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Supporting Material

IONIC MECHANISMS FOR ELECTRICAL HETEROGENEITY BETWEEN RABBIT PURKINJE AND VENTRICULAR CELLS

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Online Supplement

IONIC MECHANISMS FOR ELECTRICAL HETEROGENEITY BETWEEN RABBIT PURKINJE FIBER AND VENTRICULAR CELLS

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TABLE S1: AP CHARACTERISTICS (see Fig. 8)

Property	Cell	Source	Symbol
APD	PF	Lu *et al.* (2004)	Square
		Gluais *et al.* (2003)	Circle
		Gluais *et al.* (2002)	Inverted triangle
		Ducroq *et al.* (2007)	Hexagon
		Noguchi *et al.* (2001)	Triangle
	Endo	Verkerk *et al.* (2004)	Triangle
		McIntosh *et al.* (2000)	Hexagon
		Yan *et al.* (2001)	Inverted triangle
		Idriss & Wolf (2004)	Circle
		Biagetti *et al.* (2006)	Diamond
	M	McIntosh *et al.* (2000)	Hexagon
		Lu *et al.* (2001)	diamond
	Epi	Verkerk *et al.* (2004)	Triangle
		McIntosh *et al.* (2000)	Hexagon
		Yan *et al.* (2001)	Inverted triangle
		Idriss & Wolf (2004)	Circle
		Biagetti *et al.* (2006)	diamond
dV/dt_{max}	PF	Lu *et al.* (2005)	Hexagon
		Gluais *et al.* (2003)	Diamond
		Gluais *et al.* (2002)	Inverted triangle
		Ducroq *et al.* (2007)	Square
		Lu *et al.* (2002)	Triangle
		Noguchi *et al.*01	Circle
	Endo	Lu *et al.* (2005)	Hexagon
		Gluais *et al.* (2002)	Inverted triangle
		Noguchi *et al.* (2001)	Circle
		Golod *et al.* (1998)	Square
		Gluais *et al.* (2003)	Diamond

	M	Lu *et al.* (2005) Gluais *et al.* (2002) Noguchi *et al.* (2001) Golod *et al.* (1998) Gluais *et al.* (2003)	Hexagon Inverted triangle Circle Square Diamond
	Epi	Lu *et al.* (2005) Gluais *et al.* (2002) Noguchi *et al.* (2001) Golod *et al.* (1998) Gluais *et al.* (2003)	Hexagon Inverted triangle Circle Square Diamond
APA	PF	Lu *et al.* (2005) Lu *et al.* (2002) Gluais *et al.* (2002) Noguchi *et al.* (2001) Ducroq *et al.* (2007) Gluais *et al.* (2003)	Square Inverted triangle Triangle Diamond Hexagon Circle
	Endo	Lu *et al.* (2005) Noguchi *et al.* (2001) Gluais *et al.* (2003) Gluais *et al.* (2002) McIntosh *et al.* (2000)	Square Diamond Circle Triangle Inverted triangle
	M	Lu *et al.* (2005) Noguchi *et al.* (2001) Gluais *et al.* (2003) Gluais *et al.* (2002) McIntosh *et al.* (2000)	Square Diamond Circle Triangle Inverted triangle
	Epi	Lu *et al.* (2005) Noguchi *et al.* (2001) Gluais *et al.* (2003) Gluais *et al.* (2002) McIntosh *et al.* (2000)	Square Diamond Circle Triangle Inverted triangle
MDP	PF	Gluais *et al.* (2003) Lu *et al.* (2002) Ducroq *et al.* (2007) Noguchi *et al.* (2001)	Square Diamond Inverted triangle Hexagon
	Endo	Gluais *et al.* (2003) Noguchi *et al.* (2001) Fedida *et al.* (1991) McIntosh *et al.* (2000) Golod *et al.* (1998)	Square Hexagon Triangle Diamond Circle
	M	Gluais *et al.* (2003)	Square

		Noguchi *et al.* (2001) McIntosh *et al.* (2000) Golod *et al.* (1998)	Hexagon Diamond Circle
	Epi	Gluais *et al.* (2003) Noguchi *et al.* (2001) Fedida *et al.* (1991) McIntosh *et al.* (2000) Golod *et al.* (1998)	Square Hexagon Triangle Diamond Circle

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APPENDIX S2: PF CELL MODEL

General equations

$$\frac{\mathrm{d}V}{\mathrm{d}t} = -\frac{I_{\mathrm{ion}}}{C_m}$$

$$I_{\mathrm{ion}} = I_{\mathrm{Na}} + I_{\mathrm{NaL}} + I_{\mathrm{Ca,L}} + I_{\mathrm{Ca,T}} + I_{\mathrm{to}} + I_{\mathrm{Kr}} + I_{\mathrm{Ks}} + I_{\mathrm{K1}} + I_{\mathrm{Kp}} + I_{\mathrm{NaCa}} + I_{\mathrm{NaK}} + I_{\mathrm{Na,b}} + I_{\mathrm{Ca,b}} + I_{\mathrm{K,b}} + I_{\mathrm{Cl,b}} + I_{\mathrm{SLCa,p}}$$

Fast Na^+ current

$$I_{\mathrm{Na}} = g_{\mathrm{Na}} m^3 hj\left(V - E_{Na}\right)$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \frac{m_\infty - m}{\tau_m}$$

$$m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}, \quad \tau_m = \frac{1.0}{\alpha_m + \beta_m}$$

$$\alpha_m = \frac{0.32\left(V + 47.13\right)}{1 - e^{-0.1(V+47.13)}}, \quad \beta_m = 0.08 e^{-V/11.0}$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = \frac{h_\infty - h}{\tau_h}, \quad \frac{\mathrm{d}j}{\mathrm{d}t} = \frac{j_\infty - j}{\tau_j}$$

$$h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h}, \quad \tau_h = \frac{1.0}{\alpha_h + \beta_h}$$

$$j_\infty = \frac{\alpha_j}{\alpha_j + \beta_j}, \quad \tau_j = \frac{1.0}{\alpha_j + \beta_j}$$

If V >= -40 mV

$$\alpha_h = 0, \quad \beta_h = \frac{1.0}{0.13\left(1.0 + e^{-(V+10.66)/11.1}\right)}$$

$$\alpha_j = 0, \quad \beta_j = \frac{0.3e^{\left(-2.535\times10^{-7}V\right)}}{1.0 + e^{-0.1(V+32.0)}}$$

Else

$$\alpha_h = 0.135e^{-(V+80)/6.8}, \quad \beta_h = 3.56e^{0.079V} + 3.1\times10^5 e^{0.35V}$$

$$\alpha_j = \frac{-1.2714\times10^5 e^{0.2444V} - 3.474\times10^{-5} e^{-0.04391V}(V + 37.78)}{1.0 + e^{0.311(V+79.23)}}$$

$$\beta_j = \frac{0.1212e^{-0.01052V}}{1.0 + e^{-0.1378(V+40.14)}}$$

Late Na⁺ current

$$I_{\mathrm{NaL}} = g_{\mathrm{NaL}} m_L h_L (V - E_{Na})$$

$$\frac{\mathrm{d}m_L}{\mathrm{d}t} = \frac{m_{L\infty} - m_L}{\tau_{mL}}$$

$$m_{L_\infty} = \frac{\alpha_{mL}}{\alpha_{mL} + \beta_{mL}}, \quad \tau_{mL} = \frac{1.0}{\alpha_{mL} + \beta_{mL}}$$

$$\alpha_{m_l} = \frac{0.32(V + 47.13)}{1 - e^{-0.1(V+47.13)}}, \quad \beta_{m_l} = 0.08e^{-V/11.0}$$

$$\frac{\mathrm{d}h_L}{\mathrm{d}t} = \frac{h_{L\infty} - h_L}{\tau_{hL}}$$

$$h_{L\infty} = \frac{1.0}{1.0 + e^{((V+69)/6.1)}}$$

$$\tau_{h_L} = 132.4 + 112.8e^{0.02325V}$$

L-type Ca²⁺ current

$$I_{\mathrm{Ca,L}} = g_{\mathrm{Ca,L}} d f (1 - f_{Ca})(V - 60.0)$$

$$\frac{\mathrm{d}d}{\mathrm{d}t} = \frac{d_\infty - d}{\tau_d}$$

$$d_\infty = \frac{1.0}{1 + e^{-(V-4.0)/6.74}}, \quad \tau_d = \frac{0.59 + 0.8e^{0.52(V+13.0)}}{1 + e^{0.132(V+13.0)}}$$

$$\frac{\mathrm{d}f}{\mathrm{d}t} = \frac{f_\infty - f}{\tau_f}$$

$$f_\infty = \frac{1.0}{1.0+e^{(V+25.0)/10.0}}, \quad \tau_f = 0.005(V-2.5)^{2.0} + 4.0$$

$$\frac{f_{\text{Ca}}}{\mathrm{d}t} = 0.7[\text{Ca}^{2+}]_{\text{jct}}(1-f_{\text{Ca}}) - 0.0119 f_{\text{Ca}}$$

T-type Ca^{2+} current

$$I_{\text{Ca,T}} = g_{\text{Ca,T}} bg (V-50.0)$$

$$\frac{\mathrm{db}}{\mathrm{d}t} = \frac{b_\infty - b}{\tau_b}$$

$$b_\infty = \frac{1.0}{1+e^{-(V+28.0)/6.1}}, \quad \tau_b = \frac{1.0}{\alpha_b + \beta_b}$$

$$\alpha_{\text{b}} = 1.068 e^{(V+16.3)/30.0}, \quad \beta_{\text{b}} = 1.068 e^{-(V+16.3)/30.0}$$

$$\frac{\mathrm{dg}}{\mathrm{d}t} = \frac{g_\infty - g}{\tau_g}$$

$$g_\infty = \frac{1.0}{1.0+\mathrm{e}^{(V+60.0)/6.6}}, \quad \tau_{f_{\text{T}}} = \frac{1.0}{\alpha_{\text{g}} + \beta_{\text{g}}}$$

$$\alpha_g = 0.015 e^{-(V+71.7)/83.33}, \quad \beta_g = 0.015 e^{(V+71.7)/15.38}$$

Transient outward K^+ current

$$I_{\text{to}} = g_{\text{to}} r (0.75 q_1 + 0.25 q_2)(V - E_{\text{K}})$$

$$\frac{\mathrm{d}r}{\mathrm{d}t} = \frac{r_\infty - r}{\tau_r}$$

$$r_\infty = \frac{\alpha_r}{\alpha_r + \beta_r}, \ \tau_r = \frac{0.2}{\alpha_r + \beta_r}$$

$$\alpha_r = 0.0451 e^{0.0304V}, \quad \beta_r = 0.0989 e^{-0.053V}$$

$$\frac{\mathrm{d}q_1}{\mathrm{d}t} = \frac{q_\infty - q_1}{\tau_{q_1}}, \frac{\mathrm{d}q_2}{\mathrm{d}t} = \frac{q_\infty - q_2}{\tau_{q_3}}$$

$$q_\infty = \frac{\alpha_q}{\alpha_q + \beta_q}, \tau_{q_1} = 0.7\left(15 + \frac{20.0}{\alpha_q + \beta_q}\right), \tau_{q_x} = \frac{4.0}{\alpha_q + \beta_q}$$

$$\alpha_q = \frac{0.05415 e^{-(V+12.5)/15}}{1.0 + 0.0513 e^{-(V+12.5)/15}}, \quad \beta_q = \frac{0.05415 e^{(V+33.5)/15}}{1.0 + 0.0513 e^{(V+33.5)/15}}$$

