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# ON THE DETERMINANTS OF CALCIUM WAVE PROPAGATION DISTANCE IN ASTROCYTE NETWORKS: NONLINEAR GAP JUNCTIONS AND OSCILLATORY MODES

Mati Goldberg<sup>1</sup>, Maurizio De Pitta<sup>2</sup>, Vladislav Volman<sup>3</sup>, Hugues Berry<sup>4</sup> and Eshel Ben-Jacob<sup>5</sup>

1. School of Physics and Astronomy, Tel Aviv University, 69978 Ramat Aviv, Israel, mati.goldberg@gmail.com

2. School of Physics and Astronomy, Tel Aviv University, 69978 Ramat Aviv, Israel, mauriziodepitta@gmail.com

3. Center for Theoretical Biological Physics, UCSD, La Jolla, CA 92093-0319, USA & Computational Neurobiology Lab, The Salk Institute, La Jolla, CA 92037, USA, volman@salk.edu

4. COMBINING Team, INRIA Rhône-Alpes, 69621 Villeurbanne, France, hugues.berry@inria.fr

5. School of Physics and Astronomy, Tel Aviv University, 69978 Ramat Aviv, Israel & Center for Theoretical Biological Physics, UCSD, La Jolla, CA 92093-0319, USA, eshel@tamar.tau.ac.il

## ABSTRACT

A new paradigm has recently emerged in brain science whereby glial cells should be considered on a par with neurons to understand higher brain functions. In particular, astrocytes, the main type of glial cells in the cortex, are thought to form a gap-junction-coupled syncytium supporting cell-cell communication via propagating calcium ( $\text{Ca}^{2+}$ ) waves. The propagation properties of these waves and their relations to intracellular signalling dynamics are however poorly understood. Here, we propose a novel model of the gap-junctional route for intercellular  $\text{Ca}^{2+}$  wave propagation in astrocytes that yields two major predictions. First, we show that long-distance regenerative signalling requires gap junctions with nonlinear transport properties. Second, we show that even with nonlinear gap junctions, long-distance regenerative signalling is favoured when internal  $\text{Ca}^{2+}$  dynamics implements frequency modulation-encoding oscillations with pulsating dynamics, while amplitude modulation-encoding dynamics tends to restrict the propagation range. As a result, spatially heterogeneous molecular properties and/or weak couplings give rise to rich spatiotemporal dynamics and support complex propagation behaviours. These results suggest that the large variability of the wave propagation range that is consistently reported by experimental studies, is a result of the association of nonlinear gap junctions with heterogeneous astrocyte populations and/or low coupling.

## KEY WORDS

Glial cells, Calcium signalling, Mathematical model

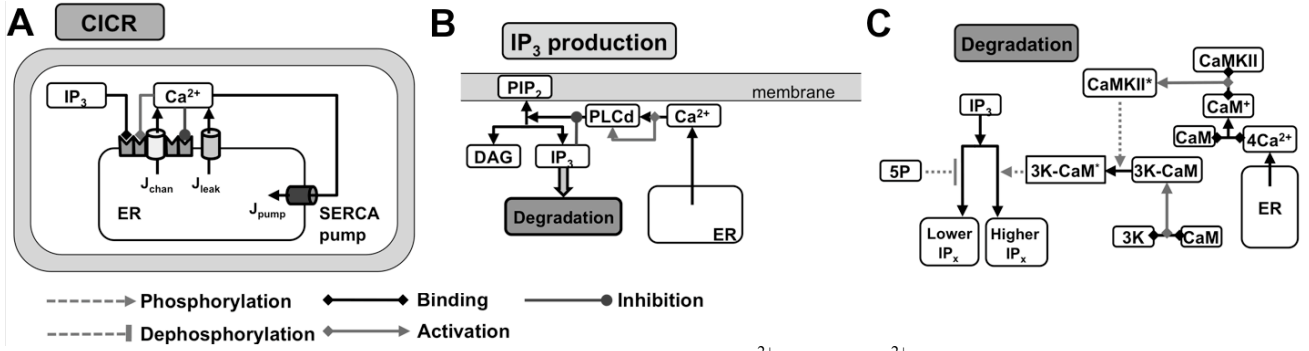
## 1. Introduction

Recent experimental evidence suggests that glial cells provide a role much more than support in the brain, including control of synapse function and formation, adult neurogenesis and regulation of cerebral blood flow (see e.g. [1] for a review). In particular, astrocytes, the main type of glial cells in the cortex, have attracted much attention because they can integrate neuronal inputs and modulate the synaptic activity between two neurons [2].

