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Dynamics of coupled-cell systems

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Abstract

Cells interact/communicate among themselves to form structures that perform specialised functions. Here, we review the different types of multicellular organisation observed in living systems whose constituent cells exhibit collective behaviour that may or may not be identical to the single cell dynamics. We present a simple one-dimensional lattice model of a ring of cells, as observed in real tissues, where each cell incorporates a model biochemical reaction having realistic regulatory processes. We study the dynamics exhibited by this coupled-cell system when the constituent pathway in the cells is at different dynamic regimes, or cells have heterogeneous dynamics. Our results show that the synchronised dynamical behaviour of the coupled-cell system can be both similar or different than its constituent cells depending on their intrinsic dynamics. The collective behaviour is robust even when the constituent single cell dynamics is unpredictable under noise.

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Keywords: Multicellularity; Coupled lattice model; Collective behaviour; Cellular networks

1. Introduction

Life on earth is organised in layers—from ecosystem to populations to organisms to cells to molecules that make up the cells. Any complex organised biological structure is composed of interacting elements/modules whose emergent properties

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are largely determined by their function on the whole. The major success of molecular biology has been to use the reductionist approach and dissect the layers of organisation in physiological systems—from whole organisms to molecules that carry genetic information and regulate biochemical functions. With all this information in hand, now the major challenge is to rebuild or "reverse engineer" the levels of organisation upward.

One of the tools in the synthetic approach, to study the structure and emergent properties of groups of interacting elements, is network analysis. A large body of literature has been accumulated over the past few years on networks of amino acids [1], genes [2], proteins [3], and biochemical pathways [4,5]. At higher levels of organisation, network theory has also been used to describe social interactions [6], and ecological networks such as food webs [7]. There has not been much study, using this framework, at the intermediate level where many cells interact to form a multicellular structure/group such as, tissues, organs, organisms and cell populations. From bacteria to humans, all that populate the earth, are composed of cells—single or multicellular. A single cell can do *almost* all the functions required for living and propagating itself. Thus, evolution of multicellularity is one of the major unsolved problems in biology.

Properties of living organisms are derived from the structure and function of its constituent cells. Many multicellular organisms, including humans, begin their existence as a single cell, a fertilised egg. A newborn human is made up of about 10^{13} cells. Such an evolving system can be viewed as a growing, branching, and hierarchical network of cells. At a different level, groups of cells develop specialisations in structures and biochemical properties that give them particular functional capabilities. For example, muscle cells contract, nerve tissue conduct signals, and red blood cells transport oxygen. These are reminiscent of sub-networks or modules. Thus, there is a range of possibilities to be explored in this level of organisation, which we term as "cellular networks" or "coupled-cell systems".

A few examples of different types of coupled-cell systems are—(a) cell colonies or organisms; (b) structured group of cells or organised assemblies—tissues and organs; and, (c) density-dependent cell population behaviour. The colonial eukaryotes present a good example of evolution of multicellularity [8]. The flagellated green algae Chlamydomonas are known to exist as single cells, and in related genera, many such flagellated cells are known to remain associated in colonies inside a jelly-like membrane. Each cell is capable of independent existence and divides to give rise to a new colony. Similar organisms (e.g., Volvox) are known that have over 50,000 such cells, but only a small number of specialised cells can reproduce, and the other cells cannot live independently. The latter is an example of a multicellular organism. The transition from single cell to cell collective (aggregates), and then to a single organism (fruiting body) in the life cycle of the cellular slime moulds is also a classic example of a coupled-cell system. Here, active communication and interaction among the cells in a population lead to higher levels of organisation [9].

Biological tissues and organs are well-known examples of structured group of cells, where the arrangement and types of contacts complement their specific functions. Pancreatic islet is an organised assembly of primarily β cells which secrete

insulin. Well-synchronised electrical activity of the β cells in the islet precedes insulin secretion. The isolated β cells show electrical activity with very different time scales and do not secrete insulin effectively [10]. Thus, the intercellular communication in the organised islet structure is a necessary prerequisite for effective functioning in this example of a coupled-cell system.

The phenomena of Community Effect [11], Quorum Sensing [12], and Biofilms [13], are examples of cell density-dependent behaviour, where a population of similar cells respond to a signal factor and induce new gene expression only when the number of cells reach a certain density. Density-dependent inhibition of cell division in normal cells is an example of cell–cell communication in a population. Loss of density-dependent inhibition in transformed cells in culture has been shown to lead to tumourigenesis [8].

