Synaptic Depression in Conjunction With A-Current Channels Promote Phase Constancy in a Rhythmic Network

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Greenberg, Idan and Yair Manor. Synaptic depression in conjunction with A-current channels promote phase constancy in a rhythmic network. J Neurophysiol 93: 656–677, 2005. First published September 8, 2004; doi:10.1152/jn.00640.2004. In many central pattern generators, pairs of neurons maintain an approximately fixed phase despite large changes in the frequency. The mechanisms underlying phase maintenance are not clear. Previous theoretical work suggested that inhibitory synapses that show short-term depression could play a critical role in this respect. In this work we examine how the interaction between synaptic depression and the kinetics of a transient potassium (A-like) current could be advantageous for phase constancy in a rhythmic network. To demonstrate the mechanism in the context of a realistic central pattern generator, we constructed a detailed model of the crustacean pyloric circuit. The frequency of the rhythm was modified by changing the level of a ligand-activated current in one of the pyloric neurons. We examined how the time difference of firing activities between two selected neurons in this circuit is affected by synaptic depression, A-current, and a combination of the two. We tuned the parameters of the model such that with synaptic depression alone, or A-current alone, phase was not maintained between these two neurons. However, when these two components came together, they acted synergistically to maintain the phase across a wide range of cycle periods. This suggests that synaptic depression may be necessary to allow an A-current to delay a postsynaptic neuron in a frequency-dependent manner, such that phase invariance is ensured.

INTRODUCTION

Many motor activities, such as respiration, swimming, terrestrial locomotion or chewing, are repetitive. The neuronal networks responsible for producing such rhythmic activity are collectively known as central pattern generators (CPGs) (Marder and Calabrese 1996). Within a CPG, different neurons are active at different times, to ensure the activation of motoneurons and their muscle targets in an optimal sequence. Most CPGs produce rhythms that are highly variable, often several fold, in the cycle period. Nevertheless, in many of these cases the firing pattern is kept such that the repetitive activity remains coherent despite changes in speed.

A central question in central pattern generation is what mechanisms allow the production of robust patterns of activity in the face of large variations in the cycle period. One possible strategy is that any temporal interval in the rhythm is expanded when the cycle period increases, or contracted when the cycle period decreases, such that the phase (ratio of time interval and cycle period) of this event remains constant when the cycle period changes. Indeed, a number of experimental studies have shown that within a neuronal network some of the neurons fire with an approximately fixed phase difference with respect to each other (DiCaprio et al. 1997; Fischer et al. 2001; Friesen and Pearce 1993; Hill et al. 2003; Hooper 1997a,b).

Maintenance of phase in rhythmic networks, especially in cases where the cycle period can vary several fold, is not a simple problem. The mechanisms that underlie phase constancy are still unclear. A recent theoretical study proposed that short-term synaptic depression of inhibitory synapses could be instrumental to maintain phase when the cycle period changes (Manor et al. 2003). When an oscillator was coupled by an inhibitory synapse to a follower neuron, if (and only if) the synapse showed depression the 2 neurons fired with little phase variation with respect to each other, in some range of cycle periods. When the rhythm was fast, the synapse was mostly depressed and thus less effective in delaying the follower neuron. With a slower rhythm, the synapse could increasingly recover and delay the follower neuron. As the cycle period changed the delay of the follower neuron was proportionally adjusted such that the 2 cells could fire with an approximately fixed phase difference with respect to each other, independent of cycle period.

The mechanism proposed by Manor et al. (2003) exclusively depended on short-term depression of an inhibitory synapse, and did not take into account other possible sources of delay, such as intrinsic conductances in the follower neuron. A number of experimental studies established that several types of intrinsic conductances, in particular transient potassium current (A-currents), could play an important role in setting the phase of follower neurons in CPG circuits (Harris-Warrick et al. 1995a; Hartline and Gassie 1979; McCormick 1991; Strom 1988). To our knowledge the possibility that intrinsic currents or synaptic depression (not saying a combination of the 2) are involved in the mechanisms underlying phase invariance was not experimentally explored.

Taking a modeling approach, in the present study we examine this question. We explore the dynamical interaction between synaptic depression and a particular type of current, a slowly inactivating form of A-current, in the context of phase maintenance and under the constraints of a complex and realistic CPG. To this end, we chose the pyloric circuit as a representative example. The choice of this well-studied CPG as our working model was motivated by the fact that it includes all the ingredients necessary for the proposed mechanism: the oscillator produces a rhythm that is variable in the cycle period; follower neurons are entrained by inhibitory synapses; the synapses are graded and show short-term depression; most
followers are endowed with a slowly inactivating A-current; and some of the neuronal pairs burst with a relatively fixed phase with respect to each other. We now describe the pyloric circuit in greater detail.

The pyloric circuit is involved in the feeding behavior of crustaceans. Depending on the species it consists of 12 to 14 neurons, which together produce a triphasic pattern of firing activity. Although the cycle period of the pyloric rhythm is commonly around 1 s, it can vary between about 0.5 to 5 s, depending on various factors such as temperature or the neuromodulatory environment (Hooper and Marder 1987; Nusbaum and Marder 1989b). The rhythm originates from a pacemaker ensemble of neurons [the anterior burster (AB) and the 2 pyloric dilators (PD)], and is propagated to the other neurons of the network by inhibitory synapses. The 3 pacemaker neurons fire together in the first phase of the rhythm. One class of follower neurons, to which the lateral pyloric (LP) neuron belongs, is active in the second phase. The third class of follower neurons consists of 6–8 pyloric constrictor (PY) neurons, depending on species. In the crab Cancer borealis, these PY neurons are subdivided to early pyloric constrictors (PE) and late pyloric constrictors (PL). The LP, PE, and PL neurons are all directly inhibited by the PD neurons, and are thus silent when the PD neurons are bursting. Earlier work suggested that the follower neurons rebound from synaptic inhibition at different rates, and thus become active at different times because of different densities or kinetics of their A-current (Harris-Warrick et al. 1995a,b; Hartline and Gassie 1979). Indeed, in pyloric neurons several types of A-currents were measured, including a rapid form ($I_A$) and a slowly inactivating form ($I_{AS}$) (Golowasch and Marder 1992; Turrigiano et al. 1995).

In the first part of this work we constructed a model of the pyloric network, which consisted of 5 representative members of the pyloric circuit and their connections: the AB, PD, LP, PL, and PE neurons. We used a realistic way of modifying the cycle period of the rhythm by incorporating a proctolin-like current in the AB neuron, and modifying its maximal conductance. The proctolin current is elicited by the endogenous neuropeptide proctolin (Freschi 1989; Hooper and Marder 1987; Nusbaum and Marder 1989a,b). It is active in many of the pyloric neurons, in particular the AB neuron (Swensen and Marder 2001). Because of its sharp dependency on voltage, this inward current depolarizes the AB neuron and increases its excitability. Indeed, when the rhythm is slow bath application of proctolin speeds up the rhythm (Hooper and Marder 1987; Swensen and Marder 2001). In our model of the pyloric rhythm we study how changes in the cycle period, induced by different levels of the proctolin current in the AB neuron, affect the delay between the onsets of bursting in the PD and LP neurons. We find that when the dynamics of the PD to LP synapse is such that it cannot, by itself, support phase constancy, nor the dynamics per se of the A-current in the LP neuron, the combination of these 2 components can produce a synergistic interaction that promotes phase maintenance in a wide range of cycle periods.

Although the detailed model of the pyloric network clearly demonstrates this synergistic interaction, the complexity of this model obscures the mechanism and impedes a complete understanding of it. Thus in the second part of this work we reduce the full circuit to a much simpler model, based on the model of Manor et al. (2003). The insights obtained from the reduced model facilitate our understanding of the synergistic interaction between synaptic depression and A-current.

METHOds

The detailed model of the pyloric circuit

CELLULAR MODELS. The model included 5 representative members of the pyloric circuit in the stomatogastric nervous system of the crab Cancer borealis. Figure 1A is a schematic drawing of the model circuit: the anterior burster (AB) and the pyloric dilator (PD), which together form the pacemaker ensemble, were coupled by a bidirectional electrical synapse. The PD neuron formed inhibitory chemical synapses onto 3 follower neurons: the lateral pyloric neuron (LP), the early pyloric constrictor (PE), and the late pyloric constrictor (PL). The LP and PE neurons were reciprocally coupled with inhibitory chemical synapses, and also by a bidirectional electrical synapse. Similar connections were set between the LP and PL neurons. In the biological circuit, LP forms an inhibitory chemical synapse back to the PD neuron (shown with a dotted line and open circle in Fig. 1A). Recent studies suggest that this feedback synapse may play an important role in stabilizing the rhythm (Mamiya and Nadim 2004; Weaver 2003). Other works show that this synapse may not have a significant effect in a nonperturbed rhythm (Prinz et al. 2003). For simplicity, and in view of the controversial role of this synapse in frequency regulation of the pyloric rhythm, we decided not to implement it in our model of the pyloric rhythm.

All cells were modeled with 2 compartments, one representing a lumped soma + dendritic tree (hereafter referred to as the somato-dendritic compartment), $XX_{sd}$, and the other representing a lumped axon, $XX_{ax}$, where $XX = AB$, PD, LP, PE, or PL. This compartmentalization was necessary to separate the site of fast action potential generation from the recording site, such that fast action potentials recorded at the soma were small in amplitude (as is experimentally observed). Pyloric neurons have a classic invertebrate monopolar morphology (King 1976a,b): a primary neurite extends from the cell body, branches into secondary neurites and dendrites, and continues as an axon. In such neurons the surface area of the cell body + dendrites is much larger than that of the axon. Thus in our cellular models the membrane capacitance and leak conductance (in absolute terms) was an order of magnitude larger in the somatodendritic compartment, relative to the axonal compartment.

The whole system consisted of 47–48 differential equations: 10 for the AB neuron; 9 for the PD neuron; 7 for each of the LP, PE, and PL neurons; and 7–8 for the synapses. Except for the PD to LP chemical synapse, for simplicity all 6 other synapses were modeled as nondepressing, with a single differential equation that determined the time-dependent activation of the synapse. The PD to LP chemical synapse was in some cases modeled as nondepressing (with one differential equation, for activation) and in others as depressing (with an additional differential equation, for depression).

In each cell $XX$, the voltages in the somatodendritic ("$sd$") and axonal ("$ax$") compartments were governed by the following equations

$$C_{xx_{sd}} \frac{dV_{xx_{sd}}}{dt} = - \left( \sum_{\text{ion channel}=\text{ion}} g_{\text{ion}}(V_{xx_{sd}})(V_{xx_{sd}} - E_{\text{ion}}) \right) + \sum_{\text{presynaptic cell}=\text{FP}} g_{\text{ FP }\rightarrow \text{ax}}(V_{\text{FP}_{\text{ax}}})(V_{xx_{sd}} - E_{\text{ax}}) + \sum_{\text{coupled cell} = \text{ZZ}} g_{\text{ZZ }\rightarrow \text{ax}}(V_{xx_{sd}} - V_{zz_{ax}}) + g_{\text{synpl}(V_{xx_{sd}} - V_{zz_{ax}})}$$

(IA)
FIG. 1. Detailed model of the pyloric circuit: circuitry and activity. All simulations were done with no A-current in the LP neuron, and a nondepressing pyloric dilator (PD) to lateral pyloric neuron (LP) synapse. A: schematic diagram of the circuit used in the model. This circuit is a subset of the complete pyloric network, which includes 12–14 neurons, depending on species. Resistors represent electrical synapses. All other connections are chemical inhibitory synapses. PD to LP synapse (arrow) was modeled as depressing or nondepressing (see text). All other synapses were modeled as nondepressing. For simplicity, the LP to PD synapse (dotted curve and open circle) was not implemented in this model. B: top 5 traces are membrane potential time courses in each of the 5 neurons. Bottom trace: combined firing activity in the PD, LP, early pyloric constrictor (PE), and late pyloric constrictor (PL) neurons. This trace models the extracellular activity on the biological nerve lm.