Moreover, neurotransmitters released from pre-synaptic neurons can bind to specific receptors on the astrocyte membrane and evoke  $\text{Ca}^{2+}$  elevations in the astrocyte cytoplasm. These  $\text{Ca}^{2+}$  elevations can propagate to neighbouring astrocytes, forming intercellular  $\text{Ca}^{2+}$  waves [3] with variable propagation distances ranging from four [4] to up to 30 [5] astrocytes. These results bring about the hypothesis that this persistent astrocyte wave-based signalling could extend the repertoire of neural network communications, adding non-local interactions, both in space and in time [1].

In order to assess this hypothesis though, several aspects of  $\text{Ca}^{2+}$  signalling in astrocytes remain to be elucidated. Experimental data suggest that a stimulus impinging on an astrocyte is preferentially encoded in the modulation of the frequency (FM) of astrocytic  $\text{Ca}^{2+}$  oscillations [6]. This type of oscillations is often characterized by pulsating waves, i.e. the propagation of peak waveforms, with width smaller than period. However, the possibility of amplitude modulation (AM) or even coexisting AM and FM (AFM) encoding have also been inferred [7].

Intracellular  $\text{Ca}^{2+}$  dynamics in astrocytes is mainly due to  $\text{Ca}^{2+}$ -induced  $\text{Ca}^{2+}$  release (CICR) from the endoplasmic reticulum (ER) stores and its regulation by inositol trisphosphate (IP3) [7]. In the neocortex, the propagation of  $\text{Ca}^{2+}$  waves across astrocytes is mainly due to the diffusion of IP3 molecules directly from cytosol to cytosol through gap junction channels [8]. Indeed, when the IP3 in a given cell increases, some of it can be transported through a gap junction to a neighbour astrocyte. This IP3 surge in the neighbour cell can in turn trigger CICR, thus regenerating the original  $\text{Ca}^{2+}$  signal. Yet, the transported IP3 is required to reach a minimal threshold concentration to trigger CICR in the neighbour cell. If this threshold is not reached, propagation ceases [9]. In this regard, previous theoretical studies stressed the importance of a mechanism for at least partial regeneration of IP3 levels. Production of IP3 by  $\text{Ca}^{2+}$ -dependent PLC $\delta$  has been suggested as a plausible candidate regeneration mechanism [10,11]. However, the intercellular latencies of the  $\text{Ca}^{2+}$  waves simulated with this mechanism are hardly reconcilable with experimental observations, hinting a critical role for gap junction IP3 permeability [10].



**Figure 1. Sketch of the signaling pathways considered in the model.**  $Ca^{2+}$ -induced  $Ca^{2+}$  release (CICR) from the endoplasmic reticulum (ER) (A). Endogenous  $IP_3$  production from  $PIP_2$  by  $PLC\delta$  (B).  $IP_3$  Degradation by  $IP_3$  3-kinase- (3K) and inositol polyphosphate 5-phosphatase (IP-5P) (C).

In the present study, we investigated the intercellular propagation of  $Ca^{2+}$  waves through the gap-junctional route by a computer model of one-dimensional astrocyte network. To account for intracellular  $Ca^{2+}$  dynamics, we adopted the concise but biologically realistic description of  $IP_3$ -coupled  $Ca^{2+}$  dynamics in astrocytes that we previously presented in [12]. We specifically focused on the influence of gap junction linearity and internal  $Ca^{2+}$  dynamics on the wave propagation distance. By means of bifurcation analysis and numerical solutions, we show that nonlinear coupling between astrocytes can indeed favor  $IP_3$  partial regeneration thus promoting large-distance intercellular  $Ca^{2+}$  wave propagation. Our study also shows that long-distance wave propagation critically depends on the nature of intracellular  $Ca^{2+}$  encoding (i.e. whether  $Ca^{2+}$  signals are FM or AM) and the spatial arrangement of the cells. Furthermore, our results suggest that, in the presence of weak coupling, nonlinear gap junctions could also explain the complex intracellular oscillation dynamics observed during intercellular  $Ca^{2+}$  wave propagation in astrocyte networks [3].

