<Equations, parameters and initial values of the β-cell model>

1. General

<Unit>

time in ms

voltage in mV

current in pA

conductance in nS

capacitance in pF

concentration in mM

volume in fl

flux in mM ms^{-1}

J_{SERCA} or J_{rel} in amole ms^{-1} (= fl mM ms^{-1})

Thermodynamic constants

R ; 8.3143 (mV C $mmol^{-1}$ K^{-1}), Gas constant

T ; 273.15 + 37 (K), absolute temperature

F ; 96.4867 (C $mmol^{-1}$), Faraday const

Extracellular composition

$[Na^+]_o$ = 140 mM, $[K^+]_o$ = 5.4 mM, $[Ca^{2+}]_o$ = 2.6 mM

Cell parameters

Cm ; 6.158 (pF), cell capacitance

vol_i ; 764 (fl), cell volume (cytosol)

vol_{ER} ; 280 (fl), ER volume

f_i ; 0.01, cytosolic Ca^{2+} buffer strength

f_{ER} ; 0.025, ER Ca^{2+} buffer strength

2. Calculation of membrane potential and internal ion concentrations

Membrane potential

$$\frac{dV_m}{dt} = \frac{-(I_{tot} + I_{inject})}{C_m} \quad \text{(S1)}$$

$$I_{tot} = I_{CaV} + I_{TRPM} + I_{SOC} + I_{bNSC} + I_{KDr} + I_{KCa(BK)} + I_{KCa(SK)} + I_{KATP} + I_{NaK} + I_{NaCa} + I_{PMCA} \quad \text{(S}$$

2)

Internal ion concentrations

$$\frac{d[Na^+]_i}{dt} = \frac{-I_{CaV,Na} - I_{TRPM,Na} - I_{SOC,Na} - I_{bNSC,Na} - 3 \cdot I_{NaK} - 3 \cdot I_{NaCa} + I_{PMCA}}{vol_i \cdot F} \quad \text{(S3)}$$

(Assumption; the H^+ flux via PMCA is immediately converted to Na^+ flux through Na/H exchange)

$$\frac{d[K^+]_i}{dt} = \frac{-I_{KDr} - I_{KCa(BK)} - I_{KCa(SK)} - I_{KATP} - I_{CaV,K} - I_{TRPM,K} - I_{SOC,K} - I_{bNSC,K} + 2 \cdot I_{NaK} - I_{inject}}{vol_i \cdot F} \quad \text{(S4)}$$

$$\frac{d[Ca^{2+}]_i}{dt} = \frac{f_i}{vol_i} \cdot \left(\frac{-I_{CaV,Ca} - I_{SOC,Ca} + 2 \cdot I_{NaCa} - 2 \cdot I_{PMCA}}{2 \cdot F} - J_{SERCA} + J_{rel}\right) \quad \text{(S5)}$$

$$\frac{d[Ca^{2+}]_{ER}}{dt} = \frac{f_{ER}}{vol_{ER}} \cdot (J_{SERCA} - J_{rel}) \quad \text{(S6)}$$

Constant field equation and Nernst equation

$$CF_x = \frac{z_x \cdot F \cdot V_m}{R \cdot T} \frac{[X]_i - [X]_o \exp(-\frac{z_x \cdot F \cdot V_m}{R \cdot T})}{1 - \exp(-\frac{z_x \cdot F \cdot V_m}{R \cdot T})} \quad \text{(mM)} \quad \text{(S7)}$$

$$E_x = \frac{R \cdot T}{z_x \cdot F} \ln \frac{[x]_o}{[x]_i} \quad \text{(mV)} \quad \text{(S8)}$$

