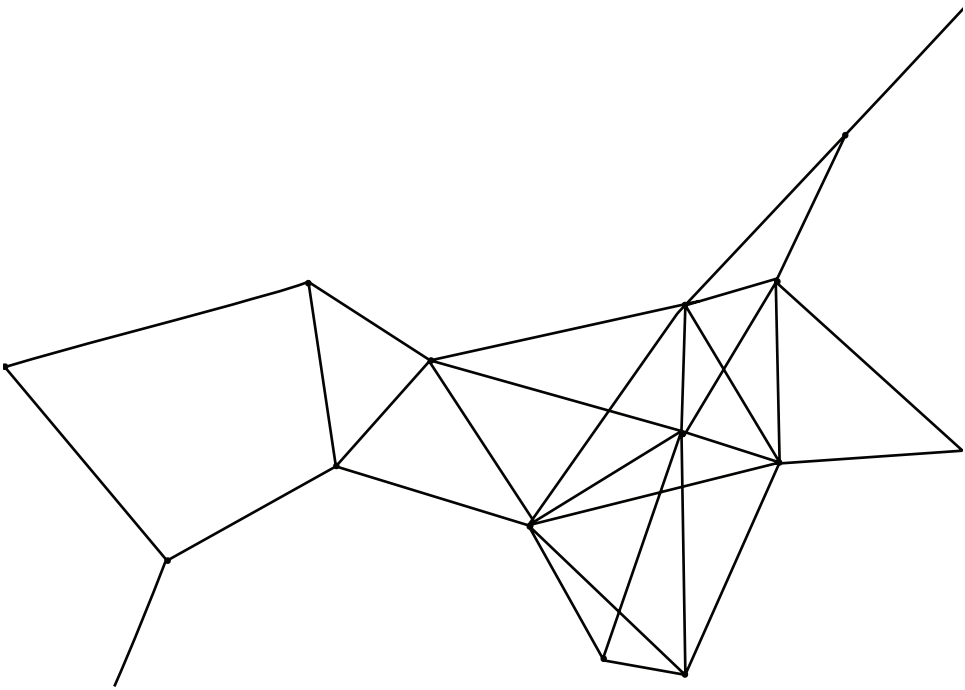
Faster.
Higher.
Stronger.



Faster. Higher. Stronger. These three powerful words are commonly linked together. They represent motivation, challenge and encouragement. They are the catalysts of success. When we hear these words we initially envision them embodied in humans. But, what about technology? Today's technological masterpieces have transcended far beyond the ordinary computer and into our biological lives. We no longer just type words on a computer but our bodies and minds work as one with computers, they help us become faster, higher, and stronger.

Meghan Smith

Fall 2017

Junior

Graphic Design 1: Typography

Faster

1

Smart Bionic Limbs are Reengineering the Human

Erik Sofge

There aren't enough bionic men on the planet to produce a proper stereotype. Even so, David the Farmer seems atypical. Ruddy, red-haired, and impossibly cheerful, he meets us on the gravel path outside his workshop. What I was expecting—a grizzled retiree limping stiffly through his daily chores—bears no resemblance to this 30-something mechanic climbing down from a massive tractor without hesitation, weaving between ATVs and scattered engine parts, moving from task to task with no evidence that he's part machine.

After a few minutes, there are clues, though: He always turns on his right leg, and his pants gather around his

left ankle, hinting at a limb that's slightly skeletal and decidedly nonbiological. Today that left leg will be replaced. That's why engineers from Össur, one of the world's largest prosthesis-makers, drove an hour west from the company's headquarters in Reykjavík, Iceland, to the farm where David Ingvason lives and works.

David the Farmer—the nickname they've given their star prosthesis tester, though he is actually employed as a full-time, on-site mechanic—is one of a limited pool of amputees fitted with the Symbionic Leg: an artificial knee, ankle, and foot that are integrated into a single bionic limb.On the farmland and surrounding terrain, in tall grass, and on moss-sprayed plains of volcanic rock, Ingvason regularly destroys his leg. He fouls the motors in muck and sludge, burns them out through unremitting use, and generally grinds one of the most sophisticated auto-adaptive devices on the planet, each one worth more than some sedans, into an inert, cybernetic paperweight. According to Össur's new technology search manager, Magnús Oddsson, all Ingvason has to do is call and they'll hand-deliver a new limb.

More often, he swings by Reykjavík himself wearing a backup leg and asking for a repair or replacement. Whatever David the Farmer

wants, he gets—the punishment he metes out to his leg, and the data that result, are simply too useful.

