Korhonen et al, http://www.jgp.org/cgi/doi/10.1085/jgp.200809961

COMPLETE MODEL EQUATIONS

The model parameters are defined in Tables S2–S5. The units in the equations are mV for voltage, μM for concentrations, pl for volume, ms for time, μm for distance, pA/pF for current, and μM/ms (in 1 pl volume) for fluxes. The scaling factors required for agreement of the units are shown within the equations.

Nernst Potentials

$$E_{Ca} = \frac{RT}{2F}\ln\frac{[\mathrm{Ca}^{2+}]_o}{[\mathrm{Ca}^{2+}]_{subSL}} \quad (1)$$

$$E_K = \frac{RT}{F}\ln\frac{[\mathrm{K}^{+}]_o}{[K^{+}]_i} \quad (2)$$

$$E_{Na} = \frac{RT}{F}\ln\frac{[\mathrm{Na}^{+}]_o}{[\mathrm{Na}^{+}]_i} \quad (3)$$

SL Membrane Currents

L-type Ca^{2+} Current.

$$I_{CaL} = G_{CaL}O\left(V - E_{CaL}\right) \quad (4)$$

$$\alpha = 0.3992\exp\left[\left(V + 12.01\right)/10.01\right] \quad (5)$$

$$\beta = 0.04308\exp\left[-\left(V + 13.19\right)/15.01\right] + 0.07274\exp\left[\left(V - 17.30\right)/3.004\right] \quad (6)$$

$$\gamma = K_{pc,max}[\mathrm{Ca}^{2+}]_{subSL} / \left(K_{pc,half} + [\mathrm{Ca}^{2+}]_{subSL}\right) \quad (7)$$

$$K_{pcf} = 15.29\left\{1 - \exp\left[-\left(V + 24.30\right)^2 / 87.81\right]\right\} \quad (8)$$

$$\frac{dO}{dt} = \alpha C_4 - 4\beta O + K_{pcb}I_1 - \gamma O + 0.001\left(\alpha I_2 - K_{pcf}O\right) \quad (9)$$

$$C_1 = 1 - \left(O + C_2 + C_3 + C_4 + I_1 + I_2 + I_3\right) \quad (10)$$

$$\frac{dC_2}{dt} = 4\alpha C_1 - \beta C_2 + 2\beta C_3 - 3\alpha C_2 \quad (11)$$

$$\frac{dC_3}{dt} = 3\alpha C_2 - 2\beta C_3 + 3\beta C_4 - 2\alpha C_3 \quad (12)$$

$$\frac{dC_4}{dt} = 2\alpha C_3 - 3\beta C_4 + 4\beta O - \alpha C_4 + 0.01\left(4K_{pcb}\beta I_1 - \alpha\gamma C_4\right) + 0.002\left(4\beta I_2 - K_{pcf}C_4\right) + 4\beta K_{pcb}I_3 - \gamma K_{pcf}C_4 \quad (13)$$

$$\frac{dI_1}{dt} = \gamma O - K_{pcb}I_1 + 0.001\left(\alpha I_3 - K_{pcf}I_1\right) + 0.01\left(\alpha\gamma C_4 - 4\beta K_{pcb}I_1\right) \quad (14)$$

$$\frac{dI_2}{dt} = 0.001\left(K_{pcf}O - \alpha I_2\right) + K_{pcb}I_3 - \gamma I_2 + 0.002\left(K_{pcf}C_4 - 4\beta I_2\right) \quad (15)$$

$$\frac{dI_3}{dt} = 0.001\left(K_{pcf}I_1 - \alpha I_3\right) + \gamma I_2 - K_{pcb}I_3 + \gamma K_{pcf}C_4 - 4\beta K_{pcb}I_3 \quad (16)$$

T-type Ca^{2+} Current.

$$I_{CaT} = G_{CaT}bg\left(V - E_{Ca} + 75\right) \quad (17)$$

$$b_\infty = \left\{1 + \exp\left[-\left(V + 23\right)/6.1\right]\right\}^{-1} \quad (18)$$

$$\tau_b = 0.6 + 5.4 \times \left\{1 + \exp\left[0.03\left(V + 100\right)\right]\right\}^{-1} \quad (19)$$

$$g_\infty = \left\{1 + \exp\left[\left(V + 75\right)/6.6\right]\right\}^{-1} \quad (20)$$

$$\tau_g = 1 + 40 \times \left\{1 + \exp\left[0.08\left(V + 65\right)\right]\right\}^{-1} \quad (21)$$

$$\frac{db}{dt} = \frac{b_\infty - b}{\tau_b} \quad (22)$$

$$\frac{dg}{dt} = \frac{g_\infty - g}{\tau_g} \quad (23)$$

Background Ca^{2+} Current.

$$I_{Cab} = G_{Cab}\left(V - E_{Ca}\right) \quad (24)$$

Fast Na^{+} Current.

