

## MODELING THE INTERCELLULAR EXCHANGE OF SIGNALING MOLECULES DEPENDING ON INTRA- AND INTER-CELLULAR ENVIRONMENTAL PARAMETERS

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**Abstract** – The exchange of biochemical substances is essential in establishing communication between bacterial cells. It is noticeable that all phases of the process are heavily influenced by perturbations of either internal or external parameters. Therefore, instead of developing an accurate quantitative model of substance exchange between bacterial cells, we are interested in the formalization of the basic shape of the process, and creating the appropriate strategy that allows further investigation of synchronization. Using a form of coupled difference logistic equations we investigated the synchronization of substance exchange between abstract cells and its sensitivity to fluctuations of environmental parameters using methods of nonlinear dynamics.

**Key words:** Intercellular communication, substances exchange, coupled logistic equations, synchronization.

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### INTRODUCTION

Communication between cells is ubiquitous in the biological world. From single cell bacteria to complex eukaryotic organisms, cellular communication is a way for creating more complex structures through the integration and maintaining of functioning. Organisms have evolved various auxiliary ways for ensuring that the transfer of signals can be performed timely and efficiently (e.g. development of vascular systems starting from early chordates). However, at the molecular level, the basic scheme of signal exchange remains the same: signaling molecules reach the cellular receptor which in turn activates a regulatory response that modulates the production of targeted molecular species. These species then either directly or indirectly influence the production of arriving signals. In this general approach, several points should be noted. Since communication is established by exchange of specific biochemical substances ("substances" in the further text) through the surrounding environment, this process is heavily influenced by environmental factors. In single cell organisms environmental fluctuations are even more prominent since substances have to be released into the

external environment, which is not included in the homeostasis created by the organism. Additionally, even in a clonal population and under a strongly controlled environment, a significant level of fluctuations of the constituting parameters will remain, due to protein disorder (Dunker et al., 2002) and so-called intrinsic noise (Elowitz et al., 2002; Swain, et al., 2002). Finally, due to thermal and conformational fluctuations, biochemical processes are inherently random (Longo & Hasty, 2006).

These facts indicate that signaling processes are able to maintain functionality despite the very strong influence of both internal and external fluctuations – a phenomenon called robustness (Barkai & Shilo, 2007; Kitano, 2007). In contrast to stability, where the achieved state is maintained, here the whole functional process is in focus. Although it is one of the main aspects of the functioning of living organisms, an understanding of robustness is still very incomplete. Due to its very general nature it is reasonable to neglect some species-specific and molecule-specific aspects in order to investigate the foundations of robust behavior. Therefore, our focus in this paper is only on the question of how the oscillating system, which is

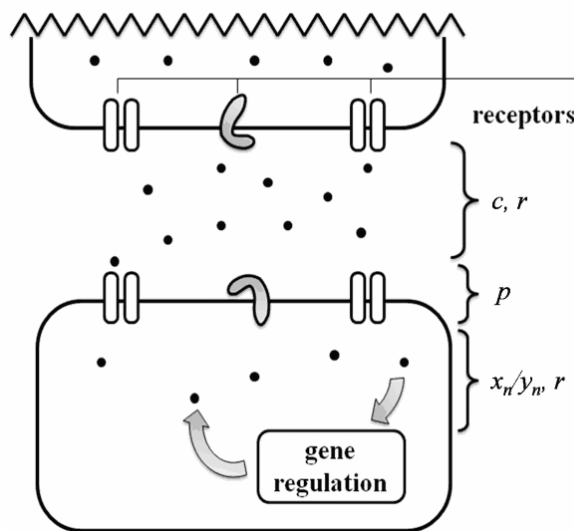
basically stochastic and is inherently influenced by internal and external perturbations, can maintain its functioning? Therefore, instead of developing an accurate quantitative model of substance exchange between cells, we are more interested in the formalization of the basic shape of the process and in creating the appropriate strategy that allows further investigation of the synchronization induced by fluctuations of intra- and inter-cellular environmental parameters. We give a short overview of the general mechanism for substance exchange between two bacterial cells, representing a cooperative communication process. Furthermore, we identify the main parameters of the process and derive a system of two coupled logistic equations as an appropriate model of the given process. In Section 3 we investigate the synchronization of the model and its sensitivity to fluctuations of environmental parameters. Concluding remarks are given at the end.

