A basic model of calcium homeostasis in non-excitable cells

Christina H. Selstø, Peter Ruoff*

Department of Chemistry, Bioscience, and Environmental Engineering, University of Stavanger, Stavanger, Norway

Supporting Information S1 Text

List of rate equations, abbreviations, and LSODE Y(i) assignments for the model in Fig 3

Rate equations for the final model with source files `CAREG65.f` and `CAREG66.f` are given here. Conditions (i), (ii), and (iii) below refer to the section *Effect of cytosolic calcium on the dissociation of $IP_3R{\bullet}IP_3$*.

The model also contains a Ca-binding indicator Ind, but results on this are not explicitly presented.

$$\begin{aligned}\frac{dCa^{2+}_{cyt}}{dt} &= k_1{\cdot}Ca^{2+}_{ext} - k_2{\cdot}Ca^{2+}_{cyt} - k_3{\cdot}\frac{(PMCA{\bullet}M^*){\cdot}Ca^{2+}_{cyt}}{k_4 + Ca^{2+}_{cyt}}\\ &- 4{\cdot}k_8{\cdot}(M){\cdot}(Ca^{2+}_{cyt}) + 4{\cdot}k_9{\cdot}(M{\bullet}Ca_4) - 4{\cdot}k_{10}{\cdot}(B){\cdot}(Ca^{2+}_{cyt})\\ &+ 4{\cdot}k_{11}{\cdot}(B{\bullet}Ca_4) - \frac{k_{23}{\cdot}(SERCA){\cdot}(Ca^{2+}_{cyt})}{k_{24} + Ca^{2+}_{cyt}} + k_{27}{\cdot}Ca^{2+}_{lum}\\ &+ \frac{k_{36}{\cdot}(R{\bullet}S){\cdot}(ARCC){\cdot}(Ca^{2+}_{ext})}{k_{37} + Ca^{2+}_{ext}} + \frac{k_{38}{\cdot}(IP_3R{\bullet}IP_3){\cdot}(Ca^{2+}_{lum})}{k_{39}{\cdot}f_{IP3R} + f_{IP3R.Ca_{ER}}{\cdot}Ca^{2+}_{lum}}\\ &- \frac{k_{63}{\cdot}(Ca^{2+}_{cyt}){\cdot}(NCX{\bullet}M^*)}{k_{64} + Ca^{2+}_{cyt}} + \frac{k_{73}{\cdot}(Ca^{2+}_{ext}){\cdot}(SOCC){\cdot}(STIM)}{k_{74} + Ca^{2+}_{ext}}\\ &+ k_{51}(Ind{\bullet}Ca) - k_{50}{\cdot}(Ca_{cyt}){\cdot}(Ind) \qquad (1)\end{aligned}$$

$$\frac{d(PMCA{\bullet}M^*)}{dt} = k_5{\cdot}Ca^{2+}_{cyt}{\cdot}(PMCA{\bullet}M) - \frac{k_6{\cdot}(PMCA{\bullet}M^*)}{k_7 + (PMCA{\bullet}M^*)} \qquad (2)$$

$$\frac{d(Ca_{ext})}{dt} = 0 \;\; \text{(extracellular Ca is kept constant at 1 or 2 mM)} \qquad (3)$$

$$\frac{dM}{dt} = k_{16} - k_{17}{\cdot}M - k_{12}{\cdot}(M){\cdot}(PMCA) + k_{13}{\cdot}(PMCA{\bullet}M) + k_9{\cdot}(M{\bullet}Ca_4) - k_8{\cdot}(Ca^{2+}_{cyt}){\cdot}(M) + k_{68}{\cdot}(NCX{\bullet}M) - k_{67}{\cdot}(M){\cdot}(NCX) \tag{4}$$

$$\frac{d(M{\bullet}Ca_4)}{dt} = k_8{\cdot}(Ca^{2+}_{cyt}){\cdot}(M) - k_9{\cdot}(M{\bullet}Ca_4) \tag{5}$$

$$\frac{dB}{dt} = k_{18} - k_{19}{\cdot}B - k_{10}{\cdot}(B){\cdot}(Ca^{2+}_{cyt}) + k_{11}{\cdot}(B{\bullet}Ca_4) \tag{6}$$

