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3D Bioelectrical Modelling of Interstitial Fibrosis Networks and Ventricular Arrhythmias in Non-ischemic Cardiomyopathy

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Abstract

I. INTRODUCTION

In the current study we develop an efficient 3D simulation methodology for cardiac tissue with networks of interstitial fibrosis, for use in patients with ventricular non-ischemic cardiomyopathies. Our method fully accounts for topological effects such as branching within the fibrosis network. Furthermore, we demonstrate in a patient specific geometry how such a network can greatly increase activation delays, and cause a reentrant arrhythmia.

II. METHODS

A. Patient MRI Dataset and 3D Geometrical Modelling

Late gadolinium enhanced cardiovascular magnetic resonance imaging (LGE-CMR) images were acquired at St. Thomas Hospital from a patient with non-ischemic dilated cardiomyopathy (NIDCM) and late gadolinium enhancement (LGE) in the basal septum. The scanning protocol consisted of details of MRI protocol. Ethical approval was given by the approval committee, approval number, and the patient gave written informed consent in accordance with the Declaration of Helsinki. The scanning resolution of the image stack was 1.3 mm in plane and 2.0 mm out of plane.

The walls of the left ventricle were segmented using the medical image software Eidolon[1], and the LGE was delineated using a semi-automated full-width at half maximum technique. Tetrahedral meshes were created using CGAL[2].

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For the purposes of limiting the computational expense of running detailed simulations, a reduced size mesh was created. This mesh consisted of all myocardial tissue within 2cm of the LGE zone. The maximum edge length of the mesh was 0.25 mm within the LGE and 0.4 mm outside of the LGE. Both the mesh and example image slices are shown in Figure 1.

In addition to the reduced mesh, a full mesh of the left ventricle was created for the determination of the local myocardial architecture. This architecture consisted of fibre, sheet and sheet normal directions, which were assigned to each element according to the rule-based method of Bayer et al. [3]. The relevant section of the local architecture was then transferred onto the reduced mesh via interpolation.

B. Generation of Interstitial Fibrosis Networks from LGE-CMR

The clefts between cardiomyocytes caused by interstitial fibrosis occur on a spatial scale that is an order of magnitude below that of our LGE-CMR image resolution. We therefore require a way to estimate the location of interstitial clefts in our meshes. One approach to this problem is to randomly assign fibrosis to mesh entities [4, 5, 6, 7, 8]. In our case this consists...
of assigning each mesh face within the LGE a probability score between 0 and 1. This creates a fibrosis probability map. Different realizations of the probability map can be created by generating a random number between 0 and 1 for each mesh face within the LGE, and assigning the face to be fibrotic if the random number is larger than the probability. The selected faces together form a simulated network of interstitial fibrosis, such as the one shown in Figure 1c.

Given that the image intensity of LGE scales with the amount of fibrosis [9], it is reasonable to assign higher fibrosis probability scores in regions with higher intensity. We achieve this by considering the normalized fibrosis intensity

\[ I^* = \frac{I - I_{ref}}{I_{max} - I_{ref}}, \]

with \( I, I_{max} \) denoting the local, and maximum LGE image intensities. The reference intensity \( I_{ref} \) is taken to be the mean intensity over all non-LGE voxels.

Furthermore, we assume that clefts of interstitial fibrosis are most likely to be aligned with the local myocardial sheet architecture, due to the substantial presence of connective tissue between sheets [10]. We therefore model the probability of a mesh face being fibrotic as

\[ p = \alpha \cos \theta I^*, \]

where \( \theta \) is the angle between the face normal and the local myocardial sheet normal direction. The parameter \( \alpha \) represents the global maximum fibrosis density that we use to control the total amount of fibrosis in a mesh. We considered \( \alpha \in \{0.2, 0.4, 0.6, 0.8, 1.0\} \), and created 5 different fibrosis network realizations for each fibrosis level, as well as a control model with no fibrosis, giving 26 different models.

**C. Element Face Disconnection Algorithm**

Once we have selected a network of fibrotic faces we are left with the task of modelling the local effect of the fibrosis on electrical propagation. Ex-vivo studies of heart tissue with Non-ischemic cardiomyopathies (NICM) [11, 12] have reported small scale conduction barriers due to fibrosis. We model this effect by creating no-flux boundaries along the fibrotic faces, using a nodal decoupling technique based on the method of Costa et al. [13]. This method consists of creating extra copies of nodes along fibrotic edges/faces that exist in the same locations as the originals. The old and new nodes are assigned to different mesh elements, thereby creating a local discontinuity. In 2D this discontinuity is typically present along a mesh edge, whereas in 3D a mesh face is more appropriate.

We now describe how extra nodes can be created and assigned in a complex 3D network of fibrosis in such a way that the correct topology is achieved. That is elements which are disconnected by split faces should not share nodes. This task is trivial when there is no branching in the network, as each face’s vertices can simply be doubled and assigned to elements on opposing sides. However, in the presence of branching, a more sophisticated procedure is required to create new nodes and assign them to the correct elements.