## 2. Model

Calcium and  $IP_3$  dynamics in astrocytes were realistically modeled by an extended version of the Li-Rinzel model that includes  $Ca^{2+}$ -dependent  $IP_3$  metabolism [12]. Briefly, this model accounts for the complex signalling pathway illustrated in Figure 1 that includes  $Ca^{2+}$  regulation by  $IP_3$ -dependent CICR as well as  $IP_3$  dynamics resulting from  $PLC\delta$ -mediated synthesis and degradation by  $IP_3$  3-kinase (3K) and inositol polyphosphate 5-phosphatase (5P). The temporal evolution of astrocytic intracellular calcium in a cell is described by three coupled nonlinear differential equations:

$$\dot{C} = J_{chan}(C, h, IP_3) + J_{leak}(C) - J_{pump}(C) \quad (1)$$

$$\dot{h} = (h_{\infty}(C, IP_3) - h) / \tau_h(C, IP_3) \quad (2)$$

$$\dot{IP}_3 = P_{PLC\delta}(C, IP_3) - D_{3K}(C, IP_3) - D_{5P}(IP_3) \quad (3)$$

where the variables  $C$ ,  $h$  and  $IP_3$  represent the cell-averaged calcium concentration, the fraction of open  $IP_3$  Receptor channels ( $IP_3R$ ) on the Endoplasmic Reticulum (ER) membrane, and the cell-averaged concentration of  $IP_3$  second messenger, respectively.

$J_{chan}$  is the  $Ca^{2+}$  flux to the cytoplasm through  $IP_3Rs$ ,  $J_{leak}$  is a passive Ca leak through the ER membrane and  $J_{pump}$  the Ca flux to the ER via the SERCA ATPase pumps.  $h_{\infty}$  denotes  $h$  equilibrium value and  $\tau_h$  the corresponding time constant.  $P_{PLC\delta}$  expresses  $IP_3$  endogenous production by  $PLC\delta$ , while  $IP_3$  degradation is accounted for by  $D_{3K}$  and  $D_{5P}$ . The exact mathematical expression for each of the terms found in the right-hand side terms of eq.(1-3) is given in [12].

To investigate intercellular  $Ca^{2+}$  wave propagation we considered a simplified setup of 1D astrocyte networks (chains) with nearest-neighbour coupling through gap junctions. Hence, in each cell  $i$ ,  $C$  and  $h$  evolution are given by eq. (1) and (2), while  $IP_3$  evolution now reads:

$$\dot{IP}_3 = P_{PLC\delta}(C, IP_3) - D_{3K}(C, IP_3) - D_{5P}(IP_3) + \dots \quad (4)$$

$$\dots J_{i-1 \rightarrow i} + J_{i+1 \rightarrow i}$$

where the last two terms designate  $IP_3$  flux from the neighbour cells.

We considered three scenarios to describe the exchange of  $IP_3$  between a pair of adjacent astrocytes: (1) *linear*, (2) *threshold-linear* (composed of a linear term operating after a threshold) and (3) *non-linear (sigmoid)* coupling. The linear model is a simple diffusive coupling:

$$J_{i \rightarrow j} = F \Delta IP_3 \quad (5)$$

where  $\Delta IP_3$  is the concentration gradient between cell  $j$  and cell  $i$ . Both the threshold-linear:

$$J_{i \rightarrow j} = 0.5F \left( 1 + \tanh \left( \frac{|\Delta IP_3| - \Delta IP_3^{threshold}}{\Delta IP_3^{scale}} \right) \right) \frac{\Delta IP_3}{|\Delta IP_3|} \quad (6)$$

and the nonlinear models:

$$J_{i \rightarrow j} = 0.5F \left[ \frac{|\Delta IP_3| - \Delta IP_3^{threshold} - \Delta IP_3^{scale}}{\Delta IP_3^{scale}} \right]^+ \frac{\Delta IP_3}{|\Delta IP_3|} \quad (7)$$

transfer  $IP_3$  only when the  $IP_3$  gradient between the two adjacent cells overcomes a threshold value. In these equations,  $[x]^+$  denotes rectification ( $[x]^+ = x$  if  $x > 0$ , 0 else) and  $\Delta IP_3^{threshold}$  and  $\Delta IP_3^{scale}$  are parameter used to adjust the couplings so as to ease their comparison. Our investigation of nonlinear coupling case was motivated by the experimental observations suggesting that gap junction permeability can be actively modulated by various factors, among which different second messengers.

