PRAMANA
— journal of
physics

Vol. 71, No. 2
August 2008
pp. 423–435

Synchronization in multicell systems exhibiting dynamic plasticity

C SUGUNA* and SOMDATTA SINHA
Centre for Cellular and Molecular Biology, Council of Scientific and Industrial Research, Uppal Road, Hyderabad 500 007, India
*Corresponding author. E-mail: suguna@ccmb.res.in

Abstract. Collective behaviour in multicell systems arises from exchange of chemicals/signals between cells and may be different from their intrinsic behaviour. These chemicals are products of regulated networks of biochemical pathways that underlie cellular functions, and can exhibit a variety of dynamics arising from the non-linearity of the reaction processes. We have addressed the emergent synchronization properties of a ring of cells, diffusively coupled by the end product of an intracellular model biochemical pathway exhibiting non-robust birhythmic behaviour. The aim is to examine the role of intercellular interaction in stabilizing the non-robust dynamics in the emergent collective behaviour in the ring of cells. We show that, irrespective of the inherent frequencies of individual cells, depending on the coupling strength, the collective behaviour does synchronize to only one type of oscillations above a threshold number of cells. Using two perturbation analyses, we also show that this emergent synchronized dynamical state is fairly robust under external perturbations. Thus, the inherent plasticity in the oscillatory phenotypes in these model cells may get suppressed to exhibit collective dynamics of a single type in a multicell system, but environmental influences can sometimes expose this underlying plasticity in its collective dynamics.

Keywords. Synchronization; multicell system; birhythmicity; biochemical pathway.

PACS Nos 05.45.Xt; 87.18.-h; 89.75.-k

1. Introduction

A vast majority of cellular functions rely on the ability of cells to maintain equilibrium or homeostasis. However, there are also many functions, which require rapid and efficient response to even small inputs or signals. Such sensitivity coupled with robustness is only possible because the biochemical pathways, which carry out all cellular functions are controlled by combinations of positive and negative feedback processes [1]. The highly non-linear regulatory mechanisms of control in cells arise from cooperativity and elicit a vast array of dynamics from equilibrium to periodic, multistable, multirhythmic, complex and chaotic oscillations [2]. There is increasing evidence of the importance of such varied dynamics in models of circadian, glycolytic, calcium, peroxidase–oxidase and neuronal rhythms [2–9]. Although the first experimental observations of periodic oscillations in cellular dynamics were

made only in the 60s, in the intermediates of the glycolytic pathway, rhythmic behaviour of living systems has been well-known for a long time [10]. Multirhythmic behaviour is more difficult to observe experimentally since such behaviour generally occurs in a very narrow range of the parameter space in many models. Birhythmicity, trirhythmicity and hysteresis have been observed in chemical systems such as the bromate–chlorite–iodide oscillators [2,11,12].

In order to show coherent, coordinated activity, cells in tissues or organs must synchronize their rhythms and phases, through exchange of information or chemicals with the environment or the other cells in their vicinity. Emergent synchronization is well-known in many areas of science. Pendulum clocks, electrical generators, electronic circuits, arrays of lasers, chirping crickets and flashing fireflies are some well-known examples of oscillators, which get synchronized due to coupling [13–15]. The exchange of information among cells (coupling) can be global (all-connected-to-all) or local (nearest neighbours). The coupling can also be direct or indirect. In many cases the oscillators are arranged in chains or lattices with each element interacting with its nearest neighbours, in which case we consider the coupling to be local. The coupling itself may be direct or indirect. Direct coupling takes place when membrane-bound molecules interact or when there is exchange of signalling molecules through gap junctions in cells. When an external medium or an intercellular matrix mediates the information exchange, the coupling is indirect. In nature, there are instances of local and global, direct and indirect couplings, depending on the structure and function of the interacting oscillators [14,16–21]. In biological tissues, local, direct coupling is useful in promoting coordinated functional activity.

Synchronization of chaotic and multistable systems has been studied in different model systems using different coupling schemes (e.g., unidirectional, bi-directional, nearest neighbour, global and star coupling), external forcing by daylight and other sources of entrainment and also coupling between populations of interacting cells [22–27]. Such studies have shown that the coupled dynamics are richer and more complicated and show different types of synchronizations such as complete synchronization, phase and lag synchronizations, intermittent phase synchronization, etc. Pisarchik *et al* [24] show that when a bistable chaotic system is coupled unidirectionally with an identical chaotic system, synchronization occurs first by intermittent switching between the two coexisting attractors and at relatively strong coupling, there are phase-synchronized, period doubling oscillations with the natural frequency of the slave system shifted towards half of the natural frequency of the master oscillator [24]. It is not clear as to how inherently birhythmic oscillators may behave when coupled. It is important to understand, for the robust functioning of the coupled system, whether the dynamic plasticity gets suppressed or variability retained, especially in a noisy environment. Even though a comprehensive microscopic view of how stochastic fluctuations in gene expression can cause cells to change their phenotype has been shown recently [28,29], how cell–cell interaction may regulate such variability is not understood both experimentally and theoretically.

