Contribution of Synaptic Depression to Phase Maintenance in a Model Rhythmic Network

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1Life Sciences Department and Zlotowski Center for Neurosciences, Ben-Gurion University of the Negev, Beer-Sheva, 84105 Israel; 2Department of Mathematical Sciences, New Jersey Institute of Technology, Newark, New Jersey 07102; 3Courant Institute of Mathematical Sciences, New York University, New York City, New York 10012; 4Center for Applied Mathematics and Statistics, New Jersey Institute of Technology, Newark, 07102; and 5Department of Biological Sciences, Rutgers University, Newark, New Jersey 07102

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Manor, Yair, Amitabha Bose, Victoria Booth, and Farzan Nadim. Contribution of synaptic depression to phase maintenance in a model rhythmic network. J Neurophysiol 90: 3513–3528, 2003. First published June 18, 2003; 10.1152/jn.00411.2003. In many rhythmic neuronal networks that operate in a wide range of frequencies, the time of neuronal firing relative to the cycle period (the phase) is invariant. This invariance suggests that when frequency changes, firing time is precisely adjusted either by intrinsic or synaptic mechanisms. We study the maintenance of phase in a computational model in which an oscillator neuron (O) inhibits a follower neuron (F) by comparing the dependency of phase on cycle period in two cases: when the inhibitory synapse is depressing and when it is nondepressing. Of the numerous ways of changing the cycle period, we focus on three cases where either the duration of the active state, the inactive state, or the duty cycle of neuron O remains constant. In each case, we measure the phase at which neuron F fires with respect to the onset of firing in neuron O. With a nondepressing synapse, this phase is generally a monotonic function of cycle period except in a small parameter range in the case of the constant inactive duration. In contrast, with a depressing synapse, there is always a parameter regime in which phase is a cubic function of cycle period: it decreases at short cycle periods, increases in an intermediate range, and decreases at long cycle periods. This complex shape for the phase-cycle relationship arises because of the interaction between synaptic dynamics and intrinsic properties of the postsynaptic neuron. By choosing appropriate parameters, the cubic shape of the phase-cycle relationship is likely to be present in models where the postsynaptic neuron is sensitive to synaptic input. Consequently, we find that although a depressing synapse does not produce perfect phase maintenance, in most cases it is superior to a nondepressing synapse in promoting a constant phase difference.

INTRODUCTION

Neuronal oscillations have been implicated in cognitive functions (Eckhorn et al. 1988; Fries et al. 2001; Gray et al. 1989; Rodriguez et al. 1999), in various sensory states (Laurent et al. 1996; Patel and Baladad 2000; Perez-Orive et al. 2002) and in the production of motor patterns (Grillner et al. 2000; Marder 2000; Nusbaum and Behnacker 2002). In many cases, such neuronal networks produce rhythmic activity over a wide range of frequencies (Marder and Calabrese 1996). The output of a rhythmic network is defined by the frequency dependence of the activity of individual neurons or groups of neurons. For instance, the activity of different neurons may be separated by a fixed time latency, despite wide changes in frequency (Ahissar et al. 2000; Bartos et al. 1999; Faulkes and Paul 1998). Often, however, rather than a constant latency, neurons maintain a constant phase difference (DiCaprio et al. 1997; Friesen and Pearce 1993; Grillner 1981; O’Keefe and Recce 1993; Young 1975), where the phase difference is the ratio of latency and cycle period. In other cases, when frequency is changed neurons in the network show differences in activity times that range between constant latency and constant phase (Davis 1969; Fischer et al. 2001; Grillner 1981; Hooper 1997a,b; Pearson and Iles 1970).

Nowhere is the importance of phase adjustment more obvious than in rhythmic motor systems, which operate in a wide range of frequencies (Brodin et al. 1985; Marder and Calabrese 1996; Mercier and Wilkens 1984; Skinner and Mulloney 1998) and where mechanical restrictions dictate that the pattern in muscle activity should be adjusted in accordance to speed of movement. In the crab ventilatory system, for instance, phase constancy is necessary to produce a smooth and coordinated movement of the ventilatory pump (DiCaprio et al. 1997). In lamprey and other aquatic organisms propelled by undulatory locomotion, fixed phase lags between consecutive segments guarantee that the rostra-caudal axis of the body forms exactly one wavelength. This ensures the minimization of lateral thrust and the optimization of swimming at all possible speeds (Grillner 1974; Sigvardt 1981).

Despite its importance in central pattern generation, the mechanisms underlying phase constancy across different cycle frequencies are not well understood. Several studies have addressed the problem of phase maintenance in chains of coupled oscillators and have proposed that the mechanism underlying phase constancy is embedded within the circuitry. In Williams (1992), for example, the synapses that make up a unit oscillator are repeated in neighboring segments, albeit with a reduced synaptic strength. In Skinner and Mulloney (1998), each segment one neuron makes equal excitatory and inhibitory connections to two identical neurons in the previous segment.

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In both works, even though phase constancy was demonstrated, the essence of the mechanism remains unclear.

In this work, we propose a novel mechanism involving short-term synaptic depression to create phase maintenance between neurons in rhythmic networks. We consider a simple model network consisting of an oscillatory neuron that has an inhibitory synapse onto a follower neuron. The mechanism is based on the simple idea that the latency of firing in the postsynaptic cell is directly affected by the synaptic strength. In a nondepressing synapse, the latency and time course of the synapse are independent of cycle frequency. In contrast, when the synapse is depressing, synaptic strength varies with cycle frequency, allowing postsynaptic latency to vary as well. With the correct choice of synaptic dynamics, we show that it is possible to vary the postsynaptic latency in a way that is approximately proportional to the change in cycle frequency, thereby allowing the phase to be relatively well maintained.

We have intentionally chosen a very simple oscillator-follower model to illustrate our proposed mechanism for phase maintenance. In spite of the simplicity of this model, the explanation of how a depressing synapse contributes to maintaining phase is surprisingly complicated. As we will show, this complexity arises because of the interaction between synaptic dynamics and intrinsic properties of the postsynaptic neuron. At certain cycle periods, the latency is determined by the intrinsic properties alone, whereas in other cycle periods, it is mostly affected by the synaptic dynamics. In principle, there can be numerous ways in which cycle period of an oscillatory system can change. We explore in detail three cases where cycle period is varied while preserving the duration of the active state, the duration of the inactive state, or both durations proportionally. Despite their simple nature, these three representative ways of changing the cycle period provide results that are insightful for the general case. Indeed, in all three cases synaptic depression provides a degree of flexibility that can be used to automatically adjust the time difference between the activities of the two neurons, such that their phase difference is approximately maintained. Although a depressing synapse does not produce perfect phase maintenance, we show that in most cases it is superior to a nondepressing synapse in promoting a constant phase difference.

**METHODS**

The circuit consists of an oscillator neuron (O) and a follower neuron (F) coupled with an inhibitory synapse from O to F. In this study, we focus only on the effects of changing the period of the oscillator on the activity of the follower cell F. Thus for simplicity, neuron O is modeled as a square-wave oscillator that steps from a low voltage of −50 mV (the inactive state) to a high voltage of +50 mV (the active state). The durations of the active and inactive states (black rectangles), and the intervals between them, are defined as $T_{\text{active}}$ and $T_{\text{inactive}}$, respectively (bottom). Middle: time courses of the variable $s$ (thick line), which represents the fraction of open synaptic channels, and the depression variable $d$ (thin line), which represents the fraction of available synaptic resources. At the instant that neuron O switches from its inactive to its active state, $s$ is set to the value of $d$. The time constants that govern the growth and decay of $s$ and $d$ are indicated.

**RESULTS**

1) $T_{\text{active}}$ remains constant and $T_{\text{inactive}}$ varies ($T_{\text{inactive}}$ = 750 ms in **RESULTS**).

2) $T_{\text{inactive}}$ remains constant and $T_{\text{active}}$ varies ($T_{\text{active}}$ = 400 ms in **RESULTS**).

We now describe the model of the follower neuron F and the synapse from O to F. For each case of changing the period, we refer to the model with the parameter values given below as the “reference model.” When noted, the reference model will be changed to assess the dependence of our model on parameters (see **RESULTS**).

