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Physiological Insights from Cellular and Network Models of the Stomatogastric Nervous System of Lobsters and Crabs[1]

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SYNOPSIS. The stomatogastric nervous system of decapod crustaceans is an ideal system for the study of the processes underlying the generation of rhythmic movements by the nervous system. In this chapter we review recent work that uses mathematical analyses and computer simulations to understand: 1) the role of individual currents in controlling the activity of neurons, and 2) the effects of electrical coupling on the activity of neuronal oscillators. The aim of this review is to highlight, for the physiologist, what these studies have taught us about the organization and function of single cell and multicellular neuronal oscillators.

INTRODUCTION

The reductionist approach to neuroscience has taught us to seek to understand the nervous system by attempting to identify, isolate, and analyze each of its components. At the level of cellular biophysics this has led to the study of single ionic currents and the second messenger systems that underlie many of these processes. At the level of systems neuroscience, the reductionist approach has led us to attempt to identify the neurons involved in a given behavior and to define the connections among them. In both cellular and systems neuroscience, however, it is always easier to define the individual components of a system, than it is to understand what each identified component, be it a current or a neuron, contributes to the dynamic activity of the whole. Indeed, conventional electrophysiological and biophysical methods are almost totally inadequate to analyze the role individual components play in defining the activity of a system. On the other hand, this is an area where mathematical and computer models can provide substantial insights.

The crustacean stomatogastric ganglion (STG) contains 30 neurons, and generates two motor patterns, the pyloric rhythm (period $\approx$1 sec) and the gastric rhythm (period 5–10 sec). The pyloric rhythm consists of repeating bursts of action potentials in the motor neurons that innervate muscles that alternately dilate and constrict the pyloric valve. The pyloric rhythm depends for its rhythmicity on a bursting pacemaker neuron, the Anterior Burster (AB) neuron. The AB neuron is electrically coupled to the Pyloric Dilator (PD) neurons, which therefore fire in bursts. Inhibitory connections from the pacemaker group (AB and PD neurons) cause the constrictor neurons (Lateral Pyloric (LP) and Pyloric (PY) neurons) to fire out of phase with the dilator neurons.

In this article, we will describe our first attempts to construct models of the neurons and networks in the STG. For each example, rather than describe the form of the model in detail (these are described elsewhere), we will describe the neurobiological problem that led us to formulate the model, summarize the salient features of the model, and then focus on what experimental neuroscientists can learn from this enterprise.

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CELLULAR MODELS

AB neuron

The amplitude and frequency of the membrane potential oscillations of the AB neuron are modulated in characteristic and different ways by a large number of both peptidergic and aminergic neurotransmitters (Marder and Eisen, 1984*b*; Flamm and Harris-Warrick, 1986; Hooper and Marder, 1987). Because the AB neuron is a target for so many different neuromodulatory substances, it is interesting to determine, for each, the mechanism underlying the modulation of burst amplitude and frequency (Harris-Warrick and Flamm, 1987). There are at least two different classes of general mechanisms by which such a large number of neuromodulatory substances could induce specific changes in AB neuron activity. First, the AB neuron's rhythmic oscillations could, in all cases, depend on the same ensemble of conductances, with the changes induced by neuromodulatory substances resulting from only quantitative alterations in the expression of these conductances. Second, AB neuron oscillations could arise from qualitatively different sets of conductances, each set induced by different neuromodulators. The ultimate answer to this question requires the complete description of the ionic currents found in the AB neuron, as well as an analysis of the mechanisms by which each modulatory substance influences the AB neuron. Although we are far from having these data, a first attempt to model the activity of the AB neuron gives us some new insights into this problem.

Harris-Warrick and Flamm (1987) compared the AB neuron bursts obtained in the presence of three different amines, serotonin, octopamine, and dopamine. These workers noted that under a given set of experimental conditions TTX failed to abolish dopamine-enhanced bursts, but suppressed serotonin-enhanced bursts. From these and other observations, Harris-Warrick and Flamm (1987) suggested that there might be an essential difference in the nature of the burst generating mechanism found in the presence of these different amines. Partly motivated by these data, Epstein and Marder (1990) constructed an *ad hoc* model of an AB-like burster. This model was not based on specific data from biophysical studies of AB neurons, but is an isopotential, conductance-based model that contains five ionic currents found in almost all central nervous system neurons.

This "AB" model consists of a Hodgkin-Huxley type TTX-sensitive Na^+ current, a delayed-rectifier K^+ current, a voltage-dependent Ca^{++} current, a Ca^{++}-dependent K^+ current, and a Cl^- leakage current. Epstein and Marder (1990) showed that variations in the values of the maximal conductances of the Na^+, Ca^{++} and Cl^- leakage currents produced bursts with significantly different waveforms (Fig. 1A, B) and current-voltage properties. In one form of the model (Fig. 1A), the Ca^{++} conductance is low, and when TTX application was simulated by turning off the Na^+ conductance, bursting was suppressed (not shown). In another form of the model in which the Ca^{++} conductance is higher, bursting persists in the absence of the Na^+ current (Fig. 1C). The currents active during bursting in these forms of the model are shown in Figure 1D, E.

