Supplementary Information

Mathematical Model Equations:

(1) Calcium Dynamics

$$\nu plc = (Vplc + basal) * \left(\frac{[Ca^{2+}]^2}{Kplc^2 + [Ca^{2+}]^2}\right)$$

$$\nu deg = (k5p + k3k * \left(\frac{[Ca^{2+}]^2}{K3k^2 + [Ca^{2+}]^2}\right)) * [IP3]$$

$$\nu rel = \left(k1 * \left([IP3r] * \frac{[Ca^{2+}]}{Ka + [Ca^{2+}]} * \frac{[IP3]}{Kp + [IP3]}\right)^3 + k2\right) * ([Ca^{2+}(ER)] - [Ca^{2+}])$$

$$\nu serca = Vserca * \left(\frac{[Ca^{2+}]^2}{Kserca^2 + [Ca^{2+}]^2}\right)$$

$$\nu in = \nu 0 + \emptyset * Vplc * (\frac{1}{k3k + k5p})$$

$$\nu out = Vpm * \left(\frac{[Ca^{2+}]^2}{Kpm^2 + [Ca^{2+}]^2}\right)$$

$$\frac{d[IP3]}{dt} = \nu plc - \nu deg$$

$$\frac{d[Ca^{2+}]}{dt} = \nu rel - \nu serca + \varepsilon * (\nu in - \nu out)$$

$$\frac{d[Ca^{2+}(ER)]}{dt} = \left(\frac{1}{\beta}\right) * (\nu serca - \nu rel)$$

$$\frac{d[IP3r]}{dt} = \left(\frac{1}{Tr}\right) * (1 - [IP3r] * \frac{Ki + [Ca^{2+}]}{Ki})$$

(2) Conservation equations

R = receptor available for binding, Rtot = total receptor, [LR] = Ligand-Receptor Complex, G = available G-protein for activation, Gtot = total G-protein, [GGTP] = Active G-protein, [GGDP] = Inactive G-protein, [PLC*] = activated PLC, PLCtot = total PLC, Gβγ = G-protein subunit, [LRp] = Ligand-phosphorylated Receptor complex, [Rp] = phosphorylated Receptor, [Rrec] = Recycled Receptor

$$R = Rtot - [LR] - [LRp] - [Rp] + Rrec$$

$$G = Gtot - [GGTP] - [GGDP] - [PLC*]$$

$$G\beta\gamma = [GGTP] + [GGDP] + [PLC*]$$

$$PLC = PLCtot - [PLC*]$$

(3) Ligand, Receptor, G-protein dynamics

$$\frac{d[LR]}{dt} = k1L * R * L - k2L * [LR] - kgrk1f * [LR] + kgrk1r * [LRp]$$

$$\frac{d[GGTP]}{dt} = -k4 * [GGTP] + k5 * G * [LR] - k6 * PLC * [GGTP] + k3 * G$$

$$\frac{d[GGDP]}{dt} = k4 * [GGTP] + k4 * [PLC*] - k7 * [GGDP] * G\beta\gamma$$

$$\frac{d[PLC*]}{dt} = k6 * PLC * [GGTP] - k4 * [PLC*]$$

(4) Receptor Phosphorylation Dynamics

$$\frac{d[LRp]}{dt} = kgrk1f * [LR] - kgrk1r * [LRp] + kgrk2r * [Rp] - kgrk2f * [LRp]$$

$$\frac{d[Rp]}{dt} = -kgrk2r * [Rp] + kgrk2f * [LRp] - kgrk3r * [Rp]$$

$$\frac{d[Rrec]}{dt} = kgrk2r * [Rp] - k1L * L * [Rrec]$$

Model Parameters:

Parameter	Description	Value
K3k	Half-activation constant of IP3K	0.465 μM
k5p	IP3 dephosphorylation rate constant	0.56 s^{-1}
β	Ratio of effective volumes of the ER/cytosol	0.185
Kserca	Half-activation constant for SERCA pump	0.076 μM
Kpm	Half-activation constant for PMCA pump	0.076 μM
ϕ	Stimulation-dependent influx	0.0024 s^{-1}
Ctot	Total Calcium concentration	2 μM
k2	Calcium leak	0.014 s^{-1}
Ki	Calcium binding to inhibiting site	0.469 μM
Tr	Characteristic time of IP3r inactivation	7 s
k3k	IP3 phosphorylation rate constant	0
Kplc	Half-activation constant of PLC	0.213 μM
Vserca	Maximal SERCA pump rate	0.27 μM s^{-1}

Vpm	Maximal PMCA pump rate	0.014 μM s^{-1}
ν0	Basal calcium flux	0.0001 μM s^{-1}
ε	Calcium flux strength	5
k1	Maximal rate of calcium release	0.85 s^{-1}
Ka	Calcium binding to activating site	0.059 μM
Kp	IP3 binding	0.13 μM
basal	Basal IP3 production rate by PLC	0.3 μM s^{-1}
k1L	Ligand-receptor association rate constant	2.3 μM^{-1} s^{-1}
k2L	Ligand-receptor dissociation rate constant	0.07 s^{-1}
k3	Basal exchange rate of GTP for GDP on Gα subunit	0.008 s^{-1}
k4	Rate constant for hydrolysis of GαGTP to GαGDP	2 s^{-1}
k5	Encounter rate constant for ligand-receptor complex and G-protein	$2*10^{-5}$ s^{-1}
k6	Encounter rate constant for PLC and GαGTP	$2*10^{-5}$ s^{-1}
k7	Encounter rate constant for βγ and GαGDP	$1*10^{-5}$ s^{-1}
Rtot	Receptor total	0.068 μM
Gtot	G-protein total	0.2 μM
PLCtot	PLC total	0.1 μM
kgrk1f	GRK-mediated receptor phosphorylation rate constant	0.0324 s^{-1}
kgrk1r	Receptor dephosphorylation rate constant	$6*10^{-4}$ s^{-1}
kgrk2f	Ligand dissociation rate constant with phosphorylated receptor	0.0919 s^{-1}
kgrk2r	Ligand association rate constant with phosphorylated receptor	$1*10^{-4}$ s^{-1}
kgrk3r	Receptor dephosphorylation rate constant without ligand	0.007 s^{-1}

Model Schematic: