Semi Automated Pipeline to Create Anatomical Twins and Perform Electrophysiology Simulations for Hypertrophic Cardiomyopathy

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Abstract

Cardiomyocyte properties and ventricular anatomy play a critical role in the propagation of electrical signals, the timing of contractions, and the coordination of ventricular function. This is especially important in hypertrophic cardiomyopathy (HCM), where genetic mutations lead to altered contractile function and abnormal myocardial thickening. Although the effects of these anatomical and cellular changes remain underexplored, gaining a deeper understanding of these mechanisms could enhance disease management. We propose a semi-automated pipeline to create anatomical twins for HCM patients, aiming to study the disease's impact on cardiac activation. By integrating cardiac magnetic resonance imaging with thorax computed tomography scans, we construct torso models and employ the ToR-ORd-dynCl ionic model to investigate cardiomyocyte properties. Our findings indicate that alterations in HCM cellular electrophysiology have a limited influence on the overall heart activation pattern, which appears to be primarily governed by anatomical factors. Further research is required to assess the impact of tissue-level fibrosis on patient electrocardiograms.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is one of the most common genetic cardiac disorders, with an estimated prevalence of 1 in 500 worldwide [1]. It is characterised by thickening of the heart muscle, especially of the left ventricle, which can interfere with the heart's ability to pump out blood efficiently and thus lead to morbidities such as hypertension and remodelling. While some patients, with proper management, can have relatively normal lives, others are at risk of atrial fibrillation, stroke and sudden cardiac death [2]. This variability in presentation and heterogeneous outcomes makes HCM challenging to diagnose. Cardiologists, therefore, need a multidisciplinary approach, such as genetic screening and risk stratification, along with standard diagnostic and electrophysiological testing, to provide optimal care for affected individuals.

Imaging modalities such as cardiac magnetic resonance imaging (MRI) and cardiac computed tomography (CT) scans provide valuable information about the heart's anatomy and function, thus allowing precise measurements of wall thickness, assessment of myocardial fibrosis, and evaluation of blood flow patterns. Recent advancements have led to the development of electrocardiographic imaging (ECGI), which maps the heart's electrical activity. A wearable ECGI vest allows for continuous monitoring and the ability to detect subtle changes in cardiac electrical activity associated with HCM. While these tools delineate electrophysiology, underlying cellular changes caused by HCM-associated mutations in genes encoding sarcomeric proteins are yet to be fully understood.

Computational modelling to simulate and analyse the behaviour of the heart affected by HCM can help researchers and clinicians better understand the underlying mechanisms, predict disease progression, and test the efficacy of treatment strategies. Patient-specific models, tailored to an individual's unique data, help create a link between the anatomy, function and presentation of HCM. This study proposes a semi-automated pipeline to efficiently create patient-specific anatomical twins by combining MRI and CT data to simulate ECGI cardiac activation mapping in HCM patients.

2. Methods

The data used in this study comprised whole torso non-contrast CT scans along with high-resolution cine-cardiac

