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Supporting Material

Modeling cardiac action potential shortening driven by oxidative stress-induced mitochondrial oscillations

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Supplemental materials: ECME-RIRR model equations and parameters

S1. Model equations

S1.1 Sarcolemmal membrane ionic currents

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

$$I_{Na} = \overline{G}_{Na}\, m^3\, h\, j\, \left(V - E_{Na}\right) \tag{E1}$$

$$E_{Na} = \frac{RT}{F} \ln\left(\frac{[Na^+]_o}{[Na^+]_i}\right) \tag{E2}$$

$$\frac{dm_{Na}}{dt} = \alpha_m\left(1-m_{Na}\right) - \beta_m m_{Na} \tag{E3}$$

$$\frac{dh_{Na}}{dt} = \alpha_h\left(1-h_{Na}\right) - \beta_h h_{Na} \tag{E4}$$

$$\frac{dj_{Na}}{dt} = \alpha_j\left(1-j_{Na}\right) - \beta_j j_{Na} \tag{E5}$$

$$\alpha_m = 0.32\, \frac{V + 47.13}{1 - e^{-0.1\,(V+47.13)}} \tag{E6}$$

$$\beta_m = 0.08\, e^{-V/11} \tag{E7}$$

For V ≥ -40 mV

$$\alpha_h = 0.0 \tag{E8}$$

$$\alpha_j = 0.0 \tag{E9}$$

$$\beta_h = \left(0.13\left(1 + e^{\left(\frac{V+10.66}{-11.1}\right)}\right)\right)^{-1} \tag{E10}$$

$$\beta_j = 0.3\, \frac{e^{-2.535 \times 10^{-7} V}}{1 + e^{-0.1\,(V+32)}} \tag{E11}$$

For V< -40 mV

$$\alpha_h = 0.135\, e^{\frac{80 + V}{-6.8}} \tag{E12}$$

$$\alpha_j = \frac{\left(-127{,}140\ e^{0.2444\ V} - 3.474 \times 10^{-5}\ e^{-0.04391\ V}\right) \times (V + 37.78)}{1 + e^{0.311\ (V+79.23)}} \tag{E13}$$

$$\beta_h = 3.56\ e^{0.079\, V} + 3.1 \times 10^{5}\ e^{0.35\, V} \tag{E14}$$

$$\beta_j = 0.1212 \frac{e^{-0.01052\ V}}{1 + e^{-0.1378\ (V + 40.14)}} \tag{E15}$$

Time-dependent delayed rectifier K^+ current (I_K)

$$I_K = \overline{G}_K\ X_1\ X^2 \left(V - E_K\right) \tag{E16}$$

$$E_K = \frac{RT}{F} \ln\left(\frac{[K^+]_o + P_{Na,K}\ [Na^+]_o}{[K^+]_i + P_{Na,K}\ [Na^+]_i}\right) \tag{E17}$$

$$\overline{G}_K = 0.282 \sqrt{\frac{[K^+]_o}{5.4}} \tag{E18}$$

$$X_1 = \left(1 + e^{(V-40)/40}\right)^{-1} \tag{E19}$$

$$\frac{dX}{dt} = \alpha_\chi\ \left(1 - X\right) - \beta_\chi\ X \tag{E20}$$

$$\alpha_\chi = 7.19\ 10^{-5}\ \frac{V + 30}{1 - e^{-0.148(V+30)}} \tag{E21}$$

$$\beta_\chi = 1.31\ 10^{-4}\ \frac{V + 30}{-1 + e^{0.0687(V+30)}} \tag{E22}$$

Time-independent K^+ current (I_{K1})

$$I_{K_1} = \overline{G}_{K_1}\ K_{1\infty}\left(V - E_{K_1}\right) \tag{E23}$$

$$E_{K_1} = \frac{RT}{F} \ln\left(\frac{[K^+]_o}{[K^+]_i}\right) \tag{E24}$$

$$\overline{G}_{K_1} = 0.75 \sqrt{\frac{[K^+]_o}{5.4}} \tag{E25}$$

$$K_{1\infty} = \frac{\alpha_{K_1}}{\alpha_{K_1} + \beta_{K_1}} \tag{E26}$$

$$\alpha_{K_1} = \frac{1.02}{1 + e^{0.2385\left(V - E_{K_1} - 59.215\right)}} \tag{E27}$$

$$\beta_{K_1} = \frac{0.4912\, e^{0.08032\left(V - E_{K_1} + 5.476\right)} + e^{0.06175\left(V - E_{K_1} - 594.31\right)}}{1 + e^{-0.5143\left(V - E_{K_1} + 4.753\right)}} \tag{E28}$$

Plateau K^+ current (I_{Kp})

$$I_{K_P} = \overline{G}_{K_P}\; K_P \left(V - E_{K_P}\right) \tag{E29}$$

$$E_{K_P} = E_{K_1} \tag{E30}$$

$$K_p = \left(1 + e^{(7.488 - V)/5.98}\right)^{-1} \tag{E31}$$

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

$$I_{NaCa} = k_{NaCa}\; \frac{1}{K_{m,Na}^3 + [Na^+]_o^3}\; \frac{1}{K_{m,Ca} + [Ca^{2+}]_o} \left(1 + k_{sat}\, e^{(\eta-1)\frac{VF}{RT}}\right)^{-1} \left\{ e^{\eta\frac{VF}{RT}}\, [Na^+]_i^3\, [Ca^{2+}]_o - e^{(\eta-1)\frac{VF}{RT}}\, [Na^+]_o^3\, [Ca^{2+}]_i \right\} \tag{E32}$$

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

$$I_{NaK} = \bar{I}_{NaK}\; f_{NaK}\; f_{NaK}^{ATP} \left(1 + \left(\frac{K_{m,Na_i}}{[Na^+]_i}\right)^{1.5}\right)^{-1} \frac{[K^+]_o}{[K^+]_o + K_{m,K_o}} \tag{E33}$$

$$f_{NaK} = \left(1 + 0.1245\, e^{-0.1\frac{VF}{RT}} + 0.0365\, e^{-\frac{VF}{RT}} \left(\frac{e^{[Na^+]_o/67.3} - 1}{7}\right)\right)^{-1} \tag{E34}$$

$$f_{NaK}^{ATP} = \left(1 + \frac{K_{NaK}^{1,\,ATP}}{[ATP]_i} \left(1 + \frac{[ADP]_i}{K_{NaK}^{i,\,ADP}}\right)\right)^{-1} \tag{E35}$$

Nonspecific Ca^{2+} activated current ($I_{ns(Ca)}$)

$$I_{ns(Ca)} = I_{ns(Na)} + I_{ns(K)} \tag{E36}$$

$$I_{ns(Na)} = \bar{I}_{ns(Na)} \left(1 + \left[\frac{K_{m,ns(Ca)}}{[Ca^{2+}]_i}\right]^3\right)^{-1} \tag{E37}$$

$$\bar{I}_{ns(Na)} = P_{ns(Na)}\; \frac{VF^2}{RT}\; \frac{0.75\left([Na^+]_i\, e^{VF/RT} - [Na^+]_o\right)}{e^{VF/RT} - 1} \tag{E38}$$

$$I_{ns(K)} = \bar{I}_{ns(K)} \left(1 + \left[\frac{K_{m,ns(Ca)}}{[Ca^{2+}]_i}\right]^3\right)^{-1} \tag{E39}$$

$$\bar{I}_{ns(K)} = P_{ns(K)} \frac{VF^2}{RT} \frac{0.75\left([K^+]_i\ e^{VF/RT} - [K^+]_o\right)}{e^{VF/RT} - 1} \tag{E40}$$

Background Ca^{2+} current ($I_{Ca,b}$)

$$I_{Ca,b} = \bar{G}_{Ca,b}\left(V - E_{Ca,N}\right) \tag{E41}$$

$$E_{Ca,N} = \frac{RT}{2F} \ln\left(\frac{[Ca^{2+}]_o}{[Ca^{2+}]_i}\right) \tag{E42}$$

Background Na^+ current ($I_{Na,b}$)

$$I_{Na.b} = \bar{G}_{Na,b}\left(V - E_{Na,N}\right) \tag{E43}$$

$$E_{Na,N} = E_{Na} \tag{E44}$$

Sarcolemmal Ca^{2+} pump current (I_{pCa})

$$I_{pCa} = I_{pCa\_max}\ F_{pCa}^{ATP} \frac{[Ca^{+2}]_i}{K_m^{pCa} + [Ca^{+2}]_i} \tag{E45}$$

$$F_{pCa}^{ATP} = \left(1 + \frac{K_{m1\_pCa}^{ATP}}{[ATP]_i}\left(1 + \frac{[ADP]_i}{K_{i\_pCa}^{ADP}}\right)\right)^{-1} + \left(1 + \frac{K_{m2\_pCa}^{ATP}}{[ATP]_i}\right)^{-1} \tag{E46}$$

SERCA pump (J_{up})

$$J_{up} = \frac{V_{max\,f}\ f_b - V_{max\,r}\ r_b}{1 + f_b + r_b}\ f_{ATP}^{SERCA} \tag{E47}$$

$$f_b = \left(\frac{[Ca^{2+}]_i}{K_{fb}}\right)^{Nfb} \tag{E48}$$

$$r_b = \left(\frac{[Ca^{2+}]_{NSR}}{K_{rb}}\right)^{Nrb} \tag{E49}$$

$$\mathrm{f}_{\mathrm{ATP}}^{\mathrm{SERCA}} = \left(\frac{\mathrm{K}_{\mathrm{m,up}}^{\mathrm{ATP}}}{[\mathrm{ATP}]_{\mathrm{i}}} . \left(1 + \frac{[\mathrm{ADP}]_{\mathrm{i}}}{\mathrm{K}_{\mathrm{i,up}}} \right) + \left[1 + \frac{[\mathrm{ADP}]_{\mathrm{i}}}{\mathrm{K}_{\mathrm{i,up}}^{'}} \right] \right)^{-1} \tag{E50}$$

