# Slow delayed rectifier current protects ventricular myocytes from arrhythmic dynamics across multiple species

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Integrative Cardiac Dynamics
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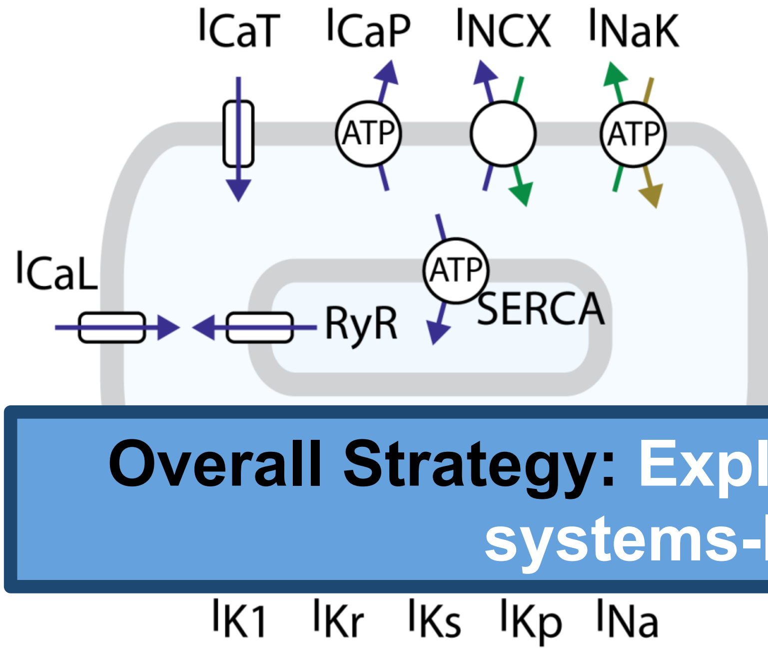
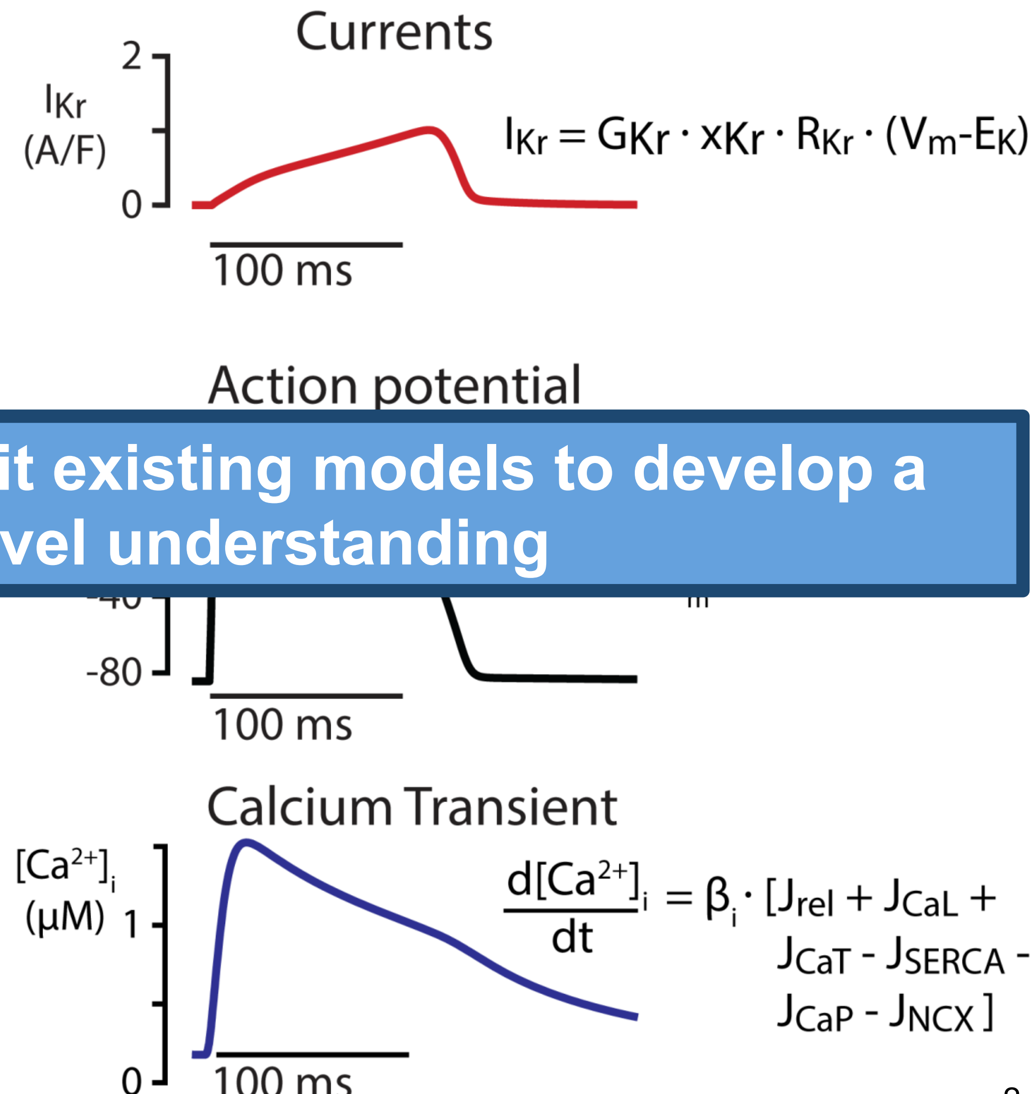
# Studying the cardiac myocyte with mathematical models

## First cardiac cell model published in 1962 – hundreds of subsequent models




**Overall Strategy: Exploit existing models to develop a systems-level understanding**

- 10-20 ion channels, pumps, and transporters
- 20-60 ordinary differential equations

# Outline

## Control of ventricular action potential duration

- Coupling of modeling and experiments (guinea pigs)
- Developing more predictive mathematical models
- Implications for cellular arrhythmia dynamics
- Hypothesis: slow delayed rectifier $I_{Ks}$ is stabilizing

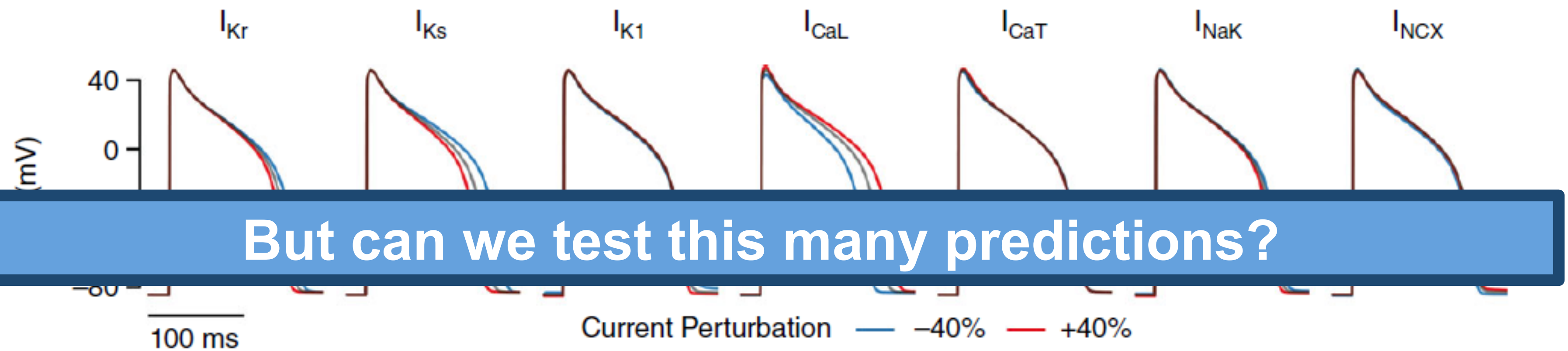
## Extending the $I_{Ks}$ stabilization hypothesis

- Testing multiple mathematical models
- Mechanistic explanations
- Physiological importance: β-adrenergic stimulation

# How do we choose parameters and improve the existing models?

## Test how the system responds to perturbations

**Model predictions: augmenting/inhibiting guinea pig ionic currents**




**But can we test this many predictions?**

**model of Livshitz & Rudy (2009) *Biophys. J.* 97:1265-76.**

**Ryan Devenyi, M.D., Ph.D.**

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### Differential roles of two delayed rectifier potassium currents in regulation of ventricular action potential duration and arrhythmia susceptibility

Ryan A. Devenyi[1,*], Francis A. Ortega[2,*], Willemijn Groenendaal[3,4], Trine Krogh-Madsen[3], David J. Christini[2,3] and Eric A. Sobie[1]

