Intercellular synchronization of diffusively coupled Ca^{2+} oscillators

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Abstract We examine the synchrony in the dynamics of localized $[\text{Ca}^{2+}]_i$ oscillations among a group of cells exhibiting such complex Ca^{2+} oscillations, connected in the form of long chain, via diffusing coupling where cytosolic Ca^{2+} and inositol 1,4,5-triphosphate are coupling molecules. Based on our numerical results, we could able to identify three regimes, namely desynchronized, transition and synchronized regimes in the $(T - k_e)$ (time period-coupling constant) and $(A - k_e)$ (amplitude-coupling constant) spaces which are supported by phase plots ($\Delta\phi$ verses time) and recurrence plots, respectively. We further show the increase of synchronization among the cells as the number of coupling molecules increases in the $(T - k_e)$ and $(A - k_e)$ spaces.

Keywords Cell signaling · Synchronization · Diffusive coupling · Network topology · Chemical coupling

Introduction

The astrocytes in the central nervous system have various important roles, namely taking active part in

signal processing [1–3], interact with the neighbouring neurons [4–6] etc. which leads to important responsibility of the cells in predicting disease states [7]. Since these cells interact with the environment, Ca^{2+} waves propagated through the cells display oscillation in the nonpropagating internal stored $[\text{Ca}^{2+}]_i$ inside the cells [8]. These oscillations are sustained due to interaction of inositol 1,4,5-triphosphate (IP3) with extracellular, cytosolic and endoplasmic Ca^{2+} through inositol cross coupling and calcium-induced calcium release mechanisms [9–11].

The coupling among a group of these cells in a certain network topology is done through the process of cell signaling. This cell signaling is being considered as a means of complex communication and information processing among individual cells, for example, astrocytes with neurons, governing basic cellular activities and to coordinate various actions involving various complex coupling mechanisms [12]. It has been predicted that Ca^{2+} variation in IP3 concentration is necessary for the intercellular Ca^{2+} wave propagation and this variation is initiated by IP3 diffusion through gap junctions to communicate neighbouring cells [13]. Therefore, synchrony in the dynamics of the local $[\text{Ca}^{2+}]_i$ oscillations is believed to be due to chemical coupling, i.e. due to exchange of cytosol Ca^{2+} waves and IP3 [14–17], and can exhibit synchronization of the cells over long distances [18]. However, this idea of synchrony of $[\text{Ca}^{2+}]_i$ oscillation by chemical coupling is considered to be weak by claiming that these chemical waves propagate relatively slow and coupling through release of Ca^{2+} is very weak as the effective diffusion of it is limited to very short distance [19]. They proposed electrochemical rather than chemical coupling, in which strong electrical coupling combined with weak

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chemical coupling is responsible for the synchrony of these cells and is an effective means of long-range signaling [19]. However, it has been predicted that in astrocytes, the intercellular Ca^{2+} waves can travel over several hundred micrometers and may provide a long-range synchrony [1].

The aim of this work is to try to raise this issue and try to look for a reasonable solution regarding synchrony of a group of these cells via chemical coupling and possible long-range interaction among the cells. We organize our work as in the following: We first study the model of Ca^{2+} oscillations in a single cell developed by Houart et al. [20] in “Materials and methods” section. We introduce possible diffusive coupling mechanisms among a group of coupled cells arranged in a certain topology to see whether there is synchrony behaviours in the local $[\text{Ca}^{2+}]_i$ oscillations and look for long-range communication among them. We present our simulation results based on the model discussed in “Results” section, and some conclusions based on our results are drawn in “Discussions” section.

Materials and methods

The basic single-cell model which is described in Fig. 1 involves three key variables: the free calcium concentration in the cytosol (X), the concentration of stored Ca^{2+} in the internal pool (Y) and the IP3 (Z) [20–22].