Each state variable x was modeled with the following type of equation

\[
\frac{dx}{dt} = \frac{x_s(V) - x}{\tau_x(V)} \quad x = m, h
\]

with the steady-state function \(x_s(V)\) described by

\[
x_s(V) = \frac{1}{1 + \exp[-(V - V_{1/2})/k_s]}\]

where \(V_{1/2}\) (in mV) represents the slope at which \(x_s(V) = 0.5\), and \(k_s\) (in mV) represents the slope steep when close to 0. In agreement with the model described in Turrigiano et al. (1995), in all our cellular models the time constant of inactivation of the sodium current was described with a bell-shaped function

\[
\tau_{x,ln}(V) = \frac{3}{1 + \exp[-(V + 40)/10]} \left[ \frac{1.5 + 1}{1 + \exp[(V + 10)/3.6]} \right]
\]

As in Turrigiano et al. (1995), all other times constants of conductance activation/inactivation were described by sigmoid functions of the form

\[
\tau_x(V) = \tau_x,hi + \frac{\tau_{x,hi} - \tau_{x,lo}}{1 + \exp[(V - V_{1/2})/k_x]}
\]

where \(\tau_{x,hi}\) and \(\tau_{x,lo}\) (in ms) are the time constant values at low \((V \rightarrow -\infty)\) and high \((V \rightarrow +\infty)\) voltages, respectively. Instantaneous variables (i.e., dependent on voltage but not on time) were modeled by

\[
\frac{dx}{dt} = x(V)
\]

Ion conductances. The voltage- and time-dependent conductance \(g_{ion}(V, t)\) of ionic conductance \(ion\) obeyed the following equation

\[
g_{ion}(V, t) = g_{ion,rest} m^n h^p
\]

where \(m\) and \(h\) are state variables describing activation and inactivation, and \(p\) and \(q\) are gating powers. For a non-voltage-dependent (leak) current, \(p = q = 0\), and \(g(V, t) = \bar{g}_f\). For a voltage-dependent persistent current (no inactivation) \(p > 0\), \(q = 0\), and \(g_{ion}(V, t) = \bar{g}_f n^p h^p\). For a voltage-dependent transient current, \(p > 0\), \(q > 0\), and \(g_{ion}(V, t) = \bar{g}_f m^n h^p\).
An empty entry indicates that the current represented in the corresponding column was not implemented in the compartment of the corresponding row. Parameters that were modified from run to run of the simulations are denoted as “Variable.”

Values for \( \varepsilon_{\text{syn}} \) in nS were: 2 (LP, \( \text{sd} \rightarrow \text{PD, sd} \)), 6 (LP, \( \text{sd} \rightarrow \text{PL, sd} \)), 2.5 (PD, \( \text{sd} \rightarrow \text{AB, sd} \)), 0 (PE, \( \text{sd} \rightarrow \text{LP, sd} \)), and PL, \( \text{sd} \rightarrow \text{LP, sd} \)).

### Table 1. Maximal conductances (g) in nS in the various compartments

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<tr>
<th></th>
<th>( I_{\text{Leak}} )</th>
<th>( I_{C_a} )</th>
<th>( I_{N_a} )</th>
<th>( I_K )</th>
<th>( I_A )</th>
<th>( I_H )</th>
<th>( I_{\text{Procolin}} )</th>
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<tr>
<td>ABa</td>
<td>0.05</td>
<td>12</td>
<td>3</td>
<td>3</td>
<td>1.4</td>
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<td>PDs</td>
<td>6</td>
<td>1.3</td>
<td>50</td>
<td>30</td>
<td>2.5</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>PDa</td>
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<td>5</td>
<td>50</td>
<td>10</td>
<td>Variable</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>LPs</td>
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<td>5</td>
<td>500</td>
<td>150</td>
<td>35</td>
<td>2</td>
<td></td>
</tr>
<tr>
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<td>0.5</td>
<td>500</td>
<td>200</td>
<td>30</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>PEa</td>
<td>0.5</td>
<td>0.5</td>
<td>500</td>
<td>200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLas</td>
<td>0.5</td>
<td>0.5</td>
<td>500</td>
<td>200</td>
<td></td>
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### Table 2. Reversal potentials (E) in mV

<table>
<thead>
<tr>
<th></th>
<th>( I_{\text{Leak}} )</th>
<th>( I_{C_a} )</th>
<th>( I_{N_a} )</th>
<th>( I_K )</th>
<th>( I_A )</th>
<th>( I_H )</th>
<th>( I_{\text{Procolin}} )</th>
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<tr>
<td>ABa</td>
<td>−60</td>
<td>100</td>
<td>−80</td>
<td>−80</td>
<td>−80</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PDs</td>
<td>−72</td>
<td>45</td>
<td>−80</td>
<td>−80</td>
<td>−80</td>
<td>−10</td>
<td></td>
</tr>
<tr>
<td>PDa</td>
<td>−60</td>
<td>100</td>
<td>−80</td>
<td>−80</td>
<td>−80</td>
<td>−10</td>
<td></td>
</tr>
<tr>
<td>LPs</td>
<td>−72</td>
<td>45</td>
<td>−80</td>
<td>−80</td>
<td>−80</td>
<td>−10</td>
<td></td>
</tr>
<tr>
<td>PEa</td>
<td>−52</td>
<td>45</td>
<td>−80</td>
<td>−80</td>
<td>−80</td>
<td>−10</td>
<td></td>
</tr>
<tr>
<td>PLs</td>
<td>−52</td>
<td>45</td>
<td>−80</td>
<td>−80</td>
<td>−80</td>
<td>−10</td>
<td></td>
</tr>
<tr>
<td>PLa</td>
<td>−52</td>
<td>45</td>
<td>−80</td>
<td>−80</td>
<td>−80</td>
<td>−10</td>
<td></td>
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</table>

### Table 3. Midpoint voltages (\( V_{m,1/2} \)) of steady-state activation/inactivation curves (in mV)

<table>
<thead>
<tr>
<th></th>
<th>( I_{C_a} )</th>
<th>( I_{N_a} )</th>
<th>( I_K )</th>
<th>( I_A )</th>
<th>( I_H )</th>
<th>( I_{\text{Procolin}} )</th>
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<tr>
<td>ABa</td>
<td>−57.5−54</td>
<td>−57.5−60−61</td>
<td>−50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDs</td>
<td>−57.5−54</td>
<td>−18−23</td>
<td>−61−66−65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDa</td>
<td>−57.5−54</td>
<td>−18−23</td>
<td>−61−66−65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPs</td>
<td>−57.5−54</td>
<td>−21−23</td>
<td>−61−66−65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEa</td>
<td>−57.5−54</td>
<td>−21−23</td>
<td>−61−66−65</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PLs</td>
<td>−57.5−54</td>
<td>−21−23</td>
<td>−61−66−65</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 4. Slopes (\( k_a; k_p \)) of steady-state activation/inactivation curves (in mV)

<table>
<thead>
<tr>
<th></th>
<th>( I_{C_a} )</th>
<th>( I_{N_a} )</th>
<th>( I_K )</th>
<th>( I_A )</th>
<th>( I_H )</th>
<th>( I_{\text{Procolin}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABa</td>
<td>3−1</td>
<td>3</td>
<td>1.25</td>
<td>1.25</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>PDs</td>
<td>3−3</td>
<td>12.5−7.7</td>
<td>5</td>
<td>1.25</td>
<td>1.25</td>
<td>−5</td>
</tr>
<tr>
<td>PDa</td>
<td>12.5−7.7</td>
<td>12.5−7.7</td>
<td>1.25</td>
<td>1.25</td>
<td>1.25</td>
<td>1.25</td>
</tr>
<tr>
<td>LPs</td>
<td>12.5−7.7</td>
<td>12.5−7.7</td>
<td>1.25</td>
<td>1.25</td>
<td>1.25</td>
<td>1.25</td>
</tr>
<tr>
<td>PEa</td>
<td>12.5−7.7</td>
<td>12.5−7.7</td>
<td>1.25</td>
<td>1.25</td>
<td>1.25</td>
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<tr>
<td>PLs</td>
<td>12.5−7.7</td>
<td>12.5−7.7</td>
<td>1.25</td>
<td>1.25</td>
<td>1.25</td>
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</tr>
</tbody>
</table>

**The reduced model**

The complexity of the detailed model prevented us from gaining a clear and complete understanding of the mechanism. Thus we decided to dissect the mechanism by reducing this model to a much simplified one. The reduced model consisted of an oscillator (O) coupled by a single inhibitory synapse to a follower F. Both O and F were modeled with Morris–Lecar equations (Morris and Lecar 1981). In O, the selected set of conductances produced spontaneous oscillations. Cell F was endowed with a set of ionic conductances that, in the absence of any input from cell O, yielded a high stable resting membrane potential. The synapse from O to F was modeled with 2 variables: one represented the fraction of open synaptic channels (which decayed between bursts; this decay represented the closure of synaptic channels after the onset of transmitter release) and the other represented the depression state of the synapse (which decreased when cell O was active, and increased when it was nonactive). Equations for the cellular and synaptic variables were as described in Manor et al. (2003), with the exception that an A-like current was introduced in cell F.

In the reduced model, the cycle period was modified by changing the value of the time constant of the recovery variable in cell O when the membrane potential of cell O was low. This computational manipulation changed the cycle period by modifying the duration of time that cell O was not active, while keeping the duration of the active state (high-voltage) fixed.

**COMPUTATION OF TIME INTERVAL AND PHASE.** Numerical simulations and analysis were done with a MatLab program using the
Symulink environment. All simulations were run for 30-s simulation time. In each run we ignored the first 20 s, to eliminate transient effects and allow the system to reach a stationary state. We then divided the last 10 s of the run to n individual cycles. We arbitrarily decided that each cycle starts at the onset time of PD burst (in the detailed model), or the time that the voltage exceeds 0 mV in the O neuron (in the reduced model). This time was defined as the reference time. In any one cycle, all temporal events were measured relative to this time. In each cycle, we measured the following temporal events for cell XX:

1.) $T_{XX,on}$, the time of the onset of activity in neuron XX. In the PD, LP, PE, or PL neurons (detailed pyloric model) this time was equal to the time of the first action potential peak in a burst. In all cases, we empirically found that the interspike interval was always <250 ms. Thus in these neurons an action potential was defined as first action potential in a burst if no spike occurred within the 250 ms preceding this action potential. The action potentials in the AB neuron were very small in amplitude and could not be used to define the burst limits. Thus in this case we defined the onset of burst as the time at which the voltage of the cell became more positive than 0 mV.

2.) $T_{XX,off}$, the time of the termination of activity in cell XX. In the PD, LP, PE, or PL neurons (detailed pyloric model) this time was equal to the time of the last action potential peak in a burst. An action potential was defined as last in a burst if no spike occurred within the 250 ms after this action potential. In the case of the AB neuron, the end of the burst was defined as the time at which the membrane potential of AB became more negative than −55 mV. In the simplified model, the end of activity was defined as the time at which the voltage of the cell became more negative than 0 mV.

3.) Burst duration in neuron XX was calculated as $T_{XX,off} - T_{XX,on}$.

### Table 5. Gating powers (p:q) of activation:inactivation processes

<table>
<thead>
<tr>
<th></th>
<th>$I_{Ca}$</th>
<th>$I_{Na}$</th>
<th>$I_{K}$</th>
<th>$I_A$</th>
<th>$I_H$</th>
<th>$I_{Procuslin}$</th>
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</thead>
<tbody>
<tr>
<td>ABs</td>
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<td>2:1</td>
<td>4:1</td>
<td></td>
<td>2:1</td>
<td>1:1</td>
</tr>
<tr>
<td>ABa</td>
<td>3:1</td>
<td>2:1</td>
<td>4:1</td>
<td></td>
<td>1:1</td>
<td>1:1</td>
</tr>
<tr>
<td>PDs</td>
<td>3:1</td>
<td>2:1</td>
<td>4:1</td>
<td></td>
<td>1:1</td>
<td>1:1</td>
</tr>
<tr>
<td>PDa</td>
<td>3:1</td>
<td>2:1</td>
<td>4:1</td>
<td></td>
<td>1:1</td>
<td>1:1</td>
</tr>
<tr>
<td>LPs</td>
<td>3:1</td>
<td>2:1</td>
<td>4:1</td>
<td></td>
<td>1:1</td>
<td>1:1</td>
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<td>4:1</td>
<td></td>
<td>1:1</td>
<td>1:1</td>
</tr>
<tr>
<td>LPe</td>
<td>3:1</td>
<td>2:1</td>
<td>4:1</td>
<td></td>
<td>1:1</td>
<td>1:1</td>
</tr>
<tr>
<td>PLs</td>
<td>3:1</td>
<td>2:1</td>
<td>4:1</td>
<td></td>
<td>1:1</td>
<td>1:1</td>
</tr>
<tr>
<td>PLA</td>
<td>3:1</td>
<td>2:1</td>
<td>4:1</td>
<td></td>
<td>1:1</td>
<td>1:1</td>
</tr>
</tbody>
</table>

A value of 0 indicates an instantaneous activation. Identical values for $\tau_m,lo$ and $\tau_m,hi$ indicate a constant (voltage independent) time constant.