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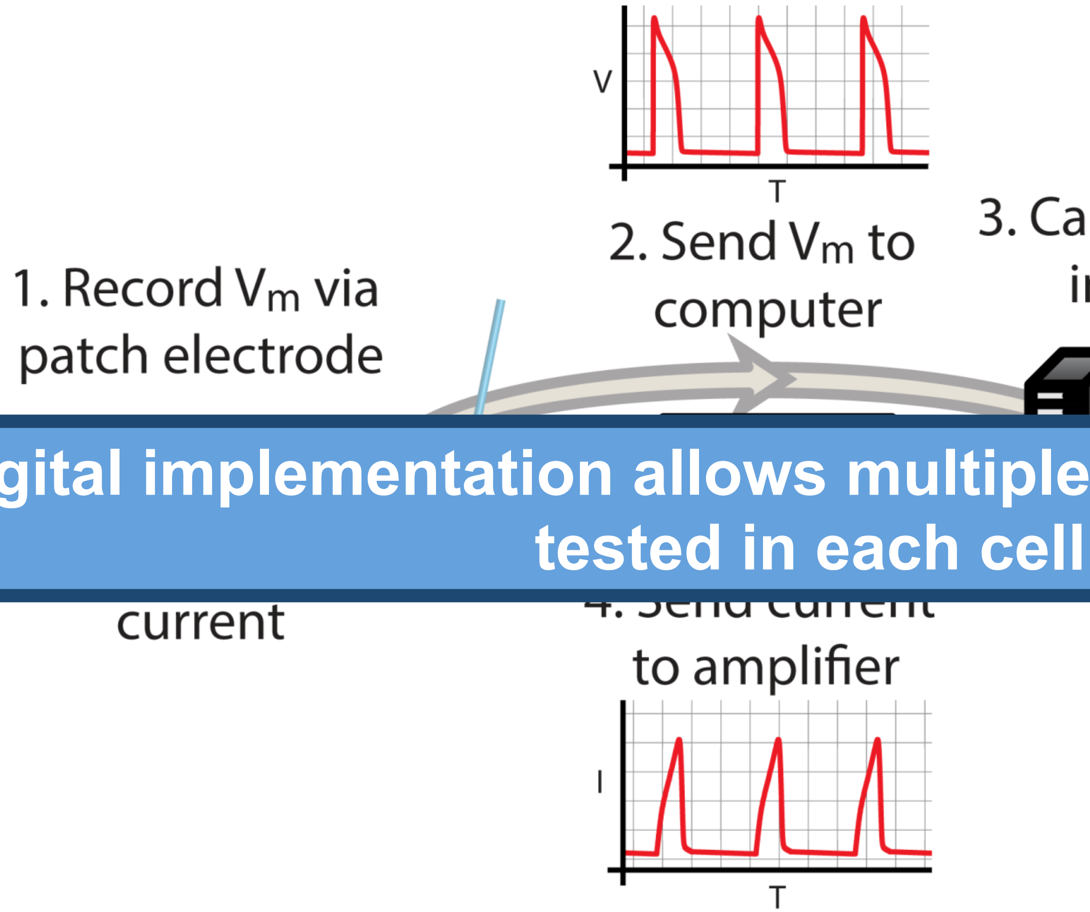
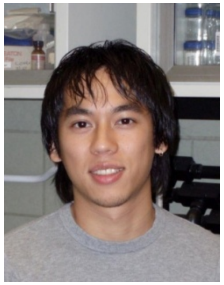
***Journal of Physiology*, (2017) 595:2301-2317.**

# Dynamic Clamp: a real-time, closed loop system for altering ionic current levels



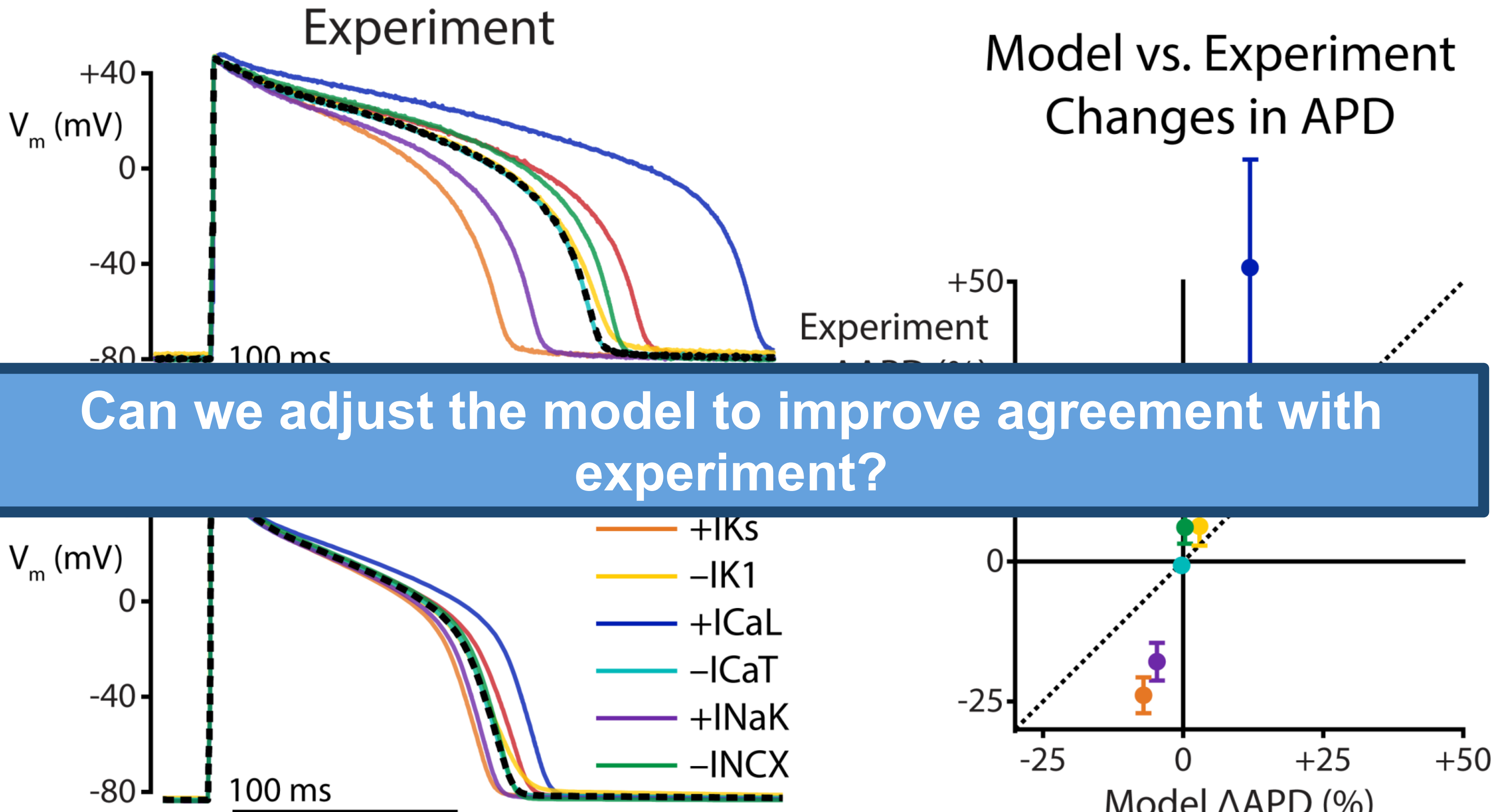

**Digital implementation allows multiple perturbations to be tested in each cell**



**Prof. David Christini, Francis Ortega**
**Weill-Cornell Medical College**

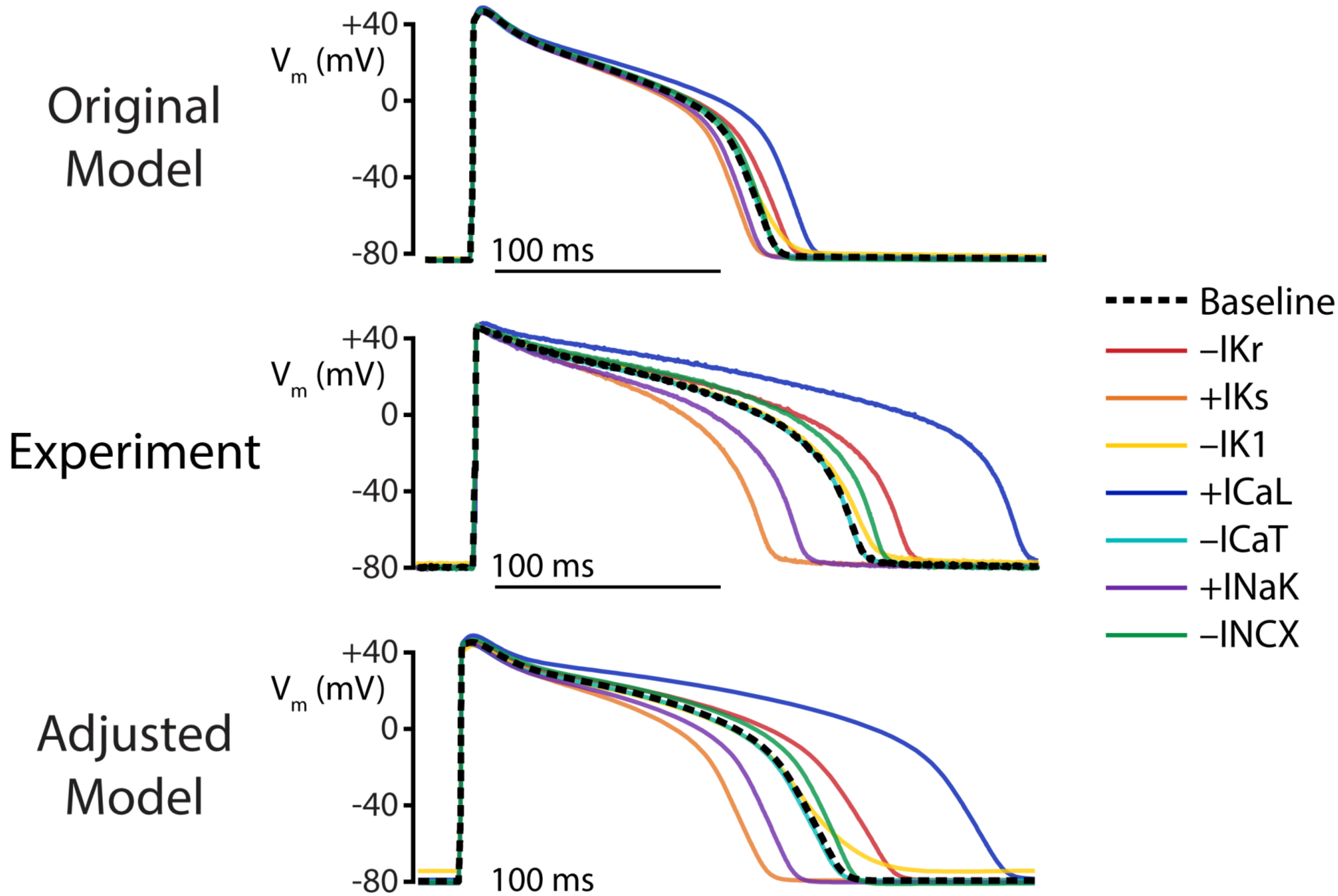
# Larger changes in experiments than in model

