

Contents

<i>Foreword by Venki Ramakrishnan</i>	ix
Introduction	1
1 The Measure of You	14
2 Beyond Bacon's Ants, Spiders and Bees	39
3 From Analogue to Digital You	69
4 Big AI	95
5 A Simulating Life	115
6 The Virtual Cell	141
7 How to Create a Human Heart	163
8 The Virtual Body	189
9 Virtual You 2.0	217
10 From Healthcasts to Posthuman Futures	240
<i>Acknowledgments</i>	257
<i>Appendix: Towards a Virtual Cosmos</i>	261
<i>Glossary</i>	267
<i>References</i>	279
<i>Index</i>	305

Introduction

Imagine a virtual human, not made of flesh and bone but one made of bits and bytes, and not just any human, but a virtual version of you, accurate at every scale, from the way your heart beats down to the letters of your DNA code.

—*Virtual Humans* movie premiere, Science Museum, London

Within the walls of a nineteenth-century chapel on the outskirts of Barcelona, a heart starts to contract. This is not a real heart but a virtual copy of one that still pounds inside a patient's chest. With its billions of equations, and 100 million patches of simulated cells, the digital twin pumps at a leisurely rate of around one beat per hour as it tests treatments, from drugs to implants.

Though it was deconsecrated many decades ago, the Chapel Torre Girona is still adorned with a cross above its entrance. You can sense a higher power and purpose inside its romantic architecture. There, as sunlight streams through its stained-glass windows, you are confronted by an enormous glass-and-steel room, within which stand three ranks of black cabinets dotted with green lights.

This is MareNostrum (the Roman name for the Mediterranean Sea), a supercomputer on the campus of the Polytechnic University of Catalonia that is used by Peter Coveney along with colleagues across Europe to simulate electrical, chemical, and mechanical processes within the human body. These simulations look just like the real thing, whether a fluttering heart or a lung expanding into the chest. Much more important, however, is that these virtual organs behave like the real thing.

To show the dazzling range and potential of virtual human research, we used MareNostrum to create a movie, with the help of simulations run on other supercomputers, notably SuperMUC-NG in Germany (the suffix *MUC* refers to the code of nearby Munich Airport). Working with an international team, we wanted our *Virtual Humans* movie to showcase where these diverse efforts to create a body *in silico* could take medicine.

2 INTRODUCTION



FIGURE 1. Still from the *Virtual Humans* movie. (CompBioMed and Barcelona Supercomputing Centre)

In September 2017, we held the premiere in the cavernous IMAX Cinema of the Science Museum in London with Fernando Cucchietti and Guillermo Marin, our colleagues from the Barcelona Supercomputing Centre. Even though we had worked for many months on the movie, gazing up at a pounding virtual heart the size of four double-decker buses still left us a little breathless.

SuperMUC-NG and MareNostrum 4 are among a few hundred or so great computational machines dotted around the world that are being harnessed to model the cosmos, understand the patterns of nature and meet the major challenges facing our society, such as studying how the Earth will cope with climate change, developing low-carbon energy sources and modelling the spread of virtual pandemics.

Just as great medieval cathedrals were raised by architects, masons, geometers and bishops to give humankind a glimpse of the infinite, supercomputers are the cathedrals of the information age, where novel worlds of endless variety, even entire universes, can be simulated within these great engines of logic, algorithms and information.

You can also re-create the inner worlds of the human body, and not just any body, or an average body, but a particular person, from their tissues and organs down to the molecular machines at work within their cells, their component proteins along with their DNA.



FIGURE 2. The MareNostrum supercomputer. (Wikimedia Commons: Gemmaribasmaspoch. CC-BY-SA-4.0)

The eventual aim of this endeavour is to capture life's rhythms, patterns and disorders in a computer, not just of any life or an average life, but of one particular body and one particular life—yours.¹

At the premiere, we were joined by colleagues who had developed virtual hearts, arteries and veins along with the skeleton and its musculature. On that great IMAX screen in the Science Museum, the packed audience glimpsed a future when drugs can be designed to suit an individual patient, when we can visualise the shimmering movements of a mutated protein in the body, track the turbulent flow of drug particles deep into the lungs, study the surges of blood cells through the brain, and simulate the stresses and strains that play on weakened bones.

Rise of Digital Twins

In engineering, virtual copies are known as digital twins. The concept is usually attributed to a paper by John Vickers and Michael Grieves

4 INTRODUCTION

at the University of Michigan in 2002,² which talked of a “Mirrored Spaces Model.” NASA coined the term *digital twin* in 2010,³ and applied this way of thinking to spacecraft.⁴ However, the origins of this approach can be glimpsed much earlier. Many cite the Apollo moon programme as one notable example, when simulators on the ground were used as analogue twins of spacecraft. This approach was famously employed in 1970 to help return three astronauts safely to Earth in the aftermath of an explosion 200,000 miles out in space on board the ill-fated Apollo 13 mission.⁵

Today, digital twins are well established. Many industrial processes and machines are too complex for one brain to grasp, so experimenting with their digital twins makes their behaviour easier to explore and understand.⁶ Lessons learned this way are transforming the future of manufacturing and, by accelerating automation, altering the future of work. Digital copies of machines, even entire factories, are helping to anticipate hurdles, perfect designs and prevent mistakes before they occur.

Digital twins are used to optimise supply chains and store layouts; General Electric used a twin to boost efficiency at an aluminium smelter in India; a twin of the route of a proposed railway line in north west England—in the form of 18 billion data points harvested by drones—was created to help manage this vast transport project; a “factory of the future” in Australia honed a virtual copy of a robotic workstation before building the real thing; engineers use digital twins to estimate the lifetime of a jet engine and how to maintain it efficiently. Digital twins have been used to help create wind turbines, oil rigs, cars, jet engines, aircraft, spacecraft and more besides. Some believe that digital twin cities hold the key to future urban planning.

Digital twins are emerging in medicine too, thanks to the data revolution in biology. One of the legions of people sifting through health data is Leroy Hood of the Institute for Systems Biology, Seattle. Among the most influential of today’s biotechnologists, Hood has worked at the leading edge of medicine, engineering and genetics for decades, dating back to the first human genome programme meeting in 1985. In 2015, he launched a venture that gathered a plethora of data on 5000 patients for five years. All their data were

stored in what Hood calls “personal health clouds.”* Analysis of a patient’s cloud can reveal telltale signals of what Hood calls “pre-pre-disease” that doctors could use to anticipate problems, then intervene to maintain their health.

Hood talks of “scientific wellness,” which “leverages personal, dense, dynamic data clouds to quantify and define wellness and identify deviations from well states toward disease.” A living embodiment of his approach, the 82-year-old was on sprightly form (“I plan never to retire”) when we talked to him about his vision of a “P4” future, where treatments are predictive, preventive, personalised, and participatory. Simulations of the body will help usher in that future by making sense of what patterns in a patient’s data hold in store for them.

