

Calibrating computational models to study electrophysiological variation in human iPSC-derived cardiomyocytes

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Outline

Background

- Electrophysiological variability in human iPSC-derived cardiomyocytes
- Computational models of iPSC-CM electrophysiology
- Model calibration pipeline outline and approach

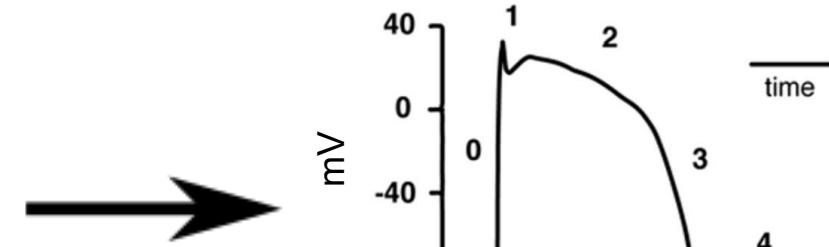
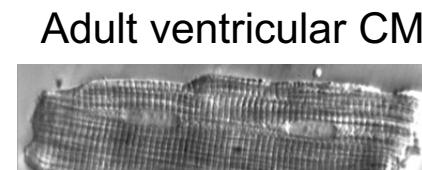
Results

- Pipeline optimization findings
- Preliminary model calibrations with *in vitro* data

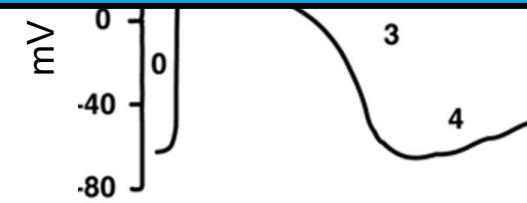
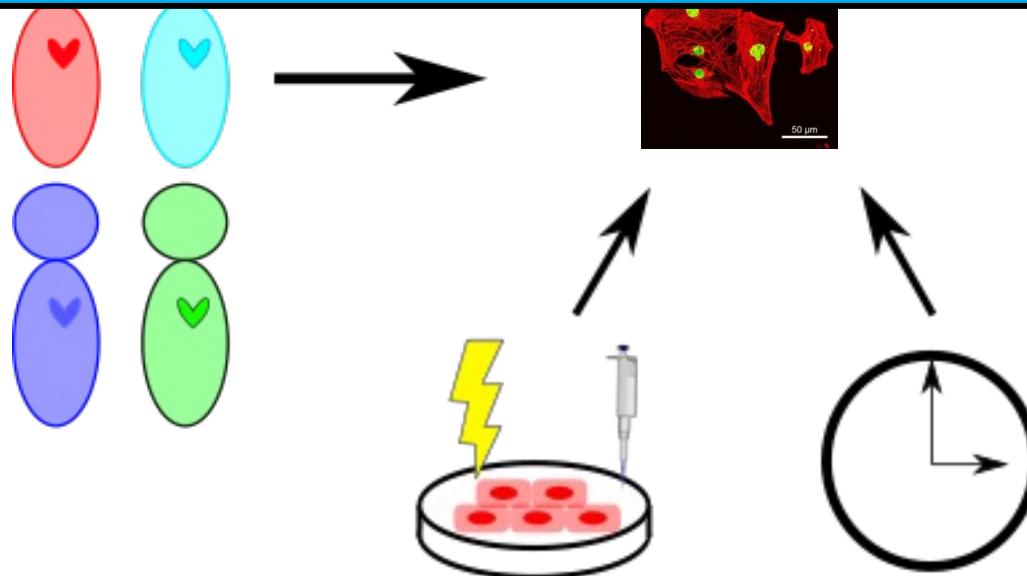
Summary & next steps

Human iPSC-CM electrophysiology varies by cell source and maturity

- hiPSC-CMs can be derived from healthy individuals
- Easier to acquire and maintain than primary heart tissue

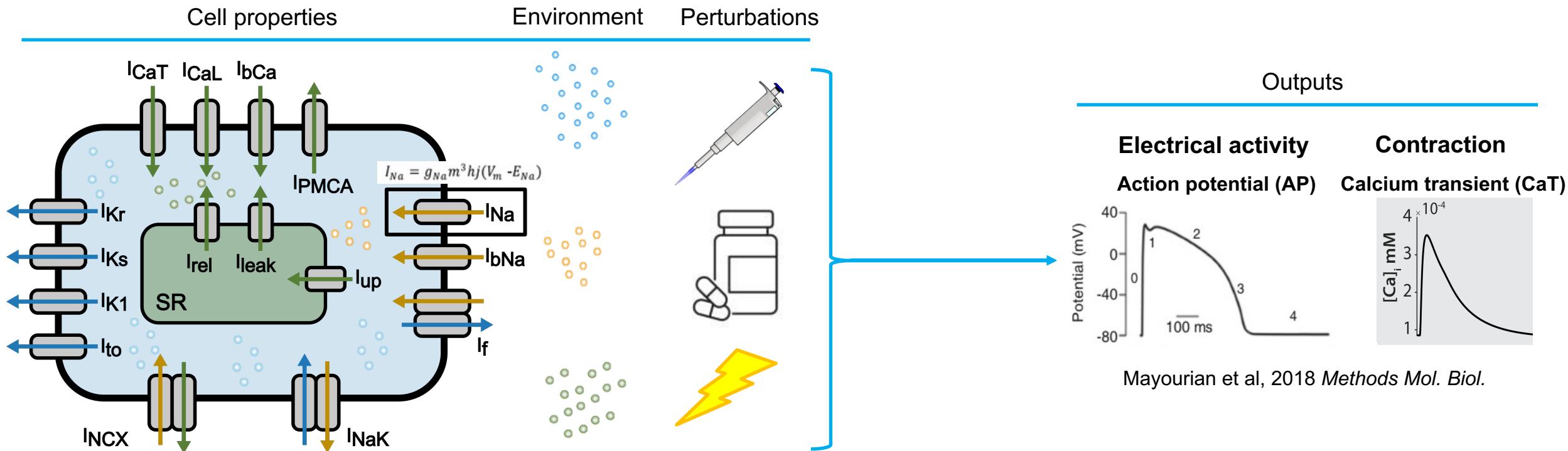


Electrophysiological variability limits reproducibility and clinical relevance of iPSC-CM findings



Karakikes et al, 2015 *Circ Res*

Computational models bridge mechanism and phenotype of cardiac electrophysiological responses

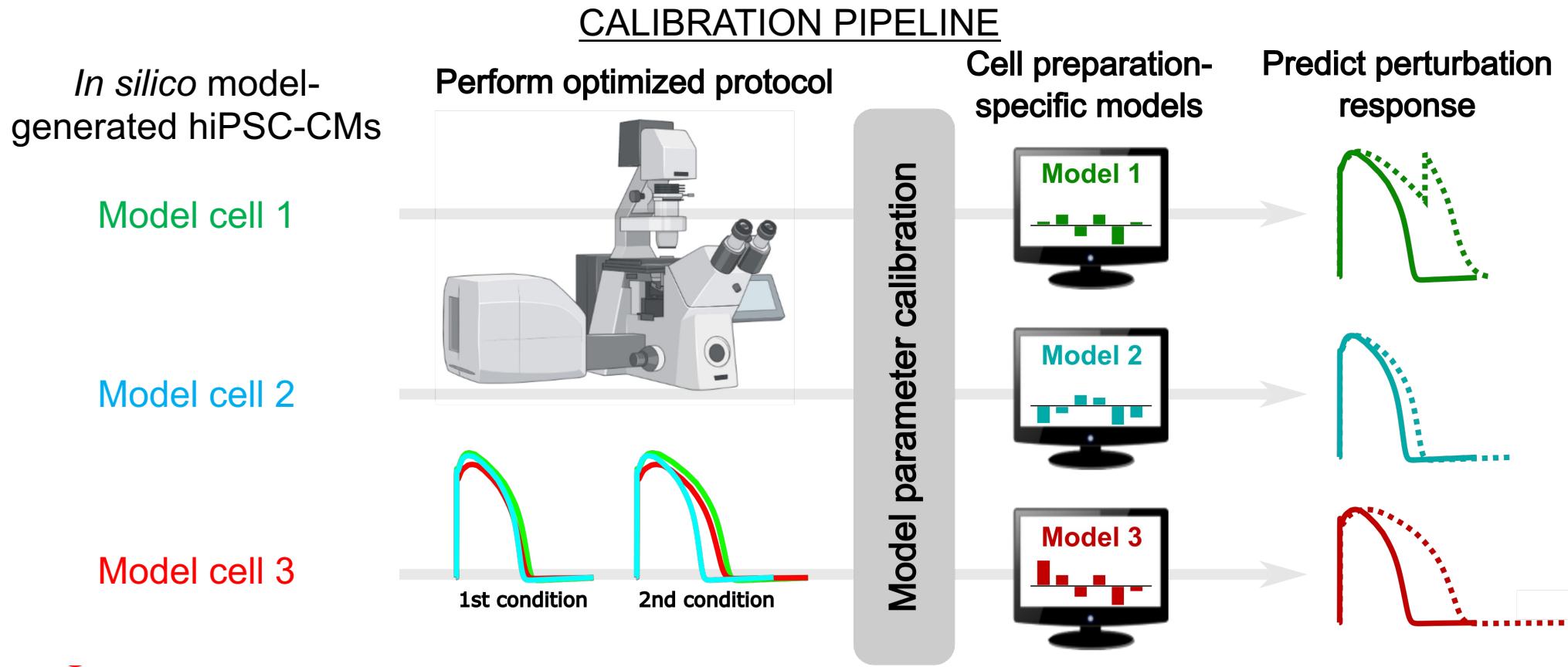


Adapted from Kernik et al, 2019 *J. Physiol.*

- Baseline model parameters are usually determined using patch clamp recordings of individual channel currents, often from one or few specific cell preparations
- Baseline models can't capture the observed iPSC-CMs electrophysiological variability

