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Supplemental Information

Na-K-2Cl Cotransporter and Store-Operated Ca^{2+} Entry in Pacemaking by Interstitial Cells of Cajal

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Supplement equations

A1. Membrane potential

$$\frac{dV}{dt} = \frac{-(I_{total} + I_{ext})}{C_m} \#(1)$$

$$I_{total} = I_{CaL} + I_{CaT} + I_{K1} + I_{NaLCN} + I_{ClCa} + I_{Clb} + I_{Orai} + I_{NaCa} + I_{NaK} \#(2)$$

A2. Constant field equation

$$CF_X = z_X \cdot \frac{F \cdot V}{R \cdot T} \cdot \frac{[X]_i - [X]_o \cdot e^{-z_X \cdot \frac{F \cdot V}{R \cdot T}}}{1 - e^{-z_X \cdot \frac{F \cdot V}{R \cdot T}}} \#(3)$$

$$CF_{X,md} = z_X \cdot \frac{F \cdot V}{R \cdot T} \cdot \frac{[X]_{md} - [X]_o \cdot e^{-z_X \cdot \frac{F \cdot V}{R \cdot T}}}{1 - e^{-z_X \cdot \frac{F \cdot V}{R \cdot T}}} \#(4)$$

A3. L-type Ca^{2+} current (I_{CaL})

$$I_{CaL} = I_{CaL}Ca + I_{CaL}Na + I_{CaL}K \#(5)$$

$$I_{CaL}Ca = P_{CaL} \cdot CF_{Ca} \cdot m \cdot h \#(6)$$

$$I_{CaL}Na = 0.00005 \cdot P_{CaL} \cdot CF_{Na} \cdot m \cdot h \#(7)$$

$$I_{CaL}K = 0.001 \cdot P_{CaL} \cdot CF_K \cdot m \cdot h \#(8)$$

$$P_{CaL} = 57.6 \#(9)$$

$$\alpha_m = 0.002175 \cdot \frac{V + 30}{1 - e^{-\frac{V+30}{2.5}}} \#(10)$$

$$\beta_m = 0.0006315 \cdot \frac{V}{e^{\frac{V}{2.5}} - 1} \#(11)$$

$$\alpha_h = 1.775 \cdot 10^{-6} \cdot \frac{V + 34}{e^{\frac{V+34}{5.633}} - 1} \#(12)$$

$$\beta_h = 0.427 \cdot [Ca^{2+}]_i \cdot \frac{V + 64}{1 + e^{-\frac{V+44}{4.16}}} \#(13)$$

A4. T-type Ca^{2+} current (I_{CaT})

$$I_{CaT} = P_{CaT} \cdot CF_{Ca} \cdot d \cdot f \#(14)$$

$$P_{CaT} = 7.92 \#(15)$$

$$\mathrm{d}_\infty = \frac{1}{1 + e^{-\frac{V+26}{6}}} \#(16)$$

$$\tau_\mathrm{d} = 0.6 + \frac{5.4}{1 + e^{0.03\cdot(V+100)}} \#(17)$$

$$\alpha_\mathrm{d} = \frac{\mathrm{d}_\infty}{\tau_\mathrm{d}} \#(18)$$

$$\beta_\mathrm{d} = \frac{1 - \mathrm{d}_\infty}{\tau_\mathrm{d}} \#(19)$$

$$\mathrm{f}_\infty = \frac{1}{1 + e^{\frac{V+66}{6}}} \#(20)$$

$$\tau_\mathrm{f} = 10 + \frac{400}{1 + e^{0.02\cdot(V+65)}} \#(21)$$

$$\alpha_\mathrm{f} = \frac{\mathrm{f}_\infty}{\tau_\mathrm{f}} \#(22)$$

$$\beta_\mathrm{f} = \frac{1 - \mathrm{f}_\infty}{\tau_\mathrm{f}} \#(23)$$

A5. Inward rectifier K^+ current (I_{K1})

$$I_\mathrm{K1} = G_\mathrm{K1} \cdot \left(\frac{[\mathrm{K}^+]_\mathrm{o}}{5.4}\right)^{0.4} \cdot \frac{(V - E_\mathrm{K} - 1.73)}{1 + e^{\frac{1.613\cdot\mathrm{F}}{\mathrm{R}\cdot\mathrm{T}}\cdot(V - E_\mathrm{K} - 1.73)}} + a_\mathrm{K1} \cdot b_\mathrm{K1} \#(24)$$

$$G_\mathrm{K1} = 18.0 \#(25)$$

$$E_\mathrm{K} = \frac{\mathrm{R}\cdot\mathrm{T}}{\mathrm{F}} \cdot \log \frac{[\mathrm{K}^+]_\mathrm{o}}{[\mathrm{K}^+]_\mathrm{i}} \#(26)$$

$$a_\mathrm{K1} = 10 + \frac{48}{e^{\frac{V+37}{25}} + e^{-\frac{V+37}{25}}} \#(27)$$

$$b_\mathrm{K1} = \frac{0.0001}{1 + e^{-\frac{V - E_\mathrm{K} - 76.77}{17}}} \#(28)$$

A6. Na^+-leak current (I_{NaLCN})

$$I_\mathrm{NaLCN} = I_\mathrm{NaLCN}\mathrm{Na} + I_\mathrm{NaLCN}\mathrm{K} \#(29)$$

$$I_\mathrm{NaLCN}\mathrm{Na} = P_\mathrm{NaLCN} \cdot \mathrm{CF}_\mathrm{Na} \#(30)$$

$$I_\mathrm{NaLCN}\mathrm{K} = 0.9 \cdot P_\mathrm{NaLCN} \cdot \mathrm{CF}_\mathrm{K} \#(31)$$

$$P_{\mathrm{NaLCN}} = 0.1485\#(32)$$

A7. Ca^{2+}-activated Cl^- current (I_{ClCa})

$$I_{\mathrm{ClCa}} = g_{\mathrm{ClCa}} \cdot O_{\mathrm{ClCa}} \cdot (V - E_{\mathrm{Cl}})\#(33)$$

$$g_{\mathrm{ClCa}} = 20.0\#(34)$$

$$E_{\mathrm{Cl}} = \frac{\mathrm{R{\cdot}T}}{\mathrm{F}} \cdot \log \frac{[\mathrm{Cl}^-]_{\mathrm{cld}}}{[\mathrm{Cl}^-]_{\mathrm{o}}}\#(35)$$

