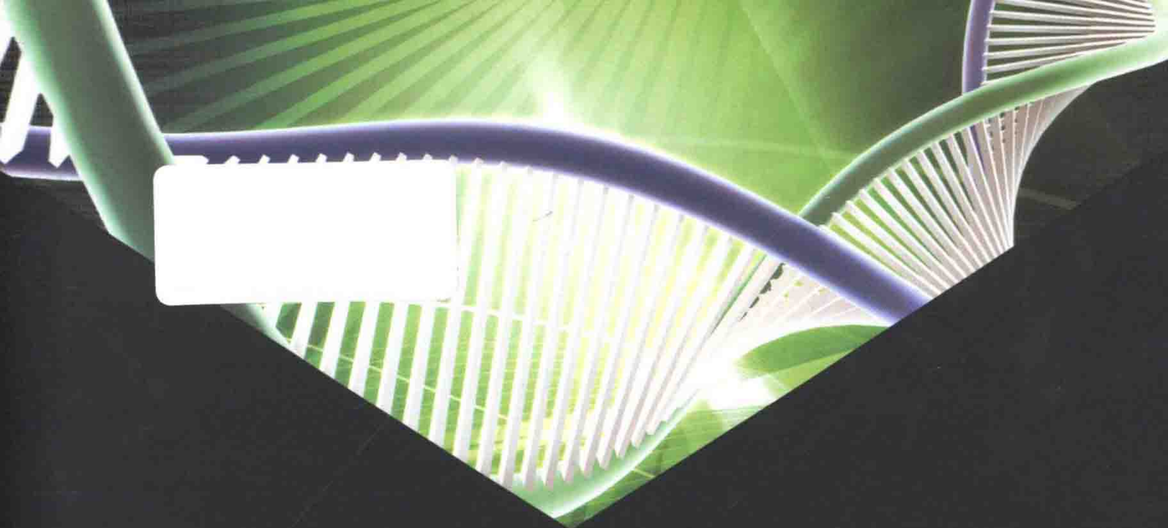

WILLIAM HOFFMAN & LEO FURCHT

THE BIOLOGIST'S IMAGINATION

Innovation in the Biosciences

The Biologist's Imagination

INNOVATION IN THE BIOSCIENCES

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and
Leo Furcht

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INTRODUCTION

The ability of human societies to modify and transform biological systems will increase more in this century than it has in the hundred centuries since the dawn of agriculture. . . .

—*Nature*

Without deviation from the norm, progress is not possible.

—Frank Zappa

During an interview in 1929, Albert Einstein was asked if he trusted more to his imagination than to his knowledge. His answer has echoed through the decades since. "I am enough of an artist to draw freely upon my imagination," he said in "What Life Means to Einstein," published in *The Saturday Evening Post*. "Imagination is more important than knowledge. Knowledge is limited. Imagination encircles the world."

Imagination is a mysterious thing. Springing from the provinces and principalities of the unconscious, imagination takes us from what we know to the infinite realm of what we do not know, a poet once said. Imagination is the life force of our literature, which has its ancient roots in the oral tradition of storytelling; our art, which continues to keep archeologists and anthropologists busy; and our music, which probably filled the air long before recorded history when the acoustics of some prehistoric cave chambers are taken into account. Imagination is what has brought human beings from the earliest days of cave painting and tool making to the days of moon shots and iPhones and genomes decoded to reveal how life works as an information system, a bioinformation system. Imagination is the wellspring of creativity and the key to health, wealth, and well-being. The twentieth century established what Einstein called "the democracy of the intellect," a new epoch in which intellect, imagination, and creativity can blossom anywhere in the world, not just in elite enclaves among a privileged few.

It was imagination that drove James Watson and Francis Crick in their search for the structure of DNA in the middle of the twentieth century. Their discovery was one of the most socially and economically valuable in the history of science, "ranking alongside the transistor and laser," reflected a veteran science journalist on its sixtieth anniversary. Less than a quarter century after the discovery, venture capitalist Robert Swanson and biochemist Herbert Boyer imagined and then founded Genentech, giving birth to a new industry based on the idea that value could be created by moving DNA from one organism to another. Their dream was to harness recombinant DNA technology to design and manufacture new types of drugs. Today those drugs, called biologics, are used to treat millions of patients, enabling many to live normal lives. Swanson and Boyer located their new company in the technological field of dreams south of San Francisco: Silicon Valley, the *über*-cluster of innovation.