We propose a vertex based algorithm with a local connectivity analysis to correctly assign new nodes to elements. This algorithm consists of looping over every vertex that is located on at least one split face, and performing a local connectivity analysis, as shown in Figure 2. In the connectivity analysis a graph is built whose nodes are the elements which contain the current vertex (e.g. Figure 2b). Two elements are connected in the graph if they share a face which is not split. The connected components of this local element graph then determine the number and assignment of the new vertices needed to achieve the local discontinuity.

It is possible that a particular splitting face does not disconnect the local connectivity graph. In 2D this can only occur if the target vertex is connected to a single split edge. Consequently, the local graph will only have a single component. In this case we can disconnect the connectivity graph along the mesh edge whose angle to the split edge is closest to 180 degrees. In 3D the situation is slightly more complicated, and we need to check that the elements on opposite sides of a split face are disconnected in the element graph. If they are not then we need a set of element faces to form a splitting plane among the local elements. This can be achieved by ranking all faces neighbouring the current vertex by the dot product of the face normals with the normal of the face that we wish to disconnect. The faces with the smallest dot product can then be progressively removed from the local element connectivity until two disconnected element groups are created.

A pseudocode description of the 3D nodal splitting algorithm is given in Algorithm 1. As a preprocessing step to this algorithm we build a global element connectivity graph that is disconnected along all split faces, and then remove all connected components from the mesh expect for the largest one. This removes all electrically isolated mesh elements and simplifies later calculations.

**D. Electrophysiology Simulation**

Electrical activity was simulated with the standard monodomain representation, and piecewise linear basis functions. Cellular kinetics were specified by the 2006 Ten-Tusscher model [14] of the human ventricular action potential, integrated with step size 20 \( \mu \text{s} \). Both monodomain and cellular kinetics were implemented in the software package CARP [15]. The primary output of interest from the monodomain model was the transmembrane potential \( v_m \). Activation times were recorded at the first time that \( v_m \) crossed 0 mV with a positive derivative.

Conductivities were tuned to match experimentally observed conduction velocities [12]. In the non-LGE areas fibre conduction velocity (CVF) was 84 cm/s and transverse conduction velocity (CVT) was 23 cm/s. LGE areas were assigned reduced conductivities as in our previous study [4], that is regions in the intensity range 0-25% and 25-50% above the reference intensity, \( I_{ref} \), had CVT reduced by 25% and 50% respectively, with normal CVF. Regions in the intensity ranges 50-75% and 75-100% above \( I_{ref} \) had CVF reduced by 25% and 50% respectively, and CVT reduced by 50%.

All electrical stimuli were applied with a strength of 500 \( \mu \text{A/cm}^2 \) for 2 ms.
Fig. 2: An example of local connectivity analysis to create a topologically consistent set of extra vertices. a) The vertex 6 in the middle of the mesh is visited by the algorithm, with neighbouring elements $e_1 - e_5$. The edges between $e_2 - e_3, e_3 - e_4$ and $e_1 - e_5$ are to be split and are marked in red. b) The local element connectivity graph. c) Mesh with elements coloured according to their connectivity. d) Two extra vertices are added (7, 8) and assigned to elements according to the local connectivity. Note that later iterations of the algorithm can be expected to visit nodes 2, 3, 5 and complete the required discontinuities along the red edges.

**E. Simulated Programmed Electrical Stimulation**

Simulated programmed electrical stimulation was used to test for the possibility of each 3D model to initiate an electrical reentry. The protocol consisted of a preconditioning cycle of 3 beats at 600 ms intervals, followed by up to 3 beats with dynamically determined intervals. The timing of the dynamic beats was determined by algorithmically finding the local effective refractory period using a binary search. This search began with the intervals (200 ms, 450 ms) and ended when two consecutive timings were found such that the second one initiated a new wave of activation whereas the first one did not. A new wave was detected by the presence of any activations within 4.2 cm of the stimulus site at 110-120 ms after the stimulus initiation. After each dynamic beat 800 ms of electrical activity were simulated and a reentry was determined if any activations were present within 1 cm of the stimulus site after 300 ms.

**F. 2D test meshes with differing fibrosis topology**

To demonstrate the need for a topologically correct vertex disconnection algorithm we created a simple 2D test case consisting of 2 meshes with the same arrangement of split edges, but with differing element topologies. Each mesh had dimensions 9.5 mm x 9.5 mm, and was divided into 38x38 boxes, with each box consisting of two triangular elements sharing a diagonal line going from left to right. Fibrotic edges were designated in a row of 10 crosses spaced 1 element apart (see Figure 3). In the correct topology (tight) each cross separates the surrounding elements into 4 groups, whereas in the incorrect topology (leaky) there are diagonal connections resulting in only 2 separate element groups. Conductivities were assigned to both meshes corresponding to an effective conduction velocity of 17 cm/s.

