Uncertainty Quantification of the Effect of Variable Conductivity in Ventricular Fibrotic Regions on Ventricular Tachycardia

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Abstract

Ventricular tachycardia (VT) is a life-threatening cardiac arrhythmia for which a common treatment pathway is electroanatomical mapping and ablation. Recent advances in both noninvasive ablation techniques and computational modeling have motivated the development of patient-specific computational models of VT. Such models are parameterized by a wide range of inputs, each of which is associated with an often unknown amount of error and uncertainty. Uncertainty quantification (UQ) is a technique to assess how variability in a the inputs to a model affects its outputs. UQ has seen increased attention in computational cardiology as an avenue to further improve, understand, and develop patient-specific models. In this study we applied polynomial chaos based UQ to explore the effect of varying the tissue conductivity of fibrotic border zones in a patient-specific model on the resulting VT simulation. We found that over a range of inputs, the model was most sensitive to fibrotic sheet direction, and uncertainty in fibrotic conductivity resulted in substantial variability in the VT reentry duration and cycle length. Overall this study paves the way for future UQ applications to improve and understand VT models.

1. Introduction

Ventricular tachycardia (VT) is a life-threatening arrhythmia often seen in failing hearts or in the context of ischemia-related myocardial injury and scar.[1] Treatment for such VT often includes ablation of critical regions of the myocardium to prevent the reentrant circuit, and computational modeling has emerged as a powerful tool to inform ablation treatment.[2, 3] Patient-specific computational models can provide pre-operative insight into possible reentrant circuits, predict the success of proposed ablation strategies, and even estimate latent reentrant circuits that may arise after the dominant one is treated.[3] Recent studies exploring the use of radiation-based ablation of cardiac tissue further motivate increased application of computational models which can noninvasively predict putative ablation sites.[2] This rising popularity of such computational models demands improved understanding of the effects of uncertainty and variability of model inputs.

Uncertainty quantification (UQ) offers techniques to efficiently and robustly explore the effects of parameterized variability of the inputs of a model on the output.[4] UQ has seen increased attention and application to biomedical modeling problems as it provides statistical expressions of the sensitivity of a model to various inputs and their inevitable uncertainties. [5] Patient-specific models of VT have a large number of input parameters, including descriptions of the cellular ionic currents in healthy, fibrotic, and scarred tissue, bulk extra- and intracellular conductivity values, and many more, all of which are associated with some degree of uncertainty and variability.[3] Uncertainty quantification in this context can be difficult because of the number of inputs and because of the likelihood that changes to these parameters could drastically change the path of a VT circuit. It remains challenging to identify outputs of models outputs which are both sufficiently detailed to provide insight into the behavior of the model given input uncertainty while also remaining consistent enough to produce interpretable UQ outputs.

In the study we sought to address these challenges by narrowing the UQ focus to a select set of parameters and model outputs that could be reliably assessed in all simulations, regardless of VT morphology. As input parameters, we focused on variability in the conductivity of the fibrotic tissue defined in the border zone between healthy tissue

and an infarct scar, as this region is a common clinical target for ablation therapies as it plays a key role in reentry. We applied forward parametric uncertainty quantification to assess the effect of varied intracellular conductivity in the fibrotic region in longitudinal, transverse, and normal directions on simulated VT in a human patient-specific model. Specifically, we explored the effect on activation maps of the final beat of a VT induction protocol as well as global metrics such as VT cycle length and duration of the VT.

2. Methods

Patient Specific Model: Structural and late Gadolinium-enhanced (LGE) MRI images were acquired from a single patient at the University of Utah Hospitals. Ventricular anatomy, as well as scar and fibrosis patterns, were segmented using Seg3D (www.seg3d.org), where LGE MRI intensity was used to define scar (¿70% of total intensity) and border zone fibrotic (between 70% and 40% total intensity) regions in the tissue. Segmentations were converted to computational meshes using a combination of in-house processing tools, leveraging tetgen and the iso2mesh library.[6] Models were further refined and prepared for VT simulation using the mesh refinement tools present in the openCARP simulation package.[7] All procedures and data acquisition were completed with University of Utah IRB approval.

