Computational Modelling of Low Voltage Resonant Drift of Scroll Waves in the Realistic Human Atria

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Abstract. This study evaluated the effects of human atrial anatomy and fibre orientation on the effectiveness of a low voltage resonant defibrillation method. The Courtemanche-Ramirez-Nattel model was modified to simulate scroll wave re-entry that may represent a form of atrial fibrillation. The cell models were incorporated into a 3D anatomical model to simulate re-entry. The single shock threshold to eliminate re-entry in the isotropic and anisotropic 3D models was estimated as the reference point for the low energy defibrillation effectiveness. The low voltage scroll wave termination protocol was based on the resonant drift of stationary scroll waves due to feedback-controlled periodic stimulation. The global resonant feedback stimulation can work in the realistic anatomy model in principle. Further investigation to find optimal parameters for the resonant low energy defibrillation in anatomically realistic models must include optimal location of electrodes as well as stimulation protocol improvement.

Keywords: Atrial arrhythmia, electrical cardioversion, computational cardiology, mathematical modelling.

1 Introduction

Atrial arrhythmias cause loss in quality of life and are often driven by scroll waves, which require electrical stimulation for their termination. Low voltage stimulation protocols may potentially improve defibrillation. Modern computational cardiology allows the study of re-entry termination using detailed atrial electrophysiology and atrial anatomy. The locations of pacing electrodes for internal scroll wave termination can be investigated using mathematical modelling [1].

The present work draws upon theoretical developments by Biktashev and Holden [2] where feedback-controlled repetitive low voltage global shocks were proposed to be effective. Using a 2D Fitz-Hugh Nagumo model, they showed that a train of small amplitude stimuli applied at appropriate times (i.e. applied "resonantly" with respect to the stationary re-entry) were sufficient to eliminate spiral waves. This work was extended by the same authors to further demonstrate the principles of low voltage defibrillation. [3]. Subsequently, Morgan et al. [4] considered two stimulation electrode and point or line registration electrodes providing the feed-back in 2D human atrial sheets. The goal of this study was to verify the effectiveness of a resonant drift low-voltage pacing protocol in a 3D human realistic atrial geometry by estimation of scroll wave termination parameters.

2 Methods

Atrial excitation model: The established human atrial action potential (AP) cell model by Courtemanche et al. [5] (CRN) was used in this study. Atrial fibrillation (AF) induced electrophysiological changes were implemented as in our previous study [6]. Thus defined AF condition gave stationary re-entry in isotropic homogeneous sheets of atrial tissue.

Conduction velocity in atrium: In the 3D anisotropic cases, the larger eigenvalue of the diffusion tensor $\boldsymbol{D}$ was taken to be 0.21 mm^2/ms to give a conduction velocity of 0.7 mm/ms along the fibres, and the smaller eigenvalue of $\boldsymbol{D}$ was 0.07 mm^2/ms, giving conduction velocity of 0.4 mm/ms across the fibres. In the isotropic case, $\boldsymbol{D}$ was taken to be 0.07 mm^2/ms. The mono-domain reaction-diffusion system was solved using a second order finite-difference approximation of the diffusion operator using 7 point (3D, isotropic) or 19 point (3D, anisotropic) stencils. A 3D human atrium model with rule based fibre orientation in the conduction pathways [7] was used in this study.

Initiation of scroll waves: Scroll wave initiation was implemented using the phase distribution method [8]. It involves pacing of the cell model rapidly till steady transients over one period in all state variables are obtained. The transients are then used to pace a 1D tissue with the same $\boldsymbol{D}$ values as in the 3D model. The state variables recorded from the middle of the 1D tissue during one steady propagating pulse are then used to distribute the phase of the electrical excitation to induce a spiral or scroll wave according to an Archimedean spiral formula. Using such a protocol ensures the initiation of a scroll wave at a prescribed location in the 3D models. As the atrial wall in the anatomical model is approximately 3 mm thick with a maximum of 6 computational nodes transmurally, the initiated scroll waves has filaments that were short and stubby.

Tip tracing: The tips of the transmural filaments, i.e. the centres of the quasi two-dimensions epicardial surface spiral waves, were tracked by the software EZView (http://empslocal.ex.ac.uk/people/staff/vnb262/software/EZView/) based on the Marching Cubes algorithm [9] as implemented by Dowle and Barkley [10].

