrillation (VF), are major causes of morbidity and mortality in the developed world, yet remain incompletely understood [1]. As arrhythmias are inherently an organ-scale phenomenon, quantitative

characterisation requires visualisation of excitation-propagation processes throughout the three-dimensional (3D) *in vivo* beating heart [2]. This is not yet technically feasible, and thus the study of arrhythmias presents a significant research challenge. Mapping electrical activity during arrhythmias, using techniques such as depth-resolved optical imaging, is one approach which has been used with some success to shed light on VF mechanisms [3]. Reaction-diffusion models of cardiac electrophysiology, incorporating both dynamic action potential (AP) behaviour and image-based myocardial architecture, offer an alternative way of studying the complex organisation of excitation waves during arrhythmias, which enable direct control of important determinants of arrhythmia dynamics such as ion current properties and tissue structure and anisotropy [4].

The field of computational cardiac modelling is beginning to move beyond the single virtual heart paradigm, as the importance of accounting for inter-subject variability is emerging [5]. Recent efforts have focused overwhelmingly on electrophysiological variability, with particular emphasis on how this might affect arrhythmia dynamics and drug response [6]. In this study, we sought to determine to what extent variability in cardiac anatomy and microstructure manifests as differences in arrhythmia dynamics. Quantitative study of this important relationship can improve understanding of the role of structural variability in ventricular arrhythmogenesis, and thus how myocardial structure influences proarrhythmic risk and drug response.

2. Methods

2.1. DTI reconstructions

Five healthy rat heart reconstructions at 100 μm isotropic resolution from *ex vivo* diffusion tensor MRI (DTI) [7] were used to provide myocardial structure for reaction-diffusion models of cardiac electrophysiology, from which five ventricular geometries were extracted. The helix and transverse angles and the sheetlet angle, derived from the primary and secondary eigenvectors obtained from DTI, respectively, were computed for each of the ventricular geometries using the coordinate system and method described previously [3]. Variability in tissue

microstructure (helix, transverse, and sheetlet angles) existed between the five data sets (Figure 1).

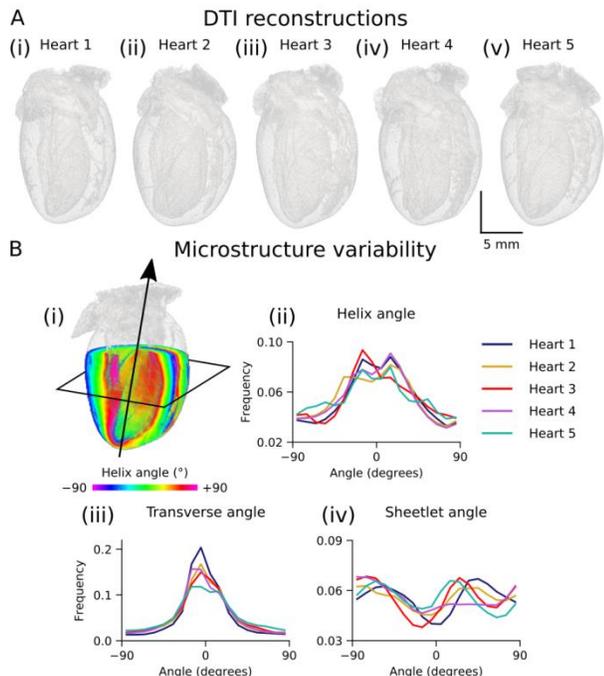


Figure 1: (A) Five healthy rat heart reconstructions from *ex vivo* DTI [7]. (B) (i) Co-ordinate system used to compute myocyte and sheetlet orientation angles [3] and microstructure variability in (i) helix angle, (ii) transverse angle, and (iii) sheetlet angle between the five geometries.

2.2. Ventricular tissue simulations

The Fenton-Karma three variable (FK3V) minimal AP model [8] was modified to reproduce the short (~50 ms) rat AP duration (APD) and its restitution, using experimental data from our laboratory [9] (Figure 2). Propagation of APs in 3D tissue geometries was described using the monodomain equation,

$$\frac{\partial V}{\partial t} = \nabla(\mathbf{D}\nabla V) - \frac{I_{\text{ion}}}{C_m}, \quad (1)$$

where V is the transmembrane voltage, \mathbf{D} is the global conductivity tensor, I_{ion} is the total ionic current, and C_m is the membrane capacitance. Equation (1) was solved using a finite difference PDE solver based on the explicit forward Euler method with $\Delta t = 0.01$ ms and a Strang splitting scheme. The global conductivity tensor, \mathbf{D} , from Equation (1) is given by,

$$\mathbf{D} = D_1 \mathbf{e}_1 \mathbf{e}_1^T + D_2 \mathbf{e}_2 \mathbf{e}_2^T + D_3 \mathbf{e}_3 \mathbf{e}_3^T, \quad (2)$$

where D_1 , D_2 , and D_3 correspond to electrical diffusion in directions along the myocyte orientation axis, perpendicular to myocyte orientation in the sheetlet plane,

and normal to the sheetlet plane, respectively, \mathbf{e}_1 , \mathbf{e}_2 , and \mathbf{e}_3 are the corresponding eigenvectors obtained from DTI, and the superscript T denotes the vector transpose. D_1 was set to a value which gave a conduction velocity of 0.6 m/s along the myocyte orientation axis [10]. For isotropic simulations, the diffusion coefficients, D_i , were set equal to each other, and were scaled (by reducing values radial to the myocyte direction) in the ratios $D_1:D_2:D_3 = 4:1:1$ and $D_1:D_2:D_3 = 36:9:1$ for anisotropic and orthotropic simulations, respectively [2].

