Published in final edited form as:

Neurocomputing. 2007 June ; 70(10-12): 1863–1869.

Functional penetration of variability of motor neuron spike timing through a modulated neuromuscular system

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Abstract

Variability of the neuronal spike pattern is usually thought of in terms of the information that the different interspike intervals might be encoding. However, the very presence of the variability can have other kinds of functional significance. Here we consider the example of the B15/B16-ARC neuromuscular system of *Aplysia*, a model system for the study of neuromuscular modulation and control. We show that variability of motor neuron spike timing at the input to the system penetrates throughout the system, affecting all downstream variables including modulator release, modulator concentrations, modulatory actions, and the contraction of the muscle. Furthermore, not only does the variability penetrate through the system, but it is actually instrumental in maintaining its modulation and contractions at a robust, physiological level.

Keywords

Motor control; neuromuscular system; neuromodulation; pattern dependence; behavioral variability

Introduction

Irregularity or variability of the neuronal spike pattern is usually considered from a coding perspective, with the idea that the different times at which successive spikes are fired, the varying lengths of the successive interspike intervals, serve to individually encode and convey information. Here we point out that, quite apart from this, the overall degree of variability that is present in the spike pattern will automatically modulate in a global way a great variety of downstream variables, many of which would not be thought of from the information-coding perspective at all. We study the phenomenon in a well-understood invertebrate model system.

The B15-B16/ARC neuromuscular system of *Aplysia*

The B15-B16/ARC neuromuscular system of *Aplysia* ([9], Fig. 1), which participates in the animal's rhythmic consummatory feeding behaviors such as biting, swallowing, and rejection, is a model system for the study of neuromuscular modulation and control. The ARC muscle is innervated by two motor neurons, B15 and B16, which, when they fire (Fig. 1, top), release their classical transmitter, ACh, to contract the muscle ("Basal neuromuscular transform," down the left-hand side of Fig. 1). In addition, however, both motor neurons release modulatory peptide cotransmitters. B15 releases the small cardioactive peptides (SCPs) and B16 releases the myomodulins (MMs). Through a network of modulatory actions in the muscle

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(“Modulation,” down the right-hand side of Fig. 1), the released peptides then shape the basal ACh-induced contractions (Fig. 1, bottom). Extensive studies over the past 30 years have characterized many aspects of the system to the point where integrative, functional questions can be asked. In particular, these studies have allowed the construction of a reasonably complete dynamical model of the system, covering the variables shown in Fig. 1 [3,6,7].

Question

During each cycle of the feeding behavior *in vivo*, the two ARC motor neurons fire a burst of spikes, producing a contraction of the muscle. Experimentally and in the model, the system has always been probed, however, with completely *regular* bursts, as indicated at the top of Fig. 1. This was taken to be adequate on the basis of two assumptions: (1) that the feeding behavior is stereotyped, very similar in all its parameters from cycle to cycle; and (2) that, in any case, the ARC is a “slow” muscle that will respond only to the overall, integrated spike rate of the motor neurons, so that the precise timing of the individual spikes should not much matter. Both of these assumptions now have to be revised.

First, it has been found that essentially all parameters of the feeding behavior exhibit great variability from cycle to cycle [11,12,15,16]. Fig. 2, for example, shows how the spike bursts of the ARC motor neurons vary in overall cycle-level parameters such as the cycle period, burst duration, and overall spike frequency during an entire ~2½-hour “meal” of 749 cycles recorded *in vivo* [from 3, 11]. And, as can be seen, there is variability also within each cycle, in the irregular timing of the individual spikes within each burst. Fig. 3 further documents the statistical properties specifically of this low-level intraburst spike timing variability. Fig. 3A plots the distributions of all the intraburst interspike intervals of the motor neurons B15 (left) and B16 (right) within the 2½-hour meal. To eliminate from this total variability any components arising from slow trends over multiple interspike intervals [3,11,12], Fig. 3B plots the corresponding distributions of the differences between successive interspike intervals, normalized by the mean interval. With this normalization, +1 and -1 on the abscissa represent, respectively, increases and decreases in interspike interval from one interval to the next that are equal in magnitude to the mean interval. There are many differences as large or even twice as large as this—a large variability. The standard deviation of the distributions, σ , which with the normalization is comparable to the standard coefficient of variation, is 1.02 for B15 and 1.16 for B16. Finally, Fig. 3C shows the first return maps of the interspike intervals. These maps have essentially no structure, suggesting that, apart from slow trends, successive interspike intervals were drawn from the distributions in Fig. 3A essentially at random, without significant second-order interaction between intervals.

The second reason to revise the existing assumptions is that recent experiments have suggested that the ARC muscle is not really slow. Rather, it operates at the interface between the slow and fast regimes, so that, while it does integrate over the spikes, it can also respond to each individual one [16].

What, in that case, is the impact of the variability found in the motor neuron spike patterns on the contractions, and on the modulatory actions that are also set in motion by the motor neuron firing? Here we ask this question specifically with respect to the low-level intraburst variability, that in the timing of successive spikes within each burst.

Method

We drive our model of the B15/B16-ARC system (Fig. 1) with either the real, irregular spike patterns of the motor neurons recorded during the 2½-hour meal in Fig. 2, or, in comparison, the corresponding “regularized” patterns, replacing each irregular burst with a regular burst with the same overall parameters—the same spike number, mean spike frequency, and duration

—as the irregular burst, but with all interspike intervals equal. This eliminates just the low-level intraburst variability of spike timing, and its functional contribution. Fig. 4A shows an example of the real, irregular (gray) and regularized (black) patterns.

Results

Fig. 5 compares, in the two cases, the trajectories of key variables of the model (see Fig. 1)—from top to bottom, first the driving spike patterns, in the form of the instantaneous firing frequencies of the two motor neurons, f_{B15} and f_{B16} ; then the released concentrations of the respective modulators, C_{SCP} and C_{MM} ; the resulting enhancement of Ca current in the muscle, C ; activation of K current, K ; acceleration of the muscle's relaxation rate, R ; the overall modulation of contraction size, S , given by the balance of C and K ; the basal, unmodulated contraction, c_{basal} ; and finally the modulated contraction, c . Clearly, the regularization of the spike patterns decreases the peak amplitude of essentially all of the downstream variables. While this is not especially surprising, it does show that the variability of spike timing at the input to the system *penetrates* throughout the system, affecting the modulator concentrations, modulatory actions, and the contraction.

More interestingly, not only is the peak amplitude affected, but so is the mean amplitude. Fig. 6A plots, for each of the variables in Fig. 5 as well as the actual release of the modulators from the motor neurons, r_{B15} and r_{B16} , a measure that in previous theoretical work on these kinds of phenomena [4] we have termed *pattern-dependence*, Φ . Given an input-output relationship, Φ seeks to quantify the impact of the presence of a pattern in the input—in this case, the intraburst variability of the motor neuron spike timing—on the output. In Fig. 6A, Φ is therefore computed as the ratio of the mean amplitude of each variable, integrated over the 2½-hour meal, that is produced by the real, irregular spike patterns to that produced by the regularized patterns. It is evident that the variable timing of the real spikes greatly increases not merely the peak amplitudes, but also the total amounts of the modulators released, the total modulator concentrations in the muscle, the total “amounts” of the modulatory actions, and the total “amount” of contraction generated.

Qualitatively similar pattern-dependence is in fact generated also by the pattern at the overall, whole-cycle level, that is, by the fact that the motor neuron spikes are grouped into bursts at all. If the bursts are completely dispersed—regularized even beyond the regularization studied here—into the equivalent number of spikes fired tonically, the peak and mean amplitudes of the model variables are decreased still further, below even the regularized levels in Fig. 5B [see 2–5]. However, this component of pattern-dependence, on a slower and coarser scale, is less unexpected [4]. What is striking is that a very strong pattern-dependence continues to be generated by the spike pattern even down to the level of the timing of the individual spikes.

The pattern-dependence Φ , and the changes in Φ on passage through a network of input-output steps such as that constituting the B15/B16-ARC system (Fig. 1, repeated under Fig. 6A), can be quantitatively explained by the nonlinearity of each input-output transformation as well as its time scale [4]. The shapes of four of the input-output transformations (for simplicity, in the steady state) are sketched in Fig. 6B. Bearing out the theoretical analysis presented in [4], the $f_{B15} \rightarrow r_{B15}$ step, with a supralinear transformation, increases Φ (B1), as does the $f_{B15} \rightarrow c_{\text{basal}}$ step (B4). Conversely, the $C_{SCP} \rightarrow C$ step, with a sublinear transformation, decreases Φ (B3). The linear step $r_{B15} \rightarrow C_{SCP}$ does not change Φ (B2).

Given a particular input-output transformation, Φ then depends on the amplitude as well as the time scale of the input pattern [4]. Here we have simply contrasted the presence of the entire pattern recorded *in vivo* with its complete absence. However, intermediate, or larger, degrees of spike timing variability would generate intermediate, or larger, Φ . With a pattern occurring

across multiple inputs, Φ will also be accentuated by any correlation between the inputs and any synergism between their convergent actions. In the ARC system, however, there appears to be no correlation between the spike patterns of the motor neurons B15 and B16 [9,15] nor any obvious synergism between their actions where they converge within the network in Fig. 1 [6,7].

Can the pattern-dependence be confirmed experimentally? Fig. 4 is in fact from an experiment in which we replayed the real, irregular and the regularized spike patterns in Fig. 4A, not into the model, but into the real motor neurons *in vitro* [16]. Fig. 4B then shows the resulting contractions of the real ARC muscle. A strong pattern-dependence is obvious. On the overall, whole-cycle level, too, the predicted pattern-dependence has been experimentally confirmed on contractions [4,5] as well as directly-measured release of the modulators [2].

Conclusion

It appears, therefore, that the intraburst variability of motor neuron spike timing not only penetrates through the entire network of the B15/B16-ARC neuromuscular system, but is actually instrumental in maintaining its modulation and contractions at a robust, physiological level.

Insofar as the variable spike timing produces variable modulation and contractions, the detailed information that, formally, is encoded in the varying interspike intervals is of course passed to these downstream variables. However, there are reasons to believe that, in this system, the detailed information is functionally less important than the global consequences of the variability. Far from fine-tuning the detailed shape of the contractions, the varying spike pattern may in fact serve to randomize the contraction shape as part of a trial-and-error search mechanism through the space of possible feeding movements, the animal's strategy for dealing with an uncertain and changing feeding environment [11,12]. Such randomization does not require any specific set of spike patterns, merely spike patterns with the proper overall degree of variability.

Are the phenomena that we have studied here in some way special to the *Aplysia* system? We do not believe so. The underlying principles [4] do not depend on the particular identities of the processes involved but only on abstract properties such as the shapes of the input-output transformations and their time scales. The *Aplysia* transformations have standard shapes (Fig. 6B). In terms of time scales, the fact that the variability of the spike pattern, with a characteristic time scale of ~100 ms (Fig. 3A), penetrates the processes that we have studied simply means that they have components that are faster than this [4]. But this is not especially fast: many spike-dependent processes, particularly in vertebrates, are considerably faster. We therefore expect that the phenomena that we have described here will be found to occur generally. Indeed, one such phenomenon is already well known in sensory systems. Formally, the mechanism by which the spike timing variability maintains the contractions in the system studied here—as variable noise superimposed on a more slowly oscillating base waveform that is then passed through a threshold nonlinearity—is essentially identical to the “iceberg effect” [14] of simple “threshold” stochastic resonance that allows detection of otherwise subthreshold sensory stimuli in numerous sensory systems [1,10,13].

Acknowledgements

Supported by NIH grant R01 NS41497 to V.B.

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Biography

Vladimir Brezina received his Ph.D. from UCLA in 1988. He did postdoctoral work at Columbia University and the Mount Sinai School of Medicine before becoming a faculty member at Mount Sinai. He uses both experimental and computational approaches to study modulated neuromuscular networks in *Aplysia*, and, more generally, the principles of operation of complex neurobiological networks.

Fig. 1. Schematic summary of the modulated B15/B16-ARC neuromuscular system. The variables shown are the variables of our dynamical model.

Fig. 2.

Variability of B15 and B16 spike bursts *in vivo*. *Top*: instantaneous firing frequency functions of B15 and B16 during an entire ~2½-hour meal comprising 749 cycles of feeding behavior [from3,11]. *Bottom*: expansion of the indicated excerpt with a schematic representation of the individual spikes.

Fig. 3.

Statistics of the intraburst interspike intervals of B15 and B16 during the 2½-hour meal in Fig. 2. Intraburst intervals were taken to be those <1 s [3]. *A*: distributions of all 7,847 B15 (*left*) and 25,116 B16 (*right*) intraburst intervals, scaled so as to approximate the probability density functions. The *thin vertical lines* mark the 10th, 25th, 50th (median), 75th, and 90th percentiles of each distribution. *B*: the corresponding distributions of the 7,125 B15 (*left*) and 24,163 B16 (*right*) successive intraburst interval differences, normalized by the means of all of the B15 and B16 intervals. As well as the percentiles, the standard deviation, σ , of each distribution is shown. The first and last bars contain pooled smaller and larger values, respectively, indicated

by the *small left- and right-pointing arrows*. *C*: first return maps of the B15 (*left*) and B16 (*right*) intraburst intervals.

Fig. 4. Real, irregular and regularized spike patterns. *A*: excerpt from the real, irregular spike patterns of B15 and B16 in Fig. 2 (gray) and the corresponding regularized patterns (black). *B*: contractions of a real ARC muscle *in vitro* produced by replaying into its motor neurons the patterns in *A* [from16].

Fig. 5. Trajectories of key variables of the B15/B16-ARC model in Fig. 1 driven with the real, irregular spike patterns of B15 and B16 from Fig. 2 (A) or with the corresponding regularized patterns (B).

Fig. 6.

A: pattern-dependence Φ of mean amplitude of the key modeled variables (labels in the network directly below each bar), computed as described in the text. B: steady-state input-output transformations for the four steps indicated in the network in A, sketched schematically.