J Physiol 597.17 (2019) pp 4533–4564

A computational model of induced pluripotent stem-cell derived cardiomyocytes incorporating experimental variability from multiple data sources

Divya C. Kernik[1], Stefano Morotti[2], HaoDi Wu[3], Priyanka Garg[3], Henry J. Duff[7], Junko Kurokawa[6], José Jalife[4,5], Joseph C. Wu[3], Eleonora Grandi[2] and Colleen E. Clancy[1]

[1] *Department of Physiology and Membrane Biology, Department of Pharmacology, School of Medicine, University of California, Davis, Davis, CA, USA*
[2] *Department of Pharmacology, School of Medicine, University of California, Davis, CA, USA*
[3] *Stanford Cardiovascular Institute, Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA, USA*
[4] *Department of Internal Medicine, Center for Arrhythmia Research, Cardiovascular Research Center, University of Michigan, Ann Arbor, MI, USA*
[5] *Centro Nacional de Investigaciones Cardiovasculares (CNIC), and CIBERV, Madrid, Spain*
[6] *Department of Bio-Informational Pharmacology, School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, Japan*
[7] *Libin Cardiovascular Institute of Alberta, Faculty of Medicine, University of Calgary, Calgary, AB, Canada*

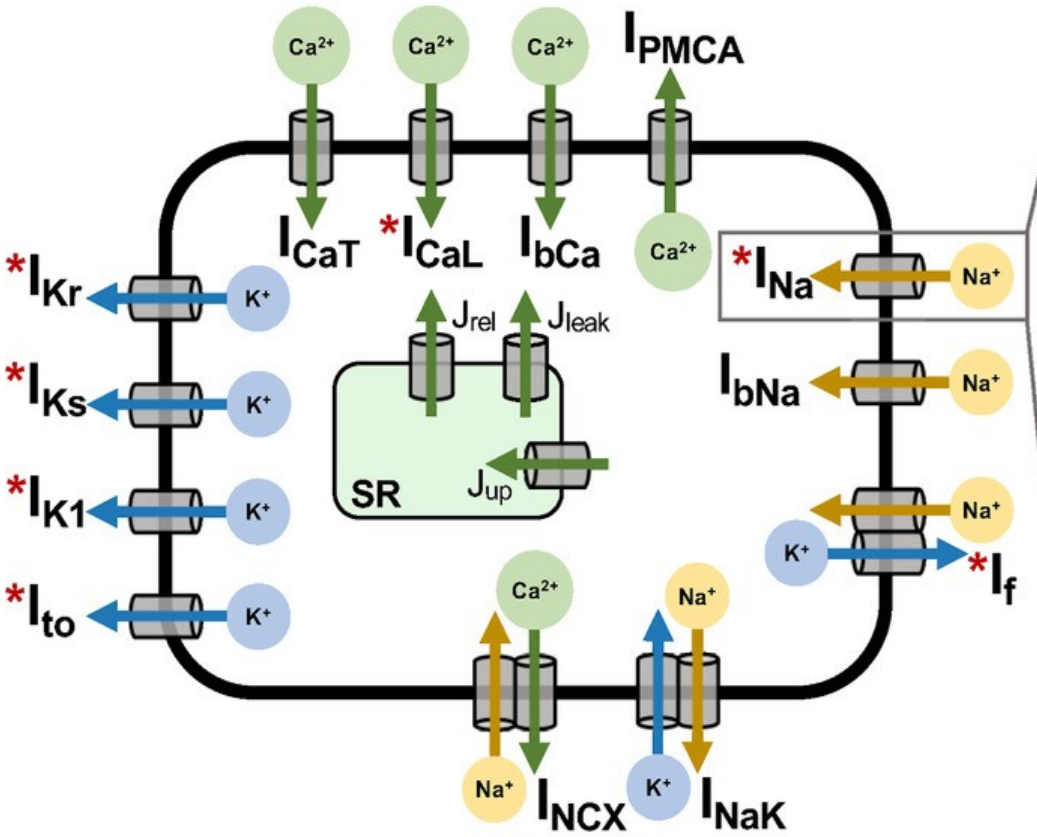
iPSC-CMs have vast variability

Strengths	Limitations
• Recapitulate cellular electrical properties of normal and diseased phenotypes • Preserve patient-specific genotype • Demonstrate expected pharmacological responses of adult cardiomyocytes	• immature phenotype • immature calcium handling • **Vast diversity of phenotypes**

Main Goal:

Use in vitro kinetic data to implement the experimentally informed variation of IPSC-CMs into a computation model to capture the wide range of “normal” iPSC-CM behaviors observed experimentally.

Kernik-Clancy computational iPSC-CM model



Example: *Sodium Current*

For gate x, where x=m, h, or j in I_{Na}

$$C \underset{\beta_x}{\overset{\alpha_x}{\rightleftharpoons}} O$$

$$\alpha_x = x_1 e^{V_m/x_2} \qquad \beta_x = x_3 e^{V_m/x_4}$$

$$x_\infty = \frac{\alpha_x}{\alpha_x+\beta_x} \qquad \tau_x = \frac{1}{\alpha_x+\beta_x} + x_5$$

