Theory in motion

Eve Marder and LF Abbott

Brandeis University, Waltham, USA

Modeling studies are now a significant part of mainstream research in motor control. Novel and classical modeling techniques used in recent work on small and large motor systems illustrate the different roles that models play in furthering our understanding of motor systems. The models presented reveal single neuron short-term memory, unexpected effects of reciprocal inhibition and methods for decoding activity in large populations of neurons.

Current Opinion in Neurobiology 1995, **5**:832–840

Introduction

Theoretical methods, including mathematical analyses and computer simulations, have been used to illuminate numerous problems in motor control [1–3,4•]. The use of theory so pervades modern work in this field that it is impossible to do justice to its scope in a brief review. Theoretical work is best discussed in the context of the neurobiological problem it is meant to illuminate. Indeed, it is now common to see computational models of all kinds embedded within papers describing fundamental experimental findings. We cannot possibly review all areas of motor control in which significant theoretical work is being done. Rather, we will use a small number of examples (often chosen from our own work for the usual obvious reasons) to illustrate the different roles that modeling can play in enhancing and consolidating our understanding of experimental data, and in suggesting new ideas and directions.

There are at least three quite different functions that models serve in studies of the nervous system, each with a different relationship to experimental data and prediction. Confirmatory models can determine whether existing experimental data are sufficient to account for the observed behavior of a system. These models are built to match data closely and are useful for pinpointing shortcomings or discovering missing components. Common confirmatory models include conductance-based models of single neurons constructed from biophysical data characterizing membrane currents (see [5••,6•,7••,8••,9,10,11••,12••] for recent examples). These are often used to see whether a set of measured conductances is complete or accurate enough to account for the behavior of a given neuron.

Speculative models tend to be more loosely based on experimental data and attempt to address fundamentally puzzling and unanswered questions in neuroscience. Such models can be applied in two opposite ways. First, they can be used to suggest the neural mechanisms underlying a particular behavior. We will discuss a particular example closely related to a problem that arises during the construction of confirmatory conductance-based models [13–15]. Alternatively, speculative models can take a known mechanism, such as an identified property of a channel, receptor, or cell, and explore its logical and behavioral consequences. To illustrate this we will present a number of different examples [16,17••,18••,19•,20–27,28••,29•,30•]. In either case, speculative models (at least good ones) should point to new research directions and experiments.

Finally, modeling can be used essentially as a sophisticated form of data analysis. We call such cases interpretive models. An example of this type of work is the application of decoding methods to neuronal responses [31,32,33••,34–36,37•], as described in the last section of this review. One consequence of a useful interpretive model is that, often, the manner in which data are collected is modified.

Dynamics of single neurons

Neurons that are intrinsically oscillatory or display conditional oscillatory properties that depend on the presence of modulatory substances are commonly found in rhythmic motor systems (see [38]), as well as in many other brain regions. Computational models of oscillatory neurons have a long history. Recent theoretical work [7••,8••,16] on neuron R15 of *Aplysia* and its modulation by neurotransmitters provides a particularly impressive illustration of the remarkable dynamic repertoire of realistic model neurons [39,40•,41,42••]. Canavier *et al.* [16] showed that a semi-realistic, conductance-based model of R15 has a number of stable oscillatory modes (Fig. 1a), and that transient synaptic inputs can switch among these modes. A consequence of this is that a

Abbreviations

$[Ca^{2+}]_i$—concentration of intracellular Ca^{2+}; **I_H**—hyperpolarization-activated inward conductance; **IPSP**—inhibitory postsynaptic potential.

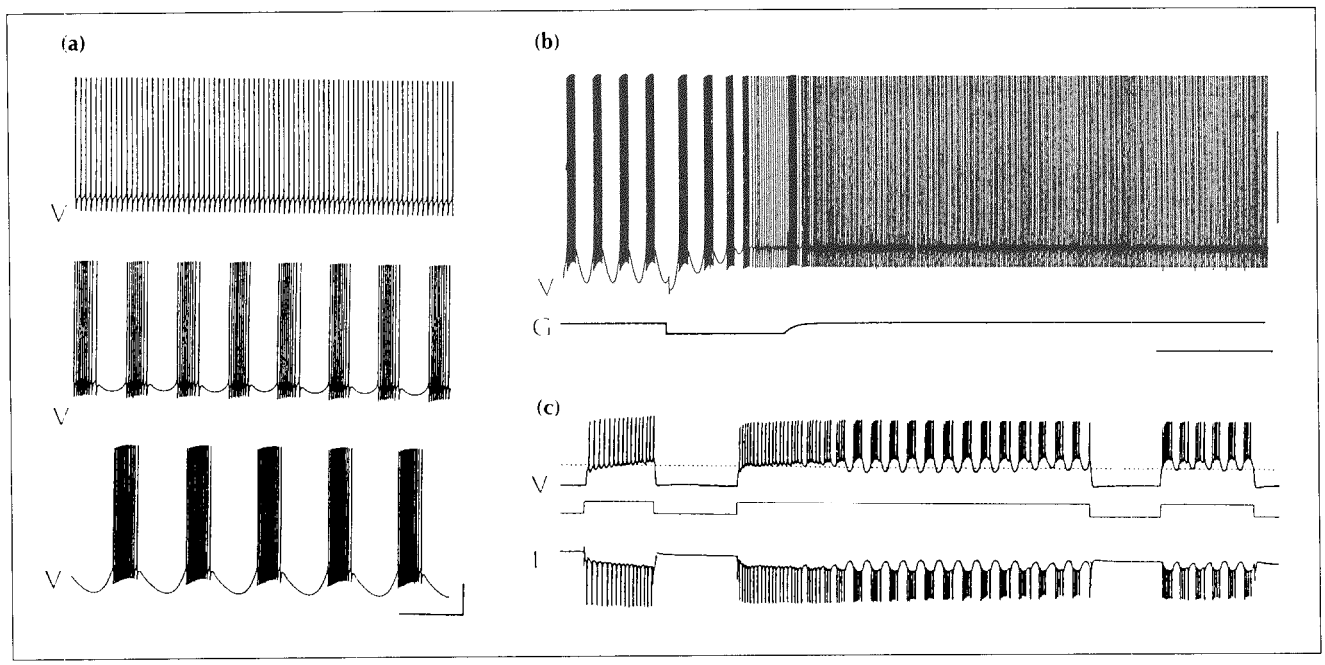

Fig. 1. Intrinsic cellular short-term memory. **(a)** Model of the R15 neuron from *Aplysia* displays multiple modes of activity for a given set of parameters. These include tonic firing (top) and bursting (middle, bottom). Reproduced with permission from [16]. **(b)** The R15 model is switched stably from bursting mode to tonic firing mode by a transient inhibitory input. Modified from [7••]. **(c)** Cultured stomatogastric ganglion neuron into which a Kv1.3 conductance has been added using the dynamic clamp. A short depolarization triggers tonic firing. A longer depolarization triggers a switch from tonic firing to bursting. A subsequent short depolarization elicits bursting. G, modulatory conductance; I, current injected into the cell; V, membrane potential. Modified from [45•].

