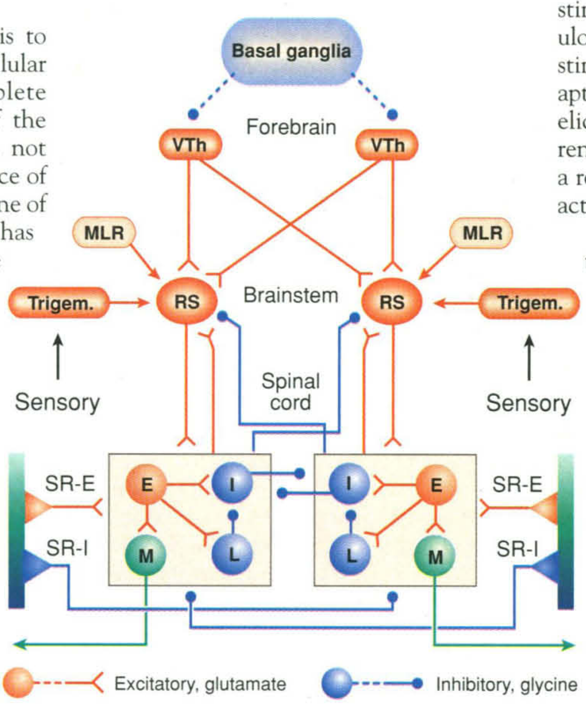
NEUROSCIENCE

Ion Channels and Locomotion

Sten Grillner

A major challenge of neuroscience is to bridge the gap between molecular-cellular events and behavior. Even a complete molecular description of each cell of the central nervous system (CNS) would not describe its function, because the essence of the CNS is its intricate organization. One of the few cases in vertebrates in which it has been possible to bridge this gap is in the contol system underlying locomotion.



Moving about. Sensory stimulation (Trigem.) produces long-lasting responses in reticulospinal (RS) neurons (7), which in turn excite all classes of spinal interneurons [excitatory (E), inhibitory (I), lateral (L), and motor neurons (M)]. The motor pattern is produced by the interaction between E and I interneurons on the same side and crossed I interneurons. Locomotion can also be initiated by the diencephalic (VTH) or mesopontine (MLR) locomotor centers. Sensory stretch receptor neurons (SR-E, SR-I) feed back onto spinal interneurons and help adapt locomotion to external events. Blue neurons are inhibitory and red, excitatory.

Most behaviors of vertebrates require the animal, or parts of it, to move from place to place. In the process, the brain recruits a dedicated neural network that executes this locomotion. This control system is designed similarly in all classes of vertebrates (*1*), as might be expected from an evolutionary perspective. Thus, the same mesopontine and diencephalic centers initiate locomotion in lampreys and primates, through an activation of lower brainstem reticulospinal neurons. These in turn activate the spinal networks of nerve cells (CPG), which generate the motor pattern, be it swimming or walking. Sensory feedback on the CPG is an integral part of the control system and helps adapt the motor pattern to external events. The larger building blocks of the control system have been defined in mammals (*2*), but the cellular and molecular function of the network is now being revealed in simple model systems of vertebrates like frog embryo (*3*) and lamprey (*4*).

An impressive example of the power of these simple vertebrate systems is reported on page 1122 by Viana Di Prisco *et al.* (*5*). These authors used the lamprey CNS to analyze brainstem mechanisms that initiate locomotion. The brainstem and spinal cord of this primitive vertebrate can be isolated together and maintained in vitro for several days. Moreover, the neural activity underlying locomotion can be elicited under these conditions by activation of sensory input or stimulation of the brainstem locomotor centers (*4*). The different components of the spinal network (see the figure) with its sensory and supraspinal control have been identified, and the pattern of interaction is understood, at least to a first approximation.

The brainstem-spinal cord network uses glutamate and glycine as transmitters for fast synaptic interaction. The motor pattern is initiated and maintained by an excitatory glutamatergic drive from the brainstem acting on all spinal network interneurons. Both *N*-methyl-D-aspartate (NMDA) and AMPA/kainate receptors mediate the fast glutamatergic synaptic transmission. NMDA receptors give rise to excitatory postsynaptic potentials (EPSPs) with a slow rise time and long decay, but in addition they are voltage sensitive and can therefore elicit long-lasting plateau depolarizations for many seconds (*6*). This is a very useful property, because a short-lasting stimulus can be translated into a more long-lasting effect. Both with short-lasting activation of the trigeminal cranial nerves (*5*) or the diencephalic locomotor centers (*7*), a long-lasting plateau can be produced in the reticulospinal neurons, which in turn activate the spinal cord networks.

Viana Di Prisco *et al.*'s report concerns the cellular processes that control the reticulospinal system—what makes it respond with long-lasting periods of locomotor activity to short-lasting input signals? Sensory cutaneous stimuli applied to the head excites reticulospinal neurons (see the figure). Moderate stimuli give rise to a transient excitatory synaptic potential, whereas a stronger stimulus elicits a plateau depolarization and concurrent locomotor activity. The plateau arises as a result of NMDA receptor activation interacting with intrinsic cellular properties.

The dynamic properties of single cell types are of critical importance for the network. For instance, one type of calcium-dependent K$^+$ channel (K_{Ca}) regulates the frequency of action potentials and adaptation in single cells by controlling the afterhyperpolarization, which also contributes to burst termination at the network level (*8*). Factors intrinsic to the nerve cells thus combine with the synaptically induced signals to regulate locomotion.

