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Physiology & Behavior 77 (2002) 629–633

PHYSIOLOGY & BEHAVIOR

Modeling neural oscillations

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Received 30 July 2002; accepted 6 September 2002

Abstract

A brief review of oscillatory activity in neurons and networks is given. Conditions required for neural oscillations are provided. Three mathematical methods for studying the coupling between neural oscillators are described: (i) weak coupling, (ii) firing time maps, and (iii) leaky integrate-and-fire methods. Several applications from macroscopic motor behavior to slice phenomena are provided.

Keywords: Neural oscillators; Synchronization; Mathematical models

1. Introduction

Oscillatory activity is ubiquitous in neural systems. Rhythms play a major role in motor, sensory, and possibly even cognitive functioning. A number of recent experiments have pointed to the possible roles of neural oscillators in visual perception, olfaction, and memory formation [1–3]. The mechanisms for the production of rhythmic firing vary considerably from single pacemaker neurons, whose membrane properties endow them with the ability to produce rhythmic activity, to large cortical networks, where the interactions of many excitatory and inhibitory neurons are responsible for the rhythmic behavior.

Rhythmic behavior is seen at every level in the nervous system. Some of the earliest experiments in physiology were aimed at understanding the underlying mechanisms of rhythmicity in nerve axons. The most obvious roles for rhythmic activity occur in motor activities such as animal gaits, respiratory rhythms, and feeding and mating patterns. Oscillatory activity in pathologies like epilepsy and Parkinsonian tremors is well known and the subject of much theoretical effort. Recently, there has been a great deal of interest in the possible role of several different cortical rhythms (such as coherent behavior in the gamma range of 40–80 Hz) in cognitive function such as attention. Several theories have been proposed which suggest that binding of different parts of a perceived object could be accomplished by using oscillatory codes [2,4].

There are many ways in which one can define rhythmicity, particularly when the systems are not always perfectly regular. We will take the point of view that a neural network is oscillatory if the recorded variables (e.g., the membrane potentials, currents, or calcium concentrations) are periodic with a well-defined period, T. Another important property is stability to perturbations. That is, if the oscillation is briefly perturbed, for example, by a short-lasting small stimulus, then the rhythm will return to its original magnitude and period with a possible phase-shift. This phase-shift is quite important and can be systematically used to model oscillators about which few details are known. The absence of a phase effect due to a perturbation is often a hint that the perturbed network is not the source of the rhythm but rather is simply following the output of some "upstream oscillator."

Another important concept in oscillatory neural networks is the pattern of timings or phases of the individual elements. That is, if one records from two different cells, then the time-difference between the two action potentials (or burst onsets, etc.) divided by the period defines the *relative phase*. The phase is easily defined between two elements if they have identical waveforms. For different waveform shapes, there is no single best way to determine relative phase, but one method is to choose a single prominent feature of the waveform and measure relative to that feature.

In a typical oscillatory network, there will be many cells firing at different times but with the same period. Choosing

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PII: S0031-9384(02)00898-3

one cell to fire at *zero phase* allows us to uniquely define the relative phase of all the remaining cells. *Synchrony* is defined as a relative phase of zero and *antiphase* is a phase-difference of one-half a cycle. The relative phases of the elements in an oscillatory network serve to define the behavior of that network. In many cases, the system is able to switch from one pattern of phases to another. For example, a horse can switch from walking to trotting to galloping and the relative phases of the legs are different for each gait. In trotting, the legs on one side are synchronous but in antiphase with those of the other side. In galloping, there is a complicated phase relationship among the four legs. If these gaits are controlled by a neural "central pattern generator," then such changes in phase will be reflected in changes in neuronal firing.

We will introduce some of the underlying theoretical methods and issues that arise in the study of neural oscillations. We first describe the requirements for oscillations at the single cell and network level. Next, we discuss a general method for the analysis of networks of intrinsically oscillating neurons. Finally, we provide different examples of the theory at work.

2. Neural oscillations

The basic requirement for any type of oscillation is a positive action followed by a delayed negative feedback. Thus, oscillatory activity can occur in the membrane of a neuron, in the interactions between regions of a neuron, and in networks of neurons. In a typical fast-spiking neuron, injected current raises the potential, opening sodium channels and causing the potential to rise quickly. A slower outward potassium current develops and at the same time the sodium channels begin to close (due to inactivation at high potentials). These two processes conspire to bring the potential down. At the lower potential, the potassium channels close down and the sodium channels recover from the block allowing the process to repeat itself. This leads to repetitive firing of action potentials. Interactions between the soma and dendrites can also produce rhythmic behavior [5].

