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Mixed-mode synchronization between two inhibitory neurons with post-inhibitory rebound

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ABSTRACT

We study an array of activity rhythms generated by a half-center oscillator (HCO), represented by a pair of reciprocally coupled neurons with post-inhibitory rebounds (PIR). Such coupling-induced bursting possesses two time scales, one for fast spiking and another for slow quiescent periods, is shown to exhibit an array of synchronization properties. We discuss several HCO configurations constituted by two endogenous bursters, by tonic-spiking and quiescent neurons, as well as mixed-mode configurations composed of neurons of different type. We demonstrate that burst synchronization can be accompanied by complex, often chaotic, interactions of fast spikes within synchronized bursts.

1. Introduction

Synchronization of coupled oscillators is a fundamental phenomenon in nonlinear systems that has been observed in a wide range of diverse applications [1]. The mathematical concept of synchronization [2], first introduced and developed for periodic oscillators has been further generalized for other aperiodic systems, including ones with chaotic dynamics. In life sciences, of a keen interest is synchronization or phase locking among oscillators with multiple time scales. They may include mixed-mode and slow–fast relaxation-type oscillators [3], whose interaction can give rise to the onset of a variety of synchronization patterns [4–7]. In neuroscience, a plethora of rhythmic motor behaviors with diverse time scales, such as heartbeat, respiration, chewing, and locomotion on land and in water are produced and governed by neural networks called Central Pattern Generators (CPGs) [8,9]. The CPG is a microcircuit of neurons that is able to autonomously generate an array of polyrhythmic bursting patterns, underlying various motor behaviors.

Endogenous (self-sustained) bursting and network (coupling-induced) bursting are composite oscillatory behaviors, featuring active phases during which a neuron or a group of neurons generates trains of fast action potentials, which are alternated with long interburst intervals during which it remains inactive or quiescent, until a new cycle of bursting occurs. In this paper we examine synchronization of bursting patterns emerging through interactions of two interneurons coupled reciprocally by fast inhibitory synapses. This study has been driven by two major motivations: first, a general one concerning questions on

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synchronization of mixed-mode oscillators. The second is a neuroscience related one, aimed at a progress in understanding of intrinsic mechanisms of rhythmogenesis in CPGs, composed, often symmetrically, of such small networks of interneurons, as outlined below. It is still unclear how CPGs can achieve the level of synergy, flexibility, and robustness to produce a plethora of rhythmic patterns observed in nature.

Recent experimental and theoretical studies have disclosed a distinct role of CPGs in generation of adaptive and coordinated motor activity of animals [9–12]. An important feature of CPGs is their ability to produce various types of rhythmic bursting activity, what causes flexible and adaptive locomotion of an organism. To robustly govern motor patterns, CPGs are in a position to flexibly adjust their oscillatory properties (such as bursts duration, frequency of spiking, phase relations of bursts) due to a feedback from sensory inputs, for example, in response to changes of an environment [9,10]. Up to a certain extent, the flexibility of CPG behaviors may be attributed to its multistability (of several coexistent attractors representing different bursting rhythms in a phase space of the dynamical system) allowing for fast switching between operating modes [7,13].

From the theoretical point of view, a CPG is modeled as a small network of coupled oscillatory, or quiescent, interneurons, each described by a system of nonlinear ordinary differential or difference equations (dynamical system) [11,14,15]. The study of CPGs allows one to progress in a general understanding of synchronization patterns in mixed-mode oscillators, applicable to systems of various physical and biological origin.

