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James T. Buchanan

Marquette University, james.buchanan@marquette.edu

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Spinal Cord of Lamprey: Generation of Locomotor Patterns

James T. Buchanan

Introduction

The successes in revealing the structure and function of rhythm-generating networks in invertebrates led to the insight that although there are recurring "building blocks" in the evolution of neuronal networks, there is also a great deal of variation in the details of network construction between different classes of organisms (Getting, 1989). Thus, to understand vertebrate neuronal networks, one must study vertebrate nervous systems, and this realization has led to a proliferation of vertebrate models for investigating the cellular and synaptic mechanisms of locomotor rhythm generation (Pearson and Gordon, 2000) (see LOCOMOTION, VERTEBRATE). One of the most favorable adult vertebrate preparations is the lamprey, a jawless fish with close ties to the earliest vertebrates of the fossil record. Significant progress has been made toward revealing features of the lamprey locomotor network, and this preparation has been the focus of numerous modeling studies.

The Lamprey Spinal Cord

The adult lamprey spinal cord has numerous advantages for neurophysiological studies aimed at understanding the cellular and synaptic mechanisms of rhythmic locomotor activity. In overall structure and organization, the lamprey spinal cord resembles the spinal cords of higher vertebrates. For example, the spinal cord consists of a core of nerve cell bodies surrounded by axon tracts, and there are dorsal and ventral roots of sensory and motor functions, respectively. However, when compared with other adult vertebrates, the lamprey spinal cord contains relatively few nerve cells (ca. 1,000 per segment), and the cell bodies of many of these neurons are clearly visible in the thin (ca. 0.3 mm), transparent spinal cord. In addition, the lamprey spinal cord survives and functions well when isolated and can be readily manipulated by adding pharmacological agents to the bathing fluid. This is particularly important in the study of locomotor activity because one can activate the spinal swimming network by adding the excitatory neurotransmitter, glutamate, to the bathing fluid. One disadvantage to using the lamprey nervous system is the lack of uniquely identifiable cells in the spinal cord, a feature that made invertebrate preparations, such as the crustacean stomatogastric ganglion, so successful in the study of network structure and function (see CRUSTACEAN STOMATOAGASTRIC SYSTEM). In the lamprey spinal cord we must characterize classes of nerve cells rather than unique individuals, and thus we face the uncertainties associated with defining cell classes.

Fictive Swimming

Like most fish, lampreys swim with lateral body undulations that propagate from head to tail (Figure 1A). These body waves are created by contractions of muscles that alternate between the two sides and propagate down the body. The speed of wave propagation is scaled to the swim frequency so that as the animal swims faster, the propagation speed of the waves increases. In this way, the lamprey maintains about one full wave of body curvature over the length of its body for a wide range of swimming speeds. When the spinal cord is isolated and exposed to glutamate, similar rhythmic activity can be recorded from the ventral roots, the nerves that contain the axons of the motor neurons innervating the body muscles (Figure 1B). As the motor neurons fire action potentials, their

spikes are recorded as rhythmic bursts (ca. 0.5–4 bursts/s) that alternate with ventral roots on the opposite side of the spinal cord (Figure 1B). Ventral roots located more distant from the head show a progressive delay in burst onset. Again, this delay is scaled to the swim frequency, so that there is a constant phase lag in the head-to-tail propagation of the ventral root bursts. This phase lag is about 1% of a cycle period per segment (ca. 100 spinal segments total). Thus, there is a close match between the pattern of muscle electrical activity in the swimming lamprey and the pattern of ventral root bursting in the isolated spinal cord, indicating that the latter represents the neuronal correlate of swimming and is therefore referred to as fictive swimming.