### Table 6. Time constant ($\tau_m,lo$–$\tau_m,hi$) of activation at low and high voltages (in ms)

<table>
<thead>
<tr>
<th></th>
<th>$I_{Ca}$</th>
<th>$I_A$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABs</td>
<td>300–1,200</td>
<td>200–200</td>
</tr>
<tr>
<td>ABa</td>
<td>300–1,200</td>
<td>200–200</td>
</tr>
<tr>
<td>PDs</td>
<td>300–1,200</td>
<td>200–200</td>
</tr>
<tr>
<td>PDa</td>
<td>300–1,200</td>
<td>200–200</td>
</tr>
<tr>
<td>LPs</td>
<td>300–1,200</td>
<td>200–200</td>
</tr>
<tr>
<td>LPe</td>
<td>300–1,200</td>
<td>200–200</td>
</tr>
<tr>
<td>PLs</td>
<td>300–1,200</td>
<td>200–200</td>
</tr>
</tbody>
</table>

Time constant of inactivation of sodium current is given in Eq. 6.

4.) $P$, the cycle period. This time was equal to the time difference between $T_{XX,on}$ in the current cycle and $T_{XX,on}$ in the subsequent cycle, where XX = PD in the detailed model and XX = O in the simplified model.

5.) The phase of the onset of the burst in cell XX: $\phi_{XX,on} = T_{XX,on}/P$.

6.) The phase of the termination of the burst in cell XX: $\phi_{XX,off} = T_{XX,off}/P$.

A CRITERION FOR PHASE CONSTANCY. To compare how well phase was maintained in different cases, we developed the following criterion: we found the phase at a cycle period of $P = 1,000$ ms, and referred to this phase as the “pivot point.” In the plot of phase versus cycle period, we defined a window of ±0.05 around the pivot point, and found the largest continuous range of cycle periods ($\Delta P$) for which the phase varied within this window only. Larger $\Delta P$ values indicate better phase maintenance.

### Results

A detailed model of the pyloric rhythm produced a triphasic rhythm similar to the biological pyloric rhythm.

The parameters of the model were tuned such that the network produced a triphasic rhythm with a cycle frequency (frequency of slow waves) of 1 Hz, which is the typical frequency of the pyloric rhythm. Five top traces in Fig. 1B are voltage traces of the somatodendritic compartments of the AB, PD, LP, PE, and PL neurons. The AB and PD neurons produced simultaneous bursts. The fast action potentials rising on the slow wave of the PD and AB neurons were of small amplitude, reflecting the fact that the site of fast action potentials generation was electrically distant from the somatodendritic compartment. After a brief interval, the LP neuron produced a burst, followed by bursts in the PE and then the PL neurons. There was a brief overlap in the bursting times of the LP neuron and the 2 PY (PE and PL) neurons. The onset of activities in the PE and PL neurons terminated the LP burst. The bursts of PE and PL terminated when PD started the subsequent burst. These activity profiles are characteristic of the intracellular activities that can be recorded in a typical biological pyloric network (Bal et al. 1994; Marder and Calabrese 1996). The bottom trace in Fig. 1B represents the spiking activity in a nerve constituting axons of the 4 motoneurons PD, LP, PE, and PL (the AB neuron is an interneuron and does not send an axon through this nerve). This trace was constructed by first detecting the times of action potential peak in these 4 neurons. Then, for each spike detected, a vertical stroke was
Increasing a proctolin current in the AB neuron produced a biphasic effect on the cycle period

The cycle period of the rhythm was modified by changing the level of the proctolin current in the AB neuron. We assumed that larger levels (greater concentrations) of proctolin recruit more proctolin channels. Thus we modeled the effect of proctolin concentration by changing the maximal conductance of the proctolin current, $g_{\text{proc}}$. In the simulations shown in Fig. 2, the synapse from PD to LP was nondepressing, and there was no A-current in LP (the effects of synaptic depression in the PD to LP synapse and existence of A-current in the LP neuron are studied in later sections). In Fig. 2A are plotted voltage traces of the somatodendritic compartment in the PD neuron, with different $g_{\text{proc}}$ values in the AB neuron. When $g_{\text{proc}} = 0$ (top trace), the cycle period of the rhythm was 1,888 ms, which is within the physiological range of slow pyloric rhythms. At low levels of the proctolin current, increasing the proctolin current sped up the rhythm: compare top trace to 2nd trace ($g_{\text{proc}} = 2.5$ nS), and 2nd trace to 3rd trace ($g_{\text{proc}} = 5$ nS). At higher levels of proctolin, increasing the proctolin current had an opposite effect: it slowed down the rhythm (compare 3rd trace to 4th trace, $g_{\text{proc}} = 7.5$ nS).

To understand the biphasic effect of the proctolin current on cycle period, we examined how different levels of this current affect the burst and interburst durations in the AB and PD neurons. Figure 2B plots the burst and interburst durations in the AB neuron (thin curves), the burst and interburst durations in the PD neuron (thick curves), and the cycle period (dashed curve). With $g_{\text{proc}} = 0$, the burst durations were 240 and 197 ms in the AB and PD neuron, respectively. As $g_{\text{proc}}$ was increased, the burst duration in the AB neuron gradually became longer, as a result of the addition of an inward current that delayed the termination of the AB burst. Because of the electrical coupling between the AB and PD neurons, the PD burst duration gradually became longer as well. The interburst duration in the AB neuron (and, consequently, in the PD neuron) decreased as $g_{\text{proc}}$ was increased because the addition of inward current in AB facilitated the depolarization of the AB neuron and advanced its activity time. As long as the burst duration, which in general increased, was smaller than the interburst duration, which in general decreased, the cycle period (= burst + interburst) decreased as a function of $g_{\text{proc}}$. This occurred for $g_{\text{proc}} < 6.1$ nS. Above this value, the burst duration exceeded the interburst duration, and the cycle period increased with larger $g_{\text{proc}}$ values, until the rhythm collapsed when $g_{\text{proc}}$ was greater than 7.7 nS (the AB and PD neurons became permanently active). We see that, in general, increasing the proctolin current produced a gradual change in the cycle period and the durations of burst and interburst in the AB and PD neurons. This effect is illustrated in Fig. 2C, where PD bursts at 3 different $g_{\text{proc}}$ values are superimposed. The transition of $g_{\text{proc}}$ from 1.0 to 1.6 nS demonstrates the gradual effect of the proctolin current: the addition of inward current in the AB neuron prolonged the AB burst and thus delayed the last (7th) spike in the PD burst. Recall that in the PD neuron the burst duration is calculated as the interval from the first to the
last action potential in the burst. Thus the duration of the PD burst gradually increased.

At several discrete points, increasing the proctolin current in AB produced a stepwise change in the durations of PD burst and interburst

At several discrete \( \text{g}_{\text{proc}} \) values, the PD burst and interburst durations abruptly changed. These results were obtained when the number of action potentials in the PD burst decremented, or incremented, by one. Note that this effect was observed only for the PD neuron, and not the AB neuron. Because the PD burst duration is calculated as the interval from the first to the last action potential in the burst, the addition or subtraction of a single spike resulted in a step change (about 60 ms) in the durations of the PD burst and interburst. This effect was not observed in the AB neuron because, in this case, the calculation of burst duration did not rely on the times of first and last action potentials in the burst (see methods).

The number of action potentials in the PD burst incremented at \( \text{g}_{\text{proc}} = 4.9 \) (from 5 to 6 spikes), 6.6 (6 to 7 spikes), 7.12 (7 to 8 spikes), 7.4 (8 to 9 spikes), 7.58 (9 to 10 spikes), and 7.7 nS (10 to 11 spikes). In these cases, the increase in inward current prolonged the AB burst and, consequently, delayed the repolarization of the PD burst. Thus the number of action potentials in the PD burst incremented and the PD burst duration abruptly increased (by about 60 ms).

At \( \text{g}_{\text{proc}} = 1.8 \) and 4.2 nS, the number of action potentials in the PD burst decreased (from 7 to 6 and from 6 to 5, respectively). A possible explanation is that when \( \text{g}_{\text{proc}} \) was increased, the addition of an inward current tended not only to prolong the AB burst, but also to increase the amplitude of the AB burst (as observed in our simulations; not shown). A larger amplitude of the AB burst could increase speed up the inactivation of calcium currents, thereby acting as a negative feedback and accelerating the rate of repolarization in both AB and PD. This effect would cause each spike in the PD burst to occur incrementally later, and at a lower membrane potential. Let \( n \) be the number of spikes in the PD burst at some \( \text{g}_{\text{proc}} \) value. As \( \text{g}_{\text{proc}} \) is increased, eventually the membrane potential of PD would fall below threshold shortly after the \( n - 1 \) spike, and the number of action potentials would suddenly decremented from \( n \) to \( n - 1 \).

This effect is illustrated in Fig. 2C when \( \text{g}_{\text{proc}} \) was increased from 1.6 to 1.8: the addition of inward current in the AB neuron slightly increased the rate of repolarization in the PD burst, as can be seen from the slightly lower membrane potential at the time of the 6th spike in the PD burst. The 7th spike failed because at the time this action potential should have been generated, the membrane potential was already too negative; thus the duration of the PD burst sharply decreased.

Dependency of frequency of the onset and termination times of bursting in the pyloric neurons

Next, we examined the dependency of burst onset and termination as a function of the cycle period (as a result of changing \( \text{g}_{\text{proc}} \)) in the PD, LP, PE, and PL neurons (Fig. 3, A–D). In each panel, the dotted line \( T = P \) represents the time of the subsequent burst in the PD neuron. Black and gray curves represent times of burst onset and termination, respectively. On any of these curves, each point was obtained with a different \( \text{g}_{\text{proc}} \) value. The reference time, relative to which all other times were measured, was the onset of bursting in the PD neuron (\( T_{\text{PD,on}} = 0 \), lies on the x-axis in Fig. 3A). As function of cycle period, the end of the PD burst (\( T_{\text{PD,off}} \), Fig. 3A) and onset of the LP burst (\( T_{\text{LP,on}} \), Fig. 3B) showed a wedgelike shape, which consisted of lower and upper branches. We emphasize that the wedgelike shape of these 2 curves does not indicate a bistability phenomenon: the 2 branches were separated because the value of a parameter was different, that is \( \text{g}_{\text{proc}} \), and not the initial conditions of the system variables. On the 2 curves \( T_{\text{PD,off}} \) and \( T_{\text{LP,on}} \), \( \text{g}_{\text{proc}} \) was incremented from 0 to 6 nS when following the lower branch from the right (\( P = 1,888 \) ms) to the left (\( P = 597 \) ms). In general \( T_{\text{PD,off}} \) gradually increased along the lower branch, except at 2 points where it sharply decreased (see Fig. 2). Thus overall the change in \( T_{\text{PD,off}} \) was relatively small along this branch. Because of the strong inhibitory synapse from PD to LP, as long as the PD neuron was bursting the LP burst was delayed. Consequently \( T_{\text{LP,on}} \) was vertically shifted relative to \( T_{\text{PD,off}} \). Because the synapse was nondepressing, this shift was almost constant and \( T_{\text{LP,on}} \) was mostly fixed. There was a weak decrease of \( T_{\text{LP,on}} \) along the lower branch, mainly because of the gradual nature of the PD to LP synapse. When following the upper branch from the left (\( P = 598 \) ms) to the right (\( P = 918 \) ms), \( \text{g}_{\text{proc}} \) was incremented from 6.1 to 7.7 nS. At these large \( \text{g}_{\text{proc}} \) values, the increased excitability in the AB neuron delayed the termination of the AB and PD bursts, and \( T_{\text{PD,off}} \) increased along its upper branch. Note that the slope of the upper branch was parallel to the linear curve \( T = P \), indicating that along this branch the increase in cycle period was a direct result of the increase in PD burst duration. The burst of the LP neuron was delayed accordingly, and \( T_{\text{LP,on}} \) increased along its upper branch as well.

