# Assessing and Improving the Credibility of Multiscale Cardiac Electrophysiology Models


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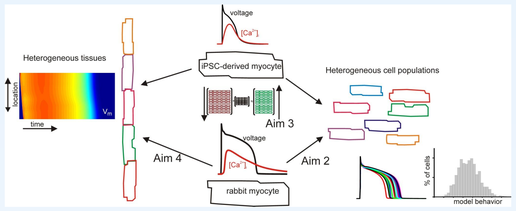
U01HL136297: ”Multiscale modeling to map cardiac electrophysiology between species”

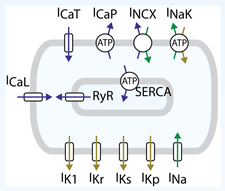

## OVERALL PROJECT GOALS

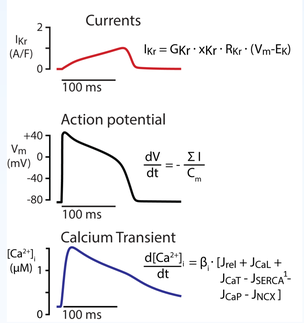
***Aim 1:*** Develop improved cellular models through rigorous experimental calibration protocols.
***Aim 2:*** Calibrate models of cell populations to infer variation and co-variation in ionic currents
***Aim 3:*** Develop and experimentally test models that map behavior between species
***Aim 4:*** Predict tissue-level physiological consequences of cellular heterogeneity.




## METHODS – CELLULAR ELECTROPHYSIOLOGY MODELS

Models typically are built from data from multiple cell types, from many labs, under varying conditions – composite models can struggle to reproduce biology

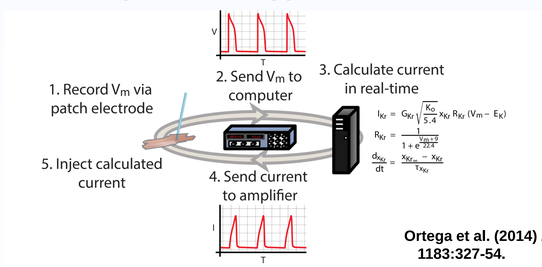



- 10-20 ion channels, pumps, and transporters
- 20-60 ordinary differential equations

## METHODS – DYNAMIC CLAMP ELECTROPHYSIOLOGY

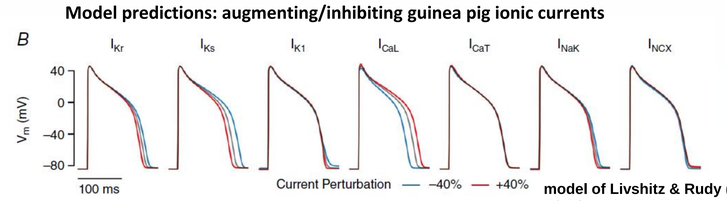
**Dynamic Clamp: real-time approach to alter ionic current levels**




Ortega et al. (2014) *Methods Mol Biol.* 1183:327-54.

## CREDIBILITY ASSESSMENT 1 – CELLULAR PERTURBATION

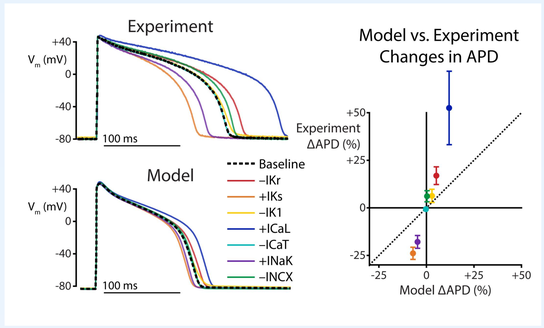
**Model predictions: augmenting/inhibiting guinea pig ionic currents**



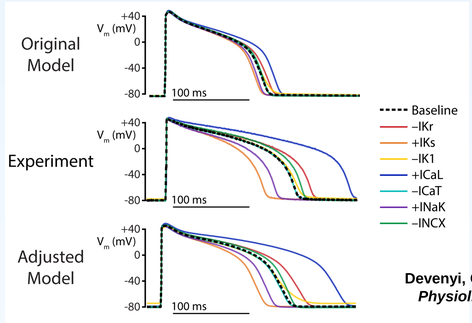

model of Livshitz & Rudy (2009) *Biophys. J.* 97:1265-76.

