Biophysical Journal, Volume *117*

Supplemental Information

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A spatiotemporal ventricular myocyte model incorporating mitochondrial calcium cycling

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Supplemental Information

The overall structure of the ventricular myocyte model is described in the Methods section and Fig.1 in the main text. Here we describe the detailed mathematical formulations and the parameters of the model.

1. Membrane potential and ionic currents

The governing differential equation for the membrane potential (V) is

$$C_m \frac{dV}{dt} = I_{Na} + I_{Na,L} + I_{K1} + I_{Kr} + I_{Ks} + I_{to,f} + I_{to,s} + I_{NaK} + I_{K,ATP} + I_{Ca,b} + I_{Ca,L} + I_{NCX} - I_{sti},$$

where I_{sti}=-50 μA/cm^2 is the stimulus current density and C_m=1 μF/cm^2 is the cell membrane capacitance. The equations and functions for the ionic currents are detailed in the sub-sections below and their maximum conductance are listed in Table S1 except the ones stated in their corresponding sub-sections. The formulations for the ionic currents are mainly based on those from the rabbit ventricular myocyte model by Mahajan et al (1) except for the ones specifically stated. The physical constants and ion concentrations are listed in Table S2.

Table S1. Maximum ionic current conductance

Parameter	Description	Value
g_{Na}	Maximum I_{Na} conductance	12.0 mS/μF
$g_{Na,L}$	Maximum $I_{Na,L}$ conductance	0.0065 mS/ μF
$g_{to,f}$	Maximum $I_{to,f}$ conductance	0.1 mS/μF
$g_{to,s}$	Maximum $I_{to,s}$ conductance	0.04 mS/μF
g_{K1}	Maximum I_{K1} conductance	0.6 mS/μF
g_{Kr}	Maximum I_{Kr} conductance	0.0078 mS/μF
g_{Ks}	Maximum I_{Ks} conductance	0.2 mS/μF
g_{NaK}	Maximum I_{NaK} conductance	1.5 mS/μF

1.1. Na^+ current (I_{Na})

The I_{Na} formulation is from Hund and Rudy (2), which incorporates CaMKII-dependent activation.

$$I_{Na} = g_{Na} m^3 h j (V - E_{Na}),$$
$$E_{Na} = \frac{RT}{F} \ln\left(\frac{[Na^+]_o}{[Na^+]_i}\right),$$
$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h,$$
$$\frac{dj}{dt} = \alpha_j (1 - j) - \beta_j j,$$
$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m,$$

Table S2. Physical constants and ionic concentrations

Parameter	Description	Value
F	Faraday constant	96.5 C/mmol
R	Universal gas constant	8.315 $Jmol^{-1}K^{-1}$
T	Temperature	308 K
$[Na^+]_o$	External sodium concentration	136 mM
$[K^+]_o$	External potassium concentration	5.4 mM
$[K^+]_i$	Internal potassium concentration	140 mM
$[Ca^{2+}]_o$	External calcium concentration	1.8 mM

$$\alpha_m = 0.32 \frac{V + 47.13}{1 - e^{-0.1(V+47.13)}},$$
$$\beta_m = 0.08 e^{-\frac{V}{11}},$$

For $V - \Delta V_{Na} \geq -40$ mV,

$$\alpha_h = 0,$$
$$\alpha_j = 0,$$
$$\beta_h = \frac{1}{0.13\left(1 + e^{\frac{V+10.66-\Delta V_{Na}}{-11.1}}\right)},$$
$$\beta_j = 0.3 \frac{e^{-2.535\times10^{-7}(V-\Delta V_{Na})}}{1 + e^{-0.1(V+32-\Delta V_{Na})}},$$

For $V - \Delta V_{Na} < -40$ mV,

$$\alpha_h = 0.135 e^{\frac{V+80-\Delta V_{Na}}{-6.8}},$$
$$\beta_h = 3.56 e^{0.079(V-\Delta V_{Na})} + 3.1\times10^5 e^{0.35(V-\Delta V_{Na})},$$
$$\alpha_j = \left(1 + \Delta\alpha_j\right) \cdot \frac{\left(-127140 e^{0.2444(V-\Delta V_{Na})} - 0.03474 e^{-0.04391(V-\Delta V_{Na})}\right) \times (V + 37.78 - \Delta V_{Na})}{1 + e^{0.311(V+79.23-\Delta V_{Na})}},$$
$$\beta_j = \frac{0.1212 e^{-0.01052(V-\Delta V_{Na})}}{1 + e^{-0.1378(V+40.14-\Delta V_{Na})}},$$

where

$$\Delta V_{Na} = \frac{-3.25}{1 + \left(\frac{K_{m,CaMK}}{[CaMKII]_{act}}\right)^4},$$

$$\Delta\alpha_j = \frac{-0.18}{1 + \left(\frac{K_{m,CaMK}}{[CaMKII]_{act}}\right)^4}.$$

$K_{m,CaMK}$=0.3 was used.

1.2. Late Na^+ current ($I_{Na,L}$)

The $I_{Na,L}$ formulation is from Hund and Rudy (2) , which incorporates CaMKII-dependent activation.

$$I_{Na,L} = (g_{Na,L} + \Delta g_{Na,L}) \cdot m_L^3 h_L \cdot (V - E_{Na}),$$

$$\frac{dm_L}{dt} = \alpha_{m,L}(1 - m_L) - \beta_{m,L} m_L ,$$

$$\frac{dh_L}{dt} = \frac{h_{L,\infty} - h_L}{\tau_{h,L}},$$

For $V \geq -47.13$ mV,

$$\alpha_{m,L} = 0.32 \frac{V + 47.13}{1 - e^{-0.1(V+47.13)}},$$

else

$$\alpha_{m,L} = 3.2,$$

$$\beta_{m,L} = 0.08 e^{-\frac{V}{11}},$$

$$h_{L,\infty} = \frac{1}{1 + e^{\frac{V+91}{6.1}}},$$

$$\tau_{h,L} = 600 \text{ ms},$$

$$\Delta g_{Na,L} = \frac{0.0095}{1 + \left(\frac{K_{m,CaMK}}{[CaMKII]_{act}}\right)^4}.$$

$K_{m,CaMK}$=0.3 was used.

1.3. L-type Ca^{2+} current ($I_{Ca,L}$)

L-type Ca^{2+} channels (LCCs) are simulated by a stochastic 9-state Markov model (see Fig.1C) that were developed based a Hodgkin-Huxley formulation (3). However, a directly randomized version of the Hodgkin-Huxley-type formulation is not appropriate for an LCC, because the maximum open probability of an LCC is 100% in the Hodgkin-Huxley-type model at high voltages, whereas that of real channels is much smaller (~5%-10%). Therefore, we added a new state (the final open state) to simulate a much lower channel open probability (~5%-10%) observed in experiments.