Biological modes of communication among the cells in a coupled-cell system are varied. It can be both direct and indirect. Direct signalling involves interaction between membrane-bound molecules, or via gap junctions. Indirect ones can be through secreted chemicals or matrix mediated. Inter-cellular signalling during any physiological process may use any one, or combination of the above-mentioned mechanisms [9].

Modelling coupled-cell system, thus, involves studying many cells interacting in space and time in different scenario. The whole system behaviour is the emergent collective behaviour. The three important elements are—(a) cells with identical or heterogeneous biochemical properties, (b) different types of interactions (all-to-all, nearest neighbour, random, etc), and, (c) the environment/structure on which the cells exist, which may be constant for all cells, or have gradient in properties, or constitute a noisy environment. Thus, a coupled-cell system has cells that are discrete entities having localised reaction dynamics, and are coupled to each other through different information transfer mechanisms. The reactions in a cell are parts of a large network of biochemical pathways that are regulated through single, multiple and coupled, negative and positive feedback processes. A combination of negative and positive feedback processes is useful for optimal performance requiring stability, sensitivity, and multiplicity of dynamics.

This paper considers a simple model of a one dimensional coupled-cell system—a ring of cells—where the cells incorporate a model biochemical pathway, and can interact with their nearest neighbours through diffusion of a signal molecule. We consider a coupled lattice model, where each lattice node represents the model cell with a dynamical system describing a three-step pathway regulated by endproduct inhibition (negative feedback) and auto-induction (positive feedback) processes. We study the dynamics exhibited by a single cell and the collective dynamics of the coupled-cell system at different parameter regimes. Our results show that even when the single cell behaviour is robust or sensitive to concentration and parameter variations, the behaviour of the coupled-cell system shows quite robust and synchronised dynamics at all parameter regimes. Given the biological and medical importance of cell population behaviour, and the modular and hierarchical nature of these levels of organisation, this remains a relatively unexplored field for theoretical studies, especially network analysis.

2. Model and methods

2.1. Single cell dynamics

The model cell incorporates a three-step biochemical reaction, which is regulated by end product inhibition and autocatalytic activation of the end-product by an allosteric enzyme. The time evolution of the normalised concentrations of the substrates x and y and end-product z in the pathway in each cell is given by

$$\frac{dx}{dt} = F(z) - kx; \quad \frac{dy}{dt} = x - G(y,z); \quad \frac{dz}{dt} = G(y,z) - qz\,,$$

$$F(z) = \frac{1}{(1+z^4)} \quad \text{and} \quad G(y,z) = \frac{Ty(1+y)(1+z)^2}{L+(1+y)^2(1+z)^2}\,.$$

$F(z)$ and $G(y,z)$ are the functions describing the negative and positive feedback processes. The parameters k, and q are related to the rates of degradation of x and z, and L and T are to the properties of the enzyme [14–16]. The basal parameter values, obtained from experiments on other cellular processes having similar regulatory mechanisms [17–19], are $L = 10^6, T = 10, k = 1$, and $q = 0.01$.

2.2. Coupled-cell dynamics

As a model of a one-dimensional coupled-cell system (e.g., cellular arrangement in plant roots), we consider a one-dimensional lattice with periodic boundary conditions, as shown in Fig. 1. Each lattice node contains a model cell which is coupled to the neighbouring cells by diffusion of the end-product z. The concentration of z in the ith cell at time $(r+1)$ is described by

$$z(i,r+1) = (1-e)z(i,r) + (e/2)[z(i-1,r) + z(i+1,r)]\,,$$

where e is the strength of diffusive coupling, and, r, the earlier instant of time. The dynamical behaviour of the coupled-cell system is simulated numerically, and

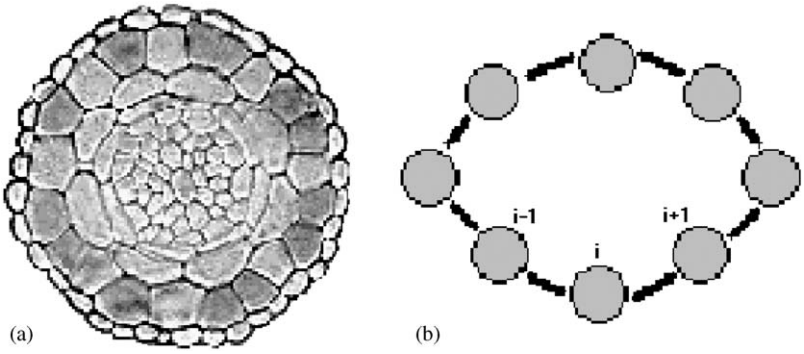

Fig. 1. (a) Ring-like arrangement of cells in section of a plant root. (b) A circular lattice model of a ring of cells where the ith cell is diffusively coupled to the $(i-1)$th and $(i+1)$th cells.

