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Phase Dynamics for Weakly Coupled Hodgkin-Huxley Neurons.

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Abstract. – Hodgkin-Huxley model neurons coupled by weak excitatory interactions are studied by a phase reduction technique. All the information about the coupling between the neurons and their synchronization is then contained in an effective interaction between their phases. One shows analytically that an excitatory coupling can result in an effective inhibition between the neurons reducing their firing rates. Systems of two neurons exhibit bistability and out-of-phase locking. It is suggested that these features may have significant consequences for networks.

Systems of coupled non-linear oscillators keep on attracting a considerable interest in physics [1, 2], chemistry [3] and biology [4]. In the field of neurobiology an important motivation is the study of synchronized activity in neuronal systems [5, 6]. Oscillating neurons are described by a system of non-linear differential equations with a stable limit cycle. The coupling appears as an additional term in the evolution equations for the membrane potentials of the neurons. For weak interaction, phase reduction methods [1, 7] enable one to replace the original system by only one equation of motion per oscillator, that governs the phase of this oscillator, thus leading to a drastic reduction of the problem. The phase dynamics is completely defined by an effective interaction Γ, that can be evaluated in terms of the original system and describes the slowing-down or acceleration of the phase due to the interaction. This approach is valid as long as the shape of the limit cycle is only weakly altered by the interaction; this does not entail that effects on the phase are small too.

In the context of neural modelling phase reductions have been used to study oscillations in assemblies of analog [8, 9], «integrate and fire» [10] or Morris-Lecar neurons [7]. We consider here the more realistic Hodgkin-Huxley (H-H) model [11]. This model of excitable membrane, originally introduced to describe the behaviour of the squid's giant axon, provides a simple and useful paradigm that accounts naturally for both the generation of spikes, due to voltage-dependent membrane conductances, and the existence of absolute and relative refractory periods. This paradigm is representative of all the conductance-based models of tonically spiking neurons. It also serves as a starting point in the building of models with more complex dynamical behaviour such as bursting.

In what follows we focus mainly on excitatory *chemical* connections [12] (*i.e.* a pulsed-type

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interaction) between pairs of neurons. We consider two kinds of effects. First, the system of two neurons reaches asymptotically a phase-locked state characterized by a phase shift that can be non-zero. A similar effect was recently discussed by Sherman and Rinzel; they observed monostable antiphase locking in the case of two electrically coupled conductance-based-model neurons [13]. A second and more surprising effect is that in the asymptotic regime the firing rate of the neurons is reduced although the interaction that couples them is excitatory. Both effects are interpreted in the framework of phase reduction methods.

A Hodgkin-Huxley neuron is described by a set of four variables $\boldsymbol{X} = (V, m, h, n)$, where V is the membrane potential, m and h the activation and inactivation variables of the sodium current and n the activation variable of the potassium current. The corresponding equations of motion read [14]

$$C\frac{\mathrm{d}V}{\mathrm{d}t} = I - g_{\mathrm{Na}} m^3 h(V - V_{\mathrm{Na}}) - g_{\mathrm{K}} n^4 (V - V_{\mathrm{K}}) - g_{\mathrm{l}}(V - V_{\mathrm{l}}), \tag{1}$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \frac{(m_\infty(V) - m)}{\tau_m(V)}, \tag{2}$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = \frac{(h_\infty(V) - h)}{\tau_h(V)}, \tag{3}$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \frac{(n_\infty(V) - n)}{\tau_n(V)}. \tag{4}$$

