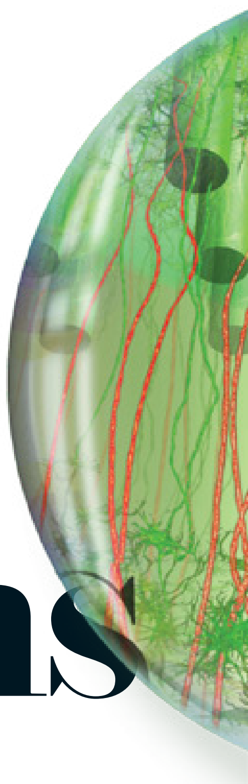
MEDICAL ENGINEERING

Bionic Connections



A new way to link artificial arms and hands to the nervous system could allow the brain to control prostheses as smoothly as if they were natural limbs

By D. Kacy Cullen and Douglas H. Smith

IN ONE OF THE MOST ICONIC SCENES IN SCIENCE-FICTION FILMS, LUKE SKYWALKER casually examines his new synthetic forearm and hand. The *Star Wars* hero is able to move the fingers by extending and contracting pistons shown through an open flap along the wrist. Then he senses the robotic surgeon's pinprick of one of the fingers. Not only can the prosthesis be moved with Skywalker's thoughts, it *feels* to him like his own hand.

What the audience does not see, however, is the actual connection between man and machine. And yet to neuroscientists like the two of us, it is precisely this hidden interface that should have been at the center the scene. In order for such a linkup to work, it would have to have converted nerve impulses from the brain into electrical signals in the artificial arm, and vice versa. In the world beyond movies, however, no one has yet figured out how to splice together nerves and electrical wires in a way that allows them to control an artificial limb as if it were a natural extension of the body.

The failure is not surprising. For one thing, nerves and the electrical wires needed to regulate the electronics in a prosthesis transmit entirely different kinds of signals. Electronic devices depend on the flow of electrons across conductive materials

IN BRIEF

Bioengineers would like to connect prosthetic arms and hands directly to the nervous system.

Two-way communication would allow the brain to control a limb's movements and to feel its presence.

The first step is to develop a kind of adapter cord that translates nerve impulses into electrical signals.

The authors are developing such an interface with laboratory-grown nerve fibers and electricity-conducting polymers.

Illustration by Jean-François Podevin

REACH: Advances in neuroengineering are starting to catch up to the tremendous progress that has recently been made in prosthetic design.

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and through semiconductors and transistors; the nervous system relies on the depolarization of cell membranes and the release of signaling chemicals in the gaps between nerve cells. For another, the linkage would require implanting wires and other kinds of electronics into the body, which normally perceives such implants as foreign and thus unleashes attacks that would generate scar tissue around an interface and disrupt its functioning.

Advances in nanotechnology and tissue engineering over the past few years, however, are addressing both challenges. Rather than trying to force nerves to communicate directly with the standard electronics in modern prostheses, we and others are building new kinds of bridges between nerves and artificial limbs—linkages that take advantage of the nervous system's inborn ability to adapt itself to new situations. Indeed, recent research in the laboratory has brought us closer to the goal of developing an artificial limb that, like Luke Skywalker's, can be moved and sensed by the brain.

COMBINING MOTOR AND SENSORY INPUT

For better or worse, much of the progress in prosthetic design has occurred as a result of armed conflict—most recently, the wars in Afghanistan and Iraq. Until the past few years, however, designers focused more on artificial limbs for the lower rather than the upper body. Developing prosthetic legs that allow users to walk and run is a more straightforward engineering proposition than devising an artificial hand that enables its user to open jars, for example, or to touch-type on a computer keyboard. Since 2006 and the launch of the Revolutionizing Prosthetics program of the Defense Advanced Research Projects Agency, researchers have made impressive strides in creating sophisticated artificial upper limbs as well.

Part of the challenge in designing highly functional upper limbs is the need to replicate (at least in part) the hand's exquisite fine-motor control. The effort requires being able to tap into the brain's own mental maps, which it uses to transmit nerve signals to specific muscle fibers controlling the forearm, and to know when it receives nerve signals about pressure, position, tension, momentum, and force from the arm and hand, from whence those messages originate. This sensory feedback helps the brain to determine just how many muscle fibers should be recruited to power any given effort.

In an intact limb, these motor and sensory signals work together to create, among other things, the sense known as proprioception—the awareness of where the various parts of the body exist in space and in relation to one another without having to actually look at them. Without proprioception, even what appear to be simple tasks, such as writing with a pen, would be nearly impossible. Thanks to a symphony of nervous system signaling from the brain to the extremities and back again, you are able to move your hand exactly to the pen, gently lift it while seamlessly shifting it into position and lightly touch it down to write.