Össur began selling the Symbionic model as the world's first commercially available bionic leg last fall. It represents a significant shift in prostheses. The traditional half-measures, the stand-ins for lost limbs and senses, are now being imbued with machine intelligence. Ingvason's leg is, in fact, a robot, with sensors that detect its environment and gauge his intentions, and processors that determine the angle of his carbon-fiber foot as it swings forward. The same approach is being applied to prosthetic arms, in which complex algorithms determine how hard to grasp a water bottle or when to absorb the impact of a fall. Vision- and hearing-based prostheses bypass faulty organs and receptors entirely, processing and translating raw sensor data into signals that the brain can interpret. All of these bionic systems actively adapt to their users, restoring the body by serving it.

Take, for example, one of the most common prosthesis failures. A mechanical knee typically goes rigid as the heel lands, supporting the user's weight, then unlocks when pressure is applied to the toe. If that toe contact comes too early the leg collapses under its owner. The Symbionic Leg isn't so

easily fooled. Force sensors and accelerometers keep track of the leg's position relative to the environment and the user. Onboard processors analyze this input at a rate of 1000 times per second, deciding how best to respond—when to release tension and when to maintain it.

Since the leg knows where it is throughout each stride, achieving a rudimentary form of proprioception, it takes more than a stubbed toe to trigger a loose knee. If the prosthesis still somehow misreads the situation, the initial lurch of the user falling should activate its stumble-recovery mode. Like antilock brakes for the leg, the actuators will slow to a halt, and magnetically controlled fluid in the knee will become more viscous, creating resistance, as the entire system strains to keep the person from crumpling toppling.The result, Ingvason says, is that he rarely falls, or no more often than someone with two biological legs. He can drive ATVs, hike across glaciers, even ride a horse while herding sheep. "I don't have to think about it," he says. Before he went bionic, Ingvason fell constantly.

"With the old knee, it was every day, often more than once in a day," he says. "If I was walking and the toe hit something while swinging forward and I stepped on it, then I just went down. Now I'm walking on uneven ground

and high grass and sand and mud and everything." Ingvason's newly delivered limb is another Symbionic Leg, loaded with upgraded software that will allow the knee and the ankle to communicate with each other. Össur plans to develop this feature over the coming years, establishing what Oddsson calls networked intelligence. After putting it on, Ingvason limps, awkwardly at first, across dirt and gravel, past the rusting hulks of trucks and cars. Within a few minutes, the robot has calibrated itself.

With Ingvason's pant leg hitched up, it's impossible not to watch the limb in action. It's harsh and alien. The gray polymer shell,which partially conceals aircraft-grade aluminum, seems too skinny to support his weight; the ankle, too delicate for the 10,000 newtons of force it was built to withstand. But the leg is nimble and so quick to react, it's as though he were born with it.

The goal of current bionic research is to recover what was taken. In Ingvason's case, it's the leg he lost nearly 12 years ago, when he stopped to help a couple whose car had broken down in the rain. While he was working, another vehicle slipped off the wet road and plowed into him. Others' losses include arms torn off by industrial accidents or improvised bombs, and senses dulled or snuffed out

by disease. Despite decades of study, the prostheses developed to replace lost functions have been at once ingenious and disappointing.

Most prosthetic devices create their own health problems. Purely mechanical legs use a complex system of gears and analog triggers to allow people to walk, but users must hike up one hip with each step to keep the artificial toe from scraping the ground. Powered prosthetic arms tend to be locked in place during walking—and that dead weight throws off the user's balance and posture. Roughly 70 percent of amputees develop back and joint problems, and experts suggest that such "co-morbidities" force those who might be obese or in chronic pain to become even less mobile and less healthy, ultimately shortening their lives. The answer, for now, is in the algorithms. Össur's Symbionic Leg eliminates hip hiking through a simple robotic twitch: The toe actuates upward during each step, performing what's called dorsiflexion.

Other algorithms are more sophisticated, interpreting a torrent of sensor data as specific types of terrain. If the foot lands at a higher elevation, with the knee bent, the leg assumes the presence of stairs and adjusts accordingly. If the toe tips up on contact and the heel dips down, the artificial intelligence (AI)

suspects a slope and shifts the angle and resistance to assist in climbing.

The new generation of prosthetic arms has a different set of software challenges and solutions. DEKA, the research firm founded by inventor (and 2009 PM Breakthrough Award winner) Dean Kamen, is developing the third generation of its bionic limb, known internally as Gen 3. It's backed by DARPA's Revolutionizing Prosthetics program—a $100 million effort to create devices that are roughly equivalent in function to biological arms.

Now awaiting FDA approval, Gen 3 has 10 degrees of freedom (typical motorized arms have only two or three) and a range of algorithms that mimic the precise control of its flesh-and-blood counterpart. By moving his or her foot, which operates a wireless controller, the user can engage various preset grasping patterns. Previous upper-limb models have used foot switches but with nowhere near the number of grip -options, nor the machine intelligence and the force sensors that guide the artificial fingers and determine how much power should drive them. "The results have been incredible," says Stewart Coulter, the Gen 3 project manager.