Fig. 1 The schematic diagram of biochemical reaction network of Ca^{2+} oscillation model

The time evolution of these three variables is governed by the following differential equations:

$$\begin{aligned}\frac{dX}{dt} &= V_0 + V_1\beta - V_2 + V_3 + k_fY - kX \\ \frac{dY}{dt} &= V_2 - V_3 - k_fY \\ \frac{dZ}{dt} &= \beta V_4 - V_5 - \epsilon Z \\ V_2 &= V_{M2} \frac{X^2}{K_2^2 + X^2} \\ V_3 &= V_{M3} \frac{X^m}{K_X^m + X^m} \frac{Y^2}{K_Y^2 + Y^2} \frac{Z^4}{K_Z^4 + Z^4} \\ V_5 &= V_{M5} \frac{Z^p}{K_5^p + Z^p} \frac{X^n}{K_d^n + X^n}\end{aligned}\quad (1)$$

where V_0 indicates the constant input of Ca^{2+} and V_1 returns to maximum rate of stimulus-induced influx of Ca^{2+} from extracellular medium. The parameter β is the degree of stimulation of the cell, and V_1 and V_2 are the pumping and release of Ca^{2+} from cytosol to internal store and internal store to cytosol, respectively, in the Ca^{2+} -induced Ca^{2+} release process with the maximum rates V_{M2} and V_{M3} . K_2 , K_x , K_y and K_z are the threshold value release, pumping and activation of release by Ca^{2+} and IP3 (Z), respectively. k_f is the passive, linear leak rate constant of X and Y ; k is the rate of Ca^{2+} diffuse into extracellular medium; V_4 relates to rate of stimulus-induced synthesis of Z ; V_5 is the phosphorylation rate of Z by the 3-kinase; V_{M2} is the maximum value and half saturation constant K_5 ; K_d corresponds to the threshold Ca^{2+} level; ϵ is the reflected Z to mobilize in Ca^{2+} ; m , n and p are Hill coefficients.

The oscillations in the variables X , Y and Z exhibit various types, namely simple oscillation, bursting, chaotic and quasiperiodic subject to different values of reaction constants and parameters in the set of Eq. 1 [20, 23]. These complex oscillations of the variables are in fact significantly stimulated by the variation of populations of IP3 (Z) and stored Ca^{2+} in the internal pool (Y) supported by some experimental reports [22, 24].

Consider a group or network of N such identical cells which are coupled by the exchange of free cytosolic Ca^{2+} ions (X) and IP3 (Z) by allowing these molecules to diffuse through the ion-channels on each cell surface. Among these cells, the information of individual cell reactions is transmitted via these diffusing molecules to each neighbouring cells in the network and a unique globally coordinated behaviour of the localized molecules, i.e. $[\text{Ca}^{2+}]_i$ stored in internal pool

(Y) of each individual cells in the network will be exhibited. In this present work, we consider a simple network of these cells diffusively coupled in series in the form of a chain as shown in Fig. 2a, b, and we study the following two diffusing coupling mechanisms: (a) coupling via Ca^{2+} diffusion: In this coupling mechanism, X is being taken as coupling molecule such that the species $X^{[i-1]}$, $X^{[i]}$ and $X^{[i+1]}$ in $(i-1)$ th, i th and $(i+1)$ th cells in the network can interconvert via additional reaction channels, $X^{[i]} \xrightarrow{k_{x1}} X^{[i-1]}$, $X^{[i-1]} \xrightarrow{k_{x2}} X^{[i]}$, $X^{[i]} \xrightarrow{k_{x3}} X^{[i+1]}$, $X^{[i+1]} \xrightarrow{k_{x4}} X^{[i]}$, where $i = 1, 2, 3, \dots, N$ and the diffusing rates in all these additional reactions are k_{x1} , k_{x2} , k_{x3} and k_{x4} . Deterministically, this corresponds to two bi-directional diffusive couplings, i.e. $[k_{x1}(X^{[i]} - X^{[i-1]})$ and $k_{x2}(X^{[i-1]} - X^{[i]})]$ and $[k_{x3}(X^{[i]} - X^{[i+1]})$ and $k_{x4}(X^{[i+1]} - X^{[i]})]$ are, respectively, incorporated bi-directionally. Therefore, the synchronization in other variables Y_k , ($k = 1, 2, \dots, N$) occurs when the rates k_{x1} , k_{x2} , k_{x3} and k_{x4} are sufficiently large. Now, taking $k_{x1} = k_{x2} = k_{x3} = k_{x4} = k_e$ for simplicity, we have the following diffusively coupled differential equations of the cells in the network of cells we consider,

