# SUPPLEMENTARY MATERIALS

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Definitions and Abbreviations

ORd model  O’Hara-Rudy dynamic human ventricular cell model
TP model   ten-Tusscher-Panfilov1 human ventricular cell model
GB model   Grandi-Bers2 human ventricular cell model
AP         action potential
APD        action potential duration (ms)
APDX       action potential duration to X% of resting membrane potential (ms)
CL         pacing cycle length (ms)
DI         diastolic interval, relative to APD90 (ms)
I-V Curve  current voltage relationship
CDI        Ca2+ dependent inactivation of L-type Ca2+ current
VDI        voltage dependent inactivation of L-type Ca2+ current
RyR        ryanodine receptor
V, or Vm   membrane voltage (mV)
R          gas constant, 8314 J/kmol/K
T          temperature, 310° K
F          Faraday constant, 96485 coul/mol
C_M        total membrane capacitance, 1 µF
E_s        reversal potential for ion S (mV)
R_{CG}     ratio between capacitive and geometric membrane areas (= 2)
A_{geo}    geometric area (cm2)
A_{cap}    capacitive area (cm2)
v_S        volume of compartment S (µL)
s_∞        steady state value of gate S
τ_s        time constant of gate S (ms)
τ_{s,fast}, τ_{s,slow} fast/slow time constant of gate S (ms)
A_{s,fast}, A_{s,slow} fraction of channels with gate S undergoing fast/slow process
z_s        valence of ion S
I_{stim}   stimulus current (µA/µF)
I_S        current through ion channel S (µA/µF)
G_{S}      maximum conductance of ion channel S (mS/µF)
K_{m,S}    half-saturation concentration of molecule S (mM)
I_{S}      maximum current carried through ion channel S (µA/µF)
P_S        permeability to ion S (cm/s)
PR_{Q,S} \quad \text{permeability ratio of ion Q to ion S}
\gamma_S \quad \text{activity coefficient of ion S}
J_S \quad \text{ion flux S (mM/ms)}
[S]_Q \quad \text{concentration of ion S, in sub-cellular compartment Q (mM)}
\bar{[S]} \quad \text{maximum concentration of buffer S (mM)}
myo \quad \text{myoplasmic compartment (also abbreviated by small letter “i”)}
ss \quad \text{subspace compartment (representing submembrane space near t-tubules)}
SR \quad \text{sarcoplasmic reticulum}
jsr \quad \text{junctional SR compartment}
nsr \quad \text{network SR compartment}
Y \quad \text{compartment Y (e.g. “i”, “ss”), as in } I_{NaCa} \text{ equations}
CaMK \quad \text{Ca}^{2+}/\text{calmodulin-dependent protein kinase II}
CaMK_{bound} \quad \text{fraction of CaMK binding sites bound to Ca}^{2+}/\text{calmodulin}
CaMK_{trap} \quad \text{fraction of autonomous CaMK binding sites with trapped calmodulin}
CaMK_{active} \quad \text{fraction of active CaMK binding sites}
CaMK_o \quad \text{fraction of active CaMK binding sites at equilibrium}
\alpha_{CaMK}, \beta_{CaMK} \quad \text{(de)phosphorylation rates of CaMK (ms}^{-1})
PLB \quad \text{phospholamban}
\varnothing_{S,CaMK} \quad \text{fraction of channels of type S phosphorylated by CaMK}

\textbf{Currents (µA/µF)}

\begin{align*}
I_{Na} & \quad \text{Na}^+ \text{ current} \\
I_{to} & \quad \text{transient outward K}^+ \text{ current} \\
I_{CaL} & \quad \text{Ca}^{2+} \text{ current through the L-type Ca}^{2+} \text{ channel} \\
I_{CaNa} & \quad \text{Na}^+ \text{ current through the L-type Ca}^{2+} \text{ channel} \\
I_{CaK} & \quad \text{K}^+ \text{ current through the L-type Ca}^{2+} \text{ channel} \\
I_{Kr} & \quad \text{rapid delayed rectifier K}^+ \text{ current} \\
I_{Ks} & \quad \text{slow delayed rectifier K}^+ \text{ current} \\
I_{K1} & \quad \text{inward rectifier K}^+ \text{ current} \\
I_{NaCa,i} & \quad \text{myoplasmic component of Na}^+/\text{Ca}^{2+} \text{ exchange current} \\
I_{NaCa,ss} & \quad \text{subspace component of Na}^+/\text{Ca}^{2+} \text{ exchange current} \\
I_{NaCa} & \quad \text{total Na}^+/\text{Ca}^{2+} \text{ exchange current} \\
I_{NaK} & \quad \text{Na}^+/K^+ \text{ ATPase current} \\
I_{Nab} & \quad \text{Na}^+ \text{ background current} \\
I_{Cab} & \quad \text{Ca}^{2+} \text{ background current} \\
I_{Kb} & \quad \text{K}^+ \text{ background current} \\
I_{pCa} & \quad \text{sarcolemmal Ca}^{2+} \text{ pump current}
\end{align*}

\textbf{Time Dependent Gates}

\begin{align*}
m & \quad \text{activation for fast } I_{Na} \\
h_{fast} & \quad \text{fast development of inactivation for fast } I_{Na} \\
h_{slow} & \quad \text{slow development of inactivation for fast } I_{Na} \\
j & \quad \text{recovery from inactivation for fast } I_{Na} \\
h_{CaMK,fast} & \quad \text{fast development of inactivation for CaMK phosphorylated fast } I_{Na}
\end{align*}
\( h_{\text{CaMK,slow}} \) slow development of inactivation for CaMK phosphorylated fast \( I_{\text{Na}} \)

\( J_{\text{CaMK}} \) recovery from inactivation for CaMK phosphorylated fast \( I_{\text{Na}} \)

\( m_L \) activation for late \( I_{\text{Na}} \)

\( h_L \) inactivation for late \( I_{\text{Na}} \)

\( h_{L,CaMK} \) inactivation for CaMK phosphorylated late \( I_{\text{Na}} \)

\( a \) activation for \( I_{\text{to}} \)

\( i_{\text{fast}} \) fast inactivation for \( I_{\text{to}} \)

\( i_{\text{slow}} \) slow inactivation for \( I_{\text{to}} \)

\( a_{\text{CaMK}} \) activation for CaMK phosphorylated \( I_{\text{to}} \)

\( i_{\text{CaMK,fast}} \) fast inactivation for CaMK phosphorylated \( I_{\text{to}} \)

\( i_{\text{CaMK,slow}} \) slow inactivation for CaMK phosphorylated \( I_{\text{to}} \)

\( d \) activation for \( I_{\text{CaL}} \)

\( f_{\text{fast}} \) fast voltage dependent inactivation for \( I_{\text{CaL}} \)

\( f_{\text{slow}} \) slow voltage dependent inactivation for \( I_{\text{CaL}} \)

\( f_{\text{Ca,fast}} \) fast development of \( Ca^{2+} \) dependent inactivation for \( I_{\text{CaL}} \)

\( f_{\text{Ca,slow}} \) slow development of \( Ca^{2+} \) dependent inactivation for \( I_{\text{CaL}} \)

\( j_{\text{Ca}} \) recovery from \( Ca^{2+} \) dependent inactivation for \( I_{\text{CaL}} \)

\( n \) fraction in \( Ca^{2+} \) dependent inactivation mode for \( I_{\text{CaL}} \)

\( f_{\text{CaMK,fast}} \) fast development of \( Ca^{2+} \) dependent inactivation for CaMK phosphorylated \( I_{\text{CaL}} \)

\( f_{\text{Ca,CaMK,fast}} \) slow development of \( Ca^{2+} \) dependent inactivation for CaMK phosphorylated \( I_{\text{CaL}} \)

\( x_{r,\text{fast}} \) fast activation/deactivation for \( I_{\text{Kr}} \)

\( x_{r,\text{slow}} \) slow activation/deactivation for \( I_{\text{Kr}} \)

\( x_1 \) activation for \( I_{\text{Ks}} \)

\( x_2 \) deactivation for \( I_{\text{Ks}} \)

\( x_{K1} \) inactivation for \( I_{\text{K1}} \)

\( J_{\text{diff,Na}} \) diffusion of \( Na^+ \) from subspace to myoplasm

\( J_{\text{diff,K}} \) diffusion of \( K^+ \) from subspace to myoplasm

\( J_{\text{diff,Ca}} \) diffusion of \( Ca^{2+} \) from subspace to myoplasm

\( J_{\text{rel,LP}} \) non-phosphorylated \( Ca^{2+} \) release, via ryanodine receptors, from jsr to myoplasm

\( J_{\text{rel,CalM}} \) CaMK phosphorylated \( Ca^{2+} \) release, via ryanodine receptors, from jsr to myoplasm

\( J_{\text{rel}} \) total \( Ca^{2+} \) release, via ryanodine receptors, from jsr to myoplasm

\( J_{\text{up,LP}} \) non-phosphorylated \( Ca^{2+} \) uptake, via SERCA pump, from myoplasm to nsr

\( J_{\text{up,CalM}} \) CaMK phosphorylated \( Ca^{2+} \) uptake, via SERCA pump, from myoplasm to nsr

\( J_{\text{up}} \) total \( Ca^{2+} \) uptake, via SERCA pump, from myoplasm to nsr

\( J_{\text{tr}} \) \( Ca^{2+} \) translocation from nsr to jsr

**Calcium Buffers**

| CMDN   | calmodulin, \( Ca^{2+} \) buffer in myoplasm |
|--------|-----------------------------------------------|
| TRPN   | troponin, \( Ca^{2+} \) buffer in myoplasm     |
| BSR    | anionic SR binding sites for \( Ca^{2+} \) in subspace |
| BSL    | anionic sarcolemmal binding sites for \( Ca^{2+} \) buffer in subspace |
| CSQN   | calsequestrin, \( Ca^{2+} \) buffer in JSR      |
$\beta_Y$ buffer factor for compartment Y

**ORd Human Model Basic Parameters**

**Stimulus**

amplitude = $-80.0 \frac{\mu A}{\mu F}$, duration = 0.5 ms

For charge conservation sake, stimulus has K$^+$ identity as described by Hund et al.$^3$.

