Uncertainty Quantification in Simulations of Myocardial Ischemia

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Abstract

Computational models of myocardial ischemia are parameterized using assumptions of tissue properties and physiological values such as conductivity ratios in cardiac tissue and conductivity changes between healthy and ischemic tissues. Understanding the effect of uncertainty in these parameter selections would provide useful insight into the performance and variability of the modeling outputs. Recently developed uncertainty quantification tools allow for the application of polynomial chaos expansion uncertainty quantification to such bioelectric models in order to parsimoniously examine model response to input uncertainty. We applied uncertainty quantification to examine reconstructed extracellular potentials from the cardiac passive bidomain based on variation in the conductivity values for the ischemic tissue. We investigated the model response in both a synthetic dataset with simulated ischemic regions and a dataset with ischemic regions derived from experimental recordings. We found that extracellular longitudinal and intracellular longitudinal conductivities predominately affected simulation output, with the highest standard deviations in regions of extracellular potential elevations. We found that transverse conductivity had almost no effect on model output.

1. Introduction

Myocardial ischemia is a complex pathophysiological event that can result in lethal complications such as sudden cardiac death in as little as a few minutes.[1,2] The cardiac passive bidomain is a computational modeling tool that has been used to examine the bioelectric presentation of myocardial ischemia.[3,4] The passive bidomain predicts the static extracellular potentials throughout the heart given a distribution of transmembrane potentials. Transmembrane potentials during the plateau phase of the cardiac action potential are depressed in ischemic tissue, resulting in intracellular and extracellular currents that can be characterized using the passive bidomain model.[3] Formulation of the passive bidomain model requires assumptions of cellular-, tissue-, and organ-scale parameters, including changes to conductivity due to ischemic stress.[3,5] Many of these parameter choices are based on either literature values or heuristics, and it is uncertain which parameters may be important to tune for the generation of patient specific models and which can be left at default values. Previous studies have investigated ischemia-specific changes in conductivity, but no studies have investigated how variation in the ischemic conductivity affects the passive bidomain output in whole heart models.[3,5–7]

The study of model output sensitivities to input uncertainty, known as uncertainty quantification (UQ), has emerged as an active area of research in the field of computational biological models. Previous studies have investigated the role of a handful of parameters of the passive bidomain on the solution variability; however, these studies have been limited by the lack of experimental data, simple slab models, and limited UQ techniques.[7] UQ methods such as range finding or Monte Carlo are limited by either minimal sampling of the parameter space or intractable computational demand. Modern UQ methods such as polynomial chaos expansions (PCE) allow us to assess variability in model outputs given uncertainty in the input parameters by employing sophisticated sampling techniques and statistical models to dramatically reduce computational demand while still being able to describe the entire parameter space accurately.[8] PCE provides accurate statistical analysis of the model outputs such as standard deviations, specific parameter sensitivities, and parameter interaction effects.

In this study, we performed PCE UQ to analyze the effects of variability in the ratio between healthy and ischemic conductivity on the cardiac passive bidomain. We made use of two datasets, one consisting of synthetically generated regions of myocardial ischemia, and another

Table 1. Conductivity ratios for each tissue label. The first subscript indicates tissue domain (i = intracellular, e = extracellular). The second subscript indicates either the direction (L = longitudinal, T = transverse) or if the domain is also the blood pool (b). The base conductivity values used was 0.16 S/cm^2

Conductivity	Healthy Tissue	Ischemic Tissue
σ_{iL}	1	1/10
σ_{eL}	1	1/2
σ_{iT}	1/10	1/1000
σ_{eT}	1/3	1/4
σ_{iB}	0	0
σ_{eB}	3	3

consisting of experimentally measured regions of myocardial ischemia.

2. Methods

Forward Model Formulation: The passive bidomain describes the forward problem from transmembrane potentials to extracellular potentials during a particular phase of the cardiac action potential.[3, 4] Specifically during the plateau phase, we assume that the healthy tissue has a transmembrane potential of 0 mV whereas ischemic tissue has a transmembrane potential between 0 and -40 mV. The passive bidomain is defined in EQ 1, where the transmembrane potentials (Φ_m) source is defined throughout the myocardium and coupled via intracellular (σ_i) and tissue (σ_h) conductivity tensors to the extracellular potentials (Φ_e). Tissue conductivity is defined as the sum of extracellular and intracellular conductivity ($\sigma_h = \sigma_i + \sigma_e$).

$$\nabla \cdot (\sigma_i \nabla \Phi_m) = -\nabla \cdot (\sigma_h \nabla \Phi_e), \tag{1}$$

To generate a solution for the extracellular potentials given transmembrane potentials, we applied Green's divergence theorem to attain a finite element weak formulation of Equation 1, as described previously.[3, 4] We then solved the resulting linear system of equations using a conjugate gradient solver with a Jacobi preconditioner.