$$\frac{d(B{\bullet}Ca_4)}{dt} = k_{10}{\cdot}(B){\cdot}(Ca^{2+}_{cyt}) - k_{11}{\cdot}(B{\bullet}Ca_4) \tag{7}$$

$$\frac{d(PMCA{\bullet}M)}{dt} = k_{12}{\cdot}(PMCA){\cdot}(M) - k_{13}{\cdot}(PMCA{\bullet}M) + \frac{k_6{\cdot}(PMCA{\bullet}M^*)}{k_7 + (PMCA{\bullet}M^*)} - k_5{\cdot}(Ca^{2+}_{cyt}){\cdot}(PMCA{\bullet}M) \tag{8}$$

$$\frac{d(PMCA)}{dt} = k_{14} - k_{15}{\cdot}(PMCA) - k_{12}{\cdot}(PMCA){\cdot}(M) + k_{13}{\cdot}(PMCA{\bullet}M) \tag{9}$$

$$\frac{d(SERCA)}{dt} = k_{20} - \frac{k_{21}{\cdot}(SERCA){\cdot}(Ca^{2+}_{lum})}{k_{22} + (SERCA)} \tag{10}$$

$$\frac{dCa^{2+}_{lum}}{dt} = \frac{k_{23}{\cdot}(SERCA){\cdot}(Ca^{2+}_{cyt})}{k_{24} + Ca^{2+}_{cyt}} - k_{27}{\cdot}Ca^{2+}_{lum} - 30{\cdot}k_{25}{\cdot}(Ca^{2+}_{lum}){\cdot}(L) + 30{\cdot}k_{26}{\cdot}(L{\bullet}Ca_{30}) - n{\cdot}k_{71}{\cdot}(STIM){\cdot}(Ca^{2+}_{lum})^n + k_{72}{\cdot}n{\cdot}(STIM{\bullet}Ca_n) - \frac{k_{38}{\cdot}(IP_3R{\bullet}IP_3){\cdot}(Ca^{2+}_{lum})}{k_{39}{\cdot}f_{IP3R} + f_{IP3R.Ca_{ER}}{\cdot}(Ca^{2+}_{lum})} \tag{11}$$

$$\frac{dL}{dt} = k_{28} - k_{29} \cdot L - k_{25} \cdot (Ca^{2+}_{lum}) \cdot (L) + k_{26} \cdot (L \bullet Ca_{30}) \tag{12}$$

$$\frac{d(L \bullet Ca_{30})}{dt} = k_{25} \cdot (Ca^{2+}_{lum}) \cdot (L) - k_{26} \cdot (L \bullet Ca_{30}) \tag{13}$$

$$\frac{dS}{dt} = k_{30} - k_{31} \cdot S - k_{34} \cdot (S) \cdot (R) + k_{35} \cdot (R \bullet S) \tag{14}$$

$$\frac{dR}{dt} = k_{32} - k_{33} \cdot R - k_{34} \cdot (S) \cdot (R) + k_{35} \cdot (R \bullet S) \tag{15}$$

$$\frac{d(R \bullet S)}{dt} = k_{34} \cdot (S) \cdot (R) - k_{35} \cdot (R \bullet S) \tag{16}$$

$$\frac{dARCC}{dt} = k_{44} - k_{45} \cdot ARCC \tag{17}$$

$$\frac{d(IP_3R \bullet IP_3)}{dt} = k_{77} \cdot (IP_3) \cdot (IP_3R) - k_{78} \cdot (IP_3R \bullet IP_3) \cdot (Ca^{2+}_{cyt}), \ \ \text{condition (i)} \tag{18}$$

$$\frac{d(IP_3R \bullet IP_3)}{dt} = k_{77} \cdot (IP_3) \cdot (IP_3R) - k_{78} \cdot (IP_3R \bullet IP_3) \cdot (1 + Ca^{2+}_{cyt}), \ \ \text{condition (ii)} \tag{19}$$

$$\frac{d(IP_3R \bullet IP_3)}{dt} = k_{77} (IP_3)(IP_3R) - k_{78} \cdot (IP_3R \bullet IP_3), \ \ \text{condition (iii)} \tag{20}$$