**External Concentrations**

$[\text{Na}^+]_o = 140 \text{ mM}$
$[\text{Ca}^{2+}]_o = 1.8 \text{ mM}$
$[\text{K}^+]_o = 5.4 \text{ mM}$

**ORd Model Initial Conditions**

Single endocardial cell, at 1 Hz steady state, in diastole. There are 41 state variables.

- $V = -87.84 \text{ mV}$
- $[\text{Na}^+]_i = 7.23 \text{ mM}$
- $[\text{Na}^+]_{ss} = 7.23 \text{ mM}$
- $[\text{K}^+]_i = 143.79 \text{ mM}$
- $[\text{K}^+]_{ss} = 143.79 \text{ mM}$
- $[\text{Ca}^{2+}]_i = 8.54 \cdot 10^{-5} \text{ mM}$
- $[\text{Ca}^{2+}]_{ss} = 8.43 \cdot 10^{-5} \text{ mM}$
- $[\text{Ca}^{2+}]_{n_{sr}} = 1.61 \text{ mM}$
- $[\text{Ca}^{2+}]_{j_{sr}} = 1.56 \text{ mM}$
- $m = 0.0074621$
- $h_{fast} = 0.692591$
- $h_{slow} = 0.692574$
- $j = 0.692477$
- $h_{CaMK,slow} = 0.448501$
- $j_{CaMK} = 0.692413$
- $m_l = 0.000194015$
- $h_l = 0.496116$
- $h_{L,CaMK} = 0.265885$
- $a = 0.00101185$
- $i_{fast} = 0.999542$
- $i_{slow} = 0.589579$
- $a_{CaMK} = 0.000515567$
- $i_{CaMK,fast} = 0.999542$
- $i_{CaMK,slow} = 0.641861$
- $d = 2.43015 \cdot 10^{-9}$
- $f_{fast} = 1.0$
- $f_{slow} = 0.910671$
- $f_{Ca,fast} = 1.0$
- $f_{Ca,slow} = 0.99982$
- $j_{Ca} = 0.999977$
- $n = 0.00267171$
- $f_{Ca,CA MK,fast} = 1.0$
- $x_{r,fast} = 8.26608 \cdot 10^{-6}$
- $x_{r,slow} = 0.453268$
- $x_{s1} = 0.270492$
- $x_{s2} = 0.0001963$
- $x_{k1} = 0.996801$
- $J_{rel,NP} = 2.53943 \cdot 10^{-5} \text{ mM/ms}$
- $J_{rel,CaMK} = 3.17262 \cdot 10^{-7} \text{ mM/ms}$
- $CaMK_{trap} = 0.0124065$

**Reversal Potentials**
\[
E_{\text{Na}} = \frac{RT}{F} \cdot \ln \left( \frac{[\text{Na}^+]_o}{[\text{Na}^+]_i} \right)
\]
\[
E_{\text{K}} = \frac{RT}{F} \cdot \ln \left( \frac{[\text{K}^+]_o}{[\text{K}^+]_i} \right)
\]
\[
PR_{\text{Na,K}} = 0.01833, \quad E_{\text{Ks}} = \frac{RT}{F} \cdot \ln \left( \frac{[\text{K}^+]_o + PR_{\text{Na,K}} \cdot [\text{Na}^+]_o}{[\text{K}^+]_i + PR_{\text{Na,K}} \cdot [\text{Na}^+]_i} \right)
\]

Cell Geometry

Cell geometry was approximated by a cylinder. Cell length (L) was about ten times longer than the radius (Forbes and Sperelakis)\(^4\).

\[L = 0.01 \text{ cm}, \quad r = 0.0011 \text{ cm}\]

\[
v_{\text{cell}} = \pi \cdot r^2 \cdot L = 38 \cdot 10^{-6} \mu \text{L}
\]

\[
A_{\text{geo}} = 2 \pi \cdot r^2 + 2 \pi \cdot r \cdot L = 0.767 \cdot 10^{-4} \text{ cm}^2
\]

\[
A_{\text{cap}} = R_{\text{CG}} \cdot A_{\text{geo}} = 2 \cdot A_{\text{geo}} = 1.534 \cdot 10^{-4} \text{ cm}^2
\]

\[
v_{\text{myo}} = 0.68 \cdot v_{\text{cell}} = 25.84 \cdot 10^{-6} \mu \text{L}
\]

\[
v_{\text{nsr}} = 0.0552 \cdot v_{\text{cell}} = 2.098 \cdot 10^{-6} \mu \text{L}
\]

\[
v_{\text{jsr}} = 0.0048 \cdot v_{\text{cell}} = 0.182 \cdot 10^{-6} \mu \text{L}
\]

\[
v_{\text{ss}} = 0.02 \cdot v_{\text{cell}} = 0.76 \cdot 10^{-6} \mu \text{L}
\]

ORd Human Model Currents

Sodium Current (\(I_{\text{Na}}\))

\[
m_{\infty} = \frac{1}{1 + \exp \left( \frac{-(V + 39.57)}{9.871} \right)}
\]

\[
\tau_m = \frac{6.765 \cdot \exp \left( \frac{V + 11.64}{34.77} \right) + 8.552 \cdot \exp \left( \frac{-(V + 77.42)}{5.955} \right)}{1}
\]

\[
\frac{dm}{dt} = \frac{m_{\infty} - m}{\tau_m}
\]

\[
h_{\infty} = \frac{1}{1 + \exp \left( \frac{V + 82.9}{6.086} \right)}
\]

\[
\tau_{h,\text{fast}} = \frac{1}{1.432 \cdot 10^{-5} \cdot \exp \left( \frac{-(V + 1.196)}{6.285} \right) + 6.149 \cdot \exp \left( \frac{V + 0.5096}{20.27} \right)}
\]

\[
\tau_{h,\text{slow}} = \frac{1}{0.009764 \cdot \exp \left( \frac{-(V + 17.95)}{28.05} \right) + 0.3343 \cdot \exp \left( \frac{V + 5.730}{56.66} \right)}
\]

\[A_{h,\text{fast}} = 0.99, \quad A_{h,\text{slow}} = 0.01\]

\[
\frac{dh_{\text{fast}}}{dt} = \frac{h_{\infty} - h_{\text{fast}}}{\tau_{h,\text{fast}}}
\]
\[
\begin{align*}
\frac{dh_{\text{slow}}}{dt} &= \frac{h_\infty - h_{\text{slow}}}{\tau_{h,\text{slow}}} \\
h &= A_{h,\text{fast}} \cdot h_{\text{fast}} + A_{h,\text{slow}} \cdot h_{\text{slow}} \\
j_\infty &= h_{\infty} \\
\tau_j &= 2.038 + \frac{1}{0.02136 \cdot \exp \left( \frac{-(V + 100.6)}{8.281} \right) + 0.3052 \cdot \exp \left( \frac{V + 0.9941}{38.45} \right)} \\
\frac{dj}{dt} &= \frac{j_\infty - j}{\tau_j} \\
h_{\text{CaMK},\infty} &= \frac{1}{1 + \exp \left( \frac{V + 99.1}{6.086} \right)} \\
\tau_{h,\text{CaMK,slow}} &= 3.0 \cdot \tau_{h,\text{slow}} \\
A_{h,\text{CaMK,fast}} &= A_{h,\text{fast}}, \quad A_{h,\text{CaMK,slow}} = A_{h,\text{slow}} \\
h_{\text{CaMK,fast}} &= h_{\text{fast}} \\
\frac{dh_{\text{CaMK,slow}}}{dt} &= \frac{h_{\text{CaMK,\infty}} - h_{\text{CaMK,slow}}}{\tau_{h,\text{CaMK,slow}}} \\
h_{\text{CaMK}} &= A_{h,\text{CaMK,fast}} \cdot h_{\text{CaMK,fast}} + A_{h,\text{CaMK,slow}} \cdot h_{\text{CaMK,slow}} \\
j_{\text{CaMK,\infty}} &= j_\infty \\
\tau_{j,\text{CaMK}} &= 1.46 \cdot \tau_j \\
\frac{dj_{\text{CaMK}}}{dt} &= \frac{j_{\text{CaMK,\infty}} - j_{\text{CaMK}}}{\tau_{j,\text{CaMK}}} \\
K_{m,\text{CaMK}} &= 0.15, \quad \phi_{\text{INa,CaMK}} = \frac{1}{1 + \frac{K_{m,\text{CaMK}}}{CaMK_{\text{active}}}} \\
G_{\text{Na,fast}} &= 75 \text{ mS/\mu F} \\
I_{\text{Na,fast}} &= G_{\text{Na,fast}} \cdot (V - E_{\text{Na}}) \cdot m^3 \cdot \left( (1 - \phi_{\text{INa,CaMK}}) \cdot h \cdot j + \phi_{\text{INa,CaMK}} \cdot h_{\text{CaMK}} \cdot j_{\text{CaMK}} \right) \\
m_{L,\infty} &= \frac{1}{1 + \exp \left( \frac{-(V + 42.85)}{5.264} \right)} \\
\tau_{m,L} &= \tau_m \\
\frac{dm_L}{dt} &= \frac{m_{L,\infty} - m_L}{\tau_{m,L}} \\
h_{\infty} &= \frac{1}{1 + \exp \left( \frac{V + 87.61}{7.488} \right)} \\
\tau_{h,L} &= 200 \text{ ms} \\
\frac{dh_L}{dt} &= \frac{h_{\infty} - h_L}{\tau_{h,L}} \\
h_{\text{L,CaMK,\infty}} &= \frac{1}{1 + \exp \left( \frac{V + 93.81}{7.488} \right)} \\
\tau_{h,\text{L,CaMK}} &= 3 \cdot \tau_{h,L} \\
\frac{dh_{\text{L,CaMK}}}{dt} &= \frac{h_{\text{L,CaMK,\infty}} - h_{\text{L,CaMK}}}{\tau_{h,\text{L,CaMK}}} 
\end{align*}
\]
\[ K_{m, \text{CaMK}} = 0.15, \quad \varphi_{\text{INaL, CaMK}} = \frac{1}{1 + \frac{K_{m, \text{CaMK}}}{\text{CaMK}_{\text{active}}}} \]

\[ \overline{\varphi}_{\text{INa, late}} = 0.0075 \text{ mS/\mu F} \]

\[ I_{\text{INa, late}} = \overline{\varphi}_{\text{INa, late}} \cdot (V - E_{\text{Na}}) \cdot m_L \cdot \left( (1 - \varphi_{\text{INaL, CaMK}}) \cdot h_L + \varphi_{\text{INaL, CaMK}} \cdot h_{L, \text{CaMK}} \right) \]

\[ I_{\text{Na}} = I_{\text{Na, fast}} + I_{\text{Na, late}} \]

