MODEL PARAMETERS

Cell compartments

$C = 32$ pF: Cell electric capacitance

$L_{cell} = 70$ µm: Cell length

$L_{sub} = 0.02$ µm: Distance between jSR and surface membrane (submembrane space)

$R_{cell} = 4$ µm: Cell radius

$V_{i_{part}} = 0.46$: Part of cell volume occupied with myoplasm

$V_{jSR_{part}} = 0.0012$: Part of cell volume occupied by junctional SR

$V_{nSR_{part}} = 0.0116$: Part of cell volume occupied by network SR

$V_{cell} = \pi \cdot {R_{cell}}^2 \cdot L_{cell}$: Cell volume

$V_{sub} = 2 \cdot \pi \cdot L_{sub} \cdot \left(R_{cell} - \frac{L_{sub}}{2}\right) \cdot L_{cell}$: Submembrane space volume

$V_i = V_{i_{part}} \cdot V_{cell} - V_{sub}$: Myoplasmic volume

$V_{jSR} = V_{jSR_{part}} \cdot V_{cell}$: Volume of junctional SR (Ca2+ release store)

$V_{nSR} = V_{nSR_{part}} \cdot V_{cell}$: Volume of network SR (Ca2+ uptake store)

Fixed ion concentrations, mM

$Cao = 2$: Extracellular Ca^{2+} concentration

$Ki = 140$: Intracellular K^{+} concentration

$Ko = 5.4$: Extracellular K^{+} concentration

$Nao = 140$: Extracellular Na^{+} concentration

$Mgi = 2.5$: Intracellular Mg^{2+} concentration.

Variable ion concentrations

Cai: Intracellular Ca^{2+} concentration

Ca_{jsr}: Ca^{2+} concentration in the junctional SR

Ca_{nsr}: Ca^{2+} concentration in the network SR

Ca_{sub}: Subspace Ca^{2+} concentration

Nai: Intracellular Na^{+} concentration.

Ionic values

$F = 96485$ C/M: Faraday constant

$R = 8.314$ J/(kM·K): Universal gas constant

$T = 310$ K: Absolute temperature for 37°C

RTONF is "R·T/F" factor = 26.72655 mV

$E_{Na} = RTONF \cdot \ln\frac{Nao}{Nai}$: Equilibrium potential for Na^{+}

$E_K = RTONF \cdot \ln\frac{Ko}{Ki}$: Equilibrium potential for K^{+}

$E_{Ca} = 0.5 \cdot RTONF \cdot \ln\frac{Cao}{Ca_{sub}}$: Equilibrium potential for Ca^{2+}

Sarcolemmal Ion currents and their conductances

I_f: Hyperpolarization-activated current ($g_{f_{Na}} = 0.03$ μS, $g_{f_k} = 0.03$ μS)

I_{CaL}: L-type Ca^{2+} current ($P_{CaL} = 0.2\ nA/mM$)

I_{CaT}: T-type Ca^{2+} current ($P_{CaT} = 0.02\ \ nA/mM$)

I_{Kr}: Delayed rectifier K^{+} current rapid component ($g_{Kr} = 0.0021637$ μS)

I_{Ks}: Delayed rectifier K^{+} current slow component ($g_{Ks} = 0.0016576$ μS)

I_{KACh}: Ach-activated K^{+} current ($g_{KACh} = 0.00864$ μS)

I_{to}: Transient outward K^{+} current ($g_{to} = 0.002$ μS)

I_{Na}: Na^{+} current ($g_{Na} = 0.0125$ μS)

I_{NaK}: Na^{+}/K^{+} pump current ($I_{NaK_{max}} = 0.063$ nA)

I_{NaCa}: Na^{+}/Ca^{2+} exchanger current ($K_{NaCa} = 4$ nA)

Modulation of sarcolemmal ion currents by ions

$Km_{fCa} = 0.00035$ mM: Dissociation constant of Ca^{2+} -dependent I_{CaL} inactivation