The end of the LP burst (\( T_{\text{LP,off}} \)) depended on the activity of the PE (Fig. 3C) and PL (Fig. 3D) neurons. Thus its dependency on cycle period cannot be understood before analyzing how the cycle period affected the onset of burst in the PE and PL neurons. We therefore start by describing the dependency of \( T_{\text{PE,on}} \) (onset of PE burst) and \( T_{\text{PL,on}} \) (onset of PL burst) on the cycle period. The PE neuron included a large A-current. After inhibition from the PD neuron, the large A-current in PE strongly decreased the rate of depolarization, and PE started to burst about 250 ms after the onset of LP burst. The PE neuron included an even larger A-current and therefore its burst was further delayed, and \( T_{\text{PE,off}} \) and \( T_{\text{PL,off}} \) were vertically shifted with respect to \( T_{\text{LP,on}} \) and with respect to each other. Because the PD to PE and PL synapses were nondepressing, \( T_{\text{PE,off}} \) and \( T_{\text{PL,off}} \) were almost constant. As soon as the PD neuron started to depolarize, it ended the bursts in PE and PL (thus \( T_{\text{PE,off}} \) and \( T_{\text{PL,off}} \) were close to the linear line \( T = P \)). As \( \text{g}_{\text{proc}} \) increased and the cycle period decreased, as seen in Fig. 2, the PD interburst duration approached a minimal value. Because PL and PE could burst only when PD was not active, the burst duration in these 2 cells became shorter. In the PL neuron, between \( 742 < P < 803 \) ms the burst shortened down to the duration of a single spike (note the merging of \( T_{\text{PL,on}} \) and \( T_{\text{PL,off}} \) in Fig. 3D). At \( P < 742 \) ms, the interburst of the PD neuron was too short to allow the PL neuron to produce even a single spike, and the PL neuron stopped firing. Likewise for the PE neuron (Fig. 3C): the burst shortened down to a single spike.
between 617 < P < 693 ms, and at P = 617 ms the PE neuron stopped firing. \( T_{P,E,\text{on}} \) and \( T_{P,L,\text{on}} \) lacked the wedgelike shape seen for \( T_{P,D,\text{off}} \) and \( T_{P,L,\text{on}} \) because the PE and PL neurons stopped firing at large \( g_{\text{proc}} \) values.

The strong inhibitory synapses from the PE to LP and PL to LP neurons ensured that LP stopped firing slightly after PE started to fire, and slightly before PL started to fire. Thus at low and intermediate values of \( g_{\text{proc}} \), \( T_{P,E,\text{on}} \) (Fig. 3B) was larger than \( T_{P,L,\text{on}} \), and \( T_{P,L,\text{off}} \) because the PE and PL neurons stopped firing. Thus in this case the burst of the LP neuron was terminated by the subsequent burst in the PD neuron, and \( T_{P,L,\text{off}} \) was close to the linear curve \( T_P \).

We hereafter focus our attention to the onset of bursting in the LP neuron. In the DISCUSSION, we briefly elaborate how other temporal events may be affected by the cycle period as well, using principles similar to those outlined for the onset of bursting in the LP neuron.

With no A-current in LP, the delaying effect of a depressing synapse was similar to a nondepressing synapse.

In this section we study the frequency-dependent contribution of synaptic depression per se to the onset of bursting in the LP neuron. All simulations were done when the LP neuron did not include an A-current. To properly compare between the depressing and nondepressing cases, we tuned the maximal synaptic conductance \( g_{\text{syn}} \) of the depressing PD to LP synapse such that at a cycle period of 1,000 ms the delay it produced onto the LP burst \( (T_{P,L,\text{on}}) \) was identical to that of the nondepressing case. With a nondepressing synapse, at \( P = 1,000 \) ms \( T_{P,L,\text{on}} \) was 330 ms. The maximal conductance \( g_{\text{syn}} \) of the nondepressing synapse was 3.1 nS. When the synapse was implemented as a depressing synapse, we found that at \( P = 1,000 \) ms a \( g_{\text{syn}} \) value of 20 nS produced a delay \( T_{P,L,\text{on}} \) of 330 ms. We therefore chose a maximal conductance of 20 nS for the depressing synapse.

In Fig. 4A we show voltage traces of the PD neuron (top row) and the LP neuron when the PD to LP synapse was nondepressing (middle row, –Dep–A) or depressing (bottom row, +Dep–A), at 4 values of \( g_{\text{proc}} \): 7.5 nS (\( P = 762 \) ms, leftmost column), 6.5 nS (\( P = 598 \), 2nd column), 2.7 nS (\( P = 1,005 \), 3rd column), and 0 nS (\( P = 1,888 \), rightmost column). The length of the 2 gray rectangles on top of the PD traces represents the delay of LP burst when the synapse was nondepressing (top rectangle) or depressing (bottom rectangle). When the synapse was nondepressing, in all 4 cases the depth of inhibition (lowest voltage in LP) was almost identical (compare troughs on middle row traces); the durations of inhibition depended only on the duration of the PD burst and were not significantly different. Thus as expected, the effect of the synapse on the delay of the LP burst was nearly fixed and independent of cycle period. When the synapse showed depression, the depth of hyperpolarization was strongly correlated with \( g_{\text{proc}} \) and cycle period (compare troughs on bottom...
row traces). The lowest voltages of LP were: −55.0 mV with \( \tilde{g}_{\text{proc}} = 7.5 \) (\( P = 762 \) ms); −57.6 mV with \( \tilde{g}_{\text{proc}} = 6.5 \) (\( P = 598 \) ms); −63.3 mV with \( \tilde{g}_{\text{proc}} = 2.7 \) (\( P = 1,005 \) ms); and −65.8 mV with \( \tilde{g}_{\text{proc}} = 0 \) (\( P = 1,888 \) ms); With \( \tilde{g}_{\text{proc}} \) values of 0, 2.5, or 5 nS (2nd, 3rd, and rightmost columns), the onset of LP burst was not different whether the synapse was depressing or nondepressing (compare widths of gray rectangles in the 2nd, 3rd, and rightmost columns).

At first sight, this result is unexpected because with synaptic depression longer cycle periods produce larger voltage differences (trajectories) from the trough of inhibitory to the onset of burst in the LP neuron. The result that delay did not increase, despite the larger trajectory in the LP neuron, suggests that the rate of depolarization in LP increased, possibly because of the postinhibitory rebound properties in the LP neuron. Indeed, a larger hyperpolarization in the LP neuron is expected to produce a larger deinactivation of the calcium current in the LP neuron and this in turn should increase the magnitude of the calcium current in the LP neuron on depolarization, thereby accelerating the depolarization rate and acting to reduce the delay of the LP burst. In contrast, with \( \tilde{g}_{\text{proc}} = 7.5 \) nS (leftmost column) there was a marked difference when the synapse was depressing or nondepressing: With a nondepressing synapse, as the duration of the PD burst increased the LP neuron was inhibited for a longer time, and the LP burst was delayed (note the longer length of the bottom gray rectangle, compared with all other cases). When the synapse was depressing, because of the short interburst in the PD neuron the PD to LP synapse did not recover from inhibition and became weak. The weak synapse was not sufficient to inhibit the LP neuron for as long as PD was active, and LP started to burst before the end of the PD burst (the bursts of LP and PD overlapped in this case). Thus the LP burst was advanced (note the shorter length of the upper gray rectangle, compared with all other cases).

These results are quantitatively presented in Fig. 4B. With \( \tilde{g}_{\text{proc}} \) values <3.4 nS (\( P < 856 \) ms), \( T_{\text{LP,on}} \) was almost identical (up to 1 ms difference) whether the synapse was nondepressing (thin curve, −Dep − A) or depressing (thick curve, +Dep − A); it weakly decreased as \( \tilde{g}_{\text{proc}} \) increased and the cycle period decreased, between 370 ms at \( P = 1,888 \) and 320 ms at \( P = 856 \) ms. With higher values of \( \tilde{g}_{\text{proc}} \) (>3.3 nS), the dependency of \( T_{\text{LP,on}} \) on \( \tilde{g}_{\text{proc}} \) and the cycle period became different in the 2 cases: when the synapse was nondepressing synapse, \( T_{\text{LP,on}} \) increased as \( \tilde{g}_{\text{proc}} \) in-
creased, as can be seen on the top branch of the curve \( -\text{Dep}\text{--A} \), and also on the bottom branch of this curve for \( 597 < P < 856 \) ms. In contrast, when the synapse was depressing synapse, \( T_{\text{LP, on}} \) decreased as \( g_{\text{proc}} \) increased, as can be seen on the bottom branch of the curve \( +\text{Dep}\text{--A} \), and also on the top branch of this curve for \( 597 < P < 856 \) ms.

As explained in the methods, the pivot point was defined as the phase \( \phi_{\text{LP, on}} \) at \( P = 1,000 \) ms. Because of the tuning process of the depressing synapse, by definition the pivot points for the depressing and nondepressing cases were identical and equal to 0.33 (dashed linear curve in Fig. 4B represented a fixed phase of 0.33; this curve crossed the 2 curves, \( -\text{Dep}\text{--A} \) and \( +\text{Dep}\text{--A} \), at \( P = 1,000 \) ms). In Fig. 3C, the width of the gray rectangle represented a phase variation of \( \pm 0.05 \) around the pivot points; the length of this rectangle represented the range \( \Delta P \) of cycle periods for which phase varied within this rectangle (i.e., \( \pm 0.05 \) around the pivot point). Because, in this range of cycle periods, the phases were identical with a depressing or a nondepressing synapse, the gray rectangles corresponding to the 2 cases were identical (only one rectangle is shown in Fig. 4C). In both the nondepressing and depressing versions of the synapse, \( \Delta P \) was \( 1,250 - 838 = 412 \) ms. This relatively narrow range represented a poor level of phase maintenance.

These results suggest that with no A-current in the follower neuron, and with the kinetics chosen for synaptic depression in this model, a depressing synapse may not be advantageous for phase maintenance.

When the synapse was nondepressing, the delaying effect of an A-current was constant and independent of cycle period

In this section we study the frequency-dependent contribution of an A-current per se to the onset of bursting in the LP neuron. All simulations were done when the synapse from PD to LP was nondepressing. In Fig. 5A, voltage traces of the PD (top traces) and LP neuron without A-current (middle row traces, \( -\text{Dep}\text{--A} \)) and with A-current (bottom row traces, \( -\text{Dep}\text{+A} \)) are shown for 4 values of \( g_{\text{proc}} \): 7.5 nS (\( P = 762 \) ms, leftmost column), 6.5 nS (\( P = 598 \), 2nd column), 2.7 nS (\( P = 1,005 \), 3rd column), and 0 nS (\( P = 1,888 \), rightmost column). Because the synapse from PD to LP was nondepressing, in all 4 cases the depth of synaptic inhibition was similar, whether the LP current included or did not include an A-current (troughs of bottom traces and middle traces, respectively). The addition of A-current slightly delayed the burst of LP in all 4 cases, but this additional delay was too short to be visually distinguishable when comparing the lengths of the gray rectangles in Fig. 5A.

Figure 5B plots the onset time of bursting in the LP neuron (\( T_{\text{LP, on}} \)) as a function of cycle period \( P \), with and without A-current in the LP neuron. At any \( P \) value, the A-current added a small and approximately fixed difference delay of about 10 ms. For example, at \( P = 1,000 \) ms, \( T_{\text{LP, on}} \) was 330 ms with no A-current, and 340 ms when the LP neuron included an A-current. Because the depth of synaptic inhibition was independent of cycle period, at different cycle periods the deinactivation level of the A-current was similar, adding a similar (small) delay in the onset of LP burst. Dashed linear curves represent constant phases of 0.33 and 0.34 (the pivot points in
the 2 corresponding cases). These linear functions crossed the corresponding phase curves at \( P = 1,000 \) ms, but did not remain close to the phase curves when \( P \) was smaller or larger than 1,000 ms. This implies that the level of phase maintenance was poor in both cases.

The onset phase of LP burst was plotted against the cycle period in Fig. 5C. Each of the 2 gray rectangles represented a phase variation of \( \pm 0.05 \) around the corresponding pivot point of 0.33 (without A-current in LP) and 0.34 (with A-current in LP). The ranges \( \Delta P \) of cycle periods for which phase satisfied the criterion for phase maintenance (i.e., variation within \( \pm 0.05 \) of the pivot point, as illustrated by the gray rectangles) were almost identical with and without A-current: 420 and 412 ms, respectively.

These results demonstrate that when the synapse is not depressing, the existence of A-current in the follower neuron is not advantageous for phase constancy.