**Transient Outward Potassium Current (\( I_{t_o} \))**

\[ a_{\infty} = \frac{1}{1 + \exp \left( \frac{-(V - 14.34)}{14.82} \right)} \]

\[ \tau_a = \frac{1}{1.0515} - \frac{1}{1.2089 \cdot \left( 1 + \exp \left( \frac{-(V - 18.41)}{29.38} \right) \right) + \frac{3.5}{1 + \exp \left( \frac{V + 100}{29.38} \right)}} \]

\[ \frac{da}{dt} = \frac{a_{\infty} - a}{\tau_a} \]

\[ i_{\infty} = \frac{1}{1 + \exp \left( \frac{V + 43.94}{5.711} \right)} \]

\[ \tau_{i, \text{fast}} = 4.562 + \frac{1}{0.3933 \cdot \exp \left( \frac{-(V + 100)}{100} \right) + 0.08004 \cdot \exp \left( \frac{V + 50}{16.59} \right)} \]

\[ \tau_{i, \text{slow}} = 23.62 + \frac{1}{0.001416 \cdot \exp \left( \frac{-(V + 96.52)}{59.05} \right) + 1.7808 \cdot 10^{-8} \cdot \exp \left( \frac{V + 114.1}{8.079} \right)} \]

\[ A_{i, \text{fast}} = \frac{1}{1 + \exp \left( \frac{V - 213.6}{151.2} \right)}, \quad A_{i, \text{slow}} = 1 - A_{i, \text{fast}} \]

\[ \frac{di_{\text{fast}}}{dt} = \frac{i_{\infty} - i_{\text{fast}}}{\tau_{i, \text{fast}}} \]

\[ \frac{di_{\text{slow}}}{dt} = \frac{i_{\infty} - i_{\text{slow}}}{\tau_{i, \text{slow}}} \]

\[ i = A_{i, \text{fast}} \cdot i_{\text{fast}} + A_{i, \text{slow}} \cdot i_{\text{slow}} \]

\[ a_{\text{CaMK, \infty}} = \frac{1}{1 + \exp \left( \frac{-(V - 24.34)}{14.82} \right)} \]

\[ \tau_{a, \text{CaMK}} = \tau_a \]

\[ \frac{da_{\text{CaMK}}}{dt} = \frac{a_{\text{CaMK, \infty}} - a_{\text{CaMK}}}{\tau_{a, \text{CaMK}}} \]

\[ i_{\text{CaMK, \infty}} = i_{\infty} \]

\[ \delta_{\text{CaMK, develop}} = 1.354 + \frac{10^{-4}}{\exp \left( \frac{V - 167.4}{15.89} \right) + \exp \left( \frac{-(V - 12.23)}{0.2154} \right)} \]

\[ \delta_{\text{CaMK, recover}} = 1 - \frac{0.5}{1 + \exp \left( \frac{V + 70}{20} \right)} \]
\[ \tau_{i,\text{CaMK,fast}} = \tau_{i,\text{fast}} \cdot \delta_{\text{CaMK,develop}} \cdot \delta_{\text{CaMK,recover}} \]
\[ \tau_{i,\text{CaMK,slow}} = \tau_{i,\text{slow}} \cdot \delta_{\text{CaMK,develop}} \cdot \delta_{\text{CaMK,recover}} \]
\[ A_{i,\text{CaMK,fast}} = A_{i,\text{fast}} \cdot \quad A_{i,\text{CaMK,slow}} = A_{i,\text{slow}} \]
\[ \frac{di_{\text{CaMK}}}{{dt}} = \frac{i_{\text{CaMK,\infty}} - i_{\text{CaMK,fast}}}{{\tau_{i,\text{CaMK,fast}}}} \]
\[ \frac{di_{\text{CaMK,slow}}}{{dt}} = \frac{i_{\text{CaMK,\infty}} - i_{\text{CaMK,slow}}}{{\tau_{i,\text{CaMK,slow}}}} \]
\[ i_{\text{CaMK}} = A_{i,\text{CaMK,fast}} \cdot i_{\text{CaMK,fast}} + A_{i,\text{CaMK,slow}} \cdot i_{\text{CaMK,slow}} \]
\[ K_{m,\text{CaMK}} = 0.15, \quad \phi_{\text{Ito, CaMK}} = \frac{1}{{1 + \frac{K_{m,\text{CaMK}}}{\text{CaMK}_{\text{active}}}}} \]
\[ \bar{\alpha}_{\text{to}} = 0.02 \, \text{mS/\mu F} \]
\[ \text{I}_{\text{to}} = \overline{\alpha}_{\text{to}} \cdot (V - E_{K}) \cdot \left( 1 - \phi_{\text{Ito, CaMK}} \cdot a \cdot i + \phi_{\text{Ito, CaMK}} \cdot a \cdot i \cdot \text{CaMK} \right) \]

**L-type Calcium Current (I_{CaL})**

\[ d_{\infty} = \frac{1}{{1 + \exp \left( \frac{-(V + 3.940)}{{4.230}} \right)}} \]
\[ \tau_{d} = 0.6 + \frac{1}{{\exp \left( -0.05 \cdot (V + 6.0) \right) + \exp \left( 0.09 \cdot (V + 14.0) \right)}} \]
\[ \frac{df}{{dt}} = \frac{1}{{\tau_{d}}} \]
\[ f_{\infty} = \frac{1}{{1 + \exp \left( \frac{V + 19.58}{{3.696}} \right)}} \]
\[ \tau_{f,\text{fast}} = 7.0 + \frac{1}{{0.0045 \cdot \exp \left( \frac{-(V + 20.0)}{{10.0}} \right) + 0.0045 \cdot \exp \left( \frac{V + 20.0}{{10.0}} \right)}} \]
\[ \tau_{f,\text{slow}} = 1000 + \frac{1}{{0.000035 \cdot \exp \left( \frac{-(V + 5.0)}{{4.0}} \right) + 0.000035 \cdot \exp \left( \frac{V + 5.0}{{6.0}} \right)}} \]
\[ A_{f,\text{fast}} = 0.6, \quad A_{f,\text{slow}} = 1 - A_{f,\text{fast}} \]
\[ \frac{df}{{dt}} = \frac{f_{\infty} - f}{{\tau_{f,\text{fast}}}} \quad \frac{df}{{dt}} = \frac{f_{\infty} - f}{{\tau_{f,\text{slow}}}} \]
\[ f = A_{f,\text{fast}} \cdot f_{\text{fast}} + A_{f,\text{slow}} \cdot f_{\text{slow}} \]
\[ f_{\text{Ca,}\infty} = f_{\infty} \]
\[ \tau_{f,\text{Ca,fast}} = 7.0 + \frac{1}{{0.04 \cdot \exp \left( \frac{-(V - 4.0)}{{7.0}} \right) + 0.04 \cdot \exp \left( \frac{V - 4.0}{{7.0}} \right)}} \]
\[ \tau_{f,\text{Ca,slow}} = 100 + \frac{1}{{0.00012 \cdot \exp \left( \frac{-(V - 7.0)}{{3.0}} \right) + 0.00012 \cdot \exp \left( \frac{V - 7.0}{{3.0}} \right)}} \]
\[ A_{f,\text{Ca,fast}} = 0.3 + \frac{0.6}{{1.0 + \exp \left( \frac{-(V - 10.0)}{{10.0}} \right)}}, \quad A_{f,\text{Ca,slow}} = 1 - A_{f,\text{Ca,fast}} \]
\[
\begin{align*}
\frac{df_{Ca,\text{fast}}}{dt} &= f_{Ca,\infty} - f_{Ca,\text{fast}} \\
\frac{df_{Ca,\text{slow}}}{dt} &= f_{Ca,\infty} - f_{Ca,\text{slow}} \\
f_{Ca} &= A_{f, Ca, \text{fast}} \cdot f_{Ca, \text{fast}} + A_{f, Ca, \text{slow}} \cdot f_{Ca, \text{slow}} \\
j_{Ca, \infty} &= f_{Ca, \infty} \\
\tau_{f, Ca, \text{fast}} &= 75.0 \\
\frac{dj_{Ca}}{dt} &= j_{Ca, \infty} - j_{Ca} \\
f_{Ca, \text{MK, fast}} &= A_{f, Ca} \cdot f_{Ca, \text{fast}} + A_{f, Ca} \cdot f_{Ca, \text{slow}} \\
\frac{df_{Ca,\text{MK, fast}}}{dt} &= f_{Ca,\text{MK,}\infty} - f_{Ca,\text{MK, fast}} \\
f_{Ca,\text{MK, slow}} &= f_{Ca,\text{slow}} \\
\frac{df_{Ca,\text{MK, fast}}}{dt} &= f_{Ca,\text{MK,}\infty} - f_{Ca,\text{MK, fast}} \\
f_{Ca,\text{MK, slow}} &= f_{Ca,\text{slow}} \\
\frac{df_{Ca,\text{MK, fast}}}{dt} &= f_{Ca,\text{MK,}\infty} - f_{Ca,\text{MK, fast}} \\
K_{m,n} &= 0.002, \quad k_{+2,n} = 1000.0, \quad k_{-2,n} = |Ca| \cdot 1.0 \\
\alpha_n &= \frac{k_{+2,n}}{k_{-2,n}} + \left(1 + \frac{K_{m,n}}{[Ca^{2+}]_{ss}}\right)^{4.0} \\
\frac{dn}{dt} &= \alpha_n \cdot k_{+2,n} - n \cdot k_{-2,n} \\
P_{Ca} &= 0.0001 \text{ cm} \cdot \text{s}^{-1} \\
\gamma_{Ca} &= 1.0, \quad \gamma_{Ca} = 0.341, \quad z_{Ca} = 2 \\
\psi_{Ca} &= \frac{z_{Ca}^2 \cdot VF^2}{RT} \cdot \frac{Y_{Ca} \cdot [Ca^{2+}]_{ss} \cdot \exp\left(\frac{Z_{Ca} VF}{RT}\right) - Y_{Ca} \cdot [Ca^{2+}]_o \cdot \exp\left(\frac{Z_{Ca} VF}{RT}\right) - 1.0}{\exp\left(\frac{Z_{Ca} VF}{RT}\right)} \\
\bar{I}_{Ca} &= P_{Ca} \cdot \psi_{Ca} \\
P_{CaNa} &= 0.00125 \cdot P_{Ca} \cdot \gamma_{Na} = 0.75, \quad \gamma_{Na} = 0.75, \quad z_{Na} = 1 \\
\psi_{CaNa} &= \frac{z_{Na}^2 \cdot VF^2}{RT} \cdot \frac{Y_{Na} \cdot [Na^{+}]_{ss} \cdot \exp\left(\frac{Z_{Na} VF}{RT}\right) - Y_{Na} \cdot [Na^{+}]_o \cdot \exp\left(\frac{Z_{Na} VF}{RT}\right) - 1.0}{\exp\left(\frac{Z_{Na} VF}{RT}\right)} \\
\bar{I}_{CaNa} &= P_{CaNa} \cdot \psi_{CaNa} \\
P_{CaK} &= 3.574 \cdot 10^{-4} \cdot P_{Ca} \cdot \gamma_{K} = 0.75, \quad \gamma_{K} = 0.75, \quad z_{K} = 1 \\
\psi_{CaK} &= \frac{z_{K}^2 \cdot VF^2}{RT} \cdot \frac{Y_{K} \cdot [K^{+}]_{ss} \cdot \exp\left(\frac{Z_{K} VF}{RT}\right) - Y_{K} \cdot [K^{+}]_o \cdot \exp\left(\frac{Z_{K} VF}{RT}\right) - 1.0}{\exp\left(\frac{Z_{K} VF}{RT}\right)} \\
\bar{I}_{CaK} &= P_{CaK} \cdot \psi_{CaK} 
\end{align*}
\]
\[
\begin{align*}
P_{\text{Ca,CMK}} &= 1.1 \cdot P_{\text{Ca}} \\
I_{\text{Ca,CMK}} &= P_{\text{Ca,CMK}} \cdot \Psi_{\text{Ca}} \\
P_{\text{CaNa,CMK}} &= 0.00125 \cdot P_{\text{Ca,CMK}} \\
I_{\text{CaNa,CMK}} &= P_{\text{CaNa,CMK}} \cdot \Psi_{\text{CaNa}} \\
P_{\text{CaK,CMK}} &= 3.574 \cdot 10^{-4} \cdot P_{\text{Ca,CMK}} \\
I_{\text{CaK,CMK}} &= P_{\text{CaK,CMK}} \cdot \Psi_{\text{CaK}} \\
K_{m,CMK} &= 0.15, \quad \emptyset_{I_{\text{CaL,CMK}}} = \frac{1}{1 + K_{m,CMK}^{\text{active}}} \]
\[
x_{s1,\infty} = \frac{1}{1 + \exp\left(\frac{-(V + 11.60)}{8.932}\right)}
\]

