

APPENDIX 1

Formulation of the model

- 5 The basic units in which the equations were solved are: mV for membrane voltage, μA for membrane currents, mS for conductivities, $ml\ s^{-1}$ for permeabilities, $\mu mol\ s^{-1}$ for ionic fluxes, $mmol\ l^{-1}$ for ionic concentrations, ml for volumes and s for time. The suffix 'x' stands for surface ('s') or tubular ('t') membrane variables, and the suffix 'o' stands for extracellular ('e') or tubular ('t') ionic concentrations. Table A1 lists physical constants, Table A2, the
10 geometric parameters of the cell and the TATS.

Membrane currents

- 15 Table A3 lists parameters for membrane currents.

Na^+ current, I_{Na}

The underlined values in the description of I_{Na} are corrections introduced to adapt I_{Na} properties from 16°C to 37°C (see the main text).

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$$I_{Na,x} = g_{Na,x} m_x^3 h_x (V_{m,x} - E_{Na,x}) \quad (A1)$$

$$\frac{dm_x}{dt} = \frac{\bar{m}_x - m_x}{\tau_{m,x}}, \quad \frac{dh_x}{dt} = \frac{\bar{h}_x - h_x}{\tau_{h,x}} \quad (A2)$$

$$\bar{m}_x = \frac{1}{1 + e^{-(V_{m,x} + 52.2 - 9)/7.4}} \quad (A3)$$

$$\bar{h}_x = \frac{1}{1 + e^{(V_{m,x} + 85.6 - 9)/5.5}} \quad (A4)$$

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$$\tau_{m,x} = \underline{0.207} \left[\frac{0.001}{101.6e^{0.1135V_{m,x}} + 0.02268e^{-0.0717V_{m,x}}} + 0.0001 \right] \quad (A5)$$

$$\tau_{h,x} = \underline{0.207} \left[\frac{0.001}{1.1381 \times 10^{-6} e^{-0.1017V_{m,x}} + 6.537e^{0.08016V_{m,x}}} + 0.0005 \right] \quad (A6)$$

$$E_{\text{Na},x} = \frac{RT}{F} \frac{[\text{Na}^+]_o + 0.12[\text{K}^+]_o}{[\text{Na}^+]_i + 0.12[\text{K}^+]_i} \quad (\text{A7})$$

30 *Persistent Na⁺ current, I_{Naps}*

$$I_{\text{Naps},x} = g_{\text{Naps},x} k_{\text{Naps},x} (V_{m,x} - E_{\text{Naps},x}) \quad (\text{A8})$$

$$k_{\text{Naps},x} = \frac{1}{1 + e^{-(V_{m,x} + 54)/8}} \quad (\text{A9})$$

$$E_{\text{Naps},x} = E_{\text{Na},x} \quad (\text{A10})$$

35 *L-type Ca²⁺ current, I_{CaL}*

Numerical values of parameters specific to I_{CaL} are listed in Table A4.

$$I_{\text{CaL},x} = P_{\text{CaL},x} (O_x + O_{\text{Ca},x}) y_x V_{m,x} \frac{4F^2}{RT} \frac{0.001e^{2V_{m,x}F/(RT)} - 0.341[\text{Ca}^{2+}]_e}{e^{2V_{m,x}F/(RT)} - 1} \quad (\text{A11})$$

$$\frac{dC_{0,x}}{dt} = \beta_x C_{1,x} + \omega C_{\text{Ca}0,x} - (4\alpha_x + \gamma) C_{0,x} \quad (\text{A12})$$

$$40 \quad \frac{dC_{1,x}}{dt} = 4\alpha_x C_{0,x} - 2\beta_x C_{2,x} + \frac{\omega}{b} C_{\text{Ca}1,x} - (\beta_x + 3\alpha_x + \gamma a) C_{1,x} \quad (\text{A13})$$

$$\frac{dC_{2,x}}{dt} = 3\alpha_x C_{1,x} + 3\beta_x C_{3,x} + \frac{\omega}{b^2} C_{\text{Ca}2,x} - (2\beta_x + 2\alpha_x + \gamma a^2) C_{2,x} \quad (\text{A14})$$

$$\frac{dC_{3,x}}{dt} = 2\alpha_x C_{2,x} + 4\beta_x C_{4,x} + \frac{\omega}{b^3} C_{\text{Ca}3,x} - (3\beta_x + \alpha_x + \gamma a^3) C_{3,x} \quad (\text{A15})$$

$$\frac{dC_{4,x}}{dt} = \alpha_x C_{3,x} + g O_x + \frac{\omega}{b^4} C_{\text{Ca}4,x} - (4\beta_x + f + \gamma a^4) C_{4,x} \quad (\text{A16})$$

$$\frac{dO_x}{dt} = f C_{4,x} - g O_x \quad (\text{A17})$$

$$45 \quad \frac{dC_{\text{Ca}0,x}}{dt} = \beta'_x C_{\text{Ca}1,x} + \gamma C_{0,x} - (4\alpha'_x + \omega) C_{\text{Ca}0,x} \quad (\text{A18})$$

