Neuromuscular Modulation in *Aplysia*. II. Modulation of the Neuromuscular Transform in Behavior

Vladimir Brezina, Irina V. Orekhova, and Klaudiusz R. Weiss

*Department of Physiology and Biophysics and Fishberg Research Center for Neurobiology, Mount Sinai School of Medicine, New York, New York 10029*

Submitted 6 December 2002; accepted in final form 5 July 2003

Brezina, Vladimir, Irina V. Orekhova, and Klaudiusz R. Weiss. Neuromuscular modulation in *Aplysia*. II. Modulation of the neuromuscular transform in behavior. *J Neurophysiol* 90: 2613–2628, 2003. First published July 9, 2003; 10.1152/jn.01093.2002. In this work we use mathematical modeling and complementary experiments to study the dynamics of modulation in the accessory radula closer (ARC) neuromuscular system of *Aplysia*. Here we join a dynamic model of the modulation from the preceding paper to a model of the basal neuromuscular transform (NMT). The resulting complete model of the NMT allows us to predict, test, and analyze the actual modulated contraction shapes in different types of feeding behavior, through entire quasi-realistic meals. The model reproduces a variety of published and new experimental observations. We find that components of the modulatory network act in interdependency and mutual complementarity, one or another playing a key role depending on the behavior and its past history. The history is remembered by slow dynamical components whose persistence prepares the system for future behavior of the same kind. The persistence becomes counterproductive, however, when the behavior suddenly changes. Superposition of fast dynamical components alleviates the problem under most, but not all, circumstances. In the quasi-realistic meals, the modulation improves functional performance on average, but degrades it after certain behavioral switches, when the model predicts sharp contraction transients. These are indeed seen in the real muscle. We propose that the real system does not switch the underlying motor neuron firing patterns abruptly, but relaxes them gradually, matching the relaxation of the peripheral modulatory state, through such behavioral transitions. We model food-induced arousal, a known phenomenon of this kind. The peripheral dynamics of the modulated NMT thus constrain the motor commands of the CNS.

**INTRODUCTION**

The accessory radula closer (ARC) neuromuscular system of *Aplysia* is a model system for the study of neuromuscular modulation and control. The ARC muscle is one of the muscles of the buccal mass, a complex structure that produces rhythmic movements of the animal’s food-grasping organ, the radula, in several types of consummatory feeding behavior such as biting, swallowing, and rejection of unsuitable food. The muscle is innervated by 2 motor neurons, B15 and B16, which release their classical transmitter, acetylcholine (ACh), to contract the muscle. In addition, however, both motor neurons release modulatory peptide cotransmitters that shape the basal ACh-induced contractions. B15 releases the small cardioactive peptides (SCPs) and B16 releases the myomodulins (MMs). The SCPs and MMs shape contractions through 3 main actions on the muscle. They potentiate the contractions by enhancing the muscle’s Ca current, they depress them by activating a K current, and they accelerate their relaxation rate. The combination of these 3 effects then gives the final shape of the contraction (for references see the preceding paper, Brezina et al. 2003; referred to hereafter as Paper I).

In Paper I we constructed a dynamic model of this neuro-modulatory system. We modeled the firing of the motor neurons B15 and B16, the release and concentrations of SCP and MM, and the 3 effects on the muscle. The model allowed us to study the dynamics of the modulation as the motor neurons were fired in various quasi-realistic patterns including hour-long meals consisting of many cycles of biting, swallowing, and rejection. We found a number of dynamical features of interest. The modulatory effects have very disparate dynamical time scales. The Ca-current and relaxation-rate effects react to the motor neuron firing only over many cycles of behavior, but the K-current effect is fast enough to respond to each individual cycle. Switches between the behaviors are therefore followed by rapid relaxations of contraction size, critically controlled by the degree of activation of the K current, but not of the relaxation rate. The trajectory of the modulatory state is a transient throughout the meal, ranging widely over regions of the modulatory space not accessible in the steady state. There is a pronounced history-dependency: the modulatory state associated with a cycle of a particular behavior depends on when that cycle occurs and what behaviors preceded it. On average, nevertheless, each behavior is associated with a different modulatory state.

However, although the model allowed us to examine the dynamics of the “neuro-modulation” transform, it did not yet predict the actual modulated contraction shapes because it did not include a model of the basal neuromuscular transform (NMT)—that is, of the transformation of the motor neuron firing patterns to the basal contraction shapes on which the modulators then act (Brezina and Weiss 2000; Brezina et al. 2000a,b). Here we join a model of the basal NMT to that of the modulation. The resulting complete model of the modulated...
NMT allows us to predict, test, and analyze the actual modulated contraction shapes in different types of feeding behavior.

METHODS

Methods were as in Paper I, and as follows.

Modeling

THE B15/B16-ARC NEUROMUSCULAR TRANSFORM. As its primary output, the NMT yields \(c(t)\), the waveform of contraction amplitude \(c\) as a function of time \(t\) (Brezina et al. 2000a). We model first the unmodulated, basal contraction \(c_{basal}\), then apply the modulation to convert \(c_{basal}\) to \(c\).

To model \(c_{basal}\), we used the data previously published, in part, by Brezina et al. (1997, 2000a), reproduced here in Fig. 1A1. In this experiment, contractions of the ARC muscle were elicited by tonic firing of motor neuron B15. The experiment was done at room temperature, which minimizes release of the motor neurons’ modulatory cotransmitters (see Vilim et al. 1996a; Whim and Lloyd 1990; Paper I). Previous work with this data (Brezina et al. 1997, 2000a) suggested that the B15-ARC NMT is sufficiently simple that sections of these contraction waveforms elicited by tonic firing, when assembled appropriately, can well reproduce contraction waveforms elicited by burst-firing patterns of the kind used throughout this work. We employed essentially this strategy here.

The waveforms in Fig. 1A1 were normalized to the maximal, saturating contraction amplitude observed with the highest firing frequency; thus too, \(0 \leq c_{basal} \leq 1\) (although the modulated \(c\) can exceed 1). To a first approximation, the waveforms can be taken to have single-exponential rising (contraction) and falling (relaxation) phases (Brezina et al. 1997, 2000a). Treating the shapes as exponentials, we measured from the waveforms in Fig. 1A1/3 parameters, plotted in Fig. 1, B–D: the steady-state basal contraction amplitude \(c_{basal,ss}\) as a function of the firing frequency \(f\); the contraction rate \(r_{contr}\) as a function of \(f\); and the relaxation rate \(r_{relax}\) as a function of \(c_{basal,ss}\). The measurements (points) were fitted with the continuous interpolation functions \(c_{basal,ss}(f)\), \(r_{contr}(f)\), and \(r_{relax}(c)\), respectively (curves), that were then used when running the model [extrapolation of \(r_{relax}(c)\) was used when necessary for the modulated \(c > 1\)].

