Cardioversion Using Feedback Stimuli in Human Atria

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Abstract

Beatbox, a novel cardiac simulation environment, was used to study low amplitude human atrial cardioversion.

Chronic atrial fibrillation (CAF) was simulated using the Courtemanche et al. cell model with reduced I_{CaL} and increased I_{K1} current conductances. In 2D and 3D models, re-entry was induced using the phase distribution method. The feedback stimulation method was applied to eliminate such re-entry under CAF conditions.

CAF dramatically reduced action potential duration by 47%. Under CAF conditions, a single threshold amplitude shock of 4.5 pA/pF eliminated the stable re-entry. In 2D simulations, multiple feedback induced stimuli of 1 pA/pF caused re-entrant waves to migrate out of the 2D tissue. In 3D CAF simulation, feedback induced stimuli also caused the re-entrant wave migration eventually eliminating the re-entry.

The effectiveness of the cardioversion method is affected by the 3D anatomy and warrants further studies.

1. Introduction

Chronic atrial fibrillation (CAF) is the most frequently encountered cardiac arrhythmia in clinical practice. The increasing prevalence of CAF with advancing age [1] exacts a significant burden on healthcare systems and is a major clinical concern. Pharmacological intervention being a preferred strategy in the treatment of atrial fibrillation (AF) [2], electrical cardioversion provides an effective rapid method for termination of underlying mother rotors [3]. Current clinical methods of applying a single large transthoracic shock may damage cardiac tissue and cause loss in quality of life. Patients will subsequently often develop post-treatment episodes of AF. Implantable cardioversion devices apply a series of significantly smaller shocks to the organ during recurring AF episodes and have proven effective in recent times.

The efficacy of many local and global control methods, including feedback [4, 5] and non-feedback [6, 7] pacing protocols used by ICDs is being continually evaluated using advanced cardiac computational tools. In a extending previous theoretical and computational efforts, this ongoing study extends the investigation to realistic 3D human atria. A novel cardiac simulation environment, Beatbox [8], was used in the multi-scale simulations. The CAF induced shortening of atrial action potential (AP), and re-entrant wave evolution under CAF conditions were simulated. The single shock threshold required to terminate re-entry was established. The efficacy of a low energy feedback induced stimulation pacing protocol was then tested in 2D as well as realistic 3D models of human atria.

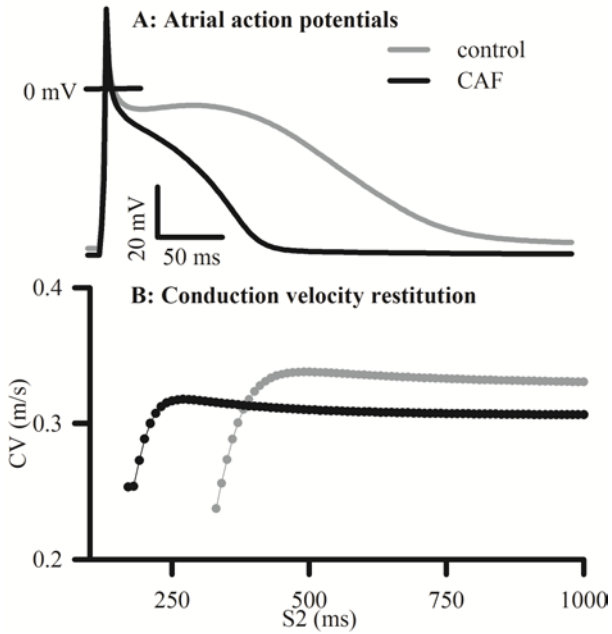

Figure 1. A: AP profiles under control (gray line) and CAF (solid line) conditions. B: CV restitution under control (gray line) and CAF (solid line) conditions.