## Dynamic clamp in guinea pig myocytes

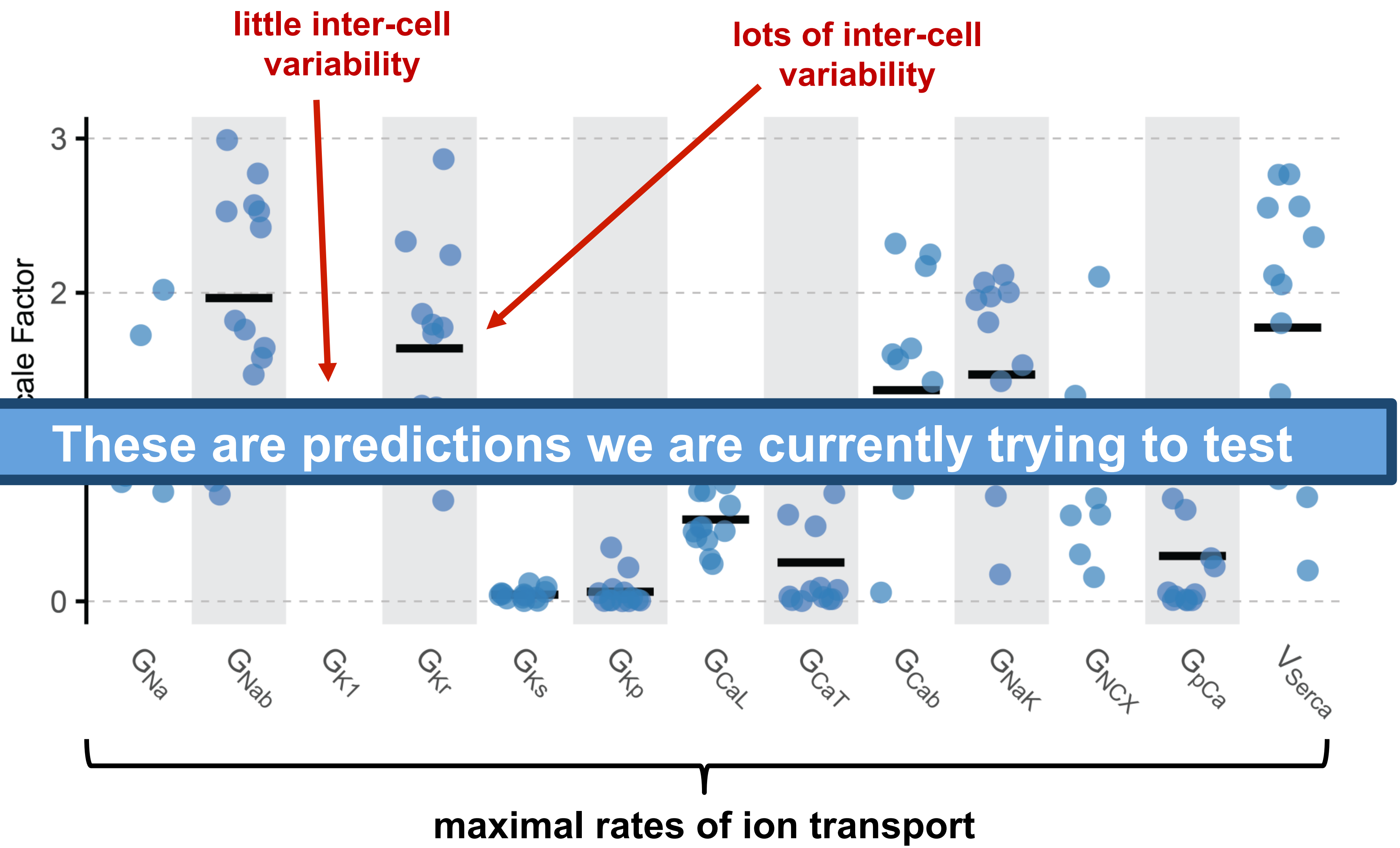



**Can we adjust the model to improve agreement with experiment?**

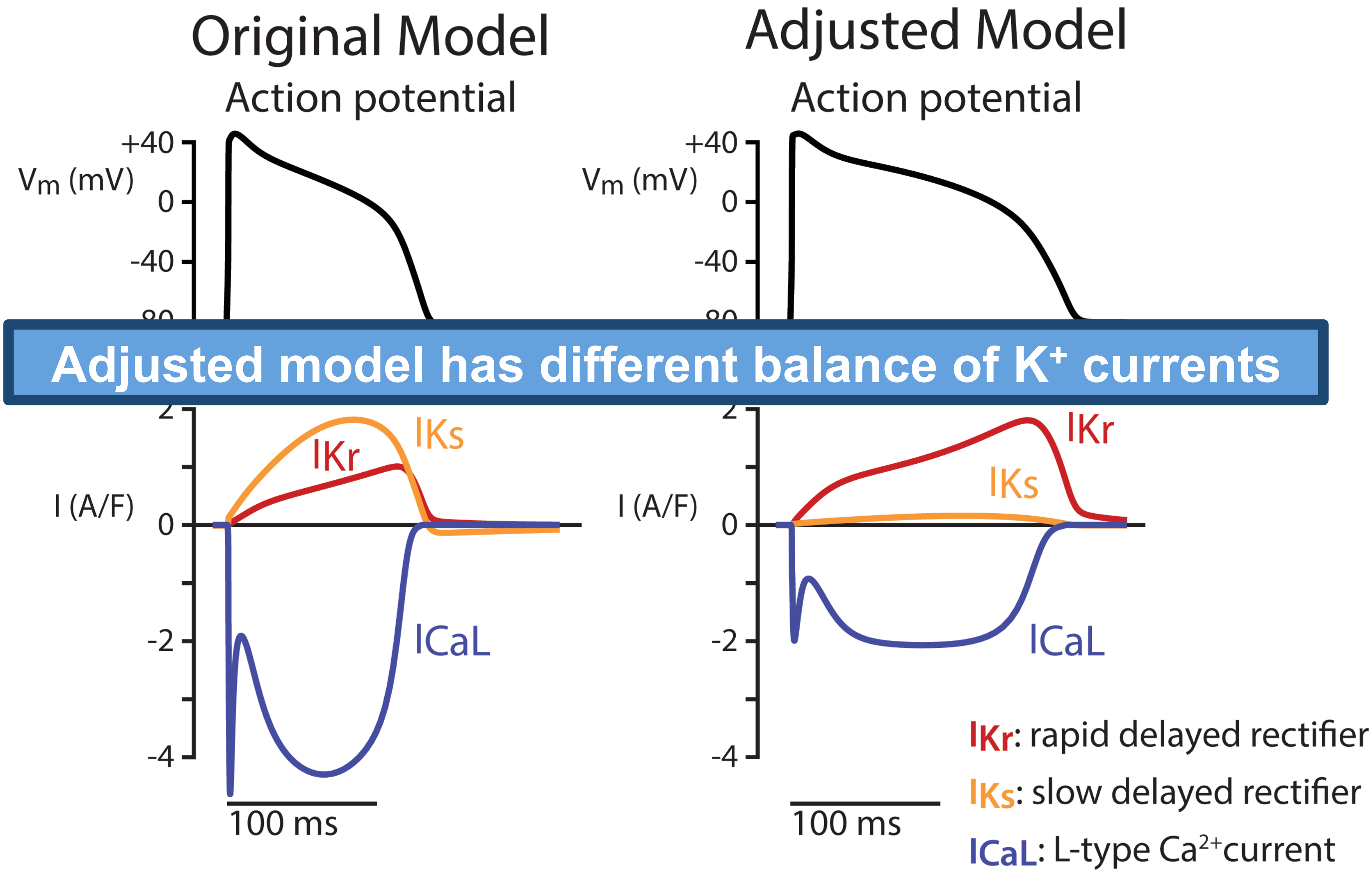
# A Genetic Algorithm improves agreement between simulation and experiment