We assume that \(c_{basal}\) is governed by the schema

\[
1 - c_{basal}(t) = e^{\alpha t} c_{basal}(0) = 0
\]

with corresponding differential equation

\[
\frac{dc_{basal}(t)}{dt} = \alpha(t)[1 - c_{basal}(t)] - \beta(t)c_{basal}(t)
\]

For constant \(\alpha\) and \(\beta\), solutions of Eq. 1b are indeed exponential, with \(c_{basal,ss} = \alpha(1 + \beta)\) and \(r_{contr,relax} = \alpha + \beta\). Thus \(\alpha = c_{basal,ss}r_{contr,relax}\) and \(\beta = (1 - c_{basal,ss})r_{contr,relax}\). For running the model, in particular, with the complete input firing pattern \(f_{NMT}(t)\) given by Eq. 1f below, we therefore use

\[
\alpha(t) = c_{basal,ss}f_{NMT}(t)r_{contr,relax}(t)
\]

FIG. 1. Basal, unmodulated NMT. A1: contractions of real accessory radula closer (ARC) muscle elicited by tonic firing of motor neuron B15 at frequencies \(f\) indicated, in protocol sketched below. Relaxation of muscle after end of firing is shown on expanded time scale. Complete data from experiment previously shown in Fig. 3, A and B of Brezina et al. (1997) and Fig. 3A of Brezina et al. (2000a). A2: corresponding contractions produced by model. Model was run with \(S(f) = 0\), \(R(t) = 0\), \(f_{NMT}(t) = 0\), and \(f_{firing}(t)\) as in A1. B–D: parameters of real contractions in A1 used by model. B: steady-state basal contraction amplitude \(c_{basal,ss}\) as function of \(f\). C: contraction rate \(r_{contr}\) as function of \(f\). \(r_{contr}\) was measured as rate constant of single exponential fitted to rising phase of each contraction in A1. D: relaxation rate \(r_{relax}\) as function of \(c_{basal,ss}\). \(r_{relax}\) was measured as rate constant of single exponential fitted to initial 1–3 s of falling phase of each contraction in A1. In B–D points are measured values, curves are interpolation functions through points or through smoothed set of points. See further THE B15/B16-ARC NEUROMUSCULAR TRANSFORM in METHODS.
and

$$\beta(t) = \begin{cases} 1 - c_{basal}(f_{cort}(t)) r_{cort}(t) & \text{if } f_{cort}(t) > 0 \\ \gamma & \text{otherwise} \end{cases} \quad (Id)$$

where, for the computation of $c_{basal}$ only.

$$\gamma = t_{relax}(c_{basal}(t^*)) \quad (Ic)$$

where $t^*$ is the start time of the current cycle. In other words, during the contraction phase in biting, swallowing, and rejection behaviors, when $f_{cort}(t) > 0$, $\alpha(t)$ and $\beta(t)$ are computed using Eq. $Ic$ and the first alternative in Eq. $Id$. During the relaxation phase, when $f_{cort}(t) = 0$, Eq. $Ic$ yields $\alpha(t) = 0$, and $\beta(t)$ remains fixed, by Eq. $Ie$, at the value corresponding to $c_{basal}$ at $t^*$, when the current cycle, and the relaxation, started.

In making $\beta$ a function of $c$ rather than $f$ in the relaxation phase, the model departs from the pure first-order formulation used previously (Brezina et al. 1997, 2000a). However, there is clear experimental support for an inverse dependency of the relaxation rate on contraction amplitude, not only in Fig. 1, A and D, but also in the work of Cropper et al. (1988) and Whim and Lloyd (1990). Yu et al. (1999) similarly found that force measured in another buccal muscle, D2, decays more slowly when starting from higher amplitude. Morris and Hooper (2001) reported a similar phenomenon in crustacean muscle.

The 2 different formulations of $\beta$ introduce a discontinuity into the model as $f_{cort}(t)$ makes the transition from small values to exactly zero. However, this never occurs with the large burst-firing patterns used in this work, where always either $f_{cort}(t) > 0$ or $f_{cort}(t) = 0$.

As can be seen in Fig. IA2, this formulation of the model NMT is well able to reproduce the real waveforms in Fig. IA1. The root mean square error between the real and modeled waveforms is 0.024, that is, 2.4% of the maximal contraction amplitude. The fit is least good at firing frequencies just above the contraction threshold, where the real contraction responds to the firing only with a significant latency (Brezina et al. 1997; Orekhova et al. 2003), and then appears in Fig. IA1 to develop in multiple phases. However, most simulations in this study used much greater frequencies; in particular, in the behaviorally realistic firing patterns used in Figs. 5–12, the intraburst $f_{cort}$ was never <14 Hz.

The waveforms in Fig. IA1 were obtained with motor neuron B15 firing. Published reports (e.g., Jordan et al. 1993) and preliminary experiments show that the B16-ARC NMT is broadly similar, but differs in one important respect: the contraction threshold is several Hertz higher for B16 than for B15. Accordingly, to compute the input to the overall B15/B16-ARC NMT, the overall NMT-relevant firing frequency $f_{cort}(t)$, we use the formula

$$f_{cort}(t) = f_{hit}(t) + \max(f_{hit}(t) - 4, 0) \quad (If)$$

where $f_{hit}(t)$ and $f_{hit}(t)$ are given by Eq. I of Paper I (or are similar functions tailored to reproduce specific experimental protocols, as noted in the figure legends), and max $(x, y)$ selects the larger of $x$ and $y$.

To implement the modulation of contraction size $S$, we apply the formula

$$c(t) = c_{mod}(t) S(t) \quad (Ig)$$

First dividing $S(t)$ by 100 if it was computed as a percentage, as in Paper I.

To implement the increase of relaxation rate $R$, we replace Eq. $Ie$ with

$$\gamma = r_{cort}(c(t^*) (1 + \delta_R(t^*))) \quad (Ih)$$

after selecting $\delta_R$ according to the absolute fold increase of relaxation rate that $R$ represents. The data in Brezina et al. (1995, 1996) suggest that $R = 100\%$ may correspond to a 4-fold multiplication of the relaxation rate. Accordingly, we used $\delta_R = 0.03$ [when $R(t)$ was computed as a percentage], or in some simulations, as noted in their figure legends, $\delta_R = 0.05$.

The complete model of the modulated NMT consists of Eqs. 1a–e, 2a–c, 3, 5a and 5c for $X \in \{C, K, R\}$, and Eq. 6, and the parameter values in Tables 1 and 2 of Paper I, and Eqs. 1b–d and 1f–h here.