**Cellular model**

The follower neuron F is modeled with standard current balance equations based on the Morris-Lecar model (Morris and Lecar 1981). The ion conductances of this neuron include a fast activating conductance (the “calcium” conductance), a slow activating conductance with low equilibrium potential (the “potassium” conductance), and a non-voltage-dependent conductance (the “leak” conductance)

$$dV_f/dt = -\frac{g_C m_F(V_f - E_C)}{C_m} - \frac{g_K w_F(V_f - E_K)}{C_m} - g_L (V_f - E_L) - I_{\text{syn}} + I_{\text{ext}}$$

where $V_f$ is the membrane potential and $w_F$ governs the gating of the potassium conductance. The maximal conductances are (in mS/cm^2) $g_C = 0.3$, $g_K = 0.6$, and $g_L = 0.15$; the reversal potentials are (in mV) $E_C = 100$, $E_K = -70$, and $E_L = -50$; the steady-state activation functions are $m_{\text{ss}}(V_f) = 0.5 [1 + \tanh((V_f - 1)/14.5)]$ for the calcium conductance, and $w_{\text{ss}}(V_f) = 0.5 [1 + \tanh((V_f + 20)/15)]$ for the potassium conductance; the applied current $I_{\text{ext}}$ is 7.5 μA/cm^2. The parameter $\tau_p$, which determines the speed of the intrinsic dynamics in neuron F, is equal to 150 ms in the constant $T_{\text{active}}$ case and 100
ms in the other two cases. With these parameters, neuron F is a quiescent cell with a high-voltage equilibrium point.

**Synaptic model**

The current balance equation for neuron F includes an additional term that represents the synaptic current from O to F

\[ I_{syn} = g_{syn}(V_F - E_{syn}) \]  

(2)

where the synaptic reversal potential \( E_{syn} \) is \(-70 \text{ mV} \), and the maximal synaptic conductance \( g_{syn} \) (in \( \text{mS/cm}^2 \)) is: 0.185 in the constant \( T_{Active} \) case, 0.22 in the constant duty cycle case, and 0.35 in the constant \( T_{Inactive} \) case.

The gating variable \( s \) represents the fraction of open synaptic channels. In general, except for the single time point when neuron O switches from its nonactive to its active state, \( s \) decays toward 0. This decay represents the closure of synaptic channels after the onset of transmitter release. When neuron O switches to its active state, \( s \) is set to the fraction of available synaptic resources at that time. This fraction is described by a second variable \( d \), which decreases toward 0 when the presynaptic cell O is active (representing the decay of available synaptic resources, i.e., the synaptic depression), and increases toward 1 when the presynaptic cell O is not active (representing the recovery of available synaptic resources).

Figure 1 shows time traces of the postsynaptic voltage \( V_F \) (top), \( s \) (thick, middle), and \( d \) (thin, middle). At the onset time of the active state in neuron O, \( s \) is set to the value of \( d \). Except for this single time point, \( s \) decays to 0 in two steps: 1) during the active state of neuron O (black bars, bottom trace), \( s \) decays with a slow time constant \( \tau_s \). This slow decay represents the fatigue of the synapse, for example as a result of desensitization of synaptic receptors. In our study, we assumed that the synaptic fatigue is small. Hence, we set \( \tau_s \) to 25 s such that \( s \) remains essentially constant for the duration of the active state. And 2) during the nonactive state of neuron O (between black bars, bottom trace), \( s \) decays with a faster time constant \( \tau_s \). This decay represents the closing of synaptic channels as the neurotransmitter is removed from the synaptic cleft. The value of \( \tau_s \) is 1.5 s in the constant \( T_{Active} \) case, 0.5 s in the constant duty cycle case, and 0.3 s in the constant \( T_{Inactive} \) case. Hence, except for the single time point where \( s \) is set to the value of \( d \), the dynamics of \( s \) are governed by the following equation

\[ \frac{ds}{dt} = \begin{cases} -s/\tau_s & \text{neuron O is non-active} \\ -s/\tau_s & \text{neuron O is active} \end{cases} \]  

(3)

where neuron O is defined as active when its membrane potential is above 0 mV and nonactive otherwise.

The variable \( d \) represents the fraction of available synaptic resources (depression). It evolves independently of \( s \), decreasing toward 0 with time constant \( \tau_d \) when neuron O is active and recovering toward 1 with time constant \( \tau_d \) when neuron O is nonactive

\[ \frac{dd}{dt} = \begin{cases} (1-d)/\tau_d & \text{neuron O is non-active} \\ -d/\tau_d & \text{neuron O is active} \end{cases} \]  

(4)

where \( \tau_d = 3 \text{ s} \); \( t_{df} = 1.5 \text{ s} \) for the constant \( T_{Active} \) case and 0.5 s for the other two cases. For a depressing synapse, the peak strength of the synaptic current depends on the peak value of \( d \) during the cycle.

To make a synapse nondepressing, we assume that the fraction of available synaptic resources is constant, that is, independent of the period. Thus for a nondepressing synapse the value of \( d \) is not determined by Eq. 4 but is fixed to \( d = 1 \). We can tune a nondepressing synapse to have dynamics identical to a depressing synapse at a specific value of the period by setting \( g_{syn} \) in the nondepressing case to the maximum value of \( g = \frac{\bar{g}_{syn}}{s} \) for that specific case of the depressing synapse.

**Definitions of key values of the synaptic conductance**

To facilitate the understanding of how synaptic conductance determines the onset of activity in neuron F, we define several key values of the synaptic conductance. The synaptic conductance itself, \( g \), is simply the product of the maximal conductance \( g_{syn} \) and the fraction of open synaptic channels \( s \).

Note that if the synaptic conductance is too large, activity in neuron F is suppressed. Thus a necessary, but not sufficient, condition for neuron F to become active is that the synaptic conductance \( g \) is less than some value \( g^* \) defined here as the critical conductance.

The conductance immediately before the onset of activity in neuron F is defined as the transition conductance \( g_{trans} \). It is important to emphasize that the transition conductance \( g_{trans} \) is not identical to the critical conductance \( g^* \). For example, if the inhibition is weak (i.e., the maximal synaptic conductance \( g_{syn} \) is small), the synaptic conductance \( g \) may never be sufficiently large to reach the critical conductance \( g^* \), but by definition it will reach the value of \( g_{trans} \) immediately before the onset of activity in neuron F. On the other hand, when the inhibition is strong (\( g_{syn} \) is large), at the onset of activity in neuron O, the synaptic conductance \( g \) may be larger than the critical conductance \( g^* \). If the duration of the nonactive state in neuron O is sufficiently long, \( s \) can decay to a sufficiently small value such that the synaptic conductance \( g \) reaches the critical conductance \( g^* \) and at that time neuron F becomes active. It is only in this latter case that the critical conductance \( g^* \) and the transition conductance \( g_{trans} \) are equal, and the condition \( g < g^* \) becomes a sufficient condition for the transition to the active state.

We further define \( g_{peak} \) as the synaptic conductance at the onset of activity in neuron O, i.e., at the instant that \( s \) is set to the value of \( d \). Because \( s \) decays at all other times, \( g_{peak} \) is the peak synaptic conductance reached during a cycle. Depending on the period, \( g_{peak} \) may be greater than or less than the critical conductance \( g^* \). In the former case, the synapse is defined as weak; it is strong in the latter case.

**Definition of time interval and phase**

For the analysis of the effects of the depressing synapse on the firing time of neuron F, we arbitrarily define the onset of firing of a neuron as the time at which the membrane potential of this neuron increases past 0 mV. The period \( P \) is defined by the interval between consecutive onsets of firing in neuron O. \( \Delta t \) is defined as the time interval between the onset of firing in neuron O and the subsequent onset of firing in neuron F. The phase \( \phi \) of firing in neuron F is defined as \( \Delta t/P \). Thus the phase ranges between 0 and 1 with both extremes corresponding to the case where neurons O and F start their active states at the same time. Whenever the period is changed, we allow the system to equilibrate before we measure \( \Delta t \) and \( \phi \).

All numerical simulations were done with the software XPPAUT (Ermentrout 2002).

