Neural Networks for Vertebrate Locomotion

The motions animals use to swim, run and fly are controlled by specialized neural networks. For a jawless fish known as the lamprey, the circuitry has been worked out

by Sten Grillner

It is difficult to grasp how the human brain is able to keep up with the requirements of running or even walking: deciding what joint needs to be moved, exactly when it should bend and by how much, and then sending the proper series of impulses along nerves to activate the appropriate combination of muscles. The dexterity that even lowly creatures display as they swim, fly, run or otherwise propel their bodies through their surrounds is truly marvelous. Even the most sophisticated mobile robots perform poorly in comparison.

Although many mysteries of animal locomotion are yet unsolved, scientists are beginning to comprehend the way vertebrates (creatures with backbones, including humans) can almost effortlessly coordinate complicated movements that may involve hundreds of muscles. The formidable task of managing the body's various motions is simplified by a remarkable form of neural organization, one that distributes the responsibility for coordinating such acts to distinct networks of nerve cells. Some of these specialized circuits, such as the one that keeps a person constantly breathing, are ready to operate flawlessly from birth. Others, such as those that control crawling, walking or running, can take time to mature.

The neural networks that govern specific, oft-repeated motions are sometimes called central pattern generators. They can steadfastly execute a particular action over and over again without the need for conscious effort. The key neural-control circuits that humans use for breathing, swallowing, chewing and certain eye movements are contained within the brain stem, which surrounds the uppermost spinal cord. Oddly enough, the circuits for walking and running (as well as some protective reflexes) are not located in the brain at all but reside in the spinal cord itself.

Since the late 1960s, my colleagues and I have been attempting to unravel the design of the neural systems that coordinate locomotion in various experimental animals in hopes that this research will help scientists understand some of the intricacies of the human nervous system. Much is yet to be learned, but we have finally produced a blueprint for the neural networks responsible for movement in a simple vertebrate, a type of jawless fish known as a lamprey.