$$\frac{dx}{dt} = \frac{x_\infty - x}{\tau_x}$$

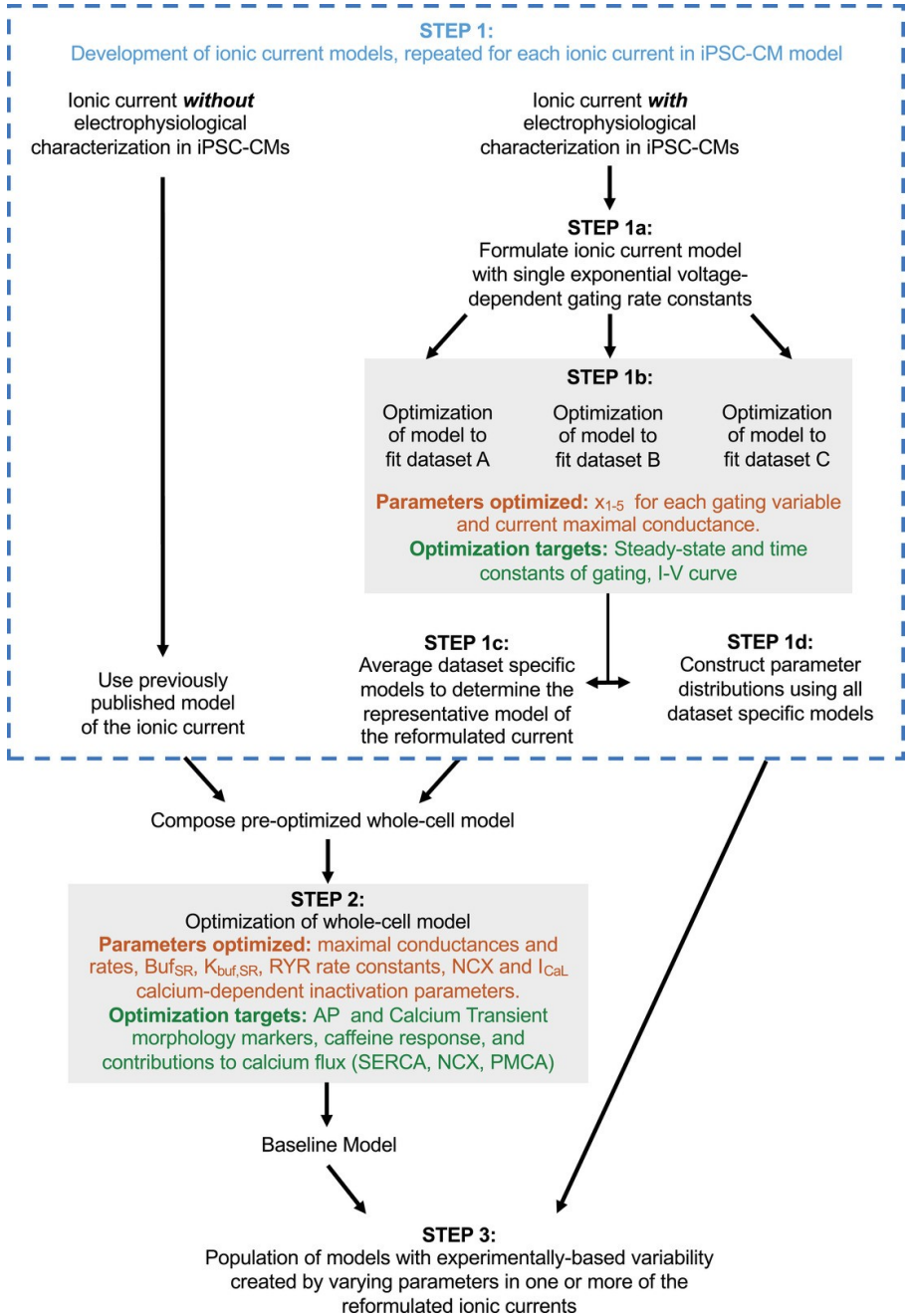
$$I_{Na} = g_{Na} m^3 h j (V_m - E_{Na})$$

C: *Closed State*, **O:** *Open State*

V_m: *Membrane Voltage*

g_{Na}: *Maximal I_{Na} Conductance*

$x_{1\text{-}5}$: *Parameters Optimized*



Example: *Sodium Current*

For gate x, where x=m, h, or j in I_{Na}

$$C \underset{\beta_x}{\overset{\alpha_x}{\rightleftharpoons}} O$$

$$\alpha_x = x_1 e^{V_m/x_2} \qquad \beta_x = x_3 e^{V_m/x_4}$$

$$x_\infty = \frac{\alpha_x}{\alpha_x+\beta_x} \qquad \tau_x = \frac{1}{\alpha_x+\beta_x} + x_5$$

