Capturing the Influence of Conduction Velocity on Epicardial Activation Patterns Using Uncertainty Quantification

Anna Busatto[1,2,3], Lindsay C Rupp[1,2,3], Karli Gillette[5], Akil Narayan[1,4], Gernot Plank[5], Rob S MacLeod[1,2,3]

[1] Scientific Computing and Imaging Institute, University of Utah, SLC, UT, USA
[2] Nora Eccles Cardiovascular Research and Training Institute, University of Utah, SLC, UT, USA
[3] Department of Biomedical Engineering, University of Utah, SLC, UT, USA
[4] Department of Mathematics, University of Utah, SLC, UT, USA
[5] Institute of Biophysics, Medical University of Graz, Graz, Austria

Abstract

Individual variability in parameter settings, due to either user selection or disease states, can impact accuracy when simulating the electrical behavior of the heart. Here, we aim to test the impact of inevitable uncertainty in conduction velocities (CVs) on the output of simulations of cardiac propagation, given three stimulus locations on the left ventricular (LV) free wall. To understand the role of physiological variability in CV in simulations of cardiac activation, we generated detailed maps of the variability in propagation simulations by implementing bi-ventricular activation simulations and quantified the effects by deploying robust uncertainty quantification techniques based on polynomial chaos expansion (PCE). PCE allows efficient stochastic exploration with reduced computational demand by utilizing an emulator for the underlying forward model. Our results suggest that CV within healthy physiological ranges plays a small role in the activation times across all stimulation locations. However, we noticed differences in variation coefficients depending on the stimulation site, i.e., *LV endocardium, midmyocardium, and epicardium. We observed low levels of variation in activation times near the earliest activation sites, whereas there was higher variation toward the termination sites. These results suggest that CV variability can play a role when simulating healthy and diseased states.*

1. Introduction

Conduction velocity in the myocardium can vary between individuals, especially in diseased states, and such changes can affect both normal and abnormal spread of activation in the heart, even leading to re-entrant arrhythmia. For example, the conduction velocity in the ventricular myocardium can be reduced to almost half of the healthy ranges during acute ischemia. [1] Simulations of the spread of activation in the heart play an increasing role in exploring mechanisms, supporting diagnosis, and guiding therapy, so it is essential to explore their response to variations in conduction velocity. The direct effect of increases or decreases in conduction velocity values on the spread of activation is well known, but what is considerably less understood is the impact of unknown variability in conduction velocity, *i.e.,* the inevitable error around estimates of conduction velocity that are input to a simulation of even an otherwise healthy heart. The goal of this study is to provide a rigorous, comprehensive statistical quantification of the effect of variability in conduction velocity on a simulation model of propagation in a healthy heart.

There are several mathematical approaches to study the effects of input parameter variability on model predictions, including brute force, Monte Carlo, and range-finding techniques.[2, 3] Polynomial chaos expansion (PCE) provides a more sophisticated and efficient means to carry out uncertainty quantification (UQ) methodology. [4, 5]

PCE can achieve highly precise approximations of model output statistics with significantly fewer forward model evaluations than other approaches; to accomplish this, it relies on mathematical assumptions regarding the stochastic nature of fields. Our approach was to apply this technique to simulations of cardiac propagation to enable efficient exploration of model sensitivity to the uncertainty in conduction velocity.

To understand the influence of conduction velocity variability, we tested a subject-specific geometric model of a porcine heart using assigned ranges of conduction velocity based on values from the literature and three stimulus locations. [6, 7] The output values were the mean, standard deviation (STD), and coefficient of variation of the

activation times on the epicardial surface. Our results suggest that uncertainty in conduction velocity only mildly impacts the activation patterns when considering physiological ranges across all stimulation locations. The mean activation times, as expected, were the smallest for the epicardial stimulation and the largest following endocardial stimulation. The values of variance (or standard deviation) also followed a predictable pattern, smallest near the stimulus site and growing over the duration of activation. Notable relative differences in response to the pacing site arose in the coefficient of variation. Thus, we conclude that even relatively simple distributions of conduction velocity can produce localized variability in the dispersion of data points in a data series around the mean, suggesting a possible substrate for life-threatening arrhythmias.

2. Methods

Simulation Model

For our analysis, we used a bi-ventricular geometric model of a porcine heart generated from MRI scans, segmented and made into a finite-element mesh (average edge length, 700 μm). [8] The Eikonal activation patterns were calculated via the *Cardiac Arrhythmia Research Package* (CARP) using the reaction-Eikonal technique. [9–11] The mean longitudinal conduction velocity was set to 100 cm/s and assumed to vary according to a uniform distribution with bounds of 90 cm/s and 110 cm/s, according to ranges found in previous studies. [6, 7] In the CARP simulations, the sheet and transverse conduction velocities were set to 1/3 and 2/3 of the longitudinal value, respectively. [12]