There is a growing body of experimental evidence that a universal building block of most identified CPGs is a half-center oscillator (HCO) [16]. A HCO is a pair of reciprocally inhibitory interneurons bursting in alternation. Such a pair can be comprised of endogenously bursting interneurons, as well as of intrinsically tonic spiking or quiescent interneurons that start anti-phase bursting only when they are coupled. Theoretical studies [17–21] have indicated that the formation of an anti-phase bursting rhythm is always based on some slow-time-scale dynamics. In the biophysically plausible models, the slow dynamics is firmly associated with the slow membrane currents, such as persistent sodium or slow calcium-dependent current (e.g., potassium after-hyperpolarization current [25]); following [22] we term currents associated with slow-varying concentrations and gating variables as slow ones. There are three basic mechanisms to generate alternating bursting in the HCO: release, escape, and post-inhibitory rebound (PIR). The first mechanism is typical for endogenously bursting neurons [4,6,23]. The other two mechanisms underlie coupling-induced bursting in HCOs comprised of neurons, which are initially depolarized or hyperpolarized quiescent in isolation [9,18,20,24–26].

The PIR mechanism uses reciprocal inhibition to maintain coupling-induced bursting in otherwise hyperpolarized quiescent neurons. As such, either neuron of the HCO must receive a sufficiently strong pulse of some external negative current that initiates the chain reaction in the coupled neurons. PIR triggers an onset of a single or a series of action potentials in the post-synaptic neuron after it has been prolongedly hyperpolarized and abruptly released from inhibition generated by the pre-synaptic neuron during an active, tonic spiking phase of bursting. After that, the neurons of the HCO swap their opposite roles to repeat the PIR mechanism. PIR promotes the action potential generation after a period of sufficiently strong hyper-polarizing (inhibiting) input, as illustrated in Fig. 2. PIR is often caused by a low-threshold activated calcium current in neurons and their biophysically plausible models.

Formation of the antiphase dynamics in inhibitory coupled neurons forming homogeneous HCOs has been extensively studied in Refs. [17–19,21,27] where the primary scope is focused on the dynamics of *identical* neurons, which are either intrinsically excitable or tonically spiking neurons represented by phenomenologically reduced models. Much is yet unknown about the rhythmogenesis of an anti-phase coupling-induced bursting in heterogeneous HCOs described by biologically plausible models derived within the framework of the Hodgkin–Huxley approach. We focus our study on the properties of the emergent bursting in HCOs comprised of non-identical neurons, demonstrating qualitatively different activity types in isolation, i.e. initially chosen at the opposite sides of the transition thresholds between bursting, tonics-spiking, and quiescent behaviors.

An examination of an set of non-identical neurons gives rise to the following issues: (i) the first one concerns with the dynamical robustness and the structural stability (in the parameter space) of the ensemble dynamics against perturbations in the form of a heterogeneity in the ensemble; (ii) the second problem deals with the phase synchronization of a network of oscillatory units. In the case of strong heterogeneity, one should expect possible emergence of additional dynamical phenomena occurring in the system.

Therefore, in this paper, following and capitalizing on the previous studies of PIR mechanisms in homogeneous networks, we examine how PIR contributes to formation, synchronization and robustness of multiple bursting rhythms in heterogeneous HCOs with inhibitory coupled neurons. We focus our consideration upon the oscillatory dynamics occurring in a heterogeneous setup with slightly non-identical neurons, as well as in various mixed-mode HCOs where constituent neurons are chosen to operate in different dynamical regimes: bursting and tonic spiking, or hyperpolarized quiescence.

In this paper, we employ a modification of the Hodgkin–Huxley-type model introduced in [22] to plausibly describe the PIR mechanism. Depending on its parameters, the model is known to produce an array of generic neuronal activities such as excitable dynamics emerging from a hyperpolarized quiescent state, periodic spiking, and bursting.

First, we will examine the conditions that stably reproduce the PIR mechanism in the neurons. We will argue that the PIR is a pivotal component that promotes an alternating bursting rhythm in the HCO made of intrinsically spiking and excitable neurons. Finally, we will show that the PIR mechanism enhances anti-phase coupling-induced bursting that occurs in a pair of endogenously bursting neurons.

Below in this paper we present different dynamical behaviors in coupled neurons, choosing the following structuring: we first describe the dynamics of lumped neurons, and then separately present studies of pairs with different types of lumped dynamics. So, we arrange the results not according to the resulting behavior of the CPG, but according to the properties of uncoupled