In reality, of course, we make do with incomplete understanding and incomplete data. But, as advances in weather forecasting have shown, these shortcomings can be overcome to make useful predictions. We have come a long way since 1922 when, in his remarkable book *Weather Prediction by Numerical Process*, the British mathematician Lewis Fry Richardson (1881–1953) outlined the idea of a fantastic forecast factory, where thousands of human “computers,” using slide rules and calculators, are coordinated by a “conductor.” Richardson mused on whether “some day in the dim future it will be possible to advance the computations faster than the weather advances.” But even he went on to admit that his forecast factory was only a dream.

A century later, his extraordinary vision has become a reality. Supercomputers can make predictions a few days into the future with reasonable accuracy by constantly updating sophisticated computer models with data from orbiting satellites, buoys, aircraft, ships and weather stations.

A typical forecasting model relies on a system of equations to simulate whether it is going to rain or shine. There is an equation for momentum, density, and temperature in each of water’s three phases (vapour, liquid and solid), and potentially for other chemical variables too, such as the ozone that absorbs harmful ultraviolet radiation. In

* Leroy Hood, interview with Peter Coveney and Roger Highfield, August 12, 2021.

6 INTRODUCTION

Chapter Two, we spell out why these nonlinear differential equations, notably partial differential equations, rule the climate system. In all, it takes *billions* of equations to model the planet down to a resolution of, currently, around 60 kilometres.* Overall, the model has to take account of ever-changing thermodynamic, radiative and chemical processes working on scales from hundreds of metres to thousands of kilometres, and from seconds to weeks.⁷ That represents a tour de force of simulation, one that some claim already approaches the complexity required to model the human brain.

Thanks to the torrent of biomedical data available today, along with ever more powerful theory and computation, we believe simulations will revolutionise biology just as much as they have transformed meteorology. The American meteorologist Cleveland Abbe (1838–1916) once declared how progress in his field depended on “the consecration of the physicist and mathematician to this science.”⁸ To echo his 1895 vision of forecasting, we look forward to the day when it is not enough to know someone is unwell—we want to be able to understand if they will fall sick and why, so that we can make them better and for longer.

Optimism about the potential of digital twins in medicine is bolstered by our current ability to forecast weather, which would amaze Abbe. We take the daily forecasts for granted, but this feat of prediction is truly extraordinary. Markus Covert of Stanford University, who has developed virtual cells, remarked that “prediction of storms such as Hurricane Sandy ten days in advance of landfall—with the corresponding evacuation of hundreds of residents, saving both lives and property—could arguably be ranked as among the great technical triumphs in human history.”⁹

When it comes to climate forecasts, plans are under way to create a “digital twin” of Earth that would simulate the atmosphere, ocean, ice, and land down to a resolution of one kilometre, providing forecasts of the risks of floods, droughts, and fires, along with the swirling ocean eddies that shift heat and carbon around the planet. This European model, Destination Earth, will fold in other data, such as energy use, traffic patterns and human movements (traced by mobile

* Tim Palmer, email to Peter Coveney, June 2, 2021.

phones), to reveal how climate change will affect society—and how society could alter the trajectory of climate change in what some already call the Anthropocene, a geological epoch where human activity is having a significant impact on our planet.¹⁰

The details of creating a digital twin of our own planet Earth are staggering. Take clouds, as one example. They are made of water, which is also the main ingredient of the human body (around 68%¹¹). Unlike us, however, clouds seem simple—great plumes of water droplets or ice crystals floating in the sky. Their formation is critical to our ability to predict weather, important for our understanding of the effects of global heating and central to controversial schemes to curb climate change through geoengineering.¹²

From cumulus tufts with beguiling shapes to great sheets of grey, clouds are a beautiful example of how complexity can result from simplicity, as droplets of water are borne on air currents of convection. As these droplets condense inside clouds, a little heat is released, making the clouds buoyant. At great heights, where temperatures fall well below freezing, the droplets turn into ice crystals, giving the resulting cirrus clouds a wispy, feathery look.

Within a cloud, processes at the smallest scales govern the formation of droplets. But, though microscopic, these features and interactions have large-scale, macroscopic, effects. The smaller and more numerous the droplets, the more that light is scattered. At the scale of micrometres, turbulence accelerates cloud formation and triggers rain showers.¹³ Large-scale air motions can create vast cloud systems that can span a continent. By reflecting light into space, clouds can cool the Earth's surface, which is why some believe they should be nurtured to help curb runaway global warming.¹⁴

Essentially all the laws that underpin cloud formation are known, so we should be able to represent how they evolve in terms of known mathematical equations. The hope is to achieve the same for virtual humans, even down to the last water molecule. This may sound fantastical, but optimism that mathematics can describe the warm, complex, dynamic world of the body dates back centuries. The English physician William Harvey (1578–1657) relied on calculations in his demonstration of the circulation of the blood,¹⁵ while in 1865 the French physiologist Claude Bernard (1813–1878) stated that

8 INTRODUCTION

“the application of mathematics to natural phenomena is the aim of all science.”¹⁶

Our ability to create a virtual copy of a person depends on describing the body with the language of mathematics. Although a work in progress, equations written using calculus, which express rates of change, can already depict complex processes uncovered by molecular biologists, cell biologists and many others in the biosciences. These mathematical expressions—ordinary and partial differential equations—can describe at every instant how blood pressure varies depending on where you make a measurement in the body or track an electrical impulse as it speeds along a neuron in the brain, or how quickly a virus steals into a person’s airway.

To put these equations to work, all that is needed to start calculating are the boundary conditions for the problem at hand. This could mean the state of a neuron or an infected cell at a given time or at various time intervals, their rates of change at various instants or the upper and lower limits of a given quantity. These conditions tether the mathematics to reality so we can make forecasts about the body, or “healthcasts,” by analogy with the weather.

But while we accept that the laws of nature are universal, in one critical and practical sense the life sciences—by which we mean biology and medicine—are quite different from the physical sciences—physics and chemistry—that we use to describe clouds. They are more empirical, more dependent on making measurements and doing experiments and, until now, less dependent on theoretical understanding.

Theory, that is, the mathematical representation of the laws of nature, plays a relatively diminished role in medicine and biology. Even the Darwin-Wallace theory of evolution, regarded by some as the greatest scientific theory of all, does not admit a mathematical description. This might sound shocking, but the reality is that, while basic predictions about the patterns of inheritance have been made since Gregor Mendel studied peas in the nineteenth century, the course of evolution is not possible to predict in any quantitative manner.¹⁷

Some influential figures are only too aware of this shortcoming. Paul Nurse, director of the Francis Crick Institute in London and former assistant editor of the *Journal of Theoretical Biology*, told us how he was weary of reading papers that use clever technology to make

measurements that come to “barely any significant conclusions.”* In an opinion article for the journal *Nature*, he cited Sydney Brenner (1927–2019), his old friend and fellow Nobel: “We are drowning in a sea of data and starving for knowledge.”¹⁸ He complained to us that the importance of theory and the principles of life are relatively neglected in favour of cramming facts, knowledge and information. Biology “does have ideas, so why aren’t we talking about them?”