compared to the behaviour of single non-interacting cells. For numerical integration, we have used the scheme of Oono and Puri [20]. The temporal simulation of the local dynamics is done using a fourth-order Runge–Kutta scheme, and the stability of the solutions has been checked with different integration steps in the range (0.001–0.2). The results are shown for 0.1. Simulations (50 or more in each case) have been performed on lattices of 50 cells with random initial conditions and parameter variation. Long-term simulations ($t = 20\,000$) are shown as space time plots and time series. The latter plots are shown by superposition of the time evolution of all 50 cells in the uncoupled and coupled state.

3. Results

3.1. Single cell dynamics

The biochemical pathway in the model cells is known to exhibit a wide range of dynamics—equilibrium, limit cycle, period-doubling, birhythmic, complex, and chaotic oscillations—with variation in parameters k and q [16].

In this study on collective dynamics of the coupled-cell system, we have chosen three dynamic regimes as shown in the three-dimensional phase plots in Fig. 2. These are—(a) simple limit cycle oscillations, (b) the birhythmic state having coexistence of two types of oscillations, termed Type I and II, of widely different amplitudes and time periods, and, (c) chaotic oscillations. The phase space of the coexisting Type I and II attractors in the birhythmic region overlap considerably, and their basins of attraction are found to be fractal [16,21].

3.2. Coupled-cell dynamics

Here, we consider two types of coupled-cell systems—*homogeneous* and *heterogeneous*. The homogeneous lattice is made up of cells having the same

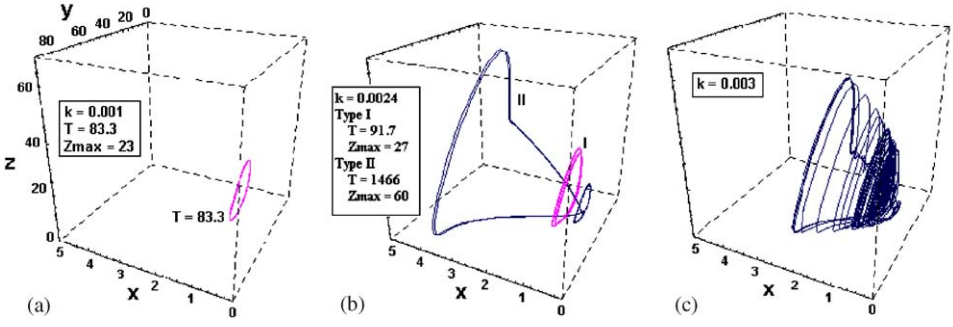

Fig. 2. Phase plots of the attractors for varying k, with $q = 0.1$. (a) Simple periodic oscillations. (b) Birhythmic behaviour—Type I and II attractors superimposed. (c) Chaotic dynamics. Value of k, time period of oscillations (T), and maximum of z (z_{max}) are given for comparison.

properties (same parameters), and the heterogeneous lattices have cells with different dynamics (different parameters). First, we show the homogeneous cell systems for the three dynamic regime. We then state our results for lattices whose cells have the parameter k randomly distributed within a certain range.

3.2.1. Homogeneous lattice

Three types of homogeneous lattices are considered with cells having intrinsic dynamics as shown in Fig. 2.

Cells with periodic dynamics: The lattice is composed of cells exhibiting simple limit cycle oscillations at different phases (as in Fig. 2(a)). Fig. 3(a and c) show the space–time plot and time series of z in the uncoupled cells in the lattice. The behaviour of the cells, on coupling, are shown in Fig. 3(b and d). The plots show that the coupled cells are fully synchronised, with the same periodicity and nearly the same amplitude as the individual cells. Thus, the collective dynamics of the coupled-cell system is identical to that of a single cell in this regime. In absence of cell communication (through diffusion of molecules), their dynamics is asynchronous; whereas, cell–cell communication leads to synchronised activity leading to collective regular output.

