

Creating Cell-specific Computational Models of Stem Cell-derived Cardiomyocytes Using Optical Experiments

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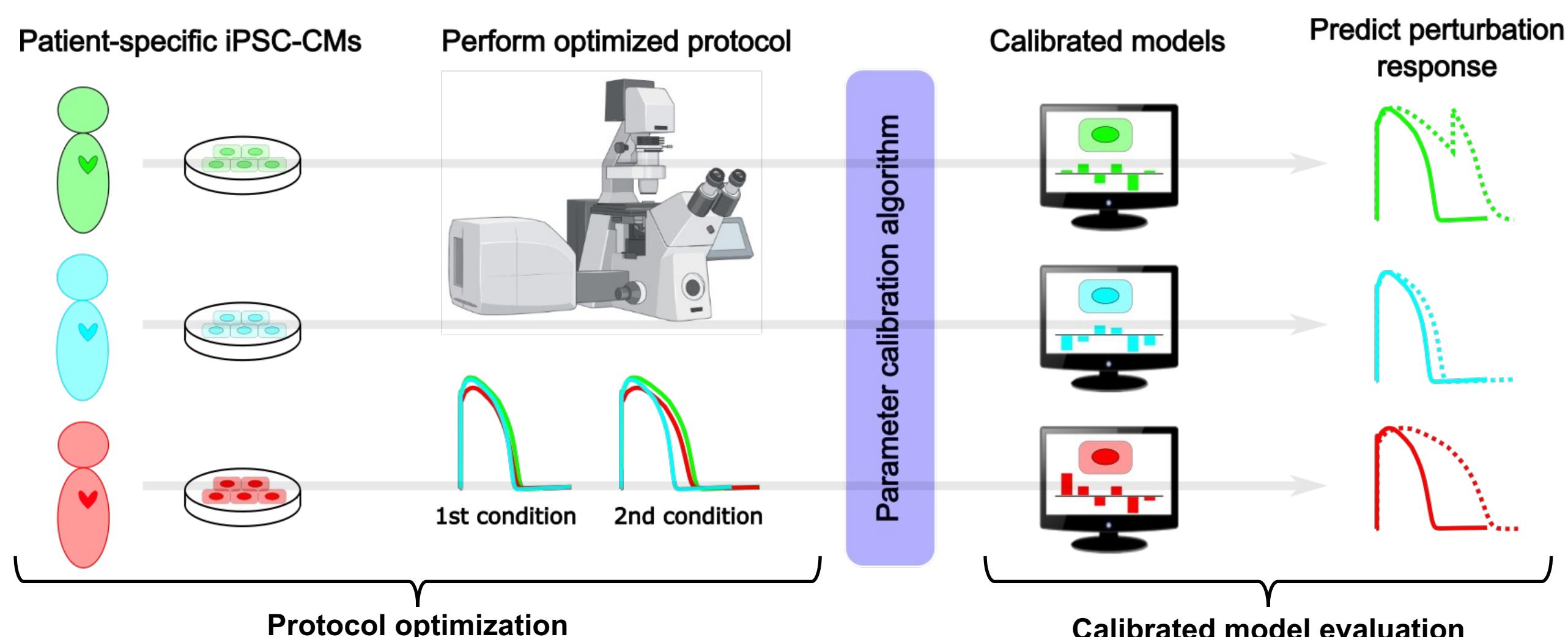
Introduction

Human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) are a powerful model in cardiac disease and therapeutics research, since iPSCs are self-renewing and can be derived from healthy and diseased patients without invasive surgery. However, this *in vitro* platform is affected by several limitations [1]: current differentiation methods produce cells with an **immature electrophysiological phenotype**; varied differentiation protocols yields **phenotypic differences** between labs; and the **genetic background** of iPSC donors can produce additional variability. We aim to address these limitations by developing a **computational pipeline to predict cell preparation-specific iPSC-CM electrophysiological parameters**. This model calibration pipeline can be applied broadly to examine cell line-specific ion channel properties and predict perturbation responses.

Objectives

Objective: Create a pipeline that can calibrate computational models of iPSC-CM electrophysiology to data from practical, accessible experiments. These calibrated models should predict cell-specific properties and behaviors.

