Automated model parameterization for studying electrophysiological variation in hiPSC-CMs

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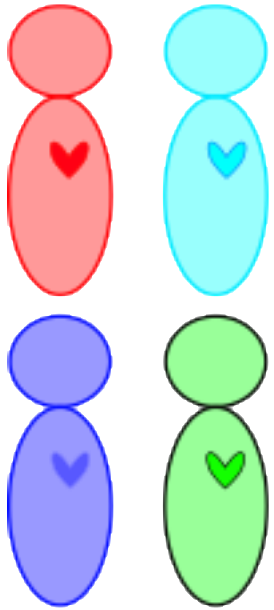
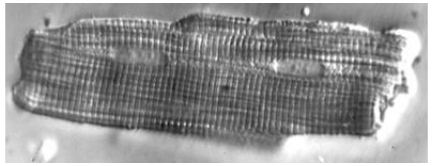
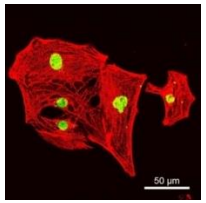
Human iPSC-CM electrophysiology varies by cell source and maturation stage

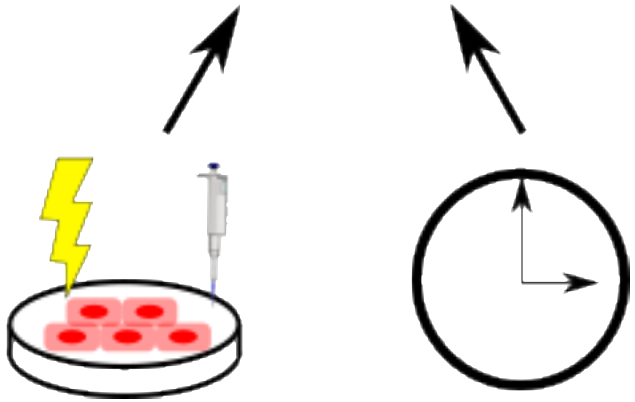


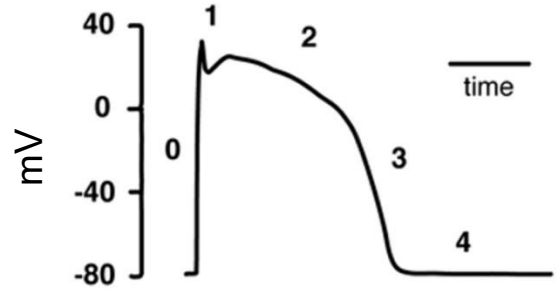
Adult ventricular CM

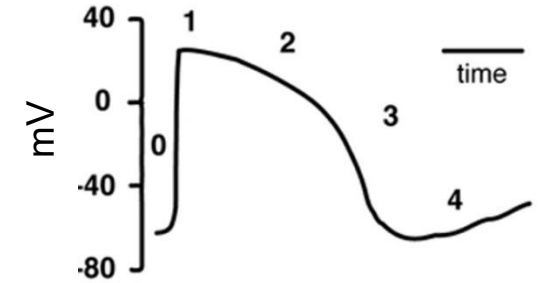


Human iPSC-CM







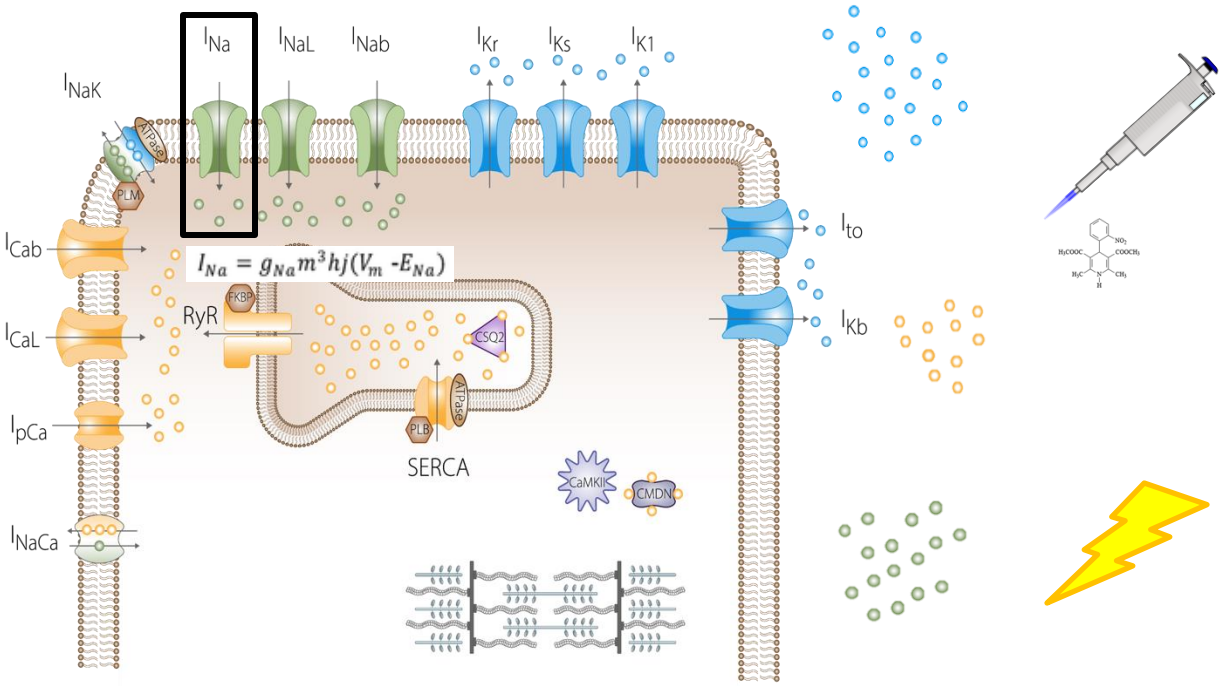


Karakikes et al, 2015

Cell source- and maturity-related variability prevents full realization of iPSC-CM potential

Computational models can reveal mechanisms of (and predict) cardiac electrophysiological responses

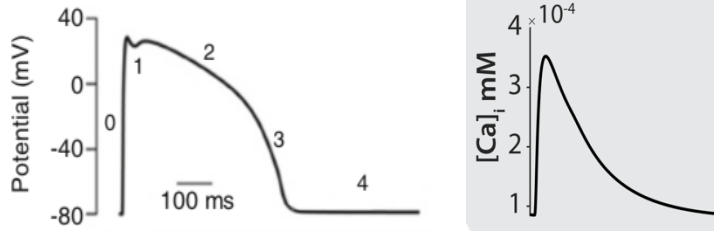
Cell properties | Environment | Perturbations



O'Hara et al, 2011 *PLOS Comp. Bio.*

Outputs

Action potential (AP) | Calcium transient (CaT)



Mayourian et al, 2018 *Methods Mol. Biol.*

Baseline model parameters are usually determined using recordings of individual channel currents, often from one or few specific cell preparations