$$I_{Na} = G_{Na} O_{Na}\left(V - E_{Naf}\right) \quad (25)$$

$$E_{Naf} = \frac{RT}{F}\ln\left(\frac{0.9[\mathrm{Na}^+]_\mathrm{o} + 0.1[\mathrm{K}^+]_\mathrm{o}}{0.9[\mathrm{Na}^+]_\mathrm{i} + 0.1[\mathrm{K}^+]_\mathrm{i}}\right) \quad (26)$$

$$\alpha_{Na11} = 3.802 / \left\{0.1027\exp\left[-\left(V + 2.5\right)/17\right] + 0.20\exp\left[-\left(V + 2.5\right)/150\right]\right\} \quad (27)$$

$$\alpha_{Na12} = 3.802 / \left\{0.1027\exp\left[-\left(V + 2.5\right)/15\right] + 0.23\exp\left[-\left(V + 2.5\right)/150\right]\right\} \quad (28)$$

$$\alpha_{Na13} = 3.802 / \left\{0.1027\exp\left[-\left(V + 2.5\right)/12\right] + 0.25\exp\left[-\left(V + 2.5\right)/150\right]\right\} \quad (29)$$

$$\beta_{Na11} = 0.1917\exp\left[-\left(V + 2.5\right)/20.3\right] \quad (30)$$

$$\beta_{Na12} = 0.20\exp\left[-\left(V - 2.5\right)/20.3\right] \quad (31)$$

$$\beta_{Na13} = 0.22\exp\left[-\left(V - 7.5\right)/20.3\right] \quad (32)$$

$$\alpha_{Na3} = \beta_{Na4} = 7 \times 10^{-7}\exp\left[-\left(V + 7\right)/7.7\right] \quad (33)$$

$$\beta_{Na3} = 0.0084 + 0.00002\left(V + 7\right) \quad (34)$$

$$\alpha_{Na2} = \left\{0.1885\exp\left[-\left(V + 7\right)/16.6\right] + 0.3940\right\}^{-1} \quad (35)$$

$$\beta_{Na2} = \alpha_{Na13}\alpha_{Na2}\alpha_{Na3} / \left(\beta_{Na13}\beta_{Na3}\right) \quad (36)$$

$$\alpha_{Na4} = \alpha_{Na2} / 1000 \quad (37)$$

$$\alpha_{Na5} = \alpha_{Na2} / 95000 \quad (38)$$

$$\beta_{Na5} = \alpha_{Na3} / 50 \quad (39)$$

$$C_{Na3} = 1 - \left(O_{Na} + C_{Na1} + C_{Na2} + IF_{Na} + I1_{Na} + I2_{Na} + IC_{Na2} + IC_{Na3}\right) \quad (40)$$

$$\frac{dC_{Na2}}{dt} = \alpha_{Na11}C_{Na3} - \beta_{Na11}C_{Na2} + \beta_{Na12}C_{Na1} - \alpha_{Na12}C_{Na2} + \alpha_{Na3}IC_{Na2} - \beta_{Na3}C_{Na2} \quad (41)$$

$$\frac{dC_{Na1}}{dt} = \alpha_{Na12}C_{Na2} - \beta_{Na12}C_{Na1} + \beta_{Na13}O_{Na} - \alpha_{Na13}C_{Na1} + \alpha_{Na3}IF_{Na} - \beta_{Na3}C_{Na1} \quad (42)$$

$$\frac{dO_{Na}}{dt} = \alpha_{Na13}C_{Na1} - \beta_{Na13}O_{Na} + \beta_{Na2}IF_{Na} - \alpha_{Na2}O_{Na} \quad (43)$$

$$\frac{dIF_{Na}}{dt} = \alpha_{Na2}O_{Na} - \beta_{Na2}IF_{Na} + \beta_{Na3}C_{Na1} - \alpha_{Na3}IF_{Na} + \beta_{Na4}I1_{Na} - \alpha_{Na4}IF_{Na} + \alpha_{Na12}IC_{Na2} - \beta_{Na12}IF_{Na} \quad (44)$$

$$\frac{dI1_{Na}}{dt} = \alpha_{Na4}IF_{Na} - \beta_{Na4}I1_{Na} + \beta_{Na5}I2_{Na} - \alpha_{Na5}I1_{Na} \quad (45)$$

$$\frac{dI2_{Na}}{dt} = \alpha_{Na5}I1_{Na} - \beta_{Na5}I2_{Na} \quad (46)$$

$$\frac{dIC_{Na2}}{dt} = \alpha_{Na11}IC_{Na3} - \beta_{Na11}IC_{Na2} + \beta_{Na12}IF_{Na} - \alpha_{Na12}IC_{Na2} + \beta_{Na3}C_{Na2} - \alpha_{Na3}IC_{Na2} \quad (47)$$

$$\frac{dIC_{Na3}}{dt} = \beta_{Na11}IC_{Na2} - \alpha_{Na11}IC_{Na3} + \beta_{Na3}C_{Na3} - \alpha_{Na3}IC_{Na3} \quad (48)$$