I is the external current injected into the neuron and fixes the neuron's firing rate. In the following all neurons will be identical. The parameters g_{Na}, g_{K} and g_{l} are the maximum conductances per surface unit for the sodium, potassium and leak currents, V_{Na}, V_{K} and V_{l} are the corresponding reversal potentials and C is the capacitance per surface unit. For the squid's axon typical values of the parameters (at 6.3 °C) are: $V_{\mathrm{Na}} = 50\,\mathrm{mV}$, $V_{\mathrm{K}} = -77\,\mathrm{mV}$, $V_{\mathrm{l}} = -54.4\,\mathrm{mV}$, $g_{\mathrm{Na}} = 120\,\mathrm{mS/cm^2}$, $g_{\mathrm{K}} = 36\,\mathrm{mS/cm^2}$, $g_{\mathrm{l}} = 0.3\,\mathrm{mS/cm^2}$, and $C = 1\,\mu\mathrm{F/cm^2}$. The functions $m_\infty(V)$, $h_\infty(V)$ and $n_\infty(V)$ and the characteristic times (in milliseconds) τ_m, τ_n, τ_h are given by: $x_\infty(V) = a_x/(a_x + b_x)$, $\tau_x = 1/(a_x + b_x)$ with $x = m, n, h$ and $a_m = 0.1(V + 40)/(1 - \exp[(-V - 40)/10])$, $b_m = 4\exp[(-V - 65)/18]$, $a_h = 0.07\exp[(-V - 65)/20]$, $b_h = 1/(1 + \exp[(-V - 35)/10])$, $a_n = 0.01(V + 55)/(1 - \exp[(-V - 55)/10])$, $b_n = 0.125\exp[(-V - 65)/80]$.

Let us recall that for small values of I the system reaches a stable fixed point ($V_{\mathrm{eq}} = -65\,\mathrm{mV}$ for $I = 0$). At $I_1 = 9.78\,\mu\mathrm{A/cm^2}$ the system undergoes an inverted Hopf bifurcation to the spiking regime. This behaviour agrees with the electrophysiological observation on the squid's axon that the oscillations start with finite amplitude and frequency. The periodic emission of spikes stops at $I_2 = 154.5\,\mu\mathrm{A/cm^2}$, where the fixed point becomes again stable through a normal Hopf bifurcation.

The chemical interaction between coupled neurons can be modelled as follows. The emission of a spike by a given neuron triggers postsynaptic events in all the neurons it is connected to. To account for this synaptic effect, one must add a synaptic current I_{syn} to the right-hand side of the equation for membrane potential evolution. The simplest way to model a single synaptic event is to use an «alpha function» [15]:

$$I_{\mathrm{syn}} = -g\alpha(t - t_0)[V(t) - V_{\mathrm{syn}}], \tag{5}$$

where $\alpha(t) = (t/\tau)\exp[-t/\tau]$, g is the peak synaptic conductance, τ is the characteristic time of the interaction, and t_0 is the instant when the interaction starts (the time of the emission of a spike by the presynaptic neuron when all delays are neglected). For multiple events, I_{syn} becomes a sum of such terms as above, each characterized by its time of occurrence. Note the

pulsed nature of the interaction, that takes place in a time of order τ. The synaptic effect is traditionally classified as excitatory or inhibitory depending on the value of V_{syn} with respect to the resting potential V_{eq}. If $V_{\text{syn}} > V_{\text{eq}}$, $I_{\text{syn}}(V) < 0$ in most of the potential range ($V_{\text{K}} < V < V_{\text{Na}}$) and tends *a priori* to induce firing in the postsynaptic neuron. In this case the interaction is excitatory. In the inhibitory case ($V_{\text{syn}} \leqslant V_{\text{eq}}$) the interaction tends to hyperpolarize the target neuron and to stabilize it in a quiescent state.

An isolated neuron is moving on its stable limit cycle (for $I_1 < I < I_2$) with period $T(I)$. One can associate to any point $\boldsymbol{X}$ in the attraction basin of the cycle a phase $\Phi(\boldsymbol{X})$ in such a way that points with the same phase display the same asymptotic behaviour on the limit cycle. Thus one defines a family of isochrons. The phase increases uniformly with time $\mathrm{d}\Phi(\boldsymbol{X})/\mathrm{d}t = 1$. In a coupled network the evolution equation for the phase becomes $\mathrm{d}\Phi_i(\boldsymbol{X}_i)/\mathrm{d}t = 1 + \sum_{j \neq i} (\partial \Phi_i / \partial \boldsymbol{X}_i) \cdot \boldsymbol{p}(\boldsymbol{X}_i, \boldsymbol{X}_j)$, where $\boldsymbol{p}(\boldsymbol{X}_i, \boldsymbol{X}_j)$ is the coupling between neurons i and j. For weak coupling this term can be evaluated on the unperturbed trajectories. The first-order motion equation for the phase now reads $\mathrm{d}\Phi_i/\mathrm{d}t = 1 + \sum_{j \neq i} \boldsymbol{Z}(\Phi_i) \cdot \boldsymbol{p}(\Phi_i, \Phi_j)$, where $\boldsymbol{Z}$ is the phase gradient, and $\boldsymbol{Z}$ and $\boldsymbol{p}$ are periodic functions of all their arguments. We can define for each unit i a phase perturbation Ψ_i by $\Psi_i(\boldsymbol{X}_i) = \Phi_i(\boldsymbol{X}_i) - t$. Its equation of motion is then [1]

