# Contents

# INTRODUCTION

## SCIENCES CONVERGE IN BIOLOGY TO TRANSFORM HEALTH

Biology is the most intensely investigated subject of modern science. Beyond perpetual human preoccupations with health, mortality, and finding our place and identity in the universe, the power hidden in biology's complexity is causing almost all the branches of science and technology to gravitate toward the study of life. Biology ceases to be the sovereign territory of biologists, biochemists, and medical scientists; in the twenty-first century, physical, mathematical, and engineering sciences converge with the more traditional biological disciplines to seek a deeper understanding of life in all its multifaceted, dynamic structures and functions. In our turbulent and disoriented times, the inner workings of biology and its profound insight into the meaning of life have become the focus of human creativity, spawning technological and cultural innovations that may contribute either to our survival or to our extinction.

The sciences' appetite for biology seeks satisfaction on all its spatial scales—from nanometer-size molecules to cells tens of micrometers large to meter-scale eukaryotes[1]—and in all its manifestations, from the mind-boggling diversity of shape and action found in its molecular inventory to the forces and processes that drive the precise assembly of an intricate protein, lipid membrane, or coil of DNA. Science seeks knowledge about individual molecules, cells, tissues, organisms, and ecosystems; this includes the study of how biological structures give rise to the individual and collective "intelligences"[2] that enable living creatures to persist on Earth.

Apart from the pure search for knowledge, economic gain and social influence are the workaday drivers of science (and even more so of research funding); thus one can observe that the motivation of the current scientific desire for all things biological is often technological. The potential technological payoffs of biology are as diverse as the new disciplines evolving out of the knowledge extracted from it. For example, computer scientists are keen to learn the fine details of the human brain's organization so that they can mirror the layered connectivity between its neurons in the structure of their algorithms; they hope this will lead to much-improved artificial intelligence (AI) as well as to better understanding of our own thinking ability. Materials scientists and roboticists look to the assembly of biological structures for inspiration in the design of novel bioinspired materials and robots. In physics departments, scientists study the plant proteins responsible for photosynthesis, prospecting for biological recipes that can be adopted in the quantum computers of the future.

However vigorous and dedicated the biological research activity of these new players, medicine still takes center stage as the main intellectual, social, and economic engine of biological research. Medicine helps to attract the money, but more fundamentally, plays the role of integrator of knowledge. The sciences and technologies drawn to biology arrive by different paths and aim at disparate goals, but medicine dispels the cultural barriers among disciplines, facilitating their fusion in the pursuit of better strategies for uncovering the ultimate causes of disease and better interventions to preserve and restore health.

Understanding disease and curing it is such a complex challenge that it requires “all hands on deck”—all the technical and scientific knowledge available. Cutting-edge medical research already combines the latest advances in AI, materials science, and robotics, and will undoubtedly use quantum computers as they become available. As anyone who has been in a modern hospital can attest, most human technologies end up being adapted for use in the clinic in one way or another: from the humble thermometer to the physics of positrons in PET scans for imaging tumors, and from mobile phone apps to control fertility to gene editing to eradicate diseases. The hospital is the most nourishing culture medium for scientific and technical knowledge to combine and grow in.

The diversity, intensity, and speed of advance of current research unequivocally indicate that we are living in prerevolutionary times in both biology and medicine. Confident answers to the long-standing questions that have enthralled humans, such as the origin and diversity of life and the source of our intelligence and consciousness, are perhaps still far from being found. However, the accelerating and ever-more-potent interdisciplinary mergers make us feel that we are now at an inflection point, and will soon slide irrevocably toward the advent of the technologies that will transform our understanding and control of our biology. In extraordinarily novel and efficient ways, these will give us the powers to heal ourselves and to prolong and transform our lives.

## NANOTECHNOLOGY IN BIOLOGY AND MEDICINE

A necessary step toward this brink of breakthrough was, and continues to be, the development of nanotechnology—the capacity to visualize, interact with, manipulate, and create matter at the nanometer scale. This is primarily because the main molecular players in biology, and the main drug and treatment targets in medicine—proteins and DNA—are nano-size. Nanotechnology is the technological interface with the nanoscale. It directly links the macroscopic world of our perceptions with the nanoscopic world of individual biomolecules. To arrive in medical heaven—the power to restore perfect health—we would need to know how molecules work in a specific environment, why and how they malfunction in a disease, and most importantly, how to reach them, to target them, and to deactivate or activate them. In this "spatial" sense, medicine parallels nanotechnology: to cure, we need to traverse the spectrum of scale from the macroscopic size of the doctor to the nanometer scale of biomolecules, navigating the very intricate "multiscale" landscape of organs, tissues, and cells in between. Since the early days of nanotechnology, one of its main missions has been to create tools that are able to interact with key biological molecules one at a time, directly in their complex medium, and in this way to bring closer to realization the targeting of individual molecules in the medical context. We are still working on it, and this book is in part an effort to show how far we have come.