## MATERIALS AND METHODS

### *Simple model of intercellular exchange: empirical background*

Starting from bacteria where quorum sensing (Waters & Bassler, 2007) and colony formation (Stoodley et al., 2002) are efficient mechanisms for the rapid switching between different phenotypes to the sophisticated humoral control in vertebrates which ensures the proper functioning of the organism as an integrated system, communication between cells is one of the main prerequisites for assembling them into higher organized structures. Despite the great variety of specific mechanisms and the even greater number of molecules included, the general scheme, especially in unicellular organisms, remains fairly universal [see, for example Purves et al. (2003)] as is seen in Fig. 1, which is adopted as a scheme of the intercellular exchange model we propose in this paper.

Signaling molecules are those which are deliberately extracted by the cell into the intracellular environment, and which can affect the behavior of other cells of the same or different type (species or



**Fig. 1.** Schematic representation of intercellular communication. Here,  $c$  represents the concentration of signaling molecules in the intercellular environment coupled with the intensity of response they can provoke, while  $r$  includes the collective influence of environment factors which can interfere with the process of communication.  $x_n$  and  $y_n$  represent the concentration of signaling molecules in the cell's environment, while  $p$  denotes cellular affinity to the uptake the substances.

phenotype) by means of active uptake and subsequent changes in genetic regulations. They can be excreted as either a side product of other metabolic processes, or as purposefully synthesized, and transported from the cell. Once in the intercellular environment, they can be transported to other cells that can be affected. Let us note that the term *environment*, in this paper, comprises both (i) *intracellular environment* (inside the cell) and (ii) *intercellular environment* (that surrounds cells). Since active uptake is one of the milestones of the process, a very important factor in establishing communication is a current set of receptors and transporters in the cellular membrane during the communication process. At the same time they constitute the backbone of the whole process while simultaneously being a very important source of perturbations of the process due to protein disorder and intrinsic noise. As a result, the process of exchange is constantly under the inherent fluctuations of the aforementioned parameters. Another important factor is the intercellular environment which

could interfere in the process of exchange. It includes: the distance between the cells, the mechanical and dynamic properties of the fluid which serve as a channel for exchange and various abiotic and biotic factors influencing the physiology of the involved cells. Finally, in order to define the exchange process as communication, received molecules should induce change in genetic regulations. Signaling molecules can influence the production of a number of different genes, but the synthesis of molecules that are able to directly or indirectly affect the production of arriving signals is necessary to call this process a communication. Therefore, the concentration of the signaling molecules inside the cell that are destined to be extracted, can serve as an indicator of the dynamics of the whole process of communication. These signaling molecules can be either the same for all involved cells or they can be different, acting directly or indirectly on the production of arriving signals.

Additionally, the influence of affinity in the functioning of living systems is also an important issue. It can be divided into the following aspects: (a1) the affinity of genetic regulators towards arriving signals which determine the intensity of cellular response, and (a2) the affinity for uptake of signaling molecules. The first aspect is genetically determined and therefore species specific. The second aspect is more complex and is influenced by the affinity of receptors to binding specific signaling molecules, the number of active receptors and their conformational fluctuations (protein disorder).

#### *An outline of the model*

As is obvious from the empirical description, we can infer the success of the communication process by monitoring: (i) the number of signaling molecules, both inside and outside the cell, and (ii) their mutual influence. The concentration of signaling molecules in the intercellular environment is subject to various environmental influences, and taken alone can often indicate more about the state of the environment than about the communication itself. Therefore, we chose to follow the concentration of signaling molecules inside the cell as the main

indicator of the process. In that case, the parameters of the system are: (i) the affinity  $p$  by which cells perform the uptake of signaling molecules (a2) that depends on the number and state of the appropriate receptors, (ii) the concentration  $c$  of signaling molecules in the intercellular environment within the radius of interaction, (iii) the intensity of cellular response (a1)  $x_n$  and  $y_n$ , and (iv) the influence of other environmental factors which can interfere with the process of communication. In this case we postulate parameter  $r$ , that can be taken collectively for the intra- and inter- cellular environment, inside the one variable, indicating the overall disposition of the environment to the communication process.