In this paper, we have studied the synchronization properties of a multicell system, diffusively coupled by the end product of an intracellular model biochemical pathway, exhibiting birhythmic dynamics. Our model multicell system has cells located at the nodes of a closed one-dimensional lattice. Such structures are found

in the arrangement of cells in intestinal muscles, walls of blood vessels, plant roots, etc. The communication among the cells is assumed to be through the diffusion of the end product of an activator–inhibitor biochemical pathway to the two nearest neighbours in the lattice. Our aim is to examine the role of intercellular interaction in stabilizing the non-robust dynamics in the emergent collective behaviour in the ring of cells.

We have shown earlier [30] that, with changing parameters, a wide variety of dynamics can be exhibited by the model activator–inhibitor, such as equilibrium, periodic, chaotic and complex oscillations. In particular, we had shown coexistence of two types of oscillations (birhythmic attractors – termed Type-I and II) with very different amplitudes and frequencies for certain parameter values, whose basin of attraction is fractal [30]. That is, in this regime, single cells, with the same parameter values, can exhibit two different 'dynamic phenotypes' (that are non-robust with variable frequencies), which can switch from one to the other in response to a small amount of noise [22,31].

In an earlier work, we had shown that a coupled multicell system in which cells show periodic or chaotic dynamics, can exhibit partial to complete synchronization in parameter regimes where the cells show periodic or chaotic dynamics [22,32,33]. Here we show that, birhythmic cells synchronize their dynamics completely, but at low and medium coupling strengths, for small lattice sizes, it is impossible to predict the type of emergent phenotype (Type-I or II). For larger lattices, the emergent collective dynamics stabilizes to only one type (Type-I), irrespective of the inherent frequency of the individual cells. To study the robustness of the synchronized state, we use two-perturbation analyses. The long-term behaviour of the lattices show that the synchronized state (Type-I) is fairly robust to noise, and only a few of them exhibit variable dynamic phenotypes that depend on the strength of the perturbation and not on the composition of the lattice. Our results show that the inherent plasticity in the oscillatory phenotypes in these model cells gets suppressed to exhibit collective dynamics of a single type in a multicell system, which is fairly robust under environmental influences.

2. Model and methods

Our model of a multicell system is a one-dimensional lattice, with each lattice node containing a single cell, which is directly coupled to its nearest neighbours by the diffusion of the end product. The imposition of periodic boundary conditions renders all the cells equivalent, leading to a ring of cells (figure 1a). Each cell is assumed to have a model biochemical pathway that incorporates a coupled positive and negative feedback process as shown in figure 1b.

The model biochemical pathway consists of a three-step reaction process with substrates S1, S2 and S3, regulated by an autocatalytic activation of the end product, S3, through an allosteric enzyme, E, and negative feedback with end product inhibition of S1 by S3 (figure 1b). The time evolution of the normalized substrates of this simple pathway in each cell is modelled as in refs [34–37]. Diffusion to the nearest neighbours is included and modelled using the discretization scheme of Oono–Puri [38]. The resultant dynamics of the coupled systems is described by the

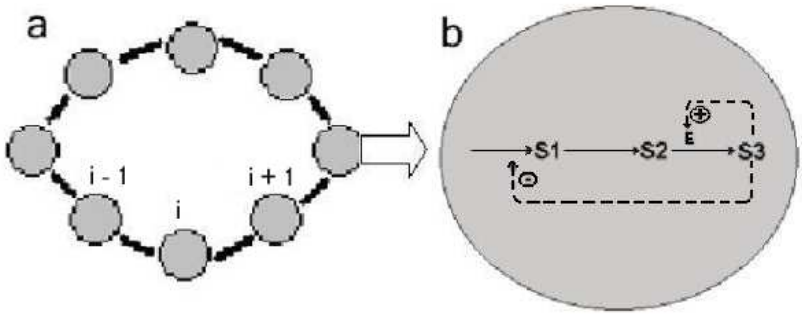

Figure 1. (**a**) The multicell system showing diffusion to the nearest neighbours. (**b**) A model cell incorporating a three-step biochemical pathway with coupled positive and negative feedback processes.

following differential equations:

$$\begin{aligned}
\frac{\mathrm{d}x_i}{\mathrm{d}t} &= F(z_i) - kx_i, \\
\frac{\mathrm{d}y_i}{\mathrm{d}t} &= x_i - G(y_i, z_i), \\
\frac{\mathrm{d}z_i}{\mathrm{d}t} &= G(y_i, z_i) - qz_i + \frac{e}{2}(z_{i-1} + z_{i+1} - 2z_i),
\end{aligned} \tag{1}$$

where

$$F(z_i) = \frac{1}{(1 + z_i^n)} \quad \text{and} \quad G(y_i, z_i) = \frac{Ty_i(1 + y_i)(1 + z_i)^2}{L + (1 + y_i)^2(1 + z_i)^2}.$$