Evaluation of single shock threshold: To estimate the minimum single shock required to eliminate re-entry, a mono-phasic rectangular waveform constant electrical shock was applied to the whole model for 5 ms. The shocks were applied at 12 different timings to cover an entire 80 ms rotor cycle. A single shock was deemed successful if no re-entry was detectable at 500 ms after termination of the shock.

Pacing protocol: Global resonant drift pacing: The resonant drift pacing is based on previous theoretical developments [2-4, 11] and involves:

- A registration electrode registers electrical activity, locally at a point or globally over the selected area, to provide a feedback signal.
- A "trigger event" is defined with respect to the registered signal.
- A time delay between the trigger event and a subsequent shock is defined.
- A global rectangular shaped electric shock is issued upon expiry of the time delay.

Each weak electrical shock is supposed to cause a displacement of the scroll wave, and the feedback ensures that these displacements accumulate causing the "resonant drift", which drives the scroll wave towards an inexcitable boundary. The amplitude of the shock may be lower than the threshold of excitation; however, exact parameters of the protocol required for efficient work depend on the model. In our simulations, the protocol was implemented as follows:

- We used point electrodes measuring transmembrane potential. A single registration electrode was chosen near an inexcitable boundary.

- The trigger event was defined as the moment when the signal crossed -40 mV while increasing at the registration electrode site.
- We used fixed time delays of 0 ms, 20 ms, 40 ms, and 60 ms.
- The electric shocks were the same form as for single-shock protocol, only with smaller amplitude.

The resonant drift pacing was deemed successful if the scroll waves were eliminated in 40 s after the start of applying the feedback-driven stimulation.

Cardiac simulation environment: BeatBox, a multi-functional High Performance Computing cardiac simulation environment was used in this study [12, 13]. In the 3D human atrium simulations of this study, 256 processors yielded the 40 s of simulated electrical activity within 48 hours, reflecting its highly scalable nature [13, 14].

3 Results

Evolution of scroll waves in the isotropic and anisotropic atrium: In a previous study [6], we have shown that anatomical features such as pectinate muscles (PMs) (see **Fig. 1,** A and B) serve as perturbation and may cause spontaneous drift of scroll waves. It has also been shown that the drift might be due to a gradient of the surface curvature [15]. In addition, the main conduction pathways in the human atrium have fibre orientation shown in **Fig. 1**, C. An example of the isotropic anatomy induced drift is illustrated in **Fig. 1**, D. Therefore, before the scroll wave termination, the externally unperturbed scroll waves were simulated in the anatomy. We choose 4 scroll wave initiation locations, named L1, L2, L3, L4, shown in **Fig. 2**, where the isotropic anatomy induced spontaneous drift was known to be insignificant in a 15 s duration. In the isotropic case, the scroll waves remained localised. L1 and L2 are in the predominantly isotropic regions of the 3D model, far away from the fibre orientation regions of the conduction pathways. In contrast, when the scroll wave was initiated at location L3 with anisotropy "on", it showed a definite spontaneous drift. The drift was in the direction away from the complex regions to the isotropic region. In case of the scroll wave initiated at L4 in the anisotropic model, the scroll wave moved along the pectinate muscle. This movement can be expected as there are anatomical as well as fibre orientation effects. The pectinate muscle is thicker than the atrial wall, see the recent theoretical results that sharp variations in thickness may also cause drift [16]. In addition, conduction along the pectinate muscle is faster due to fibre orientation thus promoting the scroll wave core to move along the pectinate muscle. Note that spatial variations of anisotropy can be viewed as geometric features in terms of Riemannian geometry [17]. Thus, we note that anisotropy also causes a spontaneous drift of the scroll wave. This drift may not be towards any model boundaries, but will affect the effectiveness of the feedback stimulated resonant drift protocol of scroll wave termination.