# The GA fit generates a parameter set for each experimental sample



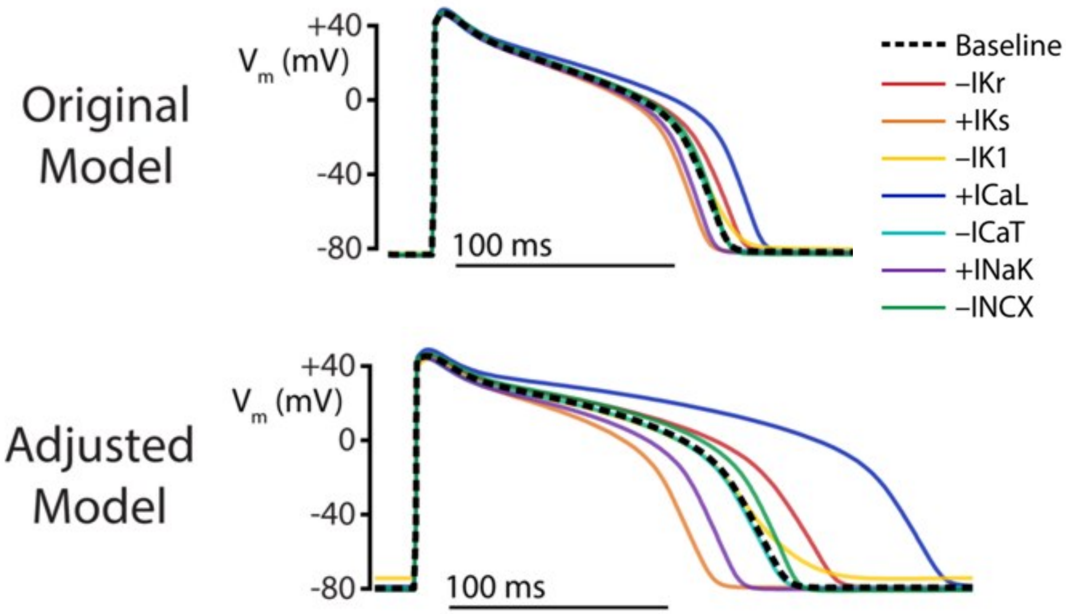
# The new model behaves differently



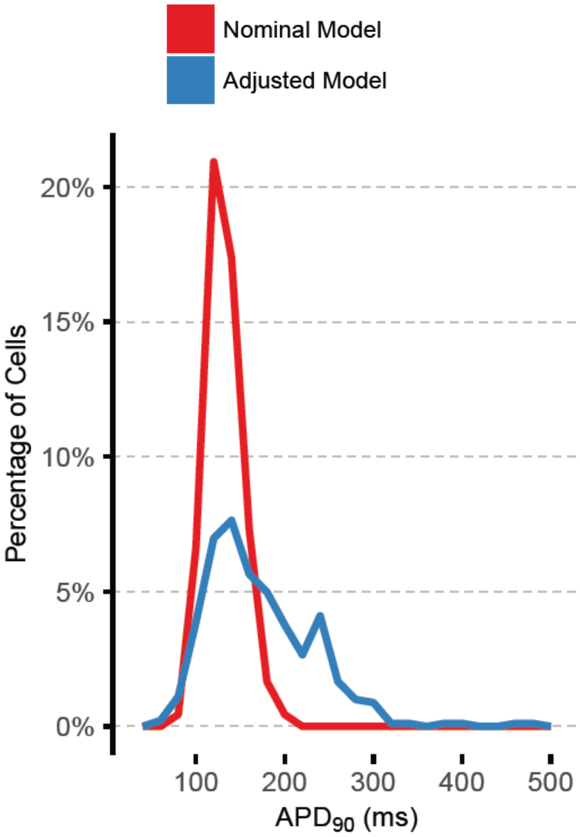

**Adjusted model has different balance of $K^+$ currents**

# Decreased stability in the adjusted model

## Response to perturbations

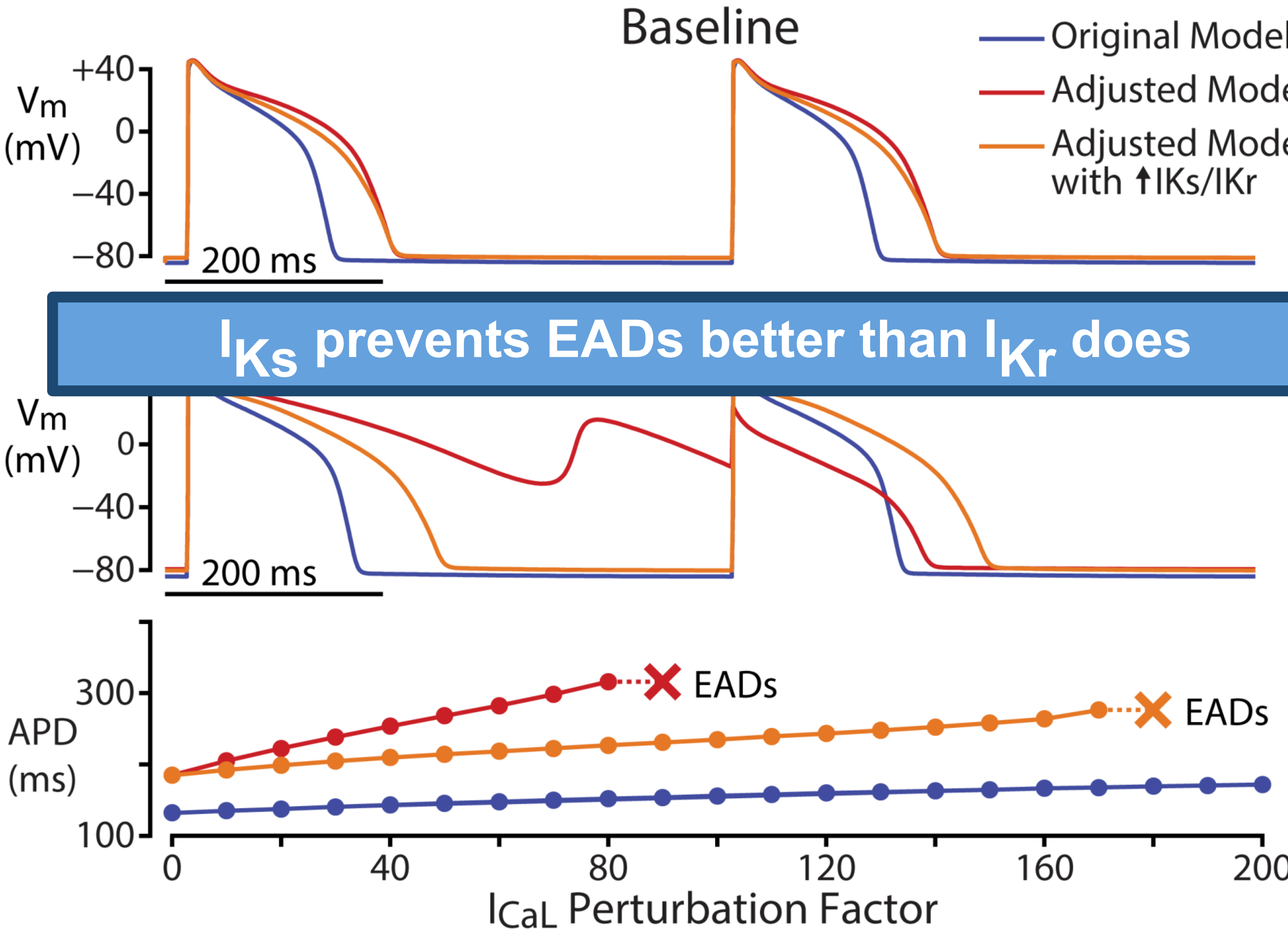



## Population simulations




**Hypothesis:** decreased stability may predispose cells to arrhythmic dynamics

# Different K⁺ currents have different effects on pro-arrhythmic EADs

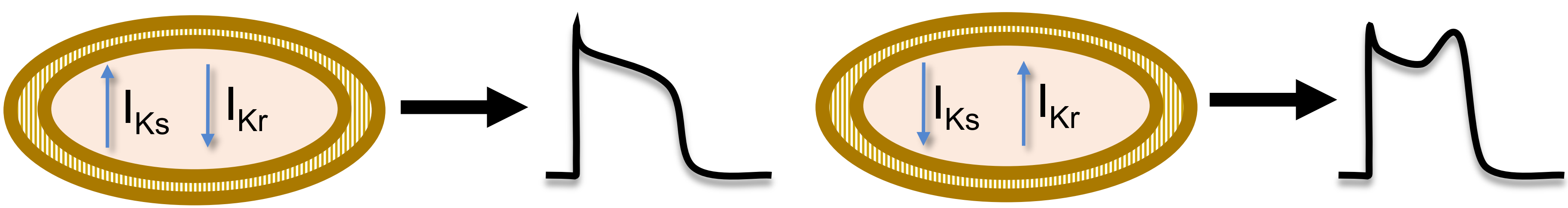



**$I_{Ks}$ prevents EADs better than $I_{Kr}$ does**

# Summary

**Combining perturbation modeling with thorough experimental tests gives insight into AP dynamics**

1. Roles of complementary $K^+$ currents, $I_{Kr}$ and $I_{Ks}$
2. Predictions about pro-arrhythmic events (EADs)
3. A more predictive mathematical model

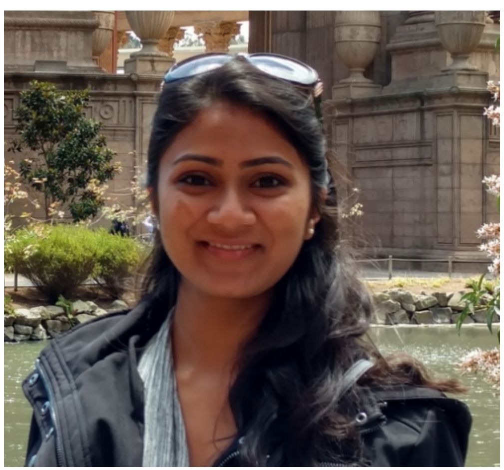


# Goals

(1) Is this concept true in other animal and human models?

(2) What is the underlying mechanism that allows $I_{Ks}$ to be protective?

(3) Is this concept true only at baseline or during other physiological conditions such as during β-adrenergic activation?



