S1 Appendix

The full model consists of fifteen variables:

$$\frac{d}{dt}C_{cyt} = f_c\bigg[(1-R_{\mathrm{S1}})(J_{\mathrm{IPR}} - J_{\mathrm{SERCA}}) + \frac{1-R_{\mathrm{S2}}}{R_{\mathrm{V3}}}(J_{\mathrm{NCX}} - J_{\mathrm{MCU}}) + J_{\mathrm{diff}} + J_{\mathrm{in}} - J_{\mathrm{pm}}\bigg] \tag{1}$$

$$\frac{d}{dt}C_{MAM} = f_c\bigg[R_{\mathrm{V1}}R_{\mathrm{S1}}(J_{\mathrm{nIPR}} - J_{\mathrm{nSERCA}}) + \frac{R_{\mathrm{V1}}R_{\mathrm{S2}}}{R_{\mathrm{V3}}}(J_{\mathrm{nNCX}} - J_{\mathrm{nMCU}}) - R_{\mathrm{V1}}J_{\mathrm{diff}}\bigg] \tag{2}$$

$$\frac{d}{dt}C_{mito} = f_m\bigg[R_{\mathrm{S2}}(J_{\mathrm{nMCU}} - J_{\mathrm{nNCX}}) + (1-R_{\mathrm{S2}})(J_{\mathrm{MCU}} - J_{\mathrm{NCX}})\bigg] \tag{3}$$

$$\frac{d}{dt}C_t = J_{\mathrm{in}} - J_{\mathrm{pm}} \tag{4}$$

$$\frac{d}{dt}P = \tau_p(P_{\mathrm{s}} - P) + \mathrm{pulse} \tag{5}$$

$$\frac{d}{d\hat{t}}h_{42} = \lambda_{h_{42}}(h_{42}^{\infty} - h_{42}) \tag{6}$$

$$\frac{d}{d\hat{t}}h_{\mathrm{n}42} = \lambda_{h_{n42}}(h_{\mathrm{n}42}^{\infty} - h_{\mathrm{n}42}) \tag{7}$$

$$\frac{d}{d\hat{t}}m_{42} = \lambda_{m_{42}}(m_{42}^{\infty} - m_{42}) \tag{8}$$

$$\frac{d}{d\hat{t}}m_{\mathrm{n}42} = \lambda_{m_{42}}(m_{\mathrm{n}42}^{\infty} - m_{\mathrm{n}42}) \tag{9}$$

$$\frac{d}{d\hat{t}}h_{24} = \lambda_{h_{24}}(h_{42}^{\infty} - h_{42}) \tag{10}$$

$$\frac{d}{d\hat{t}}m_{24} = \lambda_{m_{24}}(m_{42}^{\infty} - m_{42}) \tag{11}$$

$$\frac{d}{dt}ADP_c = I_{\mathrm{hyd}} - \frac{I_{\mathrm{ant}}}{R_{\mathrm{V3}}} \tag{12}$$

$$\frac{d}{dt}ADP_m = I_{\mathrm{ant}} - I_{\mathrm{F1FO}} \tag{13}$$

$$\frac{d}{dt}N = I_{\mathrm{pdh}} - I_{\mathrm{o}} + I_{\mathrm{agc}} \tag{14}$$

$$\frac{d}{dt}V_m = \frac{1}{C_p}(a_1 I_{\mathrm{o}} - a_2 I_{\mathrm{F1FO}} - I_{\mathrm{ant}} - I_{\mathrm{Hleak}} - (1-R_{\mathrm{S2}})(J_{\mathrm{NCX}} + 2J_{\mathrm{MCU}}) - R_{\mathrm{S2}}(J_{\mathrm{nNCX}} + 2J_{\mathrm{nMCU}}) - I_{\mathrm{agc}}) \tag{15}$$

To non-dimensionalize the model, we first redefined the model variables with dimensionless variables,

$$\begin{aligned}
C_{cyt} &= Q_{cyt} \cdot \widehat{C_{cyt}}, & C_{MAM} &= Q_{MAM} \cdot \widehat{C_{MAM}} \\
C_{mito} &= Q_{mito} \cdot \widehat{C_{mito}}, & C_t &= Q_t \cdot \widehat{C_t} \\
P &= Q_p \cdot \widehat{P}, & ADP_m &= Q_{Am} \cdot \widehat{ADP_m}, \\
ADP_c &= Q_{Ac} \cdot \widehat{ADP_c}, & N &= Q_N \cdot \widehat{N}, \\
V_m &= Q_{Vm} \cdot \widehat{V_m}, & t &= T \cdot \widehat{t},
\end{aligned} \tag{16}$$

and dimensionless fluxes and rates

$$\begin{aligned}
\bar{J}_\star &= \frac{J_\star}{V_{\text{nSERCA}}} && \text{for } \star = \text{IPR, nIPR, SERCA, nSERCA, diff,} \\
&&& \qquad \text{MCU, nMCU, NCX, nNCX} \\
\bar{J}_\dagger &= \frac{V_{\text{SOCC}} J_\dagger}{V_{\text{pm}}^2} && \text{for } \dagger = \text{leakin, SOCC, ROCC, pm} \\
\bar{I}_\triangle &= \frac{I_\triangle}{V_{\text{nSERCA}}} && \text{for } \triangle = \text{hyd, ant, F1FO, pdh, o, agc, Hleak}
\end{aligned} \tag{17}$$

