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In-phase and anti-phase synchronization in noisy Hodgkin–Huxley neurons

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ABSTRACT

We numerically investigate the influence of intrinsic channel noise on the dynamical response of delay-coupling in neuronal systems. The stochastic dynamics of the spiking is modeled within a stochastic modification of the standard Hodgkin–Huxley model wherein the delay-coupling accounts for the finite propagation time of an action potential along the neuronal axon. We quantify this delay-coupling of the Pyragas-type in terms of the difference between corresponding presynaptic and postsynaptic membrane potentials. For an elementary neuronal network consisting of two coupled neurons we detect characteristic stochastic synchronization patterns which exhibit multiple phase-flip bifurcations: The phase-flip bifurcations occur in form of alternate transitions from an in-phase spiking activity towards an anti-phase spiking activity. Interestingly, these phase-flips remain robust for strong channel noise and in turn cause a striking stabilization of the spiking frequency.

1. Introduction

Time-delayed feedback presents a common mechanism which is found in many biological systems including neuronal systems. Signal transmission time delays in neuronal systems either result from (i) chemical processes in the neuronal synapses where neurotransmitters are released and diffusively overcome the synaptic cleft and/or (ii) from the finite propagation speed of electrical excitations along the neuronal axon. Time delays stemming from chemical synapses are of the order of a few milliseconds, while the axonal conduction delays in both, delay-coupled neurons and autaptic feedback loops, reach values up to tens of milliseconds [1–4].

As the time scale of the delayed coupling and of the neuronal dynamics become comparable, the delay-coupling gives raise to peculiar synchronization phenomena [5]. In particular, phase synchronization phenomena in neuronal systems are commonly thought to be the basis for many biological relevant processes occurring in the brain [6,7]. Synchrony of neurons from small brain regions up to large-scale networks of different cortices comes along with transmission time delays. Theoretical and computational studies on neuronal networks with delay-coupling recently highlighted the occurrence of so-called phase-flip bifurcations [8–10]. The ensemble activity of the coupled neurons change abruptly from in-phase to anti-phase oscillations or vice versa.

With this work we research this objective by considering the influence of internal noise. It is an established fact that noise leads to various prominent effects in neuronal dynamics [11]. Some typical examples that come to mind are stochastic resonance features [12–15], and noise-assisted synchronization [5,16–18]. Within our work the intrinsic noise is due to the stochastic gating of the ion channels, i.e. the so-called channel noise which is inherently coupled to the electrical properties of the axonal cell membrane [19–21]. Interestingly, it has been shown that intrinsic channel noise does not only lead to the generation of spontaneous action potentials [22], but as well affects the neuronal dynamics at different levels, namely: (i) it can boost the signal quality [14,15], (ii) enhance the signal transmission reliability [23], (iii) cause frequency- and phase-synchronization features [24–28] and (iv) may result in a frequency stabilization [29], to name but a few.

The present work is organized as follows: In Section 2 we introduce the biophysical model. We review the standard Hodgkin–Huxley model and its generalizations with respect to intrinsic channel noise and a delay-coupling. Numerical methods for simulation are introduced after that. In Section 3, the dynamics of a network of two delay-coupled Hodgkin–Huxley neurons is explored both, in the deterministic limit and under consideration of channel noise. As a comparison, we retrospect on the previous work on a single neuron subjected to a delayed feedback loop resulting from autapse in Section 4. Our conclusions are given in Section 5.

2. Biophysical model setup

We consider a minimal building block of a neuronal network composed of two coupled neurons. As an archetype model for nerve excitation of the individual neuron, we utilize a stochastic generalization of the common Hodgkin–Huxley model. The stochastic generalization accounts for intrinsic membranal

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conductance fluctuations, i.e. channel noise, being caused by random ion channel gating. Moreover, we account for a delay in the coupling which accounts for a finite propagation time of the action potential along the axon.