Delayed Rectifier K⁺ Current.

$$I_{Kdr} = I_{Kx}K_{Kdr}[\mathrm{K}^+]_\mathrm{o}^{0.59}\left[[\mathrm{K}^+]_\mathrm{i} - [\mathrm{K}^+]_\mathrm{o}\exp\left(-\frac{VF}{RT}\right)\right] \quad (49)$$

$$I_{Kx\infty} = \left\{1 + \exp\left[-(V + 25.1)/7.4\right]\right\}^{-1} \quad (50)$$

$$\tau_{IKx} = 2000/\left[17\exp(0.0398V) + 0.211\exp(-0.051V)\right] \quad (51)$$

$$\frac{dI_{Kx}}{dt} = \frac{I_{Kx\infty} - I_{Kx}}{\tau_{IKx}} \quad (52)$$

Time Independent K⁺ Current.

$$I_{K1} = K_{K1}[\mathrm{K}^+]_\mathrm{o}^{0.37}\left[[\mathrm{K}^+]_\mathrm{i} - [\mathrm{K}^+]_\mathrm{o}\exp\left(-\frac{VF}{RT}\right)\right] \quad (53)$$

Hyperpolarization Activated Current.

$$I_{fNa} = 0.2G_f y(V - E_{Na}) \quad (54)$$

$$I_{fK} = 0.8G_f y(V - E_K) \quad (55)$$

$$I_f = I_{fNa} + I_{fK} \quad (56)$$

$$y_\infty = \left\{1 + \exp\left[(V + 70.7742)/11.9531\right]\right\}^{-1} \quad (57)$$

$$\tau_y = 65.88 + 7429\exp\left[V/16.86\right] \quad (58)$$

$$\frac{dy}{dt} = \frac{y_\infty - y}{\tau_y} \quad (59)$$

NaK-ATPase.

$$I_{NaK} = I_{NaK}^{\max} f_{NaK} \times \left[1 + \left(K_{m,Nai}/[\mathrm{Na}^+]_\mathrm{i}\right)^{\eta_{NaK}}\right]^{-1} \times \left[1 + \left(K_{m,Ko}/[\mathrm{K}^+]_\mathrm{o}\right)\right]^{-1} \quad (60)$$

$$f_{NaK} = \left[1 + 0.1245\exp\left(-0.1VF/RT\right) + 0.0365\sigma\exp\left(-VF/RT\right)\right]^{-1} \quad (61)$$

$$\sigma = 1/7 \times \left[\exp\left([\mathrm{Na}^+]_\mathrm{o}/67300\right) - 1\right] \quad (62)$$

Na^+/Ca^{2+}-Exchanger.

$$I_{NCX} = k_{NCX}\frac{[\mathrm{Na}^+]_\mathrm{o}^3}{K_{m,Na}^3 + [\mathrm{Na}^+]_\mathrm{o}^3}\frac{[\mathrm{Ca}^{2+}]_\mathrm{o}}{K_{m,Ca} + [\mathrm{Ca}^{2+}]_\mathrm{o}}\frac{\frac{[\mathrm{Na}^+]_\mathrm{i}^3}{[\mathrm{Na}^+]_\mathrm{o}^3}\exp\left[\eta VF/RT\right] - \frac{[\mathrm{Ca}^{2+}]_\mathrm{i}}{[\mathrm{Ca}^{2+}]_\mathrm{o}}\exp\left[(\eta-1)VF/RT\right]}{1 + k_{sat}\exp\left[(\eta-1)VF/RT\right]} \quad (63)$$

$$\frac{dV}{dt} = -\left(I_{NCX} + I_{CaL} + I_{CaT} + I_{Cab} + I_{Kdr} + I_{K1} + I_{NaK} + I_{Na} + I_f + I_{stim}\right) \quad (64)$$

SR

Ryanodine Receptors.

$$J_{RyR} = \nu_1\left(P_{O1} + P_{O2}\right)\left(\left[\mathrm{Ca}^{2+}\right]_\mathrm{SR} - \left[\mathrm{Ca}^{2+}\right]_\mathrm{subSR}\right) \quad (65)$$

$$J_{RyR-caffeine} = \nu_1 \times 0.2 \times \left(\left[\mathrm{Ca}^{2+}\right]_\mathrm{SR} - \left[\mathrm{Ca}^{2+}\right]_\mathrm{subSR}\right) \quad (66)$$

$$P_{C1} = 1 - \left(P_{C2} + P_{O1} + P_{O2}\right) \quad (67)$$

$$\frac{dP_{O1}}{dt} = k_a^+\left[\mathrm{Ca}^{2+}\right]_\mathrm{subSR}^n P_{C1} - k_a^- P_{O1} - k_b^+\left[\mathrm{Ca}^{2+}\right]_\mathrm{subSR}^m P_{O1} + k_b^- P_{O2} - k_c^+ P_{O1} + k_c^- P_{C2} \quad (68)$$

$$\frac{dP_{O2}}{dt} = k_b^+[\mathrm{Ca}^{2+}]_\mathrm{subSR}^\mathrm{m} P_{O1} - k_b^- P_{O2} \quad (69)$$

$$\frac{dP_{C2}}{dt} = k_c^+ P_{O1} - k_c^- P_{C2} \quad (70)$$

IP_3 Receptors.