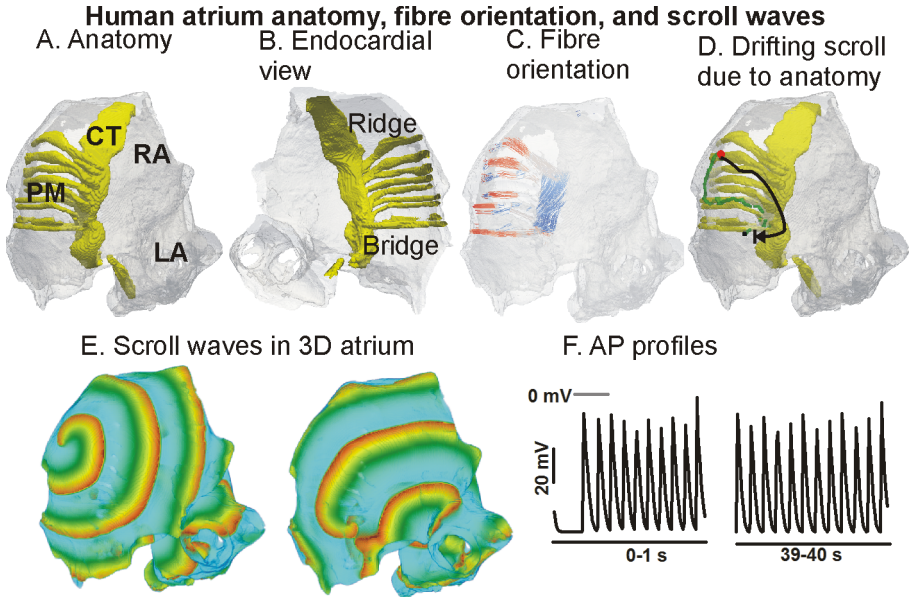

Fig. 1 Human atrial anatomy, fibres and anatomical effect on scroll. A: Epicardial view of the right atrial surface showing pectinate muscles (PM), cristae terminalis (CT), right atrium (RA) and left atrium (LA). B: Endocardial view of the atria showing anatomical heterogeneity of PM and CT that form "bridges" and "ridges" in the tissue. C: Fibre orientation in the human atrial model where the fibres are colour coded by their horizontal axis component. D: Drift of a scroll wave due to anatomical heterogeneity. The scroll wave initiation location is shown by the red dot, trajectory by the green line, and pinning location by the black square after 40 s. (colour online).

Single Shock Scroll Wave Termination Threshold: Multiple single shock amplitudes and timings were experimented with in the 2D isotropic model. Small stimulation amplitudes (between 0.1 to 1 pA/pF) caused the spirals to displace without termination. Stronger stimuli (1 to 4 pA/pF) eliminated original spiral waves but boundary effects gave rise to secondary wavelets that left the re-entry persistent. A shock of 5 pA/pF was found to terminate the spiral wave activity in the 2D isotropic sheet. In the 3D isotropic anatomy case, the single shock threshold was found to be between 5 and 5.2 pA/pF, while in the anisotropic case it was found to be between 5.2 and 5.6 pA/pF.

Resonant Drift Pacing in 3D isotropic and anisotropic cases: After quantifying the scroll wave behaviour in 2D, resonant drift pacing was applied to scroll waves in the 3D model as illustrated in **Fig. 3**. A registration electrode at the right AV border (**Fig. 3**, A), registered a signal, after which a global stimulus was applied. In all simulations, isotropic and anisotropic, it should be noted that the small amplitude of the global periodic simulation of 0.5 pA/pF did not give rise to secondary wavelets and stimulus induced AF, but simply caused the scroll wave to incrementally change its location. Four representative delays of 0 ms, 20 ms, 40 ms, and 60 ms were chosen at each of the four locations to span the scrolls unperturbed period of 80 ms. In the isotropic case with initiation at L1 or L2, a correlation between the stimulation delay and the resonant feedback drift of the scroll wave can be seen from **Fig. 3** (top panels). At delay 0, the filament of the scroll wave drifts approximately orthogonally to the line joining the initiation site and the registration electrode (**Fig. 3**, A for electrode location, **Fig. 3**, B, for the *isotropic case*). Therefore, in case of L1 and L2,

an appropriate choice of delay may be chosen to cause the scroll waves to drift towards a model boundary, a large blood vessel opening. The resonant drift trajectory changes as the delay was increased. When the scroll waves are initiated at L3, the anatomical features (locally altering thickness or ridge structures) inhibit a strong