\[
\tau_{x,s1} = 817.3 + \frac{2.326 \cdot 10^{-4} \cdot \exp\left(\frac{V + 48.28}{17.80}\right)}{1 + \exp\left(\frac{-(V + 210.0)}{230.0}\right)}
\]

\[
\frac{dx_{s1}}{dt} = \frac{x_{s1,\infty} - x_{s1}}{\tau_{x,s1}}
\]

\[
x_{s2,\infty} = x_{s1,\infty}
\]

\[
\tau_{x,s2} = \frac{1}{0.01 \cdot \exp\left(\frac{V - 50}{20}\right) + 0.0193 \cdot \exp\left(\frac{-(V + 66.54)}{31}\right)}
\]

\[
\frac{dx_{s2}}{dt} = \frac{x_{s2,\infty} - x_{s2}}{\tau_{x,s2}}
\]

\[
\overline{G}_{Ks} = 0.0034 \text{ mS/\mu F}
\]

\[
I_{Ks} = \overline{G}_{Ks} \cdot \left(1 + \frac{0.6}{1 + \left(\frac{3.8 \cdot 10^{-5}, 1.4}{[Ca^{2+}]_{i}}\right)}\right) \cdot x_{s1} \cdot x_{s2} \cdot (V - E_{Ks})
\]

---

**Inward Rectifier Potassium Current (I_{K1})**

\[
x_{K1,\infty} = \frac{1}{1 + \exp\left(\frac{-(V + 2.5538 \cdot [K^+]_o + 144.59}{1.5692 \cdot [K^+]_o + 3.8115}\right)}
\]

\[
\tau_{x,K1} = \frac{1}{\exp\left(\frac{-(V + 127.2)}{20.36}\right) + \exp\left(\frac{V + 236.8}{69.33}\right)}
\]

\[
\frac{dx_{K1}}{dt} = \frac{x_{K1,\infty} - x_{K1}}{\tau_{x,K1}}
\]

\[
R_{K1} = \frac{1}{1 + \exp\left(\frac{V + 105.8 - 2.6 \cdot [K^+]_o}{9.493}\right)}
\]

\[
\overline{G}_{K1} = 0.1908 \text{ mS/\mu F}
\]

\[
I_{K1} = \overline{G}_{K1} \cdot \sqrt{[K^+]_o} \cdot x_{K1} \cdot R_{K1} \cdot (V - E_K)
\]

---

**Sodium/Calcium Exchange Current (I_{NaCa})**

For, \( Y \in \{i, ss\} \)

\[
k_{Na1} = 15 \text{ mM, } k_{Na2} = 5 \text{ mM, } k_{Na3} = 88.12 \text{ mM, } k_{asymm} = 12.5
\]

\[
\omega_{Na} = 6 \cdot 10^4 \text{ Hz, } \omega_{Ca} = 6 \cdot 10^4 \text{ Hz, } \omega_{NaCa} = 5 \cdot 10^3 \text{ Hz}
\]

\[
k_{Ca,on} = 1.5 \cdot 10^6 \frac{\text{mM}}{\text{ms}}, \ k_{Ca,off} = 5 \cdot 10^3 \text{ Hz}
\]

\[
q_{Na} = 0.5224, \ q_{Ca} = 0.1670
\]

\[
h_{Ca} = \exp\left(\frac{q_{Ca}VF}{RT}\right), \ h_{Na} = \exp\left(\frac{q_{Na}VF}{RT}\right)
\]
\[ h_1 = 1 + \frac{[\text{Na}^+]_Y}{k_{Na3}}(1 + h_{Na}) \]
\[ h_2 = \frac{[\text{Na}^+]_Y \cdot h_{Na}}{k_{Na3} \cdot h_1} \]
\[ h_3 = \frac{1}{h_1} \]
\[ h_4 = 1 + \frac{[\text{Na}^+]_Y}{k_{Na1}} \left( 1 + \frac{[\text{Na}^+]_Y}{k_{Na2}} \right) \]
\[ h_5 = \frac{[\text{Na}^+]_Y^2}{h_4 \cdot k_{Na1} \cdot k_{Na2}} \]
\[ h_6 = \frac{1}{h_4} \]
\[ h_7 = 1 + \frac{[\text{Na}^+]_o}{k_{Na3}} \left( 1 + \frac{1}{h_{Na}} \right) \]
\[ h_8 = \frac{k_{Na3} \cdot h_{Na} \cdot h_7}{1} \]
\[ h_9 = \frac{1}{h_7} \]
\[ h_{10} = k_{\text{asymmm}} + 1 + \frac{[\text{Na}^+]_o}{k_{Na1}} \left( 1 + \frac{[\text{Na}^+]_o}{k_{Na2}} \right) \]
\[ h_{11} = \frac{[\text{Na}^+]_o^2}{1} \]
\[ h_{12} = \frac{1}{h_{10}} \]
\[ k_1 = h_{12} \cdot [\text{Ca}^{2+}]_o \cdot k_{Ca,\text{on}} \]
\[ k_2 = k_{Ca,\text{off}} \]
\[ k_3' = h_9 \cdot \omega_{\text{Ca}} \]
\[ k_3'' = h_8 \cdot \omega_{\text{NaCa}} \]
\[ k_3 = k_3' + k_3'' \]
\[ k_4' = h_3 \cdot \omega_{\text{Ca}} \]
\[ k_4'' = h_3 \cdot \omega_{\text{NaCa}} \]
\[ k_4 = k_4' + k_4'' \]
\[ k_5 = k_{Ca,\text{off}} \]
\[ k_6 = h_6 \cdot [\text{Ca}^{2+}]_Y \cdot k_{Ca,\text{on}} \]
\[ k_7 = h_5 \cdot h_2 \cdot \omega_{Na} \]
\[ k_8 = h_8 \cdot h_{11} \cdot \omega_{Na} \]
\[ x_1 = k_2 \cdot k_4' \cdot (k_7 + k_6) + k_5 \cdot k_7 \cdot (k_2 + k_3) \]
\[ x_2 = k_1 \cdot k_7 \cdot (k_4 + k_5) + k_6 \cdot (k_1 + k_8) \]
\[ x_3 = k_1 \cdot k_3 \cdot (k_7 + k_6) + k_8 \cdot k_6 \cdot (k_2 + k_3) \]
\[ x_4 = k_2 \cdot k_8 \cdot (k_4 + k_5) + k_3 \cdot k_5 \cdot (k_1 + k_8) \]
\[ E_1 = \frac{x_1 + x_2 + x_3 + x_4}{x_2} \]
\[ E_2 = \frac{x_1 + x_2 + x_3 + x_4}{x_3} \]
\[ E_3 = \frac{x_1 + x_2 + x_3 + x_4}{x_1 + x_2 + x_3 + x_4} \]
\[
E_4 = \frac{x_4}{x_1 + x_2 + x_3 + x_4}
\]