The time development ( $n$  is the number of time step) of the concentration in cells ( $x_n, y_n$ ) can be expressed as

$$x_{n+1} = (1-c)\Psi(x_n) + h(\Psi(y_n)), \quad (1a)$$

$$y_{n+1} = (1-c)\Psi(y_n) + h(\Psi(x_n)). \quad (1b)$$

The map,  $h$ , represents the flow of materials from cell to cell, and  $h(x)$  and  $h(y)$  are defined by a map that can be approximated by a power map,

$$h(x) \sim cx^p, \quad (2a)$$

$$h(y) \sim cy^q. \quad (2b)$$

If  $h(x) \sim cx^p$  and  $h(y) \sim cy^q$ , the interaction is expressed as a nonlinear coupling between two cells. The dynamics of intracellular behavior is expressed as a logistic map (e.g., (Deverney, 1986; Gunji & Kamiura, 2004)),

$$\Psi(x_n) = r x_n (1 - x_n), \quad (3a)$$

$$\Psi(y_n) = r y_n (1 - y_n). \quad (3b)$$

Since concentration of signaling molecules can be regarded as their population for a fixed volume, and since we are focused on the mutual influence of these populations, the use of coupled logistic

equations is indicated. Instead of considering the cell-to-cell coupling of two explicit  $n$ -gene oscillators (Ullner et al., 2008) we consider a generalized case of gene oscillator coupling. In this case the investigation of the conditions under which two equations are synchronized and how this synchronization behaves under changes in the intra- and inter- cellular environment, can give some answers to the question of maintaining functionality in the system. Therefore, having in mind that (i) cellular events are discrete (Barkay & Shilo, 2007), and (ii) the aforementioned reasoning, we consider system of difference equations of the form

$$X_{n+1} = F(X_n) \equiv L(X_n) + P(X_n), \quad (4)$$

with notation

$$L(X_n) = ((1-c)rx_n(1-x_n), (1-c)ry_n(1-y_n)), \quad P(X_n) = (cy_n^p, cx_n^{1-p}), \quad (5)$$

where  $X_n = (x_n, y_n)$  is a vector representing the concentration of signaling molecules inside of the cell, while  $P(X_n)$  denotes the stimulative coupling influence of members of the system which is here restricted only to positive numbers in the interval  $(0,1)$ . The starting point  $X_0$  is determined so that  $(x_0, y_0) \in (0,1)$ . Parameter  $r \in (0,4)$  is a so-called logistic parameter, which in logistic difference equations determines an overall disposition of the environment to the given population of signaling molecules and exchange processes. Affinity to uptake signaling molecules is indicated by  $p$ . Let us note that we require that the sum of all affinities of cells  $p_i$  exchanging substances has to satisfy condition  $\sum_i p_i = 1$  or in the case of two cells  $p + q = 1$ . Since the fixed point is  $F(0) = 0$ , in order to ensure that zero is not at the same time the point of attraction, we defined  $p \in (0,1)$  as an exponent. Finally,  $c$  represents the coupling of two factors: the concentration of the signaling molecules in the intracellular environment and the intensity of response they can provoke. This form is taken because the effect of the same intracellular concentration of signaling molecules can vary greatly with the variation of the affinity of genetic regulators for that

signal, which is further reflected in the ability to synchronize with other cells. Therefore,  $c$  influences both the rate of intracellular synthesis of the signaling molecules, as well as the synchronization of the signaling processes between two cells, so the parameter  $c$  is taken to be a part of both  $L(X_n)$  and  $P(X_n)$ . However, the relative ratio of these two influences depends on the current model setting. For example, if for both cells  $X_n$  is strongly influenced by an intracellular concentration of signals, while they can provoke a relatively smaller response then the form of equation will be

$$x_{n+1} = (1-c)rx_n(1-x_n) + cy_n^p, \quad (6a)$$

$$y_{n+1} = (1-c)ry_n(1-y_n) + cx_n^{1-p}. \quad (6b)$$

*Analysis of the coupled maps representing the intercellular exchange of substances using methods of nonlinear dynamics*

In order to further investigate the behavior of the coupled maps, we performed a numerical analysis of the coupled system (6) through its parameters  $c$ ,  $r$  and  $p$ , using the largest Lyapunov exponent and cross sample entropy as measures of the chaotic behavior and border between synchronized and non-synchronized system states in the intercellular exchange of substances.

