Digital Twin of a Rabbit Heart in a Langendorff Setup

Daniel M P Leme[1], Saleem Ullah[2], Angélica Quadros[2], Jimena Paredes[2], Mayra U Barbosa[1], João Salinet[2], Joventino O Campos[1], Rodrigo W dos Santos[1]

[1] FISOCOMP, Federal University of Juiz de Fora, Juiz de Fora, Brazil
[2] HEartLab, Federal University of ABC, São Bernardo do Campo, Brazil

Abstract

This study presents the development of a digital twin of a rabbit heart, constructed using magnetic resonance imaging (MRI) and data acquired from a Langendorff perfusion setup, including optical mapping of the epicardial surface and ECG-like electrograms. The digital twin pipeline comprises several key steps: segmentation of MRI images and finite element mesh generation; mechanical heart simulation to align the geometry with the heart's configuration obtained with photogrammetry; fitting of action potential waveforms based on epicardial optical mapping data; and simulation of action potential propagation and ECG-like signals for comparison with experimentally recorded electrograms. The results demonstrated a good agreement between the simulated and experimental data. This integrated experimental-simulation framework offers a promising platform for investigating cardiac arrhythmias, testing pharmacological interventions, and developing new biomedical technologies.

1. Introduction

In the context of precision medicine, there is a growing demand for continuous acquisition and processing of patient-specific data in order to define more effective and personalized therapeutic strategies. Within this framework, the concept of the digital twin emerges as a computational representation that integrates anatomical, physiological, and dynamic patient data over time. This tool employs mechanical, statistical, and mathematical models to generate a realistic simulation of the individualized functioning of an organ or system, offering a new paradigm for diagnosis, monitoring, and therapeutic planning [1].

The Langendorff perfused heart model is an experimental technique widely used for studying cardiac activity under isolated conditions. In this approach, retrograde perfusion of the heart is performed through the aorta, allowing for the maintenance of cardiac function ex vivo. This technique enables the analysis of physiological and electrophysiological parameters in a controlled environment, making it valuable for the investigation of arrhythmias, coronary vascular function, physiological regulation, and pathological mechanisms associated with conditions such as hypertension, diabetes, heart failure, and ischemia-reperfusion injury [2].

The present work proposes the construction of a digital twin of the rabbit heart using magnetic resonance imaging and electric signals obtained from the experimental Langendorff model. The aim is to assess the accuracy of the computational modeling approach in representing cardiac dynamics, with a view toward its future application in optimizing preclinical drug testing and the development of new therapies.

2. Materials and methods

2.1. Ex-vivo dual mapping

The research protocol for the experiments was approved by the local Ethics Committee on Animal Use (CEUA), under protocol number 3947230519. A female New Zealand rabbit (3.1 kg, heart size: 3.5x2.5 cm and heart weight: 8.0 g) was anesthetized by infusion of buprenorphine hydrochloride (0.05 mg/kg), injected intramuscularly. After 30 minutes, a mixture of ketamine (100 mg/kg) and xylazine (14 mg/kg) was infused. After 10 minutes, 1,250 U/kg (Eq. 4) of heparin was injected intravenously into the rabbit's ear. Then a left thoracotomy is performed and the heart is extracted, cannulated to the Langendorff system, where a modified Krebs solution is carbonated by a mixture of carbogen (95% O2 and 5% CO2) and heated (37.5 ° C) perfusing the coronary arteries through the aorta.

Then the heart was immersed in a custom designed hexagonal tank, filled with a sucrose solution (in mM: 23 NaCl, 260 sucrose (C6H12O6)). Ten surface-mounted electrodes are strategically placed on each face of the hexagonal tank. The 60 electrodes are connected to a 64-channel recording head stage (RHD 64 Channel Recording Head stages, C3315, Intan Technologies). This setup allows high-density electrocardiogram acquisition at a 4 kHz.