To date, robotic hands have been developed that permit varying, indirect levels of motor control. In some cases, for example, repeated contracting and relaxing of muscles in the limb stump or in the chest can activate specialized relays that trigger different movements in the artificial limb. Ideally, however, bioengineers would like to build a prosthetic that is linked to, and controlled by, the original motor nerves—which do not die after amputation but merely retreat a bit from the edge of the stump.

Use of motor neurons is just part of the vision, however. Many simple tasks still prove difficult even with today's very advanced prosthetic devices because no sensory signals travel from the artificial limb back to the brain. Amputees have to consciously direct every discrete movement of their prosthesis, relying on what their eyes see for feedback rather than on their natural sense of proprioception. This level of effort results in clumsy and slow movements that leave people exhausted by the concentration and time needed to accomplish such tasks as buttoning a shirt.

A critical goal, then, is to engineer an interface between the nervous system and the prosthesis that allows direct two-way communication of both motor and sensory information. Such a "neuromechanical" interface would permit the development of prosthetic hands that can be controlled by intuitive thought and that feel real. Several research laboratories, including our own, are now pursuing this objective. Although we have each adopted somewhat different approaches with their own advantages and challenges, success will probably depend on some combination of everyone's insights and technological innovations.

TWO MAIN APPROACHES

The first step in creating a useful interface between the body and a prosthetic limb is deciding where in the nervous system to position it. Designers have two main options—interact with the central nervous system (linking to either the brain or the spinal cord) or work further out, in what is known as the peripheral nervous system, with nerves that stretch primarily between the spinal cord and the rest of the body.

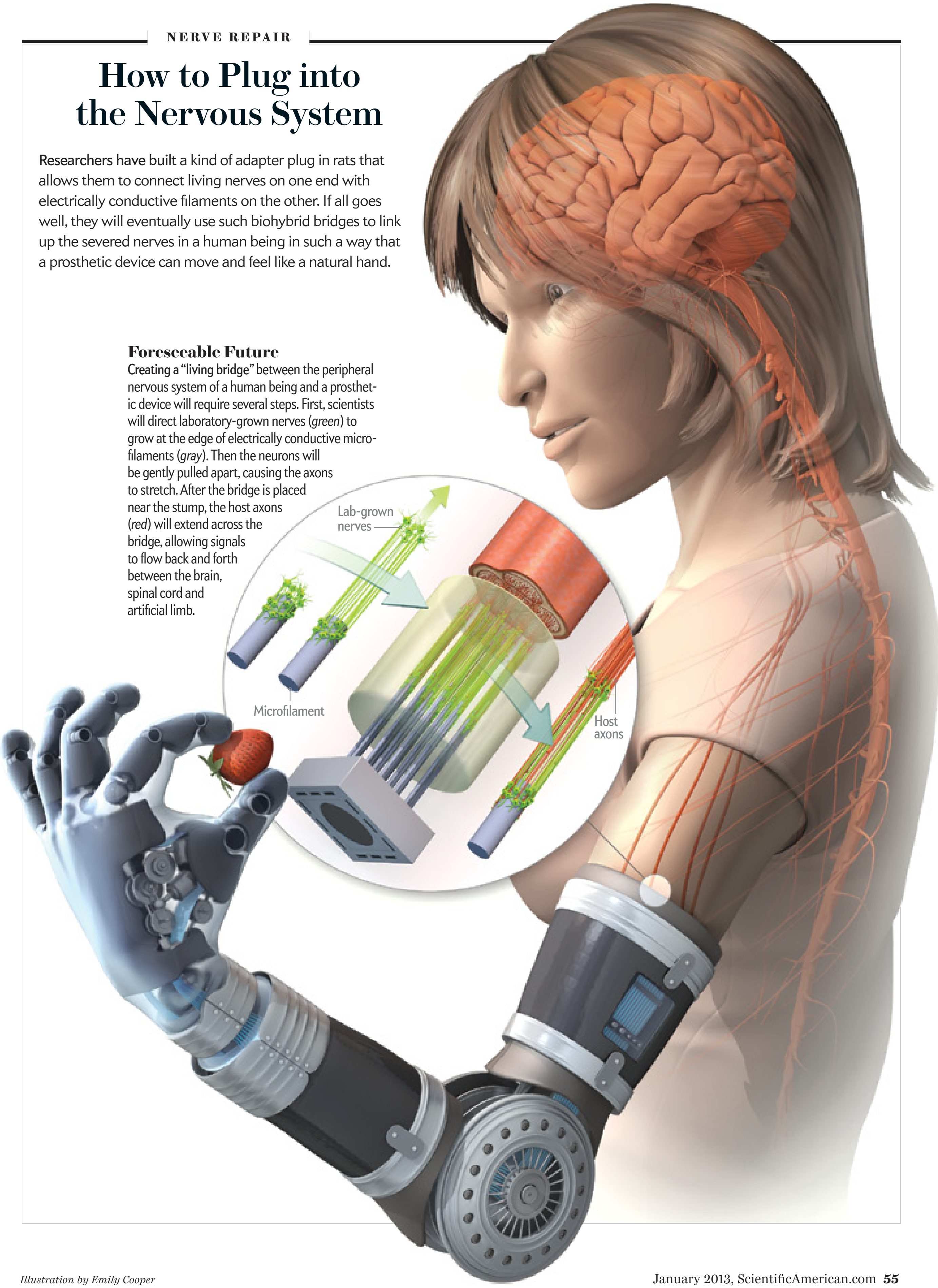
To date, most researchers have focused on the brain as a starting point. The least invasive approaches listen in on its neural activity via external electrodes on the scalp or just under the skull on the surface of the brain itself. The electrodes pick up electrical signals from the brain, which a computer then analyzes to signal the desired movement. These methods have the advantage of not poking holes into the brain, but they are susceptible to interference from other electronics. The electrical signals are also rather coarse representations of what the brain is actually doing, which makes it difficult for the computer to predict which movements should occur.