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

$$\alpha = 0.4\ \mathrm{e}^{(\mathrm{V}+2)/10} \tag{E51}$$

$$\beta = 0.05\ \mathrm{e}^{-(\mathrm{V}+2)/13} \tag{E52}$$

$$\alpha' = \mathrm{a}\ \alpha \tag{E53}$$

$$\beta' = \frac{\beta}{\mathrm{b}} \tag{E54}$$

$$\gamma = 0.1875\ [\mathrm{Ca}^{2+}]_{\mathrm{ss}} \tag{E55}$$

$$\frac{\mathrm{dC_o}}{\mathrm{dt}} = \beta\ \mathrm{C}_1 + \omega\ \mathrm{C}_{\mathrm{CaO}} - (4\alpha + \gamma)\mathrm{Co} \tag{E56}$$

$$\frac{\mathrm{dC_1}}{\mathrm{dt}} = 4\alpha\mathrm{C_o} + 2\beta\ \mathrm{C}_2 + \frac{\omega}{\mathrm{b}}\ \mathrm{C}_{\mathrm{Ca1}} - (\beta + 3\alpha + \mathrm{a}\gamma)\mathrm{C}_1 \tag{E57}$$

$$\frac{\mathrm{dC_2}}{\mathrm{dt}} = 3\alpha\mathrm{C}_1 + 3\beta\ \mathrm{C}_3 + \frac{\omega}{\mathrm{b}^2}\ \mathrm{C}_{\mathrm{Ca2}} - \left(2\beta + 2\alpha + \mathrm{a}^2\gamma\right)\mathrm{C}_2 \tag{E58}$$

$$\frac{\mathrm{dC_3}}{\mathrm{dt}} = 2\alpha\mathrm{C}_2 + 4\beta\ \mathrm{C}_4 + \frac{\omega}{\mathrm{b}^3}\ \mathrm{C}_{\mathrm{Ca3}} - \left(3\beta + \alpha + \mathrm{a}^3\gamma\right)\mathrm{C}_3 \tag{E59}$$

$$\frac{\mathrm{dC_4}}{\mathrm{dt}} = \alpha\mathrm{C}_3 + \mathrm{g\ O} + \frac{\omega}{\mathrm{b}^4}\ \mathrm{C}_{\mathrm{Ca4}} - \left(4\beta + \mathrm{f} + \mathrm{a}^4\gamma\right)\mathrm{C}_4 \tag{E60}$$

$$\frac{\mathrm{dO}}{\mathrm{dt}} = \mathrm{f\ C}_4 - \mathrm{g\ O} \tag{E61}$$

$$\frac{\mathrm{dC_{Ca0}}}{\mathrm{dt}} = \beta'\mathrm{C}_{\mathrm{Ca1}} + \gamma\ \mathrm{C}_0 - (\ 4\alpha' + \omega)\quad \mathrm{C}_{\mathrm{Ca0}} \tag{E62}$$

$$\frac{\mathrm{dC_{Ca1}}}{\mathrm{dt}} = 4\alpha'\mathrm{C}_{\mathrm{CaO}} + 2\beta'\mathrm{C}_{\mathrm{Ca2}} + \mathrm{a}\gamma\ \mathrm{C}_1 - \left(\beta' + 3\alpha' + \frac{\omega}{\mathrm{b}}\right)\mathrm{C}_{\mathrm{Ca1}} \tag{E63}$$

$$\frac{\mathrm{dC_{Ca2}}}{\mathrm{dt}} = 3\alpha'\mathrm{C}_{\mathrm{Ca1}} + 3\beta'\mathrm{C}_{\mathrm{Ca3}} + \mathrm{a}^2\gamma\ \mathrm{C2} - \left(2\beta' + 2\alpha' + \frac{\omega}{\mathrm{b}^2}\right)\mathrm{C}_{\mathrm{Ca2}} \tag{E64}$$

$$\frac{\mathrm{dC_{Ca3}}}{\mathrm{dt}} = 2\alpha'\mathrm{C}_{\mathrm{Ca2}} + 4\beta'\mathrm{C}_{\mathrm{Ca4}} + \mathrm{a}^3\gamma\ \mathrm{C}_3 - \left(3\beta' + \alpha' + \frac{\omega}{\mathrm{b}^3}\right)\mathrm{C}_{\mathrm{Ca3}} \tag{E65}$$

$$\frac{dC_{Ca4}}{dt} = \alpha' C_{Ca3} + g' O_{Ca} + a^4 \gamma\, C_4 - \left(4\beta' + f' + \frac{\omega}{b^4}\right) C_{Ca4} \tag{E66}$$

$$\frac{dO_{Ca}}{dt} = f'\, C_{Ca4} - g'\, O_{Ca} \tag{E67}$$

$$I_{Ca_{max}} = 4\, \bar{P}_{Ca} \frac{VF^2}{RT} \frac{0.001\, e^{2VF/RT} - 0.341\, [Ca^{2+}]_o}{e^{2V/RT} - 1} \tag{E68}$$

$$I_{Ca} = 6\, I_{Ca_{max}}\, y\, [O] \tag{E69}$$

$$I_{Ca,K} = P_K^{'}\, y\left[O + O_{Ca}\right] \frac{VF^2}{RT} \frac{[K^+]_i\, e^{VF/RT} - [K^+]_o}{e^{VF/RT} - 1} \tag{E70}$$

$$P_K^{'} = \frac{\bar{P}_K}{1 + \dfrac{I_{Ca_{max}}}{I_{Ca_{half}}}} \tag{E71}$$

$$\frac{dy}{dt} = \frac{y_\infty - y}{\tau_y} \tag{E72}$$

$$y_\infty = \frac{1}{1 + e^{(V+55)/7.5}} + \frac{0.5}{1 + e^{(-V+21)/6}} \tag{E73}$$

$$\tau_y = 20 + \frac{600}{1 + e^{(V+30)/9.5}} \tag{E74}$$

Sarcolemmal membrane potential

$$\frac{dV}{dt} = -\frac{1}{C_m}\left(\begin{aligned} I_{Na} + I_{Ca} + I_{Ca,K} + I_K + I_{K_1} + I_{Kp} + I_{NaCa} \\ + I_{NaK} + I_{ins(Ca)} + I_{pCa} + I_{Ca,b} + I_{Na,b} + I_{K,ATP} \end{aligned}\right) \tag{E80}$$

S1.2. Ca^{2+} handling system

Ca^{2+} Release channel current (J_{rel})

$$\frac{dP_{C1}}{dt} = -k_a^+\, [Ca^{2+}]_{ss}^n\, P_{C1} + k_a^-\, P_{O1} \tag{E75}$$

$$\begin{aligned} \frac{dP_{O1}}{dt} = {} & k_a^+\, [Ca^{2+}]_{ss}^n\, P_{C1} - k_a^-\, P_{O1} - k_b^+\, [Ca^{2+}]_{ss}^m\, P_{O1} \\ & + k_b^-\, P_{O2} - k_c^+\, P_{O1} + k_c^-\, P_{C2} \end{aligned} \tag{E76}$$

$$\frac{dP_{O2}}{dt} = k_b^+ \, [Ca^{2+}]_{ss}^m \, P_{O1} - k_b^- \, P_{O2}$$ E77

$$\frac{dP_{C2}}{dt} = k_c^+ \, P_{O1} - k_c^- \, P_{C2}$$ E78

$$J_{rel} = v_1 \left(P_{O_1} + P_{O_2}\right) \left([Ca^{2+}]_{JSR} - [Ca^{2+}]_{SS}\right)$$ E79

Ca^{2+} buffering and diffusive transport between compartments

$$J_{trpn} = \frac{d[HTRPNCa]}{dt} + \frac{d[LTRPNCa]}{dt}$$ E81

$$J_{tr} = \frac{[Ca^{2+}]_{NSR} - [Ca^{2+}]_{JSR}}{\tau_{tr}}$$ E82

$$J_{xfer} = \frac{[Ca^{2+}]_{SS} - [Ca^{2+}]_{i}}{\tau_{xfer}}$$ E83

$$\beta_i = \left(1 + \frac{K_m^{CMDN}[CMDN]_{tot}}{\left(K_m^{CMDN} + [Ca^{2+}]_i\right)^2}\right)^{-1}$$ E84

$$\beta_{SS} = \left(1 + \frac{K_m^{CMDN}[CMDN]_{tot}}{\left(K_m^{CMDN} + [Ca^{2+}]_{SS}\right)^2}\right)^{-1}$$ E85

$$\beta_{JSR} = \left(1 + \frac{K_m^{CSQN}[CSQN]_{tot}}{\left(K_m^{CSQN} + [Ca^{2+}]_{JSR}\right)^2}\right)^{-1}$$ E86

$$\frac{d[HTRPNCa]}{dt} = k_{htrpn}^+ \, [Ca^{2+}]_i \left([HTRPN]_{tot} - [HTRPNCa]\right) - k_{htrpn}^- [HTRPNCa]$$ E87

$$\frac{d[LTRPNCa]}{dt} = k_{ltrpn}^+ \, [Ca^{2+}]_i \left([LTRPN]_{tot} - [LTRPNCa]\right) - k_{ltrpn}^- \left(1 - \frac{2}{3} \, Force_{Norm}\right) [LTRPNCa]$$ E88