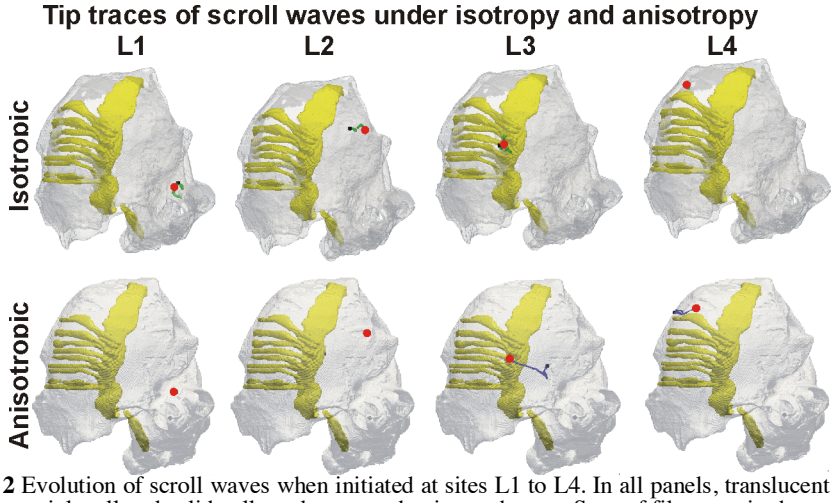

Fig. 2 Evolution of scroll waves when initiated at sites L1 to L4. In all panels, translucent grey shows atrial wall and solid yellow shows conduction pathways. Start of filaments is shown by a red dot (time t = 0), while end is shown by a black square (time t = 40 s). Isotropic filament tip traces (top panels) are shown in green, while anisotropic filament tip traces are shown in blue (bottom panels). In several instances, the drift of the scroll wave was minimal. Therefore, the start and end points, as well as the tip trajectories are virtually indistinguishable.

correlation between the feedback parameters and the drift trajectory. The drift trajectories show that the resonant drift pacing may not move the scroll waves in a desired direction. In case of L4, the scroll waves drifted along the pectinate muscle ridge. In this case, the resonant drift stimulation combined with the anatomical perturbation due to the ridge formed by the PM-atrial wall and caused the scroll to drift along the PM ridge.

With anisotropy "on" and scroll wave being initiated at L1, there was only marginal drift due to the feedback stimulation, see L1 bottom row in **Fig. 3**. In the L2 case (**Fig. 3**, bottom row), the combination of anatomy and fibre orientation results in all 4 delay cases giving almost identical tip trajectories. In cases of L3 and L4, the scroll wave drift due to the fibre orientation anisotropy was substantially larger. This caused a large scroll wave drift (**Fig. 3**, L3 and L4 bottom panels). Due to the combined high degree of anatomical and fibre orientation heterogeneity, the scroll wave drifted, led to spiral wave break up, and formation of secondary scroll waves.

4 Conclusions and Discussion

We have demonstrated that feedback-controlled resonant pacing can cause drift of scroll waves in the atrial geometry. The trajectory of the spiral drift depends on the relative position of the spiral core and the registration electrode of the feedback loop, and the delay in the feedback. This trajectory is also affected by the atrial geometry and anisotropy. Feedback controlled resonant pacing can push the spiral wave onto an inexcitable boundary, i.e. a "hole", of which in the human atrium geometry there are

several, including the right and left AV border and the openings of the blood vessels, and this can be achieved at the amplitude of the electric shocks as small as 1/10 of the single shock scroll wave termination threshold. Thus, we have demonstrated that feedback controlled pacing is capable in principle of eliminating re-entrant activity in the atria.