When the synapse was depressing, the delaying effect of an A-current was incrementally larger as cycle period increased.

In this section we examined whether, when the synapse from LP to PD synapse showed depression, the existence of A-current in the LP neuron promoted phase constancy. All simulations were done when the LP to PD synapse was depressing. In Fig. 6A, voltage traces of the PD (top traces) and LP neuron without A-current (middle row traces, +Dep−A) and with A-current (bottom row traces, +Dep+A) are shown for 4 values of \( g_{\text{proc}} \): 7.5 nS (\( P = 762 \) ms, leftmost column), 6.5 nS (\( P = 598 \), 2nd column), 2.7 nS (\( P = 1,005 \), 3rd column), and 0 nS (\( P = 1,888 \), rightmost column). When the synapse was nondepressing, in all 4 cases the LP burst occurred at similar times. In contrast, with a depressing synapse the delaying effect of the A-current became highly dependent on the cycle period. Except for the case \( g_{\text{proc}} = 7.5 \) nS (leftmost column), the LP burst was incrementally delayed as the cycle period was increased. At \( P = 1,888 \) ms, with an A-current the LP neuron fired a single action potential: here the onset of firing in the LP neuron was delayed for so long that it occurred just slightly before the onset of firing in the PE and PL neurons. As soon as the PL neuron started its burst, it inhibited the LP neuron and prevented it from generating additional spikes.

These results are quantitatively presented in Fig. 6B. Without A-current in the LP neuron, when \( g_{\text{proc}} \) was incremented from 0 to 6 nS and cycle period decreased from 1,888 to 597 ms, \( T_{\text{LP,on}} \) decreased from 368 to 309 ms (+Dep−A, thin curve in Fig. 6B). Thus at low and intermediate values of \( g_{\text{proc}} \), \( T_{\text{LP,on}} \) weakly decreased as the cycle period decreased because the interburst in the PD neuron became shorter, the synapse had less time to recover from depression, and was less effective in delaying the burst in the LP neuron. However, it is important to emphasize that with no A-current in the LP neuron this effect was subtle relative to the case where LP included an A-current (see following text). With further increment of \( g_{\text{proc}} \) from 6.1 to 7.7 nS (bottom branch +Dep−A curve in Fig. 6B), the cycle period increased from 598 to 918 ms and \( T_{\text{LP,on}} \) decreased because the synapse became too weak to inhibit the LP neuron, and the LP burst started to burst before the end of the PD burst.

**FIG. 6.** Detailed model of the pyloric circuit: phasing effects of a depressing PD to LP synapse with and without A-current in LP. All simulations were done when the synapse from PD to LP was depressing. A–C as in Fig. 4.
A different picture emerged when the LP neuron was endowed with an A-current. As $g_{\text{proc}}$ was increased from 0 to 6 nS and the cycle period decreased from 1,888 to 597 ms in the LP neuron, $T_{\text{LP, on}}$ decreased from 752 to 314 ms (+Dep+A curve in Fig. 6B, when following the top branch of the curve from right to left). Note that this part of the +Dep+A curve was close to the linear function 0.45$P$ (dashed curve in Fig. 6B), implying that with low and intermediate values of $g_{\text{proc}}$, the phase $\phi_{\text{LP}}$ was well maintained around 0.45 (see also Fig. 6C). At higher values of $g_{\text{proc}}$, when $g_{\text{proc}}$ was increased from 6.1 to 7.7 nS and the cycle period increased from 598 to 918 ms, $T_{\text{LP, on}}$ decreased, again because the synapse became incrementally weak and ineffective in delaying the burst of LP. Focusing on the low and intermediate values of $g_{\text{proc}}$ (see Discussion), these results demonstrate that the existence of A-current greatly amplified the tendency of $T_{\text{LP, on}}$ to increase as the cycle period increased, thereby promoting phase constancy in this regime.

These results are also presented in Fig. 6C, where the onset phase $\phi_{\text{LP, on}}$ of the LP burst is plotted against cycle period. Without A-current, when $g_{\text{proc}}$ was incremented from 0 to 6 nS and cycle period decreased from 1,888 to 597 ms, the phase rose from 0.19 to 0.52 (+Dep−A curve in Fig. 6C). As $g_{\text{proc}}$ was further increased from 6.1 to 7.7 nS and the cycle period increased from 598 to 918 ms, the phase decreased to 0.21. The pivot point on this curve (i.e., the phase at $P = 1,000$ ms) was 0.33. The range $\Delta P$ of cycle period values for which phase varied by less than $\pm 0.05$ around the pivot point (length of bottom gray rectangle in Fig. 5C) was 412 ms. This range represented a poor level of phase maintenance.

In contrast, with an A-current in the LP neuron, the phase was approximately constant and around 0.45 in a wide range of cycle period values (thick curve in Fig. 6C). This occurred with low and intermediate values of $g_{\text{proc}}$, but not with $g_{\text{proc}}$ values $>6$ nS, where the cycle period increased with $g_{\text{proc}}$ and the phase decreased (bottom branch of the curve +Dep+A). The pivot point on this phase curve was 0.45. Considering only the low and intermediate values of $g_{\text{proc}}$, the range $\Delta P$ of cycle period values for which phase varied by less than $\pm 0.05$ around the pivot point (upper gray rectangle) was 1,245 ms. This represents a 3.02-fold improvement in the range of cycle periods for which phase was well maintained, according to the criterion defined in Methods, compared with all other cases (no A-current with and without depression, A-current with no depression).

These results support our hypothesis that when the synapse is depressing, the existence of A-current in the follower neuron promotes phase constancy.

Sensitivity analysis of the kinetics of the A-current in the detailed model

Next, we investigated how the kinetics of the A-current affects the relationship between $\phi_{\text{LP, on}}$ and the cycle period $P$. In Fig. 7, each panel illustrates the effect of a different parameter of the A-current. In each panel, the thick curve represents the phase obtained with the set of canonical parameters outlined in Methods. Other curves were obtained with a different value of the parameter, as indicated on the graphs. The dotted curve represents the phase obtained with no A-current. The A-current started to affect the phase at the $P$ value at which $\phi$ diverged from this dotted curve.

The canonical value of the maximal conductance of the A-current, $g_A$, was 22 nS. With larger or smaller maximal conductance of the A-current, $g_A$, the delaying effect of the A-current was stronger or weaker, respectively, and $\phi_{\text{LP, on}}$ increased or decreased, respectively (Fig. 7A). These effects were particularly emphasized with small and intermediate values of the procoltin current, where the cycle period was long or moderate and the A-current could sufficiently deinactivate (during the interburst of the LP neuron) and become active. Note that with larger values of $g_A$, the $\phi_{\text{LP, on}}$ curve was truncated at long $P$ values. In these conditions, the LP burst was excessively delayed such that the PL neuron became active before the onset of burst in the LP neuron. Thus $\phi_{\text{LP, on}}$ was not defined in these cases. For example, with $g_A = 26$ nS the LP neuron stopped to burst at $P > 1,100$ ms.

The onset phase of LP burst was also sensitive to the midpoint ($V_{1/2,h}$) of the inactivation current of the A-current (Fig. 7B). The canonical value of $V_{1/2,h}$ was $-65$ mV. More depolarized values increased the phase because it allowed A-current to incrementally deinactivate during the interburst of the LP neuron. With more depolarized values of $V_{1/2,h}$, the $\phi_{\text{LP, on}}$ curve was truncated at long $P$ values, again because in these conditions, the LP burst was excessively delayed such that the PL neuron became active before the onset of burst in the LP neuron.

The effect of the slope ($k_h$) of the inactivation curve of the A-current is presented in Fig. 7C. The canonical value of $k_h$ was $-1.5$ mV. Less-negative values (e.g., $k_h = -0.5$ mV) yielded a steeper inactivation curve. At all cycle periods, with the parameters used for this model the lowest membrane potential of LP was more depolarized than the midpoint of the inactivation curve, $V_{1/2,h} = -65$ mV. For example, when $P = 1,000$ ms, the lowest membrane potential of LP was $-64.2$ mV. Therefore at the lowest membrane potential of LP the value of $h_s(V)$ was smaller when $k_h$ was less negative. The deinactivation of the A-current was smaller and thus the A-current was less effective in delaying the LP neuron. The phase was therefore smaller when $k_h$ was less negative (opposite effects would have been obtained if the lowest membrane potential of LP was more hyperpolarized than $V_{1/2,h}$ in that case less-negative values of $k_h$ would have increased the phase; see also Fig. 9C). This effect was emphasized at small $P$ values because at short cycle periods the synapse from PD to LP was weaker and the hyperpolarization level of the LP neuron was smaller. When $k_h$ was more negative and the slope of the steady-state curve was more shallow, the phase increased, causing the LP neuron to stop bursting at large cycle periods (again, because of the strong inhibitory synapse from PL to LP, which terminated the LP burst). For example, with $k_h = -2$ mV the LP neuron stopped to burst at $P > 1,080$ ms.

The effect of the time constant ($\tau_h$) of inactivation of the A-current on phase was examined in Fig. 7D. The canonical value of $\tau_h$ was 500 ms. Around this value, the phase was weakly sensitive to differences in $\tau_h$ because the interburst duration of the LP neuron was long relative to $\tau_h$. When the time constant was too small ($\tau_h = 100$ ms in Fig. 7D), the A-current rapidly inactivated during the depolarization phase of the LP neuron, and it became ineffective in delaying the LP neuron. The phase was therefore smaller compared with the
canonical case, and thus a critical assumption of our model is that the A-current is a slowly inactivating current. As elaborated in the DISCUSSION, this is not an unrealistic assumption.

A simplified model was instrumental in gaining insights to understand the interaction of A-current and synaptic depression

The detailed model of the pyloric rhythm demonstrated that synaptic depression together with A-current was advantageous for phase maintenance, but the complexity of this model impeded us from gaining a clear and complete understanding of the mechanism. For this reason, we decided to examine how synaptic depression combined with A-current in a much simpler set of equations based on the model of Manor et al. (2003). This simplified model consisted of only 2 cells, an oscillator O and a follower neuron F, coupled by an inhibitory synapse. Both cells were modeled with Morris–Lecar equations. The synapse was modeled with 2 variables, one representing the fraction of open synaptic channels, and the second representing the fraction of available synaptic resources (depression and recovery). At the onset of activity in O, the first variable was set to the value of the second (representing the event of transmitter release, immediately after the presynaptic cell became active). To model the synapse as depressing, we forced the second variable to be dependent on the cycle period: it decreased during the burst of O and increased during the interburst. Thus with longer interbursts in O, transmitter release was increased, and the synapse was stronger.

Figure 8A shows voltage traces of O (top traces) and F without A-current (middle row traces, +Dep–A) and with A-current (bottom row traces, +Dep+A) at cycle periods of 514 (leftmost column), 1,350 (2nd column), 3,090 (3rd column), and 4,600 ms (rightmost column). Vertical dashed lines represented the time of firing in F (TF) when it did not include an A-current, at each cycle period. At P/514 and 1,350 ms, this time was identical or similar to the time of firing in F when it included an A-current (compare lengths of gray rectangles). At P/3,090 and 4,600 ms, there were incrementally larger differences (270 and 990 ms) between the 2 cases. With these P values, the A-current had a significant contribution to the delay of F.

Next, we quantitatively examined the relationship between TF and cycle period P. In Fig. 8B, thin and thick curves plotted TF as function of P without A-current (thin curve, +Dep–A) and with A-current (thick curve, +Dep+A) in F (Fig. 8B). The dashed linear curves represented constant phases of 0.35 and 0.45.

We first describe the relationship between TF and P when there was no A-current in F. At P < 514 ms, there was no
rhythmic activity in F because the nonactive state of O was too brief to allow F to escape from the inhibition of O. At $P = 514$ ms, $T_F$ was 181 ms and tangent to the linear curve 0.35P, implying that the phase was 0.35. As $P$ was increased, $T_F$ became longer. The increase in $T_F$ was proportionally larger than the increase in $P$, and thus $T_F > 0.35P$ and the phase increased above 0.35. At $P = 1,160$ ms, $T_F$ was 516 ms and tangent to the linear curve 0.45P, and the phase reached a maximum of 0.45. With larger $P$ values, $T_F$ continued to increase but the increase was now proportionally smaller than the increase in $P$, and thus $T_F < 0.45P$ and the phase decreased below 0.45. At $P = 2,180$ ms, $T_F$ crossed the linear curve 0.35P (and the phase further decreased, below 0.35). Eventually, $T_F$ reached a plateau of 5,000 ms at $P > 5,000$ ms.