"The other day, one of our testers was eating with chopsticks, doing a better job than I could."

The second arm funded by the Revolutionizing

Prosthetics program, the Modular Prosthetic Limb (MPL), developed at Johns Hopkins University, may lead to what many believe is the endgame for bionics: direct neural control. By embedding electrodes into a subject's existing nerves, or going through the skull and implanting them directly onto his or her cortex, researchers have been able to turn thoughts into action.

In a study conducted in 2010 at the University of Pittsburgh, a quadriplegic pressed the MPL's hand against his girlfriend's. Through trial and error, processors are taught to decrypt a user's thoughts and recognize a growing list of intentions. "The system's smart. It has to be," says Michael McLoughlin, Revolutionary Prosthetics' project manager at Johns Hopkins. "The algorithms interpret what the patient is trying to do, then do it."The MPL, in other words, isn't truly mind-controlled. The electrodes deliver orders, but it's the arm that decides how to carry them out. Or, rather, it's the network of machines—each jointed segment and finger with its own processor—that makes up the arm. The state of the art in powered prostheses is in some ways stranger than science fiction: a swarm of bots that obey the human mind, either through cables that snake out of the skull or by taking their best collective guess at those thoughts. Stranger still, this is just the beginning.

I tip my foot upward. The bionic foot that's bolted to the side of the table does the same. I press my toes into the floor and the prosthesis pivots downward into empty space. It's mirroring what I do, responding to the vibrations in my calf muscles, which are picked up by silicone embedded microphones strapped to my bare leg. The system isn't detecting the full-blown tremors of muscle activity but a set of lower-level, initial rumblings that begin when the subject first intends to move.

Unlike the tests run in Össur's Gait Lab, where users wearing sensor rigs climb ramps and cross gravel and sand, this research is happening behind closed doors. It's part of the company' own quest to find an alternative to invasive neural control. "What we would like to do," Oddsson says, "is exactly what the user wants. And for that we need some kind of a brain–computer interface."

Like other efforts, it's a work in progress: The 125 milliseconds it takes for vibrations to be processed into action is still painfully slow compared with the near-instant reflexes of a biological limb. A foot muscle can respond to input within 40 milliseconds faster than even the brain can deliver a response. But it's a technology worth pursuing. In the long term, experts agree that while implanted interfaces could change the

lives of millions of patients with amputations, spinal cord injuries, or neurological disorders, bionics that require major surgery will always be expensive, niche devices. For the millions suffering from debilitating strokes, or people with no serious disability but the money to pay for a wearable bionic system, a noninvasive BCI would change everything.

In other words, it's how we could reach that persistent fantasy of the able-bodied—true bionic augmentation. Even the most evasive experts I spoke with agreed that, while visions of superhuman amputees may be ridiculous, a combination of noninvasive BCIs and exoskeletons could turn decades of bionic research into a mainstream tool. California-based Ekso Bionics released the first commercially available exoskeleton in February; it's designed for patients with neurological or spinal cord damage. Billed as a "wearable robot," the system walks under its own power, currently via a remote control. An advanced version translates shifts in balance and feedback from canes into a natural stride. "That's the right use of the technology now, as a medical device," Ekso spokeswoman Beverly Millson says. "But it's really a technology platform. It's the beginning of wearing your devices, for whatever purpose you might have."

At MIT's Media Lab, prosthetics pioneer (and 2005 PM Breakthrough Award winner) Hugh Herr is still in the early stages of bionic augmentation research, with a lower-limb exoskeleton system that cuts in half the forces associated with walking. Herr, who lost both legs below the knee as a teenager, understands the need for restoration.

He's spun off a company, iWalk, to market his BiOM robotic ankle-and-foot system, now in clinical trials. Yet he says the endgame of his own work would be some kind of bionic vehicle that commuters might use to literally run to the office. Imagine sprinting 60 miles without breathing hard, across terrain that would stop an ATV in its tracks. "Something like the mountain bike will be completely laughable," Herr says. "We'll still have trucks to transport goods. At that point, though, driving alone across town in a metal box with four wheels would be just absurd."

Before leaving Össur, I coax a few specifics out of Oddsson. He's a scientist through and through. But he must have some sci-fi-tinged vision of what's beyond the Symbionic Leg. He tells me he wants to take what Össur has learned about the human body and the intricacies of gait—the tremendous forces and physics at work in a single step—and create

something that hijacks the nervous system directly. "It's not an exoskeleton. 'Smart trousers' might be more accurate," Oddsson says a little sheepishly. The goal at first would be to help stroke victims. The device would stimulate the muscles, providing commands that the brain or damaged nerves can't. "We would use the actuators that are already there, the muscles, and simply provide a new central controller," he says.