*Lyapunov exponent of the coupled maps (6) for  $r = \text{const.}$*

We calculated the Lyapunov exponent by analysis of orbits. The orbit of the point  $X_0$  is the sequence  $X_0, F(X_0), \dots, F^n(X_0), \dots$  where  $F^0(X_0) \equiv X_0$  and for  $n \geq 1$ ,  $F^n(X_0) = F(F^{n-1}(X_0))$ . We say that the orbit is periodic with a period  $k$  if  $k$  is the smallest natural number so that  $F^k(X_0) = X_0$ . If  $k = 1$ , then the point  $X_0$  is the fixed point. The periodic point  $X_0$  with period  $k$  is an attraction point if the norm of the Jacobi matrix for the mapping  $F^k(X) = (f_k(x, y), g_k(x, y))$  is less than one, i.e.,  $\|J^k(X_0)\| < 1$ , where

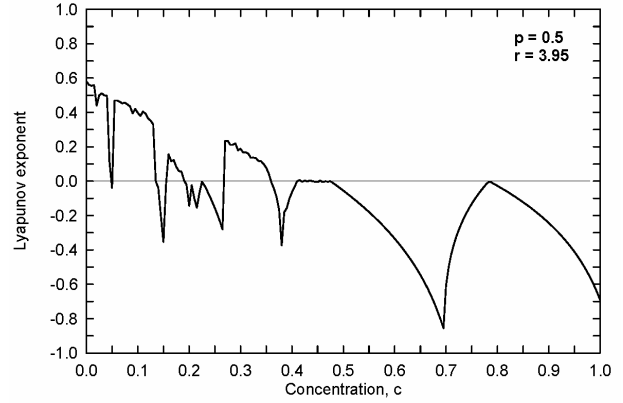
$$J^k(X_0) = \begin{bmatrix} \frac{\partial f_k}{\partial x} & \frac{\partial f_k}{\partial y} \\ \frac{\partial g_k}{\partial x} & \frac{\partial g_k}{\partial y} \end{bmatrix}_{X=X_0} \quad (7)$$

Here, we define  $\|J^k(X_0)\|$  as  $\max \{|\lambda_1|, |\lambda_2|\}$ , where  $\lambda_1$  and  $\lambda_2$  are the eigenvalues of the matrix. In order to characterize the asymptotic behavior of the orbits, we need to calculate the largest Lyapunov exponent, which is given for the initial point  $X_0$  in the attracting region by

$$\lambda = \lim_{n \rightarrow \infty} (\ln \|J^n(X_0)\| / n). \quad (8)$$

With this exponent, we measured how rapidly two nearby orbits in an attracting region converge or diverge. In practice, we computed the approximate value of  $\lambda$  by substituting in (8) successive values from  $X_{n_0}$  to  $X_{n_1}$ , for  $n_0, n_1$  large enough to eliminate transient behaviors and provide a good approximation. If  $X_0$  is part of a stable periodic orbit of period  $k$ , then  $\|J^k(X_0)\| < 1$  and the exponent  $\lambda$  is negative, which characterizes the rate at which small perturbations from the fixed cycle decay, and we can call such a system a synchronized one.

