Supporting Information S1 to:

"Activation of store-operated calcium entry in airway smooth muscle cells: insight from a mathematical model"

Huguette Croisier[1,*], Xiahui Tan[2], Jose F. Perez-Zoghbi[3], Michael J. Sanderson[2], James Sneyd[4], Bindi S. Brook[1]

1 School of Mathematical Sciences, University of Nottingham, Nottingham, UK.
2 Department of Microbiology and Physiological Systems, University of Massachusetts Medical School, Worcester, MA, USA.
3 Department of Cell Physiology and Molecular Biophysics, Texas Tech University Health Sciences Center, Lubbock, TX, USA.
4 Department of Mathematics, University of Auckland, Auckland, New Zealand.
∗ E-mail: Huguette.Croisier@nottingham.ac.uk

Parameter estimation procedure

In this section, we give more detail about the rationale which has guided our parameter estimation. From Eq. (13b), in the absence of agonist, the equilibrium Ca^{2+} concentrations obey:

$$c_s^* = c^* + \frac{V_e}{J_{SR}} \frac{c^{*2}}{K_e^2 + c^{*2}}.$$

Assuming $c^* \sim K_e$ (that is, assuming $K_e \sim 0.1\mu$M), to satisfy the experimental constraint $c_s^*/c^* \gg 1$, we must have $\frac{J_{SR}}{V_e/K_e} \ll 1$. Also, as J_{leakSR} represents a small Ca^{2+} leak through the SR membrane, it must be that $\frac{J_{SR}}{k_{IPR}} \ll 1$. These are our first two constraints on parameter values.

We must also have $\frac{k_{RyR}}{J_{SR}} \gg 1$ for the SR to be largely depleted by the Rya-Caf treatment, so that (i) SOCE is activated ($c_s \lesssim K_s$) and (ii) agonist stimulation is no longer able to trigger substantial Ca^{2+} release from the SR after the treatment.

The IPR rate k_{IPR} must also be large enough so that for $p/K_1 \gg 1$ (for which P_{IPR} is saturated as a function of p, cf. Eq. (7)), Ca^{2+} oscillations cease to exist. Otherwise, stable Ca^{2+} oscillations persist in an unphysiologically large, and possibly semi-infinite, range of agonist concentrations (this can happen if the ROCE rate is zero, because then, for $p/K_3 \gg 1$, increasing p no longer influences Ca^{2+} dynamics, as Φ_1 and Φ_2 are saturated (Eq. (9)).

Moreover, in order to have $c_s^* > 100\mu$M (to match the experimental estimation $c_s^* \sim 500\mu$M [1]), which is equivalent to $c_s^* > 1000c^*$, the quantity $\frac{V_e/K_e}{J_{SR}}$ must be so large that to keep the $[Ca^{2+}]_i$oscillation amplitude reasonable, we have to set simultaneously the maximum PMCA rate V_p to $V_p \sim V_e$ and the PMCA affinity to $K_p \sim 1\mu$M. Increasing only V_p kills the oscillations, and changing k_{IPR} has little effect on the oscillation amplitude. At the same time, SOCE must be large enough compared with the PMCA Ca^{2+} flux to maintain an elevated $[Ca^{2+}]_i$after the Rya-Caf treatment. As a consequence, the Ca^{2+} fluxes through the PM are not negligible in our model, and the total Ca^{2+} concentration $c_t = c + c_s/\gamma$ cannot be considered as a slow variable for model reduction purpose, as it is in several models of Ca^{2+} dynamics (e.g., [2–4]). In order to make that approximation, we would need $c_s \lesssim 100\,c$, but this would disagree with the current experimental estimations.

Finally, it is instructive to consider non-dimensional estimates of the relative magnitudes of the different Ca^{2+} fluxes in the model, since these ratios control the qualitative dynamics of Ca^{2+}. This is done in Table S1, together with a comparison with the same quantities in the Wang *et al.* model [4]. We note, in particular, that the ratio between the PMCA and SERCA rates is much smaller in the Wang *et al.* model than in our model, while it is the contrary for the ratio between the IPR and SERCA rates. The equilibrium Ca^{2+} concentrations of the two models are also compared in Table S1.

quantity	expression	this work	Wang *et al.* [4]	ratio
J_{SOCC}/J_{PMCA}	$\frac{V_s}{K_s}\frac{K_p}{V_p}$	0.00628	0	0
J_{leakin}/J_{PMCA}	$\frac{\alpha_0}{V_p}$	0	0.0111	/
J_{ROCC}/J_{PMCA}	$\alpha_1\frac{K_p}{V_p}$	0.000209	0.0889	424
J_{VOCC}/J_{PMCA}	$\frac{V_s}{K_s}\frac{K_p}{V_p}$	0	0.2	/
J_{PMCA}/J_{SERCA}	$\frac{V_p}{K_p}\frac{K_e}{V_e}$	0.1	0.0125	0.125
J_{IPR}/J_{SERCA}	$k_{IPR}\frac{K_e}{V_e}$	0.0133	0.123	9.25
J_{RyR}/J_{SERCA}	$k_{RyR}\frac{K_e}{V_e}$	0	0.0371	/
J_{leakSR}/J_{SERCA}	$J_{SR}\frac{K_e}{V_e}$	0.0002	0.00222	11.1
J_{leakSR}/J_{IPR}	$\frac{J_{SR}}{k_{IPR}}$	0.015	0.018	1.2
resting $[Ca^{2+}]_i(\mu M)$	c^*	0.0681	0.161	N.A.
resting $[Ca^{2+}]_{SR}(\mu M)$	c_s^*	158	27.4	N.A.

Table S1. Relative magnitudes of the different Ca^{2+} fluxes in our model and in the Wang *et al.* model [4]. The last column gives the ratio of the previous two. The equilibrium Ca^{2+} concentrations are also given.

References

1. Demaurex N, Frieden M (2003) Measurements of the free luminal ER Ca2+ concentration with targeted cameleon fluorescent proteins. Cell Calcium 34: 109–119.

2. Tang Y, Stephenson JL, Othmer HG (1996) Simplification and analysis of models of calcium dynamics based on IP3-sensitive calcium channel kinetics. Biophys J 70: 246–63.

3. Sneyd J, Tsaneva-Atanasova K, Yule DI, Thompson JL, Shuttleworth TJ (2004) Control of calcium oscillations by membrane fluxes. PNAS 101: 1392–6.

4. Wang IY, Bai Y, Sanderson MJ, Sneyd J (2010) A mathematical analysis of agonist- and KCl-induced Ca2+ oscillations in mouse airway smooth muscle cells. Biophys J 98: 1170–81.