**Meera Varshneya**
**Ph.D. candidate**

# (1) Is this concept true in other species models?

(1) Fox et al.
DOI: 10.1152/ajpheart.00612.2001
(2) Hund et al.
DOI: 10.1161/01.CIR.0000147231.69595.D3

(3) Shannon et al.
DOI: 10.1529/biophysj.104.047449

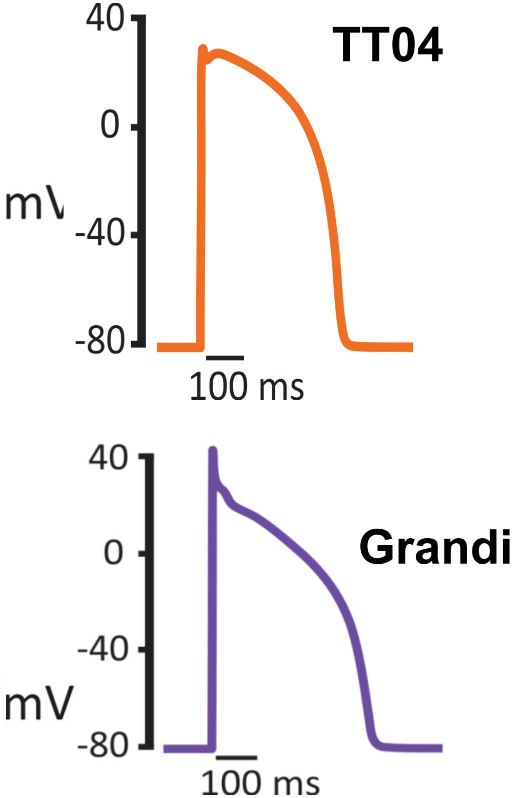
(4) Livshitz et al.
DOI: 10.1016/j.bpj.2009.05.062
(5) Devenyi et al.
DOI: 10.1113/JP273191

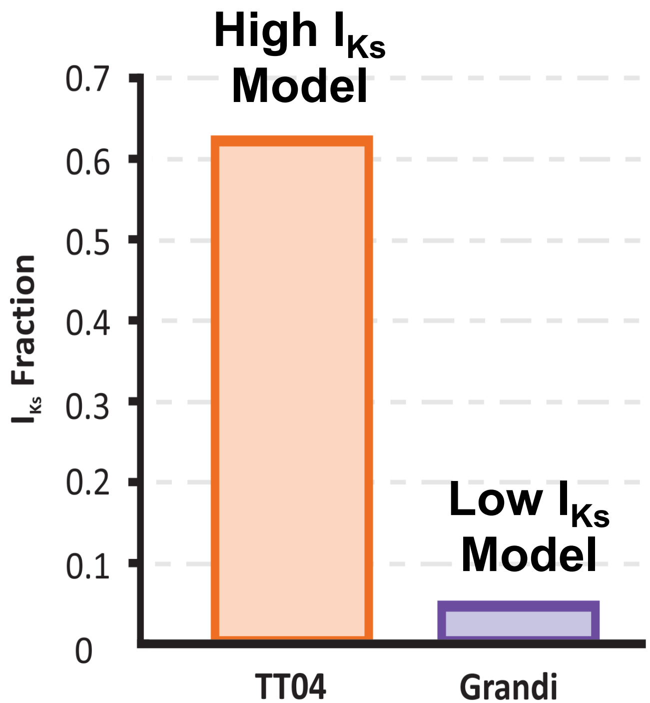
(6) TT04 et al.
DOI: 10.1152/ajpheart.00794.2003
(7) TT06 et al.
DOI: 10.1152/ajpheart.00109.2006
(8) Grandi et al.
DOI:10.1016/j.yjmcc.2009.09.019
(9) O'Hara et al.
DOI:10.1371/journal.pcbi.1002061

**Nine ventricular myocyte mathematical models**

- **Endocardial variant of models with multiple layers**
- **Constant pacing at 1 Hz**

