Appendix

Equations and Parameters for Model Simulations

Goforth et al, J. Gen. Physiol. 120(3):307-322, 2002

Model I (no subspace; Fig. 6)

Units:

Conductances	pS
Currents	fA
Ca concentrations	μM
Time	ms
Capacitance	fF

Differential Equations:

$$C_m \frac{dv}{dt} = -I_{\mathrm{Ca}} - I_{\mathrm{Kv}} - I_{\mathrm{KATP}} - I_{\mathrm{KCa}} - I_{\mathrm{Leak}} \quad (1)$$

$$\frac{dn}{dt} = \frac{n_\infty(v) - n}{\tau_n} \quad (2)$$

$$\frac{dc}{dt} = f_{\mathrm{CYT}} \left(-\alpha I_{\mathrm{Ca}} - J_{\mathrm{PMCA}} - J_{\mathrm{SERCA}} + J_{\mathrm{RELEASE}}\right) \quad (3)$$

$$\frac{dc_{\mathrm{ER}}}{dt} = f_{\mathrm{ER}} \frac{V_{\mathrm{CYT}}}{V_{\mathrm{ER}}} \left(J_{\mathrm{SERCA}} - J_{\mathrm{RELEASE}}\right) \quad (4)$$

(For voltage-clamp protocol, equation for V is replaced by a given function of time.)

Initial Conditions:

v	-65.0
n	0.0001
c	0.014
c_{ER}	110.0

Ionic Currents:

$$
\begin{aligned}
I_{\mathrm{Ca}} &= g_{\mathrm{Ca}} m_{\infty}(v)(v - v_{\mathrm{Ca}}) && (5)\\
I_{\mathrm{KCa}} &= g_{\mathrm{KCa}} \omega(v - v_{\mathrm{K}}) && (6)\\
I_{\mathrm{KATP}} &= g_{\mathrm{KATP}}(v - v_{\mathrm{K}}) && (7)\\
I_{\mathrm{K}} &= g_{\mathrm{K}} n(v - v_{\mathrm{K}}) && (8)\\
I_{\mathrm{Leak}} &= g_{\mathrm{Leak}}(v - v_{\mathrm{Leak}}) && (9)
\end{aligned}
$$

where:

$$
\begin{aligned}
n_{\infty}(v) &= \frac{1}{1 + \exp((v_n - v)/s_n)} && (10)\\
m_{\infty}(v) &= \frac{1}{1 + \exp((v_m - v)/s_m)} && (11)\\
\omega(c) &= \frac{c^q}{c^q + K_d^q} && (12)
\end{aligned}
$$

and parameters are:

for I_{Kv}:

g_{Kv}	2500
v_{K}	-70
v_n	-15
s_n	5.6
τ_n	11.1

for I_{Ca}:

g_{Ca}	1200
v_{Ca}	30
v_m	-15
s_m	8

for I_{KCa}:

g_{KCa}	800
K_d	0.6
q	5

for I_{Leak}:

g_{Leak}	15
v_{Leak}	-30

for I_{KATP}:

g_{KATP}	60

Calcium fluxes: (μM ms^{-1})

$$J_{\mathrm{PMCA}} = k_{\mathrm{PMCA}}\, c \tag{13}$$

$$J_{\mathrm{SERCA}} = k_{\mathrm{SERCA}}\, c \tag{14}$$

$$J_{\mathrm{RELEASE}} = p_{\mathrm{ER}}\, (c_{\mathrm{ER}} - c) \tag{15}$$

with rates: (ms^{-1})

p_{ER}	0.0001
k_{PMCA}	0.08
k_{SERCA}	0.08

and buffer parameters*:

f_{CYT}	0.01
f_{ER}	0.005

*(dimensionless fraction of calcium that is free in each compartment)

Volume ratios:

$$\frac{V_{\mathrm{CYT}}}{V_{\mathrm{ER}}} = 25.0 \tag{16}$$

Miscellaneous:
Unit Conversion for ICa (converts fA to μM ms^{-1}):

$$\alpha = \frac{1}{2FV_{\mathrm{CYT}}} = 4.5 \times 10^{-6} \mu\mathrm{M\ fA}^{-1}\ \mathrm{ms}^{-1}$$