Fast delayed rectifier K^+ current

$$I_{\text{Kr}} = g_{\text{Kr}} X_r R_\infty (V - E_{\text{K}})$$

$$g_{\text{K,r}} = 0.0156 \sqrt{[K^+]_0 / 5.4}$$

$$X_{r\infty} = \frac{1.0}{1.0 + e^{-(V+20.0)/10.5}}, \quad \tau_{Xr} = \frac{1.0\left(1 - e^{-0.123(V+7)}\right)}{0.00138(V+7.0)} + \frac{0.00061(V+10.0)}{e^{0.145(V+10.0)} - 1.0}$$

$$\frac{\mathrm{d}X_r}{\mathrm{d}t} = \frac{X_{r\infty} - X_r}{\tau_{X_r}}$$

$$R_\infty = \frac{1.0}{1.0 + \mathrm{e}^{\mathrm{V}/50}}$$

Slow delayed rectifier K^+ current

$$I_{\mathrm{Ks}} = g_{\mathrm{Ks}} X (V - E_{\mathrm{Ks}})$$

$$g_{\mathrm{Ks}} = 0.07\left(0.057 + \frac{0.19}{1.0 + e^{(-7.2 + p_{Ca})/0.6}}\right)$$

$$p_{Ca} = -1.0 \log_{10}\left([\mathrm{Ca}^{2+}]_i \times 10^{-3}\right) + 3.0$$

$$\frac{\mathrm{d}X}{\mathrm{d}t} = \frac{X_\infty - X}{\tau_X}$$

$$X_\infty = \frac{1.0}{1.0 + e^{-(V-1.5)/20.0}}, \quad \tau_X = \frac{600.0}{1 + \mathrm{e}^{(\mathrm{V}\text{-}20)/15}} + 250.0$$

Inward rectifier K^+ current

$$I_{\mathrm{K1}} = g_{\mathrm{K1}}\left(K1_\infty + 0.008\right)\left(V - E_K\right)$$

$$g_{\mathrm{K1}} = 0.5\sqrt{\left([\mathrm{K}^+]_o / 5.4\right)}$$

$$K1_\infty = \frac{\alpha_{K1}}{\alpha_{K1} + \beta_{K1}}$$

$$\alpha_{K1} = \frac{0.3}{1 + e^{(0.2385(V - E_K - 59.215))}}$$

$$\beta_{K1} = \frac{0.49e^{(0.0803(V - E_K + 5.5))} + e^{(0.06175(V - E_K - 594.31))}}{1.0 + e^{(-0.5143(V - E_K + 4.753))}}$$

Plateau K^+ current

$$I_{\mathrm{Kp}} = g_{\mathrm{Kp}} I_{Kp_{Kp}} \left(V - E_K\right)$$

$$I_{\mathrm{Kp_{Kp}}} = \frac{1.0}{1.0 + e^{(7.488 - V)/5.98}}$$

Ca^{2+} activated Cl^- current

$$I_{\mathrm{Cl}} = \frac{0.3 A_\infty I}{1.0 + 0.1/[\mathrm{Ca}^{2+}]_i}\left(V - E_{Cl}\right)$$

$$A_\infty = \frac{1.0}{1.0 + e^{-(V+5.0)/10.0}}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \frac{I_\infty - I}{\tau_I}$$

$$I_\infty = \frac{1.0}{1.0 + e^{(V+75.0)/10.0}}, \quad \tau_I = \frac{20.0}{\left(1.0 + e^{(V+33.5)/10.0}\right)} + 20.0$$

Na^+-Ca^{2+} exchanger current

$$I_{\mathrm{NaCa}} = \frac{1.8[\mathrm{Na}^+]_i^{\,3}[\mathrm{Ca}^{2+}]_o e^{0.35VF/RT} - 1.5[\mathrm{Na}^+]_o^3[\mathrm{Ca}^{2+}]_i e^{(0.35-1)VF/RT}}{\left(1.0 + \left(0.125/1.5[\mathrm{Ca}^{2+}]_i\right)^2\right)\left(1.0 + 0.27e^{(0.35-1)VF/RT}\right)\left(d_{\mathrm{NaCa}_1} + d_{\mathrm{NaCa2}}\right)}$$

$$d_{\mathrm{NaCa}_1} = K_{mCao}[\mathrm{Na}^+]_i^{\,3} + K_{mNa_o}{}^3 1.5[\mathrm{Ca}^{2+}]_i + K_{mNa_i}{}^3[\mathrm{Ca}^{2+}]_o \left(1.0 + 1.5[\mathrm{Ca}^{2+}]_i / K_{mCa_i}\right)$$

$$d_{\mathrm{NaCa}_2} = K_{mCa_i}[\mathrm{Na}^+]_o^{\,3}\left(1 + ([\mathrm{Na}^+]_i / K_{mNa_i})^3\right) + [\mathrm{Na}^+]_i^{\,3}[\mathrm{Ca}^{2+}]_o + [\mathrm{Na}^+]_o^{\,3} 1.5[\mathrm{Ca}^{2+}]_i$$

Na^+-K^+ pump current

$$I_{\mathrm{NaK}} = 0.6187 f_{\mathrm{NaK}} \frac{[\mathrm{K}^+]_o}{1 + \left(10.0/[\mathrm{Na}^+]_i\right)^2\left([\mathrm{K}^+]_o + 1.5\right)}$$

$$f_{\mathrm{NaK}} = \frac{1.0}{1.0 + 0.1245e^{-0.1VF/RT}} + 0.0365\sigma e^{-0.1VF/RT}$$

$$\sigma = \frac{e^{[Na^+]o/67.3} - 1}{7.0}$$

Ca^{2+} pump current

$$I_{\mathrm{SLCa,p}} = \frac{0.033625}{1.0 + \left(0.5/[\mathrm{Ca}^{2+}]_i\right)^{1.6}}$$

Background currents

$$I_{\mathrm{Na,b}} = g_{\mathrm{Na,b}}(V - E_{\mathrm{Na}}), \quad I_{\mathrm{Ca,b}} = g_{\mathrm{Ca,b}}(V - E_{\mathrm{Ca}}), \quad I_{\mathrm{K,b}} = g_{\mathrm{K,b}}(V - E_{\mathrm{K}}),$$
$$I_{\mathrm{Cl,b}} = g_{\mathrm{Cl,b}}(V - E_{\mathrm{Cl}})$$

TABLE S2. Model parameter values

C_m	66 pF
g_{Na}	2×10^{-2} μS/pF
g_{NaL}	1.62×10^{-5} μS/pF
$g_{Ca,L}$	2.7×10^{-4} μS/pF
$g_{Ca,T}$	2.0×10^{-4} μS/pF
g_{to}	1.12×10^{-4} μS/pF

g_{Kp}	1×10^{-6} μS/pF
$g_{\mathrm{Na,b}}$	2.97×10^{-8} μS/pF
$g_{\mathrm{Ca,b}}$	3.52×10^{-7} μS/pF
$g_{\mathrm{K,b}}$	5×10^{-8} μS/pF
$g_{\mathrm{Cl,b}}$	2.7×10^{-7} μS/pF
K_{mCao}	1.3 mM
K_{mNao}	87.5 mM
K_{mNai}	12.29 mM
K_{mCai}	3.59×10^{-3} μM
$[Na^+]_o$	140.0 mM
$[Ca^{2+}]_o$	1.800 mM
$[K^+]_o$	5.400 mM
$[Cl^-]_o$	150 mM
$[Na^+]_i$	8.8 mM
$[Ca^{2+}]_i$	0.100 μM
$[K^+]_i$	135 mM
$[Cl^-]_i$	30 mM
R	8314 mJ/mol ^{o}C
F	96487 C/mol
T	35^{o}C

APPENDIX S3: VENTRICULAR CELL MODEL

General equations

$$\frac{\mathrm{d}V}{\mathrm{d}t} = -\frac{I_{\mathrm{ion}}}{C_m}$$

$$I_{\mathrm{ion}} = I_{\mathrm{Na}} + I_{\mathrm{Ca,L}} + I_{\mathrm{to}} + I_{\mathrm{Kr}} + I_{\mathrm{Ks}} + I_{\mathrm{K1}} + I_{\mathrm{Kp}} + I_{\mathrm{NaCa}} + I_{\mathrm{NaK}} + I_{\mathrm{Na,b}} + I_{\mathrm{Ca,b}} + I_{\mathrm{Cl,b}} + I_{\mathrm{K,b}} + I_{\mathrm{SLCa,p}}$$

Fast Na$^+$ current

$$I_{\mathrm{Na}} = g_{\mathrm{Na}} m^3 hj\left(V - E_{Na}\right)$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \frac{m_\infty - m}{\tau_m}$$

$$m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}, \quad \tau_m = \frac{1.0}{\alpha_m + \beta_m}$$

$$\alpha_m = \frac{0.32(V+47.13)}{1-e^{-0.1(V+47.13)}}, \quad \beta_m = 0.08e^{-V/11.0}$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = \frac{h_\infty - h}{\tau_h}, \quad \frac{\mathrm{d}j}{\mathrm{d}t} = \frac{j_\infty - j}{\tau_j}$$

$$h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h}, \quad \tau_h = \frac{1.0}{\alpha_h + \beta_h}$$

$$j_\infty = \frac{\alpha_j}{\alpha_j + \beta_j}, \quad \tau_j = \frac{1.0}{\alpha_j + \beta_j}$$

If V >= -40 mV

$$\alpha_h = 0, \quad \beta_h = \frac{1.0}{0.13\left(1.0 + e^{-(V+10.66)/11.1}\right)}$$

$$\alpha_j = 0, \quad \beta_j = \frac{0.3e^{\left(-2.535\times10^{-7}V\right)}}{1.0 + e^{-0.1(V+32.0)}}$$

