Homogenized model

$$\frac{\partial[Ca^{2+}]}{\partial t} = J_{flux} - J_{SERCA} + J_{media} + D_{Ca^{2+}}\nabla^2[Ca^{2+}]$$

$$\frac{d[IP_3R]}{dt} = k_6\left(\frac{K_i^2}{K_i^2 + [Ca^{2+}]^2} - [IP_3R]\right)$$

$$\frac{d[Ca_{ER}^{2+}]}{dt} = -\frac{V}{V_{ER}}\left(J_{flux} - J_{SERCA}\right)$$

$$\frac{\partial[IP_3]}{\partial t} = v_{PLC} - k_{deg}[IP_3] + D_{IP_3}\nabla^2[IP_3]$$

$$J_{flux} = \frac{(k_1 + k_2[IP_3R][Ca^{2+}]^2[IP_3]^2)([Ca_{ER}^{2+}] - [Ca^{2+}])}{(K_{Ca^{2+}}^2 + [Ca^{2+}]^2)(K_{IP_3}^2 + [IP_3]^2)}$$

$$J_{SERCA} = \frac{v_{SERCA}[Ca^{2+}]^2}{k_{SERCA}^2 + [Ca^{2+}]^2}$$

$$J_{media} = v_{leak} - k_{leak}[Ca^{2+}]$$

$$v_{PLC} = \Gamma(1, \mu_{PLC})$$

Boundary and initial conditions

No-flux boundary conditions:

$$\nabla[IP_3] = 0 \; at \; x = \{0, L\}$$

$$\nabla[Ca^{2+}] = 0 \; at \; x = \{0, L\}$$

Spatial domain is 0 to L

Steady-state initial conditions:

$at \; t = 0$:

$$[Ca^{2+}] = 0.05 \; \mu M$$

$$[IP_3] = 0.15 \; \mu M$$

$$[Ca^{2+}_{ER}] = 80 \; \mu M$$

$$[IP_3R] = 1$$

Parameter	Description	Value
k_1	Rate constant of calcium leak from ER[1]	4e-4 [1/s]
k_2	Rate constant of calcium release through IP3R[1]	0.08 [1/s]
$K_{Ca^{2+}}$	Half-saturation constant for calcium activation of IP3R[1]	0.2 [uM]
K_{IP_3}	Half-saturation constant for IP3 activation of IP3R[1]	0.3 [uM]
v_{SERCA}	Maximum rate of calcium pumping into the ER[2]	0.08 [uM/s]
k_{SERCA}	Half-saturation constant for calcium pumping into the ER[2]	0.02 [uM]
v_{leak}	Rate of calcium leak from medium[1]	0.51 [1/s]
k_{leak}	Rate constant of calcium flux to the medium[1]	0.035 [uM]
V_{ER}/V	Volumetric fraction of ER[2]	20
k_6	Rate constant of IP3R inactivation[1,2]	11.3 [1/s]
K_i	Half-saturation constant for calcium inhibition of IP3R[1,2]	0.09 [uM]
k_{deg}	Rate constant of IP3 degradation[1]	0.08 [1/s]
μ_{PLC}	Mean rate of IP3 generation	1e-2 [uM/s]
D_{IP_3}	Diffusivity of IP3[1,2,3]	280 [uM/s^2]
$D_{Ca^{2+}}$	Diffusivity of calcium[1,2,3]	20 [uM/s^2]
D_{IP_3}	Permeability of IP3[1,2,3]	1 [uM/s]
$D_{Ca^{2+}}$	Permeability of calcium[1,2,3]	0.01 [uM/s]

1. Höfer, Thomas, Laurent Venance, and Christian Giaume. "Control and plasticity of intercellular calcium waves in astrocytes: a modeling approach." *The Journal of neuroscience* 22.12 (2002): 4850-4859.
2. Sneyd, J. A. M. E. S., et al. "Intercellular calcium waves mediated by diffusion of inositol trisphosphate: a two-dimensional model." *American Journal of Physiology-Cell Physiology* 268.6 (1995): C1537-C1545.
3. Keener, James P., and James Sneyd. *Mathematical physiology*. Vol. 1. New York: Springer, 1998.

