THE AGE OF LIVING MACHINES

HOW BIOLOGY WILL BUILD THE NEXT TECHNOLOGY REVOLUTION

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CONTENTS

PROLOGUE

For the last couple of decades, as a dean and then provost at Yale, and then as president and now president emerita of the Massachusetts Institute of Technology (MIT), I've had the privilege of looking over the scientific horizon, and what I've seen is breathtaking. Ingenious and powerful biologically based tools are coming our way: viruses that can self-assemble into batteries, proteins that can clean water, nanoparticles that can detect and knock out cancer, prosthetic limbs that can read minds, computer systems that can increase crop yield.

These new technologies may sound like science fiction, but they are not. Many of them are already well along in their development, and each of them has emerged from the same source: a revolutionary convergence of biology and engineering. This book tells the story of that convergence—of remarkable scientific discoveries that bring two largely divergent paths together and of the pathbreaking researchers who are using this convergence to invent tools and technologies that will transform how we will live in the coming century.

We need new tools and technologies. Today's world population of around 7.6 billion is projected to rise to well over 9.5 billion by 2050. In generating the power that fuels, heats, and cools our current population, we've already pumped enough carbon dioxide into the atmosphere to change the planet's climate for centuries to come, and we're now grappling with the consequences. Temperatures and sea levels are rising, and large portions of the globe are plagued with drought, famine, and drug-resistant disease. Simply scaling up our current tools and technologies will not solve the daunting challenges that face us globally. How can we generate more abundant yet cleaner energy, produce sufficient clean water, develop more effective medicines at lower cost, enable the disabled among us, and produce more food without disrupting the world's ecological balance? We need new solutions to these problems. Without them, we are destined for troubled times.

We have overcome prospects as dire as these before. In 1798, the Reverend Thomas Robert Malthus, a British cleric, economist, and demographer, observed that population growth inevitably outpaced the growth in food production. His analysis led him to warn of only one possible outcome: widespread outbreaks of famine, war, and disease. These outbreaks, Malthus claimed, would keep population growth in check—but only by the deaths of many people. "The superior power of population," he wrote, "cannot be checked without producing misery or vice."

But Malthus got it wrong. Farmers in his day had already begun to adopt new technologies, including four-field crop rotation and applying fertilizer from new sources to their crops. These new technologies fundamentally changed the equation. They made land more productive and sent more food into the marketplace. With more food available, England's population grew even more rapidly than Malthus projected, which helped to meet the workforce demands of the industrial revolution. The technology-driven agricultural revolution of the nineteenth century contributed to launching a new age of innovation and economic growth.

We've arrived at a similar moment today. Dire problems confront us with potentially disastrous consequences. Unchecked, they spell misery and devastation for much of the planet, and we do not have in hand the means to overcome them—not yet. But as I peer over the scientific horizon, I see a future that looks surprisingly bright. Biology and engineering are converging in previously unimaginable ways, and this convergence could soon offer us solutions to some of our most significant and seemingly most intractable problems. We are about to enter an era of unprecedented innovation and prosperity, and the prospects for a better future could not be more exciting.

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1

WHERE THE FUTURE COMES FROM

At an early morning meeting of the MIT Corporation on August 26, 2004, I was elected MIT's sixteenth president. My selection for the role surprised a lot of observers. Many called out the fact that I was the first woman to hold the office—a big change from my fifteen predecessors, all of whom had been men. But others noted something perhaps even more surprising: I was a biologist. I had devoted my graduate work and scientific career to understanding the physical, chemical, and structural development of the brain—not exactly the sort of thing MIT was best known for. No life scientist had previously served as the Institute's president.

When I took office, MIT had a well-deserved reputation as one of the world's premier engineering institutions and was home to internationally renowned physics, chemistry, mathematics, and computer science departments. The university had a long-standing history—based on its founding "ideas into action" mission—of collaborating with industry to transform campus discoveries into useful and marketable technologies. MIT faculty and alumni had founded an array of companies, including Intel, Analog Devices, Hewlett-Packard, Qualcomm, TSMC (Taiwan Semiconductor Manufacturing Company), and Bose Corporation. When people thought of MIT, these were the sorts of achievements that came to mind: revolutionary products from engineering and physics that helped make the United States a leader during the explosive development of the twentieth century's electronics and digital industries.

