# High Performance Computer Simulations for the Study of Biological Function in 3D Heart Models Incorporating Fibre Orientation and Realistic Geometry at Para-Cellular Resolution

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## Abstract

*Information regarding the propagation dynamics of intramural electrical wavefronts in the 3D volume of the ventricles is critical in gaining a better understanding of normal and pathological cardiac function. However, investigation into such phenomena using cardiac modelling has so far been impaired due to limitations in the structural details included in current cardiac computational models. Here, we describe the technological pipeline required for the construction of realistic, highly-detailed and personalised whole ventricular models directly from high-resolution MR images and their use within a reliable, fully tested cardiac simulation software (Chaste). Simulations of cardiac propagation in the structurally-detailed model are presented that reveal the importance of complex structural geometry, fibre orientation, blood vessels and other heterogeneities in propagation of activation wavefronts through the ventricular volume. The tools and techniques presented in this study are expected to be key in the development and application of the next generation of cardiac models.*

## 1. Introduction

Knowledge of the specific dynamics of intramural propagating electrical activation wavefronts throughout the heart is critical in gaining a better understanding of cardiac function in both healthy and pathological conditions. However, the way in which wavefronts interact with, and propagate through, heterogeneous regions of tissue has not been thoroughly assessed due to limitations in the detail and complexity of current whole ventricular models. The goal of this study is to develop the techniques to build realistic, highly-detailed and personalised whole ventricular models directly from high-resolution MR images for use within a reliable, fully tested cardiac simulation software. The software and models developed here are used to simulate electrical propagation in the 3D volume of the rabbit ventricles, with unprecedented resolution in myocardial structure.

To achieve this goal, a realistic anatomically-detailed finite element ventricular model was constructed directly from a high-resolution (voxel size $\approx 25\mu\text{m}^3$), 3D rabbit MR data set. The images were segmented using a combination of level-set techniques and used to generate tetrahedral meshes. The model includes detailed structural information including blood vessels, papillary muscles, trabeculations and a representation of realistic fibre orientation. Propagation of electrical activation within the realistic rabbit ventricular model was simulated by solving the monodomain equations using Chaste, a novel biological simulation environment. Chaste has been developed using state-of-the-art numerical and computational techniques, as well as professional software engineering practices, and provides a rigorously-tested library of computational biology software.

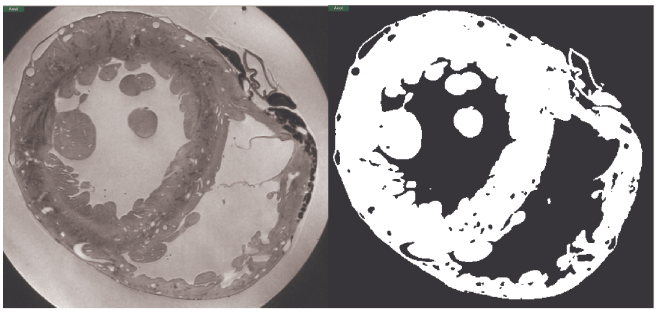
## 2. Development of computation model

### 2.1. MR data acquisition and processing

MR scans were performed on a fixed and agar embedded female rabbit heart ($\approx$ 1.2kg) using an 11.7 T (500 MHz) MR system. For specific details of the MR system and scan protocols used see [1]. Scans were acquired with an in-plane resolution of $26.4$ $\mu$m $\times$ $26.4$ $\mu$m and out-of-plane resolution of $24.4$ $\mu$m producing a MR image stack containing $1024 \times 1024 \times 2048$ voxels. Due to computational memory restraints, however, this was downsampled once by a factor of 2 using Matlab (The MathWorks, Inc.) to produce a more managable data set containing $512 \times 512 \times 1024$ voxels. Fig. 1a shows a cross-section of the MR data set taken along the short-axis of the heart viewed using the freely available software Seg3D (`software.sci.utah.edu/`).

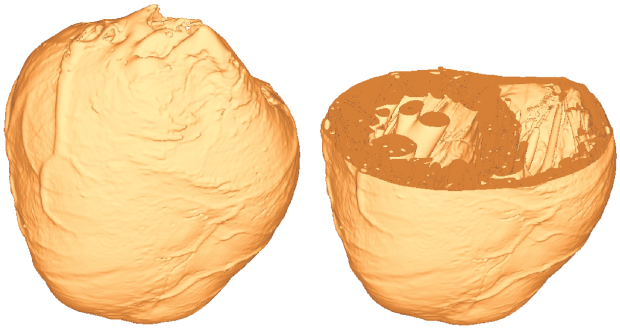
### 2.2. Segmentation of MR data set

Segmentation is the critical first stage in extracting geometrical information from the MR data set to build a



(a) (b)

Figure 1. Anatomical high-resolution MR image (a) with final result of segmentation pipeline (b).



(a) (b)

Figure 2. Finite element rabbit ventricular mesh.

high-resolution anatomically-detailed computational cardiac model. Our goal is to create a binary mask allowing discrimination of the heart's tissue volume from the surrounding background volume and cavities, as well as the extracellular cleft space and vessels. The downsampled data set was segmented using a segmentation pipeline application based on level sets algorithms and developed using the Insight Toolkit libraries (ITK, `www.itk.org`).