This book is about the history and current state of innovation in the biosciences in our changing world. It is about how imagination pushes back the frontiers of what we understand about living things. It is about how imagination challenges conventional thinking and norms by bringing together the sciences of life, creative enterprise, and a restless entrepreneurial drive. And it is about the places where these interactions tend to occur, the fertile soil where ideas take root.

What we know about biology figures into the medications we take, the vaccines we use to immunize our children, the food we eat, the water we drink, the air we breathe, and the way we dispose of our waste. Biology gives us fabrics that clothe us and ecosystems that sustain us. From biological knowledge we create genetic tests that enable us to learn about our health and risks for developing disease, about where we came from and possibly about where we are headed. Detailed understanding of biological components and processes plus converging domains of knowledge and the explosion in sharing information are accelerating the pace of discovery. The technology of biology has already entered our economic affairs in a big way. Today our ability to make changes in the DNA molecule, shuttle DNA from one life form to another, manipulate biological processes, alter biological endowment, and test biological response accounts for more than 2 percent of what the US economy produces every year in revenues. Those revenues are growing 15 percent annually by some estimates (see Figure I.1).

The tools of bioscience innovation are also telling us a lot about the living systems of which we are part. As the biologist Rachel Carson was writing and publishing her 1962 environmental classic *Silent Spring*, Marshall Nirenberg and Har Gobind Khorana and other geneticists and biochemists were deciphering the genetic code and protein synthesis and explaining the chemistry of life. Today the tools of bioscience and genetics are showing that healthy ecosystems are critical for economic development. They help us understand that clean air and water are vital for human health and productivity, that biodiversity may ease the burden of infectious disease, and that forests are important carbon storehouses for greenhouse gas emissions. They also help us connect ocean acidification to declining coral reefs and commercial fish stocks and empower us to develop new food crop lines that are better suited to thrive in a changing climate, yielding more food from less land using less water, fertilizers, and pesticides.

We have grown accustomed to taking the remarkable advances in the biosciences fairly in stride. That was highlighted by what happened in just one week in the spring of 2013. First, geneticists confirmed the hybrid ancestry of New World cattle such as Texas Longhorns with their rich genetic diversity and ability to adapt

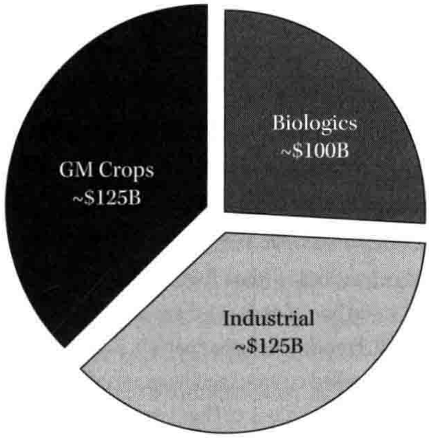

FIGURE I.1 United States biotech revenue in billions of US dollars (B). Genetically modified products in the US Bioeconomy (2012 estimate): 350B or equivalent to 2.5 percent of GDP.
Source: Robert Carlson, Biodesic, synthesis.cc blog, January 1, 2014, with permission.

to drought. Their DNA is derived from cattle that spanned the globe, from the Iberian cattle that came with Columbus to the ancestral aurochs of the Middle East and India, telling a story of human and cattle co-migration. Then scientists reported the genetic sequence of the mountain pine beetle, a notorious pest that has destroyed more than 15 million hectares of forest in western North America and made them vulnerable to wildfires. Unusually dry conditions in the pine forests, a consequence of climate change, enable the beetle to expand its range northward. In a pernicious feedback loop, the beetle itself contributes to a warming planet by destroying forests. Shortly thereafter, bioengineers reported eyebrow-raising experimental results. They constructed functional transistor-like logic gates inside cells, paving the way for living computers. Cancer researchers then reported that mutated-driver genes responsible for most if not all malignancies operate through as few as twelve cell-signaling pathways, giving innovative drug designers a clearer pathway to developing safe and effective therapies.

To innovate stems from the root Latin word *innovare*, to renew or change, which in turn stems from *novare,* to make new. *Innovation* is a word that gained currency in published materials beginning in the eighteenth century with the Industrial Revolution (Figure I.2), although the word *innovation* does not appear in Adam Smith's *The Wealth of Nations* (1776). *Innovation* is a word inextricably bound with the American democratic experiment. Indeed, America's form of democracy has itself proved to be an unparalleled innovation. James Madison, the father of the Constitution and a student of the "science of Government," employed the term in the *Federalist Papers* to describe the way critics saw the Framers' proposed structure of a national government. "And it is asked by what authority this bold and radical innovation was undertaken."

To Madison, innovation in the structure of republican government was both desirable and necessary for the American experiment to work. To his *Federalist*

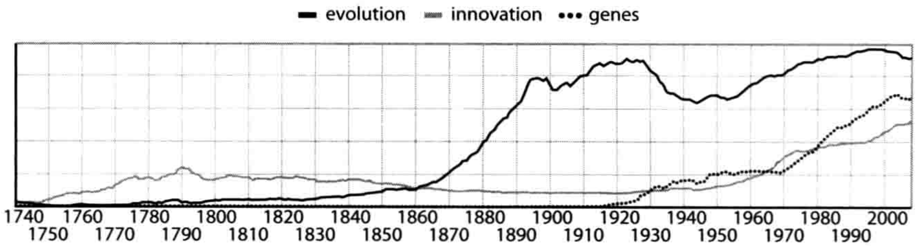

FIGURE I.2 Innovation (light line), evolution (dark line), and genes (broken line) 1700–2008. The graph illustrates the frequency trend line of each word appearing in 5.2 million books published in American English, British English, French, German, Spanish, Russian, and Chinese scanned by Google Books in an exercise that has been called cultural genomics or culturomics. Jean-Baptiste Michel et al., "Quantitative Analysis of Culture Using Millions of Digitized Books." *Science* 331 (2011):176–182.
Source: Google Books Ngram Viewer, http://books.google.com/ngrams.

Papers coauthor Alexander Hamilton, innovation could be a creative and beneficial action or a mischief-making nuisance when it came to administration and governance. Yet it was Hamilton more than any of his contemporary nation-builders who understood that innovation in economic affairs—the mix of diverse ideas, experimentation, and capital—was the dynamo of the capitalist system and the secret to material affluence. The role of government is to ensure that the dynamo performs its task as efficiently as possible consistent with the public good. Hamilton wrote in the *Federalist Papers* that "*in the usual progress of things, the necessities of a nation, in every stage of its existence, will be found at least equal to its resources*" (emphasis in original). His idea of energetic government and Madison's idea of individual liberty were in some tension with each other in 1787. That tension still exists. Will today's *necessities* for long-term economic growth find the *resources* to support federally funded research and development essential for that growth? Or will the current and projected decline in federal research funding as a percentage of the nation's overall economic output—headlined as the "The Coming R&D Crash"—put Hamilton's emphatic belief at risk?

Living things respond to changes in their ecosystems through experimentation, adaptation, and natural selection. When viewed as dynamic systems, economies also seem to respond organically, from the ground up, to changing environments. Entrepreneurship is the source of capitalism's "creative destruction," an ongoing process that economist Joseph Schumpeter likened to evolution. Innovation can be thought of as the means by which dynamic economies adapt to new realities, new necessities, new forces in the economic ecosystem, producing economic growth and social change. Today human ingenuity, the application of imagination, is expressed in the economic arena principally through technology. New tools, devices, products, processes, methods, and practices that arise from the adoption and use of technologies generate positive feedbacks, stimulating further technology development and economic activity. We reorchestrate the parts and processes that constitute technology to better serve our needs. We adapt to new economic realities by creating new technologies and then find ways to expedite their entry into the marketplace and society.

Innovation systems in the biosciences build wealth through brainpower using micro-amounts of elements and natural resources: DNA, RNA, proteins, enzymes, carbohydrates, cells, silicon, carbon, gallium, platinum, phosphorous, and a host of other elements, molecules, compounds, substances, fibers, and materials. Innovation is shrinking industrial machines and medical devices to the scale of atoms and molecules and building microbial factories. Among the biological technologies flowing into our economic ecosystem are tools to read (sequence), write (synthesize), and edit with exquisite precision the code of life—DNA—and engineer the fundamental unit of life—the cell. New instruments have driven down the cost of reading and writing DNA dramatically in the past decade, at a much faster pace than the drop in the cost of computing power over the past five decades. These tools and instruments are or will be available to more and more people—creative individuals, research teams, entrepreneurs, college and high-school students, even do-it-yourself hobbyists working at home, in garages, or in community laboratories.