$$O_{\mathrm{ClCa}\infty} = \left[\left(1 + e^{(V_{\mathrm{h}} - V)/0.0156}\right)\left(1 + \left(\frac{\mathrm{EC}_{50}}{[\mathrm{Ca}^{2+}]_{\mathrm{Ano1}}}\right)^2\right)\right]^{-1}\#(36)$$

$$V_{\mathrm{h}} = -100\ \mathrm{mV}\#(37)$$

$$\tau = t_1 + t_2 \cdot e^{V/t_3}\#(38)$$

$$t_1 = 48.978 \cdot e^{-0.57[\mathrm{Ca}^{2+}]_{\mathrm{Ano1}}}\#(39)$$

$$t_2 = 45.702 \cdot e^{-0.05374[\mathrm{Ca}^{2+}]_{\mathrm{Ano1}}}\#(40)$$

$$t_3 = 133.57 \cdot e^{0.153[\mathrm{Ca}^{2+}]_{\mathrm{Ano1}}}\#(41)$$

$$\mathrm{EC}_{50(0\mathrm{mV})} = 1.39 \cdot 10^{-3}\ \mathrm{mM}\#(42)$$

$$\mathrm{EC}_{50} = \mathrm{EC}_{50(0\mathrm{mV})} \cdot e^{-k_{\mathrm{c}} \cdot V}\ \mathrm{mM}\#(43)$$

$$k_{\mathrm{c}} = 5.4912 \cdot 10^{-3}\#(44)$$

$$[\mathrm{Ca}^{2+}]_{\mathrm{Ano1}} = \frac{\left(-D_{\mathrm{c}} \cdot K_{\mathrm{m}} + \frac{\sigma}{2\pi r} + C_2 + \sqrt{\left(D_{\mathrm{c}} \cdot K_{\mathrm{m}} + \frac{\sigma}{2\pi r} + C_2\right)^2 + 4D_{\mathrm{c}} \cdot D_{\mathrm{m}} \cdot B_{\mathrm{m}} \cdot K_{\mathrm{m}}}\right)}{2D_{\mathrm{c}}}\#(45)$$

$$D_{\mathrm{c}} = 250 \cdot 10^{-3}\ \mu\mathrm{m}^2 \cdot \mathrm{ms}^{-1}\#(46)$$

$$D_{\mathrm{m}} = 75 \cdot 10^{-3}\ \mu\mathrm{m}^2 \cdot \mathrm{ms}^{-1}\#(47)$$

$$B_{\mathrm{m}} = 50 \cdot 10^{-3}\ \mathrm{mM}\#(48)$$

$$K_{\mathrm{m}} = 0.1 \cdot 10^{-3}\ \mathrm{mM}\#(49)$$

$$r = 0.05\ \mu\mathrm{m}\#(50)$$

$$\mathrm{n}_{\mathrm{Orai}} = 250\#(51)$$

$$C_2 = D_c \cdot [Ca^{2+}]_i - \frac{D_m \cdot B_m \cdot K_m}{K_m + [Ca^{2+}]_i} \#(52)$$

$$\sigma = \frac{J_{Orai} \cdot Vol_{cyt}}{n_{Orai}} \#(53)$$

$$J_{Orai} = \frac{-I_{Orai}}{F \cdot Vol_{cyt}} \#(54)$$

A8. Background Cl^- current (I_{Clb})

$$I_{Clb} = P_{Clb} \cdot CF_{Cl} \#(55)$$

$$P_{Clb} = 0.1 \#(56)$$

A9. Current carried by store-operated Ca^{2+} entry (I_{Orai})

$$I_{Orai} = g_{Orai} \cdot O_{Orai} \cdot (V - E_{Ca}) \#(57)$$

$$E_{Ca} = \frac{R \cdot T}{2 \cdot F} \cdot \log \frac{[Ca^{2+}]_o}{[Ca^{2+}]_i} \#(58)$$

$$g_{Orai} = 0.028 \#(59)$$

$$O_{Orai} = \frac{(K_{m,Ca})^8}{(K_{m,Ca})^8 + (0.021 \cdot [Ca]_{rel})^8} \#(60)$$

$$K_{m,Ca} = 0.2 \text{ mM} \#(61)$$

A10. Na^+/Ca^{2+} exchange current (I_{NaCa})

$$\begin{array}{ccccccc} E_2Na & \overset{K_{m,Nao}}{\longleftrightarrow} & E_2 & \overset{K_{m,Cao}}{\longleftrightarrow} & E_2Ca & & 1 - y_{NaCa} \\ k_1 \uparrow\downarrow k_2 & & & & k_3 \uparrow\downarrow k_4 & & \beta_y \uparrow\downarrow \alpha_y \\ E_1Na & \overset{K_{m,Nai}}{\longleftrightarrow} & E_1 & \overset{K_{m,Cai}}{\longleftrightarrow} & E_1Ca & & y_{NaCa} \end{array}$$

$$I_{NaCa} = P_{NaCa} \cdot \left(k_1 \cdot E_1Na \cdot y_{NaCa} - k_2 \cdot E_2Na \cdot (1 - y_{NaCa})\right) \#(62)$$

$$P_{NaCa} = 8.458 \text{ pA} \#(63)$$

$$k_1 = e^{\frac{0.32 \cdot F \cdot V}{R \cdot T}} \#(64)$$

$$k_2 = e^{\frac{(0.32-1) \cdot F \cdot V}{R \cdot T}} \#(65)$$

$$k_3 = 1 \#(66)$$

$$k_4 = 1\#(67)$$

$$K_{\mathrm{m,Nao}} = 87.5\ \mathrm{mM}\#(68)$$

$$K_{\mathrm{m,Cao}} = 1.38\ \mathrm{mM}\#(69)$$

$$K_{\mathrm{m,Nai}} = 4.375\ \mathrm{mM}\#(70)$$

$$K_{\mathrm{m,Cai}} = 0.00138\ \mathrm{mM}\#(71)$$

$$\alpha_y = k_2 \cdot E_2\mathrm{Na} + k_4 \cdot E_2\mathrm{Ca}\#(72)$$

$$\beta_y = k_1 \cdot E_1\mathrm{Na} + k_3 \cdot E_1\mathrm{Ca}\#(73)$$

$$E_1\mathrm{Na} = \left(1 + \frac{1 + [\mathrm{Ca}^{2+}]_{\mathrm{cld}}/K_{\mathrm{m,Cai}}}{([\mathrm{Na}^+]_{\mathrm{cld}}/K_{\mathrm{m,Nai}})^3}\right)^{-1}\#(74)$$