$$\frac{dx}{dt} = \frac{x_\infty - x}{\tau_x}$$

Figure 3. Sodium current (*I*Na) model optimization

Example: *Sodium Current*

For gate x, where x=m, h, or j in I_{Na}

$$C \underset{\beta_x}{\overset{\alpha_x}{\rightleftharpoons}} O$$

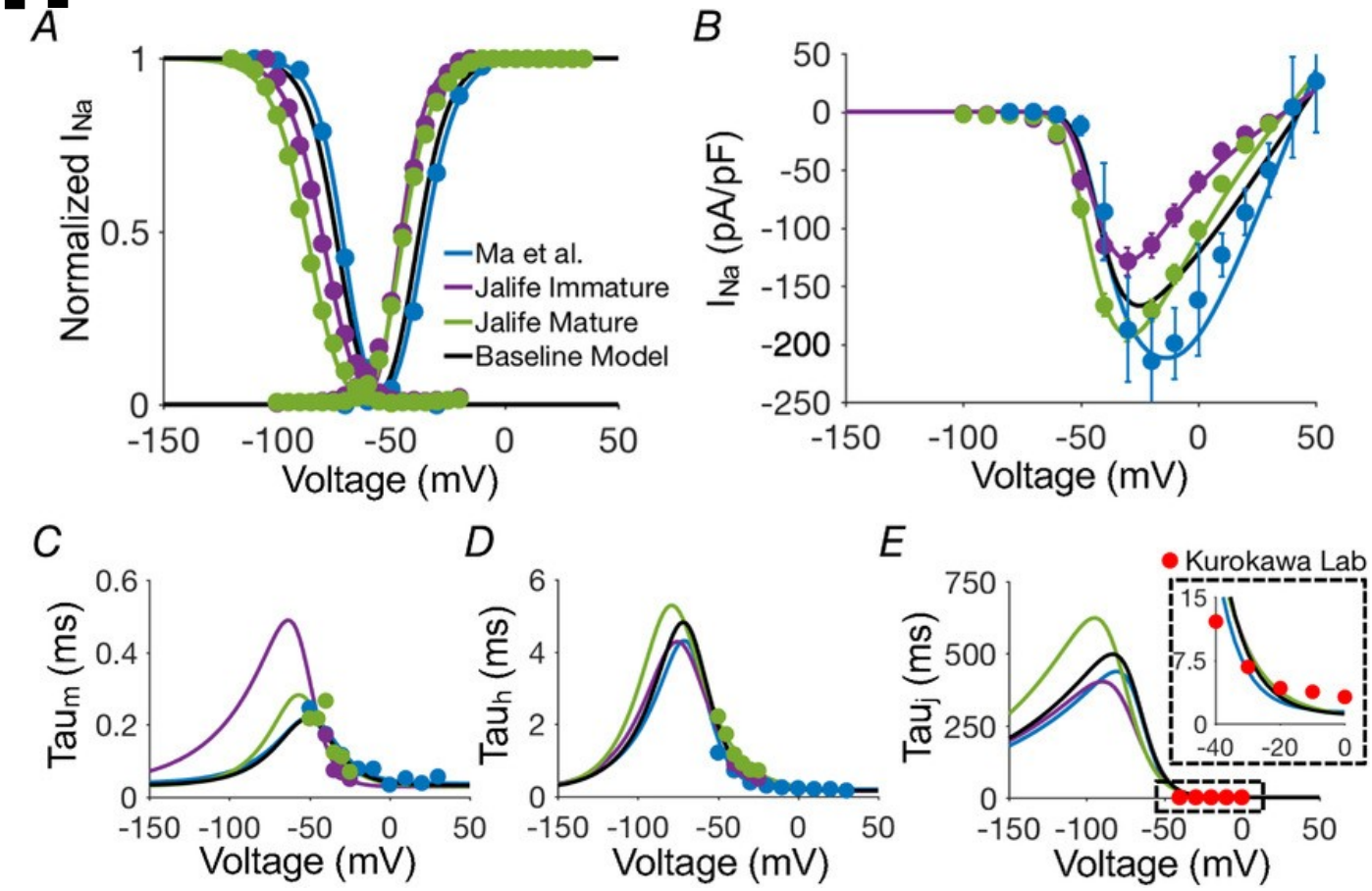
$$\alpha_x = x_1 e^{V_m/x_2} \qquad \beta_x = x_3 e^{V_m/x_4}$$

$$x_\infty = \frac{\alpha_x}{\alpha_x+\beta_x} \qquad \tau_x = \frac{1}{\alpha_x+\beta_x} + x_5$$

$$\frac{dx}{dt} = \frac{x_\infty - x}{\tau_x}$$

$$I_{Na} = g_{Na} m^3 hj(V_m - E_{Na})$$

C: *Closed State*, **O:** *Open State*
V_m: *Membrane Voltage*
g_{Na}: *Maximal I_{Na} Conductance*
$x_{1\text{-}5}$: *Parameters Optimized*