Eventually, Oddsson says, prosthetics research will disappear, replaced by advanced reconstructive technology. By 2050, he ballparks, limbs will be re-created—printed, grown, who knows?—and all of the arcane, biomechanical secrets collected by companies like Össur will be harnessed to finally restore flesh and bone. It's a strange best-case scenario: that an industry will innovate itself out of existence, its research seeding other scientific fields while all of that sophisticated technology migrates toward devices that change the way millions of us, abled or disabled, live and work.

Higher

2

The Rise of the Biobot: Mixing Biology and Technology

Reuven Cohen

In a recent article posted on the The Guardian website, author and new-age guru Deepak Chopra made an interesting observation. "A cyborg future is coming. Man's relationship with machine is merging and machines are an extension of our own intelligence. I'm so into it. I wear all kinds of bio-sensors to tell me what's going on inside me. It's the future," said Chopra.

Anyone who has read my posts lately will know that I've been going through a bit of an obsession, not just with bitcoin, but with biologically inspired technology. From wearable tech, to medical implants to complex interfaces between brain, mind and machine, recent developments in

combining machines and organisms of various types is a fascinating subject, but it also gives rise to some major ethical concerns. In a recent paper published in the renowned journal Angewandte Chemie International Edition, German scientists discuss the state of the art of research, opportunities, and risks facing so called "Cyborgs." Although published in German, the paper explores the latest developments at the interface between technical systems and living organisms.

First a bit of background, a "cyborg" is an acronym for a cybernetic organism. More simply, it describes a kind of chimera, a living organism combined with a machine. For many this may sound like some far-fetched Sci-fi novel, but today many people use intracorporeal medical systems (occurring within the body) such as pacemakers, complex prostheses or cochlear and retinal implants.

In a technical sense, many humans can already be considered as cyborgs. The report's authors note that in recent years, the current needs in the field of biomedicine and the enormous advances in micro-and nanotechnology have driven the original idea of cybernetic organism to new levels. They describe a compound yet functional interaction between living tissue and technical

systems that have reached an astonishing level of complexity. Modern man made systems are now able to interact or even replace central body functions. One common example is the frequently of implanted cardiac pacemakers. These types of implants help to compensate for diminished sensory abilities, for example using cochlear implants for hearing. Often they can complement nonfunctional body structures, such as arms or legs that can be partially or completely replaced by technical prostheses that can interact directly with your brain.

The use of prostheses or implants certainly isn't a new idea. Humans have been using implanted technical aids of various types for thousands of years to compensate for defects and impairments caused by traumatic events or illnesses or just vanity. Back as far back as Roman times, artificial dentures made of forged iron were used as dental implants to replace lost teeth.

Today, when a technical system or machine is used to replace a complex function within the body, such as gripping a hand, it is essential that the system be closely related to the living organism. Ideally, the system itself should be capable of receiving and sending the appropriate signals for the movement and control directly from the

central nervous system and especially the brain itself. Such "hardware / wetware interfaces" are typically referred to as brain-machine interfaces. They represent the interface to receive control commands from the technical systems and to which they may return feedback or stimulation.

Low-cost brain-machine interfaces make interfacing with our central nervous systems more accessible then ever before even for laymen. One example is the SpikerBoxthat is commercially sold by Backyard Brains. The company describes the product as "a great way to get introduced to hands-on neuroscience." Technically it is a" bioamplifier" that allows you to hear and see spikes (i.e. action potentials) of real living neurons in invertebrates (cricket, earthworm, or cockroach) which you can order from us or pick up in a local pet store or backyard. The company even offers a Smartphone Cable to plug your SpikerBox into your smartphone or tablet to look at the neurons firing in real time.

Needless to say, there are some pretty serious ethical concerns when you start talking about experimenting on backyard invertebrates. Ethical concerns aside, interfacing directly with lower forms of life opens up the potential for variety of interesting usages. The brains of lower organisms, such as insects, are much

less complex. They allow us to more easily understand how a certain movements are programmed, such as running or flying. The use of autonomous electronics implanted with in insects has enabled researchers with the able to remotely control insects for up to 3 hours. In many ways, insects provide the gold standard in terms of aerodynamics, sustainability, energy efficiency and biochemical sensor capabilities.

By understanding these core biological processes, the opportunity for so-called biobots, (i.e. large insects with implanted electronic and microfluidic control units) can be used in a new generation of tools, such as small flying objects for monitoring or even autonomous drones, which can based upon real life processes found within organisms. Moreover, these systems could also be powered by the organism's own thermal, kinetic, electric or chemical energy making them extremely energy efficient.