Yet biology, like the rest of science, is undoubtedly governed by the laws of nature. To be sure, there are no-go areas for moral and ethical reasons based on human arguments, but there is absolutely every reason to believe that we should be able to understand a particular scientific aspect of how an organism works and capture that insight in the form of mathematics. To create Virtual You, we need to go beyond the current use of theory in making post hoc rationalisations in biology, after studies are carried out, to using theory to guide experiments and make predictions.

Uniting Science

Science is balkanised. The notion of dividing academic inquirers into tribes dates back to ancient Greece with Socrates (c. 469–399 BCE), his student Plato (c. 428–347 BCE) and, in turn, Plato’s student Aristotle (384–322 BCE).¹⁹ Within a few decades, however, Timon of Philius (c. 320–230 BCE) moaned about the squabbling of “bookish cloisterlings” at the Museum of Alexandria. By the sixteenth century, Francis Bacon (1561–1626) and other philosophers were mourning the splintering of human knowledge.

By the mid-nineteenth century, the disciplinary boundaries of the modern university had taken root, each with its own customs, language, funding streams, establishments and practices. In *Virtual You*, we intend to show that today’s research is more than a baggy collection of fragmented efforts—it is a grand and complementary mosaic of data, models, mechanisms and technology. The big picture of how the human body works is beginning to heave into view.

* Paul Nurse, interview with Peter Coveney and Roger Highfield, September 25, 2021.

10 INTRODUCTION

Just as there is no privileged point of view of the human body, so each perspective from each discipline is equally important. Each is complementary and, if united and consistent, remarkable new insights can emerge. If we look, for example, at the great molecular biology revolution that dates from the 1950s, when physicists and chemists tackled biology, and biologists used techniques developed by physicists, we can see that this vital atomic view of proteins, enzymes and other molecules of living things perfectly complements existing insights into heredity and evolution, marking a powerful unification of knowledge known as consilience.

The simple idea at the heart of this book is that the convergence of many branches of science—patient data, theory, algorithms, AI and powerful computers—is taking medicine in a new direction, one that is quantitative and predictive. We will show how mathematics can capture an extraordinary range of processes at work in living things, weigh up developments in computer hardware and software and then show how the human body can be portrayed *in silico*, holding up a digital mirror to reflect our possible futures.

This is a story that builds on multidisciplinary ideas we set out in our earlier books, *The Arrow of Time*²⁰ and *Frontiers of Complexity*.²¹ In the first, we discussed how to reconcile a deep problem at the heart of science: that time is represented in different ways by different theories and at different length scales, ranging from the microscopic to the macroscopic. In the latter, we showed how complexity in mathematics, physics, biology, chemistry and even the social sciences is transforming not only the way we think about the universe, but also the very assumptions that underlie conventional science, and how computers are essential if we are to explore and understand this complexity. Nowhere is this more relevant than in the efforts to create the virtual human. In *Virtual You*, we draw these threads together within a broad tapestry of research, both historical and contemporary.

Virtual You

This is the first account of the global enterprise to create a virtual human aimed at the general reader. Hundreds of millions of dollars

have been spent in the past two decades on the effort that has been organised through initiatives such as the International Physiome Project,²² America's Cancer Patient Digital Twin,²³ the European Virtual Physiological Human,²⁴ the Human Brain Project²⁵ and another Europe-wide effort led by University College London to which we both contribute, Computational Biomedicine, or CompBioMed for short.

All are united by a single objective. As one workshop held in Tokyo declared: "The time is now ripe to initiate a grand challenge project to create over the next 30 years a comprehensive, molecules-based, multi-scale, computational model of the human ('the virtual human'), capable of simulating and predicting, with a reasonable degree of accuracy, the consequences of most of the perturbations that are relevant to healthcare."²⁶ That virtual vision was unveiled more than a decade ago—in February 2008—and its future is fast approaching.

In the following pages, we will take you on a fantastic voyage through the body, its organ systems, cells and tissues along with the deformable protein machines that run them. We hope to convince you that, in coming decades, virtual twins of cells, organs, and populations of virtual humans will increasingly shape healthcare. This organising principle for twenty-first-century medicine will enable doctors for the first time to look forward to—and predict—what is in store for you, including the effects of proposed therapies. This marks a stark contrast with today's approach where doctors, in effect, look back at what happened to similar (though nonidentical) patients in similar (though nonidentical) circumstances.

In the long term, virtual cells, organs and humans—along with populations of virtual humans—will help to evolve the current generation of one-size-fits-all medicine into truly personalised medicine. Your digital twin will help you understand what forms of diet, exercise and lifestyle will offer you the healthiest future. Ultimately, the rise of these digital twins could pave the way for methods to enhance your body and your future. As we discuss in our concluding chapter, virtual humans will hold up a mirror to reflect on the very best that you can be.

The following four chapters focus on the fundamental steps that are required to create a digital twin: harvest diverse data about the body (Chapter One); craft theory to make sense of all these data

12 INTRODUCTION

(Chapter Two) and use mathematics to understand the fundamental limits of simulations; harness computers to put the spark of life into mathematical understanding of the human body (Chapter Three); blend the insights of natural and artificial intelligence to interpret data and to shape our understanding (Chapter Four).

In Chapters Five to Eight, we show the consequences of taking these steps and begin to build a digital twin, from virtual infections (Chapter Five) to cells, organs, metabolism and bodies. Along the way, in Chapter Six, we encounter the fifth step necessary for the creation of Virtual You. Can we stitch together different mathematical models of different physical processes that operate across different domains of space and time within the body? We can, and the ability to customise a virtual heart to match that of a patient marks one extraordinary example (Chapter Seven), along with modelling the body and its organ systems (Chapter Eight). In Chapter Nine, we discuss “Virtual You 2.0,” when the next generation of computers will overcome shortcomings of the current generation of “classical” digital computers.

In our last chapter, we examine the many opportunities, along with ethical and moral issues, that virtual humans will present. Digital twins will challenge what we mean by simple terms such as “healthy.” Are you really healthy if your digital twin predicts that—without a treatment or a change in lifestyle—you will not live out your potential life span? You may feel “well,” but are you really well if simulations suggest that you are destined to spend a decade longer in a care home than necessary? If a virtual human can become the substrate for human thought, how will we come to regard our digital copy? Finally, in an appendix, we examine a provocative question raised by using computers to simulate the world: Is it possible to re-create the fundamental physics of the cosmos from simple algorithms?

