

## **MODEL CREDIBILITY PLAN**

One of the weaknesses of many published modeling studies is that model behavior is validated only under a limited range of conditions. For instance, the model output may closely match action potential morphology at a particular pacing rate, but since the simulated response of the model to ionic current perturbations is not presented, the user of the model is never sure whether this behavior will be realistic. One of the strengths of this proposal is that we will develop new methods to validate cardiac electrophysiology models under a broader range of conditions, thereby producing more predictive models, as our preliminary data already indicate (see Research Strategy).

Rigorous tests of model credibility are therefore already built into the proposal and are a fundamental aspect of the planned research. For instance: (1) Aim 1 will include dynamic clamp experimental tests of model predictions regarding how perturbations to ionic currents influence cellular action potentials and calcium transients; (2) Aim 2 will directly test predictions about how ionic conductances vary and co-vary across a population; (3) Aim 3 will include direct experimental tests of models that map from one cell type to another.

In addition to these tests, however, we recognize the importance of 3<sup>rd</sup> party use of mathematical models to ensure their broadest applicability. We therefore plan to make our models freely available and to encourage the broader community to use and test the predictive power of our models. Dr. Blanca Rodriguez of Oxford University, one of the world's foremost experts in cardiac electrophysiology modeling, has already agreed to participate in this effort (see letter of support). In addition to working with Dr. Rodriguez and her team, we will find partners for 3<sup>rd</sup> party testing through the MSM consortium and our own interactions with the broader scientific community. Specific questions that can be addressed through these evaluations include the following:

- Do the models of heterogeneous cell populations exhibit variability that is consistent with variability observed experimentally? We plan to calibrate our populations based on our own data (see Aim 2), but calibration by 3<sup>rd</sup> parties against additional published datasets will also be valuable. (this is one of Dr. Rodriguez's particular areas of expertise).
- Under what conditions do the cellular models exhibit grossly unphysiological behavior such as an inability to fire action potentials? Dramatic changes in parameters can cause qualitatively different behaviors (bifurcations), and these can often be compared with the results of pharmacological or genetic experiments (overexpression or knockdown).
- How well do tissue-level behaviors match experimental data on conduction velocity, electric field potentials (e.g. electrocardiograms), and spatial dispersion of action potential waveforms? The results from our tissue simulations in Aim 4 can be compared directly with electrical and optical mapping data obtained from whole hearts.

In addition to these questions, we are sure that colleagues will think of additional methods for assessing model credibility, which is why the participation of 3<sup>rd</sup> parties such as Dr. Rodriguez will be critical.

We intend to engage with the community in this way according to the following timeline:

- 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.