Grasping the fundamental way our biological processes work offers a huge potential to tap into some of the efficiencies we as humans enjoy. One such example is the energy efficiency of the human brain. It is both the most powerful and most efficient computer ever created. Running on just 23.3 watts, the brain makes up 2% of a person's weight. Despite this, even

at rest, the brain consumes 20% of the body's energy. The brain consumes energy at 10 times the rate of the rest of the body per gram of tissue. Even though your brain is the most energy intensive organ in your body, by computing technology standards, your brain uses extremely low amount of energy for an estimated 1exaFLOP (exaSCALE) computing capability.

Theoretically, an exaSCALE computing system – 100 times more computing capability than today's fastest systems – could be built with only more common x86 processors, but it would require as much as 2 gigawatts of power or roughly the peak power generation of the Hoover Dam. In terms of bang for your computing buck, your brain is by far the winner, at the rate of about 86,956,521 times more powerefficient than conventional computing systems. Some believe that the relationship between technology and biology may provide the next step in our evolution. For me this both fascinating and terrifying.

Stronger

3

The Interplay of Biology and Technology

Stanley Fields

Abstract.
Technologies for biological research arise in multiple ways—through serendipity, through inspired insights, and through incremental advances—and they are tightly coupled to progress in engineering. Underlying the complex dynamics of technology and biology are the different motivations of those who work in the two realms. Consideration of how methodologies emerge has implications for the planning of interdisciplinary centers and the training of the next generation of scientists.

Biologists now operate in a time when technology is not merely appreciated, but acclaimed. Research not based on specific

hypotheses and carried out by using methods to analyze a complete set of genes or proteins has been termed "discovery science," a moniker that comes uncomfortably close to suggesting that traditional research is incapable of discoveries. Funding agencies actively solicit proposals to develop techniques, especially those that will assist the analysis of the vast quantities of DNA sequence that are accumulating. Universities seek to build institutes that bring biologists into contact with mathematicians, computer scientists, physicists, and engineers.

Because technology provides the tools and biology the problems, the two should enjoy a happy marriage. But this relationship is complicated: methods may develop adventitiously and independent of the needs of the biological community; settings conducive to the advancement of technology are formidable to establish; and the ability to generate novel methodology may require training in multiple disciplines. Those who want answers to biological questions may not be concerned with the engineering and machinery that are necessary to reach them, and those who like to tinker with methods may not care about the answers at all.

Technology development is unlike most other research

in the biological sciences—so much so that one of the first postdoctoral fellows in my laboratory told me that it was not science at all. For one thing, technology development is totally unconstrained by the exigencies of billions of years of evolution.

It presents none of the surprising quirks of cellular processes that must be painstakingly deduced from a succession of clues, or suddenly glimpsed in a fragment of data. The technologist is free to imagine the use of tools that do not conform to those used by cells at any time in the earth's history. Another difference is that technology can be an all-or-nothing affair: because half of a novel method is not a method, this type of research may not be rewarded in the same way as progress in biological understanding. Yet another contrast is that critical incremental improvements in technology may be due as much to the acumen of engineers as to the cleverness of biologists.

With the current widespread efforts to foster the development and application of technologies, it is instructive to consider how methodologies for biology have arisen in the past. No universal pattern holds: discoveries emerge from varying venues, from contrasting personalities, and from distinct sources of inspiration. These variables should be kept

in mind when planning for scientific enterprises, research funding, and student training.

The Unforeseeable. Technologies may emerge in a completely unpredictable and unplanned fashion. Consider the method that is arguably most central to molecular biology over the last two decades: the polymerase chain reaction (PCR). Not only is it difficult to envision contemporary biology without PCR, but the procedure has made its way into the world beyond laboratory research: forensics, evolutionary studies, clinical applications, and much more. Kary Mullis, its inventor, describes (1) how in 1983, while employed at the Cetus Corporation to synthesize oligonucleotides, he had time on his hands to think about an improvement—not in DNA amplification but in DNA sequencing. He hoped to modify dideoxy sequencing (2) for the simple determination of the identity of the nucleotide at any position in a DNA molecule.

On a drive up the California coast, he imagined an experiment with four reactions, each containing a DNA template, primer, DNA polymerase, and one of the dideoxynucleotides carrying a label, with the label incorporated into the primer providing the means to identify the nucleotide immediately 3' to the primer. Mullis (1) writes, "I decided

the determination would be more definitive if, instead of just one oligonucleotide, I used two.

