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When Inhibition not Excitation Synchronizes Neural Firing

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Abstract. Excitatory and inhibitory synaptic coupling can have counter-intuitive effects on the synchronization of neuronal firing. While it might appear that excitatory coupling would lead to synchronization, we show that frequently inhibition rather than excitation synchronizes firing. We study two identical neurons described by integrate-and-fire models, general phase-coupled models or the Hodgkin-Huxley model with mutual, non-instantaneous excitatory or inhibitory synapses between them. We find that if the rise time of the synapse is longer than the duration of an action potential, inhibition not excitation leads to synchronized firing.

Introduction

It is commonly assumed that excitatory synaptic coupling tends to synchronize neural firing while inhibitory coupling pushes neurons toward anti-synchrony. Such behavior has been seen in models of neuronal circuits (Winfree, 1967; Peskin, 1975; Kuramoto, 1984 & 1991; Ermentrout and Kopell, 1984; Ermentrout, 1985; Mirollo and Strogatz, 1988; Abbott, 1990). However, in some studies (Sorti and Rand, 1986; Lytton and Sejnowski, 1991; Sherman and Rinzel, 1992; Wang and Rinzel, 1992 & 1993; Kopell and Sommers, 1994) just the opposite effect has been observed. In the reticular nucleus of the thalamus, synchronized oscillations occur through purely inhibitory synapses (Wang and Rinzel, 1992; Steriade, McCormick and Sejnowski, 1993; Golomb, Wang and Rinzel, 1994). In the cases we discuss here, we will show that such 'reversed' behavior is the rule rather than the exception. The key feature that determines whether excitation or inhibition synchronizes spiking is the rise time of the synaptic response. In models with instantaneous (zero rise times) or extremely rapid synaptic responses, excitatory coupling leads to synchronization. However, if synaptic rise times are slower than the width of an action potential, we find that inhibition rather than excitation produces synchrony. We first consider a simple circuit of two identical integrate-and-fire neurons mutually coupled by identical, excitatory or inhibitory synapses. We then extend our results to any model that can be described by averaging as a phase-coupled model. Using both the phase description and computer simulation, we show how inhibition and not excitation synchronizes two Hodgkin-Huxley model neurons. In all the models we consider, perfectly synchronized firing cannot be produced by excitatory synaptic coupling unless the synaptic rise time is extremely rapid. Instead, a stable synchronous state can only occur when the neurons are coupled through inhibitory synapses. In many cases, excitatory synapses produce anti-synchronous firing.

Integrate and Fire Models

To illustrate the basic phenomenon, we begin by considering two integrate-and-fire neurons with mutual excitatory or inhibitory coupling. The neurons are described by activation variables x_i with $i = 1, 2$ satisfying the equations

$$\frac{dx_i}{dt} = X - x_i + E_i(t) \tag{2.1}$$

in the range $0 < x_i < 1$. When $x_i = 1$, neuron i fires and is reset to $x_i = 0$. E_i is the synaptic input to neuron i. If cell $j \neq i$ fires at time t_j, the function E_i gets augmented by

$$E_i(t) \to E_i(t) + E_s(t - t_j) \tag{2.2}$$

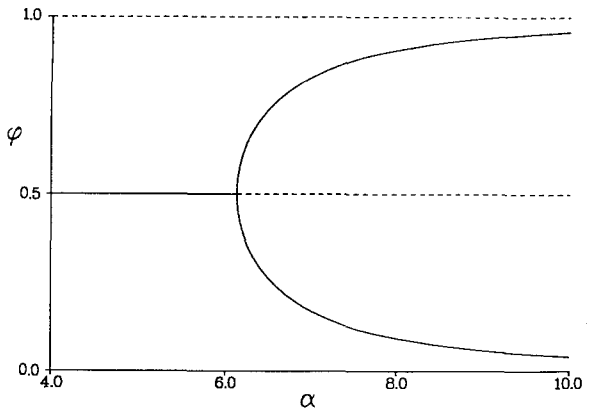

Fig. 1. Equilibrium phase differences between two identical integrate-and-fire neurons with mutual excitatory coupling through alpha functions. The phase difference ϕ is plotted as a function of the synaptic rate constant α. Solid lines correspond to stable states and dashed lines to unstable states. Parameter values were $X = 1.3$ and $g = 0.4$. Note that this figure starts at $\alpha = 4.0$. Below this value the behavior remains unchanged.