Our story about the history and current state of innovation in the biosciences is divided into seven chapters, all bound by recurrent themes woven throughout the narrative. We cover subjects as seemingly disparate as the history of technology, economics, molecular biology and genetics, neuroscience, geography, evolution, education, globalization, clinical trials, technology transfer, the digital revolution, patent law, and public policy.

To put the remarkable world of technological change we entered more than two centuries ago into context, we reflect on the history of technology in chapter 1. Technological innovation has is roots both in myth and in the observations of pre-Socratic natural philosophers. It came to the fore in late Middle Ages and exploded beginning with the Industrial Revolution. The Lunar Society of Birmingham linked science, industry, and society for the first time, setting the stage for the technology-driven modern economy. What science historian Horace Judson calls "the great endeavor of biology" beginning in the nineteenth century provided the foundation for the rise of molecular biology and the biotechnology industry in the twentieth century and completion of the Human Genome Project early in the twenty-first century.

In chapter 2, we describe how the pharmaceutical industry came to account for 90 percent of economic output in today's trillion-dollar-plus global life sciences sector. Its small-molecule drugs still dominate the market, though biopharmaceutical drugs based on advances in molecular biology constitute a growing proportion of innovation in the industry and of drug sales. U.S. Food and Drug Administration approvals of new molecular entities have grown in recent years after a period of stagnation, yet R&D efficiency in pharmaceutical industry has declined with increases in investment. High-throughput screening of candidate molecules together with advances in "omics" technologies (genomics, transcriptomics, proteomics, metabolomics) and biomarker identification may help reverse this trend, as may patient selection for early-stage trials based on their genetic profile. Meanwhile, manufacturing of biopharmaceutical drugs has become highly efficient. We explain how the offshoring of pharmaceutical R&D, biomanufacturing, and clinical trials gives host countries greater opportunity to innovate themselves with domestic talent and explore differences in the way their ethnic groups respond to drugs based on their genetic makeup (pharmacogenomics). Regulatory bodies and public health agencies are hard pressed to keep up with these rapid, technology-driven developments.

The European "Age of Discovery" five centuries ago opened up global trade, including the exchange of animal, plant, and microbial species between the Old and New Worlds. Today genomic sequences of many species are transported over high-speed data networks rather than in organisms aboard ships, as in Columbus's day. Yet even in an era of global networks, bioscience startups continue to show a strong tendency to cluster in specific regions with strong research assets, which is the focus of chapter 3. Bioscience tends to catalyze itself in these urban regions, making the landscape of bioscience innovation spiky rather than flat on the global map. Technology clusters that join entrepreneurship with finance, support services, research, and education tend to emerge spontaneously. Around the world, nations and regions are trying to seed clusters by building incubators, accelerators, and science parks, typically near research facilities. Innovation and location like to march together, especially in drug, diagnostic testing, and medical device entrepreneurship. The global distribution of entrepreneurial bioscience will depend on the forces of technological innovation, urbanization, globalization, and research investment.

The Augustinian monk Gregor Mendel's pea experiments laid the foundation for modern genetics. Mendel's aptitude for math gives us license to track his legacy from pea genetics to petabytes of genomic information in chapter 4. Yet Mendel's heavy use of statistics made his famous paper practically impenetrable to the botanists of his day. Today's communications technologies, search engines, and open access make specialized scientific information readily available to scientists and innovators alike. The biostatistical analysis Mendel did in his head is done now with powerful computers and bioinformatics software that generate cumulative genomic data measured in petabytes. Biological and digital technologies will be critical for mitigating the effects of greenhouse gas emissions on biogeochemical cycles and food production. They are beginning to revolutionize how we think about human health and disease. Though direct-to-consumer (DTC) genetic testing companies marketing disease-risk information face regulatory hurdles, the market for DTC testing services is expected to grow because many people want to know what their disease risks may be. In the laboratory, next-generation DNA sequencing is developing at a faster pace than Moore's Law in computing. The expected deluge of whole genome sequence information will challenge our ability to interpret it accurately so that clinical genomics can realize its promise of improving health outcomes and reducing costs. Meanwhile, mobile devices that carry applications for biomedical research, community health reporting, and clinical genomics have made their debut.