Up to $P < 2,000$ ms, $T_F$ was identical in the 2 cases +Dep−A and +Dep+A. At larger $P$ values, $T_F$ in the case +Dep+A (Fig. 7B, thick curve) was larger than its value in the case +Dep−A. At $P = 2,650$ ms, $T_F$ was 946 ms tangent to the linear curve 0.35P; thus the phase was 0.35. At larger $P$ values the increase in $T_F$ was again proportionally larger than the increase in $P$, and thus $T_F > 0.35P$ and the phase increased above 0.35. At $P = 3,900$ ms, $T_F$ was 1,768 ms and tangent to the linear curve 0.45P, and the phase again reached a maximum of 0.45. With larger $P$ values, $T_F$ continued to increase but the increase became again proportionally smaller than the increase in $P$; thus $T_F < 0.45P$ and the phase decreased below 0.45. Eventually $T_F$ reached a plateau of 2,040 ms at $P > 5,000$ ms.

In summary, when F included an A-current, $T_F$ increased with $P$ in 2 well-separated ranges: the first range (at $P$ values <2,000 ms) was attributed to the depressing synapse: the synapse incrementally recovered when $P$ increased, producing increasingly longer $T_F$ values. At $P$ values >2,000 ms, the synapse was totally recovered from depression and increasing $P$ did not cause further change in the contribution of the synapse to the delay of F. The second range was attributed to the A-current. The A-current started to affect the timing of F at $P$ values incrementally deinactivated the A-current. The A-current started to affect the timing of F at $P$ values incrementally deinactivated the A-current.

The phase ($\phi_F = T_F/P$) as a function of $P$ is plotted in Fig. 8C. With no A-current in F, the shape of $\phi_F$ versus $P$ curve (+Dep−A, thin curve) was cubic, with a single local minimum of 0.35 at $P = 550$ ms, and a single local maximum of 0.45 at
$P = 1,160 \text{ ms}$. At low $P$ values the synapse was mostly depressed and $T_F$ was only weakly sensitive to changes in cycle periods and therefore almost constant. Thus $\phi_F$ decreased with $P$ (not shown in the figure because this decrease occurred in a very small range of cycle periods). At intermediate $P$ values the synapse incrementally recovered from depression. $T_F$ became sensitive to changes in the cycle period. In the case shown here, the increase in $T_F$ was larger than the increase in the cycle period, and thus $\phi_F$ increased with $P$. At high $P$ values the synapse was fully recovered, and $T_F$ was again constant; thus $\phi_F$ decreased with $P$. The cubic shape of the $\phi_F$ versus $P$ curve created a range of cycle periods in which the variation in phase was relatively small: with no A-current in $F$ (thin curve in Fig. 8C), $\phi_F$ varied from 0.35 and 0.45 between cycle periods of 514 and 2,180 ms, a range of 1,666 ms (length of the smaller gray rectangle in Fig. 8C).

When we included an A-current in $F$, the $\phi_F$ versus $P$ curve assumed a quintic shape, with 2 peaks consisting of 2 local minima of 0.35 at $P = 550$ and 2,650 ms, and 2 local maxima of 0.45 at $P = 1,160$ and 3,900 ms: as for the case with no A-current, the left peak (at lower $P$ values) was attributed to synaptic depression. Because of the slow kinetics chosen for the A-current, in the range of $P$ values at which this peak appeared, the A-current was still inactivated and did not contribute to the phase. At larger $P$ values, the O to $F$ synapse became incrementally efficient in inhibiting $F$. Eventually the voltage of $F$ reached sufficiently hyperpolarized values at which the A-current started to deinnactivate. As $P$ increased, the level of deinnactivation of the A-current increased, such that it was incrementally more effective in delaying the activity in $F$. The A-current was thus responsible for the right peak (at larger $P$ values). For simplicity, hereafter we refer to the 2 peaks of the quintic phase curve as the primary (left) and secondary (right) humps. With the canonical set of parameters used to produce the phase curve shown in Fig. 8C, the 2 humps were relatively shallow, thereby creating a wide range of $P$ values for which the variation in phase small: the phase varied within 0.35 and 0.45 between cycle periods of 514 and 5,770 ms (long gray rectangle), a range of 5,256 ms. This represented a 3.15-fold improvement, compared with the case when no A-current was present in $F$.

The simplified model thus demonstrates that, with respect to phase constancy, 2 delay mechanisms are at work at distinct ranges of cycle periods. Whereas synaptic depression was useful to maintain phase at short and intermediate cycle periods, the A-current contributed to the delay at longer cycle periods, but only when the synapse is depressing. Each of these 2 mechanisms was responsible for increasing the phase over a nonoverlapping range of cycle periods. If both phase increases were not too large (for our criterion of phase maintenance, $<0.1$), and these 2 ranges of cycle periods were not too separated from each other, this interaction could create a wide range of cycle periods in which the phase had little variation, and thus largely extended the range of phase maintenance.

The possibility of the A-current interacting with synaptic depression in a way that promotes phase constancy is thus critically dependent on the kinetics of the A-current. For example, an A-current that is too strong could excessively increase the size of the secondary hump in the quintic $\phi_F$ versus $P$ curve, and therefore work against phase maintenance. As another example, an A-current that is elicited only at very long cycle periods, such that the 2 humps in the phase curve are too separated from each other, may also be disadvantageous for phase maintenance. It was therefore important to test the effect of different parameters of the A-current on the phase.

**Sensitivity analysis of the kinetics of the A-current in the simplified model**

We examined the sensitivity of the reduced model by modifying several key parameters related to the dynamics of the A-current (Fig. 9). In all panels, we plotted $\phi_F$ versus $P$ for 5 different values of some A-current related parameter. The dotted line represented the reference model when no A-current was included in $F$. The thick line represents the canonical set of parameters used in Fig. 8. In general, manipulation of the parameters of the A-current affected mainly the secondary hump of the phase curve. In some cases, however, such manipulations could influence the shape of the primary hump as well (see following text, Fig. 9B).

Figure 9A shows the effect of the maximal conductance of the A-current, $g_A$. With a larger $g_A$, the delaying effect of the A-current was larger, and therefore the peak of the secondary hump increased; in addition, the secondary hump shifted to the left (i.e., to smaller $P$ values) because with a larger $g_A$ less deinactivation of the I–A current was required to obtain the same delaying effect. Note that with smaller $g_A$ values, the secondary hump flattened because the A-current became weak and was less effective in delaying the activity of the follower neuron when the synapse was no longer active. Changing the value of $g_A$ scaled the delaying effect of the A-current, but it scarcely changed the cycle period at which the A-current started to become effective: in the 5 cases displayed in Fig. 9A, the phase curve diverged from the case of no A-current (dotted curve) at approximately the same $P$ value of 2,000 ms.

Figure 9B examines how the midpoint $V_{1/2}$ of the steady-state inactivation curve of the A-current affected the phase. A more positive value of $V_{1/2}$ allowed the I–A conductance to deinactivate more for the same level of hyperpolarization in $F$. Thus the peak of the secondary hump increased. In addition, the secondary hump shifted to the left. In other words, with a more positive $V_{1/2}$ value the A-current started to affect the phase at a smaller $P$ value. The reason for this is that in the reduced model, the most negative potential of $F$ ($V_{f_{min}}$) was a decreasing function of $P$; it became more hyperpolarized when $P$ increased (not shown). This occurred whether the synapse was depressing or nondepressing. This relationship is revealed from the fact that as $P$ was increased (and the duration of time that O was nonactive, and $F$ was active, increased), the recoverable variable in the Morris–Lecar model of F (representing a potassium-like current) was activated for a longer time, and thus incrementally increased. Therefore when O became active and started to inhibit $F$, the intrinsic outward current in $F$ was larger and thus $F$ hyperpolarized to a lower voltage. Going back to describe the effect of $V_{h_{1/2}}$, we now understand that with a more positive $V_{h_{1/2}}$ value, the A-current started to deinactivate at a less hyperpolarized membrane potential of $F$, and therefore at a smaller $P$ value. At these small $P$ values the synapse was not totally recovered. Thus the effect of the A-current invaded the region that was dominated by the kinetics of the depressing synapse, and the shape of the primary hump was also affected.
In Fig. 9C the slope of the steady-state inactivation curve of the A-current, \( k_h \), was modified. A less negative \( k_h \), which generated a steeper steady-state inactivation curve, increased the peak of the secondary hump. In addition, the A-current started to affect the delay occurred at a longer \( P \) value. Note that the effect of \( k_h \) in this model was qualitatively different from the effect of \( k_h \) in the detailed model of the pyloric rhythm (Fig. 7C). In fact, the effect here was opposite to the effect observed in the detailed model. The reason for this discrepancy is that in the detailed model of the pyloric rhythm, the lowest membrane potential of LP was more depolarized compared with the midpoint of the steady-state inactivation curve, \( V_{h,1/2} = -65 \) mV. Thus a steeper steady-state inactivation curve yielded less deinactivation of the A-current, for the same hyperpolarization in the LP neuron. Therefore at the same \( P \) value the phase was smaller. In the reduced model, the lowest membrane potential of F was more hyperpolarized compared with midpoint of the steady-state inactivation curve, \( V_{h,1/2} = -48 \) mV. Thus a steeper steady-state inactivation curve produced more inactivation of the A-current, for the same hyperpolarization in F, and therefore a steeper inactivation curve yielded more deinactivation and the A-current was more effective in delaying F. Thus at the same \( P \) value the phase was larger, and the peak of the secondary hump increased.

Figure 9D shows the effects of the time constant of inactivation of the A-current, \( \tau_h \). In general the effect of decreasing \( \tau_h \) was similar to the effect of increasing \( g_A \) (Fig. 9A): smaller values scaled up the peak of the secondary hump, shifted the peak to the left, but did not change the \( P \) value at which the A-current started to affect the delay of F. With a smaller \( \tau_h \) value, for the same duration of hyperpolarization in F the extent to which the A-current deinatedivated was larger, therefore increasing the efficiency of the A-current in delaying F and increasing the phase. Here as well, the effect of \( \tau_h \) was different from the effect of this parameter in the detailed model of the pyloric rhythm (Fig. 7D).

This last panel illustrates that the detailed and reduced are different in some respects. The difference between the 2 models is attributed to the different ways that the depressing synapse was modeled, and the consequences for the frequency dependency of such synapses. In the detailed model of the pyloric rhythm, the PD to LP synapse was modeled with an activation variable (\( m \)) and an inactivation variable (\( h \)), similar to a transient intrinsic conductance. When the cycle period was increased, the maximal value of \( h \) (i.e., the deinactivation level) incremented toward 1. As a result the PD to LP synapse became more efficient in the sense that it hyperpolarized the LP neuron to a more negative value. There was little or no effect.

**FIG. 9.** Reduced model: phase sensitivity to parameters of the A-current. Each panel shows the phase vs. cycle period with different values of some specific parameter. In each panel, the thick curve was the canonical case (parameter values as detailed in METHODS). Dotted curve represents the case of no A-current in F. A: effect of maximal conductance (\( g_A \)). Values from bottom to top: 3.45, 3.65, 3.85 (canonical value), 4.05, and 4.25 mS/cm\(^2\). B: effect of midpoint voltage (\( V_{h,1/2} \)) of the steady-state inactivation curve of the A-current. Values from bottom to top: \(-48.5 \), \(-48.25 \), \(-48 \) (canonical value), \(-47.75 \), and \(-47.5 \) mV. C: effect of slope of steady-state inactivation curve \( k_h \). Less-negative values represent steeper functions. Values from bottom to top: \(-1.5 \), \(-1.25 \), \(-1 \) (canonical value), \(-0.75 \), and \(-0.5 \) mV. D: effect of time constant (\( \tau_h \)) of inactivation of the A-current. Values from top to bottom: 1,200, 1,100, 1,000 (canonical value), 900, and 800 ms.
on the duration of the hyperpolarization in LP; when the PD neuron terminated its burst, the inhibition ended and the LP neuron started to depolarize and eventually burst. In contrast, in the reduced model the O to F synapse was modeled with a variable \((s)\) that represented the fraction of open synaptic and a variable \((d)\) that represented the depression state of the synapse (see Manor et al. 2003). When the cycle period increased, \(d\) reached larger values during the time that \(O\) was not active. At the onset of activity in \(O\), \(s\) was set to the value of \(d\), and from this value it started to decay until the next time that \(O\) became active. As a result, when the cycle period was increased the O to F synapse became more efficient not only because it hyperpolarized F to a more negative value, but also because it hyperpolarized F for a longer time (the synapse continued to inhibit F even after O terminated its activity). The fundamental difference between these 2 models of synaptic depression explains the qualitative differences in the effect of \(\tau_h\) on phases, in the 2 models.