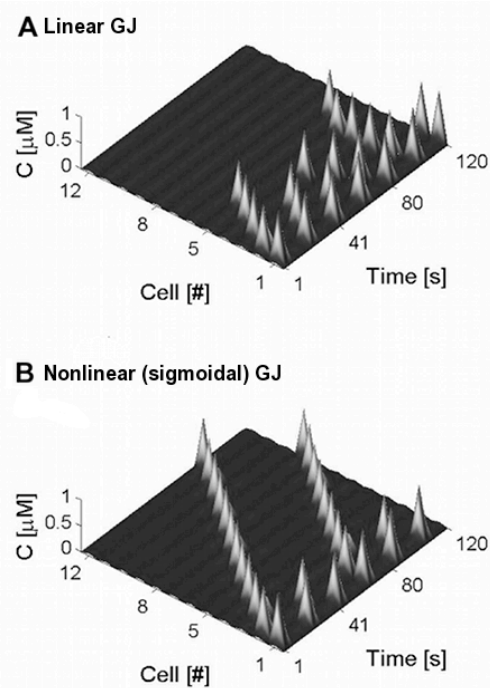
To trigger a  $Ca^{2+}$  wave in the astrocyte chain, a single cell (the “driving” cell) is subject to a supplementary

exogenous constant IP3 input through a gap junction. Its intensity ( $\mu\text{M}$ ) defines the stimulation strength.

### 3. Results

**Dynamical modes.** We first performed a detailed bifurcation analysis of our model astrocytes in the absence of coupling (isolated cells). A wealth of dynamical regimes was discovered, allowing model astrocytes to encode input information as amplitude modulated (AM), frequency modulated (FM) or mixed (AFM) modes (see [12,13]). Briefly, with large affinity of the SERCA pumps and large IP3 turnover rates, oscillations appear via a saddle-node-on-an-invariant-circle bifurcation and lead to FM type oscillations: stimuli of increasing strength give rise to Ca oscillations of increasing frequency but nearly constant amplitude. Conversely, lower affinity SERCA pumps and smaller IP3 turnover rates yield oscillations through a Hopf bifurcation, which generates AM or mixed AFM oscillation modes.

Bifurcation analysis for systems of a few coupled model astrocytes (utilizing different types of coupling) essentially evidenced the same quantitative behaviours. Note however that stable oscillation regimes often coexist in the bifurcation diagrams with stable fixed points, so that it cannot be predicted from these diagrams whether an IP3 input to the cell would trigger pulse-like oscillations or not, i.e. whether it would switch the system from the fixed point to the oscillatory regime. Thus, we resorted to extensive numerical simulations to investigate under what conditions one could observe propagation of  $\text{Ca}^{2+}$  waves along the astrocyte chain.

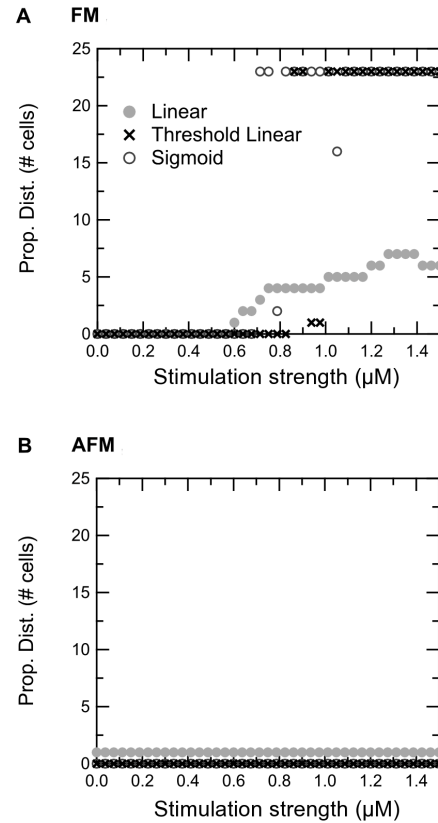


**Figure 2. Ca propagation in networks with linear (A) and non-linear sigmoidal (B) gap junctions.** Astrocyte chain of 12 FM-encoding cells with reflective boundary conditions. The stimulation ( $1.0 \mu\text{M}$ ) was delivered to cell # 1.