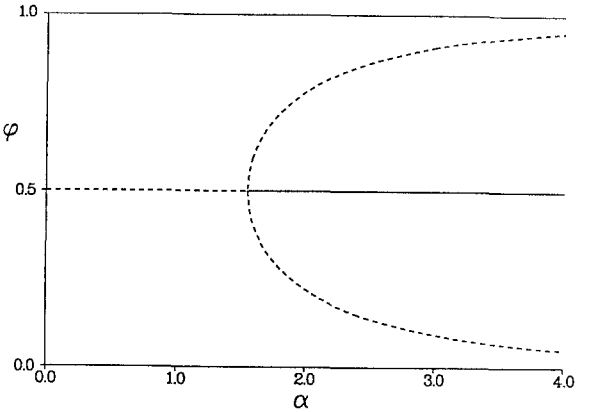

Fig. 2. Equilibrium phase differences between two identical integrate-and-fire neurons with mutual inhibitory coupling through alpha functions. The phase difference ϕ is plotted as a function of the synaptic rate constant α. Solid lines correspond to stable states and dashed lines to unstable states. Parameter values were $X = 1.3$ and $g = -0.4$.

where E_s is the contribution coming from one spike. For this particular example, we take E_s to be an alpha function

$$E_s(t) = g\alpha^2 t e^{-\alpha t} \tag{2.3}$$

where g and α are parameters determining the strength and speed of the synapse respectively and the factor of α^2 in (2.3) normalizes the integral of E_s over time to the value g. The discussion and proofs are not limited to this particular form. We take the constant $X > 1$ so both neurons fire spikes spontaneously in the absence of coupling. We consider cases where the two neurons continue firing periodically when they are coupled together. Suppose that neuron 1 fires at times $t = nT$ where T is the period and n is an integer, while neuron 2 fires at $t = (n - \phi)T$. Thus, both neurons are firing at the same frequency but are separated by a phase ϕ. We wish to determine possible values of the phase difference ϕ and conditions under which they arise.

In Fig. 1, we plot the asymptotic values of the phase difference ϕ obtained in this model with excitatory coupling ($g > 0$) for different values of the synaptic rate constant α. Small α corresponds to a slow synapse and in this case there are two possible states exhibiting either complete synchrony ($\phi = 0$ or equivalently $\phi = 1$) or complete anti-synchrony ($\phi = 1/2$). Only the anti-synchronous state is stable. As α increases, representing progressively faster synapses, there is a pitchfork bifurcation at a critical value of α (Abbott and van Vreeswijk, 1993) and two additional equilibrium states arise. At this point, the anti-synchronous state becomes unstable and the synchronous state remains unstable. The two new states are stable and are neither synchronous nor anti-synchronous. Instead, the phase difference is variable lying between 0 and 1/2 (or equivalently between 1/2 and 1). As $\alpha \to \infty$, the phase difference between the two oscillators approaches 0 (or 1) but for no value of α does the system achieve a stable synchronous state.

The situation for excitatory synapses should be contrasted with that for inhibitory synapses ($g < 0$) shown in Fig. 2. Here, the synchronous state ($\phi = 0$ or $\phi = 1$) is always stable. For slow synapses (small α), this is the only stable state, the anti-synchronous state is unstable. At the pitchfork bifurcation, the anti-synchronous state becomes stable and, again, two additional variable phase states arise but these are unstable. For fast synapses (large α), both the synchronous and anti-synchronous states are stable. As α increases, the domain of attraction of the synchronous state decreases while the domain of attraction of the anti-synchronous state increases. From Figs. 1 and 2 we see that exact synchronization with non-instantaneous synapses can be achieved in this model using inhibitory coupling but not excitatory coupling.

To analyze what is happening in this circuit, we note that with neuron 1 firing at times $t = nT$, the input to neuron 2 at $t = \theta T$ with $0 < \theta < 1$ is