So, to the first of our foundational chapters. This poses the most basic question of all. If we are to create digital twins, how well do we have to know ourselves? To create Virtual You, we need to understand how much data and what kinds are sufficient for a digital twin to be animated by a computer.

As Aristotle once remarked, knowing yourself is the beginning of all wisdom.



FIGURE 3. Virtual anatomical twin. One of the detailed high-resolution anatomical models created from magnetic resonance image data of volunteers. (IT'IS Foundation)

Index

A page number in *italics* refers to a figure.

- Abbe, Cleveland, 6
- ablation: for cardiac arrhythmias, 177, 181–82; for gastric dysrhythmias, 204
- acetaminophen overdose, 201
- action potentials: cardiac, 77–79, 79, 137; Hodgkin-Huxley model of, 45–47, 76; memristors and, 222–23; SpiNNaker supercomputer and, 223–24
- active learning, 160
- adaptive mesh refinement (AMR), 165, 233
- Aerts, Hannelore, 210
- affordances, 51
- agent-based models, 160, 161, 162
- aging, 92, 195, 248, 250, 252
- Aguado-Sierra, Jazmin, 138
- AI (artificial intelligence): biases in our system and, 105; Big AI, 94, 96, 112–14, 166; in cancer diagnosis, 99; in cancer drug development, 113; consumer uses of, 242; digital twins and, 214, 215; efficient chip design and, 82; fusion technologies and, 86; goal of general AI, 114; in *Mycoplasma* modelling, 147; nonalgorithmic thinking and, 50, 51; protein folding problem and, 104–5. *See also* machine learning
- air pollution, and respiratory modelling, 199–200, 201
- AI winter, 96
- “alchemical” calculations, 132, 133–34
- Alder, Berni, 74–75
- algorithms: carefully selected for deep learning, 106; categorised by execution time, 90–91; classical compared to quantum advantage, 235; computability theory and, 47; consciousness and, 214; genetic, 109, 160; Hilbert’s programme and, 47–49; origin of the word, 47; situational reasoning and, 50–51; thinking beyond the reach of, 50
- Allen, Paul, 151
- AlphaFold, 100–105, 103, 106
- alternative splicing, 29
- Alya Red, 174, 174–75
- Alzheimer’s disease, 29, 211, 247, 248
- analogue computers: Antikythera as, 71, 217; finding solutions not digitally computable, 50; Jiuzhang quantum computer, 235, 237, 237, 238; making a comeback, 218; in Manhattan Project, 72; metamaterials and, 218–21, 220; neuromorphic, 225–26; optical, 219, 220, 221; replaced by 1970s, 217; to solve digital pathologies, 66; with synthetic neurons, 222–23; for Virtual You, 238–39
- analogue processing, in deep neural network, 110–11
- anatomy, history of, 19–22
- Anfinsen, Christian, 32
- Anthropocene, 7
- Antikythera, 70–71, 71, 217
- antimicrobial resistance, 112, 133–34, 154, 247
- aortic valve stenosis, 179
- Apollo moon programme, 4, 80
- ARCHER and ARCHER2, 131
- Aristotle, 37
- arrhythmias, cardiac: ablation for, 177, 181–82; atrial fibrillation, 177, 181–82; cardiologists’ data on, 173; customised virtual hearts and, 177; defibrillator implanted for, 182; drug-related, 137, 138–39, 175, 182; predicting electrocardiograms in, 174; sick sinus syndrome, 159; spiral waves in, 162; tachycardia, 178; ventricular, 177

306 INDEX

- arrhythmias, digestive, 203–4
- arteriovenous fistula (AVF), 186
- artificial neurons, 222–23, 224–25, 226
- artificial synapses, 224–25, 226
- Aspuru-Guzik, Alán, 230–31
- asthma, 198, 199, 201
- ATOM AI-driven cancer platform, 113
- ATP (adenosine triphosphate), in cardiac model, 170–71
- ATP synthase, 26
- atrial fibrillation, 177, 181–82
- attention-based neural network, 102
- attractor, 58–59; strange, 58, 59, 84
- Auckland Bioengineering Institute, 190–91, 192–95, 196–97, 198, 201–2, 203–4, 210–11
- Aurora, 81, 82, 85
- Autin, Ludo, 152
- autoimmunity, 128–29
- autonomic nervous system, 192–94

- Babbage, Charles, 71, 72, 217
- backpropagation, 97
- Bacon, Francis, 9, 39, 40, 69–70, 96, 105, 117
- bacterium, virtual, 146–54. *See also E. coli; Mycoplasma genitalium*
- Balasubramanian, Shankar, 23–24
- Barrow, John, 48
- basal ganglia circuits, 91
- Bayes, Thomas, 118
- Bayesian methods, 118, 122, 128
- Bayley, Hagan, 24
- bell curve, 107, 107–8
- Belousov-Zhabotinsky reaction, 142, 142, 162
- Benioff, Paul, 229
- Berloff, Natalia, 221
- Bernard, Claude, 7–8
- Bernoulli, Jacob, 60–61
- Bernoulli map, 60–63, 64
- Besier, Thor, 197
- biases: in artificial intelligence, 105; in digital twins, 251–52
- bicycle, autonomous, 226
- Biden, Joe, 113
- bidomain model, 170
- Big AI, 94, 96, 112–14, 166; defined, 96
- Big Data: machine learning and, 105; magnitude of, 95; making sense of, 244; for medicine and biology, 32–33, 111; theory and, 67
- bits, 229
- “black swans” in data, 106, 108
- Blinov, Michael, 156, 157
- blood clots, 186, 199, 210
- blood pressure, 184, 186, 193, 208. *See also* hypertension
- Blue Waters, 131
- Blumberg, Baruch, 120
- Boghossian, Bruce, 60, 61, 62
- Bohr, Niels, 228, 255
- Boltzmann, Ludwig, 16, 56, 60, 166
- Boltzmann machine, 109
- Boolean algebra: lac operon as logic gate in, 158; in Stanford *Mycoplasma* model, 148
- Borges, Jorge Luis, 14, 38, 109
- Born, Max, 227–28
- boson sampling, 235, 237
- Boyett, Mark, 172
- Boys, S. Francis, 129
- Brahe, Tycho, 40
- brain, 206–12; blood supply to, 210, 210–11; difference from digital computer, 206, 212, 217; epilepsy and, 206, 208–9; Framework to integrate data on, 211; gut microbiome and, 204; imagery of tissue samples from, 92, 206–7; sense of smell and, 211–12; simulating connectivity in, 91–92, 206–7; stroke and, 181, 196, 210, 211; transcranial electromagnetic stimulation of, 208. *See also* Human Brain Project, of EU
- brain cells, studied with VCell, 156
- brain injury, 211
- BrainScaleS, 224–26, 225
- brain tumours, 209–10
- Braithwaite, Richard, 69
- breast cancer, 99, 132–33, 135, 136
- breathing, simulation of, 199, 200, 200–201
- Brenner, Sydney, 9, 19, 116, 145, 147, 151
- bromodomain, 131–32
- Brout, Robert, 37
- Burrowes, Kelly, 198
- butterfly effect, 56, 58, 66, 108