$$J_{IP3} = k_f\left(0.1O_{IP3} + 0.9A_{IP3}\right)^4\left([\mathrm{Ca}^{2+}]_\mathrm{SR} - [\mathrm{Ca}^{2+}]_\mathrm{subSR}\right) \quad (71)$$

$$\phi_1 = \frac{\left(k_1L_1 + l_2\right)[\mathrm{Ca}^{2+}]_\mathrm{subSR}}{L_1 + [\mathrm{Ca}^{2+}]_\mathrm{subSR}\left(1 + L_1/L_3\right)} \quad (72)$$

$$\phi_2 = \frac{k_2L_3 + l_4[\mathrm{Ca}^{2+}]_\mathrm{subSR}}{L_3 + [\mathrm{Ca}^{2+}]_\mathrm{subSR}\left(1 + L_3/L_1\right)} \quad (73)$$

$$\phi_{-2} = \frac{k_{-2} + l_{-4}[\mathrm{Ca}^{2+}]_\mathrm{subSR}}{1 + [\mathrm{Ca}^{2+}]_\mathrm{subSR}/L_5} \quad (74)$$

$$\phi_3 = \frac{k_3L_5}{L_5 + [\mathrm{Ca}^{2+}]_\mathrm{subSR}} \quad (75)$$

$$\phi_4 = \frac{\left(k_4L_5 + l_6\right)[\mathrm{Ca}^{2+}]_\mathrm{subSR}}{L_5 + [\mathrm{Ca}^{2+}]_\mathrm{subSR}} \quad (76)$$

$$\phi_{-4} = \frac{L_1\left(k_{-4} + l_{-6}\right)}{L_1 + [\mathrm{Ca}^{2+}]_{\mathrm{subSR}}} \quad (77)$$

$$\phi_5 = \frac{\left(k_1 L_1 + l_2\right)[\mathrm{Ca}^{2+}]_{\mathrm{subSR}}}{L_1 + [\mathrm{Ca}^{2+}]_{\mathrm{subSR}}} \quad (78)$$

$$S_{IP3} = 1 - \left(R_{IP3} + O_{IP3} + A_{IP3} + I1_{IP3} + I2_{IP3}\right) \quad (79)$$

$$\frac{dR_{IP3}}{dt} = \phi_{-2} O_{IP3} - \phi_2 p R_{IP3} + \left(k_{-1} + l_{-2}\right) I1_{IP3} - \phi_1 R_{IP3} \quad (80)$$

$$\frac{dO_{IP3}}{dt} = \phi_2 p R_{IP3} - \left(\phi_{-2} + \phi_4 + \phi_3\right) O_{IP3} + \phi_{-4} A_{IP3} + k_{-3} S_{IP3} \quad (81)$$

$$\frac{dA_{IP3}}{dt} = \phi_4 O_{IP3} - \phi_{-4} A_{IP3} - \phi_5 A_{IP3} + \left(k_{-1} + l_{-2}\right) I2_{IP3} \quad (82)$$

$$\frac{dI1_{IP3}}{dt} = \phi_1 R_{IP3} - \left(k_{-1} + l_{-2}\right) I1_{IP3} \quad (83)$$

$$\frac{dI2_{IP3}}{dt} = \phi_5 A_{IP3} - \left(k_{-1} + l_{-2}\right) I2_{IP3} \quad (84)$$

SERCA.

$$J_{up} = \nu_2 \Big/ \left[1 + \left(K_{m,up} / [\mathrm{Ca}^{2+}]_{\mathrm{subSR}}\right)^2\right] \quad (85)$$

Ca^{2+} Concentration in SR.

$$\beta_{SR} = \left[1 + [\mathrm{CLRT}]_{\mathrm{tot}} K_{mCLRT} / \left([\mathrm{Ca}^{2+}]_{\mathrm{SR}} + K_{mCLRT}\right)^2\right]^{-1} \quad (86)$$

$$\frac{d[\mathrm{Ca}^{2+}]_{\mathrm{SR}}}{dt} = \beta_{SR}\left(-J_{RyR} - J_{IP3} + J_{up}\right) V_{SR} \quad (87)$$

$$V_{SR} = \frac{4}{3}\pi\left(r_{SR}^3 - r_{nucleus}^3\right) \times 10^{-3} \text{ pl/fl} \quad (88)$$

Cytosol

Capacitive Membrane Area.