Uncertainty Quantification

Uncertainty in the epicardial activation patterns given variable conduction velocity was quantified using PCE. PCE facilitates the evaluation of the variation in the model outputs based on predefined distributions of particular input parameters; it determines the statistical effects of uncertainty in model-based computations. UQ was implemented using UncertainSCI, an in-house, open-source software. [4] For all the PCE evaluations, we employed an emulator of polynomial order five to approximate the underlying forward problem. For the sampling strategy, we used the Gaussian quadrature rule with 10 samples. The computed statistical parameters were mean, standard deviation (STD), and coefficient of variation. The coefficient of variation represents the ratio of the STD to the mean, and it is a useful tool to statistically compare the degree of variation between different data sets even when their means are drastically different from one another. A lower coefficient of variation is more desirable, as it implies a lower spread of data values relative to the mean.

Simulation Protocols

We stimulated an individual location in the model on the left ventricular endocardial surface, midmyocardium (0.5 wall thickness), and epicardial surface, respectively. The points to be stimulated were selected manually using the universal ventricular coordinates for the geometric model.[10, 13]

3. Results

The baseline and mean activation sequences maintained similar activation time patterns and ranges for all three stimulation locations. Figure 1A shows the mean, STD, and coefficient of variation for the left ventricular **endocardial** stimulation site. Mean activation times ranged from 22 ms to 94 ms, with the lowest values observed around the epicardial breakthrough region. The epicardial STD pattern closely matched the activation times, lowest near the breakthrough location (1.3 ms) and rising to 5.4 ms near the termination site. The coefficient of variation seems to have a heterogeneous pattern, with areas of higher variation around the breakthrough site and lower variation moving away from it. However, looking at the range of values, small changes occur throughout the epicardial surface, with a minimum of 0.054 on the left ventricular wall and a maximum of 0.066 on the right ventricular wall.

Figure 1B shows the mean, STD, and coefficient of variation for the left ventricular **midmyocardial** stimulation site. The mean and STD returned similar values to the endocardial stimulation. The earliest activation time was, as expected, slightly earlier than for endocardial stimulation (11 ms) and the latest time marginally smaller (92 ms). The pattern of STD again followed activation time with a marginally smaller minimum value (1.1 ms) and the same maximum (5.4 ms). The coefficient of variation returned a maximum value of 0.11 at the breakthrough site and progressively decreased to 0.059 approaching the termination site.

Figure 1C shows the mean, STD, and coefficient of variation for the left ventricular **epicardial** stimulation site. The mean and STD followed patterns similar to those in the previous two cases but with the expected lower values of activation time. The smallest mean activation time was 2 ms, and the highest was 97 ms at the termination site. The minimum STD was also the lowest of any case at 0.0 ms near the stimulus location, increasing to 5.6 ms on the basal right ventricular region. Here, the coefficient of variation showed an opposite pattern compared to the LV endocardial and midmyocardial stimulation, with a minimum value of 0 at the breakthrough site and progressively increasing to 0.059 approaching the termination site.

