Optimization of Cardiac Myocyte Model for CiPA Initiative

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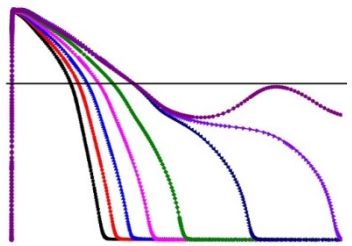
In Silico Working Group

Goals: Integrate in vitro data into a computational model of human ventricular myocyte and identify a mechanistic metric that can quantify the relative risk of inducing EAD/TdP

In silico **Reconstruction of Human Ventricular Cardiomyocyte Electrophysiology**

$$I_{stim} = C\frac{dV_m}{dt} + I_m$$



- Select a consensus base cardiomyocyte model for CiPA
- The base model is to be further optimized based on experimental data of drug effects on selected human cardiac currents
- A set of 12 training drugs classified into 3 torsade de pointes (TdP) risk categories (high, intermediate and low) is used to calibrate the model and develop the metric; Another set of 16 drugs for independent validation

The Selection of the Base Model for CiPA

- Cardiac Modeling Experts Meeting (July 2013) held at FDA to kick off CiPA In Silico Workstream
  - Modeling experts from academics, industry, FDA – hosted by HESI
- Affirmed the use of single cell vs. more complex 2D or 3D models
  - Simple but experimentally determined mechanistic representation of electrophysiology and pharmacology
  - Concerns about the degree of uncertainty generated by the large number of free parameters in a more complex model
  - Interest in quantitative metric(s) that could assign a level of risk vs. simulating proarrhythmia
- Recommended O'Hara Rudy (ORd) human ventricular myocyte model as most tightly linked to human ventricular cell data
- Identified the probable need to consider dynamic drug-channel interactions for hERG (and other channels)

Improving the ORd Model for CiPA

- Making the IKr/hERG component temperature dependent
- Modeling dynamic drug-hERG interactions rather than using simple IC50s
- Optimizing model parameters based on experimentally recorded drug effects on human ventricular myocytes

Development of a Temperature Sensitive hERG Model

Contents lists available at ScienceDirect

Journal of Pharmacological and Toxicological Methods

journal homepage: www.elsevier.com/locate/jpharmtox

A temperature-dependent *in silico* model of the human *ether-à-go-go*-related (hERG) gene channel