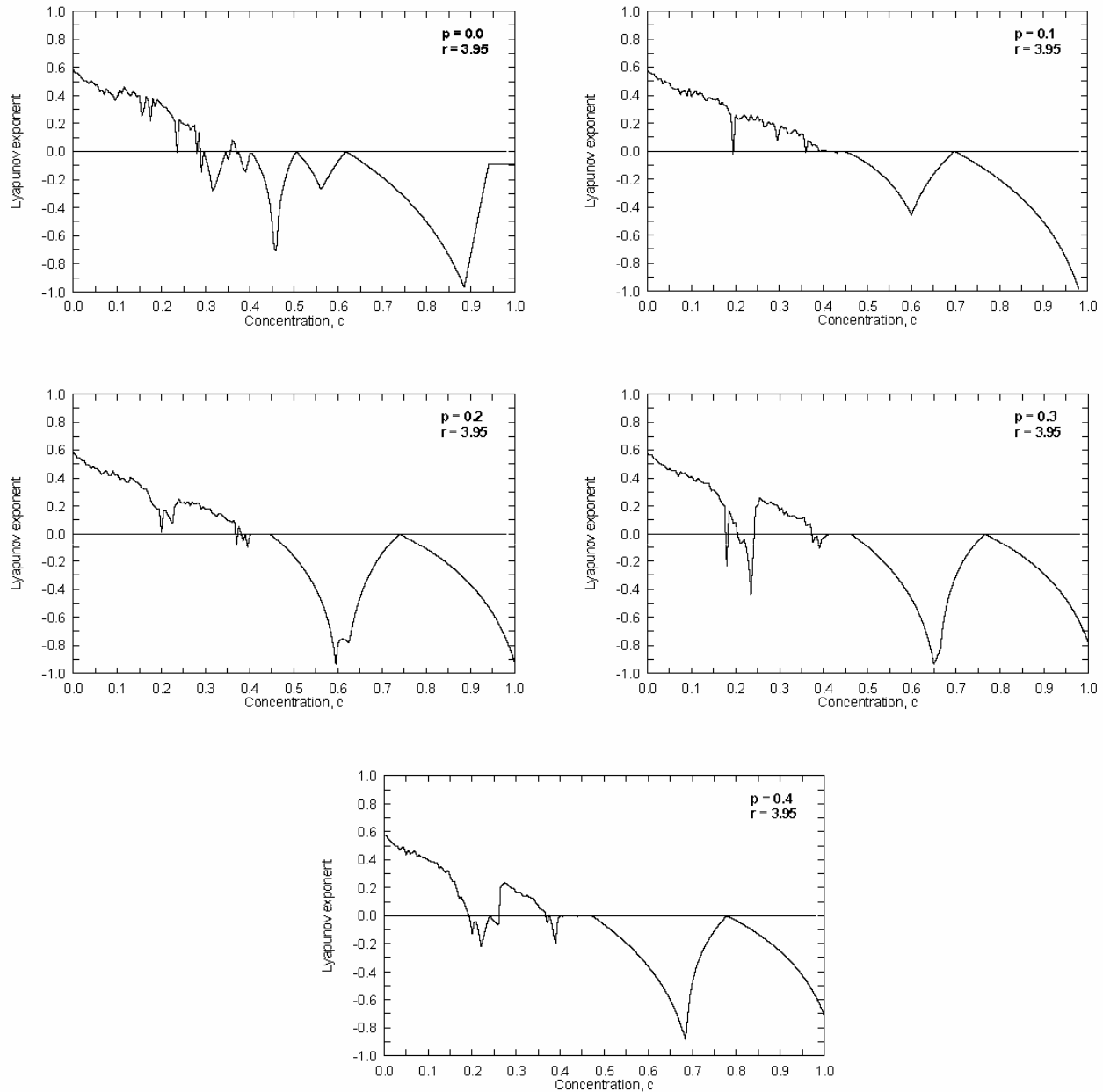
We considered a two-cell system, where each of them is able to release and uptake the same substance. According to the assumption in the model design, the dynamical behavior of the substance concentrations  $x_n$  and  $y_n$  depends on three factors: (i) its own concentration  $c$  within the radius of interaction in the surrounding environment, (ii) parameter  $r$ , and (iii) affinity  $p$  for the binding on cellular receptors. The first factor is determined by the underlying feedback mechanism of intracellular regulations, while the second one represents the level of suitability of the environment to the communication between two cells (Mihailović et al., 2010). The third factor depends on protein disorder (Dunker et al., 2002). The variation of Lyapunov exponent  $\lambda$  as a function of concentration  $c$  is depicted in Fig. 2 for  $p = 0.5$  and  $r = 3.95$ .



**Fig. 2.** Lyapunov exponent of the coupled maps, given as a function of the coupling parameter  $C$  ranging from 0.0 to 1.0, for a value of the affinity  $p = 0.5$ . Each point in the above graphs was obtained by iterating many times (2000 iterations) from the initial condition to eliminate transient behavior and then averaging over another 500 iterations. Initial condition:  $x = 0.3, y = 0.5$ , with 200  $C$  values.