3. Channel currents

I_{CaV} : voltage-dependent Ca^{2+} current

P_{CaV} ; 48.9 (pA mM^{-1}), converting factor of I_{CaV}

po_{CaV} ; open probability of the Ca^{2+} channel

d_{CaV} ; voltage-dependent activation gate of I_{CaV}

α_d, β_d ; (ms^{-1}), rate constants for d_{CaV}

U_{CaV} ; Ca^{2+}-dependent inactivation gate of I_{CaV}

α_U, β_U ; (ms^{-1}), rate constants for u_{CaV}

i_{Ca} ; (pA), amplitude of single channel current of I_{CaV}

f_{us} ; V-dependent ultra-slow inactivation gate of I_{CaV}

α_{fus}, β_{fus} ; (ms^{-1}), rate constants for f_{us}

$$I_{CaV} = I_{CaV,Ca} + I_{CaV,Na} + I_{CaV,K} \tag{S9}$$

$$I_{CaV,Ca} = P_{CaV} \cdot po_{CaV} \cdot CF_{Ca} \tag{S10}$$

$$I_{CaV,Na} = 0.0000185 \cdot P_{CaV} \cdot po_{CaV} \cdot CF_{Na} \tag{S11}$$

$$I_{CaV,K} = 0.000367 \cdot P_{CaV} \cdot po_{CaV} \cdot CF_{K} \tag{S12}$$

$$po_{CaV} = d_{CaV}{}^{2} \cdot U_{CaV} \cdot (0.4 + 0.6 \cdot f_{us}) \cdot \frac{1}{1 + (\frac{1.4}{[ATP]_i})^3} \tag{S13}$$

$$\frac{dd_{CaV}}{dt} = \alpha_d \cdot (1 - d_{CaV}) - \beta_d \cdot d_{CaV} \tag{S14}$$

$$\alpha_d = \frac{1}{0.9344 \cdot \exp(-\frac{V_m}{50}) + 0.09045 \cdot \exp(-\frac{V_m}{600})} \tag{S15}$$

$$\beta_d = \frac{1}{4.2678 \cdot \exp(\frac{V_m}{12}) + 1.1265 \cdot \exp(\frac{V_m}{30})} \tag{S16}$$

$$\frac{dU_{CaV}}{dt} = \alpha_u \cdot (1 - U_{CaV}) - \beta_u \cdot U_{CaV} \tag{S17}$$

$$\alpha_u = 0.0084$$

$$\beta_u = 0.2318 \cdot (-1.15 \cdot i_{Ca} \cdot d_{CaV}{}^{2} + [Ca^{2+}]_i) \tag{S18}$$

$$i_{Ca} = 0.0676 \cdot CF_{Ca} \tag{S19}$$

$$\frac{df_{us}}{dt} = \alpha_{fus} \cdot (1 - f_{us}) - \beta_{fus} \cdot f_{us} \tag{S20}$$

$$\alpha_{fus} = \frac{1}{75000 \cdot \exp(\frac{V_m}{34})} \tag{S21}$$

$$\beta_{fus} = \frac{1}{5000\exp(-\frac{V_m}{19}) + 500\exp(-\frac{V_m}{100})} \quad \text{(S22)}$$

I_{KDr} ; deleyed rectifier K^+ current

P_{KDr} ; 2.1 (pA mM^{-1}), converting factor of I_{KDr}

po_{KDr} ; open probability of I_{KDr} channel

r_{KDr} ; voltage-dependent activation gate of I_{KDr}

q_{KDr} ; voltage-dependent inactivation gate of I_{KDr}

α_r, β_r ; (ms^{-1}), rate constants of r_{KDr}

α_q, β_{qr} ; (ms^{-1}), rate constants of q_{KDr}

$$I_{KDr} = P_{KDr} \cdot po_{KDr} \cdot CF_K \quad \text{(S23)}$$

$$po_{KDr} = r_{KDr}{}^2 \cdot (0.6 \cdot q_{KDR} + 0.4) \quad \text{(S24)}$$

$$\frac{dr_{KDr}}{dt} = \alpha_r \cdot (1 - r_{KDr}) - \beta_r \cdot r_{KDr} \quad \text{(S25)}$$

$$\alpha_r = \frac{1}{33.07 \cdot \exp(\frac{V_m}{-8}) + 0.937 \cdot \exp(\frac{V_m}{-100})} \quad \text{(S26)}$$

$$\beta_r = \frac{1}{22.73 \cdot \exp(\frac{V_m}{100})} \quad \text{(S27)}$$

$$\frac{dq_{KDr}}{dt} = \alpha_q \cdot (1 - q_{KDr}) - \beta_q \cdot q_{KDr} \quad \text{(S28)}$$

$$\alpha_q = \frac{1}{800} \quad \text{(S29)}$$

$$\beta_q = \frac{1}{1000 \cdot \exp(-\frac{V_m}{8}) + 100 \cdot \exp(-\frac{V_m}{100})} \quad \text{(S30)}$$