- cadavers, frozen and digitized, 190–91; of Yoon-sun, 184–86, 185, 190
- calcium currents, 79

- calculus, 42–43, 43, 264; photonic calculus, 221
- cancer: AI used in diagnosis of, 99; brain tumor surgery, 209–10; breast cancer, 99, 132–33, 135, 136; drug development for, 113, 130, 131–33, 134–36; exascale initiatives on, 92–93; immunotherapy for, 160; metastatic, 134, 159, 161, 196; molecular dynamics simulations of, 122; multiscale, multiphysics modelling of, 165–66; pathogenesis of, 134–35; Physi-Cell model and, 160, 161, 162; T cells and, 128–29; of unknown primary, 99
- Cantor, Georg, 52
- Captur, Gaby, 176
- cardiovascular system, 168, 184; blood supply to brain and, 210–11; first closed-loop model of, 187. *See also* circulatory system models; heart twins
- Carrel, Alexis, 168
- Cartesius, 131
- cave art, 240–41
- cell cycle, 149, 151, 153
- cells: agent-based models of, 160, 161, 162; cardiac myocyte model, 214; chemical processes in, 116–19; of eukaryotes, 154–55; experiments on simulations of, 146, 159; imaging methods for, 155; number in human body, 26, 140; organelles of, 140, 143, 154–55; 3D models of, 152–53, 153; VCell model, 155–57. *See also* bacterium, virtual; heart cell models; neurons
- cellular automata, 261, 261–64
- cerebral autoregulation, 211
- chaotic dynamical systems: analogue module of supercomputer and, 238; attractors of, 58, 59, 84; Bernoulli map, 60–63, 64; in biology, 63–64; in drug binding to target, 130–31, 136; ensembles and, 56–58, 62, 65–66; ergodicity and, 65; flaws in machine learning and, 106–7. *See also* deterministic chaos; edge of chaos; turbulence
- chaperone proteins, 32, 124
- Cheng, Leo, 203
- chloroquine, and COVID-19, 138–39
- chromosomes, 25–26, 28
- Chua, Leon, 221–22, 223
- Chuang, Isaac, 232
- Church, Alonzo, 48, 213
- Church-Turing thesis, 49
- CiPA (comprehensive in vitro proarrhythmia assay), 137, 138
- Circle of Willis, 210
- circulatory system models, 184–86, 185; cellular automata and, 262–63; computer architecture and, 185–86; exascale computing and, 216; Guyton regulation model, 184, 192; including heart, 184, 187; liver circulation and, 202
- Clancy, Colleen E., 139
- Clark, Alfred, 119
- Clarke, Kieran, 170
- climate change, 7, 110
- clinical trials, based on modelling, 180
- cloaking by metamaterials, 218–19
- cloud formation, 7
- code, and reproducibility, 87–88
- coherence time, 232–33
- Cole, Kenneth, 22, 76
- Collins, Francis, 246
- complexity, 7–10, 17–18; Baruch Blumberg and, 120; big data and, 32–33; DNA and, 25; multiscale modelling and, 164; normal distribution and, 108; optimisation and, 109; Virtual You and, 215–16. *See also* emergent properties
- computable numbers, 51–52, 60
- computation, limits of, 47–49, 213
- confocal microscopy: discovery of fluid “highway” and, 191; VCell and, 155, 156
- Connection Machine, 170, 172, 185
- consciousness, 50, 212–14, 254
- consilience, 10, 116
- Conway, John, 261–62
- Copenhagen interpretation, 228
- coronary artery disease, 180, 194
- coronary blood flow, 172
- coronavirus, 133
- correlations: vs. causation, 111–12; from machine learning, 126, 165–66; non-Gaussian statistics and, 108; random data dredging for, 111; theory needed to understand, 67
- cosmology: exascale machines and, 85; simulations of, 261; Wolfram’s discrete worldview and, 264–66

308 INDEX

- cotranslational folding, 32
- Covert, Markus, 6, 147–48, 150, 151–54
- COVID-19: AI diagnosis from chest scans, 100; biological age and, 248; cardiotoxicity of potential drugs for, 138–39; code sharing and, 88; data sharing and, 36; drug resistance in, 134; drugs used to treat, 247; flawed machine learning models, 99–100; physics-informed neural network and, 114; politics of health policy and, 253; uncertainty in CovidSim, 88–90; vaccines for, 247. *See also* SARS-CoV-2
- CovidSim, 88–90
- cranial nerves, 193
- Crick, Francis, 37–38, 41, 145, 147, 151, 152
- cryo-electron microscopy: of protein structures, 100, 104; of viruses, 120, 121
- CT scans, and heart models, 174, 180
- Cucchietti, Fernando, 2
- curated training data, 99, 100, 105
- curse of dimensionality, 89, 109
- curve fitting, 102, 105, 109–10
- Cvitanović, Predrag, 59

- Dalchau, Neil, 124, 125
- dark energy, 266
- dark matter, 261, 266
- data, 32–36; “black swans” in, 106, 108; broad range available, 190; commercialisation and, 35–36; curated for training, 99, 100, 105; experimental brain sources of, 208; FAIR principles (findable, accessible, interoperable, reproducible), 36; floating-point numbers and, 54–55, 55; in Hood’s personal health clouds, 4–5; integrity of, 35–36; of large medical databases, 214; on neuroscience from many sources, 211; principles ensuring trust in, 251–52; statistical distribution of, 107–8; structured and unstructured, 33–34; theory to make sense of, 36–38. *See also* Big Data
- Davies, Paul, 229
- Davy, Humphry, 187
- decision problem, 48
- decoherence, 232, 233
- deep learning neural networks, 97, 97–98; AlphaFold as, 102; failures of, 105; to make sense of healthcare data, 93–94; proliferating parameters in, 105–6. *See also* machine learning
- deep physical neural networks (PNNs), 110–11, 221
- deep reinforcement learning, 86
- dementia: in Alzheimer’s disease, 29, 211, 247, 248; blood flow and water transport in brain and, 192; brain injury and, 211
- dendrites, 207
- dendritic cells, 160
- Dennard scaling, 81, 82
- Descartes, René, 264
- deterministic chaos, 18; in Lorenz’s convection model, 55–56; Poincaré’s discovery of, 44. *See also* chaotic dynamical systems
- Deutsch, David, 229, 233
- diabetes, 29, 128, 194, 203
- Diesmann, Markus, 91
- differential equations, 8, 42–45. *See also* ordinary differential equations; partial differential equations; stochastic differential equations
- diffusion: logic modules of cell and, 158; in Turing’s pattern model, 143–44; in VCell, 155, 156
- DiFrancesco, Dario, 79
- digital computers: difference from brain, 206, 212, 217; noncomputable numbers and, 52; rise of, 217–18
- digital pathologies, 60–63; denial of, 64; efforts to deal with, 63–66
- digital twins: achieving reliability and robustness, 88; cancer treatment and, 92–93; data integrity and, 35; depending on mathematics, 7–8; discrimination enabled by, 252; of Earth for climate forecasts, 6–7; emerging in medicine, 4–5, 6, 10–12, 243–44; established concept of, 3–4; as lifelong, personalised clone, 250; multiple versions for a person, 250, 251; possibilities offered by, 242; “precision medicine” compared to, 248; regulators turning to, 180, 189–90; responsibility for our