# Two human ventricular with radically different $I_{Ks}$ levels



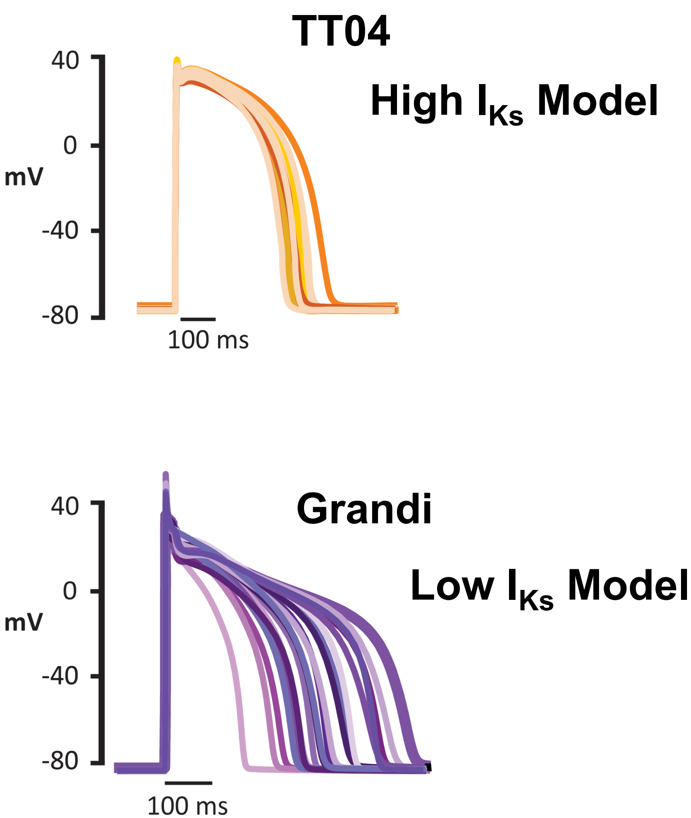



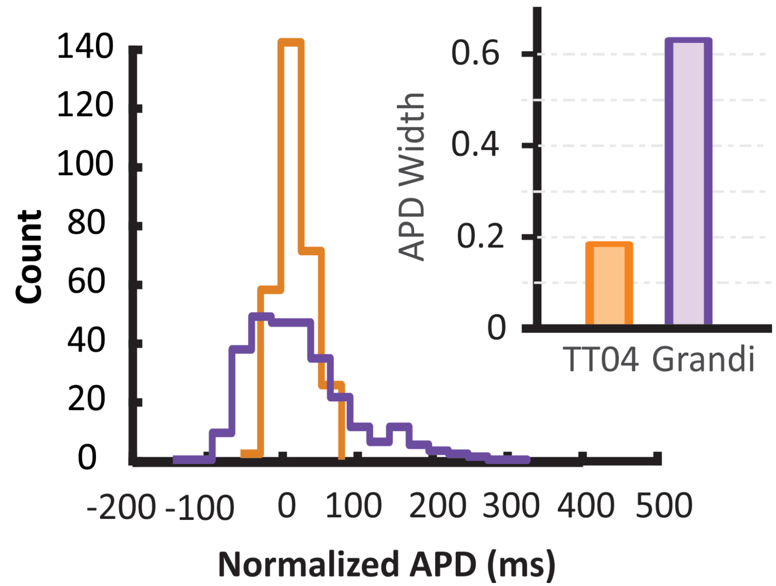

$$\text{IKs Fraction} = \frac{\int IKs}{\int IKs + \int IKr}$$

# Examine variability in heterogeneous populations

## Randomize parameters control ion transfer rates

$$\text{APD Spread} = \frac{90^{th}\%ile - 10^{th}\%ile}{median}$$

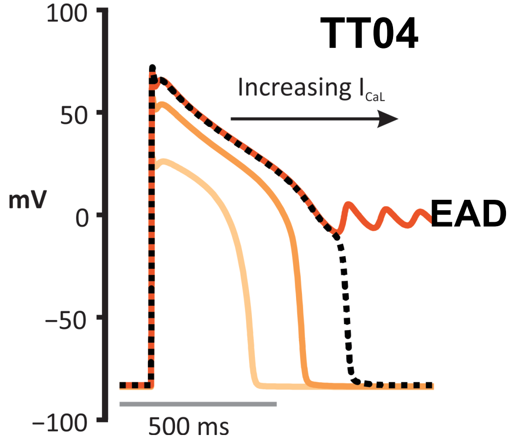


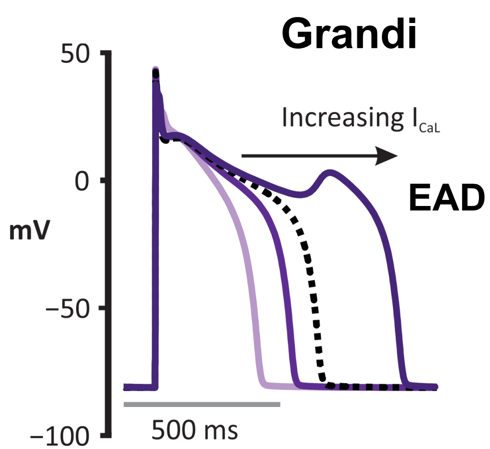



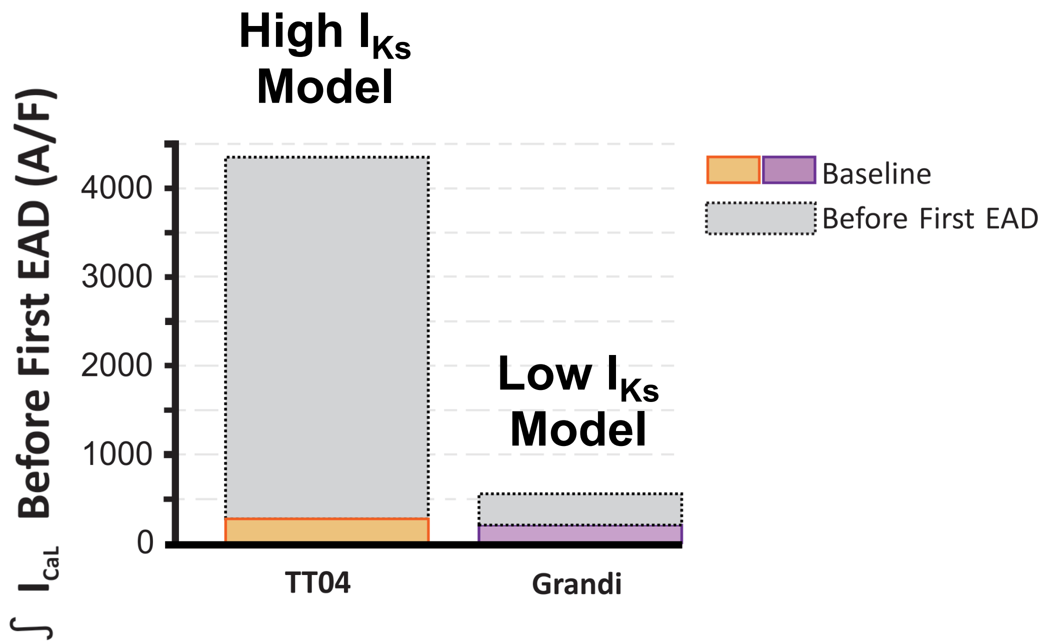

***High $I_{Ks}$ model has less population variablity***

# Test susceptibility to EADs

## Increase inward current through L-type Calcium Channel ($I_{CaL}$ )



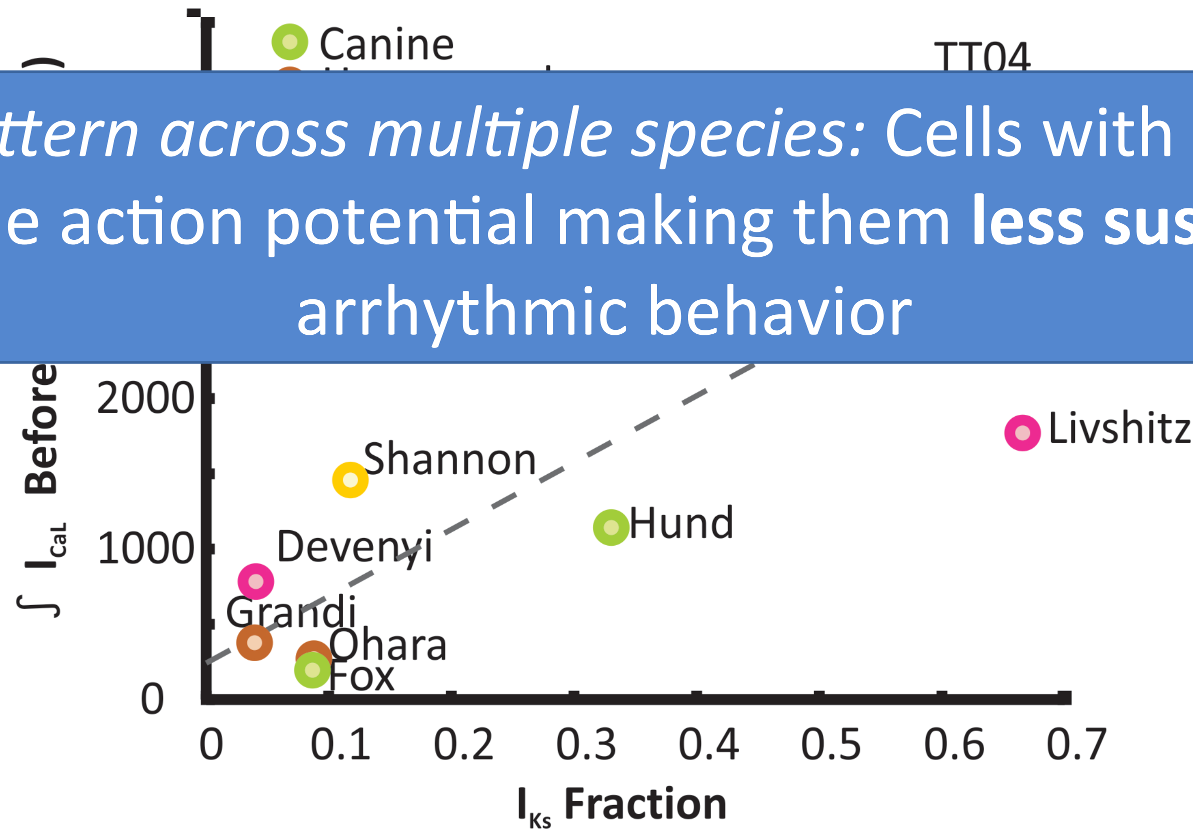




***High $I_{Ks}$ model is less susceptible to EADs***

# Study concept across multiple models

## Examine variability within a population

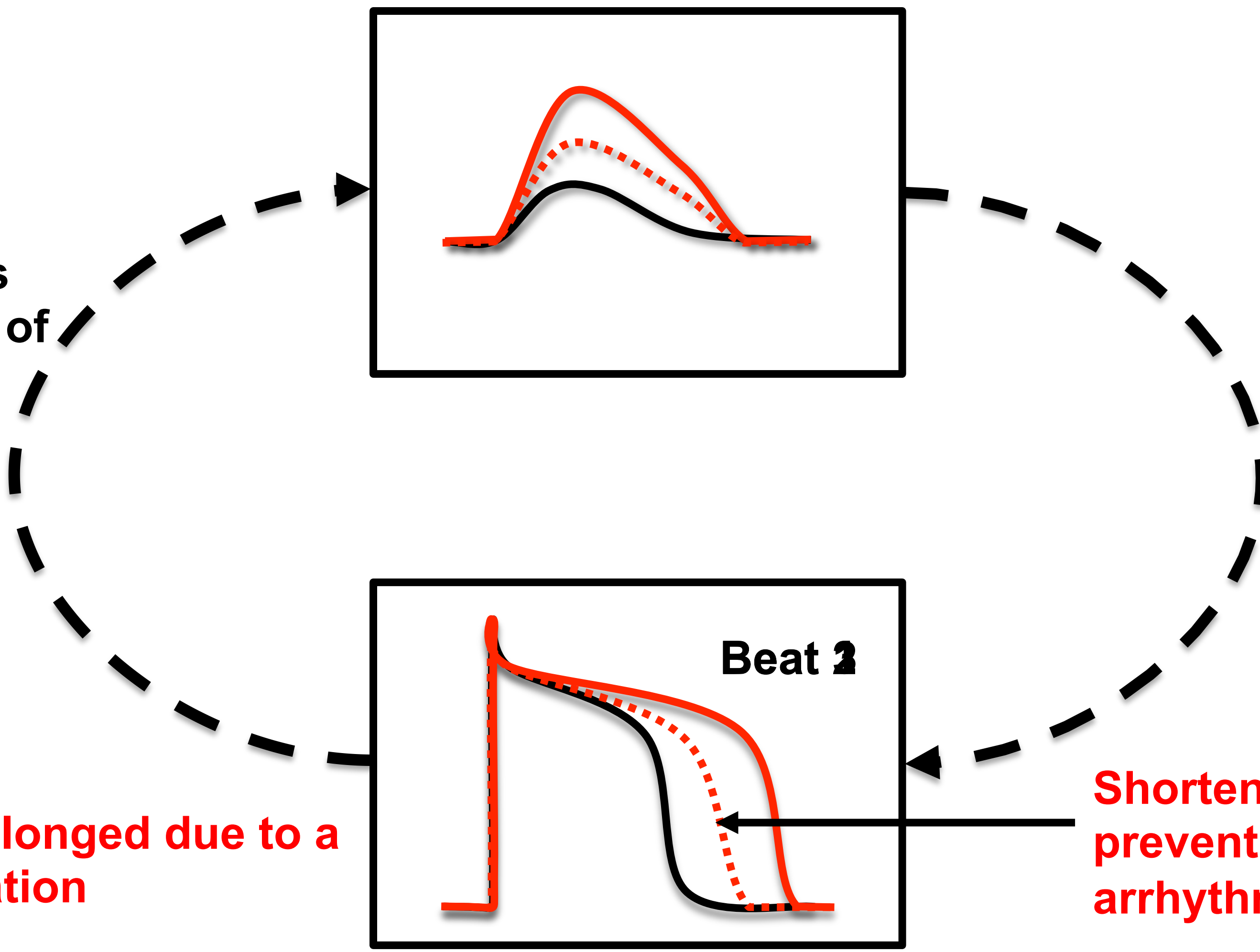
## Test susceptibility to EADs




*Same pattern across multiple species:* Cells with **higher $I_{Ks}$** stabilize the action potential making them **less susceptible** to arrhythmic behavior