Figures 4 – 9

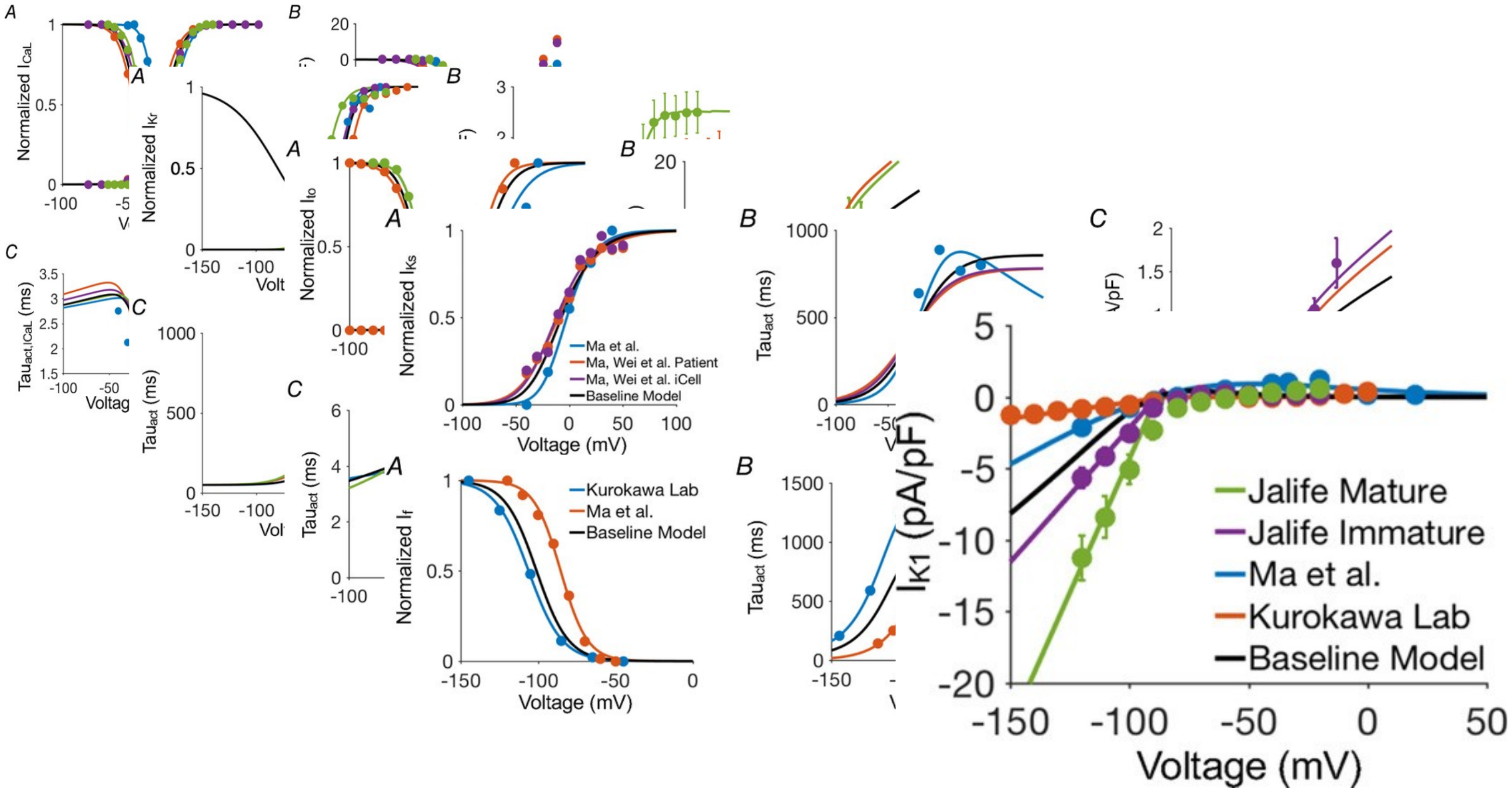
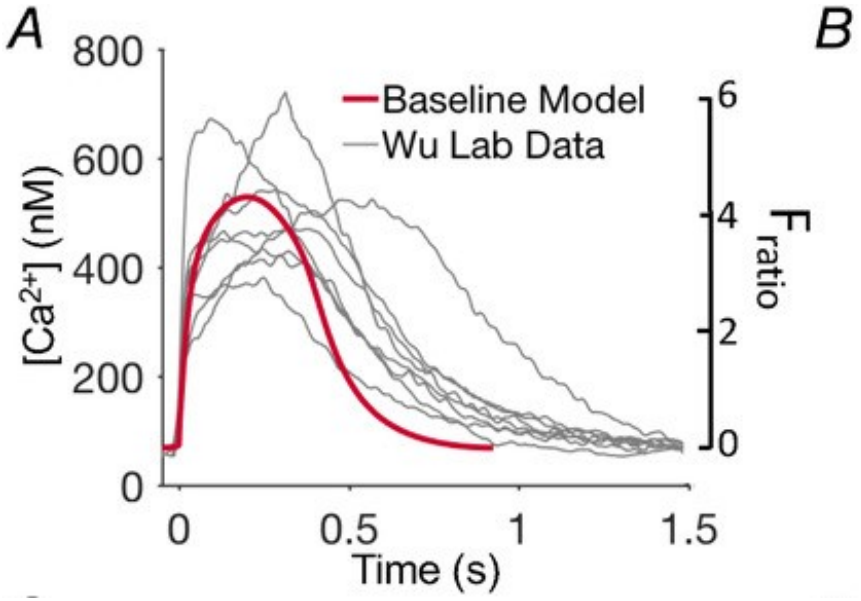

Normalized I_{CaL}
Normalized I_{Kr}
$Tau_{act,ICaL}$ (ms)
Tau_{act} (ms)
Normalized I_{to}
Normalized I_{Ks}
Ma et al.
Ma, Wei et al. Patient
Ma, Wei et al. iCell
Baseline Model
Voltage (mV)
Normalized I_f
Kurokawa Lab
Ma et al.
Baseline Model
Voltage (mV)
Tau_{act} (ms)
Tau_{act} (ms)
I_{K1} (pA/pF)
Jalife Mature
Jalife Immature
Ma et al.
Kurokawa Lab
Baseline Model
Voltage (mV)

Figure 10. Optimization of calcium handling in the iPSC-CM baseline model



Ca^{2+} Transient	Wu Lab *Experimental Data*	Baseline Model
Time to Peak (ms)	245.0 ± 81.3	202.4
Tau Decay (ms)	295.0 ± 108.4	263.6
Diastolic $[Ca^{2+}]$ (nM)	71.8 ± 39.4	68.4
Peak $[Ca^{2+}]$ (nM)	525.2 ± 148.9	528.5