Simulation of VT: All simulations were performed using the open-source simulation package openCARP using the monodomain formulation.[7] Ionic membrane models simulating the behaviors of healthy endo-, mid-, and epicardial cells, fibrotic cells, and scar cells were assigned using the Ten Tusscher and Panfilov (TTP) formulation[8], with adjustments for fibrotic and scar regions based on Dun *et al.*[9]. A rule-based method was used to assign myocardial fiber direction throughout the model.[10] Conductivities were tuned to achieve a conduction velocity of 0.8 m/s isotropically in healthy tissue, and 0.4 m/s isotropically in fibrotic tissue. Conductivity in the scar region was set to 0 S/m. A stimulus site was chosen near the intraventricular septum, which has been previously found to reliably induce simulated VT. The stimulation protocol consisted of two S1 pulses at a cycle length of 600 ms, followed by a single S2 pulse 340 ms after the last S1. Simulation was then continued for 5 seconds after the S2 pulse.

Uncertainty Quantification: We applied uncertainty quantification to assess the effect of varied intracellular conductivity in the fibrotic region via polynomial chaos expansion (PCE) as described previously and implemented in the open-source UQ framework UncertainSCI.[4] Briefly, PCE formulates a d-degree polynomial emulator of the underlying forward process, trained using sampled parameter value-model output pairs. Using a $d = 5$ emulator, we parameterized our model according to three conductivity values (fibrotic intracellular longitudinal, transverse, and normal conductivities), whose ranges are summarized in Table 1. We utilized a truncated normal distribution for all parameters. UncertainSCI then provided $n = 66$ samples of parameter values for which we ran VT induction simulations as described above, adjusting the fibrotic conductivity values according to each parameter sample. As model outputs, we then computed the following to train PCE emulators: an activation map of the S2 beat, the cycle length of the resulting VT, and the overall length of the reentry. Length of reentry was calculated as the time between the initiation of the S2 pulse and the last time instant at which electrical activity was detected in the simulation. In some cases, reentry continued for the entire 5 seconds following the S2 pulse and these were considered to be stable VT circuits, for which the reentry length was set to the duration from S2 to the end of simulation time. For each of these three outputs (S2 activation map, VT cycle length, and reentry length), a separate PCE emulator was trained using the outputs for each parameter sample. From these emulators, we then extracted statistics of the mean value, standard deviation, and global sensitivity to each parameter and parameter combination.

Table 1. intracellular conductivity ranges for each direction in the fibrotic region. Each conductivity value is reported in units of S/m.

Conductivity	Mean	Range
longitudinal	0.033	± 0.006
sheet	0.035	±0.006
normal	0.04	±0.008

3. Results

Variation of the conductivity in the fibrotic region of the patient-specific model according to a truncated normal distribution and the ranges detailed in table 1 resulted in an average reentry time of 2.64 seconds with a standard deviation of 2.83 seconds. The average cycle length was 0.43 seconds, with a standard deviation of 0.24 seconds. Figure 1 contains a sample VT simulation in which the activation wavefront for the S2 beat can be seen in frames F1 and F2, followed by the first cycle of reentry in frames F3 and F4. The reentry originated near the top of the transmural left ventricular scar in a region of fibrosis, as indicated by the red arrow. Figure 2 shows the sensitivity, mean, and standard deviation for the activation map of the S2 stimulus.