$$E_2\mathrm{Na} = \left(1 + \frac{1 + [\mathrm{Ca}^{2+}]_{\mathrm{o}}/K_{\mathrm{m,Cao}}}{([\mathrm{Na}^+]_{\mathrm{o}}/K_{\mathrm{m,Nao}})^3}\right)^{-1}\#(75)$$

$$E_1\mathrm{Ca} = \left(1 + \frac{1 + ([\mathrm{Na}^+]_{\mathrm{cld}}/K_{\mathrm{m,Nai}})^3}{[\mathrm{Ca}^{2+}]_{\mathrm{cld}}/K_{\mathrm{m,Cai}}}\right)^{-1}\#(76)$$

$$E_2\mathrm{Ca} = \left(1 + \frac{1 + ([\mathrm{Na}^+]_{\mathrm{o}}/K_{\mathrm{m,Nao}})^3}{[\mathrm{Ca}^{2+}]_{\mathrm{o}}/K_{\mathrm{m,Cao}}}\right)^{-1}\#(77)$$

A11. Na^+/K^+ pump current (I_{NaK})

$$I_{\mathrm{NaK}} = I_{\mathrm{NaK}}A + I_{\mathrm{NaK}}B\#(78)$$

$$I_{\mathrm{NaK}}A = P_{\mathrm{NaK}} \cdot \frac{0.7}{1 + (K_{\mathrm{m,Nai}}/[\mathrm{Na}^+]_{\mathrm{i}})^{1.36}} \cdot \frac{1 - \left((V + 50)/250\right)^2}{1 + K_{\mathrm{m,Ko}}/[\mathrm{K}^+]_{\mathrm{o}}}\#(79)$$

$$I_{\mathrm{NaK}}B = P_{\mathrm{NaK}} \cdot \frac{7}{1 + (K_{\mathrm{m2,Nai}}/[\mathrm{Na}^+]_{\mathrm{i}})^{3}} \cdot \frac{1 - \left((V + 50)/250\right)^2}{1 + K_{\mathrm{m,Ko}}/[\mathrm{K}^+]_{\mathrm{o}}}\#(80)$$

$$P_{\mathrm{NaK}} = 27.65\#(81)$$

$$K_{\mathrm{m,Nai}} = 3.5\ \mathrm{mM}\#(82)$$

$$K_{\mathrm{m2,Nai}} = 18\ \mathrm{mM}\#(83)$$

$$K_{\mathrm{m,Ko}} = 0.27\ \mathrm{mM}\#(84)$$

A12. Na-K-2Cl cotransporter (NKCC1)

$$J_{\mathrm{NKCC,Na}} = P_{\mathrm{NKCC}} \cdot \left(J_{\mathrm{NKCC,Na\ influx}} - J_{\mathrm{NKCC,Na\ efflux}}\right)\#(85)$$

$$J_{\mathrm{NKCC,K}} = J_{\mathrm{NKCC,Na}}\#(86)$$

$$J_{\mathrm{NKCC,Cl}} = 2 \cdot J_{\mathrm{NKCC,Na}}\#(87)$$

$$P_{\mathrm{NKCC}} = 0.168\#(88)$$

$$J_{E_1 \rightarrow E_1\mathrm{NaCl}} = \frac{v_1 \cdot v_2}{v_2 + v_{-1}}\#(89)$$

$$J_{E_1 \leftarrow E_1\mathrm{NaCl}} = \frac{v_{-2} \cdot v_{-1}}{v_2 + v_{-1}}\#(90)$$

$$J_{E_1 \rightarrow E_1\mathrm{NaClK}} = \frac{\left(J_{E_1 \rightarrow E_1\mathrm{NaCl}}\right) \cdot v_3}{v_3 + \left(J_{E_1 \leftarrow E_1\mathrm{NaCl}}\right)}\#(91)$$

$$J_{E_1 \leftarrow E_1\mathrm{NaClK}} = \frac{\left(J_{E_1 \leftarrow E_1\mathrm{NaCl}}\right) \cdot v_{-3}}{v_3 + \left(J_{E_1 \leftarrow E_1\mathrm{NaCl}}\right)}\#(92)$$

$$J_{E_1 \rightarrow E_1\mathrm{NaClKCl}} = \frac{\left(J_{E_1 \rightarrow E_1\mathrm{NaClK}}\right) \cdot v_4}{v_4 + \left(J_{E_1 \leftarrow E_1\mathrm{NaClK}}\right)}\#(93)$$

$$J_{E_1 \leftarrow E_1\mathrm{NaClKCl}} = \frac{\left(J_{E_1 \leftarrow E_1\mathrm{NaClK}}\right) \cdot v_{-4}}{v_4 + \left(J_{E_1 \leftarrow E_1\mathrm{NaClK}}\right)}\#(94)$$

$$J_{E_1 \rightarrow E_2\mathrm{NaClKCl}} = \frac{\left(J_{E_1 \rightarrow E_1\mathrm{NaClKCl}}\right) \cdot v_5}{v_5 + \left(J_{E_1 \leftarrow E_1\mathrm{NaClKCl}}\right)}\#(95)$$

$$J_{E_1 \leftarrow E_2\mathrm{NaClKCl}} = \frac{\left(J_{E_1 \leftarrow E_1\mathrm{NaClKCl}}\right) \cdot v_{-5}}{v_5 + \left(J_{E_1 \leftarrow E_1\mathrm{NaClKCl}}\right)}\#(96)$$

$$J_{\mathrm{NKCC,Na\ influx}} = J_{E_1 \rightarrow E_2\mathrm{ClKCl}} = \frac{\left(J_{E_1 \rightarrow E_2\mathrm{NaClKCl}}\right) \cdot v_6}{v_6 + \left(J_{E_1 \leftarrow E_2\mathrm{NaClKCl}}\right)}\#(97)$$

$$J_{\mathrm{NKCC,Na\ efflux}} = J_{E_1 \leftarrow E_2\mathrm{ClKCl}} = \frac{\left(J_{E_1 \leftarrow E_2\mathrm{NaClKCl}}\right) \cdot v_{-6}}{v_6 + \left(J_{E_1 \leftarrow E_2\mathrm{NaClKCl}}\right)}\#(98)$$