Then we derived the following dimensionless version of the system:

$$\begin{aligned}
\frac{d}{d\hat{t}}\widehat{C_{cyt}} = \frac{T V_{\text{nSERCA}} f_c R_{\text{V2}}}{Q_{cyt} R_{\text{V3}}} \Bigg[\frac{R_{\text{V3}}}{R_{\text{V2}}}(1 - R_{\text{S1}})(\bar{J}_{\text{IPR}} - \bar{J}_{\text{SERCA}}) \\
+ \frac{1}{R_{\text{V2}}}(1 - R_{\text{S2}})(\bar{J}_{\text{NCX}} - \bar{J}_{\text{MCU}}) + \frac{R_{\text{V3}}}{R_{\text{V2}}} \bar{J}_{\text{diff}} \Bigg] + \frac{T V_{\text{pm}}^2 f_c}{Q_{cyt} V_{\text{SOCC}}} \Big[\bar{J}_{\text{in}} - \bar{J}_{\text{pm}} \Big]
\end{aligned} \tag{18}$$

$$\begin{aligned}
\frac{d}{d\hat{t}}\widehat{C_{MAM}} = \frac{T V_{\text{nSERCA}} f_c R_{\text{V1}}}{Q_{MAM} R_{\text{V3}}} \Bigg[R_{\text{V3}} R_{\text{S1}} (\bar{J}_{\text{nIPR}} - \bar{J}_{\text{nSERCA}}) \\
+ R_{\text{S2}}(\bar{J}_{\text{nNCX}} - \bar{J}_{\text{nMCU}}) - R_{\text{V3}} \bar{J}_{\text{diff}} \Bigg]
\end{aligned} \tag{19}$$

$$\frac{d}{d\hat{t}}\widehat{C_{mito}} = \frac{T V_{\text{nSERCA}} f_m R_{\text{V2}}}{Q_{mito} R_{\text{V3}}} \Bigg[\frac{R_{\text{V3}}}{R_{\text{V2}}} R_{\text{S2}} (\bar{J}_{\text{nMCU}} - \bar{J}_{\text{nNCX}}) + \frac{R_{\text{V3}}}{R_{\text{V2}}}(1 - R_{\text{S2}})(\bar{J}_{\text{MCU}} - \bar{J}_{\text{NCX}}) \Bigg] \tag{20}$$

$$\frac{d}{d\hat{t}}\widehat{C_t} = \frac{T V_{\text{pm}}^2}{Q_t V_{\text{SOCC}}} \Big[\bar{J}_{\text{in}} - \bar{J}_{\text{pm}} \Big] \tag{21}$$

$$\frac{d}{d\hat{t}}\widehat{P} = T\tau_p\left[\frac{P_\mathrm{s}}{Q_p} - \widehat{P}\right] + \text{pulse} \tag{22}$$

$$\frac{d}{d\hat{t}}h_{42} = T\lambda_{h_{42}}\left[h_{42}^\infty - h_{42}\right] \tag{23}$$

$$\frac{d}{d\hat{t}}h_{\mathrm{n}42} = T\lambda_{h_{n42}}\left[h_{\mathrm{n}42}^\infty - h_{\mathrm{n}42}\right] \tag{24}$$

$$\frac{d}{d\hat{t}}m_{42} = T\lambda_{m_{42}}\left[m_{42}^\infty - m_{42}\right] \tag{25}$$

$$\frac{d}{d\hat{t}}m_{\mathrm{n}42} = T\lambda_{m_{42}}\left[m_{\mathrm{n}42}^\infty - m_{\mathrm{n}42}\right] \tag{26}$$

$$\frac{d}{d\hat{t}}h_{24} = T\lambda_{h_{24}}\left[h_{24}^\infty - h_{24}\right] \tag{27}$$

$$\frac{d}{d\hat{t}}m_{24} = T\lambda_{m_{24}}\left[m_{24}^\infty - m_{24}\right] \tag{28}$$

$$\frac{d}{d\hat{t}}\widehat{ADP_c} = \frac{TV_\mathrm{nSERCA}}{Q_{Ac}R_\mathrm{V2}}\left[R_\mathrm{V2}\bar{I}_\mathrm{hyd} - R_\mathrm{V2}\bar{I}_\mathrm{ant}/R_\mathrm{V3}\right] \tag{29}$$