$$\frac{d(IP_3)}{dt} = k_{46}\cdot(PLC)(PIP_2) - k_{47}\cdot(IP_3) - k_{77}\cdot(IP_3)\cdot(IP_3R) + k_{78}\cdot(IP_3R\bullet IP_3)\cdot(Ca^{2+}_{cyt}), \text{ condition (i)} \tag{21}$$

$$\frac{d(IP_3)}{dt} = k_{46}\cdot(PLC)(PIP_2) - k_{47}\cdot(IP_3) - k_{77}\cdot(IP_3)\cdot(IP_3R) + k_{78}\cdot(IP_3R\bullet IP_3)\cdot(1 + Ca^{2+}_{cyt}), \text{ condition (ii)} \tag{22}$$

$$\frac{d(IP_3)}{dt} = k_{46}\cdot(PLC)(PIP_2) - k_{47}\cdot(IP_3) - k_{77}\cdot(IP_3)\cdot(IP_3R) + k_{78}\cdot(IP_3R\bullet IP_3), \text{ condition (iii)} \tag{23}$$

$$\frac{d(PIP_2)}{dt} = 0, \text{ constant } \mathrm{PIP}_2 \text{ at } 1\mu\mathrm{M} \tag{24}$$

$$\frac{d(S2)}{dt} = k_{52} - k_{53}\cdot S2 - k_{54}\cdot(S2)\cdot(G) + k_{55}\cdot(G\bullet S2) \tag{25}$$

$$\frac{d(Ind\bullet Ca)}{dt} = -k_{51}(Ind\bullet Ca) + k_{50}\cdot(Ca_{cyt})\cdot(Ind) = -\frac{d(Ind)}{dt} \tag{26}$$

$$\frac{dG}{dt} = -k_{54}\cdot(S2)\cdot(G) + k_{55}\cdot(G\bullet S2) + k_{58} - k_{59}\cdot G \tag{27}$$

$$\frac{d(G \bullet S2)}{dt} = k_{54} \cdot (S2) \cdot (G) - k_{55} \cdot (G \bullet S2) \tag{28}$$

$$\frac{d(PLC)}{dt} = k_{56} \cdot (G) \cdot (S2) - k_{57} \cdot (PLC) \tag{29}$$

$$\frac{d(NCX \bullet M^{*})}{dt} = k_{60} \cdot (NCX \bullet M) \cdot (Ca^{2+}_{cyt}) - \frac{k_{61} \cdot (NCX \bullet M^{*})}{k_{62} + (NCX \bullet M^{*})} \tag{30}$$

$$\begin{aligned} \frac{d(NCX \cdot M)}{dt} &= k_{67} \cdot (M) \cdot (NCX) - k_{68} \cdot (NCX \bullet M) \\ &\quad - k_{60} \cdot (NCX \bullet M) \cdot (Ca^{2+}_{cyt}) + \frac{k_{61} \cdot (NCX \bullet M^{*})}{k_{62} + (NCX \bullet M^{*})} \end{aligned} \tag{31}$$

$$\frac{d(NCX)}{dt} = k_{65} - k_{66} \cdot (NCX) - k_{67} \cdot (M) \cdot (NCX) + k_{68} \cdot (NCX \bullet M) \tag{32}$$

$$\frac{d(STIM)}{dt} = k_{69} - k_{70} \cdot (STIM) - k_{71} \cdot (STIM) \cdot (Ca^{2+}_{lum})^{n} + k_{72}(STIM \bullet Ca_{n}) \tag{33}$$

$$\frac{d(STIM \bullet Ca_{n})}{dt} = k_{71} \cdot (STIM) \cdot (Ca^{2+}_{lum})^{n} - k_{72} \cdot (STIM \bullet Ca_{n}) \tag{34}$$

$$\frac{d(SOCC)}{dt} = k_{75} - k_{76} \cdot (SOCC) \tag{35}$$

$$\frac{d(IP_3R)}{dt} = k_{48} - k_{49}{\cdot}(IP_3R) - k_{77}{\cdot}(IP_3R){\cdot}(IP_3) \\ + k_{78}{\cdot}(IP_3R{\bullet}IP_3){\cdot}(Ca^{2+}_{cyt}), \quad \text{condition (i)} \tag{36}$$