$Km_{Kp} = 1.4$ mM: Half-maximal K_o for I_{NaK}

$Km_{Nap} = 14$ mM: Half-maximal Na_i for I_{NaK}

$\alpha_{fCa} = 0.01$ ms^{-1}: Ca^{2+} dissociation rate constant for I_{CaL}

Na^{+}/Ca^{2+} exchanger (NaCa) function, mM

$K1ni = 395.3$: intracellular Na^{+} binding to first site on NaCa

$K1no = 1628$: extracellular Na^{+} binding to first site on NaCa

$K2ni = 2.289$: intracellular Na^{+} binding to second site on NaCa

$K2no = 561.4$: extracellular Na^{+} binding to second site on NaCa

$K3ni = 26.44$: intracellular Na^{+} binding to third site on NaCa

$K3no = 4.663$: extracellular Na^{+} binding to third site on NaCa

$Kci = 0.0207$: intracellular Ca^{2+} binding to NaCa transporter

$Kcni = 26.44$: intracellular Na^{+} and Ca^{2+} simultaneous binding to NaCa

$Kco = 3.663$: extracellular Ca^{2+} binding to NaCa transporter

$Qci = 0.1369$: intracellular Ca^{2+} occlusion reaction of NaCa

$Qco = 0$: extracellular Ca^{2+} occlusion reaction of NaCA

$Qn = 0.4315$: Na^{+} occlusion reactions of NaCa

Ca^{2+} diffusion

$\tau_{dif_{Ca}} = 0.00004$ s: Time constant of Ca^{2+} diffusion from the submembrane to myoplasm

$\tau_{tr} = 0.04$ s: Time constant for Ca^{2+} transfer from the network to junctional SR

SR Ca^{2+} ATPase function

$K_{up} = 0.0006$ mM: Half-maximal Ca_i for Ca^{2+} uptake in the network SR

$P_{up} = 12$ mM/s: Rate constant for Ca^{2+} uptake by the Ca^{2+} pump in the network SR

RyR function

$kiCa = 500$ mM$^{-1}\cdot$s^{-1}

$kim = 5$ s^{-1}

$koCa = 10000$ mM$^{-2}\cdot$s^{-1}

$kom = 60$ s^{-1}

$ks = 250000000$ s^{-1}

$EC50_{SR} = 0.45$ mM

$HSR = 2.5$

$MaxSR = 15$

$MinSR = 1$

Ca^{2+} and Mg^{2+} buffering

$CM_{tot} = 0.045$ mM: Total calmodulin concentration

$CQ_{tot} = 10$ mM: Total calsequestrin concentration

$TC_{tot} = 0.031$ mM: Total concentration of the troponin-Ca^{2+} site

$TMC_{tot} = 0.062$ mM: Total concentration of the troponin-Mg^{2+} site

$kb_{CM} = 542$ s^{-1}: Ca^{2+} dissociation constant for calmodulin

$kb_{CQ} = 445$ s^{-1}: Ca^{2+} dissociation constant for calsequestrin

$kb_{TC} = 446$ s^{-1}: Ca^{2+} dissociation constant for the troponin-Ca^{2+} site

$kb_{TMC} = 7.51$ s^{-1}: Ca^{2+} dissociation constant for the troponin-Mg^{2+} site

$kb_{TMM} = 751$ s^{-1}: Mg^{2+} dissociation constant for the troponin-Mg^{2+} site

$kf_{CM} = 227700$ s^{-1}: Ca^{2+} association constant for calmodulin

$kf_{CQ} = 534$ s^{-1}: Ca^{2+} association constant for calsequestrin

$kf_{TC} = 88.8$ s^{-1}: Ca^{2+} association constant for troponin

$kf_{TMC} = 227700$ s^{-1}: Ca^{2+} association constant for the troponin-Mg^{2+} site

$kf_{TMM} = 2277$ s^{-1}: Mg^{2+} association constant for the troponin-Mg^{2+} site

EQUATIONS

Membrane potential

$$\frac{\mathrm{dV}}{\mathrm{d}time} = \frac{-I_{tot}}{C}$$

$$I_{tot} = I_f + I_{Kr} + I_{Ks} + I_{to} + I_{NaK} + I_{NaCa} + I_{Na} + I_{CaL} + I_{CaT} + I_{KACh}$$

Ion currents

x_∞: Steady-state curve for a gating variable *x*

τ_x: Time constant for a gating variable *x*

α_x and β_x: Opening and closing rates for channel gating

Hyperpolarization-activated, "funny" current (I_f)

$$I_f = \left(I_{fNa} + I_{fK}\right)$$

$$I_{fNa} = \frac{y^2 \cdot Ko}{Ko + Km_f} \cdot g_{f_{Na}} \cdot (V - E_{Na})$$

$$I_{fK} = \frac{y^2 \cdot Ko}{Ko + Km_f} \cdot g_{f_K} \cdot (V - E_K)$$

$$Km_f = 45 \text{ mM}$$

$$y_\infty = \frac{1}{1 + e^{\frac{V+52.5}{9}}}$$

$$\tau_y = \frac{0.7}{0.0708 \cdot e^{\frac{-(\mathrm{V}+5)}{20.28}} + 10.6 \cdot e^{\frac{V}{18}}}$$