Each CRU has a LCC cluster of 5 LCCs under the control condition. The Ca^{2+} current through the LCC cluster into the proximal space (dyadic space) of a CRU is given by

$$\bar{I}_{Ca,L} = n \cdot i_{Ca,L}$$

where $n \leq 5$ is the number of open LCCs in the CRU, and $i_{Ca,L}$ is the single LCC current, which is:

$$i_{Ca,L} = \frac{4P_{Ca} z F \left(\gamma_i [Ca^{2+}]_p e^{2z} - \gamma_o [Ca^{2+}]_o\right)}{e^{2z} - 1},$$

$$z = \frac{VF}{RT}.$$

$[Ca^{2+}]_p$ is the Ca^{2+} concentration in the corresponding proximal space of the CRU. Therefore, the whole-cell L-type Ca^{2+} current ($I_{Ca,L}$) is a summation of the Ca^{2+} currents of all CRUs in the cell,

i.e.,

$$I_{Ca,L} = \sum_{m=1}^{M} \bar{I}_{Ca,L}^{(m)}$$

where M is total number of CRUs in the cell, and $\bar{I}_{Ca,L}^{(m)}$ is the LCC current in the m^{th} CRU.

The transition rates of the LCC model are as follows:

$$\alpha_d = \frac{d_\infty}{\tau_d}, \qquad \beta_d = \frac{1 - d_\infty}{\tau_d},$$

where

$$d_\infty = \frac{1}{1 + e^{-\frac{V-5}{6.24}}},$$

$$\tau_d = \frac{1 - e^{-\frac{V-5}{6.24}}}{0.035(V-5)}\, d_\infty.$$

$$\alpha_f = \frac{f_\infty}{\tau_f}, \qquad \beta_f = \frac{1 - f_\infty}{\tau_f}$$

where

$$f_\infty = \frac{1}{1 + e^{\frac{V+16.06}{8.6}}},$$

$$\tau_f = \frac{1}{0.0197 e^{-[0.0337(V-9)]^2} + 0.02} + \Delta\tau_{f,CaMK}.$$

$$\alpha_{fCa} = \frac{f_{Ca,\infty}}{\tau_{fCa}}, \qquad \beta_{fCa} = \frac{1 - f_{Ca,\infty}}{\tau_{fCa}},$$

where

$$f_{Ca,\infty} = \frac{1}{1 + \left(\frac{[Ca^{2+}]_p}{\bar{c}_p}\right)^2},$$

$$\tau_{fCa} = 15 + \Delta\tau_{fCa,CaMK}.$$

The rate constants r_1 and r_2 are constants, which are chosen to account for 5%-10% open probability of LCC (1).

CaMKII-dependent Ca^{2+} channel phosphorylation results in a slower inactivation (4). Here, we use the formulation by Hund et al (5) to change the LCC inactivation time constants as follows:

$$\Delta\tau_{fCa,CaMK} = \frac{\Delta\tau_{fCa,CaMK,max}}{1 + \left(\frac{k_{mCaMLCC}}{[CaMKII]_{act}}\right)^{h_{CaMLCC}}},$$

$$\Delta\tau_{f,CaMK} = \frac{\Delta\tau_{f,CaMK,max}}{1 + \left(\frac{k_{mCaMLCC}}{[CaMKII]_{act}}\right)^{h_{CaMLCC}}}.$$

The corresponding parameters for the $I_{Ca,L}$ model are listed in Table S3.

Table S3. L-type Ca^{2+} current parameters

Parameter	Description	Value
P_{Ca}	LCC permeability	11.9 μmol$C^{-1}ms^{-1}$
γ_i, γ_o	Activity coefficient of Ca^{2+}	0.341
$k_{mCaMLCC}$	K_D of CaMKII activation on LCC	0.1
h_{CaMLCC}	Hill coefficient of CaMKII activation on LCC	4
$\bar{c}_p$	Ca^{2+}-dependent inactivation constant of LCC	20 μM
r_1	Opening rate	0.3 ms^{-1}
r_2	Closing rate	6 ms^{-1}
τ_{fCa}	Time constant of Ca^{2+}-dependent inactivation	15 ms
$\Delta\tau_{fCa,CaMK,max}$	Maximum increase of the time constant of Ca^{2+}-dependent inactivation	5 ms
$\Delta\tau_{f,CaMK,max}$	Maximum increase of the time constant of voltage-dependent inactivation	5 ms

1.4. Na^+-Ca^{2+} exchange current (I_{NCX})

The Na^+-Ca^{2+} exchangers are spatially distributed in the CRUs, which senses the Ca^{2+} concentrations of their local sub-membrane spaces ($[Ca^{2+}]_s$). The Na^+-Ca^{2+} exchange current in a single CRU is

$$\bar{I}_{NCX} = \frac{K_a \nu_{NaCa}\left(e^{\eta z}[Na^+]_i^3[Ca^{2+}]_o - e^{(\eta-1)z}[Na^+]_o^3[Ca^{2+}]_s\right)}{(t_1 + t_2 + t_3)(1 + k_{sat}e^{(\eta-1)z})},$$

where

$$t_1 = K_{mCai}\,[Na^+]_o^2\left[1 + \left(\frac{[Na^+]_i}{K_{mNai}}\right)^3\right],$$

$$t_2 = K_{mNao}^3[Ca^{2+}]_s\left(1 + \frac{[Ca^{2+}]_s}{K_{mCai}}\right)$$

$$t_3 = K_{mCao}^3[Na^+]_i^3 + [Na^+]_i^3[Ca^{2+}]_o + [Na^+]_o^3[Ca^{2+}]_s,$$

$$K_a = \left[1 + \left(\frac{K_{da}}{[Ca^{2+}]_s}\right)^3\right]^{-1},$$

$$z = \frac{VF}{RT},$$

and the whole-cell I_{NCX} is

$$I_{NCX} = \sum_m^M \bar{I}_{NCX}^{(m)},$$

where M is total number of CRUs in the cell, and $\bar{I}_{NCX}^{(m)}$ is the LCC current in the m^{th} CRU.
The parameters are listed in Table S4.

Table S4. Na^+-Ca^{2+} exchange current parameters

Parameter	Value	Units
ν_{NaCa}	21	$\mu M \cdot ms^{-1}$
K_{mCai}	3.59	μM
K_{mCao}	1.3	mM
K_{mNai}	12.3	mM
K_{mNao}	87.5	mM
K_{da}	0.11	μM
K_{sat}	0.27	
η	0.35	

1.5. Inward rectifier K^+ current (I_{K1})

$$I_{K1} = g_{K1}\sqrt{\frac{[K^+]_o}{5.4}}\,\frac{A_{K1}}{A_{K1}+B_{K1}}(V-E_K),$$

$$A_{K1} = \frac{1.02}{1+e^{0.2385(V-E_K-59.215)}},$$

$$B_{K1} = \frac{0.49124e^{0.08032(V-E_K+5.476)} + e^{0.06175(V-E_K-594.31)}}{1+e^{-0.5143(V-E_K+4.753)}},$$

$$E_K = \frac{RT}{F}\ln\left(\frac{[K^+]_o}{[K^+]_i}\right).$$

1.6. The rapid component of the delayed rectifier K^+ current (I_{Kr})

$$I_{Kr} = g_{Kr}\sqrt{\frac{[K^+]_o}{5.4}}\,x_{Kr}R(V)(V-E_K),$$

$$R(V) = \frac{1}{1+e^{\frac{V+33}{22.4}}},$$

$$\frac{dx_{Kr}}{dt} = \frac{x_{Kr,\infty}-x_{Kr}}{\tau_{Kr}},$$

$$x_{Kr,\infty} = \frac{1}{1+e^{-\frac{V+50}{7.5}}},$$

$$\tau_{Kr} = \frac{1}{\frac{0.00138(V+7)}{1-e^{-0.123(V+7)}} + \frac{0.00061(V+10)}{-1+e^{0.145(V+10)}}}.$$