S1.3. Ionic concentrations balance equations

$$\frac{d[\mathrm{Ca}^{2+}]_{\mathrm{i}}}{dt} = \beta_{\mathrm{i}}\left[\begin{array}{r} J_{\mathrm{xfer}} - J_{\mathrm{up}} - J_{\mathrm{trpn}} - \left(I_{\mathrm{Ca,b}} - 2\, I_{\mathrm{NaCa}} + I_{\mathrm{pCa}}\right)\dfrac{A_{\mathrm{cap}}}{2V_{\mathrm{myo}}F} \\ + \left(V_{\mathrm{NaCa}} - V_{\mathrm{uni}}\right)\dfrac{V_{\mathrm{mito}}}{V_{\mathrm{myo}}} \end{array}\right] \qquad \text{E89}$$

$$\frac{d[\mathrm{Ca}^{2+}]_{\mathrm{ss}}}{dt} = \beta_{\mathrm{ss}}\left[J_{\mathrm{rel}}\frac{V_{\mathrm{JSR}}}{V_{\mathrm{ss}}} - J_{\mathrm{xfer}}\frac{V_{\mathrm{myo}}}{V_{\mathrm{ss}}} - \left(I_{\mathrm{Ca}}\right)\frac{A_{\mathrm{cap}}}{2V_{\mathrm{ss}}F}\right] \qquad \text{E90}$$

$$\frac{d[\mathrm{Ca}^{2+}]_{\mathrm{JSR}}}{dt} = \beta_{\mathrm{JSR}}\left[J_{\mathrm{tr}} - J_{\mathrm{rel}}\right] \qquad \text{E91}$$

$$\frac{d[\mathrm{Ca}^{2+}]_{\mathrm{NSR}}}{dt} = J_{\mathrm{up}}\frac{V_{\mathrm{myo}}}{V_{\mathrm{NSR}}} - J_{\mathrm{tr}}\frac{V_{\mathrm{JSR}}}{V_{\mathrm{NSR}}} \qquad \text{E92}$$

$$\frac{d[\mathrm{Ca}^{2+}]_{\mathrm{m}}}{dt} = \delta\left(V_{\mathrm{uni}} - V_{\mathrm{NaCa}}\right) \qquad \text{E93}$$

$$\frac{d[\mathrm{Na}^{+}]_{\mathrm{i}}}{dt} = -\left(I_{\mathrm{Na}} + I_{\mathrm{Na,b}} + I_{\mathrm{ns,Na}} + 3\, I_{\mathrm{NaCa}} + 3\, I_{\mathrm{NaK}}\right)\frac{A_{\mathrm{cap}}}{V_{\mathrm{myo}}F} \qquad \text{E94}$$

$$\frac{d[\mathrm{K}^{+}]_{\mathrm{i}}}{dt} = -\left(I_{\mathrm{K}} + I_{\mathrm{K_1}} + I_{\mathrm{Kp}} + I_{\mathrm{ns,K}} + I_{\mathrm{Ca,K}} - 2\, I_{\mathrm{NaK}}\right)\frac{A_{\mathrm{cap}}}{V_{\mathrm{myo}}F} \qquad \text{E95}$$

S1.4. Force generation model (1)

$$\frac{d[P_o]}{dt} = -\left(k_{pn}^{trop} + f_{01}\right)[P_o] + k_{np}^{trop}\,[N_0] + g_{01}(SL)\,[P_1] \qquad \text{E96}$$

$$\frac{d[P_1]}{dt} = -\left(k_{pn}^{trop} + f_{12} + g_{01}(SL)\right)[P_1] + k_{np}^{trop}\,[N_1] + f_{01}\,[P_0] + g_{12}(SL)\,[P_2] \qquad \text{E97}$$

$$\frac{d[P_2]}{dt} = -\left(f_{23} + g_{12}(SL)\right)[P_2] + f_{12}\,[P_1] + g_{23}(SL)\,[P_3] \qquad \text{E98}$$

$$\frac{d[P_3]}{dt} = -\, g_{23}(SL)\,[P_3] + f_{23}\,[P_2] \qquad \text{E99}$$

$$\frac{d[N_1]}{dt} = k_{pn}^{trop}[P_1] + \left(k_{np}^{trop} + g_{01}^{'}(SL)\right)[N_1] \qquad \text{E100}$$

$$[N_0] = 1 - \left([N_1] + [P_0] + [P_1] + [P_2] + [P_3]\right) \tag{E101}$$

$$f_{01} = 3 \times f_{XB} \tag{E102}$$

$$f_{12} = 10 \times f_{XB} \tag{E103}$$

$$f_{23} = 7 \times f_{XB} \tag{E104}$$

$$g_{01} = 1 \times g_{XB}^{min} \tag{E105}$$

$$g_{12} = 2 \times g_{XB}^{min} \tag{E106}$$

$$g_{23} = 3 \times g_{XB}^{min} \tag{E107}$$

$$g_{01}(SL) = 1 \times \phi \times g_{XB}^{min} \tag{E108}$$

$$g_{12}(SL) = 2 \times \phi \times g_{XB}^{min} \tag{E109}$$

$$g_{23}(SL) = 3 \times \phi \times g_{XB}^{min} \tag{E110}$$

$$\phi = 1 + \frac{2.3 - SL}{\left(2.3 - 1.7\right)^{1.6}} \tag{E111}$$

$$k_{np}^{trop} = k_{pn}^{trop} \left[\frac{[LTRPNCa]}{K_{1/2}^{trop} \ [LTRPN]_{tot}} \right]^{N^{trop}} \tag{E112}$$

$$K_{1/2}^{trop} = \left(1 + \frac{K_{Ca}^{trop}}{1.7\ 10^{-3} - 0.8\ 10^{-3} \ \dfrac{\left(SL - 1.7\right)}{0.6}} \right)^{-1} \tag{E113}$$

$$N^{trop} = 3.5 \times SL - 2.0 \tag{E114}$$

$$K_{Ca}^{trop} = \frac{k_{ltrpn}^{-}}{k_{ltrpn}^{+}} \tag{E115}$$

$$\sum PATHS = g_{01}\ g_{12}\ g_{23} + f_{01}\ g_{12}\ g_{23} + f_{01}\ f_{12}\ g_{23} + f_{01}\ f_{12}\ f_{23} \tag{E116}$$

$$P1_{max} = \frac{f_{01}\ g_{12}\ g_{23}}{\sum PATHS} \tag{E117}$$

$$P2_{max} = \frac{f_{01}\ f_{12}\ g_{23}}{\sum PATHS} \tag{E118}$$

$$P3_{max} = \frac{f_{01}\ f_{12}\ f_{23}}{\sum PATHS} \tag{E119}$$

$$Force = \zeta \frac{P_1 + N_1 + 2\ P_2 + 3\ P_3}{P1_{max} + 2\ P2_{max} + 3\ P3_{max}} \tag{E120}$$

$$\mathrm{Force}_{\mathrm{Norm}} = \frac{P_1 + N_1 + P_2 + P_3}{P1_{\mathrm{max}} + P2_{\mathrm{max}} + P3_{\mathrm{max}}} \tag{E121}$$

$$V_{\mathrm{AM}} = V_{\mathrm{AM}}^{\mathrm{max}} \left(\frac{f_{01}\ [P_0] + f_{12}\ [P_1] + f_{23}\ [P_2]}{f_{01} + f_{12} + f_{23}} \right) \times \left(1 + \frac{K_{\mathrm{M,AM}}^{\mathrm{ATP}}}{[\mathrm{ATP}]_{\mathrm{i}}} \left[1 + \frac{[\mathrm{ADP}]_{\mathrm{i}}}{K_{\mathrm{i,AM}}} \right] \right)^{-1} \tag{E122}$$

S1.5. Mitochondrial membrane potential ($\Delta\Psi_{\mathrm{m}}$)

$$\frac{d\ \Delta\Psi_{\mathrm{m}}}{dt} = \frac{V_{\mathrm{He}} + V_{\mathrm{He(F)}} - V_{\mathrm{Hu}} - V_{\mathrm{ANT}} - V_{\mathrm{HLeak}} - V_{\mathrm{NaCa}} - 2\ V_{\mathrm{uni}} - V_{\mathrm{IMAC}}}{C_{\mathrm{mito}}} \tag{E123}$$