transient synaptic input can markedly alter the firing pattern of a neuron, long after the synaptic input is terminated (Fig. 1b). The model was also studied with its balance of conductances altered to simulate the effects of modulatory substances such as dopamine and serotonin [7••,8••]. These studies explored alterations in neuronal activity that come from parameter changes, such as those produced by neuromodulators, superimposed on a model that can also display mode changes triggered by transient events. This is an example of a model that was originally confirmatory, becoming speculative and serving a predictive role to direct new experiments.

The R15 model can be switched among several stable modes of operation by transient synaptic input, and it thus effectively 'stores' information. In other words, the R15 model is an example of a 'short-term memory' mechanism that depends solely on the intrinsic properties of a single neuron. We will discuss another example of intrinsic, cellular short-term memory below.

Conductance-based models: problems and solutions

Despite a number of impressive successes, such as the work on R15 described above, conductance-based models are frequently only partially satisfying for two fundamental reasons. First, it is often difficult or even impossible to isolate and characterize adequately all the voltage- and time-dependent conductances that play important roles in the dynamics of a given neuron. Indeed, the most interesting neurons to study — those that take part in complex functions (e.g. [5••,6•,41,42••]) — are likely to have the most complex intrinsic dynamics and are thus the most difficult to characterize completely. Second, conductance-based models are notoriously sensitive to the specific values of their numerous free parameters (e.g. [5••,6•,7••,8••,9,10,11••,12••,41,42••]). Both these problems make it difficult to trust the validity of such a model if one frankly assesses the potential impact of the errors or inadequacies of the biological data from which it is built. These problems become even more severe when single-compartment models are extended to multi-compartment models with spatial structure.

These problems led us to propose two new approaches. To address the difficulty of characterizing all of the conductances in a neuron, we developed the dynamic clamp method [43,44]. In response to the excessive sensitivity of conductance-based models to parameter values, we developed a class of models that 'tune' themselves so that they robustly maintain constant activity levels despite perturbations [13–15].

The dynamic clamp

The dynamic clamp technique is based on the premise that, although it may be impossible to characterize all the conductances contributing to a given neuron's

behavior, it is usually possible to measure some important conductances quite accurately. In such a situation, it is possible to assess the role of the measured conductances by using a hybrid computer–biological 'modeling' technique. The dynamic clamp is essentially a computer-controlled discontinuous current clamp. The membrane potential of a neuron is monitored and then sent to a computer that is programmed with equations describing the voltage dependence and dynamics of a particular current [43,44]. The current that would flow through the membrane at the recorded potential, as described by programmed equations, is computed in real time and injected into the cell. This accurately introduces the current corresponding to the modeled membrane conductance into the neuron [43,44]. The resulting hybrid system gives the experimenter complete control over one or more conductances in a biological neuron without having to resort to pharmacological manipulations. One of the major advantages of dynamic clamp simulations, compared to conventional models, is that the critical parameters for all the poorly characterized currents are properly specified by the neuron itself, so they do not have to be either measured or modeled. When small changes in parameters produce large effects in modeling studies, the investigator is often uncertain whether the sensitivity is biologically relevant. Because dynamic clamp experiments use biological neurons as their modeling platform, this problem is alleviated.

Figure 1c shows the use of the dynamic clamp to study the consequence of adding a Kv1.3 conductance to a cultured stomatogastric ganglion neuron [19•,45•]. Kv1.3 is a slowly and cumulatively inactivating K^+ conductance. Conventional simulations [19•] showed that when Kv1.3 is added to a Hodgkin–Huxley model neuron, it produces a short-term memory effect. To see if a similar phenomenon could occur in a biological neuron, we used the dynamic clamp to add the Kv1.3 current to a cell that did not express this conductance itself [45•]. Cultured stomatogastric ganglion neurons can fire tonically or in bursts, depending on the balance of their conductances [5••]. The cultured stomatogastric ganglion neuron shown in Figure 1c displayed bursting behavior in the absence of Kv1.3 (not shown, but see [45•]). When Kv1.3 was added using the dynamic clamp (Fig. 1c), the neuron fired tonically when it was depolarized for a short period of time. However, when the neuron was depolarized for longer, Kv1.3 inactivated slowly, resulting in the neuron moving into a bursting regime. The neuron then remained bursting as long as the depolarization was maintained. Thus, with an added Kv1.3 conductance, the stomatogastric neuron exhibited the same sort of mode switching as the R15 model discussed previously. Furthermore, the cell displayed another form of short-term memory. If the depolarization was removed, the neuron stopped firing. However, because the recovery from inactivation of Kv1.3 is very slow, subsequent depolarization (Fig. 1c) still elicited bursting activity. Only a prolonged period (many seconds) of hyperpolarization caused a return to the tonic firing mode. Thus, as a consequence of the slow kinetics of Kv1.3, the neuron retains information about its prior history of depolarization.

Self-tuning models

Because conductance-based models are capriciously sensitive to parameter values, we reasoned that mechanisms must exist in biological neurons to ensure robust behavior throughout the lifetime of the cell (which in most organisms is much longer than the lifetime of any of the channel proteins that determine the cell's excitability). We thus constructed speculative models designed to adjust their parameters automatically to maintain robustly a given pattern of activity. In these models [13–15], the maximal conductances of membrane currents are not fixed parameters, as in most neuronal models, but are dynamic variables that depend on the activity of the neuron.

The basic idea of these models is a negative feedback between the electrical activity of the neuron and its balance of conductances [13–15]. In such models, the concentration of intracellular Ca^{2+} ($[Ca^{2+}]_i$) is used as a measure of activity. The maximal conductances of membrane currents are slowly modified in a Ca^{2+}-dependent manner because $[Ca^{2+}]_i$ is known to follow activity and to influence many of the processes that alter channel expression and function. However, it should be stressed that in these first-generation, highly speculative models, $[Ca^{2+}]_i$ as a measure of electrical activity is 'standing in' for a complex network of unspecified biochemical and molecular processes. There are three important results of these models: first, they can self-assemble the conductances needed to produce a target pattern of electrical activity [12••,15]; second, in response to perturbations, they adjust the balance of their conductances to maintain stable activity patterns [12••,15]; and third, a non-uniform distribution of membrane conductances can arise in a spatially extended model neuron [14].