Else

$$\alpha_h = 0.135e^{-(V+80)/6.8}, \quad \beta_h = 3.56e^{0.079V} + 3.1\times10^5 e^{0.35V}$$

$$\alpha_j = \frac{-1.2714\times10^5 e^{0.2444V} - 3.474\times10^{-5} e^{-0.0439V}(V+37.78)}{1.0 + e^{0.311(V+79.23)}}$$

$$\beta_j = \frac{0.1212e^{-0.01052V}}{1.0 + e^{-0.1378(V+40.14)}}$$

Late Na^+ current

$$I_{\mathrm{NaL}} = g_{\mathrm{NaL}} m_L h_L (V - E_{Na})$$

$$\frac{\mathrm{d}m_L}{\mathrm{d}t} = \frac{m_{L\infty} - m_L}{\tau_{mL}}$$

$$m_{L\infty} = \frac{\alpha_{mL}}{\alpha_{mL} + \beta_{mL}}, \quad \tau_{mL} = \frac{1.0}{\alpha_{mL} + \beta_{mL}}$$

$$\alpha_{m_l} = \frac{0.32(V+47.13)}{1-e^{-0.1(V+47.13)}}, \quad \beta_{m_l} = 0.08e^{-V/11.0}$$

$$\frac{\mathrm{d}h_L}{\mathrm{d}t} = \frac{h_{L\infty} - h_L}{\tau_{hL}}$$

$$h_{L\infty} = \frac{1.0}{1.0 + e^{((V+69)/6.1)}}$$

$$\tau_{h_L} = 132.4 + 112.8e^{0.02325V}$$

L-type Ca^{2+} current

$$I_{\mathrm{Ca,L}} = g_{\mathrm{Ca,L}} d(0.8f_1 + 0.2f_2)(1 - f_{\mathrm{Ca}})(V - 60.0)$$

$$\frac{\mathrm{d}d}{\mathrm{d}t} = \frac{d_\infty - d}{\tau_d}$$

$$d_\infty = \frac{1.0}{1 + e^{-(V+8.5)/4.0}}, \quad \tau_d = 0.4\left(\frac{1.0}{1.0 + e^{-(V+8.5)/4.0}}\right)\left(\frac{1 - e^{-(V+8.5)/4.0}}{0.035(V+8.5)}\right)$$

$$\frac{\mathrm{d}f_1}{\mathrm{d}t} = \frac{f_\infty - f_1}{\tau_{f_1}}, \quad \frac{\mathrm{d}f_2}{\mathrm{d}t} = \frac{f_\infty - f_2}{\tau_{f_2}}$$

$$f_\infty = \frac{1.0}{1.0 + e^{(V+28.06)/6.0}},$$

$$\tau_{f_1} = 8 + \frac{20.0}{1.0 + e^{-(V-20)/5}} - \frac{20.0}{1.0 + e^{-(V-40)/5}}, \tau_{f_2} = 5 + \frac{30.0}{1.0 + e^{-(V-30)/5}} + 55.0$$

$$\frac{f_{\mathrm{Ca}}}{\mathrm{d}t} = 0.275[\mathrm{Ca}^{2+}]_{\mathrm{jct}}(1 - f_{\mathrm{Ca}}) - 0.0029 f_{\mathrm{Ca}}$$

Transient outward K$^+$ current

$$I_{\mathrm{to}} = I_{tos} + I_{tos}$$
$$I_{\mathrm{tos}} = g_{\mathrm{tos}} X_{tos}(Y_{tos} + 0.5R_{s\infty})(V - E_K)$$
$$I_{\mathrm{tof}} = g_{\mathrm{tof}} X_{tof} Y_{tof}(V - E_K)$$

$$\frac{\mathrm{d}X_{tos}}{\mathrm{d}t} = \frac{X_{tos_\infty} - X_{tos}}{\tau_{Xtos}}, \quad \frac{\mathrm{d}Y_{tos}}{\mathrm{d}t} = \frac{Y_{tos_\infty} - Y_{tos}}{\tau_{Ytos}}, \frac{\mathrm{d}X_{tof}}{\mathrm{d}t} = \frac{X_{tof_\infty} - X_{tof}}{\tau_{Xtof}}, \frac{\mathrm{d}Y_{tof}}{\mathrm{d}t} = \frac{Y_{tof_\infty} - Y_{tof}}{\tau_{Ytof}}$$

$$X_{tos_\infty} = \frac{1.0}{(1.0 + e^{-(V+3.0)/15})}, \tau_{Xtos} = \frac{9.0}{1.0 + \mathrm{e}^{(V+3.0)/15}} + 0.5$$

$$Y_{tos_\infty} = \frac{1.0}{(1.0 + e^{(V+33.5)/10})}, \tau_{Ytos} = \frac{3000.0}{1.0 + \mathrm{e}^{(V+60.0)/10}} + 30$$

$$X_{tof_\infty} = \frac{1.0}{(1.0 + e^{-(V+3.0)/15})}, \tau_{Xtof} = 3.5e^{-(V/30)^2} + 1.5$$

$$Y_{tof_\infty} = \frac{1.0}{(1.0 + e^{(V+33.5)/10})}, \tau_{Ytof} = \frac{20.0}{1.0 + \mathrm{e}^{(V+33.5)/10}} + 20$$

$$R_{s_\infty} = \frac{1.0}{(1.0 + e^{(V+33.5)/10})}$$

Fast delayed rectifier K$^+$ current

$$I_{\mathrm{Kr}} = g_{\mathrm{Kr}} X_r R_\infty (V - E_{\mathrm{K}})$$
$$g_{\mathrm{Kr}} = 0.03\sqrt{[\mathrm{K}^+]_0 / 5.4}$$

$$X_{r\infty} = \frac{1.0}{1.0 + e^{-(V+50.0-35)/7.5}}, \quad \tau_{Xr} = \frac{1.0(1 - e^{-0.123(V+7-35)})}{0.00138(V + 7.0 - 35)} + \frac{0.00061(V + 10.0 - 35)}{e^{0.145(V+10.0-35)} - 1.0}$$

$$\frac{\mathrm{d}X_r}{\mathrm{d}t} = \frac{X_{r\infty} - X_r}{\tau_{X_r}}$$

$$R_{\infty} = \frac{1.0}{1.0 + 6.0\,\mathrm{e}^{0.05\mathrm{V}}}$$

Slow delayed rectifier K+ current

$$I_{\mathrm{Ks}} = g_{\mathrm{ks}} g_{\mathrm{Ks,SL}} X^2 (V - E_{\mathrm{K}})$$

$$g_{\mathrm{Ks,SL}} = 0.14\left(0.057 + \frac{0.19}{1.0 + e^{(-7.2 + p_{Ca})/0.6}}\right)$$

$$p_{Ca} = -1.0\log_{10}\left([\mathrm{Ca}^{2+}]_i \times 10^{-3}\right) + 3.0$$

$$\frac{\mathrm{d}X}{\mathrm{d}t} = \frac{X_{\infty} - X}{\tau_X}$$

$$X_{\infty} = \frac{1.0}{1.0 + e^{-(V-1.5)/13.0}}, \quad \tau_X = \frac{300.0}{1.0 + \mathrm{e}^{(\mathrm{V-20})/15.0}} + 125.0$$

Inward rectifier K+ current

$$I_{\mathrm{K1}} = g_{\mathrm{K1}} K1_{\infty} (V - E_K)$$

$$K1_{\infty} = \frac{\alpha_{K1}}{\alpha_{K1} + \beta_{K1}}$$

$$\alpha_{K1} = \frac{1.02}{1 + e^{(0.2385(V - E_K - 59.215 - 5))}}$$

$$\beta_{K1} = \frac{0.49 e^{(0.0803(V - E_K + 5.5 - 5))} + e^{(0.06175(V - E_K - 594.31 - 5))}}{1.0 + e^{(-0.5143(V - E_K + 4.753 - 5))}}$$

Plateau K+ current

$$I_{\mathrm{Kp}} = g_{\mathrm{Kp}} I_{Kp_{Kp}} (V - E_K)$$

$$I_{\mathrm{Kp_{Kp}}} = \frac{1.0}{1.0 + e^{(7.488 - V)/5.98}}$$

Ca2+ actvation Cl- Current

$$I_{\mathrm{Cl}} = \frac{g_{Cl} A_{\infty} I}{1.0 + 0.1/[\mathrm{Ca}^{2+}]_i} (V - E_{\mathrm{Cl}})$$

$$A_{\infty} = \frac{1.0}{1.0 + e^{-(V+5.0)/10.0}}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \frac{I_{\infty} - I}{\tau_I}$$

$$I_{\infty} = \frac{1.0}{1.0 + \mathrm{e}^{(\mathrm{V}+75.0)/10.0}}, \quad \tau_I = \frac{10.0}{\left(1.0 + \mathrm{e}^{(\mathrm{V}+33.5)/10.0}\right)} + 10.0$$

Na^+-Ca^{2+} exchanger current

$$I_{\mathrm{NaCa}} = \frac{\mathrm{A} - [\mathrm{Na}^+]_o^3 [\mathrm{Ca}^{2+}]_i e^{(0.35-1)VF/RT}}{\left(1.0 + 0.27 e^{(0.35-1)VF/RT}\right)\left(d_{\mathrm{NaCa}_1} + d_{\mathrm{NaCa}2}\right)}$$

$$\mathrm{A} = 9.0\left(\left([\mathrm{Na}^+]_i{}^3 [\mathrm{Ca}^{2+}]_o e^{0.35VF/RT}\right)\right)\frac{1.0}{1.0 + \left(0.256/[\mathrm{Ca}^{2+}]_i\right)^3}$$

$$d_{\mathrm{NaCa}_1} = K_{mCao}[\mathrm{Na}^+]_i{}^3 + K_{mNa_o}{}^3[\mathrm{Ca}^{2+}]_i + K_{mNa_i}{}^3[\mathrm{Ca}^{2+}]_o\left(1.0 + [\mathrm{Ca}^{2+}]_i / K_{mCa_i}\right)$$

$$d_{\mathrm{NaCa}_2} = K_{mCa_i}[\mathrm{Na}^+]_o{}^3\left(1 + ([\mathrm{Na}^+]_i / K_{mNa_i})^3\right) + [\mathrm{Na}^+]_i{}^3[\mathrm{Ca}^{2+}]_o + [\mathrm{Na}^+]_o{}^3[\mathrm{Ca}^{2+}]_i$$

Na^+-K^+ pump current

$$I_{\mathrm{NaK}} = 1.907 f_{Nak}\frac{[\mathrm{K}^+]_o}{1 + \left(11.0/[\mathrm{Na}^+]_i\right)^4}\left([\mathrm{K}^+]_o + 1.5\right)$$

$$f_{NaK} = \frac{1.0}{1.0 + 0.1245 e^{-0.1VF/RT}} + 0.0365\sigma e^{-0.1VF/RT}$$

$$\sigma = \frac{e^{[\mathrm{Na}^+]_o/67.3} - 1}{7.0}$$

Ca^{2+} pump current

$$I_{\mathrm{SLCa,p}} = \frac{0.067}{1.0 + \left(0.5/[\mathrm{Ca}^{2+}]_i\right)^{1.6}}$$

Background currents

$$I_{\mathrm{Na,b}} = g_{\mathrm{Na,b}}(V - E_{\mathrm{Na}}), \quad I_{\mathrm{Ca,b}} = g_{\mathrm{Ca,b}}(V - E_{\mathrm{Ca}}), \quad I_{\mathrm{Cl,b}} = g_{\mathrm{Cl,b}}(V - E_{\mathrm{Cl}})$$