**Linear vs. non-linear gap junctions.** Examples of propagation patterns both for the linear and non-linear

cases are presented in Figure 2 for a chain of 12 FM-encoding cells. Here, the stimulation was applied to the first cell of the chain. For the linear coupling case (A), wave propagation fails at the 6th-7th cell from the driving one. By contrast, in the nonlinear coupling scenario (B),  $\text{Ca}^{2+}$  pulses can propagate along the whole length of the chain. Reporting the distance travelled by the propagating  $\text{Ca}^{2+}$  waves as a function of the stimulation amplitude (Figure 3A) generalizes this observation. With linear gap junctions (closed gray circles), the propagation distance increases with stimulus strength, but never exceeds one third of the chain length. On the contrary, with nonlinear sigmoid coupling (open circles),  $\text{Ca}^{2+}$  waves propagate along the whole chain as soon as the oscillatory regime is engaged (that is for stimulus strength larger than  $0.72 \mu\text{M}$ , in agreement with bifurcation studies). Similarly, threshold-linear GJs (times signs) exhibit almost the same response as sigmoid ones but with different effective threshold IP3 concentrations.

The above results, that are robust with respect to the changes in boundary conditions, suggest that a critical factor for long-distance propagation of  $\text{Ca}^{2+}$  waves across astrocytes is the existence of a threshold concentration for cell-to-cell IP3 diffusion, similar to the one displayed by our nonlinear gap junction models.



**Figure 3. Distance travelled by Ca waves as a function of stimulus intensity.** The stimulus is applied to the first cell in a chain of 25 FM (A) or AFM (B) cells. The traveled distance is expressed in number of cells. Coupling used linear (closed gray circles), non-linear sigmoid (open circles) or threshold-linear (times signs) GJs.

**AFM vs. FM cells.** We next examined the influence of the stimulus encoding mode. Figure 3B shows that whatever the stimulation strength of the driving cell or

the nature of the connecting gap junctions, i.e. linear or non-linear, Ca waves do not propagate in our AFM cell networks. In particular Figure 3B reports propagation failure even when the stimulation applied to the driving cell is as strong as  $1.5 \mu\text{M}$ , an intensity deeply inside the oscillatory region of the bifurcation diagrams.

Therefore, these results suggest a neat functional difference between AFM and FM oscillations in astrocytes: while FM could support long distance propagation of pulse-like  $\text{Ca}^{2+}$  waves, AFM is expected to give rise to localized  $\text{Ca}^{2+}$  signalling. Hence, any parameter relevant to intra-cellular  $\text{Ca}^{2+}$  signalling and able to switch the cell between AFM and FM modes (e.g. the affinity or activity of the SERCA pumps) is predicted to play a key role in the inter-cellular propagation of  $\text{Ca}^{2+}$  signals in astrocytes.

**Propagation in composite chains.** Because the astrocyte population within the brain is heterogeneous [14], the results reported above question the possibility of intercellular  $\text{Ca}^{2+}$  wave propagation across astrocytes with different properties. Here we tackled this issue using composite astrocyte chains, namely chains constituted of both FM and AFM cells.

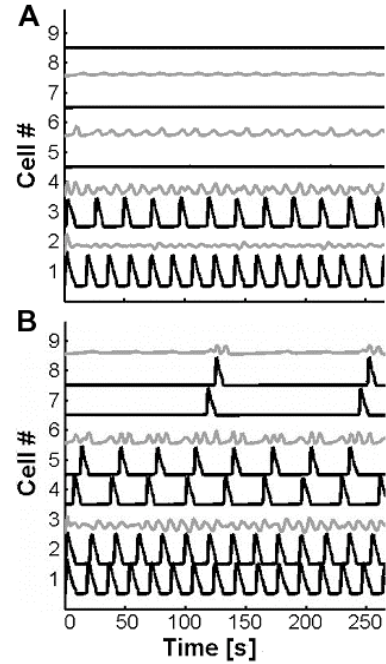
Figure 4A illustrates the propagation of a  $\text{Ca}^{2+}$  wave in a chain of alternating FM (black traces) and AFM (gray traces) cells and shows that propagation abruptly terminates at the second AFM cell in the chain (cell 4). Notably, closer inspection of IP<sub>3</sub> dynamics reveals that propagation stops because the IP<sub>3</sub> concentration in FM cell 5 does not maintains long enough above the oscillation threshold in this cell (not shown).