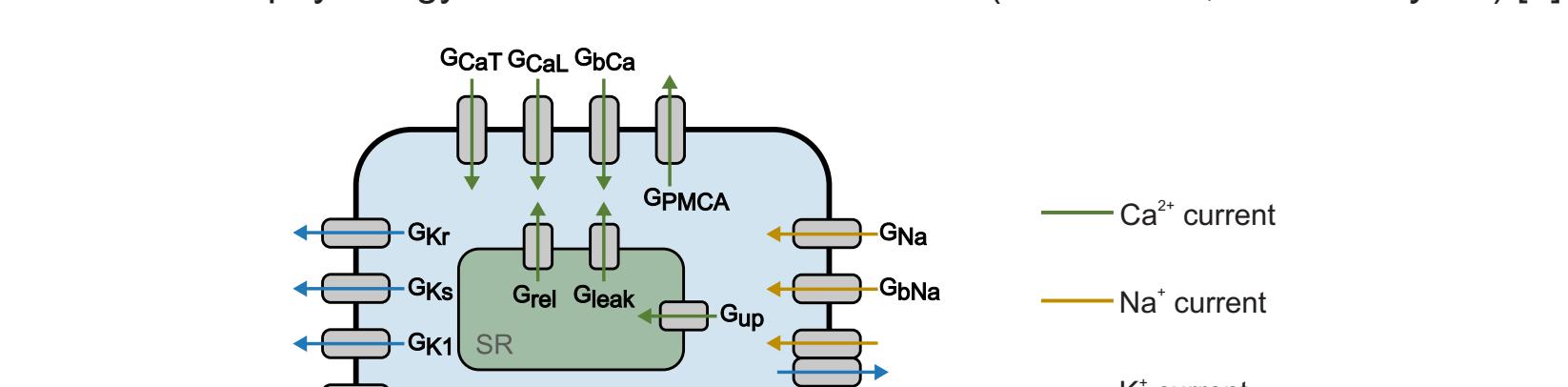
Hypothesis: Voltage and calcium recordings under multiple experimental conditions inform ion channel properties, which can be incorporated into cell line-specific iPSC-CM mathematical models.



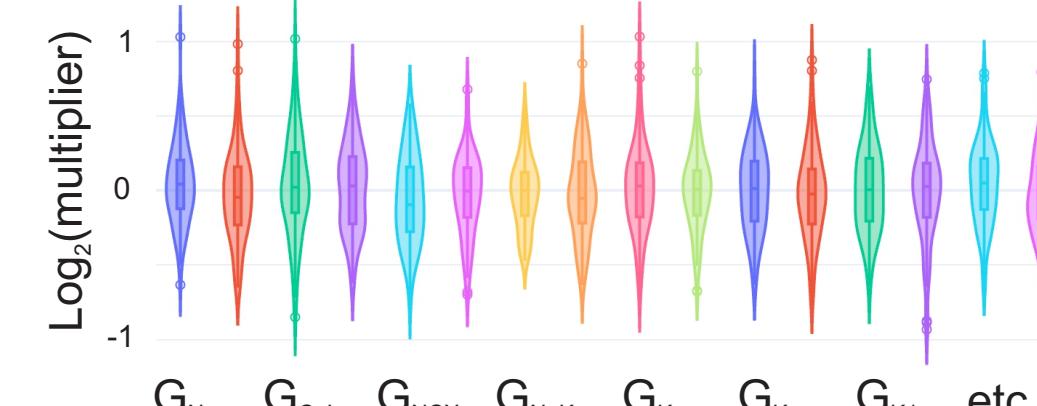
Protocol optimization strategy

- 1) Generate dataset containing simulated APs, CaTs, or both from Kernik models with varied conductance parameters, under varied cellular conditions.