$$A_{cap} = 4\pi r_{SL}^2 \times 10^{-8}\,\mathrm{cm}^2 / \text{ì m}^2 \quad (89)$$

Cytosol Volume.

$$V_{myo} = \frac{4}{3}\pi\left(r_{SL}^3 - r_{SR}^3\right) \times 10^{-3} \text{ pl/fl} \quad (90)$$

Na^+ Concentration

$$\frac{d[\mathrm{Na}^+]_{\mathrm{i}}}{dt} = -\left(I_{Na} + 3I_{NCX} + 3I_{NaK} + I_{fNa}\right) \frac{A_{cap} C_m}{F V_{cyto} \times 10^{-6} \text{ì 1/ pl}} \quad (91)$$

K^+ Concentration

$$\frac{d[\mathrm{K}^+]_{\mathrm{i}}}{dt} = -\left(I_{Kdr} + I_{K1} + I_{fK} - 2I_{NaK} + I_{stim}\right) \frac{A_{cap} C_m}{F V_{cyto} \times 10^{-6} \text{ì 1/ pl}} \quad (92)$$

Ca^{2+} Concentration

In the following equations $c = [Ca^{2+}]_i$. The general equation for Ca^{2+} diffusion in spherical coordinates with radial symmetry is

$$\frac{\partial c(r,t)}{\partial t} = D_{Ca}\frac{\partial^2 c(r,t)}{\partial r^2} + \frac{2D_{Ca}}{r}\frac{\partial c(r,t)}{\partial r} + J_{Ca}(r,t). \quad (93)$$

We calculate the radial derivatives with steps length of Δr, i.e., the cytosol is divided to spherical cores with thickness of Δr. For calculating the concentrations at the centers of these spherical cores we define a vector

$$\mathbf{j} = \left[r_{SR} + 0.5\Delta r \quad r_{SR} + 0.5\Delta r + \Delta r \quad r_{SR} + 0.5\Delta r + 2\Delta r \quad \ldots \quad r_{SL} - 0.5\Delta r\right]/\Delta r. \quad (94)$$

Thus, $j_n \Delta r$ is the spatial coordinate for concentration c_n. With the reflecting boundary conditions at r_{SL} and r_{SR} and with SR and SL Ca^{2+} fluxes we obtain for the change in total (free + buffered) Ca^{2+} for $n = 1$

$$\frac{dc_n}{dt} = \frac{D_{Ca}}{j_n(\Delta r)^2}\left[(1+j_n)c_{n+1} - 2j_n c_n + (j_n - 1)c_n\right] + \frac{J_{CaSR}}{V_{subSR}} \quad (95)$$

for $n = 2,3,4,\ldots, a\text{-}1$

$$\frac{dc_n}{dt} = \frac{D_{Ca}}{j_n(\Delta r)^2}\left[(1+j_n)c_{n+1} - 2j_n c_n + (j_n - 1)c_{n-1}\right] \quad (96)$$

for $n = a$

$$\frac{dc_n}{dt} = \frac{D_{Ca}}{j_n(\Delta r)^2}\left[(1+j_n)c_n - 2j_n c_n + (j_n - 1)c_{n-1}\right] + \frac{J_{CaSL}}{V_{subSL}}, \quad (97)$$

where a is the number of components in the vector $\mathbf{j}$ and

$$J_{CaSR} = J_{RyR} + J_{IP3} - J_{up} \quad (98)$$

$$J_{CaSL} = (2I_{NCX} - I_{CaL} - I_{CaT} - I_{Cab})\frac{A_{cap}C_m}{2F \times 10^{-6}\text{ì l/pl}} \quad (99)$$

$$V_{subSR} = \left[\frac{4}{3}\pi(r_{SR} + \Delta r)^3 - \frac{4}{3}\pi r_{SR}^{\ 3}\right] \times 10^{-3} \text{ pl/fl} \quad (100)$$

$$V_{subSL} = \left[\frac{4}{3}\pi r_{SL}^{\ 3} - \frac{4}{3}\pi(r_{SL} - \Delta r)^3\right] \times 10^{-3} \text{ pl/fl}. \quad (101)$$

The new value for each c_n ($c_{n\text{-}new}$) at each time-step (Δt) is computed as described in Hund and Rudy (2004):

$$c_{n-new} = \frac{2}{3}\sqrt{b^2 - 3c}\cos\left[\frac{1}{3}\cos^{-1}\left(\frac{9bc - 2b^3 - 27d}{2(b^2 - 3c)^{1.5}}\right)\right] - \frac{b}{3}, \quad (102)$$

where

$$b = [\text{CMDN}]_{\text{tot}} + [\text{TRPN}]_{\text{tot}} - c_{total-new} + K_{m,CMDN} + K_{m,TRPN} \quad (103)$$

$$c = K_{m,CMDN}K_{m,TRPN} - c_{total-new}(K_{m,CMDN} + K_{m,TRPN}) + [\text{TRPN}]_{\text{tot}}K_{m,CMDN} + [\text{CMDN}]_{\text{tot}}K_{m,TRPN} \quad (104)$$

$$d = -K_{m,TRPN}K_{m,CMDN}c_{total-new} \quad (105)$$

$$c_{total-new} \approx \text{CMDN} + \text{TRPN} + c_n + \frac{dc_n}{dt}\Delta t \quad (106)$$

$$\text{TRPN} = [\text{TRPN}]_{\text{tot}} / (1 + K_{m,TRPN}/c_n) \quad (107)$$

$$\mathrm{CMDN} = [\mathrm{CMDN}]_{\mathrm{tot}} / \left(1 + K_{m,CMDN} / c_n\right). \quad (108)$$