The two primers would bracket the targeted base pair I hoped to identify. . . . By directing one oligonucleotide to each strand of the sample DNA target, I could get complementary sequencing information about both strands." Yet Mullis (1) was troubled by a potential difficulty with this hypothetical method. "It would complicate the interpretation of the gel, I figured, if stray nucleotides introduced with the sample added themselves to the 3' end of the primers before the planned addition of the labeled ddNTP's [dideoxynucleotide triphosphates] I hit on an idea that appealed to my sense of esthetics and economy: I would apply the same enzyme, DNA polymerase, twice—first to eliminate the extraneous nucleotide triphosphates from the sample, then to incorporate the labeled ddNTP's. . . . Yet some questions still nagged at me.

Would the oligonucleotides extended by the mock reaction interfere with the subsequent reactions? What if they had been extended by many bases, instead of just one or two? What if they had been extended enough to create a sequence that included a binding site for the other primer molecule? Surely that would cause trouble. . . . No, far from it!

I was suddenly jolted by a realization. . . . the mock reaction would have doubled the number of DNA targets in the sample!" Analogous to the technological revelation leading to PCR, any extraordinary finding about a fundamental biological process that later forms the foundation for ingenious methodology may come from research in a wholly different direction.

The basis for the entire biotechnology industry—recombinant DNA methods—derives from studies on such topics as the defense of bacteria against phages, the enzymology of DNA replication, and the life cycle of retroviruses. Often it is laboratories interested in seemingly obscure topics, like the effect of calcium on bacterial DNA uptake, that make essential contributions.

The sort of flash of lightning that resulted in PCR or the fortuitously crucial findings that resulted in DNA cloning cannot, by definition, be planned or possibly even encouraged. These breakthroughs will occur in laboratories large and small, in universities with greater or lesser emphasis on research, and in the biotechnology and pharmaceutical industries, as well as in academia. The very unpredictability in where and when these events will take place is a powerful rationale for efforts to ensure that

public research funding is widely distributed and that large-scale projects do not consume a disproportionate share of available budgets.

Although these may not seem to be major concerns during the current period of bountiful appropriations for biomedical research in the United States and the heady afterglow of the draft human sequence, a slowdown in scientific funding is inevitable, so this debate will eventually come back to the fore.

The Insightful. Technologies that arise less serendipitously than did PCR often come from the efforts of innovative tinkerers to address specific biological problems. But even for the most revolutionary of methods, the antecedents are clear. Looking beyond Kary Mullis's epiphany, we can ask whether technology developments are typically the product of solitary inventors on late night drives. The answer is straightforward and not nearly so fanciful: new technologies come from good ideas based on previous technologies.

Working backwards, PCR arose from dideoxy sequencing, developed in Frederick Sanger's laboratory about 6 years earlier. This is a familiar method, made even more so with the recent determinations of the human genome sequence. And where did dideoxy

sequencing come from? This technique followed from another method of Sanger's called the "plus and minus system", a highly original technique from someone who spent his whole career developing novel methods. In this approach, a polymerization reaction is carried out with a primer/template combination, DNA polymerase, and all four nucleotides under conditions in which a variable number of bases is added to the primer, such that synthesis randomly terminates at essentially every nucleotide in the template in the region immediately downstream of the primer 3' terminus. Then, the extended primer/templates are split into eight reactions. In the four "minus" reactions, extension occurs with only three nucleotides, and synthesis terminates at positions corresponding to the nucleotide that has been omitted. In the four "plus" reactions, T4 DNA polymerase is used in the presence of a single nucleotide to degrade DNA from the 3' end of the extended primer until the enzyme reaches a position where it can incorporate the single nucleotide present. Fractionation of the eight reactions by PAGE and comparison of the products of the four minus and four plus reactions allows the sequence to be read. Sanger writes: "If successfully carried out, it is possible to deduce a sequence of 50 nucleotides in a few days."

Two exceptional features of this method were the direct readout of a sequence generated by extension of a template by DNA polymerase and the demonstration that denaturing gel electrophoresis can be used to separate relatively large DNA molecules that differ in length by a single nucleotide.

Going back earlier to ask where "plus and minus" comes from, we would find eventually many tools that enabled this strategy, including the introduction of radioactive precursors to follow DNA molecules, other separation methods for DNA fragments, restriction enzymes to prepare fragments that can be sequenced and that can act as primers, oligonucleotide synthesis to generate primers, isolation and characterization of DNA polymerases, etc. So by the early 1980s, all of the reagents and procedures were in place for PCR to come about. Many molecular biologists other than Kary Mullis could have invented PCR, making its eventual introduction inevitable. All that was needed was the inspiration of one individual with the willingness to putter about with enzymes and primers.

Others have also noted the fact that there are always precursors to any invention. For example, Diamond points out that for the light bulb, many

incandescent light bulbs were patented in the 40 years preceding Edison's version, and for the Wright brothers' plane he points to manned unpowered gliders and unmanned powered airplanes. Diamond's view is that the pattern of world history would not have been significantly different if some genius inventor had not lived at some particular time and place.

