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How Nanotechnology Is Transforming Medicine and the Future of Biology

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Preface and Acknowledgments

The progressive convergence of sciences in the twenty-first century, and in particular, the merging of disciplines at the interface of physics, nanotechnology, biology and medicine, has composed the landscape of my own scientific career across sciences, continents, and cultures. After a study and work journey that led me from physics to nanotechnology to biology and back to physics, through Spain, China, Czechia, Japan, Denmark and the UK, in 2007 I became the co-director of the Institute of Nanoscience for Medicine, a research program at the Oxford Martin School of the University of Oxford. The school was created with an endowment from James and Lillian Martin to become a hub where all the relevant academic disciplines would convene to investigate and debate the challenges and opportunities of the twenty-first century. Encouraged by the Oxford Martin School's founding mandate to communicate with the public, I started to deliver public lectures about nanotechnology and the future of medicine and biology that were strongly rooted in my physicist's way of looking at the world. Despite the quickening pace of scientific convergence, the scientific community has been slower to reflect on how the merging of disciplines is transforming the ways we work and think about nature, so my lectures were also attempts to satisfy my own needs as a practitioner of science. Speaking about these issues in public to scientific and nonscientific audiences has become an important part of my academic activity, and has led me to reflect more on the implications, history, and context of my research. I now deliver these lectures in many countries and to a wide variety of audiences. This has allowed me to connect with many communities and to become aware of the public's great curiosity about these converging technologies that so define our present and will most likely shape our future.

So when I was approached by my editor, Ingrid Gnerlich, to write this book, I decided to do so despite having a heavy academic and research load and two small children. People of all backgrounds seem to enjoy the scientific stories I tell. We are living in exciting times; breakthroughs in our understanding of the physical and biological reality around and within us are speeding up exponentially. The convergence of the sciences is bringing a revolution not only in technology, but also in our physical, cultural, and philosophical relationship to the material world. It is a time to think and talk about the fast-changing present, and to collectively imagine positive futures our new technologies make possible. I hope that this book will contribute to the conversation in a meaningful way.

I am grateful for the support and patience of my family, and for the kind encouragement of my editor; I am grateful, also, to the friends and colleagues that have read and commented on the first versions of the manuscript: Charles Olsen, Rosario Ruibal Villaseñor, Alberto Merchante, Ibon Santiago, and Lina Gálvez. I have also benefited from the generosity of Iwan Schaap, and of teamLab, who gave me beautiful images and inspired some of the ideas in the book. Many conversations have been important in shaping my thinking here, especially those with the physicist Jacob Seifert, my PhD supervisor Hiroshi Iwasaki, the film director Alison Rose, and the historian of mathematics Agathe Keller.

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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.

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

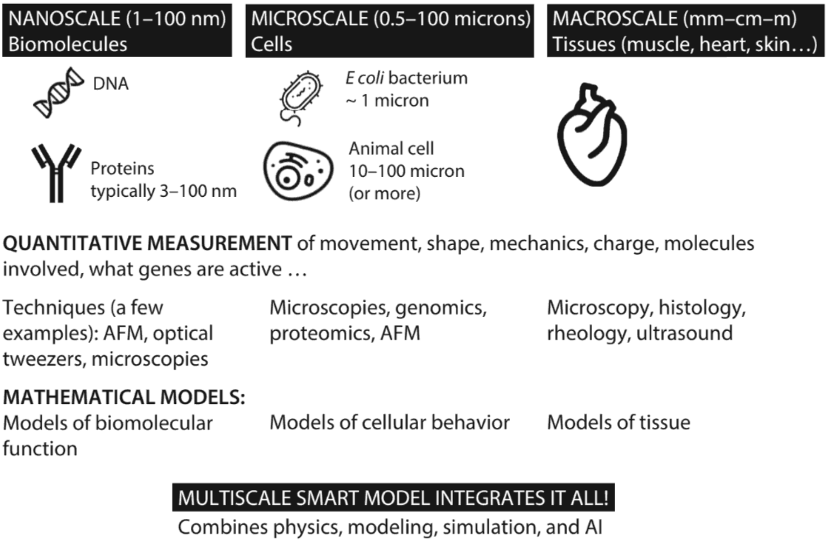

Fig 0.1. The new physics of life tries to build mechanistic models of biology at each of the relevant scales, and then integrate the models into larger "multiscale" models that include all the relevant scales. (nm = nanometer)

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 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

In this chapter, I will explore how science in the twenty-first century is reassessing the adequacy of this simplistic plan to reduce biology to molecules and genes. The roadblocks encountered in the biological and medical sciences, coinciding with the arrival of powerful tools that can image and interact directly with biological matter at the nanoscale, have made it both imperative and possible to question the views of the previous generation. Knowledge of genes alone is now considered insufficient to explain life or to solve the challenges of medicine. The combined efforts of quantitative experimental techniques and mathematical descriptions of biology are pushing scientists to dare to bravely embrace life in all its complexity as a "symphonic interplay between genes, cells, organs, body, and environment."[2]

Fundamental new ways of looking at life beyond individual molecules include the study of the physical mechanisms that underpin molecules' function and their assembly into "living shapes" capable of displaying very diverse behaviors at different temporal and spatial scales. These new views seek to bridge the scientific and intellectual gulfs between the nanoscale (molecules), the micron scale (cells), the millimeter and centimeter scales of tissues and organs, the meter size of large organisms, and so on, up to whole-planet-size ecosystems.

