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A theory of synchrony by coupling through a diffusive chemical signal

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HIGHLIGHTS

- A PDE–ODE model that couples two active compartments is formulated and analyzed.
- Phase diagrams where anti-phase and in-phase oscillations occur are found.
- Analysis predicts a wild parameter range where stable in-phase oscillations occur.
- Our theory of bulk-mediated oscillations is extended to a periodic chain of units.

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ABSTRACT

We formulate and analyze oscillatory dynamics associated with a model of dynamically active, but spatially segregated, compartments that are coupled through a chemical signal that diffuses in the bulk medium between the compartments. The coupling between each compartment and the bulk is due to both feedback terms to the compartmental dynamics and flux boundary conditions at the interface between the compartment and the bulk. Our coupled model consists of dynamically active compartments located at the two ends of a 1-D bulk region of spatial extent $2L$. The dynamics in the two compartments is modeled by Sel'kov kinetics, and the signaling molecule between the two-compartments is assumed to undergo both diffusion, with diffusivity D, and first-order, linear, bulk degradation. For the resulting PDE–ODE system, we construct a symmetric steady-state solution and analyze the stability of this solution to either in-phase synchronous or anti-phase synchronous perturbations about the midline $x = L$. The conditions for the onset of oscillatory dynamics, as obtained from a linearization of the steady-state solution, are studied using a winding number approach. Global branches of either in-phase or anti-phase periodic solutions, and their associated stability properties, are determined numerically. For the case of a linear coupling between the compartments and the bulk, with coupling strength β, a phase diagram, in the parameter space D versus β is constructed that shows the existence of a rather wide parameter regime where stable in-phase synchronized oscillations can occur between the two compartments. By using a Floquet-based approach, this analysis with linear coupling is then extended to determine Hopf bifurcation thresholds for a periodic chain of evenly-spaced dynamically active units. Finally, we consider one particular case of a nonlinear coupling between two active compartments and the bulk. It is shown that stable in-phase and anti-phase synchronous oscillations also occur in certain parameter regimes, but as isolated solution branches that are disconnected from the steady-state solution branch.

1. Introduction

Individuals in a large network communicate with each other to engage and coordinate their activities. This happens at almost all levels of the living world ranging from a colony of unicellular amoebae to highly sophisticated social networks of people. In many cases, this communication is carried out through diffusive chemicals. Examples of such kind of systems range from the signaling of the amoebae *Dictyostelium discoideum* through the release of cAMP into the medium [1] where it diffuses and acts on each individual, to some endocrine neurons that secrete a hormone to the extracellular medium where it influences the secretion of this

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hormone from a pool of such neurons [2,3], and to girls sharing a dormitory room leading to the synchronization of their menstrual cycles [4] presumably through the secretion of a pheromone [5,6] in the shared space. Further examples where this kind of signaling occurs are related to quorum sensing behavior (cf. [7–9]). In many of these systems, the individual cells or localized units, can, under appropriate conditions, exhibit sustained temporal oscillations. In this way, signaling through a diffusive chemical often can switch on and/or off the oscillations and to synchronize the oscillations among all the individuals. The present paper is a theoretical investigation of the mechanism through which this kind of synchronization occurs.

Biological rhythms are ubiquitous in living organisms, especially in mammals including human being. Some of the best known examples are the circadian periodicity observed in the blood level of most hormones in mammals. Many hormones also exhibit rhythmicity with a period much shorter than the circadian rhythm. These rhythms are referred to as the ultradian rhythms. The rhythmicity in these hormones often plays a fundamental role in their physiological function. One of the best understood examples, and the one that we are motivated by, is the pulsatile variation in the concentration of gonadotropin-releasing hormone (GnRH) in the portal blood that circulates from the hypothalamus to the pituitary gland. This periodic signal of about one pulse per hour has been shown to be crucial in maintaining the normal reproductive activities in mammals [10]. It is now believed that 800–2000 GnRH neurons are scattered in a few areas of the hypothalamus. In order to generate a coherent pulsatile GnRH signal, such as is observed in the portal blood, synchronization of the secretory activities of the neurons is essential. In [11] a synchronization mechanism was proposed, whereby neurons are coupled through GnRH secreted into the extracellular space. Results from this model were shown to be consistent with *in vivo* experiments. The key limitation of this model of [11], however, was that it was assumed that extracellular space was continuously stirred so as to average out any spatial effects resulting from any chemical secretions. A more realistic model, would be to couple the diffusion of GnRH in the extracellular space to the localized secretory activity of individual neurons.