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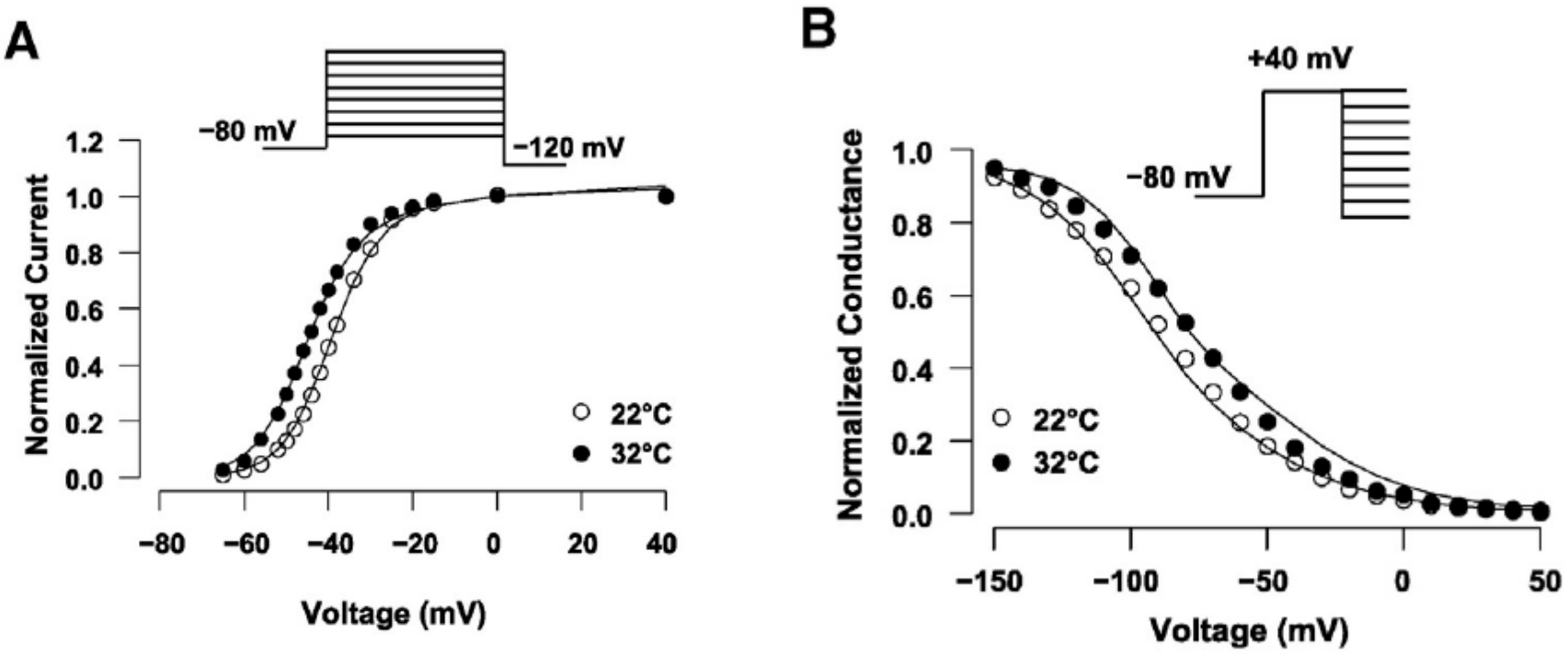
- Because O'Hara-Rudy model operates at physiological temperature, while industry-generated hERG data are often obtained at room temperature, a dynamic, temperature-sensitive hERG model is required
- We developed a modified hERG model that can reproduce temperature-induced changes in major channel gating processes

Examples of Temperature Effects