Figure 11. Characterization of the baseline model AP

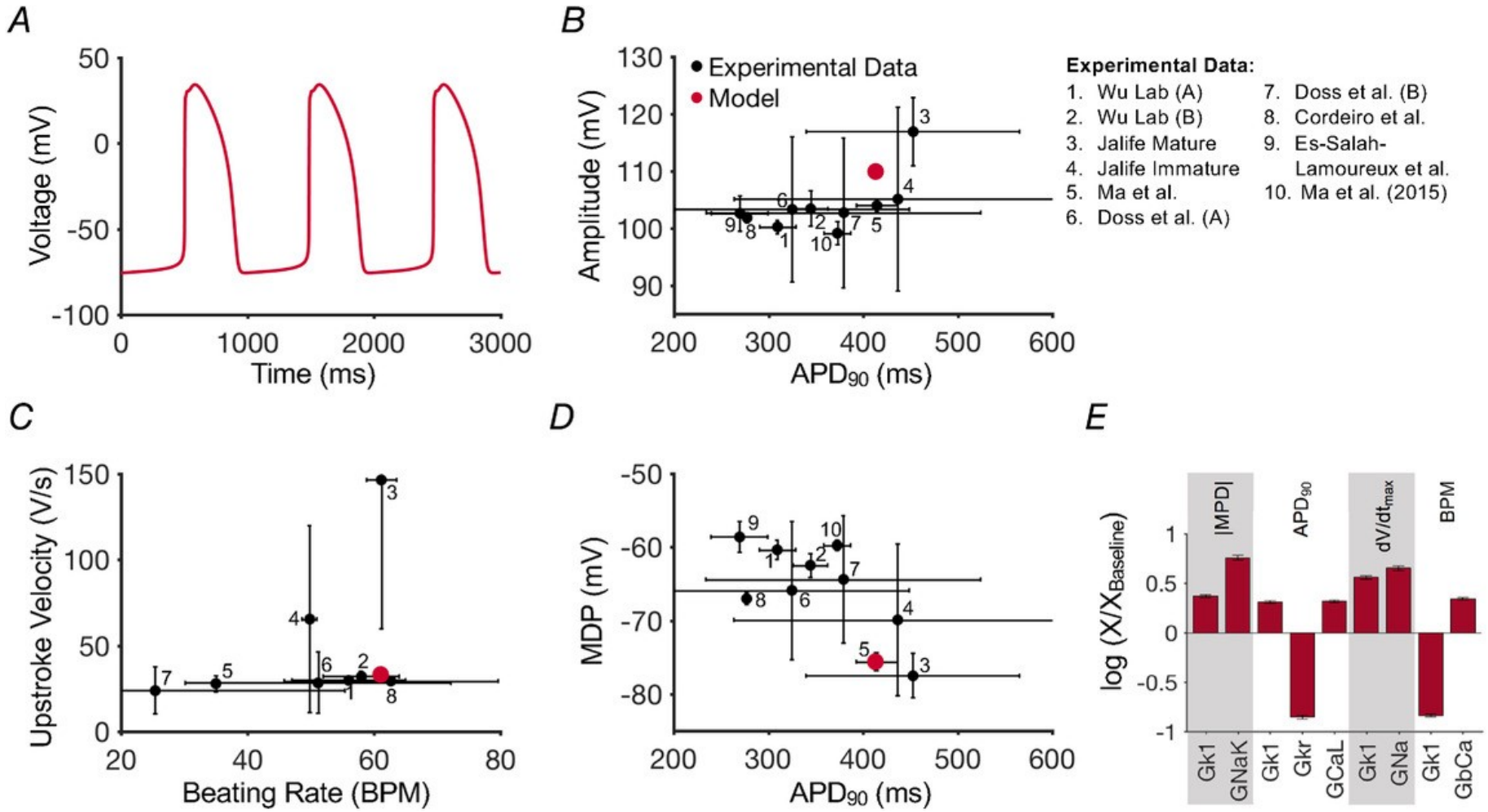


Figure 12. Kinetic variability generated by varying individual current model parameters

Example: *Sodium Current*

For gate x, where x=m, h, or j in I_{Na}

$$C \underset{\beta_x}{\overset{\alpha_x}{\rightleftharpoons}} O$$

$$\alpha_x = x_1 e^{V_m/x_2} \qquad \beta_x = x_3 e^{V_m/x_4}$$

$$x_\infty = \frac{\alpha_x}{\alpha_x+\beta_x} \qquad \tau_x = \frac{1}{\alpha_x+\beta_x} + x_5$$