**Dynamic Clamp approach allows a complete set of perturbations to be tested in each cardiac myocyte**

## CREDIBILITY ASSESSMENT 1: RESULTS




**A Genetic Algorithm was used to correct the discrepancy between experiments and simulations and produce a more predictive model**

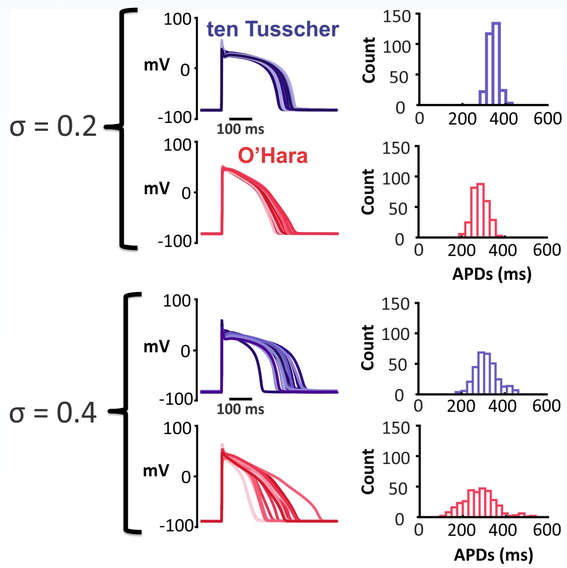



Devenyi, Ortega et al. (2017) *J Physiol.* 595:2301-17.

**Testing multiple ionic current perturbations in each cell allows us to develop more credible models**

## CREDIBILITY ASSESSMENT 2: POPULATION BEHAVIOR

**Heterogeneous populations are generated through parameter randomization – calibrating population results with experimental data will provide inferences about molecular-level variability.**




model of ten Tusscher & Panfilov (2006) *AJP Heart* 291:H1088-100.
model of O'Hara et al (2011) *PLOS Comp. Bio.* 7:e1002061.

## CREDIBILITY ASSESSMENT 3: EXTERNAL VALIDATION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### Population-based mechanistic modeling allows for quantitative predictions of drug responses across cell types


Jingqi Q. X. Gong[1] and Eric A. Sobie[1]



Quantitative mismatches between human physiology and experimental models can be problematic for the development of effective therapeutics. When the effects of drugs on human adult cardiac electrophysiology are of interest, phenotypic differences with animal cells, and more recently stem cell-derived models, can present serious limitations. We addressed this issue through a combination of mechanistic mathematical modeling and statistical analyses. Physiological metrics were simulated in heterogeneous populations of models describing cardiac myocytes from adult ventricles and those derived from induced pluripotent stem cells (iPSC-CMs). These simulated measures were used to construct a cross-cell type regression model that predicts adult myocyte drug responses from iPSC-CM behaviors. We found that (1) quantitatively accurate predictions of responses to selective or non-selective ion channel blocking drugs could be generated based on iPSC-CM responses under multiple experimental conditions; (2) altering extracellular ion concentrations is an effective experimental perturbation for improving the model's predictive strength; (3) the method can be extended to predict and contrast drug responses in diseased as well as healthy cells, indicating a broader application of the concept. This cross-cell type model can be of great value in drug development, and the approach, which can be applied to other fields, represents an important strategy for overcoming experimental model limitations.



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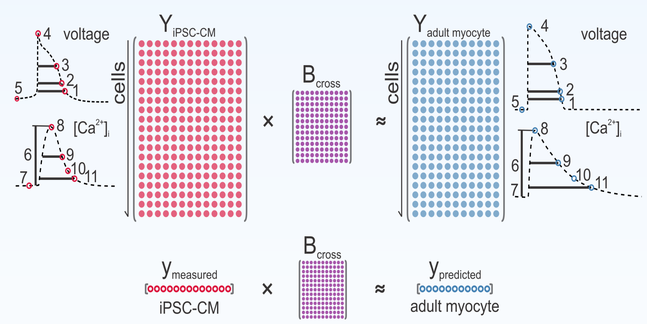
**Code and data availability**

An implementation of the cross-cell type modeling approach is available at https://github.com/JQXGong/cross-cell-type-regression.git. The repository contains implementations of the mathematical models used in the study, a sample simulated data set, and customized scripts to generate a cross-cell type regression model. Code is written in MATLAB.

**… also shared directly as requested (Beatriz Trenor, Universitat de Valencia; Colleen Clancy, UC Davis)**




**Third-party validation will ensure that results are reproducible, and that code is clear and understandable.**

## MODEL-CREDIBILITY SUMMARY

- The traditional paradigm of building cardiac cell models from data collected from many cell types, from many labs, under varying experimental conditions has led to a few decades of published models that, while useful, often fail in one or more ways.
- This project utilizes intact cardiac myocytes and dynamic experimental/computational protocols to acquire rich data sets that, coupled with global parameter fitting algorithms, produce more credible models.
- Thus, in addition to open model-sharing practices (github) to enable third-party validation, model credibility is essentially “baked into” the very goals of this project.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