Simultaneously, panoramic optical mapping was performed using the voltage-sensitive dye Di-4-ANBDQPQ (Vm), where the heart is excited by six deep red 650 nm LEDs. For fluorescence acquisition, the emitted fluorescence is passed through a long pass filter of 715 nm cut-on wavelength on each of the three high-speed cameras (HB-1800-S, Emergent technologies, 500 frames/s, 1600x1000 pixels) with C-mount 25 mm focal length lens, and the cameras separated from each other by 120°.

2.2. MRI acquisition

The MR images were acquired by the Siemens MAGNETOM 7 Tesla machine. The rabbit heart was placed in a sample cup, which was filled with fomblin and foam to anchor the heart, preventing it from floating; the heart was also injected with fomblin. Before positioning the heart in the equipment, it was fixated with sandbags and tape to minimize its movement during the exam.

2.3. Digital twin pipeline

The pipeline for obtaining the digital twin of the rabbit heart consists of segmenting magnetic resonance images and converting the surface into a volumetric format. The volumetric mesh is then converted into a specific format for mechanical simulation in Cardiax [3], where a pressure is applied to the endocardial surfaces, generating an expanded heart model, which resembles the one obtained through photogrammetry. This model is subsequently converted and used in the MonoAlg3D [4] for electrophysiological simulations. The simulations are performed using the monodomain model and the minimal cellular model [5], which propagate the electrical wave and compute the ECG-like electrograms to compare them with experimental data.

Anatomical computational model. First, the MR images were segmented using the 3D Slicer software. As illustrated in Figure 1(a), the endocardial surface of the right ventricle appears to be fused, possibly due to the effect of positioning the heart in the equipment during image acquisition. At this stage, the intersection region between the septum and the right ventricle is estimated using the Segmentation Erase tool to approximately open this area. This process is repeated for all slices until reaching the surface that separates the atria from the ventricles.

The resulting surface model is exported in STL format and subsequently processed in Meshmixer software. At this stage, the model is approximately sectioned at half of its height, allowing the separation of surfaces into four distinct anatomical regions: right ventricle (RV), left ventricle (LV), epicardium (EPI), and basal surface (BASE), as seen in Figure 1(b). The segmented surfaces are then used in GMSH to generate the finite element volumetric mesh, as illustrated in Figure 1(c).

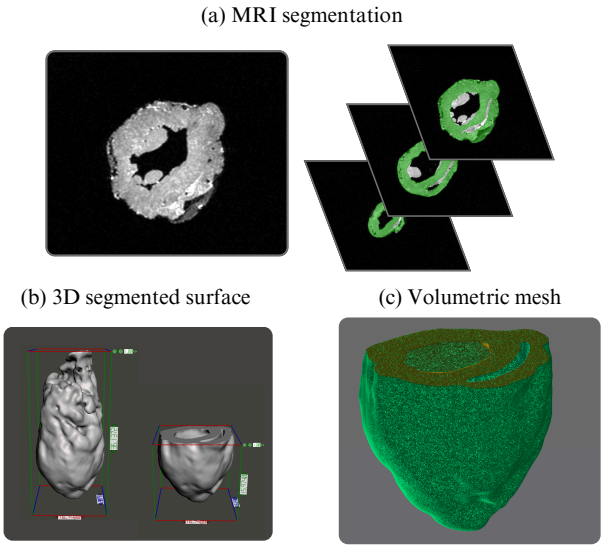


Figure 1. Anatomical computational model (a) Rabbit MR images and the segmentation performed on some slices. (b) 3D geometry reconstructed from segmentation. (c) 3D volumetric mesh.

This volumetric mesh is converted into the format of the cardiac mechanics simulator Cardiax [3], where a pressure of 1 kPa is applied to the heart's endocardial surfaces with 10 load increments. The $z-$displacements were restricted at the BASE and the heart tissue was represented through the Guccione constitutive model [6], with parameters $C = 0.6$ kPa, $b_f = 6.62$, $b_t = 3.65$, $b_{fs} = 2.65$ and $\kappa = 200$ kPa. Figure 2 shows the undeformed mesh and its resulting deformation with respect to the surface obtained from optical reconstruction during Langendorff experiment. Then, the deformed geometry obtained with Cardiax was exported in STL format to create a new mesh to be used in electrophysiological simulations.