That's why my appointment came as a surprise. A more predictable pick would have been an engineer or a computer scientist, a physicist or a mathematician. But, in fact, ever since the end of World War II, MIT has been committed to the emerging new field of molecular biology. By the time I arrived on campus, MIT's Department of Biology had taken its place among the top programs in the world. Some of its biology faculty had won the Nobel Prize for their discoveries, and several had helped to launch some of the world's top biotech companies.

With dual strengths in engineering and biology, new kinds of collaborations began. Not long after I arrived, the dean of the School of Engineering reported to me that one-third of MIT's almost four hundred engineering faculty were using the tools of biology in their work. The Institute recognized that this convergence of disciplines could create exciting ways of transforming ideas into action in the twenty-first century. In that light, my appointment made sense: we could seize the opportunity to foster the integration of biology and engineering on campus and in the international academic and industry communities.

I had to think hard about the opportunity to lead MIT. At the time, I was the provost at Yale University, where I was helping to plan a major expansion in the sciences, medicine, and engineering—a role I enjoyed immensely. A central theme in that expansion was redesigning departments and buildings to foster cross-disciplinary work. My passion for amplifying cross-disciplinary opportunities caught the attention of MIT's presidential search committee, which recognized that this sort of convergence of disciplines offered almost boundless possibilities for the future.

Could it work? Would it work? The stakes in moving between two very different institutions were high, both for me and for MIT. But in some way I had been preparing my whole life for this new assignment. So I accepted the role and embarked on what would become a fascinating journey into new fields, new ideas, and new responsibilities.

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I have always had an insatiable desire to understand how things work, and I have always satisfied that curiosity by taking things apart. I dissected all kinds of objects even as a young child, long before I knew I wanted to be a scientist. My curiosity drove me to reduce things down to their component parts and to learn how those parts come together to give the objects their function. Emboldened by watching my father fix seemingly anything in our home, I disassembled my mother's iron and her vacuum cleaner. I opened up my favorite watch to examine its mainspring and minute gears—only to have the unwinding mainspring explode the watch out of my hands, scattering into dozens of irretrievable parts. I took my curiosity outdoors, too: I dissected daffodils in our garden and acorns that had just put forth the first sprigs of new oak trees.

How an iron worked became apparent to me after I took one apart, but how daffodils bloomed and oak trees germinated did not. How did a daffodil's brilliantly yellow petals emerge from a green bud? Why were the petals yellow instead of red? What was it inside an acorn that suddenly prompted a sprig to grow? The mysteries of living things captivated me from the very beginning. What were their mainsprings and gears?

This childhood passion for taking things apart turned into my life's work. As I came of age as a scientist, I was fortunate to grow up in the midst of two major biological revolutions. The first, molecular biology, revealed the basic building blocks of all living organisms; the second, genomics, gave molecular biology the scale necessary to identify the genes responsible for diseases and trace them across populations and species.

The importance of these two biological revolutions is impossible to overstate. Molecular biology emerged in earnest in the late 1940s and early 1950s, when a cadre of scientists, many of them physicists by training, commandeered a set of new technologies (many of which came out of the technologies developed during World War II) to describe biological mechanisms at a new, finer-grained level of resolution. They advanced our understanding of how biology works down to the level of individual molecules, hence the name "molecular" biology. Famously, James Watson, Francis Crick, Maurice Wilkins, and Rosalind Franklin used new X-ray diffraction techniques to determine the structure of DNA. This discovery opened up vast new possibilities. Scientists could now begin to understand biology at the level of the cell's "hardware"—the DNA, RNA, and protein building blocks of all living things. In time, the new tools they developed allowed them to probe the inner workings of healthy cells and advance our understanding of what goes awry in disease. Along the way, they also created important biotechnology companies, among them Genentech, Biogen, and Amgen. These companies have developed new treatments for cancer, multiple sclerosis, and hepatitis, which have saved countless lives, created tens of thousands of jobs, and contributed significantly to our economic growth.