The most invasive approach inserts arrays of microelectrodes directly into the outer layers of the brain. (The microelectrodes used are typically high-density silicon probes, each generally less than a human hair's width in diameter.) As a di-

NERVE REPAIR

How to Plug into the Nervous System

Researchers have built a kind of adapter plug in rats that allows them to connect living nerves on one end with electrically conductive filaments on the other. If all goes well, they will eventually use such biohybrid bridges to link up the severed nerves in a human being in such a way that a prosthetic device can move and feel like a natural hand.



Foreseeable Future

Creating a "living bridge" between the peripheral nervous system of a human being and a prosthetic device will require several steps. First, scientists will direct laboratory-grown nerves (*green*) to grow at the edge of electrically conductive microfilaments (*gray*). Then the neurons will be gently pulled apart, causing the axons to stretch. After the bridge is placed near the stump, the host axons (*red*) will extend across the bridge, allowing signals to flow back and forth between the brain, spinal cord and artificial limb.

Illustration by Emily Cooper

rect interface, this approach offers the tremendous advantage of providing extremely precise and rich data—including the strength and frequency of "firing" for individual nerve cells. The idea is to use specially designed software to decode or translate this information into the appropriate action. Such highly detailed information would, in theory, permit exquisitely fine control of an artificial limb.

Direct brain linkages are already being tested in dozens of humans. In one case, a woman who had been paralyzed by a stroke was able to use a robotic arm to drink coffee from a container using just her thoughts to guide the device. And in 2012 DARPA launched an initiative that, for the first time, will use brain-penetrating electrodes to control state-of-the-art prosthetic arms in a few individuals who have lost upper limbs. In both cases, the neuron-recording electrodes are connected to wires that emerge from the skull. The signal is then decoded by a powerful computer, which in turn relays instructions to the robotic arm. Ultimately researchers hope to transmit the information wirelessly so that a recipient does not have to be tethered to a computer to use the synthetic arm. Unfortunately, the necessary computer power does not yet come in a package small enough to be internalized, as would be desirable in a real-world setting.

Another drawback is that the brain tissue treats the penetrating electrodes as foreign invaders and launches an inflammatory response that eventually leads to the buildup of minute scar tissue around the electrodes. The scar tissue, in turn, exponentially decreases the number of nerve cells that can be monitored, which causes the signal to grow weaker and less informative over time. In some patients, electrodes have reportedly continued recording from one or more neurons for several years after implantation, but these cases are the exception. Investigators are now searching for ways to minimize the body's intense reaction against foreign objects in the brain.

PERIPHERAL ADVANTAGES

SUCH CHALLENGES prompted the two of us to try to tap into the peripheral nervous system. Whereas the central nervous system consists of up to 100 billion nerve cells, the peripheral nervous system is mostly made up of fibers, known as axons, which are bundled together to form nerves. These axons are, in essence, very long projections—sometimes up to one meter in length—from nerve cells that transmit electrical signals between the central nervous system and the rest of the body.