$$\frac{\mathrm{d}\Psi_i}{\mathrm{d}t} = g \sum_{j \neq i} \Gamma(\Psi_i - \Psi_j), \tag{6}$$

where, in the present limit of weak coupling,

$$\Gamma(\Psi_i - \Psi_j) = \frac{1}{T} \int_0^T \boldsymbol{Z}(t + \Psi_i) \cdot \boldsymbol{p}(t + \Psi_i, t + \Psi_j)\, \mathrm{d}t \tag{7}$$

is obtained through an averaging procedure by integrating over the cycle. The net effect of the interaction between two neurons is then a convolution between the local response of the neuron on its limit cycle, implicit in the structure of isochrons, and the form of the interaction. In our case the perturbation appears only in the evolution equation for the potentials. More precisely

$$\boldsymbol{p}(t + \Psi_i, t + \Psi_j) = -g[V(t + \Psi_i) - V_{\text{syn}}] \sum_{\text{spikes}} \alpha(t + \Psi_j - t_{\text{spike}}), \tag{8}$$

where the sum is taken over all the spikes emitted by neuron j (at respective times t_{spike}). Therefore, we need only to evaluate the derivative of the phase with respect to the voltage.

For the H-H model the reduction had to be performed numerically. The limit cycle was computed by integrating the H-H system of equations for one neuron using a second-order scheme. The derivative of the phase was evaluated by computing the dephasing induced at large time by small initial perturbations. The convolution integral of eq. (7) was then calculated numerically. It is important to note that the effective interaction depends on the bias current I.

The Fourier analysis of Γ shows that several Fourier modes must be considered. For instance for bias current $I = 10\ \mu\text{A/cm}^2$, $\tau = 2$ ms and $V_{\text{syn}} = 30$ mV, one finds $\Gamma(\Psi) \approx 0.383 + 1.379 \sin((2\pi/T)\Psi + 3.93) + 0.568 \sin((4\pi/T)\Psi + 0.11) + 0.154 \sin((6\pi/T)\Psi + 2.387)$. This is at variance with the simpler situations where the reduction to phase models concerns oscillations emerging through a normal Hopf bifurcation and yields a phase interaction with only one Fourier mode ($\Gamma(\Psi) \propto \sin(\Psi + \Psi_0)$ with Ψ_0 a constant dephasing). As shown in the following, the involvement of several Fourier modes leads to dynamical phenomena that cannot be observed in the framework of the widely used single-mode approximation.

The phase dynamics can then be written in terms of the two variables $\Psi^- = \Psi_1 - \Psi_2$ and

$\Psi^+ = \Psi_1 + \Psi_2$. It is important to note that the evolution of Ψ^-, that is, the dephasing, is governed by Γ^-, the *antisymmetric* part of Γ. The values $\Psi^- = 0$, $T/2$ and $-T/2$ are always fixed points of the phase dynamics equation, as Γ^- is a periodic and odd function, but they will be stable only if the derivative of Γ^- at these points is negative. Extra fixed points may exist, depending on the parameters of the neurons (firing rate) and the features of the interaction (time constant), as illustrated in fig. 1 for an excitatory coupling, and for different values of the bias current. In that figure one sees that for small I the only stable fixed point corresponds to in-phase neurons ($\Psi^- = 0$). But if the current I is increased beyond a critical value I^* this point becomes unstable and two stable fixed points with a *non-zero* dephasing $\pm \Psi^*(I)$ emerge via a normal pitch-fork bifurcation. The neurons will then not lock in phase.