**Results**

In this study, we examine how the existence of synaptic depression affects the activity time \( \Delta t \) of follower neurons when the period changes. \( \Delta t \) is a direct function of the synaptic strength. When the synapse is nondepressing, the synaptic strength is independent of the period. In contrast, with a depressing synapse, the synaptic strength changes as a function of the period. Hence, a depressing and a nondepressing synapse affect the activity time of a follower neuron in different ways. Figure 2 illustrates this fact by comparing the activity of a follower neuron with a depressing and nondepressing synapse, for three different period values. Here, when the synapse was nondepressing, \( \Delta t \) was fixed for all three periods; with a depressing synapse, \( \Delta t \) was larger for larger period values. If
Dependence of synaptic conductance on cycle period

The oscillatory activity of neuron O dictates an oscillatory time course for the synaptic conductance $g \equiv \bar{g}_{\text{syn}}$. At the onset of activity in neuron O, the synaptic conductance $g$ is at its peak value $g_{\text{peak}}$. The synaptic conductance then decays, first with time constant $\tau_\text{in}$ (when neuron O is active) and then with time constant $\tau_\text{r}$ (when neuron O is nonactive; see Fig. 1). Immediately before the onset of activity in neuron F, the synaptic conductance is equal to the transition conductance $g_{\text{jump}}$. $\Delta t$ measures the time during which the synaptic conductance decays from $g_{\text{peak}}$ to $g_{\text{jump}}$. Analytical derivations for $g_{\text{peak}}$ and $\Delta t$ are provided in the APPENDIX. An analytical expression for $g_{\text{jump}}$ depends on the intrinsic properties of neuron F and will not be derived here. However, we will show that for a wide range of period values, $g_{\text{jump}}$ is constant.

The primary effect of synaptic depression was to change the value of $g_{\text{peak}}$. The following equation defines $g_{\text{peak}}$, regardless of how the period is changed (see APPENDIX)

$$g_{\text{peak}} = \bar{g}_{\text{syn}}(1 - \exp(-T_{\text{inactive}}/\tau_\text{r}))(1 - \exp(-T_{\text{inactive}}/\tau_\text{r} \exp(-T_{\text{active}}/\tau_\text{d})))$$

Equation 5 shows that $g_{\text{peak}}$ depends not only on the period ($= T_{\text{inactive}} + T_{\text{active}}$), but also on the time constants of recovery ($\tau_\text{r}$) and depression ($\tau_\text{d}$) and the maximal conductance $\bar{g}_{\text{syn}}$.

Figure 4 shows how the peak conductance $g_{\text{peak}}$ and the transition conductance $g_{\text{jump}}$ depended on period for the three different cases when the synapse was depressing. The effect of the synapse on the firing time of neuron F depended on the relationship of $g_{\text{peak}}$ and $g_{\text{jump}}$ to $g^*$, the critical synaptic conductance below which the synapse was too weak to keep neuron F inactive (see METHODS). The critical conductance $g^*$ is constant. In general, two factors can determine the firing time of neuron F: the intrinsic properties of neuron F (determined by $\tau_\text{r}$ and the synaptic dynamics (determined by $\tau_\text{d}$, $E_{\text{syn}}$ and $g_{\text{syn}}$). The extent to which the synapse recovered from depression determined which of these two factors affected the firing time of neuron F. For example, if the synapse was recovered enough so that $g_{\text{peak}}$ was larger than the critical conductance $g^*$ and the transition conductance $g_{\text{jump}}$ was equal to $g^*$, then the firing time of neuron F was completely determined by the synapse. In this case, the necessary condition for firing of neuron F ($g_{\text{jump}} \leq g^*$) became a sufficient condition. On the other hand, if the synapse was depressed and $g_{\text{peak}}$ was smaller than $g^*$, the firing of neuron F was mainly determined by its intrinsic properties because the synapse was too weak to...
greatly affect it. In this case, \( g_{\text{jump}} \) was not fixed; its variation with period resulted from the variation of \( g_{\text{peak}} \) with period.

In Fig. 4A, the membrane potential of neuron F (\( V_F \)) and the synaptic conductance (\( g \)) are shown for the constant \( T_{\text{Active}} \) case when the period is 500, 1,000, and 2,000 ms. At a period of 500 ms, both the peak conductance \( g_{\text{peak}} \) and the transition conductance \( g_{\text{jump}} \) were less than the critical conductance \( g^* \) (---). At periods of 1,000 and 2,000 ms, \( g_{\text{peak}} \) was larger than

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the critical conductance $g^*$, whereas $g_{\text{jump}}$ was equal to $g^*$. Figure 4B shows the dependencies of $g_{\text{peak}}$ and $g_{\text{jump}}$ on the period for a continuous range of period values. Because the period was increased by increasing $T_{\text{inactive}}$ as the period increased, the synapse had more time to recover from depression, and thus $g_{\text{peak}}$ increased (as can also be seen directly from Eq. 5). For a period $<500$ ms, the synapse was too weak to inhibit neuron F, and neuron F remained at its equilibrium point and displayed no rhythmic activity (not shown). For period values $>500$ ms, both $g_{\text{peak}}$ and $g_{\text{jump}}$ increased with the period. For period values $<750$ ms, $g_{\text{peak}}$ was smaller than the critical conductance $g^*$: the synapse was weak and the firing of neuron F was mainly affected by the intrinsic properties of neuron F. For period values $>750$ ms but $<1,250$ ms, $g_{\text{peak}}$ was larger than the critical conductance $g^*$, but $g_{\text{jump}}$ was smaller than $g^*$. In this range, the synapse affected the firing time of neuron F together with the intrinsic properties of neuron F. When the period was $>1,250$ ms, $g_{\text{jump}}$ was equal to the critical conductance $g^*$ (a constant value) and the firing of neuron F was completely determined by the synapse.

Figure 4, C and D, shows the corresponding situation for the constant duty cycle case. This case is similar to the constant $T_{\text{active}}$ case in the peak dependencies of the conductance $g_{\text{peak}}$ and the transition conductance $g_{\text{jump}}$ on period. Note that $g_{\text{peak}}$ and $g_{\text{jump}}$ increased with the period, and this result was independent of the choice of time constants of recovery and depression (not shown). Here the synapse completely determined the firing time of neuron F ($g_{\text{peak}} > g^*$ and $g_{\text{jump}} = g^*$) when the period was $>2,500$ ms. This value is relatively large, compared with the constant $T_{\text{active}}$ case (where the synapse completely determined the firing time of neuron F when the period was $>1,250$ ms). This is because here the period was increased by increasing both $T_{\text{active}}$ and $T_{\text{inactive}}$. Hence, not only the recovery from depression increased when the period increased but also the extent of depression.

Figure 4, E and F, shows the situation for the $T_{\text{inactive}}$ constant case. Here the dependencies of the peak conductance $g_{\text{peak}}$ and the transition conductance $g_{\text{jump}}$ on the period were opposite to those found in the previous two cases. Both $g_{\text{peak}}$ and $g_{\text{jump}}$ decreased when the period increased. This is because the period was increased by increasing $T_{\text{active}}$ only, and a larger value of $T_{\text{active}}$ produced a greater depression of the synapse and thus a smaller value of $g_{\text{peak}}$. This can also be seen directly from Eq. 5. In this case, the two conditions for which the synapse totally determined the firing time of neuron F, $g_{\text{peak}} > g^*$ and $g_{\text{jump}} = g^*$, were obtained for periods smaller than 1,750 ms. For periods $>1,750$ ms, $g_{\text{jump}}$ decreased from the critical conductance $g^*$ as the period increased, and the firing time of neuron F was mostly determined by its intrinsic dynamics (the synapse was too depressed).