$$\frac{\mathrm{d}y}{\mathrm{d}time} = \frac{y_\infty - y}{\tau_y}$$

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

$$I_{CaL} = (I_{siCa} + I_{siK} + I_{siNa})$$

$$I_{siCa} = \frac{2 \cdot P_{CaL} \cdot \mathrm{V}}{RTONF \cdot \left(1 - e^{\frac{-2\cdot \mathrm{V}}{RTONF}}\right)} \cdot \left(Ca_{sub} - Cao \cdot e^{\frac{-2\cdot \mathrm{V}}{RTONF}}\right) \cdot dL \cdot fL \cdot fCa$$

$$I_{siK} = \frac{0.000365 \cdot P_{CaL} \cdot \mathrm{V}}{RTONF \cdot \left(1 - e^{\frac{-\mathrm{V}}{RTONF}}\right)} \cdot \left(Ki - Ko \cdot e^{\frac{-1\mathrm{V}}{RTONF}}\right) \cdot dL \cdot fL \cdot fCa$$

$$I_{siNa} = \frac{0.0000185 \cdot P_{CaL} \cdot \mathrm{V}}{RTONF \cdot \left(1 - e^{\frac{-\mathrm{V}}{RTONF}}\right)} \cdot \left(Nai - Nao \cdot e^{\frac{-\mathrm{V}}{RTONF}}\right) \cdot dL \cdot fL \cdot fCa$$

$$dL_{\infty} = \frac{1}{1 + e^{\frac{-(V+20.3)}{4.2}}}$$

$$\alpha_{dL} = \frac{-0.02839 \cdot (V + 41.8)}{e^{\frac{-(V+41.8)}{2.5}} - 1} - \frac{0.0849 \cdot (V + 6.8)}{e^{\frac{-(V+6.8)}{4.8}} - 1}$$

$$\beta_{dL} = \frac{0.01143 \cdot (V + 1.8)}{e^{\frac{V+1.8}{2.5}} - 1}$$

$$\tau_{dL} = \frac{0.001}{\alpha_{dL} + \beta_{dL}}$$

$$\frac{\mathrm{d}dL}{\mathrm{d}time} = \frac{dL_{\infty} - dL}{\tau_{dL}}$$

$$fL_{\infty} = \frac{1}{1 + e^{\frac{V+37.4}{5.3}}}$$

$$\tau_{fL} = 0.001 \cdot \left(44.3 + 230 \cdot e^{-\left(\frac{V+36}{10}\right)^2}\right)$$

$$\frac{\mathrm{d}fL}{\mathrm{d}time} = \frac{fL_{\infty} - fL}{\tau_{fL}}$$

$$fCa_{\infty} = \frac{Km_{fCa}}{Km_{fCa} + Ca_{sub}}$$

$$\tau_{fCa} = \frac{0.001 \cdot fCa_{\infty}}{\alpha_{fCa}}$$

$$\frac{\mathrm{d}fCa}{\mathrm{d}time} = \frac{fCa_{\infty} - fCa}{\tau_{fCa}}$$

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

$$I_{CaT} = \frac{2 \cdot P_{CaT} \cdot V}{RTONF \cdot \left(1 - e^{\frac{-2 \cdot V}{RTONF}}\right)} \cdot \left(Ca_{sub} - Cao \cdot e^{\frac{-2 \cdot V}{RTONF}}\right) \cdot dT \cdot fT$$

$$dT_{\infty} = \frac{1}{1 + e^{\frac{-(V+38.3)}{5.5}}}$$

$$\tau_{dT} = \frac{0.001}{1.068 \cdot e^{\frac{V+38.3}{30}} + 1.068 \cdot e^{\frac{-(V+38.3)}{30}}}$$

$$\frac{\mathrm{d}dT}{\mathrm{d}time} = \frac{dT_{\infty} - dT}{\tau_{dT}}$$

$$fT_{\infty} = \frac{1}{1 + e^{\frac{V+58.7}{3.8}}}$$

$$\tau_{fT} = \frac{1}{16.67 \cdot e^{\frac{-(V+75)}{83.3}} + 16.67 \cdot e^{\frac{V+75}{15.38}}}$$

$$\frac{\mathrm{d}fT}{\mathrm{d}time} = \frac{fT_{\infty} - fT}{\tau_{fT}}$$

Rapidly activating delayed rectifier K+ current (I_{Kr})

$$I_{Kr} = g_{Kr} \cdot (V - E_K) \cdot (0.9 \cdot paF + 0.1 \cdot paS) \cdot pi$$

$$pa_{\infty} = \frac{1}{1 + e^{\frac{-(V+14.8)}{8.5}}}$$

$$\tau_{paF} = \frac{1}{30 \cdot e^{\frac{V}{10}} + e^{\frac{-V}{12}}}$$

$$\frac{\mathrm{d}paF}{\mathrm{d}time} = \frac{pa_{\infty} - paF}{\tau_{paF}}$$

$$\tau_{paS} = \frac{0.84655}{4.2 \cdot e^{\frac{V}{17}} + 0.15 \cdot e^{\frac{-V}{21.6}}}$$