$$v_1 = k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{Na}^+]_{\mathrm{o}} \cdot [E_1]\#(99)$$

$$v_{-1} = \left(k_{\mathrm{on}}^{\mathrm{ion}} / K_{\mathrm{Na}}\right) \cdot [E_1\mathrm{Na}]\#(100)$$

$$v_2 = k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{Cl}^-]_{\mathrm{o}} \cdot [E_1\mathrm{Na}]\#(101)$$

$$v_{-2} = \left(k_{\mathrm{on}}^{\mathrm{ion}} / K_{\mathrm{Cl}}\right) \cdot [E_1\mathrm{NaCl}]\#(102)$$

$$v_3 = k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{K}^+]_{\mathrm{o}} \cdot [E_1\mathrm{NaCl}] \#(103)$$

$$v_{\text{-}3} = \left(k_{\mathrm{on}}^{\mathrm{ion}}/K_{\mathrm{K}}\right) \cdot [E_1\mathrm{NaClK}] \#(104)$$

$$v_4 = k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{Cl}^-]_{\mathrm{o}} \cdot [E_1\mathrm{NaClK}] \#(105)$$

$$v_{\text{-}4} = \left(k_{\mathrm{on}}^{\mathrm{ion}}/K_{\mathrm{Cl}}\right) \cdot [E_1\mathrm{NaClKCl}] \#(106)$$

$$v_5 = k_{\mathrm{f}}^{\mathrm{full}} \cdot [E_1\mathrm{NaClKCl}] \#(107)$$

$$v_{\text{-}5} = k_{\mathrm{b}}^{\mathrm{full}} \cdot [E_2\mathrm{NaClKCl}] \#(108)$$

$$v_6 = \left(k_{\mathrm{on}}^{\mathrm{ion}}/K_{\mathrm{Na}}\right) \cdot [E_2\mathrm{NaClKCl}] \#(109)$$

$$v_{\text{-}6} = k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{Na}^+]_{\mathrm{cld}} \cdot [E_2\mathrm{ClKCl}] \#(110)$$

$$v_7 = \left(k_{\mathrm{on}}^{\mathrm{ion}}/K_{\mathrm{Cl}}\right) \cdot [E_2\mathrm{ClKCl}] \#(111)$$

$$v_{\text{-}7} = k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{Cl}^-]_{\mathrm{cld}} \cdot [E_2\mathrm{KCl}] \#(112)$$

$$v_8 = \left(k_{\mathrm{on}}^{\mathrm{ion}}/K_{\mathrm{K}}\right) \cdot [E_2\mathrm{KCl}] \#(113)$$

$$v_{\text{-}8} = k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{K}^+]_{\mathrm{i}} \cdot [E_2\mathrm{Cl}] \#(114)$$

$$v_9 = \left(k_{\mathrm{on}}^{\mathrm{ion}}/K_{\mathrm{Cl}}\right) \cdot [E_2\mathrm{Cl}] \#(115)$$

$$v_{\text{-}9} = k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{Cl}^-]_{\mathrm{cld}} \cdot [E_2] \#(116)$$

$$v_{10} = k_{\mathrm{f}}^{\mathrm{empty}} \cdot [E_2\mathrm{Cl}] \#(117)$$

$$v_{\text{-}10} = k_{\mathrm{b}}^{\mathrm{empty}} \cdot [E_1] \#(118)$$

$$\begin{bmatrix} a_1 & a_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_3 \\ b_1 & b_2 & b_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & c_1 & c_2 & c_3 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & d_1 & d_2 & d_3 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & e_1 & e_2 & e_3 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & f_1 & f_2 & f_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & g_1 & g_2 & g_3 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & h_1 & h_2 & h_3 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & i_1 & i_2 & i_3 \\ 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \end{bmatrix} \cdot \begin{bmatrix} [E_1] \\ [E_1\mathrm{Na}] \\ [E_1\mathrm{NaCl}] \\ [E_1\mathrm{NaClK}] \\ [E_1\mathrm{NaClKCl}] \\ [E_2\mathrm{NaClKCl}] \\ [E_2\mathrm{ClKCl}] \\ [E_2\mathrm{KCl}] \\ [E_2\mathrm{Cl}] \\ [E_2] \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{bmatrix} \#(119)$$

$$\begin{bmatrix} a_1 & a_2 & a_3 \\ b_1 & b_2 & b_3 \\ c_1 & c_2 & c_3 \\ d_1 & d_2 & d_3 \\ e_1 & e_2 & e_3 \\ f_1 & f_2 & f_3 \\ g_1 & g_2 & g_3 \\ h_1 & h_2 & h_3 \\ i_1 & i_2 & i_3 \end{bmatrix} = \begin{bmatrix} -k_{\mathrm{b}}^{\mathrm{empty}} - k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{Na}^{+}]_{\mathrm{o}} & k_{\mathrm{off}}^{\mathrm{Na}} & k_{\mathrm{f}}^{\mathrm{empty}} \\ k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{Na}^{+}]_{\mathrm{o}} & -k_{\mathrm{off}}^{\mathrm{Na}} - k\mathrm{ion}_{\mathrm{on}} \cdot [\mathrm{Cl}^{-}]_{\mathrm{o}} & k_{\mathrm{off}}^{\mathrm{Cl}} \\ k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{Cl}^{-}]_{\mathrm{o}} & -k_{\mathrm{off}}^{\mathrm{Cl}} - k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{K}^{+}]_{\mathrm{o}} & k_{\mathrm{off}}^{K} \\ k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{K}^{+}]_{\mathrm{o}} & -k_{\mathrm{off}}^{K} - k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{Cl}^{-}]_{\mathrm{o}} & k_{\mathrm{off}}^{\mathrm{Cl}} \\ k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{Cl}^{-}]_{\mathrm{o}} & -k_{\mathrm{off}}^{\mathrm{Cl}} - k_{\mathrm{f}}^{\mathrm{full}} & k_{\mathrm{b}}^{\mathrm{full}} \\ k_{\mathrm{f}}^{\mathrm{full}} & -k_{\mathrm{b}}^{\mathrm{full}} - k_{\mathrm{off}}^{\mathrm{Na}} & k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{Na}^{+}]_{\mathrm{cld}} \\ k_{\mathrm{off}}^{\mathrm{Na}} & -k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{Na}^{+}]_{\mathrm{cld}} - k_{\mathrm{off}}^{\mathrm{Cl}} & k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{Cl}^{-}]_{\mathrm{cld}} \\ k_{\mathrm{off}}^{\mathrm{Cl}} & -k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{Cl}^{-}]_{\mathrm{cld}} - k_{\mathrm{off}}^{\mathrm{K}} & k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{K}^{+}]_{\mathrm{cld}} \\ k_{\mathrm{off}}^{\mathrm{K}} & -k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{K}^{+}]_{\mathrm{cld}} - k_{\mathrm{off}}^{\mathrm{Cl}} & k_{\mathrm{on}}^{\mathrm{ion}} \cdot [\mathrm{Cl}^{-}]_{\mathrm{cld}} \end{bmatrix} \#(120)$$