TABLE S3. Model parameter values

	Endo	M	Epi
C_m	88 pF	88 pF	88 pF
g_{Na}	8.0 ×10^{-3} µS/pF	8.0 ×10^{-3} µS/pF	8.0 ×10^{-3} µS/pF
g_{NaL}	1.62 ×10^{-6} µS/pF	1.62 ×10^{-6} µS/pF	1.62 ×10^{-6} µS/pF
g_{Ks}	1.0	0.7	1.5
g_{tos}	1.7×10^{-5} µS/pF	8.5×10^{-6} µS/pF	3.12×10^{-5} µS/pF
g_{tof}	9×10^{-5} µS/pF	5.1×10^{-5} µS/pF	1.17×10^{-4} µS/pF
$g_{Ca,L}$	4.0×10^{-4} µS/pF	4.4×10^{-4} µS/pF	4.0×10^{-4} µS/pF
g_{K1}	4.5×10^{-4} µS/pF	4.2×10^{-4} µS/pF	5.4×10^{-4} µS/pF

g_{Kp}	1×10^{-6} μS/pF	1×10^{-6} μS/pF	1×10^{-6} μS/pF
g_{Cl}	1×10^{-4} μS/pF	1×10^{-4} μS/pF	1×10^{-4} μS/pF
$g_{Na,b}$	1.49×10^{-6} μS/pF	1.49×10^{-6} μS/pF	1.49×10^{-6} μS/pF
$g_{Ca,b}$	2.513×10^{-7} μS/pF	2.513×10^{-7} μS/pF	2.513×10^{-7} μS/pF
$g_{K,b}$	0.0×10^{-3} μS/pF	0.0×10^{-3} μS/pF	0.0×10^{-3} μS/pF
$g_{Cl,b}$	6.75×10^{-6} μS/pF	2.25×10^{-6} μS/pF	7.2×10^{-6} μS/pF
K_{mCao}	1.3 mM	1.3 mM	1.3 mM
K_{mNao}	87.5 mM	87.5 mM	87.5 mM
K_{mNai}	12.29 mM	12.29 mM	12.29 mM
K_{mCai}	3.59×10^{-3} μM	3.59×10^{-3} μM	3.59×10^{-3} μM
$[Na^+]_o$	140.0 mM	140.0 mM	140.0 mM
$[Ca^{2+}]_o$	1.800 mM	1.800 mM	1.800 mM
$[K^+]_o$	5.400 mM	5.400 mM	5.400 mM
$[Cl^-]_o$	150 mM	150 mM	150 mM
$[Na^+]_i$	8.8 mM	8.8 mM	8.8 mM
$[Ca^{2+}]_i$	0.100 μM	0.100 μM	0.100 μM
$[K^+]_i$	135 mM	135 mM	135 mM
$[Cl^-]_i$	30 mM	30 mM	30 mM
R	8314 mJ/mol °C	8314 mJ/mol °C	8314 mJ/mol °C
F	96487 C/mol	96487 C/mol	96487 C/mol
T	35°C	35°C	35°C

APPENDIX S4: Ca^{2+} HANDLING

Intracellular Ca^{2+} handling

$$\frac{d[Ca^{2+}]_i}{dt} = -\frac{Vol_{SR}}{Vol_{cyt}} J_{pump,SR} + \frac{J_{Ca,SL\text{-}cyt}}{Vol_{cyt}} - dCa_{cyt,bound}$$

In PF cells

$$\frac{d[Ca^{2+}]_{SL}}{dt} = -0.5\frac{I_{Ca,b} + I_{Ca,p} - 2I_{NaCa}}{2Vol_{SL}F} + \frac{J_{Ca,jct\text{-}SL} - J_{Ca,SL\text{-}cyt}}{Vol_{SL}} - dCa_{SL,bound}$$

$$\frac{d[Ca^{2+}]_{jct}}{dt} = -0.5\frac{I_{Ca,L} + I_{Ca,T}}{2Vol_{jct}F} + \frac{Vol_{SL}}{Vol_{jct}} J_{rel,SR} + \frac{Vol_{cyt}}{Vol_{jct}} J_{leak,SR} - \frac{J_{Ca,jct\text{-}SL}}{Vol_{jct}} - dCa_{jct,bound}$$

In ventricular cells

$$\frac{\mathrm{d}[\mathrm{Ca}^{2+}]_{\mathrm{SL}}}{\mathrm{d}t} = -0.65\frac{I_{\mathrm{Ca,b}} + I_{\mathrm{Ca,p}} - 2I_{\mathrm{NaCa}}}{2\mathrm{Vol}_{\mathrm{SL}}F} + \frac{J_{\mathrm{Ca,jct\text{-}SL}} - J_{\mathrm{Ca,SL\text{-}cyt}}}{\mathrm{Vol}_{\mathrm{SL}}} - \mathrm{dCa}_{\mathrm{SL,bound}}$$

$$\frac{\mathrm{d}[\mathrm{Ca}^{2+}]_{\mathrm{jct}}}{\mathrm{d}t} = -0.65\frac{I_{\mathrm{Ca,L}} + I_{\mathrm{Ca,T}}}{2\mathrm{Vol}_{\mathrm{jct}}F} + \frac{\mathrm{Vol}_{\mathrm{SL}}}{\mathrm{Vol}_{\mathrm{jct}}}J_{\mathrm{rel,SR}} + \frac{\mathrm{Vol}_{\mathrm{cyt}}}{\mathrm{Vol}_{\mathrm{jct}}}J_{\mathrm{leak,SR}} - \frac{J_{\mathrm{Ca,jct\text{-}SL}}}{\mathrm{Vol}_{\mathrm{jct}}} - \mathrm{dCa}_{\mathrm{jct,bound}}$$

$$\frac{\mathrm{d}[\mathrm{Ca}^{2+}]_{\mathrm{SR}}}{\mathrm{d}t} = J_{\mathrm{pump,SR}} - \left(J_{\mathrm{rel,SR}} + \frac{\mathrm{Vol}_{\mathrm{cyt}}}{\mathrm{Vol}_{\mathrm{SR}}}J_{\mathrm{leak,SR}}\right) - \mathrm{dCa}_{\mathrm{CQSN}}$$

$$J_{\mathrm{Ca,jct\text{-}SL}} = 0.8241\left([\mathrm{Ca}^{2+}]_{\mathrm{jct}} - [\mathrm{Ca}^{2+}]_{\mathrm{SL}}\right), \quad J_{\mathrm{Ca,SL\text{-}cyt}} = 3.7243\left([\mathrm{Ca}^{2+}]_{\mathrm{SL}} - [\mathrm{Ca}^{2+}]_{\mathrm{i}}\right)$$

In PF cells

$$J_{\mathrm{pump,SR}} = 2.0V_{\mathrm{max}}\frac{\mathrm{Vol}_{\mathrm{cyt}}}{\mathrm{Vol}_{\mathrm{SR}}}\frac{\left([\mathrm{Ca}^{2+}]_{\mathrm{i}}/K_{\mathrm{m,f}}\right)^{\mathrm{H}} - \left([\mathrm{Ca}^{2+}]_{\mathrm{SR}}/K_{\mathrm{m,r}}\right)^{\mathrm{H}}}{1.0 + \left([\mathrm{Ca}^{2+}]_{\mathrm{i}}/K_{\mathrm{m,f}}\right)^{\mathrm{H}} + \left([\mathrm{Ca}^{2+}]_{\mathrm{SR}}/K_{\mathrm{m,r}}\right)^{\mathrm{H}}}$$

$$J_{\mathrm{rel,SR}} = 2.0k_{\mathrm{s}}O\left([\mathrm{Ca}^{2+}]_{\mathrm{SR}} - [\mathrm{Ca}^{2+}]_{\mathrm{jct}}\right), \quad J_{\mathrm{leak,SR}} = 0.5k_{\mathrm{leak,SR}}\left([\mathrm{Ca}^{2+}]_{\mathrm{SR}} - [\mathrm{Ca}^{2+}]_{\mathrm{jct}}\right)$$

In ventricular cells

$$J_{\mathrm{pump,SR}} = V_{\mathrm{max}}\frac{\mathrm{Vol}_{\mathrm{cyt}}}{\mathrm{Vol}_{\mathrm{SR}}}\frac{\left([\mathrm{Ca}^{2+}]_{\mathrm{i}}/K_{\mathrm{m,f}}\right)^{\mathrm{H}} - \left([\mathrm{Ca}^{2+}]_{\mathrm{SR}}/K_{\mathrm{m,r}}\right)^{\mathrm{H}}}{1.0 + \left([\mathrm{Ca}^{2+}]_{\mathrm{i}}/K_{\mathrm{m,f}}\right)^{\mathrm{H}} + \left([\mathrm{Ca}^{2+}]_{\mathrm{SR}}/K_{\mathrm{m,r}}\right)^{\mathrm{H}}}$$

$$J_{\mathrm{rel,SR}} = k_{\mathrm{s}}O\left([\mathrm{Ca}^{2+}]_{\mathrm{SR}} - [\mathrm{Ca}^{2+}]_{\mathrm{jct}}\right), \quad J_{\mathrm{leak,SR}} = k_{\mathrm{leak,SR}}\left([\mathrm{Ca}^{2+}]_{\mathrm{SR}} - [\mathrm{Ca}^{2+}]_{\mathrm{jct}}\right)$$

$$k_{\mathrm{Ca\text{-}SR}} = Max_{\mathrm{SR}} - \frac{Max_{\mathrm{SR}} - Min_{\mathrm{SR}}}{1.0 + \left(EC_{50\text{-}\mathrm{SR}}/[\mathrm{Ca}^{2+}]_{\mathrm{SR}}\right)^{2.5}}, \quad k_{\mathrm{o,Ca\text{-}SR}} = \frac{k_{\mathrm{o,Ca}}}{k_{\mathrm{Ca\text{-}SR}}}, \quad k_{\mathrm{i,Ca\text{-}SR}} = k_{\mathrm{i,Ca}}k_{\mathrm{Ca\text{-}SR}}$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \left(k_{\mathrm{i,m}}RI - k_{\mathrm{i,Ca\text{-}SR}}[\mathrm{Ca}^{2+}]_{\mathrm{jct}}R\right) - \left(k_{\mathrm{o,Ca\text{-}SR}}[\mathrm{Ca}^{2+}]_{\mathrm{jct}}^2R - k_{\mathrm{o,m}}O\right)$$

$$\frac{\mathrm{d}O}{\mathrm{d}t} = \left(k_{\mathrm{o,Ca\text{-}SR}}[\mathrm{Ca}^{2+}]_{\mathrm{jct}}^2R - k_{\mathrm{o,m}}O\right) - \left(k_{\mathrm{i,Ca\text{-}SR}}[\mathrm{Ca}^{2+}]_{\mathrm{jct}}O - k_{\mathrm{i,m}}I\right)$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \left(k_{\mathrm{i,Ca\text{-}SR}}[\mathrm{Ca}^{2+}]_{\mathrm{jct}}O - k_{\mathrm{i,m}}I\right) - \left(k_{\mathrm{o,m}}I - k_{\mathrm{o,Ca\text{-}SR}}[\mathrm{Ca}^{2+}]_{\mathrm{jct}}^2RI\right)$$

$$\frac{\mathrm{d}RI}{\mathrm{d}t} = \left(k_{\mathrm{o,m}}I - k_{\mathrm{o,Ca\text{-}SR}}[\mathrm{Ca}^{2+}]_{\mathrm{jct}}^2RI\right) - \left(k_{\mathrm{i,m}}RI - k_{\mathrm{i,Ca\text{-}SR}}[\mathrm{Ca}^{2+}]_{\mathrm{jct}}R\right)$$