Sensitivity values for each parameter and parameter

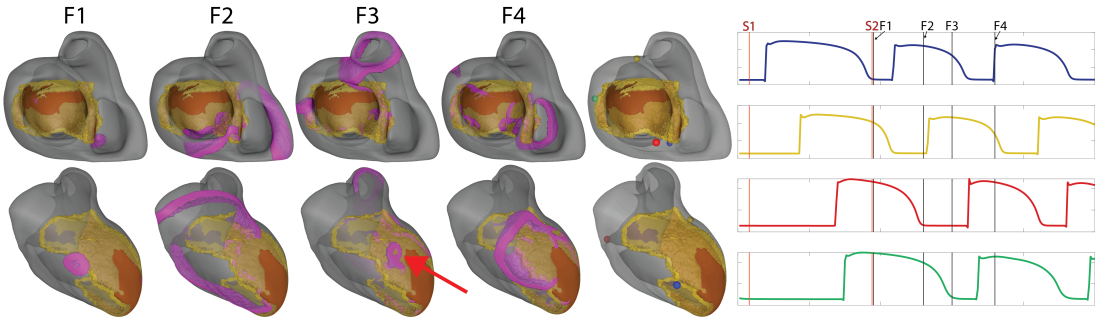

Figure 1. Patient-specific computational model. Healthy myocardium is shown in gray, fibrotic regions in yellow, and scar in brown. The top views show a basal perspective with the right ventricle to the right. The bottom views show a posterior apical view with the left ventricle on the right and the right ventricle high and to the left. In each of the frames (F1 through F4), activated tissue is shown in pink. Each frame corresponds to a time instant indicated in the time signals to the right. S1 and S2 indicate the timing of the S1 and S2 stimuli. Each time signal originates from the corresponding colored node in the right-most geometry. From top to bottom, the time signals are from (blue) the posterior apical intraventricular septum, (yellow) the anterior intraventricular septum, (red) the posterior basal intraventricular septum, and (green) the left ventricular free wall. Simulation results are shown using the nominal (mean) conductivities for the fibrotic region. The site of the first reentry is indicated with the red arrow.