# Cardiac currents & Negative Feedback

AP dictates magnitude of current

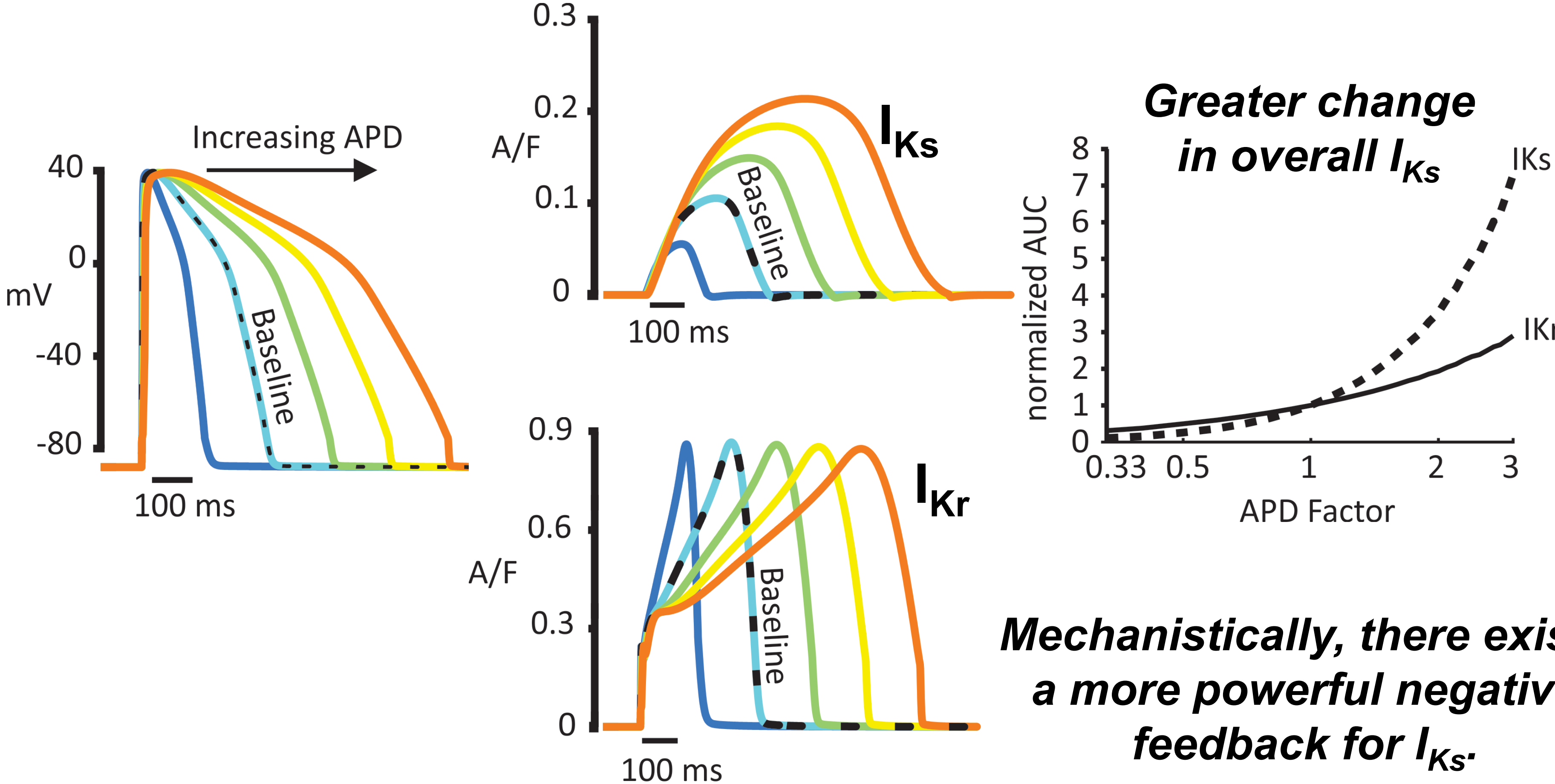



Current dictates AP shape

APD prolonged due to a perturbation

Shortens AP to prevent potential arrhythmia

# AP Clamp Simulation Results

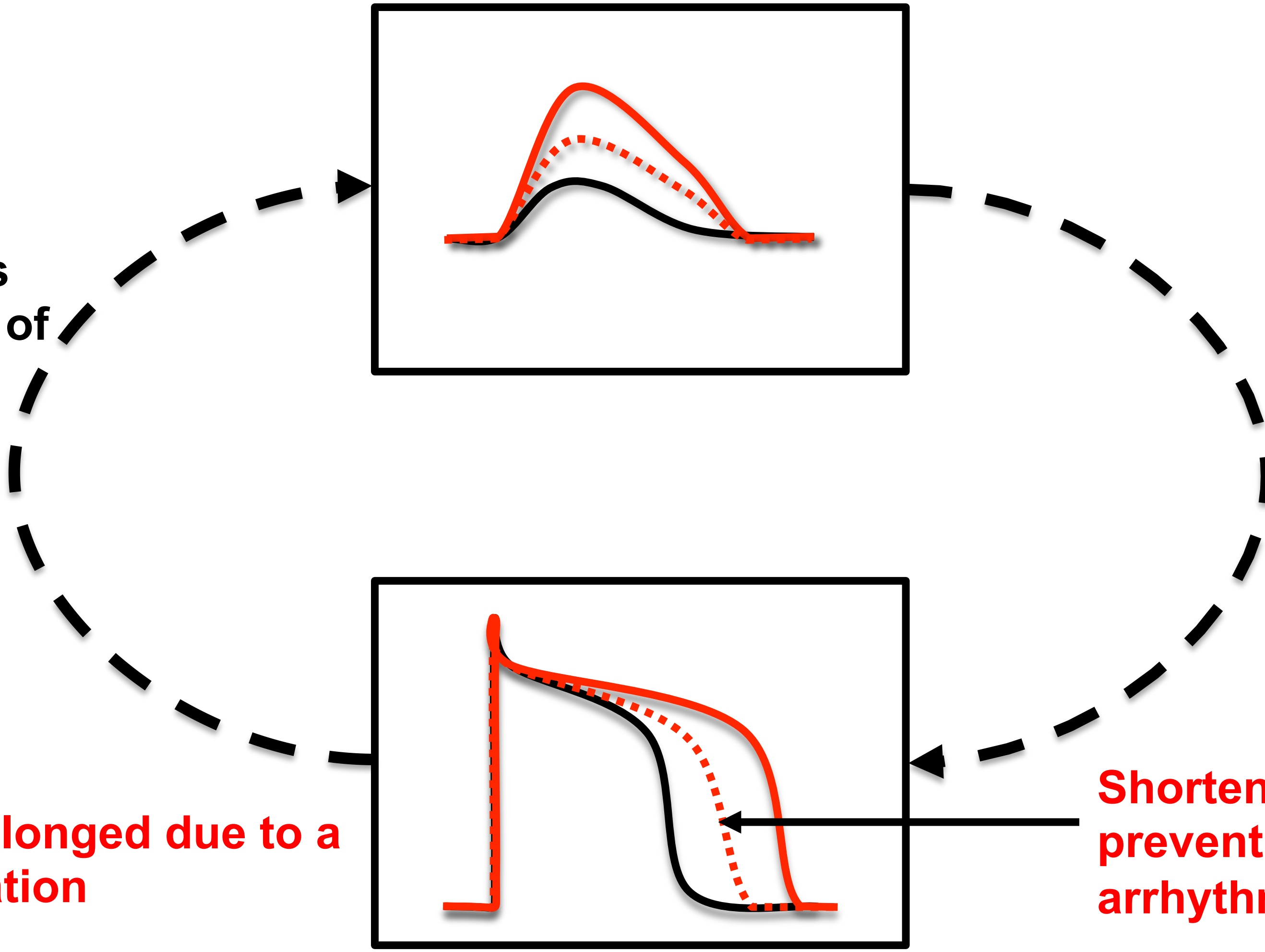



***Greater change in overall $I_{Ks}$***

***Mechanistically, there exists a more powerful negative feedback for $I_{Ks}$.***

# Cardiac currents & Negative Feedback

AP dictates magnitude of current



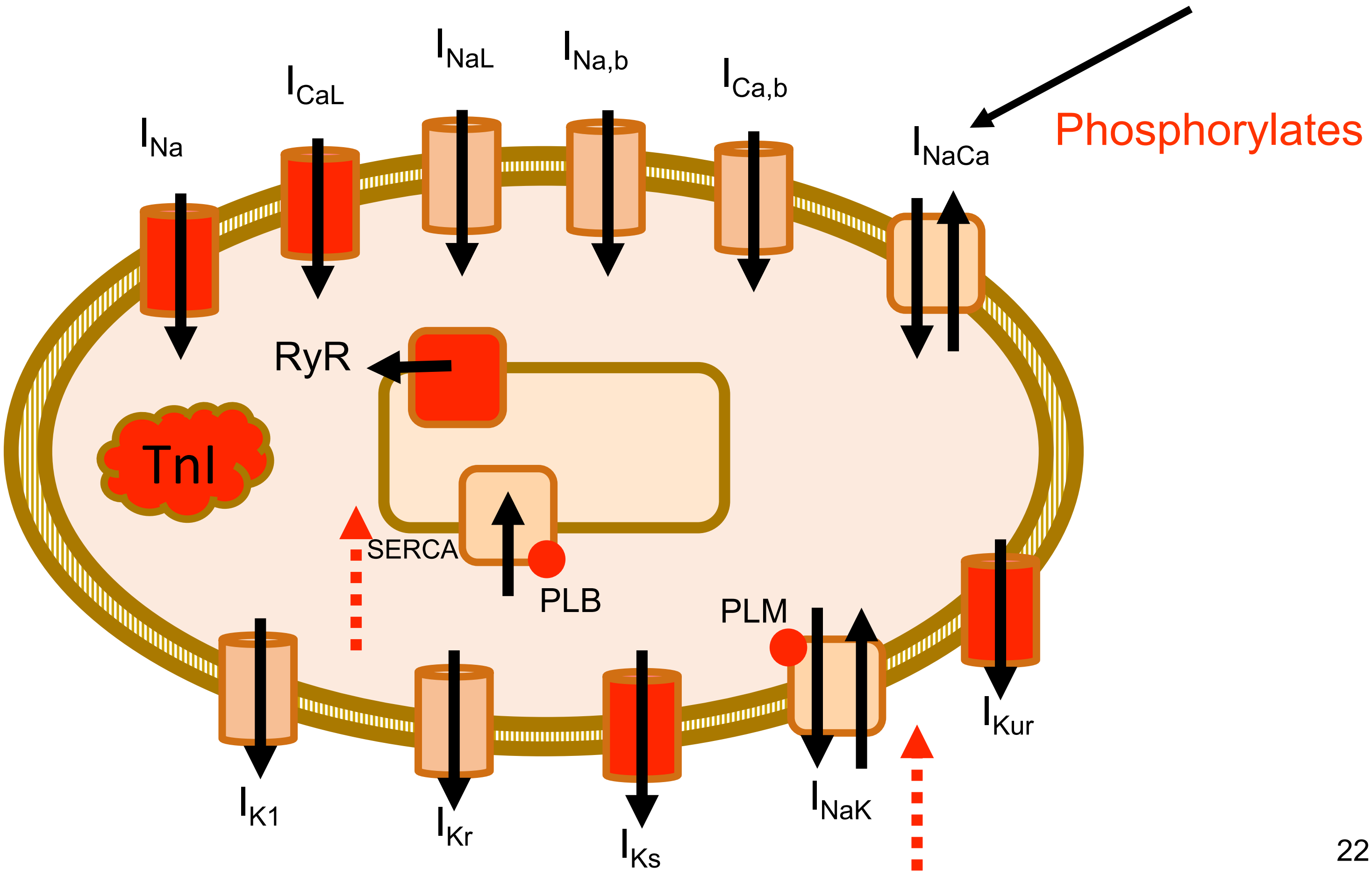
Current dictates AP shape

APD prolonged due to a perturbation

Shortens AP to prevent potential arrhythmia

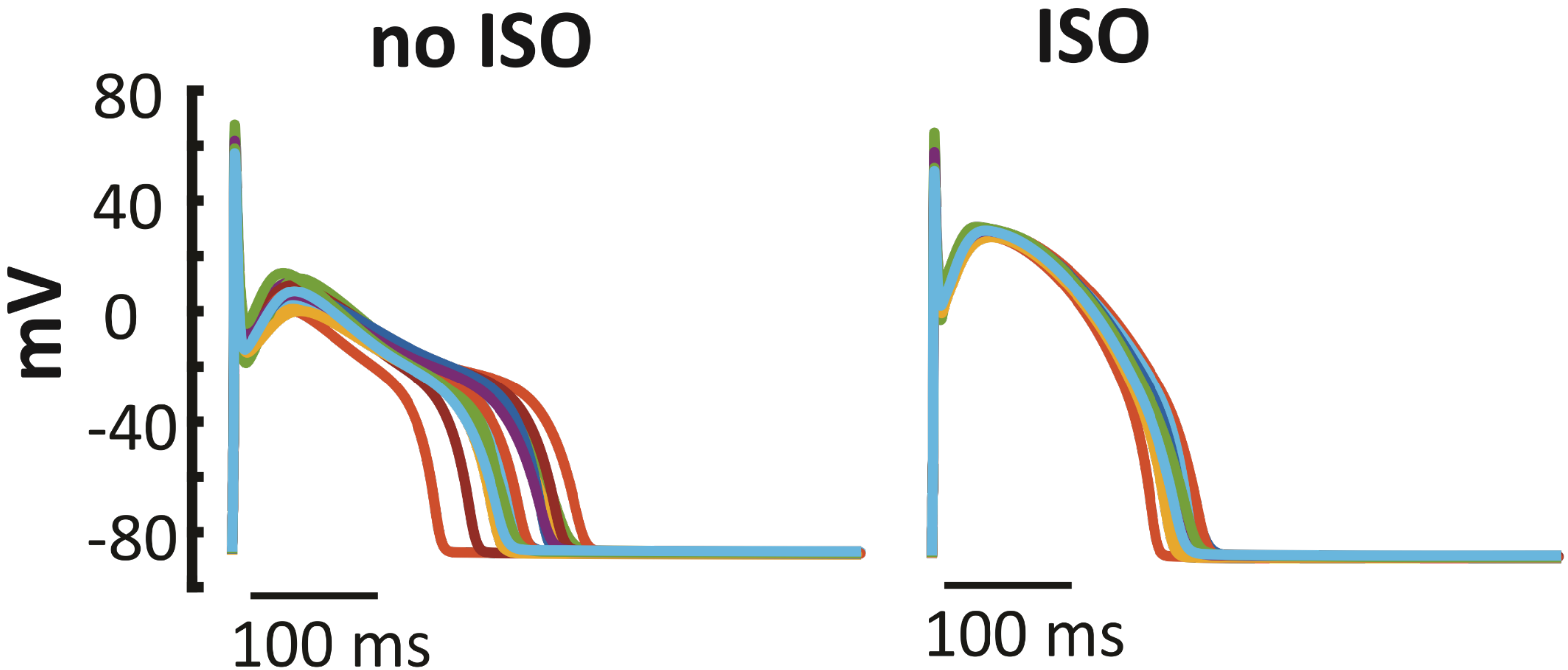