$$\frac{\mathrm{d}paS}{\mathrm{d}time} = \frac{pa_{\infty} - paS}{\tau_{paS}}$$

$$pi_{\infty} = \frac{1}{1 + e^{\frac{V+28.6}{17.1}}}$$

$$\tau_{pi} = \frac{1}{100 \cdot e^{\frac{-V}{54.645}} + 656 \cdot e^{\frac{V}{106.157}}}$$

$$\frac{\mathrm{d}pi}{\mathrm{d}time} = \frac{pi_{\infty} - pi}{\tau_{pi}}$$

Slowly activating delayed rectifier K+ current (I_{Ks})

$$I_{Ks} = g_{Ks} \cdot (V - E_K) \cdot n^2$$

$$n_{\infty} = \frac{\frac{14}{1+e^{\frac{-(V-40)}{9}}}}{\frac{14}{1+e^{\frac{-(V-40)}{9}}} + 1 \cdot e^{\frac{-V}{45}}}$$

$$\tau_n = \frac{1}{\frac{28}{1+e^{\frac{-(V-40)}{3}}} + e^{\frac{-(V-5)}{25}}}$$

$$\frac{\mathrm{d}n}{\mathrm{d}time} = \frac{n_{\infty} - n}{\tau_n}$$

Ach-activated K$^+$ current (I_{KACh})

$$I_{KACh} = \begin{cases} g_{KACh} \cdot (V - E_K) \cdot \left(1 + e^{\frac{V+20}{20}}\right) \cdot a, \text{if } ACh > 0 \\ 0, \text{otherwise} \end{cases}$$

$$a_{\infty} = \frac{\alpha_a}{\alpha_a + \beta_a}$$

$$\alpha_a = \frac{3.5988 - 0.0256}{1 + \frac{0.0000012155}{(1 \cdot ACh)^{1.6951}}} + 0.0256$$

$$\beta_a = 10 \cdot e^{0.0133 \cdot (V+40)}$$

$$\tau_a = \frac{1}{\alpha_a + \beta_a}$$

$$\frac{\mathrm{d}a}{\mathrm{d}time} = \frac{a_{\infty} - a}{\tau_a}$$

Transient outward K$^+$ current (I_{to})

$$I_{to} = g_{to} \cdot (V - E_K) \cdot q \cdot r$$

$$q_{\infty} = \frac{1}{1+e^{\frac{V+49}{13}}}$$

$$\tau_q = 0.001 \cdot 0.6 \cdot \left(\frac{65.17}{0.57 \cdot e^{-0.08 \cdot (V+44)} + 0.065 \cdot e^{0.1 \cdot (V+45.93)}} + 10.1\right)$$

$$\frac{\mathrm{d}q}{\mathrm{d}time} = \frac{q_{\infty} - q}{\tau_q}$$

$$r_{\infty} = \frac{1}{1+e^{\frac{-(V-19.3)}{15}}}$$

$$\tau_r = 0.001 \cdot 0.66 \cdot 1.4 \cdot \left(\frac{15.59}{1.037 \cdot e^{0.09 \cdot (V+30.61)} + 0.369 \cdot e^{-0.12 \cdot (V+23.84)}} + 2.98\right)$$

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

Na$^+$ current (I_{Na})

$$I_{Na} = g_{Na} \cdot m^3 \cdot h \cdot (V - E_{mh})$$

$$E_{mh} = RTONF \cdot \ln \frac{Nao + 0.12 \cdot Ko}{Nai + 0.12 \cdot Ki}$$

$$E0_m = V + 41$$

$$\delta_m = 1 \cdot 10^{-5}\ \mathrm{mV}$$

$$\frac{\mathrm{d}m}{\mathrm{d}time} = \alpha_m \cdot (1 - m) - \beta_m \cdot m$$

$$\alpha_m = \begin{cases} 2000, \mathrm{if} |E0_m| < \delta_m \\ \dfrac{200 \cdot E0_m}{1 - e^{-0.1 \cdot E0_m}}, \mathrm{otherwise} \end{cases}$$

$$\beta_m = 8000 \cdot e^{-0.056 \cdot (V+66)}$$

$$\frac{\mathrm{d}h}{\mathrm{d}time} = \alpha_h \cdot (1 - h) - \beta_h \cdot h$$

$$\alpha_h = 20 \cdot e^{-0.125 \cdot (V+75)}$$

$$\beta_h = \frac{2{,}000}{320 \cdot e^{-0.1 \cdot (V+75)} + 1}$$

Na$^+$-K$^+$ pump current (I_{NaK})

$$I_{NaK} = I_{NaK_{max}} \cdot \left(1 + \left(\frac{Km_{Kp}}{Ko}\right)^{1.2}\right)^{-1} \cdot \left(1 + \left(\frac{Km_{Nap}}{Nai}\right)^{1.3}\right)^{-1} \cdot \left(1 + e^{\frac{-(V - E_{Na} + 110)}{20}}\right)^{-1}$$