$I_{KCa(BK)}$; V- and $[Ca^{2+}]_i$-dependent transient outward K^+ current

$G_{KCa(BK)}$; 2.13 (pA mV^{-1}), conductance of $I_{KCa(BK)}$

$m_{KCa(BK)}$; activation gate for $I_{KCa(BK)}$

$po_{KCa(BK)}$; open probability of $I_{KCa(BK)}$ channel

α_m, β_m ; (ms^{-1}), rate constants for $m_{KCa(BK)}$

$h_{KCa(BK)}$; inactivation gate for $I_{KCa(BK)}$
α_h, β_h ; (ms^{-1}), rate constants for $h_{KCa(BK)}$

$$po_{KCa(BK)} = m_{KCa(BK)} \cdot h_{KCa(BK)}$$

$$I_{KCa(BK)} = G_{KCa(BK)} \cdot po_{KCa(BK)} \cdot (V_m - E_K) \qquad \text{(S31)}$$

$$\frac{dm_{KCa(BK)}}{dt} = \alpha_m \cdot (1 - m_{KCa(BK)}) - \beta_m \cdot m_{KCa(BK)} \qquad \text{(S32)}$$

$$\alpha_m = \frac{1}{13.65 \cdot \exp(-\frac{V_m}{20})} \qquad \text{(S33)}$$

$$\beta_m = \frac{1}{6.2 \cdot \exp(\frac{V_m}{60})} \qquad \text{(S34)}$$

$$\frac{dh_{KCa(BK)}}{dt} = \alpha_h \cdot (1 - h_{KCa(BK)}) - \beta_h \cdot h_{KCa(BK)} \qquad \text{(S35)}$$

$$\alpha_h = \frac{1}{570 \cdot \exp(\frac{V_m}{500})} \qquad \text{(S36)}$$

$$\beta_h = \frac{1}{7.765 \cdot \exp(-\frac{V_m}{9}) + 4.076 \cdot \exp(-\frac{V_m}{1000})} \qquad \text{(S37)}$$

$I_{KCa(SK)}$; Ca^{2+}-activated K^+ current
$P_{KCa(SK)}$; 0.2 (pA mM^{-1}), converting factor of $I_{KCa(SK)}$
$po_{KCa(SK)}$; open probability of $I_{KCa(SK)}$

$$po_{KCa(SK)} = \frac{1}{1 + (\frac{0.00074}{[Ca^{2+}]_i})^{2.2}} \qquad \text{(S38)}$$

$$I_{KCa(SK)} = P_{KCa(SK)} \cdot po_{KCa(SK)} \cdot CF_K \qquad \text{(S39)}$$

I_{bNSC} ; background non-selective cation current

P_{bNSC} ; 0.00396 (pA mM^{-1}), converting factor of I_{bNSC}

$$I_{bNSC} = I_{bNSC,Na} + I_{bNSC,K} \tag{S40}$$

$$I_{bNSC,Na} = P_{bNSC} \cdot CF_{Na} \tag{S41}$$

$$I_{bNSC,K} = 2.525 \cdot P_{bNSC} \cdot CF_{K} \tag{S42}$$

I_{SOC} ; store-operated current

P_{SOC} ; 0.00764 (pA mM^{-1}), converting factor of I_{SOC}

po_{SOC} ; open probability of I_{SOC}

$K_{0.5,ER}$; 0.003 (mM), half activation concentration of Ca^{2+} in the ER

$$I_{SOC} = I_{SOC,Na} + I_{SOC,K} + I_{SOC,Ca} \tag{S43}$$

$$po_{SOC} = \frac{1}{1 + \exp(\frac{[Ca^{2+}]_{ER} - K_{0.5,ER}}{0.003})} \tag{S44}$$

$$I_{SOC,Na} = 0.8 \cdot P_{SOC} \cdot po_{SOC} \cdot CF_{Na} \tag{S45}$$

$$I_{SOC,K} = P_{SOC} \cdot po_{SOC} \cdot CF_{K} \tag{S46}$$

$$I_{SOC,Ca} = 20 \cdot P_{SOC} \cdot po_{SOC} \cdot CF_{Ca} \tag{S47}$$

I_{TRPM} ; Ca^{2+}-activated non-selective cation current (TRPM channel)