Here x, y and z are the normalized concentrations of the substrates; i is the index of the cell number, with $i = 1, 2, 3, \ldots, N$; the parameters are assumed to be the same for all the cells, where k and q are parameters controlling the rates of degradation of S1 and S3; n is the number of molecules of S3 required for the cooperative inhibition of S1; L and T are the allosteric constant and maximum velocity, respectively, of the allosteric enzyme, E. $F(z)_i$ and $G(y_i, z_i)$ are the functions expressing the negative and positive feedback processes; e is the strength of coupling. N is the number of cells in the lattices. When $e = 0$, the equations describe the dynamics of the individual cells. The basal parameter values for this pathway have been obtained from other cellular processes with similar regulatory mechanisms as $n = 4, L = 10^6$, $T = 10$, $k = 1$ and $q = 0.01$ [34–37]. For these values the system shows simple periodic oscillations. Numerical simulations of these equations were performed in Mathematica 4.0 and Fortran 90 programs, using fourth-order Runge–Kutta integration method and some results plotted using MATLAB 6. For each set of parameter values, 50 realizations were considered with random initial conditions, for about 8×10^4 time steps. The first 50,000 steps were discarded as transients and the figures show the last 3000 time steps of the end product concentration, z.

3. Results and discussion

3.1 *Single cell behaviour*

3.1.1 *Birhythmic dynamics.* For the parameter values chosen here, the pathway exhibits two types of coexisting limit cycles, one a period-two oscillation of high frequency and low amplitude ($T = 183.4, A = 27$), which we call Type-I limit cycle. The other is a low frequency, high amplitude oscillation ($T = 1466, A = 64$), called Type-II limit cycle. Figure 2a shows the two types of attractors in the (x, y, z) phase space, superimposed for comparison. It is clear that there is considerable overlap in the phase space of the two attractors – the Type-I attractor has a very narrow range of variation in the x-direction and hence is almost two-dimensional, while the Type-II oscillations have a larger spread. The basin of attraction shown in figure 2b has been mapped in the yz plane, in the region around the steady state ($x = 0.53, y = 37.1, z = 5.3$) and is found to be riddled, with no well-defined boundary [30].

This indicates that the system is sensitive to initial conditions, leading to unpredictability and non-robust long-term dynamics of the pathway in the birhythmic region, even under small levels of noise [31]. Thus, depending on the initial conditions the pathway can show either Type-I or Type-II behaviour, so that cells with the same parameter values can have different phenotypes, exhibiting widely differing periodicities.

3.1.2 *Robustness of the birhythmic state.* A consequence of the riddled basin of attraction and the overlap of the two types of attractors in the phase space (figures 2a and 2b) is that even a small perturbation is sufficient to push the system from one kind of dynamics to the other. We have mapped the long term response to perturbation for both types of attractors, by externally adding varying levels of end products, at different phases of one complete oscillation, and observing the

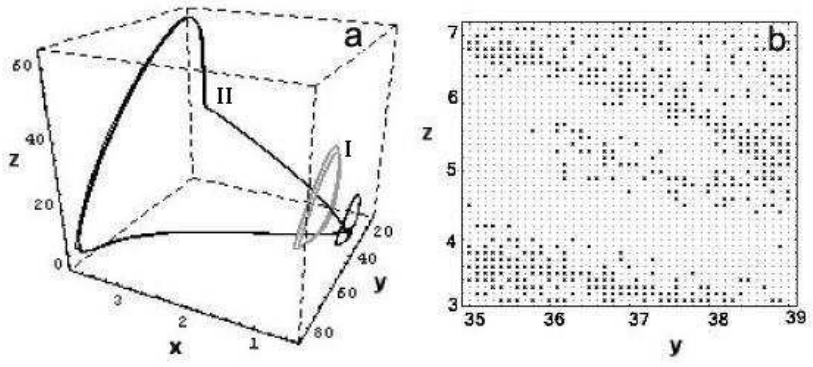

Figure 2. (**a**) Overlapped three-dimensional phase plots of end product of model pathway for $k = 0.0024$, $q = 0.1$, showing coexisting attractors of Type-I and II. (**b**) The basin of attraction around the steady state in the y–z plane where crosses represent initial conditions that lead to Type-I and dots to Type-II oscillations. Here $e = 0$ for single cells.