$$E_2(\theta T) = E_T(\theta) \tag{2.4}$$

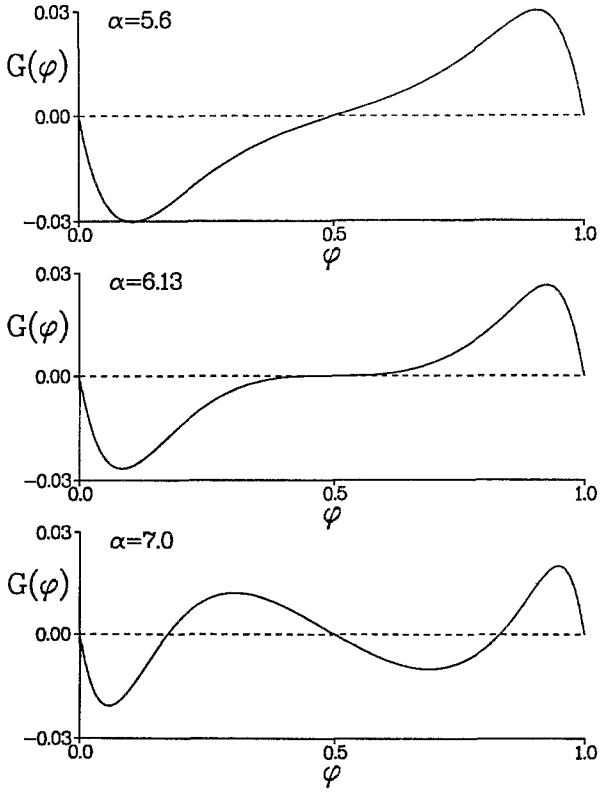

Fig. 3. G plotted as a function of the phase ϕ for excitatory alpha-function coupling. Three different α values are shown. Stable equilibium states correspond to zero crossings with positive slopes and unstable equilibrium states to zero crossings with negative slopes. Note that the synchronous state $\phi = 0$ or 1 is never stable and that the stability of the anti-synchronous state switches when two new stable states arise.

where

$$E_T(\theta) = \sum_{n=-\infty}^{0} E_s((\theta - n)T) \tag{2.5}$$

When E_s is an α-function as in equation (2.3), we find by summing the appropriate geometric series

$$E_T(\theta) = \frac{g\alpha^2 T e^{-\alpha\theta T}(\theta(1 - e^{-\alpha T}) + e^{-\alpha T})}{(1 - e^{-\alpha T})^2} \tag{2.6}$$

Outside the range $0 < \theta < 1$, E_T is defined by making it a periodic function. With neuron 2 firing at $t = (n - \phi)T$, the synaptic input to neuron 1 is

$$E_1((\theta + n)T) = E_T(\theta + \phi) \tag{2.7}$$

Since neuron 1 fires at $t = 0$, we have $x(0^+) = 0$ and by integrating equation (2.1) we find

$$x_1(T) = X(1 - e^{-T}) + Te^{-T} \int_0^1 d\theta e^{\theta T} E_T(\theta + \phi) = 1 \tag{2.8}$$

The last equality follows from the fact the neuron 1 fires again at time T. Similarly, neuron 2 fires at $t = -\phi T$ and again at $t = (1 - \phi)T$ so, after shifting the integral,

$$x_2((1 - \phi)T) = X(1 - e^{-T}) + Te^{-T} \times \int_0^1 d\theta e^{\theta T} E_T(\theta - \phi) = 1 \tag{2.9}$$

These two equations determine both the period T and the phase difference ϕ. Subtracting (2.8) from (2.9) and dividing by T gives the condition

$$G(\phi) = e^{-T} \int_0^1 d\theta e^{\theta T}[E_T(\theta + \phi) - E_T(\theta - \phi)] = 0 \tag{2.10}$$

An obvious solution is $\phi = 0$. Also, since $E_T(\theta + 1/2) = E_T(\theta - 1/2)$ by the periodicity of E_T, $\phi = 1/2$ is also a solution. These two solutions correspond to synchronous and anti-synchronous firing.

The stability of these and any other solution is determined by

$$G'(\phi) > 0 \tag{2.11}$$

where the prime signifies differentiation with respect to ϕ. To see why this is the case, we combine the second equality of equation (2.8) and the first equality of (2.9) and use (2.10) to note that

$$x_2((1 - \phi)T) = 1 - TG(\phi) \tag{2.12}$$

Suppose ϕ is slightly larger than a stable equilibrium value. Then, neuron 2 should fire later to restore the correct value of ϕ. This requires that $x_2((1 - \phi)T)$ given by the above formula should be smaller than 1, or equivalently, that G should be an increasing function of ϕ near the equilibrium value.

The function $G(\phi)$ is plotted in Fig. 3 for different values of α for the case of excitatory coupling. When $\alpha = 5.6$, there are solutions at $\phi = 0$, $1/2$, and 1 but only the anti-synchronous solution at $\phi = 1/2$ is stable. At the critical value $\alpha = 6.13$, this solution becomes unstable and two additional stable solutions arise from the point $\phi = 1/2$. This value corresponds to the bifurcation point in Fig. 1. As α increases further,