P_{TRPM} ; 0.0234 (pA mM^{-1}), converting factor of I_{TRPM}

po_{TRPM} ; open probability of I_{TRPM}

$$po_{TRPM} = \frac{1}{1 + (\frac{0.00076}{[Ca^{2+}]_i})^{1.7}} \tag{S48}$$

$$I_{TRPM} = I_{TRPM,Na} + I_{TRPM,K} \tag{S49}$$

$$I_{TRPM,Na} = 0.8 \cdot P_{TRPM} \cdot po_{TRPM} \cdot CF_{Na} \tag{S50}$$

$$I_{TRPM,K} = P_{TRPM} \cdot po_{TRPM} \cdot CF_{K} \tag{S51}$$

I_{KATP} ; ATP-sensitive K^+ current

G_{KATP} ; 2.31 ($pA\ mV^{-1}$), maximum conductance of I_{KATP}

po_{KATP} ; open probability of I_{KATP}

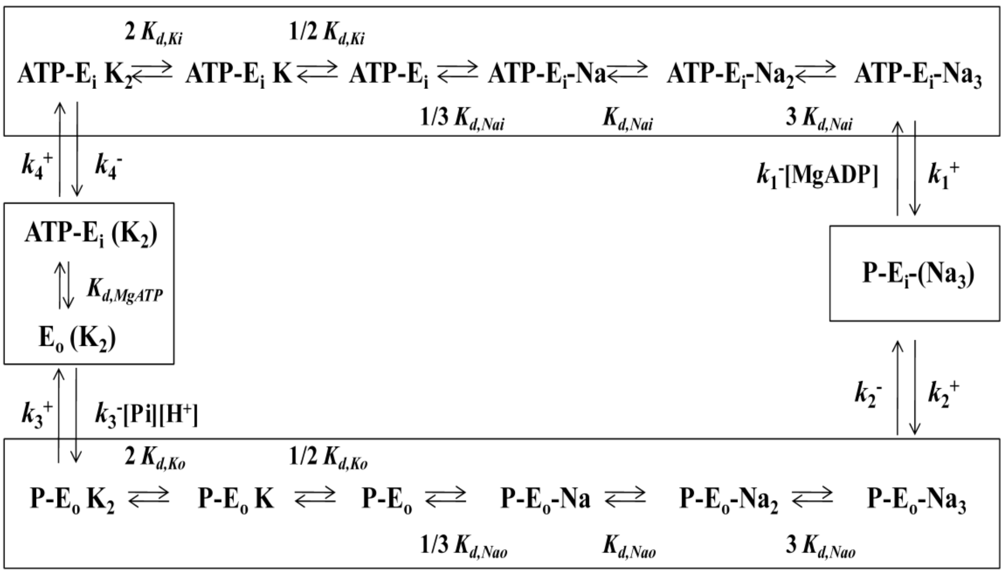
$$po_{KATP} = \frac{0.08 \cdot (1 + \frac{2 \cdot [MgADP]}{0.01}) + 0.89 \cdot (\frac{[MgADP]}{0.01})^2}{(1 + \frac{[MgADP]}{0.01})^2 (1 + \frac{0.45 \cdot [MgADP]}{0.026} + \frac{[ATP]}{0.05})} \tag{S52}$$

$$I_{KATP} = G_{KATP} \cdot po_{KATP} \cdot (V_m - E_K) \tag{S53}$$

4.Transporters

I_{NaK} : Na^+/K^+ pump current

* The rate constants, $k^{\pm}$s in their Table1 were multiplied by 1.74 according Oka et al. (2010). [Pi] of 1.9 mM and $[H^+]$ of 0.0001 mM were assumed only for calculating $I_{Na/K}$.



P_{NaK} ; 350 (pA ms), limiting amplitude of I_{NaK}
v_{cyc} ; turnover rate (ms^{-1})
F_{glc} ; inhibition factor of glucose ([G]) on I_{NaK}
$k^{\pm}$; (ms^{-1}), rate constants
$K_{d,X}$; (mM), dissociation constant of ion X

$$I_{NaK} = P_{NaK} \cdot v_{cyc} \cdot F_{glc} \tag{S54}$$

$$F_{glc} = 0.4 + 0.6\exp(-\frac{[G]}{5.84}) \tag{S55}$$

$$v_{cyc} = \frac{\alpha_1^+\alpha_2^+\alpha_3^+\alpha_4^+ - \alpha_1^-\alpha_2^-\alpha_3^-\alpha_4^-}{\sum} \tag{S56}$$

$$\begin{aligned}\sum\ &= \alpha_1^-\alpha_2^-\alpha_3^- + \alpha_1^+\alpha_2^-\alpha_3^- + \alpha_1^+\alpha_2^+\alpha_3^- + \alpha_1^+\alpha_2^+\alpha_3^+ \\ &+ \alpha_2^-\alpha_3^-\alpha_4^- + \alpha_2^+\alpha_3^-\alpha_4^- + \alpha_2^+\alpha_3^+\alpha_4^- + \alpha_2^+\alpha_3^+\alpha_4^+ \\ &+ \alpha_3^-\alpha_4^-\alpha_1^- + \alpha_3^+\alpha_4^-\alpha_1^- + \alpha_3^+\alpha_4^+\alpha_1^- + \alpha_3^+\alpha_4^+\alpha_1^+ \\ &+ \alpha_4^-\alpha_1^-\alpha_2^- + \alpha_4^+\alpha_1^-\alpha_2^- + \alpha_4^+\alpha_1^+\alpha_2^- + \alpha_4^+\alpha_1^+\alpha_2^+\end{aligned} \tag{S57}$$