2.1. Hodgkin–Huxley-type modelling of two delay-coupled neurons

According to Hodgkin and Huxley, the dynamics of the membrane potential V_i with $i = 1, 2$ of two coupled neuronal cells is given by Hodgkin and Huxley [30]

$$C\frac{\mathrm{d}}{\mathrm{d}t}V_i + G_{\mathrm{K}}(n)(V_i - V_{\mathrm{K}}) + G_{\mathrm{Na}}(m,h)(V_i - V_{\mathrm{Na}}) + G_{\mathrm{L}}(V_i - V_{\mathrm{L}}) = I_i(t). \tag{1}$$

Here, V_i denotes the membrane potential of the i-th cell. The stimulus $I_i(t)$ acting on the i-th neuron reads:

$$I_i(t) = I_{i,\ \mathrm{ext}}(t) + I^{\tau}_{ij}(t), \quad i,j = 1,2, i \neq j, \tag{2}$$

where the bi-directional delay-coupling of Pyragas-type [31] between the two neurons is assumed to be linear in the difference of the membrane potentials of a primary, i-th neuron at time t and a secondary, j-th neuron at an earlier time, $t - \tau$. The coupling thus reads:

$$I^{\tau}_{ij}(t) = \kappa[V_j(t-\tau) - V_i(t)], \tag{3}$$

where κ corresponds to the coupling strength and τ denotes the finite delay time. The coupling defined in Eq. (3) is of "electrotonic" type, i.e. we consider an idealized situation wherein the coupling is proportional to the difference of presynaptic and postsynaptic membrane potentials. This kind of coupling then corresponds to so-called gap-junctions which allow the bi-directional transport of ions and small molecules from one neuronal cell into another. Unlike the conductance of chemical synapses, the conductance of gap-junctions is independent of the presynaptic and postsynaptic membrane potentials and can therefore be modelled by the constant coupling parameter κ. Possible chemical mechanisms occurring at the synaptic cleft are assumed to be instantaneous as the time scale for signal propagation along the neuron's axon is much larger than the corresponding one for the transport process in the synaptic cleft. Note, that the delayed stimulus in Eq. (3) results in an excitatory coupling mechanism in which the spiking of neuron i at an earlier time $t - \tau$ time favors the initiation of a action potential of the other cell at time t.

In addition to the delayed, bilinear coupling current we apply a constant current stimulus $I_{i,\mathrm{ext}}$ on the neurons, mimicking the common stimulus of the neuronal environment on the so considered two-neuron network. In absence of the bi-directional coupling the dynamics of each neuron exhibits a bifurcation scenario exhibiting a subcritical Hopf bifurcation. As a consequence, the membranal dynamics displays (i) a stable fix-point, i.e. the so-called *rest state* for $I_{i,\mathrm{ext}} < I_1 \approx 6.26\ \mu\mathrm{A/cm^2}$, (ii) a stable spiking solution for $I_{i,\mathrm{ext}} > I_2 \approx 9.763\ \mu\mathrm{A/cm^2}$ and (iii) a bistable regime for which the stable rest state and a stable oscillatory spiking solution coexist, i.e. for $I_1 < I_{i,\mathrm{ext}} < I_2$ [32–36]. In particular, for $I_{i,\mathrm{ext}} = 0$ the membrane potential is $V_{\mathrm{rest}} = -65.0$ mV.

Throughout this work the membrane potentials are measured in units of mV and time in units of ms. For a squid giant axon, the parameters in Eq. (1) read $V_{\mathrm{Na}} = 50$ mV, $V_{\mathrm{K}} = -77$ mV, $V_{\mathrm{L}} = -54.4$ mV, and $C = 1\ \mu\mathrm{F/cm^2}$. Furthermore, the leakage conductance is assumed to be constant, $G_{\mathrm{L}} = 0.3\ \mathrm{mS/cm^2}$. On the contrary, the sodium and potassium conductances are controlled by the voltage-dependent gating dynamics of single ion channels and are proportional to their respective numbers. In the Hodgkin–Huxley model [30], the opening of the potassium ion channel is governed by four identical activation gates, being characterized by the opening probability n. The channel is open when all four gates are open. In the case of sodium channel, the dynamics is governed by a set of three independent and identical fast activation gates (m) and an additional slow, so-termed inactivation gate (h). The independence of the gates implies that the probability of the occurrence of the conducting conformation is $P_{\mathrm{K}} = n^4$ for a potassium channel and $P_{\mathrm{Na}} = m^3\,h$ for a sodium channel, respectively. In a mean field description, the macroscopic potassium and sodium conductances then read:

$$G_{\mathrm{K}}(n) = g^{\max}_{\mathrm{K}}\, n^4, \quad G_{\mathrm{Na}}(m,h) = g^{\max}_{\mathrm{Na}}\, m^3 h, \tag{4}$$

where $g^{\max}_{\mathrm{K}} = 36\ \mathrm{mS/cm^2}$ and $g^{\max}_{\mathrm{Na}} = 120\ \mathrm{mS/cm^2}$ denote the maximal conductances (when all channels are open). The two-state, opening–closing dynamics of the gates is governed by the voltage dependent opening and closing rates $\alpha_x(V)$ and $\beta_x(V)$ ($x = m, h, n$), i.e. [30]

$$\alpha_n(V) = \frac{0.01(V+55)}{1-\exp[-(V+55)/10]}, \tag{5}$$

$$\beta_n(V) = 0.125\exp[-(V+65)/80], \tag{6}$$

$$\alpha_m(V) = \frac{0.1(V+40)}{1-\exp[-(V+40)/10]}, \tag{7}$$

$$\beta_m(V) = 4\exp[-(V+65)/18], \tag{8}$$

$$\alpha_h(V) = 0.07\exp[-(V+65)/20], \tag{9}$$

$$\beta_h(V) = \frac{1}{1+\exp[-(V+35)/10]}. \tag{10}$$

Hence, the dynamics of the opening probabilities for the gates read:

$$\dot{x} = \alpha_x(V)\ (1-x) - \beta_x(V)x, \quad x = m, h, n. \tag{11}$$

The voltage Eq. (1), Eq. (4) and the rate equations of the gating dynamics Eqs. (6)–(11) then constitute the original, strictly deterministic Hodgkin–Huxley model for spiking activity of the squid giant axon.

2.2. Modelling channel noise

In this study, however, each channel defines a bistable stochastic element which fluctuates between its *closed and open states*. As a consequence, the number of open channels undergoes a birth–death stochastic process. Applying a diffusion approximation to this discrete dynamics, the resulting Fokker–Planck equation can be obtained from a Kramers–Moyal expansion [37,38]. The corresponding Langevin dynamics, interpreted here in the stochastic Itô calculus [39], reads:

$$\frac{\mathrm{d}}{\mathrm{d}t}x = \alpha_x(V)\,(1-x) - \beta_x(V)\,x + \xi_x(t), \quad x = n, m, h. \tag{12}$$

It is driven by independent Gaussian white noise sources $\xi_x(t)$ of vanishing mean which account for the fluctuations of the number of open gates. The (multiplicative) noise strengths depend on both, the membrane voltage and the gating variables. Explicitly, these noise correlations assume the following form for a neuron consisting of N_{Na} sodium and N_{K} potassium ion channels:

$$\langle \xi_m(t)\xi_m(t')\rangle = \frac{(1-m)\alpha_m + m\beta_m}{N_{Na}}\,\delta(t-t'), \tag{13}$$

$$\langle \xi_h(t)\xi_h(t')\rangle = \frac{(1-h)\alpha_h + h\beta_h}{N_{Na}}\,\delta(t-t'), \tag{14}$$

$$\langle \xi_n(t)\xi_n(t')\rangle = \frac{(1-n)\alpha_n + n\beta_n}{N_K}\,\delta(t-t'). \tag{15}$$

The fluctuations of the number of open ion channels result in conductances fluctuations of the cell membrane eventually leading to spontaneous action potentials. These spontaneous spiking events occur even for sub-threshold, constant external current

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