Of Mice and Men

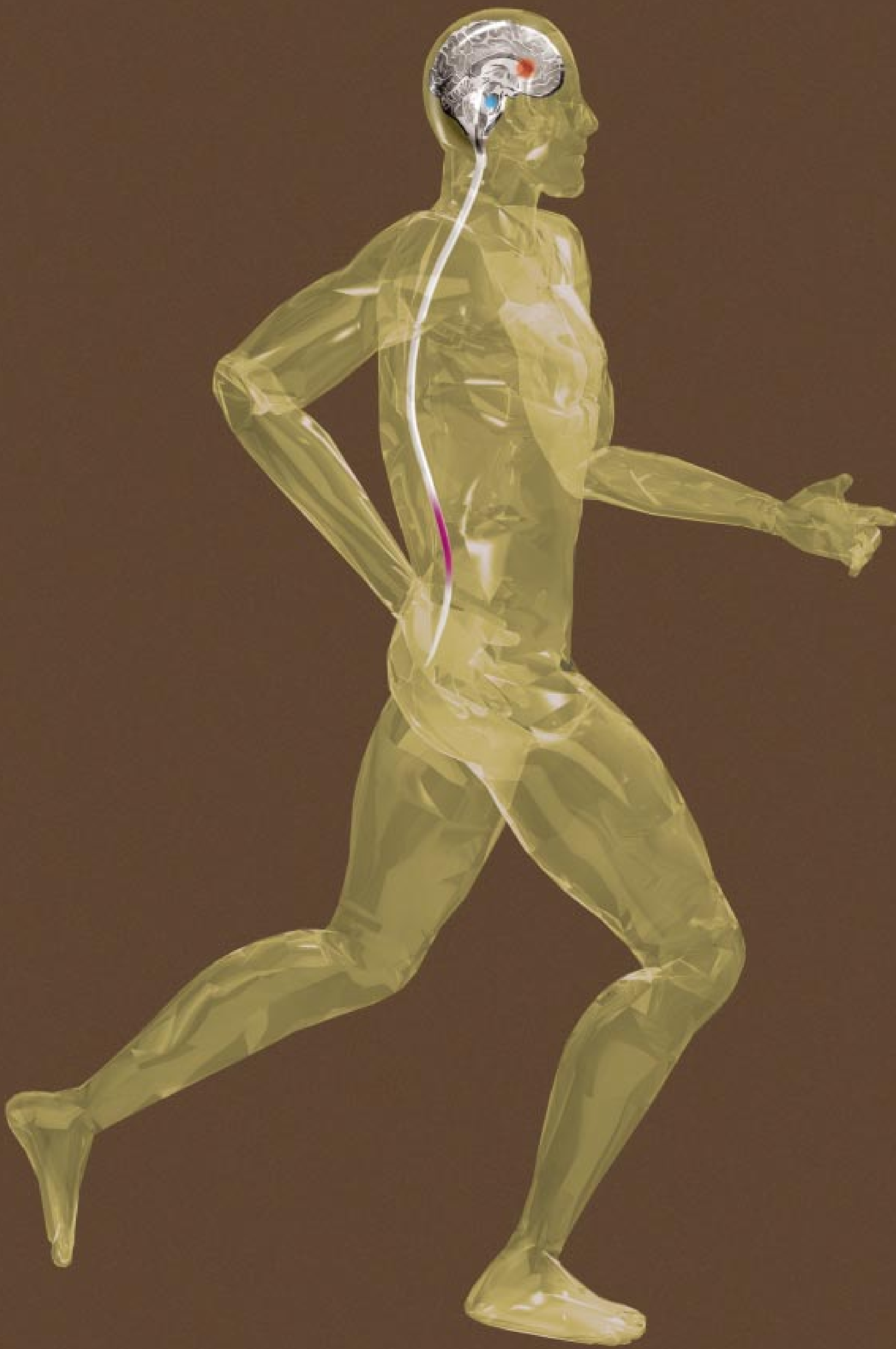
Scientists have deduced much about the organization of the human central nervous system from studies of laboratory animals. Appreciation for the significance of the spinal cord to locomotion first came just after the turn of the century, when pioneering British neurophysiologists Charles S. Sherrington and T. Graham Brown observed that mammals with severed spinal cords could produce alternating leg movements even though the connection to the brain had been cut. Much later my colleagues and I were able to show definitively that such motions corresponded to those movements used for locomotion. Thus, we could conclude that the essential nerve signal patterns for locomotion are generated completely within the spinal cord.

Yet it remained a question how the brain controls these circuits and chooses which should be active at a given instant. Much insight into this process came during the 1960s, when the Russian investigators Grigori N. Orlovski and Mark L. Shik, then at the Academy of Science in Moscow, demonstrated that the more that specific parts of the brain stem of a cat were activated, the faster the animal under study would move. With increasing stimulation, the cat would proceed from a slow walk to a trot and finally to a gallop. A very simple control signal from a restricted area of the brain stem could thus generate intricate patterns involving a large number of muscles in the trunk and limbs by activating the pattern generators for locomotion housed within the animal's spinal cord.

Beyond providing clues to the interactions between brain and spinal cord, this experiment helped to explain how animals can move about even after much of their brain is surgically removed. Some mammals (such as the common laboratory rat) can have their entire forebrain excised and are still able to walk, run and even maintain their balance to some extent. Although they move with a robotic stride, without making any attempt to avoid obstacles placed in their path, these animals are fully able to operate their leg muscles and to coordinate their steps.

The details of how the brain activates neural networks in the spinal cord took years to lay out. It is now known that large groups of nerve cells in the fore-

LOCOMOTION for humans, like all vertebrate animals, is orchestrated by the central nervous system. Specialized neural circuits in the forebrain (*red*) select among an array of "motor programs" by activating specific parts of the brain stem (*blue*). The brain stem in turn initiates locomotion and controls the speed of these movements by exciting neural networks (called central pattern generators) located within the spinal cord (*purple*). These local networks contain the necessary control circuitry to start and stop the muscular contractions involved in locomotion at the appropriate times. Networks of neurons in the brain stem also control breathing, chewing, swallowing, eye movements and other frequently repeated motor patterns.