$$\alpha_1^+ = \frac{k_1^+\overline{Na_i}^3}{(1+\overline{Na_i})^3 + (1+\overline{K_i})^2 - 1} \tag{S58}$$

$$\alpha_2^+ = k_2^+ \tag{S59}$$

$$\alpha_3^+ = \frac{k_3^+\overline{K_o}^2}{(1+\overline{Na_o})^3 + (1+\overline{K_o})^2 - 1} \tag{S60}$$

$$\alpha_4^+ = \frac{k_4^+\overline{MgATP}}{1+\overline{MgATP}} \tag{S61}$$

$$\alpha_1^- = k_1^-[MgADP] \tag{S62}$$

$$\alpha_2^- = \frac{k_2^-\overline{Na_o}^3}{(1+\overline{Na_o})^3 + (1+\overline{K_o})^2 - 1} \tag{S63}$$

$$\alpha_3^- = \frac{k_3^-[\mathrm{Pi}][\mathrm{H}^+]}{1+\overline{\mathrm{MgATP}}} \tag{S64}$$

$$\alpha_4^- = \frac{k_4^-\overline{\mathrm{K}_i}^2}{(1+\overline{\mathrm{Na}_i})^3 + (1+\overline{\mathrm{K}_i})^2 - 1} \tag{S65}$$

$k_1^- = 0.139\ \mathrm{mM^{-1}ms^{-1}}$, $k_2^- = 0.0139\ \mathrm{ms^{-1}}$, $k_3^- = 13900\ \mathrm{mM^{-2}ms^{-1}}$, $k_4^- = 0.348\ \mathrm{ms^{-1}}$

$$\overline{\mathrm{Nai}} = \frac{[\mathrm{Na}^+]_i}{K_{d,Nai}}, \tag{S66}$$

$$\overline{\mathrm{Ki}} = \frac{[\mathrm{K}^+]_i}{K_{d,Ki}} \tag{S67}$$

$$\overline{\mathrm{Na}_o} = \frac{[\mathrm{Na}^+]_o}{K_{d,Nao}}, \tag{S68}$$

$$\overline{\mathrm{K}_o} = \frac{[\mathrm{K}^+]_o}{K_{d,Ko}} \tag{S69}$$

$$\overline{\mathrm{MgATP}} = \frac{[\mathrm{MgATP}]}{K_{d,MgATP}} \tag{S70}$$

$$K_{d,Nao} = K_{d,Nao}^0 \cdot \exp\frac{\Delta_{Nao}\cdot FV_m}{RT} \tag{S71}$$

$$K_{d,Nai} = K_{d,Nai}^0 \cdot \exp\frac{\Delta_{Nai}\cdot FV_m}{RT} \tag{S72}$$

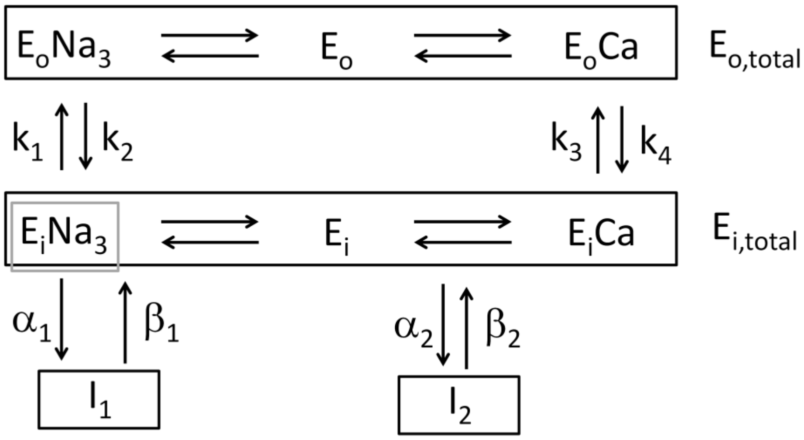
$$K_{d,Ko} = K_{d,Ko}^0 \cdot \exp\frac{\Delta_{Ko}\cdot FV_m}{RT} \tag{S73}$$

$$K_{d,Ki} = K_{d,Ki}^0 \cdot \exp\frac{\Delta_{Ki}\cdot FV_m}{RT} \tag{S74}$$

$K_{d,MgATP} = 0.6\ \mathrm{mM}$, $K_{d,Nao}^0 = 26.8\ \mathrm{mM}$, $K_{d,Ko}^0 = 0.8\ \mathrm{mM}$, $K_{d,Nai}^0 = 5.0\ \mathrm{mM}$, $K_{d,Ki}^0 = 18.8\ \mathrm{mM}$,