In the case of biology, too, examples are hard to come by in which history would be different had some specific biologist not made a particular contribution. This is true not only of technological advances, but even of the most idiosyncratic of biological choices—say, that of Sydney Brenner to analyze the nematode worm Caenorhabditis elegans; although this choice would likely not have been made by anyone else, doubtless other model organisms would have emerged.

In the case of Sanger, his especial contributions to protein sequencing, RNA sequencing, and DNA sequencing probably advanced the pace at which molecular biology developed by several years. Notably, Sanger spent much of his career at the Medical Research Council Laboratory of Molecular Biology, where he was free from the necessity to apply for grants, teach, or carry out much administration. Sanger was the quintessential

methodologist, pushing the envelope of how biological questions could be asked because of an intense drive to create tools, rather than a compelling interest in the results—often spectacular—that these tools wrought. In addition, he benefited from being surrounded by a small, but stellar set of colleagues interested, for example, in developing methodologies, the flow of genetic information, mechanisms of early development, and protein structure. Perhaps not so surprisingly, this atmosphere led as well to such seminal ideas as monoclonal antibodies and crystallographic electron microscopy techniques.

The Improved.
Many technological advances are incremental refinements of existing methods that make them faster, more sensitive, or more efficient. These are not trivial considerations—for technology, unlike most other aspects of biology, has always been tightly coupled to engineering. Consider again the example of PCR. The original description of the technique was little more than a proof of concept, not the protocol now carried out by the sleek ranks of machines found in many laboratories.

This method would be monumentally less powerful if it required the removal of an incubation tube from a water bath every 2 minutes, and the return of the tube to a bath of a

different temperature. That these tedious steps are not manually carried out is a testament to the rapid perception that automated equipment was needed. In the generic sense of "engineering," even the DNA polymerase was tinkered with to produce some of the accurate, thermostable enzymes of today's PCR.

With the commitment more than a decade ago to determine the human genome sequence, it became clear that major enhancements in DNA sequencing procedures were essential, and that individual small laboratory science could not achieve biology's version of the Manhattan Project. Deciphering the 3 billion nucleotides of human DNA did not require a wholly new method: Sanger's approach of 1977 was up to the job more than 20 years later. But not, of course, as Sanger originally described it. The procedure had to be massively retooled akin to the way that today's flight from Seattle to Tokyo only vaguely resembles that first spin around Kitty Hawk. The method had to be converted to a fluorescent-based technology that allowed a machine to read off the sequence of bases. The machines had to be improved for faster separations, smaller volumes, increased numbers of reactions, automated reloading, and the like. Programs were necessary to assign a quality score to

every determined base, to assemble the data from the phenomenal ramp-up in output, and to coordinate the millions of clones and reactions and sequence. Biologists alone could not do this. The technology developments required expertise in engineering, physics, chemistry, and computer science, not to mention management. The engineers building DNA sequencers had to work side by side with those knowledgeable about the likes of nucleotide analogues, gel matrices, fluorescent compounds, and electrophoretic separations.

Computer scientists had to know about the properties of polymerases and substrates, as well as the ratio of repeat sequences in organisms. PCR and DNA sequencing are but two examples in which significant industrial enterprises grew up around a technology. Indeed, most technological advances require commercial involvement at two distinct stages in their evolution: first, to convert a prototype to a robust device, and second, to manufacture and market these devices for worldwide use. This potential to spin off newfangled industries is a major economic benefit of technological research. But it is noteworthy that—PCR notwithstanding—nearly every important technology in use in biology today originated in an academic laboratory. These include the above-mentioned

developments in DNA sequencing, oligonucleotide synthesis, recombinant DNA, and monoclonal antibodies, as well as others in cell sorting and imaging techniques, in vitro mutagenesis, and biological mass spectrometry. In the broadest sense of technology, innovations derived from basic research include the transgenic and knockout animals that have revolutionized mammalian genetics.

The Next Generation.
With biology now moving in directions that can require experiments of a bigger scale, faster analysis, and smaller reagent volume than ever before, waiting for the next fortuitous breakthrough is not an appealing option. Instead, a wave of interdisciplinary institutes is rolling across the scientific horizon, with the mandate to devise and employ cutting edge technologies for the solution of biological problems.

These institutes potentially will be the focal point of many universities' commitment to buildings and faculty hirings for the biomedical sciences over the next several years. A primary goal in establishing such enterprises is often to unite biologists and technologists of different stripes in a common locale.

It is worth keeping in mind that the prototype for these nontraditional institutes—although perhaps the

antithesis in its current realization—is the modern genome center. Here is where the continuing efforts to sequence additional organisms and additional versions of the human have of necessity come to be sited.

