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

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Abstract

Individual variability in parameter settings, either due to user selection or disease states, can have an impact on accuracy when simulating the electrical behavior of the heart. Here, we aim to test the impact of inevitable uncertainty in conduction velocities on the output of simulations of cardiac propagation, given three different stimulus locations on the left ventricular free wall. To understand the impact of physiological variability in conduction velocity on simulations of cardiac activation, we generated detailed maps of the variability in simulations of propagation by implementing bi-ventricular activation simulations; to quantify these effects, we employed robust uncertainty quantification techniques based on polynomial chaos expansion. Polynomial chaos expansion allows for efficient stochastic exploration with reduced computational demand by utilizing an emulator for the underlying forward model. Our results suggest that conduction velocity within healthy physiological ranges plays a small role in the activation times across all stimulation locations. However, areas of strong positive skew in the activation times are present on the epicardial surface during mid-myocardial stimulation. We observed low levels of variation in activation times near the earliest activation sites, while higher variation was observed toward the termination sites. These results suggest that variability of conduction velocity 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 reduce 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 inputs 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.

To study the effects of variability of input parameters on model predictions, there are several mathematical approaches, 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 on a subject-specific geometric model of a porcine heart using assigned ranges of conduction velocity based on values from the literature and three different

stimulus locations; [6, 7] The output values included the mean, standard deviation (STD), and skewness of the activation times on the epicardial surface. Our results suggest that uncertainty in conduction velocity has only mild impacts on 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 differences in response to pacing site arose in the skewness of the distribution of activation times, especially from the mid-myocardial pacing site. Thus we conclude that even relatively simple, symmetric distributions of conduction velocity can produce localized asymmetric variability in activation, 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) [9]. 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.[10]

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. For all the PCE evaluations, we employed an emulator of polynomial order five to approximate the underlying forward problem. UQ was implemented using UncertainSCI, an in-house, open-source software.[4] The computed statistical parameters included mean, standard deviation (STD), and skewness. Skewness is a measure of the asymmetry of the data, *i.e.,* it describes both the degree and direction of deviation of symmetry within a distribution. Skewness in the context of uncertainty quantification suggests asymmetry in the response of the model to values above and below the mean of the input parameters, which can indicate a bias or systematic error in the model. Additionally, the skewness of a distribution can also affect the choice of statistical methods used to analyze the data. For the purpose of analyses, we considered data with skewness $\pm$ 0.5 to be symmetrical, between $\pm$ 0.5 and $\pm$ 1 to be moderately skewed, and below -1 or above 1 to be highly skewed.

Simulation Protocols

We stimulated the model from the left ventricular endocardial surface, mid-myocardium (0.5 wall thickness), and epicardial surface. These locations were determined using the universal ventricular coordinates for the geometric model.[11]

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 skewness for the left ventricular **endocardial** stimulation site. Mean activation times ranged from 23 ms to 94 ms, with the lowest values observed around the epicardial breakthrough region. The epicardial STD pattern matched very closely that of the activation time, lowest near the breakthrough location (1.3 ms) rising to 5.4 ms near the termination site. The activation times were moderately skewed near the breakthrough location (with a maximum skewness of 0.78), while the activation times were symmetrical everywhere else, with skewness close to zero (-0.05) over most of the epicardium.

Figure 1B shows the mean, STD, and skewness for the left ventricular **mid-myocardial** 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 (12 ms) and the latest time marginally smaller (92 ms). The pattern of STD again followed activation time with a marginally smaller minimum value (1.0 ms) and the same maximum (5.4 ms). The most notable difference was in the skewness, which was close to zero (0.15) around the stimulus location, followed by a band of moderate skewness (shown in yellow) and a larger band of high skewness (shown in red, up to 1.6) covering most of the rest of left ventricular freewall. Skewness remained moderate (0.8) over most of the right ventricle.

Figure 1C shows the mean, STD, and skewness for the left ventricular **epicardial** stimulation site. The mean and STD followed similar patterns as the previous two cases, but with the expected lower values of activation time. The smallest mean activation time was 2 ms, while 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 5.5 ms on the basal right ventricular region. The data appears to be symmetrical (with skewness