It is seen that when values of  $c$  exceed values of 0.4 then complete synchronization (Lyapunov exponent is less than zero) in the intercellular exchange of substances is achieved. In contrast to this, for values of  $c$  smaller than 0.4 there exists a region of non-synchronized states in exchange with some windows where the exchange of substances between two cells is synchronized.

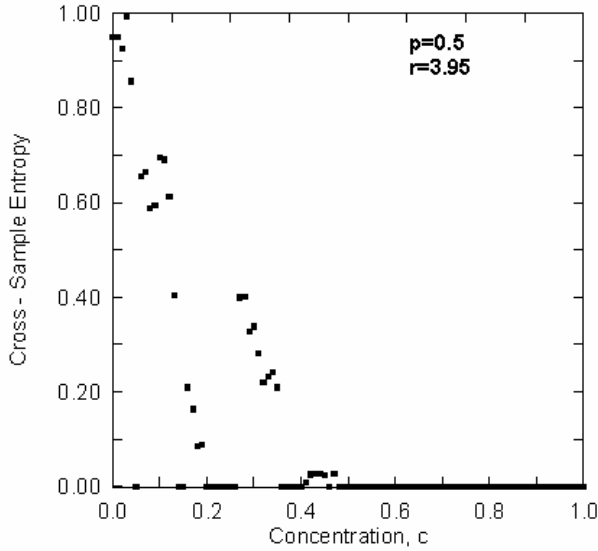
Here we further consider the behavior of coupling, and estimate how a coupled map system can achieve synchronization in the intercellular exchange of substances depending on parameter  $c$  (concentration), for a fixed value of  $r$  (in our case 3.95) and different values of affinity  $p$ . To that purpose we calculated the Lyapunov exponent of the coupled maps, given as a function of the coupling parameter  $c$  ranging from 0 to 1.0, for different values of the affinity  $p$  as depicted in Fig. 3 where Lyapunov exponents are calculated for  $p = 0.4, 0.3, 0.2, 0.1$  and 0.0. If we look at all panels it is seen that there is a border in the values of concentration  $c$  (around 0.4), that splits the domain of concentration into two regions. The first one that is located between 0 and 0.4, with the non-synchronized states including sporadic windows where synchroni-



**Fig. 3.** Lyapunov exponent of the coupled maps, given as a function of the coupling parameter  $c$  ranging from 0.0 to 1.0, for different values of the affinity  $p$ . The same graphs will be able to be obtained for values  $p = 0.6, 0.7, 0.8, 0.9$  and  $1.0$  corresponding to those for  $p = 0.4, 0.3, 0.2, 0.1$  and  $0.0$ . Each point in the above graphs was obtained by iterating many times (2000) from the initial condition to eliminate transient behavior and then averaging over another 500 iterations. Initial condition:  $x = 0.3, y = 0.5$ , with  $200c$  values.

zation is reached. In contrast to this, the second region (between 0.4 and 1.0) is a region where the process of exchange between two cells is fully synchronized. Because of the symmetry of

the coupled system (6), the same results will be obtained for values  $p = 0.6, 0.7, 0.8, 0.9$  and  $1.0$  corresponding to those for  $p = 0.4, 0.3, 0.2, 0.1$  and  $0.0$ .



**Fig. 4.** Cross sample entropy of the coupled maps, given as a function of the coupling parameter  $c$  ranging from 0.0 to 1.0, for value of the affinity  $p = 0.5$ . The  $x_n$  and  $y_n$  time series in the above graphs was obtained by iterating many times (2000 iterations) from the initial condition to eliminate transient behavior and then averaging over another 2000 iterations. Initial condition:  $x = 0.3$ ,  $y = 0.5$ , with  $200c$  values.