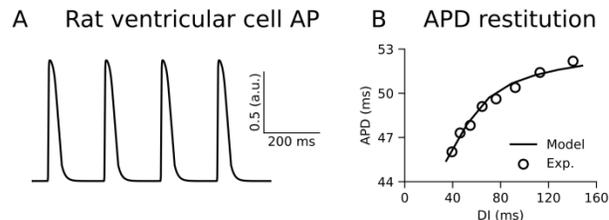


Figure 2: (A) Rat ventricular cell APs from the modified FK3V model at a 5 Hz pacing rate. (B) Comparison of APD as a function of diastolic interval (DI) from model (solid line) and experiment (points) [9].

For arrhythmia simulations, conduction velocity was decreased by 50% (through a four-fold reduction in the diffusion coefficient) to facilitate sustenance of re-entry in the limited ventricular mass. The phase distribution method [11] was used to initiate a scroll wave which developed into re-entry at ten different locations in each of the five ventricular geometries for three microstructure scenarios (isotropic, anisotropic, and orthotropic), giving 150 simulations in total. Scroll wave filaments were tracked by locating phase singularities [12] and counted using a grassfire algorithm [13]. Lifespan of re-entry was computed from pseudo ECG signals [14].

3. Results

3.1. Effects of anisotropy on scroll wave filament dynamics

Snapshots of scroll waves and corresponding filaments from a representative heart for the three microstructure scenarios (isotropic, anisotropic, orthotropic) are shown in Figure 3, as well as mean filament length averaged from ten simulations for all five hearts. In the representative simulation shown, introducing myocyte and sheetlet orientations (isotropic \rightarrow anisotropic \rightarrow orthotropic) progressively increased the number of scroll wave filaments over a 1200 ms period. However, as single filaments can be broken into multiple filaments by the intricate myocardial structure [2], filament length was chosen as a more useful way of quantifying scroll wave behaviour. In 5/5 hearts, including myocyte orientations

(isotropic \rightarrow anisotropic) in simulations increased scroll wave filament length, a measure of the complexity of re-entrant activity. In 4/5 hearts, including sheetlet orientations (anisotropic \rightarrow orthotropic) further increased filament length.

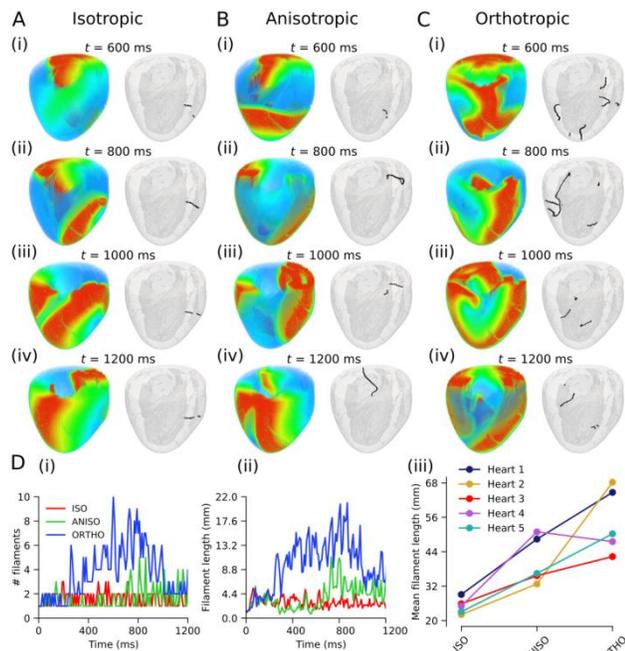


Figure 3: Representative snapshots of scroll waves (left) and corresponding filaments (right) under (A) isotropic (ISO), (B) anisotropic (ANISO), and (C) orthotropic (ORTHO) conditions at times (i) $t = 600$ ms, (ii) $t = 800$ ms, (iii) $t = 1000$ ms, and (iv) $t = 1200$ ms. (D) (i) Number of filaments in a representative simulation for different microstructure scenarios over a 1200 ms period, and corresponding (ii) filament length. (iii) Mean filament length over a 5000 ms period, averaged from ten simulations in each case.