The Lamprey Locomotor Network

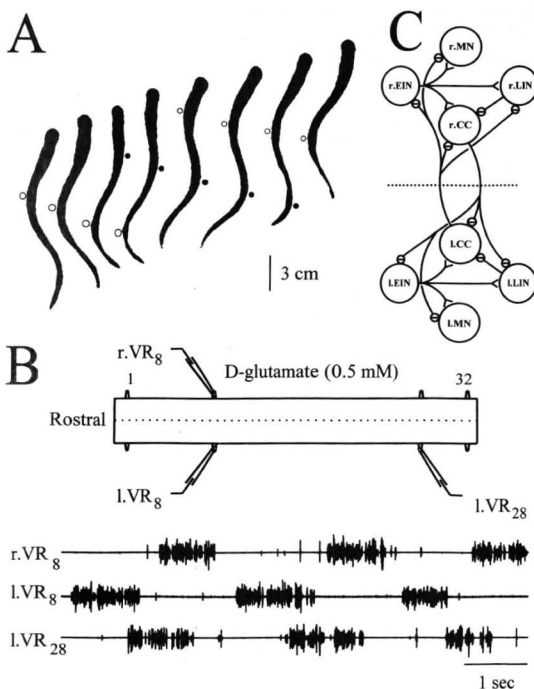
The presence of swimming activity in the isolated spinal cord demonstrates that, like other vertebrate and invertebrate preparations, the lamprey spinal cord contains a central pattern generator for locomotion. That is, the neuronal machinery required to produce the detailed locomotor pattern is an emergent property of spinal nerve cells and their synaptic interactions.

One goal of locomotor studies is to understand the structure and function of the locomotor central pattern generator. What do we know about the cells comprising this network and their synaptic interactions? Although uniquely identifiable neurons have not been found in the lamprey spinal cord, several classes of spinal neurons have been characterized on the basis of physiological and anatomical criteria (Figure 1C) (Buchanan, 2001). The alternating pattern of rhythmic activity between the two sides of the spinal cord and the disruption of rhythmic activity by midline cuts suggest that cells with midline-crossing axons (commissural interneurons) are important for locomotor activity (Buchanan, 1999). Therefore, commissural interneurons (CCINs) have been a focus of intracellular studies. One class of CCINs has been shown to make inhibitory glycinergic synapses on motor neurons and interneurons on the opposite side of the spinal cord. These inhibitory CCINs are thought to provide a mechanism for alternation between the two sides and for basic rhythm generation via their reciprocal inhibitory interactions (see HALF-CENTER OSCILLATORS UNDERLYING RHYTHMIC MOVEMENTS). In addition to the inhibitory CCINs, there is a class of small excitatory interneurons (EINs) with short axons confined to the same side of the spinal cord. The EINs provide rhythmic excitation of nearby motor neurons and interneurons via glutamatergic excitatory synapses. Finally, there is a third class of interneurons that are active during fictive swimming, the lateral interneurons (LINs). The LINs inhibit CCINs on the same side of the spinal cord via glycinergic synapses. The LINs have been proposed to provide the early inhibition that is observed in the CCINs and thus to terminate the firing of the CCINs on one side of the cord, allowing the inhibitory CCINs on the opposite side to begin firing.

Modeling Lamprey Locomotion

The lamprey locomotor network has been simulated with a variety of models, from connectionist-style to more detailed biophysical models. These simulations have demonstrated the feasibility of the proposed circuit (Figure 1C), have helped to assess the importance of various electrophysiological parameters in the function of the

Figure 1. Lamprey swimming and the locomotor network. **A**, Images of a swimming lamprey showing the lateral undulations of the body that propagate from head to tail. Images are separated by 67 msec. **B**, Fictive swimming in a 32-segment length of isolated spinal cord exposed to 0.5 mM of D-glutamate. Ventral roots (VR) were recorded with extracellular electrodes. **C**, The proposed lamprey locomotor network consists of three types of interneurons. Each cell represents many neurons. Open triangles indicate excitatory synapses, circles indicate inhibitory synapses, and the dashed line indicates the midline. MN, motor neuron; CC, commissural interneuron; EIN, excitatory interneuron; LIN, lateral interneuron.



network, and have provided insights into various network issues.