Experimental data (circles) from Vandenberg et al. 2006; Simulation (lines) from Li et al. 2016.

- Our model was able to reproduce the experimentally observed left shift of steady state activation curve (A)
- And a right shift of steady state inactivation curve (B)

Modeling Dynamic drug-hERG Interactions

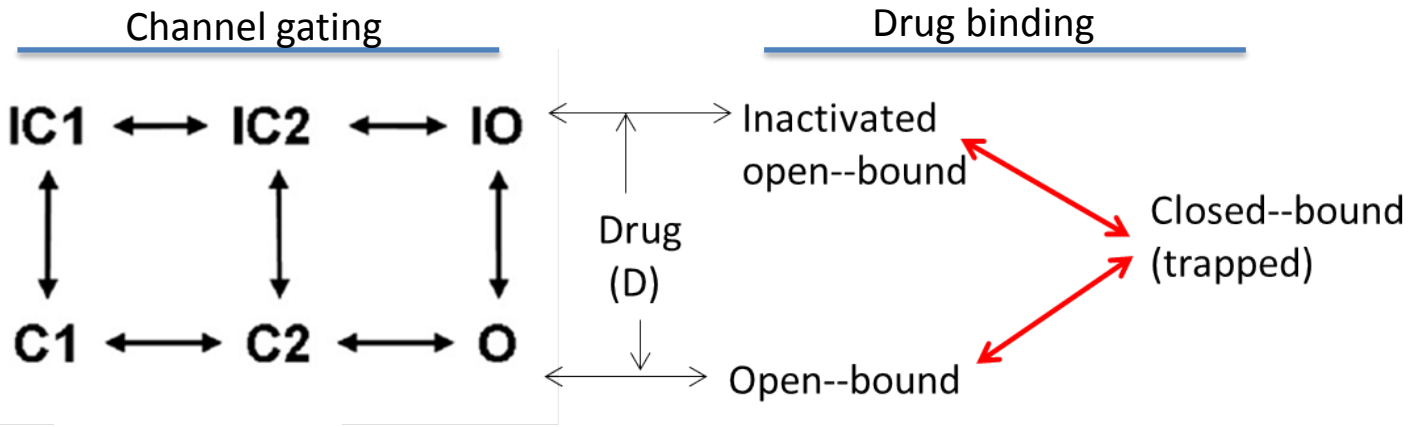
Improving the In Silico Assessment of Proarrhythmia Risk by Combining hERG (Human Ether-à-go-go-Related Gene) Channel–Drug Binding Kinetics and Multichannel Pharmacology