\[
K_{mCaAct} = 150 \cdot 10^{-6} \text{ mM}
\]

\[
\text{allo}_Y = \frac{1}{1 + \left(\frac{K_{mCaAct}}{[Ca^{2+}]_Y}\right)^2}
\]

\[
J_{\text{NaCa},Na,Y} = 3 \cdot \left(E_4 \cdot k_7 - E_1 \cdot k_8\right) + E_3 \cdot k'_4' - E_2 \cdot k'_3'
\]

\[
J_{\text{NaCa},Ca,Y} = E_2 \cdot k_2 - E_1 \cdot k_1
\]

\[
z_{\text{Na}} = 1, \quad z_{\text{Ca}} = 2
\]

\[
G_{\text{NaCa}} = 0.0008 \mu A/\mu F
\]

\[
I_{\text{NaCa},i} = G_{\text{NaCa}} \cdot 0.8 \cdot \text{allo}_i \cdot \left( z_{\text{Na}} \cdot J_{\text{NaCa},Na,i} + z_{\text{Ca}} \cdot J_{\text{NaCa},Ca,i}\right)
\]

\[
I_{\text{NaCa},ss} = G_{\text{NaCa}} \cdot 0.2 \cdot \text{allo}_i \cdot \left( z_{\text{Na}} \cdot J_{\text{NaCa},Na,ss} + z_{\text{Ca}} \cdot J_{\text{NaCa},Ca,ss}\right)
\]

**Sodium/Potassium ATPase Current (I_{NaK})**

\[
k_1^+ = 949.5 \text{ Hz}, \quad k_1^- = 182.4 \text{ mM}^{-1}, \quad k_2^+ = 687.2 \text{ Hz}, \quad k_2^- = 39.4 \text{ Hz}
\]

\[
k_3^- = 1899 \text{ Hz}, \quad k_3^+ = 79300 \text{ Hz} \cdot \text{mM}^{-2}, \quad k_4^+ = 639.0 \text{ Hz}, \quad k_4^- = 40 \text{ Hz}
\]

\[
K_{o\text{Nai}} = 9.073 \text{ mM}, \quad K_{o\text{NaO}} = 27.78 \text{ mM}
\]

\[
\Delta = -0.1550
\]

\[
K_{\text{Nai}} = K_{o\text{Nai}} \cdot \exp\left(\frac{\Delta \cdot V \cdot F}{3 \cdot R \cdot T}\right), \quad K_{\text{Nao}} = K_{o\text{NaO}} \cdot \exp\left(\frac{(1 - \Delta) \cdot V \cdot F}{3 \cdot R \cdot T}\right)
\]

\[
K_{\text{Ki}} = 0.5 \text{ mM}, \quad K_{\text{Ko}} = 0.3582 \text{ mM}
\]

\[
[M\text{gADP}] = 0.05, \quad [M\text{gATP}] = 9.8
\]

\[
K_{\text{MgATP}} = 1.698 \cdot 10^{-7} \text{ mM}
\]

\[
[H^+] = 10^{-7} \text{ mM}
\]

\[
[\Sigma P] = 4.2 \text{ mM}
\]

\[
K_{\text{H,P}} = 1.698 \cdot 10^{-7} \text{ mM}, \quad K_{\text{Na,P}} = 224 \text{ mM}, \quad K_{\text{K,P}} = 292 \text{ mM}
\]

\[
[\text{P}] = [\Sigma P]/\left(1 + \frac{[H^+]_{\text{K,H,P}}}{K_{\text{H,P}}} + \frac{[\text{Na}^+]_{\text{i}}}{K_{\text{Na,P}}} + \frac{[\text{K}^+]_{\text{i}}}{K_{\text{K,P}}}ight)
\]

\[
\alpha_1 = \frac{k_1^+ \left(\frac{[\text{Na}^+]_{\text{i}}}{K_{\text{Nai}}}\right)^3}{(1 + \left(\frac{[\text{Na}^+]_{\text{i}}}{K_{\text{Nai}}}\right)^3)^3 + (1 + \left(\frac{[\text{K}^+]_{\text{i}}}{K_{\text{Ki}}}\right)^2 - 1}
\]

\[
\beta_1 = k_1^- \cdot [\text{MgADP}]
\]

\[
\alpha_2 = k_2^+
\]

\[
\beta_2 = \frac{k_2^+ \left(\frac{[\text{Na}^+]_{\text{o}}}{K_{\text{NaO}}}\right)^3}{(1 + \left(\frac{[\text{Na}^+]_{\text{o}}}{K_{\text{NaO}}}\right)^3)^3 + (1 + \left(\frac{[\text{K}^+]_{\text{o}}}{K_{\text{Ko}}}\right)^2 - 1}
\]

\[
\alpha_3 = \frac{k_3^- \left(\frac{[\text{K}^+]_{\text{o}}}{K_{\text{Ko}}}\right)^2}{(1 + \left(\frac{[\text{Na}^+]_{\text{o}}}{K_{\text{NaO}}}\right)^3 + (1 + \left(\frac{[\text{K}^+]_{\text{o}}}{K_{\text{Ko}}}\right)^2 - 1}}
\]
\[
\beta_3 = \frac{k_3 \cdot [P] \cdot [H^+]}{1 + \frac{[MgATP]}{K_{MgATP}}} \\
\alpha_4 = \frac{k_4^+ \cdot [MgATP]}{1 + \frac{[MgATP]}{K_{MgATP}}} \\
\beta_4 = \frac{k_4^- \left( \frac{[K^+]_i}{K_{Ki}} \right)^2}{\left( 1 + \frac{[Na^+]_i}{K_{Na}} \right)^3 \left( 1 + \frac{[K^+]_i}{K_{K_i}} \right)^2 - 1}
\]

\[
x_1 = \alpha_4 \cdot \alpha_1 \cdot \alpha_2 + \beta_2 \cdot \beta_4 \cdot \beta_3 + \alpha_2 \cdot \beta_4 \cdot \beta_3 + \beta_3 \cdot \alpha_1 \cdot \alpha_2 \\
x_2 = \beta_2 \cdot \beta_1 \cdot \alpha_2 \cdot \alpha_3 + \alpha_3 \cdot \beta_1 \cdot \beta_4 + \alpha_2 \cdot \alpha_3 \cdot \beta_4 \\
x_3 = \alpha_2 \cdot \alpha_3 \cdot \alpha_4 + \beta_3 \cdot \alpha_4 \cdot \beta_2 + \beta_1 \cdot \alpha_4 + \alpha_3 \cdot \alpha_4 \cdot \beta_1 \\
x_4 = \beta_4 \cdot \beta_3 \cdot \beta_2 + \alpha_3 \cdot \alpha_4 \cdot \alpha_1 + \beta_2 \cdot \alpha_4 \cdot \alpha_1 + \beta_3 \cdot \beta_2 \cdot \alpha_1
\]

\[E_1 = \frac{x_1 + x_2 + x_3 + x_4}{x_2} \]
\[E_2 = \frac{x_1 + x_2 + x_3 + x_4}{x_3} \]
\[E_3 = \frac{x_1 + x_2 + x_3 + x_4}{x_4} \]
\[E_4 = \frac{x_1 + x_2 + x_3 + x_4}{x_4} \]

\[z_{Na} = 1, \quad z_{K} = 1 \]
\[J_{Na,K,Na} = 3 \cdot (E_1 \cdot \alpha_3 - E_2 \cdot \beta_3) \]
\[J_{Na,K,K} = 2 \cdot (E_4 \cdot \beta_1 - E_3 \cdot \alpha_1) \]
\[J_{Na,K} = 30 \cdot (z_{Na} \cdot J_{Na,K,Na} + z_{K} \cdot J_{Na,K,K}) \]

---

**Background Currents (I_{Nab}, I_{Cab}, I_{kb}) and Sarcolemmal Calcium Pump Current (I_{pCa})**

The formulations for \(I_{Nab}, I_{Cab}, I_{kb}\) and \(I_{pCa}\) were taken from the Hund-Decker-Rudy model\(^5,6\). \(I_{kb}\) represents small amplitude, rapidly activating K\(^+\) current observed in the ventricle (\(I_{k}\)-like\(^7\) or \(I_{kur}\)-like\(^8\) current). The amplitudes of these currents were reduced compared to values used by Decker et al\(^5\). These choices were made consistent with the following: 1) so that resting [Na\(^+\)] would be similar to values shown in nonfailing human ventricle at 37 °C by Pieske et al\(^9\) at very slow pacing rates (0.25 Hz), 2) so that the resting [Ca\(^{2+}\)] would be similar to values shown in nonfailing human ventricle at 37 °C by Schmidt et al\(^10\), and 3) so that the generally lower major current conductances used to match human data in construction of this model would be properly balanced.