**Analytical description of $\Delta t$**

In this section, we show how the values of the peak conductance $g_{\text{peak}}$ and the transition conductance $g_{\text{jump}}$ determine $\Delta t$, the time delay between the activity in neuron O and neuron F. Because $\Delta t$ is determined by the rates at which the conductance decays from $g_{\text{peak}}$ to $g_{\text{jump}}$, the following equation describes the dependence of $\Delta t$ on model parameters for a sufficiently large maximal conductance $g_{\text{syn}}$ (see also APPENDIX)

$$\Delta t = \tau_e \ln \left( g_{\text{peak}}/g_{\text{jump}} \right) + T_{\text{active}}(1 - \tau_e/\tau_d)$$

(6)

where $\tau_e$ and $\tau_d$ are decay time constants of the synapse during the inactive and active states of neuron O, respectively. In general, both $\Delta t$ and $g_{\text{jump}}$ are values that are a priori not known. When the O to F synapse is weak, the firing time of neuron F is largely controlled by its intrinsic properties. Thus at this time the transition conductance $g_{\text{jump}}$ is mostly determined by the intrinsic dynamics of neuron F. In this case, Eq. 6 cannot be used to compute $\Delta t$ without resolving the dependence of $g_{\text{jump}}$ on the dynamics of neuron F. However, with a stronger O to F synapse, $g_{\text{jump}}$ becomes equal to the critical conductance $g^*$ (a constant value), as seen in Fig. 4, and hence

$$\Delta t = \tau_e \ln \left( g_{\text{peak}}/g^* \right) + T_{\text{active}}(1 - \tau_e/\tau_d)$$

(7)

In this case, all terms on the right-hand side of Eq. 7 are known and $\Delta t$ can be analytically calculated. Equations 6 and 7 apply when the synapse is recovered enough to determine the firing time of neuron F. In other words, these equations apply to the constant $T_{\text{active}}$ and duty cycle cases when the period is large and to the constant $T_{\text{inactive}}$ case when the period is small. For simplicity, in our model we assumed that $\tau_e$ is large relative to $\tau_d$, such that during the active state of neuron O the synaptic decay is minimal. In this case, Eq. 7 can be approximated by the following equation

$$\Delta t = \tau_e \ln \left( g_{\text{peak}}/g^* \right) + T_{\text{active}}$$

(8)

We now describe in detail the dependence of $\Delta t$ and phase of firing in neuron F on the period, in each of these three cases.

**Dependence of $\Delta t$ and phase on period in the constant $T_{\text{active}}$ case**

As we saw from Fig. 4, A and B, increasing the period by keeping $T_{\text{active}}$ constant allowed the synapse to recover from depression without changing the extent of depression. In Fig. 5A, we compare the activity of neuron F when the synapse is nondepressing and depressing at period values of 1,000 and 2,000 ms. The **top** and **bottom traces** show the membrane potential of neuron F and the synaptic conductance, respectively. For the sake of comparison, we tuned the parameters of the nondepressing synapse such that its effect was identical to the effect of a depressing synapse when the period was 1,000 ms (see **METHODS**). Thus, at a period of 1,000 ms, the time courses of the synaptic conductance and the membrane potential of F were identical for the depressing and the nondepressing synapses (traces are superimposed, Fig. 5A, **left**). In both cases, the peak of the synaptic conductance was 120 $\mu$S/cm$^2$. At a period of 2,000 ms, in the nondepressing case the strength of the synapse was identical to when the period was 1,000 ms (compare the peak values of the synaptic conductance, horizontal dotted line). Thus $\Delta t$ was unchanged. In contrast, in the depressive case, the peak of the synaptic conductance was 155 $\mu$S/cm$^2$ because the synapse recovered more from depression. This caused $\Delta t$ to increase almost 1.5-fold.

Figure 5B shows the relationship between the period and $\Delta t$ (computed numerically) for the depressing (black) and nondepressing (blue) cases. To compare the two cases, the maximal synaptic conductance ($g_{\text{syn}}$) for the nondepressing synapse was chosen such that the phase was equal to 1 when the period was 500 ms (the smallest period value that sustained a rhythm in neuron F when the synapse was depressing). The red line represents an idealized relationship in which phase is perfectly...
The black, blue, and red curves represent the depressing synapse, nondepressing synapse, and idealized constant phases. In the case of a depressing synapse, the curve was cubic shaped with a local minimum at the point \((P_1, \phi_1)\) and a local maximum at \((P_2, \phi_2)\). In the nondepressing case, \(\Delta t\) was constant in this case and hence the phase monotonically decreased like \(1/P\). Consequently, between periods of 500 and 1,500 ms (1-s interval marked by the vertical dotted lines in Fig. 5C), the change in phase for the depressing case (0.063) was much less than that of the nondepressing case (0.668).

In the depressing case, the dependence of phase on period followed a cubic shape. This shape was obtained because \(\Delta t\) was controlled by different mechanisms in different ranges of period values. With small period values \((P < P_1)\), the synapse was largely depressed and hence \(\Delta t\) was mostly determined by the intrinsic dynamics of neuron F. Because these intrinsic dynamics did not change with period, \(\Delta t\) was almost constant and thus the phase behaved like \(1/P\). For \(P > P_1\), the synapse increasingly recovered from depression. Between \(P = P_1\) and \(P = P_2\), the phase increased because \(\Delta t\) increased more rapidly than the period (Fig. 5C). This was due to the choice of synaptic parameters, in particular the fact that the synaptic decay (governed by \(\tau_d\)) was much slower than the intrinsic dynamics of neuron F (governed by \(\tau_i\)). To understand the existence of the local maximum point at \((P_2, \phi_2)\), consider the situation when the period was very large. In this case, the synapse maximally recovered and \(g_{\text{peak}}\) and \(g_{\text{jump}}\) approached constant values (the maximal conductance \(g_{\text{syn}}\) and the critical conductance \(g^*\), respectively), hence \(\Delta t\) approached a constant value. Therefore for large periods the phase decreased like \(1/P\). The increase and then decrease of the phase, at intermediate and then large period values, imply the existence of a local maximum for the phase.

**Dependence of \(\Delta t\) and phase on period in the constant duty cycle case**

In contrast to the constant \(T_{\text{Active}}\) case, when period was increased by keeping the duty cycle constant, both the recovery from depression and the extent of depression increased. Nevertheless, the effect of the depressing synapse in the constant duty cycle case was qualitatively similar to the constant \(T_{\text{Active}}\) case because the dependence of the peak conductance \(g_{\text{peak}}\) and the transition conductance \(g_{\text{jump}}\) on period was similar in these two cases (Fig. 4, B and D). Figure 6A compares the activity of neuron F when the synapse was nondepressing (dotted traces) and depressing (solid traces) at periods of 1,000 and 2,000 ms. The description of this figure is similar to that of Fig. 5A.

It is important to emphasize that in the constant duty cycle case the O to F synapse could affect the activity of neuron F in two distinct ways, depending on whether the maximal conductance \(g_{\text{syn}}\) is smaller or larger than the critical conductance \(g^*\). This is true whether the synapse is depressing or not. When the synapse is nondepressing, \(g_{\text{syn}} > g^*\) implies that neuron F remains inhibited as long as neuron O is active independent of the period. We shall refer to this case as the strong nondepressing synapse. In contrast, when \(g_{\text{syn}} < g^*\) (weak nondepressing synapse), neuron F need not remain inhibited for the entire duration of the active state in neuron O (see for example the \(P = 2,000\) ms traces of Fig. 6A). The weak depressing synapse

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**FIG. 5.** Dependence of \(\Delta t\) and phase on period in the constant \(T_{\text{Active}}\) case. Intervals of activity in neuron O (black rectangles) had a fixed duration \((T_{\text{Active}})\) of 250 ms. A: Voltage of neuron F (top) and synaptic conductance (bottom) at \(P = 1,000\) ms (left) and \(P = 2,000\) ms (right), when the synapse was depressing (solid line) and nondepressing (dotted line). B and C: plot of \(\Delta t\) vs. \(P\) and the phase \(\phi\) vs. \(P\) when the synapse was depressing (black) and nondepressing (blue). The parameter \(\bar{g}_{\text{syn}}\) of the nondepressing case was tuned to obtain \(\phi = 1\) at \(P = 500\) ms. The red curves show the idealized case of phase constancy \(\phi = 0.643\) (the phase of the depressing case when \(P = 500\) ms). Vertical dotted lines in C mark the 1-s interval 500 ms \(\leq P \leq 1,500\) ms.

Note that the depressing synapse case remained close to phase constancy for a large range of periods extending from 500 to 1,200 ms, whereas the nondepressing synapse case did not.

Figure 5C plots the phase \((\phi)\) as a function of the period \((P)\).
behaves essentially the same way as the weak nondepressing synapse. This is not true for a strong synapse ($g_{\text{syn}} > g^*$). Thus, when discussing the effect of a depressing synapse in the following text, we treat the case of a strong depressing synapse.