REFERENCES

Hund, T.J., and Y. Rudy. 2004. Rate dependence and regulation of action potential and calcium transient in a canine cardiac ventricular cell model. *Circulation.* 110:3168–3174.

Table S1. Solutions (in mM) for the Electrophysiological Recordings

Target	Bath solution	Pipette solution	Recording method
I_{NCX}	NaCl 140, $CaCl_2$ 1, $MgCl_2$ 1, HEPES 10, glucose 10, nifedipine 0.01, niflumic acid 0.01, pH 7.40 (Tris) + $NiCl_2$ 10	NaCl 10, CsCl 20, CsOH 80, glutamic acid 80, TEA-Cl 20, HEPES 10, Tris-ATP 5, $MgCl_2$ 5.7, BAPTA 5, $CaCl_2$ 2.69 (=> 200 nM free Ca^{2+}), pH 7.20 (CsOH)	Measured as Ni^{2+}-sensitive current using voltage ramp from +100 to −100 mV. The solutions and the protocol were as described previously.[a]
I_{Na}	NaCl 140, TEA-Cl 140, $NiCl_2$ 1, $MgCl_2$ 2, HEPES 10, glucose 10, pH 7.40 (TEA-OH)	Cs-methanesulfonate 120, TEA-Cl 10, EGTA 10, Na_2-phosphocreatine 5, Mg-ATP 1, Na-GTP 1, HEPES 10, pH 7.20 (CsOH)	Measured using −100 mV holding potential and voltage clamps ranging from −70 to +70 mV with 10-mV steps.
I_{Kdr}	NMDG 140, KCl 5.4, $MgCl_2$ 0.5, $CaCl_2$ 1, HEPES 10, glucose 10, nifedipine 0.01, pH 7.40 (HCl).	KCl 80, K-aspartic acid 60, Na_2-phosphocreatine 5, Mg-ATP 5, $CaCl_2$ 0.65, EGTA 10, HEPES 5, pH 7.20 (KOH)	Measured using −40 mV holding potential and voltage clamps ranging from −30 to +40 mV with 10-mV steps.
I_{K1}	NaCl 137, KCl 5.4, MgCl 0.5, $CaCl_2$ 1, HEPES 11.8, glucose 10, pH 7.40 (NaOH) + $BaCl_2$ 2	KCl 80, K-aspartic acid 60, Na_2-phosphocreatine 5, Mg-ATP 5, $CaCl_2$ 0.65, EGTA 10, HEPES 5, pH 7.20 (KOH)	Measured as the Ba^{2+} sensitive current using −50 mV holding potential and voltage clamps ranging from −60 to −110 mV with 10-mV steps. I_{K1} was defined as the initial current at the beginning of the voltage clamp when the I_f has not yet activated.
I_f	NaCl 137, KCl 5.4, MgCl 0.5, $CaCl_2$ 1, HEPES 11.8, glucose 10, $BaCl_2$ 2, $NiCl_2$ 2, 4-AP 0.5, pH 7.40 (NaOH)	KCl 80, K-aspartic acid 60, Na_2-phosphocreatine 5, Mg-ATP 5, $CaCl_2$ 0.65, EGTA 10, HEPES 5, pH 7.20 (KOH)	Measured using 0 mV holding potential and voltage clamps ranging from −50 to −120 mV with 10-mV steps. I_f was defined as the difference between the initial current at the beginning of the voltage clamp and the current at the end of the voltage clamp. The solutions and the protocol were based on the work of Yasui et al.[b]
I_{CaL}, I_{CaT}	TEA-Cl 140, $CaCl_2$ 1, $MgCl_2$ 2, HEPES 10, glucose 10, pH 7.40 (TEA-OH)	Cs-methanesulfonate 120, TEA-Cl 10, EGTA 10, Na_2-phosphocreatine 5, Mg-ATP 1, Na-GTP 1, HEPES 10, pH 7.2 (CsOH)	Ca^{2+} currents were measured using −40 and −100 mV holding potentials and voltage clamps ranging from −30 to +40 mV and from −50 to +40 mV with 10-mV steps. The current measured from −40 mV holding potential was defined as the L-type Ca^{2+} current. The T-type current was defined as the difference between current measured from −100 and −40 mV holding potential to a same test potential.[c] The solutions were modified from the work of Yang et al.[d]