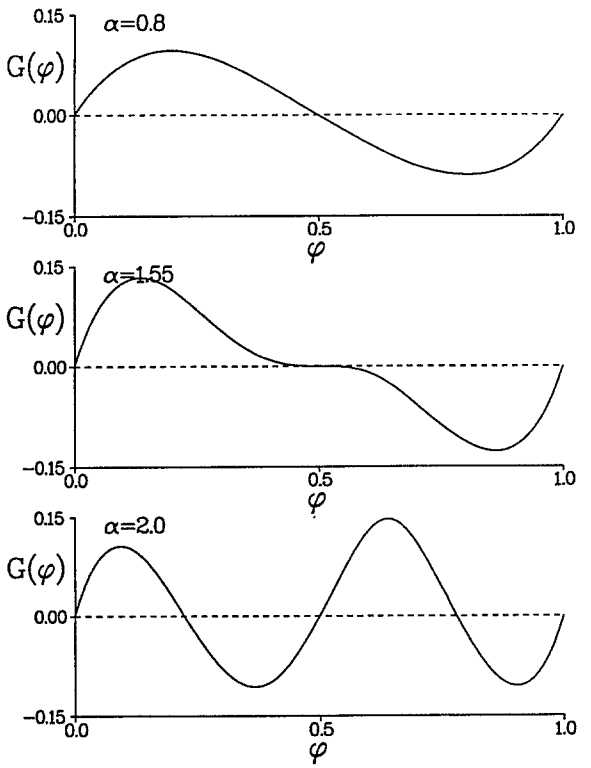

Fig. 4. G plotted as a function of the phase ϕ for inhibitory alpha-function coupling. Three different α values are shown. Stable equilibium states correspond to zero crossings with positive slopes and unstable equilibrium states to zero crossings with negative slopes. Note that the synchronous state $\phi = 0$ or 1 is always stable and the stability of the anti-synchronous state switches when two new unstable states arise.

these points move outward toward 0 and 1. In Fig. 4, the same series is shown for the case of inhibitory coupling. Since the slope of the curve with inhibitory coupling is generally opposite to that for excitatory coupling, the same set of solutions exist but their stability is reversed. New zero crossings appear in Fig. 4 at the value of α that produces the bifurcation in Fig. 2.

We can use the above results to prove that the solution $\phi = 0$ (or equivalently $\phi = 1$) is always unstable for excitatory synapses with any reasonable synaptic response function E_s. From equation (2.10) after integration by parts,

$$G'(0) = 2e^{-T}\left((e^T - 1)E_T(0) - T\int_0^1 d\theta e^{\theta T} E_T(\theta)\right) \quad (2.13)$$

The only condition we need to impose is that for excitatory coupling with finite rise time $E_T(\theta) > E_T(0)$ for $0 < \theta < 1$ so that

$$G'(0) < 2e^{-T}\left((e^T - 1)E_T(0) - T\int_0^1 d\theta e^{\theta T} E_T(\theta)\right) = 0 \quad (2.14)$$

The last equality follows from doing the integral. Thus, the synchronous state is always unstable. If instead, $E_T(\theta) < E_T(0)$ (for $0 < \theta < 1$) we have

$$G'(0) > 2e^{-T}\left((e^T - 1)E_T(0) - T\int_0^1 d\theta e^{\theta T} E_T(0)\right) = 0 \quad (2.15)$$

and the synchronous state is always stable. This is the reason that inhibitory rather than excitatory coupling produces a stable synchronous state. For example, the function E_T given by equation (2.6) satisfies $E_T(\theta) > E_T(0)$ for $g > 0$ and $E_T(\theta) < E_T(0)$ for $g < 0$.

Phase-Coupled Models

Since we are primarily interested in the relative phases of the model neurons we are studying, it is convenient to describe the state of each neuron directly in terms of a phase variable. This allows us to make our discussion more general and provides a more intuitive understanding of the synchronous and anti-synchronous states we find. To introduce and derive such a phase description, we consider a more general integrate-and-fire model of the form

$$\frac{dx_i}{dt} = f_1(x_i) + f_2(x_i)E_i(t) \quad (3.1)$$

for two model neurons, $i = 1, 2$. Equation (3.1) applies in the range $0 < x_i < 1$ and when $x_i = 1$ neuron i fires. We assume that the coupling is weak ($|f_2 E_i| \ll f_1$) and make a change of variables to a phase description by defining

$$\phi_i = \omega\int_0^{x_i} \frac{dx'}{f_1(x')} - \omega t \quad (3.2)$$

with

$$\frac{1}{\omega} = T = \int_0^1 \frac{dx'}{f_1(x')} \quad (3.3)$$

The phase variables satisfy

$$\frac{d\phi_i}{dt} = F(\omega t + \phi_i)E_i(t) \quad (3.4)$$

where

$$F(\omega t + \phi_i) = \omega \frac{f_2(x_i)}{f_1(x_i)} \tag{3.5}$$

with the right side re-expressed as a function of $\omega t + \phi_i$. F is defined to be a periodic function with period 1. Neuron i fires when $\omega t + \phi_i = n$ for integer n, or equivalently, when $t = (n - \phi_i)T$. Thus, as in equations (2.4) and (2.7)

$$E_1(t) = E_T(\omega t + \phi_2) \tag{3.6}$$

and

$$E_2(t) = E_T(\omega t + \phi_1) \tag{3.7}$$

with E_T given by equation (2.5). The phase variable equations of the model are then

$$\frac{d\phi_1}{dt} = F(\omega t + \phi_1) E_T(\omega t + \phi_2) \tag{3.8}$$

and

$$\frac{d\phi_2}{dt} = F(\omega t + \phi_2) E_T(\omega t + \phi_1) \tag{3.9}$$

In these equations, the function F is the phase response function of the model. To see this, note that if E_T were a δ function then, by integrating the above equations, we find that F would give the resulting change in phase.