Another interesting feature can be seen on the firing rates of the neurons, f_i, that depend on the *symmetric* part of Γ, Γ^+. At large time, when the two neurons are phase locked, their firing rates are equal: $f = f_1 = f_2 = (1/T)(\mathrm{d}\Phi/\mathrm{d}t)$. Using the motion equation for Φ (and the fact that $\Gamma^-(\Psi^*) = 0$) one finds

$$f(g) = f(0)(1 + g\Gamma^+(\Psi^*)). \tag{9}$$

This common firing rate depends linearly on the coupling constant. Switching on the interaction leads to an increase or to a reduction of the firing rate, depending on the sign of $\Gamma^+(\Psi^*)$. For the set of parameters and the range of bias current considered in this work, this sign is always negative: the interaction between the two neurons decreases their firing rate, *i.e.* the neurons are effectively inhibiting each other even when V_{syn} is chosen high enough (30 mV) to ensure that $V - V_{\mathrm{syn}} < 0$ all over the cycle [1]. The firing rates obtained for a given bias current ($I = 10\ \mu\mathrm{A/cm^2}$) and various couplings g are plotted in fig. 2 for both the original system and the phase reduction. The validity of the phase reduction prediction is good up to

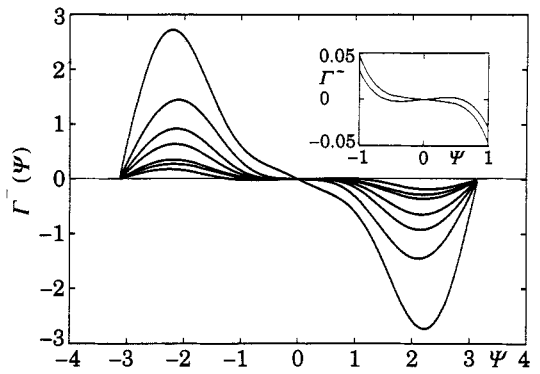

Fig. 1.

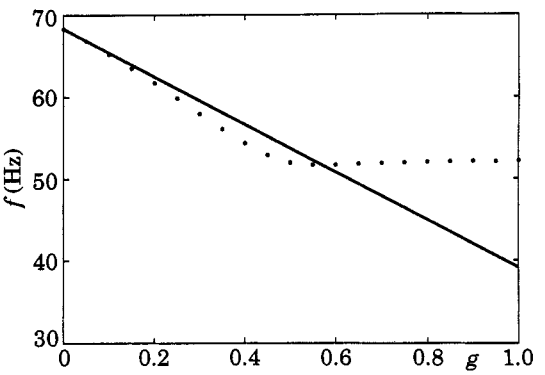

Fig. 2.

Fig. 1. – The antisymmetric part Γ^- of the effective interaction for a symmetrical excitatory synaptic coupling ($V_{\mathrm{syn}} = 30$ mV, $\tau = 2$ ms) and bias current 10, 15, 20, 25, 35, 40 and 50 $\mu\mathrm{A/cm^2}$ (the amplitude of Γ^- decreases with I). The period T was normalized to 2π. Insert: blowing up the central region for $I = 35$ and 40 $\mu\mathrm{A/cm^2}$ reveals the bifurcation of the in-phase fixed point.

Fig. 2. – The firing rate f in Hz as a function of the coupling g for two interacting H-H neurons ($I = 10\ \mu\mathrm{A/cm^2}$ and $V_{\mathrm{syn}} = 30$ mV). The dots are the results of the numerical simulation, whereas the line shows the prediction of the phase reduction method.

[1] This value of V_{syn} was chosen throughout this paper. It corresponds to an intermediate situation between the two more physiological values: $V_{\mathrm{syn}} = 0$ mV and $V_{\mathrm{syn}} = V_{\mathrm{Na}}$. We have checked that the results remain qualitatively the same within this range.

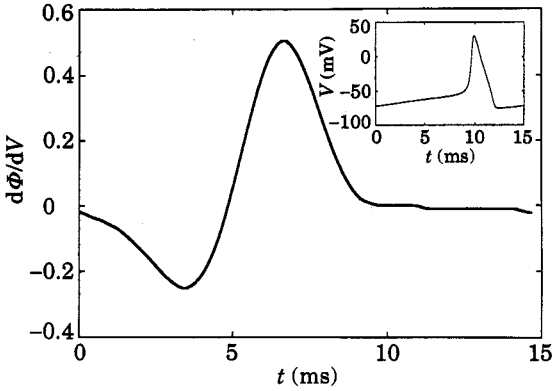

Fig. 3. – Derivative of the phase as a function of time (in ms) ($I = 10\,\mu A/cm^2$). Insert: membrane potential (in mV) as a function of time (ms) during one cycle.