$$\begin{bmatrix} [E_1] \\ [E_1\mathrm{Na}] \\ [E_1\mathrm{NaCl}] \\ [E_1\mathrm{NaClK}] \\ [E_1\mathrm{NaClKCl}] \\ [E_2\mathrm{NaClKCl}] \\ [E_2\mathrm{ClKCl}] \\ [E_2\mathrm{KCl}] \\ [E_2\mathrm{Cl}] \\ [E_2] \end{bmatrix} = \begin{bmatrix} a_1 & a_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_3 \\ b_1 & b_2 & b_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & c_1 & c_2 & c_3 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & d_1 & d_2 & d_3 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & e_1 & e_2 & e_3 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & f_1 & f_2 & f_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & g_1 & g_2 & g_3 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & h_1 & h_2 & h_3 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & i_1 & i_2 & i_3 \\ 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \end{bmatrix}^{-1} \cdot \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{bmatrix} \#(121)$$

$$K_{\mathrm{Na}} = 15.8 \cdot 10^{-3}\ \mathrm{L} \cdot \mathrm{mmol}^{-1} \#(122)$$

$$K_{\mathrm{Cl}} = 216.9 \cdot 10^{-3}\ \mathrm{L} \cdot \mathrm{mmol}^{-1} \#(123)$$

$$K_{\mathrm{K}} = 9.22 \cdot 10^{-3}\ \mathrm{L} \cdot \mathrm{mmol}^{-1} \#(124)$$

$$k_{\mathrm{f}}^{\mathrm{full}} = 1002.0 \cdot 10^{-3}\ \mathrm{ms}^{-1} \#(125)$$

$$k_{\mathrm{b}}^{\mathrm{full}} = 2255.0 \cdot 10^{-3}\ \mathrm{ms}^{-1} \#(126)$$

$$k_{\mathrm{f}}^{\mathrm{empty}} = 37767 \cdot 10^{-3}\ \mathrm{ms}^{-1} \#(127)$$

$$k_{\mathrm{b}}^{\mathrm{empty}} = \frac{K_{\mathrm{Na}} \cdot K_{\mathrm{Cl}} \cdot K_{\mathrm{K}} \cdot K_{\mathrm{Cl}} \cdot k_{\mathrm{f}}^{\mathrm{full}} \cdot k_{\mathrm{f}}^{\mathrm{empty}}}{K_{\mathrm{Na}} \cdot K_{\mathrm{Cl}} \cdot K_{\mathrm{K}} \cdot K_{\mathrm{Cl}} \cdot k_{\mathrm{b}}^{\mathrm{full}}}\ \mathrm{ms}^{-1} \#(128)$$

$$k_{\mathrm{on}}^{\mathrm{ion}} = 100\ \ \mathrm{L} \cdot \mathrm{mmol}^{-1} \#(129)$$

$$k_{\mathrm{off}}^{\mathrm{Na}} = k_{\mathrm{on}}^{\mathrm{ion}} / K_{\mathrm{Na}} \#(130)$$

$$k_{\mathrm{off}}^{\mathrm{K}} = k_{\mathrm{on}}^{\mathrm{ion}} / K_{\mathrm{K}} \#(131)$$

$$k_{\mathrm{off}}^{\mathrm{Cl}} = k_{\mathrm{on}}^{\mathrm{ion}} / K_{\mathrm{Cl}} \#(132)$$

A13. ER Ca^{2+} pump current ($\boldsymbol{I}_{\mathbf{pCa}}$)

$$\begin{array}{ccccc} E_2\mathrm{Ca} & \overset{K_{\mathrm{m,Cao}}}{\longleftrightarrow} & E_2 & & 1-\mathrm{y}_{\mathrm{pCa}} \\ k_1 \upharpoonleft\downharpoonright k_2 & & k_3 \upharpoonleft\downharpoonright k_4 & & \beta_{\mathrm{y}} \upharpoonleft\downharpoonright \alpha_{\mathrm{y}} \\ E_1\mathrm{Ca} & \overset{K_{\mathrm{m,Cai}}}{\longleftrightarrow} & E_1 & & \mathrm{y}_{\mathrm{pCa}} \end{array}$$

$$I_{\mathrm{pCa}} = P_{\mathrm{pCa}} \cdot \left(k_2 \cdot E_2Ca \cdot \left(1 - y_{\mathrm{pCa}}\right) - k_1 \cdot E_1Ca \cdot y_{\mathrm{pCa}}\right) \#(133)$$

$$P_{\mathrm{pCa}} = 772.8 \#(134)$$

$$k_1 = 0.01 \#(135)$$

$$k_2 = 1 \#(136)$$

$$k_3 = 1 \#(137)$$

$$k_4 = 0.01 \#(138)$$

$$\alpha_y = k_2 \cdot E_2Ca + k_4 \cdot E_2 \#(139)$$

$$\beta_y = k_1 \cdot E_1Ca + k_3 \cdot E_1 \#(140)$$

$$E_1\mathrm{Ca} = \left(1 + \frac{K_{\mathrm{m,Cai}}}{[\mathrm{Ca}^{2+}]_{\mathrm{up}}}\right)^{-1} \#(141)$$

$$E_2\mathrm{Ca} = \left(1 + \frac{K_{\mathrm{m,Cao}}}{[\mathrm{Ca}^{2+}]_{\mathrm{i}}}\right)^{-1} \#(142)$$

$$E_1 = \left(1 + \frac{[\mathrm{Ca}^{2+}]_{\mathrm{up}}}{K_{\mathrm{m,Cai}}}\right)^{-1} \#(143)$$