We now assume that the term ωt varies much more quickly than either of the ϕ_i. This will be true, for example, if the coupling is weak enough. In this case, we can average the right sides of the above two equations over one period T to obtain

$$\frac{d\phi_1}{dt} = H(\phi_2 - \phi_1) \tag{3.10}$$

and

$$\frac{d\phi_2}{dt} = H(\phi_1 - \phi_2) \tag{3.11}$$

with

$$H(\phi) = \frac{1}{T} \int_0^T dt\, F(\omega t - \phi) E_T(\omega t) \tag{3.12}$$

The fact that H can be written as a function of the phase difference follows from the periodicity of F and E_T. We can change the expression for H to an integral involving E_s instead of E_T by using the periodicity of F and the definition (2.5),

$$H(\phi) = \int_0^\infty d\theta\, F(\theta - \phi) E_s(\theta T) \tag{3.13}$$

Finally, if we define the phase difference between the two oscillators as $\phi = \phi_1 - \phi_2$, it is determined by the equation

$$\frac{d\phi}{dt} = -G(\phi) \tag{3.14}$$

where

$$G(\phi) = H(\phi) - H(-\phi) \tag{3.15}$$

Equation (3.13), has a simple interpretation. If the coupling between the two oscillators was instantaneous with unit strength so that E_S was a delta function at $\theta = 0$, then the instantaneous phase-coupling interaction function would be

$$H_\infty(\phi) = F(-\phi) \tag{3.16}$$

However with non-instantaneous coupling, the interaction function is a convolution, obtained from equation (3.13),

$$H(\phi) = \int_0^\infty d\theta\, H_\infty(\phi - \theta) E_s(\theta T) \tag{3.17}$$

Thus, if we know the interaction function for an instantaneous synapse, we can determine the dynamic interaction function simply by performing the appropriate convolution integral. This convolution has profound effects on the stability and the number of phase-locked states of the model.

Equations (3.14), (3.15) and (3.17) are extremely general. Any pair of oscillators coupled with arbitrary synaptic dynamics can be reduced to a pair of phase equations as above if the interactions are sufficiently weak (Ermentrout and Kopell, 1984). In particular, the phase interaction function H can be written as a convolution of the instantaneous interaction function H_∞ with the synaptic response function as in (3.17). If the two oscillators are identical and symmetrically coupled, we can determine the phase lags between them by looking at the zeros of G defined in (3.15) as the odd part of the interaction function. These are stable if G' is positive. Since H is periodic with period 1, G must have zeros at $\phi = 0$, 1/2 and 1. We need only look at the slopes of G at these zeros to determine the stability of the synchronous and anti-synchronous states.

We will consider a particularly simple case,

$$H_\infty(\phi) = \sin(2\pi\phi) \tag{3.18}$$

For this interaction function, the instantaneous model has a stable synchronous solution and an unstable anti-synchronous solution for excitatory coupling. For

inhibitory coupling the stability is reversed between these two states. To reveal the role of the finite synaptic rise time, we will treat two types of synaptic interaction functions, a simple exponential

$$E_s(t) = g\alpha \exp(-\alpha t) \tag{3.19}$$

and the alpha function of (2.3). For the exponential synapse, we find from equations (3.15) and (3.17) and by doing the exponential integrals that

$$G(\phi) = \frac{2g\alpha^2 T^2}{(\alpha^2 T^2 + 4\pi^2)} \sin(2\pi\phi) \tag{3.20}$$

Thus, for an exponential synaptic response function the stability is the same as it is for the instantaneous case for all values of α. The synchronous state is stable for excitatory coupling ($g > 0$) and the anti-synchronous state is stable for inhibitory coupling ($g < 0$). This is because the exponential response has an instantaneous rise time. If instead we use the alpha-function synaptic response, we find

$$G(\phi) = \frac{2g\alpha^2 T^2(\alpha^2 T^2 - 4\pi^2)}{(\alpha^2 T^2 + 4\pi^2)^2} \sin(2\pi\phi) \tag{3.21}$$

From this we see that for excitatory coupling ($g > 0$) the synchronous state $\phi = 0$ is stable and the asynchronous state $\phi = 1/2$ is unstable if $\alpha > 2\pi/T$. If $\alpha < 2\pi/T$ however, excitatory coupling leads to a stable asynchronous state. For inhibitory coupling ($g < 0$) the reverse is true.