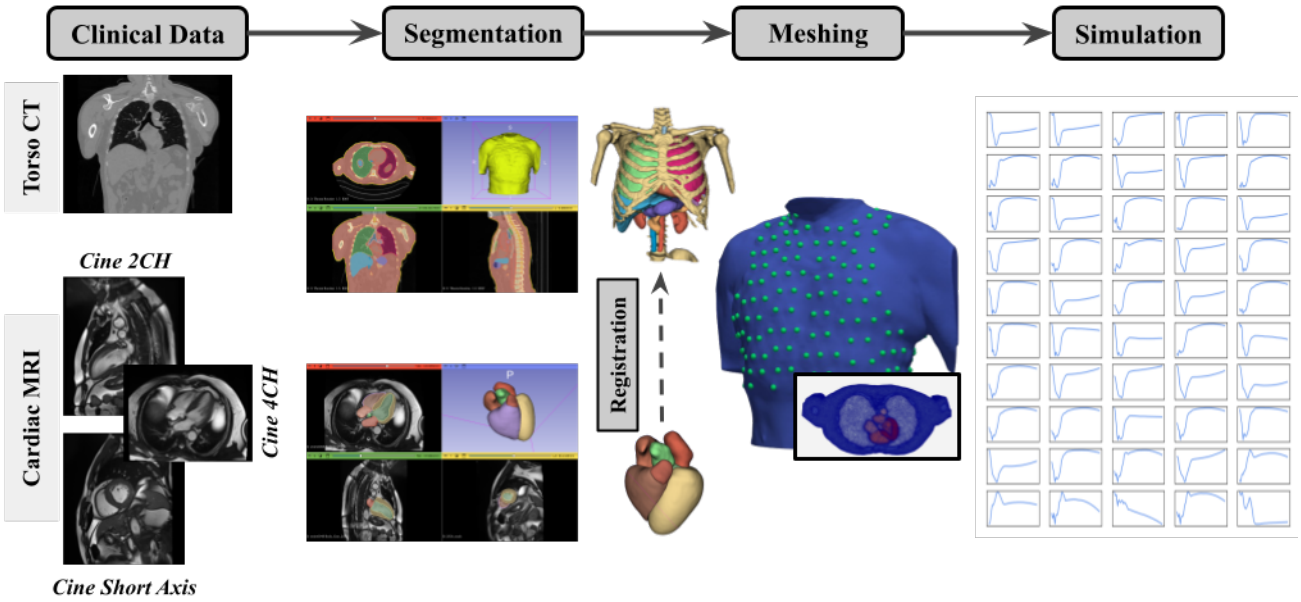

Figure 1. Generalized semi-automated workflow for anatomical twin generation.

MRI scans of HCM patients acquired by clinicians at Hammersmith Hospital. *Figure 1* shows the workflow developed to create patient-specific anatomical twins.

2.1. Segmentation

Segmentation of major organs in the abdominal and thoracic cavity, bones and skin was performed using 3D Slicer (Version 5.6.1). CT thorax routine series (thickness = 1.5 mm) was automatically segmented using the TotalSegmentator AI model [3] plugin in the 'fast' mode on a CPU machine. The post-processing step of the generated whole torso segments included smoothing segmentation boundaries and removing regions irrelevant to the study.

Hearts were segmented separately from 2D long-axis single slices and 3D cine short-axis volumes using a hybrid encoder-decoder convolutional neural network proposed by Qayyum et al [4]. The whole four-chamber heart, with individual labels for each chamber and the left myocardium, was then reconstructed using a label completion U-Net (LC-U-Net) by Xu et al [5]. Mislabeled hypertrophy regions were corrected manually to be included in the myocardium label. Subsequently, the walls of the right ventricle and the left and right atria were segmented manually in 3D Slicer by dilating the blood pools to 3mm and 2mm, respectively.

2.2. Registration

Although the thorax CT provides a heart segmentation, it fails to differentiate between cardiac chambers and myocardium. Therefore, to account for contrast and soft tissue resolution limitations of CT, the detailed cardiac MRI segmentation generated above was rigidly registered onto the torso using landmark matching in 3D Slicer. A list of fiducials at the apex of the heart, pulmonary valve and aortic valve was defined manually for heart segmentations of both imaging modalities. Using SlicerIGT [6], a spatial transformation was determined based on fiducial coordinates and applied to the MRI heart.

2.3. Finite element model

Unstructured, conformal, boundary-fitted volumetric torso meshes were generated directly from the multi-label segmentations using Simpleware (Synopsys, Inc.).

Using the Laplace-Dirichlet rule-based method [7], ventricular myofibre orientations were assigned to the mesh. For this purpose, the bi-ventricle mesh was first extracted from the torso, and the bi-ventricular base was defined as the intersection between the atrioventricular valves and the ventricles. The point on the left ventricle epicardium at the furthest distance was then set as the apex. Additionally, epicardial and endocardial surfaces of the bi-ventricle were extracted from the mesh to define Laplace equations to be solved. Endocardial/epicardial fibre and sheet angles were set as +40°/-50°and -65°/+25°, respectively, followed by solving the Laplace to assign fibre orientations.

Extraction of the surfaces mentioned above required the generation of UVCs, as defined by Gillette et al [8]. This process involved performing boolean operations according to tissue labels and establishing a mapping between the parent mesh and the extracted sub-mesh or surface, which was automated using CARPentry meshtool [9].

2.4. Electrophysiology Simulations

A 1-element thick subendocardium (SE) layer was defined for the bi-ventricular mesh to set up the ventricular conduction system. The His-Purkinje System (HPS) was assumed to be a fascicular conduction system comprising N fascicles, as noted by Gillette et al [8]. The earliest sites of ventricular activation of a given fascicle were identified and set as 'root points'. Tissue patches adjacent to the root points were assumed to activate instantly due to the high conduction velocity (CV) of HPS and the dense distribution of Purkinje fibres.

All organs in the torso (except the left ventricle (LV) and right ventricle (RV) myocardium) and the bath are considered to be resistive conductors with homogeneous constant conductivities, as listed in Table 1. The myocardium and SE layer conductivities are transversely isotropic with different values for the fibre and cross-fibre direction within intra- and extracellular space, as shown in Table 2.

