A basic model of calcium homeostasis in non-excitable cells

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Supporting Information S4 Program

Rate equations, parameters, initial concentrations, and calculations for Figs 7C and 7D

Calculations in Figs 7C,D are based on the model shown in Fig S1.

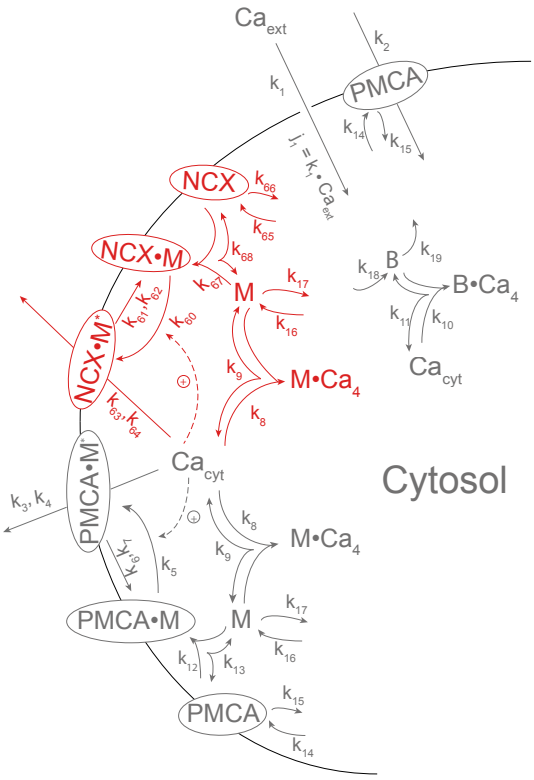

Figure S1. Model including both PMCA and NCX for cytosolic Ca^{2+} extrusion. The added NCX part is outlined in red.

The rate equations are:

$$\frac{dCa^{2+}_{ext}}{dt} = k_1 \times Ca^{2+}_{ext} - k_2 \times Ca^{2+}_{cyt} \times PMCA - k_3 \times \frac{(PMCA \bullet M^*) \times Ca^{2+}_{cyt}}{k_4 + Ca^{2+}_{cyt}} - 4 \times k_8 \times M \times Ca^{2+}_{cyt} + 4 \times k_9 \times (M \bullet Ca_4) - 4 \times k_{10} \times B \times Ca^{2+}_{cyt} + 4 \times k_{11} \times (B \bullet Ca_4) - \frac{k_{63} \times Ca^{2+}_{cyt} \times (NCX \bullet M^*)}{k_{64} + Ca^{2+}_{cyt}} \tag{S1}$$

$$\frac{d(PMCA \bullet M^*)_{ext}}{dt} = k_5 \times Ca^{2+}_{cyt} \times (PMCA \bullet M) - \frac{k_6 \times (PMCA \bullet M^*)}{k_7 + (PMCA \bullet M^*)} \tag{S2}$$

$$\frac{dM}{dt} = k_{16} - k_{17} \times M - k_{12} \times M \times PMCA + k_{13} \times (PMCA \bullet M) \tag{S3}$$

$$+ k_9 \times (M \bullet Ca_4) - k_8 \times Ca^{2+}_{cyt} \times M + k_{68} \times (NCX \bullet M) \tag{S4}$$

$$- k_{67} \times M \times NCX \tag{S5}$$

$$\frac{d(M \bullet Ca_4)}{dt} = k_8 \times Ca^{2+}_{cyt} \times M - k_9 \times (M \bullet Ca_4) \tag{S6}$$

$$\frac{dB}{dt} = k_{18} - k_{19} \times B - k_{10} \times B \times Ca^{2+}_{cyt} + k_{11} \times (B \bullet Ca_4) \tag{S7}$$

$$\frac{d(B \bullet Ca_4)}{dt} = k_{10} \times B \times Ca^{2+}_{cyt} - k_{11} \times (B \bullet Ca_4) \tag{S8}$$

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

$$\frac{dPMCA}{dt} = k_{14} - k_{15}\times PMCA - k_{12}\times PMCA\times M + k_{13}\times(PMCA\bullet M)$$

$$\frac{d(NCX\bullet M^*)}{dt} = k_{60}\times(NCX\bullet M)\times Ca_{cyt}^{2+} - \frac{k_{61}\times(NCX\bullet M^*)}{k_{62}+(NCX\bullet M^*)}$$

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

$$\frac{dNCX}{dt} = k_{65} - k_{66}\times NCX - k_{67}\times M\times NCX + k_{68}\times(NCX\bullet M)$$

The time steps during LSODE integration is 1.0×10^{-2}s, with 5 phases having intervals of 48s, 144s, 210s, 148s, and 290s.