Na$^+$-Ca^{2+} exchanger current (I_{NaCa})

$$I_{NaCa} = \frac{K_{NaCa} \cdot (x2 \cdot k21 - x1 \cdot k12)}{x1 + x2 + x3 + x4}$$

$$x1 = k41 \cdot k34 \cdot (k23 + k21) + k21 \cdot k32 \cdot (k43 + k41)$$

$$x2 = k32 \cdot k43 \cdot (k14 + k12) + k41 \cdot k12 \cdot (k34 + k32)$$

$$x3 = k14 \cdot k43 \cdot (k23 + k21) + k12 \cdot k23 \cdot (k43 + k41)$$

$$x4 = k23 \cdot k34 \cdot (k14 + k12) + k14 \cdot k21 \cdot (k34 + k32)$$

$$k43 = \frac{Nai}{K3ni + Nai}$$

$$k12 = \frac{\frac{Ca_{sub}}{Kci} \cdot e^{\frac{-Qci \cdot V}{RTONF}}}{di}$$

$$k14 = \frac{\frac{\frac{Nai}{K1ni} \cdot Nai}{K2ni} \cdot \left(1 + \frac{Nai}{K3ni}\right) \cdot e^{\frac{Qn \cdot V}{2 \cdot RTONF}}}{di}$$

$$k41 = e^{\frac{-Qn \cdot V}{2 \cdot RTONF}}$$

$$di = 1 + \frac{Ca_{sub}}{Kci} \cdot \left(1 + e^{\frac{-Qci \cdot V}{RTONF}} + \frac{Nai}{Kcni}\right) + \frac{Nai}{K1ni} \cdot \left(1 + \frac{Nai}{K2ni} \cdot \left(1 + \frac{Nai}{K3ni}\right)\right)$$

$$k34 = \frac{Nao}{K3no + Nao}$$

$$k21 = \frac{\frac{Cao}{Kco} \cdot e^{\frac{Qco \cdot V}{RTONF}}}{do}$$

$$k23 = \frac{\frac{\frac{Nao}{K1no} \cdot Nao}{K2no} \cdot \left(1 + \frac{Nao}{K3no}\right) \cdot e^{\frac{-Qn \cdot V}{2 \cdot RTONF}}}{do}$$

$$k32 = e^{\frac{Qn \cdot V}{2 \cdot RTONF}}$$

$$do = 1 + \frac{Cao}{Kco} \cdot \left(1 + e^{\frac{Qco \cdot V}{RTONF}}\right) + \frac{Nao}{K1no} \cdot \left(1 + \frac{Nao}{K2no} \cdot \left(1 + \frac{Nao}{K3no}\right)\right)$$

Ca^{2+} release flux (J_{rel}) from SR via RyRs

$$J_{rel} = ks \cdot O \cdot \left(Ca_{jsr} - Ca_{sub}\right)$$

$$kCaSR = MaxSR - \frac{MaxSR - MinSR}{1 + \left(\frac{EC50_{SR}}{Ca_{jsr}}\right)^{HSR}}$$

$$koSRCa = \frac{koCa}{kCaSR}$$

$$kiSRCa = kiCa \cdot kCaSR$$

$$\frac{\mathrm{d}R}{\mathrm{d}time} = kim \cdot RI - kiSRCa \cdot Ca_{sub} \cdot R - \left(koSRCa \cdot {Ca_{sub}}^{2} \cdot R - kom \cdot O\right)$$

$$\frac{\mathrm{d}O}{\mathrm{d}time} = koSRCa \cdot {Ca_{sub}}^2 \cdot R - kom \cdot O - (kiSRCa \cdot Ca_{sub} \cdot O - kim \cdot I)$$

$$\frac{\mathrm{d}I}{\mathrm{d}time} = kiSRCa \cdot Ca_{sub} \cdot O - kim \cdot I - \left(kom \cdot I - koSRCa \cdot {Ca_{sub}}^2 \cdot RI\right)$$

$$\frac{\mathrm{d}RI}{\mathrm{d}time} = kom \cdot I - koSRCa \cdot {Ca_{sub}}^2 \cdot RI - (kim \cdot RI - kiSRCa \cdot Ca_{sub} \cdot R)$$