Therefore, a possible mechanism to facilitate wave propagation across AFM cells in such heterogeneous conditions consists in increasing the frequency of the wave pulses in the FM cell preceding the AFM one. This effect is actually naturally obtained when several successive FM cells are placed between two AFM ones. We illustrate this in Figure 4B, where the same conditions as in Figures 4A were used, except that one has now two successive FM cells between two AFM ones. The interactions between the two successive FM cells increase the frequency of the  $\text{Ca}^{2+}$  pulses, thus the frequency of elementary diffusion events of IP<sub>3</sub> in the next AFM cell. In turn this allows  $\text{Ca}^{2+}$  wave propagation in the subsequent FM cells.

The presence of homogenous FM cell domains between AFM cells is therefore likely to enable long traveling distances for propagating  $\text{Ca}^{2+}$  waves. One may even assume that if the number of successive FM cells in the FM domains is large enough, the  $\text{Ca}^{2+}$  wave should propagate over the entire heterogeneous network, whatever its size.

**Propagation of complex waves.** The  $\text{Ca}^{2+}$  and IP<sub>3</sub> dynamics observed so far were all obtained using a high value of the coupling strength ( $F = 2.0 \mu\text{M}\cdot\text{s}^{-1}$ , see eq.(5-7)). In these conditions, the properties of the propagated waves are rather simple: a pulse-like (or not) wave front travels across astrocytes, with conserved shape and either stops after a few cells or invades the whole cell chain. However, our system being a spatially extended dynamical system with large

numbers of degrees of freedom (e.g. coupled map lattices), we can expect complex spatiotemporal behaviours when the coupling strength changes. To get an insight on the possible propagation behaviour at weaker coupling, we finally considered reduced levels of GJ permeability.



**Figure 4. Ca wave propagation in composite astrocyte chains composed of repeated -[AFM-FM]- (A) or -[AFM-FM-FM]- sequences (B).** Black traces locate FM cells while AFM cells are displayed with gray traces. The stimulation ( $1.2 \mu\text{M}$ ) was applied to cell # 1.

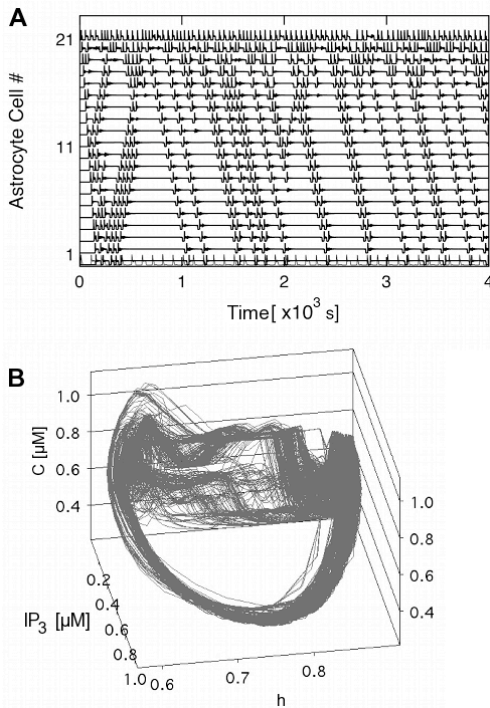
Figure 5 shows the  $\text{Ca}^{2+}$  dynamics of 41 coupled FM cells with  $F = 0.23 \mu\text{M}\cdot\text{s}^{-1}$ . Here, the stimulation was a square wave periodic IP<sub>3</sub> input applied to the central cell # 21. Visual inspection of the  $\text{Ca}^{2+}$  traces in each cell (Figure 5A) evidences the occurrence of occasional propagation failures that do not seem to result from a simple spatiotemporal pattern. Actually, observation of the temporal traces of each individual cell reveals the occurrence of pulse-like events showing up with no apparent regularity (not shown).

To further illustrate the complexity of the obtained dynamics, we plot in Figure 5B the trajectory of the system in the phase space of the driving cell. It is very tempting to compare the resulting trajectories to those observed with classical low-dimensional strange attractors. In this regard, preliminary analysis of the three time series of the driving cell using nonlinear time series analysis tools [15] suggested that the dynamics indeed corresponds to deterministic chaos, with sensitivity to initial conditions testified by a positive maximal Lyapunov exponent that we estimated between  $0.020$  and  $0.050 \text{ s}^{-1}$  (depending on the time series under consideration).