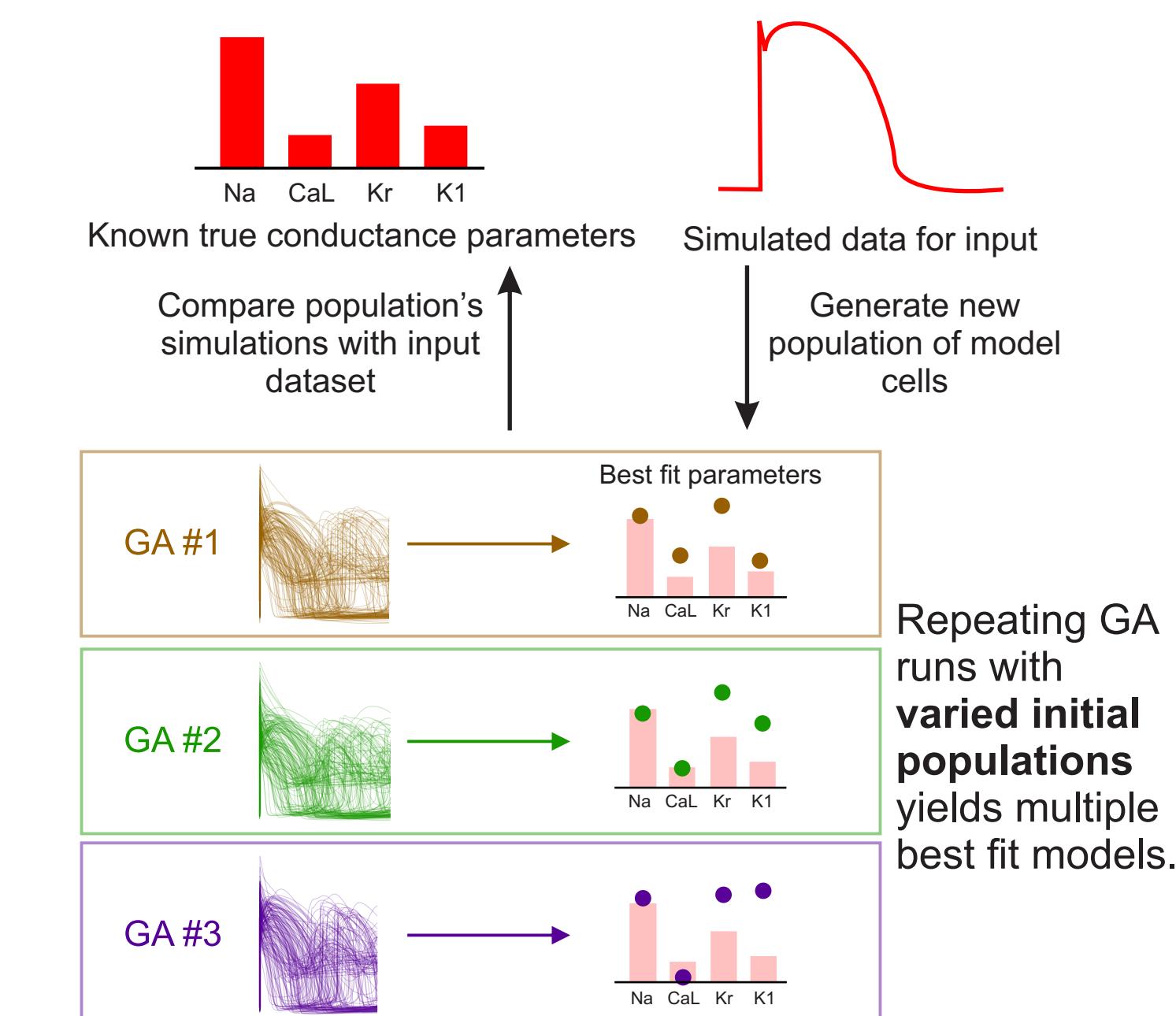
Whole-cell physiology model for human iPSC-CMs (Kernik et al, 2019 *J Physiol*) [2]