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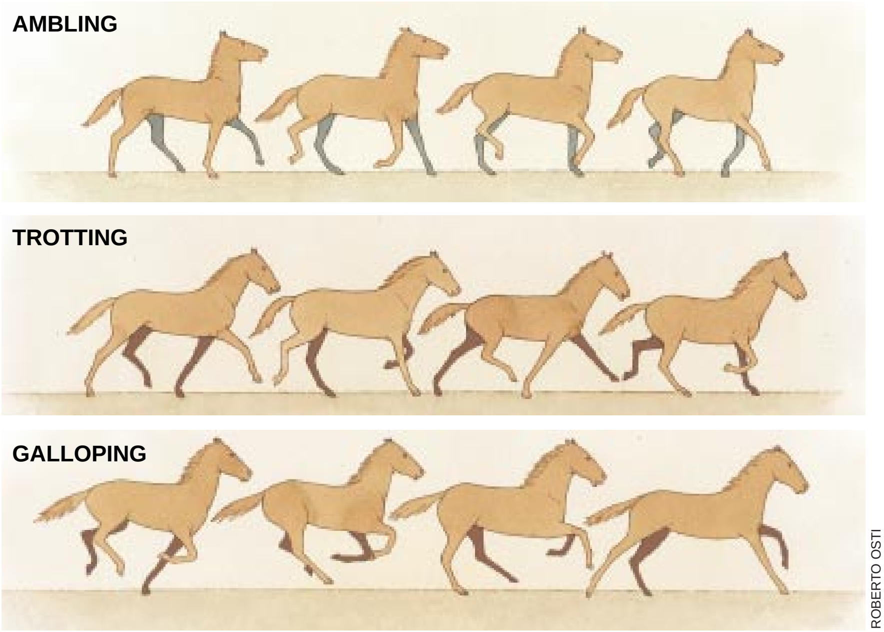


PATTERN GENERATORS, separate neural networks that control each limb, can interact in different ways to produce various gaits, such as the amble, trot and gallop of a horse. In ambling (*top*), the animal must move the foreleg and hind leg of one flank in parallel. Trotting (*middle*) requires movement of diagonal limbs (front right and back left, or front left and back right) in unison. Galloping (*bottom*) involves the forelegs, and then the hind legs, acting together.

brain, called basal ganglia, connect (either directly or through relay cells) to target neurons in the brain stem that in turn can initiate different "motor programs." Under resting conditions, the basal ganglia continuously inhibit the brain's sundry motor centers so that no movements occur. But when the active inhibition is released, coordinated motions may begin. The basal ganglia thus function to keep the various motor programs of the nervous system under strict control. This suppression is essential: renegade operation of a motor program could be disastrous for most any animal.

In humans, for instance, diseases of the basal ganglia can cause involuntary facial expressions and hand or limb movements. Such hyperkinesis occurs commonly in cerebral palsy and Huntington's disease and as a side effect of some medications. Other diseases of the basal ganglia can lead to the opposite situation, with more inhibition than desired being applied; victims then have difficulty initiating movements. The best known example of such a disability is Parkinson's disease.

Ferrari or Model T?

Although medical researchers keenly desire to understand how such neurological disorders arise and what might be done to correct them, progress has been difficult to achieve because the human nervous system (which houses nearly a trillion neurons) is extraordinarily complicated. It is not yet feasible to examine the neural circuits in humans, or indeed in any mammal, in much detail. My colleagues and I have therefore focused our studies on much simpler vertebrates. We sought an experimental animal with the same basic neural organization as humans but with far fewer components.

Our fundamental approach has been similar to something an imaginary researcher from outer space might undertake to deduce the basic mechanics of an automobile. An extraterrestrial scientist would fare best by beginning such an analysis with a Model T Ford (if one could be obtained), because that vintage vehicle has all the essential components of a car—internal-combustion engine, transmission, brakes and steering—manufactured from a simple design and arranged for easy inspection. Investigations that began by directly probing a more advanced model, such as a modern turbocharged Ferrari, might prove far more frustrating. One presumes that knowledge of a Model T would serve as the foundation needed to understand the anatomy of the more elegant and sophisticated car.