Zhihua Li, PhD; Sara Dutta, PhD; Jiansong Sheng, PhD; Phu N. Tran, PhD; Wendy Wu, PhD; Kelly Chang, PhD; Thembi Mdluli, PhD; David G. Strauss, PhD; Thomas Colatsky, PhD

Li Z et al. Improving the In Silico Assessment of Proarrhythmia Risk by Combining hERG-Drug Binding Kinetics and Multi-channel Pharmacology. Circulation: Arrhythmia & Electrophysiology. 2017;10:e004628

- Because the same drug may show different block potency under different conditions (i.e. heart rate), a novel model was developed to capture this dynamic drug-hERG interaction
- This model can distinguish between hERG blockers with similar IC50s but different TdP liabilities because of some drugs' tendency to be trapped in closed hERG channel

Modeling Dynamic drug-hERG Interactions



O = Open
C = Closed
I = Inactivated

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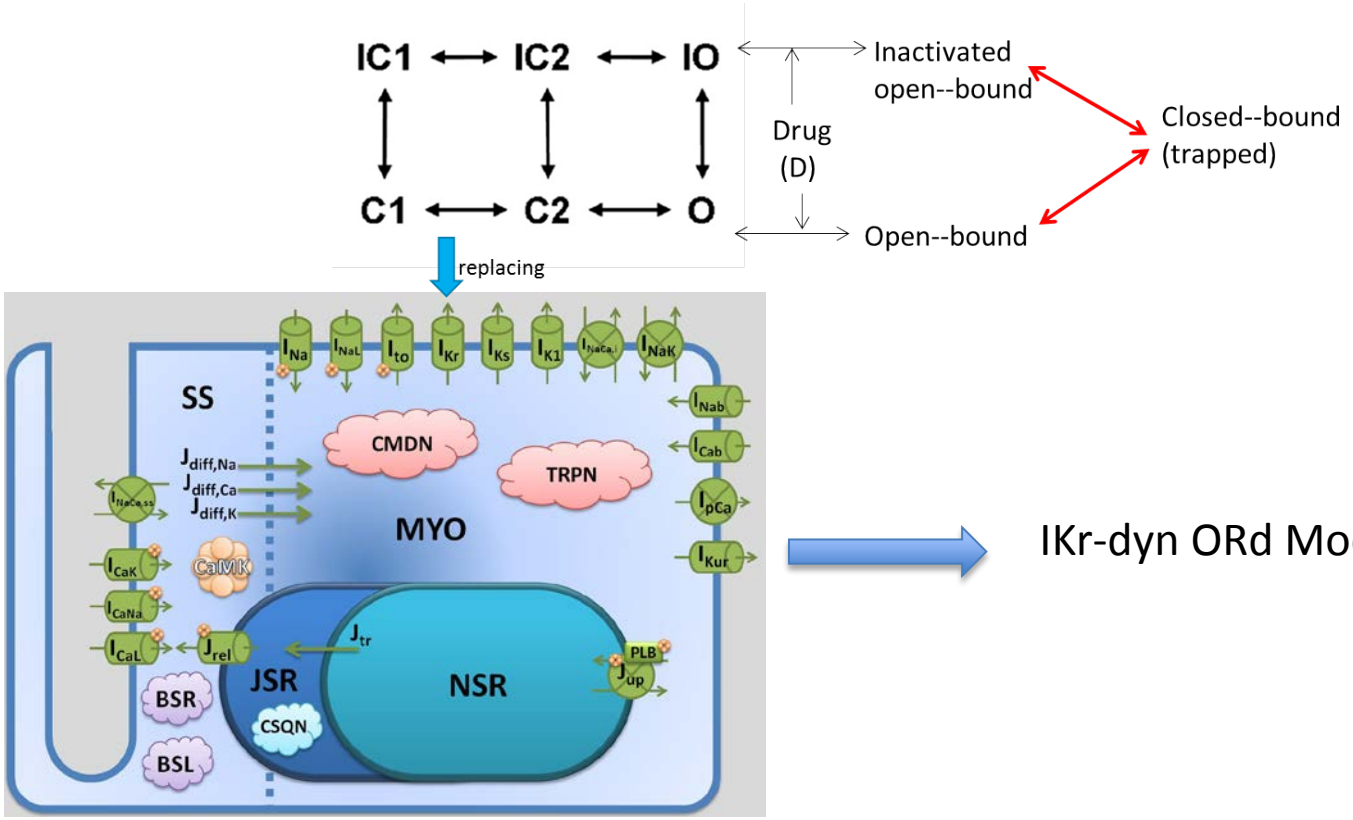
- The model allows drugs to be trapped in closed-bound state with varying propensities, a realistic feature often missing from published hERG models
- Modeling shows that High TdP Risk compounds tend to have a higher propensity to be trapped within hERG channel during repolarization