# Is $I_{Ks}$ is upregulation during β-adrenergic activation important for arrhythmia suppression?

Sympathetic Nervous System Activation → β-adrenergic signaling pathway activated → Protein Kinase A (PKA) activated



# Heterogeneous population variability

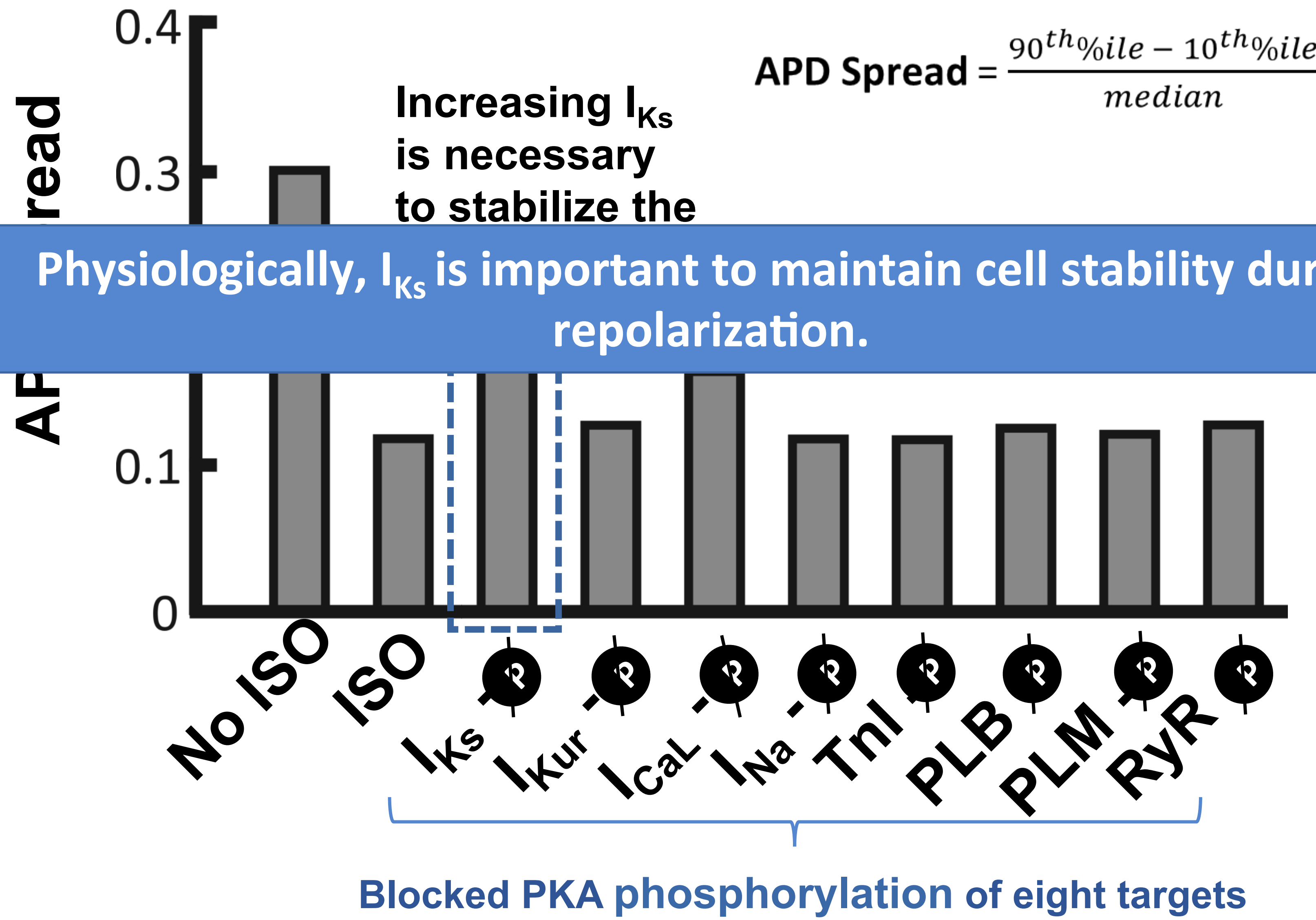
## Randomize parameters that control ion transfer rates




Simulated in the Heijman Canine Electrophysiology + Signaling Model
Heijman et al (2011) *J Mol Cell Cardiol.* 50:863-71.

**Adding β-agonist Isoproterenol (ISO) shortens the AP**

# $I_{Ks}$ phosphorylation is necessary to stabilize the AP during β-adrenergic activation.




**Physiologically, $I_{Ks}$ is important to maintain cell stability during repolarization.**

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