S1.6. Energy metabolism system

Mitochondrial metabolites balance equations

$$\frac{d\ [\mathrm{ATP}]_{\mathrm{i}}}{dt} = V_{\mathrm{ANT}} \frac{V_{\mathrm{mito}}}{V_{\mathrm{myo}}} - V_{\mathrm{CK}}^{\mathrm{mito}} - V_{\mathrm{AM}} - \frac{1}{2} J_{\mathrm{up}} - \left(I_{\mathrm{pCa}} + I_{\mathrm{NaK}} \right) \frac{A_{\mathrm{cap}}}{V_{\mathrm{myo}} F} \tag{E124}$$

$$\frac{d\ [\mathrm{ATP}]_{\mathrm{ic}}}{dt} = -V_{\mathrm{CK}}^{\mathrm{cyto}} - V_{\mathrm{ATPase}}^{\mathrm{cyto}} \tag{E125}$$

$$\frac{d\ [\mathrm{CrP}]_{\mathrm{i}}}{dt} = V_{\mathrm{CK}}^{\mathrm{mito}} - V_{\mathrm{tr}}^{\mathrm{CrP}} \tag{E126}$$

$$\frac{d\ [\mathrm{CrP}]_{\mathrm{ic}}}{dt} = V_{\mathrm{tr}}^{\mathrm{CrP}} + V_{\mathrm{CK}}^{\mathrm{cyto}} \tag{E127}$$

$$\frac{d\ [\mathrm{ADP}]_{\mathrm{m}}}{dt} = V_{\mathrm{ANT}} - V_{\mathrm{ATPase}} - V_{\mathrm{SL}} \tag{E128}$$

$$[\mathrm{ATP}]_{\mathrm{m}} = C_{\mathrm{A}} - [\mathrm{ADP}]_{\mathrm{m}} \tag{E129}$$

$$\frac{d[\mathrm{NADH}]}{dt} = -\ V_{\mathrm{O2}} + V_{\mathrm{IDH}} + V_{\mathrm{KGDH}} + V_{\mathrm{MDH}} \tag{E130}$$

$$\frac{d[\mathrm{ISOC}]}{dt} = V_{\mathrm{ACO}} - V_{\mathrm{IDH}} \tag{E131}$$

$$\frac{d[\alpha\mathrm{KG}]}{dt} = V_{\mathrm{IDH}} - V_{\mathrm{KGDH}} + V_{\mathrm{AAT}} \tag{E132}$$

$$\frac{d[\mathrm{SCoA}]}{dt} = V_{KGDH} - V_{SL}$$
E133

$$\frac{d[\mathrm{Suc}]}{dt} = V_{SL} - V_{SDH}$$
E134

$$\frac{d[\mathrm{FUM}]}{dt} = V_{SDH} - V_{FH}$$
E135

$$\frac{d[\mathrm{MAL}]}{dt} = V_{FH} - V_{MDH}$$
E136

$$\frac{d[\mathrm{OAA}]}{dt} = V_{MDH} - V_{CS} - V_{AAT}$$
E137

$$[\mathrm{CIT}] = C_{Kint} - \left(\begin{array}{l} [\mathrm{ISOC}] + [\alpha\mathrm{KG}] + [\mathrm{SCoA}] + [\mathrm{Suc}] \\ \qquad\qquad\qquad + [\mathrm{FUM}] + [\mathrm{MAL}] + [\mathrm{OAA}] \end{array} \right)$$
E138

Cytosolic metabolic reaction rates

$$V_{ANT} = V_{maxANT} \frac{0.75\left(1 - \dfrac{0.25\,[\mathrm{ATP}]_i \times 0.45\,[\mathrm{ADP}]_m}{0.17\,[\mathrm{ADP}]_i \times 0.025\,[\mathrm{ATP}]_m}\right)\left(e^{-\frac{F}{RT}\Delta\Psi_m}\right)}{\left(1 + \dfrac{0.25\,[\mathrm{ATP}]_i}{0.225\,[\mathrm{ADP}]_i}\, e\left(\dfrac{-h^{ANT}\ F\,\Delta\Psi_m}{RT}\right)\right)\left(1 + \dfrac{0.45\,[\mathrm{ADP}]_m}{0.025\,[\mathrm{ATP}]_m}\right)}$$
E139

$$V_{CK}^{cyto} = k_{CK}^{cyto}\left([\mathrm{ATP}]_{ic}\ [\mathrm{Cr}]_{ic} - \frac{[\mathrm{ADP}]_{ic}\ [\mathrm{CrP}]_{ic}}{K_{EQ}}\right)$$
E140

$$V_{CK}^{mito} = k_{CK}^{mito}\left([\mathrm{ATP}]_i\ [\mathrm{Cr}]_i - \frac{[\mathrm{ADP}]_i\ [\mathrm{CrP}]_i}{K_{EQ}}\right)$$
E141

$$V_{tr}^{CrP} = k_{tr}^{Cr}\left([\mathrm{CrP}]_i - [\mathrm{CrP}]_{ic}\right)$$
E142

Tricarboxylic acid cycle reaction rates

$$V_{CS} = k_{cat}^{CS}\ E_T^{CS}\left(1 + \frac{K_M^{AcCoA}}{[\mathrm{AcCoA}]} + \frac{K_M^{OAA}}{[\mathrm{OAA}]} + \frac{K_M^{AcCoA}}{[\mathrm{AcCoA}]}\ \frac{K_M^{OAA}}{[\mathrm{OAA}]}\right)^{-1}$$
E143

$$V_{ACO} = k_f^{ACO}\left([\mathrm{CIT}] - \frac{[\mathrm{ISOC}]}{K_E^{ACO}}\right)$$
E144

$$f_{a}^{IDH} = \left[\left(1 + \frac{[ADP]_{m}}{K_{ADP}^{a}} \right) \left(1 + \frac{[Ca^{2+}]_{m}}{K_{Ca}^{a}} \right) \right]^{-1} \tag{E145}$$

$$f_{i}^{IDH} = \left(1 + \frac{[NADH]}{K_{i,NADH}} \right) \tag{E146}$$

$$V_{IDH} = k_{cat}^{IDH}\ E_{T}^{IDH} \left[\begin{array}{l} \left(1 + \dfrac{[H^{+}]}{k_{h,1}} + \dfrac{k_{h,2}}{[H^{+}]} \right) + f_{i}^{IDH} \left(\dfrac{K_{M}^{NAD}}{[NAD]} \right) \\ + f_{a}^{IDH} \left(\dfrac{K_{M}^{ISOC}}{[ISOC]} \right)^{ni} + f_{a}^{IDH}\ f_{i}^{IDH} \left(\dfrac{K_{M}^{ISOC}}{[ISOC]} \right)^{ni} \left(\dfrac{K_{M}^{NAD}}{[NAD]} \right) \end{array} \right]^{-1} \tag{E147}$$

$$f_{a}^{KGDH} = \left[\left(1 + \frac{[Mg^{2+}]}{K_{D}^{Mg^{2+}}} \right) \left(1 + \frac{[Ca^{2+}]_{m}}{K_{D}^{Ca^{2+}}} \right) \right]^{-1} \tag{E148}$$

$$V_{KGDH} = \frac{k_{cat}^{KGDH}\ E_{T}^{KGDH}}{1 + f_{a}^{KGDH} \dfrac{K_{M}^{\alpha KG}}{[\alpha KG]} + f_{a}^{KGDH} \left(\dfrac{K_{M}^{NAD}}{[NAD]} \right)^{n_{aKG}}} \tag{E149}$$

$$V_{SL} = k_{f}^{SL} \left([SCoA][ADP]_{m} - \frac{[Suc][ATP]_{m}[CoA]}{K_{E}^{SL}} \right) \tag{E150}$$

$$V_{SDH} = \frac{k_{cat}^{SDH}\ E_{T}^{SDH}}{1 + \left(\dfrac{K_{M}^{Suc}}{[Suc]} \right) \left(1 + \dfrac{[OAA]}{K_{i,sdh}^{OAA}} \right) \left(1 + \dfrac{[FUM]}{K_{i}^{FUM}} \right)} \tag{E151}$$

$$V_{FH} = k_{f}^{FH} \left([FUM] - \frac{[MAL]}{K_{E}^{FH}} \right) \tag{E152}$$

$$f_{h,a} = \left(1 + \frac{[H^{+}]}{k_{h1}} + \frac{[H^{+}]^{2}}{k_{h1}\ k_{h2}} \right)^{-1} + k_{offset} \tag{E153}$$

$$f_{h,i} = \left(1 + \frac{k_{h3}}{[H^{+}]} + \frac{k_{h3}\ k_{h4}}{[H^{+}]^{2}} \right)^{-2} \tag{E154}$$

$$V_{MDH} = \frac{k_{cat}^{MDH}\ E_{T}^{MDH}\ f_{h,a}\ f_{h,i}}{1 + \dfrac{K_{M}^{MAL}}{[MAL]} \left(1 + \dfrac{[OAA]}{K_{i}^{OAA}} \right) + \dfrac{K_{M}^{NAD}}{[NAD]} + \dfrac{K_{M}^{MAL}}{[MAL]} \left(1 + \dfrac{[OAA]}{K_{i}^{OAA}} \right) \dfrac{K_{M}^{NAD}}{[NAD]}} \tag{E155}$$

$$V_{AAT} = k_f^{AAT}[OAA][GLU]\,\frac{k_{ASP}\,K_E^{AAT}}{\left(k_{ASP}\,K_E^{AAT} + [\alpha KG]\,k_f^{AAT}\right)} \qquad \text{E156}$$