$$\frac{dC_{\text{Ca}1,x}}{dt} = 4\alpha'_x C_{\text{Ca}0,x} + 2\beta'_x C_{\text{Ca}2,x} + \gamma a C_{1,x} - (\beta'_x + 3\alpha'_x + \frac{\omega}{b}) C_{\text{Ca}1,x} \quad (\text{A19})$$

$$\frac{dC_{\text{Ca}2,x}}{dt} = 3\alpha'_x C_{\text{Ca}1,x} + 3\beta'_x C_{\text{Ca}3,x} + \gamma a^2 C_{2,x} - (2\beta'_x + 2\alpha'_x + \frac{\omega}{b^2}) C_{\text{Ca}2,x} \quad (\text{A20})$$

$$\frac{dC_{\text{Ca}3,x}}{dt} = 2\alpha'_x C_{\text{Ca}2,x} + 4\beta'_x C_{\text{Ca}4,x} + \gamma a^3 C_{3,x} - (3\beta'_x + \alpha'_x + \frac{\omega}{b^3}) C_{\text{Ca}3,x} \quad (\text{A21})$$

$$\frac{dC_{Ca4,x}}{dt} = \alpha'_x C_{Ca3,x} + g'_x O_{Ca,x} + \gamma a^4 C_{4,x} - (4\beta'_x + f' + \frac{\omega}{b^4}) C_{Ca4,x} \quad (A22)$$

$$50 \quad \frac{dO_{Ca,x}}{dt} = f C_{Ca4,x} - g' O_{Ca,x} \quad (A23)$$

$$\alpha_x = 400 e^{(V_{m,x} + 12)/10} \quad (A24)$$

$$\beta_x = 50 e^{-(V_{m,x} + 12)/13} \quad (A25)$$

$$\alpha'_x = a \alpha_x \quad (A26)$$

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$$\beta'_x = \frac{\beta_x}{b} \quad (A27)$$

$$\gamma = 187.5 [Ca^{2+}]_{ss} \quad (A28)$$

$$\frac{dy_x}{dt} = \frac{\bar{y}_x - y_x}{\tau_{y,x}} \quad (A29)$$

$$\bar{y}_x = \frac{1}{1 + e^{(V_{m,x} + 35)/6}} \quad (A30)$$

$$60 \quad \tau_x = \frac{0.001}{0.02 + 0.0197 e^{-((V_{m,x} + 10)/29.67)^2}} + \frac{0.55}{1 + e^{(V_{m,x} + 40)/2.375}} \quad (A31)$$

L-type K⁺ current, I_{KL}

$$I_{KL,x} = P_{KL,x} (O_x + O_{Ca,x}) y_x V_{m,x} \frac{F^2}{RT} \frac{[K^+]_i e^{V_{m,x} F/(RT)} - [K^+]_o}{e^{V_{m,x} F/(RT)} - 1} \quad (A32)$$

$$65 \quad P_{KL,x} = \frac{P_{KL,x}}{1 + \frac{I_{CaL}}{I_{CaL, half}}} \quad (A33)$$

Rapid component of delayed rectifier K⁺ current, I_{Kr}

$$I_{Kr,x} = g_{Kr,x} c_{Kr,x} x_{r1,x} \bar{x}_{r2,x} (V_{m,x} - E_{Kr}) \quad (A34)$$

$$c_{Kr,x} = \left([K^+]_o / 5.4 \right)^{0.5} \quad (A35)$$

$$70 \quad \frac{dx_{r1,x}}{dt} = \frac{\bar{x}_{r1,x} - x_{r1,x}}{\tau_{r1,x}} \quad (A36)$$

$$\bar{x}_{r1,x} = \frac{1}{1+e^{-(V_{m,x}+21.5)/7.5}} \quad (\text{A37})$$

$$\bar{x}_{r2,x} = \frac{1}{1+e^{-(V_{m,x}+9)/22.4}} \quad (\text{A38})$$

$$\tau_{r1,x} = \frac{1}{\frac{1.38(V_{m,x}+14.2)}{1-e^{-(V_{m,x}+14.2)/8.13}} - \frac{0.61(V_{m,x}+38.9)}{1-e^{-(V_{m,x}+38.9)/6.89}}} \quad (\text{A39})$$

$$E_{Kr,x} = \frac{RT}{F} \ln \left(\frac{[\text{K}^+]_o}{[\text{K}^+]_i} \right) \quad (\text{A40})$$

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Slow component of delayed rectifier K⁺ current, I_{Ks}

$$I_{Ks,x} = g_{Ks,x} c_{Ks} x_{s,x} (V_{m,x} - E_{Ks}) \quad (\text{A41})$$

$$c_{Ks} = 0.23058 + 0.7692 / \left(1 + e^{-(\log([\text{Ca}^{2+}]_i) + 4.2)/0.6} \right) \quad (\text{A42})$$

$$\frac{dx_{s,x}}{dt} = \frac{\bar{x}_{s,x} - x_{s,x}}{\tau_{s,x}} \quad (\text{A43})$$