$$E_2 = \left(1 + \frac{[\mathrm{Ca}^{2+}]_{\mathrm{i}}}{K_{\mathrm{m,Cao}}}\right)^{-1} \#(144)$$

$$K_{\mathrm{m,Cao}} = 0.00258\ \mathrm{mM} \#(145)$$

$$K_{\mathrm{m,Cai}} = 0.08\ \mathrm{mM} \#(146)$$

A14. IP_3-mediated Ca^{2+} release current from the ER ($\boldsymbol{I}_{\mathbf{IP3R}}$)

$$\mathrm{U} \underset{k_{\mathrm{cu}}}{\overset{k_{\mathrm{uc}}\cdot[\mathrm{IP}_3]}{\rightleftharpoons}} \mathrm{C} \underset{k_{\mathrm{oc}}}{\overset{k_{\mathrm{co}}\cdot[\mathrm{Ca}^{2+}]_{\mathrm{i}}}{\rightleftharpoons}} \mathrm{O} \underset{k_{\mathrm{io}}}{\overset{k_{\mathrm{oi}}\cdot[\mathrm{Ca}^{2+}]_{\mathrm{i}}}{\rightleftharpoons}} \mathrm{I}$$

$$I_{\mathrm{IP3R}} = P_{\mathrm{IP3R}} \cdot \left([\mathrm{Ca}^{2+}]_{\mathrm{rel}} - [\mathrm{Ca}^{2+}]_{\mathrm{i}}\right) \cdot P_{\mathrm{o(IP3R)}} \#(147)$$

$$P_{\mathrm{IP3R}} = 217.2\#(148)$$

$$P_{\mathrm{o(IP3R)}} = \mathrm{O}^3\#(149)$$

$$k_{\mathrm{uc}} = 400\ \mathrm{mM}^{-1} \cdot \mathrm{ms}^{-1}\#(150)$$

$$k_{\mathrm{cu}} = 0.37736\ \mathrm{ms}^{-1}\#(151)$$

$$k_{\mathrm{co}} = 20\ \mathrm{mM}^{-1} \cdot \mathrm{ms}^{-1}\#(152)$$

$$k_{\mathrm{oc}} = 0.0016468\ \mathrm{ms}^{-1}\#(153)$$

$$k_{\mathrm{oi}} = 0.2\ \mathrm{mM}^{-1} \cdot \mathrm{ms}^{-1}\#(154)$$

$$k_{\mathrm{io}} = 0.0002098\ \mathrm{ms}^{-1}\#(155)$$

A15. Ca^{2+} leak from ER uptake pool (I_{leak})

$$I_{\mathrm{leak}} = P_{\mathrm{leak}} \cdot \left([\mathrm{Ca}^{2+}]_{\mathrm{up}} - [\mathrm{Ca}^{2+}]_{\mathrm{i}}\right)\#(156)$$

$$P_{\mathrm{leak}} = 1.9125\#(157)$$

A16. Ca^{2+} transfer between ER uptake and release pool (I_{tr})

$$I_{\mathrm{tr}} = P_{\mathrm{tr}} \cdot \left([\mathrm{Ca}^{2+}]_{\mathrm{up}} - [\mathrm{Ca}^{2+}]_{\mathrm{rel}}\right)\#(158)$$

$$P_{\mathrm{tr}} = 205\#(159)$$

A17. Ca^{2+} concentration in ER uptake pool

$$\frac{\mathrm{d}[\mathrm{Ca}^{2+}]_{\mathrm{up}}}{\mathrm{dt}} = \frac{I_{\mathrm{pCa}} - I_{\mathrm{tr}} - I_{\mathrm{leak}}}{2\mathrm{F} \cdot Vol_{\mathrm{up}}}\#(160)$$

A18. Ca^{2+} concentration in ER release pool

$$[\mathrm{Ca}^{2+}]_{\mathrm{rel}} = 0.5 \cdot \left(-\mathrm{b}_{\mathrm{CSQN}} + \sqrt{\mathrm{b}_{\mathrm{CSQN}}{}^2 + 4 \cdot \mathrm{c}_{\mathrm{CSQN}}}\right)\#(161)$$

$$\mathrm{b}_{\mathrm{CSQN}} = [\mathrm{CSQN}]_{\mathrm{total}} - [\mathrm{Ca}]_{\mathrm{rel}} + K_{\mathrm{m}}\#(162)$$

$$\mathrm{c}_{\mathrm{CSQN}} = K_{\mathrm{m}} \cdot [\mathrm{Ca}]_{\mathrm{rel}}\#(163)$$

$$K_{\mathrm{m}} = 0.8\ \mathrm{mM}\#(164)$$

$$[\mathrm{CSQN}]_{\mathrm{total}} = 10\ \mathrm{mM}\#(165)$$

$$\frac{\mathrm{d[Ca]_{rel}}}{\mathrm{dt}} = \frac{I_{\mathrm{tr}} - I_{\mathrm{IP3R}}}{2\mathrm{F} \cdot Vol_{\mathrm{rel}}} \#(166)$$

A19. Ion concentrations in cytosol

$$\frac{\mathrm{d[Na^+]_i}}{\mathrm{dt}} = \frac{-I_{\mathrm{net}}\mathrm{Na}}{\mathrm{F} \cdot Vol_{\mathrm{cyt}}} + D_{\mathrm{Na}} \cdot \left([\mathrm{Na^+}]_{\mathrm{cld}} - [\mathrm{Na^+}]_{\mathrm{i}}\right) \#(167)$$

$$I_{\mathrm{net}}\mathrm{Na} = I_{\mathrm{CaL}}\mathrm{Na} + I_{\mathrm{NaLCN}}\mathrm{Na} + 3 \cdot I_{\mathrm{NaK}} \#(168)$$

$$D_{\mathrm{Na}} = 0.3\ \mathrm{ms^{-1}} \#(169)$$

$$\frac{\mathrm{d[K^+]_i}}{\mathrm{dt}} = \frac{-I_{\mathrm{net}}\mathrm{K}}{\mathrm{F} \cdot Vol_{\mathrm{cyt}}} + D_{\mathrm{K}} \cdot \left([\mathrm{K^+}]_{\mathrm{cld}} - [\mathrm{K^+}]_{\mathrm{i}}\right) \#(170)$$