Due to spatial variations in coil sensitivity, a significant overlap of intensity levels between tissue and background exists. This makes basic approaches such as thresholding insufficient in this case. We developed a pipeline of three separate level-set segmentation steps (respectively intensity-based, geodesic active contour and Laplacian-based), ordered to provide good robustness to initialization in the first steps and excellent accuracy at the end, with the output of each stage in the pipeline acting as an initial segmentation to the next stage. The final result of the segmentation pipeline can be seen in Fig. 1b.

## 2.3. Segmentation post-processing

Following the segmentation pipeline, the binary mask was further improved by a series of morphological operations. Isolated segmentation artifacts were removed by the use of a connected component algorithm, to ensure that all structures in the heart are electrically connected. Thin-walled blood vessels on the outer-surface of the heart volume, which were not sufficiently defined in the downsampled MR data set to be extracted during the segmentation process, were manually modified. Small air bubbles were also manually removed. Finally, to produce a purely ventricular model, a B-splines surface was manually fitted to separate the ventricles from the atria. All tissue voxels above this plane were removed, thereby removing the atria.

## 2.4. Mesh generation

The majority of the leading cardiac electrophysiology simulators (such as the one used in this study, Chaste, described in the next section) usually utilise tetrahedral finite element meshes as an input. Therefore, the final segmented and post-processed data set was used to generate a tetrahedral finite element mesh using the meshing software Tarantula (`www.meshing.at`). Tarantula is an Octree-based mesh generator that generates unstructured, boundary fitted, locally refined conformal finite element meshes, and has been custom designed for cardiac modelling.

The final mesh consisted of 3717056 finite element node points making-up 20401874 tetraheral elements (with mean edge-length of approximately 130$\mu$m) and with 1194070 bounding triangular faces. Epicardial as well as left ventricular (LV) and right ventricular (RV) endocardial surfaces were defined as separate surfaces. Fig. 2 shows the final cardiac mesh; panel (a) shows the full data set, whilst (b) shows a slice along the short axis.

# 3. Chaste: reliable heart simulations

Mathematical modelling of cardiac physiology, and, in particular, cardiac electrophysiology, is a mature discipline. Several advanced software packages for modelling cardiac electrophysiology have been developed by different groups around the world. The Chaste project started with the aim of addressing some of the limitations presented by these software packages. In particular, Chaste was developed with the following specific requirements: i) to use state-of-the-art software engineering methods, so correctness is ensured, ii) to achieve maximum efficiency on High Performance Computing (HPC) platforms by using state-of-the-art numerical and computational techniques, iii) to be freely available (including source code) to the scientific community, and iv) to be generic enough, and not constrained to a particular application. For a more

complete description of the philosophy and methodology behing Chaste, the reader is referred to [2].

## 3.1. Capabilities

Currently, Chaste can solve both monodomain and bidomain models of cardiac electrical activation on any given mesh. Input files for the simulations are written in XML. Parameters are structured in three categories, i) simulation description: duration of the simulation, mono/bidomain model selection, cellular model selection, stimuli to be applied, and output details, ii) physiological properties: intracellular and extracellular conductivities, cell model heterogeneites, and physical constants defined in the mono/bidomain equations (i.e. capacitance or surface area to volume ratio), and iii) numerical parameters: partial and ordinary differential equations time steps, tolerances, and linear solver and preconditioner selection.

The Chaste team has worked in many of the mathematical, computational, and physiological aspects of electromechanical heart simulation. The most remarkable features of Chaste are:

*Cell models* Easy integration of any cell model written in CellML with PyCML [3].

*Finite Element Methods* Semi-implicit solution schema for accuracy and performance [4].

*Linear algebra* Use of state-of-the-art linear solvers and preconditioners via PETSc.

*Parallel performance* Mesh partitioning for parallel communication reduction with METIS.

*Input/Output* Use of XML for extensible and platform independent input definition. Scalable and platform independent output with HDF5.

*User requested features* Interface for cell model parameterisation in different heart regions.

The first fully-functional version of Chaste was released a few months ago and can be downloaded from `chaste.ediamond.ox.ac.uk`.

## 3.2. Fibre orientation support

Fibre orientation is known to play a crucial role in heart electrical activation. DT-MRI images, which can be used to estimate fibre orientation, were not available in this case. To overcome this, we implemented a variation of the mathematical model for ventricular fibre orientation originally presented by Streeter [5, 6], described below.