The rate constants/parameters are given as:
k_1, phase 1 = $1\times10^{-4}s^{-1}$, k_2 = $0.0s^{-1}$, k_3, phase 1 = $5.0\times10^{3}s^{-1}$, k_4 = 1.2μM, k_5 = $16.0\mu M^{-1}s^{-1}$, k_6 = $8.0\times10^{-3}\mu$M/s, k_7 = $1.0\times10^{-6}\mu$M, k_8 = $2.5s^{-1}$, k_9 = $5.0s^{-1}$, k_{10} = $1.0\times10^{2}\mu M^{-1}s^{-1}$, k_{11} = $80.0s^{-1}$, k_{12} = $1.0*10^{-2}\mu M^{-1}s^{-1}$, k_{13} = $1.0\times10^{-1}\mu M^{-1}s^{-1}$, k_{14} = 0.0μM/s, k_{15} = $0.0s^{-1}$, k_{16} = 0.0μM/s, k_{17} = $0.0s^{-1}$, k_{18} = 0.0μM/s, k_{19} = $0.0s^{-1}$, k_{60} = $16.0\mu M^{-1}s^{-1}$, k_{61} = $8.0\times10^{-3}\mu$M/s, k_{62} = $1.0\times10^{-6}\mu$M, k_{63} = $1\times10^{5}s^{-1}$ (all 5 phases), k_{64} = $1.0\times10^{2}\mu$M, k_{65} = 0.0μM/s, k_{66} = $0.0s^{-1}$, k_{67} = $1.0\times10^{-2}\mu M^{-1}s^{-1}$, k_{68} = $1.0\times10^{-1}s^{-1}$, k_1, phase 2 = $1.4\times10^{-2}s^{-1}$, α, phase 2 = $4.5\times10^{-2}s^{-1}$, k_3, phase 2 = $5.0\times10^{3}s^{-1}$, β, phase 2 = $200s^{-1}$, k_1, phase 3 = $1\times10^{-4}s^{-1}$, k_3, phase 3 = $5.0\times10^{3}s^{-1}$, k_1, phase 4 = $1.4\times10^{-2}s^{-1}$, α, phase 4 = $4.5\times10^{-2}s^{-1}$, k_3, phase 4 = $5.0\times10^{3}s^{-1}$, β, phase 4 = $200s^{-1}$, k_1, phase 5 = $0.0s^{-1}$, α, phase 5 = $0.0s^{-1}$, k_3, phase 5 = $0.0s^{-1}$, β, phase 5 = $0.0s^{-1}$.

Initial concentrations (all in μM): Ca_{cyt}^{2+} = 1.0652×10^{-1}, PMCA•M* = 3.7450×10^{-4}, Ca_{ext}^{2+} = 2×10^{3}, M = 9.4988, M•Ca4 = 5.0588×10^{-1}, B = 1.7785×10^{2}, B•Ca4 = 23.679, PMCA•M = 4.6826×10^{-3}, PMCA = 4.9428×10^{-3}, NCX•M* = 3.7450×10^{-4}, NCX•M = 4.6836×10^{-3}, NCX = 4.9428×10^{-3}.

Compiling `CAREG64v6.f`

We have compiled `CAREG64v6.f` with 64 bits encoding using the Mac Terminal and Windows Cmd prompt together with Absoft's ProFortran compilers for Mac OSX and Windows:

Mac OSX: `f77 -o careg64v6 -m64 -O2 CAREG64v6.f libV77.a`
Windows: `f77 -o careg64v6.exe -m64 -O2 CAREG64v6.f vms.lib`
with the (enclosed) 64 bits libraries `libV77.a` and `vms.lib`.