$$\frac{dx}{dt} = \frac{x_\infty - x}{\tau_x}$$

$$I_{Na} = g_{Na} m^3 hj (V_m - E_{Na})$$

C: *Closed State,* **O:** *Open State*

V_m: *Membrane Voltage*

g_{Na}: *Maximal I_{Na} Conductance*

$x_{1\text{-}5}$: *Parameters Optimized*

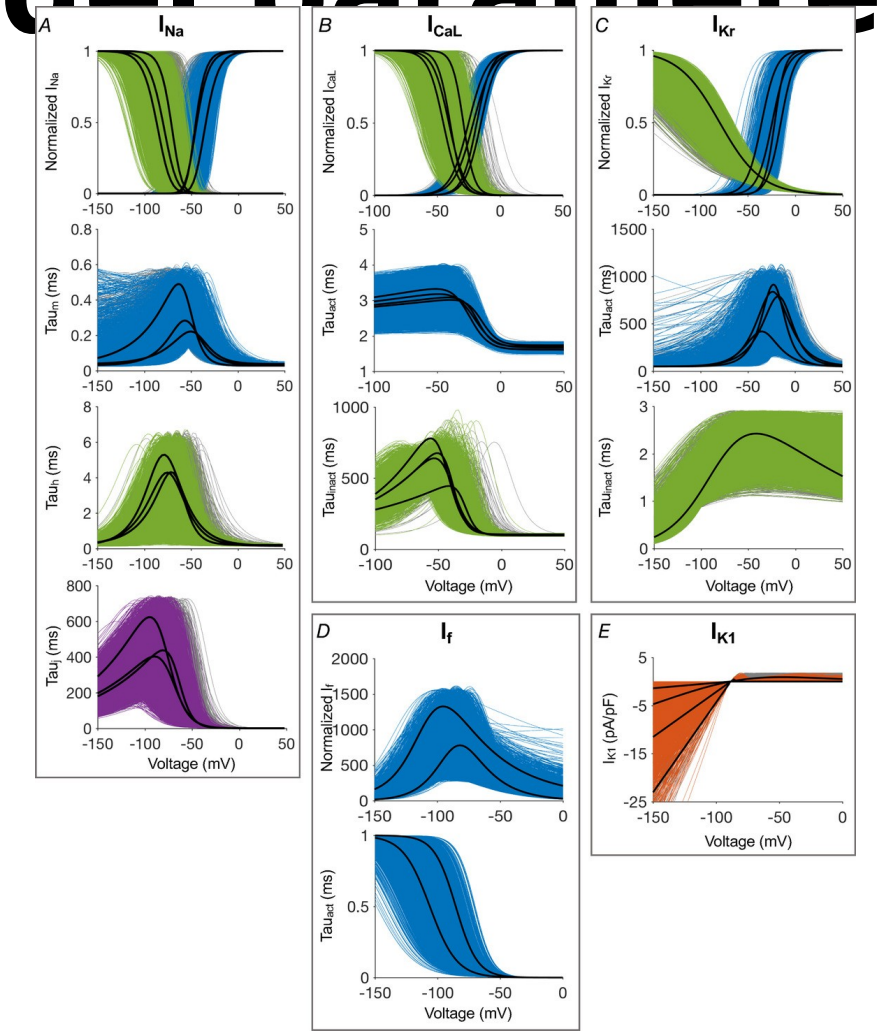


Figure 13. Variation of action potential morphology in model iPSC-CM populations

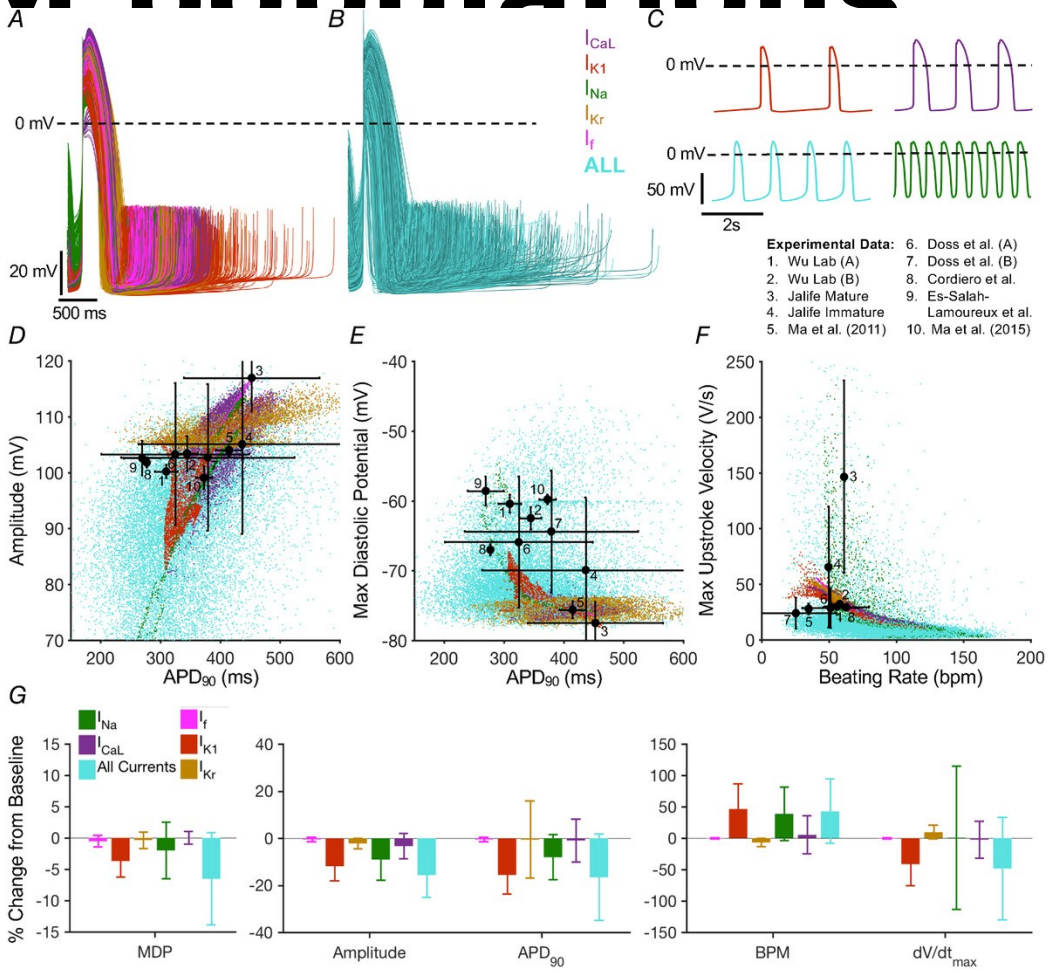


Figure 14. Sample APs showing the effect of ion channel blockers within the model population

