coupled equations:

$$\begin{aligned}
c_m \frac{dV_1}{dt} &= -i_1 + \frac{I_e}{A_1} + g_{1,2}(V_2 - V_1) \\
c_m \frac{dV_2}{dt} &= -i_2 + g_{2,3}(V_3 - V_2) + g_{2,1}(V_1 - V_2) + g_{2,4}(V_4 - V_2) \\
c_m \frac{dV_3}{dt} &= -i_3 + g_{3,2}(V_2 - V_3) \\
c_m \frac{dV_4}{dt} &= -i_4 + g_{4,2}(V_2 - V_4)
\end{aligned}$$

This can be written in matrix/vector format and solved numerically:

$$c_m \begin{pmatrix} \frac{dV_1}{dt} \\ \frac{dV_2}{dt} \\ \frac{dV_3}{dt} \\ \frac{dV_4}{dt} \end{pmatrix} = - \begin{pmatrix} i_1 \\ i_2 \\ i_3 \\ i_4 \end{pmatrix} + \begin{pmatrix} \frac{I_e}{A_1} \\ 0 \\ 0 \\ 0 \end{pmatrix} + \begin{pmatrix} -g_{1,2} & g_{1,2} & 0 & 0 \\ g_{2,1} & -(g_{2,3} + g_{2,1} + g_{2,4}) & g_{2,3} & 0 \\ 0 & g_{3,2} & -g_{3,2} & 0 \\ 0 & g_{4,2} & 0 & -g_{4,2} \end{pmatrix} \begin{pmatrix} V_1 \\ V_2 \\ V_3 \\ V_4 \end{pmatrix}$$

General purpose simulators, such as NEURON, solve such coupled ODE equations numerically. There is a large body of numerical methods dedicated to solving such problems, which will be subject to a later chapter.

4.3 Intracellular calcium dynamics

Intracellular calcium dynamics play an important role in relaying electrical activity to an intracellular, biochemical machinery relevant for learning and cell survival. Intracellular calcium signals that enter the cell nucleus selectively activate gene transcription relevant cascades, where the amplitude, duration, and frequency of the calcium signal determine which cascades are activated and at what intensity. The question then becomes: how are calcium signals, that eventually enter the cell nucleus through nuclear pore complexes, shaped and how do they propagate over long distances from synapses to the nucleus?
Neurons have a large set of calcium regulating components. This section will discuss a number of these to explain the spatio-temporal, intracellular calcium dynamics. The cell's plasma membrane is equipped with calcium exchangers that can bidirectionally exchange calcium ions between the intra- and extracellular space. In the intracellular space, calcium ions diffuse and react with second messenger molecules. Given these circumstances, calcium signals would be confined to a small microdomain around a given calcium source. To overcome this microdomain confinement, neurons make use of intracellular calcium stores, that can be activated through free calcium ions, and other signaling molecules. One such calcium store is the endoplasmic reticulum (ER).
Similar to the plasma membrane, neurons can bidirectionally exchange calcium across the ER membrane, thus allowing a calcium-induced calcium release mechanism to propagate calcium signals over longer distances towards the cell nucleus. In the following we will discuss these exchange mechanisms.

4.3.1 Inositol-3-phosphate receptors

Inositol-3-phosphate receptors (IP3R) have three binding sites, one for the molecule IP3, one for activating calcium ions, and one for inactivating calcium ions.

Definition 12. *Let x_{ijk} be the fraction of IP3 receptors in one of the 8 states s_{ijk}, $i, j, k \in 0, 1$.*

Then the kinetics in the front plane between s_{000}, s_{100}, s_{001}, and s_{101} is of the following form:

$$\begin{array}{ccc} s_{110} & \underset{b_2}{\overset{a_2[Ca^{2+}]}{\rightleftarrows}} & s_{101} \\ a_1[IP3] \uparrow \downarrow b_1 & & a_3[IP3] \uparrow \downarrow b_3 \\ s_{000} & \underset{b_4}{\overset{a_4[Ca^{2+}]}{\rightleftarrows}} & s_{001} \end{array} \tag{4.24}$$

The front to back plane kinetics are described by:

$$s_{i0j} \underset{b_5}{\overset{a_5[Ca^{2+}]}{\rightleftarrows}} s_{i1j} \tag{4.25}$$

Taken together this leads to 8 differential equations:

$$\begin{aligned}
\frac{x_{000}}{dt} &= b_4 x_{001} + b_5 x_{010} + b_1 x_{100} - (a_4[Ca^{2+}] + a_5[Ca^{2+}] + a_1[IP3])x_{000} \\
\frac{x_{001}}{dt} &= a_4[Ca^{2+}] x_{000} + b_5 x_{011} + b_3 x_{101} - (b_4 + a_5[Ca^{2+}] + a_3[IP3])x_{001} \\
\frac{x_{010}}{dt} &= a_5[Ca^{2+}] x_{000} + b_4 x_{011} + b_1 x_{110} - (b_5 + a_4[Ca^{2+}] + a_1[IP3])x_{010} \\
\frac{x_{011}}{dt} &= a_5[Ca^{2+}] x_{001} + a_4[Ca^{2+}] x_{010} + b_3 x_{111} - (b_5 + b_4 + a_3[IP3])x_{011} \\
\frac{x_{100}}{dt} &= a_1[IP3] x_{000} + b_2 x_{101} + b_5 x_{110} - (b_1 + a_2[Ca^{2+}] + a_5[Ca^{2+}])x_{100} \\
\frac{x_{101}}{dt} &= a_3[IP3] x_{001} + a_2[Ca^{2+}] x_{100} + b_5 x_{111} - (b_3 + b_2 + a_5[Ca^{2+}])x_{101} \\
\frac{x_{110}}{dt} &= a_1[IP3] x_{010} + a_5[Ca^{2+}] x_{100} + b_2 x_{111} - (b_1 + b_5 + a_2[Ca^{2+}])x_{110} \\
\frac{x_{111}}{dt} &= a_3[IP3] x_{011} + a_5[Ca^{2+}] x_{101} + a_2[Ca^{2+}] x_{110} - (b_3 + b_5 + b_2)x_{111}
\end{aligned} \tag{4.26}$$

In thermodynamic equilibrium the sum of reactions is zero. Therefore we get:

$$\begin{aligned}
0 &= a_2[Ca^{2+}][S_{1k0}] - b_2[S_{1k1}] \\
\Rightarrow \frac{b_2}{a_2} &= \frac{[Ca^{2+}][S_{ik0}]}{[S_{1k1}]}
\end{aligned}$$

and

$$\begin{aligned}\frac{a_3}{b_3} &= \frac{[S_{1k1}]}{[IP3][S_{0k1}]} \\ \frac{a_4}{b_4} &= \frac{[S_{0k1}]}{[Ca^{2+}][S_{0k0}]} \\ \frac{b_1}{a_1} &= \frac{[IP3][S_{0k0}]}{[S_{1k0}]}\end{aligned} \tag{4.27}$$

This leads to

$$\frac{b_1 b_2 a_3 a_4}{a_1 a_2 b_3 b_4} = \frac{[IP3][S_{0k0}][Ca^{2+}][S_{1k0}][S_{1k1}][S_{0k1}]}{[S_{1k0}][S_{1k1}][IP3][S_{0k1}][Ca^{2+}][S_{0k0}]} = 1. \tag{4.28}$$

Let $d_i := \frac{b_i}{a_i}$, then

$$p_O^{IP3R} = x_{110}^3 = \left(\frac{d_2[Ca^{2+}][IP3]}{([Ca^{2+}][IP3] + d_2[IP3] + d_3[Ca^{2+}] + d_1 d_2)([Ca^{2+}] + d_5)}\right)^3 \tag{4.29}$$

Computing d_1, d_2, d_3, and d_5

Using sets of experimental data, we can compute the necessary parameters. In a first step we will use K_d-values at different calcium concentrations.

Definition 13. *The K_d-value denotes the concentration of a substance at which 50 % of all binding sites are occupied.*

Joseph et al. (1989) computed the following values for IP3 binding to IP3 receptors:

1. no Ca^{2+}: $K_d = 145$ nM.
2. 1 μM Ca^{2+}: $K_d = 542$ nM.

For the model this means

$$\begin{aligned}50\% &= x_{100} + x_{101} + x_{110} + x_{111} \\ &= \frac{[Ca^{2+}] + [IP3] + d_2[IP3]}{[Ca^{2+}][IP3] + d_2[IP3] + d_3[Ca^{2+}] + d_1 d_2} \\ \Leftrightarrow d_3[Ca^{2+}] + d_1 d_2 &= [Ca^{2+}][IP3] + d_2[IP3]\end{aligned}$$

Now we can plug in our experimental data

1. $(c1, p1) = (0\mu M, 145nM)$ and
2. $(c2, p2) = (1\mu M, 542nM)$.

$$
\begin{aligned}
\Rightarrow c_1 p_1 + d_2 p_1 &= d_3 c_1 + d_1 d_2 \\
c_2 p_2 + d_2 p_2 &= d_3 c_2 + d_1 d_2 \\
\Rightarrow d_3 &= \frac{c_1 p_1 - c_2 p_2 + d_2(p_1 - p_2)}{c_1 - c_2} \\
d_1 &= \frac{d_2(c_1 p_2 - c_2 p_1) + c_1 c_2 (p_2 - p_1)}{d_2(c_1 - c_2)}
\end{aligned}
\tag{4.30}
$$