$$I_{\mathrm{net}}\mathrm{K} = I_{K1} + I_{\mathrm{CaL}}\mathrm{K} + I_{\mathrm{NaLCN}}\mathrm{K} - 2 \cdot I_{\mathrm{NaK}} \#(171)$$

$$D_{\mathrm{K}} = 0.3\ \mathrm{ms^{-1}} \#(172)$$

$$\frac{\mathrm{d[Ca]_i}}{\mathrm{dt}} = \frac{-I_{\mathrm{net}}\mathrm{Ca}}{2\mathrm{F} \cdot Vol_{\mathrm{cyt}}} + D_{\mathrm{Ca}} \cdot \left([\mathrm{Ca^{2+}}]_{\mathrm{cld}} - [\mathrm{Ca^{2+}}]_{\mathrm{i}}\right) \#(173)$$

$$D_{\mathrm{Ca}} = 0.2\ \mathrm{ms^{-1}} \#(174)$$

$$I_{\mathrm{net}}\mathrm{Ca} = I_{\mathrm{Orai}} + I_{\mathrm{CaL}}\mathrm{Ca} + I_{\mathrm{CaT}} + I_{\mathrm{pCa}} - I_{\mathrm{IP3R}} - I_{\mathrm{leak}} \#(175)$$

$$\left[\mathrm{Ca^{2+}}\right]_{\mathrm{i}} = 0.5 \cdot \left(\text{-}\mathrm{b_{CMDN}} + \sqrt{\mathrm{b_{CMDN}}^2 + 4 \cdot \mathrm{c_{CMDN}}}\right) \#(176)$$

$$\mathrm{b_{CMDN}} = [\mathrm{CMDN}]_{\mathrm{total}} - [\mathrm{Ca}]_{\mathrm{i}} + K_{\mathrm{m}} \#(177)$$

$$\mathrm{c_{CMDN}} = K_{\mathrm{m}} \cdot [\mathrm{Ca}]_{\mathrm{i}} \#(178)$$

$$K_{\mathrm{m}} = 0.00238\ \mathrm{mM} \#(179)$$

$$[\mathrm{CMDN}]_{\mathrm{total}} = 0.0005\ \mathrm{mM} \#(180)$$

$$\frac{\mathrm{d[Cl^-]_i}}{\mathrm{dt}} = \frac{I_{\mathrm{Clb}}}{\mathrm{F} \cdot Vol_{\mathrm{cyt}}} + D_{\mathrm{Cl}} \cdot ([\mathrm{Cl^-}]_{\mathrm{cld}} - [\mathrm{Cl^-}]_{\mathrm{i}}) \#(181)$$

$$D_{\mathrm{Cl}} = 0.002\ \mathrm{ms^{-1}} \#(182)$$

A20. Ion concentrations in $\mathrm{Cl^-}$ microdomain

$$\frac{\mathrm{d[Na^+]_{cld}}}{\mathrm{dt}} = \frac{-3 \cdot I_{\mathrm{NaCa}}}{\mathrm{F} \cdot Vol_{\mathrm{cld}}} + J_{\mathrm{NKCC,Na}} + D_{\mathrm{Na}} \cdot \left([\mathrm{Na^+}]_{\mathrm{i}} - [\mathrm{Na^+}]_{\mathrm{cld}}\right) \cdot \frac{Vol_{\mathrm{cyt}}}{Vol_{\mathrm{cld}}} \#(183)$$

$$\frac{d[K^+]_{cld}}{dt} = J_{NKCC,K} + D_K \cdot \left([K^+]_i - [K^+]_{cld}\right) \cdot \frac{Vol_{cyt}}{Vol_{cld}} \#(184)$$

$$\frac{d[Ca]_{cld}}{dt} = \frac{2 \cdot I_{NaCa}}{2F \cdot Vol_{cld}} + D_{Ca} \cdot \left([Ca^{2+}]_i - [Ca^{2+}]_{cld}\right) \cdot \frac{Vol_{cyt}}{Vol_{cld}} \#(185)$$

$$\left[Ca^{2+}\right]_{cld} = 0.5 \cdot \left(\text{-}b_{CMDN} + \sqrt{{b_{CMDN}}^2 + 4 \cdot c_{CMDN}}\right) \#(186)$$

$$b_{CMDN} = [CMDN]_{total} - [Ca]_{cld} + K_m \#(187)$$

$$c_{CMDN} = K_m \cdot [Ca]_{cld} \#(188)$$

$$K_m = 0.00238 \text{ mM} \#(189)$$

$$\frac{d[Cl^-]_{cld}}{dt} = \frac{I_{ClCa}}{F \cdot Vol_{cld}} + J_{NKCC,Cl} + D_{Cl} \cdot ([Cl^-]_i - [Cl^-]_{cld}) \cdot \frac{Vol_{cyt}}{Vol_{cld}} \#(190)$$

A21. IP_3 concentration

$$PIP_2 \underset{k_{ba}}{\overset{k_{ab}}{\rightleftarrows}} IP_3$$

$$k_{ca} \uparrow \qquad \qquad \downarrow k_{bc}$$

$$IP_4 \ (inactive\ metabolites)$$

$$\frac{d[IP_3]}{dt} = k_{ab} \cdot [PIP_2] - (k_{ba} + k_{bc}) \cdot [IP_3] \#(191)$$

$$\frac{d[PIP_2]}{dt} = k_{ba} \cdot [IP_3] + k_{ca} \cdot [IP_4] - k_{ab} \cdot [PIP_2] \#(192)$$

$$\frac{d[IP_4]}{dt} = k_{bc} \cdot [IP_3] - k_{ca} \cdot [IP_4] \#(193)$$

$$[PI_{total}] \ = [PIP_2] + [IP_3] + [IP_4] = 3.3 \cdot 10^{-3} \#(194)$$

$$k_{ab} = 0.2 \cdot e^{\frac{V+48.5}{18.1}} \cdot \frac{[Ca^{2+}]_i}{[Ca^{2+}]_i + K_{m,Cai(PI)}} \text{ ms}^{-1} \#(195)$$