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$$\bar{x}_{s,x} = \frac{1}{1+e^{-(V_{m,x}-1.5)/16.7}} \quad (\text{A44})$$

$$\tau_{s,x} = \frac{1}{\frac{0.0719(V_{m,x}+30)}{1-e^{-(V_{m,x}+30)/6.76}} - \frac{0.131(V_{m,x}+30)}{1-e^{-(V_{m,x}+30)/14.55}}} \quad (\text{A45})$$

$$E_{Ks,x} = \frac{RT}{F} \ln \left(\frac{[\text{K}^+]_o + 0.0183[\text{Na}^+]_o}{[\text{K}^+]_i + 0.0183[\text{Na}^+]_i} \right) \quad (\text{A46})$$

Plateau K⁺ current, I_{Kp}

$$85 \quad I_{Kp,x} = g_{Kp,x} k_{Kp,x} (V_{m,x} - E_{Kp,x}) \quad (\text{A47})$$

$$k_{Kp,x} = \frac{1}{1+e^{-(V_{m,x}-20)/5}} \quad (\text{A48})$$

$$E_{Kp,x} = E_{Kr,x} \quad (\text{A49})$$

Inward rectifying K⁺ current, I_{K1}

$$90 \quad I_{K1,x} = g_{K1,x} c_{K1,x} k_{K1,x} (V_{m,x} - E_{K1,x}) \quad (\text{A50})$$

$$c_{K1,x} = \left([K^+]_o / 5.4 \right)^{0.5} \quad (\text{A51})$$

$$k_{K1,x} = \frac{\alpha_{K1,x}}{\alpha_{K1,x} + \beta_{K1,x}} \quad (\text{A52})$$

$$\alpha_{K1,x} = \frac{1020}{1 + e^{(V_{m,x} - E_{K1,x} - 59.215)/4.193}} \quad (\text{A53})$$

$$\beta_{K1,x} = \frac{491.24e^{(V_{m,x} - E_{K1,x} + 5.476)/12.45} + 61.75e^{(V_{m,x} - E_{K1,x} - 594.31)/16.19}}{1 + e^{-(V_{m,x} - E_{K1,x} + 4.753)/1.944}} \quad (\text{A54})$$

$$95 \quad E_{K1,x} = E_{Kr,x} \quad (\text{A55})$$

Na⁺ activated K⁺ current, I_{K(Na)}

$$I_{K(Na),x} = g_{K(Na),x} c_{K(Na)} k_{K(Na),x} (V_{m,x} - E_{K(Na),x}) \quad (\text{A56})$$

$$c_{K(Na)} = \frac{0.85}{1 + \left(\frac{K_{\text{half},K(Na,i)}}{[Na^+]_i} \right)^{2.8}} \quad (\text{A57})$$

$$100 \quad k_{K(Na),x} = 0.8 - \frac{0.65}{1 + e^{(V_{m,x} + 125)/15}} \quad (\text{A58})$$

$$E_{K(Na),x} = E_{Kr,x} \quad (\text{A59})$$

ATP sensitive K⁺ current, I_{K(ATP)}

$$I_{K(ATP),x} = g_{K(ATP),x} c_{I_{K(ATP),x}} c_{K(ATP)}^2 (V_{m,x} - E_{K(ATP),x}) \quad (\text{A60})$$

$$105 \quad c_{I_{K(ATP),x}} = \left([K^+]_o / 4 \right)^{0.24} \quad (\text{A61})$$

$$c_{K(ATP)}^2 = \frac{1}{1 + \left(\frac{[ATP]_i}{K_{\text{half},K(ATP,i)}} \right)^2} \quad (\text{A62})$$

$$E_{K(ATP),x} = E_{Kr,x} \quad (\text{A63})$$

[ATP]_i was set to 6.8 mM in control conditions.

110 *Non-specific Ca²⁺ activated current, I_{ns(Ca)}*

$$I_{\text{ns(Ca),x}} = I_{\text{nsNa,x}} + I_{\text{nsK,x}} \quad (\text{A64})$$

$$I_{\text{nsNa,x}} = P_{\text{nsNa,x}} c_{\text{nsNa}} V_{\text{m,x}} \frac{F^2}{RT} \frac{0.75 [\text{Na}^+]_i e^{V_{\text{m,x}}F/(RT)} - 0.75 [\text{Na}^+]_o}{e^{V_{\text{m,x}}F/(RT)} - 1} \quad (\text{A65})$$

$$c_{\text{nsNa}} = \frac{1}{1 + \left(\frac{K_{\text{half,nsNa(Ca}_i)}}{[\text{Ca}^{2+}]_i} \right)^3} \quad (\text{A66})$$

$$I_{\text{nsK,x}} = P_{\text{nsK,x}} c_{\text{nsK}} V_{\text{m,x}} \frac{F^2}{RT} \frac{0.75 [\text{K}^+]_i e^{V_{\text{m,x}}F/(RT)} - 0.75 [\text{K}^+]_o}{e^{V_{\text{m,x}}F/(RT)} - 1} \quad (\text{A67})$$