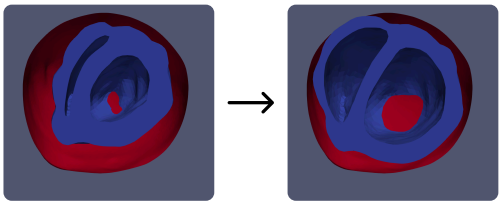


Figure 2. The comparison between the expanded surfaces at different iterations. On the left is the initial surface, and on the right, the surface after 10 iterations. The expanded surface is shown in blue, while the photogrammetry surface is shown in red.

The expanded exported surfaces are used to generate the volumetric finite volume mesh and then the fiber orientation is assigned according to the Laplace-Dirichlet

Rule-Based (LDRB) algorithm [7]. This mesh is used by MonoAlg3D [4] to solve the monodomain equation coupled to the Minimal Model and compute the electrograms.

Cellular model. The minimal ventricular model (MV) represents a simplified and computationally efficient approach for simulating the cardiac action potential, while faithfully reproducing several electrophysiological features observed experimentally. Unlike more complex models, which involve dozens of variables and parameters, the MV model captures the essential dynamics of the action potential using only four state variables: u (transmembrane potential), v (fast activation gate responsible for depolarization), w (slow recovery gate associated with repolarization), and s (slow inward current gate related to the plateau phase), as proposed by Bueno-Orovio et al [5].

Based on the action potential (AP) values obtained by optical mapping, it was observed that the duration of the rabbit action potential is approximately 100 ms, as shown in Figure 3. In order to reproduce the observed APs, first a sensitivity analysis was performed to identify the key parameters for optimization among the 28 parameters initially configured with the standard values of the MV model [5], resulting in three critical parameters that were selected for optimization: u_u, τ_{so1} and τ_v^+. The optimization objective function was formulated as a weighted error function that aimed primarily to match the APD90 value of the reference action potential curve, secondarily considering the general shape of the action potential through an L2 norm error between the simulated and reference curves. This approach prioritized the accuracy of the APD90 while maintaining reasonable fidelity to the action potential waveform. Figure 3 shows the fitted AP waveform as compared to those measured by optical mapping.

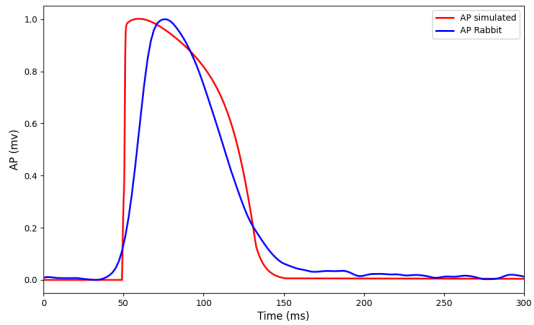


Figure 3. Experimental action potential (blue) and the fitted action potential generated by the minimal model (red).

Surface electrograms. The simulation of the electrical wave propagation through the cardiac tissue was performed using the MonoAlg3D [4], which solved the monodomain model coupled to the MV model calibrated to the rabbit AP. The conductivity of the tissue was modeled as anisotropic, incorporating the fiber orientation. A time step $\Delta t = 0.02$ ms was used, while spatial discretization was $h = 500$ μm was considered, with $C_m = 1$ $\mu F/cm^2$ and $\beta = 1400$ cm^{-1}. A single stimulus was applied at the apex, and ECG signals were computed at the electrode positions of Langendorff experiment using a pseudo-ECG algorithm. The electrodes position and the electrical simulation can be seen in Figure 4.