*Algorithm 1:* **Generation of fibre orientation data**.
INPUT: mesh $M = (N, E)$, set of nodes $N$, elements $E$
OUTPUT: $(\vec{a_f}, \vec{a_l}, \vec{a_n})_{e \in E}$, orthonormal basis defining direction of fibre, laminae sheet and laminae sheet-normal for each element in the mesh
$\forall n \in N$,

1. Compute distance from $n$ to the endocardium ($d_{endo}$) and epicardium ($d_{epi}$). $d_{endo} = min(d_{lv}, d_{rv})$. To do this, we used an ordered propagation algorithm [7]. The algorithm takes as input the mesh $M$ and a definition of the epicardium, LV, and RV surfaces and outputs a distance map from each of those surfaces to every node in the mesh.
2. Compute wall position parameter $p_n = \frac{d_{endo}}{d_{endo}+d_{epi}}$
3. Compute $p'_n$ as average of $p$ and all its neighbours

Then $\forall e \in E$

4. Compute $\vec{u} = \nabla p'$, the gradient of $p'$ at the centroid of the element and normalise.
5. Compute $\vec{v} = \vec{u} \times \hat{\imath}$ and normalise ($\hat{\imath}$ is apex-base).
6. Compute $\vec{w} = \vec{u} \times \vec{v}$
7. Compute $p'_e$, the average of $p'$ for all the nodes in $e$
8. Compute $\alpha = R(1 - 2p'_e)^3$. Set R equal to $\pi/3$ for the LV and $\pi/4$ for the RV.
9. Compute $(\vec{u}, \vec{v_r}, \vec{w_r})$ as the $\alpha$ radians rotation of $(\vec{u}, \vec{v}, \vec{w})$ about $\vec{u}$. $(\vec{a_f}, \vec{a_l}, \vec{a_n})_e = (\vec{v_r}, \vec{u}, \vec{w_r})$

## 3.3. Performance related issues

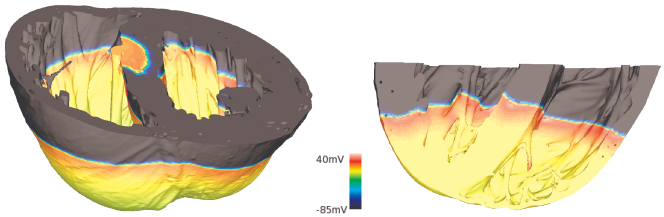
Chaste has been designed to be scalable on complex models and work on HPC platforms. However, due to the unprecedented geometric complexity of models in this work, some modifications were required to the design. First, large meshes impose a large memory footprint due to the sheer number of nodes and elements. The memory associated with each of these objects was reduced by removing some of the cached geometric data (such as the Jacobian of a tetrahedron) at the expense of having to compute data on the fly. Second, the process of loading a mesh was designed as a two-step process with the mesh first being read from disk (in any supported format) and stored in a neutral format in memory. This intermediate definition was processed and read into the mesh class. In the modified Chaste, the intermediate structure is not built in its entirety, but is read from disk and passed into the mesh constructor in a lazy manner. Third, the use of compressed formats for symmetric sparse matrices was enforced without a noticeable loss in performance.

# 4. Results

Following implementation of Algorithm 1 to generate fibre orientation, Chaste was used to simulate electrical propagation throughout the rabbit ventricular volume using the monodomain model. Cellular membrane dynamics were defined by the Luo-Rudy 1991 ionic model [8], although any other ionic model could have been used. Conductivity was considered to be orthotropic [9] and homogeneous all over the mesh with values: $0.175$, $0.875$, and $0.4375$ S/m in the fibre direction, transverse to the fibre direction in the plane of myocite laminae, and normal to this plane respectively. A stimulus of magnitude $-0.5$ A/cm$^2$

and duration 0.5 ms was applied to nodes within the apical region of the mesh, which initiated propagation of an activation wavefront of depolarisation in the direction apex-to-base. 30 ms of simulated propagation took 13 hours on one core of an Intel Xeon 3 GHz server with 16 GB of RAM.

Fig. 3 shows a snap-shot of the wavefront of depolarisation spreading through the high-resolution ventricular mesh. The use of such a highly-anatomically detailed model is seen to significantly affect the propagation patterns of the activation wavefronts with the small structures such as trabeculae and papillary muscles, absent in the majority of lower resolution cardiac models, playing particularly important roles. For example, in panel (a) conduction of the wavefront along a small trabeculae which then joins the septum (to the left) causes premature depolarisation of the septum prior to the main advancing wavefront. In addition, the complex structural geometry and inclusion of anisotropic conduction within the tissue leads to a highly non-planar wavefront morphology. This is evident in panel (b) in the LV wall where the front is seen to propagate faster close to the epicardial/endocardial surfaces than in the mid-myocardium, an effect also evident in the septum.




(a) (b)

Figure 3. Wavefront of depolarisation spreading through ventricular mesh following apical stimulation.

## 5. Discussion and conclusions

The results of this study successfully demonstrate the ability of our developed pipeline in generating individualised high-resolution cardiac models and how the use of the Chaste software can perform simulations with such detailed and computationally-challenging models within HPC environments with fast, reliable results. We have shown that the application of such tools allows direct assessment of the specific impact of complex structural geometry, fibre orientation, blood vessels and other heterogeneities on intramural wavefront dynamics. Specifically, our simulations have demonstrated that the inclusion of such heterogeneities within cardiac models significantly affects the local orientation of activation wavefronts within the ventricular walls during pacing propagation. The development of such a pipeline for the construction of highly detailed structural models directly from anatomical MR data, combined with the use of Chaste to simulate the functional behaviour of the model, provides an important step forward in the development and application of the next generation of cardiac models.

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