Uncertainty Quantification: We quantified forward parametric uncertainty in the passive bidomain using polynomial chaos expansions (PCE) as described previously.[8] This approach approximates the underlying forward model using a polynomial function emulator that is computationally inexpensive to sample. UQ was performed using the open-source library UncertainSCI.[8] We chose to examine the effects of varying the ratios that define the conductivity of ischemic tissue. Specifically, we varied σ_{iL}, σ_{iT}, σ_{eL}, and σ_{eT} of the ischemic tissue with a range of $\pm 20\%$ of the values listed in Table 1 and a uniform distribution. We used order 5 for all PCE evaluations.

Datasets: We examined the passive bidomain response to uncertainty in ischemic conductivity using both synthetic and measured ischemic potentials. The synthetic data were based on a spherical region of ischemia with a radius of 5 mm in the left ventricular free wall (Figure 1). This region was assigned a transmembrane potential of -35 mV. The transmembrane potential was then linearly decayed to 0 mV isotropically over a 2 mm border zone.

The measured potentials came from experiments that captured the development of acute myocardial ischemia using intramyocardial electrode arrays as described previously.[9] We assigned transmembrane potentials throughout the myocardium based on these measured extracellular potentials at the peak of an ischemic episode, using a core threshold of 10 mV and a linear transfer function.[5]

Conductivity tensors were constructed using myocardial fiber direction vectors and conductivity ratios for the different regions of tissue defined in Table 1. Myocardial fibers were generated using a rule-based algorithm described previously, with an endocardial fiber angle of 60 degrees, epicardial fiber angle of -60 degrees, endocardial helix angle of -35 degrees, and epicardial helix of angle 0 degrees.[10] We assumed that conductivity in the plane normal to the principal fiber direction is isotropic. For the purpose of assigning conductivity values, transmembrane potentials were used to determine if a specific area of tissue was ischemic or not. A piece-wise linear function was used to map the transmembrane value to conductivity with transmembrane values of 0 set at healthy conductivities, transmembrane values below -35 mV set as ischemic, a linear interpolation between ischemic, and healthy conductivities for TMP values between 0 mV and -35 mV.[5]

3. Results

Figure 1 shows baseline forward solutions for the synthetic dataset, which used nominal conductivity ratios, as well as the mean solution and standard deviation values from the PCE. Figure 2 shows the standard deviation contributions of the four parameters. The transverse conductivities in both extracellular and intracellular domains had little effect on the solution output, with a near zero standard deviation contribution.

Figure 3 shows the measured extracellular potentials, baseline forward solution, mean PCE forward solution, and standard deviation for the measurement dataset. Figure 4 shows the standard deviation contributions of the input parameters. As with the synthetic dataset, the transverse ischemic conductivities have little effect on the forward solution. In both the synthetic and measured dataset, we observed minimal parameter interaction sensitivity for any combination of parameters.

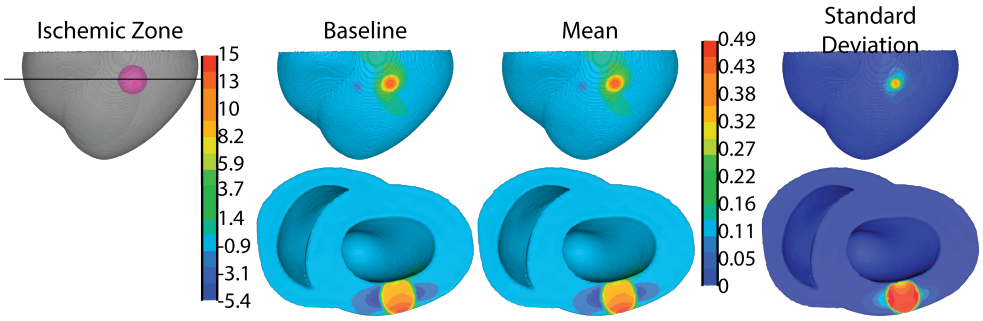

Figure 1. Forward solution from the synthetic dataset. Column one shows the 5 mm radius synthetic ischemic core. The black line shows the cut plane for subsequent visualization. Column two shows the forward solution using default conductivity parameters. Column three shows the PCE mean forward solution. Column four shows the PCE standard deviation due to all four parameters.

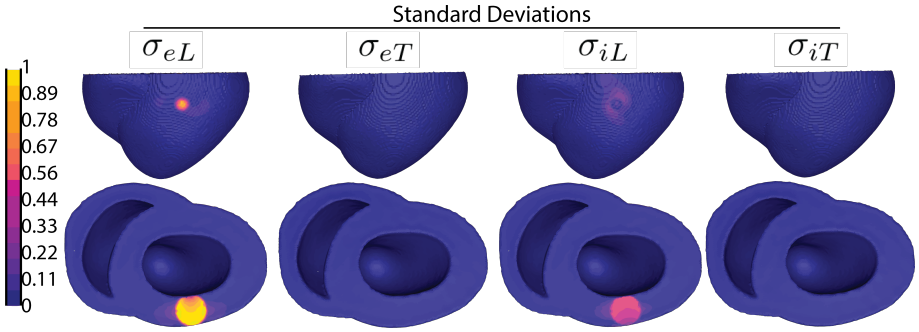

Figure 2. Per-parameter standard deviations (mV) for the synthetic dataset. Columns one through four show the standard deviation contributions to the forward solution of extracellular longitudinal, extracellular transverse, intracellular longitudinal, and intracellular transverse ischemic tissue conductivities, respectively.