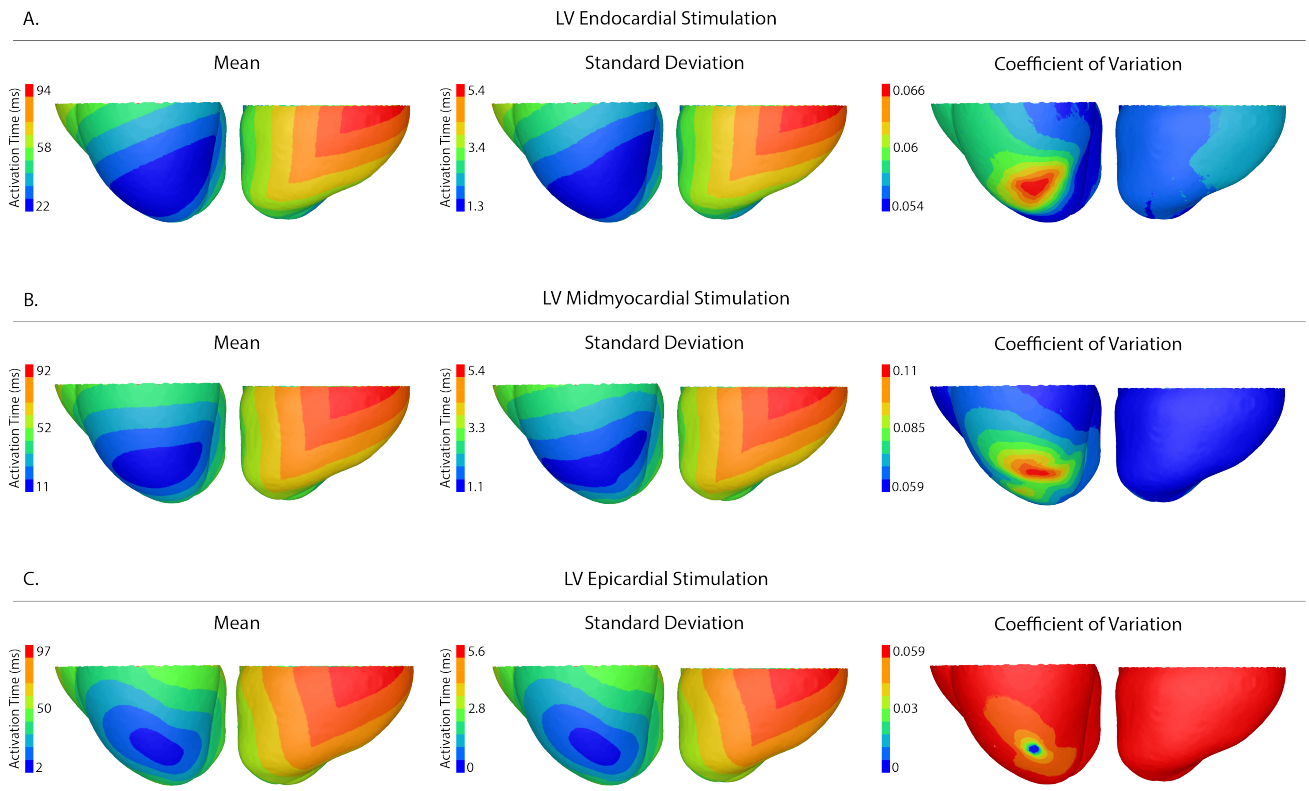

Figure 1. Uncertainty quantification of epicardial activation sequences. The top panel (A) shows the epicardial activation times for endocardial stimulation. The middle panel (B) shows the epicardial activation times for midmyocardial stimulation. The bottom panel (C) shows the epicardial activation times for epicardial stimulation. For each panel, the left column shows the mean activation sequence, the middle shows the standard deviation of the activation sequence, and the right shows the coefficient of variation of the activation sequence. In each panel, there are views from two perspectives, the left lateral and right lateral sides of the heart, respectively.

4. Discussion and Conclusions

The aim of this study was to provide an evaluation of the impact of conduction velocity variability on epicardial activation sequences using robust UQ. We utilized prescribed conduction velocities, bi-ventricular Eikonal simulations, and PCE techniques. [4, 10, 11]

Our findings suggest that uniform variations in conduction velocity between 90–110 cm/s have minimal impact on the activation times across all stimulus locations. The activation times had the smallest variability around the stimulus location and progressively increased moving toward the termination site. As expected, the mean activation times were the smallest for epicardial stimulation and the largest for endocardial stimulation because, with epicardial stimulation, the electrical wavefront does not need to travel through the ventricular wall, but it does when stimulation comes from the endocardium. The midmyocardial stimulation had the shortest total activation time because it created two propagating wavefronts. The STDs followed remarkably similar patterns as activation times, with the smallest standard deviation following the epicardial stimulation and increasing from the midmyocardial to the endocardial sites; the highest STD values were about the same across the three stimulation sites. The close match between variance and mean values suggests a closely linear response of error to distance traveled by the propagating excitation.

The coefficient of variation parameter provided clear differences related to the stimulation site. Following endocardial stimulation, the coefficient of variation was, overall, uniform across the epicardial surface, with a slight decrease moving away from the breakthrough site. The same pattern, but more pronounced, was observed following midmyocardial stimulation. Comparing the midmyocardial and epicardial stimulation, there was a uniform 5.9% variation away from the breakthrough site, but near the breakthrough site the epicardial had a lower coefficient of variation, whereas the midmyocardial had a higher one. A possible explanation of this behavior is that in endo-

cardial and midmyocardial stimulation, the signal needs to travel through the wall to reach the epicardial surface. Despite that, the variations were only 6.6% and 11%, respectively,even at the breakthrough site. The different behaviors observed in the coefficient of variation suggest nonlinear impacts of conduction velocity on propagation on the ventricular epicardial surface of the heart, mostly when the stimulation site is not located on the epicardium.

Limitations of this study include the use of only one heart geometry and three stimulation sites. However, expanded testing of two more heart geometries, two more mean longitudinal conduction velocities (90 cm/s, 110 cm/s), and additional stimulation sites yielded similar results. A further limitation was the uniform use of normal conduction velocities, which clearly will change in the face of disease or insult. Future directions follow naturally from these limitations, *e.g.,* to test other stimulation sites on multiple heart geometries and under pathophysiological conditions. We will also utilize the bidomain rather than the Eikonal simulation framework to evaluate the impact of such simplified propagation models due to the possible neglected effects of wavefront curvature.

Overall, our results suggest that the conduction velocities assigned in simulations of myocardial propagation play a relatively small role, depending on the specific objectives and research or clinical goals and whether or not the tissue is healthy or affected by underlying conditions.

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Address for correspondence:

Anna Busatto
University of Utah
72 Central Campus Dr, Salt Lake City, UT 84112
annabusatto@sci.utah.edu