In general we can express H_∞ as a Fourier series

$$H_\infty(\phi) = \sum_n C_n \exp(2\pi i n\phi) \tag{3.22}$$

We find that, in general, the presence of higher Fourier components smoothes the transition from synchronous to asynchronous behavior so that the system no longer makes a sudden jump from one to the other at a critical value of α as it does for the pure sine case. Including terms other than the sine term of (3.18) can also induce bifurcations for the case of exponential synaptic coupling.

The Hodgkin-Huxley Model

To see if the results we obtained in the previous sections carry over to more complete and accurate neuron models, we have simulated two Hodgkin-Huxley model neurons and also analyzed this circuit using the phase-coupling description. For the simulation we used two identical two-compartment neurons with active soma compartments and passive dendritic compartments. The active compartments contained the usual Hodgkin-Huxley sodium and potassium conductances. For the phase-coupling analysis, the interaction functions were computed for the Hodgkin-Huxley model numerically (see also Hansel, Mato and Meunier, 1993) and then decomposed into their first few Fourier components. The first three to four terms in the Fourier expansion (3.22) provided a sufficiently accurate description for our purposes. Then the odd part of the interaction function was computed for various types of synaptic dynamics. Both approaches produced similar results so we will focus on the results provided by the phase analysis. We consider two types of synaptic response functions E_s, either a pure exponential (3.19) or the alpha function (2.3).

Figure 5 shows the equilibrium values of the phase-difference ϕ for excitatory exponential coupling. For very large α, there are two stable states, the synchronous and anti-synchronous states. As α decreases the anti-synchronous state loses stability at $\alpha_2 \approx 14$/ms. For smaller α, a pair of new stable asynchronous states bifurcates from synchrony at $\alpha = \alpha_1 \approx 0.3$/ms and these remain stable for all smaller values of α.

In Fig. 6, we show the bifurcation diagram for excitatory alpha-function synapses. As in the case of exponential synapses, both the anti-synchronous and the synchronous states are stable for very fast synapses. At $\alpha = \alpha_3 \approx 28$/ms the anti-synchronous state loses stability and only the synchronous state remains stable. For $\alpha < \alpha_2 \approx 0.82$/ms, the synchronous state loses stability to a pair of asynchronous solutions. Unlike the exponential synapses, these states then merge with the anti-synchronous state at $\alpha_1 \approx 0.4$ ms and the anti-synchronous state remains stable for all smaller values of α. Note that Fig. 6 is similar to Fig. 1 except that the asynchronous states merge with the synchronous state at finite α and there is a second bifurcation for very large α.

Figures 7 and 8 show exponential and alpha-function coupling respectively for inhibitory synapses. The behavior is similar to that of excitatory coupling except that the stability is reversed. The detailed points of bifurcation are also different. Figure 8 is similar to Fig. 2 except that the synchronous state destabilizes at finite $\alpha = \alpha_2$ and there is a second bifurcation at $\alpha = \alpha_3$.

The overall conclusion from this analysis is that the results of both integrate-and-fire models and phase-coupled models apply to more accurate models pro-

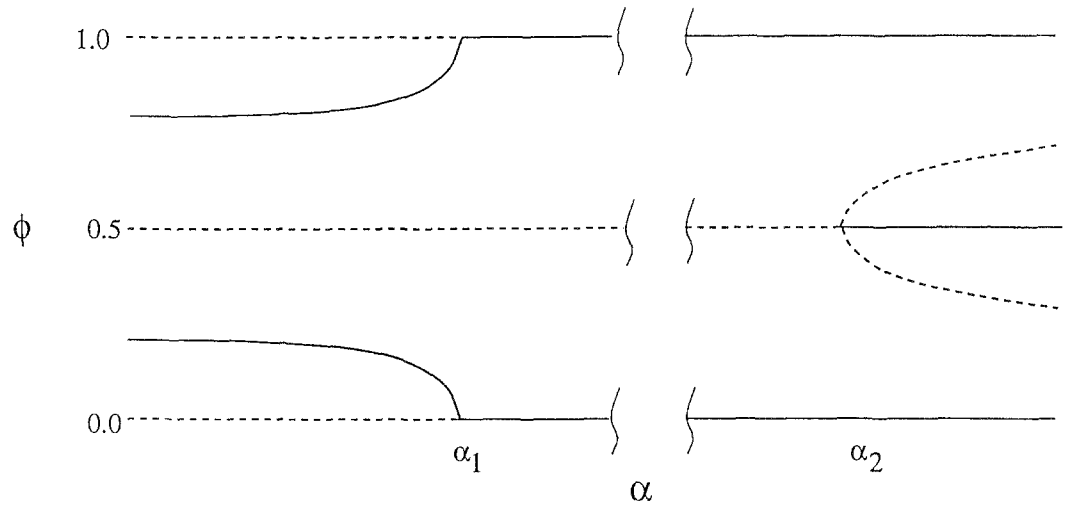

Fig. 5. Equilibrium phase differences between two identical Hodgkin-Huxley neurons with mutual excitatory coupling through exponential functions. The phase difference ϕ is plotted as a function of the synaptic decay constant α. Solid lines correspond to stable states and dashed lines to unstable states. The synaptic current was given by $0.05\ \max(\tanh(V-25),0)(E-V)$ with E set 100 mV above the resting potential.