Intracellular Ca^{2+} buffering

$$\mathrm{dCa}_{\mathrm{cyt,bound}} = \mathrm{dCa}_{\mathrm{TRPN}} + \mathrm{dCa}_{\mathrm{TRPN,Ca\text{-}Mg}} + \mathrm{dMg}_{\mathrm{TRPN,Ca\text{-}Mg}} + \mathrm{dCa}_{\mathrm{CMDN}} + \mathrm{dCa}_{\mathrm{MSN}} + \mathrm{dCa}_{\mathrm{SR\text{-}B}}$$

$$\mathrm{dCa}_{\mathrm{jct,bound}} = \mathrm{dCa}_{\mathrm{jct,SL\text{-}B}} + \mathrm{dCa}_{\mathrm{jct,SL\text{-}H}}, \quad \mathrm{dCa}_{\mathrm{SL,bound}} = \mathrm{dCa}_{\mathrm{SL,SL\text{-}B}} + \mathrm{dCa}_{\mathrm{SL,SL\text{-}H}}$$

$$\mathrm{dCa}_{\mathrm{TRPN}} = 32{,}700.0[\mathrm{Ca}^{2+}]_{\mathrm{i}}\left(0.07 - [\mathrm{Ca}^{2+}]_{\mathrm{TRPN}}\right) - 19.6[\mathrm{Ca}^{2+}]_{\mathrm{TRPN}}$$

$$\mathrm{dCa}_{\mathrm{TRPN,Ca\text{-}Mg}} = 2{,}3700.0[\mathrm{Ca}^{2+}]_{\mathrm{i}}\left(0.14 - S_{\mathrm{TRPN,Ca\text{-}Mg}}\right) - 0.032[\mathrm{Ca}^{2+}]_{\mathrm{TRPN,Ca\text{-}Mg}}$$

$$\mathrm{dMg}_{\mathrm{TRPN,Ca\text{-}Mg}} = 3.0[\mathrm{Mg}^{2+}]_{\mathrm{i}}\left(0.14 - S_{\mathrm{TRPN,Ca\text{-}Mg}}\right) - 3.33[\mathrm{Mg}^{2+}]_{\mathrm{TRPN,Ca\text{-}Mg}}$$

$$S_{\mathrm{TRPN,Ca\text{-}Mg}} = [\mathrm{Ca}^{2+}]_{\mathrm{TRPN,Ca\text{-}Mg}} + [\mathrm{Mg}^{2+}]_{\mathrm{TRPN,Ca\text{-}Mg}}$$

$$\mathrm{dCa}_{\mathrm{CMDN}} = 34{,}000.0[\mathrm{Ca}^{2+}]_{\mathrm{i}}\left(0.024 - [\mathrm{Ca}^{2+}]_{\mathrm{CMDN}}\right) - 238.0[\mathrm{Ca}^{2+}]_{\mathrm{CMDN}}$$

$$\mathrm{dCa}_{\mathrm{MSN}} = 13{,}800.0[\mathrm{Ca}^{2+}]_{\mathrm{i}}\left(0.14 - [\mathrm{Ca}^{2+}]_{\mathrm{MSN}}\right) - 0.46[\mathrm{Ca}^{2+}]_{\mathrm{MSN}}$$

$$\mathrm{dCa}_{\mathrm{SR\text{-}B}} = 100{,}000.0[\mathrm{Ca}^{2+}]_{\mathrm{i}}\left(0.0171 - [\mathrm{Ca}^{2+}]_{\mathrm{SR\text{-}B}}\right) - 60.0[\mathrm{Ca}^{2+}]_{\mathrm{SR\text{-}B}}$$

$$\mathrm{dCa}_{\mathrm{jct,SL\text{-}B}} = 100{,}000.0[\mathrm{Ca}^{2+}]_{\mathrm{jct}}\left(\frac{\mathrm{Vol}_{\mathrm{cyt}}}{\mathrm{Vol}_{\mathrm{jct}}}0.0046 - [\mathrm{Ca}^{2+}]_{\mathrm{jct,SL\text{-}B}}\right) - 1{,}300.0[\mathrm{Ca}^{2+}]_{\mathrm{jct,SL\text{-}B}}$$

$$\mathrm{dCa}_{\mathrm{jct,SL\text{-}H}} = 100{,}000.0[\mathrm{Ca}^{2+}]_{\mathrm{jct}}\left(\frac{\mathrm{Vol}_{\mathrm{cyt}}}{\mathrm{Vol}_{\mathrm{jct}}}0.00165 - [\mathrm{Ca}^{2+}]_{\mathrm{jct,SL\text{-}H}}\right) - 30{,}000.0[\mathrm{Ca}^{2+}]_{\mathrm{jct,SL\text{-}H}}$$

$$\mathrm{dCa}_{\mathrm{SL,SL\text{-}B}} = 100{,}000.0[\mathrm{Ca}^{2+}]_{\mathrm{SL}}\left(\frac{\mathrm{Vol}_{\mathrm{cyt}}}{\mathrm{Vol}_{\mathrm{SL}}}0.0374 - [\mathrm{Ca}^{2+}]_{\mathrm{SL,SL\text{-}B}}\right) - 1{,}300.0[\mathrm{Ca}^{2+}]_{\mathrm{SL,SL\text{-}B}}$$

$$\mathrm{dCa}_{\mathrm{jct,SL\text{-}H}} = 100{,}000.0[\mathrm{Ca}^{2+}]_{\mathrm{SL}}\left(\frac{\mathrm{Vol}_{\mathrm{cyt}}}{\mathrm{Vol}_{\mathrm{SL}}}0.00165 - [\mathrm{Ca}^{2+}]_{\mathrm{SL,SL\text{-}H}}\right) - 30{,}000.0[\mathrm{Ca}^{2+}]_{\mathrm{SL,SL\text{-}H}}$$

$$\mathrm{dCa}_{\mathrm{CQSN}} = 100{,}000.0[\mathrm{Ca}^{2+}]_{\mathrm{SR}}\left(\frac{\mathrm{Vol}_{\mathrm{cyt}}}{\mathrm{Vol}_{\mathrm{SR}}}0.14 - [\mathrm{Ca}^{2+}]_{\mathrm{CQSN}}\right) - 65{,}000.0[\mathrm{Ca}^{2+}]_{\mathrm{CQSN}}$$

$$\frac{\mathrm{d}[\mathrm{Ca}^{2+}]_{\mathrm{X}}}{\mathrm{d}t} = \mathrm{dCa}_{\mathrm{X}}, \quad \frac{\mathrm{d}[\mathrm{Mg}^{2+}]_{\mathrm{TPRN,Ca\text{-}Mg}}}{\mathrm{d}t} = \mathrm{dMg}_{\mathrm{TPRN,Ca\text{-}Mg}}$$

TABLE S4: Model parameter values

$\mathrm{Vol}_{\mathrm{cell}}$	33 pL
$\mathrm{Vol}_{\mathrm{cyt}}$	21.45 pL
$\mathrm{Vol}_{\mathrm{SR}}$	1.155 pL
$\mathrm{Vol}_{\mathrm{SL}}$	0.66 pL
$\mathrm{Vol}_{\mathrm{jct}}$	0.016 pL
$[\mathrm{Mg}^{2+}]_{\mathrm{i}}$	1.000 mM
V_{max}	2.860 mM s^{-1}
$K_{\mathrm{m,f}}$	0.000246 mM
$K_{\mathrm{m,r}}$	1.700 mM
H	1.787
k_{s}	125,000.0 s^{-1}
$k_{\mathrm{leak,SR}}$	0.005348 s^{-1}
Max_{SR}	15.00
Min_{SR}	1.000

$EC_{50\text{-}SR}$	0.450 mM
$k_{o,Ca}$	10,000.0 mM^{-2} s^{-1}
$k_{i,Ca}$	500.0 mM s^{-1}
$k_{o,m}$	60.00 s^{-1}
$k_{i,m}$	5.000 s^{-1}

SUPPLEMENTARY FIGURE LEGENDS

Figure S1. Simulated effects of 50% (light grey bars) and 100% (dark grey bars) block of $I_{Ca,L}$ on the APD in PF, Endo, M and Epi cell models. Black bars indicate control values. A: APD at (i) 500 ms, (ii) 1000 ms, (iii) 2000 ms basic cycle length. B: absolute changes in APD from control due to the block. C: percentage changes in APD from control.

Figure S2. Simulated effects of 50% (light grey) and 100% (dark grey) block of I_{NaL} on APD in PF, Endo, M and Epi cell models. Black bars indicate control values. A: APD at (i) 500 ms, (ii) 1000 ms, (iii) 2000 ms basic cycle length. B: absolute changes in APD from control due to the block. C: percentage changes in APD from control.

Figure S3. Simulated effects of 50% (light grey) and 100% (dark grey) block of I_{to} on APD in PF, Endo, M and Epi cell models. Black bars indicate control values. A: APD at (i) 500 ms, (ii) 1000 ms, (iii) 2000 ms basic cycle length. B: absolute changes in APD from control due to the block. C: percentage changes in APD from control.

Figure S4. Simulated effects of 50% (light grey) and 100% (dark grey) block of I_{Kr} on APD in PF, Endo, M and Epi cell models. Black bars indicate control values. A: APD at (i) 500 ms, (ii) 1000 ms, (iii) 2000 ms basic cycle length. B: absolute changes in APD from control due to the block. C: percentage changes in APD from control. Symbols represent experimental values.

Figure S5. Simulated effects of 50% (light grey) and 100% (dark grey) block of I_{Ks} on APD in PF, Endo, M and Epi cell models. Black bars indicate control values. A: APD at (i) 500 ms, (ii) 1000 ms, (iii) 2000 ms basic cycle length. B: absolute changes in APD from control due to the block. C: percentage changes in APD from control. Symbols represent experimental values.

Figure S6. Simulated effects of 50% (light grey) and 100% (dark grey) block of I_{K1} on APD in PF, Endo, M and Epi cell models. Black bars indicate control values. A: APD at (i) 500 ms, (ii) 1000 ms, (iii) 2000 ms basic cycle length. B: absolute changes in APD from control due to the block. C: percentage changes in APD from control. Note that there is no data for 100% block in PF cells, as such a block results in sustained depolarisation.

Figure S7. Simulations of Class III drug effects on PF and ventricular cells. A: effects of 100% block of I_{Kr}; B: effects of 100% block of I_{Ks}. Simulation results for PF (i), Endo (ii), M (iii) and Epi (iv) cell models are in good agreement with experimental data [33].

Figure S8. Simulations of α1-adrenergic agonist effects on PF and ventricular cell models. APs in all three ventricular cell types became shorter (primarily, in the M cell), but are substantially prolonged the PF cell, as seen in experiments [43].