Replacing the IKr component of ORd with the Dynamic hERG Model

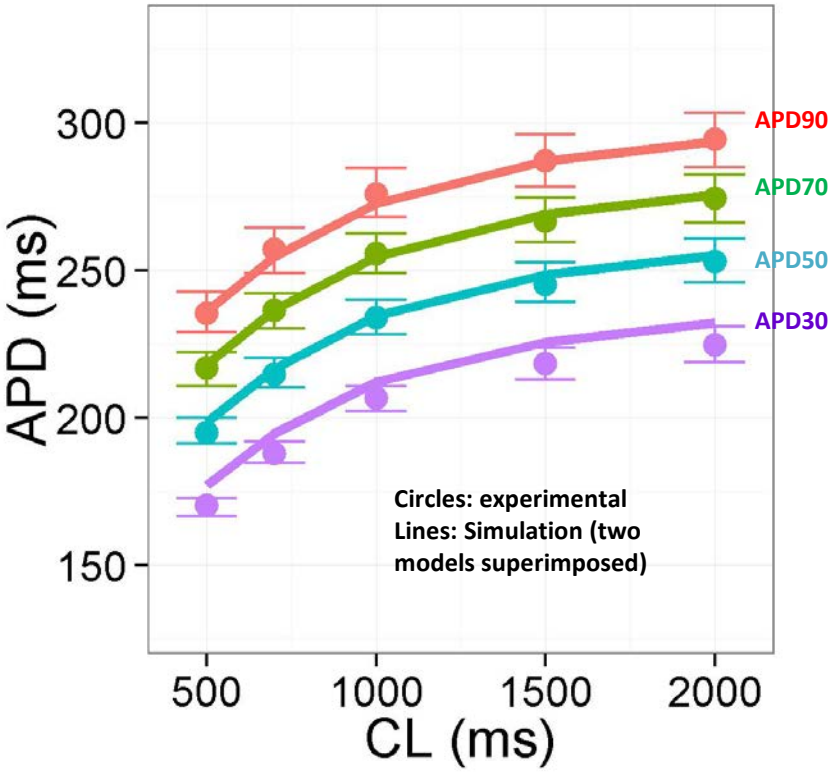


O'Hara T, Virag L, Varro A, & Rudy Y (2011) *PLoS Comput Biol 7(5):e1002061.*

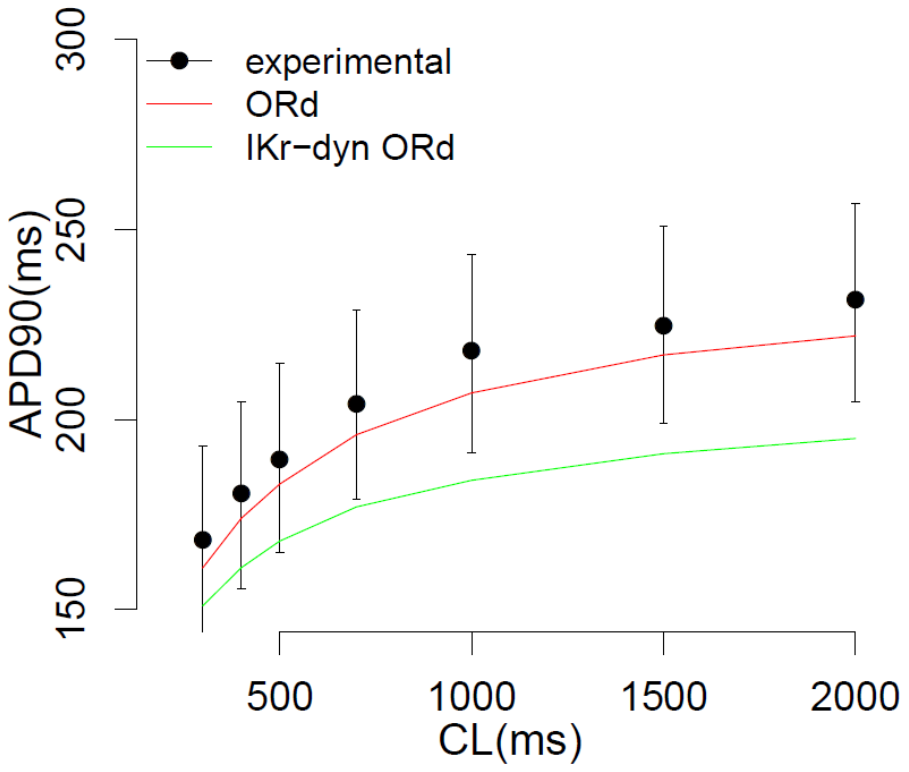
Li Z et al. Circulation: Arrhythmia & Electrophysiology. 2017;10:e004628

IKr-dyn ORd Model vs ORd Model

Control Condition (no drug)



1 μM nisoldipine (ICaL blocker)



- Under control conditions, both models fit experimental rate-dependent APD well
- In the presence of some drugs, IKr-dyn ORd model made the fitting worse

Further Optimization of IKr-dyn ORd

frontiers in Physiology

ORIGINAL RESEARCH
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Check for updates

Optimization of an *In silico* Cardiac Cell Model for Proarrhythmia Risk Assessment

*Sara Dutta, Kelly C. Chang, Kylie A. Beattie, Jiansong Sheng, Phu N. Tran, Wendy W. Wu, Min Wu, David G. Strauss, Thomas Colatsky† and Zhihua Li**