Some of these peripheral nerve fibers connect the spinal cord to the muscles and hence allow the brain to control motor functions by sending signals down to the spinal cord. Other peripheral nerve fibers relay sensory information—such as limb position, temperature or touch—from the body to the spine, which then passes it on to the brain for further processing.

Because the remaining sensory nerves in a limb stump often continue emitting signals as if they were receiving inputs from the missing arm or leg, many amputees have a feeling that their lost appendage is still there—a condition known as phantom limb syndrome. If you could hook up those misfiring sensory axons to an artificial prosthetic that would send strong signals to the nerves, the brain would readily interpret the incoming signals as coming from a forearm, a hand and fingers.

Similarly, the motor axons of the peripheral nervous system are still capable of directing movement. Because the brain retains the ability to coordinate and match these varying motor signals to different motions, it would command a properly connected artificial limb to move in a natural way.

The problem is that peripheral axons will not grow longer unless they have a biological target with which they can make contact. Moreover, as is true in the central nervous system, the body tends to react badly to wires implanted into peripheral nerves.

Todd Kuiken of Northwestern University and his group have demonstrated, in human volunteers, an ingenious work-around to this problem: they use muscles in the chest as a kind of bridge between the stump from an amputated arm and the internal electronics of a prosthetic device. First, the Northwestern scientists cut the motor nerves to a handful of superficial muscles in the chest so that they do not receive any competing signals from the brain. Then they carefully redirect the motor axons that once connected the spinal column and the severed part of the arm so that they now connect to the superficial chest muscles instead. Within a matter of weeks, the rerouted nerves completely connect up with (or innervate) the chest muscles. Commands from the brain that are meant to stimulate the no longer existent arm now travel to the chest instead, thus causing those muscles to contract.

At this point, electrodes are placed on the skin of the chest to record the electrical activity of the individual muscles as they contract. Such recordings, in turn, indirectly reveal the signaling coming from the brain. After a few weeks of training, patients can move the prosthetic devices simply by thinking about what they want the device to do. For example, thinking about clasping a cup leads to a specific pattern of contractions in the chest that in turn "tells" the electronics in the prosthesis to bend the fingers in the artificial hand.

> **The nervous system's inborn ability to adapt allows scientists to create "living bridges" between nerves in a stump and the electronics of prostheses.**

Kuiken and his group have now used this approach, known as targeted muscle reinnervation, on dozens of amputees. Yet whether this technology can provide the fine control needed to re-create all the natural moves of a real hand and arm remains to be seen.

NEURAL BRIDGES

WE BELIEVE that fine-motor control of an artificial arm will ultimately require a different kind of link between living tissue and the prosthesis. Fortunately, muscles are not the only tissue that severed nerves will innervate. Nerves will also grow toward other nerves and will even accept transplanted nerves as part of the family, so to speak. Thus, about six years ago we decided to explore the possibility of using transplanted nerve fibers instead of muscle as the intermediary between the severed axons in a stump and the electrical wiring of a prosthetic device.

To create such a neural bridge, one first has to figure out how to grow nerve fibers that are long enough to span the gap between the host axons and the electronics. One of us (Smith) has developed a technique for stretching axons grown in cell culture to help them to achieve the required lengths. This process exploits the natural ability of nerves to elongate during normal growth spurts. One of the most extreme examples of this kind of "stretch growth" occurs in axons in the blue whale's spinal cord, which can elongate more than three centimeters a day and reach up to 30 meters in length.

In essence, we take a cell culture of neurons and start dividing it into two—pulling the halves a little farther apart each day. The axons in the middle get stretched and thus must grow in both directions to release the tension. Taking advantage of this natural mechanical process, we have developed devices we call axon elongators that can stretch-grow bundles of axons at the unprecedented experimental rate of one centimeter a day, which causes them to become as long as 10 centimeters and eventually probably even longer.

One of our first applications of these stretch-grown axons was to serve as a living bridge to repair severed peripheral nerves, such as occurs during trauma or surgery. When we implanted such axon bundles so that one end was close to the tip of a severed nerve in rats, the axons in the nerve reached out and grew along the length of the bridge. In fact, many of the axons inched their way so far into the previously paralyzed limb that the nerve was completely restored and the rats were able to regain function.

In addition, we determined that our neural bridges survived for at least four months after transplantation—all without triggering an immune reaction. Indeed, our neural bridges worked so well in rats that we are now trying them out in pigs. And if those experiments are successful, we will begin trials in people who have recently suffered major nerve damage.