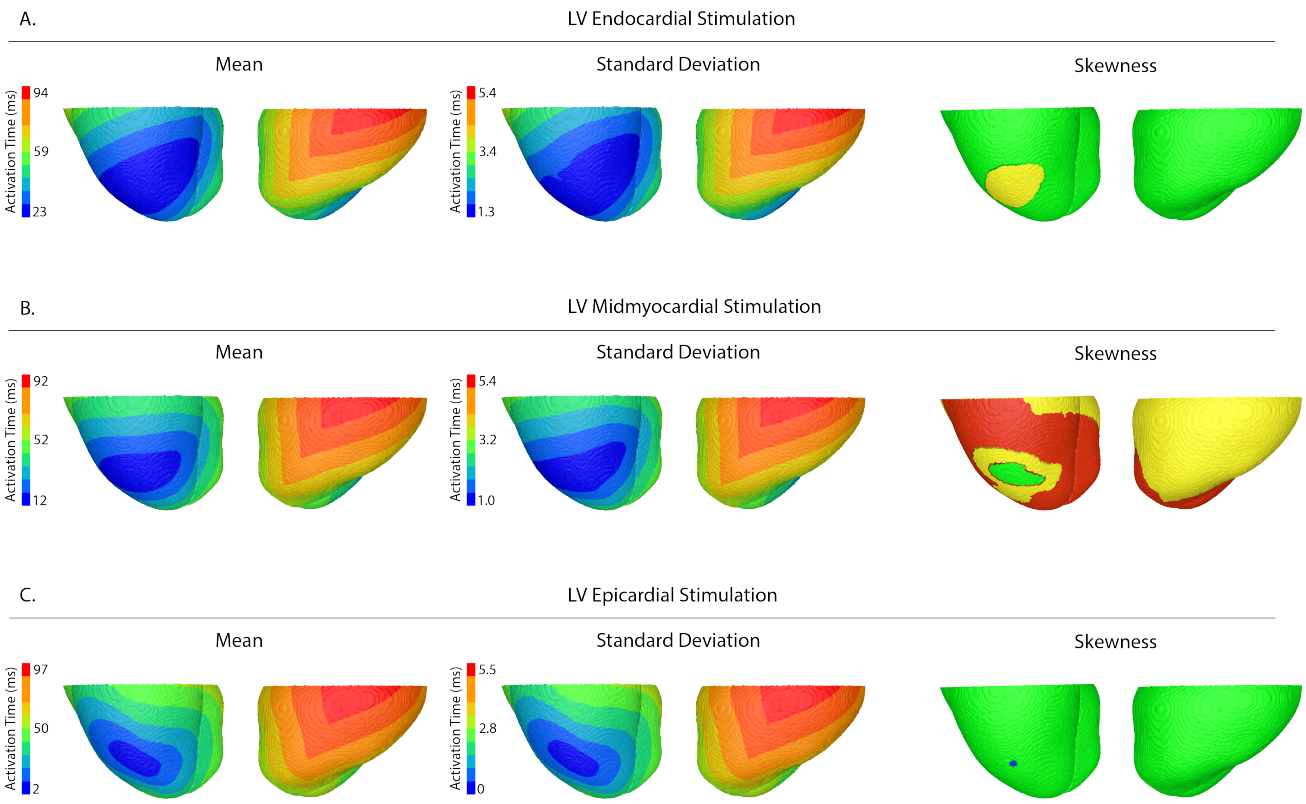

Figure 1. Uncertainty quantification of epicardial activation sequences. The top panel (A) shows the epicardial activation times for endocardial stimulation. The middle panel (B) shows the epicardial activation times for mid-myocardial stimulation. The bottom panel (C) shows the epicardial activation 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 skewness of the activation sequence. For the skewness, blue regions indicate zero skewness, green regions indicate skewness of 0 ± 0.5, yellow regions indicate skewness between $\pm$ 0.5 and $\pm$ 1, and red regions indicate skewness below -1 or above 1. In each panel, there are views from two perspectives, the left lateral and right lateral sides of the heart, respectively.

< 0.4) across the whole epicardial surface.

4. Discussion and Conclusions

The aim of this study was to provide an evaluation of the role of conduction velocity variability on epicardial activation sequences using robust UQ. We utilized prescribed conduction velocities, bi-ventricular Eikonal simulations, and PCE techniques. [4, 12]

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 site of termination. As expected, the mean activation times were smallest for epicardial stimulation because the stimulus does not need to travel through the tissue, while they were the largest for the endocardial stimulation site because the stimulus has to travel through the entire transverse direction. The mid-myocardial stimulation had the smallest 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 mid-myocardial 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 skewness parameter provided clear differences related to stimulation site. Skewness was low across the epicardial surface following both endocardial and epicardial stimulation, however, mid-myocardial stimulation generated a band of elevated skewness through much of the epicardial surface of the left ventricular freewall. This increased skewness showed that the majority of activation

times were below the mean; suggesting highly nonlinear impacts of conduction velocity on propagation in this region of the heart.

Limitations of this study include the use of only one heart geometry and only 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 models of propagation.

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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