This model, although not specifically based on real biophysical data from the AB neuron, teaches us several things. First, even a relatively modest change in the balance of conductances of a neuron can produce markedly different behavior under current clamp conditions. Although the two forms of the model respond qualitatively differently to the simulation of TTX application, this effect is produced by a relatively minor difference in the maximal Ca^{++} and leakage conductances in the two forms of the model. No new conductances are involved, and these changes are well within the kinds of effects produced by modulatory substances in many tissues. Thus, the apparent qualitative difference in the behavior of the biological AB neuron in the presence of dopamine (in which bursting continues in the presence of TTX) and serotonin (in which bursting is suppressed by TTX) (Harris-Warrick and Flamm, 1987) may result from a modest quantitative difference in the Ca^{++} current which participates in bursting in both

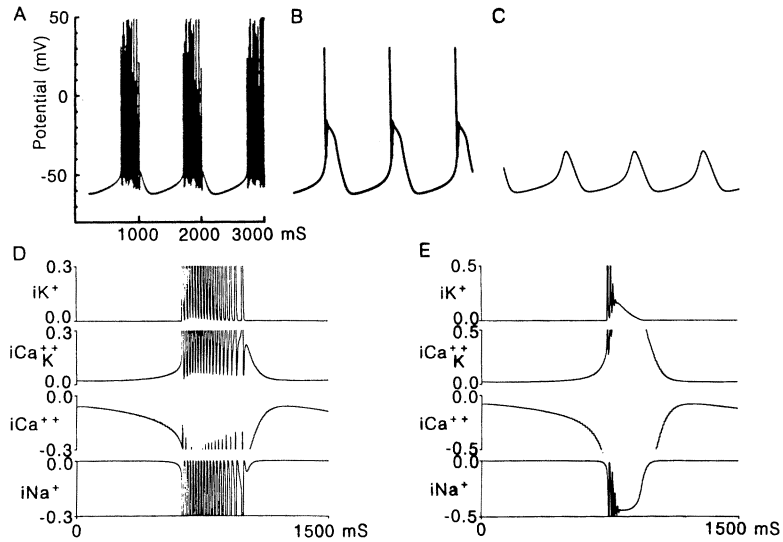

FIG. 1. Multiple forms of a burster. A. Epstein and Marder (1990) model with maximal conductances (mmho/cm^2): Na^+ = 100; Ca^{++} = 0.08; Cl^- = 0.11. B. Epstein and Marder (1990) with maximal conductances (mmho/cm^2): Na^+ = 8; Ca^{++} = 0.12; Cl^- = 0.18. All other parameters are the same for the two models. C. Conductances as in (B) with the Na^+ conductance set to 0. D. Currents flowing during burst shown in (A). E. Currents flowing during burst of (B). Adapted from Figs. 2, 3, 4, and 8 of Epstein and Marder (1990).

cases, rather than indicating that bursting in the two amines occurs by qualitatively different mechanisms. Support for this interpretation comes from recent work of Johnson *et al.* (1992) who showed that serotonin-activated bursting persists in the presence of TTX when the temperature is elevated. This may occur if the higher temperature increases the Ca^{++} current, for example. In summary, a relatively minor modification of the ratio of the maximal conductances of the currents involved in burst generation can markedly influence the dynamic activity of the neuron.

The work of Epstein and Marder (1990) makes another interesting point. In this model the only Na^+ current is the early inward Hodgkin-Huxley, TTX-sensitive current. Although this current activates and inactivates rapidly, enough current remains at the relatively hyperpolarized membrane potentials of the slow oscillations for it to play a significant role in burst generation (*e.g.*, Fig. 1E). It has often been assumed in the analysis of burst generation (Benson and Adams, 1987, 1989), that the TTX-sensitive Na^+ current which participates in bursting is a different current than that responsible for rapid action potentials. Our results suggest that in certain neurons the fast Na^+ current may play both roles.

LP neuron

Although the *ad hoc* model of the AB neuron brought us insight into several physiological processes, we wished to construct models that were based on the actual conductances measured from a real STG neuron. Therefore Golowasch and Marder (1992*a*) undertook a study of the conductances found in the Lateral Pyloric (LP) neuron of the crab, *Cancer borealis*. Each STG has a single LP neuron which is also subject to a host of neuromodulatory influences (Hooper and Marder, 1987; Nusbaum and Marder, 1988, 1989*a, b*; Golowasch and Marder, 1991*b*).

Using conventional two-electrode voltage clamp methods, Golowasch and Marder (1992*a*) characterized many of the major voltage- and time-dependent conductances in the LP neuron. The LP neuron shows three outward currents, a delayed-rectifier K^+ current (I_D), a fast transient K^+ current

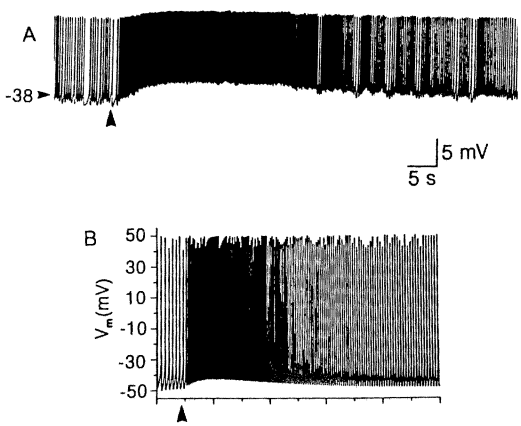

FIG. 2. Proctolin responses of the biological and model LP neurons. A. Intracellular recording from an LP neuron isolated from presynaptic inputs from the pyloric network by application of 10^{-5} M picrotoxin and a sucrose block on the input nerve. Proctolin was applied at the upward arrow from a puffer pipette (0.5 sec puff). Note the slight depolarization and the increase in firing frequency. B. Response of the model LP neuron to a simulated proctolin puff (at the arrow). Once again, note the slight depolarization and the increase in firing frequency. Time tics are 1 sec.