$$\frac{d(IP_3R)}{dt} = k_{48} - k_{49}{\cdot}(IP_3R) - k_{77}{\cdot}(IP_3R){\cdot}(IP_3) \\ + k_{78}{\cdot}(IP_3R{\bullet}IP_3){\cdot}(1 + Ca^{2+}_{cyt}), \quad \text{condition (ii)} \tag{37}$$

$$\frac{d(IP_3R)}{dt} = k_{48} - k_{49}{\cdot}(IP_3R) - k_{77}{\cdot}(IP_3R){\cdot}(IP_3) \\ + k_{78}{\cdot}(IP_3R{\bullet}IP_3), \quad \text{condition (iii)} \tag{38}$$

List of abbreviations and LSODE Y(i) assignments:

ARCC	Arachidonic acid Calcium Channel	Y(18)
B	Buffer	Y(7)
B•Ca_4	Buffer bound with 4 Ca^{2+}	Y(8)
Ca_{cyt}	Cytosolic calcium	Y(1)
Ca_{ext}	Extracellular calcium	Y(3)
Ca_{lum}/Ca_{ER}	Calcium in ER	Y(12)
DAG	Diacyl glycerol	-
ER	Endoplasmic reticulum	-
f_{IP3R}	part of dual calcium binding model	Eq 23
$f_{\mathrm{IP3R.Ca}_{ER}}$	part of dual calcium binding model	Eq 24
G	G protein	Y(24)
G•S2	Signal activated G protein	Y(25)
Ind	Indicator	Y(21)
Ind•Ca	Calcium bound to indicator	Y(22)
IP_3	Inositol 4,5-trisphosphate	Y(20)
IP_3R	Inositol 4,5-trisphosphate receptor	Y(33)
IP_3R•IP_3	IP_3 bound to IP_3R	Y(19)
L	Luminal buffers	Y(13)
L•Ca_{30}	Luminal buffers bound with 30 calcium	Y(14)
M, CaM	Calmodulin	Y(5)
M•Ca_4	Calmodulin bound with 4 calcium	Y(6)
NCX	Sodium - calcium exchanger	Y(29)
NCX•M	Sodium - calcium exchanger bound with calmodulin	Y(28)
NCX•M^*	Activated form of the sodium - calcium exchanger	Y(27)
PIP_2	Phosphatidylinositol 4,5-bisphosphate	-
PLC	Phospholipase C	Y(26)
PMCA	Plasma membrane calcium ATPase	Y(10)
PMCA•M	PMCA bound with calmodulin	Y(9)
PMCA•M^*	Activated plasma membrane calcium ATPase	Y(2)
R	Receptor	Y(16)
R•S	Signal activated receptor	Y(17)
S	Signal activating receptor in order to activate ARCC	Y(15)
S2	Signal activating G protein in order to activate PLC	Y(23)
SERCA	Sarco/endoplasmic reticulum calcium ATPase	Y(11)
SOCC	Storage operated calcium channel	Y(32)
STIM	Stromal interaction molecule	Y(30)
STIM•Ca	STIM bound with calcium	Y(31)

LSODE Y(i)'s for calculating the time averages $<Ca_{cyt}>$, $<Ca_{ER}>$, and $<(PMCA \bullet M)>$:

Y(4)	$\int_0^\tau Ca_{cyt} dt$	Fig 18A; Fig S2A in SI 'S9 Program'
Y(34)	$\int_0^\tau Ca_{ER} dt$	Fig 18C; Fig S2C in SI 'S9 Program'
Y(35)	$\int_0^\tau (PMCA \bullet M) dt$	Fig S2A in SI 'S9 Program'

Time average $<X>$ is calculated as $(1/\tau) \int_0^\tau X(t)dt$, where τ is the simulation time in seconds.

Other rate constant assignments

k_{40}=K_1^{IP3}, k_{41}=K_2^{IP3}, k_{42}=$K_1^{IP3 \cdot Ca_{ER}}$, and k_{43}=$K_2^{IP3 \cdot Ca_{ER}}$.