

Uncertainty Quantification of Fibrotic Conductivity Effects on Computational Model-Derived Ablation of Atypical Left Atrial Flutter

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Abstract

Cardiac computational models are powerful tools to improve treatment of complex cardiac arrhythmias. However, such computational models rely on many uncertain inputs, and the effects of this input uncertainty on the model-derived treatment strategies are unclear. We have developed a computational model-guided ablation planning tool to aid in the ablation of reentrant circuits found in atypical left atrial flutter (ALAF). We then applied parametric uncertainty quantification to assess the effect of errors and variability in the conductivity of fibrotic tissue on the model outputs and suggested ablation patterns. In a computational model of a patient who presented with ALAF, we found that our model-guided ablation tool reduced the number of simulated ALAF circuits from 10 preablation to 4 postablation. Uncertainty quantification revealed that fibrotic conductivity affected the suggested ablation sites substantially; however, the uncertainty quantification also provided a method to display a proposed ablation strategy in a manner that accounts for the input parameter uncertainty. The results of this study show the twofold insight of UQ. This method provides a robust means to explore the effects of input parameter variability on predictions of reentrant arrhythmia. We suggest it can also present modeling results that display the uncertainty associated with model predictions.

1. Introduction

Cardiac computational models are transitioning from research tools to platforms with research and clinical applications.[1, 2] In all such computational modeling applications, it is critical to quantify the effects of uncertainty in

input parameters on the resulting model output.[3] However, robustly characterizing the output of simulations of cardiac arrhythmias in a way amenable to robust uncertainty quantification (UQ) techniques presents many challenges.[4, 5] For example, simulated reentrant arrhythmias may change their path substantially due to subtle changes in input parameters,[5], but UQ statistics such as the mean of the path of reentry with such variability would not produce useful or clinically meaningful outputs. Instead, robust UQ requires an output metric that can accurately describe the behavior of the modeled arrhythmia while still being amenable to the calculations needed for UQ. Developing and exploring such a metric is a critical next step in advancing the robust and responsible use of cardiac computational models in clinical and research domains.

Atypical left atrial flutter (ALAF) is a common complication of atrial fibrillation ablations for which cardiac computational models have shown promise in improving treatment planning procedures.[1] Such computational models allow for the identification of possible ALAF reentrant pathways and testing of proposed ablation strategies *in silico* before patient treatment. However, the implementation of such computational models requires patient-specific measurements and parameter assumptions that are error-prone.[5] The effects of variability in these inputs have only recently become a topic of robust interrogation,[5] and initial studies show a wide range of model outputs as input parameters vary, underscoring the need to better understand these UQ relationships. One parameter of interest is the conductivity assigned to areas of fibrosis, as robust quantification of the degree of fibrosis within the atria and how this correlates to tissue conductivity lacks detail.

In this study, we applied UQ to variability in ALAF

simulations resulting from uncertainty in the fibrotic tissue conductivity. We first developed a clinically relevant metric that captured the ALAF simulation behavior that was amenable to robust UQ techniques. This metric was proposed ablation sites determined algorithmically based on simulations of ALAF in a patient-specific cardiac computational model. We explored the effect of fibrotic conductivity uncertainty on the ablation sites proposed to terminate ALAF circuits, and we present a UQ-informed method for determining ablation sites that account for input uncertainty.

2. Methods

Cardiac Computational Model: We recorded structural and late Gadolinium-enhanced (LGE) MRI images from a single patient in the University of Utah Health system who had undergone a catheter ablation for atrial fibrillation, and subsequently presented with ALAF. The anatomy of the left atrium was segmented using Seg3D (www.seg3d.org). The atrial wall was extruded by 3 voxels (1.875 mm) from the blood pool. Meshes were created using the iso2mesh and tetgen libraries.[6]. LGE image intensity ratio (IIR) was used to identify scar (threshold: 1.6) and fibrosis (threshold: 1.0) based on tuning of the IIR.[7] Atrial fibers were mapped from an atlas using universal atrial coordinates.[2, 8] All procedures and data acquisition were completed with University of Utah IRB approval.

Simulation of Atrial Flutter: All simulations were performed with the open-source simulation package open-CARP using the monodomain formulation.[9] A modified Courtemanche ionic model[10] was used for healthy and fibrotic tissue according to Table 1, which contains the default healthy and fibrotic conductivities. Regions of scar were modeled as passive with zero conductivity. Induction of a reentrant atrial flutter was achieved using an S1-S2 protocol that consisted of 8 S1 pulses at a cycle length of 500 ms followed by a single S2 pulse at a variable delay (12 trials at 380–190 ms with 10 ms intervals) from the last S1. Any activity (nodes with membrane potential above -40 mV) at 1 second after the S2 pulse were considered induced reentrant arrhythmias. This S1-S2 protocol was repeated independently at 9 stimulus sites spread across the left atrium.