Figure 6, B and C, respectively, shows the dependence of $\Delta t$ and phase on period for a range of period values for a depressing synapse (black curve), a strong (green curve), and three weak (blue curves) nondepressing synapses. The idealized constant phase case is represented as red curves. In the case of the depressing synapse, at short and intermediate period values, the dependency of $\Delta t$ (and phase) on period was similar to the constant $T_{\text{Active}}$ case. However, at large period values, the constant duty cycle case was qualitatively different from the constant $T_{\text{Active}}$ case. As the period was increased, $\Delta t$ approached a constant value in the constant $T_{\text{Active}}$ case, whereas here it continued to increase linearly. To understand why, recall that in both the constant $T_{\text{Active}}$ and constant duty cycle cases the activity in neuron F was suppressed during the activity of neuron O. Thus the activity of neuron F started at some time interval after the end of activity in neuron O ($\Delta t = T_{\text{Active}} + \delta t$, where $\delta t$ is the time interval between the end of activity in neuron O and the beginning of activity in neuron F).

At large period values, the synapse was maximally recovered. Hence, $\delta t$ no longer changed as the period continued to increase. Because in the constant duty cycle case $T_{\text{Active}}$ increased linearly with period, so did $\Delta t$. From the definition of phase $\phi = \Delta t/P = (T_{\text{Active}} + \delta t)/P$, at large period values the term $\delta t/P$ became negligible. Consequently, the phase approached the duty cycle value ($DC = T_{\text{Active}}/P$).

The dependence of $\Delta t$ on period was qualitatively different for the weak and strong nondepressing synapses. When the nondepressing synapse was strong (green curves in Fig. 6, B and C), at all period values neuron F started to fire at a fixed time after the end of activity in neuron O. Thus, $\Delta t$ was equal to $T_{\text{Active}} + \delta t$ and $\delta t$ was constant for all period values because it only depended on $\tau_e$, the decay time constant of the synapse (which is independent of the period). Hence, as period increased, $\Delta t$ increased linearly and the phase decayed toward the duty cycle DC. When the nondepressing synapse was weak (blue curves in Fig. 6, B and C, with 1 denoting the weakest synapse), the effect of the synapse on $\Delta t$ and the phase was qualitatively different for small and large period values. With large period values $\Delta t$ was constant, whereas it increased for small period values. The transition point between these two regions moved to larger period values when the maximal conductance $g_{\text{syn}}$ was increased (from curve 1 to curve 3). To explain the existence of these two regions, recall that with a weak nondepressing synapse, following the onset of inhibition neuron F depolarized according to its intrinsic dynamics. Because the synapse was not strong enough to keep neuron F inactive indefinitely, when the period was large enough neuron F eventually started its activity while neuron O was still active. In this case, $\Delta t$ was independent of the period because it only depended on the dynamics of neuron F. Hence, for large period values, $\Delta t$ was constant and the phase decayed to 0. On the other hand, when the period was small, the intrinsic dynamics of neuron F did not have sufficient time to enable it to become active before neuron O stopped its activity. Therefore, just as in the case of a strong nondepressing synapse, $\Delta t$ was equal to $T_{\text{Active}} + \delta t$. However, in contrast to the strong nondepressing synapse where $\delta t$ was fixed, here $\delta t$ decreased with the period.
To explain this, note that $\delta t$ is the time it took neuron F to reach activity after the end of activity in neuron O. As such, when the synapse was weak, $\delta t$ was determined primarily by the intrinsic properties of neuron F. When the period increased, $T_{\text{Active}}$ increased and hence during the time that neuron O was active, the membrane potential in neuron F depolarized more. Therefore, at the end of the activity in neuron O the membrane potential of neuron F was closer to its activity threshold, and consequently it took less time for neuron F to become active. Because the decrease of $\delta t$ was small relative to the increase in $T_{\text{Active}}$ (since the depolarization of neuron F was relatively slow), overall the sum $T_{\text{Active}} + \delta t$ increased as the period increased. Note that the increase in $\Delta t$ in this case was due only to the increase in $T_{\text{Active}}$ and was completely independent of changes in $T_{\text{Inactive}}$. However, the increase in period was due to increases in both $T_{\text{Active}}$ and $T_{\text{Inactive}}$, and as a result the phase decreased with period.

Note that in the 1-s interval marked by the vertical dotted lines, the change in phase for the depressing synapse (0.149) was smaller than any of the nondepressing cases (strong: 0.467; weak: 1, 0.269; 2, 0.272; 3, 0.214).

**Dependence of $\Delta t$ and phase on period in the constant $T_{\text{Inactive}}$ case**

In the constant $T_{\text{Inactive}}$ case, the time during which the synapse depressed, and hence the extent of synaptic depression grew as the period increased. Hence, the synapse was most relevant when the period was small. Figure 7A shows the activity of neuron F when the synapse was nondepressing (dotted lines) and depressing (solid lines) at period values of 1,000 and 2,000 ms. With a depressing synapse, the activity in neuron F began at a later time for a period of 1,000 ms compared with when the period was 2,000 ms. This was due to the fact that the conductance of the depressing synapse was smaller when the period increased (bottom).

Figure 7, B and C, respectively, show the dependence of $\Delta t$ and phase on period for a depressing synapse (black curve), a strong (green curve), and three weak (blue curves) nondepressing synapses. The idealized constant phase cases are shown as red curves. In the depressing case, the dependence of $\Delta t$ on period went through a clear transition from being dependent on the properties of the depressing synapse to being dependent on the intrinsic properties of neuron F. The transition occurred at the period value that corresponded to the local maximum of the $\Delta t$ versus $P$ curve (at a period value of 1,450 ms). For period values below this transition point the synapse was strong (the peak conductance $g_{\text{peak}}^*$ was larger than the critical conductance $g^*$) and hence neuron F could switch to its active state only after the end of activity in neuron O. In this regime, $\Delta t = T_{\text{Active}} + \delta t$, where $\delta t$ is the time interval from the end of activity in neuron O to the beginning of activity in neuron F. Note that both $T_{\text{Active}}$ and $\delta t$ changed as the period was increased but in opposite directions. The time interval $\delta t$ decreased because the synapse became more depressed, while $T_{\text{Active}}$ increased linearly with the period (by definition of the constant $T_{\text{Inactive}}$ case). These two time intervals were determined by completely separate parameters. We chose the reference parameters so that $\delta t$ initially decreased and then increased. For period values above the transition point (1,450 ms), the synapse became too weak ($g_{\text{peak}} < g^*$) to keep neuron

![Fig. 7. Dependence of $\Delta t$ and $\phi$ on cycle period in the constant $T_{\text{Inactive}}$ case. A: voltage of neuron F (top) and synaptic conductance (bottom) at $P = 1,000$ ms (left) and $P = 2,000$ ms (right) when the synapse was depressing (solid traces) and nondepressing (dotted traces). Black rectangles represent the intervals of activity in neuron O. Duration $T_{\text{Inactive}}$ of the inactive state in neuron O had a fixed value of 750 ms, B and C: plot of $\Delta t$ vs. $P$ and $\phi$ vs. $P$ when the synapse was depressing (black curves), weak nondepressing (blue curves, $g_{\text{peak}}$, tuned to match the depressing case at $P = 3,000$ ms, curve 2; curves 3 and 1 were obtained by doubling or halving the maximal conductance used for curve 2) and strong nondepressing (green curves, $g_{\text{peak}}$, tuned to match the depressing case at $P = 800$ ms). The red curves show the idealized case of phase constancy $\phi = 0.491$ (the phase of the depressing case at $P = 800$ ms). Vertical dotted lines in C mark the 1-s interval 800 ms $\leq P \leq 1,800$ ms.](image-url)
F silent while neuron O is active, and hence neuron F started to fire before the end of activity in neuron O. Near the transition point, the synapse still had an effect in delaying the firing of neuron F, but this effect weakened as the period was increased. Hence Δt decayed. At period values larger than 2,700 ms, the synapse was totally depressed, and the firing time of neuron F was exclusively determined by the intrinsic dynamics of neuron F. As a result, Δt approached a constant value. The phase curve had a local minimum and a local maximum. The local maximum of the phase curve occurred at the period value of the local maximum in Δt (Fig. 7B). For larger period values, Δt decreased to a constant value, and the phase decayed to 0. To explain the occurrence of the local minimum in the plot of phase versus period, recall that for period values below the local maximum there were two competing effects on Δt. As the period increased, Δt (and therefore the phase) first decreased. With further increases in the period, Δt increased rapidly, causing the phase to increase as well. This resulted in a local minimum at low period values.