Detailed biophysical models typically use Hodgkin-Huxley (HH)-style kinetic modeling of ion channels that are incorporated into compartmental models of neuronal electrotonic structure. Such models of the lamprey locomotor network suffer from the problem of an overabundance of unspecified and unconstrained parameters because we do not have good voltage-clamp characterizations of the HH parameters for lamprey neurons. An alternative to detailed voltage-clamp analysis has been to use white noise analysis (Murphy, Moore, and Buchanan, 1995). The magnitude and phase responses of lamprey neurons to small-amplitude, subthreshold white noise current or voltage signals have been used to fit model neurons containing voltage-dependent conductances and electrotonic structure. This approach provides a stronger data-based modeling of the nonlinear voltage dependencies and the contributions of dendritic electrotonic structure, but a systematic characterization of the various lamprey spinal neuron classes using this technique has not yet been done.

Although detailed HH-style modeling currently has limitations when applied to lamprey neurons, these or similar detailed bio-

physical models are essential for a full understanding of any neuronal network. For example, neuromodulators often act by subtly altering the activity of voltage-gated or ligand-gated channels, and detailed biophysical models are required to explore the consequences of these ion channel changes on network activity (see NEUROMODULATION IN INVERTEBRATE NERVOUS SYSTEMS). There are a number of neuromodulators present in the lamprey spinal cord that alter the output of the locomotor network, with serotonin, dopamine, and the tachykinins being among the best studied. These substances offer good opportunities to test our knowledge of the locomotor system by combining the cellular and synaptic actions of the modulators into detailed network models.

Interesting new work involving neuromodulators in the lamprey has come from Parker and Grillner (2000). They have been investigating the effects of substance P, a tachykinin neuropeptide. The tachykinins have been well studied in the mammalian spinal cord, where they are involved in pain processing. In the lamprey, application of substance P to the isolated spinal cord has an extremely powerful effect on fictive swimming, increasing the swim burst frequency by three to five times. What is most remarkable is that

after only a 10-minute exposure to substance P, the increase in the active swimming frequency persists for at least the next 24 hours. This essentially permanent alteration in the locomotor network requires protein and RNA synthesis for its maintenance. Tachykinins are present in the lamprey spinal cord in ventral midline cells located below the central canal, where they coexist in neurons with serotonin and dopamine. At the synaptic level, substance P and serotonin both have strong effects on activity-dependent plasticity at the synapses involved in generating the locomotor rhythm. This type of modulation of activity-dependent synaptic plasticity is referred to as metaplasticity. Not only are serotonin, dopamine, and substance P colocalized in spinal neurons, but their actions on the locomotor network are interdependent. Serotonin can block the effects of substance P on swim frequency and on synaptic metaplasticity. Detailed biophysical models of the lamprey network have demonstrated that metaplasticity can have significant effects on network behavior that are consistent with those observed experimentally (Kozlov et al., 2001). A major challenge for lamprey neurobiology will be to determine when these various neuromodulators are released. Are they coreleased or differentially released in a context-dependent manner?

Given the lack of detailed biophysical information about lamprey locomotor neurons, models that do not depend on details of individual cells have proved useful in advancing our understanding of lamprey locomotion. For example, simplified rhythm generators have been employed to look at larger-scale issues, such as the control of turning (McClellan and Hagevici, 1997). Techniques of bifurcation analysis have been used to examine the dynamic behavior of the network (Figure 1C), especially with regard to its interactions with the brain (Jung, Kiemel, and Cohen, 1996). Efforts have also been made using simpler locomotor networks to expand the levels of modeling to take into account the properties of the muscles, movement through water, and sensory feedback during movement (Ekeberg and Grillner, 1999).