#### Entropy of the system of coupled maps (6)

The estimation of the complexity of system of coupled maps (6) through analysis of the concentration in cells  $(x_n, y_n)$  depending on intra- and inter-cellular parameters, is of great interest for the modeling procedure. In this paper, we use the sample entropy (SampEn) as a measure of the complexity of the system considered. Sample entropy, a measure quantifying regularity and complexity, is believed to be an effective analyzing method of diverse settings that include both deterministic chaotic and stochastic processes, particularly operative in the analysis of physiological, sound, climate and environmental interfaces or cell signals that involve a relatively small amount of data (Pincus, 1991; Richman & Moorman, 2000). Practically, we consider cross sample entropy (*Cross-SampEn*) - the measure of asynchrony recently introduced a technique for comparing two

different time series to assess their degree of asynchrony or dissimilarity (Kennel et al., 1992; Richman & Moorman, 2000; Lake et al., 2002). Let  $u = [u(1), u(2), \dots, u(N)]$  and  $v = [v(1), v(2), \dots, v(N)]$  fix the input parameters  $m$  and  $\rho$ . The vector sequences are:  $x(i) = [u(i), u(i+1), \dots, u(i+m-1)]$  and  $y(j) = [v(j), v(j+1), \dots, v(j+m-1)]$ , while  $N$  is the number of data points of the time series,  $i, j = N - m + 1$ . For each  $i \leq N - m$  set  $B_i^m(\rho)(v \| u) = (\text{number of } j \leq N - m \text{ so that } d[x_m(i), y_m(j)] \leq \rho) / (N - m)$ , where  $j$  ranges from 1 to  $N - m$ .

And then

$$B^m(\rho)(v \| u) = \sum_{i=1}^{N-m} B_i^m(\rho)(v \| u) / N - m \quad (9)$$

which is the average value of  $B_i^m(v \| u)$ . Similarly we define  $A^m$  and  $A_i^m$  as  $A_i^m(\rho)(v \| u) = (\text{number of } j \leq N - m \text{ such that } d[x_m(i), y_m(j)] \leq \rho) / (N - m)$ .

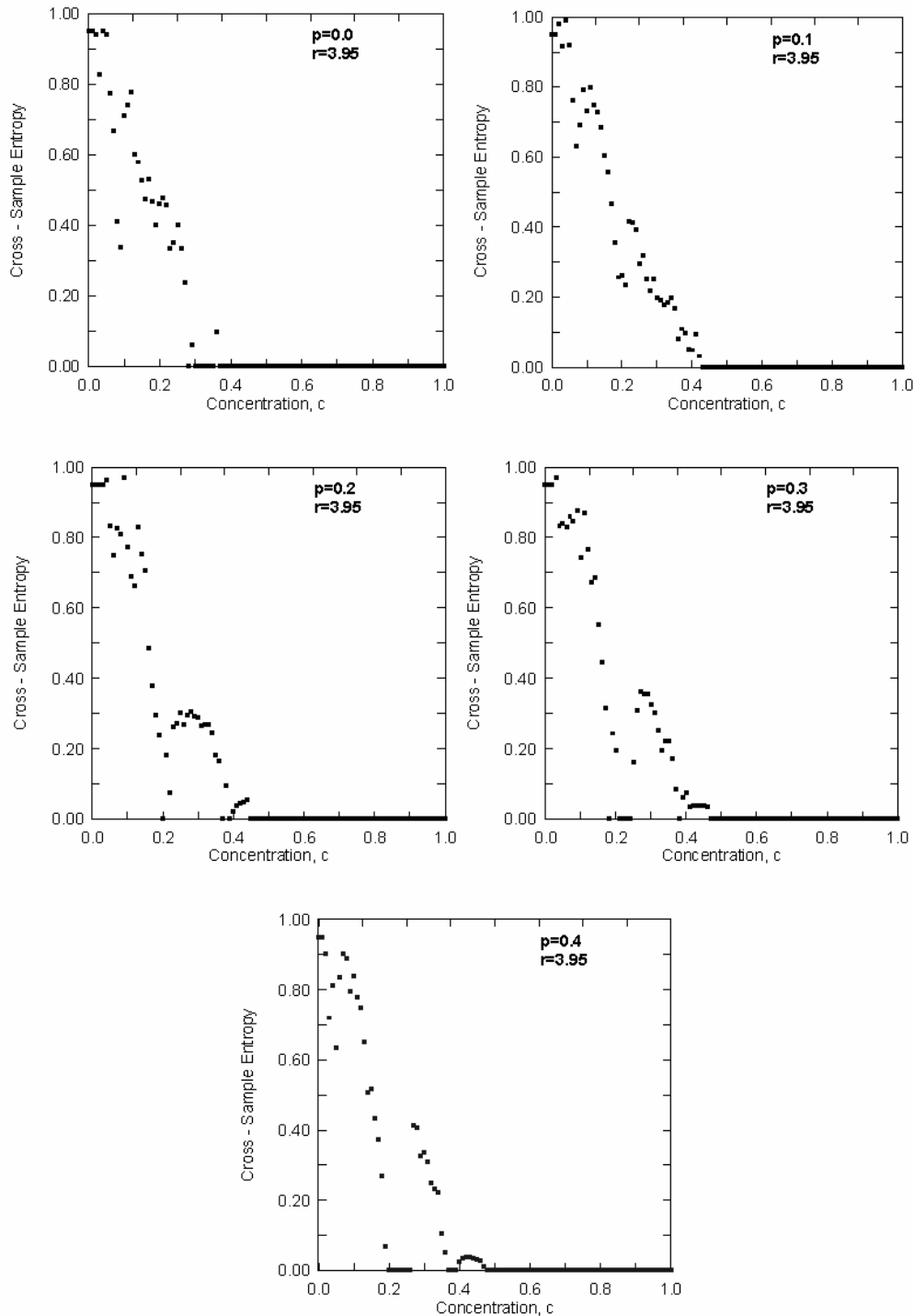
$$A^m(\rho)(v \| u) = \sum_{i=1}^{N-m} A_i^m(\rho)(v \| u) / N - m \quad (10)$$

