1 Dynamical System

The following ODEs govern calcium (c) dynamics

$$\frac{dc}{dt} = J_{IP3R} + J_{ERleak} - J_{SERCA} \quad + \delta[J_{ECSadd} - J_{PMCA} + J_{SOC}] \tag{1}$$

$$\frac{dc_{tot}}{dt} = \delta[J_{ECSadd} - J_{PMCA} + J_{SOC}] \tag{2}$$

$$\frac{dh}{dt} = \frac{h_\infty - h}{\tau_h} \tag{3}$$

where the equations related to h are

$$\tau_h = \frac{1}{a_2(Q_2 + c)} \tag{4}$$

$$h_\infty = \frac{Q_2}{Q_2 + c} \tag{5}$$

$$Q_2 = d_2\left(\frac{p + d_1}{p + d_3}\right) \tag{6}$$

The various fluxes J are given each by

$$J_{IP3R} = v_{IP3R} m_\infty^3 n_\infty^3 h^3 (c_{ER} - c) \tag{7}$$

$$m_\infty = \frac{p}{p + d_1}, \quad n_\infty = \frac{c}{c + d_5} \tag{8}$$

$$J_{SERCA} = v_{SERCA} \frac{c^{1.75}}{c^{1.75} + k_{SERCA}^{1.75}} \tag{9}$$

$$J_{PMCA} = v_{PMCA} \frac{c^2}{c^2 + k_{PMCA}^2} \tag{10}$$

$$J_{SOC} = v_{SOC} \frac{k_{SOC}^2}{k_{SOC}^2 + c_{ER}^2} \tag{11}$$

$$J_{ERleak} = v_{ERleak}(c_{ER} - c) \tag{12}$$

$$J_{ECSadd} = v_{in} - k_{out} c \tag{13}$$

and in equations (1), (2), δ is a scaling size parameter. The other dynamic variable of interest is IP3 (p), which has ODEs

$$IP3_{production} = v_\beta G^* + v_+ \frac{k_\delta}{1+p} \frac{c^2}{c^2 + k_{PLC\delta}^2} \tag{14}$$

$$IP3_{degradation} = v_- \frac{c^4}{c^4 + k_d^4} \frac{p}{p + k_3} + r_{5p} p \tag{15}$$

$$\frac{dp}{dt} = IP3_{production} - IP3_{degradation} \tag{16}$$

G^* is the strength of external stimulation to the system and our bifurcation parameter. Importantly in equations (14) and (15), v_δ is the strength of positive $c \to p$ feedback, and v_{3k} is the strength of negative $c \to p$ feedback. If $v_\delta = 0$ or $v_{3k} = 0$, we say that there is no positive or no negative feedback respectively.

The GPCR model has the following equations

$$\frac{dG^*}{dt} = k_p \gamma G - k_m G^* - k_{d1} G^* - k_{d2} G^* \lambda \tag{17}$$

$$\frac{dG_{d1}}{dt} = k_{d1} G^* - k_{r1} G_{d1} \tag{18}$$

$$\frac{dG_{d2}}{dt} = k_{d2} (G^* + G) \lambda - k_{r2} G_{d2} \tag{19}$$

$$\frac{d\lambda}{dt} = k_{\lambda+} G^* - k_{\lambda-} \lambda \tag{20}$$

All parameters are given in the following table:

Parameter	Description	Value/Units
	Calcium Parameters	
v_{IP3R}	Max IP3 Receptor Flux	0.222 s^{-1}
v_{ER_leak}	Cytosol to ER leak	0.002 s^{-1}
v_{in}	Rate of leak into Cytosol from Plasma Membrane	0.05μM s^{-1}
k_{out}	Rate of leak out of Cytosol from Plasma Membrane	1.2 s^{-1}
v_{SERCA}	Max SERCA Flux	0.9μM s^{-1}
k_{SERCA}	Half-Saturation for SERCA	0.1μM
v_{PMCA}	Max PMCA Flux	10μM s^{-1}
k_{PMCA}	Half-Saturation for PMCA	2.5μM
v_{SOC}	Max SOC channels Flux	1.57μM s^{-1}
k_{SOC}	Half-Saturation for SOC channels	90μM
δ	Scale Factor (ratio of membrane transport to ER transport)	0.2
d_1	Dissociation constant for IP3	0.13μM
d_2	Dissociation constant for Ca2+ inhibition	1.049μM
d_3	Receptor dissociation constant for IP3	0.9434μM
d_5	Ca2+ activation constant	0.08234μM
a_2	Ca2+ inhibition constant	0.04 μM^{-1} s^{-1}
	IP3 Parameters	
v_β	PLCβ IP3 Generation from GPCR	0.2
k_δ		1.5
$k_{PLC\delta}$		0.1
v_-	Negative Calcium to IP3 Feedback via Phosphorylation	0.1 (2.0)
v_+	Positive Calcium to IP3 Feedback Rate via PLCδ	0.005 (0.01)
k_d		0.7
k_3		1
r_{5p}	Natural IP3 Degradation	0.08
	GPCR Parameters	
k_p	GPCR Activation Rate	0.02 (0.03)
k_m	GPCR Deactivation Rate	0.2 (0.04)
k_{d1}	Homologous (Gd1) Deactivation Rate	0.02
k_{r1}	Homologous Reactivation Rate	0.01
k_{d2}	Heterologous (Gd2) Deactivation Rate	1.2 (0.003)
k_{r2}	Heterologous Reactivation Rate	0.005 (0.0007)
k_{lp}	Downstream PKA (λ) Production	0.0002
k_{lm}	PKA (λ) Degradation	0.004
	Diversity Transient Parameters	
r_{rise}	Rate of Exponential Growth	[0.002-12] s^{-1}
d_{decay}	Duration of IP3 decline	[15-220] s
d_{rise}	Duration of IP3 increase	[1-41] s
A	Max amplitude of IP3 transient	[0.2-0.9] μM