- own future and, 255. *See also* heart twins; Virtual You
- distributed computing, on home PCs, 85
- DNA: as digital information storage device, 158; double helix structure of, 41, 145; mitochondrial, 154; as potential storage medium, 35; variants in disease, 28, 29
- DNA sequencing: of human genome, 246–47; methods for, 23–25, 24; of *Mycoplasma genitalium*, 146
- Doorly, Denis, 200–201
- double precision floating-point numbers, 53, 54, 62, 63
- double slit experiment, 227, 227
- Dougherty, Ed, 40
- downward causation, 17
- drug binding to target, 119, 130, 130–32, 136
- drug development, 129–31; Big AI in, 112, 113–14; bile flow impairment in, 203; blending classical and quantum physics, 166; for cancer, 113, 130, 131–33, 134–36; cardiotoxicity and, 136–39; ensemble simulations in, 131–32; experiments on cell models and, 159; quantum computing for, 231; for sepsis, 160; slow and ineffective, 129–30, 245, 247; 3D images used in, 52; 3D protein structures and, 104–5
- Dushek, Omer, 126–29
- dynamical systems: attractors of, 58, 58–59, 84. *See also* chaotic dynamical systems
- Eagle, 131
- Earth system model, 86
- Eccleston, Ruth, 124
- echocardiography, 176
- E. coli*: data on enzymes of, 150; early research on, 145–46; lac operon of, 158; simulation of, 151–52; simulation of colonies, 153–54
- Eddington, Arthur, 40
- edge of chaos, 222, 223
- Einstein, Albert, 20, 37, 40, 49, 115, 140, 159, 163
- electrocardiograms: drug-related arrhythmias and, 139; whole organ simulations and, 174, 178
- electroceuticals, 193–94
- electronic structure calculations, 229–30, 231, 238
- electrophysiology: in Alya Red heart model, 174; in digestion, 203–4; early research on, 22; in heart cell models, 170, 173; in heart twins, 182; in VCell, 156. *See also* Hodgkin-Huxley model
- Elliott, Tim, 124, 126
- emergent properties, 16–18; agent-based models and, 160; cardiac oscillations as, 77, 78–79, 173; information flow and, 159; Navier-Stokes equations and, 262, 263; of synthetic bacterial cell, 151; theories and, 37, 38; of whole human, 115–16. *See also* complexity
- empiricism, 40
- energy efficiency: of analogue processors, 238; of hybrid quantum-classical machines, 238; memristors and, 222, 223; of PNNs (deep physical neural networks), 111; of quantum computers, 234
- Energy Exascale Earth System model, 86
- Engheta, Nader, 219, 221
- Englert, François, 37
- ENIAC, 73, 80, 219
- ensemble averages, 57, 58, 74
- ensembles of digital twins, 250
- ensembles of neural networks, 108
- ensembles of simulations, 56–58; for Bernoulli map, 60, 62; in biological sciences, 66–67; for chaotic systems, 56–58, 62, 65–66; drug binding to target and, 131, 136; ergodicity and, 65; limitations of digital computers and, 217; for testing CovidSim, 89–90; in weather forecasting, 57, 57
- entanglement, 230, 231, 232, 234
- Entscheidungsproblem*, 48
- enzymatic reactions: experimentally measured parameters for, 117; quantum computing and, 231
- epigenetics, 28, 246
- epilepsy, 206, 208–9
- equations, 41
- ergodicity, 64–65; spurious correlations and, 111–12
- eukaryotes, cells of, 154–55
- Everett, Hugh, III, 228–29

310 INDEX

- evolutionary theory, 8, 66–67
- exaflop speed, 85
- exascale computers, 80–86; hybrid quantum-classical machines, 238; simulations using, 83–84, 91–94, 216; for Virtual You, 238, 244. *See also* supercomputers
- exons, 29
- experiments: in drug discovery, 104–5; growing gut bacteria, 204; guided by reason, 40; mathematical structures backed by, 67; Morowitz’s ambition for virtual cell and, 146; theories to make sense of, 9, 36–37, 67; validation of computer simulations and, 88
- exponent, 52–53, 53
- Farmelo, Graham, 42–43
- Federov, Vadim, 177
- feedback: autonomic nervous system and, 194–95; cardiac oscillations and, 77–78; cellular information and, 158; in cerebral autoregulation, 211; human complexity and, 216; in multiscale, multiphysics modelling, 164; nonlinear phenomena and, 108, 158; in Turing’s model of patterns, 143
- Fenton, Flavio, 182
- Fetter, Ellen, 56
- Feynman, Richard, 69, 84, 229, 232
- Fick’s law of diffusion, 143
- finite element method: in heart simulations, 169; in predicting bone fracture, 195
- fixed point attractor, 58
- floating-point numbers, 52–54, 53; Bernoulli map and, 60–63; simulations limited by, 54–55, 55. *See also* digital pathologies
- flops, 53; of exascale machines, 81
- fluid dynamics: in Alya Red heart model, 174; of bile, 202–3; blending molecular and continuum models of, 166–67; in circulatory system models, 186; in HemeLB, 184–85, 216, 262; hybrid physics-based and data-driven modelling in, 112; in nuclear weapons, 72, 73, 74; physics-informed neural networks (PINNs) and, 114; Wolfram’s lattice description of, 262–63, 265. *See also* Navier-Stokes equations; turbulence
- fluid highway, discovered in 2018, 191
- Folding@home, 85
- Fowler, Philip, 133–34
- fractal geometry, 59
- Frankenstein* (Shelley), 45, 187
- Frankenstein data sets, 100
- Franklin, Rosalind, 40
- Frontera, 131
- Frontier, 85, 206, 285
- Furber, Steve, 223–24
- fusion power, 86
- Game of Life, 261, 262
- games, winning with AI, 98, 100
- GANs (generative adversarial networks), 98–99, 214
- Gates, Bill, 105
- Gauss, Carl Friedrich, 107
- Gaussian statistics, 107, 107–8
- gender bias, 105
- gene expression: in different cell types, 26, 28; drug interaction with cancer cells and, 113; in *E. coli* model, 152; in *Mycoplasma* cell cycle, 149; regulatory elements of DNA and, 28; in simulated *E. coli* colony, 153–54; turning data into protein, 30–31
- general relativity, Wolfram’s approach to, 264, 265
- genes: functions depending on all 20,000, 246; hugely outnumbered by proteins, 29
- genetic algorithms, 109, 160
- genetic code, 25–26
- genome: limited impact on medicine, 246–47; noncoding regions of, 28; unknowns, 28
- genome-wide association studies (GWAS), 29
- Gershenfeld, Neil, 232
- Getz, Michael, 162
- Ghaffarizadeh, Ahmadreza, 160, 161
- Gibbs, J. Willard, 57
- Gibson, Dan, 150
- glial cells, 207, 211
- global warming, 7
- Gödel, Kurt, 48, 51, 213, 217
- Goodsell, David, 152
- Gorard, Jonathan, 264–65
- Gosling, Ray, 40