Intracellular Ca^{2+} fluxes

J_{diff} : Ca^{2+} diffusion flux from submembrane space to myoplasm

J_{tr}: Ca^{2+} transfer flux from the network to junctional SR

J_{up}: Ca^{2+} uptake by the SR

$$J_{diff} = \frac{Ca_{sub} - Cai}{\tau_{dif_{Ca}}}$$

$$J_{tr} = \frac{Ca_{nsr} - Ca_{jsr}}{\tau_{tr}}$$

$$J_{up} = \frac{P_{up}}{1 + \frac{K_{up}}{Cai}}$$

Ca^{2+} buffering

f_{CMi} : Fractional occupancy of calmodulin by Ca^{2+} in myoplasm

f_{CMs} : Fractional occupancy of calmodulin by Ca^{2+} in subspace

f_{CQ}: Fractional occupancy of calsequestrin by Ca^{2+}

f_{TC} : Fractional occupancy of the troponin-Ca^{2+} site by Ca^{2+}

f_{TMC}: Fractional occupancy of the troponin-Mg^{2+} site by Ca^{2+}

f_{TMM}: Fractional occupancy of the troponin-Mg^{2+} site by Mg^{2+}

$$\frac{\mathrm{d}fCMi}{\mathrm{d}time} = \delta_{fCMi}$$

$$\delta_{fCMi} = kf_{CM} \cdot Cai \cdot (1 - fCMi) - kb_{CM} \cdot fCMi$$

$$\frac{\mathrm{d}fCMs}{\mathrm{d}time} = \delta_{fCMs}$$

$$\delta_{fCMs} = kf_{CM} \cdot Ca_{sub} \cdot (1 - fCMs) - kb_{CM} \cdot fCMs$$

$$\frac{\mathrm{d}fCQ}{\mathrm{d}time} = \delta_{fCQ}$$

$$\delta_{fCQ} = kf_{CQ} \cdot Ca_{jsr} \cdot (1 - fCQ) - kb_{CQ} \cdot fCQ$$

$$\frac{\mathrm{d}fTC}{\mathrm{d}time} = \delta_{fTC}$$

$$\delta_{fTC} = kf_{TC} \cdot Cai \cdot (1 - fTC) - kb_{TC} \cdot fTC$$

$$\frac{\mathrm{d}fTMC}{\mathrm{d}time} = \delta_{fTMC}$$

$$\delta_{fTMC} = kf_{TMC} \cdot Cai \cdot \big(1 - (fTMC + fTMM)\big) - kb_{TMC} \cdot fTMC$$

$$\frac{\mathrm{d}fTMM}{\mathrm{d}time} = \delta_{fTMM}$$

$$\delta_{fTMM} = kf_{TMM} \cdot Mgi \cdot \big(1 - (fTMC + fTMM)\big) - kb_{TMM} \cdot fTMM$$

Dynamics of Ca^{2+} concentrations in cell compartments

$$\frac{\mathrm{d}Cai}{\mathrm{d}time} = \left(\frac{J_{diff} \cdot V_{sub} - J_{up} \cdot V_{nsr}}{V_i} - \left(CM_{tot} \cdot \delta_{fCMi} + TC_{tot} \cdot \delta_{fTC} + TMC_{tot} \cdot \delta_{fTMC}\right)\right) - \frac{\mathrm{d}fBAPTA}{\mathrm{d}time}$$

$$\frac{\mathrm{d}Ca_{sub}}{\mathrm{d}time} = \left(\frac{J_{rel} \cdot V_{jsr}}{V_{sub}} - \left(\frac{I_{siCa} + I_{CaT} - 2 \cdot I_{NaCa}}{2 \cdot F \cdot V_{sub}} + J_{Ca_{dif}} + CM_{tot} \cdot \delta_{fCMs}\right)\right) - \frac{\mathrm{d}fBAPTA_{sub}}{\mathrm{d}time}$$

$$\frac{\mathrm{d}Ca_{nsr}}{\mathrm{d}time} = J_{up} - \frac{J_{tr} \cdot V_{jsr}}{V_{nsr}}$$

$$\frac{\mathrm{d}Ca_{jsr}}{\mathrm{d}time} = J_{tr} - \left(J_{rel} + CQ_{tot} \cdot \delta_{fCQ}\right)$$

Dynamics of intracellular Na^{+} concentration

$$\frac{\mathrm{d}Nai}{\mathrm{d}time} = -\frac{I_{Na} + I_{fNa} + I_{siNa} + 3 \cdot I_{NaK} + 3 \cdot I_{NaCa}}{(V_i + V_{sub}) \cdot F}$$

RATE MODULATION EXPERIMENTS

Cesium 5 mM

Voltage-dependent reduction of the I_f conductance ($g_{f_{Na}}$ and g_{f_K}): $\frac{\frac{10.6015}{5}}{\frac{10.6015}{5}+e^{\frac{-0.71 \cdot V}{25}}}$

Ivabradine 3 µM

Reduction of 66% of the I_f conductance ($g_{f_{Na}}$ and g_{f_K}).