**DISCUSSION**

Phasing of neurons is an important aspect in central pattern generation. Changes in the activity phase of CPG members cause modifications in behavior, such as from trotting to galloping in quadrupeds (Grillner 1981). Within a CPG, phase shifts among different neurons may result from differences in synaptic efficacy (Cohen and Harris-Warrick 1984; Eisen and Marder 1984) or differences in the intrinsic properties of the neurons (Harris-Warrick et al. 1995a; Nagy et al. 1988). The possibility to change synaptic efficacy and intrinsic properties by neuromodulation provides a simple way to modify the phase relationships among the CPG neurons, thereby changing the motor pattern and the behavior. Several studies investigated the mechanisms used to produce variability in phase (Eisen and Marder 1984; Hill et al. 2003; Marder and Calabrese 1996) We focus on an opposite aspect of central pattern generation: the maintenance of phase. Maintenance of phase, often referred to as phase constancy or phase invariance, ensures the robustness of the activity pattern despite wide changes in the frequency of the rhythm (DiCaprio et al. 1997; Hill et al. 2002; Hooper 1997a), although the mechanisms responsible for the maintenance of phase remain unclear.

One possibility to maintain phase in a rhythmic network is that the same signal that produced a change in the cycle frequency, such as the release of a neuromodulatory substance that excites the pacemaker, also affects synaptic or intrinsic properties in follower neurons, such that temporal relationships are modified accordingly. Such a signal would need to be spatially distributed, and to simultaneously target many components of the network, those responsible for the regulation of cycle frequency and those responsible for phasing. A much simpler strategy is that the cycle period, by itself, determines the intervals of firing between 2 neurons in the network. Thus any change in the cycle period automatically generates a change in the temporal relationships between neurons, such that the phase difference remains constant. The model of Manor et al. (2003) was constructed in the spirit of this simple idea. This model, which consisted of an oscillator coupled by an inhibitory synapse to a follower neuron, demonstrated that short-term depression in inhibitory synapses may be sufficient to maintain phase over a relatively wide range of cycle periods. However, if this simple mechanism is indeed used to promote phase maintenance, it is most probably only part of the story. It is clear that other factors can affect the time of activity of neurons, and that these factors should be considered as well. Previous studies have demonstrated that, for example, A-currents delay the activity of follower neurons in rhythm networks, thereby playing an important role in determining the timing of such neurons with respect to the oscillator, and thus in shaping the pattern of activities (Harris-Warrick et al. 1995a,b). It is therefore essential to study how intrinsic currents in general, and A-currents in particular, interact with synaptic depression in the context of phase setting and maintenance.

In this study we wanted to investigate the putative interaction between A-currents and short-term synaptic depression, in the context of phase setting and phase maintenance, under the constraints of a complex and realistic CPG. As a representative example, we chose the pyloric circuit of the stomatogastric nervous system in crustaceans. We constructed a biophysical model of the pyloric circuit, reconstructing most of the important aspects of this rhythm. The purpose of this model was not to attempt modeling the full pyloric circuit with its many details, nor to claim that synaptic depression in conjunction with A-current is the mechanism that underlies phase constancy in the pyloric rhythm. Our only goal was to demonstrate that synaptic depression in conjunction with A-current could promote phase constancy in a realistic CPG such as the pyloric rhythm.

A realistic model demonstrates that synaptic depression together with A-current can promote phase constancy among neurons of the pyloric circuit

In our model of the pyloric circuit, the rhythm was generated by 2 neurons electrically coupled to each other, representing the anterior burster (AB) and one of the 2 pyloric dilators (PD). Three other neurons in the model represented the lateral pyloric (LP) neuron, one of the 4 early constrictor (PE) neurons and one of the 4 late constrictor (PL) neurons. Other pyloric neurons such as the inferior cardiac (IC) or ventricular dilator (VD) neurons were not included in the model. The LP, PE, and PL neurons were inhibited by the PD neuron, and rebounded from inhibition at different times during the cycle (e.g., the LP neuron started firing before the PE and PL neurons). The rate of rebound was strongly affected by the kinetics of the A-current in these cells. In our model, we chose a slow dynamics for the A-currents. The slow kinetics of the A-current was an essential assumption of our model. An excessively fast inactivation time constant would cause the A-current to totally inactivate during the early stages of depolarization of LP, that is, before this current could actually contribute to the delay of LP. The assumption of slow kinetics of the A-current is not unrealistic. Indeed, in many cases the kinetics reported for A-currents are much faster. However, voltage-clamp studies reveal that in pyloric neurons several variants of A-currents exist, some of them with slow inactivation kinetics ranging in the hundreds of milliseconds to seconds (Abbott et al. 1993; Golowasch and Marder 1992; Turrigiano et al. 1995). Slowly inactivating A-currents were also found in a variety of other neuronal networks, where they contribute in the production of
In our modeling study, we changed the cycle period of the pyloric rhythm by modifying the level of a ligand-activated inward current in the AB neuron, the so-called proctolin current. We examined how the timing activity of one neuron in the pyloric network, the LP neuron, altered as a result in the change in the cycle period. We chose the kinetics of the PD to LP synapse such that, with no A-current in the LP neuron, phase between the onset of bursting activities in the PD and LP neurons was poorly maintained. Indeed, if the inhibitory synapse between PD and LP was depressing, longer cycle periods allowed it to recover more from depression, and thus to hyperpolarize LP to more negative values. This by itself delayed the firing activity of the LP neuron, and thus helped to maintain the phase of LP bursting when cycle period was increased. However, the LP neuron was also endowed with postinhibitory rebound properties. Thus a stronger synaptic inhibition produced a larger hyperpolarization, which by itself accelerated the rate of depolarization in the LP neuron, and acted to advance the onset of bursting in the LP neuron. Thus the strengthening of the LP to PD synapse, as the cycle period was increased, resulted in 2 counter effects that canceled out each other. As a result, with synaptic depression and no A-current the timing activity of the LP neuron remained approximately constant, and the phase decreased as function of cycle period.

We also found that with no synaptic depression in the PD to LP synapse, the existence of an A-current in the LP neuron was not advantageous for phase constancy. No doubt, if the non-depressing synapse from PD to LP was strong enough and the membrane potential of the LP neuron dipped low enough during a PD burst, such an A-current added a delay to the onset of bursting in the LP neuron, but this delay was nearly constant and independent of cycle period: because the synapse was nondepressing, the depth of inhibition was approximately fixed, irrespective of changes in the cycle period. Thus during the interburst of the LP neuron, its A-current deactivated to a certain level, but always to the same level, no matter what the cycle period was. Therefore when the LP neuron was released from PD inhibition and started to depolarize, its A-current added a fixed, frequency-independent delay. Consequently, the existence of A-current in the LP neuron was not advantageous for phase constancy, if the synapse between PD and LP was nondepressing.

When synaptic depression came together with an A-current in the follower neuron, however, the interaction of these 2 components created favorable conditions for phase maintenance. As the cycle period decreased, the PD to LP synapse had less time to recover and the depth of synaptic inhibition decreased. A smaller and shorter hyperpolarization in the LP neuron reduced the extent of A-current deactivation. When the LP neuron was released from the PD inhibition and started to depolarize, less A-current was activated and therefore the LP neuron was delayed to a smaller extent. Thus the onset of bursting activity in the LP neuron was automatically adjusted to the change in the cycle period, thereby promoting phase constancy.

In a previous study we proposed that synaptic depression may be sufficient to promote phase constancy in a simple oscillator–follower model (Manor et al. 2003). Our current study does not stand in opposition with these results, but complements them: it proposes that in cases where synaptic depression per se is not sufficient to support phase maintenance, the addition of A-current may unmask the role of synaptic depression in phase invariance. Moreover, our work also suggests that in cases where the kinetics of synaptic depression are sufficient to maintain phase over some range of cycle periods, the existence of A-current dramatically increases this range.

**The combination of synaptic depression and A-current can promote phase constancy at low or intermediate levels of the proctolin current, but not at high levels**

In this model, we controlled the rhythm frequency by the magnitude of a proctolin-activated current in the AB neuron. The mechanism we propose ensures phase maintenance as long as a change in the cycle period produces a directly related change in synaptic recovery. Indeed, at low and intermediate levels of the proctolin current, as the cycle period decreased the interburst duration decreased as well, the PD to LP synapse recovered less, and the delay of the LP burst became shorter.

However, beyond some level of proctolin current the interburst duration of AB reached a minimal value. With higher levels of the proctolin current, an opposite effect was revealed: as the proctolin current increased, the cycle period increased because the addition of inward current in AB delayed the termination of its burst and increased the burst duration, with no change in interburst duration. Because the interburst duration of PD reached a minimal and short duration, the PD to LP synapse became mostly depressed. Consequently, the critical component that allowed the A-current to respond in a frequency-dependent manner attained nonfunctional limits. In fact, because the synapse from PD to LP was weak in this regime, there was an overlap in the firing of the PD and LP neurons: the LP neuron escaped from inhibition and started to burst before the end of the PD burst. Thus in this range of parameters the model did not succeed in maintaining phase. We note however that the modeling results found at high levels of the proctolin current are not compatible with known experimental observations: several studies reported that proctolin accelerated the pyloric rhythm (Hooper and Marder 1987; Nusbaum 1989; Swensen and Marder 2001), but none reported decelerating effects of proctolin. Moreover, the PD to LP synapse is always sufficiently strong to inhibit the LP neuron as long as the PD neuron is bursting, even in cases where PD interburst duration is short. It is therefore possible that in the biological circuit, proctolin (or other excitatory neuromodulators that stimulate the pyloric rhythm) may never reach the high levels used in some of our simulations. Alternatively, it is possible that a second, different mechanism could promote phase constancy at higher levels of the proctolin current, but because of the low biological relevance of such conditions, we did not investigate this possibility.

**Frequency-dependent phasing of other pyloric neurons**

In modeling the pyloric circuit, we focused on the phasing of the LP neuron, and did not investigate how bursting activities of other neurons in this network are affected by changes in the cycle period. Thus for simplicity purposes, except for the PD to
LP synapse, all other synapses in the circuit were modeled as nondepressing; however, we stress that if other synapses were modeled as depressing, for example the PD to PE or PD to PL synapses, we would expect the onset of bursting in these pyloric neurons to automatically change as the cycle period changed. In principle, if no connections existed between the followers and themselves, when the frequency of the rhythm would be modified the activity pattern could remain unchanged. In practice, extensive connections exist among the follower neurons in the pyloric circuit: electrical synapses and reciprocal inhibitory synapses between the LP and PY neurons, for example. Thus the manipulations required to achieve phase constancy in one pair of pyloric neurons may affect the phase relationships of another pair, inclusive or not. However, phase constancy may be required in parts of the CPG, and not required in others. For instance, in the pyloric rhythm of Panulirus interruptus, phase is well maintained between some pairs, but poorly maintained between others (Hooper 1997b). It is tempting to speculate that in the former case the dynamics of synaptic depression is well coordinated with the dynamics of the A-current in the follower neuron such that phase can be well maintained, but in the latter case the 2 components (if they exist at all) are not in concert, for example, the A-current in the follower is too rapid or nonexistent or the strength of synaptic inhibition is too weak.

Earlier experimental work suggested that, after inhibition from the PD neurons, different levels or different kinetics of the A-current in the LP and the PY neurons are responsible for the early firing of the LP neuron and the later firing of the PY neurons (Harris-Warrick et al. 1995a,b; Hartline 1979). Our modeling work suggests an alternative explanation for the phase difference between the LP and PY neurons: it is possible that similar levels and kinetics of A-current are present in the LP and PY neurons, but variability in the kinetics and strength of the inhibitory depressing synapses from PD to LP and PD to the PY neurons is responsible for the differential effects of these A-current on the times of activity of the LP and PY neurons.