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$$c_{\text{nsK}} = \frac{1}{1 + \left(\frac{K_{\text{half,nsK(Ca}_i)}}{[\text{Ca}^{2+}]_i} \right)^3} \quad (\text{A68})$$

Background current, I_b

$$I_{\text{b,x}} = I_{\text{Nab,x}} + I_{\text{Cab,x}} \quad (\text{A69})$$

$$I_{\text{Nab,x}} = g_{\text{Nab,x}} (V_{\text{m,x}} - E_{\text{Nab,x}}) \quad (\text{A70})$$

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$$E_{\text{Nab,x}} = \frac{RT}{F} \ln \left(\frac{[\text{Na}^+]_o}{[\text{Na}^+]_i} \right) \quad (\text{A71})$$

$$I_{\text{Cab,x}} = g_{\text{Cab,x}} (V_{\text{m,x}} - E_{\text{Cab,x}}) \quad (\text{A72})$$

$$E_{\text{Cab,x}} = \frac{RT}{2F} \ln \left(\frac{[\text{Ca}^+]_o}{[\text{Ca}^+]_i} \right) \quad (\text{A73})$$

Na⁺ - Ca²⁺ exchanger current, I_{NaCa}

$$\begin{aligned}
I_{\text{NaCa},x} &= k_{\text{NaCa},x} e^{-0.85V_{m,x}F/(RT)} \\
125 \quad &\times \frac{e^{V_{m,x}F/(RT)} [\text{Na}^+]_i^3 [\text{Ca}^+]_o - [\text{Na}^+]_o^3 [\text{Ca}^+]_i}{1+0.0001e^{-0.85V_{m,x}F/(RT)} \left(e^{V_{m,x}F/(RT)} [\text{Na}^+]_i^3 [\text{Ca}^+]_o + [\text{Na}^+]_o^3 [\text{Ca}^+]_i \right)} \quad (\text{A74})
\end{aligned}$$

$\text{Na}^+ - \text{K}^+$ pump current, I_{NaK}

$$I_{\text{NaK},x} = I_{\text{NaK,max},x} c1_{\text{NaK},x} c2_{\text{NaK}} k_{\text{NaK},x} \quad (\text{A75})$$

$$c1_{\text{NaK},x} = \frac{[\text{K}^+]_o}{[\text{K}^+]_o + K_{\text{half,NaK}}(\text{K}_o)} \quad (\text{A76})$$

$$130 \quad c2_{\text{NaK}} = \frac{1}{1 + \left(\frac{K_{\text{half,NaK}}(\text{Na}_i)}{[\text{Na}^+]_i} \right)^{1.5}} \quad (\text{A77})$$

$$k_{\text{NaK},x} = \frac{1}{1+0.1245e^{-0.1V_{m,x}F/(RT)}+0.0365\sigma_x e^{-V_{m,x}F/(RT)}} \quad (\text{A78})$$

$$\sigma_x = \frac{1}{7} \left(e^{[\text{Na}^+]_o/67.3} - 1 \right) \quad (\text{A79})$$

Ca^{2+} pump current, I_{pCa}

$$I_{\text{pCa},x} = I_{\text{pCa,max},x} c_{\text{pCa}} \quad (\text{A80})$$

$$135 \quad c_{\text{pCa}} = \frac{[\text{Ca}^{2+}]_i}{K_{\text{half,pCa}}(\text{Ca}_i) + [\text{Ca}^{2+}]_i} \quad (\text{A81})$$

Circulation current, I_{circ}

$$I_{\text{circ}} = \left[\frac{V_{\text{ms}} - V_{\text{mt}}}{R_{\text{st}}} \right] \quad (\text{A82})$$

140 Stimulation current, I_{stim}

$$I_{\text{stim}} = -45 \mu\text{A cm}^{-2} \text{ for } 0.001 \text{ s} \quad (\text{A83})$$

Intracellular Ca^{2+} handling

145 See tables A5, A6 and A7 for values of related parameters.

Ca^{2+} uptake from cytoplasm into NSR, J_{SRup}

$$J_{\text{SRup}} = J_{\text{SRup,max}} \frac{[\text{Ca}^{2+}]_i^2}{K_{\text{half,up}}^2 + [\text{Ca}^{2+}]_i^2} \quad (\text{A84})$$

150 Ca^{2+} leak from NSR into cytoplasm, J_{SRleak}

$$J_{\text{SRleak}} = P_{\text{SRleak}} \left([\text{Ca}^{2+}]_{\text{NSR}} - [\text{Ca}^{2+}]_i \right) \quad (\text{A85})$$