$$\frac{d}{d\hat{t}}\widehat{ADP_m} = \frac{TV_\mathrm{nSERCA}}{Q_{Am}}\left[\bar{I}_\mathrm{ant} - \bar{I}_\mathrm{F1FO}\right] \tag{30}$$

$$\frac{d}{d\hat{t}}\widehat{N} = \frac{TV_\mathrm{nSERCA}}{Q_N R_\mathrm{V2}}\left[R_\mathrm{V2}\bar{I}_\mathrm{pdh} - R_\mathrm{V2}\bar{I}_\mathrm{o} + R_\mathrm{V2}\bar{I}_\mathrm{agc}\right] \tag{31}$$

$$\begin{aligned}\frac{d}{d\hat{t}}\widehat{V_m} = \frac{TV_\mathrm{nSERCA}}{C_p Q_V R_\mathrm{V2}R_\mathrm{V3}}\Big[&R_\mathrm{V2}R_\mathrm{V3}a_1\bar{I}_\mathrm{o} - R_\mathrm{V2}R_\mathrm{V3}a_2\bar{I}_\mathrm{F1FO} - R_\mathrm{V2}R_\mathrm{V3}\bar{I}_\mathrm{ant} - R_\mathrm{V2}R_\mathrm{V3}\bar{I}_\mathrm{Hleak} \\ &- R_\mathrm{V2}R_\mathrm{V3}(1-R_\mathrm{S2})(\bar{J}_\mathrm{NCX} + 2\bar{J}_\mathrm{MCU}) - R_\mathrm{V2}R_\mathrm{V3}R_\mathrm{S2}(\bar{J}_\mathrm{nNCX} + 2\bar{J}_\mathrm{nMCU}) \\ &- R_\mathrm{V2}R_\mathrm{V3}\bar{I}_\mathrm{agc}\Big]\end{aligned} \tag{32}$$

For every equation, the term in $\left[\cdots\right]$ is approximately of order $O(1)$. The gating variable rates are $\lambda_{m_{42}} = \lambda_{m_{24}} = 100\ \mathrm{s}^{-1}$ and $\lambda_{h_{24}} = 40\ \mathrm{s}^{-1}$. These rates are estimated directly from dynamical single channel data [1,2].

We chose $T = Q_{cyt}/(V_\mathrm{nSERCA}f_c)$. Based on numerical simulations of the model, typical concentration scale for the ions are of orders $Q_{cyt} = 1\ \mu$M, $Q_{MAM} = 10\ \mu$M, $Q_{mito} = 0.1\ \mu$M, $Q_t = 10^3$ μM, $Q_{Ac} = 10^3\ \mu$M, $Q_{Am} = 10^4\ \mu$M, $Q_N = 10^2\ \mu$M. A typical scale for mitochondrial membrane potential is $Q_V = 10^2$ mV. With these scales, the magnitudes of the right hand sides of the equations

Eq. (18) – Eq. (32) are:

$$
\begin{aligned}
&\frac{d}{d\hat{t}}\widehat{C_{cyt}} \sim O(0.1) && \frac{d}{d\hat{t}}\widehat{C_{MAM}} \sim O(10) && \frac{d}{d\hat{t}}\widehat{C_{mito}} \sim O(0.1) \\
&\frac{d}{d\hat{t}}\widehat{C_t} \sim O(0.0001) && \frac{d}{d\hat{t}}\widehat{P} \sim O(1) && \\
&\frac{d}{d\hat{t}}h_{42} \sim O(0.1) && \frac{d}{d\hat{t}}h_{\mathrm{n}42} \sim O(0.1) && \frac{d}{d\hat{t}}m_{42} \sim O(1000) \\
&\frac{d}{d\hat{t}}m_{\mathrm{n}42} \sim O(1000) && \frac{d}{d\hat{t}}h_{24} \sim O(100) && \frac{d}{d\hat{t}}m_{24} \sim O(1000) \\
&\frac{d}{d\hat{t}}\widehat{ADP_c} \sim O(0.01) && \frac{d}{d\hat{t}}\widehat{ADP_m} \sim O(0.01) && \\
&\frac{d}{d\hat{t}}\widehat{N} \sim O(0.1) && \frac{d}{d\hat{t}}\widehat{V_m} \sim O(0.001) &&
\end{aligned}
\tag{33}
$$

The model contains multiple timescales with the IPR gating variables evolving on the fastest and $\widehat{C_t}$ on the slowest. Using the quasi-steady-state approximation, we assumed that the gating variables reach their quasi-equilibria instantaneously. We note that this model reduction method is not well established for systems with multiple timescales. However, we compared model simulations of the full model with those of the reduced model, and confirmed that the dynamical characteristics are preserved under the reduction. Thus, we find that the quasi-steady-state reduction was suitable for our Ca^{2+} model.

References

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