Network interactions between different neurons can also induce oscillations. In the thalamus, large amplitude oscillatory bursts of action potentials are recorded during sleep. This is due to interactions between the excitatory thalamocortical relay cells (TC) and the cells of the thalamic reticular nucleus (nRT) [6]. TC cells contain a low-threshold calcium current, which is inactivated at rest. Hyperpolarizing the cell de-inactivates this large inward current so that when the hyperpolarization disappears, the cell fires a large burst of action potentials. This burst excites the nRT neurons causing them to fire a burst of action potentials that hyperpolarizes the TC cell starting the cycle again.

While there are innumerable biophysical mechanisms for the production of oscillatory behavior in single cells and networks, they are described by a few mathematical principles [7]. One of our goals in computational neuroscience is to classify the huge variety of models according to the underlying mathematical mechanisms that lead to oscillations. We use methods of *dynamical systems theory*, which describes how qualitatively new behavior arises as parameters in a model vary. The theory tells us that there are three mathematically distinct ways in which an excitable membrane can go from rest to rhythmic behavior: (i) saddle-node bifurcation, (i) Hopf bifurcation, and (iii) homoclinic bifurcation. Very few neural models exhibit the third type of behavior so we will only describe the first two.

These classifications actually correspond to physiologically observed behaviors. The behavior of axons subjected to depolarizing currents was categorized into two different classes [8]:

- Class I
  - All-or-none action potentials;
  - Arbitrarily long period oscillations;
  - Long delay to firing of an action potential after a transient stimulus;
  - Square root or linear FI curve. (The FI curve is the firing rate as a function of the injected current.)
- Class II
  - Graded action potential amplitudes, particularly at higher temperatures;
  - Limited range of frequencies;
  - Short latencies to firing.

In Ref. [7], it was suggested that these two classes corresponded, respectively, to the saddle-node bifurcation and the Hopf bifurcation.

One can ask why this is important. One point is that there are mathematical techniques which allow one to *reduce* many-variable conductance-based models to simplified systems *without losing too many of the observed behaviors*. Thus, if one understands these simple models, it is possible to apply that knowledge to whole classes of model cells. For example, the action-potential generation of many conductance-based models, which are Class I can be well-fit with the quadratic integrate-and-fire model [9]:

$$\frac{dx}{dt} = ax^2 + bI$$

where I is the current input into the neuron (synaptic, applied, or even slow currents like the AHP) and a, b are parameters, which depend on the details of the model. The variable x characterizes the amplitude of the all the variables in the model; in particular, the voltage is approximately given by, $V(t) = V_0 + V_1 x$, where V_0, V_1 are constants depending on the model. A second reason why such a classification is useful is that the behavior of these oscillators when coupled together in networks strongly depends on whether they are Class I or II.

3. Coupling of neural oscillators

Neurons are generally coupled together into networks either through chemical synapses or via electrotonic gap junctions that depend on the potential difference between two neurons. Consider a simplified situation of a pair of nearly identical neural oscillators coupled synaptically. In absence of coupling, the two neurons fire repetitively and their current states can conveniently be described by the time since the last action potential, which we denote $\theta_{1,2}$. Note that these variables lie between 0 and T, the intrinsic period of the cells. In the uncoupled case, these two times are independent; however, we expect that the coupling will alter their respective times so that they fall into a precise pattern. For example, typical patterns between two neurons are (i) synchrony, in which the timing difference between the two cells vanishes, and (ii) antiphase, in which the cells fire a half of a cycle out of phase.

Some of the questions that we have asked over the last two decades are (1) can we predict the pattern between two oscillators given their coupling; (2) how do environmental and other influences change this pattern; and (3) how does the nature of the neural oscillation affect this pattern? We next describe three approaches we have taken to answer these questions. The first is very general and is not necessarily restricted to neural oscillations. The second method takes advantage of the pulse-like interactions of fast chemical synapses, and the third considers a simplified Class I neuron for which mathematical results can be easily extracted.