These past studies are the motivation for formulating and investigating a relatively new modeling paradigm by which spatially segregated dynamically active units, such as cells or localized signaling compartments, communicate with each other through a signaling molecule that diffuses in the bulk medium between the active units. In our model that couples dynamically active compartments through a diffusive chemical signal, we will focus on the case where each compartment is a *conditional oscillator*. This term is adopted here to refer to a dynamical system that stays at a stable steady state when isolated from others, but is capable of generating sustained oscillations with some different choice of parameter values. Dynamics of the signal in extracellular space, referred to as the bulk region, is described by a simple diffusion equation, with diffusivity D, that undergoes first-order linear bulk degradation. Each compartment is capable of sensing the strength of the signal, through either a linear or nonlinear coupling with the bulk, and responding to it by adjusting the rate of release of the signaling molecules into the bulk. The release of the signal by each compartment into the bulk region is modeled as a flux boundary condition at the interface between the compartment and the bulk.

In Section 2 we formulate such a 1-D model on $0 < x < 2L$, which consists of a PDE–ODE system that couples diffusion in the bulk $0 < x < 2L$, with constant diffusivity D, to compartmental dynamics with Sel'kov kinetics on the boundaries $x = 0$ and $x = 2L$. The particular choice of Sel'kov kinetics, as originally used in [12] for modeling glycolysis oscillations, leads to a unique steady-state solution of the coupled system. The qualitative behavior of bulk-mediated oscillatory dynamics, as predicted from the spectral properties of the linearization, will be very similar for other choices of the compartmental kinetics where a unique steady-state occurs (see Section 6 for a further discussion of this issue). For a related PDE–ODE membrane–bulk system the numerical study of [13] has revealed the possibility of stable synchronous dynamics under Fitzhugh–Nagumo reaction-kinetics in the compartments. However, in [13], the coupling of the membrane to the bulk is different than for our Sel'kov model formulated in (2.1) in that in [13] it was assumed that both the compartment and bulk concentrations are identical at the two membranes.

For our compartment–bulk model with Sel'kov kinetics, in Section 3 we consider the case where there is a linear coupling between the two compartments at $x = 0$ and $x = 2L$ and the bulk, where β represents the strength of this coupling. For this linearly coupled model, we construct a steady-state solution that is symmetric about the midline $x = L$. In Section 3.1 we then derive a transcendental equation for the eigenvalue parameter λ associated with the linearization of the coupled compartment–bulk model around the symmetric steady-state solution. In our stability theory, we must allow for perturbations that are either symmetric or anti-symmetric about the midline, which leads to the possibility of either in-phase synchronous or anti-phase synchronous instabilities in the two compartments. To determine unstable eigenvalues of the linearization, in Appendix B we use the winding number of complex analysis to determine the number of roots in $\mathrm{Re}(\lambda) > 0$ to the transcendental equation for the eigenvalue. This linear stability analysis is supplemented by the numerical computation of global branches of periodic solutions, either in-phase or anti-phase, that bifurcate from the symmetric steady-state solution branch. These global solution branches, together with their stability properties, are determined using the numerical bifurcation software package XPPAUT [14] after first spatially discretizing the PDE–ODE system into a relatively large system of ODEs. In this way, a phase-diagram in the D versus β parameter space, characterizing the region where stable in-phase and anti-phase oscillations between the two compartments can occur is obtained. Our results show that there is a rather large parameter range where either stable in-phase or anti-phase oscillations occur. Full numerical computations from a method-of-line approach of the PDE–ODE system of coupled compartmental-bulk dynamics are used to validate the theory.

In Section 4 we illustrate oscillatory compartmental dynamics for a specific type of nonlinear coupling between the bulk and the two compartments, for which the steady-state solution is the same as that for the uncoupled compartmental dynamics. For this model, no Hopf bifurcations can occur along the steady-state solution branch. Nevertheless, we show using the numerical bifurcation software XPPAUT [14] that this model can still generate compartment–bulk oscillations. More specifically, our numerical computations show, in contrast to the case of a linear coupling between the compartments and the bulk considered in Section 3, that the branches of in-phase and anti-phase periodic solutions are disconnected and do not bifurcate off the symmetric steady-state solution branch. Our global bifurcation diagram reveals that there is a parameter range of bistability where either stable in-phase oscillations or stable anti-phase oscillations can co-exist with the stable symmetric steady-state solution branch. Although the coupled system in Section 4 is only a mathematical model, and is not motivated by a specific biological context, the analysis does indicate that the coupling of active compartments by bulk diffusion can lead to disconnected global branches of periodic solutions having a saddle–node structure. This indicates that hysteretic behavior in the compartment–bulk oscillations can be possible as parameters are varied. In Section 4.1 we study an extended ODE compartmental dynamics model, closely related to the nonlinear coupled compartment–bulk model, but where bulk diffusion is neglected.