Maximal conductance parameter multipliers drawn from a log-normal distribution

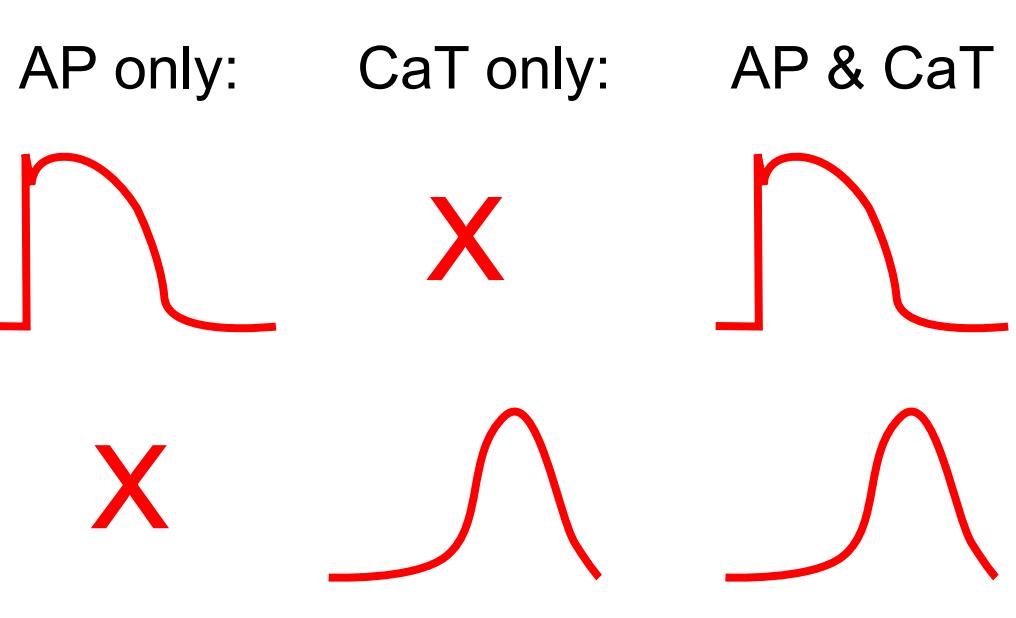


- 2) Fit model conductance parameters using the **genetic algorithm (GA)**. [2]

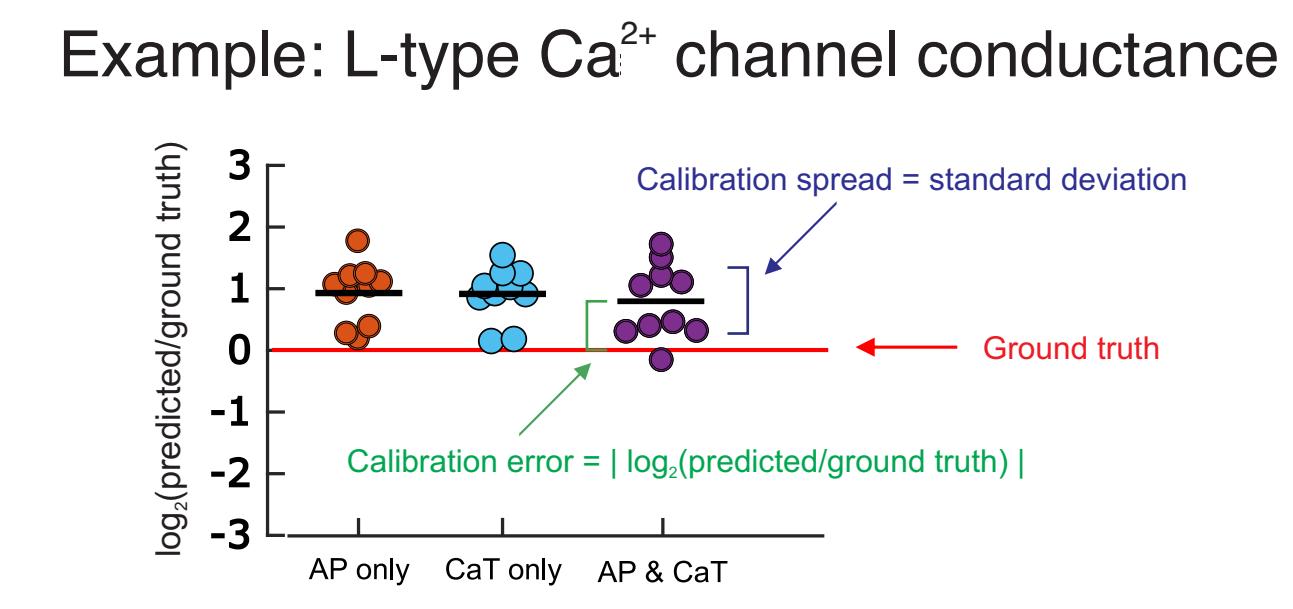


In silico dataset for protocol optimization

Types of data:



Calibrated parameter evaluations:

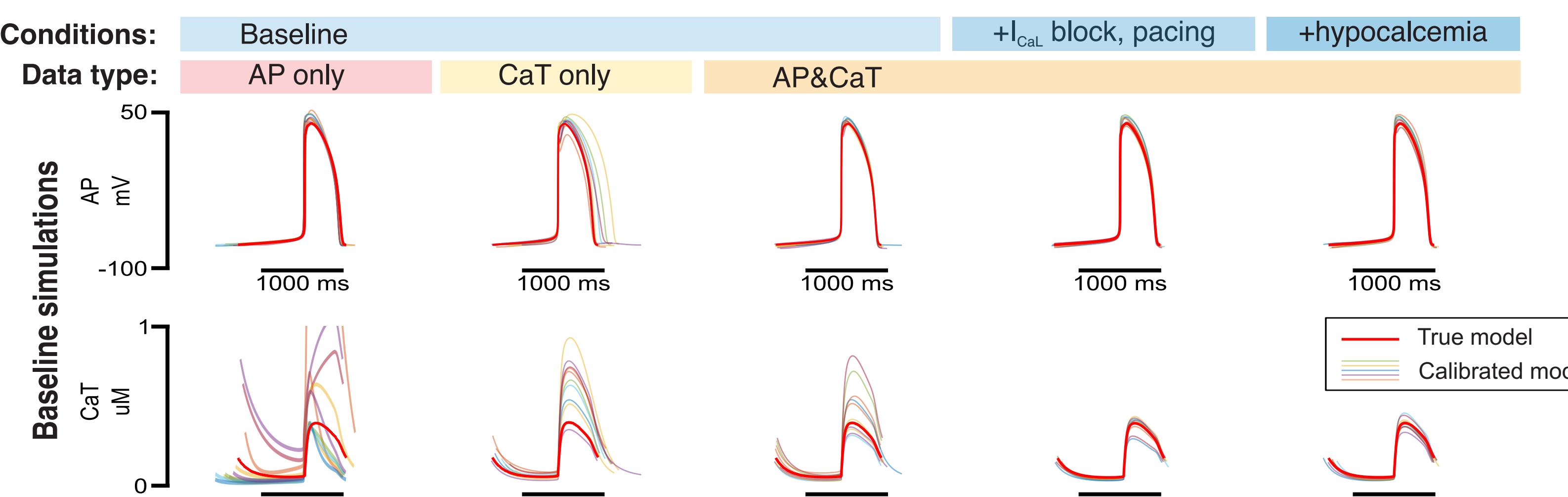


Baseline physiological conditions: 1.8 mM [Ca²⁺]_o, 5.4 mM [K⁺]_o, 151 mM [Na⁺]_o

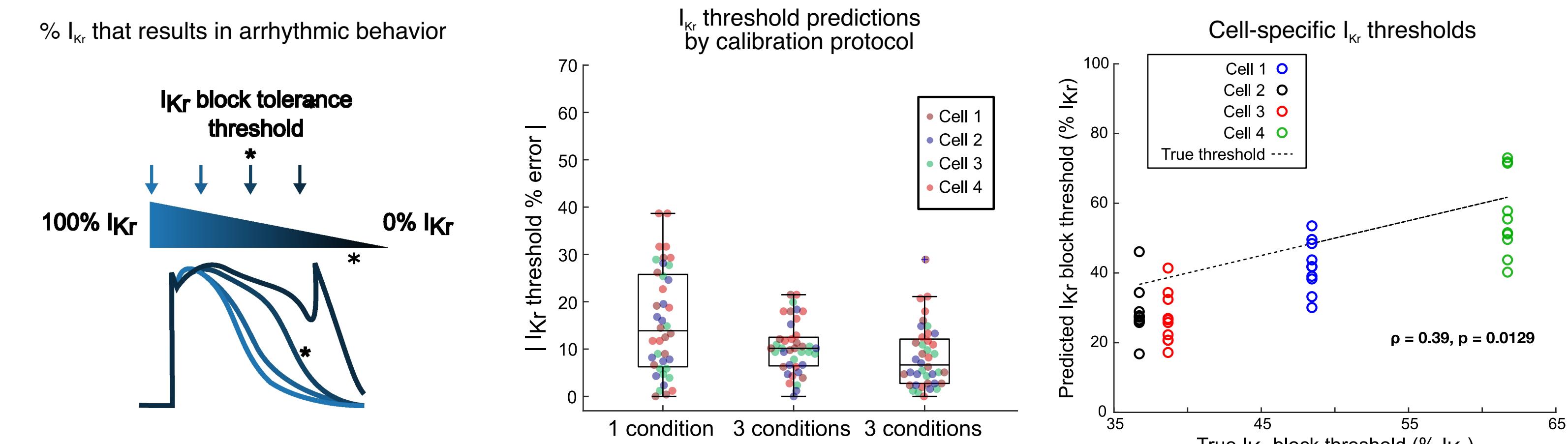
1. Hypo- & hyper-calcemia: 1.0–2.6 mM [Ca²⁺]_o
2. L-type Ca²⁺ channel block: 25% & 50% I_{CaL} block
3. Pacing stimulus: no stimulus, or 1.25 Hz