**Performance Measure.** To evaluate the functional significance of the modeled contraction waveform, we use the performance measure (Brezina and Weiss 2000) $m$, given for each cycle by

$$m = \tilde{c} - c - cP \quad (2)$$

where $\tilde{c}$ is the maximum and $c$ is the minimum contraction amplitude in the cycle, respectively, and $P$ is the cycle period. Equation 2 balances the amplitude of the phasic part of the contraction waveform $(\tilde{c} - c)$, assumed to be the functionally significant component of the waveform for a repetitive, rhythmic behavior, against the area of the tonic part $(cP)$, assumed to be a nonfunctional, but energy-consuming, component.

**Experiments.**

The experiments in this study were done in intact ARC muscle preparations as described in Paper I, except that both motor neurons B15 and B16 were stimulated to fire in behaviorally realistic patterns. These were the canonical biting, swallowing, and rejection patterns in Table 2 of Paper I, then in some cases adjusted as required to produce initial contractions of moderate size in that particular preparation. The experiments were done at physiologically low temperatures (13–17°C, varying no more than 0.5°C within any particular experiment) to allow release of the motor neurons’ modulatory cotransmitters. The results in this study were obtained from 25 muscles.

**Results.**

**Tests of the model NMT: simulation of published experiments**

As described in detail in methods, we constructed a model of the unmodulated, basal B15/B16-ARC NMT; joining it with the modulation model from Paper I, we obtained a model of the complete, modulated NMT. As shown in Fig. 1, the basal model NMT well reproduced the experimental data from which it was constructed. As a more challenging test, we ran the complete model NMT in simulations of several key published experiments.

Figure 2A shows a simulation of the simplest experiment, in Fig. 11 of Brezina et al. (1995), in which MM was simply applied exogenously at a constant concentration. The model NMT well reproduces an initial, transient net depression of contraction size, followed by a gradual net potentiation of contraction size together with an increase of the relaxation rate, $r_{relax}$. (The effects develop somewhat earlier in the model than in the real experiment, perhaps because of slow access of the applied MM to the real muscle; Paper I.) As expected from Paper I, the initial effect is due to the fast activation of the muscle’s modulator-specific K current, model variable $K$, and so a decrease in the contraction size modulation variable $S$, while the subsequent effects reflect the much slower enhancement of the muscle’s Ca current, $C$, and so a rise in $S$, and increase of the relaxation rate, $R$.

Note that $r_{relax}$ as measured in Fig. 2A and elsewhere in this study, is not identical to $R$. $R$ is relative, the increase of relaxation rate, whereas $r_{relax}$ is the actual, absolute rate. More important, whereas $R$ is an independent variable, $r_{relax}$ depends...
in a complex manner not just on \( R \) but also inversely on the absolute contraction amplitude, and thus on its modulation \( S \), in the model (see METHODS) as indeed in the real muscle (Fig. 1, A1 and D1; Brezina et al. 2000b). Whereas \( R \) is immediately produced by the model, it was necessary to measure \( \text{r}_{\text{relax}} \) from the modeled contraction waveforms in the same way as from real experimental waveforms. The complex origin of \( \text{r}_{\text{relax}} \), together with the fact that in real experiments its absolute magnitude can vary greatly with the loading of the muscle (Brezina et al. 1995), also unfortunately made it difficult to quantitatively compare the modeled with the experimental \( \text{r}_{\text{relax}} \) in cases where only single example records, rather than group data, had been published. In some cases this could be done (Fig. 2A), but in other cases (below) the comparison could be only qualitative.

Figure 2B shows a simulation of the experiment in Fig. 4 of Cropper et al. (1990a), which demonstrated modulator release from motor neuron B15, as detected by increased \( \text{r}_{\text{relax}} \) in response to some firing patterns but not others. Specifically, decreasing the interval between the bursts of firing increased \( \text{r}_{\text{relax}} \) as well as contraction size, whereas increasing the burst duration or intraburst firing frequency had only the latter effect.

As can be seen in Fig. 2B, the model NMT reproduces these findings (for contraction size in a reasonably quantitative manner, for \( \text{r}_{\text{relax}} \) only qualitatively). In the latter 2 cases, \( \text{r}_{\text{relax}} \) actually decreases, a consequence of the increased contraction size, on which \( \text{r}_{\text{relax}} \) inversely depends, not counteracted by any significant increase in \( R \). Examination of the model variables confirms that, as Cropper et al. (1990a) believed, the observed differences in the modulation of \( \text{r}_{\text{relax}} \) in the 3 cases indeed reflect differences in modulator—SCP—release. Finally, Fig. 3 shows simulations of the experiments in Figs. 3, 5, and 11 of Whim and Lloyd (1990), which demonstrated heterosynaptic modulation of motor neuron B16-elicited contractions by modulators released from B15, and vice versa. A short period of intense burst-firing of B15 elicited, of course, its own contraction, but after this had completely relaxed away, both the size and \( \text{r}_{\text{relax}} \) of test contractions elicited by B16 remained increased for many minutes. Conversely, firing of B16 increased the size and \( \text{r}_{\text{relax}} \) of test contractions elicited by B15. As can be seen in Fig. 3, A and B, the model NMT reproduces all of these effects. To demonstrate the full magnitude of the modulation, these simulations were run at 15°C, the physiological temperature at which the modulation is fully developed (Paper I), rather than 22°C as in the experiments of Whim and Lloyd (1990). The model also reproduced (not shown) the homosynaptic counterparts of these experiments, reported by Whim and Lloyd (1990), in which B15 firing modulated its own test contractions, and likewise with B16. Finally, Fig. 3C well reproduces, at the original temperature of
22°C, the quantitative relationship found by Whim and Lloyd (1990) between the intraburst B15 firing frequency in these experiments and the magnitude of the increase of B16-elicited contraction size.

Figure 3C also shows the effect of tonic B15 firing at 5 and 10 Hz. If each B15 spike had exactly the same modulatory effect on contraction size, the effect of the 5- and 10-Hz tonic firing should be equal to that of, respectively, 12.5- and 25-Hz firing in the bursting pattern. Instead, the effect of the tonic firing is significantly lower. This difference is a manifestation of the “pattern-dependency” (Brezina et al. 1997) that has been well documented experimentally in this system and analyzed in previous, partial models (Brezina et al. 1997, 2000c; Whim and Lloyd 1989). The predominantly “positive” pattern-dependency observed in the system, whereby, as in this instance, effects are greater when spikes are grouped into bursts, can largely be traced to the strong positive pattern-dependency of modulator release (Brezina et al. 2000c), although other steps in the network have their own pattern-dependency (see, e.g., Fig. 14B of Paper I).