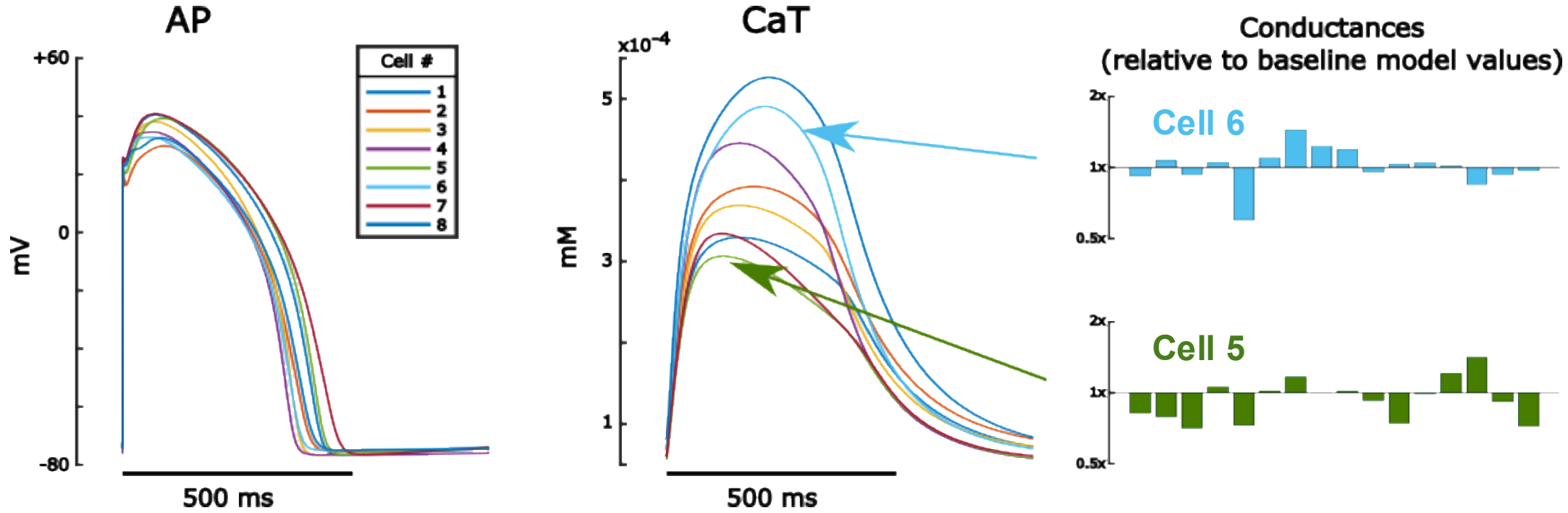
iPSC-derived CMs exhibit electrophysiological variability that isn't captured by baseline models

Can fitted iPSC-CM model parameters predict maturation- and individual-related variability?

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

Hypothesis: 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

Kernik et al (2019) model cells with varied conductances



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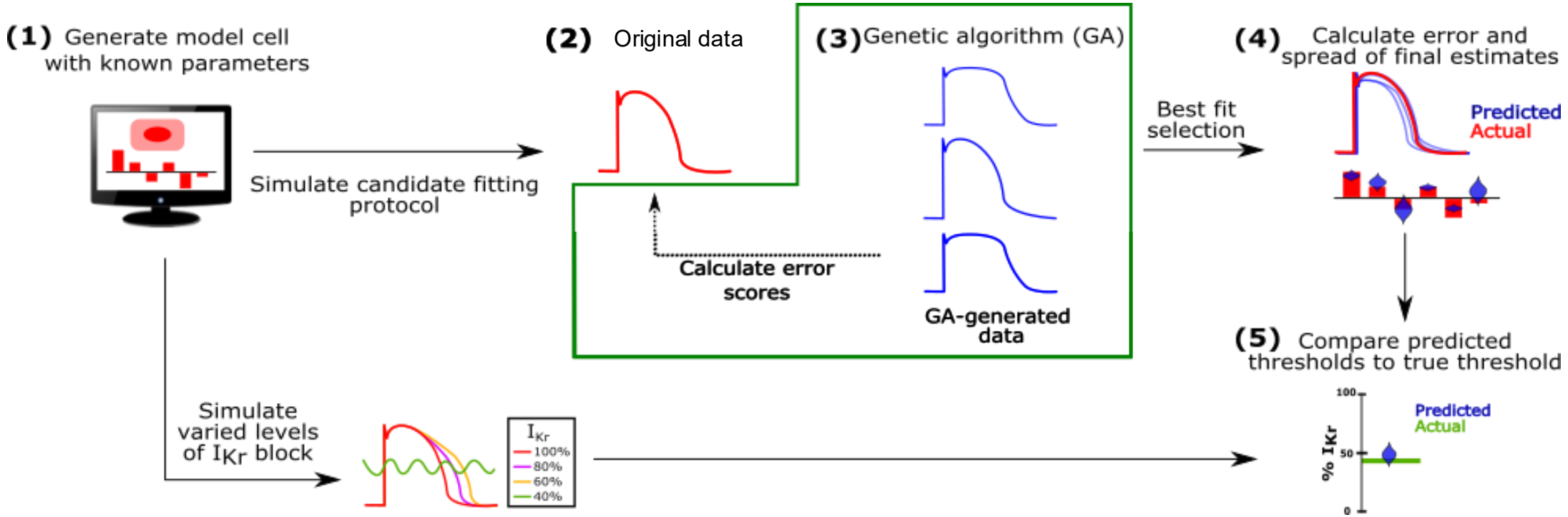