Left out for model validation: 30% I_{Kr} block without pacing stimulus

Calibrated model predictions improve with added experiment conditions and data types

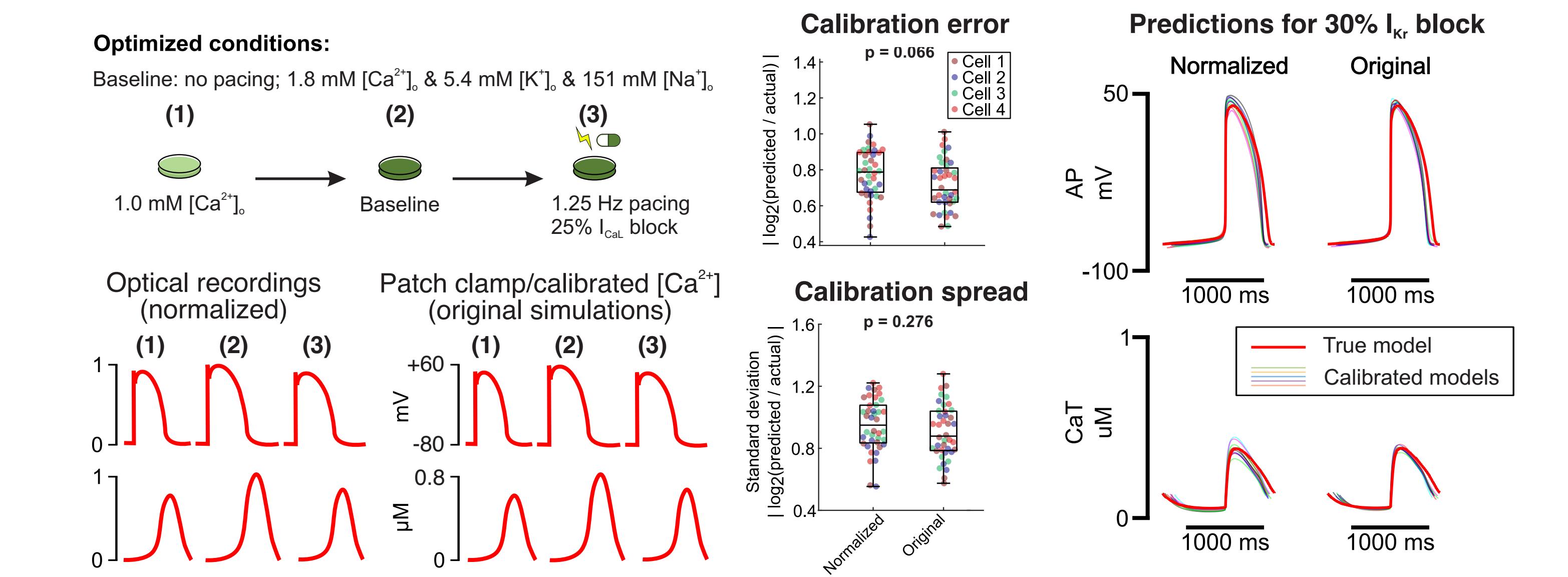


Calibrated models predict I_{Kr} block-induced arrhythmia thresholds



The optimized calibration pipeline generates iPSC-CM models which can predict cell-specific susceptibility to arrhythmia triggers, such as I_{Kr} block (e.g. dofetilide, quinidine).