[a]Despa, S., F. Brette, C.H. Orchard, and D.M. Bers. 2003. Na/Ca exchange and Na/K-ATPase function are equally concentrated in transverse tubules of rat ventricular myocytes. *Biophys. J.* 85:3388–3396.
[b]Yasui, K., W. Liu, T. Opthof, K. Kada, J.K. Lee, K. Kamiya, and I. Kodama. 2001. I-f current and spontaneous activity in mouse embryonic ventricular myocytes. *Circ. Res.* 88:536–542.
[c]Niwa, N., K. Yasui, T. Opthof, H. Takemura, A. Shimizu, M. Horiba, J.K. Lee, H. Honjo, K. Kamiya, and I. Kodama. 2004. Ca(v)3.2 subunit underlies the functional T-type Ca2+ channel in murine hearts during the embryonic period. *Am. J. Physiol. Heart Circ. Physiol.* 286:H2257–H2263.
[d]Yang, Z., W. Shen, J.N. Rottman, J.P. Wikswo, and K.T. Murray. 2005. Rapid stimulation causes electrical remodeling in cultured atrial myocytes. *J. Mol. Cell. Cardiol.* 38:299–308.

Table S2. Structural and Environmental Parameters of the Model

Parameter	Definition	Value
$r_{nucleus}$	Radius to the surface of nucleus	7.415 μm[a]
r_{SR}	Radius to the surface of SR	7.45 μm[a]
r_{SL}	Radius of the cell	11.05 μm[a]
F	Faradays constant	96.5 C/mmol
T	Temperature	34 ºC = 307 K[a]
R	Ideal gas constant	8.314 J / (mol K)
C_m	Specific membrane capacitance	1.0 μF/cm^2
$[Ca^{2+}]_o$	Extracellular Ca^{2+} concentration	1796 μM[a]
$[Na^+]_o$	Extracellular Na^+ concentration	154578 μM[a]
$[K^+]_o$	Extracellular K^+ concentration	5366 μM[a]

[a]Fitted based on experimental data or conditions.

Table S3. Parameters of the SL Membrane Currents

Parameter	Definition	Value
G_{CaL}	Maximum I_{CaL} conductance	0.1518 mS/μF[a]
E_{CaL}	Reversal potential for I_{CaL}	63.0 mV[b]
$K_{pc,max}$	Maximum time constant for Ca^{2+} induced inactivation of I_{CaL}	0.23324 ms^{-1}[b]
$K_{pc,half}$	Half-saturation constant for Ca^{2+} induced inactivation of I_{CaL}	20.0 μM[b]
K_{pcb}	Rate constant for I_{CaL} inactivation	0.0005 ms^{-1}[b]
G_{CaT}	Maximum I_{CaT} conductance	0.0655 mS/μF[a]
G_{Cab}	I_{Cab} conductance	0.003057 mS/μF[a]
G_{Na}	Maximum I_{Na} conductance	4.5 mS/μF[a]
K_{Kdr}	Scaling factor for I_{Kdr}	2.201×10^{-7} pA / (pF $(\mu M)^{1.59}$)[a]
K_{K1}	Scaling factor for I_{K1}	2.743×10^{-7} pA / (pF $(\mu M)^{1.37}$)[a]
G_f	Maximum I_f conductance	0.04836 mS/μF[a]
$I_{NaK}^{\max}$	Maximum NaK-ATPase current	4.698 pA/pF[a]
$K_{m,Nai}$	Na^+ half saturation constant for I_{NaK}	18600 μM[a]
n_{NaK}	Hill coefficient for Na^+ in I_{NaK}	3.2[a]
$K_{m,Ko}$	K^+ half saturation constant for I_{NaK}	1500 μM[c]
k_{NCX}	Scaling factor I_{NCX}	4890 pA/pF[a]
$K_{m,Na}$	Na^+ half saturation constant for I_{NCX}	87500 μM[c]
$K_{m,Ca}$	Ca^{2+} half saturation constant for I_{NCX}	1380 μM[c]
k_{sat}	Saturation factor for I_{NCX}	0.1[c]
η	Voltage-dependence parameter for I_{NCX}	0.55752[a]

[a]Fitted based on experimental data.

[b]Bondarenko, V.E., G.P. Szigeti, G.C. Bett, S.J. Kim, and R.L. Rasmusson. 2004. Computer model of action potential of mouse ventricular myocytes. *Am. J. Physiol. Heart Circ. Physiol.* 287:H1378–H1403.

[c]Luo, C.H., and Y. Rudy. 1994. A Dynamic-model of the cardiac ventricular action-potential .1. Simulations of ionic currents and concentration changes. *Circ. Res.* 74:1071–1096.