When the synapse was nondepressing, as for the constant duty cycle case, the dependence of Δt (and hence of the phase) on the period was qualitatively different if the synapse was strong ($\g_{\text{syn}} > g^*$, green curve) or weak ($\g_{\text{syn}} < g^*$, blue curves). As in Fig. 6B, the weak nondepressing cases are numbered from 1 to 3 with 1 marking the weakest case. When the nondepressing synapse was strong, neuron F started to fire at some fixed time interval after the end of activity in neuron O. Hence Δt = $T_{\text{active}} + \delta t$, where $T_{\text{active}}$ increased linearly with the period and δt was constant (as in the strong nondepressing constant duty cycle case). Hence Δt increased. Recall that $\phi = T_{\text{active}}/\rho + \delta t/\rho$. As the period was increased, the first term on the right side of this equation approached 1, whereas the second term approached 0. Thus the phase increased toward 1.

When the synapse was nondepressing and weak, the dependence of Δt on the period was identical to the constant duty cycle case because the arguments presented for the constant duty cycle case depended only on changes in $T_{\text{active}}$. In the present case, in the range of period values where Δt increased with the period, the phase also increased. This increase occurred for the same reasons that the phase increased in the strong nondepressing case. In contrast, for larger period values, where Δt was constant, the phase decayed to 0.

In contrast to the constant duty cycle and constant $T_{\text{active}}$ cases, in the constant $T_{\text{inactive}}$, a depressing synapse did not show a significantly different variation of phase in the 1-s interval between period values of 500 and 1,500 ms (vertical dotted lines), compared with a strong nondepressing synapse (0.292 and 0.302, respectively). Moreover, the weak nondepressing case gave a smaller variation in phase, compared with the depressing case (1: 0.094, 2: 0.118, 3: 0.213). These results suggest that, in the constant $T_{\text{inactive}}$ case, a depressing synapse does not promote phase maintenance better than a nondepressing synapse.

Dependence of the phase-period relationship on intrinsic and synaptic parameters when $T_{\text{active}}$ is constant

In general, the shape of the phase versus period curve was determined by the intrinsic properties of neuron F (the intrinsic time constant $\tau_f$) when the period was small and by the properties of the synapse (the synaptic time constants $\tau_{\text{syn}}, \tau_{\text{g}}, \tau_{\text{E}_{\text{syn}}}$, and the maximal synaptic conductance $g_{\text{syn}}$) when the period was large. Because these parameters were independent, the phase versus period curve could be cubic-like, depending on the choice of these parameters. Moreover, each of these parameters played a distinct role in determining the value and location of the local maximum and minimum points of the phase versus period curve. The effects of these parameters on the phase versus period curve are illustrated in Fig. 8. The effect of increasing the time constant of synaptic depression ($\tau_{\text{g}}$) was qualitatively equivalent to decreasing the time constant of synaptic recovery ($\tau_{\text{syn}}$). Hence, we only show the effect of the latter parameter. The effect of increasing $E_{\text{syn}}$ (making it less negative) was tantamount to decreasing the maximal synaptic conductance $g_{\text{syn}}$. Hence, we only show the effect of $g_{\text{syn}}$.

In each panel, the thick curve shows the reference model; other curves show variations of one of the studied parameters. The two synaptic parameters, the maximal conductance $g_{\text{syn}}$ and the time constant of synaptic recovery $\tau_{\text{syn}}$, both controlled the strength of the synapse directly. The effect of $g_{\text{syn}}$ on synaptic strength was present across all periods. Increasing the maximal conductance $g_{\text{syn}}$ caused the phase versus period curve to shift up (Fig. 8A). Decreasing the time constant of synaptic recovery $\tau_{\text{syn}}$ had a similar effect, although this effect was more diminished for sufficiently large period values because at these period values the synapse was mostly recovered from depression (Fig. 8B). In both cases, at any particular period value, strengthening the synapse caused the phase to increase because as $\Delta t$ increased. This can be explained by considering Eqs. 5 and 6. Indeed, Eq. 6 shows that for sufficiently large period values (when the transition conductance $g_{\text{jump}}$ is fixed at the critical conductance $g^*$), $\Delta t$ is an increasing function of $g_{\text{peak}}$. $g_{\text{peak}}$ itself increases when the time constant of synaptic recovery $\tau_{\text{syn}}$ is decreased or the maximal synaptic conductance $g_{\text{syn}}$ is increased, as can be seen from Eq. 5.

In Fig. 8A, the maximal phase value moved to the left as the maximal synaptic conductance $g_{\text{syn}}$ increased. Near the maximum, we recall that the phase was determined entirely by the properties of the synapse so that neuron F would only jump to its active state when the synaptic conductance $g$ decayed below the critical conductance $g^*$. Because the synaptic conductance $g$ is equal to $g_{\text{syn}}$, when the maximal synaptic conductance $g_{\text{syn}}$ increased, the synaptic conductance $g$ decayed below the critical conductance $g^*$ at a lower value of $s$, i.e., at a smaller period value. Thus the synapse would become more relevant for determining the firing time of neuron F at lower values of the period, causing the phase versus period curve to shift up and to the left. Similar trends occur in Fig. 8B, as the time constant of synaptic recovery $\tau_{\text{syn}}$ decreased. For any fixed period value, smaller values of $\tau_{\text{syn}}$ (faster recovery) caused the synaptic conductance $g$ to increase. Hence, at any fixed period value, the synaptic conductance $g$ decayed below the critical conductance $g^*$ at a lower value of $s$ when the synaptic recovery was faster. Again, this happened for smaller period values implying that, as the synaptic recovery was faster, the phase versus period curve shifted up and to the left.

Of the three synaptic parameters analyzed, the time constant of synaptic decay $\tau_{\text{syn}}$ (decay of synaptic transmission when neuron O is not active) is the only one that is not directly related to synaptic depression. Recall that the main effect of depression is to change the peak conductance $g_{\text{peak}}$ whereas...
the time constant of synaptic decay \( \tau_c \) affects the time spent between \( g_{\text{peak}} \) and the transition conductance \( g_{\text{jump}} \), but not \( g_{\text{peak}} \) itself. At small period values, where the synapse was weak, \( \tau_c \) had almost no effect on the phase (Fig. 8C). However, for larger periods, \( \tau_c \) was the predominant parameter in determining how long the synaptic conductance \( g \) had to decay to release neuron F from the inhibition of neuron O. Thus, at larger period values, changes in \( \tau_c \) had a large effect on \( \Delta t \) and consequently on the phase. Increasing \( \tau_c \) (slower decay) increased the maximum phase and shifted it to the right. This can be explained using Eqs. 6–8, which show that a simultaneous increase in both the period and \( \tau_c \) shifts the phase versus period curve up and to the right. Because \( \Delta t \) increased with \( \tau_c \), for a fixed period value, the phase increased as well, thereby shifting up the curve. Alternatively, if the phase remained fixed, an increase in \( \tau_c \) would result in an increase in \( \Delta t \) and therefore in period, thereby shifting the curve to the right.

At large period values, the intrinsic parameter \( \tau_e \) did not have any effect on the phase because the synapse was dominant in determining the firing time of neuron F (Fig. 8D). The effect on phase was restricted to smaller values of the period when the synapse was relatively weak. For such a fixed period value, decreasing \( \tau_e \) forced neuron F to spend less time in the silent state, thereby decreasing \( \Delta t \) and therefore the phase.

As seen in Fig. 8, changing any of the parameters shown could remove the local minimum and maximum of the phase versus period curve. An examination of the shown parameter ranges for which the phase versus period curve decreased monotonically revealed that, in these ranges, the effect of the intrinsic properties of neuron F was dominant over the effect of the depressing synapse in determining the phase. This shift in the dominance of the intrinsic versus synaptic effects was produced either through a change in the relative time courses of these two factors (Fig. 8, C and D) or by weakening the synapse (Fig. 8, A and B).

**Dependence of the phase-period relationship on intrinsic and synaptic parameters when the duty cycle is constant**

Figure 9 shows the dependence of the phase versus period curve on parameters when the duty cycle is constant. In principle, the different parameters affected the phase versus period curve in a way that was similar to the constant \( T_{\text{Active}} \) case. There were some differences between the two cases that are worth pointing out. In Fig. 9A, as the maximal synaptic conductance \( g_{\text{syn}} \) was decreased, the value of the local minimum of the phase curve decreased and shifted to the right. Recall that in the constant duty cycle case, a larger period means that there is not only a longer time for the synapse to recover but also a longer time for it to depress. This can be seen in Fig. 4, where \( g_{\text{peak}} > g^* \) at much larger period values for the constant duty cycle case compared with the constant \( T_{\text{Active}} \) case. Thus at smaller values of the maximal conductance \( g_{\text{syn}} \), the range of period values for which the intrinsic properties of neuron F determined phase became larger. However, despite the smaller value of \( g_{\text{syn}} \), as the period was increased to very large values.
the synapse became sufficiently large and determined phase. A similar effect was seen by increasing the time constant of synaptic recovery $\tau_{re}$ (Fig. 9B). In both A and B, the cubic shape of the phase curve persisted when the synapse was weakened because, as the period approached infinity, the phase tended to the duty cycle value (0.3).