Having demonstrated a way to direct and stimulate severed axons to regrow significantly, we next attempted to make a more complicated bridge that would allow the axons to communicate with the electronics in a prosthesis. Our vision was to find thin, conductive filaments that the body would not perceive as foreign. After some trial and error, we decided to create our filaments using various conductive polymers, one of which is polyaniline, a nitrogen-based organic compound that has long been known to carry electric current and that research by others had indicated might be tolerated by the body. So far, at least in studies of rodents, such specialized polymers do not appear to provoke a strong reaction from the immune system.

The next step was to induce a bundle of lab-grown neurons to grow around one end of those microfilaments and then stretch-grow the axons toward the host nerve. (The other end of the microfilaments would connect with the prosthesis via a wireless transmitter.) Ideally, axons from a stump would grow along our stretched axons and make contact with the filaments, which would pick up electrical signals from the stump's motor axons and convey them to the electronics; likewise, sensory signals sent from the electronics would travel up the filaments, depolarizing the sensory axons that had grown into the bridge and thereby relaying information to the spine and brain.

Using this approach in rats, we have found that the stretch-grown neural tissue provides a pathway that guides the host's regenerating axons to within a few tens of microns of the polymer filaments. That is close enough for different filaments to be able to record the signals of the nerves going in one direction (down the limb) and to stimulate the nerves going in the other direction (toward the brain). In essence, we have created a simple adapter cord that connects devices with two different kinds of plugs. Our hybrid of biological tissue (the neurons and their stretch-grown axons) and a nonbiological conductor would allow electronics in a prosthesis to plug in at one end and axons from the stump to plug in at the other end. So far these biohybrids have survived and maintained their integration with the host nerve for at least one month following transplantation, which suggests the immune system readily tolerates them because it would otherwise have destroyed them in a matter of days. Further tests at longer time points are ongoing.

NEXT STEPS

WHILE PROMISING, our biohybrid approach to neural engineering is still in its infancy. We do not yet know how long these bridges will last. Nor do we know whether the immune system will tolerate the polymer-based components over the long run. Moreover, we need to minimize interference from other electrical devices as well as improve the sensitivity of the individual nerve signals that are transmitted from the bridge to the prosthesis. Even if we can connect the neurons from a limb stump to a prosthesis, we still have no guarantee that the brain will be able to interpret the signals that originate in the prosthesis in a meaningful way.

Experience with hand transplants provides reason to believe that the brain might be up to the task. In performing such transplants, surgeons cannot possibly connect every last nerve fiber correctly from the host to the transplanted hand. Such precision turns out to be unnecessary, however. The brain essentially redraws its own internal map of which motor neurons do what, allowing it to eventually gain control of the new hand. Similarly, driving a robotic hand that is linked to the nervous system will probably require extensive retraining of the brain.

Further progress in the control of prosthetic limbs may well require a combination of advances in research on both the central and the peripheral nervous systems. Yet forming direct connections between the brain and advanced prosthetics—by tapping directly into the cerebrum, through repurposed chest muscles or linking across biohybrid bridges—offers the best chance of having an artificial arm that moves as gracefully and feels as natural as the original one. Although the interface between Luke Skywalker and his new arm was never revealed in *The Empire Strikes Back,* scientists are well on the way to figuring out how it must have been constructed.

MORE TO EXPLORE:

Stretch Growth of Integrated Axon Tracts: Extremes and Exploitations. Douglas H. Smith in *Progress in Neurobiology,* Vol. 89, No. 3, pages 231–239; November 2009.

Neural Tissue Engineering and Biohybridized Microsystems for Neurobiological Investigation in Vitro, Part 1. D. Kacy Cullen, John A. Wolf, Varadraj N. Vernekar, Jelena Vukasinovic and Michelle C. LaPlaca in *Critical Reviews in Biomedical Engineering,* Vol. 39, No. 3, pages 201–240; 2011.

Neural Tissue Engineering for Neuroregeneration and Biohybridized Interface Microsystems in Vivo, Part 2. D. Kacy Cullen, John A. Wolf, Douglas H. Smith and Bryan J. Pfister in *Critical Reviews in Biomedical Engineering,* Vol. 39, No. 3, pages 241–259; 2011.

SCIENTIFIC AMERICAN ONLINE
Listen to an interview with Cullen, as he discusses biohybrid bridges and the future of prosthetic devices, at **ScientificAmerican.com/jan2013/bionic-limb**