Oxidative phosphorylation reaction rates

$$V_{O_2} = 0.5\,\rho^{res}\,\frac{\left(r_a + r_{c1}\,e^{\left(\frac{6F\,\Delta\Psi_B}{R\,T}\right)}\right)e^{\left(\frac{A_{res}\,F}{R\,T}\right)} - r_a\,e^{\left(\frac{g\,6\,F\,\Delta\mu_H}{R\,T}\right)} + r_{c2}\,e^{\left(\frac{A_{res}\,F}{R\,T}\right)}\,e^{\left(\frac{g\,6\,F\,\Delta\mu_H}{R\,T}\right)}}{\left(1 + r_1\,e^{\left(\frac{F\,A_{res}}{R\,T}\right)}\right)e^{\left(\frac{6\,F\Delta\Psi_B}{R\,T}\right)} + \left(r_2 + r_3\,e^{\left(\frac{F\,A_{res}}{R\,T}\right)}\right)e^{\left(\frac{g\,6\,F\,\Delta\mu_H}{R\,T}\right)}} \qquad \text{E157}$$

$$V_{He} = 6\,\rho^{res}\,\frac{\left(r_a\,e^{\left(\frac{A_{res}\,F}{R\,T}\right)} - \left(r_a + r_b\right)e^{\left(\frac{g\,6F\,\Delta\mu_H}{R\,T}\right)}\right)}{\left(1 + r_1\,e^{\left(\frac{F\,A_{res}}{R\,T}\right)}\right)e^{\left(\frac{6\,F\Delta\Psi_B}{R\,T}\right)} + \left(r_2 + r_3\,e^{\left(\frac{F\,A_{res}}{R\,T}\right)}\right)e^{\left(\frac{g\,6\,F\,\Delta\mu_H}{R\,T}\right)}} \qquad \text{E158}$$

$$A_{res} = \frac{R\,T}{F}\ln\left(K_{res}\sqrt{\frac{[NADH]}{[NAD^+]}}\right) \qquad \text{E159}$$

$$[NAD^+] = C_{PN} - [\,NADH] \qquad \text{E160}$$

$$V_{He(F)} = 4\,\rho^{res(F)}\,\frac{\left(r_a\,e^{\left(\frac{A_{res(F)}\,F}{R\,T}\right)} - \left(r_a + r_b\right)e^{\left(\frac{g\,6F\,\Delta\mu_H}{R\,T}\right)}\right)}{\left(1 + r_1\,e^{\left(\frac{F\,A_{res(F)}}{R\,T}\right)}\right)e^{\left(\frac{6\,F\Delta\Psi_B}{R\,T}\right)} + \left(r_2 + r_3\,e^{\left(\frac{F\,A_{res(F)}}{R\,T}\right)}\right)e^{\left(\frac{g\,6\,F\,\Delta\mu_H}{R\,T}\right)}} \qquad \text{E161}$$

$$A_{res(F)} = \frac{R\,T}{F}\ln\left(K_{res(F)}\sqrt{\frac{[FADH_2]}{[FAD]}}\right) \qquad \text{E162}$$

$$V_{ATPase} = -\rho^{F1}\,\frac{\left(10^2\,p_a + p_{c1}\,e^{\left(\frac{3\,F\Delta\Psi_B}{R\,T}\right)}\right)e^{\left(\frac{A_{F1}\,F}{R\,T}\right)} - \left(p_a\,e^{\left(\frac{3\,F\Delta\mu_H}{R\,T}\right)} + p_{c2}\,e^{\left(\frac{A_{F1}\,F}{R\,T}\right)}\,e^{\left(\frac{3\,F\Delta\mu_H}{R\,T}\right)}\right)}{\left(1 + p_1\,e^{\left(\frac{F\,A_{F1}}{R\,T}\right)}\right)e^{\left(\frac{3\,F\Delta\Psi_B}{R\,T}\right)} + \left(p_2 + p_3\,e^{\left(\frac{F\,A_{F1}}{R\,T}\right)}\right)e^{\left(\frac{3\,F\Delta\mu_H}{R\,T}\right)}} \qquad \text{E163}$$

$$V_{Hu} = -3\,\rho^{F1}\,\frac{10^2\,p_a\left(1+e^{\left(\frac{F\,A_{F1}}{R\,T}\right)}\right) - \left(p_a+p_b\right)e^{\left(\frac{3\,F\,\Delta\mu_H}{R\,T}\right)}}{\left(1+p_1\,e^{\left(\frac{F\,A_{F1}}{R\,T}\right)}\right)e^{\left(\frac{3\,F\Delta\Psi_B}{R\,T}\right)} + \left(p_2+p_3\,e^{\left(\frac{F\,A_{F1}}{R\,T}\right)}\right)e^{\left(\frac{3\,F\,\Delta\mu_H}{R\,T}\right)}} \tag{E164}$$

$$A_{F1} = \frac{R\,T}{F}\ln\left(K_{F1}\,\frac{[\mathrm{ATP}]_m}{[ADP]_m\,\mathrm{Pi}}\right) \tag{E165}$$

$$V_{Hleak} = g_H\,\Delta\mu_H \tag{E166}$$

$$\Delta\mu_H = -2.303\frac{R\,T}{F}\,\Delta\mathrm{pH} + \Delta\Psi_m \tag{E167}$$

Mitochondrial Ca^{2+} handling rates

$$V_{uni} = V_{max}^{uni}\,\frac{\frac{[\mathrm{Ca}^{2+}]_i}{K_{trans}}\left(1+\frac{[\mathrm{Ca}^{2+}]_i}{K_{trans}}\right)^3\ \frac{2\,F\left(\Delta\Psi_m - \Delta\Psi^o\right)}{R\,T}}{\left(\left(1+\frac{[\mathrm{Ca}^{2+}]_i}{K_{trans}}\right)^4 + \frac{L}{\left(1+\frac{[\mathrm{Ca}^{2+}]_i}{K_{act}}\right)^{n_a}}\right)\left(1 - e^{\left\{\frac{-2\,F\left(\Delta\Psi_m - \Delta\Psi^o\right)}{R\,T}\right\}}\right)} \tag{E168}$$

$$V_{NaCa} = V_{max}^{NaCa}\,\frac{e^{\left(\frac{b\,F\left(\Delta\Psi_m - \Delta\Psi^\circ\right)}{R\,T}\right)}\,e^{\left(\ln\frac{[\mathrm{Ca}^{2+}]_m}{[\mathrm{Ca}^{2+}]_i}\right)}}{\left(1+\frac{K_{Na}}{[\mathrm{Na}^+]_i}\right)^n\left(1+\frac{K_{Ca}}{[\mathrm{Ca}^{2+}]_m}\right)} \tag{E169}$$

$$\frac{d[Ca^{2+}]_m}{dt} = \delta(V_{uni} - V_{NaCa}) \tag{E170}$$

ROS-induced-ROS-release rates

$$V_{SOD} = \frac{2\,\mathrm{k}_{\mathrm{SOD}}^{1}\,\mathrm{k}_{\mathrm{SOD}}^{5}\left(\mathrm{k}_{\mathrm{SOD}}^{1} + \mathrm{k}_{\mathrm{SOD}}^{3}\left(1 + \frac{[\mathrm{H_2O_2}]}{\mathrm{K_i^{H2O2}}}\right)\right)\mathrm{E}_{\mathrm{SOD}}^{T}\,[\mathrm{O_2}^{\cdot -}]}{\mathrm{k}_{\mathrm{SOD}}^{5}\left(2\,\mathrm{k}_{\mathrm{SOD}}^{1} + \mathrm{k}_{\mathrm{SOD}}^{3}\left(1 + \frac{[\mathrm{H_2O_2}]}{\mathrm{K_i^{H2O2}}}\right)\right) + [\mathrm{O_2}^{\cdot -}]\,\mathrm{k}_{\mathrm{SOD}}^{1}\,\mathrm{k}_{\mathrm{SOD}}^{3}\left(1 + \frac{[\mathrm{H_2O_2}]}{\mathrm{K_i^{H2O2}}}\right)} \tag{E171}$$

$$V_{CAT} = 2\ \ k_{CAT}^{1}\ E_{CAT}^{T}\,[\mathrm{H_2O_2}]\,e^{-fr\,[H_2O_2]} \tag{E172}$$

$$V_{GPX} = \frac{E_{GPX}^{\mathrm{T}}\,[\mathrm{H_2O_2}][\mathrm{GSH}]}{\Phi_1\,[\mathrm{GSH}] + \Phi_2\,[\mathrm{H_2O_2}]} \tag{E173}$$

$$V_{GR} = \frac{\mathrm{k}_{\mathrm{GR}}^{1}\ \mathrm{E}_{\mathrm{GR}}^{\mathrm{T}}}{1 + \frac{\mathrm{K_M^{GSSG}}}{[\mathrm{GSSG}]} + \frac{\mathrm{K_M^{NADPH}}}{[\mathrm{NADPH}]} + \frac{\mathrm{K_M^{GSSG}}}{[\mathrm{GSSG}]}\,\frac{\mathrm{K_M^{NADPH}}}{[\mathrm{NADPH}]}} \tag{E174}$$

$$V_{ROS}^{Tr} = \mathrm{j}\,.\,\frac{\mathrm{V_{IMAC}}}{\Delta\Psi_m}\left(\Delta\Psi_m\ \text{-}\ \tfrac{\mathrm{RT}}{\mathrm{F}}\log\left(\frac{[\mathrm{O_2}^{\cdot -}]_{\mathrm{m}}}{[\mathrm{O_2}^{\cdot -}]_{\mathrm{i}}}\right)\right) \tag{E175}$$

$$\mathrm{V_{IMAC}} = \left(\mathrm{a} + \frac{\mathrm{b}}{1 + \frac{\mathrm{K_{cc}}}{[\mathrm{O_2}^{\cdot -}]_{\mathrm{i}}}}\right)\left(\mathrm{G_L} + \frac{\mathrm{G_{max}}}{1 + \mathrm{e}^{\left(\kappa\left(\Delta\Psi_m^{b} - \Delta\Psi_m\right)\right)}}\right)\Delta\Psi_{\mathrm{m}} \tag{E176}$$

$$G_T = [GSH] + 2\times[GSSG] \tag{E177}$$

ROS-induced-ROS-release metabolites balance equations

$$\frac{d[O2^{\cdot -}]_m}{dt} = \mathrm{shunt}\ .\ \mathrm{V_{O_2}}\ \text{-}\ \mathrm{V_{ROS}^{Tr}} \tag{E178}$$

$$\frac{d[O2^{\cdot -}]_i}{dt} = \mathrm{V_{ROS}^{Tr}}\ \text{-}\ \mathrm{V_{SOD}} \tag{E179}$$

$$\frac{d[H_2O_2]}{dt} = \mathrm{V_{SOD}}\ \text{-}\ \mathrm{V_{CAT}}\ \text{-}\ \mathrm{V_{GPX}} \tag{E180}$$

$$\frac{d[GSH]}{dt} = \mathrm{V_{GR}}\ \text{-}\ \mathrm{V_{GPX}} \tag{E181}$$

S2. Model parameters

S2.1. General parameters

Symbol	Value	Units	Description	Eq.	Ref.
F	96.5	C mmol^{-1}	Faraday constant		
T	310	K	Absolute temperature		
R	8.314	J mol^{-1} K^{-1}	Universal gas constant		
$\mathrm{C_m}$	1.0	μF cm^{-2}	Membrane capacitance	E79	2
$\mathrm{A_{cap}}$	$1.534\ 10^{-4}$	cm^2	Capacitative cell surface area	E88	2
V_{myo}	25.84	pL	Cytosolic volume	E88	2
V_{mito}	15.89	pL	Mitochondrial volume	E92	11
V_{NSR}	1.4	pL	NSR volume	E91	3
V_{JSR}	0.16	pL	JSR volume	E89	3
V_{SS}	$0.495\ 10^{-3}$	pL	SS volume	E89	3
$[\mathrm{K}^+]_\mathrm{o}$	5.4	mM	Extracellular K^+ concentration	E17	2
$[\mathrm{Na}^+]_\mathrm{o}$	140.0	mM	Extracellular Na^+ concentration	E2	2
$[\mathrm{Ca}^{2+}]_\mathrm{o}$	2.0	mM	Extracellular Ca^{2+} concentration	E32	2

