

### Complementary model for InsP<sub>3</sub> coupling

Tanimura et al. [1] demonstrated cell type-dependent differences in InsP<sub>3</sub> dynamics: i.) Ca<sup>2+</sup> spikes are generated in the absence of synchronous InsP<sub>3</sub> fluctuations and ii.) Ca<sup>2+</sup> spikes are connected by InsP<sub>3</sub> fluctuations with a small time delay. In the second case, we have to consider additional InsP<sub>3</sub> production by c<sub>cyt</sub>-dependent phospholipase C activation and InsP<sub>3</sub> might play a role in the intercellular Ca<sup>2+</sup> synchronization. Instead of Eq. (20), we consider that the InsP<sub>3</sub> concentration, denoted here by  $I(v, t)$ , satisfies the following differential equation

$$\frac{\partial I(x, v, t)}{\partial t} = I_G(v, t) + I_{Ca}(x) - I_{DEG}(v, t) + d_I \sum_{\{v, u\} \in \mathcal{E}} (I(u, t) - I(v, t)) \quad (1)$$

where  $I_G$  denotes the G-protein dependent InsP<sub>3</sub> production,  $I_{Ca}$  the c<sub>cyt</sub>-dependent InsP<sub>3</sub> production,  $I_{DEG}$  the degradation and  $d_I$  the gap junctional permeability of InsP<sub>3</sub>.

The G-protein dependent InsP<sub>3</sub> production is related to stimulus intensity and is modeled as

$$I_G(v, t) = \begin{cases} 0.015, & \text{if } t < t_1(v) \\ i_{G, \max}(v) \frac{t - t_1(v)}{K_G + t - t_1(v)}, & \text{if } t \geq t_1(v) \end{cases} \quad (2)$$

where  $K_G$  is a positive constant and,  $i_{G, \max}(v)$  as well as  $t_1(v)$  can take different values among the cells network, enabling the actual InsP<sub>3</sub> concentration to be inhomogeneous in space. The degradation rate of InsP<sub>3</sub> is given by the following equation:

$$I_{DEG}(v) = r_{u1} \cdot I(v), \quad (3)$$

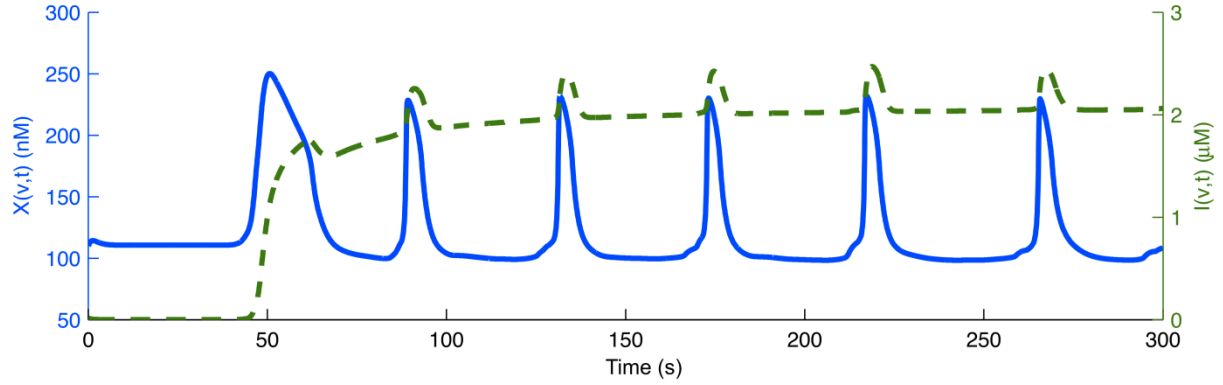
with  $r_{u1}$  a positive constant. Because the activity of c<sub>cyt</sub>-dependent phospholipases increases suddenly above resting Ca<sup>2+</sup> values [2], the c<sub>cyt</sub>-dependent InsP<sub>3</sub> production is modeled by the following function of the cytosolic Ca<sup>2+</sup> concentration  $x$ ,

$$I_{Ca}(x) = r_{u2} \cdot \frac{x^3}{K_{Ca}^3 + x^3} \quad (4)$$

with  $r_{u2}$  and  $r_{u3}$  positive constants. All parameter values are presented in Table A. For the simulations, the values of  $i_{G, \max}(v)$  are assigned in the same manner as  $i_{ip3, \max}(v)$ , see Table 1 in Main Text.