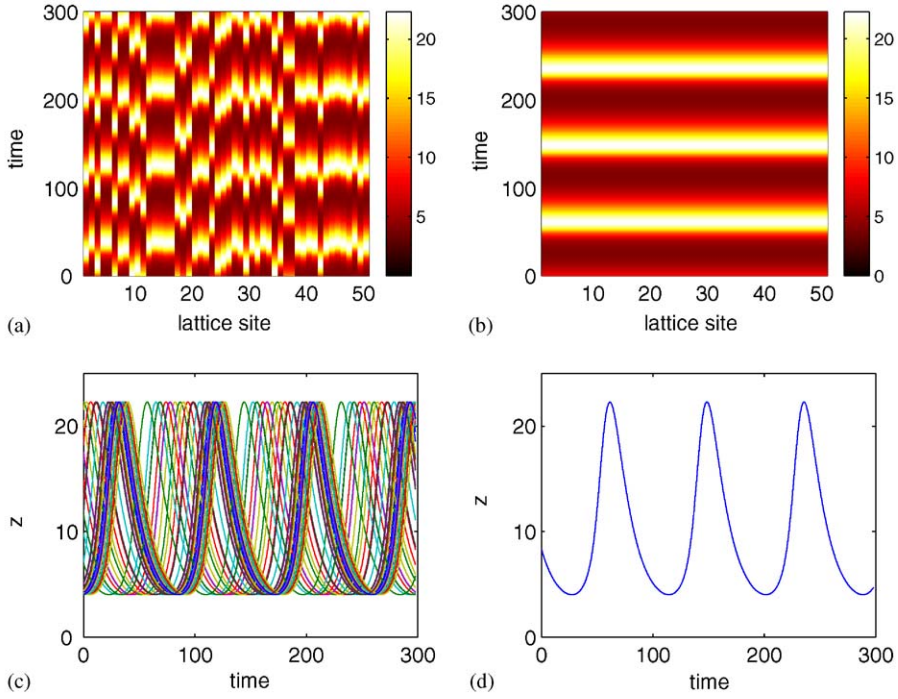

Fig. 3. Lattice with cells in the simple periodic regime. Space–time plots of z (a) without, and (b) with coupling; Time series of the cells when (c) uncoupled, and (d) coupled. The parameters are: $k = 0.001, q = 0.1, e = 0.3$.

Cells with birhythmic behaviour: We considered lattices having uncoupled cells showing either Type I (Fig. 4(a)) or Type II (Fig. 4(b)) dynamics. Fig. 4(c and d) show the emergent behaviour, on coupling, of the coupled-cell system in the space time plot and time series. Cells in both lattices synchronise to Type I dynamics. Since there is considerable overlap in the phase space of Type I and II attractors, and the basins of attraction are fractal, the behaviour of single cells under small noise is unpredictable [21]. Here we show that the collective dynamics is always Type I in the coupled-cell systems with large number of cells. Thus, irrespective of the initial dynamics of the single cells, the coupled-cell behaviour is only of Type I. This happens even if a lattice has a mixture of Type I and II cells [22].

Cells with chaotic dynamics: The coupled-cell behaviour of lattices made up of cells exhibiting chaotic dynamics (Fig. 2(c)) is shown in Fig. 5. Fig. 5(a and e) show the space–time plot and time series of z in the uncoupled cells. We show, here, three examples of the dynamic behaviour resulting from the diffusive coupling strength $e = 0.3$. The emergent dynamics is mostly synchronised but not necessarily chaotic (Fig. 5(b,c,d) and (f,g,h)). The degree of synchronisation varies from well-synchronised and more regular (Fig. 5(b and f)) to partial synchrony and irregular (Fig. 5(d and h)), where some cells in the coupled lattice show difference in