$$\begin{aligned} \frac{dX^{[i]}}{dt} &= F^{[i]} + \sum_{j=0}^1 k_e (X^{[i+2j-1]} - X^{[i]}) \\ &\quad + \sum_{j=0}^1 k'_e (X^{[i]} - X^{[i+2j-1]}) \\ \frac{dY^{[i]}}{dt} &= G^{[i]} \\ \frac{dZ^{[i]}}{dt} &= H^{[i]} \end{aligned} \quad (2)$$

Fig. 2 **a** The schematic diagram of diffusive coupling among a group of cells arranged in the form of a chain, where **a** coupling molecule is cytosolic Ca^{2+} . **b** Coupling molecules are both cytosolic Ca^{2+} and IP_3

and (b) coupling via Ca^{2+} and IP_3 : In this case, two molecular species Ca^{2+} and IP_3 are considered as diffusively coupling molecules among the cells in the network. For every diffusing molecular species, four additional reaction channels are to be added with different rates. In this model, we have two diffusively coupling molecules, i.e. X and Z . Therefore, we will have eight additional reaction channels: four for X and four for Z , respectively. Taking the diffusive rates of each molecular species to be the same as given by k_e , the coupled differential equations are given by,

$$\begin{aligned} \frac{dX^{[i]}}{dt} &= F^{[i]} + \sum_{j=0}^1 k_x (X^{[i+2j-1]} - X^{[i]}) \\ &\quad + \sum_{j=0}^1 k'_x (X^{[i]} - X^{[i+2j-1]}) \\ \frac{dY^{[i]}}{dt} &= G^{[i]} \\ \frac{dZ^{[i]}}{dt} &= H^{[i]} + \sum_{j=0}^1 k_z (Z^{[i+2j-1]} - Z^{[i]}) \\ &\quad + \sum_{j=0}^1 k'_z (Z^{[i]} - Z^{[i+2j-1]}) \end{aligned} \quad (3)$$

where $X^{[i]}$, $Y^{[i]}$ and $Z^{[i]}$ are the variables of the i th cell in the chain of cells we considered. The functions in the above equations are defined by $F^{[i]} = V_0 + V_1\beta - V_2 + V_3 + k_f Y^{[i]} - k X^{[i]}$, $G^{[i]} = V_2 - V_3 - k_f Y^{[i]}$ and $H^{[i]} = \beta V_4 - V_5 - \epsilon Z^{[i]}$. The parameters k_x , k'_x , k_z and k'_z are the coupling constants of X and Z molecular species for bi-directional coupling and are not necessary to have the same value. In our numerical simulation, we take $k_x = k'_x$ and $k_z = k'_z$ for the sake of simplicity, and equivalent rate constant is given by the parallel law, $\frac{1}{k_e} = \frac{1}{k_x} + \frac{1}{k_z}$. Further, we apply fixed boundary conditions in our model where $X^{[0]} = 0$, $Z^{[0]} = 0$, $X^{[N+1]} = 0$ and $Z^{[N+1]} = 0$, since these molecular species are not in the domain of the system we considered. However, if the chain becomes a ring by connecting the two ends, then we have to apply the periodic boundary conditions, i.e. $X^{[0]} = X_N$, $Z^{[0]} = Z_N$ and $X^{[N+1]} = X^{[1]}$, $Z^{[N+1]} = Z^{[1]}$.