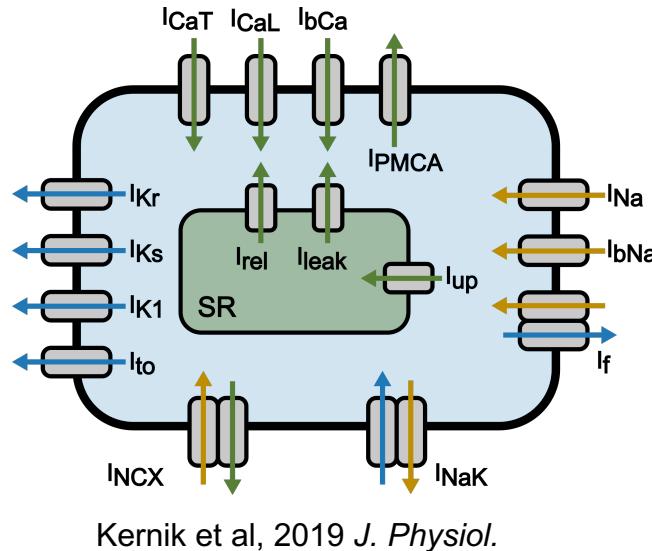
Can iPSC-CM model parameters fitted to optical fluorescence data predict electrophysiological variability?

Hypothesis: Fluorescence voltage & calcium recordings under multiple experimental conditions inform ion channel properties, which can then be incorporated into patient- and maturation stage-specific iPSC-CM mathematical models



Goal 1: Determine data types & conditions needed to estimate iPSC-CM model parameters

In silico dataset of modeled iPSC-CM population for pipeline optimization

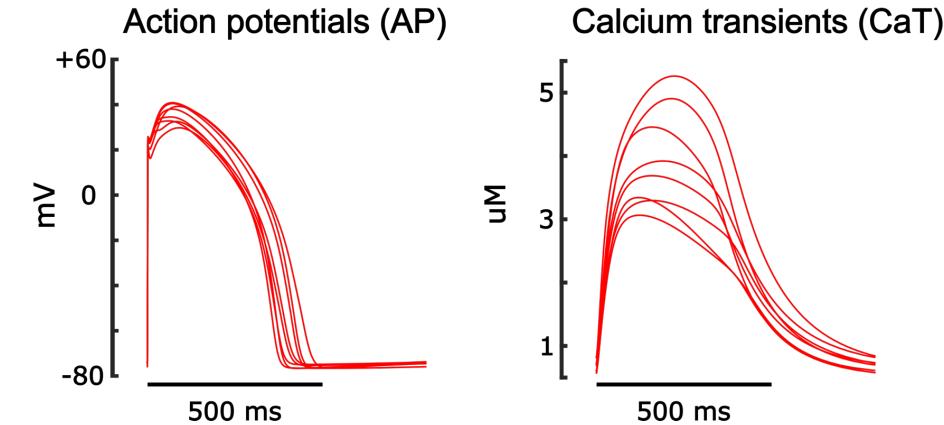


Kernik et al, 2019 *J. Physiol.*

Create a population of 100 “model cells” by drawing 100 sets of conductance parameter multipliers from a log-normal distribution ($\mu = 0$, $\sigma = 0.2$)

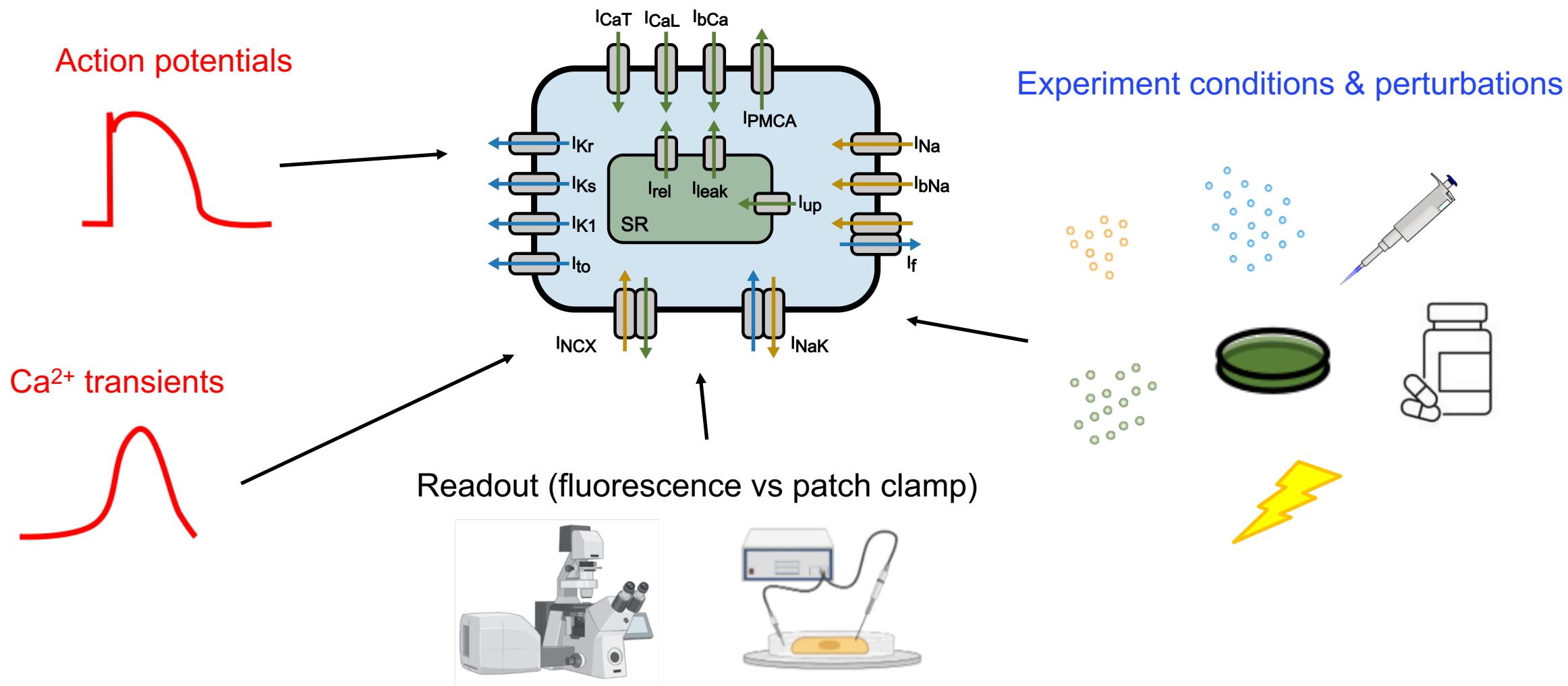
- 0.3-1 Hz spontaneous beating (Forny et al, 2018 *J. Vis. Exp.*)
- Randomly select subset of cells to simulate under various conditions

8 Kernik model cells with known conductance parameters, simulated under 30 different conditions



Model calibrations to the *in silico* dataset

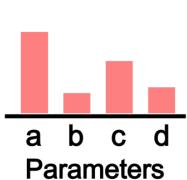
Fitting 16 ion channel conductance parameters (1 per current in the Kernik model) to selected data



Model calibrations to the *in silico* dataset

For each protocol to test:

- 1 Input data (voltage, calcium transient, or both) from each protocol

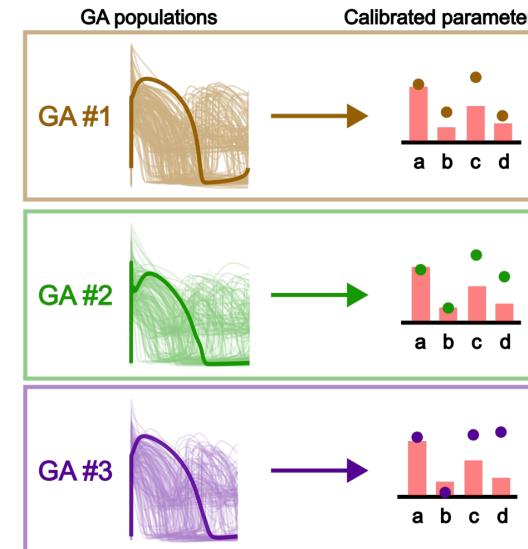


Genetic algorithm (GA)

- Creates a population of model cells
- Simulates the same protocol that generated the input data
- Error between GA-generated traces and input data determines which model cells are kept, removed, or altered for the next population.

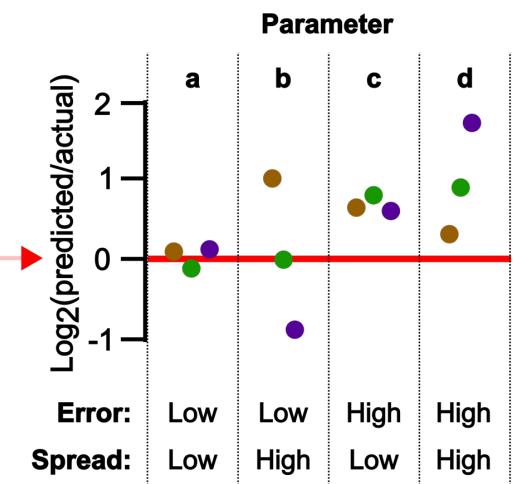
Groenendaal et al, 2015 *PLOS Comp Bio*

- 2 Calibrate all Kernik model conductances to the input data using the GA.