Acetylcholine 10 nM

I_f : shift of y_∞ and τ_y by -5 mV;

$I_{Ca,L}$: reduction of the maximal conductance of 3%;

SRCa^{2+} uptake: decrease of P_{up} by 7%.

I_{KACh} activation

Isoprenaline 1µM

I_f : shift of y_∞ and τ_y by 7.5 mV;

I_{NaK}: increase of $I_{NaK_{max}}$ of 20%;

$I_{Ca,L}$: increase of the maximal conductance of 23%, shift of dL_∞ and τ_{dL} by -8 mV; reduction of 31% of the inverse of the slope factor of dL_∞;

I_{Ks}: increase of g_{Ks} of 20%; shift of n_∞ and τ_n by -14 mV;

SRCa^{2+} uptake: increase of P_{up} by 25%.

BAPTA 10 mM

f_{BAPTA} : concentration of BAPTA bound to Ca^{2+};

$kb_{BAPTA} = 119.38$ s^{-1}: Ca^{2+} dissociation constant for BAPTA;

$kf_{BAPTA} = 940000$ mM^{-1}s^{-1}: Ca^{2+} association constant for BAPTA;

BAPTA.=10 mM: total BAPTA concentration;

$$\frac{\mathrm{d}f_{BAPTA}}{\mathrm{d}time} = kf_{BAPTA} \cdot Cai \cdot (\text{or } Ca_{sub}) \cdot (BAPTA - f_{BAPTA}) - kb_{BAPTA} \cdot f_{BAPTA}.$$

Nai was held to 7.5 mM during the simulation of this experiment

FIGURES

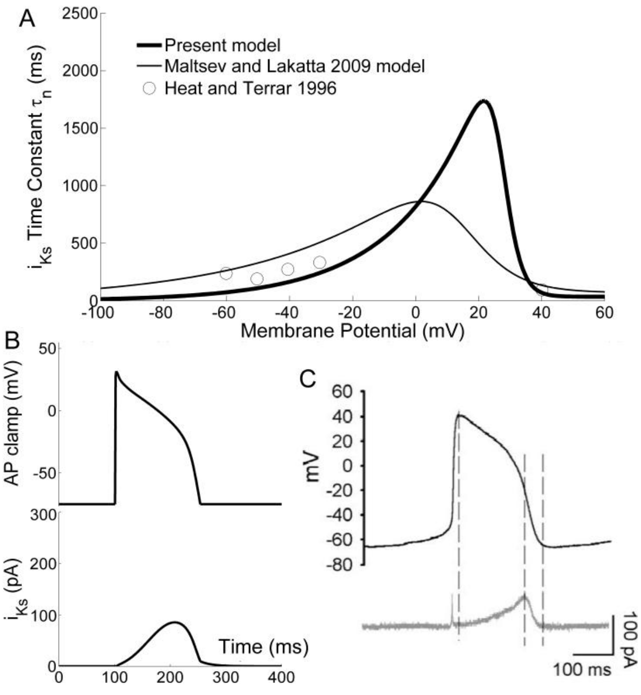

Figure S1. I_{Ks} current. A: time constant of I_{Ks} activation (τ_n), our formulation (thick line) and that from ML model (thin line); also shown are experimental data from Heath & Terrar (1996) on guinea-pig ventricular cells (open circles). B: Simulation of AP-clamp, reproducing the results of AP-clamp experiments of Lei et al. (2002) in C (redrawn with permission).

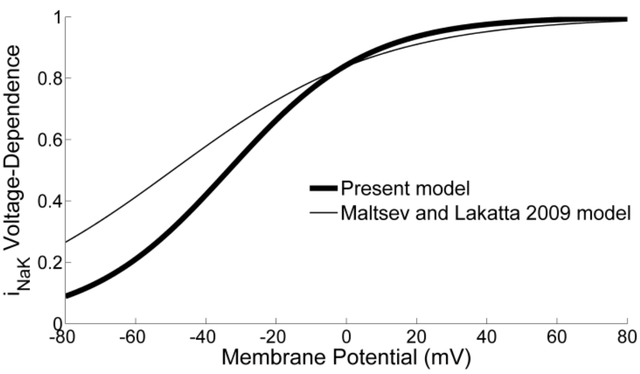

Figure S2. Voltage-dependence of Na+/K+ pump current (I_{NaK}). Our voltage-dependent component of I_{NaK} (thick line) is compared with that in ML model (thin line).