Ca^{2+} transfer from NSR into JSR, J_{SRtr}

$$J_{\text{SRtr}} = P_{\text{SRtr}} \left([\text{Ca}^{2+}]_{\text{NSR}} - [\text{Ca}^{2+}]_{\text{JSR}} \right) \quad (\text{A86})$$

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Ca^{2+} release from JSR into subspace, J_{SRrel}

$$J_{\text{SRrel}} = P_{\text{SRrel}} (P_{\text{O1}} + P_{\text{O2}}) \left([\text{Ca}^{2+}]_{\text{JSR}} - [\text{Ca}^{2+}]_{\text{ss}} \right) \quad (\text{A87})$$

$$\frac{dP_{\text{C1}}}{dt} = P_{\text{O1}} k_a^- - P_{\text{C1}} k_a^+ [\text{Ca}^{2+}]_{\text{ss}}^4 \quad (\text{A88})$$

$$\frac{dP_{\text{O1}}}{dt} = P_{\text{C1}} k_a^+ [\text{Ca}^{2+}]_{\text{ss}}^4 + P_{\text{O2}} k_b^- + P_{\text{C2}} k_c^- - P_{\text{O1}} (k_a^- + k_b^+ [\text{Ca}^{2+}]_{\text{ss}}^3 + k_c^+) \quad (\text{A89})$$

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$$\frac{dP_{\text{O2}}}{dt} = P_{\text{O1}} k_b^+ [\text{Ca}^{2+}]_{\text{ss}}^3 - P_{\text{O2}} k_b^- \quad (\text{A90})$$

$$\frac{dP_{\text{C2}}}{dt} = P_{\text{O1}} k_c^+ - P_{\text{C2}} k_c^- \quad (\text{A91})$$

Ca^{2+} transfer from subspace into cytoplasm, J_{cyt}

$$J_{\text{cyt}} = P_{\text{cyt}} \left([\text{Ca}^{2+}]_{\text{ss}} - [\text{Ca}^{2+}]_i \right) \quad (\text{A92})$$

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Ca^{2+} buffering by troponin, J_{trpn}

$$J_{\text{trpn}} = V_{\text{myo}} \left(\frac{d[\text{HTRPN}_{\text{Ca}}]}{dt} + \frac{d[\text{LTRPN}_{\text{Ca}}]}{dt} \right) \quad (\text{A93})$$

$$\frac{d[\text{HTRPN}_{\text{Ca}}]}{dt} = k_{\text{htrpn}}^+ [\text{Ca}^{2+}]_i \left([\text{HTRPN}_{\text{Ca}}]_{\text{tot}} - [\text{HTRPN}_{\text{Ca}}] \right) - k_{\text{htrpn}}^- [\text{HTRPN}_{\text{Ca}}] \quad (\text{A94})$$

$$\frac{d[\text{LTRPN}_{\text{Ca}}]}{dt} = k_{\text{ltrpn}}^+ [\text{Ca}^{2+}]_i \left([\text{LTRPN}_{\text{Ca}}]_{\text{tot}} - [\text{LTRPN}_{\text{Ca}}] \right) - k_{\text{ltrpn}}^- [\text{LTRPN}_{\text{Ca}}] \quad (\text{A95})$$

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Ca²⁺ buffering by calmodulin, B_i and B_{ss}

$$B_i = \left\{ 1 + \frac{[\text{CMDN}_{\text{Ca}}]_{\text{tot}} K_{\text{half,CMDN(Ca)}}}{\left(K_{\text{half,CMDN(Ca)}} + [\text{Ca}^{2+}]_i \right)^2} \right\}^{-1} \quad (\text{A96})$$

$$B_{\text{ss}} = \left\{ 1 + \frac{[\text{CMDN}_{\text{Ca}}]_{\text{tot}} K_{\text{half,CMDN(Ca)}}}{\left(K_{\text{half,CMDN(Ca)}} + [\text{Ca}^{2+}]_{\text{ss}} \right)^2} \right\}^{-1} \quad (\text{A97})$$

175 *Ca²⁺ buffering by calsequestrin, B_{JSR}*

$$B_{\text{JSR}} = \left\{ 1 + \frac{[\text{CSQN}_{\text{Ca}}]_{\text{tot}} K_{\text{half,CSQN(Ca)}}}{\left(K_{\text{half,CSQN(Ca)}} + [\text{Ca}^{2+}]_{\text{JSR}} \right)^2} \right\}^{-1} \quad (\text{A98})$$