Table S4. Sarcoplasmic Reticulum Parameters

Parameter	Definition	Value
v_1	*Maximum Ca^{2+} permeability for RyR*	0.01 ms^{-1}[a]
k_a^+	RyR rate constant	1.5 μM^{-4} ms^{-1}[b]
k_a^-	RyR rate constant	0.0288 ms^{-1}[b]
k_b^+	RyR rate constant	1.5 μM^{-3} ms^{-1}[b]
k_b^-	RyR rate constant	0.3859 ms^{-1}[b]
k_c^+	RyR rate constant	0.00175 ms^{-1}[b]
k_c^-	RyR rate constant	0.0001 ms^{-1}[b]
n	RyR cooperativity parameter	4[b]
m	RyR cooperativity parameter	3[b]
p	IP_3 concentration	0.075 μM (unless stated otherwise)[a]
k_f	Maximum Ca^{2+} permeability for IP_3R	0.3 ms^{-1}[a]
k_1	IP_3R kinetic parameter	0.00064 $(\mu M\ ms)^{-1}$[c]
k_{-1}	IP_3R kinetic parameter	0.00004 $(ms)^{-1}$[c]
k_2	IP_3R kinetic parameter	0.0374 $(\mu M\ ms)^{-1}$[c]
k_{-2}	IP_3R kinetic parameter	0.0014 $(ms)^{-1}$[c]
k_3	IP_3R kinetic parameter	0.00011 $(\mu M\ ms)^{-1}$[c]
k_{-3}	IP_3R kinetic parameter	0.0298 $(ms)^{-1}$[c]
k_4	IP_3R kinetic parameter	0.004 $(\mu M\ ms)^{-1}$[c]
k_{-4}	IP_3R kinetic parameter	0.00054 $(ms)^{-1}$[c]
L_1	IP_3R kinetic parameter	0.12 μM[c]
L_3	IP_3R kinetic parameter	0.025 μM[c]
L_3	IP_3R kinetic parameter	0.025 μM[c]
L_5	IP_3R kinetic parameter	54.7 μM[c]

Parameter	Definition	Value
I_2	IP_3R kinetic parameter	0.0017 $(ms)^{-1}$[c]
I_4	IP_3R kinetic parameter	0.0017 $(\mu M\ ms)^{-1}$[c]
I_6	IP_3R kinetic parameter	4.707 $(ms)^{-1}$[c]
I_{-2}	IP_3R kinetic parameter	0.0008 $(ms)^{-1}$[c]
I_{-4}	IP_3R kinetic parameter	0.0025 $(\mu M\ ms)^{-1}$[c]
I_{-6}	IP_3R kinetic parameter	0.0114 $(ms)^{-1}$[c]
v_2	Maximum SERCA flux	2 μM/ms[a]
$K_{m,up}$	Ca^{2+} half-saturation for SERCA	0.25 μM[d]
$[CLRT]_{tot}$	Total calreticulin concentration	7000 μM[a]
K_{mCLRT}	Half-saturation for calreticulin	2000 μM[e]

[a]Fitted based on experimental data.
[b]Keizer, J., and L. Levine. 1996. Ryanodine receptor adaptation and Ca2+-induced Ca2+ release-dependent Ca2+ oscillations. *Biophys. J.* 71:3477–3487.
[c]Sneyd, J., and J.F. Dufour. 2002. A dynamic model of the type-2 inositol trisphosphate receptor. *Proc. Natl. Acad. Sci. USA.* 99:2398–2403.
[d]Frank, K., C. Tilgmann, T.R. Shannon, D.M. Bers, and E.G. Kranias. 2000. Regulatory role of phospholamban in the efficiency of cardiac sarcoplasmic reticulum Ca^{2+} transport. *Biochemistry (Mosc).* 39:14176–14182.
[e]Michalak, M.E., F. Corbett, N. Mesaeli, K. Nakamura, and M. Opas. 1999. Calreticulin: one protein, one gene, many functions. *Biochem. J.* 344:281–292.

Table S5. Cytosol Parameters

Parameter	Definition	Value
Δr	Length of spatial discretization of cytosol	0.1 μm
$[TRPN]_{tot}$	Total troponin concentration	21 μM[a,b]
K_{mTRPN}	Half-saturation for troponin	0.5 μM[a]
$[CMDN]_{tot}$	Total calmodulin concentration	37.5 μM[a,b]
K_{mCMDN}	Half-saturation for calmodulin	2.38 μM[a]
D_{Ca}	Diffusion coefficient for Ca^{2+}	0.79 $\mu m^2/ms$[c]

[a]Luo, C.H., and Y. Rudy. 1994. A dynamic-model of the cardiac ventricular action-potential .1. Simulations of ionic currents and concentration changes. *Circ. Res.* 74:1071–1096.
[b]Creazzo, T.L., J. Burch, and R.E. Godt. 2004. Calcium buffering and excitation-contraction coupling in developing avian myocardium. *Biophys. J.* 86:966–977.
[c]Cussler, E.L. 1997. Diffusion mass transfer in fluid systems. Cambridge University Press, Cambridge. 580 pp.