Another application of models with less neuronal detail has been in investigations aimed at understanding the nature of the coupling among the rhythm generators. This is an interesting problem because the speed of the head-to-tail propagation of the rhythmic activity down the spinal cord varies with the speed of swimming, yet conduction delays in axons are fixed. Experimental tests of a model of coupled oscillators (Cohen et al., 1992) (see CHAINS OF OSCILLATORS IN MOTOR AND SENSORY SYSTEMS) led to the conclusion that ascending intersegmental coupling signals have a stronger influence over oscillator coupling in the lamprey spinal cord than do descending signals (Sigvardt and Williams, 1996). Williams (1992) explored coupling using connectionist-style modeling to link chains of unit locomotor networks using the same neurons that generate the rhythmic activity. By adjusting the synaptic strengths of the coupling signals, it was possible to achieve constant phase lags with values similar to that of fictive swimming. While these studies demonstrated the feasibility of this mechanism, we do not yet know sufficient details of the intersegmental connectivity to verify the mechanism experimentally.

Discussion

An underlying motivation for studying the lamprey locomotor network is to learn about vertebrate locomotor networks in general. Does the lamprey tell us anything about higher vertebrates? There is certainly reason for hope that the lamprey network shares some fundamental properties with the locomotor networks of higher vertebrates because of the striking similarities between the lamprey network and that of the frog tadpole spinal cord (Roberts et al., 1998). These two animals swim with similar patterns, so it may not be unexpected that the networks are similar, yet the organisms are evolutionarily quite distant. We would like to believe that the lam-

prey locomotor network has been conserved to some extent in higher vertebrates as a core rhythm-generating network, and evolution has provided coupling among these core oscillators to generate the more complex sequences of muscle activation required in fins and limbs. In this regard, the salamander offers a promising preparation for studying the interaction of swimming and walking networks because this animal performs both. Connectionist-style modeling has recently been used to explore how a neural circuitry can produce and modulate the two locomotor programs of swimming and walking (Ijspeert, 2001), and several laboratories are beginning to explore these issues experimentally.

Where do we go from here in our attempts to understand the generation and control of vertebrate locomotion? A major limitation to understanding the lamprey locomotor network is the large numbers of nerve cells and the inability to uniquely identify them or even to classify them with confidence. Experimentally, we need to employ techniques that will allow characterization of populations and the synaptic interactions of many cells. Optical imaging of calcium signals or of voltage-sensitive dyes offers some hope in this direction. Further exploration of neuromodulators of the locomotor network will continue to provide opportunities to test our models as we try to account for the network effects of modulators on the basis of their demonstrated cellular and synaptic actions. Modeling of the locomotor network must proceed in parallel with the experimental data; and ultimately, large-scale and detailed biophysical modeling will be necessary. However, given the current limitations in our knowledge about the lamprey locomotor network, modeling that relies less on the details of individual cells will continue to be useful in understanding how locomotion is organized within the lamprey nervous system. Finally, comparisons with other vertebrates will be important for determining what aspects of the locomotor network have been conserved and how the core rhythm-generating network of swimming was modified for walking with limbs.

Road Maps: Motor Pattern Generators; Neuroethology and Evolution

Background: Motor Pattern Generation

Related Reading: Chains of Oscillators in Motor and Sensory Systems; Locomotion, Vertebrate; Sensorimotor Interactions and Central Pattern Generators

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Statistical Mechanics of Generalization

Manfred Opper

Introduction

The theory of learning in artificial neural networks has benefited from various different fields of research. Among these, statistical physics has become an important tool for understanding a neural network's ability to generalize from examples. This article explains some of the basic principles and ideas of this approach.

In the following, we assume a feedforward network of N input nodes, receiving real-valued inputs, summarized by the vector $\mathbf{x} = (x(1), \dots, x(N))$. The configuration of the network is described by its weights and will be abbreviated by a vector of parameters \mathbf{w} . Using \mathbf{w} , the network computes a function $F_{\mathbf{w}}(\mathbf{x})$ of the inputs \mathbf{x} and returns $\sigma = F_{\mathbf{w}}(\mathbf{x})$ as its output.

