

## MODEL CREDIBILITY REPORT (October 1, 2018)

### Simulation guidance of ablation therapy for persistent atrial fibrillation (U01-HL-141074)

**Natalia Trayanova, Johns Hopkins University (PI/PD)**

**Hugh Calkins, Johns Hopkins Medicine (PI)**

**Patrick Boyle, University of Washington (Co-I)**

**Adityo Prakosa, Johns Hopkins University (Co-I)**

Predictive multiscale models to improve clinical workflow, standard operating procedures, patient-specific modeling for diagnosis and therapy planning. Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia, leading to morbidity and mortality in 1-2% of the population and contributing significantly to global health care costs. For patients in whom AF cannot be treated by drugs, the recommended therapy is catheter-based ablation to isolate arrhythmia triggers and eliminate the substrate for arrhythmia perpetuation. However, outcomes of the procedure are poor (50% success rate) in patients with persistent AF (PsAF) due to the presence of extensive atrial fibrosis, which confounds ablation strategies. There is an urgent need for new approaches that can result in swift and accurate identification of optimal ablation targets for PsAF and thereby improve the efficacy of and increase the tolerance for the therapy, as well as reduce post-procedure complications and repeated ablations. The overall objective of this application is to develop and validate a novel personalized multiscale modeling strategy for determining the optimal targets for catheter ablation of the fibrotic substrate in patients with PsAF. We propose to develop and validate atrial models reconstructed from MRI images of patients with PsAF and fibrotic remodeling. The models will integrate mechanistically functions from the molecular level to the electrophysiological interactions in the intact organ. We will parametrize and validate the simulation approach with experimental measurements in explanted human atria and animal models. We will use the validated personalized modeling strategy to determine, in retrospective patient studies, what constitutes a set of optimal ablation lesions that terminate AF with the least likelihood of recurrence. The project will culminate with a pilot prospective patient study, where AF ablation will be executed directly at the simulation-predicted targets. Successful execution of the proposed studies will pave the way for a major paradigm shift in the clinical procedure of AF ablation in patients with fibrotic remodeling, resulting in a dramatic improvement in the efficacy of the therapy. Importantly, completion of this project will result in a major leap forward in the integration of computational modeling in the diagnosis and treatment of cardiac disease.

#### 1. List of Planned Actions

*Classified as Validation (VA), Verification (VE), and Uncertainty Quantification (UQ), or Other (O)*

- ✓ **[VA-1]** Develop version-controlled code (git, <https://git-scm.com/>)
- ✓ **[VA-2]** Perform unit testing on all software sub-modules.
- ✓ **[VA-3]** Maintain a database of annotated software parameters for the multiscale modeling software used (CARP, <https://carp.medunigraz.at/>)
- ✓ **[VA-4]** Perform convergence testing in tissue wedge models extracted from all atrial models
- ✓ **[VA-5]** Re-run the complete simulation and analysis process for a subset of models in a distinct software package
  
- ✓ Calibrate model parameters corresponding to different tissue regions (LA/RA, non-fibrotic/fibrotic) to match observations from experiments conducted in atrial tissue samples recovered from rejected donor hearts of patients who had persistent AF, specifically:
  - ✓ **[VE-1A]** Establish baseline ion channel expression levels (i.e., maximal conductances) by measuring mRNA levels

- ✓ **[VE-1B]** Adjust mathematical formulations for membrane kinetics to match action potential morphology observed via optical mapping
- ✓ **[VE-1C]** Calibrate conductivity tensor values to match conduction velocities observed via optical mapping
- ✓ **[VE-2]** Systematically compare scans of canine atria with different degrees and spatial patterns of fibrotic remodeling to histology data acquired immediately post-scan
- ✓ **[VE-3]** Calibrate conductivity tensor values in canine models using in vivo intracardiac endocardial and open-heart epicardial electrogram recordings from the same dogs
- ✓ Conduct retrospective studies in models derived from persistent AF LGE-MRI scans to prove:
  - ✓ **[VE-4A]** That simulations are capable of predicting how each individual's pattern of fibrotic remodeling sustains AF
  - ✓ **[VE-4B]** That the list of targets produced by the approach constitutes an optimal set of ablation lesions that will terminate AF with the least likelihood of recurrence
- ✓ **[UQ-1]** Characterize the relationship between cell- and tissue-scale model parameters and primary model outputs (i.e., locations of persistent reentrant drivers within the fibrotic substrate)
- ✓ **[UQ-2]** Ascertain the relationship between regions of enhanced intensity in LGE-MRI and tissue identified as fibrotic via ex vivo histological examination of the same dog hearts
- ✓ **[O-1]** Work to identify groups to perform independent evaluation of our multiscale modeling strategy
- ✓ **[O-2]** Continuously update simulation platform to remain current and address intrinsic limitations associated with the relationship between MRI fidelity and quality of model prediction
- ✓ **[O-3]** Disseminate findings from model credibility actions, including detailed descriptions of each approach and results of related studies (e.g., sensitivity analyses), to interested third parties via publications or at the PD's discretion.