Using data from Bezprozvanny et al. (1991), who found that $p_O^{max} = 0.15$ at concentrations $[IP3] = 2\mu M$ and $[Ca^{2+}] = c_{max} = 0.25\mu M$, we get

$$
d_2 = \frac{(p_O^{max})^{1/3} c_{max}([IP3] + d_3)(c_{max} + d_5)}{c_{max}[IP3] - (p_O^{max})^{1/3}([IP3] + d_1)(c_{max} + d_5)} \tag{4.31}
$$

and with $0 = \frac{dx_{110}^3}{d[Ca^{2+}]}$ follows

$$
d_5 = \frac{c_{max}^2([IP3] + d_3)}{d_2([IP3] + d_1)} \tag{4.32}
$$

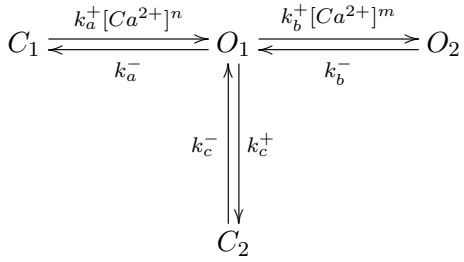
Finally, $[IP3]$ can be computed via a diffusion reaction equation:

$$
\frac{\partial [IP3]}{\partial t} = D_{IP3} \Delta [IP3] + k_{IP3}([IP3] - [IP3]^{eq}) \tag{4.33}
$$

with $[IP3]^{eq}$ equilibrium state concentration and k_{IP3} a reaction rate for free IP3. This model can then be integrated into a three-dimensional model for calcium dynamics, where the total calcium flux through a piece of membrane can be computed from the IP3-model.

4.3.2 Ryanodine receptors

Keizer and Levine (1996) propose the following model for ryanodine receptors (RyR):



(4.34)

This leads to

$$\begin{aligned}
\frac{dx_{C_1}}{dt} &= k_a^- x_{O_1} - k_a^+ [Ca^{2+}]^n x_{C_1} \\
\frac{dx_{O_1}}{dt} &= k_a^+ [Ca^{2+}]^n x_{C_1} + k_b^- x_{O_2} + k_c^- x_{C_2} - (k_a^- + k_b^+ [Ca^{2+}]^m + k_c^-) x_{O_1} \\
\frac{dx_{O_2}}{dt} &= k_b^+ [Ca^{2+}]^m x_{O_1} - k_b^- x_{O_2} \\
\frac{dx_{C_2}}{dt} &= k_c^+ x_{O_1} - k_c^- x_{C_2}
\end{aligned}$$

In equilibrium the left hand sides are zero. With $x_{C_1} + x_{C_2} + x_{O_1} + x_{O_2} = 1$ we can solve the system for

$$p_O^{RyR} = x_{O_1} + x_{O_2} = \frac{1 + K_b [Ca^{2+}]^m}{1 + K_c + (K_a [Ca^{2+}]^n)^{-1} + K_b [Ca^{2+}]^m} \tag{4.35}$$

with $K_i := \frac{k_i^+}{k_i^-}$. The values m and n are fitted using data from Keizer/Levine and K_a, K_b, and K_c are least squares fitted with data from Gyoerke and Fill (1993).

4.3.3 SERCA pumps

A model for sarco-/endoplasmic reticulum Ca^{2+}-ATPases (SERCA) was proposed by Sneyd et al. (2003). SERCA pumps operate against concentration gradients and thus are active transporters. The model is based on a Hill-type equation:

$$J_{SERCA}^{total} = \frac{g_{SERCA}^{total} [Ca^{2+}]}{K_{SERCA} + [Ca^{2+}]} \cdot \frac{1}{[Ca^{2+}]} \tag{4.36}$$

With data from Fink et al. (2000) g_{SERCA}^{total} can be broken down to a value for a single pump g_{SERCA}.

$$j_{SERCA} = \rho_{SERCA} \frac{g_{SERCA} [Ca^{2+}]}{K_{SERCA} [Ca^{2+}]} \cdot \frac{1}{[Ca^{2+}]} \tag{4.37}$$

In resting state all ER-transmembrane fluxes need to be in equilibrium. This is achieved by adding a leakage term of the type

$$j_{ER}^{leak} = g_{El}([Ca_{ER}^{2+}] - [Ca_{cyt}^{2+}]) \tag{4.38}$$

4.3.4 Plasma membrane processes

Plasma membrane Ca^{2+}-ATPases (PMCA) and sodium/calcium exchangers (NCX) can be modeled by Hill-equations

$$\begin{aligned}
j_P &= \rho_P g_P \frac{[Ca_{cyt}^{2+}]^2}{K_P^2 + [Ca_{cyt}^{2+}]^2} \\
j_{NCX} &= \rho_{NCX} g_{NCX} \frac{[Ca_{cyt}^{2+}]}{K_{NCX} + [Ca_{cyt}^{2+}]}
\end{aligned}$$

Finally, voltage-dependent Ca^{2+} channels (VDCC) are modeled by Borg-Graham (1998) in a Hodgkin-Huxley-type formalism:

$$\frac{dx_O}{dt} = \alpha(V)(1 - x_O) - \beta(V)x_O \tag{4.39}$$

where x_O is the open probability of the gate.