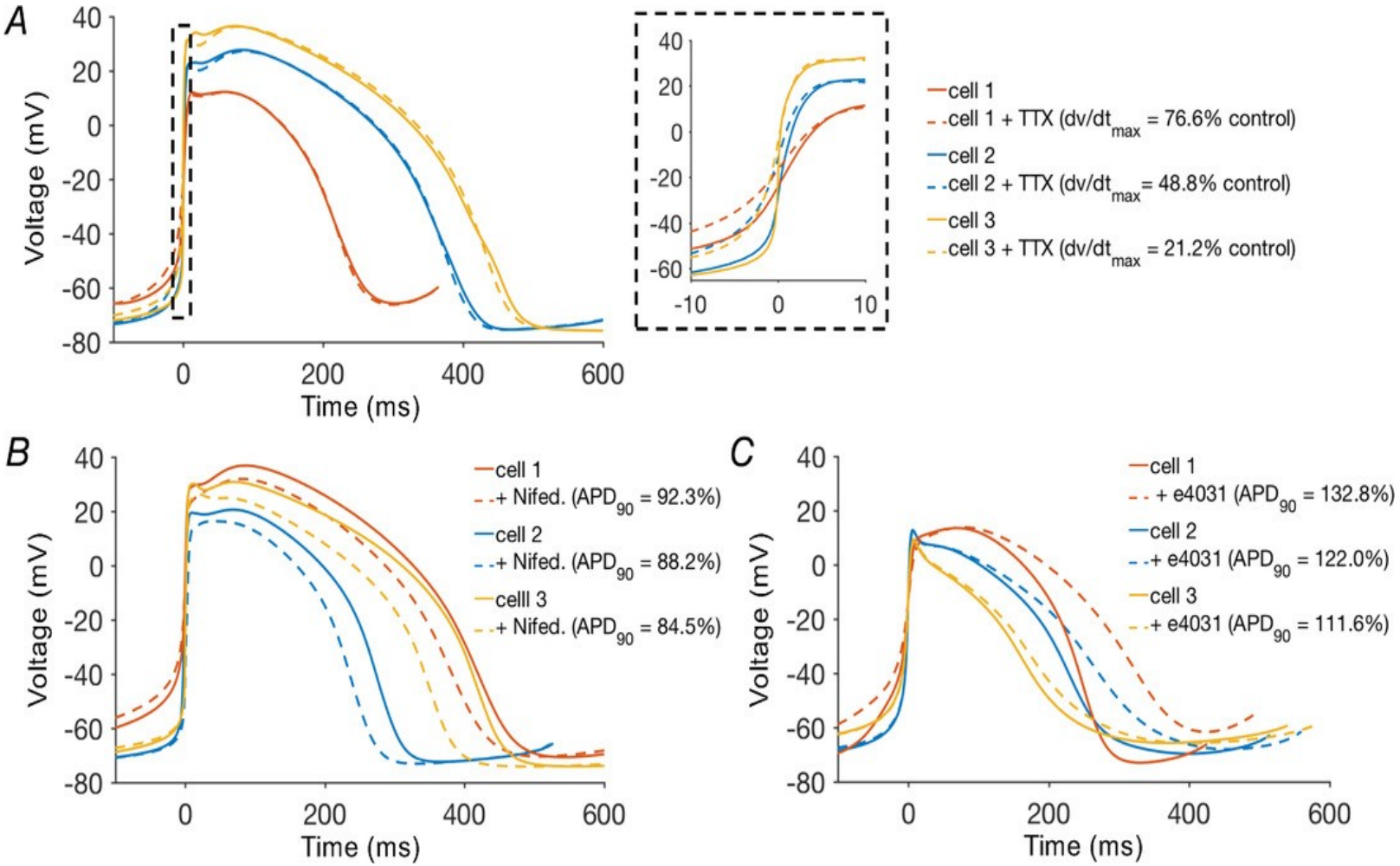


Figure 15. Comparison of immature and mature cellular models

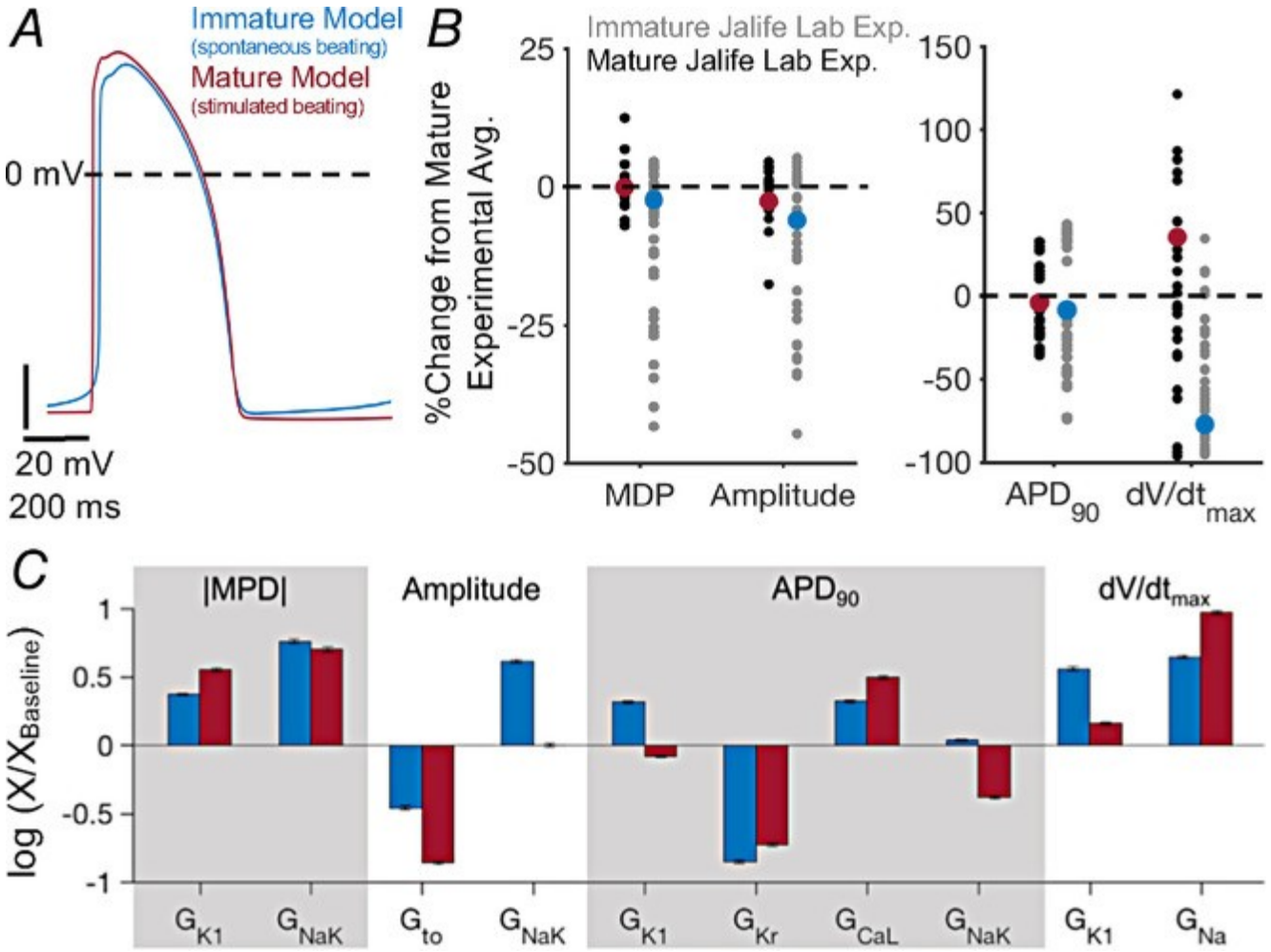
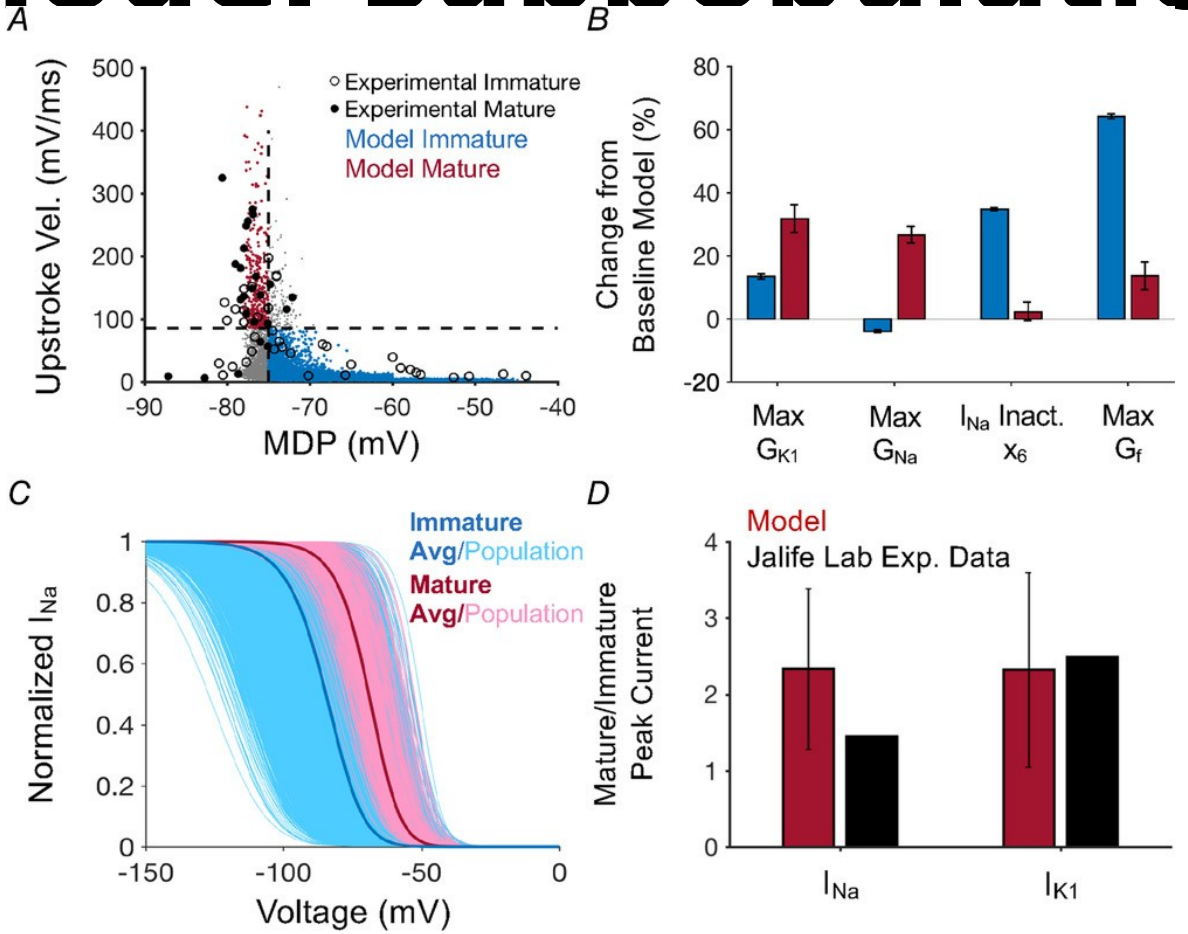


Figure 16. Comparison of mature and immature iPSC-CM model subpopulations



Mature Cells:

- hyperpolarized diastolic potentials
- high upstroke velocity