Motor neuron B16 as the source of depressive modulation

Examination of the modulation in Paper I suggests that, as the modulation of contraction size ranges from large net potentiation to large net depression, it is mostly motor neuron B16 that contributes the component of depression, because it releases MM, which has the same potentiation effect as SCP released from B15 but in addition strongly activates the depressive K current, K (see, e.g., Figs. 2B, 8, and 13 of Paper I). However, in the modulation-only model this conclusion could not take into account the fact that the firing patterns of B15 and B16 that release different amounts of SCP and MM also release different amounts of ACh and so elicit different sizes of basal contractions. Does B16 still function as a depressive modulatory neuron in the complete model, in quasi-realistic behavior?

Figure 4A1 shows a simulation in which we fired motor neuron B15 in a canonical swallowing pattern (see Paper I), then added a swallowing pattern of firing of B16. The addition of B16 immediately brings about a great increase in contraction size because the total intensity of motor neuron firing—the input to the basal NMT—is more than doubled. However, the increased contraction size is only transient, eventually decaying even below the previous size with B15 firing only (compare “a” and “b” in Fig. 4A1). This even though the intensity of motor neuron firing is much higher, the contraction size is smaller, as a result of the addition of B16 firing. The decay of the transient parallels an increase of R and t_relax (see below), but the steady-state depression is largely due to increased K. In evidence of the role of K, when B16 ceases firing, the contraction relaxes to about its previous size with B15 firing only, and it does so with a fast transient (“c”), on the time scale of K but much faster than that of R.

Are these phenomena seen in the real muscle? Fig. 4A2 shows an experiment comparable to Fig. 4A1. Qualitatively, the same features are evident (“a”–“c”). The real muscle seems to have slower dynamics, however, probably at least in part reflecting the tendency of the contractions to progressively run down and fatigue with the regular, intense firing of the motor neurons in these experiments, uninterrupted by breaks and pauses as it would be in real behavior.

Figure 4B shows the converse real experiment, in which motor neuron B16 was fired first, then B15 added. After the initial large contraction transient, B16 appears to depress its own contractions, too, much more than B15 does the contractions of B15 (compare “d” and “e” in Fig. 4B with, respectively, “d” and “c” in A2). The addition of B15 increases.
contraction size rather than depresses it. The complete model reproduces these features (not shown).

Thus there is real asymmetry between the motor neurons B15 and B16. B15 firing adds to contraction size, but B16 firing can actually subtract from it.

Switches between behaviors

As in Fig. 4 when a motor neuron was added or removed, the model predicted sharp contraction transients when the motor neuron firing pattern was switched between the different feeding behaviors.

Figure 5A shows a switch from biting to swallowing. Swallowing is characterized by longer bursts of firing of the motor neurons—a more intense input to the basal NMT—than those of biting (Paper I). The contraction therefore immediately increases in size, and even builds up an underlying tonic contracture. This buildup occurs largely because the value of $R$, and so $r_{relax}$, that was established during successive biting cycles as just sufficiently fast to relax each of their contractions fully before the next cycle, is suddenly no longer sufficient. Indeed $r_{relax}$ slows somewhat immediately after the switch because of its inverse dependency on contraction amplitude (see METHODS). However, the buildup is only transient: it decays as the longer swallowing bursts release more modulators, $R$ and $r_{relax}$ rise to a new, higher level, and the contractions reestablish their phasic character. To some extent a rise in $K$, and so a fall in $S$, is also involved, but the relaxation of the contraction transient parallels the slow relaxation of $R$, not the fast relaxation of $K$ (contrast “c” in Fig. 4A).

The same features are seen in contractions of the real muscle after such a switch (Fig. 5B). Indeed, almost every behavioral switch is followed by some kind of contraction transient in the real muscle (Fig. 6). These are very variable, however, as expected from the transient nature and strong history dependency of the modulatory state (Paper I), as well as from the progressive rundown of the contractions, which adds its own history-dependency.

Functional performance in quasi-realistic meals

Next, we simulated quasi-realistic meals, switching between biting, swallowing, rejection, and null behaviors randomly 75 times in an hour-long meal, as in Paper I but now with the complete model. Figure 7A shows the entire contraction waveform of a representative meal.

Our underlying hypothesis throughout this work is that the modulation serves to optimize functional performance. Unfortunately, the functional task of the ARC muscle within the mechanically complex buccal mass is not precisely known (see DISCUSSION). To evaluate the functional significance of the shape of the contraction waveform, we therefore devised a
simple task expressing our rough understanding (Brezina and Weiss 2000; Brezina et al. 1993) that, for the rhythmic feeding behavior, the phasic component of the contraction is functional, whereas tonic contracture is not. The task suggested a performance measure (see METHODS) that yielded one performance value per cycle, or a cumulative curve over successive cycles. Figure 7E (●) shows the rising cumulative performance curve computed for the contraction waveform in A.

Functional consequences of the modulation and its components

We compared contraction waveforms and performance in the quasi-realistic meals when the model was run with and without the modulation, or without its various components. Figure 7, B–D, shows, for example, contraction waveforms for the same meal as in A but without the modulation of relaxation rate R (B), contraction size S (C), or both—that is, with no modulation at all (D).

As can be seen in Fig. 7E, performance is worse in each of these cases than with the normal, complete modulation. The complete modulation appears to ensure that, in most cycles, the contraction relaxes fully before the next cycle, yet is as large as possible consistent with that requirement. Thus contractions are relatively small early in the meal when they occur frequently, then increase as they become less frequent (Fig. 7A). In contrast, with no modulation at all, the contractions are fixed at an intermediate size, too large early in the meal to relax fully, and too small later when they could increase without penalty (D). Without R but with S, the combination of increasing size but slow relaxation rate builds large tonic contractures whenever the motor neurons fire with any intensity in the middle part of the meal (B), giving very poor performance.

Interestingly, Fig. 7E shows that performance in the last case is worse than with no modulation at all. The modulation of contraction size is thus actually counterproductive unless it is accompanied by the modulation of relaxation rate. The converse, however, is not true. Without S but with R, there appears to be, grossly, only a relatively small deficit late in the meal when the contractions do not increase as much as they could (Fig. 7C).

Closer examination shows, however, that S makes a very significant contribution to performance after certain behavioral switches. Figure 8, A–C and F, expands, for example, the rejection→swallowing switch boxed in Fig. 7, A–D; Fig. 8G shows the performance, in this case plotted not cumulatively but individually for each cycle. It can be seen that, although the complete modulation with both R and S (● in Fig. 8G) does not provide the best performance in all cycles, it does best maintain performance over the few cycles immediately after the switch, considerably better than R without S.