S2.2. Sarcolemmal membrane current parameters

Symbol	Value	Units	Description	Eq.	Ref.
$\overline{\mathrm{G}}_{\mathrm{Na}}$	12.8	mS $\mu\mathrm{F}^{-1}$	Maximal Na channel conductance	E1	2
$\overline{\mathrm{G}}_{\mathrm{K_P}}$	8.28×10^{-3}	mS $\mu\mathrm{F}^{-1}$	Maximal plateau K channel conductance	E29	2
$\mathrm{P_{Na,K}}$	0.01833		Na+ permeability of K+ channel	E17	2
$\mathrm{k_{NaCa}}$	9000	μA $\mu\mathrm{F}^{-1}$	Scaling factor of $\mathrm{Na}^+/\mathrm{Ca}^+$ exchange	E32	3
$\mathrm{k_{m,Na}}$	87.5	mM	Na half saturation constant NCX	E32	2
$\mathrm{k_{m,Ca}}$	1.38	mM	Na half saturation constant NCX	E32	2
$\mathrm{k_{sat}}$	0.1		$\mathrm{Na}^+/\mathrm{Ca}^{2+}$ exchange saturation factor at negative potentials	E32	2
η	0.35		Controls voltage dependence of NCX	E32	2

S2.3. Na$^+$/K$^+$ pump parameters

Symbol	Value	Units	Description	Eq.	Ref.
$\bar{I}_{NaK}$	3.147	μA μF^{-1}	Maximum Na$^+$/K$^+$ pump current	E33	12,13
$K_{m,Nai}$	10	mM	Na half saturation for Na$^+$/K$^+$ pump	E33	2
$K_{m,Ko}$	1.5	mM	K half saturation for Na$^+$/K$^+$ pump	E33	2
$K_{NaK}^{1,ATP}$	8.0 × 10^{-3}	mM	ATP half saturation constant for Na$^+$/K$^+$ pump	E35	5
$K_{NaK}^{i,ADP}$	0.1	mM	ADP inhibition constant for Na$^+$/K$^+$ pump	E35	5

S2.4. Non-specific channel current parameters

Symbol	Value	Units	Description	Eq.	Ref.
$P_{ns(Na)}$	1.75 × 10^{-7}	cm s^{-1}	Non specific channel current Na permeability	E38	7
$K_{m,ns(Ca)}$	1.2 × 10^{-3}	mM	Ca^{2+} half saturation constant for non specific current	E37	2
$P_{ns(K)}$	0	cm s^{-1}	Non specific channel current K permeability	E40	3

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S2.5. Background Ca^{2+} current parameters

Symbol	Value	Units	Description	Eq.	Ref.
$\bar{G}_{Ca,b}$	3.217 × 10^{-3}	mS μF^{-1}	Maximum background current Ca^{2+} conductance	E41	*
$\bar{G}_{Na,b}$	5.45 × 10^{-4}	mS μF^{-1}	Maximum background current Na+ conductance	E43	*

Note: *. Adjusted from (2, 3) based on physiological levels of Ca^{2+} and Na$^+$ in cardiomyocytes (3, 4).

S2.6. Sarcolemmal Ca^{2+} current parameters

Symbol	Value	Units	Description	Eq.	Ref.
I_{pCa_max}	0.575	μA μF^{-1}	Maximum sarcolemmal Ca^{2+} pump current	E45	3
K_m^{pCa}	5 × 10^{-4}	mM	Ca^{2+} half saturation constant for sarcolemmal Ca^{2+} pump	E45	2
$K_{m1\_pCa}^{ATP}$	0.012	mM	First ATP half saturation constant for sarcolemmal Ca^{2+} pump	E46	14

$K_{m2\_pCa}^{ATP}$	0.23	mM	Second ATP half saturation constant for sarcolemmal Ca^{2+} pump	E46	14
$K_{i\_pCa}^{ADP}$	1.0	mM	ADP inhibition constant for sarcolemmal Ca^{2+} pump	E46	8

S2.7. Sarcoplasmic reticulum Ca^{2+} ATPase parameters

Symbol	Value	Units	Description	Eq.	Ref.
$V_{max,f}$	2.989×10^{-4}	ms^{-1}	SERCA forward rate parameter	E47	2
$V_{max,r}$	3.179×10^{-4}	ms^{-1}	SERCA reverse rate parameter	E47	2
K_{fb}	2.4×10^{-4}	mM	Forward Ca^{2+} half saturation constant of SERCA	E48	3
K_{rb}	1.64269	mM	Reverse Ca^{2+} half saturation constant of SERCA	E49	3
N_{fb}	1.4		Forward cooperativity constant of SERCA	E48	3
N_{rb}	1.0		Reverse cooperativity constant of SERCA	E49	3
$K_{m,up}^{ATP}$	0.01	mM	ATP half saturation constant for SERCA	E50	5
$K_{i,up}$	0.14	mM	ADP first inhibition constant for SERCA	E50	5
$K_{i,up}^{'}$	5.1	mM	ADP second inhibition constant for SERCA	E50	5

S2.8. L-type Ca^{2+} current parameters

Symbol	Value	Units	Description	Eq.	Ref.
a	2.0		Mode transition parameter	E53	2
b	2.0		Mode transition parameter	E54	2
ω	0.01	ms^{-1}	Mode transition parameter	E56	2
f	0.3	ms^{-1}	Transition rate into open state	E61	2
g	2.0	ms^{-1}	Transition rate out of open state	E61	2
f'	0.0	ms^{-1}	Transition rate into open state, mode Ca	E67	2
g'	0.0	ms^{-1}	Transition rate out open state, mode Ca	E67	2
$\overline{P}_{Ca}$	1.24×10^{-3}	$cm\ s^{-1}$	L-type Ca^{2+} channel permeability to Ca^{2+}	E68	3
$\overline{P}_{K}$	1.11×10^{-11}	$cm\ s^{-1}$	L-type Ca^{2+} channel permeability to K^{+}	E71	3
$I_{Ca_{half}}$	-0.4583	$\mu A\ \mu F^{-1}$	ICa level that reduces $\overline{P}_{K}$ by half	E71	3

S2.9. Ca^{2+} release channel current parameters

Symbol	Value	Units	Description	Eq.	Ref.
v_1	3.6	ms^{-1}	RyR flux channel constant	E79	3
n	4		Cooperativity parameter	E75	2
m	3		Cooperativity parameter	E76	2
k_a^+	1.215×10^{10}	$mM^{-4}\ ms^{-1}$	RyR rate constant	E75	2
k_a^-	0.576	ms^{-1}	RyR rate constant	E75	15
k_b^+	4.05×10^{6}	$mM^{-3}\ ms^{-1}$	RyR rate constant	E76	2
k_b^-	1.93	ms^{-1}	RyR rate constant	E76	2
k_c^+	0.1	ms^{-1}	RyR rate constant	E76	15
k_c^-	8.0×10^{-4}	ms^{-1}	RyR rate constant	E76	2

S2.10. Ca^{2+} transport and buffering parameters

Symbol	Value	Units	Description	Eq.	Ref.
τ_{tr}	0.5747	ms	Time constant for transfer from subspace to myoplasm	E82	16
τ_{xfer}	9.09	ms	Time constant for transfer from NSR to JSR	E83	3
K_m^{CMDN}	2.38×10^{-3}	mM	Ca^{2+} half saturation constant for calmodulin	E84	3
K_m^{CSQN}	0.8	mM	Ca^{2+} half saturation constant for calsequestrin	E85	3
k_{htrpn}^+	100	$mM^{-1}\ ms^{-1}$	Ca^{2+} on-rate for troponin high affinity sites	E86	3
k_{htrpn}^-	$3.3\ 10^{-4}$	ms^{-1}	Ca^{2+} off-rate for troponin high affinity sites	E87	3
k_{ltrpn}^+	100	$mM^{-1}\ ms^{-1}$	Ca^{2+} on-rate for troponin low affinity sites	E88	3
k_{ltrpn}^-	$4\ 10^{-2}$	ms^{-1}	Ca^{2+} off-rate for troponin low affinity sites	E88	2
$[HTRPN]_{tot}$	0.14	mM	Total troponin high-affinity sites	E87	2
$[LTRPN]_{tot}$	0.07	mM	Total troponin low-affinity sites	E88	2
$[CMDN]_{tot}$	5.0×10^{-2}	mM	Total myoplasmic calmoduling concentration	E84	2
$[CSQN]_{tot}$	15	mM	Total NSR calsequestrin concentration	E85	3

