An Example Latex File: The Success of Whole Cell Models of Ca^{2+} Signaling

Regenerative Ca^{2+} release from the endoplasmic reticulum (ER), a continuous membrane-delimited intracellular compartment, plays an important role in Ca^{2+} signaling [?, ?]. In most cell types the ER has integrative and regenerative properties analogous to the excitable membranes of neurons [?, ?, ?]. For example, agonist-induced Ca^{2+} signaling in pituitary gonadotrophs is initiated by metabotropic receptors of the plasma membrane that stimulate the production of the intracellular messenger, inositol 1,4,5-trisphosphate (IP_3) [?]. IP_3 in turn promotes Ca^{2+} release from intracellular stores by binding and activating IP_3R receptor Ca^{2+} channels (IP_3Rs) located on the ER membrane. In rat basophilic leukemia cells, an experimental model for mucosal mast cells, cross-linking the high-affinity immunoglobulin E receptor with multivalent antigen leads to tyrosine kinase-dependent activation of PLC_γ, production of IP_3, release of intracellular Ca^{2+} stores, and a sustained phase of Ca^{2+} influx—events that culminate in the secretion of histamine, serotonin, and other mediators of inflammation [?, ?].

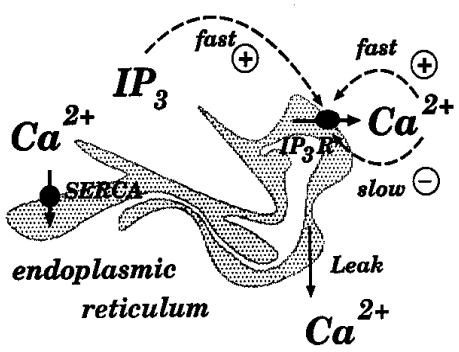

Figure 1: Schematic diagram of a whole cell model of Ca^{2+} handling. Ca^{2+} enters the cytosol from the ER via a passive leak and the IP_3R, which is activated by both Ca^{2+} and IP_3 on a fast time scale and inhibited by Ca^{2+} on a slow time scale, all at the cytoplasmic face. The ER is refilled by a SERCA-type Ca^{2+}-ATPase pump. Reproduced with permission from Jafri and Keizer, 1994.

Whole cell models of intracellular Ca^{2+} signaling have played a role in understanding the dynamics of Ca^{2+} responses of gonadotrophs, RBL cells, and other cell types (reviewed in [?, ?, ?, ?]). While such models can be diagrammed as in Fig. 1, they are in reality systems of nonlinear ODEs. For example, a whole cell model of IP_3-mediated Ca^{2+} responses might take the following form,

$$\frac{d[\mathrm{Ca}^{2+}]}{dt} = \underbrace{j_{rel} - j_{up}}_{j_{er}} + \underbrace{j_{in} - j_{out}}_{j_{pm}} \qquad \frac{d[\mathrm{Ca}^{2+}]_{er}}{dt} = -\alpha_{er} j_{er} \tag{1}$$

$$\frac{dw}{dt} = \left[w_\infty\left([\mathrm{Ca}^{2+}],[\mathrm{IP}_3]\right) - w\right]/\tau\left([\mathrm{Ca}^{2+}],[\mathrm{IP}_3]\right) \tag{2}$$

$$j_{rel} = (v_{leak} + v_{ip} f_o)\left([\mathrm{Ca}^{2+}]_{er} - [\mathrm{Ca}^{2+}]\right) \qquad j_{up} = \frac{v_p[\mathrm{Ca}^{2+}]^2}{[\mathrm{Ca}^{2+}]^2 + k_p^2} \tag{3}$$

In these equations, w is a Hodgkin-Huxley-like gating variable representing the fraction of IP_3Rs *not* inactivated and f_o, the open fraction (or open probability) of the IP_3Rs, is a function of w, $[Ca^{2+}]$, and $[IP_3]$.

Whole cell models of Ca^{2+} handling are biophysically realistic to the extent that they include details of molecular mechanism. For example, sigmoidal kinetics of the SERCA-type Ca^{2+}-ATPase [**?**] have been used in Eqs. **??**–**??** and the parameter α_{er} accounts for an ER/cytosol volume ratio of $\sim 1/6$. One of the keys to biophysical realism of whole cell models is the functional form for the open probability of the IP_3R and the equation for IP_3R kinetics. Indeed, when I present Eq. **??**, I have in mind the Li-Rinzel reduction of the DeYoung-Keizer model [**?**] in which the IP_3R is viewed as a collection of n independent subunits, each of which has one binding site for IP_3 and two binding sites for Ca^{2+} [**?**]. Thus, three processes (IP_3-potentiation, Ca^{2+}-activation, and Ca^{2+}-inactivation) produce eight possible states for each IP_3R subunit (see Fig. 3). With parameters chosen to fit binding data and the 'bell-shaped' steady-state open probability curve of the IP_3R as a function of $[Ca^{2+}]$ measured in planar lipid bilayer experiments [**?**], whole cell models of Ca^{2+} handling can exhibit Ca^{2+} oscillations for superthreshold $[IP_3]$.

Li and Rinzel derived a simplified version of the DeYoung-Keizer model IP_3R by noticing that the fast processes of IP_3-potentiation and Ca^{2+}-activation are essentially at equilibrium with the slower process of Ca^{2+}-inactivation [**?**, **?**]. In this quasi-static limit, the functional forms of $w_\infty\left([Ca^{2+}],[IP_3]\right)$ and $\tau\left([Ca^{2+}],[IP_3]\right)$ in Eq. **??** are found and the fraction of open IP_3Rs is given by $f_o = m_\infty^n w^n$ where $m_\infty([Ca^{2+}],[IP_3])$ is an instantaneously equilibrating activation gating variable.

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