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# Synchronization dynamics of chemically coupled cells with activator–inhibitor pathways

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ABSTRACT

Systems of interacting cells containing an activator–inhibitor pathway, regulating naturally in their inner parts their end-product concentrations through a sequence of biochemical reactions with feedback-loops: an end-product inhibition of the first substrate, and an autocatalytic activation of the end-product through an allosteric enzyme-mediated reaction are investigated. The individual cells are considered to be identical and are described by nonlinear differential equations recently proposed following the concerted transition model. The chemical and electrical coupling types, realized by exchange of metabolites across concentration of the cells are used in order to analyze the onset of phase and complete synchronization in the biochemical system. It is found that depending on the coupling nature and the range of coupling strength, cells enter into different synchronization regimes going from low-quality to high-quality synchronization. The synchronization manifold's stability is analyzed. The results are supported by numerical simulations using indicators such as the conditional Lyapunov exponents and the rate of change of the Lyapunov function. The results indicate that the system cannot completely synchronize under the single action of the chemical coupling. The combined effect of both chemical and electrical couplings is found to be of capital importance in the onset of complete synchronization and high quality synchronization.



## 1. Introduction

In a pioneering work on oscillating biochemical reactions Higgins [1–4] addressed the problem in which way a coupling between individual cells affects the resulting dynamics, for example, by synchronizing their oscillations. Synchronization, i.e., the ability of coupled oscillators to lock to a common frequency, is a general and ubiquitous feature of nature, since it occurs for mechanical or electrical oscillators, lasers, chemical reactions and biological clocks, to mention just some well-known examples [5–19]. In the last named fields of studies, it was observed that many living organisms naturally come together, organize themselves into coupled systems, in order to perform certain functions, with the aim of maintaining the equilibrium in their living environment and perpetuate life. This is also actually the case for the basic building blocks of any living organism: the cells [2,3,20,21].

Roughly speaking, a cell is a 'dynamical black box' that admits various types of input and that has an output which is uniquely determined by the inputs and the initial state. One fundamental property of coupled cells is that the coupling structure forces the existence of subspaces that are flow-invariant under the associated coupled cells systems: the synchrony subspaces. These should have an important role in the kinds of dynamics that can occur, and a significant step in understanding the dynamics forced by the coupling of these patterns of synchrony. The chemical coupling between cells is well known to be changing the cells synchrony subspace [22–26], however the analysis of coupled cells with activator inhibitor pathway under such circumstances has not yet been carried out. Understanding both the processes that influence the synchronization of individual biochemical oscillators and how the behaviors of living cells arise out of the properties of coupled populations of cells oscillators is an important goal in the study of biological systems, and a field of research with enormous practical applications [27].

The phenomenon of synchronization in electrically coupled cells with activator–inhibitor pathways has been extensively studied in [28,29]. However, these works on coupled cells with

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activator–inhibitor pathways have been only carried out with the so-called electrical coupling. This scenario termed as short range interaction suggests that cells be linked through electrical coupling or signal only. However, in nature, the interactions among cells sharing the same living environment are more complex and involve much more than just short range and linear interactions. They are in general nonlinear, deterministic or stochastic and involve long range interactions with one or many other cells. The chemical and electrical coupling schemes have proven their physical importance [22–25]. In the first case (electrical) the coupling is linear and made through gap junction and directly depends on the difference in the normalized concentrations of the substances in the pathway of each cell. While in the second case (chemical), the coupling is often modeled by a threshold nonlinear input or output function. In this last case, coupled cells with activator–inhibitor pathways may exhibit a variety of synchronization behavior including phase, partial and complete synchronization. Motivated by this, in the present study, we go further with the work of [28,29] by analyzing the effect of the chemical coupling on the dynamics and synchronization of coupled cells with activator–inhibitor pathways, and also analyze the combined effect of electrical and chemical coupling on the high quality synchronization process of the coupled cells. To the best of our knowledge, this problem has never been investigated. We recall that, the method used here is more appealing and provides optimal parameter for implementation and is based on the rate of change of the Lyapunov function of the coupled system.