We investigated several possible subjects before settling finally on the lamprey—an elongate, jawless fish with a large mouth adapted for sucking. The lamprey is a primitive vertebrate with a nervous system composed of comparatively few cells (only about 1,000 in each segment of the spinal cord), making it ideal for our purposes. The lamprey also suited us because Carl M. Rovainen of Washington University had shown that the fish's central nervous system could be maintained in a glass dish and studied for several days after it is removed from the animal. Moreover, motor networks in the isolated nervous system remain active.

The strategy of choosing a simple but relevant experimental animal for study has yielded key insights into many different biological processes. For example, examination of invertebrate nerve cells, such as those of the squid and lobster, provided the first important clues to how nerve impulses are generated and how networks of nerve cells function.

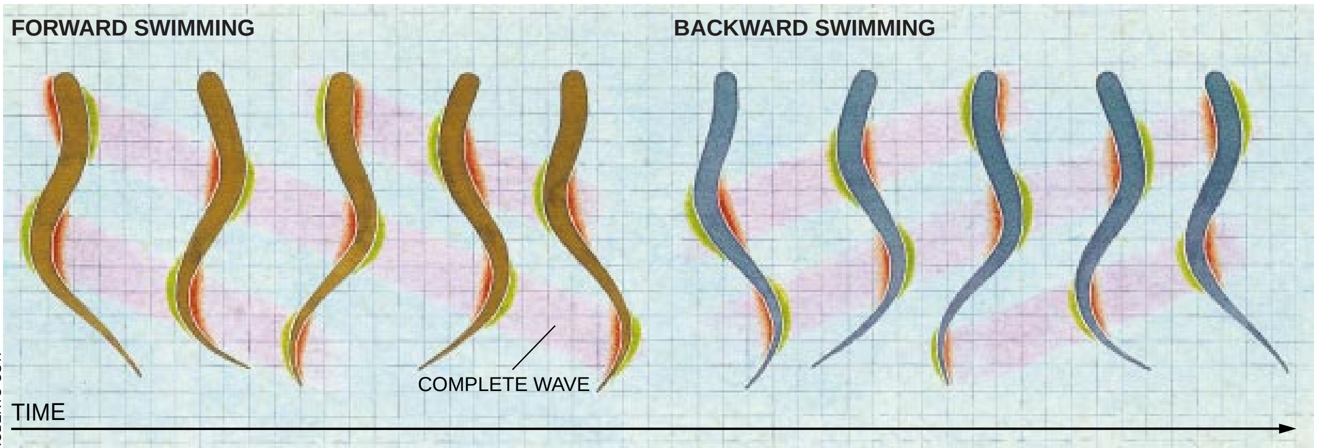
A Hardwired Fish

From the beginning of our studies with the lamprey in the late 1970s, my colleague Peter Wallén and I, along with a number of collaborators, have concentrated on understanding the fundamental features of the animal's swimming. Like other fish, the lamprey propels itself forward through the water by contracting its muscles in an undulating wave that passes along the creature's body from head to tail.

To produce a propulsive wave, the animal must generate bursts of muscle activity that bend each section of the spine toward one side and then the other in rhythmic alternation. But the lamprey also needs to coordinate the contractions of consecutive segments along its body so that a smooth wave forms. We soon discovered that the neural controls for both these abilities are distributed throughout the spinal cord. If a lamprey's spinal cord is isolated and separated into several pieces, each length can be made to show the characteristic alternating pattern, and within any given portion the activity between adjoining segments stays coordinated.

Further observations showed that the lag between activation of adjacent segments remains fixed during a given wave, as the undulatory motion propagates down the body of the lamprey. But the lag time changes with the fish's speed, so that the overall period of that wave (the time it takes for the wave to travel the entire length of the body) can vary from about three seconds during very slow swimming to as little as one tenth of a second for sudden sprints. Exactly the same characteristic contractions occur in reverse order when the fish swims backward.

