Two independent measured datasets support the direction of an iPSC-cardiomyocyte repolarization-risk model

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Abstract

We test whether a published human induced-pluripotent-stem-cell cardiomyocyte (iPSC-CM) action-potential model, run with a multi-channel Hill block and the same 1–4× free-$C_{\max}$ exposures as a measured screen, reproduces the direction and rank of repolarization prolongation in two independent datasets. Against Blinova et al. (2018), 112 matched drug-dose points give a Spearman rank correlation of 0.67 and direction agreement on 89% of measurable points. Against Lee et al. (2025), direction agrees on 9 of 10 anchored drugs, with the calcium-channel blocker verapamil as the sole disagreement. The model's measured failure modes are an overconfident population confidence signal, a null IKs addition, and a negative INaL addition. The mechanism ranking that the model produces remains untested against wet data. The two checks bound the model's repolarization direction. They do not establish waveform or mechanism equivalence.

Keywords: iPSC-cardiomyocyte, action potential, cardiotoxicity, validation, CiPA

1. Introduction

In-silico models of the human ventricular action potential are proposed as an early cardiotoxicity screen for drug candidates. A single strong current, the delayed rectifier I_{Kr} (hERG), dominates the QT-prolongation signal, so a multi-channel model must show it does more than a single-channel margin before it earns a role in a safety package. The model here is the Kernik-2019 human iPSC-CM action potential model [kernik2019]. It differs from adult-ventricular models in being an iPSC-CM substrate, which matters because iPSC-CMs are the CiPA-recommended experimental substrate.

We ask one question: when the model is run with the same multi-channel Hill block and the same drug exposures as a measured MEA field-potential-duration (FPD) screen, does its repolarization direction and rank match the measurement? We use two independent datasets: Blinova et al. (2018) [blinova2018], the CiPA multi-site myocyte validation study, and Lee et al. (2025) [lee2025], a 28-drug iPSC-CM FPDc screen.

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2. The model and the read

The model computes ionic currents and the action-potential duration (APD90) of a simulated iPSC-CM. A compound is applied as fractional block of the currents I_{Kr}, I_{CaL}, and I_{Na}, derived from measured half-maximal inhibitory concentrations at the drug's free maximal concentration ($C_{\max}$). APD90 prolongation beyond a calibrated threshold is a repolarization-risk signal; a model cell that fails to repolarize is flagged as a collapse. This is a pharmacodynamic read: it takes a concentration as input and returns a repolarization response. It does not model pharmacokinetics.

3. Validation 1: Blinova et al. 2018

Blinova et al. (2018) screened the 28 CiPA drugs across multiple sites by MEA, measuring field-potential duration (FPD) at 1–4× free $C_{\max}$ with EAD annotations [blinova2018]. We matched each measured drug-dose point to a model run at the same multiple. FPD and APD90 are different readouts, so the claim is rank and direction of repolarization prolongation, not waveform equivalence.

Across 112 matched points the Spearman rank correlation between model APD90 prolongation and measured FPD prolongation is $\rho = 0.67$ (Fig. 1). Excluding repolarization-collapse points, $\rho = 0.62$. Direction agrees on 82 of 92 measurable points (89for each of them (no false collapses, specificity 100of the 27 EAD-bearing drugs (sensitivity 22milliseconds. The agreement holds in rank and direction, without magnitude equivalence.

4. Validation 2: Lee et al. 2025

Lee et al. (2025) measured corrected FPD (FPDc) in iPSC-CMs across the same 28 CiPA drugs at CiPA reference doses and clinical-$C_{\max}$ multiples [lee2025]. The per-drug values are published as figure heatmaps rather than a numeric table, so a rank correlation over all 28 is not computable from the extractable text. What is extractable is the direction for specific anchored drugs, stated numerically in the text.

For ten anchored drugs the model direction agrees with the measured direction on nine (Table 1). The eight high-risk drugs prolong in both the measurement and the model. Ranolazine, the only low-risk drug that Lee found to prolong FPDc, also prolongs in the model; this is a counterintuitive case where two independent measurements and the model agree. The calcium blockers nifedipine, nitrendipine and diltiazem shorten in both. The sole disagreement is verapamil: Lee measured a decrease, the model prolongs. This is the known calcium-block limitation, now confirmed in a third independent place.