S2.11. Force generation parameters

Symbol	Value	Units	Description	Eq.	Ref.
k_{pn}^{trop}	0.04	ms^{-1}	Transition rate from tropomyosin permissive to non-permissive	E96	3
SL	2.15	μm	Sarcomere length	E111	3
f_{XB}	0.05	ms^{-1}	Transition rate from weak to strong cross bridge	E102	16
g_{XB}^{min}	0.1	ms^{-1}	Minimum transition rate from strong to weak cross bridge	E105	16
ζ	0.1	$N\ mm^{-2}$	Conversion factor normalizing to physiological force	E120	3
V_{AM}^{max}	7.2×10^{-3}	$mM\ ms^{-1}$	Maximal rate of ATP hydrolysis by myofibrils (AM ATPase)	E122	6
$K_{M,AM}^{ATP}$	0.03	mM	ATP half saturation constant of AM ATPase	E122	6
$K_{i,AM}$	0.26	mM	ADP inhibition constant of AM ATPase	E122	6

S2.12. Cytoplasmic energy handling parameters

Symbol	Value	Units	Description	Eq.	Ref.
C_T	25	mM	Total concentration of creatine metabolites (both compartments)		17 ,18
k_{CK}^{cyto}	1.4×10^{-4}	ms^{-1}	Forward rate constant of cytoplasmic CK	E140	21
k_{CK}^{mito}	1.33×10^{-6}	ms^{-1}	Forward rate constant of mitochondrial CK	E141	21
k_{tr}^{Cr}	2.0×10^{-3}	ms^{-1}	Transfer rate constant of CrP	E142	21
K_{EQ}	0.0095		Equilibrium constant of CK	E140	17, 16
V_{ATPase}^{cyto}	$1.0\ 10^{-5}$	$mM\ ms^{-1}$	Constitutive cytosolic ATP consumption rate	E125	19

S2.13. Tricarboxylic acid cycle parameters

Symbol	Value	Units	Description	Eq.	Ref.
[AcCoA]	1.0	mM	Acetyl CoA concentration	E143	4
k_{cat}^{CS}	0.05	ms^{-1}	Catalytic constant of CS	E143	**
E_T^{CS}	0.4	mM	Concentration of CS	E143	4
K_M^{AcCoA}	1.26×10^{-2}	mM	Michaelis constant for AcCoA	E143	4

K_M^{OAA}	6.4×10^{-4}	mM	Michaelis constant for OAA	E143	4
C_{Kint}	1.0	mM	Sum of TCA cycle intermediates' concentration	E138	4
k_f^{ACO}	1.25×10^{-2}	ms^{-1}	Forward rate constant of ACO	E144	4
K_E^{ACO}	2.22		Equilibrium constant of ACO	E144	4
K_{ADP}^{a}	0.62	mM	Activation constant by ADP	E145	**
K_{Ca}^{a}	0.0005	mM	Activation constant for Ca^{2+}	E145	*
$K_{i,NADH}$	0.19	mM	Inhibition constant by NADH	E146	4
k_{cat}^{IDH}	0.03	ms^{-1}	Rate constant of IDH	E147	*
E_T^{IDH}	0.109	mM	Concentration of IDH	E147	4
$[H^+]$	2.5×10^{-5}	mM	Matrix proton concentration	E147	4
$k_{h,1}$	8.1×10^{-5}	mM	Ionization constant of IDH	E147	4
$k_{h,2}$	5.98×10^{-5}	mM	Ionization constant of IDH	E147	4
K_M^{ISOC}	1.52	mM	Michaelis constant for isocitrate	E147	4
ni	2.0		Cooperativity for isocitrate	E147	4
K_M^{NAD}	0.923	mM	Michaelis constant for NAD^+	E147	4
$K_D^{Mg^{2+}}$	0.0308	mM	Activation constant for Mg^{2+}	E148	4
$K_D^{Ca^{2+}}$	1.27×10^{-3}	mM	Activation constant for Ca^{2+}	E148	4
E_T^{KGDH}	0.5	mM	Concentration of KGDH	E149	4
k_{cat}^{KGDH}	0.05	ms^{-1}	Rate constant of KGDH	E149	**
$K_M^{\alpha KG}$	1.94	mM	Michaelis constant for αKG	E149	4
K_M^{NAD}	38.7	mM	Michaelis constant for NAD	E149	4
$n_{\alpha KG}$	1.2		Hill coefficient of KGDH for αKG	E149	4
Mg^{2+}	0.4	mM	Mg^{2+} concentration in mitochondria	E148	4
k_f^{SL}	5.0×10^{-4}	$mM^{-1}\ ms^{-1}$	Forward rate constant of SL	E150	**

K_E^{SL}	3.115		Equilibrium constant of the SL reaction	E150	4
[CoA]	0.02	mM	Coenzyme A concentration	E150	4
k_{cat}^{SDH}	3.0×10^{-3}	ms^{-1}	Rate constant of SDH	E151	**
E_T^{SDH}	0.5	mM	SDH enzyme concentration	E151	4
K_M^{Suc}	0.03	mM	Michaelis constant for succinate	E151	4
K_i^{FUM}	1.3	mM	Inhibition constant by fumarate	E151	4
$K_{i,sdh}^{OAA}$	0.15	mM	Inhibition constant by oxalacetate	E151	4
k_f^{FH}	3.32×10^{-3}	ms^{-1}	Forward rate constant for FH	E152	**
K_E^{FH}	1.0		Equilibrium constant of FH	E152	4
k_{h1}	1.13×10^{-5}	mM	Ionization constant of MDH	E153	4
k_{h2}	26.7	mM	Ionization constant of MDH	E153	4
k_{h3}	6.68×10^{-9}	mM	Ionization constant of MDH	E154	4
k_{h4}	5.62×10^{-6}	mM	Ionization constant of MDH	E154	4
k_{offset}	3.99×10^{-2}		pH-independent term in the pH activation factor of MDH	E153	4
k_{cat}^{MDH}	0.111	ms^{-1}	Rate constant of MDH	E155	**
E_T^{MDH}	0.154	mM	Total MDH enzyme concentration	E155	4
K_M^{MAL}	1.493	mM	Michaelis constant for malate	E155	4
K_i^{OAA}	3.1×10^{-3}	mM	Inhibition constant for oxalacetate	E155	4
K_M^{NAD}	0.2244	mM	Michaelis constant for NAD^+	E155	4
[GLU]	10.0	mM	Glutamate concentration	E156	4
k_f^{AAT}	6.44×10^{-4}	ms^{-1}	Forward rate constant of AAT	E156	4
K_E^{AAT}	6.6		Equilibrium constant of AAT	E156	4
k_{ASP}	1.5×10^{-6}	ms^{-1}	Rate constant of aspartate consumption	E156	**

Note: *. The values of the Isocitrate dehydrogenase activation constants by ADP and Ca2+ have been modified to reproduce appropriately the kinetics reported by Rutter and Denton (5). **. The kinetic constants of all the TCA cycle enzyme steps have been multiplied by a factor of 1.5-

4 with respect to those indicated in g to match the fluxes of the TCA cycle (22) in the integrated model that faces additional restrictions than those of the isolated mitochondrial model.

S2.14. Oxidative Phosphorylation parameters

Symbol	Value	Units	Description	Eq.	Ref.
r_a	6.394×10^{-13}	ms^{-1}	Sum of products of rate constants	E157	4
r_b	1.762×10^{-16}	ms^{-1}	Sum of products of rate constants	E158	4
r_{c1}	2.656×10^{-22}	ms^{-1}	Sum of products of rate constants	E157	4
r_{c2}	8.632×10^{-30}	ms^{-1}	Sum of products of rate constants	E157	4
r_1	2.077×10^{-18}		Sum of products of rate constants	E157	4
r_2	1.728×10^{-9}		Sum of products of rate constants	E157	4
r_3	1.059×10^{-26}		Sum of products of rate constants	E157	4
ρ^{res}	3.0×10^{-3}	mM	Concentration of electron carriers (respiratory complexes I-III-IV)	E157	4
K_{res}	1.35×10^{18}		Equilibrium constant of respiration	E159	4
$\rho^{res(F)}$	3.75×10^{-4}	mM	Concentration of electron carriers (respiratory complexes II-III-IV)	E161	*
$\Delta\Psi_B$	50	mV	Phase boundary potential	E157	4
g	0.85		Correction factor for voltage	E157	4
$K_{res(F)}$	5.765×10^{13}		Equilibrium constant of $FADH_2$ oxidation	E162	4
[FADH2]	1.24	mM	Concentration of $FADH_2$ (reduced)	E162	4
[FAD]	0.01	mM	Concentration of FAD (oxidized)	E162	4
p_a	1.656×10^{-8}	ms^{-1}	Sum of products of rate constants	E163	4
p_b	3.373×10^{-10}	ms^{-1}	Sum of products of rate constants	E164	4
p_{c1}	9.651×10^{-17}	ms^{-1}	Sum of products of rate constants	E163	4
p_{c2}	4.585×10^{-17}	ms^{-1}	Sum of products of rate constants	E163	4
p_1	1.346×10^{-8}		Sum of products of rate constants	E163	4
p_2	7.739×10^{-7}		Sum of products of rate constants	E163	4
p_3	6.65×10^{-15}		Sum of products of rate constants	E163	4
ρ^{F1}	1.5	mM	Concentration of F_1F_0-ATPase	E163	4
K_{F1}	1.71×10^{6}		Equilibrium constant of ATP hydrolysis	E165	4
Pi	2.0	mM	Inorganic phosphate concentration	E165	**