(I_A), and a Ca^{++}-activated K^+ current (I_{oCa}). The inward currents displayed by the LP neuron include a hyperpolarization activated slow inward current (I_H), a voltage-dependent Ca^{++} current (I_{Ca}), and a Hodgkin-Huxley type TTX-sensitive Na^+ current (I_{Na}) (Golowasch and Marder, 1992*a*). To construct a model of the LP neuron, each of these currents was fit with equations of the general form of the Hodgkin-Huxley equations (Buchholtz *et al.*, 1992), and then a model neuron was constructed by combining these with a leakage conductance and capacitance. The activity of the model LP neuron was compared to the activity of the biological LP neuron by simulating a series of current and voltage-clamp experiments similar to those performed with the real neuron (Buchholtz *et al.*, 1992; Golowasch *et al.*, 1992).

One of the comparisons between the model neuron and real neuron can be seen in Figure 2, which compares the response of the biological and model neurons to the application of the peptide proctolin (the proctolin current was simulated from biophysical measurements, Golowasch and Marder, 1992*b*; Golowasch *et al.*, 1992). Proctolin is a peptide known to have important modulatory actions on the pyloric rhythm (Hooper and Marder, 1987; Nusbaum and Marder, 1989*a, b*). Figure 2A shows the response of the biological neuron to a puff of proctolin (arrow). Note the slight depolarization, and the sharp increase in the frequency of the LP neuron action potentials. In Figure 2B, the same experiment was simulated by turning on (arrow) the proctolin current in the model neuron. Note again the increase in firing frequency and the slight depolarization of the membrane potential. The similarity in the responses of the model and the real neurons is gratifying, but does not in itself provide any insight into the roles of each of the membrane currents in controlling membrane excitability.

Insight into the roles of each of the conductances in controlling the activity of the neuron can be obtained by examining the plots of the individual currents during ongoing rhythmic activity (Fig. 3). In the absence of the proctolin current, note that the outward current due to the activity of the Ca^{++}-activated K^+ current contributes significantly to the repolarization of the action potential, while the delayed rectifier contributes considerably less. Interestingly, when the proctolin current is turned on, and the neuron is thus slightly depolarized, the relative contributions of the Ca^{++}-activated K^+ current and the delayed rectifier to the repolarization of the action potentials changes. Thus even a small current that produces only a modest change in membrane potential may have pronounced effects on the role of each current in shaping the activity of the neuron, in ways that are impossible to see unless one has a model in which the activity of each current can be visualized during ongoing activity.

REDUCTION OF COMPLEX MODELS

Although detailed conductance-based and multicompartmental models allow the investigator to see what each variable in a model is doing at all times and to ask what each component of a model is providing to the output of the system, they also have several major disadvantages. Most significantly, as the number of dynamical vari-