The measure of synchronization of the time evolution of two independent and identical systems can be possible [25] by defining an instantaneous phase for an arbitrary signal $\eta(t)$ via the Hilbert transform [26]

$$\tilde{\eta}(t) = \frac{1}{\pi} P. V. \int_{-\infty}^{+\infty} \frac{\eta(\tau)}{t - \tau} d\tau \quad (4)$$

where $P. V.$ denotes the Cauchy principal value. The instantaneous phase $\phi(t)$ and amplitude $A(t)$ of a given

arbitrary signal can be obtained through the relation, $A(t)e^{i\phi(t)} = \eta(t) + i\tilde{\eta}(t)$. For any given pair of signals $[(i, j); i, j = 1, 2, \dots, N, i \neq j]$, one can therefore obtain the instantaneous phases ϕ_i and ϕ_j ; phase synchronization is then the condition that $\Delta\phi = m\phi_i - n\phi_j$ is constant with m and n being integers. Starting with different initial configurations, the temporal dynamics of the uncoupled oscillators will be uncorrelated; however, upon coupling, the dynamics can show phase synchrony [26–28].

Another way to measure the rate of synchrony of two coupled oscillators is to plot the two corresponding variables x, x' from the two oscillators along the two axes of the two-dimensional cartesian plane [29]. If the oscillators are uncoupled, then the points in the plane scattered away from the diagonal. However, if the oscillators are coupled, then the points concentrated towards the diagonal. The rate of concentration of the points towards the diagonal measures the rate of synchrony.

Results

We first present the temporal dynamics of the concentrations of the variables of a single cell by standard numerical integration technique [30] of the set of differential equations (Eq. 1) for four sets of parameter values [20] given in the figure caption of Fig. 3 showing simple oscillation, bursting, chaos and quasiperiodicity. The time is measured in minutes. Now, we take $N = 50$ such identical cells connected in the form of a chain, and then diffusive coupling is employed where X is taken as diffusive coupling molecule among the cells. We then simulate the temporal dynamics of localized Ca^{2+} , i.e. $Y^{[i]}$, where $i = 1, 2, \dots, N$ at different values of coupling constant k_e switched on at different times and solved the sets of coupled differential equations (Eq. 2) as shown in Fig. 4. The results of *simple oscillations* are shown in Fig. 4a, b; the figure (a) shows plots of the dynamics of concentrations of the variable $Y^{[i]}$ for ten different cells at positions 1, 2, 3, 4, 5, 6, 25, 30, 40 and 50, respectively, in the chain and figure (b) shows the corresponding phase plot ($\Delta\phi$ versus time) for three different coupling constants, i.e. $k_e = 0$ (uncoupled), $k_e = 5$ (transition) and $k_e = 40$ (synchronized) switched on at time intervals 0–15, 15–30 and 30–45 min, respectively. The uncoupled behaviours of the cells are shown during time interval 0–15 min proved by random fluctuation of $\Delta\phi$ with time, and recurrence plot of $Y^{[i]}$ versus $Y^{[j]}$ in Fig. 7a where the points spread randomly away from the diagonal. During time interval 15–30 min, the behaviours of the

Fig. 3 The plot showing the time evolution of concentration of X, Y and Z showing: (1) simple oscillation for the parameters [20]: $V_0=2, V_1=2, \beta=0.5, V_{M2}=6, k_2=0.1, V_{M3}=20, K_x=0.5, K_y=0.2, K_z=0.2, V_{M5}=5, k_5=1, k_d=0.4, k_f=1, k=10, \epsilon=0.1, V_4=2, m=2, p=2$ and $n=4$; (2) bursting for the parameters: $V_0=2, V_1=2, \beta=0.46, V_{M2}=6, k_2=0.1, V_{M3}=20, K_x=0.3, K_y=0.2, K_z=0.1, V_{M5}=30, k_5=1, k_d=0.6, k_f=1, k=10, \epsilon=0.1, V_4=2.5, m=4, p=1$ and $n=2$; (3) chaos for the parameters: $V_0=2, V_1=2, \beta=0.65, V_{M2}=6, k_2=0.1, V_{M3}=30, K_x=0.6, K_y=0.3, K_z=0.1, V_{M5}=50, k_5=0.3194, k_d=1, k_f=1, k=10, \epsilon=13, V_4=3, m=2, p=1$ and $n=4$ and (4) quasiperiodicity for the parameters: $V_0=2, V_1=2, \beta=0.51, V_{M2}=6, k_2=0.1, V_{M3}=20, K_x=0.5, K_y=0.2, K_z=0.2, V_{M5}=30, k_5=0.3, k_d=0.5, k_f=1, k=10, \epsilon=0.1, V_4=5, m=2, p=2$ and $n=4$

