Mathematical model of IP$_3$-induced Ca$^{2+}$ release and uptake in an isolated nucleus
This mathematical model is a one-compartment model, which represents the free Ca\(^{2+}\) concentration in the nuclear envelope ([Ca\(^{2+}\)]\(_{n}\)) and contains two major components: Ca\(^{2+}\) release via IP\(_3\) receptors (IP\(_3\)R) and Ca\(^{2+}\) uptake by SERCA (sarco-, endo-plasmic reticulum Ca\(^{2+}\) ATPase) pumps.

It is known that the rate of Ca\(^{2+}\) uptake from the cytosol to the ER in pancreatic acinar cells is sensitive to [Ca\(^{2+}\)]\(_{ER}\) (Mogami et al, 1998). Therefore, we developed a mathematical model for Ca\(^{2+}\) uptake that considers the effects of both the cytosolic and lumenal Ca\(^{2+}\) concentrations, using the data from Mogami et al. (1998), on the assumption that the Ca\(^{2+}\) uptake into the nuclear envelope is similar to that into the ER.

We assume that the lumenal sensitivity is due to an interaction between SERCA and calreticulin (CRT), which is known to have inhibitory effects on repetitive Ca\(^{2+}\) waves (Camacho and Lechleiter, 1995). We have found that Ca\(^{2+}\) inside the ER inhibits pumping activity with a Hill coefficient between 5 and 6. In our mathematical model, therefore, calreticulin binds to up to five calcium ions and binding of the fifth calcium ion to CRT enables it to bind to SERCA and thereby inhibit the Ca\(^{2+}\) pumping activity. We also assume that the interaction between CRT and Ca\(^{2+}\) is faster than other reactions, so that it can always be considered to be at a steady state. The flux of Ca\(^{2+}\) mediated by the Ca\(^{2+}\) pump can be calculated as follows:

\[
J_{pump} = V_1 + \frac{V_2 K_1}{K_1 + \left(1 + \sum_{i=1}^{5} \left(\frac{x}{K_2}\right)^i\right)}
\]
where $J_{\text{pump}}$ is the pumping rate from cytosol to the nuclear envelope, $x$ is $[\text{Ca}^{2+}]_n$, $K_1$ is the dissociation constant for the reaction between CRT and SERCA and $K_2$ is the dissociation constant for the reaction between CRT and $\text{Ca}^{2+}$. $V_1$ is the pumping rate when all pumps are completely inhibited by CRT and $V_2$ is the pumping rate when CRT is absent. Therefore, $V_1+V_2$ corresponds to the maximum pumping rate. The parameters were estimated using data from Mogami et al. (1998).

The mathematical model for the $\text{Ca}^{2+}$ flux through the IP$_3$ receptor is based on Sneyd and Dufour (2002), which deals with the type-2 IP$_3$ receptor (IP$_3$R$_2$). Since it has been suggested that the type-3 (IP$_3$R$_3$) is present around the nuclear envelope (Lee et al., 1997), we have changed some parameters in Sneyd and Dufour's model. Swatton and Taylor (2002) showed that IP$_3$R$_3$ is more strongly inhibited by ambient $\text{Ca}^{2+}$ ([Ca$^{2+}]_c$) than IP$_3$R$_2$ and we have taken this into account by decreasing $k_1$ and $l_2$ in the Sneyd and Dufour model by a factor of 10. We have also assumed that the $\text{Ca}^{2+}$ release rate is linearly proportional to $[\text{Ca}^{2+}]_n$. The resulting mathematical model is as follows:

$$J_{\text{IP}_{3R}} = V_3 x y^4$$

where $J_{\text{IP}_{3R}}$ is the release rate of $\text{Ca}^{2+}$ mediated by the IP$_3$Rs, $V_3$ is the maximum release rate, $x$ is $[\text{Ca}^{2+}]_n$ and $y$ is the open state probability of the IP$_3$R.

The open state probabilities calculated by Sneyd and Dufour’s original model and our model with $[\text{IP}_3] = 20 \mu\text{M}$ and $[\text{Ca}^{2+}]_c = 300 \text{nM}$ are shown below.
The mathematical model of the basal leak rate of Ca\(^{2+}\) from the ER is based on the data from Mogami et al. (1998):

\[
J_{\text{leak}} = V_4 e^{-\left(\frac{k_1 - \frac{k_2^3}{k_3^3 + k_4^3}}{k_3 + k_4}\right)}
\]
where $J_{\text{leak}}$ is the basal leak rate, $V_4$ is the maximum leak rate and $x$ is $[\text{Ca}^{2+}]_n$. $k_1$, $k_2$, $k_3$, $k_4$ are parameters obtained by curve fitting.

The differential equation for $[\text{Ca}^{2+}]_n$ is

$$\frac{\partial}{\partial t} x = J_{\text{leak}} + J_{\text{re}} - J_{\text{pump}}$$

where $x$ is $[\text{Ca}^{2+}]_n$. $J_{\text{leak}}$, $J_{\text{re}}$, and $J_{\text{pump}}$ have already been explained.

$V_1$, $V_2$ and $V_3$ are calibrated to fit the simulated $[\text{Ca}^{2+}]_n$ trace to the experimental traces in this article. All the computational simulations are done on MATLAB and related packages and all the curve fittings are done by TableCurve2D.

Using this mathematical model, we made a simulation to observe the time course of the change of $[\text{Ca}^{2+}]_n$ during IP$_3$ application. Application of IP$_3$ starts at $t=0$ and its time course is expressed as $20/(1+e^{-(t-10)/2})$ to reflect the gradual increase of IP$_3$ by perfusion. $[\text{Ca}^{2+}]_c$ is fixed at 300 nM and $[\text{Ca}^{2+}]_n$ is 100 µM at $t=0$.

In the simulation, $[\text{Ca}^{2+}]_n$ decreases rapidly and recovery starts when the Ca$^{2+}$ release rate is at steady state. The recovery cannot be observed when using the exact Sneyd and Dufour model, due to the larger open state probability of IP$_3$R at steady state. The recovery cannot be observed when the lumenal sensitivity of SERCA is absent. The rate of recovery is dependent on the pumping rate as the rate of release through IP$_3$Rs at steady state is considerably smaller than the SERCA pumping rate.

The result of the simulation is shown below, together with the parameter values used for the simulation:
Parameters:

\[ V_1 \] 0.996 µM/s
\[ V_2 \] 10.58 µM/s
\[ V_3 \] 1000 µM/s
\[ V_4 \] 0.63 µM/s
\[ K_1 \] 0.0001 µM
\[ K_2 \] 819.7 µM
\[ k_1 \] 2.76
\[ k_2 \] 48.7
\[ k_3 \] 1.25 µM⁻¹
\[ k_4 \] 0.01

References