3.2. Effects of microstructure variability on arrhythmia dynamics

Variability in arrhythmia dynamics following initiation of a scroll wave at a prescribed location in each of the five hearts is shown in Figure 4. It can be seen that differences in anatomy and microstructure alone were able to account for whether simulated scroll waves self-terminated, remained as VT-like, or degenerated into VF-like activity. Over simulations in which scroll waves were initiated in ten different locations, in 5/5 hearts, inclusion of myocyte orientations (isotropic \rightarrow anisotropic) increased the lifespan of self-terminating arrhythmias, and in 3/5 hearts, inclusion of sheetlet structure (anisotropic \rightarrow orthotropic) further increased the lifespan of self-terminating arrhythmias. In 4/5 hearts, including myocyte orientations (isotropic \rightarrow anisotropic) increased

the number of sustained arrhythmias, and in 1/5 hearts it decreased the number. In 3/5 hearts, including sheetlet structure (anisotropic \rightarrow orthotropic) further increased the number of sustained arrhythmias, in one heart it decreased the number, and in one heart it had no effect.

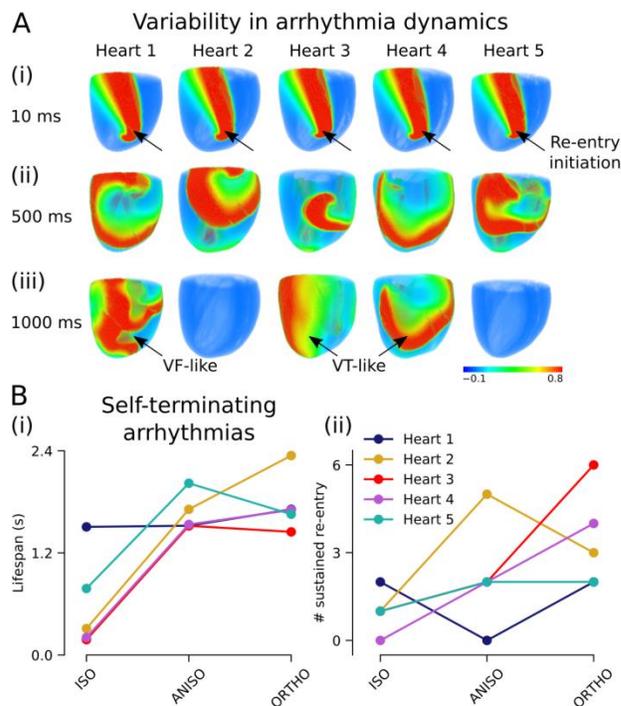


Figure 4: (A) Evolution of a scroll wave initiated at a prescribed location in five hearts at times (i) $t = 10$ ms, (ii) $t = 500$ ms, and (iii) $t = 1000$ ms, with arrows showing VT- and VF-like activity. (B) (i) Lifespan of self-terminating arrhythmias under isotropic (ISO), anisotropic (ANISO), and orthotropic (ORTHO) conditions for the five hearts, and corresponding (ii) number of sustained re-entries (those lasting 5000 ms).

4. Discussion

In this study, the role of microstructure variability in ventricular arrhythmogenesis was investigated using reaction-diffusion models of cardiac electrophysiology with modified FK3V membrane kinetics and image-based myocardial architecture from high-resolution DTI [7].

Our simulation results showed that whilst inclusion of myocyte and sheetlet orientations generally increased filament number and length and decreased the propensity for arrhythmia termination, the effects were not consistent between the five hearts. This suggests that sample-specific microstructure is necessary for improved quantitative predictive cardiac electrophysiology simulations. Integrating personalised myocardial structure with patient-specific electrophysiology is thus likely to be a crucial step towards future translation of computational models of the heart to the clinic [15].

It was also shown that, in the absence of electrophysiological differences, anatomy and microstructure alone were able to account for large variation in arrhythmia dynamics. Therefore, whereas personalised microstructure has been suggested to be of limited importance for predictive simulations of cardiac mechanics [16], our findings suggest that results from arrhythmia simulations using cardiac atlases or rule-based myocyte orientations must be interpreted with caution.

In all five hearts, the average scroll wave filament length and lifespan of self-terminating arrhythmias was greater in anisotropic and orthotropic simulations than in isotropic simulations, due to slower conduction along secondary structures. Furthermore, in 4/5 hearts the number of sustained re-entries was greater under anisotropic and orthotropic conditions than under isotropic conditions. These results indicate that tissue microstructure is a critical determinant of arrhythmia dynamics, and thus isotropic tissue simulations may be untenable for quantitative simulations of cardiac excitation-propagation and arrhythmogenesis, as they likely underestimate arrhythmia vulnerability. This further suggests that advances in imaging technologies providing high resolution microstructure and their integration with computational models of cardiac electrophysiology and mechanics are likely to drive the next generation of predictive models [17].

5. Conclusion

This study shows that ventricular anatomy and microstructure influence specific properties of arrhythmia dynamics such as lifespan and filament length, and can account for large inter-subject variation in arrhythmia dynamics. Our findings highlight the important role of structural variability in ventricular arrhythmogenesis.

Acknowledgements

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Address for correspondence.

Dominic G Whittaker,
Garstang 7.53,
University of Leeds,
Leeds, UK,
LS2 9JT,
d.whittaker@leeds.ac.uk