Repeated calibrations with different initial populations yields multiple best fit models.

- 3 Log-normalize calibrated parameter values to true parameters (red).

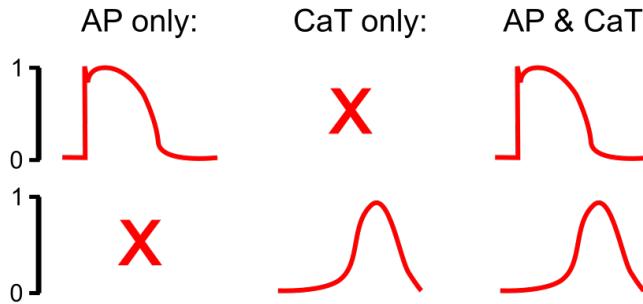


These calibrated models can be used to simulate unseen perturbation responses

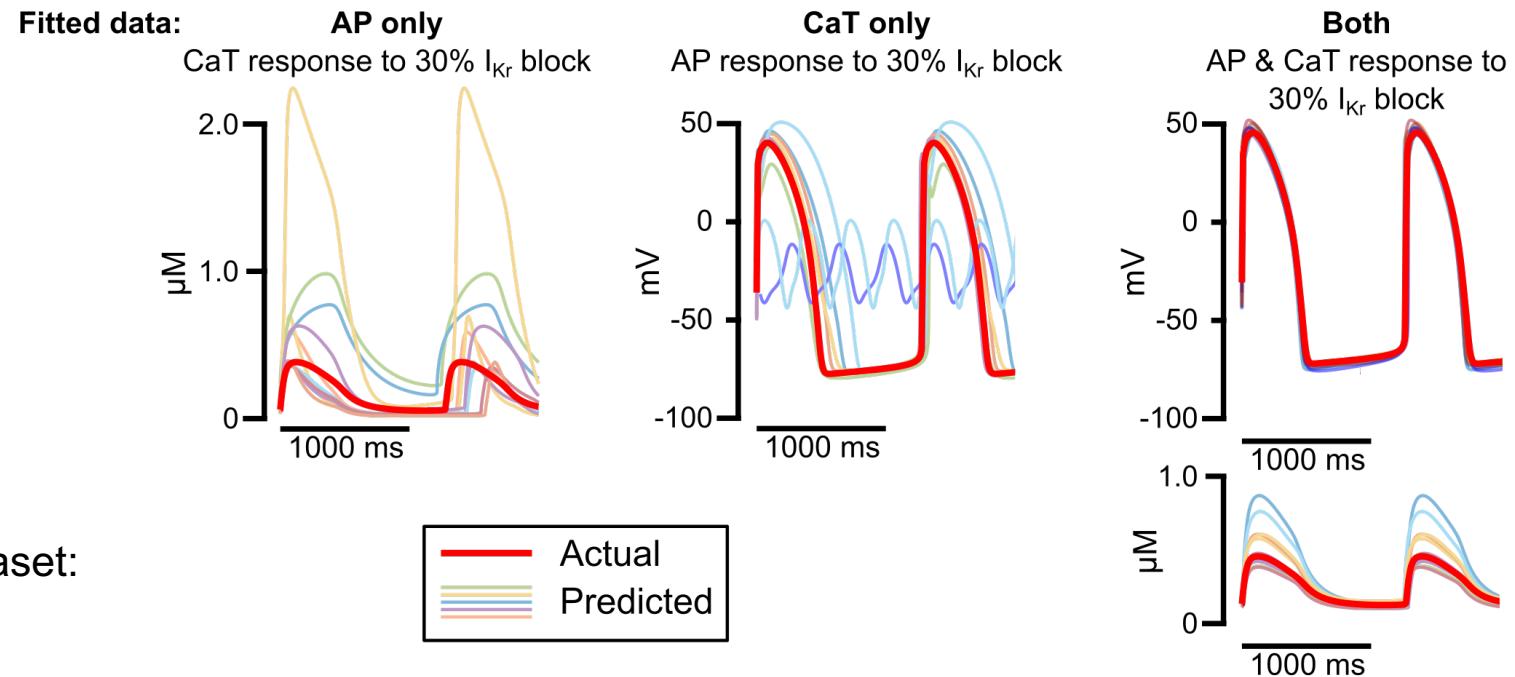
Both voltage and Ca^{2+} transient data are required to generate predictive calibrated models

Fitted data conditions & types:

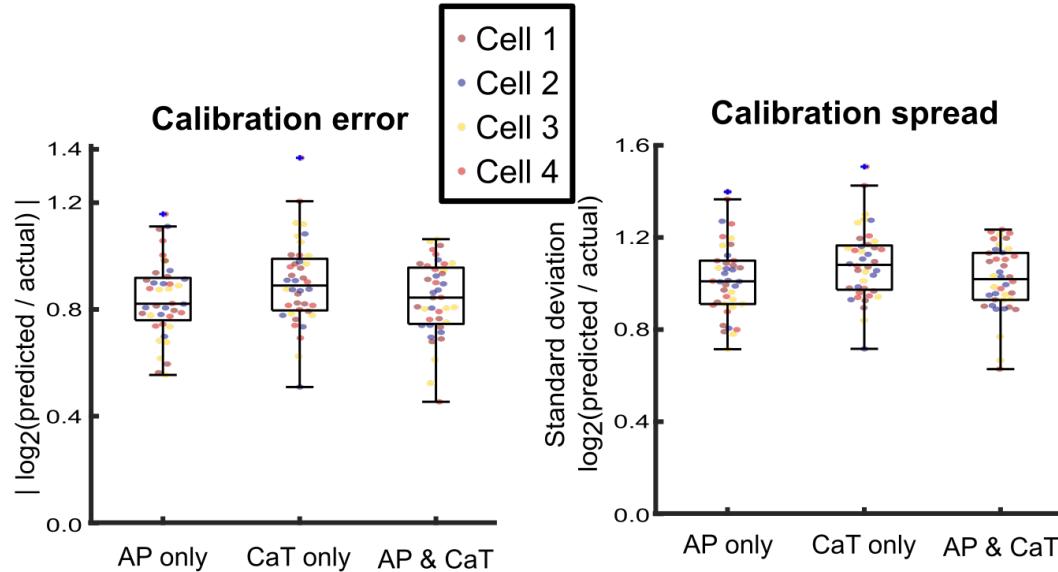
No pacing; 1.8mM $[\text{Ca}^{2+}]_o$ & 5.4mM $[\text{K}^+]_o$ & 151mM $[\text{Na}^+]_o$



Fitted data:



Tested on 4 model cells from the simulated dataset:



- Using only AP, CaT, or both has little effect on overall parameter estimate error and consistency
- Calibrated models from fitting both AP and CaT improved predictions of response to an unseen perturbation (I_{Kr} block)

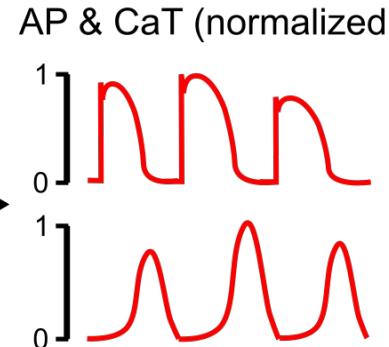
Normalized data from optimized protocol is sufficient for constraining parameters to generate predictive models

● = Baseline: no pacing; 1.8mM [Ca²⁺]_o & 5.4mM [K⁺]_o & 151mM [Na⁺]_o

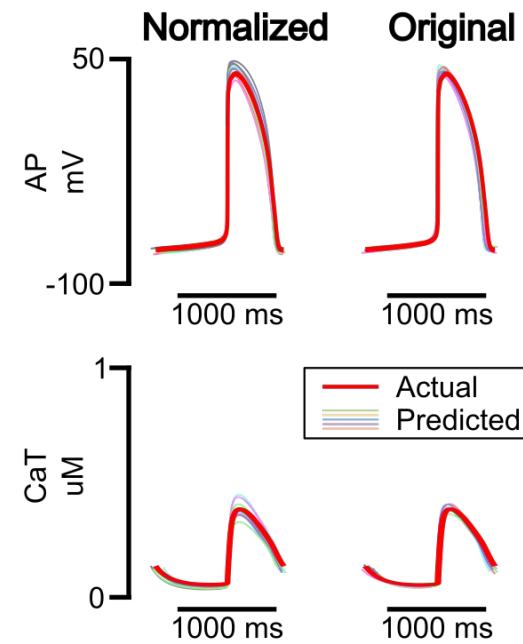
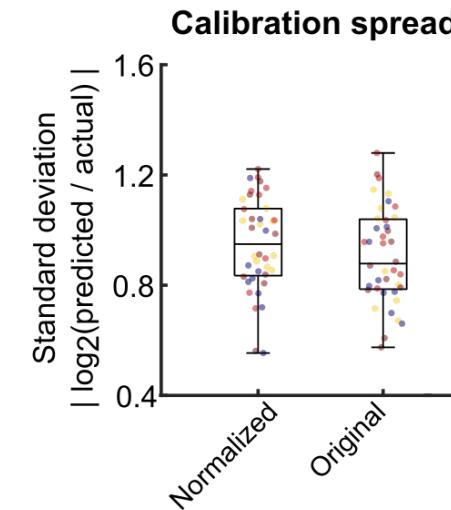
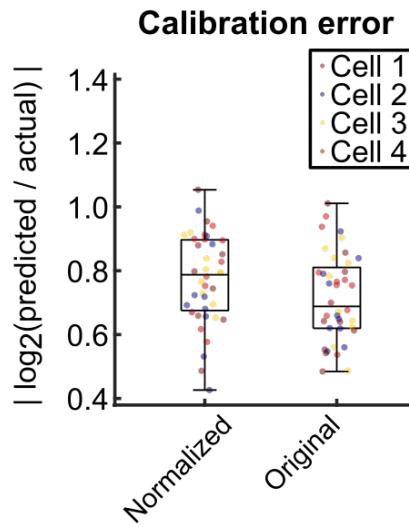
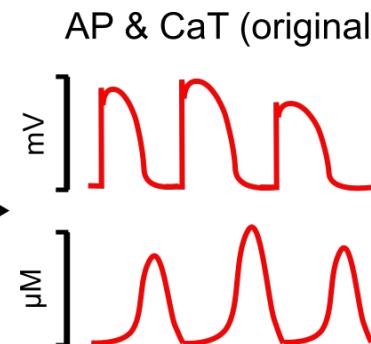
Optimized conditions:



Fluorescence recordings:



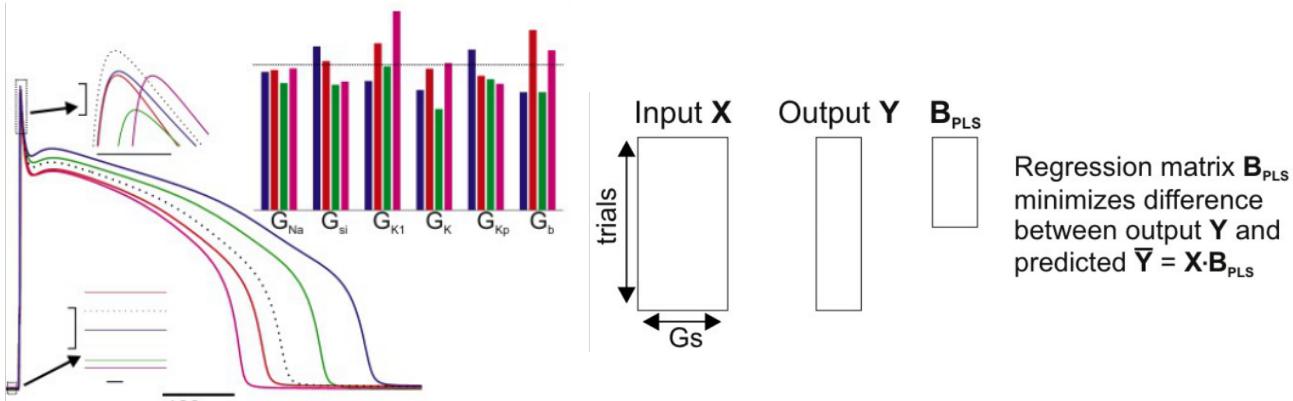
Patch clamp and calibrated calcium recordings:



- Adding different conditions improves parameter estimate accuracy & constraint, & electrophysiology predictions
- Normalized data may be sufficient for parameterization

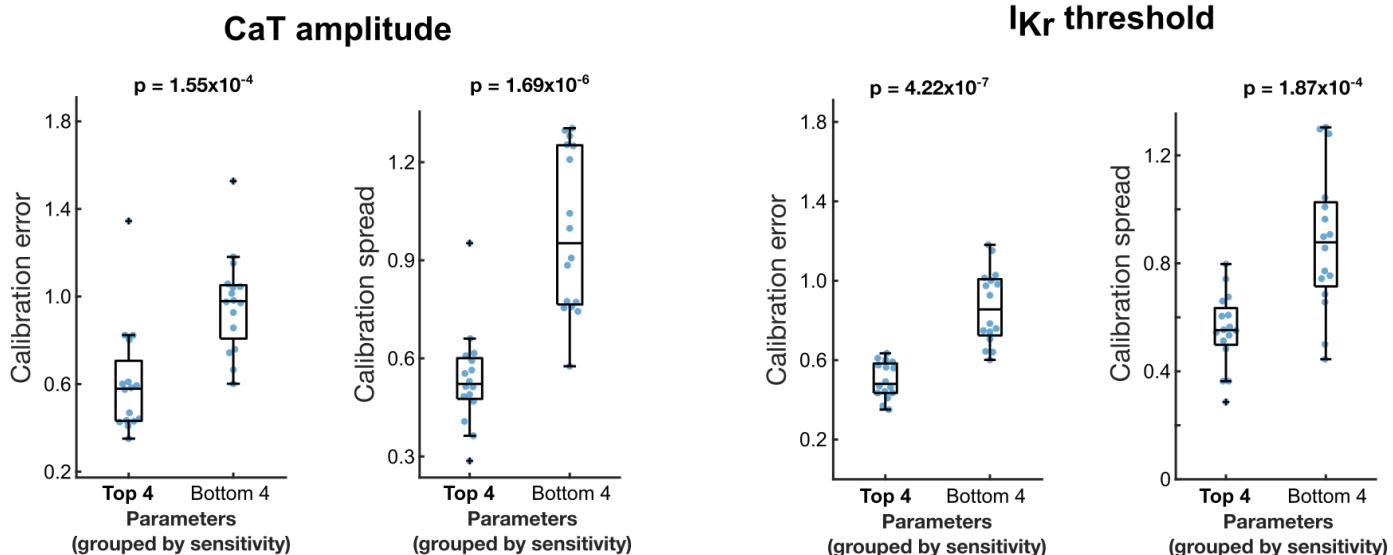
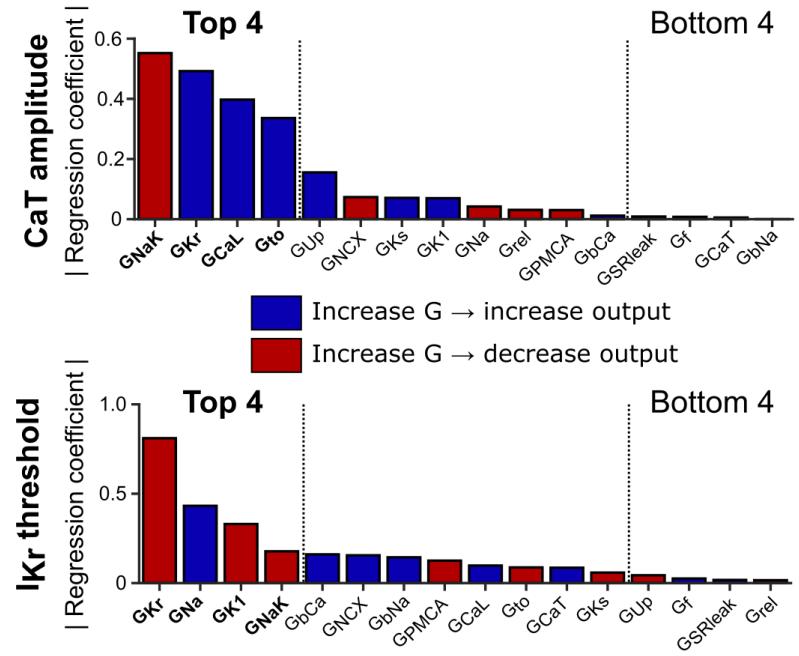
The optimized calibration pipeline constrains key conductance parameters

How much do changes in individual parameters affect output?