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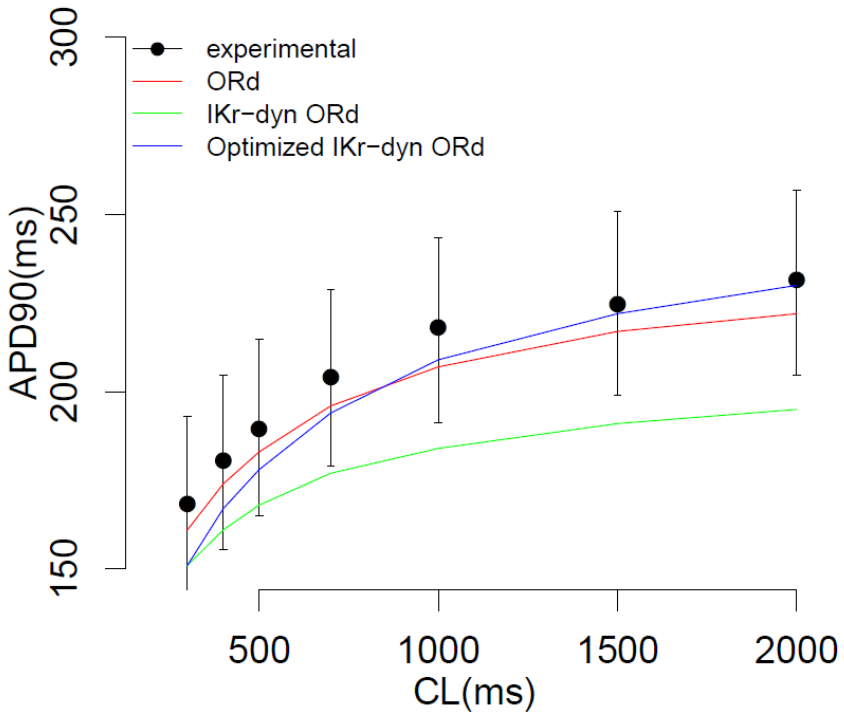
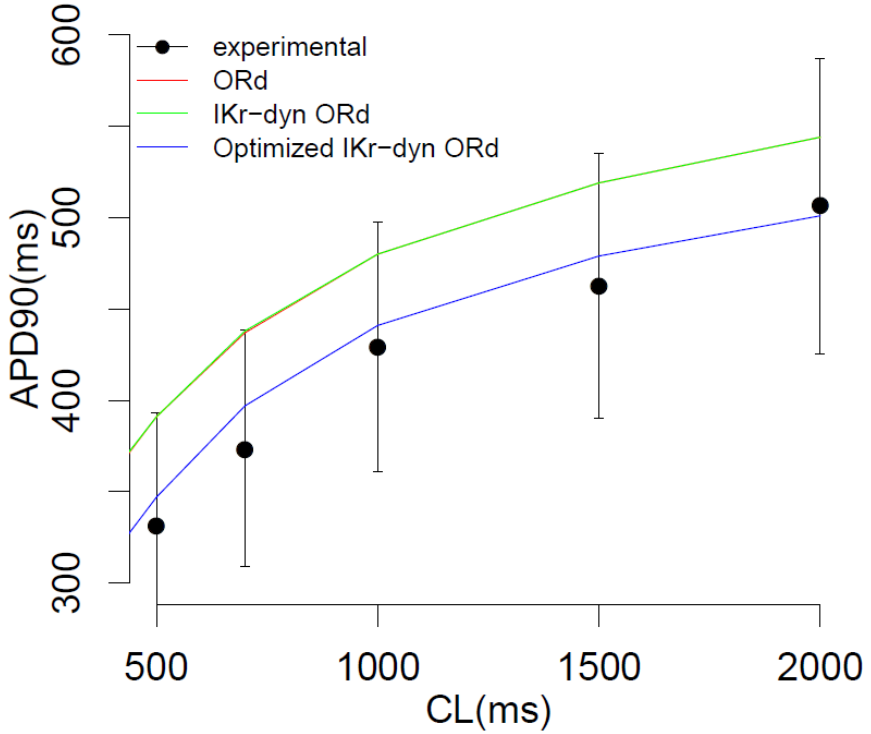
- The conductance of five major ion currents (IKr, IK1, IKs, INaL, ICaL) are adjusted
- Adjustment is based on APD rate dependence experimental data under control and drug block conditions in human cardiomyocytes (from O'Hara 2011)

Results of Optimization

1 μM nisoldipine (ICaL blocker)



1 μM E4031 (IKr blocker)



- For some drugs (nisoldipine), Optimized IKr-dyn ORd model (blue) reproduces data as faithfully as ORd (red)
- For others (E4031), Optimized IKr-dyn ORd model (blue) fits experimental data even better than ORd

Summary

- The consensus cardiac model (ORd) was selected based on its tight link to human ventricular cell data
- The choice of model complexity (1D vs 2D) and tissue/cell type is based on the assumption that the goal is to assign relative TdP risk, not to simulate TdP directly
- IKr component of ORd was replaced by a Markov hERG model that captures temperature-dependent gating and drug-hERG dynamic interaction
- Further optimization of the model improves the model's ability to reproduce rate-dependent APD experimental data from human cardiomyocytes

Acknowledgements

CiPA Steering Committee

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All CiPA Working groups

- Ion Channel working group
- In silico working group
- Cardiomyocyte working group
- Phase 1 ECG working group

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- Academic collaborators

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