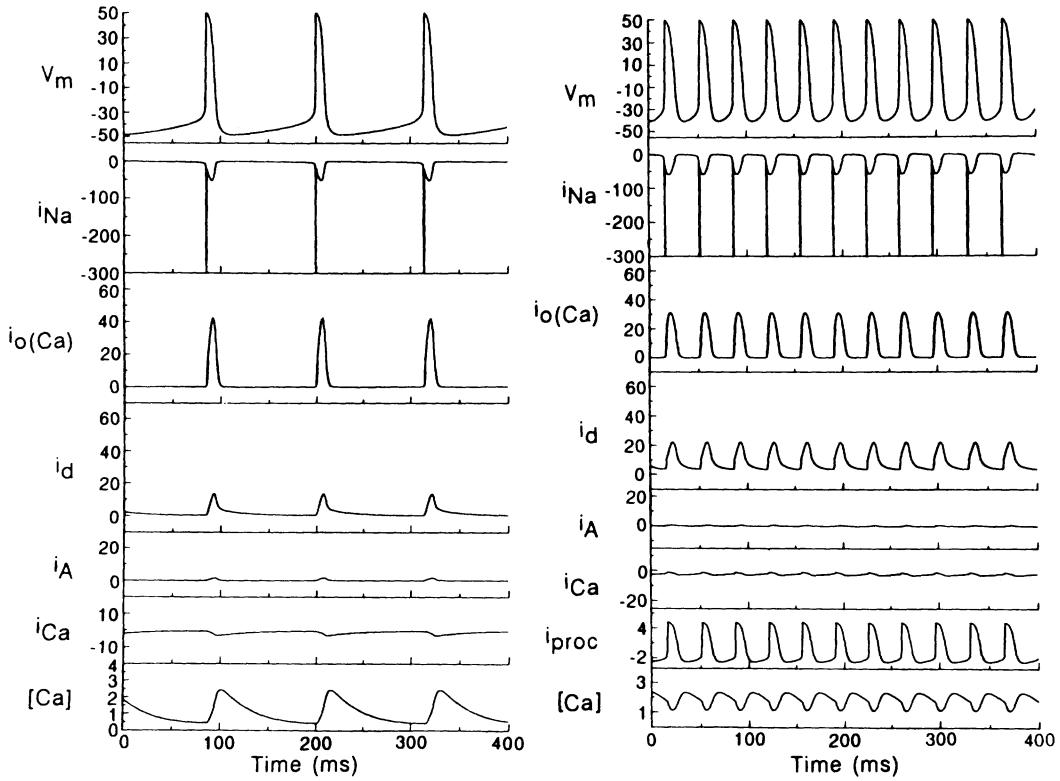

FIG. 3. Computer models allow the examination of the roles of individual membrane currents. Left: Activity of the membrane currents in the model LP neuron during spontaneous activity in the absence of the proctolin current. Right: Activity in the model LP neuron in the presence of the proctolin current, which depolarizes the neuron, and causes it to fire more rapidly. Comparison of left and right shows that the relative contributions of $i_{o(Ca)}$ and i_d currents to spike repolarization have changed. Modified from Golowasch *et al.*, 1992.

ables in a model increases, our ability to analyze the behavior of the model in formal analytic terms decreases. Therefore, the ideal situation is a model that retains the essential features of a full, realistic model, but is as simple as possible. Over the years a number of simplified neuron models have been used for simulations of neurons and neural networks. However, in most cases, these simplified models have been *ad hoc,* and their parameters bear little or no relation to the underlying biological properties of the neurons that they are meant to represent.

To remedy this situation, Kepler *et al.* (1991, 1992) have developed a method to do systematic reductions of realistic conductance-based models. Kepler *et al.* (1991, 1992) start out with the full Hodgkin-Huxley equations for an action potential. Using a method of calculating "equivalent potentials" they are able to reduce the four Hodgkin-Huxley equations to a model with only two dynamic equations. Figure 4A compares the behavior of the full Hodgkin-Huxley equations to that of the reduced model and illustrates that although the model has been reduced, this has been accomplished without sacrificing the essential characteristics of the neuron's electrical activity. To test further this method, Kepler *et al.* (1991, 1992) introduce an "A current" (I_A of Connor and Stevens, 1971). Figure 4B compares the activity of a six equation model in which the activity of these three conductances is fully simulated, and a reduction of this model with only three dynamical variables. Once again, the reduced model behaves almost identically to the full model.

The general purpose of developing this method of reducing full models is not com-