To perform multi-scale simulations the Beatbox computational package [8] was used. Beatbox incorporates repositories of biophysically detailed cell models, as well as anatomical heart models to facilitate multi-scale *in silico* cardiac simulation studies. It is a novel MPI based High Performance Computing (HPC) cardiac simulation environment developed with the aims

of simplicity, robustness, functionality, alienable, user friendliness, and based on minimal dependencies. Beatbox provides an inbuilt script interpreter to alleviate the steep learning curve for new users. It facilitates the rapid simulation construction through implementation various pacing and measurement protocols that quantify electrical behaviour in the models. The package relies on robust explicit and implicit finite difference solvers.

2. Methods

The biophysically detailed Courtemanche et al. [9] (CRN) cell model for human atrial action potential (AP) was used in this study. CAF involves a drastic reduction of AP duration (APD) and was simulated by reducing the L-type calcium current (I_{CaL}) conductance by 50%, and increasing the time independent outward rectifier potassium current (I_{K1}) conductance by 100% [10, 11]. The basal and CAF cell models were then incorporated into 1D and 2D tissue. and 3D organ models using a mono-domain reaction diffusion formulation given by:

$$C\frac{\partial V}{\partial t} = -D\nabla^2 V + I_{ion}(x_i, t) \text{ in tissue} \quad \text{Eq. (1)}$$

$$n \cdot D\nabla V = 0 \text{ at tissue boundaries}$$

where C is cell membrane capacitance, V is cell membrane voltage, D is the constant diffusion representing inter-cellular gap junctional coupling, I_{ion} is the total current generated by the cell, x_i are the ion current gating variables of the cell, t is time, and n is the unit vector normal to tissue surface. In all isotropic spatial models, the space step was taken to be 0.33 mm and discretisation carried out using standard 3 point (1D), 5 point (2D), and 7 point (3D) finite difference stencils. The time step was taken to be a constant 0.05 ms in all spatial simulations. The 1D models were taken to be 33 mm long to minimize boundary effects. The 2D model was taken to be a 37.5 x 37.5 mm^2 square sheet. The 3D models, both anatomical and box wise, are 90 mm^3 boxes consisting of void and tissue grid points. While the spatial solver used in this study is based on explicit finite differences, Beatbox provides an advanced implicit algorithm for accurate approximation of Neumann boundary conditions at irregular boundaries. The constant diffusion, representing gap junctional coupling, was adjusted to give a conduction velocity of 0.3 m/s [12, 13].

AP profiles and conduction velocity restitution (CVr) were quantified under control and CAF conditions using established pacing protocol methods to elicit stable APs and CV measurements [14]. In both the 2D and 3D cases, re-entry was initiated by means of an efficient phase distribution method [15]. This method allows the initiation of re-entry at any desired location precisely. In the 2D idealized sheets, re-entry was initiated in the middle of the sheet. In the 3D anatomical model, scroll waves (3D re-entry) were initiated in the middle of the right atrium. The evolution of the re-entry was quantified by means of re-entrant wave tip (filament in the 3D case) meander, period of rotation of re-entrant circuit, and life span of re-entry. Using 2D models, the threshold stimulus required for instant elimination of re-entry was estimated. This was done by applying an external stimulus after allowing the CAF re-entrant wave to stabilise for 1.5 s of simulated activity. Once a sufficiently accurate estimate of such a threshold stimulus was obtained, it was used to guide estimation of threshold stimulus in the 3D model. The effectiveness of low energy defibrillation was estimated using the 2D and 3D models. A suitable location was chosen to register localised excitations in the 2D and 3D models to implement a feedback stimulation cardioversion protocol. Every instant when an excitation was registered at a selected locations, a low energy global stimulus was applied to induce its migration towards the model boundaries.