Ion concentrations

180 *Intracellular ion concentrations*

$$\begin{aligned} \frac{d[\text{Na}^+]_i}{dt} = & - \left(\frac{I_{\text{Na,s}} + I_{\text{Na,t}} + I_{\text{Naps,s}} + I_{\text{Naps,t}} + I_{\text{nsNa,s}} + I_{\text{nsNa,t}}}{FV_{\text{myo}}} \right), \dots \\ & - \left(\frac{I_{\text{Nab,s}} + I_{\text{Nab,t}} + 3I_{\text{NaCa,s}} + 3I_{\text{NaCa,t}} + 3I_{\text{NaK,s}} + 3I_{\text{NaK,t}}}{FV_{\text{myo}}} \right) \end{aligned} \quad (\text{A99})$$

$$\frac{d[\text{K}^+]_i}{dt} = - \left(\frac{I_{\text{Kr},s} + I_{\text{Kr},t} + I_{\text{Ks},s} + I_{\text{Ks},t} + I_{\text{Kp},s} + I_{\text{Kp},t} + I_{\text{Kl},s} + I_{\text{Kl},t} + I_{\text{K(Na),s}} + I_{\text{K(Na),t}} + I_{\text{K(ATP),s}} + I_{\text{K(ATP),t}}}{FV_{\text{myo}}} \right) - \left(\frac{+I_{\text{nsK},s} + I_{\text{nsK},t} + I_{\text{KL},s} + I_{\text{KL},t} - 2I_{\text{NaK},s} - 2I_{\text{NaK},t} + I_{\text{stim}}}{FV_{\text{myo}}} \right) \quad (\text{A100})$$

$$185 \quad \frac{d[\text{Ca}^{2+}]_i}{dt} = B_1 \left(\frac{2I_{\text{NaCa},s} + 2I_{\text{NaCa},t} - I_{\text{Cab},s} - I_{\text{Cab},t} - I_{\text{pCa},s} - I_{\text{pCa},t}}{2FV_{\text{myo}}} \right), \dots + B_i \left(\frac{J_{\text{cyt}} + J_{\text{SRleak}} - J_{\text{SRup}} - J_{\text{trpn}}}{V_{\text{myo}}} \right) \quad (\text{A101})$$

$$\frac{d[\text{Ca}^{2+}]_{\text{ss}}}{dt} = B_{\text{ss}} \left(\frac{-I_{\text{CaL},s} - I_{\text{CaL},t} + \frac{J_{\text{SRrel}} - J_{\text{cyt}}}{V_{\text{ss}}}}{2FV_{\text{ss}}} \right) \quad (\text{A102})$$

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$$\frac{d[\text{Ca}^{2+}]_{\text{NSR}}}{dt} = \frac{J_{\text{SRup}} - J_{\text{SRleak}} - J_{\text{SRtr}}}{V_{\text{NSR}}} \quad (\text{A103})$$

$$\frac{d[\text{Ca}^{2+}]_{\text{JSR}}}{dt} = B_{\text{JSR}} \frac{J_{\text{SRtr}} - J_{\text{SRrel}}}{V_{\text{JSR}}} \quad (\text{A104})$$

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Tubular ion concentrations

$$\frac{d[\text{Na}^+]_t}{dt} = \frac{I_{\text{Na},t} + I_{\text{Naps},t} + I_{\text{nsNa},t} + I_{\text{Nab},t} + 3I_{\text{NaCa},t} + 3I_{\text{NaK},t}}{FV_t} - \frac{J_{\text{Na},t}}{V_t} \quad (\text{A105})$$

$$J_{\text{Na},t} = \frac{V_t}{\tau_{\text{Na},t}} \left([\text{Na}^+]_t - [\text{Na}^+]_e \right) \quad (\text{A106})$$

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$$\frac{d[\text{K}^+]_t}{dt} = \frac{I_{\text{Kr},t} + I_{\text{Ks},t} + I_{\text{Kp},t} + I_{\text{Kl},t} + I_{\text{K(Na),t}} + I_{\text{K(ATP),t}} + I_{\text{nsK},t} + I_{\text{KL},t} - 2I_{\text{NaK},t}}{FV_t} - \frac{J_{\text{K},t}}{V_t} \quad (\text{A107})$$

$$J_{\text{K},t} = \frac{V_t}{\tau_{\text{K},t}} \left([\text{K}^+]_t - [\text{K}^+]_e \right) \quad (\text{A108})$$

$$\frac{d[\text{Ca}^{2+}]_t}{dt} = B_i \left(\frac{I_{\text{Ca,t}} + I_{\text{Cab,t}} + I_{\text{pCa,t}} - 2I_{\text{NaCa,t}}}{2FV_t} - \frac{J_{\text{Ca,t}}}{V_t} \right) \quad (\text{A109})$$

$$J_{\text{Ca,t}} = \frac{V_t}{\tau_{\text{Ca,t}}} \left([\text{Ca}^{2+}]_t - [\text{Ca}^{2+}]_e \right) \quad (\text{A110})$$

Extracellular ion concentrations (for simulation of data by Shepherd and McDonough, 1998)

$$\frac{d[\text{Na}^+]_e}{dt} = \frac{1}{\tau_{\text{Na},e}} \left([\text{Na}^+]_b - [\text{Na}^+]_e \right) \quad (\text{A111})$$

$$\frac{d[\text{K}^+]_e}{dt} = \frac{1}{\tau_{\text{K},e}} \left([\text{K}^+]_b - [\text{K}^+]_e \right) \quad (\text{A112})$$

$$\frac{d[\text{Ca}^{2+}]_e}{dt} = \frac{1}{\tau_{\text{Ca},e}} \left([\text{Ca}^{2+}]_b - [\text{Ca}^{2+}]_e \right) \quad (\text{A113})$$