Identification of Ablation Targets: Ablation targets were based on two criteria. 1) (wave-based ablation) In cases of reentry, the activation wavefront was tracked throughout time and was considered for ablation if it spanned at least two boundaries (anatomical boundaries or regions of nonconducting scar), and if removing that region broke the path of the reentrant wave. The smallest 10 wavefront regions that fit this criterion were labeled “wavefront ablations”. 2) (boundary-based ablation) Connecting lines of

Table 1. Model parameter values. Conductivities in the longitudinal σ_l , sheet σ_s and normal σ_n directions given in S/m. Ionic conductivities given as factors times the baseline values in the Courtemanche model.

Parameter	Healthy Tissue	Fibrotic Tissue
σ_l	0.3479	0.0627
σ_t	0.1606	0.0627
σ_n	0.1606	0.0627
GKr	1.6	1.6
GNa	2.0	1.2
GK1	0.8	0.4
Gto	0.5	0.5
factorGKur	0.5	0.5
GCaL	0.3	0.15

ablation were drawn between boundaries (anatomical features, scar, and previously identified ablations). Starting at one barrier, geodesic paths were drawn to connect to the nearest barriers until all were contiguous. Ablations were performed within a radius of 2 mm of these connecting lines. We then counted the number of times each node was targeted and normalized the result into an ablation score from 0 to 1, where 1 indicates a node targeted by all ablations. Separate ablation scores were calculated for the wave-based and boundary-based ablations.

Uncertainty Quantification: We applied parametric UQ to assess the effect of the fibrotic conductivity on the resulting ablation scores using polynomial chaos expansion (PCE) as defined previously.[3, 11] PCE emulates the parameter-to-output model using a d -degree polynomial trained using n sample parameter values and model outputs. Using a $d = 5$ emulator, we parameterized the isotropic conductivity in the fibrotic regions according to a beta distribution ($\alpha = 2$, $\beta = 2$), with a mean of 0.0627 S/m and a range of ± 0.06 S/m. UncertainSCI provided $n = 16$ conductivity samples.[3] For each sample, we simulated atrial flutter and identified ablation targets as described above. Wave-based and boundary-based ablation scores were provided separately as model outputs and used to train separate PCE emulators. We then extracted the mean, standard deviation, and percentiles of the ablation scores from the PCE emulators.

3. Results

In the baseline flutter simulations, using mean fibrotic conductivity, 10 ALAF circuits were induced. Figure 1 shows an example reentry induced in the model as well as the wave-based and barrier-based ablations generated for that reentry. After applying wave-based and boundary-based ablation and repeating induction simulations, only 4 reentrant circuits were observed. The 4 remaining flutter circuits were functional reentries maintained by a unidirectional block developed within the fibrotic tissue.

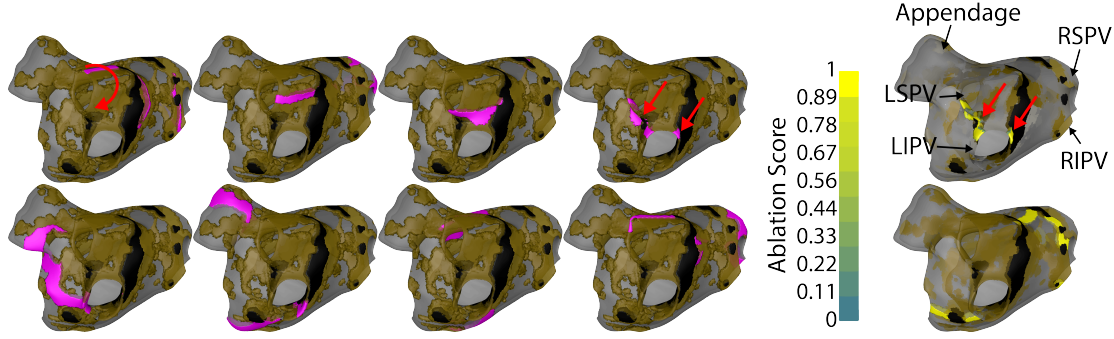


Figure 1. Cardiac computational model demonstrating simulated ALAF. Healthy myocardium is shown in gray, fibrotic regions in brown, and scar in black. The left shows time points during a reentrant flutter, where the pink surface is the activation wavefront. The red arrows indicate the path of the reentry and the critical isthmus. On the right, the wave-based ablation (top) and boundary-based ablation (bottom) are shown for this reentrant circuit.

Across the 16 parameter samples for fibrotic conductivity, in the 1,728 S1-S2 protocols simulated atrial flutter was induced 362 times. Figure 2 shows the percentile results, indicating the prescribed ablation pattern to cover 90% or 10% of the variability induced by uncertainty in the fibrotic conductivity. The mean shows the average ablation score, and the standard deviation indicates the relative variability of the ablation score across the mesh.