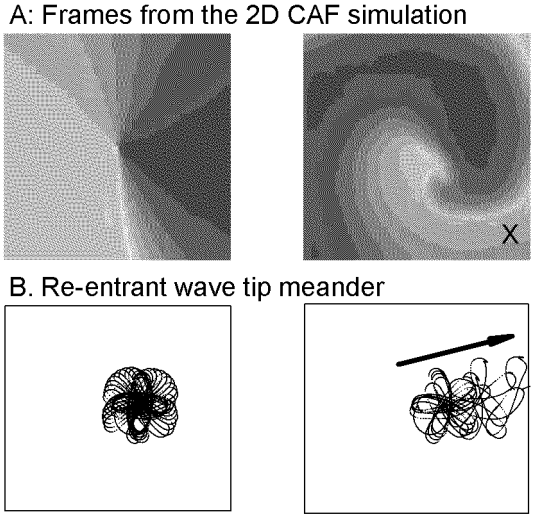

Figure 2. 2D simulation results. A: Left panel shows initiation of re-entry using the phase distribution method. Right panel shows representative frame from the CAF 2D simulation indicating location of the registration electrode as shown by "X". B: Re-entrant wave tip traces from the CAF simulation (left), and from the cardioversion simulation under CAF conditions (right). The overall direction where the spiral wave tip meanders is indicated by the gray arrow.

The scaling of Beatbox for the 3D simulations was quantified using JSC Computational resources. Two simulations were considered for the scaling. The first simulated plane wave propagation in a complete 3D box of size 235 x 269 x 298, which was the size of the box that embedded the human atrium mesh. The second simulated a plane wave propagation in the 3D human atrium model shown in Fig 3. In both simulations, file I/O was

suppressed to highlight solver efficiency. The work load on each process was quantified by estimating the allocated amount of tissue to each process. Processes (assuming there to be one process per processor) that did not have any work load were not considered in the scaling quantification.

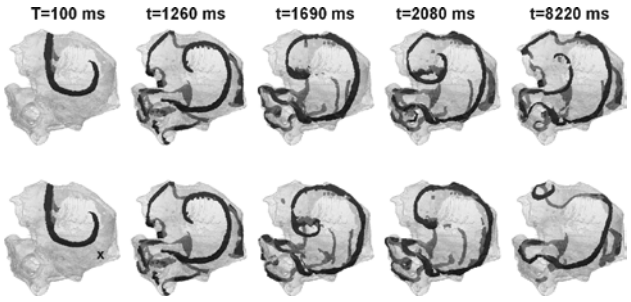

Figure 3. Frames from the 3D simulation. Top row shows representative frames from the 3D simulation under CAF conditions. Bottom row shows frames from the CAF simulation, but with feedback stimulation applied. The location of the registration electrode is indicated by "x" in the first panel of the bottom tow. After 8 s of electrical activity, the re-entry under CAF conditions was seen to be stable (top panels), while it migrated towards a model boundary (bottom panels) due to the feedback controlled stimulation.

3. Results

The CRN model has an APD of 306 ms. CAF drastically reduced the APD to 140.2 ms, a reduction of 47%. Such reduction has been observed experimentally [10]. APD reduction and the increased propensity to sustain high pacing rates under CAF conditions is reflected in the CV restitution shown in Fig 1.

The 2D simulation results are illustrated in Figure 2. In 2D simulations, re-entry under control conditions self-terminated almost immediately. In contrast, the 2D re-entrant waves under CAF conditions persisted throughout the 10 s period of simulated electrical activity. The period of re-entry was found to be 300 ms under control while 120 ms under CAF conditions. To estimate the threshold stimulus to eliminate this stable re-entry, multiple simulations were conducted with progressively reducing amplitudes of a single large global stimulus. The threshold stimulus thus estimated in the 2D CAF case was found to be 4.5 pA/pF. Further, the feedback stimulation protocol was implemented as described in the Methods section. The smallest amplitude stimulus required to abolish the CAF re-entry was estimated to be 1 pA/pF and required 10 stimuli.

The 3D simulations are illustrated in Figure 3. As in the 2D case, re-entrant waves self-terminated rapidly in the control 3D model. Under CAF conditions, the re-entrant wave was stable and the re-entry persisted for the 10 s period of simulated electrical activity.