The rest of the paper is organized as follows: in Section 2, we present the model and explore the dynamics of the single cell with activator–inhibitor pathways. We expect the cell to exhibits new dynamical behaviors ranging from limit cycle to complex and chaotic oscillations when some cell's physiological parameters change. Section 3 is devoted to the chemically coupled cells and their stability analysis. We explore different scenarios for the appearance of the synchronization in the coupled system. Numerical simulations demonstrate the capacity of such coupled cells to achieve synchronization among themselves. In Section 4 we analyze the complementary roles played by the electrical and chemical couplings in the synchronization process of the coupled cells. We show that the conjugate action of both couplings favors the onset of synchronization in the system. Later on, we present in Section 5 the analysis of the stability of the ideal complete synchronous solution by using the rate of change of the Lyapunov function of the variational system, this in order to detect coupling range for high quality synchronization in the biochemical coupled cells. We end our work with a conclusion in Section 6

## 2. Single cell and its dynamics

Since the 1980s, modeling has emerged as a novel tool to handle the rapidly growing information on the molecular parts list and the overwhelmingly complex interaction circuitry of signalling networks. Following this development, Sinha et al. [32–34] proposed in 1987 a mathematical model of a biochemical system describing the dynamics of normalized concentration of the substrates in a single cell with activator–inhibitor pathways. Since then, many studies have been carried out on this model ranging from classical nonlinear dynamical analysis to synchronization of electrically coupled network formed by units of single cell described by this model [28,29,36,35]. This cell, namely "the cell with activator–inhibitor pathway", has a biochemical pathway regulated by negative and positive feedback processes. Its model describes actually a three-step sequential reaction having two substrates, and one end product. Their concentrations are regulated by a positive and a negative feedback process respectively in terms of end product inhibition of the first substrate (i.e. when the concentration of the end product is large in the cell, the negative feedback induces an attenuation in the concentration of the substrate in the intracellular medium (see Refs. [32–34] for more details)). The model is represented by the following set of ordinary differential equations:

$$\begin{aligned}\frac{dx}{dt} &= F(z) - kx\\ \frac{dy}{dt} &= x - G(y,z)\\ \frac{dz}{dt} &= G(y,z) - qz.\end{aligned} \tag{1}$$

The present model describes a three-step sequential reaction having successively two substrates and one end product whose normalized concentrations in the intracellular medium are respectively represented by $x$, $y$ and $z$. Therefore, $x$ is the normalized concentration of the first substrate, $y$ is that of the second substrate, and $z$ is the normalized concentration of the end product. The end product is the signal molecule intended to be diffused into the extracellular medium to other cells via the cells's plasma membrane. As reported previously, these concentrations are regulated by a negative feedback process in terms of the end product inhibition of the first substrate, as well as via an autocatalytic activation of the allosteric enzyme by the end product. The functions $F(z)$ and $G(y,z)$ representing the negative and positive feedback processes, are nonlinear processes designed following the concerted transition model described in [3,4,39] and are given by

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

The parameter "$k$", called the rate of degradation of the first substrate represents the speed at which the first product's normalized concentration decreases in time. The parameters $T$ and $L$ are respectively, the maximum velocity of the enzyme which determines the maximum rate at which the biochemical reaction transforming the second substrate into end product is performed; and the allosteric constant of the enzyme determining how the alterability in the protein's (i.e. enzyme) activity takes place after reception at its binding site of the signal from the cell through positive feedback, as one form of autocrine signaling. It is noteworthy that autocrine signaling takes place when a cell sends some signals back to itself in order to regulate internal cellular mechanisms vital for a good human body functional balance. $q$ is the rate of degradation of the end product. It determines the speed at which $z$ decreases over time, especially when $z$ is sufficiently large in the intracellular medium of biological cells. Thus, the accumulations in first substrate and end product depends critically on the parameters $k$ and $q$.

### 2.1. Fixed points and their stability

In order to analyze the linear stability of the system, we start by finding the fixed points of the system (1). The fixed points are obtained by setting $\frac{dx}{dt} = \frac{dy}{dt} = \frac{dz}{dt} = 0$. These conditions can be rewritten as

$$\begin{cases} z^5 + z - \dfrac{1}{kq} = 0\\ x = qz\\ x\left[L + (1+y)^2(1+z)^2\right] - Ty(1+y)(1+z)^2 = 0 \end{cases} \tag{2}$$

From the following, the fixed points are obtained whenever the three equations in (2) are satisfied. However it is not possible to obtain analytical solution for this system. We thus proceed by solving numerically the first equation of the system using the Newton–Raphson algorithm. Substituting this solution into the two other