Initial candidate protocol evaluations

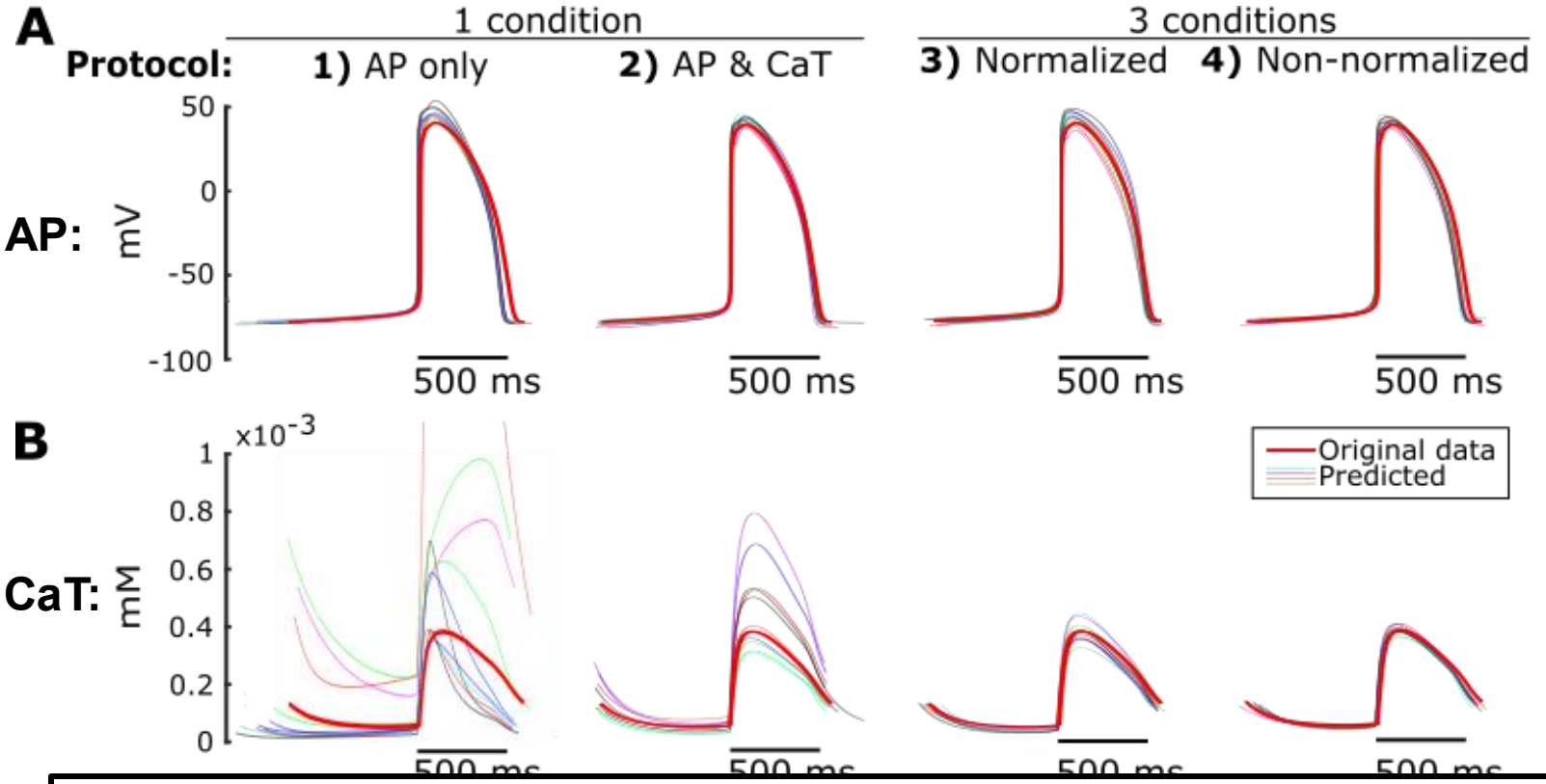
Candidate protocols – 10 GA runs each

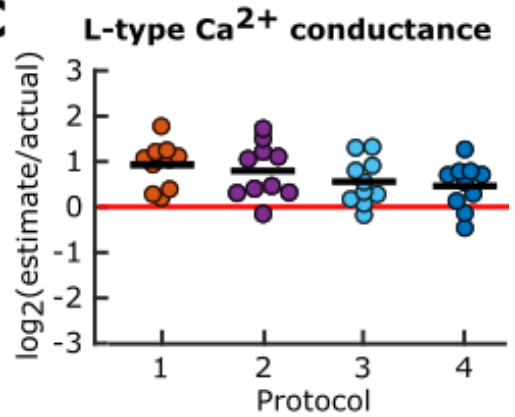
(1) = 1.8mM Ca^{2+}, 5.4mM K^{+}, 151mM Na^{+} ("baseline") without stimulus; normalized AP data

(2) = **(1)** + normalized CaT data

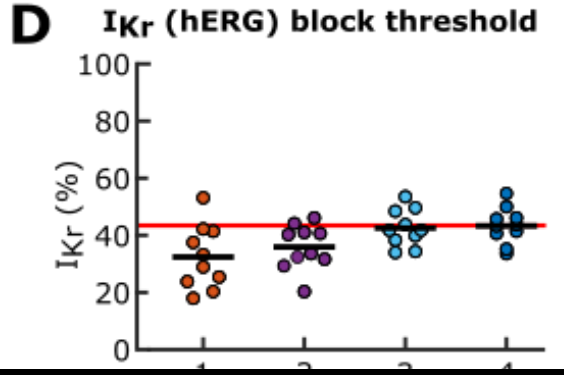
(3) = **(2)** + low Ca^{2+} + baseline, 1.25Hz pacing, 25% I_{CaL} block