Yet once this formidable array of machines, programs, and the technical workforce to operate them was in place, the enterprise has become more removed from innovation because of the necessity to operate in a production mode, whether nucleotides are determined in St. Louis, Cambridge, Hinxton, or Yokohama. There is little place within the defined tasks beginning with clone construction and ending with finished sequence for the offbeat developments that might arise when scientists and engineers in multiple disciplines rub shoulders with each other.
The fate of genome centers is emblematic of the reality that innovation and scale are rarely compatible. Although a technology may have its invention and initial elaboration occur in an academic setting, its large scale application is best done in industry.

If the competition to sequence the human genome is a signpost, we still have a distance to go to make this transition smoother.How can a community of diverse scientists be brought together—in fresh ventures

or existing circumstances—to enable unconventional advances? Mere proximity is not sufficient for productive connections to emerge, no more than physical distance, in this age of electronic communication, must inevitably be a barrier. A collaborative spirit may be engendered as part of a process to solve biological or technical questions, to reorganize administrative entities, or to educate students.

First, teams of disparate talents can be assembled to achieve a broad scientific goal, much as took place in the human genome project. However, it is difficult to conceive of a wide-ranging project targeted on the proteome—the complement of proteins encoded by the genome—that would follow the genome project and encompass the identity, abundance, modification, interaction, and function of every protein: that is too much like trying to solve all of biology itself. But it is reasonable to imagine more focused endpoints that represent a segment of such a proteome project perhaps the detailed understanding of specific cellular processes such as signaling, protein trafficking, organelle biogenesis, or gene regulation.

Such goals will of necessity engender technology developments for example, additional imaging methods at the level of molecules, cells, tissues, and organisms

will be needed.Second, interdisciplinary programs can be established with technological goals as endpoints. Efforts are already under way to array large complements of proteins for high throughput parallel assays. The continued study of human genetics demands that the genotypes of thousands of individuals be obtained to correlate polymorphisms with disease propensities. Rapid diagnostics in the future will depend on tiny lab-on-a-chip devices.

Analysis of cell function will require the ability to analyze single cells for the properties of their proteins, nucleic acids, lipids, and small molecules. Notably, both scientific and technological objectives can be addressed in the context of either a single laboratory, a group of laboratories spread across a campus or country, or a cutting-edge facility dedicated to these purposes.

Third, rather than to create new institutes based on scientific or technological rationales, another possibility for productive partnership is simply to recruit individuals of contrasting talents into existing structures. But how does a department called Genetics hire an engineer, or one called Biological Chemistry an informatics specialist, or one called Microbiology a physicist? Perhaps part of the problem lies in the current arrangement

of specializations. Faculty in delimited departments labeled Cell Biology, Developmental Biology, Molecular Biology, and Biochemistry could already be scrambled with no one realizing that affiliations have been changed. Maybe the simplicity of a broadly named department might allow all of the skills needed to make fundamental discoveries to come together within an existing structure.

Finally, the least complicated solution to bringing people together may lie in our training of the next generation of scientists. Graduate courses for biologists could be taught by teams of faculty affiliated with schools of Engineering, Arts and Sciences, and Medicine. Computational skills may require that computer scientists and mathematicians teach alongside biologists, because bioinformatics and statistics are as much the nuts and bolts of biology as cell division and protein sorting.

An understanding of bioinstrumentation encompassing the principles of cell sorters, mass spectrometers, photonics, and detector electronics may need the participation of engineers, so that biologists do not treat their instruments as black boxes. Establishing creative approaches to interdisciplinary education could provide the basis for an array of expertises

to collaborate in both pedagogical and practical enterprises. Students should be encouraged to make unorthodox choices to meet their requirements, because it is at the interfaces of biology and other sciences that many of the future discoveries will be made, at the interfaces of biology and engineering that these discoveries will come to be exploited, and at the interfaces of biology and ethics and law that their consequences for society will be decided. The challenges here should not be underestimated.
If universities establish interdisciplinary centers in sparkling new buildings, will they weaken their current academic departments by taking away faculty lines and isolating freshly recruited talent? How are the research accomplishments of collaborative individuals appropriately measured? How is tenure decided for those whose names are on multiauthor papers that include other senior investigators? Can faculty be evaluated fairly for their teaching when it is done outside of their home departments?

How will students be trained to convey their science to audiences themselves trained in distinct disciplines? Technology will continue to drive biology, and biology will continue to drive technology. The emergence of noteworthy

techniques and pivotal findings requires that the funding and facilities to pursue imaginative ideas be available and that those along the whole spectrum of knowledge be encouraged to participate together. And those who are trained in this spirit may make the most remarkable contributions.