The entire network can be viewed as having a standard configuration consisting of plateau potentials in certain cells plus other cellular mechanisms. This standard network can, however, be reconfigured by different transmitters or modulators which, through heterotrimeric GTP-binding proteins, target ion channels of one type or another. By targeting and changing the function of K_{Ca} channels, the afterhyperpolarization will be modified, thereby altering the action potential frequency in single cells. Changing the properties of network neurons will in turn produce specific changes in the network output pattern. For example, serotonin reduces the availability of K_{Ca} channels and thereby the amplitude of the afterhyperpolarization. In the network, this will result in longer bursts of locomotor activity, and the coordination between body segments will become modified. Activation of each modulator system in the spinal cord (serotonin, dopamine, tachykinins, somatostatin, and neurotensin) will affect single or groups of ion channels in certain cell types; this in turn will produce specific, predictable changes at the network level and in motor behavior. One very useful—even indispensable—tool in the analysis of these complex cellular processes that proceed in parallel is offered by modeling.

To be able to understand how the nervous system generates behavior, with nerve cells as building blocks, one needs to work on all neural levels of organization from molecule, cell,

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and synapse to network and behavior. The challenge is thus to create links between these different levels and to find simple model preparations (9) appropriate for the particular behavior of interest.

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PHYSICS

Quantum Nondemolition: Probing the Mystery of Quantum Mechanics

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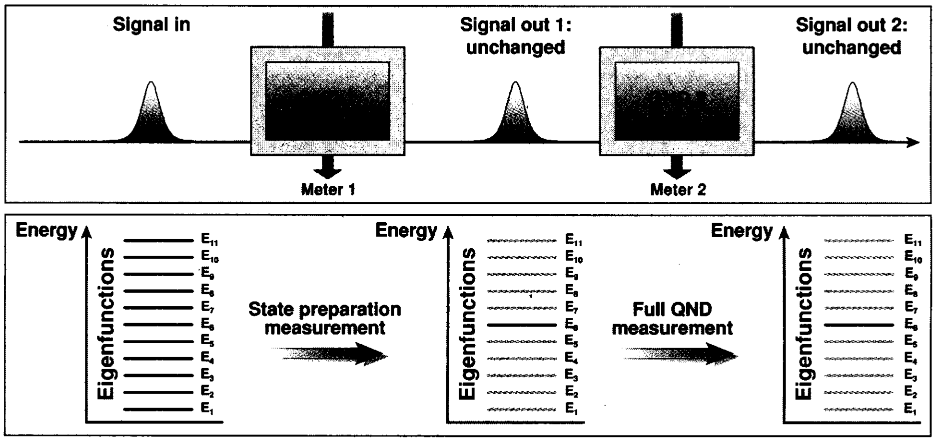
A mystery, many believe, lies at the heart of quantum mechanics. For some, it is the wavelike description of particles or the Heisenberg uncertainty principle. These descriptions, however, have counterparts in classical optics and are rather easily pictured. For others, it is the process of measurement. Our choice of measurement strategies, for example, determines whether quanta act as particles or waves. Suppose we set up a double-slit experiment and slowly send through quanta; they interfere with themselves like waves, building up a spread-out modulated interference pattern. But as we watch, the pattern builds up randomly, one quantum at a time, like particles. Nature, we are forced to confront, is intrinsically random at a fundamental level.

Recent experimental advances in quantum optics allow observation of this and other quantum measurement mysteries in a controlled laboratory environment. One important new technique is the quantum nondemolition (QND) measurement, which allows observation of the quantum measurement process in detail if losses are small. Usually the measurement is done by a nonlinear interaction that writes information from the measured "signal" to a "probe" (or meter), entangling the signal and probe at a quantum mechanical level. Reading out the probe in the usual manner (by converting it to a macroscopic classical signal) gives information about the signal without destroying it.

Current interest in QND stems from efforts by Braginsky and co-workers to enhance the sensitivity of gravitational wave antennas (*1*). The idea, however, is traceable back to "gedanken" experiments (thought experiments) in the pioneering days of quantum mechanics. Braginsky showed that the small signals caused by gravitational waves impinging on a gravitational wave antenna could be measured without the introduction of "back-action" noise, which could wash out subsequent read-outs.

At first, such back-action evasion measurements seemed to violate the Heisenberg uncertainty principle, which stipulates that a measurement always introduces noise. However, as quantum mechanical variables are invariably paired with conjugate variables (say, position with momentum), back-action evasion measurements are possible if the noise of measurement can be made to affect only the conjugate variable. This prospect implied that a gravitational wave antenna could make measurements with accuracies much better than the standard quantum limit of classical-like oscillator systems. Since this realization, there have been continual efforts to implement QND for gravitational wave detection (*2*). However, it is in quantum optics that QND measurements have been most vigorously pursued (*3*).

QND measurements can be made in two ways: single measurements that explore different interaction geometries, and double measurements that test repeatability. The state of the art for a single measurement is an elegant experiment by Roch, Grangier, and co-workers at the Institut d'Optique in Orsay, France (*4*). Using the large optical $\chi^{(3)}$ nonlinearity of cold rubidium atoms in a magneto-optical trap, these researchers achieved sensitive, back-action–evading, low-loss intensity measurements of a 15-μW signal beam by changing the phase of a 0.25-μW meter beam. If the signal is slightly detuned from the 795-nm resonance wavelength of ^{87}Rb, absorption is low. At the same time, it "depumps" the atoms to their ground state, changing the index of refraction



Double quantum nondemolition measurement. This measurement is accompanied by corresponding changes in the quantum state of the measured signal. A typical input signal is in a quantum mechanical superposition of eigenstates E_1 through E_{11} (red lines, lower left). The first back-action evasion measurement QND 1, if ideally strong, collapses the wave function to a single eigenstate, E_6 in this case (red line, lower center). If the state is measured again by QND 2, the eigenstate should be unchanged, as in the lower right. The readouts of meter 1 and meter 2 should be identical and correspond to the eigenstate after the measurement.

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