Implementation of a Multiscale Multiphysics Framework to Model Whole Heart Electrophysiological and Mechanical Behavior

Jiang Yao, Karl D'Souza, Brian Baillargeon (Dassault Systemes Simulia, USA); Birce Onal, Tom Hund (Ohio State University, USA)

1 Abstract

Cardiac electrical rhythm disturbances (arrhythmias) are responsible for the majority of sudden cardiac death related to coronary artery disease. Despite significant progress in understanding molecular mechanisms underlying both acquired and congenital forms of cardiac arrhythmia, identification of new effective and safe drugs for treatment of cardiac arrhythmia remains a major challenge for the field. Mathematical models and computational simulation have emerged as essential tools for understanding the highly nonlinear cardiac electrical rhythm. However, most studies have considered either single cell behavior, used simplified cardiac anatomical models, or have not considered the interaction between cardiac electrical and mechanical function. The current study addresses these limitations by extending the capabilities of the SIMULIA *Living Heart Human Model* (LHHM) using a modular and multiscale approach. The LHHM allows the use of high fidelity electrophysiological (EP) models to better understand the mechanistic principles involved in whole heart arrhythmia mechanisms and control as well as low fidelity models representing EP behavior at a phenomenological level better suited for parameter sensitivity analyses and device-heart interaction and optimization.

2 Introduction

The LHHM is a dynamic four-chamber heart model that considers the coupling of electrical and mechanical fields, acting in concert to regulate the heart filling, ejection, and overall pump functions [1]. The native (default) version of the LHHM includes a 2-variable tissue-level phenomenological EP model, based on the Aliev-Panfilov model [2], that allows for fast computation while providing spatial and temporal resolution of electrical propagation adequate for research and improvement of mechanical devices such as stents, valves, and pacemaker leads. However, the native electrical model in the LHHM does not explicitly allow access to or modification of cellular variables, such as ion channel currents, which control the dynamics of cellular action potentials, and ultimately the generation, longevity, and propagation of abnormal electrical signals. While advanced cellular EP models of the heart exist (e.g., [3]), there is a lack of commercially available tools that permit whole heart electromechanical modeling and are suitable for a range of potential users such as medical device makers, pharmacologists, and the clinicians.

In the current project, we systematically enhance the EP model to bridge the cell-organ scale. We first verify cell-level EP models using single elements to ensure that ion channel gradients exhibit known dynamical behavior. We then use multi-cell models with simplified geometries to validate physiological electrical impulse generation and propagation behavior with improved computational efficiency. Finally, we use the EP models integrated into the whole heart model to study electrical impulse propagation under normal (healthy) and abnormal conditions, such as those induced by cardiovascular disease or drug/device interactions in the heart. We also study the impact of various EP models and changes in cardiac electrophysiology on mechanical function of the heart. We anticipate that such multiscale multiphysics models of the heart will ultimately lead to innovative treatments for cardiac arrhythmia.

3 Methods

3.1 Cell membrane model

Choosing the right cellular model for the human heart is not a trivial matter – different regions exhibit different EP behaviors, and new models are constantly being introduced to better match experimental data. Since our goal was to develop a framework for whole heart electromechanical modeling rather than an attempt to develop our own cellular model, it was decided to work with a model of intermediate complexity. This would allow us to address the key computational challenges while users of the framework could then focus on developing models with improved physiological relevance and accuracy. We therefore decided to work with the Ten Tusscher-Panfilov model [4], wherein the cell membrane is modeled as a capacitor connected in parallel with variable resistances and batteries (Fig.

1) representing different ionic currents and sources. The electrophysiological behavior of a single cell is described by relating the change in membrane potential (V) to the transmembrane ionic current (I_{ion}), via

$$\frac{dV}{dt} = -\frac{I_{ion} + I_{stim}}{C_m}$$

where I_{stim} is the externally applied stimulus current, C_m is the cell capacitance, and the ionic current (I_{ion}) is the sum of 12 major channel ionic currents:

$$I_{ion} = I_{Na} + I_{CaL} + I_{to} + I_{Ks} + I_{Kr} + I_{K1} + I_{NaCa} + I_{NaK} + I_{pCa} + I_{pK} + I_{bCa} + I_{bNa}$$

In this model, ions such as Na^+ and K^+ are considered to flow through ion channels via a series of gates that determine the conductance of the ion channel. The macroscopic conductance arises from the combined effects of a large number of microscopic ion channels embedded in the membrane. Each individual ion channel can be thought of as containing one or more physical gates that regulate the flow of ions through the channel. Taking Na^+ current I_{Na} as an example,

$$I_{Na} = G_{Na} m^3 hj(V - E_{Na})$$

where m, h and j are activation gates. G_{Na} is the maximal I_{Na} conductance, E_{Na} is the reversal potential for Na^+. The gating variables (such as m) are described via the *Hodgkin-Huxley* type equations,

$$\frac{dm}{dt} = \frac{1}{\tau_m}(m_\infty - m)$$

where τ_m is the time constant for the evolution of m, and m_∞ is the steady state value of m. Both τ_m and m_∞ are functions of membrane potential V.