The meander of the 3D re-entry was larger than that in the 2D case, possibly due to surface curvature and other anatomical features like blood vessel openings. After characterizing the 3D CAF re-entry, the defibrillation threshold in the 3D model was estimated by means of multiple simulations. A defibrillation threshold of 4.5 pA/pF was found in the 3D model, which is identical to the 2D case. In the 3D model, the migration of the scroll wave tip was hindered by the interaction of the scroll wave arm with anatomical curvature and anatomical defects (e.g. blood vessel holes). Although the arm of the re-entry gave rise to minor secondary propagations, those were short lived and the single mother rotor meandered over a limited area of the right atrium. Notwithstanding, defibrillation was achieved by using multiple stimuli controlled by the registered signal at a low amplitude stimulus of 1 pA/pF. Defibrillation was achieved within 9 s of simulated activity by applying 58 stimuli.

In the 2D simulations, 10 s of electrical activity was simulated using 32 processors in 15 minutes. Simulation 10 s of electrical activity in the 3D model using 256 processors required 8 hours. The efficacy of Beatbox's solvers is reflected in the scaling results shown in Figure 4. When actual 3D atrial geometry was used, the scaling is close to the ideal scaling till up to 256 processors. At larger number of processors, the scaling is suboptimal. In the 3D box simulations, the scaling of Beatbox's solvers is close to the ideal scaling for several thousands of processors as shown in Figure 4.

4. Discussion

Beatbox is a portable, alienable, flexible, extensible and efficient HPC cardiac simulation environment. To extend these functionalities, Beatbox's cell and geometry repositories are being continually extended. The package is being tested in case studies such as presented in this abstract as well as collaborating groups of cardiac modellers. The strategy for parallelisation based on optimal domain decomposition is being improved. Efficient bidomain solvers based on Alternating Directions Implicit (ADI) schemes are being implemented. The efficiency of the parallel file I/O is being improved in on-going collaborative projects. Further, the scaling of the domain decomposition will be improved by addressing the issue of load balancing as discussed in the Methods section.

The efficacy of a versatile, clinically applicable cardioversion protocol is being tested in this on-going case study. As can be seen, a low energy stimulus applied at appropriate time intervals can induce the re-entry to migrate to tissue boundaries and thus eliminated it. Thus, a single high energy shock cardioversion which may lead to post therapy complications can be replaced. The low

energy protocol can be further optimised for use with implantable cardioversion devices. Further simulations using realistic pacing protocols [5] are being developed.

The source code, working scripts, documentation as well as technical support for Beatbox can be obtained from the senior authors.

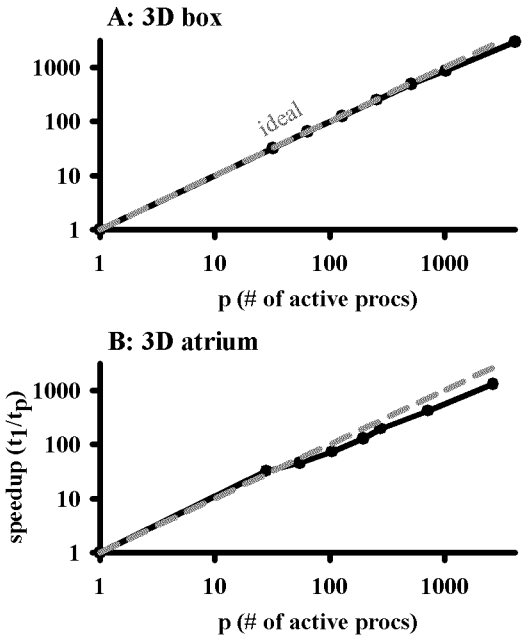

Figure 4. Scaling of Beatbox. In both panels, the gray dashed line represents ideal scaling.

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