1.7. The slow component of the delayed rectifier K^+ current (I_{Ks})

$$I_{Ks} = g_{Ks} x_{s1} x_{s2} q_{Ks} (V - E_{Ks}),$$

$$q_{Ks} = 1 + \frac{0.8}{1 + \left(\frac{0.5}{[Ca^{2+}]_i}\right)^3},$$

$$\frac{dx_{s1}}{dt} = \frac{x_{s,\infty} - x_{s1}}{\tau_{xs1}},$$

$$\frac{dx_{s2}}{dt} = \frac{x_{s,\infty} - x_{s2}}{\tau_{xs2}},$$

$$x_{s,\infty} = \frac{1}{1 + e^{-\frac{V-1.5}{16.7}}},$$

$$\tau_{xs1} = \frac{1}{\frac{0.0000719(V+30)}{1 - e^{-0.148(V+30)}} + \frac{0.00031(V+30)}{-1 + e^{0.0687(V+30)}}},$$

$$\tau_{xs2} = 4\tau_{xs1},$$

$$E_{Ks} = \frac{RT}{F} \ln\left(\frac{[K^+]_o + 0.01833[Na^+]_o}{[K^+]_i + 0.01833[Na^+]_i}\right).$$

1.8. The fast component of the outward K^+ current ($I_{to,f}$)

$$I_{to,f} = g_{to,f} X_{to,f} Y_{to,f} (V - E_K),$$

$$X_{to,f,\infty} = \frac{1}{1 + e^{-\frac{V+3}{15}}},$$

$$Y_{to,f,\infty} = \frac{1}{1 + e^{\frac{V+33.5}{10}}},$$

$$\tau_{Xto,f} = 3.5 e^{-\left(\frac{V}{30}\right)^2} + 1.5,$$

$$\tau_{Yto,f} = \frac{20}{1 + e^{\frac{V+33.5}{10}}} + 20,$$

$$\frac{dX_{to,f}}{dt} = \frac{X_{to,f,\infty} - X_{to,f}}{\tau_{Xto,f}},$$

$$\frac{dY_{to,f}}{dt} = \frac{Y_{to,f,\infty} - Y_{to,f}}{\tau_{Yto,f}}.$$

1.9. The slow component of the outward K^+ current ($I_{to,s}$)

$$I_{to,s} = g_{to,s}X_{to,s}\left(Y_{to,s} + 0.5R_{s,\infty}\right)(V - E_K),$$

$$R_{s,\infty} = \frac{1}{1 + e^{\frac{V+33.5}{10}}},$$

$$X_{to,s,\infty} = \frac{1}{1 + e^{-\frac{V+3}{15}}},$$

$$Y_{to,s,\infty} = \frac{1}{1 + e^{\frac{(V+33.5)}{10}}},$$

$$\tau_{Xto,s} = \frac{9}{1 + e^{\frac{V+3}{15}}} + 0.5,$$

$$\tau_{Yto,s} = \frac{3000}{1 + e^{\frac{V+60}{10}}} + 30,$$

$$\frac{dX_{to,s}}{dt} = \frac{X_{to,s,\infty} - X_{to,s}}{\tau_{Xto,s}},$$

$$\frac{dY_{to,s}}{dt} = \frac{Y_{to,s,\infty} - Y_{to,s}}{\tau_{Yto,s}}.$$

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

The Na^+/K^+ pump current formulation is from Cortassa et al (6) to incorporate the ATP and ADP dependence of I_{NaK}:

$$I_{NaK} = g_{NaK} \cdot f_{NaK} \cdot f_{NaK,ATP} \frac{1}{1 + \left(\frac{k_{m,Nai}}{[Na^+]_i}\right)} \frac{[K^+]_o}{[K^+]_o + k_{m,Ko}},$$

where

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

$$f_{NaK,ATP} = \frac{1}{1 + \frac{k_{i,NaK,ATP}}{[ATP]} \cdot \left(1 + \frac{[ADP]}{k_{i,NaK,ADP}}\right)}.$$

The parameters are listed in Table S5.

Table S5. Na^+/K^+ pump current parameters

Parameter	Description	Value
$k_{i,NaK,ATP}$	ATP half-saturation constant for Na^+/K^+ pump	8 μM
$k_{i,NaK,ADP}$	ADP inhibition constant for Na^+/K^+ pump	100 μM
$k_{m,Nai}$	Na^+ half-saturation for Na^+/K^+ pump	10 mM
$k_{m,Ko}$	K^+ half-saturation for Na^+/K^+ pump	1.5 mM

1.11. ATP-sensitive K^+ current (I_{KATP})

The formulation of ATP-sensitive K^+ current (I_{KATP}) is from Matsuoka et al (7):

$$I_{KATP} = 2333 \cdot \gamma \cdot (V - E_k) \cdot p_{kATP},$$

where

$$\gamma = 0.0236 \cdot ([K^+]_o)^{0.24},$$
$$E_k = \frac{RT}{F} \ln \frac{[K^+]_o}{[K^+]_i},$$
$$p_{kATP} = \frac{0.8}{1 + (10 \cdot [ATP])^2}.$$

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

The formulation of the background Ca^{2+} current is from Shannon et al (8). In this model, the background Ca^{2+} current is spatially distributed in the CRUs, which senses the Ca^{2+} concentrations of their local cytosolic space ($[Ca^{2+}]_i$). The background current in a single CRU is

$$\bar{I}_{Ca,b} = v_{cab} \cdot (V - E_{Ca}),$$

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

where $v_{cab} = 0.0002513\ mS \cdot \mu F$.

The whole-cell background Ca^{2+} current is

$$I_{Ca,b} = \sum_m^M \bar{I}_{Ca,b}^{(m)},$$

where M is total number of CRUs in the cell, and $\bar{I}_{Ca,b}^{(m)}$ is the background Ca^{2+} current in the m^{th} CRU.