Table 1. Conductivities for all regions in torso model, except LV and RV myocardium

Region	Conductivity (S/m)
Inner Body (bath)	0.2472
Skin	0.117
Bones	0.05
Kidneys, Pancreas, Liver	0.1667
Stomach, Spleen	0.1
Lungs	0.0714
Blood pools	0.6667
Atrial wall (left and right)	0.25

A Reaction-Eikonal (RE) model [10] combined with the ToR-ORd-dynCl ionic model [11], representing ventricular cardiomyocyte dynamics, was used to simulate action potential propagation and to compute source distributions driving the extracellular potential field. In the RE model, propagation of depolarization wavefronts is mediated by eikonal-based activation maps that give a solution for wavefront arrival times t_a as a function of location x. The solution t_a is then used to solve the RE model given as:

$$\beta C_m \frac{\partial V_m}{\partial t} = \nabla \cdot \sigma_i \nabla \{\Phi_i | V_m\} + I_{foot} - \beta I_{ion}$$

where β is the surface-to-volume ratio, C_m is the capacitance per unit area, V_m is the transmembrane voltage, σ_i is the harmonic mean conductivity tensor and I_{ion} is the ionic current.$\{\Phi_i|V_m\}$ represents that either Φ_i or V_m needs to be inserted, respectively if the bidomain or pseudo-bidomain model is used. I_{foot} is an additional stimulus current that initiates depolarization at site x at a time $t_a(x)$. The RE model can be further simplified by omitting the diffusion term.

Cellular dynamics were represented by the ToR-ORd-dynCl ionic model, which extends the ToR-ORd model by Grandi et al [12] by dynamically updating intracellular chloride concentrations according to its two chloride currents, calcium-sensitive Cl current ($I_{(Ca)Cl}$) and background Cl current (I_{Clb}). Finally, a lead-field-based approach was used to recover electrograms at ECGI electrode positions, as given by Poste et al [13]. Each ECGI vest had 252 electrodes with coordinates extracted from .torso files. The combined RE approach with lead-field recovery was based on the Reaction-Eikonal Lead Field (RELF) formulation proposed by Gillette et al [8], and simulations were performed using CARPentry.

3. Results

Simulations were performed on four HCM cases and a control healthy case to explore cellular and anatomical properties that drive ECGI activation patterns in HCM. ToR-ORd-dynCl model parameters were calibrated according to Tomek et al [14] to represent HCM-affected ventricular myocytes and compared against default model parameters representing healthy cells.

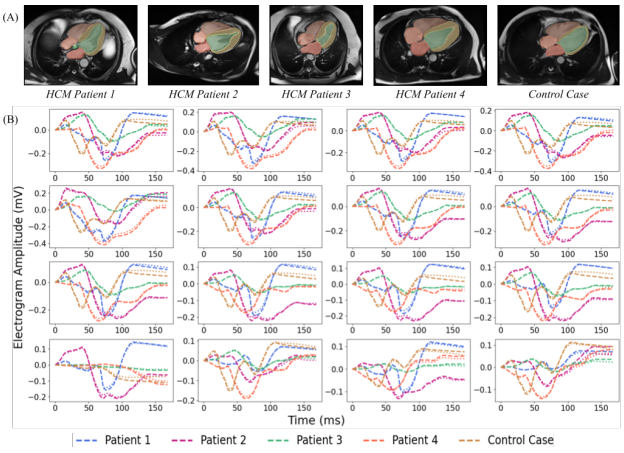

Figure 2. A) 4-chamber cine MRI segmentations showing varying degrees of hypertrophy. B) Simulated electrograms (EGMs) across 16 electrodes.

In *Figure 2B*, dotted lines represent EGMs simulated with default ToR-ORd-dynCl parameters, whereas dashed lines are those from calibrated parameters. For each patient case, slight to no variations were observed within these EGMs with changing cellular properties. On the other hand, comparing EGMs across patients, we can see significant differences in both EGM amplitude and shape. This can be explained by variations in patient anatomy, including the location and severity of hypertrophy (*Figure 2A*), apart from the overall body structure. Results were consistent across all vest electrodes.

Table 2. Conductivities for transversely isotropic regions

Region	Intracellular Conductivity (S/m)		Extracellular Conductivity (S/m)	
	Along fibre	Cross fibre	Along fibre	Cross fibre
Myocardium (LV and RV)	0.206	0.046	0.744	0.165
SE layer	1.711	—	6.059	—

3.1. Limitations

One limitation of this study is the manual delineation of hypertrophic regions. Future work should focus on automating the inclusion of these regions in heart segmentations to mitigate the limitations caused by subject variability in manual segmentation. Additionally, the electrophysiological simulations utilized generalized physiological values from existing literature for all patients. While fitting and calibrating the model to patient-specific data through sensitivity analysis was beyond the scope of this research, it is an area that warrants further exploration.

4. Conclusion

Our proposed workflow for generating torso models successfully replicated patient anatomy with minimal manual intervention. These models were also effective for conducting electrophysiology simulations. Preliminary simulation results indicate that changes in cellular properties have a limited effect on activation patterns, with alterations in the ECG QRS complex being largely driven by anatomical differences. Further investigation is needed to understand how structural variations and the degree of fibrosis influence cardiac activation.

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