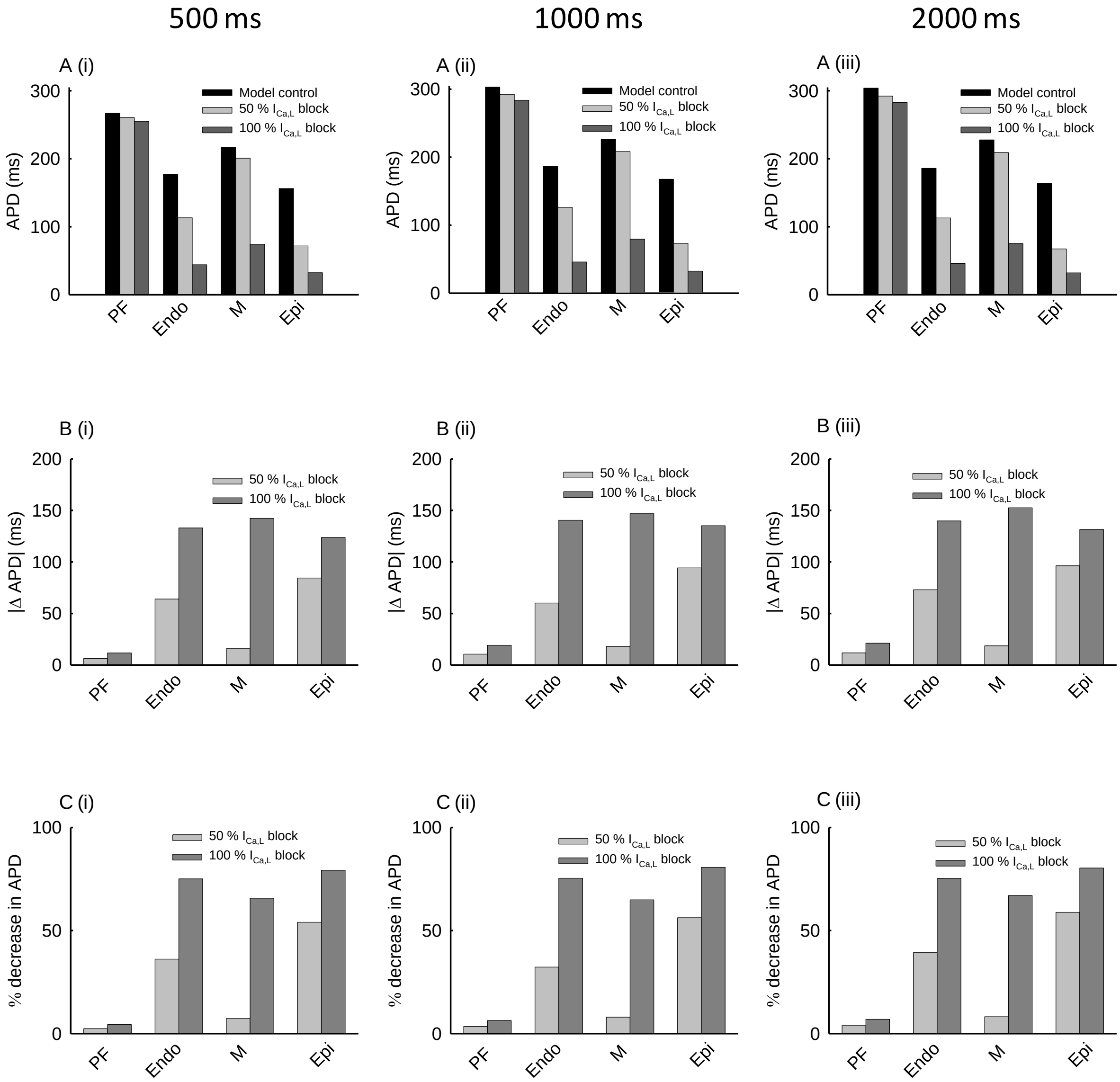
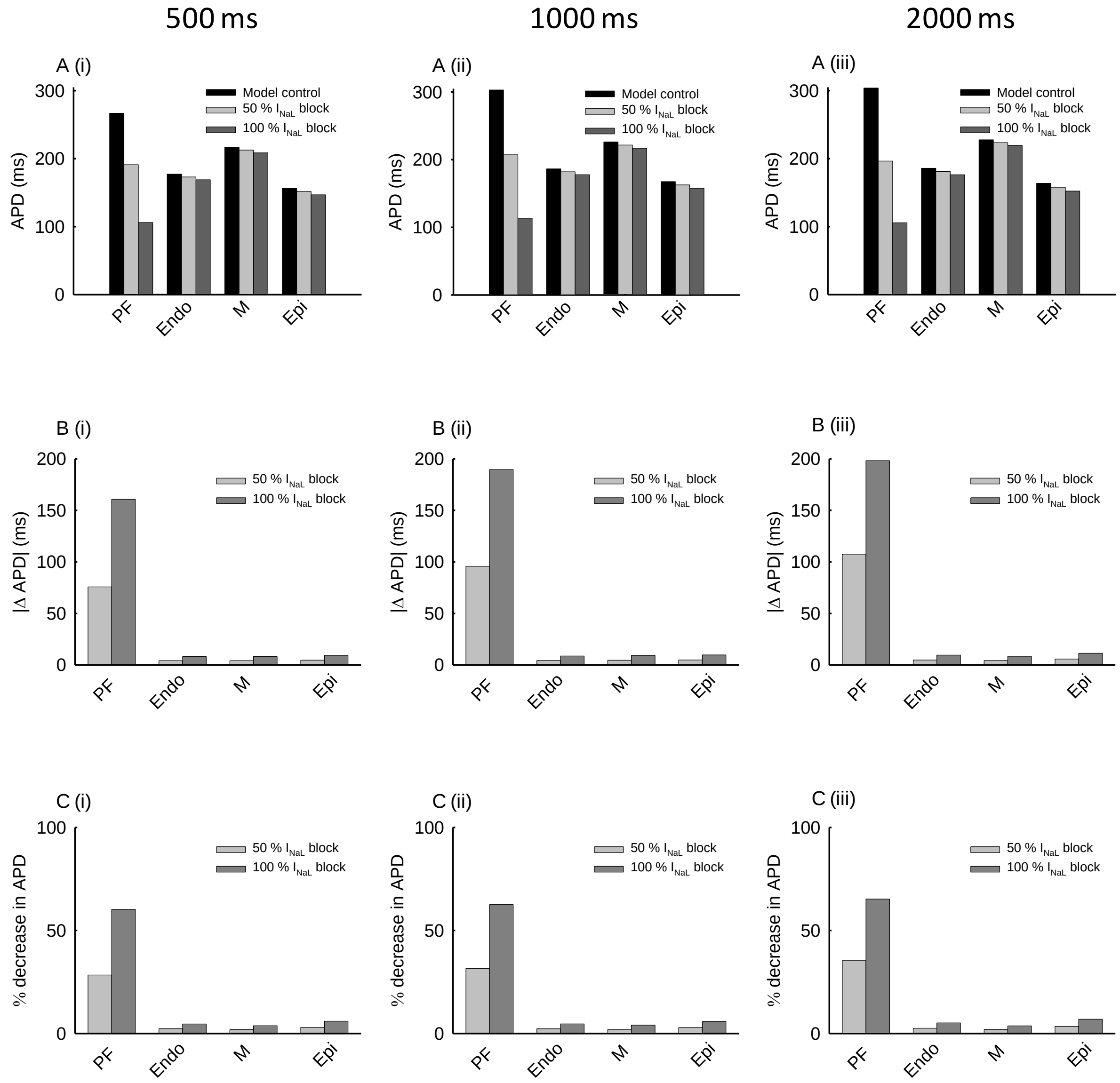

500 ms
1000 ms
2000 ms
A (i)
A (ii)
A (iii)
Model control
50 % $I_{Ca,L}$ block
100 % $I_{Ca,L}$ block
APD (ms)
0
100
200
300
PF
Endo
M
Epi
B (i)
B (ii)
B (iii)
|Δ APD| (ms)
0
50
100
150
200
C (i)
C (ii)
C (iii)
% decrease in APD
0
50
100

Figure S1



500 ms
1000 ms
2000 ms
A (i)
A (ii)
A (iii)
APD (ms)
Model control
50 % I NaL block
100 % I NaL block
PF
Endo
M
Epi
B (i)
B (ii)
B (iii)
|Δ APD| (ms)
C (i)
C (ii)
C (iii)
% decrease in APD