2. Intracellular Ca^{2+} cycling

The differential equations for the Ca^{2+} concentrations in different sub-spaces of a CRU are as follows:

$$\frac{d[Ca^{2+}]_i}{dt} = \beta_i([Ca^{2+}]_i) \left(J_{dsi} \frac{v_s}{v_i} - J_{up} + J_{leak} + J_{cab} - J_{TCi} + J_{ci} + h_{mito} \cdot \frac{v_m}{v_i} \cdot \left(J_{NCXm} - (1 - f_p - f_s) \cdot J_{uni} + J_{MPTP} \right) \right),$$

$$\frac{d[Ca^{2+}]_s}{dt} = \beta_s([Ca^{2+}]_s) \left(J_{dps} \frac{v_p}{v_s} + J_{NCX} - h_{mito} \cdot f_s \cdot J_{uni} \cdot \frac{v_m}{v_s} - J_{dsi} - J_{TCs} + J_{cs} \right),$$

$$\frac{d[Ca^{2+}]_p}{dt} = \beta_p([Ca^{2+}]_p) \left(J_r + J_{Ca} - J_{dps} - h_{mito} \cdot f_p \cdot J_{uni} \cdot \frac{v_m}{v_p} \right),$$

$$\frac{d[Ca^{2+}]_{NSR}}{dt} = \left((J_{up} - J_{leak}) \frac{v_i}{v_{NSR}} - J_{tr} \frac{v_{JSR}}{v_{NSR}} + J_{cNSR} \right),$$

$$\frac{d[Ca^{2+}]_{JSR}}{dt} = \beta_{JSR}([Ca^{2+}]_{JSR}) \left(J_{tr} - J_r \frac{v_p}{v_{JSR}} \right),$$

$$\frac{d[CaT]_i}{dt} = J_{TCi},$$

$$\frac{d[CaT]_s}{dt} = J_{TCs},$$

where h_{mito}=1, if a mitochondrion connects to the CRU, otherwise h_{mito}=0. f_p is the fraction of MCUs facing the proximal space, and f_s is the fraction of MCUs facing the submembrane space. The volumes of different compartments are listed in Table S6. Intracellular Ca^{2+} cycling parameters are listed in Table S7. The diffusion flux and buffers of the intracellular Ca^{2+} cycling remain the same as in (3, 9, 10). Mitochondrial Ca^{2+} cycling parameters are listed in Table S8.

Table S6. Effective volumes of different compartments

Parameter	Description	Value
v_i	Local cytosolic volume	0.5 μm^3
v_s	Local submembrane volume	0.025 μm^3
v_p	Local proximal space volume	0.00126 μm^3
v_{JSR}	Local JSR volume	0.02 μm^3
v_{NSR}	Local NSR volume	0.025 μm^3
v_m	Local mitochondrial volume	0.33 μm^3

2.1. Ca^{2+} diffusion within a CRU

$$J_{dsi} = \frac{[Ca^{2+}]_s - [Ca^{2+}]_i}{\tau_{si}},$$

$$J_{dps} = \frac{[Ca^{2+}]_p - [Ca^{2+}]_s}{\tau_{ps}},$$

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

The diffusion time constants are listed in Table S7.

2.2. Ca^{2+} diffusion among neighboring CRUs

The Ca^{2+} diffusive fluxes within cytosol, submembrane, and NSR are:

$$J_c^{(n)} = \sum \left(\frac{c^{(m)} - c^{(n)}}{\tau_{mn}} \right),$$

where the sum is over the six nearest neighbors. The diffusion time constants for Ca^{2+} in cytosol, submembrane and NSR in longitudinal and transverse directions are listed in Table S7.

Table S7. Intracellular calcium diffusive time scales

Parameter	Description	Value
τ_{si}	Submembrane to cytoplasm	0.1 ms
τ_{ps}	Proximal to submembrane	0.022 ms
τ_{tr}	JSR refilling	5 ms
$\tau_{i,T}$	Transverse cytosolic	2.93 ms
$\tau_{i,L}$	Longitudinal cytosolic	2.32 ms
$\tau_{NSR,T}$	Transverse NSR	7.2 ms
$\tau_{NSR,L}$	Longitudinal NSR	24 ms
$\tau_{s,T}$	Transverse submembrane	1.42 ms
$\tau_{s,L}$	Longitudinal submembrane	3.4 ms

2.3. Troponin C buffering

J_{TCi} and J_{TCs} describe the rates of change in the concentration of Ca^{2+} bound to Troponin C in the cytosolic ($[CaT]_i$) and submembrane ($[CaT]_s$) compartments,

$$J_{TCi} = k_{on,T}\,[Ca^{2+}]_i(B_T - [CaT]_i) - k_{off,T}\,[CaT]_i,$$
$$J_{TCs} = k_{on,T}\,[Ca^{2+}]_s(B_T - [CaT]_s) - k_{off,T}\,[CaT]_s.$$

The rate constants are given in Table S8.

2.4. Instantaneous cytosolic Ca^{2+} buffering

The instantaneous cytosolic Ca^{2+} buffering constant $\beta_i(c_i)$ is:

$$\beta_i(c_i) = \left[1 + \frac{\sum B_b K_b}{(c_i + K_b)^2}\right]^{-1},$$

where the sum is over the instantaneous cytosolic buffers Calmodulin, SR sites, Myosin (Ca^{2+}), and Myosin (Mg^{2+}), with buffer dissociation constants K_{CAM}, K_{SR}, K_{MCa}, and K_{MMg} and total concentration of buffering sites B_{CAM}, B_{SR}, B_{MCa}, and B_{MMg}, respectively. The parameters are listed in Table S8.

Table S8. Cytosolic buffering parameters

Parameter	Description	Value
$k_{on,T}$	Rate constant of Ca^{2+} binding to Troponin C	0.0327 $\mu M^{-1} ms^{-1}$
$k_{off,T}$	Rate constant of Ca^{2+} unbinding from Troponin C	0.0196 ms^{-1}
K_{CAM}	Dissociation constant for Calmodulin	7 μM
B_{CAM}	Total concentration of Calmodulin buffering sites	24 μM
K_{SR}	Dissociation constant for SR sites	0.6 μM
B_{SR}	Total concentration of SR sites	47 μM
K_{MCa}	Dissociation constant for Myosin (Ca^{2+})	0.033 μM
B_{MCa}	Total concentration of Myosin (Ca^{2+}) buffering sites	140 μM
K_{MMg}	Dissociation constant for Myosin (Mg^{2+})	3.64 μM
B_{MMg}	Total concentration of Myosin (Mg^{2+}) buffering sites	140 μM

2.5. Instantaneous luminal Ca^{2+} buffering

$\beta_{JSR}([Ca^{2+}]_{JSR})$ describes instantaneous luminal Ca^{2+} buffering to calsequestrin (CSQN). The expression of $\beta_{JSR}([Ca^{2+}]_{JSR})$ (denoted as $\beta(c)$ for simplicity) is

$$\beta(c) = \left(1 + \frac{K_c B_{CSQN} n(c) + \partial_c n(c)(cK_c + c^2)}{(K_c + c)^2}\right)^{-1},$$

where

$$n(c_{jsr}) = \widehat{M} n_M + (1 - \widehat{M}) n_D,$$
$$\widehat{M} = \frac{(1 + 8\rho B_{CSQN})^{\frac{1}{2}} - 1}{4\rho B_{CSQN}},$$

and

$$\rho(c_{jsr}) = \frac{\rho_\infty c^h}{K^h + c^h}.$$

The parameters are listed in Table S9.