cells start coordinating, but the coupling constant is not large enough to get synchronized, indicating weak synchronization or transition regime which is again proved by phase plot where the fluctuation is reduced enormously and by recurrence plot whose points start concentrated enormously along the diagonal. However, during time interval 30–45, the $Y^{[i]}$ dynamics exhibit strong coordinated nature, i.e. synchronized state supported by the negligible fluctuation about a constant value in the phase plot and diagonally aligned points in the recurrence plot. We also noticed from the results that the dynamics of the variables of the cells do not synchronize immediately but takes some time to get in that state after the coupling is switched on (Fig. 5).

Similarly, for the *bursting* case, the curves in Figs. 4c, d and 7b present how the dynamics of the variable Y start coordinating their behaviours from uncoupled to weak (transition), then to strong showing desynchronized, weak (transition) and strong synchronization. As explained above, the claim is based on the fluctuation rates in the phase plot (Fig. 4d) and spreading rate of the points from the diagonal in recurrence plot (Fig. 7b). The diffusing rates for desynchronization, weak and strong synchronization in this case are

Fig. 4 Plots of Y (left panels) and phase difference $\Delta\phi$ (right panels) as a function of time for different values of k_e : (1) simple oscillation in **a** and **b** for $k_e = 0, 5$ and 40 ; (2) bursting in **c** and **d** for $k_e = 0, 10$ and 28 ; (3) chaos in **e** and **f** for $k_e = 0, 8$ and 30 ; (4) quasiperiodic in **g** and **h** for $k_e = 0, 5$ and 20 ; for ten cells out of 50 cells showing desynchronized (transition regime) and strongly synchronized regimes

found to be $k_e = 0, 10$ and 28 . In the same way, the results for *chaos* and *quasiperiodic* are shown in Fig. 4e, f with Fig. 7c (for *chaos*) and Fig. 4g, h with Fig. 7d

(for *quasiperiodic*), respectively. The diffusing rates are found to be different as $k_e = 0, 8, 30$ and $k_e = 0, 5, 20$ for *chaos* and *quasiperiodic*, respectively.

Fig. 5 Similar plots of Y and $\Delta\phi$ (right panels) as a function of time for different values of k_e for simple oscillations, bursting, chaos and quasiperiodic cases

We then do the simulations for the same network of coupled oscillators where only Z (IP3) is allowed as diffusively coupling molecular species for all four types of oscillatory behaviours (Fig. 6). In this case, we found Z induced synchronization in the dynamics of $Y^{[i]}$, but at comparatively large values of coupling constant k_z , i.e. at (1) $k_z = 82$ for simple oscillation type, (2) $k_z = 63$ for bursting case, (3) $k_z = 68$ for chaotic case and (4) $k_z = 55$ for quasiperiodic case, respectively. Since the patterns are similar as shown in Fig. 4, we do not include the plots here. Even though the results give us the notion that IP3 can act as synchronizing agent at large value of k_z , there is still a question that what could be the range of k_z in real situation in this type of intercellular diffusion. However, we claim that the intercellular diffusion of IP3 is weak as compared to that of calcium diffusion to let $Y^{[i]}$ among the coupled oscillators synchronize. This claim is similar to the reported role of IP3 found in other cell types such as acinar cells [31], smooth muscle cells [32] etc.