$\Delta_{Nao} = 0.44$, $\Delta_{Nai} = -0.14$, $\Delta_{Ko} = 0.23$, $\Delta_{Ki} = -0.14$

I_{NaCa} : Na^+/Ca^{2+} exchange current



P_{NaCa} ; 204 (pA), maximum amplitude of I_{NaCa}

$E_{i,total}$, $E_{o,total}$, ; probability of active states with an internal or external binding site, respectively

I_1, I_2 ; probabilities of inactive states

k, α and β ; (ms^{-1}), rate constants

$K_{d,X}$; (mM), dissociation constant of ion X

f_{Ca} ; parameter to define the Ca^{2+}-dependency of the inactivation gates, I_1, I_2

$$I_{NaCa} = P_{NaCa} \cdot (k_1 \cdot p_{EiNa} \cdot E_{i,total} - k_2 \cdot p_{EoNa} \cdot E_{o,total}) \tag{S75}$$

$$\frac{dI_1}{dt} = \alpha_1 \cdot p_{EiNa} \cdot E_{i,total} - \beta_1 \cdot I_1 \tag{S76}$$

$$\frac{dI_2}{dt} = \alpha_2 \cdot E_{i,total} - \beta_2 \cdot I_2 \tag{S77}$$

$$k_f = k_2 \cdot p_{EoNa} + k_4 \cdot p_{EoCa} \tag{S78}$$

$$k_b = k_1 \cdot p_{EiNa} + k_3 \cdot p_{EiCa} \tag{S79}$$

$$\frac{dE_{i,total}}{dt} = k_f \cdot E_{o,total} + \beta_1 \cdot I_1 + \beta_2 \cdot I_2 - (k_b + \alpha_1 \cdot p_{EiNa} + \alpha_2) \cdot E_{i,total} \tag{S80}$$

$$E_{o,total} = 1 - (E_{i,total} + I_1 + I_2) \tag{S81}$$

$$k_1 = \exp(\frac{0.32 \cdot V_m \cdot F}{R \cdot T}) \quad \text{(S82)}$$

$$k_2 = \exp(\frac{(0.32-1) \cdot V_m \cdot F}{R \cdot T}) \quad \text{(S83)}$$

$$k_3 = 1 \quad \text{(S84)}$$

$$k_4 = 1 \quad \text{(S85)}$$

$$\alpha_1 = 0.002 \cdot f_{Ca} + 0.0015 \cdot (1 - f_{Ca}) \quad \text{(S86)}$$

$$\beta_1 = 0.0012 \cdot f_{Ca} + 0.0000005 \cdot (1 - f_{Ca}) \quad \text{(S87)}$$

$$\alpha_2 = 0.00003 \cdot f_{Ca} + 0.01 \cdot (1 - f_{Ca}) \quad \text{(S88)}$$

$$\beta_2 = 0.09 \cdot f_{Ca} + 0.0001 \cdot (1 - f_{Ca}) \quad \text{(S89)}$$

$$f_{Ca} = \frac{[Ca^{2+}]_i}{[Ca^{2+}]_i + 0.004} \quad \text{(S90)}$$

$$p_{EiNa} = \frac{(\frac{[Na^+]_i}{K_{d,Nai}})^3}{1 + (\frac{[Na^+]_i}{K_{d,Nai}})^3 + \frac{[Ca^{2+}]_i}{K_{d,Cai}}} \quad \text{(S91)}$$

$$p_{EiNa} = \frac{\frac{[Ca^{2+}]_i}{K_{d,Cai}}}{1 + (\frac{[Na^+]_i}{K_{d,Nai}})^3 + \frac{[Ca^{2+}]_i}{K_{d,Cai}}} \quad \text{(S92)}$$

$$p_{EoNa} = \frac{(\frac{[Na^+]_o}{K_{d,Nao}})^3}{1 + (\frac{[Na^+]_o}{K_{d,Nao}})^3 + \frac{[Ca^{2+}]_o}{K_{d,Cao}}} \quad \text{(S93)}$$

$$p_{EoCa} = \frac{\frac{[Ca^{2+}]_o}{K_{d,Cao}}}{1 + (\frac{[Na^+]_o}{K_{d,Nao}})^3 + \frac{[Ca^{2+}]_o}{K_{d,Cao}}} \quad \text{(S94)}$$