Table S9. Luminal buffering parameters

Parameter	Description	Value
B_{CSQN}	Concentration of calsequestrin (CSQN) molecules	460 μM
K_c	Dissociation constant of CSQN	600 μM
n_M	Buffering capacitance of CSQN monomers	15
n_D	Buffering capacitance of CSQN dimers	35
ρ_∞	Asymptotic ratio of dimers to monomers	5000
K	Dimerization constant	850 μM
h	Dimerization exponent (steepness)	23

2.6. SERCA pump

ATP, ROS regulation and CaMKII activation effects on SERCA are incorporated into the model. The flux of SERCA is formulated as

$$J_{up} = v_{up} \cdot f_{up,ATP} \cdot f_{up,ROS} \frac{[Ca^{2+}]_i^2}{[Ca^{2+}]_i^2 + \left(k_i - PLB([CaMKII]_{act})\right)^2},$$

where

$$f_{up,ATP} = \frac{1}{1 + \frac{[ADP]_f}{k'_{i,up}} + \left(1 + \frac{[ADP]_f}{k_{i,up}}\right)\frac{k_{mupATP}}{[ATP]}},$$

$$f_{up,ROS} = \frac{1}{1 + \left(\frac{[ROS]}{k_{d,ROS}}\right)^{h_{ROS,SERCA}}} + \frac{0.75}{1 + \left(\frac{k_{d,ROS}}{[ROS]}\right)^{h_{ROS,SERCA}}},$$

$$PLB([CaMKII]_{act}) = \frac{\Delta k_{m,up}}{1 + \left(\frac{k_{mCaMPLB}}{[CaMKII]_{act}}\right)^{h_{CaMPLB}}}.$$

The parameters are listed in Table S10.

2.7. SR Ca^{2+} leak flux (J_{leak})

The Hund et al formulation (2) is used for the background SR Ca^{2+} leak flux due to CaMKII-dependent phosphorylation:

$$J_{leak} = g_{leak}(1 + \Delta k_{leak})([Ca^{2+}]_{NSR} - [Ca^{2+}]_i)\frac{[Ca^{2+}]_{NSR}{}^2}{[Ca^{2+}]_{NSR}^2 + k_{JSR}^2},$$

where

$$\Delta k_{leak} = \frac{k_{leak,max}}{1 + \left(\frac{k_{mCaMleak}}{[CaMKII]_{act}}\right)^{h_{CaMleak}}}.$$

The parameters are listed in Table S10.

Table S10. SERCA uptake and leak flux parameters

Parameter	Description	Value
$^{*}v_{up}$	SERCA uptake strength	$0.3\ \mu M \cdot ms^{-1}$
$^{*}k_i$	K_d for Ca^{2+} sensitivity	0.5 μM
$k_{i,up}$	ADP first inhibition constant for SERCA	140 μM
$k'_{i,up}$	ADP second inhibition constant for SERCA	5100 μM
k_{mupATP}	ATP half-saturation constant for SERCA	10 μM

$k_{d,ROS}$	K_d for ROS inhibition on SERCA	50 μM
$h_{ROS,SERCA}$	ROS inhibition exponent	1
$\Delta k_{m,up}$	Maximal CaMKII-dependent decrease in k_i	0.17 μM
$k_{mCaMPLB}$	K_d for CaMKII activation on PLB	0.15
h_{CaMPLB}	Exponent of CaMKII activation on PLB	1
g_{leak}	Strength of leak current	1.035×10^{-5} ms^{-1}
k_{JSR}	K_d for leak current	500 μM
$k_{leak,max}$	Maximal CaMKII-dependent increase in SR leak	0.5
$k_{mCaMleak}$	K_d for CaMKII activation on SR leak	0.15
$h_{CaMleak}$	Exponent of CaMKII activation on SR leak	1

* v_{up} is 0.3 μM · ms^{-1} for all the simulations except for the simulations shown in Fig.7B, where its value is increased to 0.8.
* k_i is 0.5 μM for all the simulations except for the simulations shown in Fig.7B, where its value is decreased to 0.3.

2.8. Background Ca^{2+} flux

$$J_{cab} = \alpha_{cab} \cdot I_{Ca,b},$$

where $\alpha_{cab} = \left(\frac{2Fv_i}{C_m}\right)^{-1}$ is the factor to convert the unit of pA/pF to $\frac{\mu M}{ms}$, and $\bar{I}_{Ca,b}$ is the background Ca^{2+} current in a single CRU as described in Section **1.12**.

2.9. L-type Ca^{2+} channel flux

$$J_{Ca} = \alpha_{LCC} \cdot \bar{I}_{Ca,L},$$

where $\alpha_{LCC} = \left(\frac{2Fv_p}{C_m}\right)^{-1}$ is the factor to convert the unit of pA/pF to $\frac{\mu M}{ms}$, and $\bar{I}_{Ca,L}$ is the LCC current in a single CRU as described in Section **1.3**.

2.10. Na^+-Ca^{2+} exchange flux

$$J_{NCX} = \alpha_{NCX} \cdot \bar{I}_{NCX},$$

where $\alpha_{NCX} = \left(\frac{Fv_s}{C_m}\right)^{-1}$ is the factor to convert the unit of pA/pF to $\frac{\mu M}{ms}$, and $\bar{I}_{NCX}$ is the Na^+-Ca^{2+} exchanger current in a single CRU as described in Section **1.4**.

2.11. Ca^{2+} release flux from ryanodine receptors

$$J_r = J_{max} \cdot P_o \frac{[Ca^{2+}]_{JSR} - [Ca^{2+}]_p}{v_p},$$

where P_o is the fraction of RyR channels that are in the opening state, and J_{max} is the maximum RyR flux strength.

2.12. RyR gating model

The RyR model (see Fig.1B) is the same as the one by Restrepo et al (11), consisting of four states: closed CSQN-unbound (CU), open CSQN-unbound (OU), open CSQN-bound (OB), and closed CSQN-bound (CB). The rates of transition are:

$$k_{12} = k_{base} \cdot K_u \cdot (1 + \Delta k_{CaMK} + \Delta k_{ROS}) \cdot [Ca^{2+}]_p^2,$$
$$k_{14} = \frac{\widehat{M}\tau_b^{-1} B_{CSQN}}{B_{CSQN,0}},$$
$$k_{21} = \tau_c^{-1},$$
$$k_{23} = \frac{\widehat{M}\tau_b^{-1} B_{CSQN}}{B_{CSQN,0}},$$
$$k_{43} = K_b [Ca^{2+}]_p^2,$$
$$k_{41} = \tau_u^{-1},$$
$$k_{34} = \tau_c^{-1},$$
$$k_{32} = \frac{k_{41} k_{12}}{k_{43}},$$

where

$$\Delta k_{CaMK} = \frac{\Delta k_{CaMK,max}}{1 + \left(\frac{K_{mCaMRyR}}{[CaMKII]_{act}}\right)^{h_{CaMRyR}}},$$
$$\Delta k_{ROS} = \frac{\Delta k_{ROS,max}}{1 + \left(\frac{K_{mROSRyR}}{[ROS]}\right)^{h_{ROSRyR}}}.$$

The parameters are listed in Table S11.