Figure S2

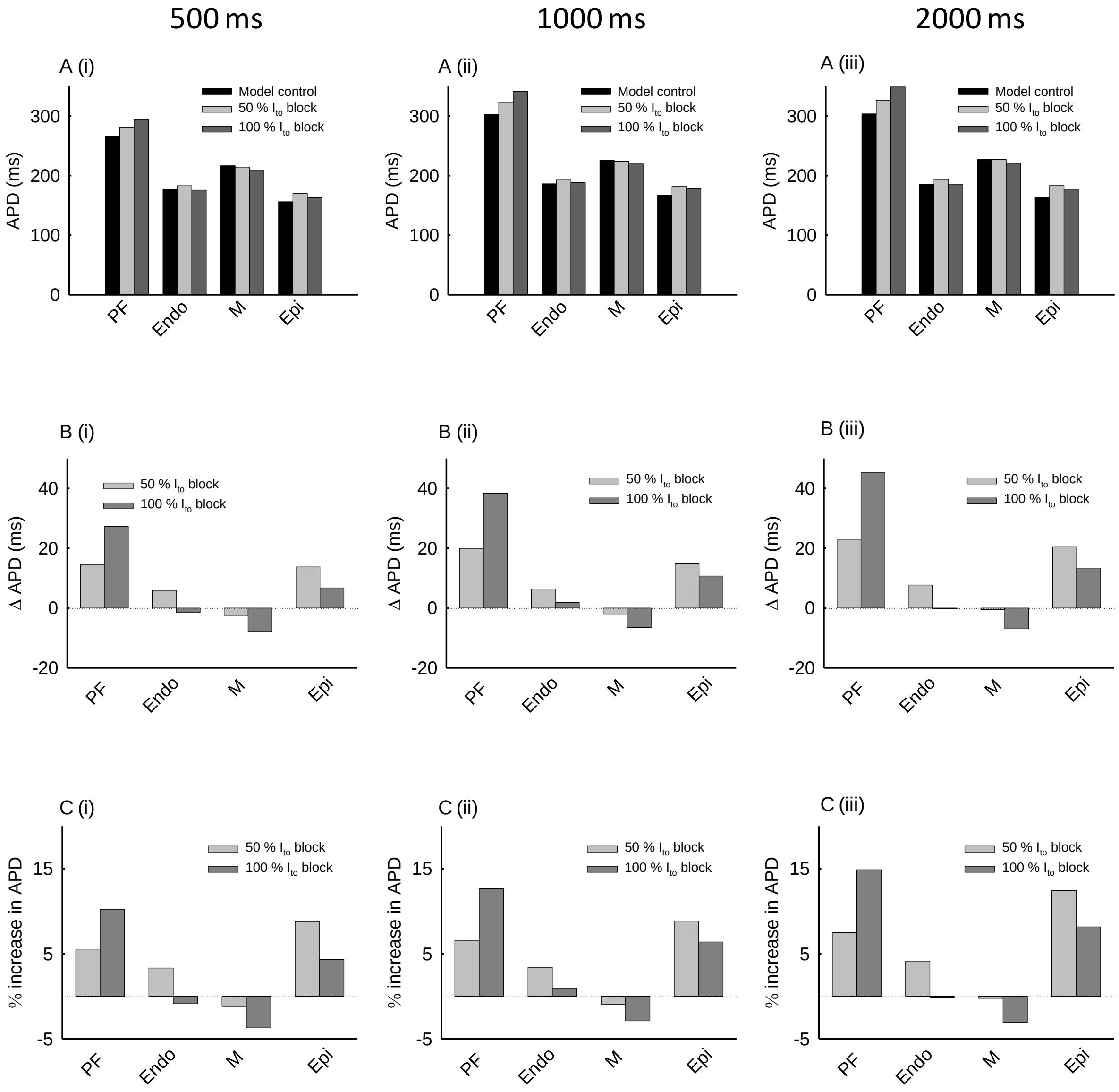
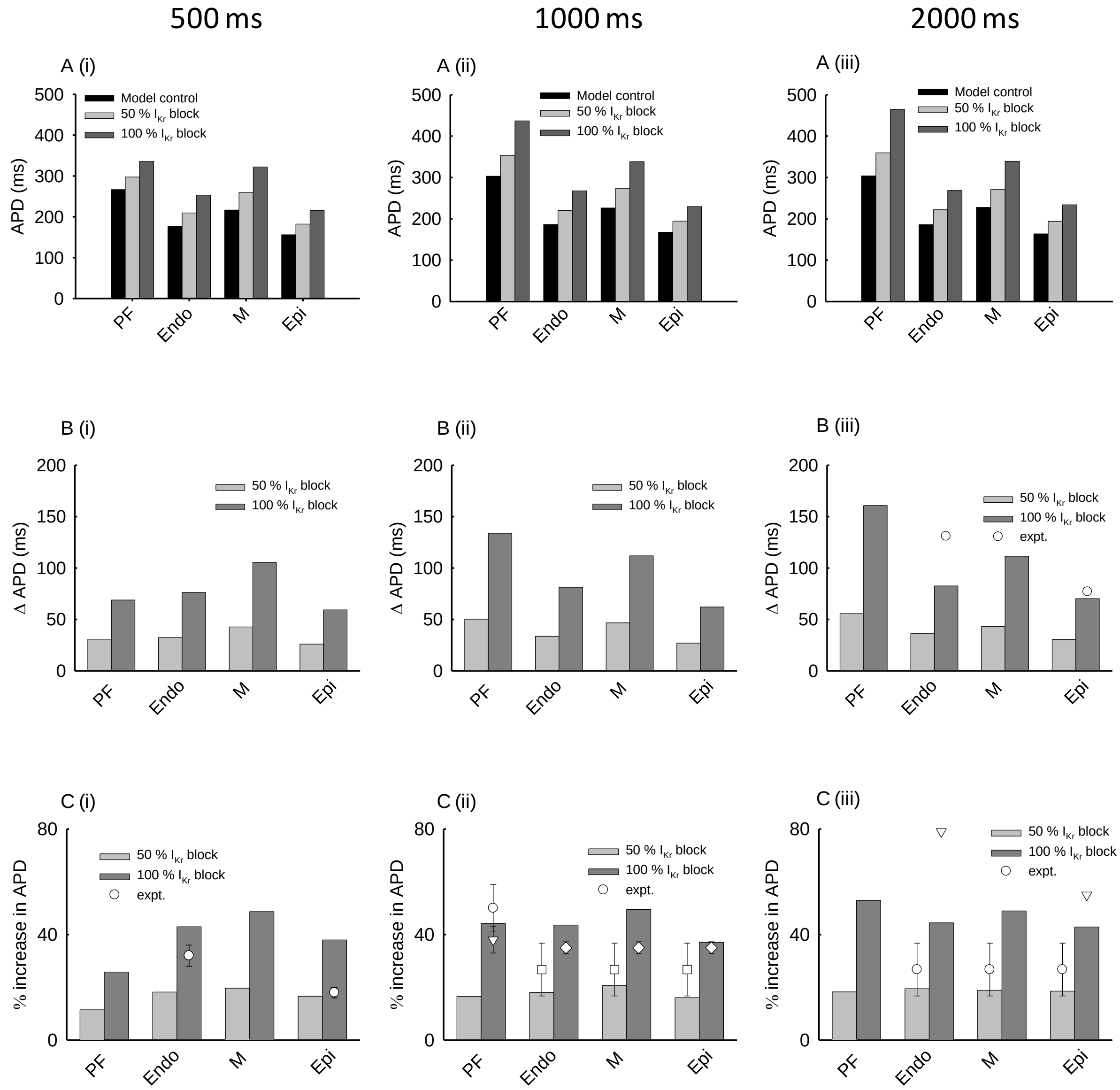

500 ms
1000 ms
2000 ms
A (i)
A (ii)
A (iii)
Model control
50 % I$_{to}$ block
100 % I$_{to}$ block
APD (ms)
B (i)
B (ii)
B (iii)
Δ APD (ms)
C (i)
C (ii)
C (iii)
% increase in APD
PF
Endo
M
Epi

Figure S3



500 ms
1000 ms
2000 ms
A (i)
A (ii)
A (iii)
Model control
50 % I_{Kr} block
100 % I_{Kr} block
APD (ms)
500
400
300
200
100
0
PF
Endo
M
Epi
B (i)
B (ii)
B (iii)
Δ APD (ms)
200
150
100
50
expt.
C (i)
C (ii)
C (iii)
% increase in APD
80
40

Figure S4

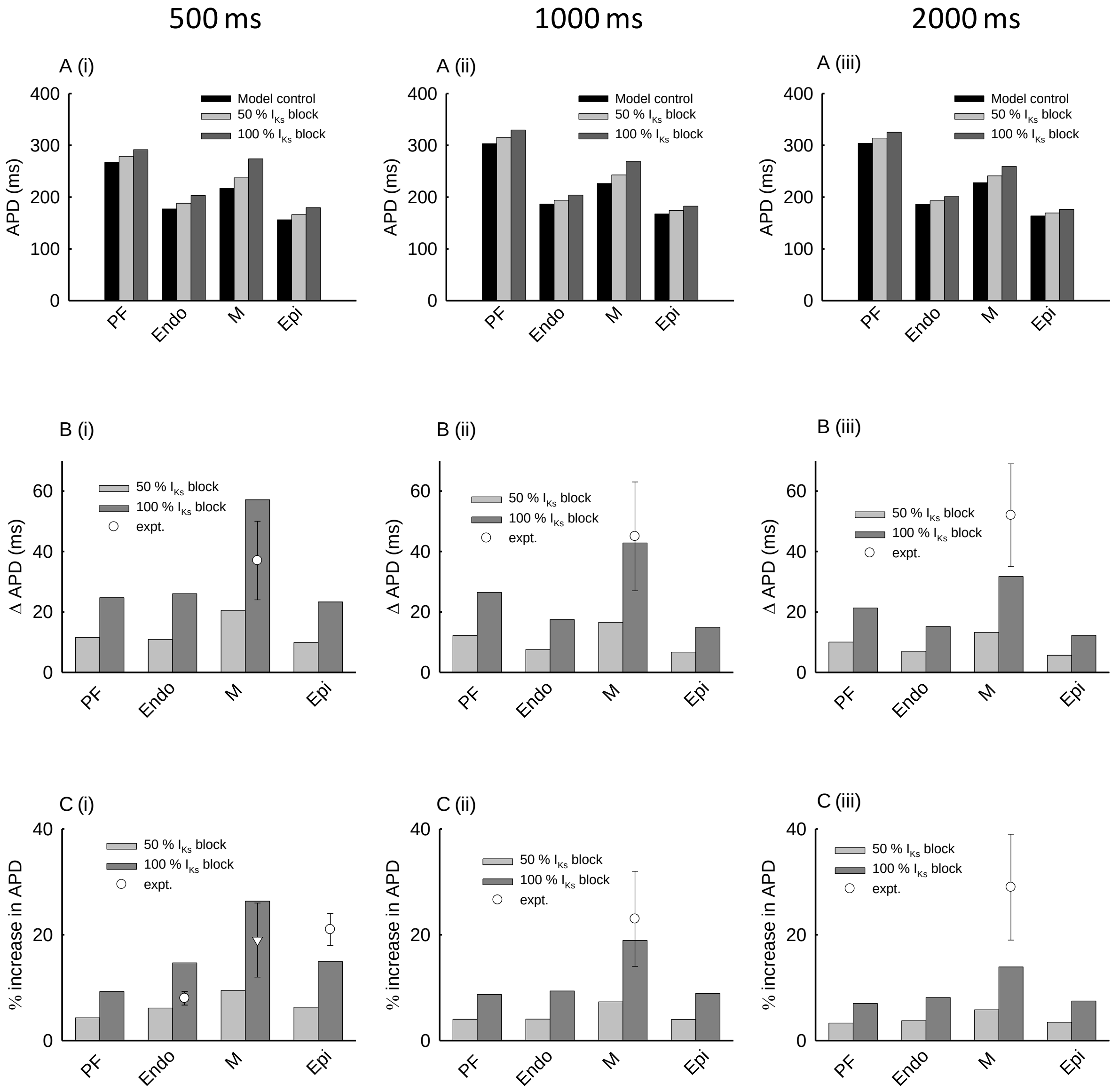

500 ms
1000 ms
2000 ms
A (i)
A (ii)
A (iii)
Model control
50 % I_{Ks} block
100 % I_{Ks} block
APD (ms)
PF
Endo
M
Epi
B (i)
B (ii)
B (iii)
expt.
Δ APD (ms)
C (i)
C (ii)
C (iii)
% increase in APD