C_A	1.5	mM	Total sum of mito adenine nucleotides	E129	**
V_{maxANT}	0.025	mM ms^{-1}	Maximal rate of the ANT	E139	4
h^{ANT}	0.5		Fraction of $\Delta\Psi_m$	E139	4
g_H	1.0×10^{-8}	mM ms^{-1} mV^{-1}	Ionic conductance of the inner membrane	E166	4
ΔpH	-0.6	pH units	pH gradient across the inner memb.	E167	4
C_{PN}	10.0	mM	Total sum of mito pyridine nucleotides	E160	4
C_{mito}	1.812×10^{-3}	mM mV^{-1}	Inner membrane capacitance	E123	4

Note: *. The respiratory complex II carriers concentration was adjusted with respect to the value in (6) to match the reported range of oxygen consumption rates (0.04 to 0.5 mM s^{-1} = 5 - 60 μmol O2/min/mg) (7). **. The total nucleotide level and inorganic phosphate were corrected with respect to previous publication (6) to follow reported experimental evidence (7, 8)

S2.15. Mitochondrial Ca^{2+} handling parameters

Symbol	Value	Units	Description	Eq.	Ref.
V_{max}^{uni}	0.0275	mM ms^{-1}	Vmax uniport Ca^{2+} transport	E168	*
$\Delta\Psi°$	91	mV	Offset membrane potential	E168	4
K_{act}	3.8×10^{-4}	mM	Activation constant	E168	4
K_{trans}	0.019	mM	K_d for translocated Ca^{2+}	E168	4
L	110.0		Keq for conformational transitions in uniporter	E168	4
n_a	2.8		Uniporter activation cooperativity	E168	4
V_{max}^{NaCa}	1.0×10^{-4}	mM ms^{-1}	Vmax of Na$^+$/Ca $^{2+}$ antiporter	E169	4
b	0.5		$\Delta\Psi_m$ dependence of Na$^+$/Ca^{2+} antiporter	E169	4
K_{Na}	9.4	mM	Antiporter Na$^+$ constant	E169	4
K_{Ca}	3.75×10^{-4}	mM	Antiporter Ca^{2+} constant	E169	4
n	3		Na$^+$/Ca^{2+} antiporter cooperativity	E169	4
δ	$3.0\ 10^{-4}$		Fraction of free [Ca^{2+}]$_m$	A93	4

Note: *. The maximal rate of the Ca^{2+} uniporter had to be adjusted to meet the transport fluxes experimentally determined (9, 10) in the new integrated model structure in which the Ca^{2+} levels in the cytoplasm are no longer steady as they were in the isolated mitochondrial model (4).

S2.16. States variables initial values

Symbol	Description	Value
V	Sarcolemmal membrane potential	-87.28
m_{Na}	Sodium channel activation gate	0.03272
n_{Na}	Sodium channel inactivation gate	0.9909
j_{Na}	Sodium channel slow inactivation gate	0.9941
X	Potassium channel activation gate	1.1212×10^{-4}
$[Na^+]_i$	Intracellular Na^+ concentration	8.2143
$[K^+]_i$	Intracellular K^+ concentration	150.8
$[Ca^{2+}]_i$	Intracellular Ca^{2+} concentration	5.8653×10^{-5}
$[Ca^{2+}]_{NSR}$	Network SR Ca^{2+} concentration	0.1948
$[Ca^{2+}]_{JSR}$	Junctional SR Ca^{2+} concentration	0.1948
$[Ca^{2+}]_{SS}$	Ca^{2+} concentration in the subspace	7.057×10^{-5}
$[Ca^{2+}]_m$	Mitochondrial free Ca^{2+} concentration	1.1324×10^{-4}
P_{C1}	Fraction of RyR channels in P_{C1} state	0.7525
P_{C2}	Fraction of RyR channels in P_{C2} state	0.2471
P_{O2}	Fraction of RyR channels in P_{O2} state	7.12×10^{-11}
P_{O1}	Fraction of RyR channels in P_{O1} state	8.309×10^{-5}
C_0	L-type Ca^{2+} channel closed – mode normal	0.9991
C_1	L-type Ca^{2+} channel closed – mode normal	8.175×10^{-5}
C_2	L-type Ca^{2+} channel closed – mode normal	2.508×10^{-9}
C_3	L-type Ca^{2+} channel closed – mode normal	3.421×10^{-14}
C_4	L-type Ca^{2+} channel closed – mode normal	1.749×10^{-20}
O	L-type Ca^{2+} channel open – mode normal	2.624×10^{-20}
C_{Ca0}	L-type Ca^{2+} channel closed – mode Ca	1.1328×10^{-3}
C_{Ca1}	L-type Ca^{2+} channel closed – mode Ca	4.7591×10^{-8}
C_{Ca2}	L-type Ca^{2+} channel closed – mode Ca	6.3826×10^{-13}
C_{Ca3}	L-type Ca^{2+} channel closed – mode Ca	1.815×10^{-15}
C_{Ca4}	L-type Ca^{2+} channel closed – mode Ca	3.712×10^{-24}
O_{Ca}	L-type Ca^{2+} channel open – mode Ca	0

y	ICa inactivation gate	0.9479
[LTRPNCa]	Ca^{2+} bound to low affinity troponin sites	0.008949
[HTRPNCa]	Ca^{2+} bound to high affinity troponin sites	0.1321
$[N_0]$	Nonpermissive tropomyosyn with 0 cross bridges	0.9979
$[N_1]$	Nonpermissive tropomyosyn with 1 cross bridges	2.243×10^{-5}
$[P_0]$	Permissive tropomyosyn with 0 cross bridges	2.601×10^{-5}
$[P_1]$	Permissive tropomyosyn with 1 cross bridges	2.248×10^{-5}
$[P_2]$	Permissive tropomyosyn with 2 cross bridges	4.199×10^{-5}
$[P_3]$	Permissive tropomyosyn with 3 cross bridges	3.657×10^{-5}
$[ATP]_i$	EC coupling linked ATP concentration	7.8707
$[ADP]_i$	EC coupling linked ADP concentration	0.1293
$[ATP]_{ic}$	Cytosolic ATP concentration not linked to EC coupling	7.7107
$[ADP]_{ic}$	Cytosolic ADP concentration not linked to EC coupling	0.2893
$[CrP]_i$	Mitochondrial linked creatine phosphate concentration	5.0297
$[CrP]_{ic}$	Cytosolic creatine phosphate concentration	5.1291
$[ADP]_m$	Mitochondrial ADP concentration	0.0477
[NADH]	Mitochondrial NADH concentration	9.0403
$\Delta\Psi_m$	Inner mitochondrial membrane potential	- 126.7
[ISOC]	Isocitrate concentration (mitochondrial)	0.6241
[αKG]	α ketoglutarate concentration (mitochondrial)	7.0596×10^{-5}
[SCoA]	Succinyl CoA concentration (mitochondrial)	0.7058
[Suc]	Succinate concentration (mitochondrial)	2.2406×10^{-4}
[FUM]	Fumarate concentration (mitochondrial)	0.01282
[MAL]	Malate concentration (mitochondrial)	0.006316
[OAA]	Oxalacetate concentration (mitochondrial)	6.6423×10^{-8}
$[ROS]_i$	ROS concentration (cytoplasmic)	6.6192×10^{-7}
$[ROS]_m$	ROS concentration (mitocondrial)	0.2838
$[H_2O_2]$	Hydrogen peroxdize (cytoplasmic)	4.6821×10^{-7}
[GSH]	Reduced glutathione (cytoplasmic)	0.9981

References

1. Rice, J. J., M. S. Jafri, and R. L. Winslow. 2000. Modeling short-term interval-force relations in cardiac muscle. Am J Physiol Heart Circ Physiol 278:H913-931.
2. Luo, C. H., and Y. Rudy. 1994. A dynamic model of the cardiac ventricular action potential. I. Simulations of ionic currents and concentration changes. Circ Res 74:1071-1096.
3. Sheu, S. S., and H. A. Fozzard. 1982. Transmembrane Na+ and Ca2+ electrochemical gradients in cardiac muscle and their relationship to force development. J Gen Physiol 80:325-351.
4. Bers, D. M. 2001. Excitation-contraction coupling and cardiac contractile force Kluwer Academic Publishers, Dordrecht, Boston.
5. Rutter, G. A., and R. M. Denton. 1988. Regulation of NAD+-linked isocitrate dehydrogenase and 2-oxoglutarate dehydrogenase by Ca2+ ions within toluene-permeabilized rat heart mitochondria. Interactions with regulation by adenine nucleotides and NADH/NAD+ ratios. Biochem J 252:181-189.
6. Cortassa, S., M. A. Aon, E. Marban, R. L. Winslow, and B. O'Rourke. 2003. An integrated model of cardiac mitochondrial energy metabolism and calcium dynamics. Biophys J 84:2734-2755.
7. Balaban, R. S. 2002. Cardiac energy metabolism homeostasis: role of cytosolic calcium. J Mol Cell Cardiol 34:1259-1271.
8. Randle, P. J., and P. K. Tubbs. 1979. Carbohydrate and fatty acid metabolism. In Handbook of Physiology. R. M. Berne, N. Sperelakis, and R. Geiger, editors. American Physiological Society, Bethesda. 805-844.
9. Gunter, K. K., and T. E. Gunter. 1994. Transport of calcium by mitochondria. J Bioenerg Biomembr 26:471-485.
10. Gunter, T. E., and D. R. Pfeiffer. 1990. Mechanisms by which mitochondria transport calcium. Am J Physiol 258:C755-786.