Table S11. RyR gating parameters

Parameter	Description	Value
k_{base}	Pre-factor of K_u	1
K_u	CSQN-unbound opening rate	0.00038 $\mu M^{-2} ms^{-1}$
K_b	CSQN-bound opening rate	0.00005 $\mu M^{-2} ms^{-1}$
$B_{CSQN,0}$	Normal CSQN concentration	400 μM
τ_u	CSQN unbinding timescale	125 ms
τ_b	CSQN binding timescale	2 ms
τ_c	RyR closing timescale	1 ms
$\Delta k_{CaMK,max}$	Maximal CaMKII-dependent increase in K_u	0.5
$K_{mCaMRyR}$	K_d for CaMKII activation on K_u	0.2
h_{CaMRyR}	Exponent of CaMKII activation on K_u	1
* $\Delta k_{ROS,max}$	Maximal ROS-dependent increase in K_u	0.3
$K_{mROSRyR}$	K_d for ROS-dependent increase on K_u	10 μM
h_{ROSRyR}	Exponent of ROS-dependent increase on K_u	1

* $\Delta k_{ROS,max}$ is 0.3 for all the simulations except for the simulations shown in Fig.7B, where its value is increased to 2 to increase the leakiness of RyR, promoting Ca^{2+} waves.

3. Mitochondrial Ca^{2+} cycling

The free Ca^{2+} concentraiton in a single mitochondrion is decribed by:

$$\frac{d[Ca^{2+}]_m}{dt} = \beta_m (J_{uni} - J_{NCXm} - J_{MPTP}),$$

where β_m is the Ca^{2+} buffering factor, which is described in Section **3.5**. The fluxes, J_{uni}, J_{NCXm}, and J_{MPTP}, are described below.

3.1. Mitochondrial uniporter Ca^{2+} flux

The formulation is taken from Williams et al (12):

$$J_{uni} = p_0 \cdot N_{MCU} \cdot \frac{i_{MCU}}{zFv_{myo}},$$

$$i_{MCU} = \frac{g_{MCU,max}}{1 + \frac{K_m}{[Ca^{2+}]}} \cdot (\Delta\psi - E_{Ca,m}),$$

$$E_{Ca,m} = \frac{RT}{zF} \ln\left(\frac{[Ca^{2+}]_{space}}{[Ca^{2+}]_m}\right),$$

where $[Ca^{2+}]_{space}$ is replaced by $[Ca^{2+}]_i$, $[Ca^{2+}]_s$, or $[Ca^{2+}]_p$ with the mitochondrial uniporter facing the cytosolic, submembrane or dyadic space. The parameters are given in Table S12.

3.2. Mitochondrial Na^+-Ca^{2+} exchange flux

The formulation is taken from Cortassa et al (6),

$$J_{NCXm} = v_{NCX,max} \cdot \frac{e^{\frac{bF}{RT}(\Delta\psi - \psi_0)} \cdot \frac{[Ca^{2+}]_m}{[Ca^{2+}]_i}}{\left(1 + \frac{k_{Na}}{[Na^+]_i}\right)^n \cdot \left(1 + \frac{k_{Ca}}{[Ca^{2+}]_m}\right)}.$$

The parameters are given in Table S12.

3.3. Mitochondrial permeability transition pore flux

$$J_{MPTP} = g_{MPTP} \cdot P_{MPTP} \cdot ([Ca^{2+}]_m - [Ca^{2+}]_i),$$

where P_{MPTP} is the open probability of MPTPs, which is governed by a stochastic Markov model described below. The parameters are given in Table S12.

3.4. Mitochondrial permeability transition pore gating model

The MPTP gating kinetics is described by a 3-state Markov model (see Fig.1F), which was developed by Korge et al (13). The transition rates are retuned to fit recent experimental data as stated in the main text. The transition rates from C_0 to C_1 is mitochondrial Ca^{2+} dependent, i.e.,

$$k_{c0c1} = \alpha_0 \left(1 + 199 \cdot \frac{[Ca^{2+}]_m^{h_{MPTP}}}{[Ca^{2+}]_m^{h_{MPTP}} + [Ca^{2+}]_0^{h_{MPTP}}}\right),$$

The other rate constants are given in Table S12.

3.5. Mitochondrial Ca^{2+} buffering factor

When MPTP opens, the buffering factor β_m is set to be $\beta_{m,on}$, and when MPTP closes, the buffering factor relaxes to $\beta_{m,off}$ with a time constant τ_m, i.e.,

$$\beta_m = \begin{cases} \beta_{m,on}, & \text{MPTP opens} \\ \beta_{m,off} - (\beta_{m,off} - \beta_m)e^{-\frac{\Delta t}{\tau_{off}}}, & \text{MPTP closes} \end{cases}$$

The parameters are given in Table S12.

Table S12. Mitochondrial Ca^{2+} dynamics parameters

Parameter	Description	Value
p_0	MCU open probability	0.9
N_{MCU}	Number of MCUs per mitochondrion	200
v_{myo}	Myoplasmic volume	18 μl
$g_{MCU,max}$	MCU maximal conductance	8.1 pS
K_m	Half-saturation constant for MCU	19 mM
$\nu_{NCX,max}$	Maximal Na^+-Ca^{2+} exchanger rate	$0.0035\ \mu M \cdot ms^{-1}$
ψ_0	$\Delta\psi$ offset for Ca^{2+} transporter	91 mV
b	Na^+-Ca^{2+} exchanger $\Delta\psi$ dependence	0.5
k_{Na}	K_d ($[Na^+]_i$) for Na^+-Ca^{2+} exchanger	9.4 mM
n	Na^+-Ca^{2+} exchanger cooperativity for $[Na^+]_i$	3
k_{Ca}	K_d ($[Ca^{2+}]_i$) for Na^+-Ca^{2+} exchanger	0.375 μM
g_{MPTP}	Maximal mPTP conductance	$100\ ms^{-1}$
α_0	Rate constant from C_0 to C_1	$3.015 \times 10^{-9}\ ms^{-1}$
$[Ca^{2+}]_0$	K_d for Ca^{2+} dependent opening	2 μM
h_{MPTP}	Exponent for Ca^{2+} dependent opening	5
α_1	Rate constant from C_1 to O	$3.03 \times 10^{-7}\ ms^{-1}$
β_0	Rate constant from C_1 to C_0	$3.015 \times 10^{-7}\ ms^{-1}$
β_1	Rate constant from O to C_1	$1.5 \times 10^{-5}\ ms^{-1}$
$\beta_{m,on}$	Ca^{2+} buffer capacitance when MPTP opens	0.1
$\beta_{m,off}$	Asymptotic Ca^{2+} buffer capacitance when MPTP closes	0.01
τ_{off}	Relaxation time constant for Ca^{2+} buffer when MPTP closes	20 s

3.6 Mitochondrial membrane potential

We used a simple formulation for mitochondrial membrane potential ($\Delta\psi$) following Korge et al (13), i.e.,

$$\frac{d\Delta\psi}{dt} = V_{\psi S} - k_{\psi U} \cdot \Delta\psi - I_{uni} - I_{NCXm},$$

$$I_{uni} = 2 \cdot \frac{1}{C_{mito}} \cdot J_{uni},$$

$$I_{NCXm} = \frac{1}{C_{mito}} \cdot J^{m}_{NaCa},$$

where $C_{mito=}1.812\ \mu M \cdot mV^{-1}$ is from Cortassa et al (14). $V_{\psi S} = 3.5\ mV \cdot ms^{-1}$ and $k_{\psi U} = 0.0192\ ms^{-1}$ are from Yang et al (15).