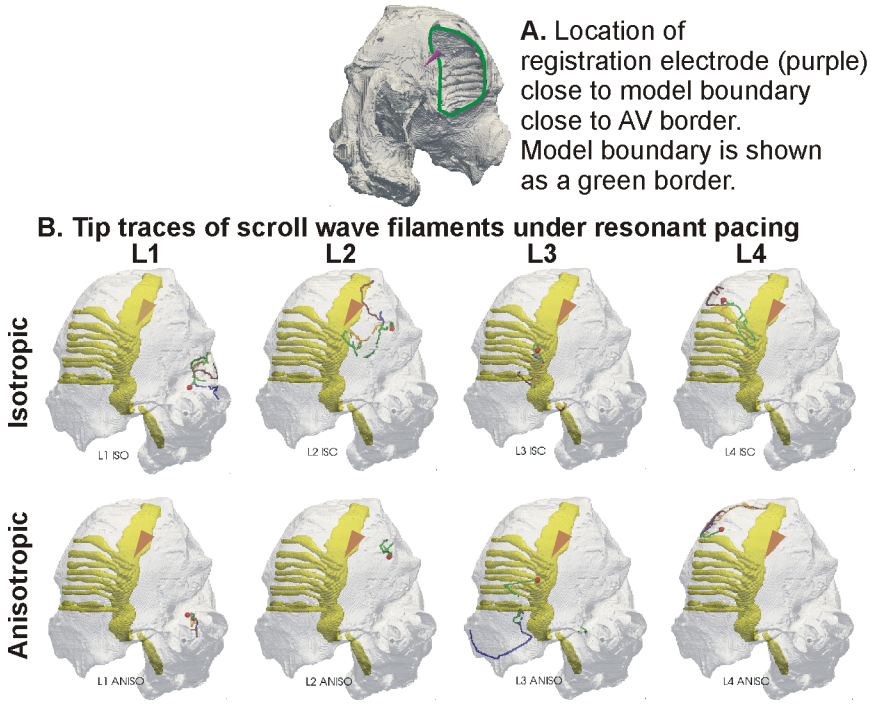

Fig. 3 3D resonant drift stimulation. A: Location of registration electrode (purple cone) on the model's back opening of the AV border. B: Registration electrode position is designated by the same purple cone, but now it is on the other side and we see its projection through two atrial walls. In each of the panels, the location of the registration electrode was the same. The stimulation amplitude was taken to be 0.5 pA/pF in all simulations. Shown are the drift trajectories for delay values of 0 ms (blue), 20 ms (brown), 40 ms (beige) and 60 ms (green) in the isotropic case (top panels) and anisotropic case (bottom panels). In case of L2 anisotropic case, the tip trajectories are coincidental at the 4 delay values. In case of L3 anisotropic case, there was a large resonant drift at delay 0 (blue) and 60 ms (green). At the delay 60 ms (green trajectory) the drift was markedly in the same direction which then became coincidental with the delay 0 case. In the L3 anisotropic case, the tip traces for delay 20 ms and 40 ms were highly fragmented and whenever a filament tip was detected there, it was almost coincidental with the delay 0 ms or delay 60 ms cases.

However, our study also reveals the new difficulties arising due to the complicated geometry of the atria. One difficulty is that pushing a scroll wave onto an inexcitable boundary alone is insufficient to terminate arrhythmia. There could be other spiral waves simultaneously present which is a known complication; as it was shown previously [4, 11] it is not an absolute deterrent: when one re-entrant source has been eliminated, the feedback loop automatically engages on another, still existing re-entrant source, and so can eliminate them one by one. Another, more significant complication for the theory of resonant drift to be applicable is that re-

entrant sources in complex media can be anatomical re-entries rather than spiral waves; and the resonant pacing is known to be not effective for anatomical re-entries [18]. Clinically, this outcome itself may be beneficial due to the anatomical re-entries have lesser frequencies and are therefore less dangerous. A more daring approach would be to try and avoid occurrence of anatomical re-entries after elimination of spirals, by directing each spiral not to any anatomical obstacle, but choosing those obstacles in such a way that the resulting topological charges of all obstacles are zero. The challenges in terms of mathematical feasibility and hardware implementation are a subject for further investigation.

Our results confirm that the anatomy including fibre orientation has an utmost effect for the feedback-controlled resonant drift pacing. Such pacing is hoped to induce cardiac re-entry to migrate to an inexcitable region or a boundary. Low-voltage protocols very similar or coinciding with ours have been successfully attempted in experiments with heart preparations [19]. There have been also other low-voltage protocols suggested recently [20]. Similar to the strengths used in this study, a recent experimental study found that multiple shocks of strength 10 fold lower than that of the threshold successfully terminated scroll waves [21]. Further work is needed to compare these methods, and fully understand the mechanisms of scroll wave termination found in experimental studies. It may be a limitation of the present study that the defibrillation shock was applied globally. Another limitation may be that a mono-domain formulation was used in the computations, whereas the effects of an external shock may be better assessed by a bidomain formulation. We are also pursuing an improvement of boundary condition implementation in a structured finite difference mesh paradigm. In any case, this study indicates that anatomy and anatomical fibre orientation of the heart impose significant perturbations on cardiac re-entry and will play a major role in the success of any low energy defibrillation protocol. Therefore, good detailed anatomical models including true fibre orientation might be the key components for further computational simulation tests. Our findings present an experimentally or clinically testable hypothesis that can provide improvements in cardioversion technology.

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