Here 2 is the valence of calcium; F is Faraday's constant; and V_{CYT} is the volume of the cytosol.
Capacitance: $C_m = 5300$ fF

To simulate delay in effect of thapsigargin do:

$$k_{\mathrm{SERCA}} = k_{\mathrm{SERCA}}^{\mathrm{max}} \cdot \exp(-(t - t_{\mathrm{THAP}})/\tau_{\mathrm{SERCA}})$$

where: $k_{\mathrm{SERCA}}^{\mathrm{max}} = 0.08$, $\tau_{\mathrm{SERCA}} = 60000$, and t_{THAP} = time that thapsigargin was added.

Output functions:

$$I_{\mathrm{TOT}} = (I_{\mathrm{Ca}} + I_{\mathrm{K}} + I_{\mathrm{KATP}} + I_{\mathrm{KCa}} + I_{\mathrm{Leak}}) \cdot 0.001\mathrm{pA}$$

Model II (subspace; Figs. 7–9)

Differential Equations:

$$C_m \frac{dv}{dt} = -I_{\mathrm{Ca}} - I_{\mathrm{Kv}} - I_{\mathrm{KATP}} - I_{\mathrm{KCa}} - I_{\mathrm{Leak}} \tag{17}$$

$$\frac{dn}{dt} = \frac{n_\infty(v) - n}{\tau_n} \tag{18}$$

$$\frac{dc}{dt} = f_{\mathrm{CYT}} \left(-\alpha I_{\mathrm{Ca}} - J_{\mathrm{PMCA}} - J_{\mathrm{SERCA}} + J_{\mathrm{X}}\right) \tag{19}$$

$$\frac{dc_{\mathrm{ER}}}{dt} = f_{\mathrm{ER}} \left(\frac{V_{\mathrm{CYT}}}{V_{\mathrm{ER}}} J_{\mathrm{SERCA}} - J_{\mathrm{RELEASE}}\right) \tag{20}$$

$$\frac{dc_{\mathrm{SS}}}{dt} = f_{\mathrm{SS}} \left(\frac{V_{\mathrm{ER}}}{V_{\mathrm{SS}}} J_{\mathrm{RELEASE}} - \frac{V_{\mathrm{CYT}}}{V_{\mathrm{SS}}} J_{\mathrm{X}}\right) \tag{21}$$

Initial Conditions:

	Fig. 7	Fig. 8	Fig. 9
V	-65.0	-56.0	-35.0
n	0.0001	0.0006	0.017
c	0.027	0.44	0.14
c_{ER}	111.17	60.0	0.14
c_{SS}	0.29	0.33	0.14

Ionic Currents:
(Same as Model I except I_{KCa} depends on c_{SS})

$$I_{\mathrm{Ca}} = g_{\mathrm{Ca}} m_\infty(v)(v - v_{\mathrm{Ca}}) \tag{22}$$

$$I_{\mathrm{KCa}} = g_{\mathrm{KCa}} \omega (v - v_{\mathrm{K}}) \tag{23}$$

$$I_{\mathrm{KATP}} = g_{\mathrm{KATP}} (v - v_{\mathrm{K}}) \tag{24}$$

$$I_{\mathrm{Kv}} = g_{\mathrm{K}} n (v - v_{\mathrm{K}}) \tag{25}$$

$$I_{\mathrm{Leak}} = g_{\mathrm{Leak}} (v - v_{\mathrm{Leak}}) \tag{26}$$

where:

$$n_\infty(v) = \frac{1}{1+\exp((v_n - v)/s_n)} \tag{27}$$

$$m_\infty(v) = \frac{1}{1+\exp((v_m - v)/s_m)} \tag{28}$$

$$\omega(c_{\mathrm{S}S}) = \frac{c_{\mathrm{S}S}^q}{c_{\mathrm{S}S}^q + K_d^q} \tag{29}$$