If molecular biology made possible the study of the hardware of cells, then genomics, the next biology revolution, made possible the study of their "software"—the code that provides the instruction set for each living organism. Genomics, powered by advances in computation, has provided a map of the human genome, along with the tools for high-resolution analysis of the sequence of DNA and RNA from any species on Earth. Advances in gene sequencing and genomic data analysis that can compare genomic information among thousands of individuals have allowed scientists to begin to unravel the complex, multifactorial genetic foundations of many diseases. They have allowed biomedicine to begin developing new treatments for patients based on each individual's unique genetic makeup and disease subtype so that we have begun to be able to target individualized therapies to individual diseases. These same tools have been used to understand plants and animals and, as we'll see in the chapters ahead, to invent new solutions to some of our most pressing industrial and societal challenges.

I studied biology as an undergraduate, but that was in the years before molecular biology and genomics had fully penetrated the field. In graduate school I decided to specialize by diving into neuroanatomy, studying the brain's circuitry and how it develops. The beauty of the brain's architecture enraptured me. Using the most advanced techniques available at the time, I examined nerve cells and their exquisitely intricate interconnections. I explored how those cells assemble themselves over the course of development into the highly regular patterns that give us the ability to see, hear, think, and dream. And I studied how early experience can permanently alter both the structure and the biochemistry of the brain. Even so, I couldn't see beyond the level of cell structures to the even more fundamental building blocks of biology—namely, the proteins and other molecules that make the machinery of the brain work. Molecular biology had not yet reached neuroscience.

Shortly after finishing my PhD, I had the great fortune to be recruited to the Cold Spring Harbor Laboratory by James Watson, one of the discoverers of the structure of DNA. There I learned how biologists in other fields were using molecular biology to show how genes direct the activities of all living organisms, plants and animals alike. Flu virus, pond scum, tulips, apple trees, butterflies, earthworms, salmon, beagle puppies, humans: molecular biologists taught us that all of these organisms rely on the same set of biological building blocks.

Well in advance of most scientists, Watson grasped that the concepts and tools of molecular biology would revolutionize the study of all living things. He understood the field's power to transform biology from an observational science to a predictive science. Under his leadership, scientists at Cold Spring Harbor advanced molecular biology to reveal the mechanisms of viruses and yeast, and then used the same technologies to understand the workings of cells taken from animals and grown in dishes. Long in advance of any available technology, Watson also foresaw the possibility that the tools of molecular biology could reveal answers to many of the mysteries of the brain.

That possibility captivated me. When I started my lab at Cold Spring Harbor, neuroscience remained among the last of the biological sciences to resist the paradigm-breaking insights of molecular biology. Against the powerful currents of mainstream neurobiology, I joined a small set of adventurous neuroscientists who embraced the tools of molecular biology and began to establish a new field: molecular neurobiology.

Revolutions, even the intellectual kind, are fraught with danger and divisive forces. Fighting to advance a new approach to neuroscience put our grants, jobs, and careers on the line. Furious arguments turned staid meetings into hotbeds of rancor. One debate at an international meeting pitted scientists who studied the human brain against those who studied insect nervous systems. The argument concerned whether anything we learned from insects could enlighten us about humans. It was, fundamentally, a debate about the molecular mechanisms of evolution. And, in truth, it was more of a shouting match than a debate, because we did not yet have a "parts list" for the nervous system that would permit a definitive comparison of a human and an insect nervous system. We neither knew its genes nor could we follow their expression over the course of development.

As a small group of renegades, our band of pioneering molecular neurobiologists gradually prevailed, and the movement we launched grew into a major force that, by bringing together classical brain research and the tools of molecular biology, has transformed neuroscience, providing previously unimaginable insights into how the brain works, along with new strategies for clinical interventions. Thanks to these and other molecular biological research breakthroughs, today we have new ways of diagnosing and treating brain diseases that were intractable only a few decades ago, among them epilepsy, neurodevelopmental disorders, stroke, and inflammatory diseases like multiple sclerosis. And, it holds out reason to hope for new insights into the many still daunting diseases, including Alzheimer's and other neurodegenerative diseases.