$$k_{ba} = 0.5 \cdot e^{-\frac{V+100}{28.5}} \text{ ms}^{-1} \#(196)$$

$$k_{bc} = 0.004 \text{ ms}^{-1} \#(197)$$

$$k_{ca} = 0.0035 \cdot e^{-\frac{V+100}{25.5}} \text{ ms}^{-1} \#(198)$$

$$K_{m,Cai(PI)} = 0.00001 \text{ mM} \#(199)$$

Supplement tables

Table A1. Glossary

Parameter	Unit	Description
I_{total}	pA	Total current of ion channels, exchanger, and pump
I_{ext}	pA	Externally applied current
I_{CaL}	pA	L-type Ca^{2+} current
$I_{CaL}X$	pA	ion X component of L-type Ca^{2+} current
I_{CaT}	pA	T-type Ca^{2+} current
I_{K1}	pA	Inward rectifier K^+ current
I_{NaLCN}	pA	Na^+-leak current
$I_{NaLCN}X$	pA	ion X component of Na^+-leak current
I_{ClCa}	pA	Ca^{2+}-activated Cl^- current
I_{Clb}	pA	Background Cl^- current
I_{Orai}	pA	Current carried by Orai (store-operated Ca^{2+} entry)
I_{NaCa}	pA	Na^+/Ca^{2+} exchange current
I_{NaK}	pA	Na^+/K^+ exchange current
J_{NKCC}	$mM\cdot ms^{-1}$	Flux by Na-K-2Cl cotransporter (NKCC1)
$J_{NKCC,X}$	$mM\cdot ms^{-1}$	ion X component of J_{NKCC}
I_{pCa}	pA	ER Ca^{2+} pump current
I_{IP3R}	pA	IP_3-mediated Ca^{2+} release current from the ER
$P_{o(IP3R)}$	unitless	Probability of IP_3 receptor in conducting state
I_{leak}	pA	Ca^{2+} leak from ER uptake pool
I_{tr}	pA	Ca^{2+} transfer between ER uptake and release pool
α_X	ms^{-1}	Forward rate constant for gating variable X
β_X	ms^{-1}	Backward rate constant for gating variable X
τ_X	ms	Time constant of gating variable X
X_∞	unitless	Steady-state value of gating variable X
E_X	mV	Equilibrium potential for ion X
V	mV	Membrane potential
t	ms	Time
CF_X	mM	Constant field for intracellular and extracellular ion X
$CF_{X,md}$	mM	Constant field for microdomain and extracellular ion X
G_X	$pA\cdot mV^{-1}$	Maximum conductance of channel X
z_X	unitless	Valence of the ion X
$[X]_i$	mM	Intracellular concentration of ion X
$[X]_{cld}$	mM	Concentration of ion X in Cl^- microdomain

$[X]_o$	mM	Extracellular concentration of ion X
$[Ca]_{rel}$	mM	Total calcium concentration in ER release pool
$[Ca^{2+}]_{rel}$	mM	Free calcium concentration in ER release pool
$[Ca^{2+}]_{up}$	mM	Free calcium concentration in ER uptake pool

Table A2. General model constants

Parameter	Value	Unit	Description
C_m	25	pF	Membrane capacitance
Vol_{cyt}	715.5	μm^3	Cell volume accessible for ion diffusion
Vol_{up}	21.465	μm^3	Volume of ER uptake pool
Vol_{rel}	7.155	μm^3	Volume of ER release pool
Vol_{cld}	35.775	μm^3	Volume of Cl^- microdomain
F	96.4867	$C \cdot mmol^{-1}$	Faraday constant
R	8.314	$C \cdot mV \cdot K^{-1} \cdot mmol^{-1}$	Gas constant
T	309.15	K	Absolute temperature

Table A3. Initial values (gating variables)

Ion carriers	Parameter	Value
I_{CaL}	m	$8.980 \cdot 10^{-8}$
	h	$0.680 \cdot 10^{-1}$
I_{CaT}	d	$4.429 \cdot 10^{-4}$
	f	$7.262 \cdot 10^{-1}$
I_{ClCa}	O_{ClCa}	$3.249 \cdot 10^{-3}$
I_{NaCa}	y_{NaCa}	$9.798 \cdot 10^{-1}$
I_{NaK}	y_{NaK}	$5.983 \cdot 10^{-1}$
I_{pCa}	y_{pCa}	$4.226 \cdot 10^{-1}$
I_{IP3R}	$P_{o(IP3R)}$	$7.009 \cdot 10^{-4}$

Table A4. Initial values (membrane potential and concentrations)

Parameter	Value	Unit
V	-72.332	mV
$[Na^+]_o$	140.0	mM
$[Na^+]_i$	6.321	mM
$[Na^+]_{cld}$	6.321	mM
$[K^+]_o$	5.4	mM
$[K^+]_i$	135.6	mM
$[K^+]_{cld}$	135.6	mM
$[Cl^-]_o$	140	mM
$[Cl^-]_i$	87.290	mM
$[Cl^-]_{cld}$	87.464	mM
$[Ca^{2+}]_o$	1.8	mM
$[Ca]_i$	$1.071 \cdot 10^{-4}$	mM
$[Ca^{2+}]_i$	$8.913 \cdot 10^{-5}$	mM
$[Ca]_{cld}$	$1.717 \cdot 10^{-4}$	mM
$[Ca^{2+}]_{cld}$	$1.433 \cdot 10^{-4}$	mM
$[Ca]_{rel}$	8.065	mM
$[Ca^{2+}]_{rel}$	1.517	mM
$[Ca^{2+}]_{up}$	1.783	mM
$[E_1]$	$1.579 \cdot 10^{-3}$	mM
$[E_1\text{Na}]$	$3.489 \cdot 10^{-3}$	mM
$[E_1\text{NaCl}]$	$1.059 \cdot 10^{-1}$	mM
$[E_1\text{NaClK}]$	$5.271 \cdot 10^{-3}$	mM
$[E_1\text{NaClKCl}]$	$1.600 \cdot 10^{-1}$	mM
$[E_2\text{NaClKCl}]$	$6.039 \cdot 10^{-2}$	mM
$[E_2\text{ClKCl}]$	$6.046 \cdot 10^{-1}$	mM
$[E_2\text{KCl}]$	$3.186 \cdot 10^{-2}$	mM
$[E_2\text{Cl}]$	$2.548 \cdot 10^{-2}$	mM
$[E_2]$	$1.340 \cdot 10^{-3}$	mM
$[IP_3]$	$3.396 \cdot 10^{-4}$	mM
$[PIP_2]$	$1.364 \cdot 10^{-3}$	mM