MODEL CREDIBILITY REPORT (February 20, 2020)

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

✓ 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)

✓ **[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-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)

✓ **[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	*Define context clearly*	**[UQ-1]**
2	*Use appropriate data*	**[VE-1] [VE-2] [VE-3] [VE-4]**
3	*Evaluate within context*	**[VA-4] [UQ-1]**
4	*List limitations explicitly*	**[VA-4] [VE-2] [VE-4] [UQ-2] [O-2]**
5	*Use version control*	**[VA-1] [VA-2]**
6	*Document adequately*	**[VA-2] [VA-3]**
7	*Disseminate broadly*	**[O-3]**
8	*Get independent reviews*	**[O-1]**
9	*Test competing implementations*	**[VA-5]**
10	*Conform to standards*	**[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 (since October 2018): We have completed the proposed convergence analysis **[VA-4]**. Mesh resolution does not have a prominent effect on reentrant driver localization. As an additional bonus, we were able to show that, in most situations pacing, from sites closer to (but not within) fibrotic regions facilitates faster revelation of a comprehensive list of each patient's ablation targets, when compared to a quasi-random distribution of evenly spaced sites. We are working on a manuscript that describes these findings and will soon be ready to submit. We have made significant progress on the sensitivity analysis proposed under **[UQ-1]**. Complete results should be available soon and will be presented at relevant scientific meetings and in publication form.

Dr. Trayanova's lab has made progress towards completion of the infrastructure for carrying out actions **[VA-1]**, **[VA-2]**, and **[VA-3]** (version control, unit testing, and parameter database). We estimate that the overall progress for these 3 actions in aggregate is 60%. The parameter database is not yet ready to be shared publicly. Moreover, extensive progress has been made in establishing the necessary modeling and simulation infrastructure that will be used to carry out the human retrospective study (**[VE-4]**). While the analysis itself has not been conducted yet, two major peer-reviewed papers describing methodology and results for models reconstructed using the same methodology were published [1,2]. Likewise, extensive sensitivity analysis work conducted in ventricular models (rather than atrial) on conceptually similar types of analysis have proved quite fruitful in terms of generating approaches that will ultimately be used in this project [3-5]. Dr. Efimov's lab has provided experimental data to inform the atrial cell models for the actions related to human tissue (**[VE-1]**).

Plans for the next reporting cycle: (1) Dr. Trayanova's lab expects to complete work on the first three VA-related actions for this project. (2) Dr. Boyle and Dr. Trayanova disseminate relevant results of will

[VA-4] via conference presentations and a peer reviewed journal article. (3) Dr. Trayanova and Dr. Efimov's labs expect to make significant progress in all sub-actions of **[VE-1]**, in which representations of left/right atrial electrophysiology will be fine-tuned based on measurements recorded from human atrial tissue samples. (4) Dr. Trayanova expects to complete the human retrospective study (**[VE-4]**), assuming suitable data can be collected from patients undergoing ablation procedures. (5) As new atrial models derived as part of this study are reconstructed, Dr. Boyle and Dr. Trayanova will continue to repeat sensitivity analysis conducted as part of two previous complementary studies that were published in 2018 [6,7]; this is to fulfil **[UQ-1]**. (6) Dr. Boyle will coordinate execution of simulations in a new cardiac electrophysiology simulator (OpenCARP: https://opencarp.org/), which is a completely refactored implementation of the finite element analysis software used in the Trayanova lab; this will fulfil **[VA-5]** and serve a complementary purpose of establishing a framework for action **[O-1]**, since it will pave the way towards identification of new outside groups to validate modeling and simulation methodology developed and used in this project.

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 Boyle, P. M. *et al.* Computationally guided personalized targeted ablation of persistent atrial fibrillation. *Nat Biomed Eng* **3**, 870-879, doi:10.1038/s41551-019-0437-9 (2019).

2 Ali, R. L. *et al.* Arrhythmogenic propensity of the fibrotic substrate after atrial fibrillation ablation: a longitudinal study using magnetic resonance imaging-based atrial models. *Cardiovasc Res* **115**, 1757-1765, doi:10.1093/cvr/cvz083 (2019).

3 Deng, D., Prakosa, A., Shade, J., Nikolov, P. & Trayanova, N. A. Characterizing Conduction Channels in Postinfarction Patients Using a Personalized Virtual Heart. *Biophys J* **117**, 2287-2294, doi:10.1016/j.bpj.2019.07.024 (2019).

4 Deng, D., Prakosa, A., Shade, J., Nikolov, P. & Trayanova, N. A. Sensitivity of Ablation Targets Prediction to Electrophysiological Parameter Variability in Image-Based Computational Models of Ventricular Tachycardia in Post-infarction Patients. *Front Physiol* **10**, 628, doi:10.3389/fphys.2019.00628 (2019).

5 Prakosa, A. *et al.* Personalized virtual-heart technology for guiding the ablation of infarct-related ventricular tachycardia. *Nat Biomed Eng* **2**, 732-740, doi:10.1038/s41551-018-0282-2 (2018).

6 Boyle, P. M. *et al.* The Fibrotic Substrate in Persistent Atrial Fibrillation Patients: Comparison Between Predictions From Computational Modeling and Measurements From Focal Impulse and Rotor Mapping. *Front Physiol* **9**, 1151, doi:10.3389/fphys.2018.01151 (2018).

7 Boyle, P. M. *et al.* Comparing Reentrant Drivers Predicted by Image-Based Computational Modeling and Mapped by Electrocardiographic Imaging in Persistent Atrial Fibrillation. *Front Physiol* **9**, 414, doi:10.3389/fphys.2018.00414 (2018).