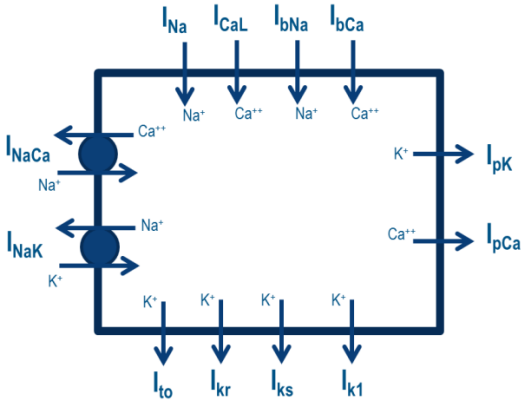

Fig. 1 Schematic of the cell model: The abbreviations represent ionic currents, pumps and exchangers, i.e. fast sodium current (I_{Na}), L-type calcium current (I_{CaL}), transient outward current (I_{to}), rapid delayed rectifier current (I_{Kr}), slow delayed rectifier current (I_{Ks}), inward rectifier current (I_{K1}), Na+/Ca2+ exchanger current (I_{NaCa}), Na+/K+ pump current (I_{NaK}), as well as plateau and background currents [1]

3.2 Coupling the cellular and organ levels in the LHHM

The cellular EP model is implemented at the material property (element integration point) level in both Abaqus/Standard and Abaqus/Explicit. In Abaqus/Standard, user subroutine HETVAL (typically used for internal heat generation in a heat transfer analysis) is used to model the cellular electrophysiology. HETVAL allows dependence of the action potential on state variables (i.e. gate variables and membrane potential) that evolve with solution. In Abaqus/Explicit, user subroutine VDFLUX is used to specify non-uniform distributed fluxes in an explicit dynamic coupled thermal-displacement analysis. Implementations in both Abaqus/Standard and Abaqus/Explicit use the inbuilt thermal conduction procedure to model the electrical propagation problem because of the equivalence of the underlying physics and the functional richness of the thermal analysis procedures in Abaqus. In both cases, cellular action potentials (computed by the cell EP model) can change in response to transmembrane

electrical potential gradients (computed from the global solution), thereby realizing bidirectional cell-organ coupling.

In addition to the underlying cellular phenomena modeled above, the heart also displays localized anatomical features (high conduction pathways such as Purkinje fibers and bundle of His) that strongly affect electrical propagation. In particular the atrioventricular (AV) node, which is the sole electrical pathway from the atria to the ventricles, introduces a conduction delay to ensure that the atria are completely drained of blood before the ventricles contract. This deliberate delay is crucial to maximize cardiac output and when affected by electrical abnormalities has an immediate impact on mechanical efficiency of the heart. To simulate the delay, a sensor-actuator mechanism was implemented in the LHHM, whereby the user can specify a delay time (default 100ms) to model the phenomena of interest (e.g., 1st or 2nd degree block). After these changes to the electrical model, the mechanical model is run in the same manner as with the native electrical model in the LHHM to examine the cardiovascular effects of electrophysiological changes.

4 Preliminary Results

4.1 Initial calibration

Using an incremental approach to add complexity, the cell EP model was first applied to a single element to verify the implementation. In Fig. 2, we show the comparison of theoretical and numerical results for a single cell (element) excited with an external stimulus of 30 mV for 0.02ms.

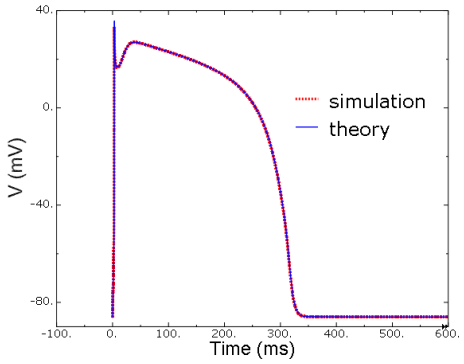

Fig. 2 Electrical potential generated by cell EP model – simulation vs. theory

The next step was to determine an appropriate mesh resolution for whole heart EP modeling. Prior studies have indicated the need for highly refined meshes to conserve the action potential wavefront propagation across the heart [4]. Conduction velocity was therefore measured in a 700mm long stack of 3D elements excited at one end with the same signal as above. Two tissue conductivities (K=0.1 mm^2/ms and K=0.2 mm^2/ms) were applied on three different element sizes (0.2mm, 0.5mm, 1mm). As can be seen in Fig. 3, both Abaqus/Standard and Abaqus/Explicit show mesh convergence around 0.2mm but underpredict and overpredict conduction velocity at higher element sizes respectively.