5. Measured failure modes

The population confidence signal is overconfident.. A population-of-models run assigns each drug a confidence equal to the fraction of cells agreeing on the risk class. That confidence is not calibrated (Fig. 2). At the top confidence band the model reports a mean confidence of 0.99 but delivers accuracy of 0.63. The signal rises weakly with confidence, so it carries ordering information, but it is not a trustworthy per-call probability. The confidently-wrong drugs are the low-risk over-call set plus sotalol, the same structural bias as the benchmark.

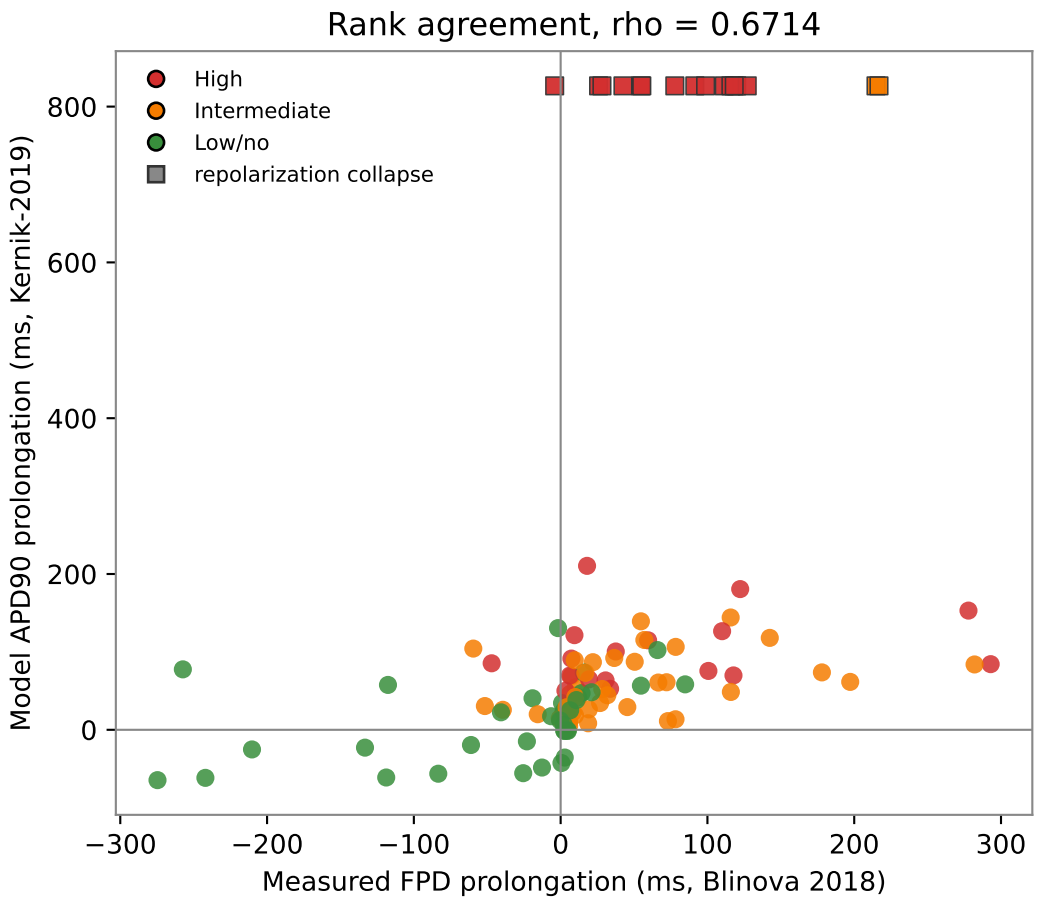

Figure 1: Model APD90 prolongation against measured FPD prolongation, 112 matched drug-dose points from Blinova et al. (2018). Squares are model repolarization collapses. The agreement is in rank and direction, not absolute magnitude.

Adding I_{Ks} changes nothing.. Adding a delayed-rectifier potassium current I_{Ks} to the risk score leaves the 28-drug accuracy unchanged (17/28) and moves no drug's class. The result is null.