3.1. Weak coupling

There are powerful mathematical techniques applicable to systems in which the oscillators are weakly coupled. One can take "weak" to mean that the shapes of the action potentials are not changed by the coupling but their timing is. The theory for weak coupling is outlined in Ref. [10].

For a system of two weakly coupled neurons, there exists a function, H, such that the time from the last spike, θ_j, satisfies:

$$\frac{d\theta_1}{dt} = 1 + g_{12}H(\theta_1 - \theta_2)$$

$$\frac{d\theta_2}{dt} = \delta + g_{21}H(\theta_2 - \theta_1) \qquad (1)$$

where δ is a parameter which allows the neurons to have slightly different periods ($\delta = 0$ is the case of identical neurons) and g is the coupling strength between the two neurons. The function H is periodic with period T and completely characterizes the interaction; it is essentially the average of the response of the postsynaptic neuron, $R(t)$, given the synaptic current from the presynaptic cell, $S(t)$. In typical models, the function $R(t)$ depends very strongly on the class of the neuron in the sense of Section 2. For example, Class I neurons have a strictly positive response function (e.g., $1+\cos\theta$), while Class II neurons have a negative response for stimuli occurring right after the action potential and a positive response function for later stimuli (e.g., $-\sin\theta$). Conversely, the synaptic function, $S(t)$, does not depend on the nature of the oscillator but does depend on standard properties like the reversal potential of the synapse and its time constant. We should point out that for gap junctions, the function $S(t)$ is just the potential difference between the pre- and postsynaptic cells so that it does depend on the nature of the oscillator. Both $R(t)$ and $S(t)$ depend on the frequency of the oscillation. This can have a profound effect on the observed patterns between neural oscillators such as the gait changes of a horse as it speeds up.

Returning to Eq. (1), the timing difference, $\phi = \theta_2 - \theta_1$ satisfies an equation obtained by subtracting the two equations for θ_j

$$\frac{d\phi}{dt} = \delta + g_{12}H(-\phi) - g_{21}H(\phi) \equiv G(\phi) \qquad (2)$$

Zeros of the function $G(\phi)$ satisfying $G'(\phi) < 0$ represent *stable* timing differences between the two oscillators. In general, unless $\delta = 0$ and $g_{12} = g_{21}$, the timing difference between the oscillators will not be zero. That is, unless the oscillators are identical and symmetrically coupled, they will not synchronize with a zero timing difference.

An interesting observation of a synchrony to antiphase transition is in an experiment cited in Ref. [11]. Subjects were asked to tap their fingers in an antiphase pattern while trying to keep up with a metronome. As the metronome increased in frequency, all subjects abruptly switched to a synchronous rhythm. These authors suggested that the phase-difference (normalized timing difference) between the oscillators satisfied an equation of the form:

$$\frac{d\phi}{dt} = -\sin\phi - a\sin 2\phi = k(\phi, a)$$

The antiphase solution, $\phi = \pi$, is stable as long as $a > 1/2$. These authors suggested that as the frequency of the oscillators increased the value of the parameter a decreased, thus destabilizing the antiphase state. It has been shown that for Class I neurons coupled with inhibition, both the synchronous and the antiphase solution are both stable for slow oscillations [12–15]. However, as the oscillation frequency increases, the antiphase solution becomes unstable leaving synchrony as the only solution. On the other hand, with mutually excitatory coupling, synchrony is stable at low frequencies and antiphase behavior is stable at high frequencies; they are never simultaneously stable. From this general theoretical result, we can explain the behavioral experiments cited in Ref. [11] if we assume that the groups of neurons driving the finger tapping are coupled in a mutually inhibitory manner.

Networks of many such oscillators can be similarly modeled with a variety of different types of coupling. The analysis of these networks in general is given in Ref. [16]. Models of this form have been used to study waves in the procerebral lobe of the slug *Limax* [17], hippocampal synchrony [18], central pattern generators in lamprey [10], visually evoked waves in turtle visual cortex [4], as well as many other oscillatory phenomena. The study of these general (and seemingly abstract) models has suggested numerous physiological experiments (see any of the papers, Refs. [4,10,17,18]).