As well as introducing nano-tools that enable new biological and medical research, nanotechnology has made a more fundamental contribution: attracting physical scientists to biology. In the last decades of the twentieth century, artificial nanomaterials and the tools of nanotechnology—microscopes and nanomanipulation devices—came into existence. Using them, a significant number of physical scientists interested in matter at the nanometer scale sought to know how and why biology first constructed itself using nano-size building blocks in the medium of (salty) water. Fascinated by the coupling of physics and chemistry that gives rise to biological function, they focused on using nanotechnology's methods to learn the workings of proteins, DNA, and other important nano-size biomolecules. In the process, they turned themselves into *biological physicists*, seeking answers to deep scientific questions such as: What was it about the properties of the nanoscale that made it special for the emergence of life? Others, more practical, saw opportunities to design nanomaterials that could be used to address disease in a more precise and rational manner, improving on current pharmacological treatments; they became *nanomedicine scientists*.

This cross-disciplinary activity led to the development of tools specifically built for studying biological processes and their nanoactors in physiological conditions (warm, salty water). As pioneering nano-bioscientists enlarged their knowledge of biology, they eroded the boundaries between materials sciences, physics, chemistry, and biology, emerging as a new generation of researchers who naturally worked across disciplines and no longer recognized intellectual or cultural barriers to interaction with any other scientific field.

## THE EMERGENCE OF QUANTITATIVE BIOLOGY: THE NEW PHYSICS OF LIFE

The arrival of nanotechnology in the life sciences has contributed to a rising wave of physical scientists entering biology, bringing fresh eyes to old problems. The experiments of these scientists differ from most biological and biochemical research in that they are driven by mechanistic hypotheses: that is, they pursue quantitative data that help to explain the actual functioning mechanism of the process under study. The usual question of a biological scientist is, "Who [which molecule] does that?" For a physicist it is, "How and why does it do that, and can I model it with mathematics?" When you look at biological systems through the eyes of a physicist, you are looking for the key parameters that explain how the biological system works: Is it size, temperature, energy, speed, structure, stiffness, charge, chemical activity?

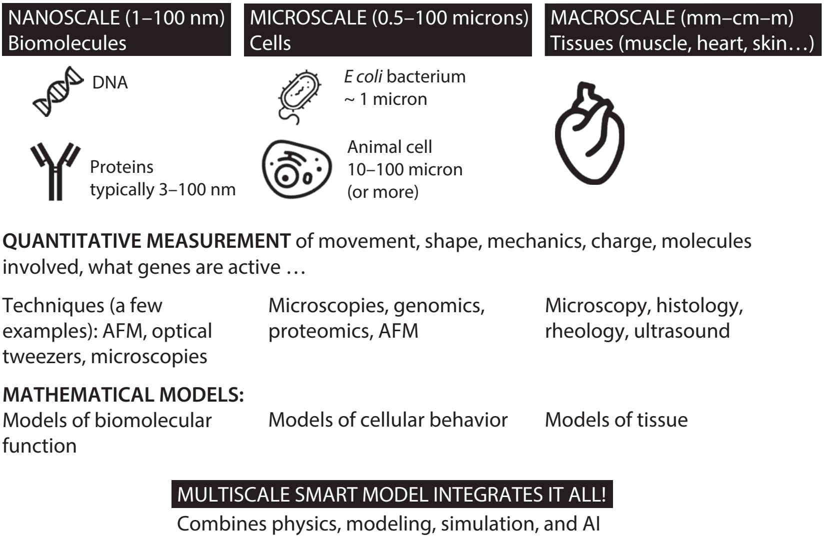
Crucially, the ultimate goal of physicists is to create mathematical models of biological processes that can be used to describe those mechanisms. If the mathematical model reproduces and even predicts the biology of the process, then we start to know the actual fundamental quantities and forces that drive it. The strength of this "quantitative approach" to biology is that it unleashes a formidable power: accurate mathematical models can be used to predict the behavior of specific biological processes in the computer, or in modern scientific jargon, *in silico*, without experiments. This means that, if successful, mathematical models can be used to progressively abandon the trial-and-error methods of the traditional biological, medical, and pharmacological sciences. These are painfully slow and costly, and, as the development of new drugs often shows, inefficient. The computer modeling approach is already in use in modern civil engineering, aeronautics, and architecture, where computer simulations combined with quantitative knowledge of the mechanical properties (e.g., elasticity, viscosity, strength, rigidity) of materials used in construction are routinely employed by engineers to test the feasibility of designs *in silico* before any actual building work is done.