\[P_{Nab} = 3.75 \cdot 10^{-10} \text{ cm/s}, \quad z_{Na} = 1 \]
\[I_{Nab} = P_{Nab} \cdot z_{Na}^2 \cdot \frac{\frac{VF^2}{RT} \cdot [Na^+]_i \cdot \exp \left( \frac{Z_{Na,VF}}{RT} \right) - [Na^+]_o}{\exp \left( \frac{Z_{Na,VF}}{RT} \right) - 1.0} \]
\[P_{Cab} = 2.5 \cdot 10^{-8} \text{ cm/s}, \quad \gamma_{CaI} = 1.0, \quad \gamma_{CaO} = 0.341, \quad z_{Ca} = 2 \]
\[I_{Cab} = P_{Cab} \cdot z_{Ca}^2 \cdot \frac{\frac{VF^2}{RT} \cdot \gamma_{CaI} \cdot [Ca^{2+}]_i \cdot \exp \left( \frac{Z_{Ca,VF}}{RT} \right) - \gamma_{CaO} \cdot [Ca^{2+}]_o}{\exp \left( \frac{Z_{Ca,VF}}{RT} \right) - 1.0} \]
\[ x_{Kb} = \frac{1}{1 + \exp\left(\frac{-(V - 14.48)}{18.34}\right)} \]

\[ G_{Kb} = 0.003 \text{ mS/\mu F} \]

\[ I_{Kb} = G_{Kb} \cdot x_{Kb} \cdot (V - E_{K}) \]

\[ G_{pCa} = 0.0005 \text{ mS/\mu F} \]

\[ I_{pCa} = G_{pCa} \cdot \frac{[Ca^{2+}]_i}{0.0005 + [Ca^{2+}]_i} \]

**Voltage**

\[ C_m = 1.0 \mu \text{F} \]

\[ \frac{dV_m}{dt} = -\frac{1}{C_m} \cdot \left( I_{Na} + I_{to} + I_{CaL} + I_{CaNa} + I_{CaK} + I_{Kr} + I_{Ks} + I_{K1} + I_{NaCa} + I_{NaK} + I_{Nab} + I_{Cab} + I_{Kb} + I_{pCa} + I_{stim} \right) \]

**Calcium/CALmodulin-Dependent Protein Kinase (CaMK)**

The CaMK model is equivalent to that used in the Hund-Decker-Rudy dog model. We assumed that CaMK kinetics are similar in human and dog, in the absence of human ventricle specific measurements.

\[ \alpha_{CaMK} = 0.05 \text{ ms}^{-1}, \quad \beta_{CaMK} = 0.00068 \text{ ms}^{-1} \]

\[ CaMK_0 = 0.05, \quad K_{mCaM} = 0.0015 \text{ mM} \]

\[ CaMK_{bound} = CaMK_0 \cdot \frac{K_{mCaM}}{1 + \frac{[Ca^{2+}]_s}{[Ca^{2+}]_i}} \]

\[ CaMK_{active} = CaMK_{bound} + CaMK_{trap} \]

\[ \frac{dCaMK_{trap}}{dt} = \alpha_{CaMK} \cdot CaMK_{bound} \cdot (CaMK_{bound} + CaMK_{trap}) - \beta_{CaMK} \cdot CaMK_{trap} \]

**ORd Human Model Fluxes**

**Diffusion Fluxes (J_{diff,Na}, J_{diff,Ca}, J_{diff,K})**

\[ \tau_{diff,Na} = \tau_{diff,K} = 2.0 \text{ ms}, \quad \tau_{diff,Ca} = 0.2 \text{ ms} \]

\[ J_{diff,Na} = \frac{\tau_{diff,Na}}{[Na^+]_s - [Na^+]_i} \]

\[ J_{diff,Ca} = \frac{\tau_{diff,Ca}}{[Ca^{2+}]_s - [Ca^{2+}]_i} \]

\[ J_{diff,K} = \frac{\tau_{diff,K}}{[K^+]_s - [K^+]_i} \]

The time constant for Na\(^+\) and K\(^+\) diffusion fluxes are larger than the time constant for Ca\(^{2+}\) diffusion flux. Physiologically, this amounts to reduced diffusivity for Na\(^+\) and K\(^+\) as they exit the subspace.
SR Calcium Release Flux, via Ryanodine Receptor ($J_{rel}$)

Ca$^{2+}$ release channels (ryanodine receptors, RyRs, formulation similar to that in Livshitz et al.\textsuperscript{11}) have been split into two separate populations in this model according to CaMK phosphorylation state, based on observations in dog ventricle\textsuperscript{12}. There is a non-phosphorylated release ($J_{rel,NP}$) and a CaMK phosphorylated release ($J_{rel,CaMK}$). When RyR channels are phosphorylated by CaMK, release amplitude is 1.25 times larger, and the decay time constant is 1.25 times longer. The proportion of the RyR population that behaves in the phosphorylated state is regulated by active CaMK.

\[
\beta_\tau = 4.75 \text{ ms} \\
\alpha_{rel} = 0.5 \cdot \beta_\tau \\
J_{rel,NP,\infty} = \frac{\alpha_{rel} \cdot (-I_{CaL})}{1 + \left( \frac{1.5}{[Ca^{2+}]_{JSR}} \right)} \\
\tau_{rel,NP} = \frac{\beta_\tau}{1 + \left( \frac{0.0123}{[Ca^{2+}]_{JSR}} \right)}, \tau_{rel,NP} \geq 0.001 \\
\frac{dJ_{rel,NP}}{dt} = J_{rel,NP,\infty} - J_{rel,NP} \\
\beta_\tau,CaMK = 1.25 \cdot \beta_\tau \\
\alpha_{rel,CaMK} = 0.5 \cdot \beta_\tau,CaMK \\
J_{rel,CaMK,\infty} = \frac{\alpha_{rel,CaMK} \cdot (-I_{CaL})}{1 + \left( \frac{1.5}{[Ca^{2+}]_{JSR}} \right)} \\
\tau_{rel,CaMK} = \frac{\beta_\tau,CaMK}{1 + \left( \frac{0.0123}{[Ca^{2+}]_{JSR}} \right)}, \tau_{rel,CaMK} \geq 0.001 \\
\frac{dJ_{rel,CaMK}}{dt} = J_{rel,CaMK,\infty} - J_{rel,CaMK} \\
K_{m,CaMK} = 0.15, \ \emptyset_{rel,CaMK} = \frac{1}{1 + \frac{K_{m,CaMK}}{CaMK_{active}}} \\
J_{rel} = (1 - \emptyset_{rel,CaMK}) \cdot J_{rel,NP} + \emptyset_{rel,CaMK} \cdot J_{rel,CaMK}
\]

Calcium Uptake via SERCA Pump ($J_{up}$)

Ca$^{2+}$ uptake channels (SERCA pumps) are phosphorylated by CaMK\textsuperscript{13,14}. Here, we used two separate Ca$^{2+}$ uptake populations: those not-phosphorylated ($J_{up,NP}$) and those phosphorylated by CaMK ($J_{up,CaMK}$). Ca$^{2+}$ leakage from the NSR was identical to the formulation used in the Hund-Decker-Rudy model. However, leak magnitude was reduced by \textasciitilde10%.

\[
J_{up,NP} = \frac{0.004375 \cdot [Ca^{2+}]_i}{0.00092 + [Ca^{2+}]_i} \\
\Delta K_{m,PLB} = 0.00017 \text{ mM} \\
\Delta J_{up,CaMK} = 1.75 \\
J_{up,CaMK} = (1 + \Delta J_{up,CaMK}) \cdot \frac{0.004375 \cdot [Ca^{2+}]_i}{0.00092 - \Delta K_{m,PLB} + [Ca^{2+}]_i}
\]
\[ K_{m, CaMK} = 0.15, \quad \phi_{up, CaMK} = \frac{1}{1 + \frac{K_{m, CaMK}}{CaMK_{active}}} \]

\[ J_{\text{leak}} = 0.0039375 \cdot [Ca^{2+}]_{nsr} \]
\[ J_{up} = \left( 1 - \phi_{up, CaMK} \right) \cdot J_{up, NP} + \phi_{up, CaMK} \cdot J_{up, CaMK} - J_{\text{leak}} \]

**Calcium Translocation from NSR to JSR (J_{tr})**

Sobie et al.\textsuperscript{15} showed that Ca\textsuperscript{2+} spark recovery required 91 ms. This measurement informed our choice of 100 ms for translocation time constant (\( \tau_{tr} \)).

\[ \tau_{tr} = 100 \text{ ms} \]
\[ J_{tr} = \frac{[Ca^{2+}]_{nsr} - [Ca^{2+}]_{jsr}}{\tau_{tr}} \]

**ORd Human Model Concentrations and Buffers**

In the absence of human ventricle specific measurements, we take Ca\textsuperscript{2+} buffering equations and kinetics from the Hund-Decker-Rudy model.

\[ [\text{CMDN}] = 0.05 \text{ mM}, \quad K_{m, \text{CMDN}} = 0.00238 \text{ mM} \]
\[ [\text{TRPN}] = 0.07 \text{ mM}, \quad K_{m, \text{TRPN}} = 0.0005 \text{ mM} \]
\[ [\text{BSR}] = 0.047 \text{ mM}, \quad K_{m, \text{BSR}} = 0.00087 \text{ mM} \]
\[ [\text{BSL}] = 1.124 \text{ mM}, \quad K_{m, \text{BSL}} = 0.0087 \text{ mM} \]
\[ [\text{CSQN}] = 10.0 \text{ mM}, \quad K_{m, \text{CSQN}} = 0.8 \text{ mM} \]

\[ \beta_{CaI} = \frac{1}{1 + \frac{[\text{CMDN}] \cdot K_{m, \text{CMDN}}}{(K_{m, \text{CMDN}} + [Ca^{2+}])^2} + \frac{[\text{TRPN}] \cdot K_{m, \text{TRPN}}}{(K_{m, \text{TRPN}} + [Ca^{2+}])^2}} \]

\[ \frac{d[Ca^{2+}]_i}{dt} = \beta_{CaI} \cdot \left( -(I_{pCa} + I_{Cab} - 2 \cdot I_{NaK,i}) \cdot \frac{A_{\text{cap}}}{2 \cdot F \cdot v_{\text{myo}}} - \frac{J_{up, v_{\text{myo}}} - J_{\text{diff, Ca}, v_{\text{myo}}} + J_{rel, v_{\text{ss}}} - J_{\text{diff, Ca}}}{v_{\text{myo}}} \right) \]

\[ \frac{d[Ca^{2+}]_s}{dt} = \beta_{CaS} \cdot \left( -(I_{pCa} - 2 \cdot I_{NaK,ss}) \cdot \frac{A_{\text{cap}}}{2 \cdot F \cdot v_{\text{ss}}} + \frac{J_{rel, v_{\text{ss}}} - J_{\text{diff, Ca}}}{v_{\text{ss}}} \right) \]
\[
\frac{d[Ca^{2+}]_{nsr}}{dt} = J_{up} - J_{tr} \cdot \frac{v_{jsr}}{v_{nsr}}
\]
\[
\beta_{Cajsr} = \frac{[CSQN] \cdot K_{m,CSQN}}{1 + (K_{m,CSQN} + [Ca^{2+}]_{jsr})^2}
\]
\[
\frac{d[Ca^{2+}]_{jsr}}{dt} = \beta_{Cajsr} \cdot (J_{tr} - J_{rel})
\]