Physics has learned to accept that when systems become very complex, they often present characteristics that cannot be explained by interactions of their building blocks, because their structures and properties at larger scales *emerge* from collective behaviors at smaller scales. Biology is the clearest example: how else could the precise assembly of nanoscale building blocks eventually give rise to sentient, social beings?

Identifying the properties that are key to understanding biological complexity and its emergent behaviors has become a fundamental objective of quantitative biology. One such property is the mechanical nature of living matter. Mechanics is the branch of physics that deals with motion and the forces and mechanical properties of materials (e.g., elasticity and viscosity) that underlie the movements of simple and complex structures. The capacity to sense, respond to, and exert mechanical forces and signals is a particularly important characteristic of life at every scale that had been almost totally overlooked in the previous century. Mechanics is currently entering the biological limelight, and is doing so in concert with another physical property: biological electricity.

In this chapter, I summarize the intellectual transformation of biological research in the last decades by new techniques and concepts originating in nanotechnology, physics, and mathematical sciences. Currently a much richer, and perhaps humbler, picture is emerging as biology gradually incorporates other sciences, which merge in the search both for new knowledge and for new technologies and medical applications. As biology becomes part of the territory of physics, its new quantitative knowledge will be applied as "engineering" in medicine, materials sciences, and even computing. Toward the end of the chapter, I argue that the new "physics of life" brings us closer to a transformation of what we understand by "matter" in general, and consequently to a technological leap in what we can do with it. More importantly, placing biology within the realm of physics changes scientific culture. Physics urges us to consider life as a whole emergent from the greater whole—emanating from the same rules that govern the entire cosmos.

HIERARCHICAL UNIVERSE, HIERARCHICAL LIFE

The opening scene of the legendary short film *Powers of Ten*, created by Ray and Charles Eames[3] in the 1960s, shows a 1-square-meter (1 meter $= 10^0$ m) overhead image of a man and a woman enjoying their picnic on a blanket, near Chicago. After ten seconds, the viewpoint starts to move out and away from the blanket, at a speed of a factor of 10 in size every ten seconds: from 1 (10^0m) square meter of the picnic blanket to 10 (10^1) square meters of Burnham Park; then it continues to move at this speed to the whole city of Chicago (10^4), followed by the Earth, the Solar System, our galaxy . . . all the way to 10^{24} square meters, a snapshot of the span of the observable universe. The film takes the viewer on a cosmic journey through magnitude to discover the effect of adding another zero to the field of vision. The effect on the viewer is wonder at the hierarchical structure of the physical reality of our universe across its temporal and spatial scales, which invites reflection on the fabric of reality. (See plate 1.)

In the second part of the film, the camera zooms back in on the man on the picnic blanket to start descending into negative powers of ten, starting from 10^{-1} m ($= 10$ cm): the back of the man's hand. The viewer is then taken through the skin of his hand to focus on the most complex of all hierarchical constructions: those in the biology of his cells, their subcellular structures, and eventually, his DNA. But we don't stop there. The film continues to zoom in: to one of the carbon atoms in the DNA, to the nucleus of that atom, and finally, to the quarks vibrating inside its protons at 10^{-16} m.

Navigating through the shapes underpinning life, the film highlights the discovery that biology is also arranged in a hierarchy of scales, resembling—in the layered nature of its structures—the rest of the universe it emerged from. Biology differs radically in one key feature, however: life's complexity of structure, variation, and behavior far surpasses that of any other assemblage so far known in the universe.

The appearance of nanometer-size molecules in the water of the young planet Earth around 4 billion years ago[4] generated matter that was destined for mind-blowing complexity and activity, unlike the simpler order emerging from inert quarks, atoms, or stars in space. Somehow, some of those early nanoscale molecules vibrating in salty water (or salty ice!)—the primordial RNAs and proteins—became able to use the energy they dissipated into their environment to become more complex and more ordered, to interact and self-assemble into increasingly sophisticated shapes and structures that eventually became capable of replication.[5]

With the appearance of early replicator molecules that were able to grow and divide, there arrived the key property that sets biological matter apart from any other matter known in the universe: evolution. Evolution is the universe's mechanism for fine-tuning the physics and chemistry of nanoscale molecular building blocks to create increasingly refined living structures. The physics of the universe ensures that biological complexity naturally increases in molecules that dissipate energy into their environment, while evolution *computes* the form and activity of the organisms that are able to succeed in that environment. In this context, by "computation" I mean that life embeds in itself the capacity to "compute" organisms that are able to survive in a complexly changing environment (as "living solutions" to the physics of life), since the organisms that don't succeed eventually disappear ("unviable solutions to the equations of life").

And so, evolution somehow produced the earliest unicellular organisms: first, archaea and bacteria; later, larger protozoa, algae,