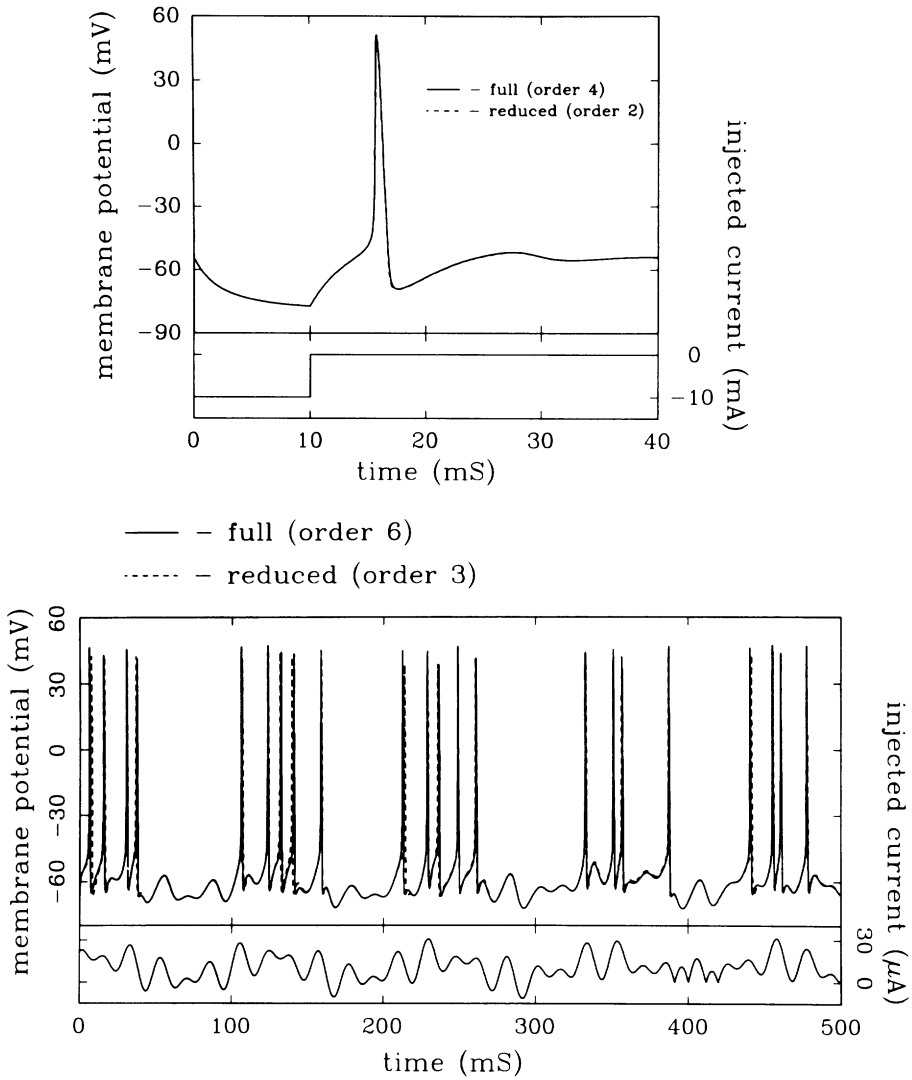

FIG. 4. Comparison of reduced and full models. Top panel: Simulation of full Hodgkin-Huxley model (solid lines) for the squid axon in response to a release from tonic hyperpolarization. Superimposed is the simulation of the reduced Hodgkin-Huxley model (dashed lines) in response to the same stimulus paradigm. Note that the reduced model duplicates the behavior of the full model (solid and dashed lines almost perfectly superimpose). Bottom panel: Simultaneous plot of the full model (six differential equations) of Connor *et al.* (1977) (solid line) and the reduced model (three equations) (dashed lines). The bottom trace of this panel shows the same randomly fluctuating current imposed on both models to probe their response to perturbation. Note that the reduced model and the full model track almost perfectly. Modified from Kepler *et al.* (1991).

putational ease, as the increasing speed and size of computers are making simulations of even large numbers of complicated neurons tractable. Instead, we hope that these reduction techniques will bring these models to an intellectually accessible point and allow us to identify which features of the complete models (and of the neurons they represent) are responsible for different aspects of the neuron's activity and modulation. Given that these reductions are from biologically realistic models, we have good reason to hope that the associations we make between specific features of the reduced

models and specific aspects of neuronal activity will be correct. Moreover, with these predictions from the models to guide us, it should be relatively easy to test them in experiments on real neurons.

NETWORK MODELS

Although recent years have seen an explosion in our understanding of the role of modulatory substances and neurons in the control of the neuronal networks in the STG (Marder and Nusbaum, 1989; Harris-Warrick and Marder, 1991), we are far from understanding the role each individual neuron and synaptic connection in the STG plays in shaping the motor patterns produced by the STG. As part of an ongoing program to develop a network model of the central pattern generating networks in the STG, we began by modeling the two celled network formed by the electrically coupled AB and PD neurons. Although the AB and PD neurons burst synchronously during ongoing rhythmic activity because they are electrically coupled, the AB and PD neurons differ in terms of their membrane properties (Bal *et al.*, 1988), their responses to inputs (Marder and Eisen, 1984*b*), and the neurotransmitters that they release (Marder and Eisen, 1984*a*). We describe below data that show that the PD neuron shapes both the frequency and the waveform of the AB neuron oscillations, thus demonstrating that the pacemaker for the pyloric rhythm is a network of several electrically coupled neurons.

The role of electrical coupling in frequency control

The first intimation that frequency control in the pyloric network results from an interaction between the intrinsic frequency of the AB neuron and network interactions came from the work of Hooper and Marder (1987). These authors noted that the isolated AB neuron in the presence of proctolin produced bursts at about 2Hz, while the full pyloric network in proctolin cycled at a frequency of about 1Hz. Thus an electrically coupled neuron could decrease the intrinsic frequency of an oscillatory pacemaker neuron (Hooper and Marder, 1987).

However, this qualitative understanding, obtained with physiological data alone, is only part of the story. Kepler *et al.* (1990) modeled the AB neuron using a Fitzhugh (1961) model, and then coupled the model AB neuron to a non-oscillatory PD neuron. In this simple model it is apparent that the effect of the non-oscillatory electrically coupled neuron depends critically on the waveform of the oscillator (Fig. 5). When the oscillatory neuron depolarizes slowly and hyperpolarizes quickly (Fig. 5, top), an inactive, hyperpolarized, electrically coupled neuron lengthens the intrinsic period of the oscillatory neuron. However, when the oscillatory neuron depolarizes quickly and hyperpolarizes slowly (Fig. 5, bottom), an inactive, hyperpolarized, electrically coupled neuron shortens the intrinsic period of the oscillatory neuron (see Fig. 1 in Kepler *et al.*, 1990). A qualitative explanation for this follows. The hyperpolarized, inactive neuron is effectively injecting outward current through the electrical junction into the oscillator throughout the oscillator cycle. When the oscillator depolarizes slowly and hyperpolarizes rapidly, the additional outward current from the coupled cell retards the depolarization of the oscillator more than it speeds up the repolarization of the oscil-

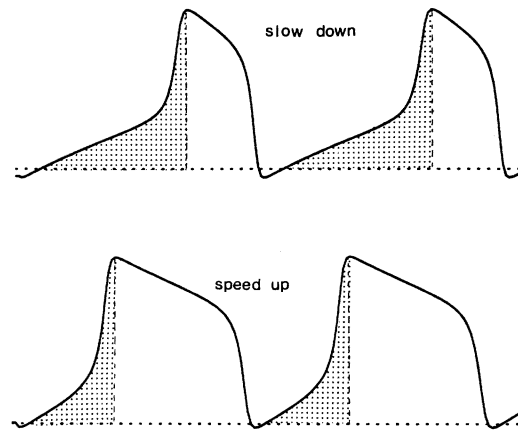

FIG. 5. Oscillator waveform is important in determining the effect of an electrically coupled neuron on oscillator frequency. This figure shows the oscillator neuron's membrane potential for both cases described, in this case with coupling coefficient = 0. Dotted horizontal lines are shown for reference and correspond to the membrane potential of the hyperpolarized cell to which the cell was coupled in the example described in the text.

lator, so the cycle period increases (Fig. 5, top). However, when the oscillator depolarizes rapidly and hyperpolarizes slowly, the outward current from the coupled cell slows the depolarization but speeds up the repolarization more (allowing the next burst to occur earlier). Therefore the cycle period decreases. A quantitative calculation of the effect of the coupled neuron on the frequency of the oscillator requires knowing the coupling conductance between the neurons, and the membrane potentials and conductances of the individual neurons (Kepler *et al.*, 1990).