4. Discussion and Conclusions

In this study, we presented both a novel automatic method to identify ablation patterns to terminate atrial flutter induced in cardiac computational models and an uncertainty quantification analysis of the effects of fibrotic conductivity variation on the generated ablation patterns. Ablations made according to our method reduced the number of inducible arrhythmias in the patient-specific model, eliminating structural reentries that rotate around scars and anatomical features such as valves and veins. However, functional reentries were not adequately addressed, since our ablation criteria could not robustly identify the spiral reentries formed within the fibrotic and healthy tissue. Although further improvements to our ablation criteria may solve this problem, an alternative approach would be to present clinicians with a suggested ablation pattern in which the structural entries have been addressed and visualize the remaining arrhythmias sustained in the model, allowing the clinician to produce the final ablation plan.

In this study, we selected variability in the fibrotic conductivity as a starting place to explore atrial flutter variability using polynomial chaos expansion. By using our automatic ablation targets as a model output, we were able to robustly characterize the effect of this input parameter variability on the behavior of the model. We found that fibrotic conductivity did cause variation in the number of observed flutter circuits and their morphology, resulting in ablation patterns that were spread out across the atria.

However, the highest ablation scores remained consistent in the face of this variation, indicating that the primary locations identified in the ablation methods were somewhat robust to this variability. Furthermore, by formulating our model output in a manner amenable to robust UQ, we were able to present an ablation strategy in a way that is aware of the uncertainty in the model in the form of a percentile. In these results, we selected the 90th, which shows the ablation pattern needed to cover 90% of the variability induced by uncertainty in the fibrotic conductivity as an upper bound, and the 10th as a lower bound. However, this percentile can easily be adjusted to the desired level, producing more or less aggressive ablation plans. Our interpretation of the proposed wave and boundary-based ablations from Figure 2 is that wave-based ablation suggests locations in between the pulmonary veins and scars that act as critical isthmuses whereas the boundary-ablation, as would be expected, suggests a connecting line between the PVs. The summary of these two approaches would be something akin to a repeated pulmonary vein isolation plus connection across the atria posterior wall. We propose that clinicians may use this information to inform their preoperative treatment plan, developing an ablation strategy that incorporates these modeling results and best clinical practices. We also propose that, as a final step, an ablation may be simulated in light of these UQ-aware proposed ablations, and any remaining functional reentries could be presented to a clinician to inform their final preprocedural planning.

This study is presently limited to one patient and one input variable to allow for exploration of the results without retractable computational load. Each S1-S2 protocol took on average an hour to complete on high-performance computing servers. While scaling up to additional parameters will increase the number of needed samples, careful selection of parameters should keep the overall computational cost low enough to be feasible to complete on a clinically relevant timeline. The results presented here pave a path

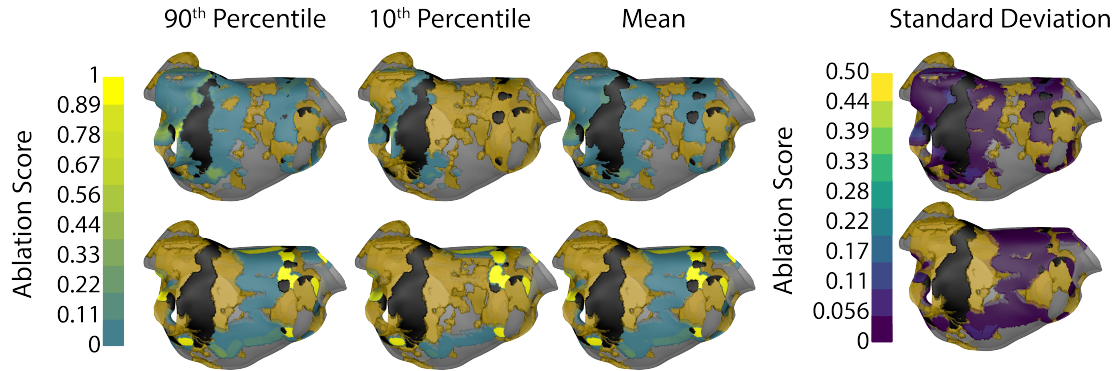


Figure 2. Uncertainty quantification results for the effects of fibrotic conductivity uncertainty on ablation pattern. The top row shows wave-based ablations, and the bottom shows boundary-based ablations. Percentile results show ablation patterns to cover X percent of the variability induced by uncertainty in fibrotic conductivity. Ablation scores below zero are removed in all cases.

for both an improved understanding of model behaviour in the face of input uncertainties, as well as the development of clinically relevant model outputs that are both informed by and robust to said uncertainties.

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