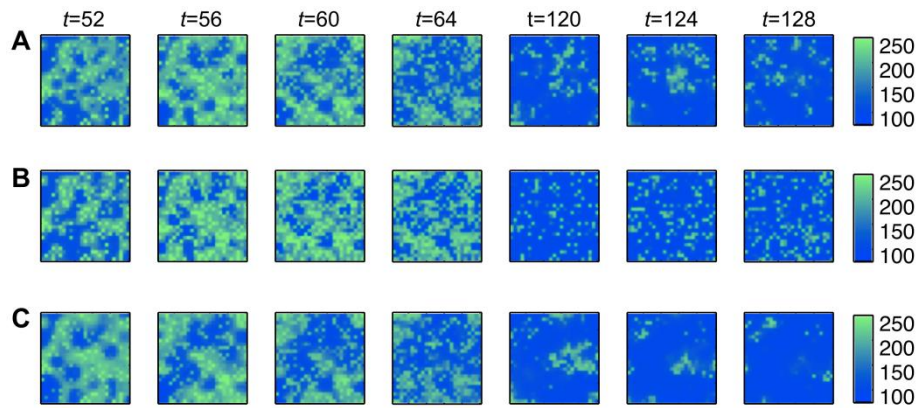
	Parameter name	Value
Constants	$K_G$	6 s
	$r_{u1}$	1.05 /s
	$r_{u2}$	200 nM/s
	$K_{Ca}$	1000 nM

**Table A. Parameters for  $\text{InsP}_3$  kinetics.**



**Fig A. Simultaneous changes of  $c_{\text{cyt}}$  and  $[\text{InsP}_3]$ , when considering both  $\text{InsP}_3$  and  $\text{Ca}^{2+}$  diffusion**

The conditions are the ones of model  $G_R$  with moderate noise and an identical gap junction coupling parameter for  $\text{Ca}^{2+}$  and  $\text{InsP}_3$ :  $d = d_I = 0.003$ . See S16 Movie.



**Fig B. Differences in  $\text{Ca}^{2+}$  propagation for different types of couplings in random model  $G_R$  (A)**

Only  $\text{Ca}^{2+}$  coupling ( $d = 0.003$  and  $d_I = 0$ , see S14 Movie). (B) Only  $\text{InsP}_3$  coupling ( $d = 0$  and  $d_I = 0.003$ , see S15 Movie). (C)  $\text{Ca}^{2+}$  and  $\text{InsP}_3$  couplings ( $d = 0.003$  and  $d_I = 0.003$ , see S16 Movie). Noise is set to moderate levels (see Table 1 in Main Text). Numerical estimations of

synchronization are reported in Table B of this supplementary text and show that  $\text{InsP}_3$  coupling is more efficiently involved in synchronization around the first  $\text{Ca}^{2+}$  peak ( $t = 52 - 64$ ). Afterwards,  $\text{Ca}^{2+}$  coupling more efficiently synchronizes  $\text{Ca}^{2+}$  oscillations.

	<b>35 – 160 (s)</b>	<b>161 – 600 (s)</b>	<b>35 – 600 (s)</b>
Only $\text{Ca}^{2+}$ coupling	$0.118 \pm 0.003$	$0.241 \pm 0.004$	$0.185 \pm 0.003$
Only $\text{InsP}_3$ coupling	$0.651 \pm 0.015$	$0.069 \pm 0.003$	$0.103 \pm 0.004$
$\text{Ca}^{2+}$ and $\text{InsP}_3$ coupling	$0.136 \pm 0.003$	$0.305 \pm 0.005$	$0.246 \pm 0.003$

**Table B. Values of the synchronization index  $m_{sync}$  (See Main Text for details)** The parameters are the ones used for producing Fig. B of this supplementary text (moderate noise). We observe how  $\text{InsP}_3$  coupling is involved in synchronization when the signal starts (around  $t_1 = 60$ , i.e. for  $35 < t < 160$ ). Afterwards,  $\text{Ca}^{2+}$  coupling is more efficient in synchronizing cell behaviors. See also S14-16 Movies.

## References

1. Tanimura A, Morita T, Nezu A, Shitara A, Hashimoto N, et al. (2009) Use of Fluorescence Resonance Energy Transfer-based Biosensors for the Quantitative Analysis of Inositol 1,4,5-Trisphosphate Dynamics in Calcium Oscillations. J Biol Chem 284: 8910-8917.
2. Pawelczyk T, Matecki A (1997) Structural requirements of phospholipase C delta1 for regulation by spermine, sphingosine and sphingomyelin. Eur J Biochem 248: 459-465.