In the simplest case, a neural network should learn a binary classification task. That is, it should decide whether a given input \mathbf{x} belongs to a certain class of objects and respond with the output: $F_{\mathbf{w}}(\mathbf{x}) = +1$, or, if the input does not belong, it should answer with $\sigma = -1$ (the choice $\sigma = \pm 1$, rather than, for example, 0, 1, is arbitrary and has no consequence for the learning curves). To learn the underlying classification rule, the network is trained on a set of m inputs $\mathbf{x}^m = \{x_1, \dots, x_m\}$ together with the classification labels $\sigma^m = \{\sigma_1, \dots, \sigma_m\}$, which are provided by a trainer or teacher. Using a learning algorithm, the network is adapted to this training set $D_m = (\sigma^m, \mathbf{x}^m)$ by adjusting its parameters \mathbf{w} such that it responds correctly on the m examples.

How well will the trained network be able to classify an input that it has not seen before? In order to give a quantitative answer to this question, a common model assumes that all inputs, those from the training set and the new one, are produced independently at random with the same probability density from the network's environment. Fixing the training set for a moment, the probability that the network will make a mistake on the new input defines the generalization error $\epsilon(D_m)$. Its average, ϵ , over many realizations of the training set, as a function of the number of examples gives the so-called learning curve. This will be the main quantity of interest in the following.

Clearly, ϵ also depends on the specific algorithm that was used during the training. Thus, the calculation of ϵ requires knowledge of the network weights generated by the learning process. In general, these weights will be complicated functions of the examples, and an explicit form will not be available in most cases.

The methods of statistical mechanics provide an approach to this problem, which often enables an exact calculation of learning curves in the limit of a very large network, i.e., for $N \rightarrow \infty$. It may seem surprising that a problem will simplify when the number of its parameters is increased. However, this phenomenon is well known for physical systems like gases or liquids which consist of a huge number of molecules. Clearly, there is no chance of esti-

imating the complete microscopic state of the system, which is described by the rapidly fluctuating positions and velocities of all particles. On the other hand, the description of the macroscopic state of a gas requires only a few parameters, like density, temperature, and pressure. Such quantities can be calculated by suitably averaging over a whole ensemble of microscopic states that are compatible with macroscopic constraints.

Applying similar ideas to neural network learning, the problems that arise from specifying the details of a concrete learning algorithm can be avoided. In the statistical mechanics approach, one studies the ensemble of all networks that implement the same set of input/output examples to a given accuracy. In this way the typical generalization behavior of a neural network (in contrast to the worst or optimal behavior) can be described.

The Perceptron

In this section I will explain this approach for one of the simplest types of networks, the single-layer perceptron (see PERCEPTRONS, ADALINES, AND BACKPROPAGATION). A study of this network is not of purely academic interest, because the single-layer architecture is a substructure of multilayer networks, and many of the steps in the subsequent calculations also appear in the analysis of more complex networks. Furthermore, by replacing the input vector \mathbf{x} with a suitable vector of nonlinear features, the perceptron (equipped with a specific learning algorithm) becomes a support vector machine, an extremely powerful learning device introduced by V. Vapnik and his collaborators (see SUPPORT VECTOR MACHINES).

The adjustable parameters of the perceptron are the N weights $\mathbf{w} = (w(1), \dots, w(N))$. The output is a weighted sum

$$\sigma = F_{\mathbf{w}}(\mathbf{x}) = \text{sign} \left(\sum_{i=1}^N w(i)x(i) \right) = \text{sign}(\mathbf{w} \cdot \mathbf{x}) \quad (1)$$

of the input values. Since the length of \mathbf{w} can be normalized without changing the performance, we choose $\|\mathbf{w}\|^2 = N$.

The input/output relation in Equation 1 has a simple geometric interpretation. Consider the hyperplane $\mathbf{w} \cdot \mathbf{x} = 0$ in the N -dimensional space of inputs. All inputs that are on the same side as \mathbf{w} are mapped onto +1, those on the other side onto -1. Perceptrons realize linearly separable classification problems. In the following, we assume that the classification labels σ_i are generated by some other perceptron with weights \mathbf{w}_i , the "teacher" perceptron. (A simple case of a student/teacher mismatch is discussed later.)

The geometric picture immediately gives us an expression for the generalization error. A misclassification of a new input \mathbf{x} by a "student" perceptron \mathbf{w}_s occurs only if \mathbf{x} is between the separating