Figure 8, D and E, further dissects S into its components, the enhancement of Ca current C and activation of K current K. Without C, performance is generally not good (Fig. 8G) because the contractions are small (D). Without K, however, performance is extremely poor because the switch to intense firing builds a very large tonic contracture (E). Clearly, especially in switches such as this early in the meal before R has had time to rise much, R is not sufficient to prevent tonic contracture and the fast dampening effect of K is required. The fast response of K is critical: slowing K to the speed of C and R (not shown, but see Fig. 11) has essentially the same effect as removing it altogether. The fast contribution of K, then, largely underlies the effectiveness of S immediately after the switch. However, examination of Fig. 8G shows that if K is present, so must C be, especially once past the immediate switch. The enhancement of Ca current and the activation of K current form another complementary pair such that either alone gives worse performance than when they are both absent—or, of course, both present.

The modulation improves performance on average, but degrades it after certain behavioral switches

We ran the model in many such quasi-realistic meals and plotted the peak contraction size (Fig. 9A) and performance (Fig. 9B) in each cycle (scatter of faintly outlined symbols), as well as the mean values for all cycles of biting, swallowing,

FUNCTIONAL CONSEQUENCES OF THE MODULATION AND ITS COMPONENTS

We compared contraction waveforms and performance in the quasi-realistic meals when the model was run with and without the modulation, or without its various components. Figure 7, B–D, shows, for example, contraction waveforms for the same meal as in A but without the modulation of relaxation rate R (B), contraction size S (C), or both—that is, with no modulation at all (D).

As can be seen in Fig. 7E, performance is worse in each of these cases than with the normal, complete modulation. The complete modulation appears to ensure that, in most cycles, the contraction relaxes fully before the next cycle, yet is as large as possible consistent with that requirement. Thus contractions are relatively small early in the meal when they occur frequently, then increase as they become less frequent (Fig. 7A). In contrast, with no modulation at all, the contractions are fixed at an intermediate size, too large early in the meal to relax fully, and too small later when they could increase without penalty (D). Without R but with S, the combination of increasing size but slow relaxation rate builds large tonic contractures whenever the motor neurons fire with any intensity in the middle part of the meal (B), giving very poor performance.

Interestingly, Fig. 7E shows that performance in the last case is worse than with no modulation at all. The modulation of contraction size is thus actually counterproductive unless it is accompanied by the modulation of relaxation rate. The converse, however, is not true. Without S but with R, there appears to be, grossly, only a relatively small deficit late in the meal when the contractions do not increase as much as they could (Fig. 7C).

Closer examination shows, however, that S makes a very significant contribution to performance after certain behavioral switches. Figure 8, A–C and F, expands, for example, the rejection→swallowing switch boxed in Fig. 7, A–D; Fig. 8G shows the performance, in this case plotted not cumulatively but individually for each cycle. It can be seen that, although the complete modulation with both R and S (● in Fig. 8G) does not provide the best performance in all cycles, it does best maintain performance over the few cycles immediately after the switch, considerably better than R without S.

Figure 8, D and E, further dissects S into its components, the enhancement of Ca current C and activation of K current K. Without C, performance is generally not good (Fig. 8G) because the contractions are small (D). Without K, however, performance is extremely poor because the switch to intense firing builds a very large tonic contracture (E). Clearly, especially in switches such as this early in the meal before R has had time to rise much, R is not sufficient to prevent tonic contracture and the fast dampening effect of K is required. The fast response of K is critical: slowing K to the speed of C and R (not shown, but see Fig. 11) has essentially the same effect as removing it altogether. The fast contribution of K, then, largely underlies the effectiveness of S immediately after the switch. However, examination of Fig. 8G shows that if K is present, so must C be, especially once past the immediate switch. The enhancement of Ca current and the activation of K current form another complementary pair such that either alone gives worse performance than when they are both absent—or, of course, both present.

The modulation improves performance on average, but degrades it after certain behavioral switches

We ran the model in many such quasi-realistic meals and plotted the peak contraction size (Fig. 9A) and performance (Fig. 9B) in each cycle (scatter of faintly outlined symbols), as well as the mean values for all cycles of biting, swallowing,

FIG. 5. Contraction transients after switches between behaviors. A: model was run with F = 6 s, fsw,sw = 10 Hz, and fsw,bit = 18 Hz throughout, starting with dsw,B15 = 1.3 s and dbit,B16 = 2 s (regular version of canonical biting pattern), then, after system had come close to steady state, switching to dsw,B15 = 3 s and dbit,B16 = 3.7 s (regular version of canonical swallowing pattern). T = 18°C. B: real experiment with same firing patterns as in A. T = 15°C. frelax was measured from portion of relaxation visible in each cycle on assumption that relaxation was exponential.
and rejection (single boldly outlined symbols), with and without the modulation. We found statistically significant differences ($P < 10^{-10}$ by Student’s $t$-test) between the means for all pairwise comparisons, of both contraction size and performance, with and without the modulation.

It can be seen that, on average, the modulation somewhat increases the contraction size and considerably improves the performance in all 3 behaviors, especially in swallowing.

At the same time, however, it greatly increases the variability of the contraction size and, more important, performance. As a consequence, there are some cycles of swallowing, in particular ($\rightarrow$ in Fig. 9B), in which performance is considerably worse with the modulation than it would have been without it. Inspection shows that these cycles occur immediately after a switch to swallowing where, although the modulatory mechanisms discussed in the preceding section are operating, they do not suffice to prevent a transient tonic contracture.

**Sensitivity of performance to parameters governing modulator concentrations**

Our definition of performance also allowed us to investigate questions of optimization of the performance with respect to the parameter values of the model. With the particular parameter values that we found, is the model—and, presumably, the real system—tuned so as to give optimal performance? Furthermore, if some of the modeled parameter values are rather uncertain, does it matter? To what extent is the performance sensitive to variation in those parameters? In particular, we investigated the 4 parameters $v_{SCP}$, $k_{SCP}$, $v_{MM}$, and $k_{CMM}$ that is, the volumes $v$ and removal rates $k_c$ that critically govern the amplitude and dynamics of the effective concentrations of SCP and MM in the ARC muscle (Paper I). Values of these parameters could not be measured directly, but were in Paper I estimated by modeling a secondary variable, cAMP elevation in the muscle.

We ran the model in quasi-realistic meals, as in Fig. 9 but varying each of the 4 parameters in turn over a 100-fold range. The resulting performance is shown in Fig. 10. Performance is relatively insensitive to variation of the SCP concentration parameters $v_{SCP}$ and $k_{SCP}$—that is, to the exact strength of the SCP modulation. In contrast, the performance is sensitive to variation of the MM concentration parameters $v_{MM}$ and $k_{CMM}$. However, the tuning is still broad: over an approximately 10-fold range around the “normal” value of either parameter—the best estimate that we arrived at in Paper I, and have been using in our simulations throughout—performance remains improved in all 3 behaviors.

Interestingly, over the full, 100-fold range of the MM concentration parameters, it can be seen that the tuning differs for the 3 behaviors. When either $v_{MM}$ or $k_{CMM}$ is small, MM reaches high concentrations in the muscle. $K$ is high, contractions are generally depressed (see, e.g., inset “$v_{MM}/10$” in Fig. 10), and performance is low in all 3 behaviors. When either $v_{MM}$ or $k_{CMM}$ is large, on the other hand, MM concentrations are low. $K$ is low, and contractions are generally potentiated (inset “$v_{MM} \times 10$”). This improves performance in rejection, which has a long cycle period so that the contractions occur far
functionality cannot react fast enough to prevent a transient tonic contracture. We propose that the solution to this problem is for the motor neuron firing patterns to relax gradually, rather than switch abruptly, through the behavioral transition (see DISCUSSION). Indeed, an example of this is already well known. The very start of the meal can also be seen as a behavioral transition, and it is well documented that the feeding rhythm starts slowly and gradually accelerates in what has been called food-induced arousal (Susswein et al. 1978; see Fig. 3A of Paper I).

Figure 11 shows contractions (A–E) and cumulative performance (F) produced by the model with and without the modulation, and with and without arousal. Again, the normal, complete modulation, with normal arousal (A), gives the best performance (● in F). Removal of the modulation degrades performance because it allows a tonic contracture to build up (B). Again, the fast speed of K is critical: simply slowing K down, even though the modulation is in all other respects intact, allows an even larger contracture (C). However, it is the contribution of arousal that is of particular interest. Elimination of arousal—that is, if the initially slow rhythm remains slow (D)—gives poor cumulative performance, as expected. Most interestingly, however, the “pre-aroused” case, in which the rhythm is fast from the very start (E), also gives worse initial performance. Although the normal modulatory mechanisms are present, they have not built up the modulatory state so as to prevent an initial tonic contracture when the motor neurons abruptly start firing at high intensity.

**DISCUSSION**

**The unmodulated NMT constrains behavior**

In our previous theoretical work on the NMT, we argued that a neuromuscular system that performs multiple behaviors—in the case of the ARC system, biting, swallowing, and rejection, each over a range of speeds—cannot, with fixed properties of the NMT, perform all of the behaviors optimally, because the properties of the NMT cannot simultaneously be optimal for all of them (Brezina and Weiss 2000). Some behaviors may not be possible at all: the entire set of motor neuron firing patterns may not include a pattern that, when filtered through the NMT, will produce the required contraction shape.

Indeed, we find such constraints here in the model and in the real muscle. The unmodulated NMT is fixed to give intermediate contraction size and slow relaxation rate (Fig. 7D; Figs. 13A, 16 of Paper I). However, this is not really optimal for any of its behaviors. When the motor neurons fire at high intensity in biting and especially in swallowing in the early part of the meal, the muscle builds up a large tonic contracture (Figs. 7D, 8F, 11B), whereas later in the meal and in rejection, the contractions are too small (Fig. 7D). Altogether, performance is poor.

The tonic contracture develops by summation of successive contractions that do not have time to relax completely before the next cycle (Brezina et al. 1997, 2000a). Although the likely resulting functional problems have been much discussed (Brezina and Weiss 2000; Weiss et al. 1993), our work here is the first actual demonstration that the speed of the B15/B16-ARC NMT is sufficiently slow that the summation occurs at the cycle speeds of normal behavior, in the model and in the real muscle (Figs. 4–6). Similar phenomena have been described in other neuromuscular systems [see, e.g., Morris and Hooper (1998, 2001); Hooper et al. (1999), and references therein].

Finding that performance degrades when modulation is simply removed from the complete system does not prove that there could not be some other firing pattern that would maintain performance under the new circumstances. However, for
the particular task of maintaining large, phasic contractions as the cycle speed accelerates, there is no such pattern (Brezina and Weiss 2000).

Modulation of the NMT alleviates the constraint

In our previous work, we argued that the solution to the functional problem posed by the fixed properties of the NMT is to tune those properties appropriately for each desired behavior by modulation (Brezina et al. 2000b). Here, we find that the modeled modulation does indeed minimize the muscle’s tonic contractures, maintaining its contractions phasic, yet as large as possible—relatively small early in the meal when they occur frequently, then increasing as they become less frequent—for significantly improved average performance (Fig. 7, A and E). The modulation is thus able to cope automatically with the range of speeds of normal behavior, as predicted (Brezina et al. 2000b; Weiss et al. 1993). On average, contraction size is somewhat increased and performance is improved in all 3 behaviors, but especially in swallowing, the key ingestive behavior (Fig. 9).

For distinct behaviors, there should be distinct modulatory states (Brezina et al. 2000b). Indeed, biting, swallowing, and rejection are associated, on average, with different states of the modulation of contraction size (Fig. 16B of Paper I). Interestingly, however, when this modulation is superimposed on the basal NMT that itself produces different contractions sizes in biting, swallowing, and rejection (Fig. 9A, left), the complementary effects of the 2 halves of the system—the “neuro-modulation” transform and the basal NMT—give a rather uniform average contraction size (Fig. 9A, right), and uniformly high performance (Fig. 9B), in all 3 behaviors.

The overall contraction size may thus be maintained within certain bounds across all 3 behaviors. However, size is only one parameter of the functionally important contraction shape (Brezina and Weiss 2000; Brezina et al. 2000b). As Fig. 12 shows, the similarly sized contractions in biting, swallowing, and rejection have very different shapes, made so by the combination of their different motor neuron firing patterns and different modulation.

Control of multiple dimensions of contraction shape

The system is able to range widely through the multidimensional space of contraction shape parameters—we have fo-
mechanisms. First, the motor neuron — by means of at least 3 may also be significant (see below) focused just on contraction size and relaxation rate, but others may also be significant (see below)—by means of at least 3 mechanisms. First, the motor neuron firing pattern, the input to the basal NMT, varies. Second, the same motor neuron firing pattern is also the input to the neuromodulation transform, where the 2 neurons B15 and B16, through their differential release of SCP and MM and consequent differential activation of the depressive K current in the muscle, differentially modulate contraction size. We emphasized this principle in our previous static analysis of the system (Brezina et al. 1996) and confirmed it again here. Thus for example, a shift of the weight of motor neuron firing from B15 to B16 that, through the basal NMT alone, would maintain or even increase contraction size, instead depresses it (Fig. 4A). Third, the system also ranges widely through the space because of its dynamics.

**Slow and fast dynamical time scales**

A key finding is that the system includes dynamical components operating on very diverse time scales. Some components, such as the enhancement of Ca current and the consequent potentiation of contraction size, as well as the acceleration of relaxation rate, are slow, much slower than the cycle speed of the behavior. In contrast, the activation of K current and the consequent depression of contraction size is as fast as the cycle speed. The basal NMT is even faster in the model, although in reality it too may include slow components (see further below).

Superposition of the slow and fast dynamics allows the system to range widely through the space of contraction shape parameters, including its non-steady-state regions, with particularly sharp transients after abrupt switches in behavior (Figs. 13 and 16 of Paper I, and Figs. 4—8 here).

**Slow dynamics embody predictive memory**

Why does the system include slow dynamical components? If the function of the modulation is simply to tune the NMT for the behavior currently being commanded by the CNS—for the current contraction shape, produced by the current motor neuron firing pattern through the fast basal NMT—why is the modulation not likewise all fast?

We propose that the slow modulatory dynamics serve to embody a memory of the history of the behavior. This history is significant because it predicts future behavior. Ultimately this reflects the slow dynamics of the interaction of the feeding animal with its environment. Once the animal makes contact with food, for example, it is likely to remain in contact with it for some time; once it begins to ingest a strip of seaweed, the strip is likely to be long enough to require multiple swallows. Runs of cycles of the same type of behavior, as in our quasi-realistic meals, are thus common (Kupfermann 1974; Morton and Chiel 1993). With slow dynamics, the modulatory state, too, is set up over the course of multiple cycles—automatically, because, with these intrinsic modulators released from the motor neurons themselves, the neuromodulation transform and the basal NMT both take as their input the same motor neuron firing pattern—and then persists to premodulate the NMT for the next cycle. In doing so, it in effect makes a prediction as to what that next cycle is going to be. With simple dynamics that tend toward unique, stable steady states, the longer a run of a particular type of behavior continues, the more firmly the system commits itself to the prediction that the next cycle will also be the same.

**Fast dynamics facilitate behavioral switches**

Sooner or later, however, the prediction is bound to fail: the CNS will change the motor neuron firing pattern to speed up the behavior, say, or even command a switch to a different type of behavior. The slow, persistent modulatory state will then suddenly be inappropriate, and actually degrade performance of the new behavior (e.g., Figs. 8E and 11C).

The solve this problem, the system superimposes on the slow modulatory dynamics the fast activation of K current that
regulates the contraction size and shape on a cycle-to-cycle basis. The K current plays a key role in maintaining adequate performance immediately after abrupt changes of firing pattern (compare, e.g., Fig. 8, A and E, and G).

The superposition of slow and fast dynamics creates a complex history-dependency (Figs. 13A and 16 of Paper I) that means that the contraction shape during each cycle of behavior, and especially after each behavioral switch, is somewhat different from any other (Fig. 7A). This can be regarded as a manifestation of the fact that, with a different history behind it, at each point the system has a somewhat different expectation of the future.

**Mutual interdependence of dynamical components**

A motif that emerges over and over again is a mutual complementarity and strong interdependency of the components of the system. Multiple components, with varying weights depending on the circumstances, contribute to each feature of contraction shape and performance, and indeed often are so strongly integrated that all are necessary: in the absence of one of them, the others are actually counterproductive.

Thus, for example, the contraction size is governed in a complex manner by the motor neuron firing pattern through the basal NMT as well as all of the modulatory effects, not only the formally modeled effect on contraction size (S) but also that on relaxation rate (R) (Fig. 7). Maintenance of contractions that are fast, large, yet still phasic depends on R, as supposed in earlier models (Weiss et al. 1993), but also, especially immediately after behavioral switches, requires S (Fig. 8). The general efficacy of S, in turn, requires both of its components, the modulation of K current as well as that of the Ca current (Fig. 8G).

Altogether, the system appears to be constituted not so much to achieve the best performance possible at any one time, but rather to maintain acceptably high performance through all the circumstances that may arise (Figs. 7E, 8G, 10). For this, a component that actually degrades performance to some extent under one set of circumstances must nevertheless be present because it may become essential under another set of circumstances.

The strong, nonlinear coupling between the components has implications for the experimental analysis of such a system. The functional role of each component depends on the context of the others, and removal of the components one at a time will not accurately reveal their roles in the intact system.

**Peripheral constraint on central motor commands**

Our previous theoretical work predicted that the most fundamental interdependency in such a system will be between the properties of the NMT and the motor neuron firing pattern (Brezina and Weiss 2000). The properties of the NMT—in particular, its modulatory state—must be such as to successfully transform the firing pattern into behaviorally appropriate contraction shapes, while the firing pattern must be such as to
successfully engage the properties of the NMT to that end. This mutual matching is likely to be most severely stressed when the firing pattern changes abruptly but the properties of the NMT, because of their slow dynamics, do not (Brezina and Weiss 2000).

Indeed, the modeled performance tends to be weakest immediately after abrupt switches in behavior (Fig. 8G). After certain switches to swallowing, in particular, the mechanisms that prevent tonic contracture can fail, even become counterproductive so that performance is transiently worse with the modulation than it would have been without it (→ in Fig. 9B). The real muscle, too, shows such contraction transients after abrupt switches in firing pattern (Figs. 5B and 6).

We propose that, to solve this problem, the CNS does not switch the motor neuron firing pattern abruptly. To command a switch in behavior, it relaxes the firing pattern gradually,

FIG. 11. Food-induced arousal. A–E: contraction waveforms produced by model. A: complete model, with normal modulation and arousal, in swallowing behavior. B: $S(t) = 0$, $R(t) = 0$. C: $K$ rate constants $k_{K^+}$ and $k_{K^-}$ divided by 250 (see Paper I). D: $P(t) = 52.85$ s (solution of Eqs. 1c–e of Paper I for $t = 0$). E: $P(t) = 5.5$ s (given by Eq. 1c of Paper I with $a(t) = 0$, $s(t) = 0$). $T = 16°C$. F: cumulative performance for waveforms in A–E.

FIG. 12. Representative contraction shapes in biting, swallowing, and rejection. Expanded view of contractions indicated by → in Fig. 7A.
essentially on a time scale that matches the relaxation of the dynamics of the NMT in the periphery.

Is there any evidence that this happens? Cropper et al. (1990b) briefly reported that, after switches to swallowing in intact, feeding animals, the swallowing motor pattern gradually develops over the next few cycles. Morton and Chiel (1993), too, reported transitional, intermediate patterns occurring particularly during switches in behavior. Such observations now need to be reproduced and extended (see below).

There is already, however, a well-known phenomenon that can be seen as belonging to the same category: the gradual acceleration of the feeding rhythm at the start of the meal in food-induced arousal (Susswein et al. 1978; Weiss et al. 1982). The model confirms that performance is worse if, instead, the fast rhythm starts abruptly, because a large tonic contracture develops in the model (Fig. 10E) as indeed in the real muscle (Fig. 6A).