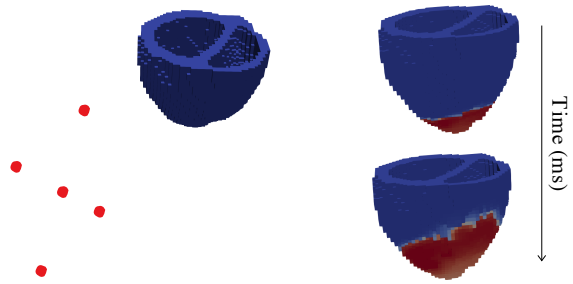


Figure 4. Electrode positions on the left. Propagation of the electrical stimulus over time, on the right.

3. Results

After segmentation, surface reconstruction and mesh generation, we performed electrophysiological simulation in order to reproduce the rabbit heart function.

A notable difference between the fitted AP waveform (Figure 3, red) and the optically mapped signal (Figure 3, blue) is in the upstroke velocity. The simulated single-cell AP exhibits a much faster upstroke, which is an expected outcome when comparing with a tissue-level optical recording. As demonstrated in literature, photon scattering within the tissue depth results in a prolongation of the optically recorded action potential upstroke [8]. Therefore, the fitting process prioritized matching the overall action potential duration while acknowledging this known artifact in the experimental signal.

The fitted minimal model was used in MonoAlg3D to perform cardiac simulations and ECG computation, with the application of two stimuli at the ventricular apex: the first at 0 ms and the second at 350 ms, both with a duration of 2 ms and a stimulus current of 0.5 mA. The total simulation time was 600 ms. The simulation was performed on a workstation equipped with a 2.3 GHz 8-Core Intel Core i9 processor and 16 GB of RAM, with a total execution time of approximately 15.5 seconds.

The experimental ECG was recorded using electrodes distributed throughout the tank containing the perfused heart, presenting variations between approximately -150 mV and 200 mV during a 1000 ms recording interval. The simulated ECG, obtained with the simulation in MonoAlg3D with the MV model, presents normalized values. Thus, the signals were mapped between the maximum and minimum values of the experimental ECG. Fig-

ure 5 shows this comparison, considering the five lower electrodes positioned on the side of the tank facing the left epicardium, chosen because they best represent the cardiac activity of the ventricles.

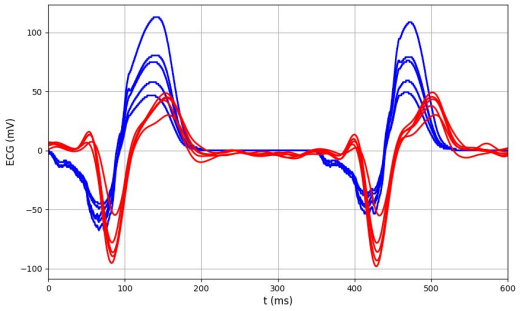


Figure 5. Comparison of the five experimental ECG traces (red) with the corresponding five simulated traces (blue).

A similar behavior was observed between the simulated and experimental electrograms curves, showing that the developed digital twin presents results consistent with those of the rabbit heart. The differences observed in the ECG peaks may be associated with discrepancies in the electrical conductivity values and action potential duration heterogeneity, which were not considered in these simulations.

Besides, the electrical current in the Langendorff experiment was applied in the atria, propagating to the ventricles through the Purkinje network, whereas our first simulations considered an apex stimulation for simplification.

4. Conclusions

The generation of a digital twin of the rabbit heart in a Langendorff setup, along with its ability to accurately reproduce ventricular electrophysiological behavior, demonstrates the method's potential as a robust platform for cardiac research. By enabling detailed simulations that align with experimental data, the approach can contribute to more informed experimental design and support the reduction of animal use in preclinical studies.

As this study represents a proof-of-concept on a single test case, the pipeline needs to be applied to a larger cohort of subjects to validate its robustness and generalizability. Further model refinements will include calibrating tissue conductivity values to match the experimentally observed conduction velocity, improving the stimulation protocol to better replicate the Purkinje system activation, incorporating cellular-level action potential heterogeneity. These developments aim to expand the digital twin's applicability in the study of cardiac arrhythmias.

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Address for correspondence:

Joventino de Oliveira Campos
Departamento de Ciência da Computação da UFJF, Juiz de Fora
joventino.campos@ufjf.br