## 2. Information Gained by each Credibility Action

- ✓ **[VA-1] Version control:** development history and tracking data on identification and resolution of programming errors
- ✓ **[VA-2] Unit testing:** benchmark data that can be used internally and by groups attempting to reproduce or replicate experiments conducted as part of the study
- ✓ **[VA-3] Annotated CARP parameter database:** systematically organized information to facilitate reproducibility and replicability, especially in other modeling platforms
- ✓ Maintain a database of annotated software parameters for the multiscale modeling software used (CARP, <https://carp.medunigraz.at/>)
- ✓ **[VA-4] Convergence testing:** range of tolerable values to ensure numerical stability (e.g., minimum requirements for time step granularity and finite element mesh resolution)
- ✓ **[VA-5] Distinct software package:** documentation of reproducibility and replicability
- ✓ **[VE-1] Human model parameter calibration:** mRNA expression, action potential properties (shape, APD restitution, dynamics of refractoriness), and conduction velocities directly measured from atrial tissue obtained from patients with persistent AF
- ✓ **[VE-2] Canine fibrosis assessment:** Correlation between LGE levels observed in clinical scans and true pattern of fibrotic remodeling observed ex vivo
- ✓ **[VE-3] Canine model parameter calibration:** In vivo action potential and conduction velocity data recorded from atria of dogs with an experimental model of AF
- ✓ **[VE-4] Retrospective human studies:** Correlation between reentrant driver locations observed in simulations conducted in models reconstructed only from data obtained non-invasively (LGE-MRI) and AF drivers observed clinically via invasive intracardiac mapping in the same individuals

- ✓ **[UQ-1] Sensitivity analysis:** Effect of model parameters on locations of persistent reentrant drivers within the fibrotic substrate as predicted by simulations, quantified in terms of the relevant clinical length scale (~7 mm)
- ✓ **[UQ-2] Canine fibrosis analysis:** Correlation between regions of LGE and locations confirmed to be fibrotic via ex vivo histological examination of the same dog hearts
- ✓ **[O-1] Model evaluation:** Independent assessment of our modeling strategy in consultation with IMAG and the MSM consortium will lend additional credibility to simulation predictions
- ✓ **[O-2] Continuous updates to bypass key limitation (MRI quality):** Working to accommodate improvements in clinical image acquisition will help us minimize the impact of an important limitation on the credibility of the overall approach
- ✓ **[O-3] Broad dissemination:** By making our VVUQ approach transparent and publicly available, we anticipate valuable feedback from interested community members (including IMAG and the MSM consortium), which will in turn help us further refine and improve our modeling strategy

### 3. Actions and Activities Classified within the CPMS TSR Framework

#	Rule	Actions/Activities
1	<i>Define context clearly</i>	[UQ-1]
2	<i>Use appropriate data</i>	[VE-1] [VE-2] [VE-3] [VE-4]
3	<i>Evaluate within context</i>	[VA-4] [UQ-1]
4	<i>List limitations explicitly</i>	[VA-4] [VE-2] [VE-4] [UQ-2] [O-2]
5	<i>Use version control</i>	[VA-1] [VA-2]
6	<i>Document adequately</i>	[VA-2] [VA-3]
7	<i>Disseminate broadly</i>	[O-3]
8	<i>Get independent reviews</i>	[O-1]
9	<i>Test competing implementations</i>	[VA-5]
10	<i>Conform to standards</i>	[VA-3] [VA-5] [O-1]

Description of how the planned activities will lead to a credible model: All aspects of the project were conceived with model credibility in mind. Successful completion of these tasks will establish a new standard of confidence in models of cardiac electrophysiology. The importance of this aspect is enormous because the work aims to break an important translational frontier by delivering custom-tailored ablation treatment to individual patients based on model predictions. The measures outlined here will require minimal additional effort from project personnel, since they will all be performed as a matter of course during the routine processes of constructing models and conducting simulations.

Progress to-date (August 2018 to present): During the first few months of work on the project, Drs. Boyle and Trayanova have made significant progress on the proposed convergence analysis [VA-4]. Complete results should be available soon and will be presented at relevant scientific meetings and in publication form. We also established an excellent framework for completing the sensitivity analysis proposed under [UQ-1], the results of which will be published in a separate study, completed prior to the beginning of the funding period, by Hakim et al. (1) This work was conducted using a previously reconstructed atrial data set derived from different LGE-MRI scans but the fundamentals of the atrial modeling methodology are the same as those in the proposed work. As such, we expect our work on [UQ-1] to proceed rapidly.

Plans for the next reporting cycle: (1) Dr. Trayanova will begin working on the infrastructure for carrying out actions [VA-1], [VA-2], and [VA-3] (version control, unit testing, and parameter database, respectively). If sufficient progress is made towards completion of [VA-3], the database will be made

publicly accessible. (2) Dr. Boyle and Dr. Trayanova will complete **[VA-4]** (convergence analysis) and disseminate relevant results via conference presentations and a peer reviewed journal article. (3) Dr. Efimov and Dr. Ranjan will begin experiments and data collection for the actions related to human tissue (**[VE-1]**) and canine experiments (**[VE-2]**, **[VE-3]**). (4) Dr. Trayanova will begin work on the human retrospective study (**[VE-4]**). Progress towards completing this action is expected to be rapid since significant work has already been done towards developing the necessary framework as part of an unrelated but complementary study has similar aims but deals with a patient cohort suffering from paroxysmal AF instead of persistent AF. (5) As new atrial models derived as part of this study are reconstructed, Dr. Boyle and Dr. Trayanova will repeat sensitivity analysis conducted as part of a previous unrelated but complementary study (now in press (1)), in fulfilment of **[UQ-1]**.

**4. Issues/concerns identified as critical or problematic**

No such issues/concerned have been identified thus far.

**5. Other factors that contribute to credibility but cannot be reported within the TSR structure**

No such factors have been discovered thus far.

**6. References**

1. Hakim JB, Murphy MJ, Trayanova NA, Boyle PM. Arrhythmia Dynamics in Computational Models of the Atria Following Virtual Ablation of Reentrant Drivers. *Europace*. 2018;in press.