To understand how the lamprey ner-

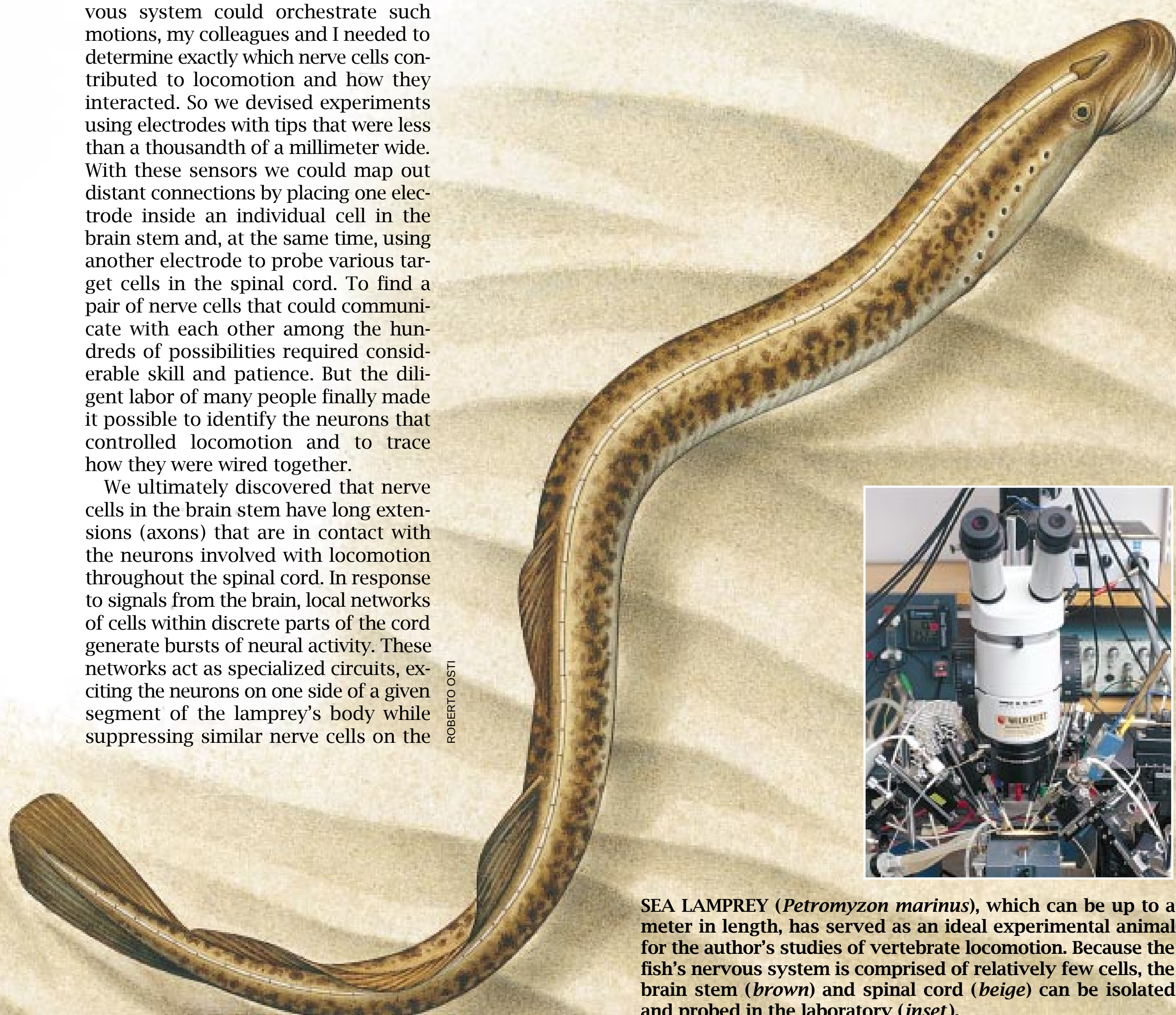


ROBERTO OSTI

UNDULATORY SWIMMING in the eellike lamprey constitutes a relatively simple form of vertebrate locomotion that neuroscientists can examine effectively. In response to signals emitted by the brain, wave after wave of muscle contraction (*red*) and extension (*green*) pass from head to tail down the body of a fish, propelling it forward through the water (*left*). Similar waves traveling from tail to head can drive the creature backward (*right*).

vous system could orchestrate such motions, my colleagues and I needed to determine exactly which nerve cells contributed to locomotion and how they interacted. So we devised experiments using electrodes with tips that were less than a thousandth of a millimeter wide. With these sensors we could map out distant connections by placing one electrode inside an individual cell in the brain stem and, at the same time, using another electrode to probe various target cells in the spinal cord. To find a pair of nerve cells that could communicate with each other among the hundreds of possibilities required considerable skill and patience. But the diligent labor of many people finally made it possible to identify the neurons that controlled locomotion and to trace how they were wired together.