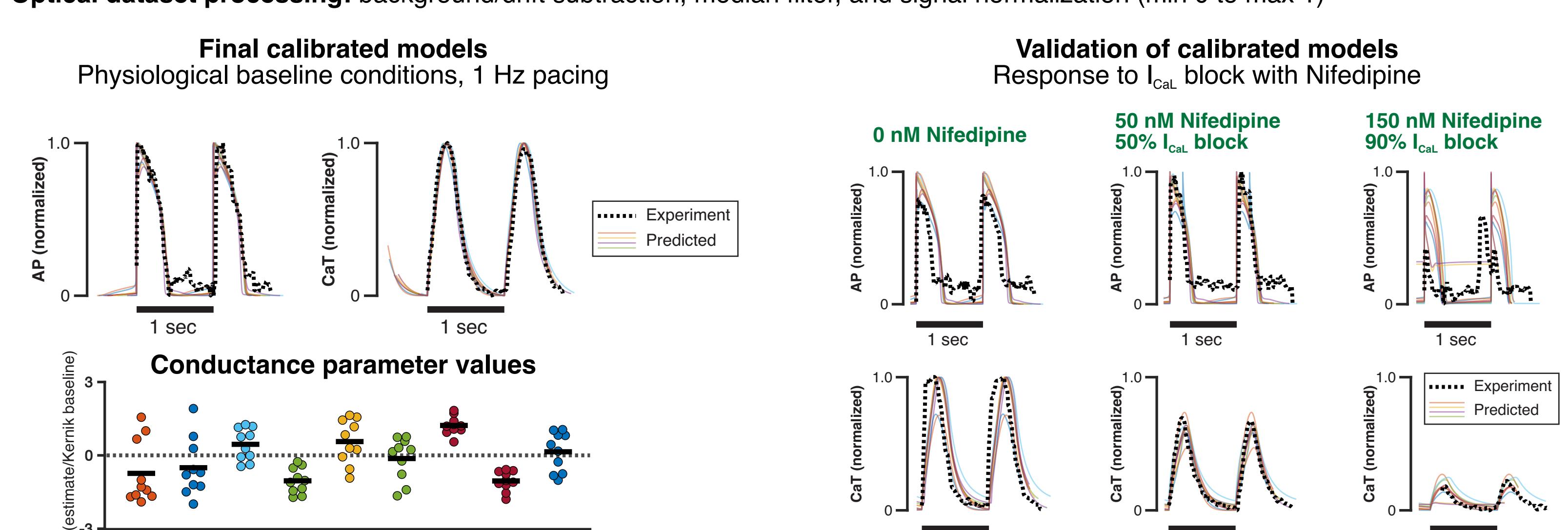
Normalized optical AP & Ca²⁺ transient data constrain model parameters



Predictive models of *in vitro* iPSC-CMs generated by calibration pipeline

iPSC lines from [4] were differentiated into iPSC-CMs in monolayer cell cultures. On day 35 post-differentiation, cells were incubated with Fluovolt and Calbryte-630 AM dyes, and fluorescence fluxes were recorded to generate paired AP and CaT line scans.

Optical dataset processing: background/drift subtraction, median filter, and signal normalization (min 0 to max 1)



Conclusions

While individual parameter calibration results varied, model calibrations using voltage and calcium transient data from an optimized 3-condition protocol improved calibration accuracy and consistency on average compared to calibrations on single-condition protocols, and the calibrated models predicted unseen channel block responses. This observation held regardless of whether the fitted data were normalized. Therefore, normalized fluorescence recordings can inform conductance parameters as well non-normalized data types, if the iPSC-CM data are collected under sufficiently varied conditions. The current optimal protocol uses normalized fluorescence data on voltage & calcium transients under 3 conditions: 1) hypocalcemia, no pacing; 2) normal calcium, no pacing; 3) normal calcium, 1.25 Hz pacing, and I_{CaL} block.

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GitHub repository

- Assess calibration pipeline performance for fitting ion channel kinetics parameters and disease-specific cell lines
- Evaluate predictions of iPSC-CM lineage (e.g. atrial, ventricular, Purkinje fiber trajectories) derived from calibrated models.



References

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