**ORd Human Model Transmural Heterogeneity**

|       | epi/endo | M/endo |
|-------|----------|--------|
| \(G_{NaL}\) | 0.6      | 1      |
| \(G_{Ito}\)   | 4.0      | 4.0    |
| \(P_{Ca}\), \(P_{CaNa}\), \(P_{CaK}\) | 1.2      | 2.5    |
| \(G_{Kr}\)     | 1.3      | 0.8    |
| \(G_{Ks}\)     | 1.4      | 1      |
| \(G_{K1}\)     | 1.2      | 1.3    |
| \(G_{NaCa,i}\), \(G_{NaCa,ss}\) | 1.1      | 1.4    |
| \(G_{NaK}\)   | 0.9      | 0.7    |
| \(G_{Kb}\)     | 0.6      | 1      |
| \(J_{rel,NP,\infty}, J_{rel,CaMK,\infty}\) | 1        | 1.7    |
| \(J_{up,NP}, J_{up,CaMK}\) | 1.3      | 1      |
| \([CMDN]\)     | 1.3      | 1      |

*Scaling Factors for Model Implementation of Transmural Heterogeneity*

Formulation changes to account for epi \(I_{to}\) differences are:

\[
\delta_{epi} = 1.0 - \frac{0.95}{1.0 + \exp\left(\frac{V + 70.0}{5.0}\right)}
\]
\[
\tau_{i,fast,\text{epi}} = \tau_{i,fast} \cdot \delta_{epi}
\]
\[
\tau_{i,slow,\text{epi}} = \tau_{i,slow} \cdot \delta_{epi}
\]

**Computational Methodology**

**Hardware and Software**

For simulation of the basic human model, we used custom code developed and run using Microsoft Visual C++ 2008 Express Edition on a Windows Vista Dell desktop PC, with an Intel Core 2 Quad processor. Integration was performed as described below (Rapid Integration). We also used custom C++ code run on an array of Dell cluster nodes with 64-bit Intel Xeon processors, running Linux and Sun Microsystems Grid Engine. Execution scripts were written in Python. A fixed time step of 0.01 ms was applied, and the Rush-Larsen Method\(^{16}\) was used. All simulations were paced to true steady state\(^{17}\), unless otherwise noted.
Validation and fitting of individual model components (i.e. time constants, steady state curves) was performed using custom code written in Matlab 2009a running on a Windows Vista Dell desktop PC, with an Intel Core 2 Quad processor. Automated parameter estimation used a sum of least squares objective function, minimized by Matlab functions “fmincon”, “ga”, and “lsqcurvefit” (interior reflexive Newton’s Method for “fmincon” and “lsqcurvefit”, genetic algorithm for “ga”). See Matlab documentation for details and references. We used the parallel implementation of “fmincon” and “ga” by opening a matlabpool (size 4). Manual parameter estimation was also used, where minimization was by simple guess and check.

**Rapid Integration**

The Rush-Larsen Method\(^\text{16}\), applied by Victorri et al.\(^\text{18}\), relies on the assumption that during sufficiently small time intervals, a system of differential algebraic equations becomes effectively uncoupled. One can then readily solve uncoupled differential equations one-by-one to obtain expressions for time evolution of state variables.

Here, identification of sufficiently small time intervals (\(dt\)) was determined by comparison to gold standard simulations with fixed \(dt = 0.005\) ms. We match the gold standard when we apply the following rules:

1. \(dt = 0.005\) ms from the start of the stimulus until 25 ms thereafter
2. maximum allowed \(dt = 1.0\) ms
3. \(dt\) was adjusted dynamically with changes in membrane voltage, as described in LR\(^\text{19}\):
   a. if \(\Delta V \leq 0.2\) mV, \(dt = 0.8 \cdot \frac{dV}{dt}\)
   b. if \(\Delta V \geq 0.8\) mV, \(dt = 0.2 \cdot \frac{dV}{dt}\)
      i. while \(\Delta V \geq 0.8\) mV, \(dt\) is reduced tenfold until the condition, \(\Delta V < 0.8\) mV, is met (minimum \(dt = 0.005\) ms)

Equations for updating gates (e.g. generic gate, \(s\))

\[
s = s_\infty - (s_\infty - s) \cdot \exp\left(\frac{-dt}{\tau_s}\right)
\]

Equations for updating the \(n\) gate, \(J_{rel,NP}\), and \(J_{rel,CaMK}\)

\[
n = \alpha_n \cdot \frac{k_{+2,n}}{k_{-2,n}} - \left(\alpha_n \cdot \frac{k_{+2,n}}{k_{-2,n}} - n\right) \cdot \exp\left(-k_{-2,n} \cdot dt\right)
\]
\[
J_{rel,NP} = J_{rel,NP,\infty} - \left(J_{rel,NP,\infty} - J_{rel,NP}\right) \cdot \exp\left(\frac{-dt}{\tau_{rel,NP}}\right)
\]
\[
J_{rel,CaMK} = J_{rel,CaMK,\infty} - \left(J_{rel,CaMK,\infty} - J_{rel,CaMK}\right) \cdot \exp\left(\frac{-dt}{\tau_{rel,CaMK}}\right)
\]

The Forward Euler Method was applied to update membrane voltage, concentrations, and \(CaMK_{\text{trap}}\) at each time step.

Using the above method, it took less than one minute of runtime to pace the model to true and accurate steady state at 1 Hz (Microsoft Visual C++ 2008 Express Edition on a Windows Vista Dell desktop PC, with a 2.83 GHz Intel Core 2 Quad processor).
Figure S1. Human $I_{\text{NaCa}}$ model faithfully reproduces Kang and Hilgemann\textsuperscript{20} observations. Compare Figures 3C, 4A, 4C from Kang and Hilgemann\textsuperscript{20} with the simulations from our human $I_{\text{NaCa}}$ model, presented here (same protocols were used). A) Charge flux reversal potential is more depolarized than Ca\textsuperscript{2+} flux, a feature of this model which includes the observed Na\textsuperscript{+} leak mode. B) Charge flux (solid lines) and Ca\textsuperscript{2+} flux (dashed lines) versus voltage, for a variety of substrates (in mM, condition 1: [Na\textsuperscript{+}]\textsubscript{o}=0, [Na\textsuperscript{+}]\textsubscript{i}=40, [Ca\textsuperscript{2+}]\textsubscript{o}=4, [Ca\textsuperscript{2+}]\textsubscript{i}=0; condition 2: [Na\textsuperscript{+}]\textsubscript{o}=120, [Na\textsuperscript{+}]\textsubscript{i}=40, [Ca\textsuperscript{2+}]\textsubscript{o}=4, [Ca\textsuperscript{2+}]\textsubscript{i}=0; condition 3: [Na\textsuperscript{+}]\textsubscript{o}=120, [Na\textsuperscript{+}]\textsubscript{i}=40, [Ca\textsuperscript{2+}]\textsubscript{o}=0, [Ca\textsuperscript{2+}]\textsubscript{i}=0.1; condition 4: [Na\textsuperscript{+}]\textsubscript{o}=120, [Na\textsuperscript{+}]\textsubscript{i}=4, [Ca\textsuperscript{2+}]\textsubscript{o}=0, [Ca\textsuperscript{2+}]\textsubscript{i}=0.1). C) Reversal potential is sensitive to ionic substrate (in mM, [Na\textsuperscript{+}]\textsubscript{o}=100, [Ca\textsuperscript{2+}]\textsubscript{o}=1.2, [Ca\textsuperscript{2+}]\textsubscript{i}=0.0005, condition 1: [Na\textsuperscript{+}]\textsubscript{i}=0; condition 2: [Na\textsuperscript{+}]\textsubscript{i}=5; condition 3: [Na\textsuperscript{+}]\textsubscript{i}=10; condition 4: [Na\textsuperscript{+}]\textsubscript{i}=20; condition 5: [Na\textsuperscript{+}]\textsubscript{i}=20, [Ca\textsuperscript{2+}]\textsubscript{i}=0).
**Figure S2.** Human $I_{\text{NaCa}}$ model faithfully reproduces observations of Weber et al.\textsuperscript{21}. Compare Weber et al.\textsuperscript{21}, their Figure 2, with simulations from our human $I_{\text{NaCa}}$ model, shown here (same protocols were used). 