We ultimately discovered that nerve cells in the brain stem have long extensions (axons) that are in contact with the neurons involved with locomotion throughout the spinal cord. In response to signals from the brain, local networks of cells within discrete parts of the cord generate bursts of neural activity. These networks act as specialized circuits, exciting the neurons on one side of a given segment of the lamprey's body while suppressing similar nerve cells on the



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TONY SICA *Gamma Liaison*

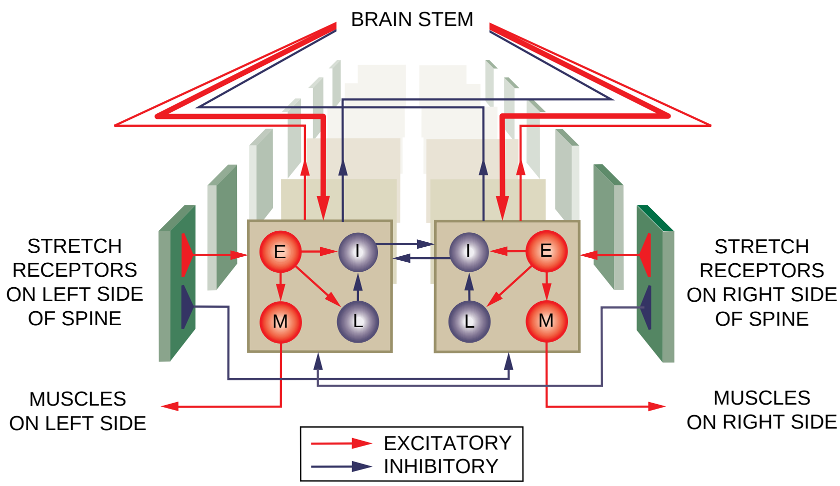
SEA LAMPREY (*Petromyzon marinus*), which can be up to a meter in length, has served as an ideal experimental animal for the author's studies of vertebrate locomotion. Because the fish's nervous system is comprised of relatively few cells, the brain stem (*brown*) and spinal cord (*beige*) can be isolated and probed in the laboratory (*inset*).

Parallel Processing

Within a single segment of the lamprey's spinal cord lies an intricate network of interconnected nerve cells. Groups of neurons (*boxes*) on the left and right sides of the cord are excited by signals sent from the animal's brain stem. Specialized neurons within these groupings respond by sending either excitatory (*red*) or inhibitory (*purple*) signals to neighboring cells. Neurons known as E cells (for excitatory) on one side of the spinal segment will activate motoneurons (M) that in turn cause the muscles on that side of the fish to contract. These E cells also induce inhibitory (I) neurons to reduce the level of excitation in the group of neurons on the opposite side of the spine, ensuring that the opposing muscles relax.

The bursts of excitation that cause one side to contract are terminated in a number of ways. Certain stretch receptor neurons (*purple triangles*) on the opposite side of the spine emit signals that inhibit the contraction. At the same time, other activated stretch receptors (*red triangles*) excite the neurons on the extended side to initiate contraction there. In addition, large (L) inhibitory nerve cells on the contracting side can be induced by the brain stem to inhibit the I cells. This allows the opposite side to become active and send inhibitory signals back. Finally, there are several electrochemical mechanisms inside cells that can force a pulse of excitation to subside, helping to control the timing of the network.

Although these local spinal cord circuits can operate autonomously, they normally feed back information to the brain about the ongoing network activity. These signals can then be combined with other forms of sensory input, such as cues from vision or from the balance system in the inner ear, to modify the animal's movements.