Without the invention of techniques able to quantitatively monitor biology in all its dynamic, hierarchically structured complexity—from the nanometer scale of proteins and DNA to cells to tissues in living bodies—adopting this quantitative approach in medicine was totally impossible. These techniques not only need to visualize structures and their movements at all the different scales, but need to be able to extract the key physical or chemical parameters (stiffness, charge, temperature, etc.) that allow the development of correct mathematical models to make computer modeling viable.

Once experimental information at the nanometer scale of single molecules becomes available, it can be used to construct models that describe the functioning of, for example, proteins or DNA in their natural environment and in disease. The capacity to model individual molecules will be progressively integrated with the emergence of techniques able to collect vast amounts of quantitative data about those molecules in complex biological environments and in real time. Furthermore, AI algorithms (such as those of machine learning) will be used more and more to aid in the analysis of biological "big data."[3] The integration of biological physics with biological big data and AI models will lead to increasingly accurate and "smart" models of life. However, twentieth-century physics teaches us that in very complex and interconnected systems, knowing the workings of the building blocks is not enough to predict the behavior of the whole: at larger scales, biology exhibits behaviors that the smaller constituents do not exhibit, or that cannot be explained from the relationships between their molecular building blocks. This is because complexly organized matter presents collective phenomena arising from cooperative interactions between the building blocks—or, as we say in physics, these properties *emerge*. Some examples of emergent behavior are cellular movements, mechanical vibrations in the brain, electrical signaling across the membranes of cells, and changes in shape or stiffness, none of which can be predicted from just knowing the molecules that constitute a particular structure. This means that in practical terms, as we zoom out from the nanoscale to the microscale, nanoscale models have to be "coarse-grained" to be integrated and consistent with models that correctly describe the cellular behaviors emergent from nanometer-scale activity.

Similarly, the cellular level then needs to be integrated into models of the tissue and organ levels. An example would be a mathematical model of a tumor that is able to relate its shape, size, and growth pattern to the properties of individual tumor cells and their molecular environment; at the next level down in size, the model should incorporate how cellular properties are connected to their molecular and genetic activity. This model could in principle be used to design a multimodal treatment regimen that targets individual molecules both directly and indirectly. Combining nano-precise drug delivery with a physical treatment such as applying electrical or mechanical signals to the tumor would single out specific molecules and also affect them through the physical and chemical phenomena that link the different spatial and temporal scales of the tumor. In other words, it would allow simultaneous targeting of the molecular, the cellular, and the tissue-level biology of the tumor. The undertaking is formidable, but the tools that would make it possible are slowly being developed and coming together.

We can draw some parallels with the past. At the beginning of the twentieth century, the arrival of tools to study atoms conduced to the development of the field of quantum mechanics.[4] This, in turn, led to the very creative mathematical models underpinning



| NANOSCALE (1–100 nm) Biomolecules | MICROSCALE (0.5–100 microns) Cells | MACROSCALE (mm–cm–m) Tissues (muscle, heart, skin…) |
|---|---|---|
| DNA<br>Proteins typically 3–100 nm | *E coli* bacterium ~ 1 micron<br>Animal cell 10–100 micron (or more) | |

**QUANTITATIVE MEASUREMENT** of movement, shape, mechanics, charge, molecules involved, what genes are active …

| | | |
|---|---|---|
| Techniques (a few examples): AFM, optical tweezers, microscopies | Microscopies, genomics, proteomics, AFM | Microscopy, histology, rheology, ultrasound |

**MATHEMATICAL MODELS:**

| | | |
|---|---|---|
| Models of biomolecular function | Models of cellular behavior | Models of tissue |

MULTISCALE SMART MODEL INTEGRATES IT ALL!