The implications of this finding for physiology are several. First, it is becoming clear that neurons with conditional oscillatory properties are important in many brain regions. We are starting to understand the role of oscillatory processes not only in the generation of rhythmic movements, but in higher order sensory processing as well. Understanding the way in which electrical coupling can modify the frequency of these oscillatory processes is fundamental to understanding how oscillatory processes are used in neural computations of all kinds (Marder *et al.*, 1992). Second, many modulatory substances modulate the plateau phase of action potentials, or change the shape of neuronal bursts. As our knowledge of the effect of modulatory substances on conditional oscillatory neurons progresses, it is important to bear in mind that substances that change the waveform of an oscillatory neuron will produce a change in frequency as well, if that oscillatory neuron is electrically coupled to other neurons. Third, there is growing evidence that electrical connections themselves are subject to modulatory substances (Dowling, 1989). Thus, in a network in which the frequency of an oscillatory neuron is controlled through coupling to other neurons, the frequency of that oscillatory neuron may be influenced by modulation of the electrical coupling in the network.

The role of electrical coupling in duty cycle modulation

The PD neurons also change the character of the AB neuron burst. Figure 6B shows an experiment in which the membrane potential and frequency of an isolated AB neuron are manipulated by the injection of current into the cell body. Note that the burst duration remains constant, while the interburst interval expands. However, if the AB neuron membrane potential is moved when the PD neurons are present, a completely different relationship is seen (Fig. 6A). Here, as the frequency is decreased, the burst duration of the AB/PD pacemaker group increases along with the interburst interval, and we see that the pacemaker group maintains an approximately constant duty cycle (ratio of the duration of the oscillator burst to the cycle period). These data are summarized in Figure 6C.

To understand how the PD neurons transform the AB neuron burst from one in which burst duration remains constant to one in which duty cycle remains constant, Abbott *et al.* (1991) developed simple models of the AB and PD neurons that retain the essential properties of these neurons when isolated, and then coupled them together electrically. The AB neuron is represented as a simple oscillator; the model AB neuron when isolated maintains constant burst duration as current is injected (Fig. 6E), just like the biological AB neuron. The PD neuron is represented as a neuron that can either oscillate significantly more slowly than the AB neuron, or fire tonically. Most critically, the model PD neuron has a slowly activating and inactivating current, which operates on a time scale considerably slower than the currents that control the burst in the AB neuron. When the model AB and PD neurons are coupled electrically, we see that the coupled network now behaves as a constant duty cycle oscillator (Fig. 6D, F). This occurs because the slow current of the PD neuron oscillates around an average value as the AB–PD ensemble oscillates; this average value is unchanging when the increase of the current during the depolarized part of the AB–PD oscillation equals the decline of the current during the hyperpolarized part. This current acts as a duty cycle governor because any time the duty cycle changes, the average value of this current acts to compensate for this change until the ratio burst duration to interburst interval is restored to the original value (Abbott *et al.*, 1991).