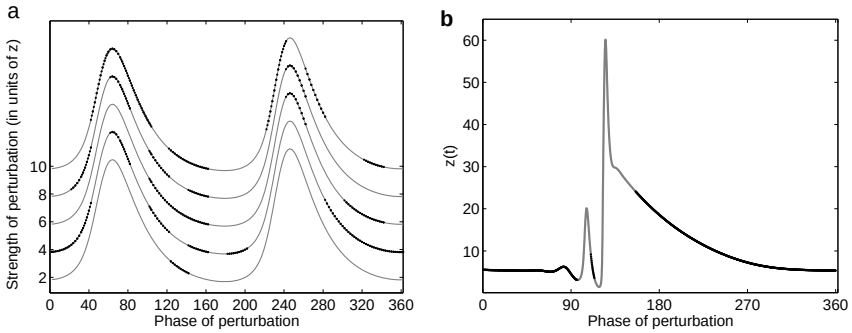

Figure 3. (**a**) Phase sensitivity to varying levels of perturbations in end product, z, shown for one complete oscillation of Type-I attractor and (**b**) Type-II attractor. Sensitive regions are shown as black dotted line and robust in gray.

long-term dynamics [31]. Sensitive regions (where the Type-I attractor switched to Type-II oscillation after perturbation) are shown as black dotted lines, while robust regions (where the dynamics remained unchanged even on perturbation) are as gray lines (figure 3a). It can be seen that although there are regions of sensitivity at all perturbation strengths, there is no overall demarcation. This makes the response of this attractor to perturbation unpredictable.

The sensitivity map for the Type-II attractor is summarized in figure 3b. The response of this attractor to perturbation is the same for all perturbation strengths from 0.5 to 10 units of z. The sensitive regions, where switching to Type-I occurs, lie near the region of the phase space where the two types of attractors overlap (figure 2a). It is also the region where the system stays most of the time during the oscillation. Therefore, neither type of attractor is robust to perturbation in this region of overlap, making large excursions into the 3D phase space before settling into either one of the attractors.

3.2 *Multicellular behaviour*

We consider a multicell system where each cell in the circular lattice can exhibit either Type-I or Type-II oscillation. We study the role of lattice size, N, as well as the coupling strength, e, on the emergent dynamics and examine the robustness of this collective state.

We have considered both homogeneous lattices (all cells exhibiting either Type-I or Type-II oscillations) and heterogeneous ones (cells exhibiting a mix of both kinds of oscillations). In figure 4 the typical long-term temporal dynamics of the end product in all cells of the uncoupled and coupled homogeneous lattices are shown, for two representative simulations with lattice size $N = 20$ and coupling strength $e = 0.3$. Figures 4a and 4b show the superposed time series of the end product, z, of the uncoupled cells in the two lattices for each phenotype – (a) Type-II and (b) Type-I oscillations. Each cell oscillates with its own phase, so that the overall dynamics is incoherent. The coupled lattices are shown in figures 4c

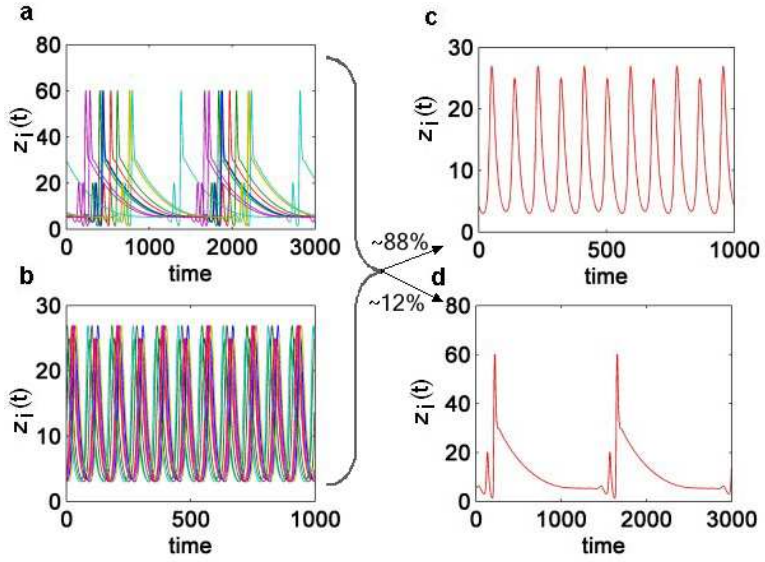

Figure 4. Incoherent dynamics of individual cells in a lattice ($N = 20$) exhibiting Type-II (**a**) or Type-I (**b**) oscillations. Superposed oscillations of the coupled cells showing synchronization either to Type-I (**c**) or Type-II (**d**) dynamics with different probabilities. Here $e = 0.3$.

and 4d (plots for the 20 cells are overlapping perfectly). On coupling ($e = 0.3$) both types of lattices synchronize their dynamics completely, but interestingly, to either type of behaviour with different probabilities as indicated by the arrows. In this case ($N = 20$), 88% lattices exhibit the emergent-coupled behaviour of Type-I, and the rest evolve to the Type-II phenotype (although the individual dynamics are different). The probability for either type of synchronized state does not depend on the dynamics of individual cells. We also found that the composition and arrangement of cells of both types within the lattices does not influence the overall dynamics of the coupled cells (results not shown). Predicting the type of the emergent synchronized state is impossible because of the riddled basin of attraction.