Combines physics, modeling, simulation, and AI

Fig 0.1. The new physics of life tries to build mechanistic models of biology at each of the relevant scales, and then integrate the models into larger “multiscale” models that include all the relevant scales. (nm = nanometer)

solid-state physics, which successfully explained how the macroscopic properties of crystalline solids[5] emerged from the order and nature of their atoms. This ultimately laid the theoretical foundation for the modern electronics present in our mobile phones and other electronic devices.

While biology is immensely more complex than crystalline solids, current trends of research in all the sciences converging on biology indisputably indicate that this colossally arduous task is already under way. We are moving, still slowly, but at an inexorable pace, toward the quantitative, mathematical description of biological phenomena—in other words, *the physics of life*.

In this new landscape, the reductionist vision of the previous generation, which strove to present organisms as mere biochemical computers executing a program, an algorithm encoded in genes, has been called into serious question. Confronting the often skeptical eyes of more-traditionally trained biologists, nano- and physics- and mathematics-savvy scientists are slowly deploying their plans to quantitatively interpret the interwoven genetic, chemical, and physical mechanisms underlying life and health, and to mathematically predict the biology underlying disease and trauma. Significantly for medicine, they seek to implement their rational health-restoring strategies one patient at a time. Their final goal is to design—using mathematics and computer models—treatments for specific problems in particular patients, rather than to discover, by endless rounds of trial and error, prescriptions that work for an acceptable majority of patients, as we do now.

## THE TRANSFORMATION OF BIOLOGY AND MEDICINE

In this book I seek to make sense of the reality that I am living and witnessing as a scientist working across disciplines. I am uniquely placed to tell the story of how the combined efforts of physical and mathematical scientists, facilitated by the rise of nanotechnology and of powerful quantitative experimental techniques, are transfiguring biology and slowly building up the capacity to identify and take on core challenges of modern medicine. Doing medicine means dealing with the intricate, dynamic, circuitous, hierarchical assembly of a myriad of nano-size building blocks that constitutes a living organism. To cure, we need to reach specific cells, proteins, and DNA with optimized concentrations of precisely designed therapeutic agents; to heal and regenerate, we need to understand and reproduce the nanoscale environment of healthy cells in tissues and organs. These are the subjects where nanotechnology, and the sciences and technologies enabled by it, are currently changing the game. They are the core of this book.

Chapter 1 describes how the deployment of nanotechnology and quantitative methods in biology is expanding the realm of science to embrace life in all its multiscale, entangled intricacy and multiplicity. I attempt to gather some of the most significant achievements to sketch a map of the changing landscape of biological research. This new landscape emerges, in part, from the realization that current medical bottlenecks will remain blocked if we linger in the previous generation's optimistic hope that life could be reduced to genes and molecules. As we dive into the complexity of biology, we are conscious that the ultimate goal of explaining life in all its detail is currently unattainable, but we rely on quantitative methods and new tools to provide solutions to specific problems that pave the way. I illustrate this picture with examples of how quantitative biology methods are being used to query the functions, structures, and interactions of key biological molecules, and to understand how these molecules' concerted actions give rise to subcellular structures that integrate their nanoscale activity into the emergent workings of whole cells and organisms.

Complementary to this approach, and in response to the doubt-inducing complexity of biology ("How do we really know that our models are correct?"), others have adopted a more pragmatic strategy, based on the engineering ethos of nanotechnologists and quantitative biologists. This strategy stems from the visionary physicist Richard Feynman's "What I cannot create, I do not understand"—in other words, learn by making. We know, for example, that the quantum theory of solid-state materials is accurate because our mobile phones work as we want them to. If the devices we design don't work, this unequivocally indicates that something is wrong or missing in the science we seek to apply. Application is the ultimate test of whether a scientific theory works.

The application of this principle at the interface of nanotechnology and biological sciences is transforming the way human-made materials are constructed and the uses they can have. Chapters 2 through 4 review how nanotechnology and the sciences and technologies converging on the nanometer scale are being used to create bioinspired and biomimetic nanostructures and nanomachines, and to integrate these nanostructures into strategies aimed at solving specific medical problems and clearing roadblocks.

In chapter 2, I summarize the development of disciplines that seek to build artificial nanostructures using both biological molecules and the organizational principles of biology. This activity began with the emergence of the DNA nanotechnology that is maturing as a distinct field of research. DNA nanotechnology pursues the design and construction of any arbitrary shape using artificial DNA building blocks. More importantly, DNA nanotech seeks to give its structures nanoscale functionality for complex tasks, such as serving as an active template for the synthesis of molecules, or even working as a programmable molecular computer or a DNA robot able to deliver drug payloads to tumors. In parallel, the field of protein nanotechnology attempts to achieve the same goals using natural or artificial proteins; this is a tougher task than making nanostructures with DNA, but can lead to many more applications. One of the most striking examples of the integration of sciences and the power of quantitative approaches in biology has been the arrival of "designer proteins." Recently scientists have been able to hack the molecular machinery of the cell to create "post-evolutionary" proteins that do not exist in nature, but have been previously designed in powerful computer programs. These technologies have made possible the realization of one of the dreams of the nanotechnology pioneers: the deployment of molecular assemblers able to construct any shape with atomic precision following a rational design, a plan previously rehearsed in a computer. A fundamental drive of biomolecular nanotechnology is to create powerful tools for nanomedical applications, ranging from molecular DNA assemblers of medicinal drugs to improved vaccines, powerful antiviral and antibacterial nanomedicines, and targeted drug delivery systems.

Chapter 3 gives an account of a key aspect of this multidisciplinary arsenal of nanomedicine: how nanotechnology is being used to improve the efficiency of current cancer chemotherapies by developing drug-delivery strategies that specifically target tumors and cancer cells. Although drug delivery via nanostructures was one of the initial goals of nanomedicine that attracted the most support, the effort put into it has not led to the breakthroughs that were hoped for. This is partly due to inertia: the application of existing trial-and-error methods to complex biological processes that are still poorly understood; the insufficient coordination of existing research; and the lack of truly quantitative approaches. And it is partly due to impatience: seeking nano-powered magic bullets and lucky shortcuts to cure disease that overlook the complexity of the biology involved has not proven fruitful. Fortunately, the lessons are being learned and new, improved initiatives are already gathering pace. In this chapter, I also discuss how nanotechnology is joining the multidisciplinary quest for new ways to combat antimicrobial resistance, coupling traditional pharmacology research with novel ways to interact with bacteria that include their physics, not only their chemistry. I also give a brief overview of how nanotechnology and its offshoots are becoming ever better at creating nanodevices that sense the chemicals in the body, thereby getting closer to the goal of responding to chemical imbalances in real time by releasing drugs when and where they are needed.

Perhaps one of the most fascinating contributions that nanotechnology can make to health and medicine is to team up with the biological research currently being done on immunotherapies (a type of cancer treatment that boosts the body's immune system to fight cancer). These combined efforts have the potential to accelerate the science of controlling and improving our immune system's innate capacity to detect and fight disease from within. In this chapter, I anticipate how the convergence of sciences is likely to lead to plans to create the "super-enhanced human immune system" of the future.

In chapter 4, I attempt to compile the science of one of the most potentially transformative scientific fields: tissue engineering. Tissue engineering is emerging not only as the field that may enable the repair and even replacement of damaged or diseased organs, but also as an arena where fundamental progress will be made in the basic science underpinning biology and medicine, with the goal of being able to monitor health and disease with molecular precision in real time. Studying all the relevant molecules in a large living organism is a daunting task; however, tissue engineering allows the construction of artificial biological tissues and organs, in which interactions between the scales can be tested in controlled environments. "Learning by creating" toy models of body parts and even trying to connect them in the lab will be useful for building mechanistic models that increasingly approach the complexity of real organisms. This activity will be leavened by mathematical modeling and simulation, and will likely incorporate AI (machine learning) algorithms.

Measurement and monitoring of the key parameters that can be used to create models of tissues are facilitated by the development of biosensors for constant surveillance of artificial tissues and new AI algorithms to integrate the data with the physics of tissues. Eventually, this will lead to the development of technology that may be used in vivo once it has been well established in tissue-engineering experiments. Creating biosensing technology and mechanistic models of tissues that link the molecular with micro- and macroscopic biology will arguably be the most important contributions to medicine and biology of tissue engineering. Tissue-engineering models are also very useful for understanding and modeling targeted drug delivery, and it is expected that tissue-engineered models of human tissues and organs will eventually replace animals in drug testing.

This book seeks both to describe the new science emerging from the convergence of disciplines on biology and human health and to reflect on how and why the sciences are converging. Each chapter, therefore, has a very short historical introduction outlining the path that led to the current situation. I hope this helps my purpose: to invite the reader to look back to where the science came from, in order to envisage the routes that can take us from here into the future.