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Membrane voltage

215 *Surface membrane voltage*

$$\begin{aligned} \frac{dV_{m,s}}{dt} = & \frac{I_{\text{circ}} - I_{\text{Na},s} - I_{\text{Naps},s} - I_{\text{CaL},s} - I_{\text{KL},s} - I_{\text{Kr},s} - I_{\text{Ks},s} - I_{\text{Kp},s} - I_{\text{Kl},s} - I_{\text{K(Na)},s} - I_{\text{K(ATP)},s} - I_{\text{ns(Ca)},s} - I_{\text{Nab},s} - I_{\text{Cab},s}}{C_{m,s}} \\ & + \frac{-I_{\text{NaCa},s} - I_{\text{NaK},s} - I_{\text{pCa},s} - I_{\text{stim}}}{C_{m,s}} \end{aligned} \quad (\text{A114})$$

Tubular membrane voltage

$$\begin{aligned} \frac{dV_{m,t}}{dt} = & \frac{-I_{\text{circ}} - I_{\text{Na},t} - I_{\text{Naps},t} - I_{\text{CaL},t} - I_{\text{KL},t} - I_{\text{Kr},t} - I_{\text{Ks},t} - I_{\text{Kp},t} - I_{\text{Kl},t} - I_{\text{K(Na)},t} - I_{\text{K(ATP)},t} - I_{\text{ns(Ca)},t} - I_{\text{Nab},t} - I_{\text{Cab},t}}{C_{m,t}} \\ & + \frac{-I_{\text{NaCa},t} - I_{\text{NaK},t} - I_{\text{pCa},t}}{C_{m,t}} \end{aligned} \quad (\text{A115})$$

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225 **TABLE A1 Physical constants**

Parameter	Definition	Value
ρ_{ext}	Specific resistance of extracellular solution	83.33 Ω cm
C_{sc}	Specific capacitance of cellular membrane	0.01 pF μm^{-2}
R	Gas molar constant	8.310 J K ⁻¹ mol ⁻¹
F	Faraday constant	96485 A s mol ⁻¹
K	Absolute temperature	310 °K

TABLE A2 Geometric parameters of ventricular guinea pig cell

Parameter	Definition	Value
L_c	Length of cell	130 μm
r_c	Radius of cell	5.93 μm
L_t	Mean length of tubules	5.93 μm
r_t	Mean radius of tubules	0.148 μm
ρ	Density of tubules in surface membrane	0.21 tubules μm^{-2}
$S_{m,s}$	Surface membrane area ($2\pi r_c^2 + 2\pi r_c L_c$)	5065 μm^2
$S_{m,t}$	Tubular membrane area ($4\pi^2 r_t L_t r_c L_c \rho$)	5623 μm^2
V_c	Volume of cell ($\pi r_c^2 L_c$)	1.436×10^{-8} ml
V_{myo}	Volume of myoplasm	0.976×10^{-8} ml
V_{NSR}	Volume of network SR	0.079×10^{-8} ml
V_{JSR}	Volume of junctional SR	0.045×10^{-9} ml
V_{ss}	Volume of subspace	0.586×10^{-12} ml
V_t	Volume of TATS	4.165×10^{-10} ml

TABLE A3 Membrane current parameters

Parameter	Definition	Value
$K_{\text{half,K(Nai)}}$	$[\text{Na}^+]_i$ half saturation constant for $I_{\text{K(Na)}}$	66 mM
$K_{\text{half,K(ATPi)}}$	$[\text{ATP}]_i$ half saturation constant for $I_{\text{K(ATP)}}$	0.1140 mM
$K_{\text{half,nsK(Cai)}}$	$[\text{Ca}^{2+}]_i$ half saturation constant for I_{nsK}	0.0025 mM
$K_{\text{half,nsNa(Cai)}}$	$[\text{Ca}^{2+}]_i$ half saturation constant for I_{nsNa}	0.0025 mM
$K_{\text{half,NaK(Ko)}}$	$[\text{K}^+]_o$ half saturation constant for I_{NaK}	1.5 mM
$K_{\text{half,NaK(Nai)}}$	$[\text{Na}^+]_o$ half saturation constant for I_{NaK}	10 mM
$K_{\text{half,pCa(Cai)}}$	$[\text{Ca}^+]_i$ half saturation constant for I_{pCa}	0.0005 mM