3.2.1 *Effect of population size.* Here we show the results of our study of the emergent behaviour of coupled cells for varying population sizes for coupling strengths $e = 0.3$ and 0.7, for lattices showing either type of behaviour (50 simulations each). The results presented seem to depend on both lattice size (N) and coupling strength (e) as we elaborate below. Figures 5a and 5b show the percentage of simulations, for which the collective dynamics synchronizes to the Type-I oscillations for the two coupling strengths, $e = 0.3$ and 0.7. The remaining simulations synchronize to the Type-II oscillations. We find that populations above a certain threshold size ($N_t \sim 30$ for $e = 0.3$ and $N_t \sim 50$ for $e = 0.7$) always get completely synchronized to the higher frequency Type-I oscillations. For populations of smaller size ($< N_t$), the emergent collective behaviour can be of either type, irrespective of that of the constituent cells, as shown in figure 4.

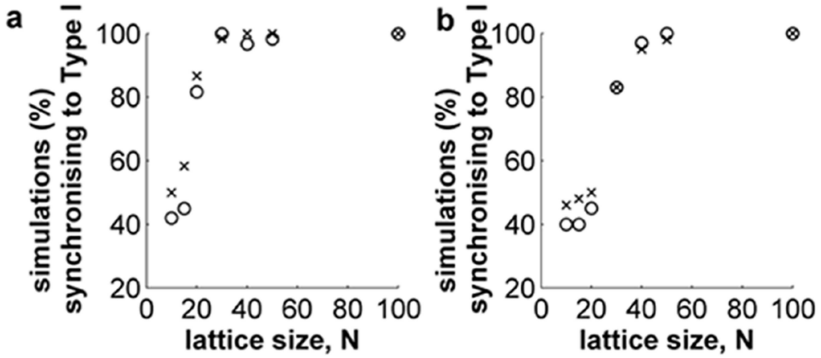

Figure 5. Percentage of simulations showing Type-I dynamics in coupled lattices of varying sizes, with coupling strengths (**a**) $e = 0.3$ and (**b**) $e = 0.7$. Lattices for which the individual cells are all Type-I are shown as crosses and Type-II as open circles.

Thus a larger number of cells in the ring have the effect of stabilizing the variability in the dynamics of populations. Such behaviours that are dependent on population size are well-known in biology. For instance, in quorum sensing, genes for functions such as bioluminescence are expressed at basal levels while the density of the bacteria is low. On achieving a critical population size, these genes are expressed at very high levels leading to enhanced emission of light, in the whole population of cells [39–41].

3.2.2 *Effect of coupling strength.* Since the behaviour of the cells in the population is influenced by the coupling to neighbouring cells, we studied the dependence of the dynamics on the coupling strength, e, for birhythmic cells, for different lattice sizes. Figures 6a–c show the percentage of simulations synchronizing to Type-I oscillations for populations of sizes (a) 20, (b) 30 and (c) 40. We observe the existence of a threshold value of coupling, below which all simulations synchronize to Type-I, and above which they synchronize to either type. Thus, we have the existence of a threshold in coupling strength, in addition to a threshold population size, for the occurrence of bistability of the synchronous state. The threshold coupling strength is higher for larger population size (threshold value, $e_t = 0.2, 0.4$ and 0.6 for $N = 20, 30$ and 40 respectively).

Figure 6d shows the positive linear correlation between the threshold population size N_t, and the threshold coupling strength e_t, at which the emergent birhythmicity is lost. As N increases, we find that only one synchronized state persists for a larger range of coupling. We also found that the heterogeneity in the dynamic composition of the lattice has little effect on its emergent behaviour or the threshold values (result not shown).

3.2.3 *Robustness of emergent behaviour.* Although the faster Type-I attractor seems to be the preferred state for synchronization of populations above the threshold size, it may not be stable, due to the riddled structure of the basin of attraction of Type-I and Type-II attractors. In the coupled system, along with the sensitivity of the individual cells to noise, the additional constraint due to coupling tends to