## TRANSMATERIAL FUTURES

Much of the science that I have briefly outlined leads to an inexorable dimming of the distinction between biological and material sciences: a new *transmaterial* science is in its embryonic state. With increasing control of matter at the nanometer scale and better knowledge of the building tricks and machinery of biology, artificial materials inspired by biology will be used to create new scaffolds for regenerating tissues and organs, or to improve the responses of the immune system. In parallel, hybrid bio-inorganic devices that mimic biology will be used in new computers and electronic devices. As biology becomes quantitative, and we gain the power of mathematics and physics to use the rules that govern it to design new applications, we release a colossal capacity for innovation, not only in medicine but in most technologies currently created by humans, from energy to electronics and from computing to materials science. By increasingly refining our ability to learn biology using the methods of physics, we will in fact be distilling the recipes of the universe to fabricate and assemble matter from the nanometer scale up, and will acquire the ultimate power to revolutionize human technology and medicine.

Forecasting the consequences of the convergence of the sciences beyond medicine (the so-called “fourth industrial revolution”) is outside the scope of this book. I have, however, included an epilogue offering a scientist’s perspective on how to navigate the promise and peril of a future in which we have snowballing power over all sorts of matter—biological and otherwise. Furthermore, I briefly explore the consequences for human identity (from my own scientist perspective) of the merger between material and biological sciences. As I read some of the predictive narratives on the fourth industrial revolution that have become international best sellers in recent years, I cannot avoid thinking that these books (more or less) unintentionally invite an additional danger, at least as powerful as technology’s effects on society: they risk unleashing the *fear* of technology, and so undermining the power of science to create a fairer society. Much of the forecasting is based on a suboptimal knowledge of the current state of the sciences, and, more importantly, a lack of knowledge of scientists themselves—their increasing sense of vocation and commitment to engage with society, to form democratic alliances that allow positive and practical transformations for the benefit of us all.

In the twenty-first century, many scientists are passionately searching for ways to create platforms and frameworks of collaboration with the public, the regulators, and the industrial developers of technologies to imagine better, more-diverse and equable futures. Much of the writing about technology in the twenty-first century forgets that scientists, more than anyone, understand the power of the knowledge that they create, and that they increasingly strive to modulate the social and economic forces that shape its development and exploitation. Scientists are a fundamental piece in the machinery that links technology with fairness in society. While it is true that the pursuit of pure knowledge motivates many of us, and that some are motivated to build successful careers that will bring them prizes, status, and money, the reality is that most scientists endure painfully long hours in the lab or at the computer in pursuit of a deep and genuine passion to improve life for all.[6] This endeavor is actually one of the main reasons why technologies converge in medicine: contributing to better health often seems the most direct pathway for scientists to improve universal well-being, or so we hope.

This book is my attempt to convey the excitement of the new worlds that the sciences at this interface of biology, physics, and medicine are uncovering, and to share and think through with the reader the opportunities now emerging from our laboratories to use technology to collectively create a fairer future of human betterment. As I introduce in chapter 1, and reflect on further in the epilogue, the incorporation of biology (including intelligence) into the realm of physics facilitates a profound and potentially groundbreaking cultural shift, because it places the study of life within the widest possible context: the study of the rules that govern the cosmos. I want to reveal this new context for studying life and the potential for human advancement that it enables. The most powerful message of this book is that in the twenty-first century life can no longer be considered just the biochemical product of an algorithm written in genes (that can potentially be modified at someone's convenience), but a complex and magnificent realization of the laws that created the universe itself. This means that as physics, engineering, computer science, and materials science merge with biology, they are actually helping to reconnect science and technology with the deep questions that humans have asked themselves from the beginning of civilization: What is life? What does it mean to be human when we can manipulate and even exploit our own biology? We have reached a point in history where these questions naturally arise from the practice of science, and this necessarily changes the sciences' relationship with societies and cultures.

We are entering a historic period of scientific convergence, feeling an urge to turn our heads to the past even as we walk toward the future, seeking to find in the origin of the ideas that brought us here the inspiration that will allow us to move forward. This book attempts to call attention to the potential for a new intellectual framework to emerge at the convergence of the sciences, one that scientists, engineers, artists, and thinkers should tap to create narratives and visions of the future that midwife our coming of age as a technological species. This might be the most important role of the physics of life that emerges from our labs: to contribute to the collective construction of a path to the preservation of (human) life on Earth.

# Index