Sobie, 2009 *Biophys J*

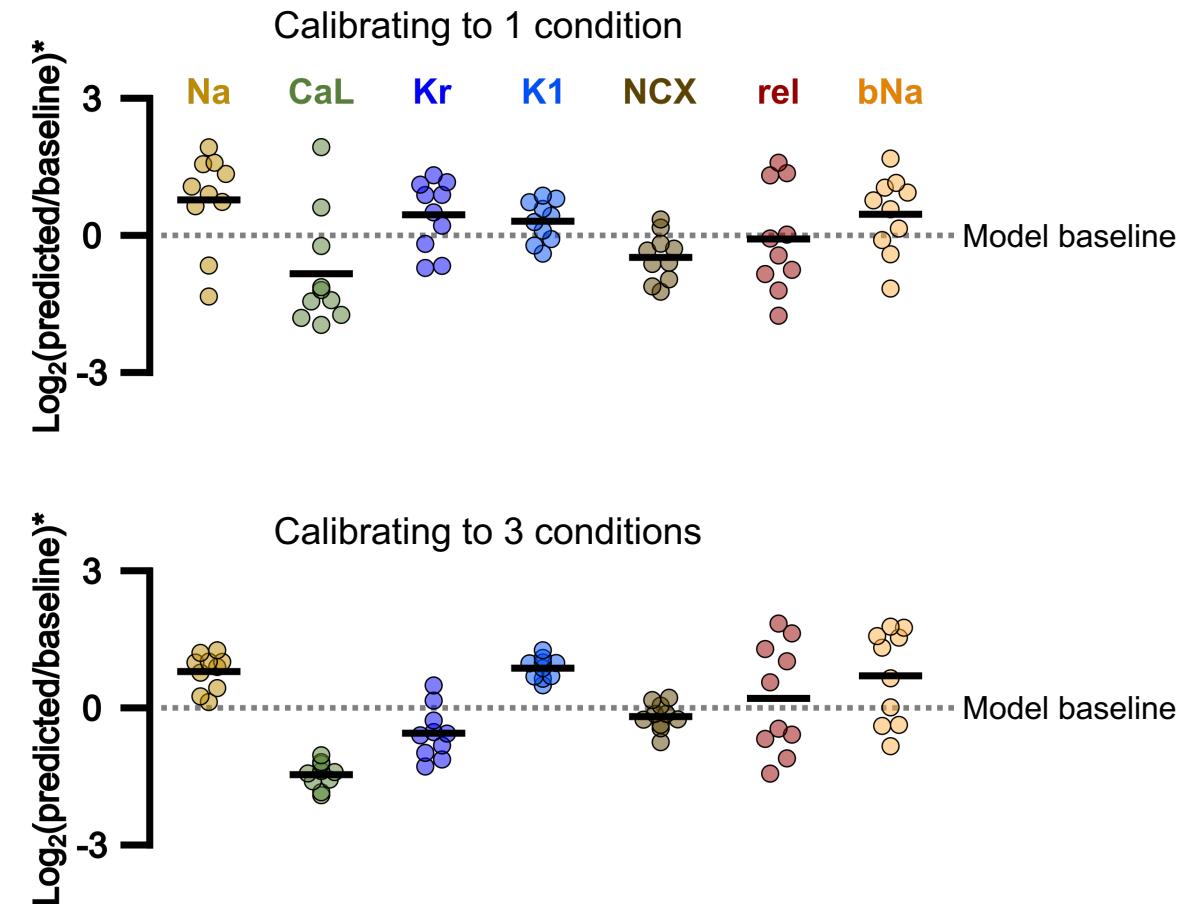
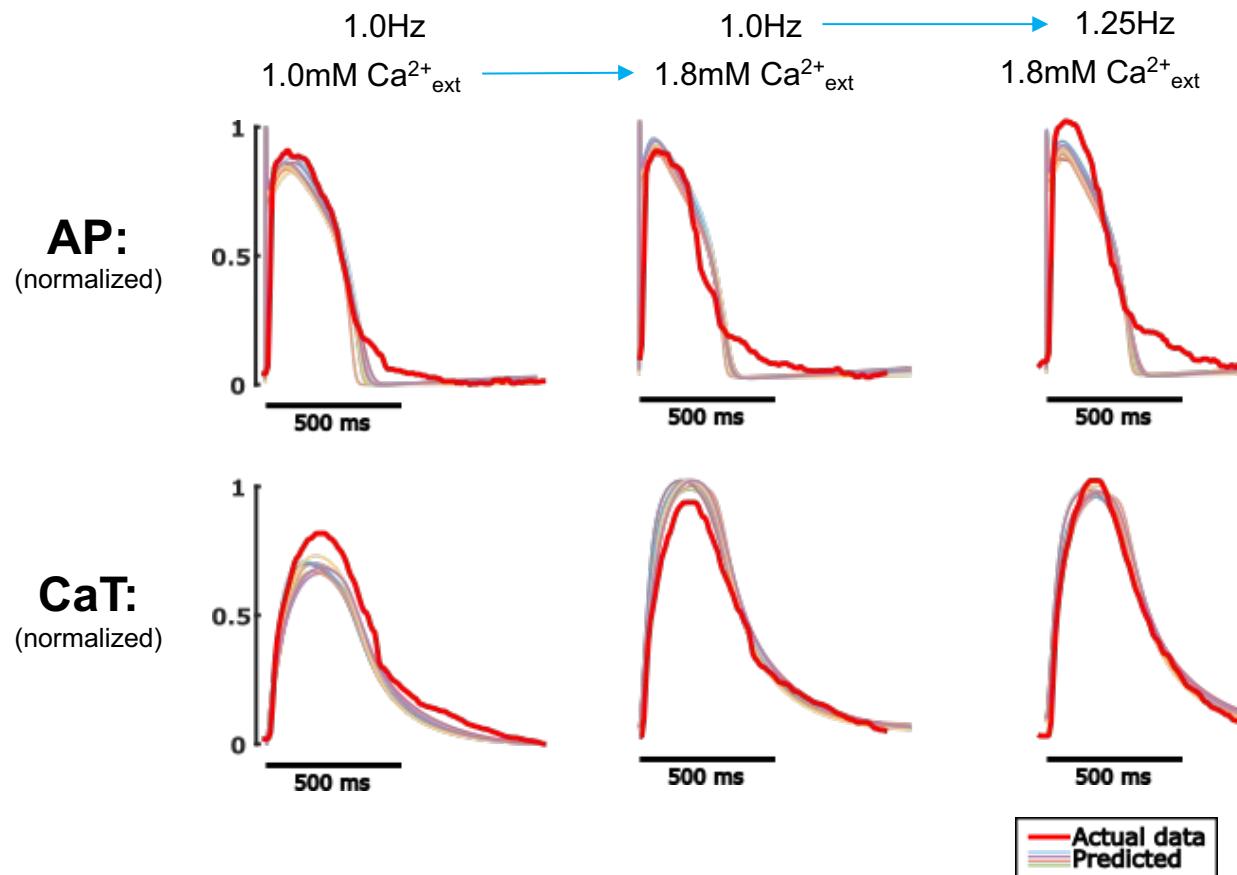
Regression matrix \mathbf{B}_{PLS}
minimizes difference
between output Y and
predicted $\bar{Y} = X \cdot \mathbf{B}_{PLS}$



- The magnitude of a parameter's sensitivity coefficient for CaT amplitude & I_{Kr} threshold correlate with the parameter's calibration accuracy and consistency

Preliminary calibrations on *in vitro* hiPSC-CM data

Fluorescence voltage and calcium recordings from Dr. Neil Daily (InVivoSciences, Inc.)



Summary

Project overview:

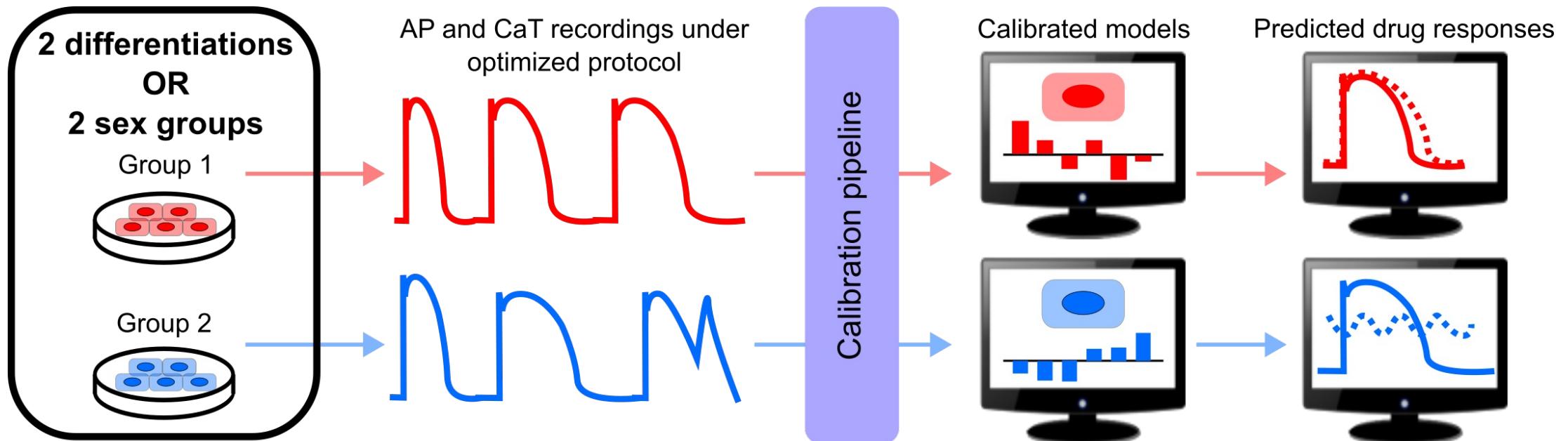
- iPSC-derived cardiomyocytes show variable electrophysiological properties & responses
- Cell line-specific computational models offer an opportunity to address this variability, but **what information is needed to generate these models is unknown**

Findings

- Calibrating parameters to voltage and calcium transient fluorescence recordings under multiple **conditions** generated predictive models that performed similarly to calibrations to corresponding non-normalized data.
- Calibrated models from these protocols produced **accurate and consistent predictions of I_{Kr} block tolerance thresholds.**
- In preliminary calibrations to *in vitro* data, **increasing protocol complexity also improved parameter constraint & phenotype prediction.**

Future goals

Predict differences & trends in baseline & drug response phenotypes between iPSC-CM lines



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My husband Vince, parents, family & friends...and my cat Ruby