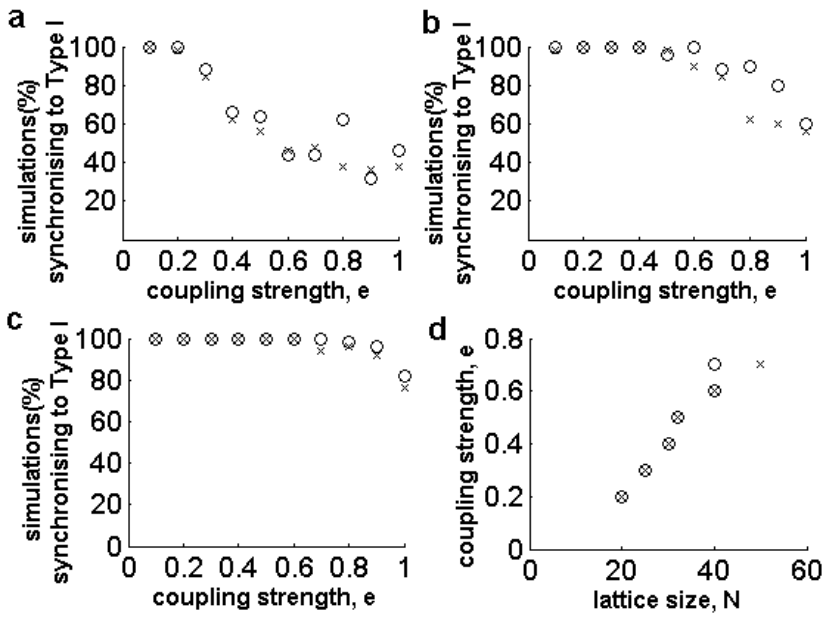

Figure 6. Percentage of simulations of coupled lattices for varying couplings, with lattice sizes, (**a**) $N = 20$, (**b**) 30 and (**c**) 40, which synchronize to Type-I. (**d**) Threshold coupling strength for definite synchronization to only Type-I phenotype, for varying lattice sizes. Crosses represent lattices for which the individual cells are all Type-I and open circles Type-II.

stabilize the emergent dynamics. In order to study the stability of the emergent state (Type-I), we have characterized its sensitivity to perturbations. We perturbed the coupled system by externally adding different levels of z to all the cells, at two time points after the system attained stable emergent behaviour (either Type-I or Type-II). We examined 50 realizations each, with different combinations of lattice sizes ($N = 10$ and 50), coupling strengths ($e = 0.3$ and 0.7) and perturbation strengths ($z_{\text{pert}} = 2$ and 10). The initial conditions were chosen randomly. The 1st and 2nd perturbations were added to the synchronized states of the lattice as shown in figure 8 by arrows 2 and 3. We show the results for one case, with $N = 50$, coupling strength of $e = 0.3$ and perturbation $z_{\text{pert}} = 2$. Figures 7a and 7b show the typical random value of $z(t)$ at which the end product, z, was perturbed both the times, in all 50 simulations. These show that the perturbations span the entire oscillation period and hence are non-specific.

Figures 8a–d show the end product dynamics of four representative simulations. The time series of 50 uncoupled cells (consisting of an equal number of Type-I and -II dynamics) have been shown superposed, for 1000 time steps (before the 1st arrow). On coupling all the lattices show Type-I oscillations (after time = 1000). The second and third arrows mark the time of the two perturbations ($z_{\text{pert}} = 2$) to the coupled system. As can be seen in figures 8a and 8b, on the first perturbation, the emergent collective state (always Type-I), can switch its dynamics (with a low probability of 16%), as shown here, or continue in the same state as in figures 8c

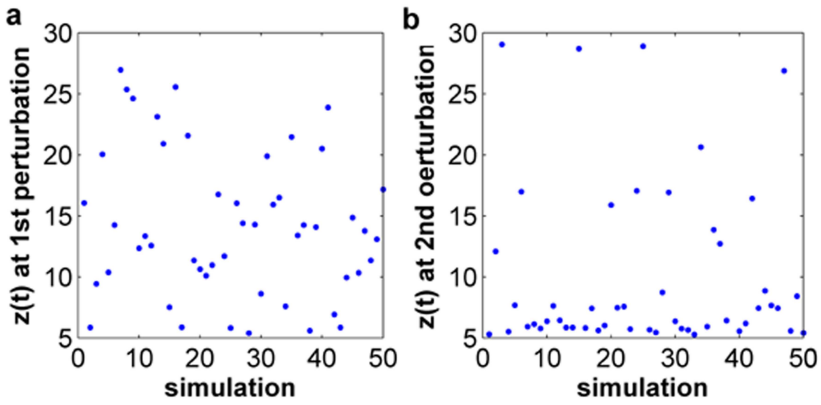

Figure 7. Phases of end product at the time of (**a**) 1st and (**b**) 2nd perturbation ($z_{\text{pert}} = 2$) for 50 simulations of coupled lattices of 50 cells, with $e = 0.3$.