(4) = (3) without data normalization





True parameter

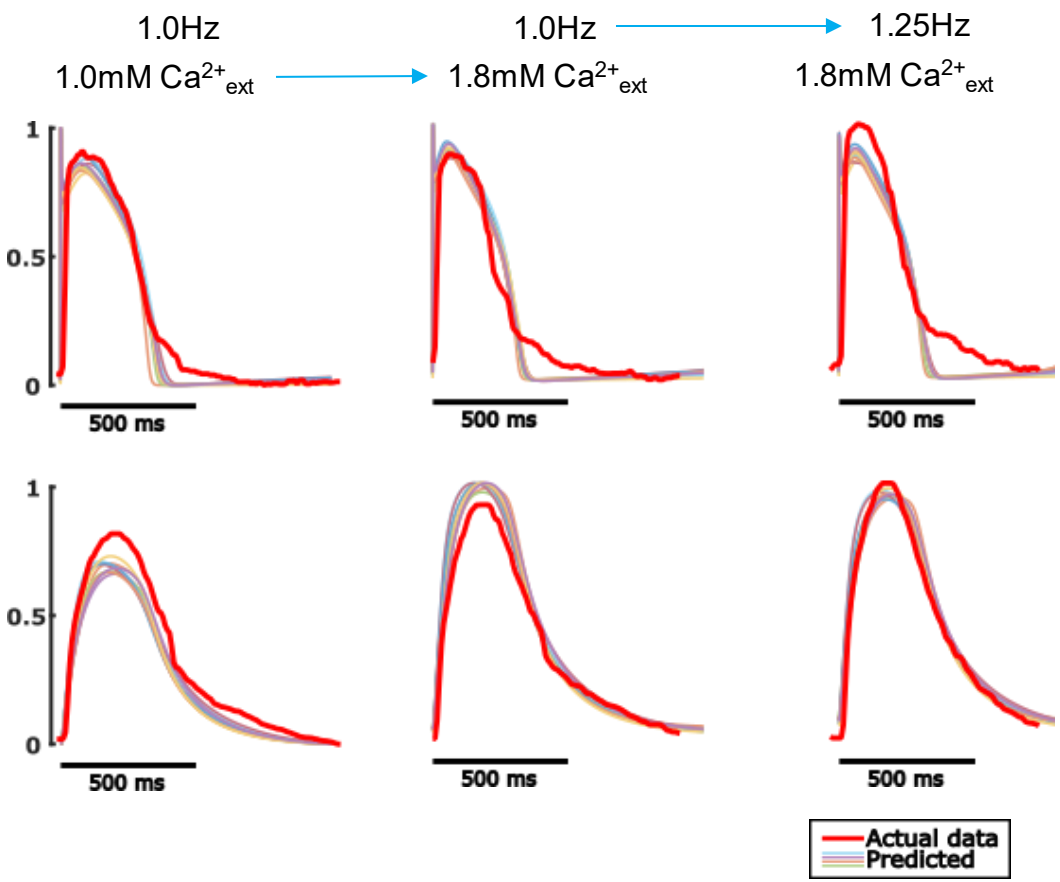


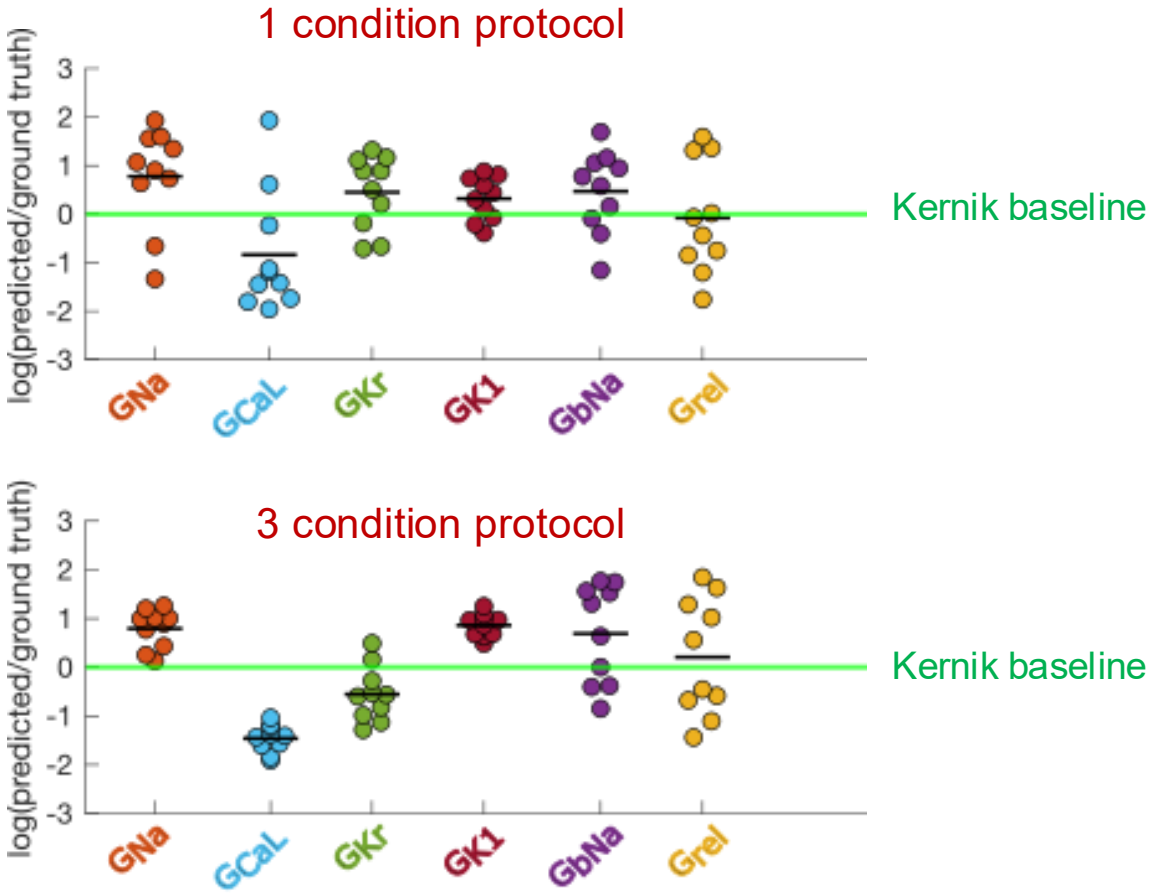
True arrhythmia threshold

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

Testing parameterization on experimental data

hiPSC-CMs from Neil Daily (InVivoSciences, Inc.)



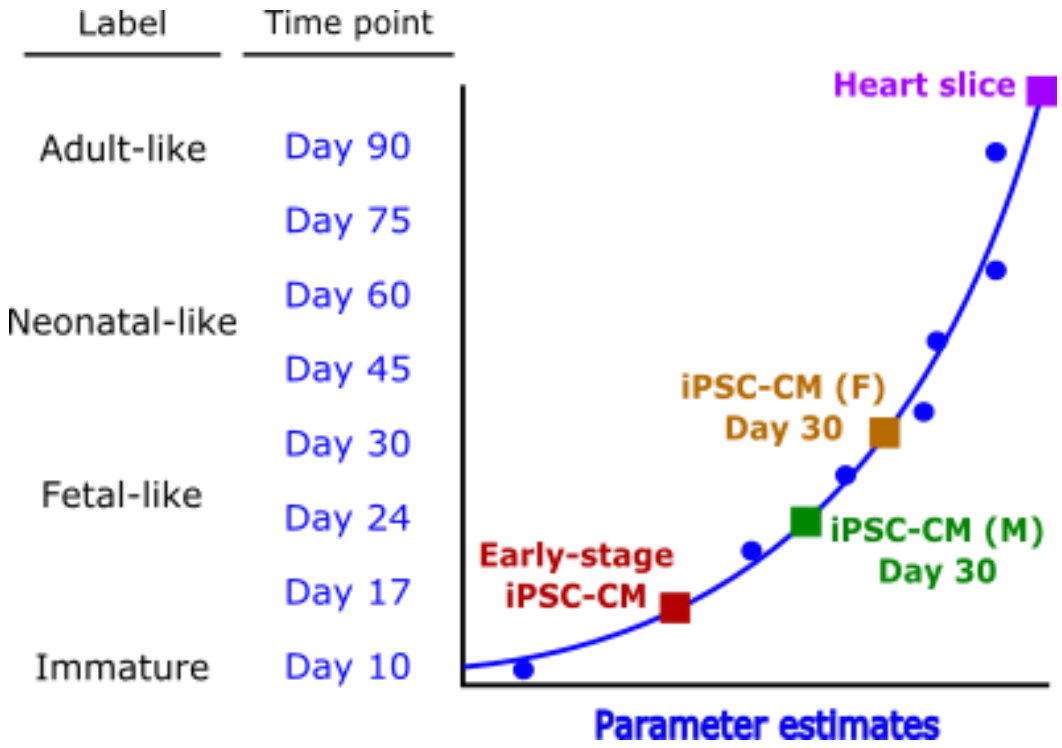


Adding different conditions improves parameter convergence between multiple GA initializations

Summary

- 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
- Initial evaluations suggest that fluorescence voltage and calcium recordings under multiple conditions may be sufficient for predicting conductances
- Adjusted models provided accurate and consistent predictions of I_{Kr} block tolerance thresholds

Next goal: Apply parameter estimates to iPSC-CM maturity & individual/group predictions



Acknowledgements

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Thank you! ☺ Questions?

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