Whether the apparent complexity of the dynamics is indeed due to some form of spatiotemporal chaos or not is beyond the scope of the current article and is left for future work. But whatever the response is, these simulations evidence that complex  $\text{Ca}^{2+}$  wave propagation patterns can manifest at low couplings,



even with spatially homogeneous cell properties and in the absence of any stochasticity source.



**Figure 5. Complex behaviours at low coupling strength ( $F = 0.23 \mu\text{M}\cdot\text{s}^{-1}$ ).** The stimulus is an oscillatory input (positive square wave, 50-second period and duty cycle of 0.4) applied to the central cell of a 41 FM-cell chain (sigmoid GJs). Calcium concentration in cells 1 to 21 (A). Trajectory in the C-h-IP3 phase space for cell 21 (i.e. the stimulated cell) (B).

### 3. Conclusion

A critical issue for the modeling studies of intercellular  $\text{Ca}^{2+}$  waves across astrocytes is to explain the observed variability of  $\text{Ca}^{2+}$  wave travelling distance [16]. Indeed, experimental measurements show travelling distances varying from 30 cells [5] (i.e. often larger than the used microscope field length) down to 3-4 cells only [4]. Models featuring purely regenerative waves (e.g. traveling waves in the usual mathematical sense) easily account for long distance propagations but hardly account for the observed short ones. Conversely, non-regenerative models (e.g. purely diffusive ones) cannot explain long-range propagation. A possible solution was suggested by Höfer et al. [11]. In the model proposed by these investigators, long-range propagating  $\text{Ca}^{2+}$  waves are obtained via IP3 regeneration in each cell by  $\text{Ca}^{2+}$ -activated  $\text{PLC}\delta$ . However, whenever  $\text{PLC}\delta$  maximal activity is lower, regeneration becomes partial and the  $\text{Ca}^{2+}$  wave propagation distance decreases. Yet this model does not include  $\text{Ca}^{2+}$ -dependent IP3 degradation, which could be critical for the occurrence of IP3-mediated  $\text{Ca}^{2+}$  oscillations [12]. This latter process in particular, can compete with  $\text{PLC}\delta$ -mediated IP3 production, thus hindering IP3 regeneration and  $\text{Ca}^{2+}$  wave propagation. This calls for additional factors to be taken into account to explain intercellular  $\text{Ca}^{2+}$  wave propagation.

In our model, the strength and the transfer properties of the gap-junction coupling are critical permissive factors

that allow long-range intercellular signalling between the astrocytes. In particular, nonlinear gap junctions were found to significantly enhance the range of  $\text{Ca}^{2+}$  wave propagation (as opposed to the classic linear gap junctions that caused fast dissipation). Gap junctions with dynamic resistance are known to exist in cardiac networks [17] and in several other cells [18]. Yet there is currently no direct evidence for nonlinear transfer of second messenger molecules through gap junctions between astrocytes. Nonetheless, the activation of PKC, which is intimately related to IP3 metabolism [12,19], is known to block astroglial gap junction communication and inhibit the spread of  $\text{Ca}^{2+}$  waves therein [20]. Hence, in light of the existing knowledge regarding the control of gap junctional permeability by various signalling molecules [21], it is plausible to assume that some nonlinearity should exist in astrocytes too.

Recent studies suggest that the astrocytes within the cortex form heterogeneous populations [22,23]. Therefore, we considered the case of intercellular  $\text{Ca}^{2+}$  wave propagation in composite 1D networks, consisting of both FM- and AFM-encoding cells. Our simulations predict that the propagation dynamics and distance of intercellular  $\text{Ca}^{2+}$  waves critically depends both on the encoding property of the cells and on their spatial arrangement. Interestingly, the cell bodies of neighbouring astrocytes within the brain are believed to distribute in space in a non-random orderly fashion called “contact spacing” [24,25]. Our study thus suggests a possible link between contact spacing and intercellular  $\text{Ca}^{2+}$  wave propagation in astrocyte networks. If, as suggested by our model, the spatial arrangement of the astrocytes, coupled to the heterogeneity of their response, conditions  $\text{Ca}^{2+}$  wave propagation, then contact spacing may play a critical role in intercellular wave propagations in the brain and the related computational properties of astrocyte networks.

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