CAREY BALLARD

opposite side. Thus, when one flank of a given section becomes active, the other is automatically inhibited. Other specialized nerve cells, called motoneurons, link the nerves of the spinal cord to the muscle fibers that actually do the job of moving the lamprey through water.

But these spinal networks are not simply passing signals sent down from the brain of the animal. Although the brain stem issues the overall command for the fish to swim, it delegates the task of coordinating the muscle movements to these local teams, which can process incoming sensory data and adjust their own behavior accordingly. In particular, they react to specific "stretch receptor neurons" that sense the bending of the lamprey's spine as it swims.

As one side of the body is contracting, the other is extending—and it is this extension that triggers the stretch receptors. These activated nerve cells then take one of two complementary actions: they either excite neurons on the extended side (inducing muscles there to contract), or they inhibit neurons on the opposite side, causing them to halt contraction. By such processes (as well as several rather complex cellular mechanisms), the fundamental oscillatory movements of the lamprey's neuromuscular system are maintained.

As we further followed the neural circuitry of the lamprey's spinal cord, we determined that some of the local neural networks extend axons along the spine. Special inhibitory cells in each segment send signals through these axons in the direction of the tail for as much as one fifth of the length of the spine. So-called excitatory cells contain somewhat shorter axons that extend in both directions. Thus, the activity at one location on the spinal cord can affect adjacent regions.

But how exactly might signals linking different segments create the characteristic wavelike motion? After much thought, we proposed that nerve signals could excite the leading segment (near the lamprey's head) so that the contractions there alternate back and forth faster than the spine would otherwise tend to oscillate. The second section behind the head would follow the quickened motions of the first (because the two segments are coupled by nerve cells), but with a slight lag as the inherently slower section tried to catch up with the leader. By similar reasoning, the third section should then follow the second with a slight delay—and so forth down the line. The series of incremental delays, we surmised, allowed the lamprey to produce a uniform wave.

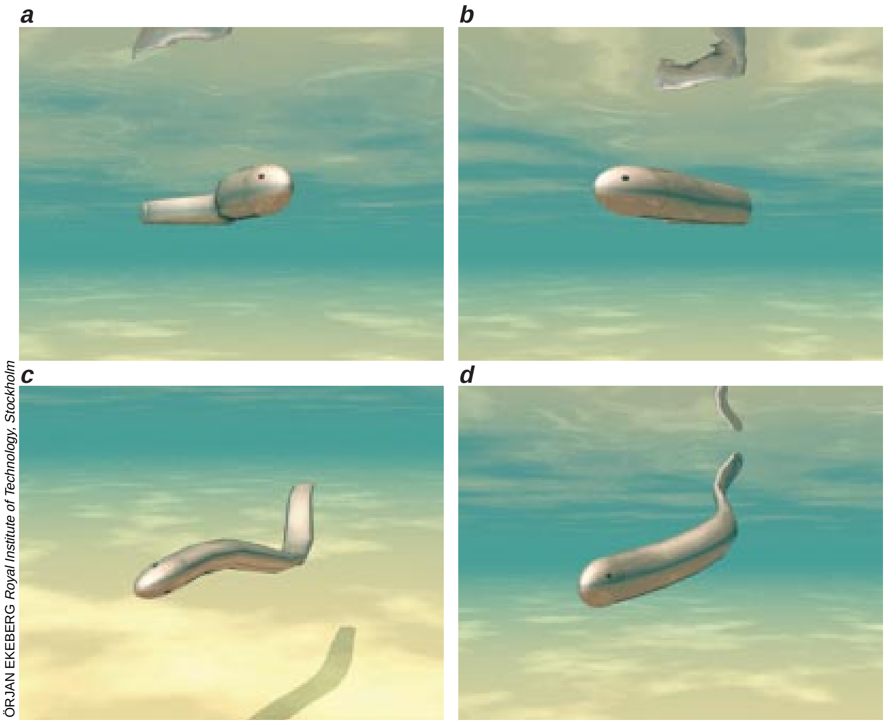
Virtual Reality

Even with our newly developed wiring diagrams and a mass of other detailed information about the properties of the different types of nerve cells involved, we were long challenged to make more than modest, general statements about how these complex neural circuits operated. To test whether the information we had gleaned truly explained how the lamprey could swim, my colleagues and I joined with Anders Lansner and Örjan Ekeberg of the Royal Institute of Technology in Stockholm to create various computer models of the process.