- government policies, tested in virtual populations, 253
- Gowans, James, 126
- graph theory: Jiuzhang quantum computer and, 237; Wolfram's model of universe and, 263–64, 265
- Grieves, Michael, 3–4
- Guldborg, Cato, 118
- Gustafson, John, 53–54
- gut microbiome, 204
- gut models, 203–4
- Guyton, Arthur, 184
- Guyton model, 184, 192
- Haemophilus influenzae*, 148
- half precision floating-point numbers, 53, 63, 107
- Hameroff, Stuart, 213–14
- Hamilton, Bill, 37–38
- hangovers, 33
- Hardy, G. H., 66, 67, 141, 142
- Harvey, William, 7, 186, 189
- HARVEY fluid dynamics code, 186
- Hassabis, Demis, 98, 103–4
- Hawking, Stephen, 41
- Haydon, Denis, 24
- healthcasts, 249–51, 252
- Heaney, Seamus, 43
- heart: autonomic nervous system and, 193, 194; kidneys and, 184; of the poet Shelley, 187. *See also* arrhythmias, cardiac; cardiovascular system; ion channels, cardiac
- heart cell models: extended to whole organ, 162, 173; gene mutations in, 159; history of, 169–73; imaging of tissue layers and, 171; incorporating patient data, 169; more than 100 used today, 80; of Noble, 76–80, 79, 136, 137, 162, 170–72, 190
- heart cells: electrical activity of, 76–80, 79, 168; muscle contractions of, 168–69; prolonged QT interval and, 137, 139
- heart failure: in Alya Red model, 175; atrial fibrillation and, 177; multiscale models of, 178, 181; neural circuitry and, 194; pacemaker and, 176; ventricular model and, 162
- HeartFlow Analysis, 180
- heart imaging: with CT, 174, 180; in customising heart models, 173; with echocardiography, 176; of layers to build 3D digital version, 171; whole organ simulations and, 174. *See also* MRI (magnetic resonance imaging) data
- heart twins, 173–77, 179; commercial simulation software and, 183; customised for a patient, 173, 175, 176–77, 178; four lanes of activity on, 173; hyperbole about, 183; limited by computer power, 182; in Living Heart Project, 174; medical devices and, 176, 176, 179, 180; multiscale modelling and, 162, 167–69, 174, 174–75, 178; patient data for use with, 172–73, 176–77, 183; predictions based on, 215; remodelling in, 173, 177. *See also* precision cardiology
- heart valves: aortic valve stenosis, 179; testing of artificial valves, 180
- Heisenberg uncertainty principle, 227
- HemeLB, 184–85, 216, 262
- Higgs, Peter, 37
- Higgs boson, 37, 85
- Hilbert, David, 47–49
- Hilbert space, 229–30, 234
- Hilgemann, Don, 79
- Hillis, Danny, 170
- Himeno, Yukiko, 205
- Hinton, Geoffrey, 97
- hip implants, 196, 197
- Hippocrates, 240
- Hisada, Toshiaki, 174
- HIV (human immunodeficiency virus): animal origin of, 120, 121; protease inhibitors for, 132
- HIV simulations, 121–26; chemical reaction network in, 122–23; compared with experiment, 123, 125–26; drug binding to target and, 130, 132; Gag protein in, 125–26; MHC presentation of peptides and, 124–25; from molecules to epidemiology, 132; ordinary differential equations in, 122–23, 124, 125; rate parameters in, 122, 124–25
- Hladky, Steve, 24
- Ho, Harvey, 201
- Hodgkin, Alan, 22

312 INDEX

- Hodgkin-Huxley model, 45–47, 70; analytical solutions to, 171–72; human heart simulations and, 169; memristors and, 222; Noble’s heart cell studies and, 76, 77, 78
- homeostasis, 164
- Hood, Leroy, 27, 245, 247–48
- Hooke, Robert, 20–21, 21
- Houzeaux, Guillaume, 174–75
- Human Brain Project, of EU, 11, 207–9, 223–26
- Human Genome Project, 247
- Hunter, Peter, 79, 171–72, 177, 190, 191, 192, 194–95, 211, 246
- Hutchison, Clyde, 148, 151
- Hutter, Otto, 76, 78
- Huxley, Andrew, 22. *See also* Hodgkin-Huxley model
- Huxley, Thomas Henry, 189
- hydroxychloroquine, and COVID-19, 138–39
- hypertension, 184, 186, 194, 211
- imaging: of the body, 21–22; of cells, 155; patient-specific radiation doses in, 190. *See also* heart imaging; MRI (magnetic resonance imaging) data
- immune system: agent-based models and, 160–62; attacking cancers, 160, 161, 162; attempted virtual versions of, 159; map of, 159; peptides from invaders and, 123–26; SARS-CoV-2 infection and, 162; sepsis and, 160. *See also* T cells
- immunological synapse, 127
- immunotherapy for cancer, 160
- Indiveri, Giacomo, 226
- inflammation, 162, 193, 194, 249
- information: in biology, 157–59; quantum computers and, 229–30
- integral equations, 219, 220
- interoperability, 215
- introns, 28, 29
- ion channels: as memristors, 222; in nanopore sequencing method, 24, 24; of nerve cells, 46–47; in patch clamp method, 22, 23
- ion channels, cardiac, 77–78, 80; in heart twin, 173; hERG potassium channel, 139; mathematical models of, 137
- irrational numbers, 51–52, 64
- ischaemia, 170
- JCVI-syn3A, 151
- Jha, Shantenu, 113
- Jirsa, Viktor, 208, 209
- Jiuzhang quantum computer, 235, 237, 237, 238
- Jumper, John, 101, 102
- Karniadakis, George, 114
- Karplus, Martin, 166
- Kauffman, Stuart, 50–51
- Kepler, Johannes, 40
- kidneys: AVF (arteriovenous fistula) for dialysis and, 186; blood pressure and, 184; studied with VCell, 156
- Klenerman, David, 23–24
- Kloewer, Milan, 62, 63
- knee implants, 197
- Kogge, Peter, 81
- Kolmogorov scale, 84
- Kranzlmüller, Dieter, 135
- Kubinec, Mark, 232
- Kuhl, Ellen, 114
- Kumar, Suhas, 221, 222
- lac operon, 158
- Lamata, Pablo, 178
- Langmuir, Irving, 119
- Large Hadron Collider (LHC), 85
- lattice Boltzmann method. *See* HemeLB
- law of mass action, 118–19; HIV simulation and, 125; in Turing’s theory of development, 143
- laws of nature: artificial intelligence and, 96; machine learning constrained by, 195; theories and, 8–9, 37; Turing’s patterns and, 144
- Leduc, Stéphane, 141
- left bundle branch block, 177
- LeGrice, Ian, 172
- Leibniz, Gottfried Wilhelm, 42, 264
- Levinthal, Cyrus, 32
- Levitt, Michael, 166
- Levy, Sam, 27
- Liesegang, Raphael, 141
- linear differential equations, 43
- linear optimisation, in *Mycoplasma* model, 148