Adding I_{NaL} is negative.. Adding a late-sodium current lowers validation accuracy. The addition does not help.

6. Limits of this validation

Established: the model's repolarization direction agrees with two independent measured datasets, and its rank agrees with Blinova et al. (2018). The calcium-block limitation is confirmed in a third place.

Not established: waveform or magnitude equivalence; a rank correlation over the full 28 drugs against Lee et al. (2025), whose per-drug values are figure-only; and the mechanism ranking that is the model's product use. That ranking has been tested only against phenotypes the same model generated, so it remains unvalidated against wet data. A fast mechanism answer is not a regulatory submission.

Table 1: Direction agreement on ten Lee et al. (2025) anchored drugs. Green marks agreement; red marks the sole mismatch (verapamil).

Drug	TdP class	Lee measured	Model
quinidine	High	prolong	prolong
dofetilide	High	prolong	prolong
droperidol	High	prolong	prolong
ibutilide	High	prolong	prolong
sotalol	High	prolong	prolong
ranolazine	Low/no	prolong	prolong
nifedipine	Low/no	shorten	shorten
nitrendipine	Low/no	shorten	shorten
diltiazem	Low/no	shorten	shorten
verapamil	Low/no	shorten	prolong

Data and code

The committed data and analysis scripts are in the repository under `science/cipa_validation/`. Figures are regenerated by `make_preprint_figures.py`.

Declarations

Funding. None.

Competing interests. The author is the sole founder of Perturb Bio, which sells the in-silico read that the model underlies.

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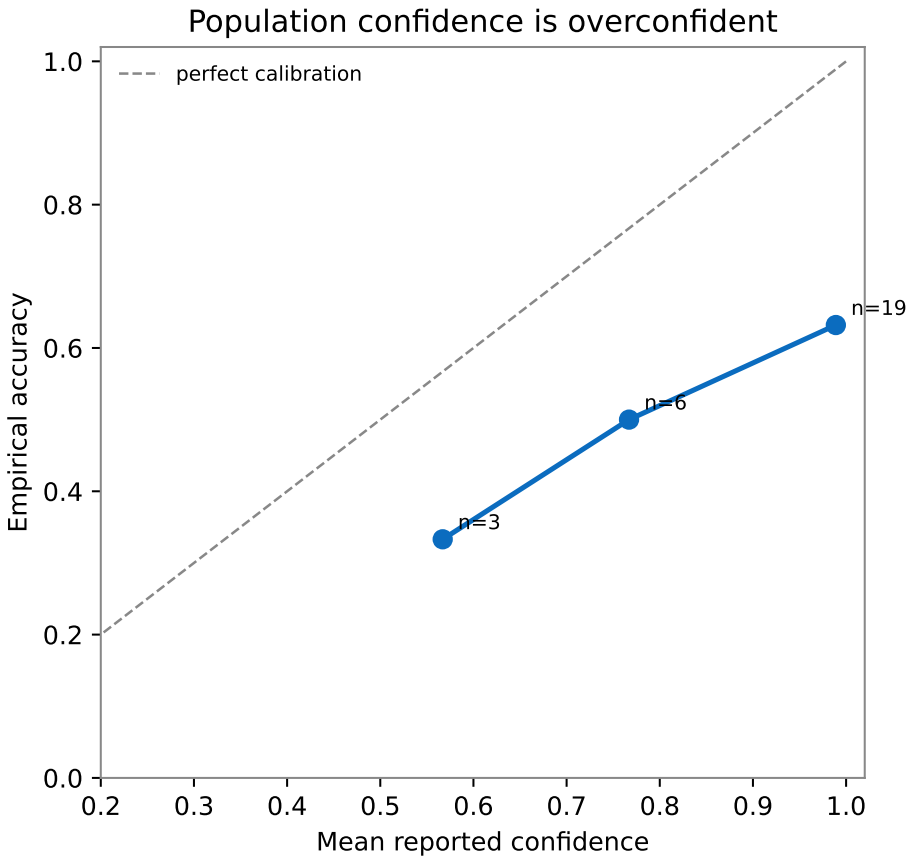

Figure 2: Reliability bands for the population confidence signal. Points fall below the identity line: reported confidence overstates achieved accuracy.