We assume that mitochondrial membrane potential is immediately depolarized to zero once the MPTP in a mitochondrion opens. Therefore, the mitochondrial membrane potential is numerically updated as follows:

$$\Delta\psi^{t+\Delta t} = \begin{cases} \Delta\psi^{t} + \frac{d\Delta\psi}{dt} \cdot \Delta t, & \text{if mPTP closes,} \\ 0, & \text{otherwise.} \end{cases}$$

4. Cytosolic ATP

A simplified ATP model is adapted from our previous study (16). We reformulated the cytosolic ATP and ADP cycling as follows:

$$[\mathrm{ATP}] + [\mathrm{ADP}] = \mathrm{TAN},$$

$$\frac{\mathrm{d}[\mathrm{ATP}]}{\mathrm{dt}} = -\mathrm{V_{ATP,consum}} + \mathrm{V_{ATPase}} + \mathrm{J_{ATP,D}},$$

$$\mathrm{V_{ATP,consum}} = \mathrm{k_{ATP,consum}}\frac{\mathrm{p_{sp}}}{\mathrm{p_{sp}} + \mathrm{k_{d,pspconsum}}},$$

where

$$\mathrm{p_{sp}} = \frac{[\mathrm{ATP}]}{[\mathrm{ADP}]_\mathrm{f}}.$$

$$\mathrm{V_{ATPase}} = \mathrm{k_{ATPase}}\left(\mathrm{f_{\Delta\psi}}\mathrm{f_{ADP}} - \mathrm{g_{\Delta\psi}}\mathrm{f_{ATP}}\right),$$

where

$$\mathrm{f_{\Delta\psi}} = \frac{\Delta\psi}{\Delta\psi + \mathrm{k_{d,\Delta\psi}}},$$

$$\mathrm{f_{ADP}} = \frac{1}{1 + \mathrm{k_{d,psn}} \cdot \mathrm{p_{sp}}},$$

$$\mathrm{g_{\Delta\psi}} = 0.3\left(1 - \mathrm{f_{\Delta\psi}}\right),$$

$$\mathrm{f_{ATP}} = \frac{\mathrm{p_{sp}}}{\mathrm{p_{sp}} + \mathrm{k_{d,psp}}}.$$

$$\mathrm{J_{ATP,D}} = \mathrm{D_{ATP}}\left(\frac{[\mathrm{ATP}]^{\mathrm{i+1,j,k}} + [\mathrm{ATP}]^{\mathrm{i-1,j,k}} - 2[\mathrm{ATP}]}{\Delta\mathrm{x}^2} + \frac{[\mathrm{ATP}]^{\mathrm{i,j+1,k}} + [\mathrm{ATP}]^{\mathrm{i,j-1,k}} + [\mathrm{ATP}]^{\mathrm{i,j,k+1}} + [\mathrm{ATP}]^{\mathrm{i,j,k-1}} - 4[\mathrm{ATP}]}{\Delta\mathrm{y}^2}\right),$$

$$\frac{\mathrm{d}[\mathrm{ADP}]_\mathrm{f}}{\mathrm{dt}} = \beta_{\mathrm{ADP}}(\mathrm{TAN} - [\mathrm{ATP}]),$$

where i, j, and k are the indices of a CRU in the model.

The parameters are given in Table S13.

Table S13. Cytosolic ATP and ADP parameters

Parameter	Description	Value
$\mathrm{k_{ATP,consum}}$	ATP consumption rate constant	0.01 μM · $\mathrm{ms^{-1}}$
$\mathrm{k_{d,pspconsum}}$	Michaelis constant for $\mathrm{p_{sp}}$	200
$\mathrm{k_{ATPase}}$	ATP synthesis/hydrolysis rate constant	0.16 μM · $\mathrm{ms^{-1}}$
$\mathrm{k_{d,\Delta\psi}}$	Michaelis constant for $\mathrm{f_{\Delta\psi}}$	150
$\mathrm{k_{d,psn}}$	Michaelis constant for $\mathrm{f_{ADP}}$	0.02
$\mathrm{k_{d,psp}}$	Michaelis constant for $\mathrm{f_{ATP}}$	0.5
$\mathrm{D_{ATP}}$	Diffusion constant of ATP	0.25 $\mu\mathrm{m}^2 \cdot ms^{-1}$
TAN	Total ATP and ADP	7000 μM
β_{ADP}	ADP buffer term	0.025

5. Cytosolic reactive oxygen species (ROS)

The equation governing the cytosolic ROS level in a single CRU is the following,

$$\frac{\mathrm{d}[\mathrm{ROS}]}{\mathrm{dt}} = \mathrm{V_{SODC}} - \mathrm{V_{DC}} + \mathrm{J_{ROS,D}},$$

where

$$V_{SODC} = \begin{cases} a_0 + \dfrac{K_{prod}}{1 + \left(\frac{170}{200 - \Delta\Psi}\right)^9}, & \text{if the CRU is attached to a mitochondrion} \\ 0, & \text{otherwise} \end{cases},$$

$$V_{DC} = K_{DC}[ROS],$$

$$J_{ROS,D} = D_{ROS}\left(\frac{[ROS]^{i+1,j,k} + [ROS]^{i-1,j,k} - 2[ROS]}{\Delta x^2} + \frac{[ROS]^{i,j+1,k} + [ROS]^{i,j-1,k} + [ROS]^{i,j,k+1} + [ROS]^{i,j,k-1} - 4[ROS]}{\Delta y^2}\right),$$

where i, j and k are the indices of the CRU in the model.

The parameters are given in Table S14.

Table S14. Cytosolic ROS parameters

Parameter	Description	Value
a_0	Baseline production rate	0.036 μM · ms^{-1}
K_{prod}	Production rate constant	100 μM · ms^{-1}
K_{DC}	Degradation rate constant	0.1 ms^{-1}
D_{ROS}	ROS diffusion constant	1.2 $\mu m^2 \cdot ms^{-1}$
Δx	CRU separation in the longitudinal direction	1.84 μm
Δy	CRU separation in the transverse direction	0.9 μm

6. Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) signaling

The 4-state Ca^{2+}-bound calmodulin model (see Fig.1D) is from Chiba et al (17):

$$\frac{d[CaMCa]}{dt} = -CA_1 + CA_2,$$
$$\frac{d[CaMCa2]}{dt} = -CA_2 + CA_3,$$
$$\frac{d[CaMCa3]}{dt} = -CA_3 + CA_4,$$
$$\frac{d[CaMCa4]}{dt} = -CA_4,$$
$$[CaM] = CaM_{tot} - [CaMCa] - [CaMCa2] - [CaMCa3] - [CaMCa4],$$

$$CA_1 = -k_{1CaM} \cdot [Ca^{2+}]_i \cdot [CaM] + k_{n1CaM} \cdot [CaMCa],$$
$$CA_2 = -k_{2CaM} \cdot [Ca^{2+}]_i \cdot [CaMCa] + k_{n2CaM} \cdot [CaMCa2],$$
$$CA_3 = -k_{3CaM} \cdot [Ca^{2+}]_i \cdot [CaMCa2] + k_{n3CaM} \cdot [CaMCa3],$$
$$CA_4 = -k_{4CaM} \cdot [Ca^{2+}]_i \cdot [CaMCa3] + k_{n4CaM} \cdot [CaMCa4],$$