Questions? Email: janice.yang@icahn.mssm.edu

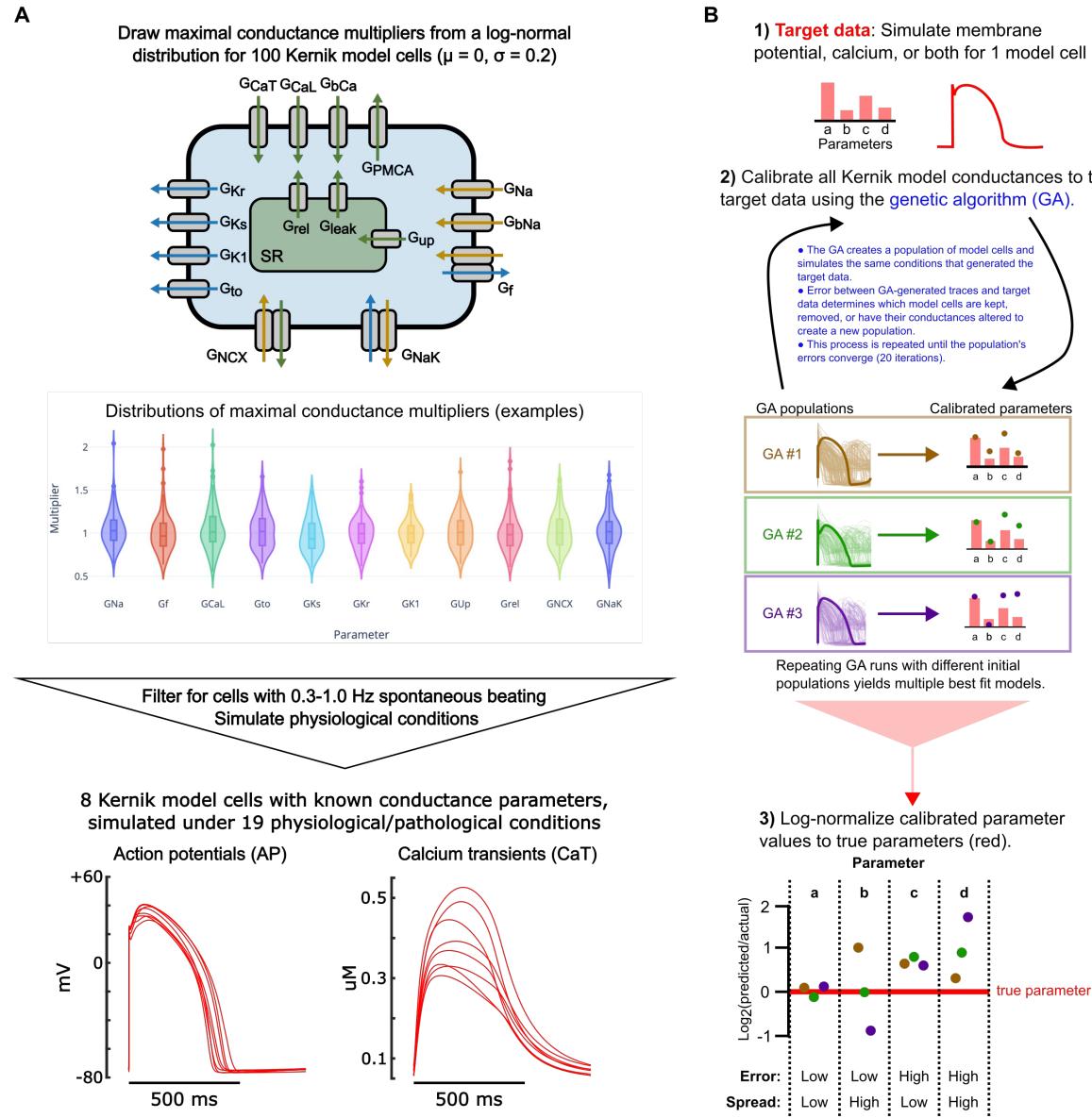
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Supplemental slides



In silico dataset of modeled iPSC-CM population for pipeline optimization



(A) Schematic of the workflow of creating the in silico membrane potential and calcium transient dataset used for optimization of the calibration pipeline. (B) Schematic of the genetic algorithm parameter calibration process, including metrics used for evaluating each candidate protocol.

Varying cell environment conditions & perturbation improves calibrations (or just I_{CaL} block?)

A

Baseline: no pacing; 1.8mM Ca^{2+}_o & 5.4mM K^+_o & 151mM Na^+_o

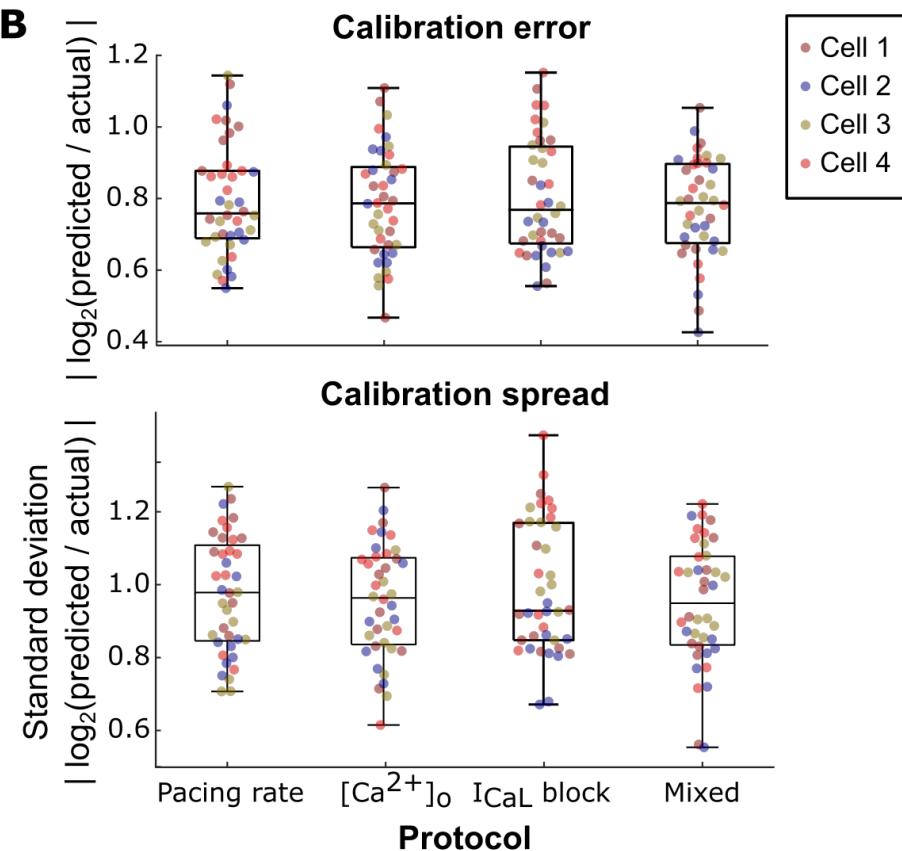
[Ca^{2+}_o]: 1.0mM Ca^{2+}_o Baseline 2.6mM Ca^{2+}_o

Pacing rate: 0 Hz 1.25 Hz 1.67 Hz

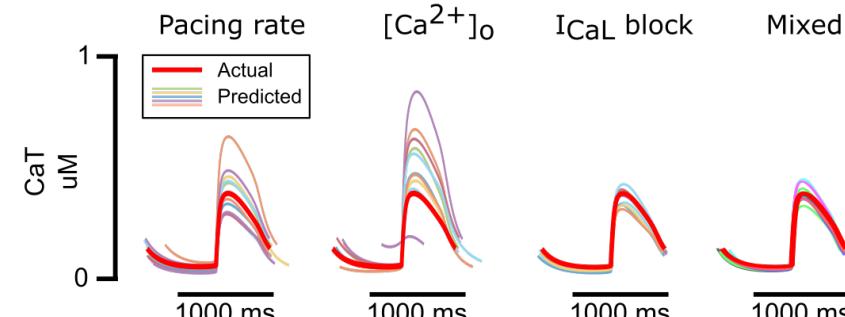
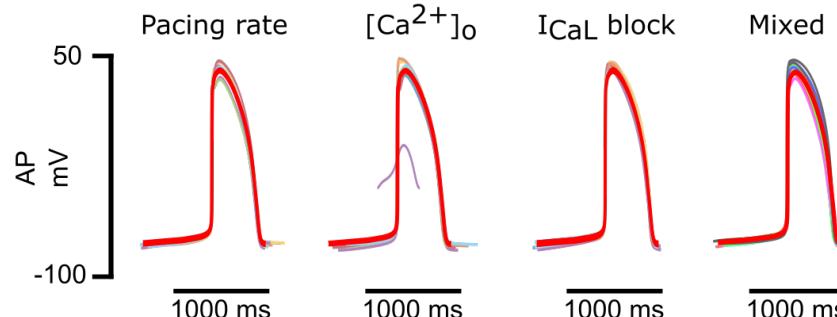
I_{CaL} block: 0% 25% 50%

Mixed: 1.0mM Ca^{2+}_o Baseline 1.25 Hz
25% I_{CaL} block

B



C



Multiple, varied cell environment conditions & perturbation improves calibrations

● Baseline: no pacing; 1.8mM $[Ca^{2+}]_o$ & 5.4mM $[K^+]_o$ & 151mM $[Na^+]_o$

Calibration protocols:

1 condition:



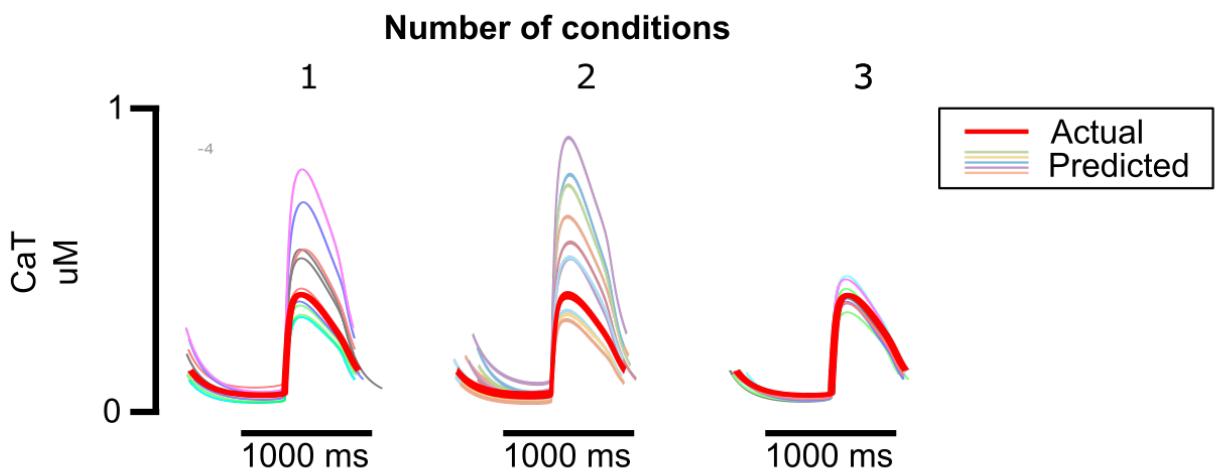
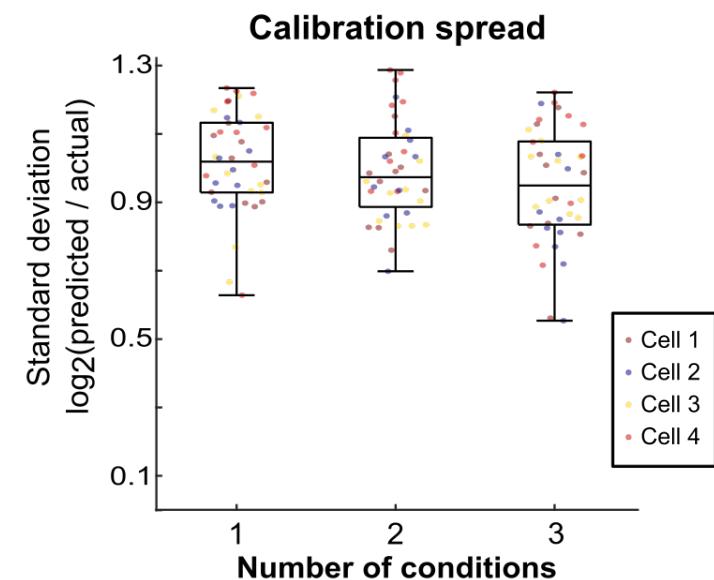
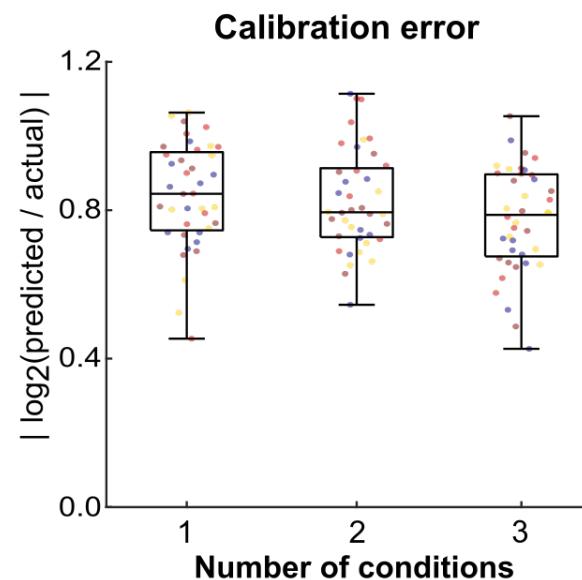
2 conditions:



3 conditions:



1.25 Hz
25% I_{CaL} block



- Calibrating parameters to data from multiple, varied conditions significantly improved model predictions of response to I_{Kr} block
- Improvement to parameter error & consistency was minimal

Multiple, varied cell environment conditions & perturbation improves calibrations

● Baseline: no pacing; 1.8mM $[Ca^{2+}]_o$ & 5.4mM $[K^+]_o$ & 151mM $[Na^+]_o$

Calibration protocols:

1 condition:



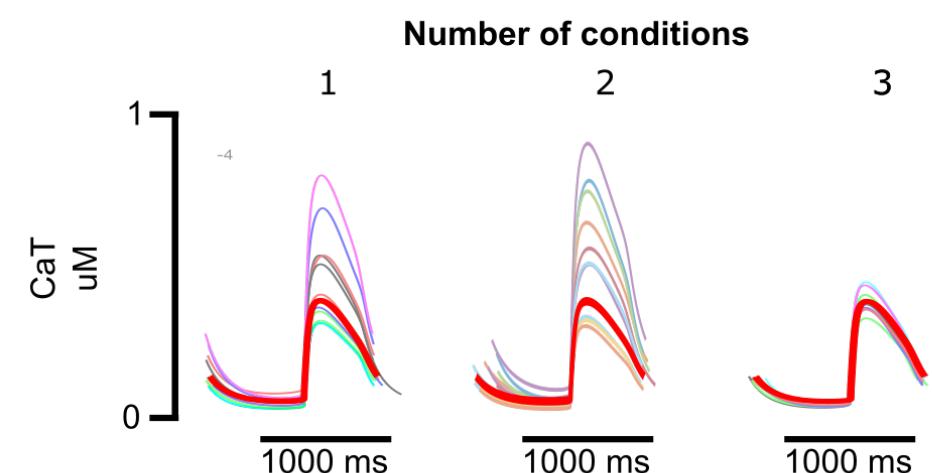
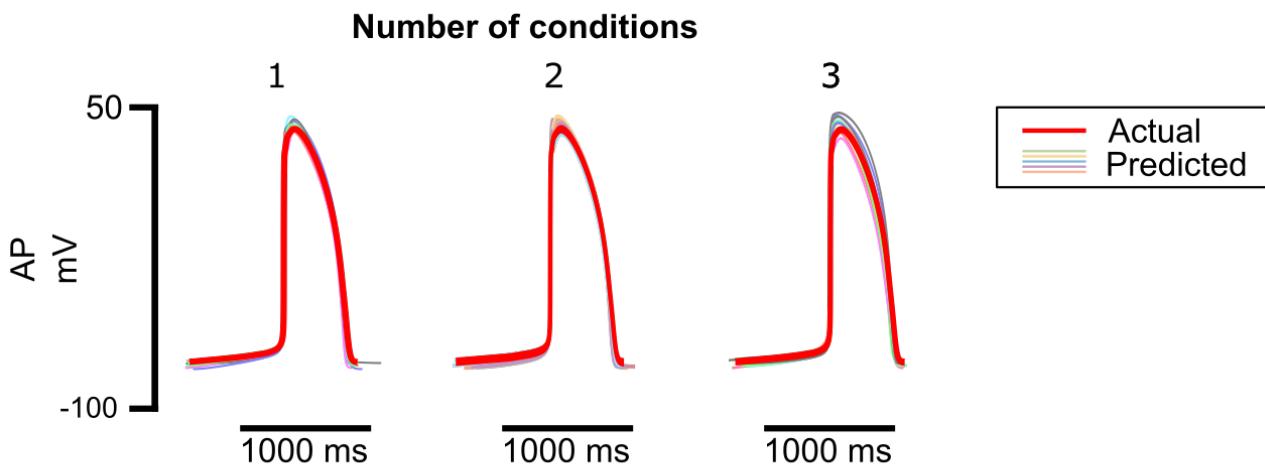
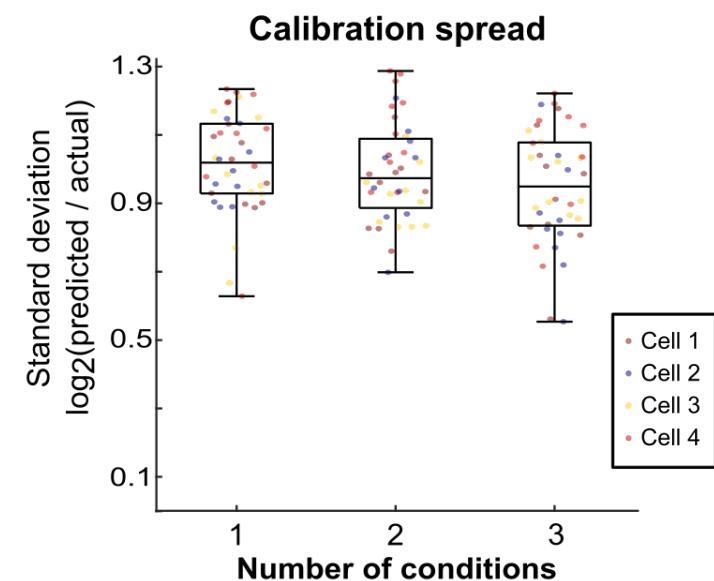
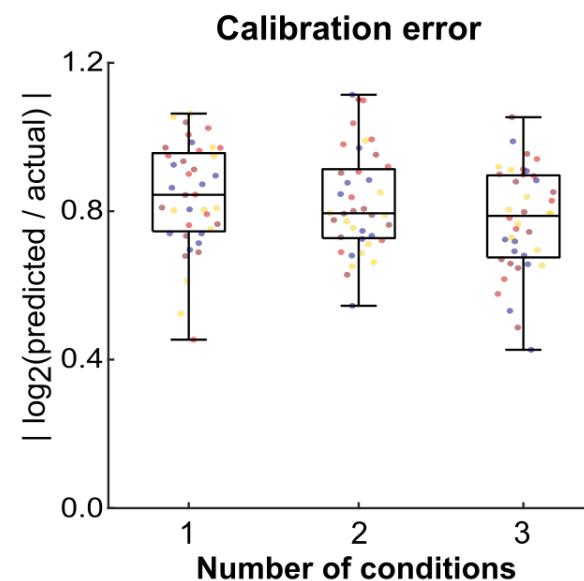
2 conditions:



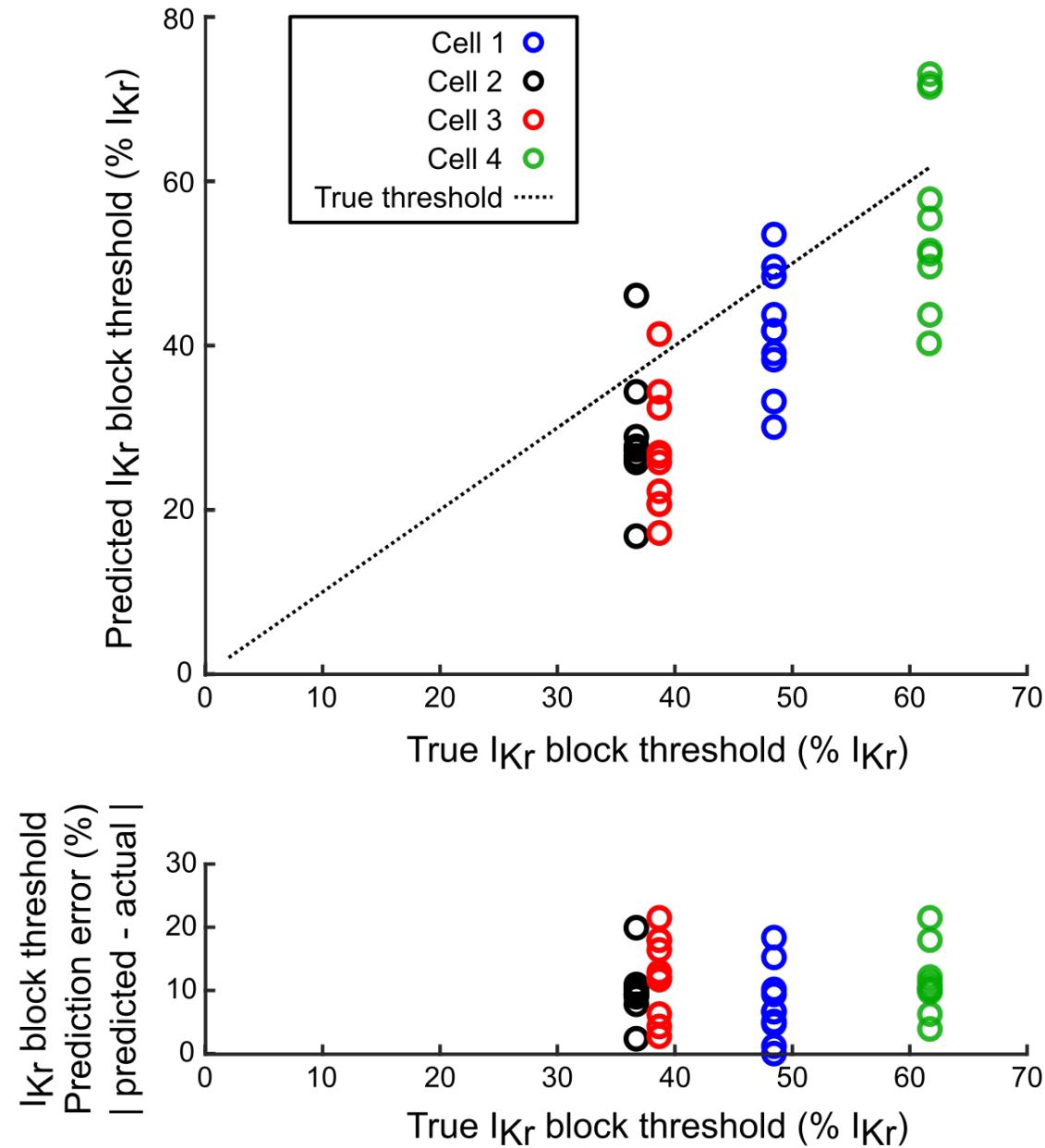
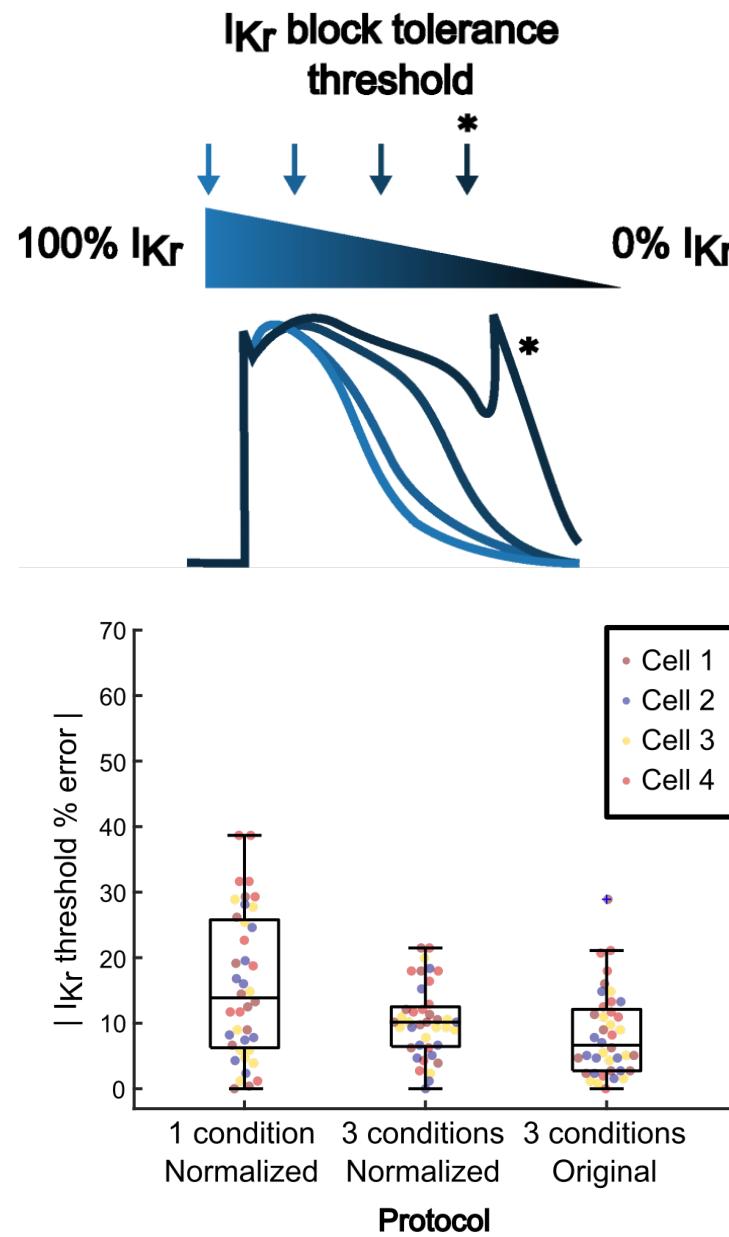
3 conditions:



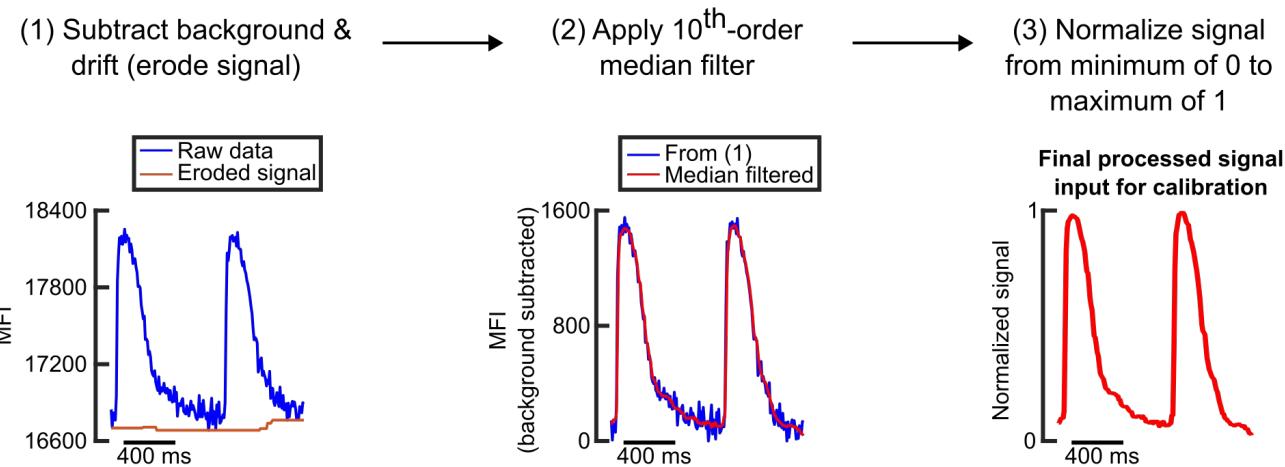
1.25 Hz
25% I_{CaL} block



Calibrated models from optimized pipeline predict cell-specific arrhythmia susceptibility



Preliminary calibrations on *in vitro* hiPSC-CM data



Sample calibrated parameters
(log₂-normalized to Kernik baseline value)