3.2. Strong coupling and maps

The weak coupling assumption gives a great deal of information about networks of neurons that are intrinsically oscillating. However, in many situations, connections between groups of neurons are sufficiently strong to cause the postsynaptic cells to fire when they are otherwise at rest. This kind of behavior cannot occur when the coupling is weak. As an example, synchronization between to two distinct areas in the hippocampus of the rat has been studied [19,20]. The oscillation frequency is in the gamma range of roughly 40 Hz. As the two areas are distant, there is a delay (due to finite axonal conduction speeds) of up to 8 ms (more than a quarter of a cycle). In spite of this delay, the two sides synchronize. The experimental data showed that when there was strong synchronization between pyramidal neurons, the inhibitory interneurons fired "doublets," that is, for each excitatory spike, the corresponding interneuron produced a pair of spikes. A large computational model for this preparation reproduces the experimental results [20].

In order to understand how this synchronization is mediated, we [21] devised a simple network model consisting of two pairs of excitatory (E) and inhibitory (I) cells. Cells within a pair were reciprocally connected without time delay. Each E cell then synapsed onto the I cell of the other pair with a time delay. The E cells were depolarized (by metabotropic receptors) so that they fired rapidly. The I cells fired because the E cells excited them. The local feedback inhibition slowed the E cell firing down to about 40 Hz due to the inhibitory time constant of 10–20 ms. The excitatory time constants were short (of the order of 2 ms). An I cell that had not fired during the cycle was induced to fire within a few milliseconds if it received input from an E cell. However, if it had fired recently, then an input from the E cell still fired it but at a delay that depended on the time difference between the input and the last time the I cell fired. This timing-dependent delay to spiking is a consequence of the refractoriness of the I cells. Mathematically, it is because of property 3 of Class I neurons, which constitute the majority of inhibitory cortical interneurons.

The strategy we employed [21] was to translate these observations into a mathematically rigorous map of spike-times for the cells. In particular, we assumed that the spike times of a periodically spiking cell are influenced by spikes from other cells within a given period. This is a good approximation for synapses that decay quickly compared to the spiking period. This allows us to generate a *first return map* of the spike time difference ψ between the E cells from one period to the next. The map has the form

$$\psi^{new} = F(\psi)$$

where $F(\psi)$ is a function that depends on the firing properties of the cells and the delay between the two sides. The dynamics of the spike time difference is obtained by iterating the map (i.e., plug a ψ into the map to obtain a new ψ and then repeat). The synchronous solution is given by $\psi = 0$ and it is stable if and only if $|F'(0)| < 1$, which turned out to imply that synchrony is stable only for delays larger than about 4–5 ms. At very long delays, synchrony remains stable; however, small differences in the two sides are magnified. Hence, the mathematics suggests that this mechanism of doublets will work in a limited range of delays.

The methods described here are quite powerful and have been used to explain why the slower beta rhythms (20 Hz) are able to synchronize with significantly larger delays [22] and how knockout mice, in which the local E to I coupling has a longer time constant, fail to synchronize their rhythms [23].

3.3. Integrate-and-fire neurons

Even with the effectiveness of weak coupling theory and first return maps, there are still situations when both are not applicable. This occurs when neurons are coupled strongly *and* the synaptic interactions are slow enough that they influence spiking beyond a single period. There are no sure-fire systematic approaches for these general situations. However, for Class I neurons, a viable approach is to use a simplified Class I model such as the classic leaky integrate-and-fire neuron:

$$C\frac{dV}{dt} = I - gV$$

This model ignores all spiking currents, integrates the inputs, and when the voltage, V, reaches a fixed threshold, resets to a new prescribed value. For this simple model, reaching the threshold constitutes a spike or action potential. The neuron fires repetitively if the external input (which includes synapses) pushes the neuron above threshold. The assumption is that the spiking currents are active for a short time, and this does not strongly influence the coupling characteristics. Numerical simulations show that coupled integrate-and-fire neurons behave qualitatively similarly to Class I conductance-based neurons. The integrate-and-fire neuron is simple enough that a spike-time map that depends on the entire spiking history of the neuron can be derived [12]. Conditions for synchrony can then be found for the map. These and other approaches [24–26] find that slow

inhibition or fast excitation is beneficial for synchronizing neurons, whereas fast inhibition or slow excitation favors antiphase. For a fixed synaptic decay time, this implies that changing network-firing frequency can change the phase relationship of oscillations. Interestingly enough, using similar methods, it is found that gap junctions also show this frequency dependent synchrony [27]. This theoretical prediction was subsequently verified in experiments on locus coeruleus where neurons are coupled electrotonically with gap junctions [28].

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