It was indescribably exciting to be a part of a scientific revolution that brought these different disciplines and ideas together. Living and working through it, I became a participant and a proponent of what I've come to think of as a "convergence" approach to discovery.

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I wasn't the first surprise pick as MIT's president. Early in 1930, in the midst of the Great Depression, the university chose Karl Taylor Compton, a Princeton physicist.

In retrospect Compton's appointment seems natural, even obvious, but at the time it struck many people as a break with tradition. Compton himself later claimed it was the biggest surprise of his life. From its founding in 1865, MIT had established physics as part of its core activities, but the school's reputation rested not on scientific research but on its success in technical domains. People knew it as a place that prepared engineers to make the tools and technologies that could advance the industrial age. An MIT student could expect to be prepared to pursue a career in the chemical industry or the fledgling electronics industry.

Compton inhabited a very different universe. At Princeton, he had chaired the physics department and run the nationally renowned Palmer Physical Laboratory. He had devoted much of his attention to atomic physics, an exciting field of as yet uncertain potential that had emerged just a generation earlier. The Department of Physics at Princeton was advancing fundamental science, laying the foundation for industrial applications that others would pursue.

The early twentieth century witnessed the astonishing transformation of fundamental scientific discoveries into marketplace products. As the basic components of the atom and its forces were revealed, they found their way into the entirely new electronics industry. The path from discoveries in basic physics to applications in useful products was and remains an arduous and unpredictable one. Few universities hosted both discovery and applications (science and engineering), and only a very few companies, most famously AT&T with its Bell Laboratories, invested in both fundamental discovery and new product development.

In 1897, the great physicist J. J. Thomson identified the electron as the particle that carries a negative electric charge. He and other physicists of his generation, among them Marie and Pierre Curie, Wilhelm Roentgen, and Ernest Rutherford, laid the groundwork for modeling the elementary particles that constitute all physical matter. While each pursued a somewhat different track, together they helped identify the “parts list” of components that make up and govern the behavior of the physical world: the protons and neutrons of the atomic nucleus and their surrounding cloud of electrons.

Having assembled this list, along with a set of laws that governed the behavior of the list’s particles, the physicists of the era began working with engineers. Together, they now had the power to make new things: lightbulbs, radios, televisions, telephones, and even electrical systems for homes and for entire cities. The electronics industry was born, and it began putting thousands of people to work and fueling economic growth. Today, in our digitally and computationally enabled world, we continue to enjoy the fruits of that industry and the convergence of physics and engineering that made it possible.

By 1930, MIT decided it had to step up its game by raising the quality of its science departments. Recalling the feeling of this moment later in life, one member of the physics faculty wrote, “We were awakening to a whole new world of science—science in its fundamental sense, which was almost totally missing from the Institute of that time—and to a new awareness of how this modern science might transform engineering of the future.” With its eye on this future and on the new integration of physics and engineering, MIT turned to Compton and offered him its presidency.

Initially taken aback, Compton was reluctant to leave his students and responsibilities at Princeton. But in the end, he came to the same realization that I would seventy-four years later: that he had been presented with the offer of a lifetime. “The magnitude of this opportunity to help science ‘make good’ in engineering education,” he told the *Daily Princetonian*, “creates an obligation which transcends other considerations.”

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From the start, Compton devoted himself to fostering the integration of physics and engineering at MIT. He embraced the Institute's mission and recognized that the best way of developing practical solutions to problems in engineering and science was to encourage high levels of interdisciplinary collaboration. And so, many decades before I did the same, he adopted a convergence approach to discovery and innovation.

The technological demands of World War II, sometimes called "the physicists' war," brought engineering and physics even closer together. And Compton played an important role in the process. In 1933, recognizing Compton's skills as a scientist and a leader, President Franklin Delano Roosevelt appointed him as the chair of the country's new Scientific Advisory Board, which in 1940 became the National Defense Research Committee (NDRC). As the head of the NDRC at the outset of the war, Compton helped orchestrate the development of technologies such as radar, jet propulsion, and digital computing that, along with an enormous array of other technologies, proved critical to the Allies' ultimate victory. The Radiation Lab he helped create at MIT, for example, brought together almost 3,500 scientists, engineers, linguists, economists, and others in an unprecedented collaboration that invented, designed, and built radar units that have been described as "the war-winning technology."