An issue related to phase invariance is how to maintain duty cycle as the cycle period changes. This problem is much more complex because it involves not only the onset of burst but also its termination. It is possible that similar mechanisms such as the one proposed in this study could be involved here as well. For example, in the case of LP the termination of burst is determined by the onset of bursting in the PE and PL neurons. In this study, for simplicity we implemented the synapses impinging on the PE and PL neurons (the PD to PL and PE synapses, the LP to PL and PE synapses) as nondepressing. Consequently, in our model the onsets of bursting in PE and PL (and thus the termination of the LP burst) were nearly fixed and not dependent on frequency in a manner that ensured phase constancy for these neurons. However, in the biological circuit all pyloric synapses, including the synapses impinging on the LP neuron, show short-term depression to some degree. Introduction of synaptic depression in these synapses could enable the A-current in these cells to delay the PE and PL bursts in a frequency-dependent manner and thus to adjust the duration of burst in LP such that its duty cycle is preserved.

The complexity of the detailed model of the pyloric circuit impeded a clear understanding of the mechanism of interaction between synaptic depression and A-current.

The benefit of modeling a realistic circuit comes at the expense of simplicity: with a larger number of variables and parameters it becomes increasingly difficult to extract principles. The multitude of variables makes it difficult to understand how the change of a single parameter affects the whole system because this parameter may produce secondary effects in ways that are difficult to anticipate or interpret. Often, analyzing a detailed model can be as difficult as analyzing the biological circuit, and in such cases simpler models are required.

We mention here a few examples that illustrate how the complexity of the detailed model of the pyloric circuit complicated the interpretations of our results.

1.) In our model cycle period was modified by changing the level ($g_{\text{proc}}$) of the proctolin current introduced in AB. The effect of $g_{\text{proc}}$ on the cycle period was complex and biphasic: At low values of $g_{\text{proc}}$, increasing $g_{\text{proc}}$ resulted in a decrease of the cycle period because it reduced the duration of the nonactive state in the AB neuron. At high values increasing $g_{\text{proc}}$ produced the opposite effect: it increased the cycle period because it increased the duration of activity in the AB neuron. As a result of this biphasic effect, there existed a range of $g_{\text{proc}}$ values for which the same cycle period was obtained with 2 different $g_{\text{proc}}$ values, for which the onset time of bursting in the LP neuron was different. However, the biphasic effect found in those simulations may be only theoretical and not relevant to the biological circuit. In experimental studies one finds that increasing levels of proctolin generally speed up the pyloric rhythm, and do not slow it down (I. Greenberg and Y. Manor, personal data, not shown). Thus it is possible that the high levels of proctolin current used in this model extend to nonphysiological conditions. In this case, the biphasic effect should not be considered. This would greatly facilitate the interpretation of our results and also increase the range of cycle periods for which phase variation is small (i.e., for which phase was well maintained).

2.) In experimental studies of the pyloric rhythm, when the cycle period is changed (e.g., by injecting various levels of DC current in the pacemaker neurons) the burst duration of pacemaker neurons changes as well. This effect was well reproduced in the detailed model, and the burst duration of PD strongly depended on the cycle period. As a result, in some parameter range when the cycle period was increased the depth of synaptic inhibition increased (because the synapse recovered more from depression) but the duration of synaptic inhibition decreased (because the burst duration of PD became shorter). Thus 2 opposing phenomena affected the timing of firing activity in LP: the stronger synapse acted to delay the firing activity in LP, but the shorter burst in PD acted to advance the firing activity in LP. Thus although the model was faithful to reality, it complicated the understanding of the interaction between synaptic depression and A-current.

3.) In the detailed model, the neurons were endowed with postsynaptic rebound properties. Thus a stronger inhibition did not necessarily imply a longer delay in the activity of the postsynaptic neuron. As explained in the RESULTS, the delay expected from a larger inhibition could be canceled out by the increase in excitability of the postsynaptic neuron.
4.) The fact that fast action potentials were superimposed on top of the slow waves of the pacemaker neurons was another complication, which produced local effects. For example, in the range of $\tilde{\gamma}_{\text{proc}}$ values, where increasing $\tilde{\gamma}_{\text{proc}}$ decreased the cycle period, at 2 discrete points a small increase in $\tilde{\gamma}_{\text{proc}}$ decremented the number of action potentials on the PD burst, and as a result the cycle period sharply decreased at these 2 points. Again, these local effects were not helpful to gain insights into the mechanism at work.

5.) In the detailed model the LP burst was terminated by firing activity in the PL neuron. Thus in the LP neuron the delay contributed by an A-current was limited and could not be too long; otherwise, the onset of activity in the PL neuron would prevent the LP neuron from firing action potentials. In some cases the delay of LP was so long that LP could produce only a single spike before the PL neuron inhibited it (see, for example, the rightmost bottom trace of the LP neuron in Fig. 5A). Consequently, we could not test the effect of parameters of the A-current that excessively increased the delay of the LP neuron, such as too large maximal conductance, too depolarized values of the midpoint of the inactivation curve, or too steep inactivation curve (see Fig. 6, A–C).

6.) In the model of the pyloric circuit the kinetics of the synaptic depression and A-current were such that these 2 components affected the timing of activity in LP in overlapping ranges of cycle periods. Thus in the phase versus cycle period curves it was difficult to assess which component affected which part of the phase curve.

To answer these shortcomings, we repeated our simulation work with a much simpler circuit that was based on the model of Manor et al. (2003). The simplicity of this reduced model allowed us to gain a better and clearer understanding of the interaction between synaptic dynamics and A-current. However, in some respects the reduced model was fundamentally different from the detailed model of the pyloric circuit. Nevertheless, by comparing the results obtained in the 2 models our understanding of the interaction between synaptic and intrinsic dynamics only increased, as explained in the next section.

**Insights obtained from a reduced model**

The reduced model consisted of a Morris–Lecar oscillator (O) coupled by synaptic inhibition to a Morris–Lecar follower (F) cell. The strength of the synapse was governed by 2 state variables, one representing the fraction of open synaptic and one representing the depression state of the synapse (see Manor et al. 2003). In total, the system included 6 differential equations (compared with 44 in the detailed model of the pyloric rhythm). In addition to the much smaller number of variables and parameters, there were several fundamental differences between the reduced model and the detailed model of the pyloric rhythm. First, in the reduced model the kinetics of the depressing synapse was such that the depression by itself (with no A-current in F) promoted phase constancy in a moderate range of cycle periods. Second, in the reduced model the change in the cycle period was better controlled and involved changes in interburst duration of the oscillator only. Third, the follower neurons had no or weak postinhibitory rebound. Fourth, the depressing synapse was modeled differently. In the reduced model, longer cycle periods resulted not only in deeper inhibition of the follower neuron, but also in longer inhibition.

Despite these differences between the detailed model of the pyloric rhythm and the reduced model, the principles underlying the synergistic interaction between the dynamics of synaptic depression and A-current were similar. In both models, because of synaptic depression longer cycle periods resulted in a stronger synapse between the oscillator and the follower, whether this increased strength was implemented as a deeper or longer inhibition of the follower neuron. As a result, the level of deinactivation of the A-current became incrementally dependent on the cycle period, and therefore the contribution of A-current in the delay of the follower neuron was automatically adjusted to a change in the cycle period; this, in essence, is the common denominator of the 2 models.

The small number of variables and parameters in the reduced model allowed us to better understand the critical importance of different parameters of the A-current in this mechanism. Because the delaying effects produced by the synapse or the A-current were well separated in the range of cycle periods at which they acted, the contribution of each parameter was easier to understand. For example, it became evident that with respect to phase constancy the steady-state inactivation curve of the A-current should not be too shifted in the depolarizing direction, nor too shifted in the hyperpolarizing direction; otherwise, changes in the strength of synaptic inhibition attributed to changes in the cycle period would produce voltage changes in the insensitive areas of the inactivation curve (full deinactivation or full inactivation), and therefore would not produce the required changes in the delaying effects of the A-current (see Fig. 8B). Phase maintenance also critically depends on the maximal conductance of the A-current: small maximal conductances of the A-current are not sufficient to produce delays that can compensate for the change in the cycle period, when the cycle period is increased. Sensitivity analysis also revealed that the inactivation of the A-current must be relatively slow; otherwise, the A-current would fully inactivate during the early stages of depolarization of the follower, and therefore would not be useful in adding any delay in the activity of the follower neuron.

Comparison of the effects of the different parameters of the A-current also exposed some qualitative differences between the detailed model of the pyloric rhythm and the reduced model, although these differences only added to our understanding. For example, in the 2 models the slope of the steady-state inactivation curve of the A-current had opposite effects on the phase: whereas a steeper slope in the reduced model increased phase, a steeper slope in the detailed model of the pyloric rhythm reduced phase. The differences between the 2 models are attributed to the relationships between the voltage at which the follower neuron dips to during inhibition, and the midpoint voltage of the inactivation curve: if the former is lower than the latter, a steeper slope of the inactivation curve yields greater deinactivation and therefore the phase increases. Opposite results are obtained when the voltage at which the follower neuron dips to during inhibition is higher than the midpoint voltage of the inactivation curve.

Another difference between the reduced model and the detailed model of the pyloric rhythm was the sensitivity of phase on the time constant of inactivation. This difference was attributed to the different ways that synaptic depression was
modeled. In the detailed model of the pyloric rhythm, an increase in the cycle period increased the depth of synaptic inhibition, but not its duration. Thus provided that the time constant was long enough to prevent the A-current to fully deaktivate during the early stages of depolarization of the follower, the phase was not very sensitive to this parameter. In contrast, in the reduced model an increase in the cycle period affected both the depth and duration of synaptic inhibition. As a result, for the same cycle period value the phase increased when the time constant of inactivation decreased because more of the A-current deactivated during the time that the follower neuron was inhibited.

In summary, although there were fundamental differences between the detailed model of the pyloric rhythm and the reduced model, they both demonstrated a similar principle: synaptic depression may be necessary to allow an A-current to delay a postsynaptic neuron in a frequency-dependent manner, such that phase invariance is ensured. Alternatively, A-current may be necessary to unmask the putative role of synaptic depression in phase maintenance. The reduced model emphasizes a result that is difficult to discern in the detailed model because of its complexity: the 2 delay mechanisms are at work in distinct (in the case of the reduced model) or overlapping (in the case of the detailed model) ranges of cycle periods. Whereas synaptic depression is useful to maintain phase at short and intermediate cycle periods, the A-current contributes to the delay at longer cycle periods, but only when the synapse is depressing. The fact that 2 very different models yield similar results hints at the generality of the underlying mechanism.

Role of other intrinsic conductances in phasing

In this study we focused on the interaction between synaptic depression and one particular type of intrinsic conductance, the slowly inactivating transient potassium (IAs) current. Many other types of currents are known to affect the phase of follower neurons, and it is more than probable that some of these currents could also be involved in phase maintenance. The insights obtained from the present work can be helpful to study the role of such currents. For example, many pyloric neurons include a slowly activating anomalous rectifier current (H-current), an inward current activated by hyperpolarization. It was previously proposed that such currents play an important role in the phasing of follower neurons (Golowasch et al. 1992; Hartline and Gassie 1979; LoFaro et al. 1994) When the synapse is depressing, larger cycle periods produce larger and longer hyperpolarization in the postsynaptic neuron, and therefore the H-current is increasingly more activated and it incrementally advances the firing of the postsynaptic neuron. In this respect, H-current works against phase maintenance because it tends to reduce time delays as the cycle period increases. Another type of current that could also play a role in the phasing of follower neurons is the low-threshold inactivating calcium current (T-current). The T-current deactivates on hyperpolarization. As in the case of the H-current it advances the firing of the postsynaptic neuron, and therefore is not advantageous for phase maintenance. It is possible that the existence of H- or T-currents is important in situations where phase should be allowed to vary as the cycle period changes. In such cases, it could be useful to increase the relative weight of such currents, perhaps by neuromodulation, that specifically increase the conductance of H- or T-channels.

In conclusion, we have described a mechanism by which interaction between the dynamics of a depressing synapse and an A-current allows the timing of activity in a follower neuron to automatically change when the cycle period changes, such that the activity phase of the follower neuron, with respect to the activity in the oscillator, shows little variation in a wide range of cycle periods. We have demonstrated that this mechanism could promote phase constancy in a realistic CPG such as the pyloric rhythm. It would be interesting to find whether experimental manipulations that reduce or enhance A-currents in follower pyloric neurons, or modify the dynamics of depressing synapses, could create or destroy phase maintenance among these neurons. The dynamic-clamp technique may be a useful tool to answer such questions.

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