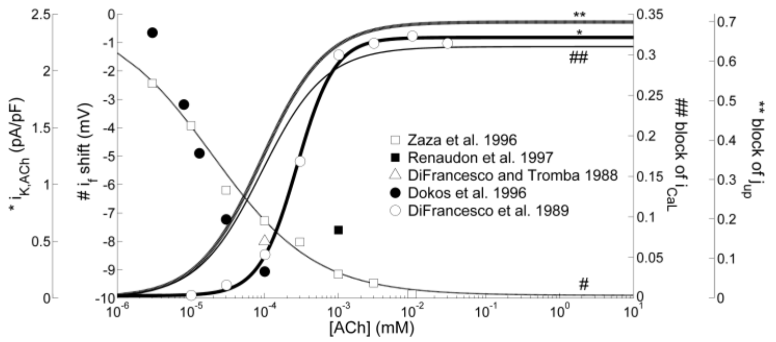

Figure S3. ACh-dependent curves used to reconstruct ACh effect in the SAN model: IK,ACh curve (*) fitted on DiFrancesco et al. (1989) data (open circles); negative shift of If kinetics (#) based on Zaza et al. (1996) (open squares), Renaudon et al. (1997) (filled squares), DiFrancesco & Tromba (1988) (open triangles) and Dokos et al. (1996) (filled circles) experimental data; inhibition of ICaL current (##) and block of Ca2+ uptake (**) were formulated as in Maltsev and Lakatta (2010).

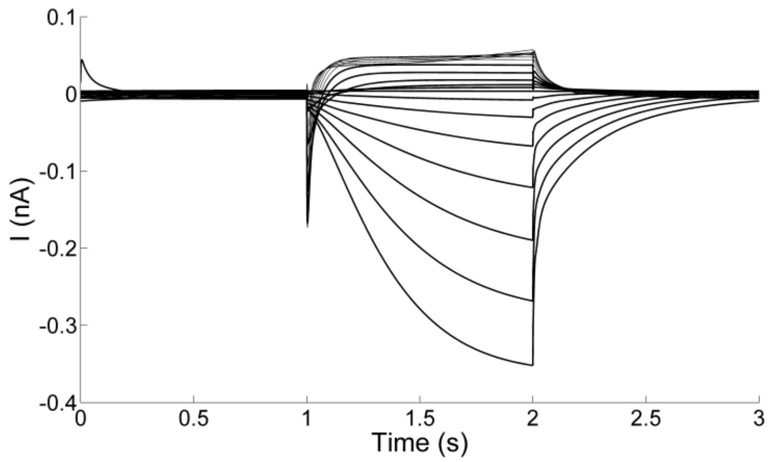

Figure S4. Simulated voltage clamp experiment. The plot shows superimposed records of the total membrane current in response to 1 s voltage clamp pulses from a holding potential of -40 mV and test potentials ranging from -75mV to 25mV (in 5 mV increments). Activation of I_f upon hyperpolarizing steps and activation of both I_{CaL} and $I_{Kr,s}$ upon depolarizing steps can be observed. Our results agree with the experimental results of DiFrancesco et al. (1986), Denyer & Brown (1990) and van Ginneken and Giles (1991).

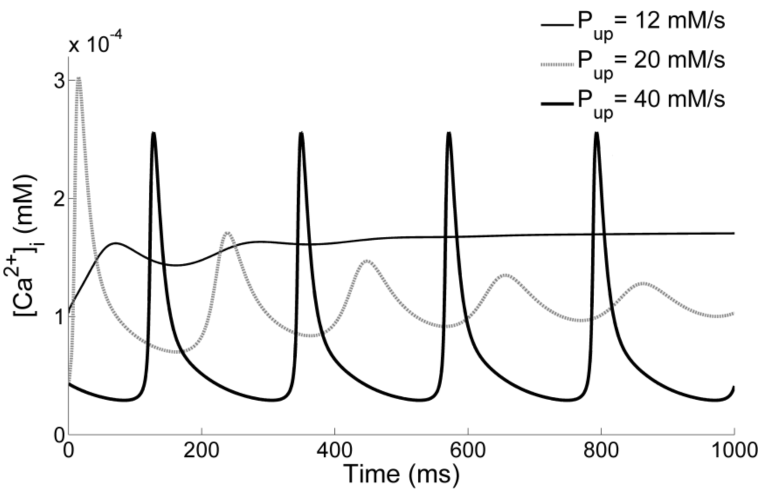

Figure S5. Isolated Ca^{2+} SR oscillator. Intracellular Ca^{2+} dynamics when all membrane currents are set to 0, at different P_{up} values. For P_{up} =12, 20 mMs^{-1} we observe damping oscillations, while there are steady oscillations for P_{up}=40 mMs^{-1}. As expected, the patterns are exactly the same as in figure 5C of Maltsev and Lakatta (2009).

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