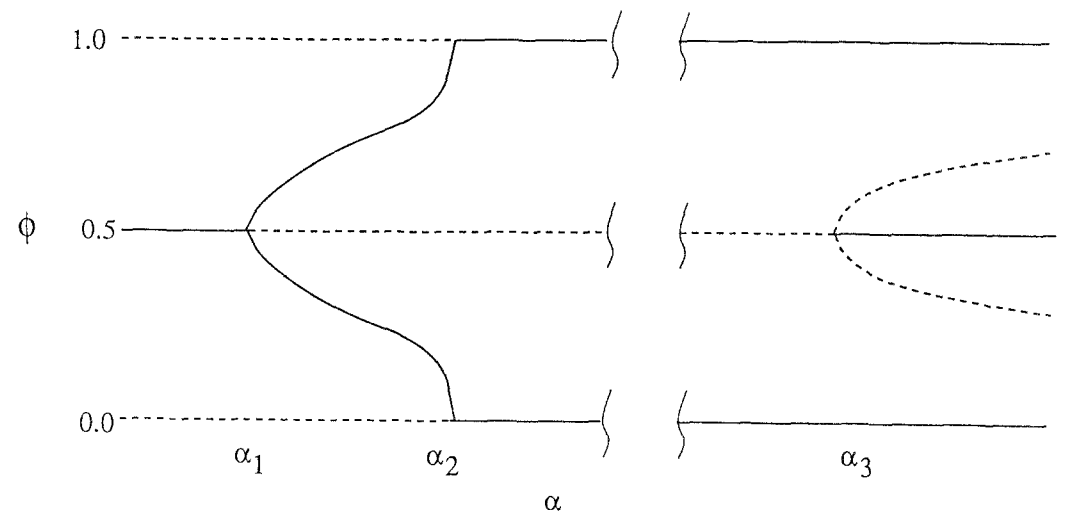

Fig. 6. Equilibrium phase differences between two identical Hodgkin-Huxley neurons with mutual excitatory coupling through alpha functions. The phase difference ϕ is plotted as a function of the synaptic rate constant α. Solid lines correspond to stable states and dashed lines to unstable states. The synaptic current was given by $0.05\ \max(\tanh(V-25),0)(E-V)$ with E set 100 mV above the resting potential.

vided that the synaptic rise time is slower than the width of the action potential.

Discussion

Our results indicate that non-instantaneous synapses have a profound effect on synchronous states of coupled oscillators and often reverse our intuitive impressions about the effects of excitatory and inhibitory coupling. The results from phase-coupled models allow us to develop an intuitive picture of why this is happening. From equations (3.15) and (3.17) we find that for the synchronous state, $\phi = 0$

$$G'(0) = 2\int_0^\infty d\theta\, H'_\infty(-\theta)E_s(\theta T)$$
$$= -2\int_0^\infty d\theta\, F'(\theta)E_s(\theta T) \qquad (5.1)$$