Thus the peripheral dynamics of the NMT constrain the motor commands of the CNS.

Other buccal-mass muscles

The ARC is just one, albeit a representative and well-studied, muscle of the buccal mass, the organ that generates the consummatory feeding movements of the radula. To generate functional and efficient movements, all of the buccal-mass muscles must act in coordination (Hooper et al. 1999; Kupfermann et al. 1997). To this end, it is very likely that all of the buccal neuromuscular circuits contain modulatory networks such as that in the ARC. Seemingly all buccal motor neurons express modulatory peptide cotransmitters (Church and Lloyd 1991), and modulatory mechanisms similar to those in the ARC have been described in a number of the other muscles (e.g., Church et al. 1993; Evans et al. 1999; Fox and Lloyd 1997; Hurwitz et al. 2000; Scott et al. 1997).

Future directions

One important role of a model such as this is to reveal, through its defects, gaps in the available data. At the same time, the model frames the questions that should now be asked. These include the following:

THE BASAL NMT. Our present model of the NMT lacks systematic data on the contribution of motor neuron B16, and especially on how B15 and B16 may interact in producing contractions. Furthermore, it does not include, except insofar as the underlying mechanisms might be reflected in the contraction time courses in Fig. 1A1, phenomena such as posttetanic potentiation (PTP) (Cohen et al. 1978). We note, however, that in another buccal muscle PTP has been attributed, as in Fig. 2B (left), to release of potentiating peptide cotransmitters (Fox and Lloyd 2001). Altogether, the NMT needs to be modeled for a wider range of motor neuron firing patterns, even arbitrary, irregular spike patterns.

ADDITIONAL MODULATORS AND MODULATORY ACTIONS. We have modeled the important postsynaptic actions of the major intrinsic modulators, SCP and MM. However, MM has recently been found to act also presynaptically, to inhibit ACh and modulator release from the terminals of B15 and B16 (Orekhova et al. 2003). Furthermore, additional modulators are active in the system. Both B15 and B16 release also the presynaptically inhibiting buccalins (Cropper et al. 1988, 1990c; Vilim et al. 1994). Extrinsic modulators of the system include the FRF peptides (Cropper et al. 1994) and serotonin (5-HT) (Weiss et al. 1978).

It may seem surprising that the model is as successful as it is without taking these other modulators and actions into account. There are several, partial answers to this. First, although the predictions of the model are indeed qualitatively correct, they are not always quantitatively so (e.g., Fig. 4A). Second, the intrinsic modulators are all obligatorily coreleased from B15 and B16 (Vilim et al. 1996b, 2000), coupling their actions and restricting the system to only parts of the modulatory space (Brezina and Weiss 1997; Brezina et al. 2000b). Third, along certain dimensions of the NMT, the modulatory actions appear redundant. For example, the presynaptic inhibition of ACh release by the buccalins, and MM, is not, to a first approximation, very different from a reduction of ACh release simply by reduction of the motor neuron firing frequency. Postsynaptically, too, not only SCP and MM but also the FRFs and 5-HT converge on the Ca-current, K-current, and relaxation-rate effects in the muscle (Brezina et al. 1994a,b; Cropper et al. 1994). Fourth, just as the actions that we have modeled play different roles under different circumstances, the additional modulators and actions might nevertheless be important, but only under special circumstances. For example, release of 5-HT from the modulatory metacerebral cells might serve to premodulate the system before the meal starts, thereby providing another solution to the problem examined in Fig. 11 (Kupfermann and Weiss 1982; Rosen et al. 1989; Weiss et al. 1978). It will be interesting to model such special circumstances once it is clearer what they are (see below).

THE FUNCTIONAL TASK OF THE MUSCLE. At the level of the whole animal, and even of the whole buccal mass, there are fairly self-evident criteria by which to evaluate the utility of the feeding movements (e.g., Hurwitz and Susswein 1992; Morton and Chiel 1993; Weiss et al. 1986). However, this is not true at the level of the single ARC muscle, embedded within the mechanically complex buccal mass and acting in complex coordination with its other muscles (see Orekhova et al. 2001).

By what criteria are we to evaluate the utility of the contraction shapes in Fig. 12? What is the functional task of the muscle (Brezina and Weiss 2000)? Here we have devised a simple task, but a much more realistic understanding is needed. This may come from the buccal-mass imaging and kinematic and kinetic modeling work of Chiel and collaborators (Drushel et al. 1997, 1998; Neustadter et al. 2002a,b).

STATISTICS OF THE BEHAVIOR AND MOTOR NEURON FIRING PATTERNS. Our finding of history-dependency in the system focuses attention on what the history typically is. How often do the behavioral switches occur; and generally what is the structure of the behavior, in real meals? What is the structure of the underlying motor neuron firing patterns? It is already clear that there is much variability in the behavior, firing patterns (e.g., Hurwitz and Susswein 1992; Morton and Chiel 1993; Rosen et al. 1982; Schwarz et al. 1988; Susswein et al. 1978, 1986; Weiss et al. 1986), and buccal-mass kinematics (e.g., Drushel et al. 1997, 1998) depending on factors such as the food type and quality, motivational state, learned experience, or simply spontaneous variability. What are the statistics of this variability? Answers to these questions will provide more realistic
input to the model. More important, however, our model has now made certain predictions about the features of the behavior and the motor neuron firing patterns. We should now look for these features in the real, behaving animal.

**How realistic is the model?**

Given the foregoing deficiencies, we regard the model, in its current form as presented here, as intermediate between a realistic and a more abstract, “speculative” model (see Marder and Abbott 1995). On the one hand, we have modeled the system as realistically as possible with the available data. Our results emerge from the data, and we believe that, at the very least qualitatively, they fairly describe what actually happens in the real system. On the other hand, the chief value of the model will ultimately lie in the broader conceptual conclusions that it affords. We believe that the concepts we have discussed here will prove to be generally applicable to a variety of systems. In the *Aplysia* system, the specific predictions of the model provide a foundation on which we can now actually begin to test the most interesting of these conclusions, concerning the constraints that the complex dynamical organization of the periphery imposes on the motor commands of the CNS.

We thank A. Proekt for stimulating discussions and two anonymous reviewers of the paper for very helpful suggestions.

**DISCLOSURES**

This work was funded by National Institutes of Health (NIH) Grants MH-50235 to K. R. Weiss and NS-41497 to V. Brezina. Some *Aplysia* were provided by the National Center for Research Resources National Resource for *Aplysia* at the University of Miami under NIH Grant RR-10294.

**REFERENCES**


Morton DW and Chiel HJ. In vivo buccal nerve activity that distinguishes ingestion from rejection can be used to predict behavioral transitions in Aplysia. J Comp Physiol A Sens Neural Behav Physiol 172: 17–32, 1993.