$K_{d,Nai}$ = 20.75 mM, $K_{d,Cai}$ = 0.0184 mM, $K_{d,Nao}$ = 87.5 mM, $K_{d,Cao}$ = 1.38 mM

I_{PMCA} : plasma membrane Ca^{2+} pump (PMCA) current

P_{PMCA} ; 1.56 (pA), maximum amplitude of I_{PMCA}

$$I_{PMCA} = P_{PMCA} \frac{1}{1+(\frac{0.00014}{[Ca^{2+}]_i})^2} \tag{S95}$$

5.ER calcium dynamics

J_{SERCA} ; Ca^{2+} uptake by SERCA

P_{SERCA} ; 0.096 (amole ms^{-1}), the maximum rate of pumping Ca^{2+} into ER.

$$J_{SERCA} = P_{SERCA} \frac{1}{1+(\frac{0.0005}{[Ca^{2+}]_i})^2} \tag{S96}$$

J_{rel} ; Ca^{2+} release from ER

P_{rel} ; 0.46 (fl ms^{-1}), converting factor for Ca^{2+} release from ER

$$J_{rel} = P_{rel} \cdot ([Ca^{2+}]_{ER} - [Ca^{2+}]_i) \tag{S97}$$

6.Glycolysis and oxidative phospholylation

J_{glc} or $J_{\beta,ox}$; NADH production through glycolysis or β-oxidation

k_{glc} ; 0.000126 (ms^{-1}), rate constant of glycolysis

$k_{\beta,ox}$; 0.0000063 (ms^{-1}), rate constant of β-oxidation

$[Re_{tot}]$; 10 (mM), total amount of pyrimidine nucleotides

$$J_{glc} = k_{glc} \cdot f_{glc} \cdot ([Re_{tot}] - [Re]) \tag{S98}$$

$$J_{\beta,ox} = k_{\beta,ox}([Re_{tot}] - [Re]) \tag{S99}$$

f_{glc} ; ATP- and glucose- dependency of glycolysis

[G] ; extracellular glucose concentration

hgl ; 2.5, Hill coefficient for glucose-dependency

K_G ; 13 (mM), half-maximal concentration of glucose

$$f_{glc} = \frac{1}{1+\frac{0.5}{[ATP]_i}} \cdot \frac{1}{1+(\frac{K_G}{[G]})^{hgl}} \tag{S100}$$

J_{op}; ATP production through oxidative phosphorylation

* P_{op} = 0.0005 ; ms^{-1} maximum rate of ATP production
* N = 2.5 ; stoichiometry of conversion from NADH to ATP
* R_{vol} = 2.5 ; volume ratio between cytosol and mitochondria

$$J_{op} = P_{op} \cdot [Re] \cdot \frac{1}{1+(\frac{0.02}{[MgADP]})^2} \tag{S101}$$

$$\frac{d[Re]}{dt} = J_{glc} + J_{\beta,ox} - \frac{R_{vol}}{N} J_{op} \tag{S102}$$

$J_{c,ATP}$; flux of Ca^{2+}-dependent/independent ATP consumption

[ATP_{tot}] ; 4 (mM), total amount of ATP species

ADP_b ; bound ADP

ADP_f ; free ADP

k_{ATP} ; 0.000062 (ms^{-1}), rate constant of Ca^{2+}-independent ATP consumption

$k_{ATP,Ca}$; 0.187 (mM^{-1} ms^{-1}), rate constant of Ca^{2+}-dependent ATP consumption

$k_{ADP,f}$; 0.0002 (ms^{-1}), rate constant from ADP_f to ADP_b

$k_{ADP,b}$; 0.00002 (ms^{-1}), rate constant from ADP_b to ADP_f

$$J_{c,ATP} = (k_{ATP} + k_{ATP,Ca} \cdot [Ca^{2+}]_i) \cdot [ATP] \tag{S103}$$

$$\frac{d[ATP]}{dt} = J_{op} - J_{c,ATP} - (\frac{I_{NaK} + I_{PMCA}}{F} + \frac{J_{SERCA}}{2})/V_i \tag{S104}$$