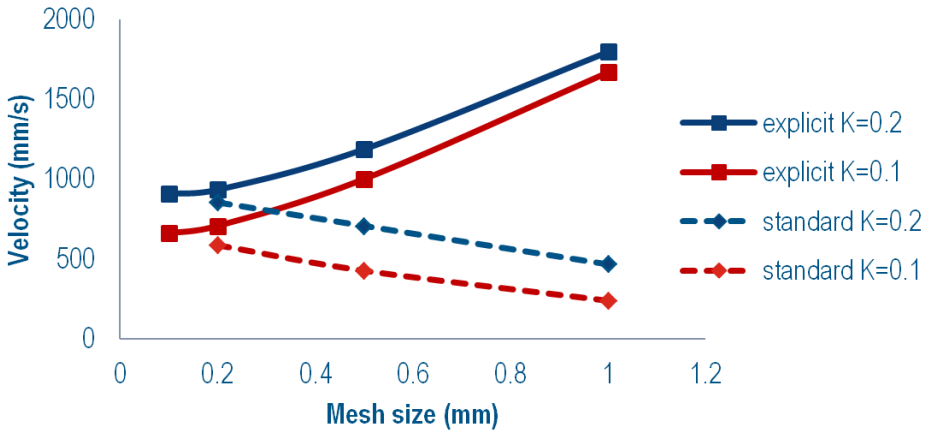

Fig. 3 Conduction velocity vs. element size – Abaqus/Standard and Abaqus/Explicit

Moreover, as shown in Table 1, the performance of Abaqus/Explicit significantly exceeds that of Abaqus/Standard for a 100ms simulation on 8 CPUs. It was therefore decided to use Abaqus/Explicit for whole heart EP modeling and with an initial element size of 0.2mm.

Mesh size (mm)	Degrees of freedom	Abaqus/ Standard	Abaqus/ Explicit
0.5	12600	6 hour	0.5 min
0.2	126000	77 hour	4.5 min

Table 1 Computation time for 100ms simulation on 8 CPUs

4.2 Whole heart modeling

The electrical potential initiates at the SA node by applying an external stimulus with a magnitude of 30mV and duration of 0.02ms. As each element is excited by the cellular EP dynamics, the potential propagates through the right atrium, and via the fossa ovalis to the left atrium. At the AV node, the potential is delayed 0.1s, and then propagates rapidly along the Purkinje network to the apex. From here, the potential once again excites cellular dynamics in the solid myocardium and is propagated throughout the ventricles (Fig.4). Overall electrical potential propagation in the modified LHHM closely matches that observed in the native LHHM model, which implies we have successfully implemented a framework to incorporate different cellular EP models and examine their impact on whole heart electrical and mechanical behavior.

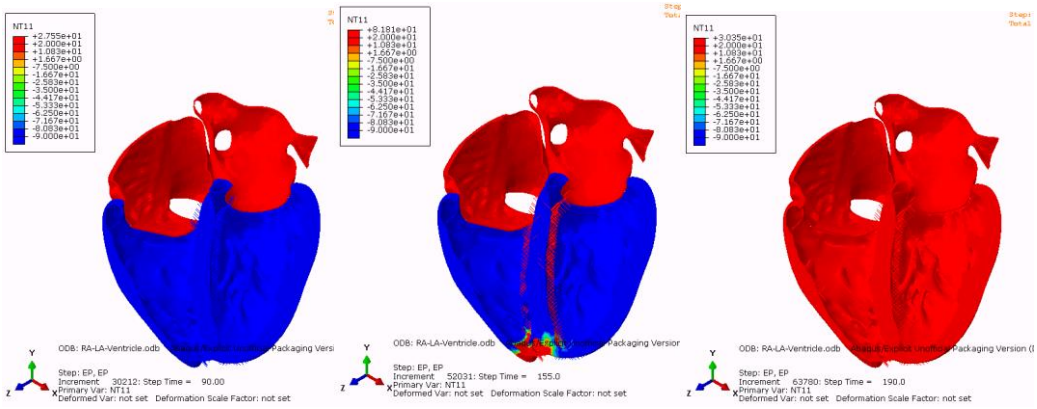

Fig. 4 Contour plots of electrical potential at 90ms, 155ms, and 190ms

Next steps include optimizing the whole heart cellular EP model for accuracy and performance and coupling the results to the mechanical simulation to study the effects of cellular models on macroscopic clinical metrics such as chamber pressures and volumes. Once this approach is validated, users will be able to introduce electrical pathologies into the model and examine the effects of surgical intervention (e.g., ablation), device interaction (e.g., TAVR, pacemaker, etc.), and pharmacological treatments on whole heart electromechanical behavior.

5 References

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