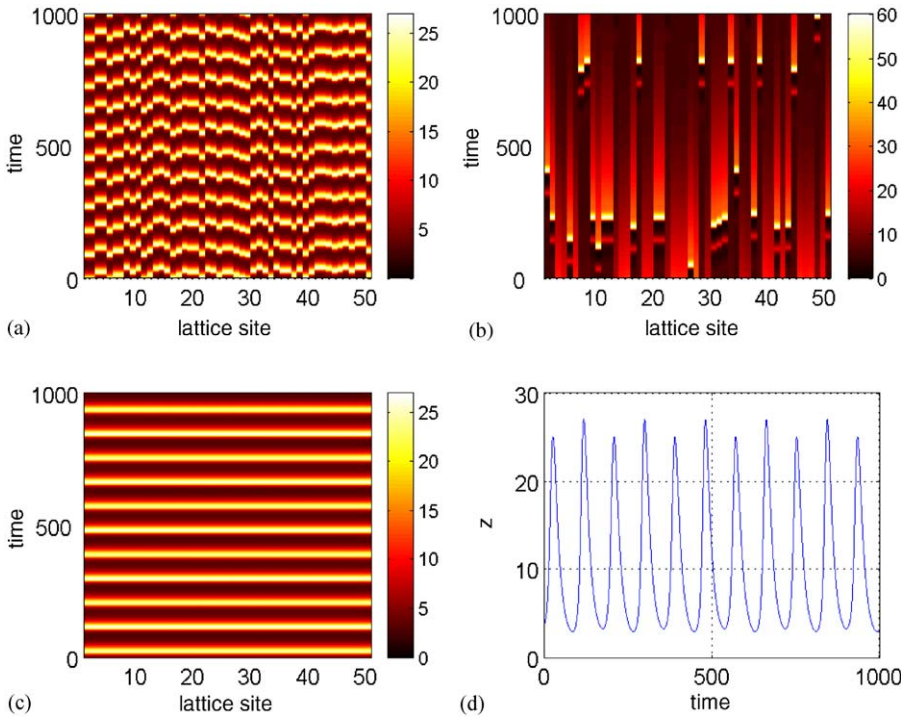

Fig. 4. Lattice with cells in the birhythmic regime. Space–time plots of z in uncoupled lattices with (a) Type I, (b) Type II dynamics. Both lattices on coupling: (c) space time plot, and (d) time series. The parameters are: $k = 0.0024, q = 0.1, e = 0.3$.

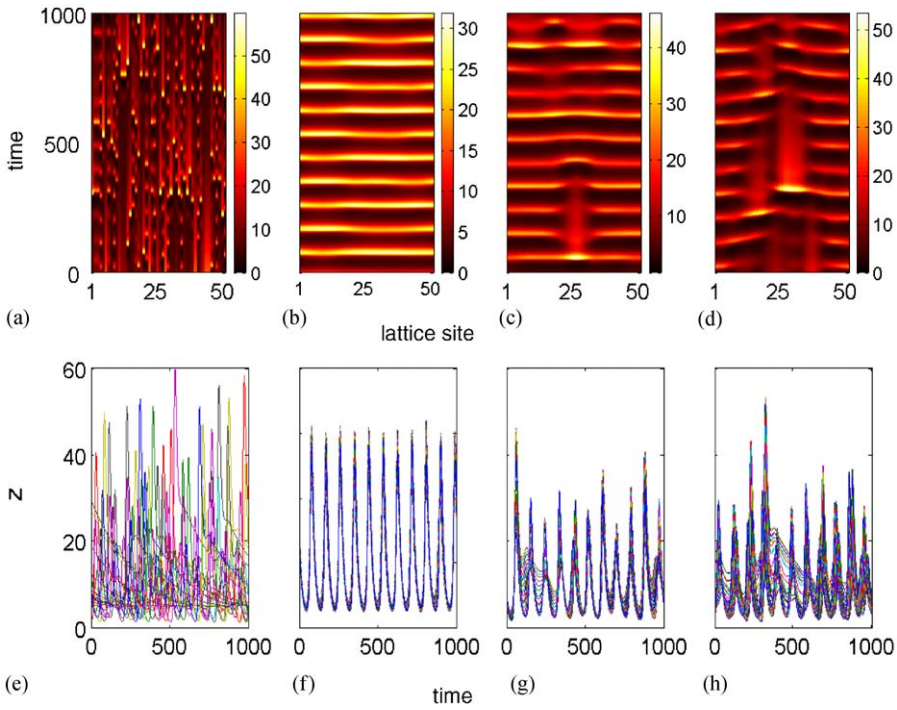

Fig. 5. Lattice with cells in the chaotic regime. Space–time plots of z for (a) uncoupled cells. (b), (c), and (d) are with coupling. Time series of the cells when (e) uncoupled, and (f), (g), and (h) when coupled, for the corresponding space–time plots. The parameters are: $k = 0.003, q = 0.1, e = 0.3$.

frequency, phase, and amplitude. Extensive simulations show that the collective dynamics depends on e, and on the number of cells in the lattice. At higher e the lattice is always synchronised to chaotic oscillations. This phenomena is being investigated further.