Now, the simulation results for the cases of simple oscillation, bursting, chaos and quasiperiodic, when two

Fig. 6 Plots of time period (T) of Y and Z as a function of coupling constant k_e for different oscillatory behaviours, i.e. (1) simple oscillations: **a** and **b** are for T and A versus k_e , (2) bursting oscillations: **c** and **d** are for T and A versus k_e , (3) chaos oscillations: **e** and **f** are for T and A versus k_e and (4) quasiperiodic oscillations: **g** and **h** are for T and A versus k_e

diffusively coupling molecular species, namely X and Z , are considered in the same network of the cells, are shown in Fig. 5a, b; c, d; e, f; g, h with Fig. 7a–d, respectively. The results are obtained by solving the set of coupled differential equations (Eq. 3). Similar behaviours of desynchronized, weakly synchronized (transition) and strongly synchronized are found as in the case of single molecular species diffusive coupling is employed. However, interestingly the mentioned behaviours are found significantly at lower values of rates, i.e. $k_e = 0, 1, 30$ for *simple oscillations*, $k_e = 0, 5, 20$ for *bursting*, $k_e = 0, 5, 25$ for *chaos* and $k_e = 0, 1.2, 15$ for *quasiperiodic*, respectively. The results show that the inclusion of Z diffusion helps $Y^{[i]}$ s among coupled oscillators to synchronize faster (Fig. 8).

We then present the results of time periods (T) and amplitudes (A) of Y and Z as a function of k_e for all cells as shown in Fig. 6. We found that the values of T and A for all cells sitting at far ends or in between are almost the same at any particular value of k_e , and therefore, the error bars at each points are within the size of the points and therefore error bars are not visible. The panels (a) and (b) are for simple oscillation, (c) and (d) are for bursting, (e) and (f) are for chaos and (g) and (h) are for quasiperiodic case. Y_1 and Y_2 are for Y dynamics for the case where (1) Ca^{2+} is used as coupling molecule and (2) Ca^{2+} and IP3 are used as coupling molecules, respectively. From the curves, we found three behaviours (1) for small values of k_e , Y and Z do not vary significantly (desynchronized regime), (2) monotonic decrease of T

Fig. 7 The recurrence plot of variable Y s of diffusively coupled first and tenth cells via Ca^{2+} for **a** oscillation, **b** bursting, **c** chaos and **d** quasiperiodic

Fig. 8 Similar plots of Y s of diffusively coupled first and tenth cells via Ca^{2+} and IP3 for **a** oscillation, **b** bursting, **c** chaos and **d** quasiperiodic

and A for moderate k_e (transition regime) and (3) T and A are not significantly changed as a function of k_e (synchronized regime). Again Y_2 gets much faster synchronization than Y_1 which indicates that the synchronization rate in the network where two molecular species (Ca^{2+} and IP3) are allowed as diffusive coupling molecules among the cells is much faster than the case where one molecular species (Ca^{2+}) is used as the diffusive coupling molecule.

Then, we simulated for each type of oscillation by taking into account next to nearest neighbour coupling contributions to each cell (the results are not shown because the dynamics are the same except shifting in the value of k which is given by $\frac{1}{k} = \frac{1}{k_e} + \frac{1}{k_r}$, where k_r is coupling constant due to next to nearest neighbour cells' contribution). The value of k for this system is found to be smaller than the value of k_e which we got in the case of nearest neighbour coupling case with the value $k_e - k \sim 1\%$ of k_e . This indicates that the rate of synchronization in this case is faster than before.

