Model Credibility Update, October 2018

1. Project Title

Multiscale modeling to map cardiac electrophysiology between species
U01 HL 136297
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2. Brief description of the project

Cardiac arrhythmias kill hundreds of thousands of people each year, but the heart's inherent complexity prevents experiments from illuminating all aspects of arrhythmias. While computational modeling fills many of the experimental voids, important limitations restrict the utility of these models. The overall goal of this project is to develop novel approaches for multiscale cardiac electrophysiology modeling, including protocols for more predictive models, rigorous representations of variability between samples, quantitative mappings between species, and the effects of heterogeneity at the tissue level.

Details about the current project can be found on the IMAG Wiki page

3. Model credibility plan details

A. Planned actions as outlined

The model credibility plans as outlined in the original proposal can be summarized as follows:

- Year 1: By the end of Year 1, MATLAB code for the re-calibrated cellular models, along with the data used to produce these models, will be publically available.
- Year 2: MATLAB code for cellular models will be converted to SBML, and a plan will be developed with other members of the MSM consortium for evaluation of the models. We will share these models with Dr. Rodriguez's group and finalize a plan for her team to perform a rigorous evaluation.
- Year 3: At the beginning of Year 3, we will host a virtual symposium (series of webinars) aimed at making outside researchers aware of our experimental data and models. By the end of Year 3, statistical models describing population behavior and mappings between cell types will be made publically available and shared with the MSM consortium.
- Year 4: By the end of Year 4, all cellular and population models will have been thoroughly evaluated by Dr. Rodriguez's group and other outside parties Tissue models will be made available.
- Year 5: All models will be archived, and a manuscript describing the lessons learned from the public evaluation process will be prepared.

B. Brief description of information gained from each credibility action

Broadly speaking, the actions planned will improve credibility in the following ways:

- third-party assessment will ensure that code is properly documented and that all simulations are reproducible
- coupling of dynamic clamp experiments to simulations will produce models that respond properly to perturbations such as ion channel block by drugs
- calibration of model populations will allow for inferences about how ion channel expression levels vary and potentially co-vary across a population

C. Actions & activities organized in the CPMS TSR framework

Rule	Actions and Activities
Rule 1 – Define context clearly	The mathematical models used in our project are of cardiac cells and tissues, appropriate for simulating the electrical behavior at these scales under a range of physiological conditions
Rule 2 – Use appropriate data	The data used to develop these models include: • voltage clamp measurements of individual ionic currents • intracellular calcium transients measured in cells at several different electrical pacing rates • responses of cells to ionic current perturbations assessed using pharmacological ion channel blockade or dynamic clamp pacing protocols • optical mapping of conduction velocity and action potential shape at the tissue level
Rule 3 – Evaluate within context	Experiments to evaluate the model credibility are an important element of the research plan. These include: • measuring the response of myocytes to pharmacological block of important ion channels • measurements from a large number of myocytes to calibrate the cell-to-cell variability in important physiological metrics These evaluations are critical for ensuring that the steps taken to develop the models are appropriate for producing robust and credible model
Rule 4 – List limitations explicitly	Limitations are always described thoroughly in publications, for instance in recent studies by Gong & Sobie (PMID: 29507757) and by Varshneya et al (in press, doi;10.1161/CIRCEP.118.006558)
Rule 5 – Use version control	At the conclusion of each study, we deposit code in github that allows for publication figures to be reproduced exactly. See, for instance, github repositories for recent studies: • https://github.com/JQXGong/cross-cell-type-regression.git • https://github.com/meeravarshneya1234/IKs_stabilizes_APs
Rule 6 – Document adequately	Models are documented in Methods sections, supplemental Methods, and in github repositories
Rule 7 – Disseminate broadly	Besides publications, research performed in this project has been discussed at several symposia, seminars, and national meetings, including: • The Kavli Institute of Theoretical Physics, Santa Barbara, CA (July 2018) • A symposium hosted by the Department of Pharmaceutical Sciences, University at Buffalo (July 2018) • A preconference workshop sponsored by the American College of Clinical Pharmacology (September 2018) • The American Conference on Pharmacometrics (upcoming October, 2018) Several of these presentations have led to new collaborations that allow for independent testing of model code, both additional simulations to test reproducibility and new experiments to test whether predictions are accurate
Rule 8 – Get	Dissemination has led to new relationships that are enabling additional

independent reviews	independent tests of concepts and model predictions, including: • following the strategy outlined by Gong & Sobie for cross-cell type predictions, the laboratory of Beatriz Trenor (PMID: 29507757) has collaboratively with Sobie's lab developed an analogous regression model to predict drug effects in diseased myocytes based on experiments performed in healthy myocytes • a collaboration has been developed with Emilia Entcheva of George Washington University in which our stem cell-derived myocyte models will be tuned to match her high-throughput recordings of drug effects in these cells
Rule 9 – Test competing implementations	This is already routine practice in our approach -- indeed, some of the keenest biological insights have been gained when two implementations produce different results. See, for instance: • Sobie, Biophysical Journal 2009 (PMID: 19217846) • Sarkar & Sobie, Heart Rhythm 2011 (PMID: 21699863) • Cummins et al, PLOS Comp Bio 2014 (PMID: 24675446) • Gong et al, JMCC 2017 (PMID: 27913283) • Varshneya et al, Circulation Arrhythmia & Electrophysiology, 2018 in press (zdoi;10.1161/CIRCEP.118.006558)
Rule 10 – Conform to standards.	Methods descriptions and github code repositories conform to standards outlined by Waltemath et al in "Minimum Information about a Simulation Experiment (PLOS Comp Bio 2011, PMID: 21552546)

D. How will these activities lead to a credible model?

Somewhat counterintuitively, in our experience the greatest gain in credibility comes after a model fails. The increase in confidence comes not from the failure itself, but from the modifications made by the investigators to address the discrepancies, and the insight gained through that process. See for instance, Devenyi & Sobie JMCC 2016 (PMID: 26235057) and Devenyi et al J Physiology 2017 (PMID: 27779762).

Similarly, when competing implementations produce different results, uncovering the reasons for the discrepancies often leads to new insights into how future experiments should be optimized for model building.

E. Progress to date & plans for next reporting cycle

One paper was published in February (Gong & Sobie PMID: 29507757), and a second paper in press will be published imminently, (Varshneya et al doi;10.1161/CIRCEP.118.006558). Code from each study, conforming to appropriate standards, has been deposited at github:

- https://github.com/JQXGong/cross-cell-type-regression.git
- https://github.com/meeravarshneya1234/IKs_stabilizes_APs

By the next reporting cycle, we expect to be able to report on progress from the recently-initiated third-party collaborations with the Trenor and Entcheva laboratories.

4. Issues/concerns identified as critical or problematic

None so far

5. What other factors contribute to credibility but cannot be reported within the TSR structure?

No factors identified so far