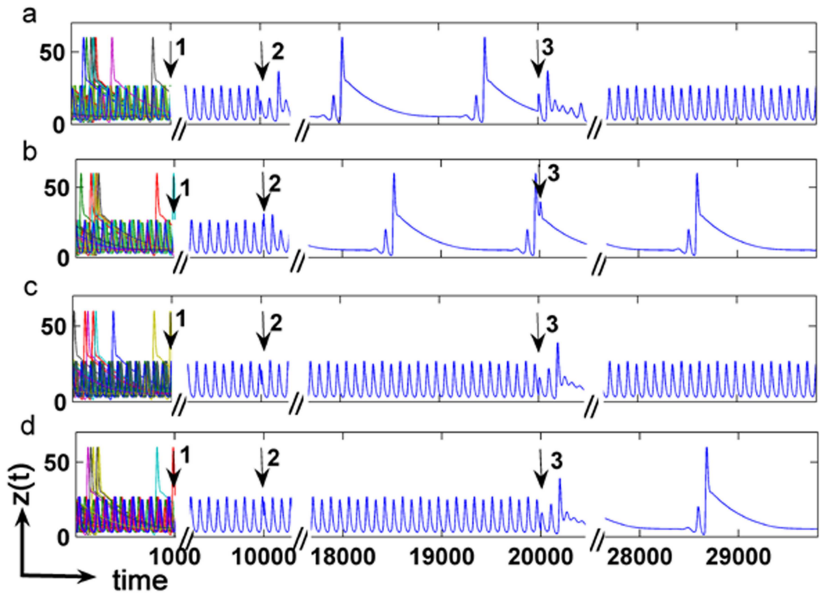

Figure 8. (**a, b, c, d**) Four typical realizations of the long-term dynamics of multicell system under perturbation. Overlapped time series of 50 cells without and with coupling ($e = 0.3$) and after two perturbations of $z_{\text{pert}} = 2$. The cells are coupled from the point shown by arrow 1. The perturbations are applied to the coupled synchronized system at points shown by arrows 2 and 3.

and 8d. After the second perturbation, 64% of the cases continued to show Type-I dynamics, and the other variations in dynamics are observed in a few of the cases as shown in figures 8a, 8b and 8d (these being 4%, 12% and 20%). The behaviour was similar for higher perturbation of $z_{\text{pert}} = 10$, with 50% of the realizations continuing

to remain in Type-I dynamics (similar to figure 8b). Thus we found that emergent Type-I behaviour was predominantly robust. The results were found to be similar for the other combinations of perturbation, coupling strength and lattice size. Hence in the multicell system, the additional constraint due to coupling quickly suppresses the unpredictable dynamics seen in the single cells (figures 3a and 3b).

4. Conclusions

Synchronization of linear chains of non-linear oscillators have been studied in lasers, Josephson junctions in physics and in vascular smooth muscles, mammalian intestinal smooth muscle and synthetic quorum sensing oscillators among other systems in biology [13–15, 42]. In these studies the oscillators considered are in regions corresponding to stable, periodic or chaotic behaviours. Such systems are also known to show behaviours such as clustering, phase locking, quenching, etc. Chaotic oscillators are synchronized partially or completely, depending on the parameters [13–15,22,32,33].

Here we have studied the role of intercellular coupling on the emergent behaviour of a diffusively coupled linear chain of cells exhibiting birhythmic behaviour. The fractal basin of attraction facilitates switching from one dynamical state to other in the presence of low levels of noise [31], and leads to non-robust behaviour of the individual cells in the lattice. We have shown that synchronization of this kind of oscillators is unique in that the two coexisting frequencies of oscillations yield complete synchronization to either of the frequencies depending on a threshold of coupling strength and lattice size. Thus, irrespective of the inherent frequencies of individual cells, depending on the coupling strength, the emergent collective behaviour synchronizes only to the higher frequency oscillations above this threshold number of cells in the ring. This indicates that, at large lattice sizes, the intercellular coupling has the effect of stabilizing the dynamic plasticity inherent in the individual cells.

Although multiplicity of dynamics is essential in situations where variability is advantageous under selection pressures, suppression of one of the birhythmic states provides for reliable and definite expression of a phenotype by the population and is important for survival as seen in the case of quorum sensing response in bacteria. Since cells function in noisy, fluctuating environment they would be subjected to repeated perturbations. The stability of the emergent synchronized state is of utmost importance for its functionality. With a two-perturbation experiment we have shown that the collective behaviour of this multicell system is mostly stable even under such perturbations. Thus, our study shows that, intercellular interactions (coupling) play a significant role on the robustness of the emergent collective behaviour of the multicell system under environmental noise by suppressing the inherent plasticity in the individual cell dynamics.

Acknowledgements

The authors thank R Maithreye and S Rajesh for discussions.