This model is satisfying, since very simple

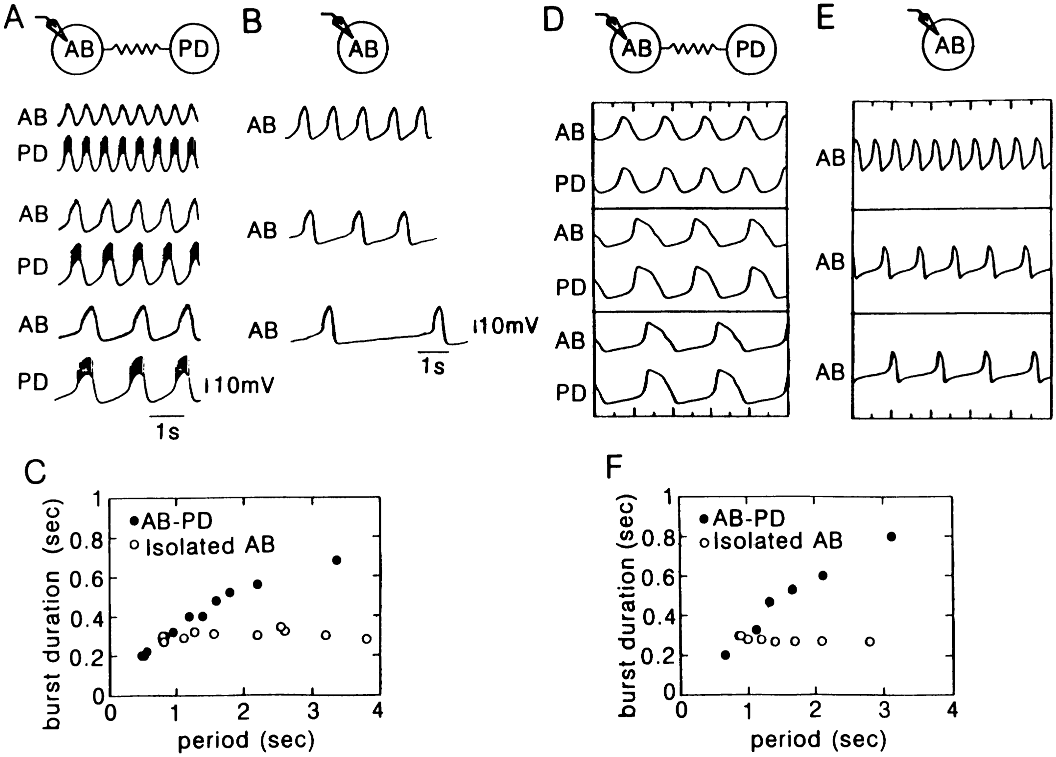

FIG. 6. Electrical coupling to the PD neurons changes the AB neuron from a constant burst duration to constant duty cycle pacemaker. A. Simultaneous intracellular recordings from the AB and PD neurons when the AB neuron was depolarized (top two traces), with no injected current (middle two traces), and with the AB neuron hyperpolarized (bottom two traces). B. Intracellular recording from isolated AB neuron. Top trace, depolarized; middle trace, no injected current; bottom trace, hyperpolarized. C. Plot of burst duration as a function of cycle period of data from the biological experiments. D. Model AB and PD neurons electrically coupled. Top two traces, depolarizing current added to the AB neuron; middle two traces, no injected current; bottom two traces, AB neuron hyperpolarized. E. Model AB neuron in the absence of PD neuron. Top, depolarized AB; middle, no injected current; bottom, AB hyperpolarized. F. Plot of burst duration as a function of cycle period for the model shown in D and E, above.

models of the individual neurons are sufficient to account for the phenomenon of interest. In this case we are able to use caricatures of neurons to represent their essential features and obtain the insight that the physiological data can arise simply from the constituent components. Specifically, we are able to represent the salient feature of the physiological difference between AB and PD neurons: AB neurons can generate "conventional" high frequency bursts when isolated from the PD neurons, but the PD neurons generate only slow oscillations with an irregular period when isolated from the AB neurons (Bal *et al.*, 1988). This model does not require that we know the nature of the ionic conductances in either the PD or the AB neurons, but only their general characteristics. It should be stressed that this kind of model cannot provide any insight into the identities of the ionic currents in the PD and AB neurons that underly these caricatures. For this we will need to develop conductance-based models, such as that for the LP neuron discussed above. In that case it will be possible to associate specific conductances with specific aspects of the behavior of the physiological neurons and the simple models.

Although we do not know which ionic currents are responsible for the transformation of the AB neuron burst by the electrical coupling to the PD neuron, this has nonetheless important implications for understanding the pyloric rhythm. The full pyloric rhythm consists of the activity of

five classes of motor neurons that fire with stereotyped phase relationships. Under standard control conditions the full pyloric rhythm maintains approximately fixed phase relationships among its elements over a significant frequency range (Eisen and Marder, 1984). The ability of the pacemaker ensemble to maintain constant duty cycles at different frequencies explains at least partially how the full network maintains fixed phase relationships at different frequencies. To maintain fixed phase relationships, the neurons must all begin to fire later in the cycle as the cycle period increases. Because the pacemaker ensemble releases transmitter in a graded fashion during the burst, as the duration of the pacemaker burst increases, the time during which inhibitory transmitter is released is extended. This in turn will retard the onset of firing of the follower neurons inhibited by the pacemaker network. Thus the maintenance of constant phase in these follower neurons depends heavily on the ability of the pacemaker ensemble to maintain a constant duty cycle as frequency is changed.

CONCLUSIONS

We have used models of several kinds to represent the neurons in the pyloric network of the STG. Some of these models are based on real ionic conductances, others are caricatures of neurons, rather than realistic representations. However, in each case the model allowed us to articulate new and different insights into the electrophysiological and biophysical processes underlying the generation of rhythmic movements.

First, we have shown that major changes in neuronal activity can stem both from modest quantitative changes in existing conductances and from the induction of small, novel conductances. Models help us understand how even small currents or small changes in currents can, under certain circumstances, produce large changes in the activity of the neuron.

Second, we have shown that whether electrically coupling non-oscillatory neurons to oscillatory neurons increases or decreases the oscillator frequency depends on the waveform of the oscillator and the membrane potential of the non-oscillator. Consequently, the effect of electrical coupling, and of neuromodulatory changes in oscillator waveform, neuronal membrane potential, and the strength of electrical coupling, can only be predicted if one has relatively detailed knowledge of the neurons and the circuitry involved.

Third, we have proposed a simple mechanism for the production of constant duty cycles at different oscillator frequencies, and argue that this helps maintain constant phase relationships for the pyloric network as a whole. While this proposal must be tested physiologically, it illustrates how even extremely simple models can suggest solutions to difficult neurobiological problems.

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REFERENCES

Abbott, L. F., E. Marder, and S. L. Hooper. 1991. Oscillating networks: Control of burst duration by electrically coupled neurons. Neural Computation. 3:487–497.

Bal, T., F. Nagy, and M. Moulins. 1988. The pyloric central pattern generator in crustacea: A set of conditional neuronal oscillators. J. Comp. Physiol. 163:715–727.

Benson, J. A. and W. B. Adams. 1987. The control of rhythmic neuronal firing. *In* L. K. Kaczmarek and I. B. Levitan (eds.), *Neuromodulation—the biochemical control of neuronal excitability,* pp. 100–118. Oxford University Press, Oxford.