**A)** Voltage dependence of $I_{\text{NaCa}}$ under different intracellular Na\textsuperscript{+} clamp conditions.

**B)** Intracellular Na\textsuperscript{+} dependence of $I_{\text{NaCa}}$ under different voltage clamp conditions.

**C)** Intracellular Ca\textsuperscript{2+} dependence of $I_{\text{NaCa}}$ under different voltage clamp conditions. The model incorporates Weber’s “allosteric activation”, seen at depolarized voltages.
Figure S3. Human $i_{NaCa}$ model faithfully reproduces Weber et al. intracellular Na⁺ dependence under AP and Ca²⁺ clamp conditions. Compare Weber et al. Figure 6A with simulations from our $i_{NaCa}$ model, shown here (same protocols were used). A) Clamped Ca²⁺ transient (similar to Weber et al., increasing instantaneously from 0.01 to 0.1 µM, and decaying over 500 ms), and action potential waveform measured in undiseased human ventricular myocytes (see Methods section of main text for details). B) Due to depolarization, exchange current was outward, briefly, until [Ca²⁺] rose. When [Na⁺] was relatively low, maximal inward exchange current increased, as Weber showed.
Figure S4. $I_{K1}$ shows voltage dependence, but not rate dependence. Top panel: Simulated action potentials, paced at different cycle lengths. Bottom panel: $I_{K1}$ in the model, at the different pacing rates. Note that the peak current reached was largely rate independent, as was shown by Jost et al.\textsuperscript{22} in undiseased human ventricle experiments.
Figure S5. $I_{Kr}$ shows voltage dependence, but not rate dependence. Top panel: Simulated action potentials, paced at different cycle lengths. Bottom panel: $I_{Kr}$ in the model, at the different pacing rates. Note that the peak current reached was rate independent, as was shown by Jost et al.\textsuperscript{22} in undiseased human ventricle experiments.
Figure S6. Schematic diagram of the human $I_{NaK}$ model, modified from Smith and Crampin$^{23}$. There are four distinct enzymatic states, with lumped substates where non-rate limiting transitions were assumed to be in rapid equilibrium. Forward pump function is clockwise cycling. From this diagram, we formulated equations for the current using the King-Altmann method$^{24}$. 
Figure S7. Human INaK model faithfully reproduces major observations of Nakao and Gadsby\textsuperscript{25}. Data (squares) are from Nakao and Gadsby\textsuperscript{25}, their Figures 2A, 4C, 7A, 9B, 10B. INaK model simulations are solid lines (same protocols used). The model is not a perfect match to these data, measured in guinea pig ventricle, but the basic voltage and concentration dependencies are duplicated, demonstrating that the model is dynamically and mechanistically correct. 

A) Voltage dependence of INaK under different extracellular Na\textsuperscript{+} clamp conditions. 

B) Voltage dependence of INaK under different intracellular Na\textsuperscript{+} clamp conditions, and [Na\textsuperscript{+}]\textsubscript{o}=150 mM. 

C) Voltage dependence of INaK under different intracellular Na\textsuperscript{+} clamp conditions, and [Na\textsuperscript{+}]\textsubscript{o}=0 mM. 

D) Voltage dependence of INaK under different extracellular K\textsuperscript{+} clamp conditions, and [Na\textsuperscript{+}]\textsubscript{o}=150 mM. 

E) Voltage dependence of INaK under different extracellular K\textsuperscript{+} clamp conditions, and [Na\textsuperscript{+}]\textsubscript{o}=0 mM.
We used microelectrode action potentials, measured in the undiseased human ventricle at 37 °C, for model validation. Since these data were measured in a multicellular preparation, the experimental protocol was simulated in a 1-dimensional multicellular fiber. In Decker et al., the subtle but complex differences in APD adaptation between single cell and a multicellular fiber were investigated. We used the conduction equations of Decker et al. (-200 µA/µF, 1 ms stimulus delivered to fiber end, zero flux boundary conditions), and measured the model APD at the 50th cell in a 100-cell homogeneous endocardial strand. Fiber results were similar to single cell results, as in Decker et al, and match the experimental data. Conduction velocity was 45 cm/sec at 1 Hz pacing, consistent with available (canine) experiments.

Figure S8. Multicellular strand simulations compared to measurements. APD30, APD50, APD70, and APD90 shown in red, green, blue, and black, respectively. Squares are experimentally measured human endocardial action potentials, at 37°C, N=140. Solid lines are simulation results from the 50th cell in a 100-cell strand (zero flux boundary).
Figure S9. Experiments (top) are from an undiseased human heart (heart #5, male, age 20, death from Tylenol overdose), measured by Glukhov et al.\textsuperscript{27}, reproduced with permission. Simulations are below. Cell types are color coded and labeled. CL = 1000 ms.
Alternans Simulation in Coupled Tissue

Figure S10. A strand composed of 100 endo cells was paced at CL = 280 ms until steady state was reached. Beat to beat APD alternans were evident at the central cell (#50, isolated from edge effects).
Alternans were Eliminated by SERCA2a Upregulation

Figure S11. Alternans were eliminated by upregulation of SERCA2a (J_{up} in the model), as in experiments by Cutler et al.\textsuperscript{28}. APD90 is on the left axes in black. Peak intracellular Ca\textsuperscript{2+} concentration ([Ca\textsuperscript{2+}]\textsubscript{Max}) is on the right axes in red. From top to bottom, J_{up} was increased from control by 10, and 20 \%. For 10\% increase in J_{up}, the alternans bifurcation shifted to faster rates. For 20\% increase, the bifurcation was eliminated.
Effects of $H^+$, $CO_2$ and $HCO_3^-$ on $Na^+$ Handling, $I_{NaK}$ and APD Rate Dependence

We kept $Cl^-$ concentration constant, since the ORd model does not systematically include $Cl^-$ handling (20 mM intracellular and 100 mM extracellular, as in Decker et al.\textsuperscript{5}). Otherwise, all Crampin and Smith equations were included exactly as described\textsuperscript{29}. The $I_{NaK}$ formulation we used, based on Smith and Crampin\textsuperscript{23}, includes pH dependence. The simulations below allow $I_{NaK}$ to respond dynamically to pH.

Figure S12. $H^+$, $CO_2$ and $HCO_3^-$ fluxes did not change the relationship between $Na^+$ accumulation, $I_{NaK}$ and APD rate dependence. Top) APD90 rate dependence with incorporation of the Crampin and Smith equations\textsuperscript{29} (black line). When intracellular $Na^+$ concentration ($[Na^+]_i$) was artificially kept low, at the CL = 2000 ms value, the ability of the APD to shorten at fast rates was substantially reduced (gray line). Bottom) Left) As pacing rate increased (indicated by arrows) $I_{NaK}$ increased due to $[Na^+]_i$ accumulation. Right) However, when $[Na^+]_i$ was clamped at the low CL = 2000 ms value, $I_{NaK}$ was rate independent. This hampered APD shortening at fast pacing rates.
Protein forming the β-subunit of $I_{Ks}$, KCNE1 was measured to be transmurally heterogeneous in the undiseased human ventricle\textsuperscript{30}. Western blots showed about two-fold greater intensity for KCNE1 in M-cells compared to epi cells. Considering that KCNE1:KCNQ1 stoichiometry is variable\textsuperscript{31}, and that the presence of KCNE1 slows $I_{Ks}$ activation by about five fold and increases $I_{Ks}$ conductance by about five fold, we simulated the effect of KCNE1 transmural heterogeneity on $I_{Ks}$ and the AP. Thus, for heterogeneous KCNE1 simulations in M-cells, $I_{Ks}$ activation was five times slower and conductance was five times greater than in the control M-cell. For epi cells, activation was five times faster, and conductance was five times smaller than in the control epi cell. These conditions are exaggerated (five fold changes compared KNCE1 overabundance to total KCNE1 absence\textsuperscript{32}), showing possible KCNE1 transmural heterogeneity effects in the extreme. As shown, even for the extreme case there was little effect on $I_{Ks}$ or especially on the AP.

Figure S13. Transmural heterogeneity of KCNE1 β-subunit had minimal effect on transmural heterogeneity of $I_{Ks}$ and the AP. Results for control conditions are solid lines (black is endo, blue is M-cell, red is epi). Dashed lines show the effect of the KCNE1 heterogeneity. Top) AP. Bottom) $I_{Ks}$.
Figure S14. APD90 Accommodation. At time = 0 seconds, pacing CL was abruptly reduced. At time = 180 seconds, the pacing CL was abruptly increased to its original value. CL change from 750 to 480 ms is shown with white circles. Black circles show CL change from 750 to 410 ms. Experiments (top) are from in vivo nonfailing human hearts, measured by Franz et al.33. Simulations are below.
**Figure S15.** Sensitivity of steady state APD90 rate dependence to variations in current conductances and to the fraction of $I_{\text{NaCa}}$ in the myoplasm (80% in the control case). The control case is shown with the thick black line. Parameter reductions are in blue (20% dashed blue, 10% solid blue). Parameter increases are shown in red (10% solid red, 20% dashed red).
Figure S16. Sensitivity of S1S2 restitution of APD90 to variations in current conductances and to the fraction of $I_{NaCa}$ in the myoplasm (80% in the control case). The control case is shown with the thick black line. Parameter reductions are in blue (20% dashed blue, 10% solid blue). Parameter increases are shown in red (10% solid red, 20% dashed red).
Figure S17. Sensitivity of rate dependence of maximum (systolic) intracellular Ca²⁺ concentration (peak [Ca²⁺]) to variations in current conductances and to the fraction of $I_{NaCa}$ in the myoplasm (80% in the control case). The control case is shown with the thick black line. Parameter reductions are in blue (20% dashed blue, 10% solid blue). Parameter increases are shown in red (10% solid red, 20% dashed red).
Figure S18. Sensitivity of rate dependence of intracellular Na⁺ concentration ([Na⁺]_i) to variations in current conductances and to the fraction of I_{NaCa} in the myoplasm (80% in the control case). The control case is shown with the thick black line. Parameter reductions are in blue (20% dashed blue, 10% solid blue). Parameter increases are shown in red (10% solid red, 20% dashed red).
Figure S19. Sensitivity of steady state rate dependence of APD90 in the different transmural cell types to changes in current conductances. The control case is shown with the thick black line. Parameter reductions are in blue (20% dashed blue, 10% solid blue). Parameter increases are shown in red (10% solid red, 20% dashed red).
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