3.2.2. *Heterogeneous lattice*

In reality, a population of cells can have different parameters due to intrinsic and extrinsic noise that permeates its environment [23]. To simulate different degrees of heterogeneity, we have considered two types of lattices with cells having $k = 0.001 + \sigma$, where σ is a random number in the range $[0, 0.003]$ and $[0, 0.03]$. We have studied the effect of increased degree of heterogeneity on the coupled-cell dynamics. In the first case, the dynamics of individual cells range from simple periodic to period-doubled, birhythmic, complex and chaotic oscillations (shown in the Left panel of Fig. 6), and in the second case with increased heterogeneity (Right panel of Fig. 6), they also include period reversals, and large-amplitude periodic oscillations whose period is comparable to the small amplitude oscillations [16].

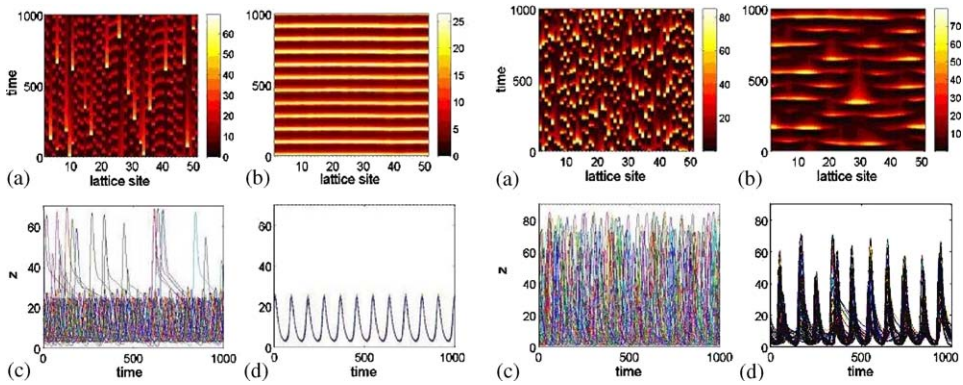

Fig. 6. Heterogeneous lattices with cells having randomly distributed k in range $0.001 + [0, 0.003]$ (Left panel) and $0.001 + [0, 0.03]$ (Right panel). Space–time plots for (a) uncoupled, and (b) coupled lattice. Time series for (c) uncoupled, and (d) coupled cells. $q = 0.1, e = 0.3$.

It is clear from the Left panel of Fig. 6, that even though the cells exhibit a large variety in their dynamics, on coupling the coupled-cell behaviour is perfectly synchronised to small periodic oscillations—similar to Type I. However, when heterogeneity of cells in the coupled-cell system is increased, the majority of cells show large amplitude oscillations as can be seen in the Right panel of Fig. 6. The cells in the lattice show partial synchronisation to complex oscillations with larger amplitude but similar time period. Comparison of the time series in the right panel shows, that though not perfectly synchronised, the dynamic behaviour of the cells in this highly heterogeneous coupled-cell system is significantly correlated compared to the uncoupled case.

4. Conclusions

Biological systems have been studied as networks at different levels—of molecules and pathways inside a cell, and of individuals and species at a higher level of organisation. In all these studies, the properties of the underlying structure of the network have been elucidated and their functional and evolutionary significance discussed. Here, the nodes of the network are single elements devoid of any intrinsic dynamics. At the level of multicellular systems, large variations in structure and function exist. There can be a whole organism as a coupled-cell system, or colonies/aggregates of cells, tissues and organs, or, groups of similar cells performing a specific function. Each cell in the organised cell system performs some biochemical function, but their collective behaviour is an outcome of the communication among them. Many diseases are due to the loss of cell communication or abnormal cell–cell interactions in the tissue.

In this paper, we have used a regular network (coupled lattice) model for simulating a simple coupled-cell system, where each cell communicates only to its

nearest neighbours through diffusion of a signal molecule which is the end-product of a regulated biochemical pathway. We have shown, that even though the collective behaviour is primarily synchronised, it may not always be the same as the constituent single cell dynamics. The collective dynamics is generally robust even if the single cell behaviour is not. Such a property confers functional advantage to the coupled-cell system in natural noisy environment. The phenomenon of collective synchronisation is well known in physics and biology, where a large number of oscillators lock to a common frequency despite the differences in their natural frequencies [24]. The regular lattice picture is appropriate in structured cell populations such as, tissues, layers, and organs. However, given the variety of complex structures that cell layers assume during development and even in adult organisms (e.g., the multiple folded layers in the brain), it would be useful to consider cellular networks with different types of branching, connectivity, and modularity in structure, to study their emergent properties and the possible relevance of various network parameters. This could shed some light in the structure–function relationship in coupled-cell systems.

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