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# Synchronization of biological clock cells with a coupling mediated by the local concentration of a diffusing substance

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ABSTRACT

The circadian rhythm in mammals is determined by the output of biological clock cells, e.g. in the brain suprachiasmatic nucleus. Each biological clock cell has its own period and can respond to photic stimulation, such that the output rhythm is given both by the coupling among cells and the external forcing. We propose a model for the coupling among biological clock cells of the suprachiasmatic nucleus where the coupling is mediated by the local concentration of a diffusing neurotransmitter which is both secreted and absorbed by the cells, influencing their individual rhythms. Such a coupling is non-local because it considers all the cells in the assembly, and the interaction strength decays exponentially with the spatial distance. We investigate the synchronization properties of this network with respect to the coupling strength and the inverse characteristic length of the coupling, which varies from zero (a global, all-to-all, coupling) to infinity (a local, nearest-neighbor, coupling). Quantitative diagnostics of phase and frequency synchronization are applied to describe the transition from a non-synchronized to a partially synchronized behavior as the coupling parameters are changed.



## 1. Introduction

The circadian rhythm is a daily periodicity (roughly a 24 h cycle) of physiological, biochemical, and behavioral processes in living beings [1]. It is produced in mammals chiefly by specialized cells (circadian clocks) belonging to the suprachiasmatic nucleus (SCN) of the anterior hypothalamus [2]. The SCN consists of multiple, single-cell circadian clocks which, when synchronized, produce a coherent circadian output that regulate overt rhythms [3–5]. The circadian master clock of the SCN is entrained by the daily light-dark cycle, which acts via retina-to-SCN neural pathways [6]. Hence, for the obtention of a coordinate circadian rhythm, the master clock cell must be coupled to the other cells in the SCN so as to synchronize them to its own rhythm as well as to the photic stimulation.

The mechanism governing the coupling of circadian clock cells in SCN is still an open issue. Many authors recently pointed out that the coupling among cells is of a chemical nature, being implemented through the action of $\gamma$-aminobutyric acid (GABA) or other neurotransmitters like vasoactive intestinal peptide (VIP) [6–18]. This is not an unanimous opinion, though, since other authors claim that the coupling is of an electric nature [19,20].

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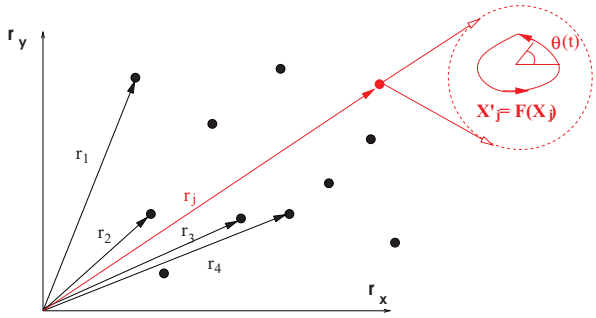


**Fig. 1.** Schematic figure of the Kuramoto's model of chemical coupling among oscillators.

The circadian clocks themselves may be regarded, in a nonlinear dynamics perspective, as limit-cycle oscillators, i.e. they are capable of self-sustained oscillations with a well-defined intrinsic period. Moreover, there is a negative feedback mechanism which gives stability and robustness with respect to environmental fluctuations. Kronauer [21] has proposed such a model, which is an adaptation of the famous Van der Pol equation, but with parameters that can be compared with laboratory data [22].

The chemical coupling between oscillators like circadian clocks will be described by means of a chemical (like GABA, for example) which is both secreted and absorbed by clock cells immersed in the intercellular medium. The coupling, in this case, is non-local in the sense that it takes into account cells which are not necessarily close to each other. An extreme situation belonging to this general category is the so-called global coupling, for which each cell interacts with the average concentration of the chemical due to all the other cells [7,23,24].

A disadvantage of this type of coupling is that the chemical is expected to diffuse through the intercellular medium in a rather complicated way, even in the limit of large times. An alternative model was proposed by Kuramoto [25], in which the equations governing the time evolution of the oscillators can be coupled by using the concentration of a substance which diffuses through the medium in which the oscillators are embedded. If the chemical diffuses in a timescale much faster than the oscillator period, the coupling - although involves virtually all oscillators like in the global case - depends on the distance between oscillators in an exponentially decaying way (in the one-dimensional case) [26,27]. This approach has been used in studies of cell interaction [28] and neural oscillators [29].

Another example of chemical coupling of biological interest involves the cellular slime mould *Dictyosteliida*. During most of their lives, these slime moulds are individual unicellular protists living in similar habitats and feeding on microorganisms. In the absence of food, however, they release signal molecules (DIF-1, short for Differentiation Inducing Factor) into their environment, so that they can find other amoeba and create swarms. In other words, when a chemical signal is secreted, they assemble into a cluster which acts as a single organism [30].

In this paper we intend to apply Kuramoto's theory of chemical coupling for studying the synchronization of circadian rhythms of clock cells whose behavior is described by Kronauer's model. The resulting model is expected to give better results than previous numerical simulations using Kronauer's oscillators with a local coupling which consider a limited number of neighborhoods of each cell [11]. In particular, we will analyze the phase and frequency synchronization of the resulting lattice system, with emphasis on the coupling parameters leading to such desired synchronized states.

This paper is organized as follows: in Section 2 we outline a mathematical model for the coupling of oscillators mediated by a diffusing chemical substance and its application to one-dimensional lattices. Section 3 presents a model proposed by Kronauer and coworkers for the oscillations of biological clocks of the SCN and the external forcing. Section 4 considers a model of coupled biological clocks of this kind with a coupling mediated by a diffusing chemical substance. In Section 5 we consider some dynamical features of the coupled oscillator model, with emphasis on the synchronization of the biological clocks. Our results concerning the synchronization with coupling and external forcing via photic stimulation, using various protocols, are reported in Section 6. The last Section is devoted to our conclusions.

## 2. Oscillator coupling mediated by a diffusing chemical substance

It is thought that the modeling of the interaction among biological clocks in the SCN would involve the presence of a diffusing chemical substance. A model for describing the coupling among oscillators mediated by a diffusing chemical substance was proposed by Kuramoto [25] leading to non-local couplings. In the following we outline the hypotheses leading to this model and its formulation, with emphasis on one-dimensional lattices, to be used in later Sections.

### 2.1. The Kuramoto model for chemical coupling

In the following we suppose that each biological clock, or oscillator cell, is located at discrete positions $\mathbf{r}_j$, where $j = 1, 2, \ldots N$, and $\mathbf{X}_j = (x_j, y_j)^T$ is the state variable for each oscillator, whose time evolution is governed by the (same) vector field $\mathbf{F}(\mathbf{X}_j)$ [Fig. 1]. We have chosen two state variables only because it is the case of oscillating biological clocks described by Kronauer's