First, we developed schemes that could reproduce the behavior of the different neurons used for locomotion. Then we succeeded in simulating on our computer the entire ensemble of interacting cells. These numerical exercises allowed us to test a variety of possible mechanisms, and they have proved to be indispensable tools in the analysis of the lamprey's neural organization. Because the computer models can generate a signal pattern that is quite similar to that occurring during actual locomotion, we can finally say with some confidence that the circuits we have deciphered do indeed capture essential parts of an extensive biological-control network.

Our computer simulations not only showed alternating contractions on either side of the spine but also refined our conception of the lag between the activation of adjoining segments. This delay arises from the neurons that reach along the cord and inhibit segments in the tailward direction. These connections ensure that the overall level of excitation will typically be highest at the head end of the animal—a condition that leads to delayed activation of the segments, one after the other, all along the animal's body. We also found that the normal pattern could be reversed by increasing the excitability in the most tailward part of the spinal cord, thereby enabling backward swimming. The "hardwired" spinal network of the lamprey thus retains a considerable degree of flexibility.

For the most part, we considered computer simulations that mimic only the lamprey's neural activity. But recent efforts led by Ekeberg have succeeded in modeling the entire lamprey, from the muscle fibers controlling the different segments to the viscous properties of the surrounding water. The neural-control circuits we had previously charted provided everything this virtual lamprey needed to swim.



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VIRTUAL SWIMMING by a simulated lamprey suggests that neural models developed in the laboratory can portray how the real creature maneuvers itself through the water. These computer-generated images show the lamprey swimming straight (*a*), turning (*b*), rolling to one side (*c*) and pitching downward (*d*).

Crawling Out of the Water

We can now be satisfied that the lamprey's capacity for locomotion can be understood in terms of the interactions of spinal nerve cells. But how certain is it that these mechanisms operate in higher forms of life? The lamprey diverged from the main vertebrate line quite early during the course of evolution, about 450 million years ago, at a time when vertebrates had not yet developed limbs. So it was not immediately obvious whether our results were relevant to other animals.

But the mechanism for locomotion in one other vertebrate—the tadpole—has also been revealed at a cellular level by Alan Roberts and his colleagues at the University of Bristol. It has been especially comforting for me to see that the tadpole's nervous system resembles in most aspects the lamprey network. For other vertebrates as well, from fish to primates, the overall neural organization is arranged along a similar plan. Discrete regions of the brain stem initiate locomotion, and the spinal cord processes the signals with specialized circuits.

Yet the cellular mechanisms used for locomotion in these other animals are still largely unknown. Researchers have shown that pattern generators are present and have probed some of their neural components, but so far it has not been possible to unravel their inner architecture. During the past few years, however, new techniques have been developed to isolate the spinal cords of the other classes of vertebrates (mammals, birds and reptiles), and it seems likely that in the next few years investigators may uncover how these animals control walking, running and flying.

Because the earliest vertebrates used only undulatory swimming for locomotion, the networks that later evolved to control fins, legs and wings may not be all that different from what my colleagues and I have already studied. Evolution rarely throws out a good design but instead modifies and embellishes on what already exists. It would be most surprising to discover that there were few similarities between lampreys and humans in the organization of control systems for locomotion. Scientists may yet devise ways to map out and to activate dormant pattern-generating circuits in people with severed spinal cords. Indeed, such miraculous medical advances might not be that far away: a turbocharged Ferrari is, after all, just another kind of car.

The Author

STEN GRILLNER received an M.D.–Ph.D. degree in 1969 from the University of Göteborg in Sweden, where he then joined the faculty. In 1975 Grillner moved to the department of physiology at the Karolinska Institute in Stockholm. He joined the Nobel Institute for Neurophysiology in 1987 and now serves both as chairman of the department of neuroscience at Karolinska and as director of the Nobel Institute. Grillner has also been a member of the Nobel Committee for Physiology or Medicine since 1987.

Further Reading

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