$g \simeq 0.5\,mS/cm^2$, where the reduction of the firing rate reaches 20%. At that point, amplitude effects start to play a significant role and the phase approximation breaks down.

The reduction of the firing rate seems at first sight paradoxical. Although the interaction between the neurons is *a priori* excitatory, the system behaves as if some inhibition existed between the two neurons. The origin of this firing-rate reduction can be understood qualitatively by analysing eq. (7). The effect of an excitatory perturbation localized in time on a H-H neuron depends on the position of the neuron on its limit cycle at the time of the perturbation. This appears clearly in fig. 3 where we have plotted the derivative of the phase. We see that a perturbation acting only on the membrane potential equation can accelerate ($\partial\Phi/\partial V > 0$) or slow down ($\partial\Phi/\partial V < 0$) the motion of the neuron. In the first case the local effect of the perturbation will be excitatory, while in the second case it will be inhibitory. The global inhibitory or excitatory nature of the interaction depends on the balance between these local excitatory and inhibitory contributions to the convolution integral in eq. (7). The existence of the negative part in $\partial\Phi/\partial V$ is a necessary condition for the reduction of the observed firing rate.

The existence of an out-of-phase locking is related to the asymmetry of $\Gamma(\Psi)$ around $\Psi = 0$, that stems from the competition between several factors: the existence of an (absolute) refractory period, the duration of the interaction (rise and decay times), the effective inhibition mentioned above and the value of V_{syn}. The phase reduction method allows us to predict a possible non-zero dephasing. For instance, studying $\Gamma(\Psi)$, one finds that the bifurcation scheme for the phase dynamics strongly depends on the characteristic time of the interaction: for $\tau = 1$ ms the in-phase fixed point never loses its stability, at variance with what we described for $\tau = 2$ ms. It is also quite sensitive to the negative part in $\partial\Phi/\partial V$. Indeed, increasing the range of the absolute refractory period by suppressing this negative part leads to a non-zero phase shift already for $I = 10\,\mu A/cm^2$. Thus the local inhibitory response decreases the phase shift by reducing the asymmetry of $\Gamma(\Psi)$ around $\Psi = 0$.

We have also studied the case of electronic coupling [12] between the neurons for which the synaptic current received by neuron 1 is: $I_{syn} = -D(V_1 - V_2)$. The phase reduction analysis predicts no frequency reduction but a multistable situation where in-phase locking and antiphase locking coexist and are simultaneously stable.

In conclusion, we have applied phase reduction techniques to study the locking of weakly coupled Hodgkin-Huxley neurons. The structure of the underlying phase equations explains the existence of different, and possibly coexisting, modes of locking. The remarkable

phenomenon of effective inhibition that leads to a reduction of the firing rate can be naturally explained in this framework. It is due to the existence of a local inhibitory response in the (relative) refractory period. This is reminiscent of paradoxical inhibition phenomena reported in recent works where an Excitatory Post Synaptic Potential (EPSP) can delay or suppress the subsequent firing of an action potential [16, 17].

The qualitative conclusions of the phase analysis can remain valid even when the coupling current exceeds 10% of the total current (external plus ionic). Thus the phase dynamics is not restricted to a limiting case; its relevance extends over a range of couplings *a priori* wide enough to encompass situations of physiological interest. In this range the coupling can induce significant effects that occur after short transients: for instance we have found that the phase locking is reached after 10 to 20 spikes.

The next step is to analyse the dynamics of networks of H-H neurons. The multistability found for two neurons will be enhanced, giving rise to a wealth of dynamical states. In addition the presence of the symmetric part of Γ entails that the dynamics is not Hamiltonian. It is easy to see that for chemical coupling and $I < I^*$ the state of global in-phase synchronization is stable at small coupling. On the other hand, for $I > I^*$ it cannot be stable. Interesting dynamical phenomena related to clustering of oscillators [18] then occur [19, 20].

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