Benson, J. A. and W. B. Adams. 1989. Ionic mechanisms of endogenous activity in molluscan burster neurons. *In* J. W. Jacklet (ed.), *Cellular and neuronal oscillators,* pp. 87–120. Dekker, New York.

Buchholtz, F., J. Golowasch, I. R. Epstein, and E. Marder. 1992. A mathematical model of an identified stomatogastric ganglion neuron. J. Neurophysiol. 67:332–340.

Connor, J. A. and C. F. Stevens. 1971. Voltage clamp studies of a transient outward membrane current in gastropod neural somata. J. Physiol. 213:21–30.

Connor, J. A., D. Walter, and R. McKnown. 1977. Neural repetitive firing: Modifications of the

Hodgkin-Huxley axon suggested by experiments from crustacean axons. Biophys. J. 18:81–102.

Dowling, J. E. 1989. Neuromodulation in the retina: The role of dopamine. Semin. Neurosciences 1:35–43.

Eisen, J. S. and E. Marder. 1984. A mechanism for the production of phase shifts in a pattern generator. J. Neurophysiol. 51:1374–1393.

Epstein, I. R. and E. Marder. 1990. Multiple modes of a conditional neural oscillator. Biol. Cybern. 63:25–34.

Fitzhugh, R. 1961. Impulses and physiological state in theoretical models of nerve membrane. Biophys. J. 55:847–881.

Flamm, R. E. and R. M. Harris-Warrick. 1986. Aminergic modulation in lobster stomatogastric ganglion. II. Target neurons of dopamine, octopamine, and serotonin within the pyloric circuit. J. Neurophysiol. 55:866–881.

Golowasch, J. and E. Marder. 1992*a*. Ionic currents of the lateral pyloric neuron of the stomatogastric ganglion of the crab. J. Neurophysiol 67:318–331.

Golowasch, J. and E. Marder. 1992*b*. Proctolin activates an inward current whose voltage-dependence is modified by extracellular Ca^{++}. J. Neurosci. 12:810–817.

Golowasch, J., F. Buchholtz, I. R. Epstein, and E. Marder. 1992. The contribution of individual ionic currents to the activity of a model stomatogastric ganglion neuron. J. Neurophysiol. 67:341–349.

Harris-Warrick, R. M. and R. E. Flamm. 1987. Multiple mechanisms of bursting in a conditional bursting neuron. J. Neurosci. 7:2113–2128.

Harris-Warrick, R. M. and E. Marder. 1991. Modulation of neural networks for behavior. Annu. Rev. Neurosci. 14:39–57.

Hooper, S. L. and E. Marder. 1987. Modulation of the lobster pyloric rhythm by the peptide, proctolin. J. Neurosci. 7:2097–2112.

Johnson, B. R., J. H. Peck, and R. M. Harris-Warrick. 1992. Elevated temperature alters the ionic dependence of amine-induced pacemaker activity in a conditional burster neuron. J. Comp. Physiol. A170:201–209.

Kepler, T. B., E. Marder, and L. F. Abbott. 1990. The effect of electrical coupling on the frequency of model neuronal oscillators. Science 248:83–85.

Kepler, T. B., L. F. Abbott, and E. Marder. 1991. Reduction of order for dynamical systems of equations describing the behavior of complex neurons. *In* R. P. Lippmann, J. E. Moody, and D. Touretzky (eds.), *Advances in neural information processing systems,* Vol. 3, pp. 55–61. Morgan Kaufmann, San Mateo.

Kepler, T. B., L. F. Abbott, and E. Marder. 1992. Reduction of conductance-based neuron models. Biol Cybern. 66:381–387.

Marder, E. and J. S. Eisen. 1984*a*. Transmitter identification of pyloric neurons: Electrically coupled neurons use different transmitters. J. Neurophysiol. 51:1345–1361.

Marder, E. and J. S. Eisen. 1984*b*. Electrically coupled pacemaker neurons respond differently to the same physiological inputs and neurotransmitters. J. Neurophysiol. 51:1362–1374.

Marder, E. and M. P. Nusbaum. 1989. Peptidergic modulation of motor pattern generators in the stomatogastric ganglion. *In* D. Kelley and T. Carew (eds.), *Perspectives in neural systems and behavior,* pp. 73–91. Alan R. Liss, Inc., New York.

Marder, E., L. F. Abbott, T. B. Kepler, and S. L. Hooper. 1992. Modification of oscillator function by electrically coupled neurons. *In* E. Basar and T. Bullock (eds.), *Induced rhythms of the brain,* pp. 287–296. Birkhäuser Boston, Inc. (In press)

Nusbaum, M. P. and E. Marder. 1988. A neuronal role for a crustacean red pigment concentration hormone-like peptide: Neuromodulation of the pyloric rhythm in the crab, *Cancer borealis.* J. Exp. Biol. 135:165–181.

Nusbaum, M. P. and E. Marder. 1989*a*. A modulatory proctolin-containing neuron (MPN). I. Identification and characterization. J. Neurosci. 9:1591–1599.

Nusbaum, M. P. and E. Marder. 1989*b*. A modulatory proctolin-containing neuron (MPN). II. State-dependent modulation of rhythmic motor activity. J. Neurosci. 9:1600–1607.