As in the case of constant $T_{Active}$ in the constant duty cycle case the time constant of synaptic decay $\tau_{dc}$ had minimal effects on the phase at small period values (Fig. 9C) and the intrinsic time constant $\tau_F$ had minimal effects on the phase at large period values (Fig. 9D).

**Dependence of the phase-period relationship on intrinsic and synaptic parameters when $T_{inactive}$ is constant**

In Fig. 10, we show the phase curves when parameters are varied in the constant $T_{inactive}$ case. Just as in the previous two cases, strengthening the synapse (by increasing the maximal synaptic conductance $g_{syn}$ in Fig. 10A or decreasing the time constant of synaptic recovery $\tau_{re}$ in Fig. 10B) had the expected effect of raising the phase versus period curves and shifting them to the right. Figure 10, A and B, also shows that if the synapse was sufficiently strong, it could determine the firing time of neuron F at all period values. For example, when $g_{syn} = 0.55 \text{ mS/cm}^2$ or $\tau_{re} = 1,500 \text{ ms}$, the phase approached 1, and not 0, as the period increased. Thus at large period values, the phase versus period curve was similar to the one obtained in the case of a strong nondepressing synapse (see Fig. 7C).

Figure 10C shows the effect of the time constant of synaptic decay ($\tau_{dc}$) on the phase versus period curve. In this case, $\tau_{dc}$ had no effect on the phase when the period was large (right of the local maximum). This is expected because, in the constant $T_{inactive}$ case, the synapse was weak at large period values, and in this range the phase was determined by the intrinsic properties of neuron F. Figure 10D shows the effect of changing the intrinsic time constant $\tau_F$ on the phase curve. The effect of $\tau_F$ was most prominent at large period values (right of the local maximum), where the synapse was weak. However, there was also a small dependence on the intrinsic time constant $\tau_F$ even at small period values (left of the local maximum) where the firing time of neuron F was mostly affected by the synaptic dynamics. This small effect on the phase curve occurred because the larger values of $\tau_F$ were comparable to (the reference value of) the time constant of synaptic decay $\tau_{dc}$. For these cases, both the synapse and the intrinsic properties of neuron F determined the phase.

**DISCUSSION**

Despite its abundance in nervous systems, it is only recently that the functional roles of short-term synaptic dynamics in general and synaptic depression in particular are beginning to be understood. It has been proposed that synaptic depression...
could be used as a mechanism for automatic gain control (Abbott et al. 1997; Tsodyks and Markram 1997). Synaptic depression has also been implicated in directional selectivity (Chance et al. 1998), burst detection (Lisman 1997), network stability (Galaretta and Hestrin 1998; Varela et al. 1999), rhythmogenesis (Friesen 1994), network synchronization (Tsodyks et al. 2000), and interval and sequence determination (Buonomano 2000). A recent set of theoretical and experimental studies raised the possibility that synaptic depression could be implicated in network reconfiguration by mediating the occurrence of multi-stable states (Bose et al. 2001; Manor and Nadim 2001; Nadim et al. 1999). The current work is an effort in the same direction. It proposes a novel function for synaptic depression.

**Effect of synaptic depression on the phase-period relationship**

In this work we developed a simple model, which demonstrates that synaptic depression can be employed as a mechanism for promoting phase constancy. Our model is not meant to reproduce the output of any particular biological network. Thus the parameters of our model were chosen to elucidate the different effects of synaptic depression on phase maintenance in different conditions. One important assumption that was used in this model is that the time constant of synaptic decay is on the order of the interburst interval. By adjusting the values of the parameters, this model can be used to simulate various biological systems, for example, circuits where neurons are fast tonic spikers and synaptic dynamics are in the milliseconds range, to circuits that consist of slow bursters and synaptic dynamics are ranging in the hundreds of milliseconds, such as in synapses of the pyloric circuit (see for example Fig. 14 in Eisen and Marder 1982). In all these cases, the essence of the model is the same. It is based on the idea that depressing synapses are frequency-dependent: longer intervals of no activity in the presynaptic neuron allow more recovery of the depressing synapses. When cycle period is varied by changing either (or both) the active or inactive durations ($T_{\text{Active}}$ or $T_{\text{Inactive}}$) of the oscillator activity, there is a range of cycle periods in which a depressing synapse maintains phase better than a nondepressing synapse.

An important result of our study is that it reveals how a synapse works together with the intrinsic properties of the postsynaptic cell to determine the firing latency. When the synapse is depressing, its strength depends on cycle period. Thus, at some range of cycle periods, the synapse determines the phase, whereas in other ranges the intrinsic properties of the postsynaptic cell control the phase. This interplay between intrinsic and synaptic properties expands the interval of periods over which phase of the postsynaptic cell can be maintained. Interestingly, our study suggests that this result is general and holds even when cycle period is changed in very different ways.

In the constant $T_{\text{Active}}$ case, when the period increases, the synapse becomes stronger and $\Delta t$ (the time delay between the

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**Fig. 10.** The effect of intrinsic and synaptic parameters on the phase-period curve in the constant $T_{\text{Inactive}}$ case. All panels show phase vs. period when the synapse was depressing and $T_{\text{Inactive}}$ was fixed at 750 ms at different parameter values. The thick curves denote the reference model (values italicized). A: maximal synaptic conductance $g_{\text{max}}$ was set to (in mS/cm$^2$): 0.55, 0.45, 0.35, 0.25, or 0.15. B: time constant of synaptic recovery $\tau_s$ was set to (in ms, from top to bottom): 1,500, 2,250, 3,000, 3,750, and 4,500. C: time constant of synaptic decay $\tau_d$ was set to (in ms, from top to bottom): 600, 450, 300, 150, and 75. D: time constant of intrinsic dynamics $\tau_F$ in neuron F was set to (in ms, from top to bottom): 200, 150, 100, 50, and 25.
activity in neuron O and neuron F) increases as well. Consequently, with the appropriate choice of parameters and range of period values, $\Delta t$ increases such that the relation between phase and period follows a cubic form. At low period values, the synapse minimally contributes to delaying the activity in neuron F and $\Delta t$ is mainly determined by the intrinsic properties of neuron F. Hence, for an incremental increase in period, $\Delta t$ increases as well but to a smaller extent. Consequently, in this range, the phase decreases. At an intermediate range, the synapse is strong enough and $\Delta t$ is mostly affected by the dynamics of the synapse. Here an increase in period causes a larger change in $\Delta t$ and the phase increases. At very large period values (relative to the time constant of synaptic recovery), the synapse is fully recovered and $\Delta t$ is constant, causing the phase to decrease like $1/P$. The cubic form of this relationship defines a range of cycle periods for which the change in phase is relatively small compared with a nondepressing synapse for which phase decreases like $1/P$ over the whole range of cycle periods.

In essence, the constant duty cycle case is similar to the constant $T_{\text{Active}}$ case except that, at large period values, the phase does not decay to 0 but approaches the duty cycle value (DC). This is because, as the period increases to very large values, $\Delta t$ approaches to $T_{\text{Active}}$ plus some fixed value, since the synapse maximally recovers from depression.

The constant $T_{\text{Inactive}}$ case is less intuitive. Here the depressing synapse becomes weaker as the period increases. In the range of small period values, the synapse is strong and its dynamics control the phase. In this range, there are two opposing effects on the phase-period relationship. On one hand, because the period is increased by increasing $T_{\text{Active}}$, as the period increases, the activity of neuron F is delayed. On the other hand, as the period increases, the synapse becomes more depressed and the activity of neuron F is advanced. The competition between these two effects causes the phase to first decrease and then increase at low and intermediate period values. At larger period values, the control of phase changes from a synaptic to an intrinsic mechanism, and the phase decreases like $1/P$.