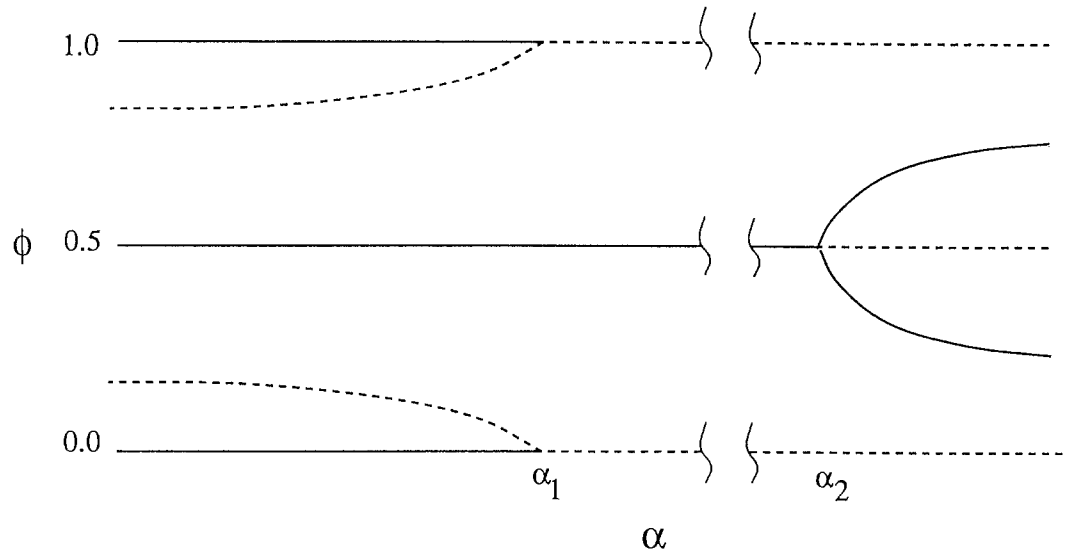

Fig. 7. Equilibrium phase differences between two identical Hodgkin-Huxley neurons with mutual inhibitory coupling through exponential functions. The phase difference ϕ is plotted as a function of the synaptic decay constant α. Solid lines correspond to stable states and dashed lines to unstable states. The synaptic current was given by 0.05 $\max(\tanh(V-25),0)(E-V)$ with E set 12 mV below the resting potential.

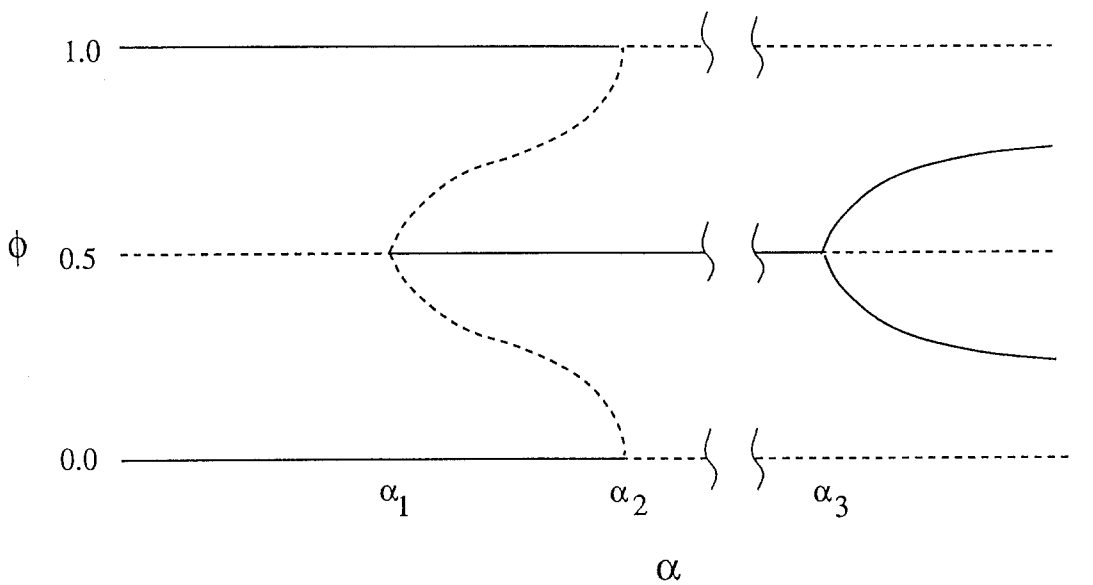

Fig. 8. Equilibrium phase differences between two identical Hodgkin-Huxley neurons with mutual inhibitory coupling through alpha functions. The phase difference ϕ is plotted as a function of the synaptic rate constant α. Solid lines correspond to stable and dashed lines to unstable states. The synaptic current was given by 0.05 $\max(\tanh(V-25),0)(E-V)$ with E set 12 mV below the resting potential.

A key feature of the phase response curve for neurons with rapid well-separated spikes is that $F'(\theta) < 0$ for a narrow region around $\theta = 0$ while $F'(\theta) > 0$ through most of the range of θ values. This is because excitation during an action potential delays the next spike while excitation during the interspike interval phase advances it. The range where $F'(\theta) < 0$ corresponds roughly to the phase width of the action potential.

If the synaptic response is very rapid, the integral in equation (5.1) is dominated by the region near $\theta = 0$.

In this region $F'(\theta) < 0$ so the integrand will be negative, $G'(0)$ will be positive and the synchronous state will be stable. This agrees with our intuitive picture of the effect of excitatory coupling. However, as we slow down the rise of the synaptic response, the region where $F'(\theta) > 0$ will start to contribute more to the integral in (5.1). When this contribution dominates over that coming from the narrow region where $F'(\theta) < 0$, the synchronous state will become unstable. For inhibitory coupling, the synaptic response has the same shape but the opposite sign. The entire argument goes through identically except that all the signs change. Thus, inhibition and not excitation will generically lead to a stable synchronous state unless the time scale for the synaptic rise is very short or the action potential is broad.

Acknowledgments

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