The interplay of biology and technology

Stanley Fields*

Howard Hughes Medical Institute, Departments of Genetics and Medicine, University of Washington, Box 357360, Seattle, WA 98195

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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

*E-mail: fields@u.washington.edu.

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 (2). This is a familiar method, made even more so with the recent determinations of the human genome sequence (3, 4). And where did dideoxy sequencing come from? This technique followed from another method of Sanger's called the "plus and minus system" (5), 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 (5) 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 (6) 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 (6). 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* (7); 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 (8) and crystallographic electron microscopy techniques (9).

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 (10), 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 (2). 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 (11). The machines had to be improved for faster separations, smaller volumes, increased numbers of reactions, automated reloading, and the like (12–14). Programs were necessary to assign a quality score to every determined base (15), to assemble the data from the phenomenal ramp-up in output (16), and to coordinate the millions of clones and reactions and sequence reads.

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 different 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 (17, 18). 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 build-

ings, 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.

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