By the war's end, under Compton's leadership, MIT was on its way to becoming the home of one of the foremost physics departments in the world, renowned for its growing strength in fundamental science, and taking its place alongside MIT's world-class engineering departments. In giving MIT dual strengths in engineering and physics, and in carrying out his broader leadership duties for the government, Compton helped chart a course for the emergence of the United States as an industrial and economic powerhouse in the decades that followed the war.

The electronics industry took off in those decades. Transistors replaced vacuum tubes, and then silicon-based circuits replaced transistors, fostering an array of discoveries and applications that opened the gates to the computer and information industries. Although Compton understood that computers would fundamentally change many aspects of communication and national defense, he could not have foreseen how the technologies he fostered would produce the digitally enabled world we live in today. Few did. That's the nature of scientific revolutions: they unfold in powerful and unpredictable ways and unleash vast possibilities. But Compton did recognize that the convergence of physics and engineering represented the beginning of a new technological age, and he did everything he could—at MIT, as a government advisor, and as a public figure—to make sure that the United States made the most of this revolution.

For these achievements alone, Compton stands as a visionary architect of the emergence of America's technological and industrial power following World War

II. But during his time at MIT, he had the remarkable foresight to see another revolution coming—namely, the convergence of biology and engineering.

Compton discussed this next convergence as early as 1936, in a lecture titled "What Physics Can Do for Biology and Medicine." In it, he presented recent advances in nuclear physics, including how a new generation of cyclotrons made it possible to incorporate radioactive labels into elements. With a radioactive label, an element could be followed as it was incorporated into a molecule and then as that molecule moved through chemical reactions and metabolic pathways of a cell or an organism. The lecture prompted a physician, Dr. Saul Hertz, to ask whether this technology could be used to understand and possibly treat thyroid disease. Hertz was chief of the Thyroid Unit at Massachusetts General Hospital (MGH) and with colleagues had studied the uptake of iodine by the thyroid gland. He asked Compton whether iodine could be made radioactive. If so, he realized, it might be possible to track iodine buildup in the thyroid. That, in turn, might make it possible to diagnose thyroid disease and, perhaps, to selectively kill diseased thyroid tissue as a therapy for hyperthyroidism and thyroid cancer.

It was a bold idea, and Compton saw its merits. He connected Hertz and the MGH endocrinology group with physics colleagues at MIT, and soon this team carried through on the idea, successfully treating a set of patients with radioactive iodine, in one of the very early examples of what we would today call "precision medicine."

Compton recognized the potential of this new convergence of biology with engineering, anticipating that it would ultimately be just as powerful and as socially and economically transformative as the convergence of physics and engineering. To educate students in the hybrid field, in 1939 he described a curriculum for Biological Engineering, and in 1942 changed the name of MIT's Department of Biology to the Department of Biology and Biological Engineering. But Compton was well ahead of his time. The biologists of his day hadn't yet developed a parts list for living things of the sort that physicists had developed for physical matter—and without that list, engineers had little to work with. Hampered by this lack of tools, the Department of Biology and Biological Engineering could not live up to its name, and within a few years it once again became the Department of Biology.

By the early 1940s, the world's attention had turned to World War II. Physics, not biology, became the necessary science. Compton worked as an extraordinarily active scientist, administrator, and public figure during the wartime years. He headed up American efforts to study radar, synthetic rubber, fire control, and thermal radiation; he ran overseas programs for the Office of Scientific Research and Development (OSRD); he served as a scientific advisor to General MacArthur; and in 1945 he became one of eight advisors appointed to guide President Truman on the use of the atomic bomb.

After the end of the war, Compton received accolades of all kinds for his contributions to the war effort. In 1946, the Army awarded him its highest civilian honor, the Medal for Merit, for his work in “hastening the termination of hostilities,” and the following year the National Academy of Sciences awarded him its Marcellus Hartley Medal, for his “eminence in the application of science to the public welfare.”