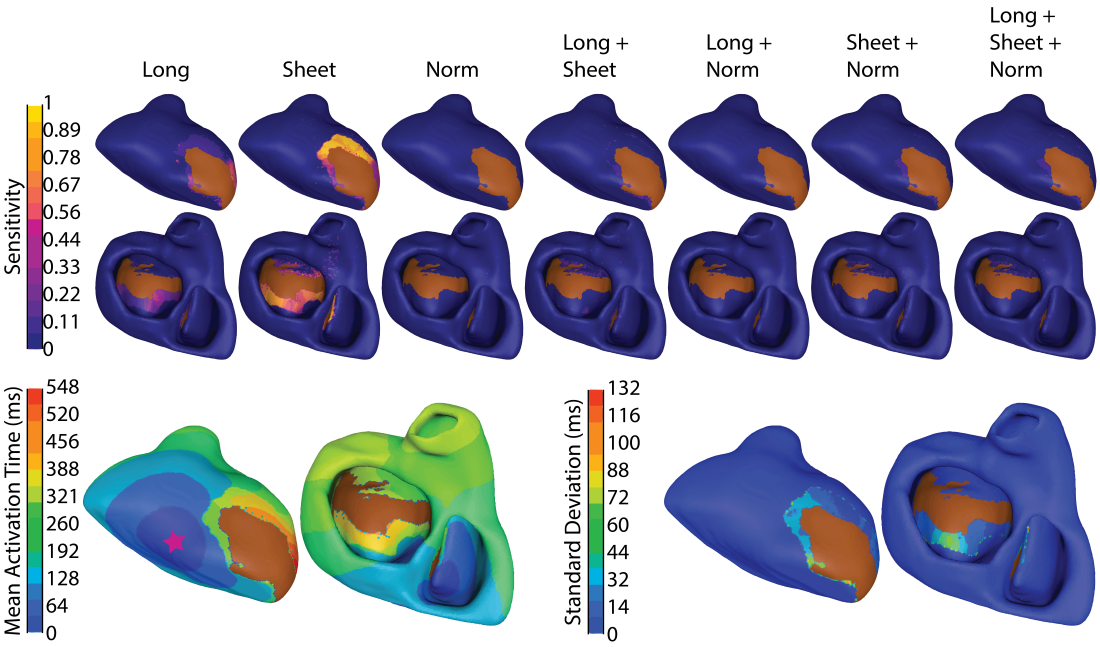

Figure 2. UQ outputs for uncertainty in the fibrotic conductivity values. Views match those in figure 1. Sensitivity (a unitless quantity from 0 to 1) for each parameter and parameter combination is shown across the top. Mean activation time for the S2 stimulus is shown on the right, while the standard deviation is shown on the left. The pink star indicates the S1 and S2 stimulus site.

combination are detailed in Table 2. The sensitivity values across each parameter combination add to 1 for reentry length and cycle length. However, because sensitivity is computed at each point in the model for the S2 activation map, the sensitivity values reported for S2 activation (which are the median of the sensitivity in the fibrotic regions) do not add to 1, but rather are meant to convey the relative sensitivities of the S2 activation map to the different parameter combinations.

Table 2. Sensitivity values for each conductivity parameter (longitudinal direction: long, sheet direction: sheet, and normal direction: norm) and combination across the three output types. For the S2 activation map, the median sensitivity in the fibrotic region is reported.

params	reentry	cycle length	S2 ActMap
long	0.056	0.039	0.063
sheet	0.229	0.139	0.307
norm	0.083	0.111	0.004
long+sheet	0.219	0.158	0.020
long+norm	0.101	0.080	0.007
sheet+norm	0.122	0.243	0.012
long+sheet+norm	0.190	0.230	0.010

4. Discussion and Conclusions

In this study, we applied PCE UQ to explore the effect of variability in the conductivity of a fibrotic border zone on simulations of VT induction. The length of the reentry varied substantially, given varied fibrotic conductivity, as evidenced by a standard deviation of 2.83 seconds. In some of the samples used to train the PCE emulator, we noted only a single beat of reentry that was not able to sustain, while in others, the VT reentry sustained for the duration of the simulation. These results alone indicate the importance of the conductivity of the fibrotic region on the resulting VT simulation and highlight the importance of properly tuning such parameters to produce robust patient-specific behavior. The simulated VT cycle length also varied substantially, with a mean of 0.43 seconds and a standard deviation of 0.24 seconds. These results suggest that the reentrant pathway may have been substantially different under different fibrotic conductivities. In future studies, we plan to investigate the changes to the reentrant pathway, using the results from this study as a foundation for the UQ-modeling pipeline.

Interpretation of VT reentry behaviors are not straightforward, however, we chose the S2 activation map as one of our UQ inputs because it was a reliable measure we were able to make in each simulation whose values did not change drastically. A possibly more intuitive metric, such as the activation map of a single reentrant cycle, would produce less interpretable UQ results, as the reentrant pathway might vary substantially, changing direction and path completely between samples. Interpretation of the resulting values such as the mean or standard deviation of such activation maps would not necessarily be useful. In the S2 activation map, we noted the highest level of standard deviation in the fibrotic region on the right and basal side of the scar (see Figure 2. The highest sensitivity values for the sheet conductivity were on the basal side of the scar, which corresponded to the site of reentry in the baseline simulation (see Figure 1). This result may suggest that sheet conductivity plays an essential role in the development of the reentrant pathway, which is corroborated by the high sensitivity to sheet conductivity seen in the reentrant length and cycle length outputs (Table 2).

This study was limited to a single patient and a limited set of both input parameters and output metrics. Future studies should develop output metrics to drive further UQ analysis and identify other parameters of interest. As conductivity heavily affects conduction velocity, our future studies will investigate these results in the context of conduction velocity changes in the fibrotic region. This study provides a solid foundation for the application of UQ to VT simulation, and demonstrates the utility of UQ in this domain by exploring the effect of variable conductivity in the fibrotic region, a highly clinically relevant and poorly understood area of tissue, on the resulting VT simulation.

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