Inhibitory synapses that show depression generally promote phase maintenance better than synapses that are nondepressing

In all three cases examined, the phase-period relationship shows a local minimum followed by a local maximum. This defines a range of cycle periods for which the change in phase is limited. A depressing synapse does not guarantee phase constancy. However, our model demonstrates that with different ways of changing cycle period, an inhibitory depressing synapse is generally better than a nondepressing synapse in promoting phase constancy. The sole exception occurs in the weak nondepressing constant $T_{\text{Inactive}}$ case, where the change in phase is smaller than with a depressing synapse. However, we emphasize that changing the period by increasing only $T_{\text{Active}}$ is a worst-case scenario where the synapse is never given a chance to increase its strength when the period is increased. Indeed, in any situation where increasing the period is accompanied with some degree of increase in $T_{\text{Inactive}}$ (no matter how $T_{\text{Active}}$ changes), our results demonstrate that a depressing synapse is superior to a nondepressing synapse in maintaining phase. This can be seen directly from Eq. 5, which shows that the peak synaptic conductance $g_{\text{peak}}$ approaches 1 with increases in $T_{\text{Inactive}}$, independent of how $T_{\text{Active}}$ may change. As a result, in such cases (which form the majority of cases), the dependence of the peak conductance $g_{\text{peak}}$ and the transition conductance $g_{\text{jump}}$ (the synaptic conductance immediately before the onset of activity in neuron F) on period will be qualitatively similar to the constant $T_{\text{Active}}$ and the constant duty cycle cases (see Fig. 4, B and D, where we demonstrated that a depressing synapse is better at maintaining phase compared with a nondepressing synapse.

The exception mentioned in the preceding text clarifies the role of synaptic depression in phase maintenance. In the uncommon cases where $T_{\text{Inactive}}$ remains fixed when period changes, a nondepressing synapse could indeed result in better phase maintenance. Our results suggest that such networks are unlikely to use depression as a means of maintaining phase.

We emphasize that, in our model, the depressing synapse improves the phase maintenance in a restricted range of, and not across all, period values. However, biological networks also operate in a limited physiological range of periods. In addition, our analysis shows that phase maintenance could be improved by choosing model parameters such that the cubic portion of the phase-period curve becomes flatter and wider.

State-dependence of phase maintenance

Several studies have shown that the extent of phase maintenance could vary under different behavioral circumstances. In insect locomotion, for example, during walking movements the coupling between the leg joints is phase-constant. In contrast, during searching movements, this relationship is lost (Fischer et al. 2001). In the crustacean pyloric circuit, it was found that some phases were almost perfectly maintained when the stomatogastric ganglion was isolated from the influence of anterior ganglia, whereas the same phases were maintained less well in intact preparations (Hooper 1997a). To reconcile the differences, this study suggested that neuromodulatory inputs could alter the degree to which different pyloric elements keep phase. If phase maintenance is indeed state-dependent, our model provides a simple explanation. We have shown that different parameters of the synaptic dynamics could alter the degree of phase maintenance. These parameters could be directly affected by neuromodulation, and it is tempting to speculate that modulation of the synaptic dynamics could affect the degree to which phase is maintained among different elements of the network.

In addition, our model provides the possibility that a neuromodulator primes the network without having an immediate effect on the frequency or the phase of neurons. Instead, the neuromodulatory action comes into effect when frequency is changed. For instance, in the constant $T_{\text{Active}}$ or constant duty cycle cases, a neuromodulator that increases the time constant of synaptic decay ($\tau_n$) has almost no effect on phase when the period is short. However, as the period is increased, the previous modification of $\tau_n$ can produce a dramatic effect on phase. This is especially useful when the network needs to change from one type of activity to another in multiple, successive steps. If two groups of neurons operate with constant phase difference in one behavior but not in the other, such a
priming mechanism would allow the transition to occur at the appropriate stage with minimal transient effects.

**Phase maintenance in more complex conditions**

In this work we studied the effect of an inhibitory depressing synapse between an oscillator neuron and a follower cell in a simple feed-forward network. To focus on the effects of synaptic dynamics, we modeled the cells with a minimal set of intrinsic properties. We are well aware that this circuit is greatly simplified. In biological networks, the presence of additional ionic conductances can interact with synaptic influences to determine the activity time of a neuron. For instance, an outward A current elicited by a postinhibitory rebound could increase the delay of a bursting neuron (Harris-Warrick et al. 1995a,b; Swensen and Marder 2001). Such a current could work in concert with the synaptic mechanism described here to increase the time delay as cycle period increases, thereby improving phase maintenance. Increased currents elicited by inhibition, such as an h current, may do the opposite. The relative timing of neuronal events could be greatly affected by modifications in the intrinsic and/or synaptic properties of neurons. For instance, a larger burst in the presynaptic neuron may increase the amount of transmitter release, thereby advancing (for an excitatory synapse) or delaying (for an inhibitory synapse) the onset of postsynaptic activity. The occurrence of feedback connections adds a new level of complexity that is beyond the scope of this discussion.

**Conclusions**

We have shown that synaptic depression can contribute to maintain phase in an oscillatory network across a range of cycle periods. Although we focused on only three representative ways to change cycle period, the results obtained from these three cases are insightful for the general case. An important characteristic of this model is that the adjustment of timing is internal and automatic. It is not regulated by external factors such as neuromodulation, but results causally from the change in cycle period through the interaction between intrinsic and synaptic dynamics within the network. It has been proposed that, in rhythmic networks, time delays are changed by neuromodulation (DiCaprio et al. 1997; Harris-Warrick et al. 1995b). However, neuromodulation is also the means for changing cycle period in such networks. Parsimonious considerations dictate that, when phase maintenance is required for proper network function, delays should be adjusted to preserve phase automatically, independent of the intrinsic input that forces the change in period. A built-in mechanism such as the one proposed in this work, in concert with excitatory modulation, provides a simple strategy for coordination of neuronal timing with cycle period.

**APPENDIX**

In this section, we abbreviate $T_{\text{Active}}$ to $T_A$ and $T_{\text{Inactive}}$ to $T_I$.

**Derivation of Eq. 5**

Suppose neuron O becomes active at $t = 0$ with $d(0) = d_0$. When neuron O is active, $dd/dt = -d/d_T$. Thus, at $t = T_A$, $d(T_A) = d_0\exp(-T_A/d_T)$. When neuron O is silent, $dd/dt = (1-d)/\tau_w$ with initial condition $d(T_A) = d_0\exp(-T_A/d_T)$. Solving this equation gives

$$d(t) = 1 - (1 - d_0\exp(-T_A/d_T))\exp(-(t - T_A)/\tau_w) \quad (A1)$$

Due to the periodicity of O, we impose the condition $d(T_A + T_I) = d_0$ in Eq. A1. Solving for $d_0$ and using the fact that $g_{\text{peak}} = g_{\text{syn}}d_0$, we obtain

$$g_{\text{peak}} = g_{\text{syn}}(1 - \exp(-T_I/\tau_w))(1 - \exp(-T_A/\tau_w)/\exp(-T_A/d_T) \quad (5)$$

**Derivation of Eq. 6**

Suppose $t = 0$ is the onset of activity in neuron O. When neuron O is active, $dg/dt = -g/\tau_a$ and $g(0) = g_{\text{peak}}$, implying that $g(T_A) = g_{\text{peak}} \exp(-T_A/\tau_a)$. When neuron O is silent, $dg/dt = -g/\tau_\omega$ with initial condition $g(T_A) = g_{\text{peak}} \exp(-T_A/\tau_a)$. Solving this equation yields

$$g(t) = g_{\text{peak}} \exp(-T_I/\tau_a) \exp(-(t - T_A)/\tau_a) \quad (A2)$$

Imposing the condition $g(\Delta t) = g_{\text{jump}}$ in Eq. A2 and solving for $\Delta t$, we obtain

$$\Delta t = \tau_a \ln (g_{\text{peak}}/g_{\text{jump}}) + T_A(1 - 1/\tau_a) \quad (6)$$

Note that if the synapse is weak and neuron F becomes active prior to the end of the activity in neuron O, Eq. 6 does not apply. In this case, $\Delta t$ satisfies the following equation

$$\Delta t = \tau_a \ln (g_{\text{peak}}/g_{\text{jump}}) \quad (A3)$$

**DISCLOSURES**

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