Running the model

If gnuplot and Perl are installed, on Mac OSX one runs the script file `careg64v6.sh` by using the terminal command `./careg64v6.sh`. On Windows computers you use the Cmd prompt and type `careg64v6.cmd`. The numerical output will be created, i.e. concentrations in file `CAREG64v6-07.txt` and fluxes in file `CAREG64v6-07_fluxes.txt`. `CAREG64v6-07` is our run identifier (which can be changed in the input file `CAREG64v6.INP`).

The following four graphs (Fig S2) (in pdf format) will be generated and should be opened automatically by the default pdf viewer.

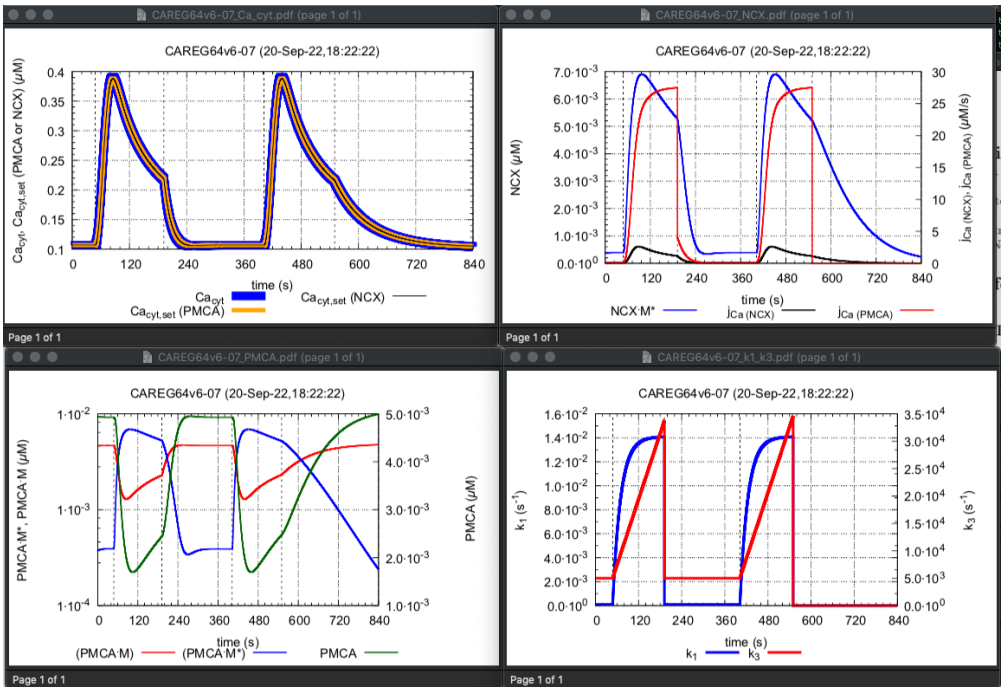

Figure S2. Graphs created when running `careg64v6.sh` or `careg64v6.exe` with Perl and gnuplot installed. $j_{Ca\ (PMCA)}$ and $j_{Ca\ (NCX)}$ are the velocities by which PMCA and NCX pump calcium out of the cell.

If Perl or gnuplot are not installed you execute the provided binary files `CAREG64v6` (Mac) or `CAREG64v6-07.exe`, which will generate the concentration and flux data files `CAREG64v6-07.txt` and `CAREG64v6-07_fluxes.txt`. Graphs can then be created by a custom graphing program if it allows to plot numerical column data. The graphs in Fig S2 involve the following columns:

File `CAREG64v6-07.txt`:
column 1: time (s)
column 2: Ca_{cyt} (μM)
column 3: (PMCA•M*) (μM)
column 10: $Ca_{cyt,\ set}$ (PMCA) (μM)

column 11: $Ca_{cyt,\ set}$ (NCX) (μM)
column 27: PMCA•M (μM)
column 29: PMCA (μM)
column 30: k_3 (1/s)
column 31: k_1 (1/s)
column 32: $(NCX{\bullet}M^*)$ (μM)

File `CAREG64v6-07_fluxes.txt`:
column 1: time (s)
column 4: $j_{Ca\ (PMCA)}$ (μM/s)
column 14: $j_{Ca\ (NCX)}$ (μM/s)