The CaMKII activation model (see Fig.1E) is from Foteinou et al (18),

$$\frac{d[CaMKII_{CaMCa4}]}{dt} = A_1 - A_2 - B_1 + B_2 - E_1 + E_2,$$
$$\frac{d[CaMKIIP_{CaMCa4}]}{dt} = B_1 - B_2 - C_1 + C_2 - I_2 + I_1,$$

$$\frac{d[CaMKIIP]}{dt} = C_1 - C_2 - D_1 - H_2 + H_1,$$
$$\frac{d[CaMKIIOXB]}{dt} = E_1 - E_2 - F_1 + F_2,$$
$$\frac{d[CaMKIIOXP]}{dt} = F_1 - F_2 - I_1 + I_2 - G_1 + G_2,$$
$$\frac{d[CaMKIIOXA]}{dt} = G_1 - G_2 + H_2 - H_1,$$

$$[CaMKII] = CaMKII_{tot} - [CaMKIIP] - [CaMKII_{CaMCa4}] - [CaMKIIP_{CaMCa4}] - [CaMKIIOXB] - [CaMKIIOXP] - [CaMKIIOXA],$$

$$[CaMKII]_{act} = [CaMKIIP] + [CaMKII_{CaMCa4}] + [CaMKIIP_{CaMCa4}] + [CaMKIIOXB] + [CaMKIIOXP] + [CaMKIIOXA].$$

$$A_1 = k_{asso} \cdot [CaMKII] \cdot [CaMCa4],$$
$$A_2 = [CaMKII_{CaMCa4}] \cdot \left(k_{disso}\left(1 - \frac{K_{mCaM}^3}{[Ca^{2+}]_i^3 + K_{mCaM}^3}\right) + k_{dissoCa} \cdot \frac{K_{mCaM}^3}{[Ca^{2+}]_i^3 + K_{mCaM}^3}\right),$$
$$B_1 = k_{cat37c} \cdot P \cdot \frac{[ATP]}{[ATP] + K_{mATP}} \cdot [CaMKII_{CaMCa4}],$$
$$P = 1 - \left(\frac{[CaMKII]}{CaMKII_{tot}}\right)^2,$$
$$B_2 = k_{catpp1new} \cdot PP1 \cdot \frac{[CaMKIIP_{CaMCa4}]}{[CaMKIIP_{CaMCa4}] + K_{mPP1}},$$
$$k_{catpp1new} = k_{catpp1} \cdot \frac{1}{1 + \frac{[ROS]}{K_{mROS}}},$$
$$C_1 = [CaMKIIP_{CaMCa4}] \cdot \left(k_{disso2}\left(1 - \frac{K_{mCaM}^3}{[Ca^{2+}]_i^3 + K_{mCaM}^3}\right) + k_{dissoCa2} \cdot \frac{K_{mCaM}^3}{[Ca^{2+}]_i^3 + K_{mCaM}^3}\right),$$
$$C_2 = k_{asso} \cdot [CaMKIIP] \cdot [CaMCa4],$$
$$D_1 = k_{catpp1new} \cdot PP1 \cdot \frac{[CaMKIIP]}{[CaMKIIP] + K_{mPP1}},$$
$$E_1 = k_{ox} \cdot [CaMKII_{CaMCa4}] \cdot [ROS],$$
$$E_2 = k_{MsrA} \cdot [CaMKIIOXB],$$
$$F_1 = k_{cat37c} \cdot P \cdot \frac{[ATP]}{[ATP] + K_{mATP}} \cdot [CaMKIIOXB],$$
$$F_2 = k_{catpp1new} \cdot PP1 \cdot \frac{[CaMKIIOXP]}{[CaMKIIOXP] + K_{mPP1}},$$
$$I_1 = k_{MsrA} \cdot [CaMKIIOXP],$$
$$I_2 = k_{ox} \cdot [CaMKIIP_{CaMCa4}] \cdot [ROS],$$
$$G_1 = [CaMKIIOXP] \cdot \left(k_{disso2}\left(1 - \frac{K_{mCaM}^3}{[Ca^{2+}]_i^3 + K_{mCaM}^3}\right) + k_{dissoCa2} \cdot \frac{K_{mCaM}^3}{[Ca^{2+}]_i^3 + K_{mCaM}^3}\right),$$
$$G_2 = k_{asso} \cdot [CaMKIIOXA] \cdot [CaMCa4],$$
$$H_1 = k_{MsrA} \cdot [CaMKIIOXA],$$
$$H_2 = k_{ox} \cdot [CaMKIIP] \cdot [ROS].$$

The parameters are given in Table S15.

Table S15. Ca^{2+}-bound calmodulin and CaMKII activation parameters

Parameter	Description	Value
CaM_{tot}	Total calmodulin concentration	50 μM
k_{1CaM}	Calcium binding rate 1	0.0025 $\mu M^{-1} ms^{-1}$
k_{n1CaM}	Calcium unbinding rate 1	0.05 ms^{-1}
k_{2CaM}	Calcium binding rate 2	0.08825 $\mu M^{-1} ms^{-1}$
k_{n2CaM}	Calcium unbinding rate 2	0.05 ms^{-1}
k_{3CaM}	Calcium binding rate 3	0.0125 $\mu M^{-1} ms^{-1}$
k_{n3CaM}	Calcium unbinding rate 3	1.25 ms^{-1}
k_{4CaM}	Calcium binding rate 4	0.25 $\mu M^{-1} ms^{-1}$
k_{n4CaM}	Calcium unbinding rate 4	1.25 ms^{-1}
$CaMKII_{tot}$	Total CaMKII concentration	1 μM
k_{asso}	CaMCa4 association rate	0.0021 $\mu M^{-1} ms^{-1}$
k_{disso}	Dissociation rate of CaMCa4 from CaMKII_CaMCa4 pathway 1	7×10^{-5} ms^{-1}
$k_{dissoCa}$	Dissociation rate of CaMCa4 from CaMKII_CaMCa4 pathway 2	9.5×10^{-4} ms^{-1}
k_{disso2}	Dissociation rate of CaMCa4 from CaMKIIP_CaMCa4 pathway 1	7×10^{-8} ms^{-1}
$k_{dissoCa2}$	Dissociation rate of CaMCa4 from CaMKIIP_CaMCa4 pathway 2	9.5×10^{-7} ms^{-1}
K_{mCaM}	Half saturation of Ca dissociation from from CaMKII_CaMCa4	0.03 μM
k_{cat37c}	Phosphorylation rate constant at 37 °C	5.4×10^{-3} ms^{-1}
K_{mATP}	Michaelis constant for the CaMKII-ATP complex	19.1 μM
k_{catpp1}	Dephosphorylation rate constant	1.72×10^{-3} ms^{-1}
K_{mROS}	Michaelis constant for the ROS-mediated autophosphorylation	1 μM
K_{mPP1}	Michaelis constant for the PP1-CaMKII complex	11 μM
k_{ox}	Oxidation dependent rate	$1.28 \times 10^{-5} \mu M^{-1} ms^{-1}$
k_{MsrA}	Reductase rate mediated by methionine sulfoxide reductase A	10^{-4} ms^{-1}
PP1	PP1 concentration	1 μM

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