The most important function of a speculative model is to suggest new directions for experimental work. Motivated by these models, Turrigiano *et al.* [5••,46••] carried out experiments with cultured stomatogastric ganglion neurons that initially showed bursting behavior as in Figure 1c. In these experiments, the bursting neurons were driven with strong, rhythmic hyperpolarizations that elicited rebound bursts. After a prolonged period of such stimulation, the neurons lost their ability to burst and only fired tonically in response to depolarization. The ratio of outward conductances to inward conductances is greater in tonically firing than bursting neurons [5••]. The additional activity provided by the external rhythmic drive led to an increase in this ratio, as predicted by the model. The notion that

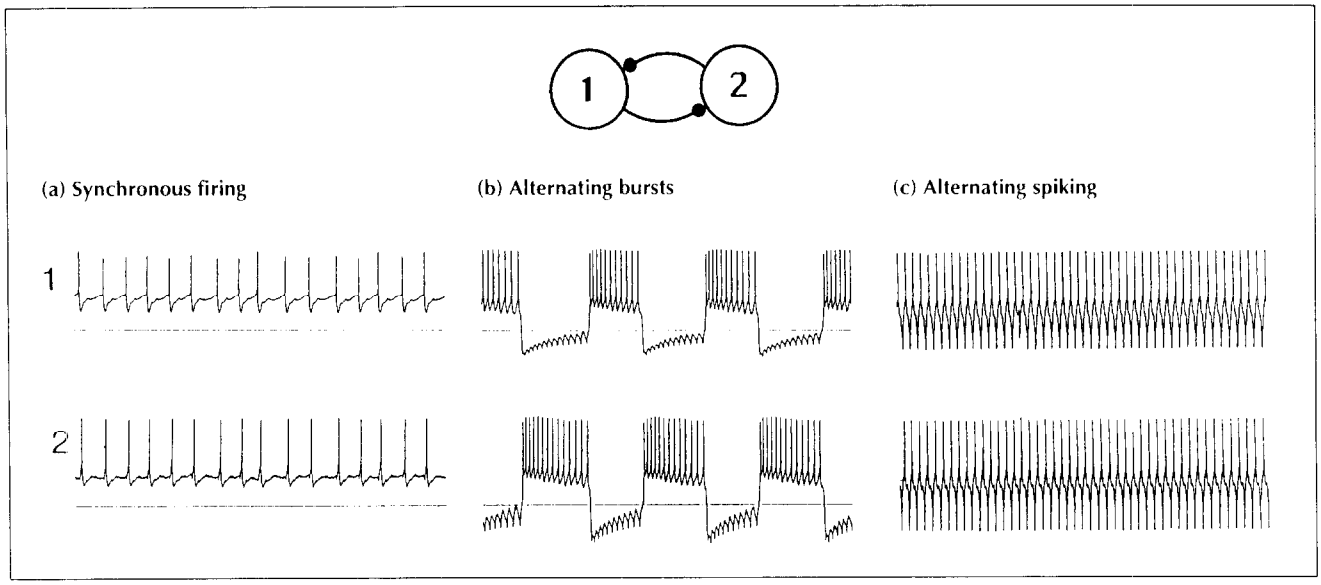

Fig. 2. The dynamic clamp was used to create reciprocal inhibitory synapses between two gastric mill neurons (labelled 1 and 2) of the crab stomatogastric ganglion. (The small black circles in the cartoon at the top of the figure denote chemical inhibitory connections.) (a–c) Simultaneous intracellular recordings from the two neurons. The threshold for transmitter release is indicated by the dotted lines. The parameters controlling the synaptic connections were modified to produce the different patterns. **(a)** Almost synchronous firing. **(b)** A stable half-center oscillator shows alternating bursts of action potentials. **(c)** The circuit displays alternating spiking. Data provided by AA Sharp and FK Skinner.

cells might regulate the balance of their conductances is also supported by recent work by Lindsell and Moody [47••,48•]. They injected Na^+ channel mRNA into *Xenopus laevis* oocytes and found that this influenced the expression of K^+ channels.

Reciprocal inhibition: models and experiments

Reciprocal inhibition is a common circuit element in many portions of the nervous system where it plays a number of roles, such as lateral inhibition in sensory systems. In motor systems, half-center oscillators formed by two reciprocally inhibitory neurons are common circuit components [49•], and they have been the subject of extensive theoretical [50,51,52•,53,54•] and experimental (reviewed in [49•]) study. Theoretical work on reciprocal inhibition has been done at a variety of levels, and it is interesting to compare the kinds of insights obtained with these different approaches.

Many experimentalists assume that reciprocal inhibition will automatically lead to alternation between inhibitory pairs, and indeed alternation is commonly found in motor systems [49•]. However, theoretical studies clearly demonstrate that reciprocal inhibition can also lead to synchrony [17••,18••,51]. For example, when the time course of the inhibition is slow relative to the time course of the spikes that trigger the inhibition, synchrony rather than alternation is the outcome [17••,18••]. We recently used the dynamic clamp to construct reciprocally inhibitory two-cell circuits (AA Sharp, FK Skinner, E Marder, unpublished data). These experiments used two stomatogastric ganglion neurons that were not biologically coupled. The dynamic clamp was used to construct artificial inhibitory synapses between the two cells, thus giving us complete control over the synaptic threshold, time course and conductance. Figure 2 illustrates three of the many different circuit outputs produced when the synaptic parameters defining the inhibitory coupling were varied. It also illustrates the use of the dynamic clamp to construct functional circuits and then to study the circuit dynamics that result when the strength and time course of the synaptic connections are altered.

The most complete description of a biological half-center oscillator comes from work on the leech heartbeat. The properties of both the cells and their reciprocally inhibitory synaptic connections were first measured [55,56•,57,58••] and then modeled [10,11••,12••]. Calabrese and his colleagues [55,56•,57,58••] focus their attention on the mechanisms underlying the transition between the 'on' and the 'off' cells, and the influence of a number of ionic and synaptic conductances on the oscillator period that results from those transitions. In this work, using highly detailed models, it is possible to see directly the roles played by graded and spike-mediated synaptic transmission.