The story of universities and technology transfer, the subject of chapter 5, begins at the University of Bologna, the first university in the West, located in a dynamic, entrepreneurial region of Italy. Since their first appearance a millennium ago, universities have been in the business of knowledge transfer and, for the past two centuries, of knowledge generation through research. Today universities, government, and industry are viewed as the triple helix of knowledge production and innovation. Enactment of the Morrill Act in 1862 laid the foundation for US federal involvement in knowledge transfer from academia to the economy. Private investment and government initiatives to spur technology transfer in the twentieth century culminated with enactment of the Bayh–Dole Act in 1980, which enabled university faculty to patent technologies and processes they invented. As we describe at length, the Bayh–Dole Act was key to the rise of the biotechnology industry and transformed academic bioscience and innovation in the United States. Subsequent federal legislation sought to enhance technology transfer from federal agencies, national laboratories, and universities to the private sector, particularly to small businesses and entrepreneurial startups. Today, universities are exploring new models for technology transfer through venture centers, partnerships, and innovation networks.

Intellectual property, information, and incentives are well understood to be keys to innovation, as we show in chapter 6. Although much has changed since enactment of the US Patent Act of 1790, "the basic idea that inventors have the right to patent their inventions has not," wrote John Roberts, chief justice of the US Supreme Court. Yet the patent system has been burdened with administrative backlogs and legal disputes. Congress sought to update the system in 2011 when it passed and President Barack Obama signed the America Invents Act, which replaces the first-to-invent with a first-to-file system and implements a post-grant review process for issued patents. In the biosciences, the public debate over whether genes can be patented went before the US Supreme Court in 2013. The gene patenting issue reveals the tension between proprietary interests important for innovation and the practice of medicine and public health uninhibited by limits imposed by proprietary interests. Successful innovation depends on a system that aligns incentives in a way that maximizes value both to the innovator and to society. Intellectual property, open-source and networked science, and precompetitive collaboration all contribute to innovation in drug discovery and development and in agriculture as well as in emerging technological fields like synthetic biology and genomic medicine.

In the twenty-first century, innovation will be broadly framed by exploration of evolution—the evolution of the universe, evolution by natural selection on Earth and perhaps beyond, and ongoing technological and cultural evolution. As we describe in chapter 7, we will see the evolution of institutions, organizations, and innovation networks; the evolution of public health agencies in response to pandemic influenza and other biothreats; and the evolution of the global middle class. The systematic practice of innovation in the industrial era—the application of ideas, inventions and technology to markets, trade, and social systems—is now being joined with the code of life. Our ability to read, write, and edit DNA and re-engineer the cell empowers new processes for discovery and development in medicine, agriculture, industry, energy production, and environmental health. It also opens a window to our evolutionary past and will influence how we live, how well we live out our years, and even how we evolve.

For the first three decades of its existence as an industrial concern, biotechnology required us "to indulge in a mass suspension of disbelief, to relax our critical facilities to allow ourselves to believe—despite all the reasons to the contrary—that we can create something that simply did not exist before." That was the way a critic described the industry's persistent lure and regular supply of gaffes and shortfalls. But biotechnology is moving beyond the drug development model that has dominated the field. Whether it is through harnessing the computational power of the code of life, the regenerative power of the cell, or the manufacturing and biomass conversion powers of microorganisms, innovators are already are already making their presence felt. Their productive handiwork is reflected in the growth of regional, national, and international collaborations in the field and in global initiatives to address the changing circumstances of life and living systems. Over time, it will be reflected in national economic growth statistics.

Finding the right combination of policies, processes, incentives, and initiatives to spur innovation from the swelling biological knowledge bank will take what the application of new knowledge normally takes and what Einstein and Hamilton understood implicitly: imagination and experimentation. It will also take new forms of organization from the self-organizing creatures that we are, as evidenced by the symphonic orchestration of our genes, our brain's ability to reorganize its neural pathways in response to new conditions and experiences, and our complex social systems.

In the late eighteenth century, scientists, philosophers, mechanics, entrepreneurs, and investors applied their individual ingenuity in a systematic way to usher in a world of labor-saving and time-liberating machines, devices, and processes. In the early twenty-first century, we imagine and experiment at will. Ingenuity is every bit as valuable in the big-data era as it was in the machine age. We gather around good ideas arising from what we know and what we learn about the codes, elements, mechanisms, and mazes of biology to build valuable and useful things. Nature has supplied innovators in the field with billions of years of experimental results. Technology has equipped them with powerful new tools, enabling them to undertake their own experiments in laboratories, *in silico*, in garages, and in the marketplace. And imagination, as Einstein said nearly a century ago, encircles the world.

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