These two awards, along with many others, made a similar point about Compton’s achievements. By bringing physics and engineering together in new ways, and by championing the revolution that this convergence enabled, he helped not only end the war but also bring about a new age of American prosperity and possibility. Compton’s vision gave us an astonishing array of new tools and technologies: not just radios, telephones, planes, TVs, radar, and computers, but also nuclear power, lasers, MRI and CT scanners, rockets, satellites, GPS devices, the Internet, and smartphones. These tools and technologies have so reshaped our world that we now have a hard time conceiving of life without them.

New digital products and the digital economy they enable continue to reshape our world. By giving rise to Big Data, the Internet of Things, and the Industrial Internet, they have made possible new business models for retail (think Amazon), hospitality (Airbnb), and transportation (Lyft, Uber). The revolution continues apace, and if Compton were still with us today, he would surely be thrilled to see its fruits.

But he would surely be just as thrilled to know that the other revolution he foresaw—the convergence of biology and engineering—is at last getting underway.

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When I arrived at MIT, I was amazed to learn just how far down this new road many of MIT’s faculty had already traveled. MIT engineers had started to incorporate the tools of biology in their work in surprising ways. Martin Polz, an environmental engineer, was using computational genomics to search for populations of plankton that capture most of the ocean’s carbon dioxide. Kristala Jones Prather, a chemical engineer, was adapting microbes to make new materials, like transportation fuels and drugs. Scott Manalis, a physicist turned biological engineer, had adapted an exquisitely sensitive measuring method he had devised to weigh individual cells and monitor their growth. And inspiring all of them was Institute Professor Robert Langer, regarded as the most prolific biological engineer in the world, with over a thousand granted or pending patents, and the founder of more than twenty-five companies.

The more I learned about the incredible projects in this new realm, not just at MIT but also in labs around the world, the more convinced I became that the convergence of biology and engineering had world-changing potential. So, I made this convergence one of the major themes of my presidency, creating resources and spaces to help make it happen as rapidly as possible.

It paid off in many ways. The biology faculty that comprised MIT's Center for Cancer Research, one of the nation's preeminent centers for fundamental biological research, joined forces with engineering colleagues and reconfigured themselves into MIT's Koch Institute for Integrative Cancer Research—an exciting mash-up of engineers, clinicians, and biologists who since 2007 have been working together to understand, diagnose, and treat cancer and other diseases in new ways. Dozens of companies have spun out of the Koch Institute, many with bioengineered products that are now in clinical trials: nanoparticles that home in on cancer cells to deliver chemotherapy directly to where it matters most; imaging technologies that allow a surgeon to more accurately spot and remove cancer cells; strategies to identify infectious agents in a small fraction of the time of current methods, so that the right drug can be prescribed fast enough to save countless lives. In similar fashion, we launched the MIT Energy Initiative, which has accelerated the development of new energy technologies, many of which use components from the parts list of biology. In its first ten years, the Energy Initiative spawned close to sixty new companies that are designing new batteries, new solar cells, and new energy-management systems.

Over the course of my career, and especially during my time at MIT, I've had the great fortune to meet many of the pioneers in this emerging arena of research, and I've seen how they have translated new lab discoveries into marketplace products, turning their ideas into action. In the chapters ahead, I'll put you on the ground and in the lab with some of these key figures, and I'll introduce you to some of the ways they're hoping to use the tools and technologies that they're developing to overcome the greatest humanitarian, medical, and environmental challenges of our time.

The work they're doing is the scientific story of this century. I have no doubt about this. A century ago, physics and engineering came together and transformed our world completely, and now biology and engineering are poised to transform our future as profoundly. This book provides a preview of that emerging future, so that you, too, can enjoy the excitement of watching it happen.

I've organized the technologies in the chapters of this book to bring you, step by step, from basic to more advanced biological concepts. The new world of biology-based technologies arises from one of the most remarkable scientific revolutions. Simply put, in 1950 we did not know the physical structure of a gene or how it gives rise to physical traits. We did not know why cancer cells divide without

quickly and as effectively as possible.

INDEX

Page numbers listed correspond to the print edition of this book. You can use your device's search function to locate particular terms in the text.

Note: Page numbers in italics indicate figures.

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