Parameters:
(**bold** denotes changes from Model I or preceding figure.)

for $I_{\mathrm{K}v}$:

g_{Kv}	2500
v_{K}	-70
v_n	-15
s_n	5.6
τ_n	**10.8**

for I_{Ca}:

g_{Ca}	**1450**
v_{Ca}	30
v_m	$\mathbf{-13}$
s_m	8

for I_{KCa}:

g_{KCa}	**1200**
K_d	**0.7** (reduced to **0.2** in Fig. 9b)
q	**8**

for I_{Leak}:

g_{Leak}	**14**
v_{Leak}	-30

for I_{KATP}:

g_{KATP}	**63**

Calcium fluxes: (μM ms^{-1})

$$J_{\mathrm{PMCA}} = k_{\mathrm{PMCA}}\, c \tag{30}$$
$$J_{\mathrm{SERCA}} = k_{\mathrm{SERCA}}\, c \tag{31}$$
$$J_{\mathrm{RELEASE}} = p_{\mathrm{ER}}\, (c_{\mathrm{ER}} - c_{\mathrm{SS}}) \tag{32}$$
$$J_{\mathrm{X}} = p_{\mathrm{X}}\, (c_{\mathrm{SS}} - c) \tag{33}$$

with rates: (ms^{-1})

	Fig. 7	Fig. 8	Fig. 9
p_{X}	**0.025**	0.025	0.025
p_{ER}	**0.0015**	**0.0030**	0.0030
k_{PMCA}	**0.18**	**0.12**	0.12
k_{SERCA}	**0.1**	0.1	**0.0**

and buffer parameters*:

f_{CYT}	0.01
f_{ER}	0.005
f_{SS}	**0.04**

*(dimensionless fraction of calcium that is free in each compartment)

Volume ratios:

$$\frac{V_{\mathrm{ER}}}{V_{\mathrm{SS}}} = \mathbf{0.1} \tag{34}$$
$$\frac{V_{\mathrm{CYT}}}{V_{\mathrm{SS}}} = \mathbf{2.5} \tag{35}$$
$$\frac{V_{\mathrm{CYT}}}{V_{\mathrm{ER}}} = \mathbf{25.0} \tag{36}$$
$$\frac{V_{\mathrm{SS}}}{V_{\mathrm{CYT}}} = \mathbf{0.4} \tag{37}$$

Miscellaneous:
(Same as Model I.)

Unit Conversion for ICa (converts fA to μM ms^{-1}):

$$\alpha = \frac{1}{2FV_{\mathrm{CYT}}} = 4.5 \times 10^{-6} \mu\mathrm{M\ fA}^{-1}\ \mathrm{ms}^{-1}$$

Here 2 is the valence of calcium; F is Faraday's constant; and V_{CYT} is the volume of the cytosol.
Capacitance: $C_m = 5300$

To simulate delay in effect of thapsigargin do:
(Same as Model I.)

$$k_{\mathrm{SERCA}} = k_{\mathrm{SERCA}}^{\mathrm{max}} \cdot \exp(-(t - t_{\mathrm{THAP}})/\tau_{\mathrm{SERCA}})$$

where: $k_{\mathrm{SERCA}}^{\mathrm{max}} = 0.1$, $\tau_{\mathrm{SERCA}} = 30000$, and t_{THAP} = time that thapsigargin was added.

Output functions:
(Same as Model I, except for additional output function, c_{AVG}.)

$$I_{\mathrm{TOT}} = (I_{\mathrm{Ca}} + I_{\mathrm{K}} + I_{\mathrm{KATP}} + I_{\mathrm{KCa}} + I_{\mathrm{Leak}}) \cdot 0.001\mathrm{pA}$$

$$c_{\mathrm{AVG}} = \frac{V_{\mathrm{SS}} c_{\mathrm{SS}} + V_{\mathrm{CYT}} c}{V_{\mathrm{SS}} + V_{\mathrm{CYT}}}$$