which is the average value of  $A_i^m(v \| u)$ . And then

$$\text{Cross-SampEn}(m, \rho, n) = -\ln \{ A^m(\rho)(v \| u) / B^m(\rho)(v \| u) \} \quad (11)$$

We applied *Cross-SampEn* with  $m = 5$  and  $\rho = 0.05$  for  $x_n$  and  $y_n$  time series.

Fig. 4 depicts the cross sample entropy of the coupled maps, given as a function of the coupling parameter  $c$  ranging from 0.0 to 1.0, for a value of the affinity  $p = 0.5$  and  $r = 3.95$ . A high disorder in the system up to the concentration  $c = 0.4$  is seen. After that value there is a complete synchronization in the substance exchange. We obtain similar behavior for different values of affinity  $p$  (Fig. 5). These data are in agreement with the analysis of the Lyapunov exponent performed above, which indicate the compatibility of used measures.



**Fig. 5.** Cross sample entropy of the coupled maps, given as a function of the coupling parameter  $c$  (concentration) ranging from 0.0 to 1.0, for different values of the affinity  $p$ . The same graphs will be able to be obtained for values  $p = 0.6, 0.7, 0.8, 0.9$  and  $1.0$  corresponding to those for  $p = 0.4, 0.3, 0.2, 0.1$  and  $0.0$ . The  $x_n$  and  $y_n$  time series in the above graphs were obtained by iterating many times (2000 iterations) from the initial condition to eliminate transient behavior and then averaging over another 2000 iterations. Initial condition:  $x = 0.3$ ,  $y = 0.5$ , with  $200c$  values.



## CONCLUSIONS

In this paper, our focus is on modeling the synchronization in the intercellular exchange of substances. We have given a short overview of the general mechanism for substance exchange between two cells, representing a cooperative communication process. We identified the main parameters of the process and derived a system of two coupled logistic equations as an appropriate model of the given process. Then we investigated the synchronization of the model and its sensitivity to fluctuations of environmental parameters using methods of nonlinear dynamics, i.e. the largest Lyapunov exponent and cross sample entropy as measures. Results show that both measures are compatible and can be used interchangeably. Both of them show the existence of stability regions where noise in the form of fluctuations in the concentration of signaling molecules in the intercellular environment and fluctuations in affinity for uptake of these molecules cannot interfere with the process of exchange. Since our model is inspired by the general scheme of intercellular communication, it naturally does not allow detailed modeling of some concrete, empirically verifiable intercellular communication processes. Instead, it is designed to serve as a starting tool in the general investigation of the robustness in mutually stimulative populations which can be readily extended to the investigation of synchronization in larger networks of interacting entities (Amritkar & Jalan, 2003; Jalan et al., 2005).

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