References

[1] A L Lehninger, D L Nelson and M M Cox, *Principles of biochemistry*, 4th edition (Worth Publishers, USA, 2004)
[2] A Goldbeter, *Biochemical oscillations and cellular rhythms* (Cambridge University Press, Cambridge, UK, 1996)
[3] T Haberichter, M Marhl and R Heinrich, *Biophys. Chem.* **90**, 17 (2001)
[4] U S Bhalla and R Iyengar, *Science* **283**, 381 (1999)
[5] J C Leloup and A Goldbeter, *J. Theor. Biol.* **198**, 445 (1999)
[6] M J Berridge, M D Bootman and P Lipp, *Nature (London)* **395**, 645 (1998)
[7] K Nielsen, P G Sorensen, F Hynne and H G Busse, *Biophys. Chem.* **72**, 49 (1998)
[8] T Hauck and F W Schneider, *J. Phys. Chem.* **97**, 391 (1993)
[9] O Decroly and A Goldbeter, *Proc Natl Acad. Sci. USA* **79**, 6917 (1982)
[10] A K Ghosh and B Chance, *Biochem. Biophys. Res. Commun.* **16**, 174 (1964)
[11] O Citri and I R Epstein, *J. Phys. Chem.* **92**, 1865 (1988)
[12] M Alamgir and I R Epstein, *J. Am. Chem. Soc.* **105**, 2500 (1983)
[13] M Rosenblum and A Pikovsky, *Contemporary Phys.* **44**, 401 (2003)
[14] M Rosenblum, A Pikovsky and J Kurths, *Synchronisation, A universal concept in nonlinear sciences* (Cambridge University Press, Cambridge, UK, 2001)
[15] S H Strogatz, *Nature (London)* **410**, 268 (2001)
[16] M Tsuchiya, S T Wong, Z X Yeo, A Colosimo, M C Palumbo, L Farina, M Crescenzi, A Mazzola, R Negri, M M Bianchi, K Selvarajoo, M Tomita and A Giuliani, *FEBS J.* **274**, 2878 (2007)
[17] C Aalkjær and H Nilsson, *British J. Pharmacology* **144**, 605 (2005)
[18] X Bonnefont, A Lacampagne, A Sanchez-Hormigo, E Fino, A Creff, M Mathieu, S Smallwood, D Carmignac, P Fontanaud, P Travo, G Alonso, N Courtois-Coutry, S M Pincus, I C A F Robinson and P Mollard, *Proc. Natl Acad. Sci. USA* **102**, 16880 (2005)
[19] R Bertram and A Sherman, *J. Biosci.* **25**, 197 (2000)
[20] M Bier, B M Bakker and H V Westerhoff, *Biophys. J.* **78**, 1087 (2000)
[21] D Somers and N Kopell, *Physica* **D89**, 169 (1995)
[22] S Rajesh, Sudeshna Sinha and Somdata Sinha, *Phys. Rev.* **E75**, 011906 (2007)
[23] L M Pecora, *Phys. Rev.* **E58**, 347 (1998)
[24] A N Pisarchik, R Jaimes-Reátegui, J R Villalobos-Salazar, J H García-López and S Boccaletti, *Phys. Rev. Lett.* **96**, 244102 (2006)
[25] D Gonze, S Bernard, C Waltermann, A Kramer and H Herzel, *Biophys. J.* **89**, 120 (1989)
[26] E Montbrio, J Kurths and B Blasius, *Phys. Rev.* **E70**, 056125 (2004)
[27] J Wolf and R Heinrich, *Biosystems* **43**, 1 (1997)
[28] H Maamar, A Raj and D Dubnau, *Science* **317**, 526 (2007)
[29] G M Süel, R P Kulkarni, J Dworkin, J Garcia-Ojalvo and M B Elowitz, *Science* **315**, 1716 (2007)
[30] C Suguna, K K Chowdhury and Somdatta Sinha, *Phys. Rev.* **E60**, 5943 (1999)
[31] C Suguna and Somdatta Sinha, *Fluctuations Noise Lett.* **2**, L313 (2002)
[32] C Suguna, R Maithreye, S Suthram and Somdatta Sinha, in: *Recent research developments in biophysical chemistry* edited by C A Condat, A Baruzzi (Research Signpost, Trivandrum, 2002) p. 91
[33] C Suguna and Somdatta Sinha, *Physica* **A346**, 154 (2005)
[34] Somdatta Sinha and R Ramaswamy, in: *Chaos in biological systems* edited by H Degn, A V Holden, L F Olsen (Plenum Press, New York, 1987) p. 59

[35] Somdatta Sinha and R Ramaswamy, *Biosystems* **20**, 341 (1987)
[36] A Goldbeter and G Nicolis, *Prog. Theor. Biol.* **4**, 65 (1976)
[37] J J Tyson, *J. Theor. Biol.* **103**, 313 (1983)
[38] Y Oono and S Puri, *Phys. Rev. Lett.* **58**, 836 (1987)
[39] C Fuqua, S C Winans and E P Greenberg, *Annu. Rev. Microbiol.* **50**, 727 (1996)
[40] M B Miller and B L Bassler, *Annu. Rev. Microbiol.* **55**, 165 (2001)
[41] J A Shapiro, *Annu. Rev. Microbiol.* **52**, 81 (1998)
[42] J Garcia-Ojalvo, M B Elowitz and S H Strogatz, *Proc. Natl Acad. Sci. USA* **101**, 10955 (2004)