Homogenization

- Cell topology was ignored through homogenization as described in[1]
- Permeability and Diffusivity terms were combined to obtain effective diffusivity for calcium and IP3

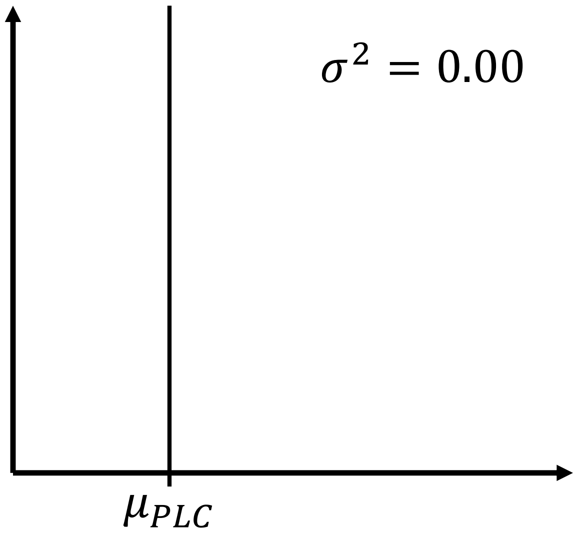
- Effective diffusivities (after accounting for cell boundaries) are:
  - IP3: 9.66 uM/s^2
  - Calcium: 0.10 uM/s^2

1. Keener, James P., and James Sneyd. *Mathematical physiology*. Vol. 1. New York: Springer, 1998.

v_{PLC} Probability density function

$$v_{PLC} = \mu_{PLC}$$

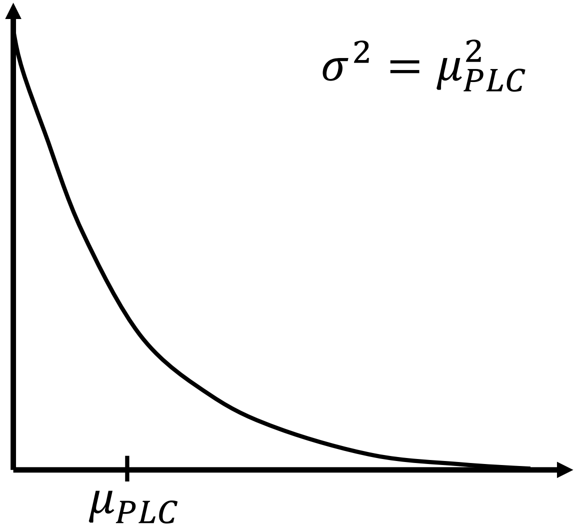
$$\sigma^2 = 0.00$$



Represents an IP_3 generation signal with no noise.

$$v_{PLC} = \Gamma(1, \mu_{PLC})$$

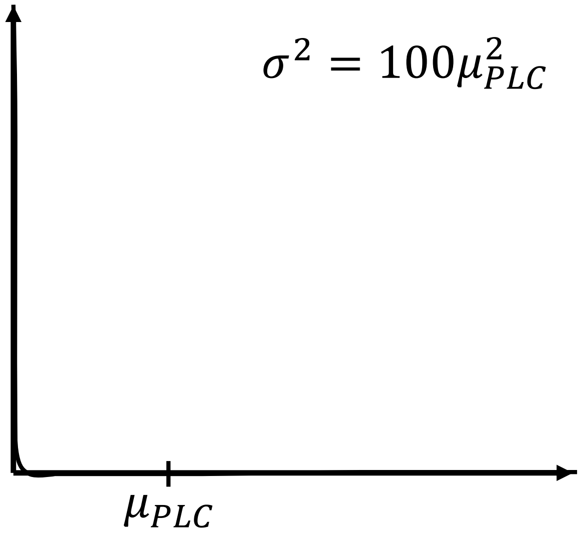
$$\sigma^2 = \mu_{PLC}^2$$



Represents variable IP_3 generation signal where very high production rates can rarely occur, but production on average is the same as in pdf 1.

$$v_{PLC} = \Gamma\left(0.01, \frac{\mu_{PLC}}{0.01}\right)$$

$$\sigma^2 = 100\mu_{PLC}^2$$



IP_3 signal with even higher variance than pdf 2. Here production rates will generally be very low but a greater frequency of high-rate events results in an average generation equal to pdf 1 and 2.

I called gamrnd in MATLAB to generate random numbers on this distribution

Stochastic term

- I used multiple pdf's including Gaussian for the stochastic term and always saw a transition as the variance increased with constant mean. I went with Gamma for this exploratory analysis because it most resembled the distribution of stimulus in discs in absence of serum
- The following is the term used for the AIChE model:

$$v_{PLC} = \Gamma(1, \mu_{PLC}) = Gamma(1, \mu_{PLC})$$

- The formal pdf for this term is:

$$P\left(x, k, \frac{\mu_{PLC}}{k}\right) = \frac{x^{k-1} e^{-\frac{xk}{\mu_{PLC}}}}{\frac{\mu_{PLC}}{k}^{k} \int_0^\infty x^{k-1} e^{-x}\, dx} \qquad P(x, 1, \mu_{PLC}) = \frac{e^{-\frac{x}{\mu_{PLC}}}}{\mu_{PLC} \int_0^\infty e^{-x}\, dx}$$

- **I called gamrnd in MATLAB to generate random numbers on this distribution**