**Algorithm 1 3D element face disconnection algorithm that produces the correct element topology.**

```plaintext
function SPLIT_VERTICES(split_faces, mesh_elements)
    Let split_vertices = all vertices in split_faces.
    For v in split_vertices
        Let G = the local element connectivity graph, disconnecting elements who share a face in split_faces.
        For split face f neighbouring v
            if elements neighbouring f are connected in G then
                G = DISCONNECT(G, f, v, mesh elems)
            end if
        End For
    End For
    Return mesh elems, and all new_vertices
end function

function DISCONNECT(G, f, v, mesh_elements)
    Let F_local = the set of all faces neighbouring v whose elements are connected in G.
    Sort F_local by the dot product of each normal to the normal of f.
    while elements neighbouring f are connected in G do
        Remove from G the connection corresponding to the next face from F_local.
    end while
    Return G.
end function
```

**III. Results**

**A. Fibrosis topology modulates transient conduction block**

We stimulated the tight and leaky test meshes twice each, with a coupling interval of 340 ms. All stimuli were located halfway across the bottom edge. The first wave crossed the row of fibrotic crosses in both meshes. The second wave however, was stopped by the tight topology but not by the leaky topology (see Figure 3). This demonstrates that the presence of transient conduction block (a known precursor to reentry) is influenced by the fibrosis topology and also motivates the use of Algorithm 1 in the 3D geometries.
B. Activation delays are increased by fibrosis and faster pacing

We tested the effects of increased interstitial fibrosis on patterns of electrical activation in our 3-D models, using a sequence of stimuli with decreasing coupling intervals. The coupling intervals were 3x600 ms, 350 ms, and finally 270 ms. Activation times were measured for the final three beats, in a plane parallel to the valves and passing through the stimulus location (see Figure 4b). These activation maps are displayed in Figure 4a for example models with fibrosis densities 1.0, 0.6 and 0 (control). The maps show that activation was progressively slowed as the coupling interval decreased and amount of fibrosis increased. Furthermore these effects were often that both decreased coupling interval and increased fibrosis contributed to the activation delays. Finally we note that the activation times in the control model smoothly increased with the distance to the stimulus site. In contrast to this the activation patterns in the models with fibrosis were more irregular. This irregularity was exacerbated by faster pacing as activation pathways became more convoluted.

C. Transmural activation times correlate with reentry incidence

Using the same stimulus location and pacing sequence as in the previous section, we measured the transmural activation time (TAT) in each model, that is the time for each wave to reach a site on the epicardium opposite to the stimulus (see Figure 5d). In Figure 5a we display the mean and standard deviation of TAT for 5 models at each level of fibrosis density. We note that both the mean and standard deviation of TAT increased with the level of fibrosis, indicating a greater influence of the fibrosis network on the electrical propagation. This increase was very modest at the 600 ms coupling interval, but became much more pronounced with the 350 ms and 270 ms intervals. Indeed the difference in mean TAT between the models with fibrosis density 1.0 and the control model was 43 ms at the 270 ms coupling interval.

Using the simulated programmed electrical stimulation protocol, we tested each model for the possibility of generating an electrical reentry. That is a signal that reactivated the tissue after the initial wave of activation was complete. The number of reentries that we observed for each fibrosis density level is given in Figure 5c. We note that there are no reentries at the fibrosis density level 0.2 and in the control model, and that the reentry incidence increased with increased fibrosis density. By comparing Figures 5a and 5c we can see a correlation of TAT values with reentry incidence. At the density level 1.0 the mean TAT score with coupling interval 270 ms increased.
dramatically and all 5 models generated a reentry.

![Fig. 5: The relationship between transmural activation times (TAT) and reentries inducible by simulated programmed electrical stimulation. a) The mean and standard deviation of the TAT values from 5 random fibrosis networks for each level of maximum fibrosis density. b) Timing of stimuli used to calculate TAT scores. The blue lines indicate stimuli for which TAT was measured. c) The number of random fibrosis networks for which reentry could be simulated at each density level. d) Epicardial view of the ventricular geometry with TAT measurement location (yellow sphere).](image)

D. Mechanism of reentry

We examined \( v_m \) of the transmembrane potential for the models that reentered in order to ascertain the mechanism of reentry. In all of the models pacing rapidly led to increasingly slowed activation and the build-up of islands of activated tissue that persisted even when most of the tissue had repolarized. With further rapid pacing these islands of delayed activation were able to survive long enough to reactivate neighbouring excitable tissue and cause a reentry. This sequence of events is depicted in Figure 6 for an example model.

![Fig. 6: Endocardial view of transmembrane voltage (\( v_m \)) maps after an extrastimulus that triggers an electrical reentry. The numbers at the top of each voltage map are the simulation time in ms, green arrows highlight directions of activation. 2450) The extrastimulus (green symbol) arrives into a heterogeneous repolarisation landscape created by the previous stimuli. 2580, 2650) The extrastimulus spreads unevenly, first activating the tissue to the left and then later to the right. 2725, 2800) Most of the tissue repolarises. 2900) Islands of activated tissue remain in the fibrotic areas. 3000) Reentrant wavefronts emerge out of the fibrosis. 3120) Most of the tissue has been reactivated due to the reentry.](image)

IV. DISCUSSION

V. CONCLUSION

REFERENCES