How well do the insights from the simple models of reciprocal inhibition capture the dynamics of real biological systems, and how well do specific systems provide general insights into the operation of neural circuits? First, detailed analyses of a single experimental preparation are unlikely to illuminate all the logical possibilities in a given circuit configuration. For example, the leech heartbeat system is built to produce alternation between the reciprocally inhibitory pairs of neurons. Therefore, if it (or other systems in which alternation is strongly favored) were studied alone, one

might draw the erroneous conclusion that alternation is a necessary consequence of this type of circuit. In this case, a speculative theory could define the universe of possible outcomes of a specific circuit architecture, providing the experimentalist with clues about the variety of possible outcomes under different conditions. However, speculative theoretical work can also be misleading in a specific experimental situation because of its inherent simplification. For example, in simplified models with reciprocal inhibition, it is easy and helpful to define different modes of circuit operation, release and escape [51,52•]. However, this distinction was blurred in the leech biological half-center oscillator because of the presence of a large number of overlapping dynamical processes [10,11••].

Interpreting neuronal activity in large networks

In most animals, motor activity is controlled by the firing of large numbers of neurons. Dealing with the quantity of data that can be recorded from such systems, and understanding how the activity of large neuronal populations correlates with behavior requires sophisticated analytic tools. This is where the third class of 'models', those involving interpretive techniques for analyzing data, can be of great value. The application of decoding methods to the analysis of neuronal firing is a prime example of interpretive theoretical work in neuroscience.

Neuronal decoding can be thought of as a method for compressing such large data sets into a compact form that is more directly related to the behavior being studied. The basic idea is to extract an estimate of the related stimulus or motor activity from the spike trains of one or more recorded neurons. A variety of methods exist for doing this (reviewed in [33••,59••]). Population decoding was developed initially in studies of limb movement in primates [34] and studies of neurons in the superior colliculus encoding saccade direction [35,36]. Decoding methods have also been used to analyze the information contained in spike trains of single neurons [31,32,60]. For single neurons, estimates of the stimulus are generated by integrating the spike train multiplied by an optimal integration kernel. For population decoding a similar technique could be applied, but typically spikes are simply counted over a fixed-size time window to determine a firing rate for each cell. Use of an optimal integration kernel, rather than a simple spike counting procedure, would probably produce better results [33••].

As motor acts involve movements through space, the neural representation of spatial vectors is of particular interest for the study of motor systems. Spatial vectors, such as the direction of an arm movement, are represented mathematically by specifying their projections along orthogonal, Cartesian coordinate axes. Many neuronal circuits appear to use a similar representation [59••,61,62•] because the firing rate of each neuron is proportional to the projection of the coded vector onto an axis or 'preferred direction' particular to that cell. The population vector decoding method [34] is based on the standard formula for reconstructing a vector from its components. However, there is a complication with neural coding of direction that is not present in the usual Cartesian system. The preferred directions defined by the neurons are rarely orthogonal [59••,63,64]. Corrections can be made for this lack of orthogonality and these produce a dramatic improvement in the quality of the decoding [59••]. Figure 3 shows the root-mean-squared average difference between the direction of a monkey's arm movement and the direction decoded from recordings of neurons in primary motor cortex. This illustrates the dramatic difference between a simple vector summation and a more optimal decoding strategy [59••].

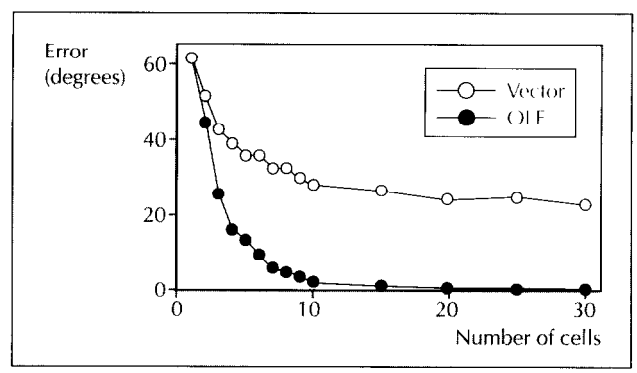

Fig. 3. The accuracy of two neuronal decoding schemes as a function of the number of cells used in the decoding. Each of the data points shows the root-mean-squared average difference between the angular direction decoded from the recorded neurons and the actual direction of movement during a reaching task. Data were provided by G Pellizzer and A Georgopoulos from recordings of 189 directionally selective neurons in the motor cortex of monkeys. Animals were trained to reach for the eight corners of a cube. Open circles (Vector) represent results derived from a method equivalent to the Cartesian representation of a vector [34]. Black circles (OLE, optimal linear estimator) depict results obtained from a method that corrects for correlations between the firing rates of the neurons caused, for example, by the fact that their preferred movement directions are not orthogonal [59••]. Modified from [59••].

In the past few years, a number of efficient and accurate decoding methods have been developed and studied [59••,63–70,71•]. A good general method for population decoding is to find the movement direction that provides the best match to the evoked activity on the basis of average-response tuning curves measured for the system. This is essentially the 'maximum likelihood' method applied to neuronal decoding. In addition to their application to experimental data, decoding methods have played an important role in a number of speculative modeling studies investigating how motor actions are generated and controlled [20–27,28••,29•,30•].

In light of the success of the population vector in predicting movement direction, it was tempting to assume that activity in motor cortex represents the

Cartesian coordinates of movement direction. However recent theoretical and experimental work supports a broader and, in many ways, more interesting point of view. The ability to decode movement parameters such as direction from the activity of a set of neurons with a population vector relies primarily on the fact that all directions are equally represented in motor cortex [72,73••,74••]. In particular, it does not depend on the precise shape of the neuronal tuning curves and it cannot uniquely characterize what coordinate system is being used [73••]. Furthermore, responses in motor cortex depend on a number of factors in addition to the direction of movement [75–79,80••]. Specifically, effects of initial hand position [78], external loads [79] and posture [80••] have been studied. These dependencies complicate both the application and the interpretation of population vector decoding.

The fact that motor cortex encodes a number of movement-related parameters complicates, but does not preclude, the possibility of decoding movement direction from population activity. Rather, it supports the idea that a neural population can simultaneously represent a number of parameters related to movement kinematics and dynamics in a coordinate-independent manner. Downstream networks (or experimentalists decoding their recordings) can read out virtually any combination of these quantities [74••]. Thus, the fact that the direction of an arm movement can be decoded from motor cortex firing does not preclude the possibility that other relevant parameters — such as joint angles, muscle tension, non-Cartesian coordinates or movement coordinates in a variety of body-part centered systems — can also be represented by the same neuronal population. Instead, it is likely that a wide variety of signals are simultaneously read out by downstream networks, each of which extracts the information most relevant to its particular function.

Conclusions

Theoretical methods of all kinds provide tools with which neuroscientists can explore the logical consequences of a set of assumptions, validate the adequacy of their data, and improve the analysis and understanding of its implications. As with all methods, the extent to which fundamental insight follows the application of theory to a problem in neuroscience depends on the dexterity with which both experimental and theoretical investigators can extract knowledge from an often recalcitrant world.

Acknowledgements

We thank Emilio Salinas for helpful comments. Supported by grants MH46742 from the National Institutes of Mental Health and DMS-9208206 from the National Science Foundation, and the Human Frontier Science Program Organization. We gratefully acknowledge the support of the WM Keck Foundation.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Cohen AH, Rossignol S, Grillner S (Eds): *Neural Control of Rhythmic Movements in Vertebrates.* New York: John Wiley & Sons; 1988.

2. Koch C, Segev I (Eds): *Methods in Neuronal Modeling.* Cambridge, Massachusetts: MIT Press; 1989.

3. Jeannerod M (Ed): *Attention and Performance XIII. Motor Representation and Control.* Hillsdale, New Jersey: Erlbaum; 1990.

4. • Arbib MA (Ed): *The Handbook of Brain Theory and Neural Networks.* Cambridge, Massachusetts: MIT Press; 1995.
This book is a compendium of useful short reviews on a variety of topics related to theoretical treatments of problems in motor control and movement.

5. •• Turrigiano G, LeMasson G, Marder E: **Selective regulation of current densities underlies spontaneous changes in the activity of cultured neurons.** *J Neurosci* 1995, **15**:3640–3652.
In the adult animal, stomatogastric ganglion motor neurons normally fire in bursts that provide rhythmic excitation to the muscles of the stomach. This paper describes the sequence of changes that individual isolated stomatogastric ganglion neurons follow after being plated in dissociated cell culture. Interestingly, after 3 days in culture, neurons become predominantly bursting, even though most of these same neurons are not intrinsic bursters in the ganglion. To determine the currents underlying these changes, the authors voltage clamped the neurons at different times, and then used a computational model to verify that the sequence of changes could be plausibly accounted for on the basis of the measured changes in current density.

6. • Harris-Warrick RM, Coniglio LM, Barazangi N, Guckenheimer J, Gueron S: **Dopamine modulation of transient potassium current evokes phase shifts in a central pattern generator network.** *J Neurosci* 1995, **15**:342–358.
Dopamine produces changes in the phase relationships among the neurons of the pyloric network of the crustacean stomatogastric ganglion. In this paper, the role played by the modulation of I_A (transient outward current) by dopamine is examined, and its possible implication is explored using a computational model.

7. •• Canavier CC, Baxter DA, Clark JW, Byrne JH: **Multiple models of activity in a model neuron suggest a novel mechanism for the effects of neuromodulators.** *J Neurophysiol* 1994, **72**:872–882.
In a previous paper [16], this group showed that a modeled bursting neuron could be switched among multiple stable oscillatory modes by transient synaptic inputs. Neuromodulators are usually thought to influence a cell's activity by altering one or more of its conductances. In this paper, the authors study the interaction between these two different ways of altering a cell's activity.

8. •• Butera RJ Jr, Clark JW Jr, Canavier CC, Baxter DA, Byrne JH: **Analysis of the effects of modulatory agents on a modeled bursting neuron: dynamic interactions between voltage and calcium dependent systems.** *J Computational Neurosci* 1995, **2**:19–44.
This paper describes the properties of a detailed model of the *Aplysia* neuron R15. The ionic currents are modeled, and the authors have included expressions for intracellular cAMP and buffers. The authors systematically compare the behavior of the model with serotonin and dopamine modulation to that of the biological neuron using a number of stimulus paradigms to perturb both the neuron and the model. One of the interesting messages of this paper is that the effects of a modulatory substance on the current clamp behavior of a neuron are of two kinds: the direct effects that arise from changes in the modulated conductance, and secondary effects that arise because alterations in any one conductance

in a dynamically interacting system are likely to alter other conductances due to changes in the dynamics of voltage or Ca^{2+}.

9. Golowasch J, Buchholtz F, Epstein IR, Marder E: **Contribution of individual ionic currents to activity of a model stomatogastric ganglion neuron.** *J Neurophysiol* 1992, **67**:341–349.

10. De Schutter E, Angstadt JD, Calabrese RL: **A model of graded synaptic transmission for use in dynamic network simulations.** *J Neurophysiol* 1993, **69**:1225–1235.

11. •• Nadim F, Olsen OH, De Schutter E, Calabrese RL: **Modeling the leech heartbeat elemental oscillator I. Interactions of intrinsic and synaptic currents.** *J Computational Neurosci* 1995, **2**:215–235.
The authors describe the development of a biophysical model of the pair of reciprocally inhibitory interneurons that make up the core of the heartbeat oscillator of the leech. The synaptic and intrinsic conductances are based on previously collected voltage-clamp data, and the model's overall activity mimics well the current-clamp recordings from these cells. Oscillations in the model depend on interactions among synaptic and intrinsic conductances. This paper is one of the finest examples of systematic biophysical work being used to develop a semi-realistic simulation of neuronal activity. Together with its companion paper [12••], this is the most complete and best characterized model of a biological half-center oscillator.

12. •• Olsen ØH, Nadim F, Calabrese RL: **Modeling the leech heartbeat elemental oscillator II. Exploring the parameter space.** *J Computational Neurosci* 1995, **2**:237–257.
This paper explores the effect of varying several parameters on the period of the half-center oscillation in the model described in the previous paper [11••]. The model circuit generates oscillations in two essentially different modes: the S-mode operates largely in the regime of spike-mediated transmitter release and the G-mode operates by predominantly graded release of transmitter. The authors compare each current's relative contribution to the period in these different modes of operation, and show that graded transmission and spike-mediated transmission have opposite effects on period. Although models of half-centers have been previously developed, the detail and richness of this model and its analysis mean that one can appreciate how the variety of membrane and synaptic currents interact in the dynamics of this two-cell circuit.

13. LeMasson G, Marder E, Abbott LF: **Activity-dependent regulation of conductances in model neurons.** *Science* 1993, **259**:1915–1917.

14. Siegel M, Marder E, Abbott LF: **Activity-dependent current distributions in model neurons.** *Proc Natl Acad Sci USA* 1994, **91**:11308–11312.

15. Abbott LF, LeMasson G: **Analysis of neuron models with dynamically regulated conductances.** *Neural Computation* 1993, **5**:823–842.

16. Canavier CC, Baxter DA, Clark JW, Byrne JH: **Nonlinear dynamics in a model neuron provide a novel mechanism for transient synaptic inputs to produce long-term alterations of postsynaptic activity.** *J Neurophysiol* 1993, **69**:2252–2257.

17. •• Van Vreeswijk C, Abbott LF, Ermentrout GB: **When inhibition not excitation synchronizes neural firing.** *J Computational Neurosci* 1994, **1**:313–321.
This paper shows clearly that excitatory and inhibitory synaptic coupling can have counterintuitive effects on the synchronization of neuronal firing. The authors use several simple neural models and prove that when the synaptic rise time is slower than the duration of the action potential, mutual inhibition leads to synchronization. This paper demonstrates the utility of investigating theoretically some commonly held assumptions about neural dynamics.

18. •• Hansel D, Mato G, Meunier C: **Synchrony in excitatory neural networks.** *Neural Computation* 1995, **7**:307–337.
A study of oscillatory neural networks with all-to-all excitatory coupling. Two cases are distinguished. In type I neurons, characterized by phase advances to small depolarizations throughout the cycle, excitation is desynchronizing. This behavior is seen for integrate-and-fire models and for models with an A-type current. Type II neurons (e.g. the Hodgkin–Huxley model) have both positive and negative phase shifts and can be synchronized by fast synapses. This paper illustrates the subtlety of synchronization, even in a fully connected network of identical units.

19. • Marom S, Abbott LF: **Modeling state-dependent inactivation of membrane currents.** *Biophys J* 1994, **67**:515–520.
This paper extends the standard formalism for modeling macroscopic currents to account for state-dependent inactivation. It includes a simulation that demonstrates that the addition of a slowly and cumulatively inactivating K^+ current (called KV3 in this paper, now known as Kv1.3) can produce a novel short-term memory effect.

20. Lukashin AV: **A learned neural network that simulates properties of the neural population vector.** *Biol Cybern* 1990, **63**:377–382.

21. Gaudiano P, Grossberg S: **Vector associative maps: unsupervised real-time error based learning and control of movement trajectories.** *Neural Networks* 1991, **4**:147–183.

22. Mussa-Ivaldi FA, Giszter SF: **Vector-field approximation: a computational paradigm for motor control and learning.** *Biol Cybern* 1992, **67**:491–500.

23. Burnod Y, Grandguillaume P, Otto I, Ferraina S, Johnson PB, Camaniti R: **Visuomotor transformation underlying arm movements toward visual targets: a neural network model of cerebral cortical operations.** *J Neurosci* 1992, **12**:1435–1452.

24. Houk JC, Keifer J, Barto AG: **Distributed motor commands in the limb premotor network.** *Trends Neurosci* 1993, **16**:27–33.

25. Lukashin AV, Georgopoulos AP: **A dynamical neural network model for motor cortical activity during movement: population coding of movement trajectories.** *Biol Cybern* 1993, **69**:517–524.

26. Berthier NE, Singh SP, Barto A, Houk JC: **Distributed representation of limb motor programs in arrays of adjustable pattern generators.** *J Cogn Neurosci* 1993, **5**:56–78.

27. Kettner R, Marcario J, Port N: **A neural network model of cortical activity during reaching.** *J Cogn Neurosci* 1993, **5**:14–33.

28. •• Lukashin AV, Wilcox GL, Georgopoulos AP: **Overlapping neural networks for multiple motor engrams.** *Proc Natl Acad Sci USA* 1994, **91**:8651–8654.
A neural network model is used to study how multiple motor sequences can be stored in, and recalled from, the same network. The network was trained to produce motor trajectories using a simulated annealing algorithm. Network output was interpreted using the population vector decoding scheme. Interestingly, the major part of the resulting network was shared by all motor patterns. A relatively small number of units were specific to a particular motor output.

29. • Lukashin AV, Georgopoulos AP: **Directional operations in the motor cortex modeled by a neural network of spiking neurons.** *Biol Cybern* 1994, **71**:79–85.
The directionality and dynamic rotation of the population vector are reproduced in a model with spiking neurons. This is an extension of the model in [20,25] to a more realistic network model.

30. • Abbott LF, Blum KI: **Functional significance of long-term potentiation for sequence learning and prediction.** *Cereb Cortex* 1995, in press.
Motor sequences are generated by an array of model neurons that encode a limb position that leads the actual position of the arm. It is argued that temporal characteristics of the induction of long-term potentiation automatically cause such a representation to arise from repeated limb movements during a learning period. Once this 'leading' representation is formed, limb movement is executed by a loop with proprioceptive input from the arm-generating activity in the coding network that represents the next position in the learned motor sequence. In this scheme, the recall of information about the learned sequence is driven by the motor response, and the retrieval rate automatically matches the rate at which the task is being performed.

31. Bialek W: **Theoretical physics meets experimental neurobiology.** In *Lectures in Complex Systems, SFI Studies in the Science of Complexity*, vol 2. Edited by Jen E. Redwood City, California: Addison-Wesley; 1989:413–595.

32. Bialek W, Rieke F, De Ruyter Van Steveninck RR, Warland D: **Reading a neural code.** *Science* 1991, **252**:1854–1857.

33. •• Abbott LF: **Decoding neuronal firing and modeling neural networks.** *Q Rev Biophys* 1994, **27**:291–331.

This is a general review of decoding methods and their application in and relation to modeling techniques for neural networks.

34. Georgopoulos AP, Schwartz A, Kettner RE: **Neuronal population coding of movement direction.** *Science* 1986, **233**:1416–1419.

35. Lee C, Rohrer WH, Sparks DL: **Population coding of saccadic eye movements by neurons in the superior colliculus.** *Nature* 1988, **332**:357–360.

36. Van Gisbergen JAM, Van Opstal AJ, Tax AMM: **Collicular ensemble coding of saccades based on vector summation.** *Neuroscience* 1987, **21**:541–555.

37. • Schwartz AB: **Direct cortical representations of drawing.** *Science* 1994, **265**:540–542.
A recent application of the population vector technique to study hand movements during a drawing task. The population vector correlates accurately with the actual drawing movement and predicts hand movement by preceding it in time during high curvature portions of the trajectory.

38. Harris-Warrick RM, Marder E: **Modulation of neural networks for behavior.** *Annu Rev Neurosci* 1991, **14**:39–57.

39. Bertram R: **A computational study of the effects of serotonin on a molluscan burster neurons.** *Biol Cybern* 1993, **69**:257–267.

40. • Bertram R: **Reduced-system analysis of the effects of serotonin on a molluscan burster neuron.** *Biol Cybern* 1994, **70**:359–368.
Geometrical methods are used to analyze the changes produced by serotonin in the sensitivity of a reduced model of R15 to synaptic input at various times during the burst cycle.

41. Guckenheimer J, Gueron S, Harris-Warrick RM: **Mapping the dynamics of a bursting neuron.** *Philos Trans R Soc Lond [Biol]* 1993, **341**:345–359.

42. •• Harris-Warrick RM, Coniglio LM, Levini RM, Gueron S, Guckenheimer J: **Dopamine modulation of two subthreshold currents produces phase shifts in activity of an identified motoneuron.** *J Neurophysiol* 1995, **74**:1404–1420.
This paper dissects the interacting roles of I_A (transient outward current) and I_H in determining the delay to firing after inhibition in the lateral pyloric neuron of the stomatogastric ganglion of the lobster, *Panulirus interruptus*. The authors combine electrophysiological methods with conventional models and dynamic clamp experiments to conclude that dopamine-evoked phase shifts are due to an interaction between changes in synaptic time course and strength, and changes in the intrinsic currents.

43. Sharp AA, O'Neil MB, Abbott LF, Marder E: **Dynamic clamp: computer-generated conductances in real neurons.** *J Neurophysiol* 1993, **69**:992–995.

44. Sharp AA, O'Neil MB, Abbott LF, Marder E: **The dynamic clamp: artificial conductances in biological neurons.** *Trends Neurosci* 1993, **16**:389–394.

45. • Turrigiano GG, Marder E, Abbott LF: **Cellular short term memory from a slow potassium conductance.** *J Neurophysiol* 1995, in press.
The dynamic clamp is used to introduce a rat brain Kv1.3 conductance into cultured stomatogastric ganglion neurons. Kv1.3 is slowly inactivating and recovers very slowly from inactivation (see references cited in this paper). These properties produce a short-term memory effect, in which depolarizations too small to bring the cell to threshold become suprathreshold subsequent to a long depolarization. This process is relatively long lasting (10–20 s). This paper demonstrates clearly that slow conductances can provide memory mechanisms that depend solely on the intrinsic properties of a neuron, independent of changes in synaptic efficacy.

46. •• Turrigiano G, Abbott LF, Marder E: **Activity-dependent changes in the intrinsic properties of cultured neurons.** *Science* 1994, **264**:974–977.
The intrinsic properties of cultured stomatogastric ganglion neurons are modified by long stretches of rhythmic inhibitory pulses that lead to large rebound bursts after termination of the inhibition. Specifically, after approximately 1h of inhibition, which led to rebound depolarization, neurons that were initially bursting fired tonically. This reverses the sequence of changes that these neurons follow in culture [5••]. These data are interpreted to suggest that the additional bursting produced by the rhythmic drive is causing these neurons to modify their conductances.

47. •• Linsdell P, Moody WJ: **Na^+ channel mis-expression accelerates K^+ channel development in embryonic *Xenopus laevis* skeletal muscle.** *J Physiol (Lond)* 1994, **480**:405–410.
In this fascinating paper, the authors injected Na^+ channel mRNA into *Xenopus* oocytes. Muscle cells that subsequently developed showed earlier than normal expression of Na^+ currents, and increased expression of K^+ currents. The increase in the K^+ current was abolished by applying tetrodotoxin, suggesting that the increased activity triggered by the exogenous Na^+ channel expression triggers a compensatory increase in K^+ channel expression.

48. • Lindsell P, Moody WJ: **Electrical activity and calcium influx regulate ion channel development in embryonic *Xenopus* skeletal muscle.** *J Neurosci* 1995, **15**:4507–4514.
The normal developmental profile of the voltage-dependent currents in *Xenopus* muscle is described. The normal developmental increase in both Na^+ and K^+ currents is blocked by tetrodotoxin, again arguing for a role for activity in controlling the balance of inward and outward currents.

49. • Friesen WO: **Reciprocal inhibition: a mechanism underlying oscillatory animal movements.** *Neurosci Biobehav* 1994, **18**:547–553.
This is a helpful review that summarizes some of the biological data on half-center oscillators in central pattern generating networks, as well as the likely mechanisms that may underlie half-center alternations.

50. Perkel DH, Mulloney B: **Motor pattern production in reciprocally inhibitory neurons exhibiting postinhibitory rebound.** *Science* 1974, **185**:181–183.

51. Wang X-J, Rinzel J: **Alternating and synchronous rhythms in reciprocally inhibitory model neurons.** *Neural Computation* 1992, **4**:84–97.

52. • Skinner FK, Kopell N, Marder E: **Mechanisms for oscillation and frequency control in reciprocally inhibitory model neural networks.** *J Computational Neurosci* 1994, **1**:69–87.
A mathematical treatment of half-center oscillation in networks of Morris–Lecar oscillators. Wang and Rinzel's [51] definitions of 'escape' and 'release' mechanisms are further defined, as the authors describe four different mechanisms of oscillation that can occur in relaxation oscillators. These include intrinsic and synaptic escape, and intrinsic and synaptic release mechanisms. The different mechanisms exhibit different dependencies of the oscillation period on the threshold for synaptic transmission.

53. Rowat P, Selverston AI: **Modeling the gastric mill central pattern generator with a relaxation–oscillator network.** *J Neurophysiol* 1993, **70**:1030–1053.

54. • LoFaro T, Kopell N, Marder E, Hooper SL: **Subharmonic coordination in networks of neurons with slow conductances.** *Neural Computation* 1994, **6**:69–84.
In this paper, the authors studied the properties of two reciprocally inhibitory model neurons. One is an endogenous burster, whereas the other is excitable and has a hyperpolarization-activated inward (I_H) conductance. The presence of this conductance allows the neurons to fire in integer subharmonics.

55. Angstat JD, Calabrese RL: **Calcium currents and graded synaptic transmission between heart interneurons of the leech.** *J Neurosci* 1991, **11**:746–759.

56. • Opdyke CA, Calabrese RL: **A persistent sodium current contributes to oscillatory activity in heart interneurons of the medicinal leech.** *J Comp Physiol [A]* 1994, **175**:781–789.
Voltage-clamp experiments were used to define and characterize a persistent Na^+ current that participates in the depolarized plateaus important for oscillation in the leech heartbeat system.

57. Simon TW, Opdyke CA, Calabrese RL: **Modulatory effects of FMRF-$_{NH2}$ on outward currents and oscillatory activity in heart interneurons of the medicinal leech.** *J Neurosci* 1992, **12**:525–537.

58. •• Simon TW, Schmidt J, Calabrese RL: **Modulation of high-threshold transmission between heart interneurons of the medicinal leech by FMRF-$_{NH2}$.** *J Neurophysiol* 1994, **71**:454–466.
In the leech heartbeat system there are two components of synaptic transmission: graded transmission, which operates in the low-voltage range, and spike-mediated transmission, which occurs in the high-

threshold range. In this paper, the authors describe the modulation of the high-threshold component of synaptic transmission by the peptide $FMRF_{NH2}$. They also construct a model of the neuron to look at the interaction between the modulated IPSP and the extent to which I_H is indirectly influenced, because I_H plays a critical role in timing. Interestingly, they find relatively little indirect effect of the changes in the amplitude of the IPSP on the I_H conductance.

59. •• Salinas E, Abbott LF: **Vector reconstruction from firing rates.** *J Computational Neurosci* 1994, **1**:89–107.
A variety of methods for neuronal population decoding are reviewed and compared. An optimal linear estimator is derived that corrects for correlations between the firing of neurons due, for example, to the non-orthogonality of their preferred direction vectors.

60. Warland D, Landolfa MA, Miller JP, Bialek W: **Reading between the spikes in the cercal filiform hair receptors of the cricket.** In *Analysis and Modeling of Neural Systems.* Edited by Eeckman F, Bower J. Norwell, Massachusetts: Kluwer Academic Publishers; 1991:163–168.

61. Touretzky DS, Redish AD, Wan HS: **Neural representation of space using sinusoidal arrays.** *Neural Computation* 1993, **5**:869–884.

62. • Redish AD, Touretzky DS: **The reaching task: evidence for vector arithmetic in the motor system.** *Biol Cybern* 1994, **71**:307–317.
Arrays of neurons with cosine tuning curves have some interesting computational capabilities. This paper proposes how such arrays could be used to perform vector sums involving load, goal direction and motor command direction vectors.

63. Gaal G: **Calculation of movement direction from firing activities of neurons in intrinsic co-ordinate systems defined by their preferred directions.** *J Theor Biol* 1993, **162**:103–130.

64. Gaal G: **Population coding by simultaneous activities of neurons in intrinsic coordinate systems defined by their receptive field weighting functions.** *Neural Networks* 1993, **6**:499–515.

65. Paradiso MA: **A theory for the use of visual orientation information which exploits the columnar structure of striate cortex.** *Biol Cybern* 1988, **58**:35–49.

66. Vogels R: **Population coding of stimulus orientation by cortical cells.** *J Neurosci* 1990, **10**:3543–3558.

67. Foldiak P: **The 'ideal homunculus': statistical inference from neural population responses.** In *Computation and Neural Systems.* Edited by Eeckman FH, Bower J. Norwell, Massachusetts: Kluwer Academic Publishers; 1993:55–60.

68. Zohary E: **Population coding of visual stimuli by cortical neurons tuned to more than one dimension.** *Biol Cybern* 1992, **66**:265–272.

69. Snippe HP, Koenderink JJ: **Discrimination thresholds for channel-coded systems.** *Biol Cybern* 1992, **66**:543–551.

70. Seung HS, Sompolinsky H: **Simple neural network models of psychophysical tasks.** *Proc Natl Acad Sci USA* 1993, **90**:10749–10753.

71. • Tanaka S: **Numerical study of coding of the movement direction by a population in the motor cortex.** *Biol Cybern* 1994, **71**:503–510.
Properties of neurons in motor cortex were simulated and the accuracy of the vector method of decoding was assessed. The accuracy increased in proportion to the square root of the number of cells used in the decoding; with 10 000 neurons, an accuracy of one degree was found. Considerably higher accuracy could have been attained using fewer neurons if a more optimal decoding scheme had been used.

72. Mussa-Ivaldi FA: **Do neurons in the motor cortex encode movement direction? An alternative hypothesis.** *Neurosci Lett* 1988, **8**:2938–2947.

73. •• Sanger T: **Theoretical considerations for the analysis of population coding in motor cortex.** *Neural Computation* 1994, **6**:29–37.
Sanger systematically studies how the results of population vector decoding depend on the basic experimental protocol. He shows that the results depend largely on the uniformity of broadly tuned neuronal responses and suggests that cosine-like tuning curves are likely to result from the methods used to analyze the data. He also argues that questions about the 'true' coordinate system used by the motor cortex may be ill-posed.

74. •• Salinas E, Abbott LF: **Transfer of coded information from sensory to motor networks.** *J Neurosci* 1995, **15**:6461–6474.
The authors examined how a sensory network that encodes target position, along with other relevant signals such as gaze direction, can evoke motor activity accurately aligned to the target position in body-centered coordinates. The accuracy of the response is determined by applying population decoding methods to the output of the model network. Properties of the required synaptic weights are derived analytically, and the authors note that these weights can develop spontaneously during the observation of random movements through correlation-based synaptic modification.

75. Alexander GE, Crutcher MD: **Preparation for movement: neural representations of intended direction in three motor areas of the monkey.** *J Neurophysiol* 1990, **64**:133–150.

76. Alexander GE, Crutcher MD: **Neural representation of the target (goal) of visually guided arm movements in three motor areas of the monkey.** *J Neurophysiol* 1990, **64**:164–178.

77. Crutcher MD, Alexander GE: **Movement-related neuronal activity selectively coding either direction or muscle pattern in three motor areas of the monkey.** *J Neurophysiol* 1990, **64**:151–163.

78. Caminiti R, Johnson PB, Galli C, Ferraina S, Burnod Y: **Making arm movements within different parts of space: the premotor and motor cortical representations of a coordinate system for reaching to visual targets.** *J Neurosci* 1991, **11**:1182–1197.

79. Kalaska JF, Cohen DAD, Hyde M, Prud'Homme MA: **A comparison of movement direction-related versus load direction-related activity of primate motor cortex using a two-dimensional reaching task.** *J Neurosci* 1989, **9**:2080–2102.

80. •• Scott SH, Kalaska JF: **Changes in motor cortex activity during reaching movements with similar hand paths but different arm postures.** *J Neurophysiol* 1995, **73**:2563–2567.
By studying reaching tasks for two different arm postures, the authors can examine the dependence of the population vector on quantities other than movement direction. Although some cells retained the same movement direction tuning in both postures, others either changed their preferred movement direction or lost tuning entirely in one of the postures. The population vector varied between the two postures and provided a poorer description of the movement direction in one posture.

E Marder and LF Abbott, Volen Center, Brandeis University, Waltham, Massachusetts 02254, USA.
E Marder e-mail: marder@volen.brandeis.edu
LF Abbott e-mail: abbott@volen.brandeis.edu