$$\frac{d[ADP_b]}{dt} = k_{ADPf} ,[ADP_f] - k_{ADP,b} \cdot [ADP_b] \tag{S105}$$

$$[ADP_f] = [ATP_{total}] - [ATP] - [ADP_b] \tag{S106}$$

$$[MgADP] = 0.55 \cdot [ADP_f] \tag{S107}$$

7. Definition of the lead potential (V_L) for calculation in Figs. 5 and 6

$$V_L = \frac{\begin{aligned}&(G_{KCa(BK)} \cdot po_{KCa(BK)} + G_{KATP} \cdot po_{KATP}) \cdot E_K \\ &+ \begin{pmatrix} P_{bNSC} + 0.8 \cdot P_{TRPM} \cdot po_{TRPM} + 0.0000185 \cdot P_{CaV} \cdot po_{CaV} \\ + 0.8 \cdot P_{SOC} \cdot po_{SOC} \end{pmatrix} \cdot \frac{\partial(CF_{Na})}{\partial V_m} \cdot E_{CFNa} \\ &+ \begin{pmatrix} 2.525 \cdot P_{bNSC} + P_{KDr} \cdot po_{KDr} + P_{TRPM} \cdot po_{TRPM} \\ + 0.000367 \cdot P_{CaV} \cdot po_{CaV} + P_{KCa(SK)} \cdot po_{KCa(SK)} + P_{SOC} \cdot po_{SOC} \end{pmatrix} \cdot \frac{\partial(CF_K)}{\partial V_m} \cdot E_{CFK} \\ &+ (P_{CaV} \cdot po_{CaV} + 20 \cdot P_{SOC} \cdot po_{SOC}) \cdot \frac{\partial(CF_{Ca})}{\partial V_m} \cdot E_{CFCa} \\ &+ G_{NaK} \cdot E_{x\_NaK} + G_{NaCa} \cdot E_{x\_NaCa} - I_{PMCA} - I_{inject}\end{aligned}}{\begin{aligned}&(G_{KCa(BK)} \cdot po_{KCa(BK)} + G_{KATP} \cdot po_{KATP}) \\ &+ \begin{pmatrix} P_{bNSC} + 0.8 \cdot P_{TRPM} \cdot po_{TRPM} + 0.0000185 \cdot P_{CaV} \cdot po_{CaV} \\ + 0.8 \cdot P_{SOC} \cdot po_{SOC} \end{pmatrix} \cdot \frac{\partial(CF_{Na})}{\partial V_m} \\ &+ \begin{pmatrix} 2.525 \cdot P_{bNSC} + P_{KDr} \cdot po_{KDr} + P_{TRPM} \cdot po_{TRPM} \\ + 0.000367 \cdot P_{CaV} \cdot po_{CaV} + P_{KCa(SK)} \cdot po_{KCa(SK)} + P_{SOC} \cdot po_{SOC} \end{pmatrix} \cdot \frac{\partial(CF_K)}{\partial V_m} \\ &+ (P_{CaV} \cdot po_{CaV} + 20 \cdot P_{SOC} \cdot po_{SOC}) \cdot \frac{\partial(CF_{Ca})}{\partial V_m} + G_{NaK} + G_{NaCa}\end{aligned}} \quad \text{(S108)}$$

where constant field equations for Na^+, K^+ and Ca^{2+} (CF_{Na}, CF_K and CF_{Ca}, respectively (Eq. S7)) were linearized with respect to V_m, as below:

$$CF_{Na} = \frac{\partial(CF_{Na})}{\partial V_m} \cdot (V_m - E_{CFNa}) \quad \text{(S109)}$$

$$CF_K = \frac{\partial(CF_K)}{\partial V_m} \cdot (V_m - E_{CFK}) \quad \text{(S110)}$$

$$CF_{Ca} = \frac{\partial(CF_{Ca})}{\partial V_m} \cdot (V_m - E_{CFCa}) \quad \text{(S111)}$$

Table S1. Initial values of independent variables (X(0))

Independent variables	Initial values
V_m	-48.9045
$[Na^+]_i$	5.80400
$[K^+]_i$	126.776
$[Ca^{2+}]_i$	0.000306139
$[Ca^{2+}]_{ER}$	0.0234849
[ATP]	2.64667
[MgADP]	0.127093
[Re]	0.641950
d_{CaL}	0.101898
U_{CaL}	0.635696
f_{us}	0.827114
r_{KDr}	0.00105694
q_{KDr}	0.970421
m_{Kto}	0.0170783
h_{Kto}	0.301612
$E_{i,tot}$	0.354892
I_1	0.151253
I_2	0.489584

* The set of values was obtained when the model shows a steady bursting rhythm at 8 mM [G]. The initial values were used for obtaining all the figures in this paper and Figs. 1, 4 & 5 in the accompanying paper. These initial values define the present model according to the charge conservation law described in the accompanying paper.