Figure S5

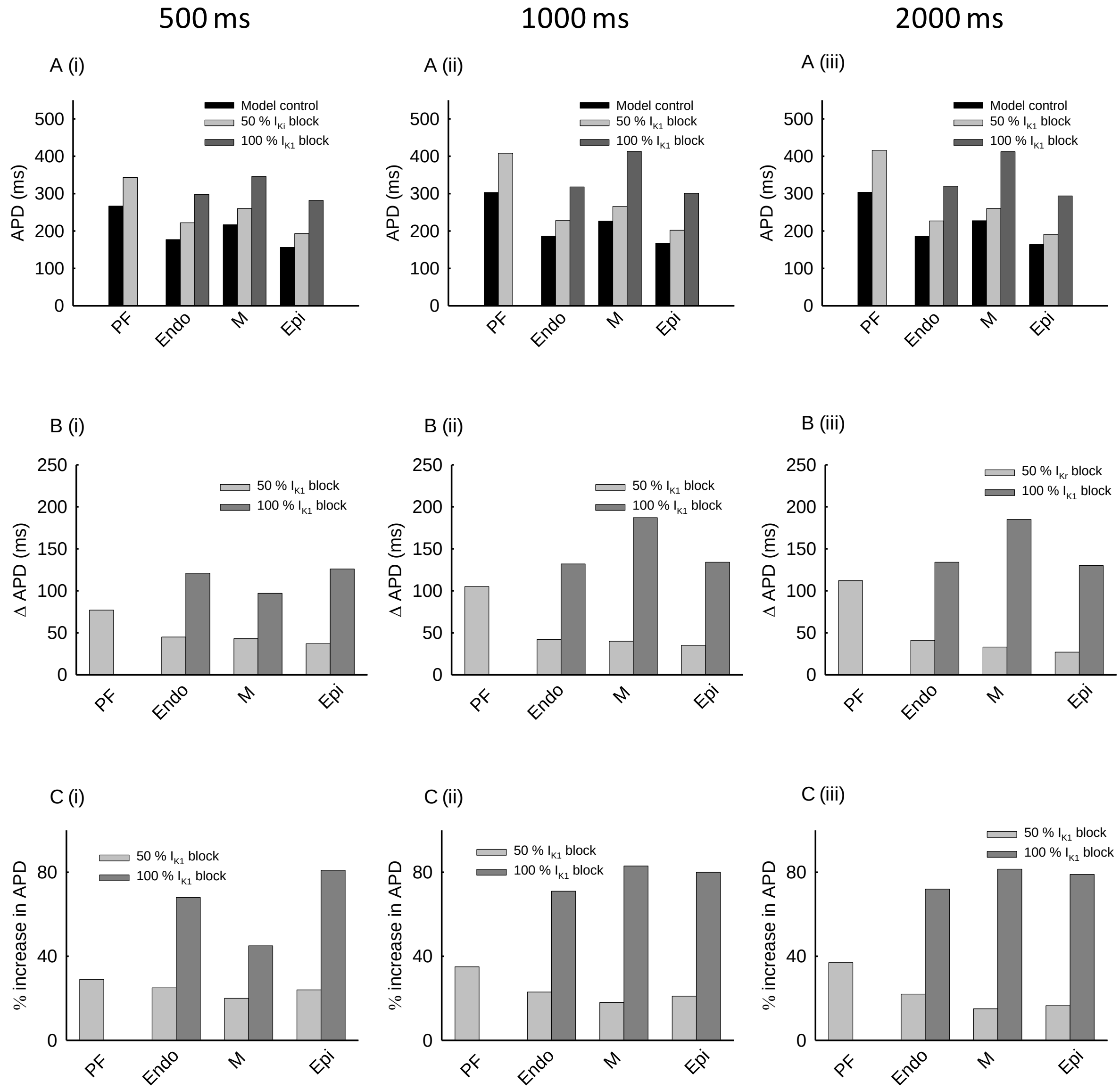
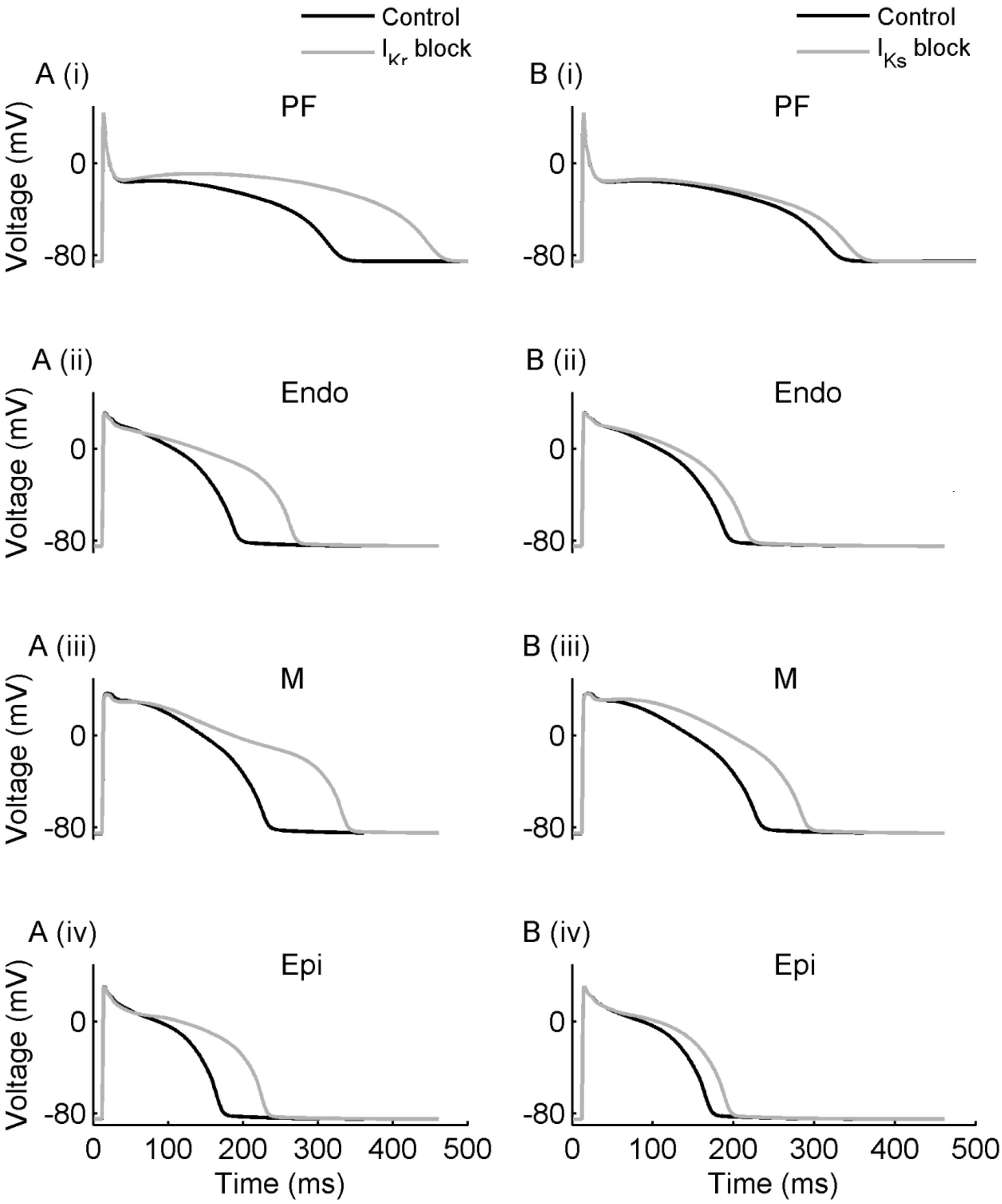

500 ms
1000 ms
2000 ms
A (i)
A (ii)
A (iii)
Model control
50 % I_{Ki} block
50 % I_{K1} block
100 % I_{K1} block
APD (ms)
0
100
200
300
400
500
PF
Endo
M
Epi
B (i)
B (ii)
B (iii)
50 % I_{Kr} block
Δ APD (ms)
0
50
100
150
200
250
C (i)
C (ii)
C (iii)
% increase in APD
0
40
80

Figure S6



Control
I_{Kr} block
Control
I_{Ks} block
A (i)
PF
B (i)
PF
A (ii)
Endo
B (ii)
Endo
A (iii)
M
B (iii)
M
A (iv)
Epi
B (iv)
Epi
Voltage (mV)
0
-80
0
100
200
300
400
500
Time (ms)

Figure S7

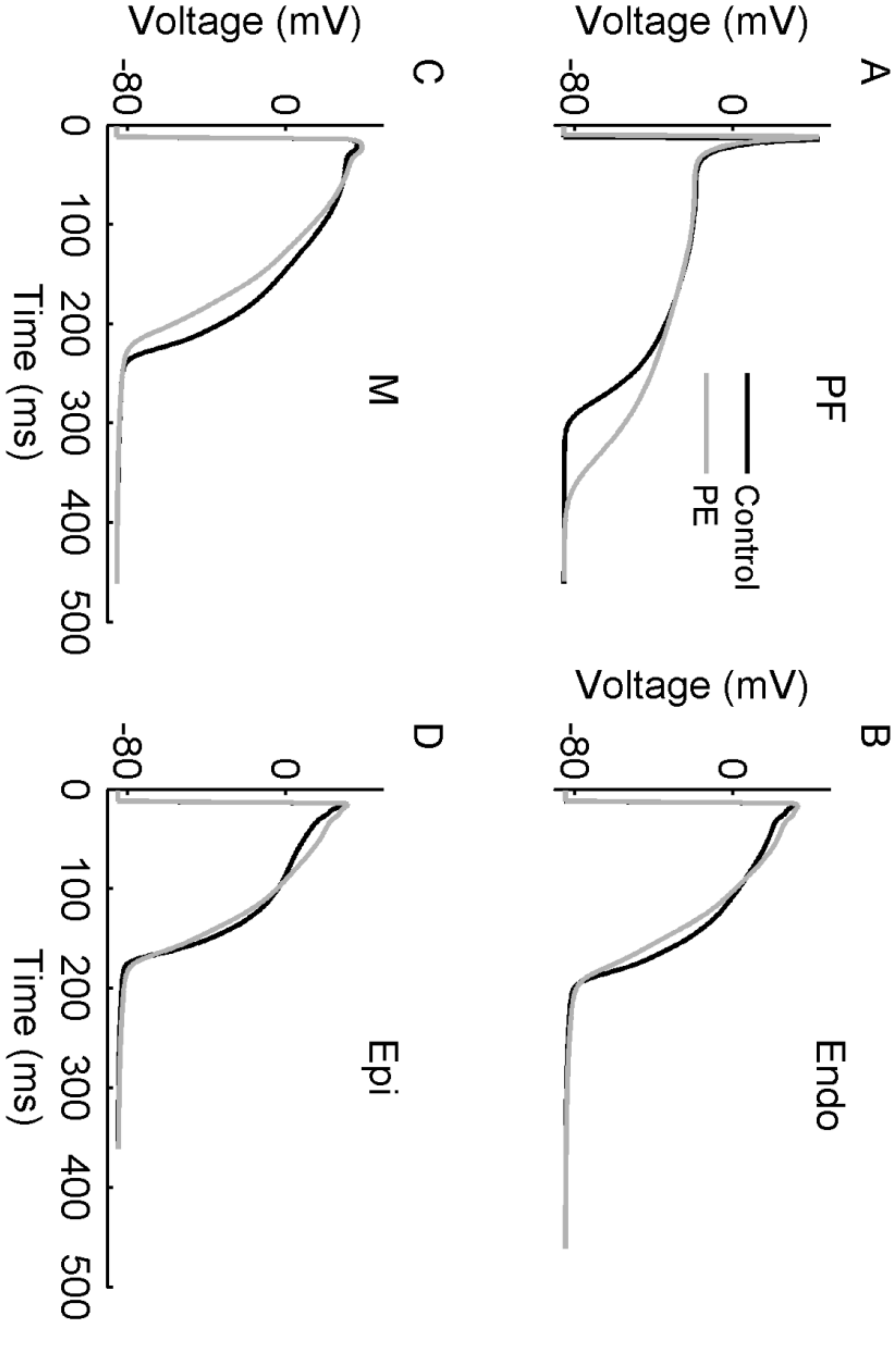

A
PF
B
Endo
C
M
D
Epi
Control
PE
Voltage (mV)
Time (ms)
0
-80
100
200
300
400
500

Figure S8