From this numerical results, one can generalize that as the number of coupling molecular species is increased to allow the cells to couple in the network, the rate of synchronization is also significantly increased. At the same time if the diffusing rates of the same molecular species are allowed to increased among the cells, the rate of synchrony will also be increased. In other words, as the number of information carrying molecules (same molecular species) or (and) molecular species (different molecular species) increases, the rate of the information processed by the cells also increases accordingly and the rate of correlation of the cells

becomes stronger. In this coupling scheme, we can write the following equation based on the results:

$$\begin{aligned} \frac{d\Lambda^{[i]}}{dt} = & \Gamma(\Lambda_u^{[i]}) + \left[\sum_{(i,j), j=0}^1 k_j (\chi^{[i+2j-1]} - \chi^{[i]}) \right. \\ & \left. + \sum_{(i,j), j=0}^1 k_j (\chi^{[i]} - \chi^{[i+2j-1]}) \right] \\ & + \left[\sum_{\langle\langle r,i \rangle\rangle, \langle\langle\langle r,i \rangle\rangle, \dots} k_r (\chi^{[r]} - \chi^{[i]}) \right. \\ & \left. + \sum_{\langle\langle r,i \rangle\rangle, \langle\langle\langle r,i \rangle\rangle, \dots} k_r (\chi^{[i]} - \chi^{[r]}) \right] \quad (5) \end{aligned}$$

where $\Lambda^{[i]} = (X^{[i]}, Y^{[i]}, Z^{[i]})^{-1}$ and $\Lambda_u^{[i]} = (X_u^{[i]}, Y_u^{[i]}, Z_u^{[i]})^{-1}$ are vectors for coupled and uncoupled cells, respectively. The vector $\chi^{[i]} = (Y^{[i]}, Z^{[i]})^{-1}$ is the vector which is used for coupling. The first term indicated by a function Γ is for uncoupled cells, second term when bi-directional coupling is introduced from the nearest neighbouring cells ((i, j)) and third term when diffusion of molecules apart from the nearest neighbouring cells in the network is allowed, for example, next to nearest neighbouring cells indicated by $\langle\langle\langle \dots \rangle\rangle$, next to next nearest neighbouring cells indicated by $\langle\langle\langle\langle \dots \rangle\rangle\rangle$ and so on. k_r are diffusive rate of molecular species to the i th cell from different cells other than nearest neighbours. These extra terms apart from $\Gamma(\Lambda^{[i]})$ are responsible for coupling of the cell with its surrounding cells in the network. Further, these terms significantly contribute to the increase in information transfer to the cell itself in the network from the other cells leading to enhance the rate of synchronization.

The oscillatory behaviours, which we get for different parameters, are not seen in different cell types such as hepatocytes etc. The calcium-induced calcium release due to Z and X pumping into the internal localized Y via PLC is important basic elements that occur in astrocytes specially. Besides that, the propagation of X in astrocytes can go few hundreds of micrometers that will give significant role in intercellular communication which we support with our simulation results.

Discussions

The diffusion of inositol 1,4,5-triphosphate and cytosolic calcium ion from one cell to another through the ion channels on the surfaces of the coupled cells gives rise to a coordinated behaviour of the cells. Moreover,

as the number of diffusing molecules among the cells increases, the amount of information transfer among the cells is also increased and the cells synchronized faster. If the number of diffusing channels is increased due to increase in neighbouring cells, then more cells will be coupled and information transfer is quicker. So we claim that the role of chemical coupling has significant contribution in the synchrony of astrocytes and long-range information transfer among them.

The diffusion of IP₃ among the coupled cells can enhance the rate of synchrony of calcium oscillations. However, if diffusion of IP₃ alone is allowed, it can act as synchronizing agent to synchronize the calcium oscillations at large coupling rate constant. This shows that the diffusion of it alone among the oscillators is very weak to let the coupled oscillators to synchronize similar to the reported role of it to other cell types such as among acinar cells [31] and smooth muscle cells [32]. However, still there are certain issues in this problem, namely the identification of k_z in real situation, impact of network structure in the modulation of calcium signaling and synchronization. There could be important role of the variable nature of gap junction connectivity of the network (which we assume to be regular in our study), whose distribution is quite broad in reality [33], in the intercellular calcium signaling mechanism. This broad connectivity and variable in global connections [34], non-linear nature of coupling function of gap junction [35] and the emerging heterogeneity of the network's architecture [35–37] can definitely affect the signal processing and intercellular synchronization in such biological network.

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