TABLE A4 L-type Ca²⁺ channel parameters

Parameter	Definition	Value
f	Transition rate into open state	300 s^{-1}
g	Transition rate out of open state	2000 s^{-1}
f'	Transition rate into open state for mode Ca	5 s^{-1}
g'	Transition rate out of open state for mode Ca	7000 s^{-1}
a	Mode transition parameter	2
b	Mode transition parameter	2
ω	Mode transition parameter	10 s^{-1}
$I_{\text{CaL, half}}$	I_{CaL} level that reduces P_{KL} by half	$-0.458 \mu\text{A cm}^{-2}$

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TABLE A5 SR parameters

Parameter	Definition	Value
$J_{\text{SRup,max}}$	SR Ca^{2+} -ATPase maximum pump rate	$1.758 \times 10^{-8} \mu\text{M s}^{-1}$
P_{SRleak}	Ca^{2+} permeability between NSR and cytoplasm	$7.08 \times 10^{-10} \text{ ml s}^{-1}$
P_{SRtr}	Ca^{2+} permeability between NSR and JSR	$1.316 \times 10^{-9} \text{ ml s}^{-1}$
P_{SRrel}	Ca^{2+} permeability between JSR and subspace	$8.169 \times 10^{-8} \text{ ml s}^{-1}$
P_{cyt}	Ca^{2+} permeability between subspace and	$3.125 \times 10^{-6} \text{ ml s}^{-1}$
P_{cyt}	Ca^{2+} permeability between subspace and	$3.125 \times 10^{-6} \text{ ml s}^{-1}$
$K_{\text{half,up}}$	Half-saturation constant for SR Ca^{2+} -ATPase	$0.5 \times 10^{-3} \text{ mM}$
k_a^+	RyR $\text{P}_{\text{c1}} - \text{P}_{\text{o1}}$ rate constant	$3.75 \times 10^{13} \text{ mM}^{-4} \text{ s}^{-1}$
k_a^-	RyR $\text{P}_{\text{o1}} - \text{P}_{\text{c1}}$ rate constant	576 s^{-1}
k_b^+	RyR $\text{P}_{\text{o1}} - \text{P}_{\text{o2}}$ rate constant	$4.05 \times 10^9 \text{ mM}^{-3} \text{ s}^{-1}$
k_b^-	RyR $\text{P}_{\text{o2}} - \text{P}_{\text{o1}}$ rate constant	1930 s^{-1}
k_c^+	RyR $\text{P}_{\text{o1}} - \text{P}_{\text{c2}}$ rate constant	18 s^{-1}
k_c^-	RyR $\text{P}_{\text{c2}} - \text{P}_{\text{o1}}$ rate constant	0.8 s^{-1}

240 **TABLE A6 Buffering parameters**

Parameter	Definition	Value
$[\text{HTRPN}_{\text{Ca}}]_{\text{tot}}$	Total myoplasmic troponin high-affinity	0.14 mM
$[\text{LTRPN}_{\text{Ca}}]_{\text{tot}}$	Total myoplasmic troponin low-affinity	0.07 mM
$[\text{CMDN}_{\text{Ca}}]_{\text{tot}}$	Total myoplasmic calmodulin concentration	0.05 mM
$[\text{CSQN}_{\text{Ca}}]_{\text{tot}}$	Total myoplasmic calsequestrin concentration	15 mM
k^+_{htrpn}	Ca^{2+} on rate for troponin high-affinity sites	$2 \times 10^4 \text{ mM}^{-1} \text{ s}^{-1}$
k^-_{htrpn}	Ca^{2+} off rate for troponin high-affinity sites	0.07 s^{-1}
k^+_{ltrpn}	Ca^{2+} on rate for troponin low-affinity sites	$4 \times 10^4 \text{ mM}^{-1} \text{ s}^{-1}$
k^-_{ltrpn}	Ca^{2+} off rate for troponin low-affinity sites	40 s^{-1}
$K_{\text{halfCMDN}(\text{Ca})}$	$[\text{Ca}^{2+}]_i$ half saturation constant for calmodulin	0.00238 mM
$K_{\text{halfCSQN}(\text{Ca})}$	$[\text{Ca}^{2+}]_i$ half saturation constant for calsequestrin	0.8 mM

TABLE A7 Time constants of ion diffusion in tubular and extracellular space

Parameter	Definition	Value
$\tau_{\text{Na,t}}$	Na ⁺ exchange between bulk and TATS	0.2 s
$\tau_{\text{K,t}}$	K ⁺ exchange between bulk and TATS	0.2 s
$\tau_{\text{Ca,t}}$	Ca ²⁺ exchange between bulk and TATS	0.24 s (1.3 s)
$\tau_{\text{Na,e}}$	Na ⁺ exchange between bulk and pericellular space	0.022 s
$\tau_{\text{K,e}}$	K ⁺ exchange between bulk and pericellular space	0.022 s
$\tau_{\text{Ca,e}}$	Ca ²⁺ exchange between bulk and pericellular space	0.024 s

245 The time constants with suffix "e" were used for modeling the data of Shepherd and McDonough (1998). An alternative $\tau_{\text{Ca,t}}$ value of 1.3 s was used in some of the simulations.