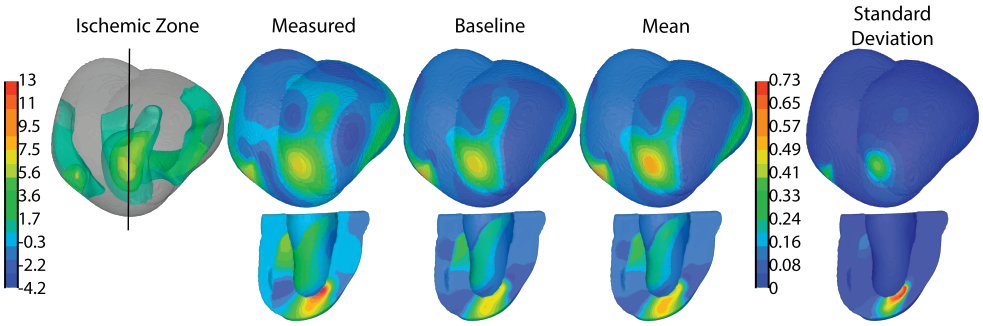

Figure 3. Forward solution from the measured dataset. Column one shows isosurfaces of the measured ischemic regions. The black line shows the cut plane for subsequent visualization. Column two shows the measured extracellular potentials. Column three shows the forward solution using default conductivity parameters. Column four shows the PCE mean forward solution. Column five shows the PCE standard deviation due to all four parameters.

4. Discussion and Conclusions

In this study, we applied PCE UQ to assess the sensitivity of the passive bidomain to variability in ischemic conductivity values. We demonstrated that the transverse conductivity values have little impact on the forward solution in both synthetic and measurement-based datasets. These results suggest that transverse ischemic conductivity does not need to be tuned to generate accurate model output, and can be set to standard values such as those in Table 1.

The standard deviation contributions of intracellular and extracellular longitudinal ischaemic tissue are highest in the area of the extracellular potential elevations, both in the simulated (Figure 1) and the measured datasets (Figure 3). In the measured dataset, we noted that the area of highest standard deviation was a region of high error between the forward solution and measurements (Figure 3. This behavior is particularly evident in the cut plane as we observe the intramyocardial potential maximum is poorly reconstructed using both mean and default forward solu-

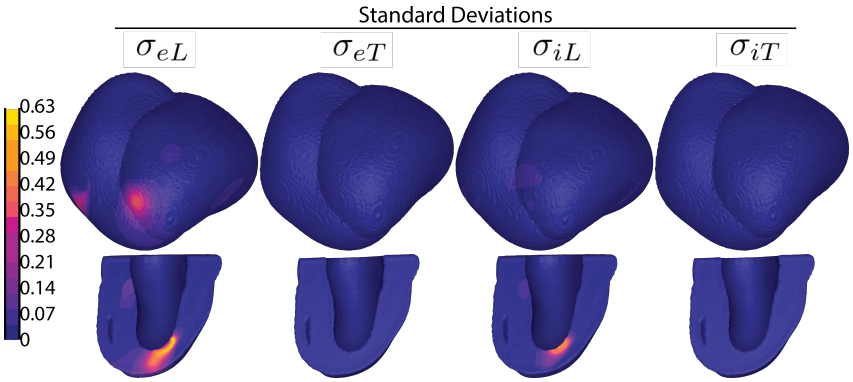

Figure 4. Parameter standard deviations for the measured dataset. Figure arrangement is the same as Figure 2

tions. This area also corresponds to the highest standard deviation, particularly with respect to changes in the extracellular longitudinal conductivity (Figure 4).

Our synthetic dataset allowed us to examine uncertainty in a controlled setting. We observed that the standard deviation was highest in regions of potential elevation, especially on the epicardium (Figure 1). We also observed that the standard deviation contribution of the extracellular longitudinal conductivity was the predominant factor in the overall standard deviation, whereas the intracellular longitudinal ischemic conductivity had an overall lower effect and was skewed toward the endocardium.

This study was limited to examinations of only a subset of the conductivity ratios used in the passive bidomain. Future studies will expand this investigation to other parameters; however, based on these initial findings, we can likely exclude the transverse ischemic conductivities from future analysis. Additionally, we plan to examine how these parameter uncertainties affect the accuracy of potential reconstructions using measured datasets. The results of these studies may help inform more accurate and compact models of myocardial ischemia that can be translated into other modeling contexts such as ischemic arrhythmogenesis and electrocardiographic imaging.

Acknowledgments

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