- liver modelling, 201–3
- Living Heart Project, 174, 180, 181
- Lloyd, Seth, 229, 232
- load balancing, 167, 185
- Loew, Les, 155–57
- Loiselle, Denis, 170
- Longhorn, 131
- Lorenz, Edward, 54–56, 59, 84
- Lorenz 96, 63
- Lorenz attractor, 58, 58–59
- Love, Peter, 230–31, 233–34
- Lovelace, Ada, 95
- Lu, Chao-Yang, 235
- lung models, 197–201
- Luthert, Philip, 253
- Luthey-Schulten, Zaida (Zan), 151
- Lyapunov time, 44, 107
- machine learning: biases in data and, 251–52; boson sampling adapted for, 237; brain network models and, 209; challenge of using real-world data in, 100; with chaotic systems, 106–7; control of simulated cancer cells and, 160, 162; correlations and, 126, 165–66; curated training data in, 99, 100, 105; digital twins' advantage over, 248; energy demand of, 110–11; as glorified curve fitting, 105; gut microbiome and, 204; half precision numbers in, 53; hints of creativity by, 98–99; local minimum on error landscape and, 108–10, 110; making sense of big data, 244; in multiscale cancer initiative, 165–66; multiscale modelling integrated with, 114; origin of, 96; of parameters in predicting arrhythmia, 139; parameters of personalised models and, 215; physics-informed, 112–14, 166; predictions and, 106; quantum mechanical, 231; in surrogate modelling, 99, 195. *See also* AI (artificial intelligence); deep learning neural networks; deep physical neural networks (PNNs); neural networks
- Macklin, Paul, 160, 162
- mammography, 190
- Mandelbrot, Benoit, 59
- Manhattan Project, 71–74
- MANIAC, 73
- Manin, Yuri, 229
- mantissa, 52, 53
- Marchant, Jo, 240
- MareNostrum supercomputer, 1, 3, 174
- Marin, Guillermo, 2
- Marinazzo, Daniele, 210
- Maritan, Martina, 152
- Martone, Maryann, 211
- Marzo, Alberto, 195
- mathematics: assisted by machine learning, 99; in biology compared to physical sciences, 66–67; describing the body with, 7–9, 10, 38; limits of computer simulations and, 47–49; reality and, 41, 213; theories in form of, 37, 41. *See also* theory in medicine and biology
- Maxwell, James Clerk, 49–50
- Maynard Smith, John, 37–38
- McClintock, Barbara, 37–38
- McCoy, Matthew, 92
- McCulloch, Andrew, 172
- McCulloch, Warren, 96
- McCullough, Jon, 184
- McIntosh, Randy, 208
- Mead, Carver, 221, 226
- mechanistic modelling. *See* physics-based simulations
- Medawar, Peter, 119
- medical devices: heart twins and, 176, 176, 179, 180; orthopaedic, 196; posthuman future and, 254; virtual cohorts of patient hearts and, 183
- medicine of twenty-first century, 245–49
- memristors, 221–23, 226
- messenger RNA, 30, 31
- metabolism, virtual, 204–6
- metabolomics, 33, 206
- metamaterials, 218–21, 220
- Metropolis, Nick, 73, 74, 118
- MHC (major histocompatibility complex), 124–25
- Michaelis-Menten equation, 117
- microbiome, 204, 206
- mitochondria, 154–55
- ModelBricks, 157

314 INDEX

- molecular dynamics simulations, 70; classical, 74–75, 75, 166–67; computer speed and, 83, 85; customised supercomputer needed for, 122; drug binding to target and, 131, 132; machine learning and, 107; Navier-Stokes equations combined with, 167; non-Gaussian statistics in, 108; of peptide binding to T cell receptors, 127
- Monte Carlo method, 73–74; cellular parameters and, 118; drug binding to target and, 131, 132; in T cell simulations, 128
- Moore's law, 81, 82
- Morowitz, Harold, 145–46, 147
- MRI (magnetic resonance imaging) data:
 - atrial fibrillation and, 177; in heart attack patients, 182; heart models and, 173, 174, 176, 178; high-resolution anatomical models and, 13, 34; virtual population models and, 93
- Müller, Viktor, 122
- multidisciplinary ideas, 9–10
- multiscale and multiphysics modelling, 164–67; with Alya series software, 175; of cancer, 165–66; of cells, 140; discrete lattice models and, 263; of drug-related arrhythmias, 139; of hearts, 162, 167–69, 174, 174–75, 178; of human body, 164; of liver lobule, 201; load imbalance in, 167; machine learning integrated with, 114; with quantum physics included, 166–67; supercomputer architectures and, 216; surrogate modelling in, 167, 195; of Virtual You, 189
- multiverse, 229, 233
- MuMMI (massively parallel multiscale machine-learned modelling infrastructure), 165
- Murphy, James, 57–58
- Murray, James, 144
- muscle fatigue, model of, 205
- musculoskeletal models, 195–97, 196, 197
- Mycoplasma*, Morowitz's work on, 145–46
- Mycoplasma genitalium*: 525 genes of, 148, 149, 150; metabolic interactions in, 146–47; models of, 146–50; synthetic cell with chromosome of, 150; 3D visualisation of, 152–53, 153
- Mycoplasma pneumoniae*, 148, 154
- Navier, Claude-Louis, 45
- Navier-Stokes equations, 45; emergent properties and, 262, 263; explosive shock waves and, 72; Lorenz's chaotic system and, 55–56; in multiscale modelling, 167. *See also* fluid dynamics
- Neher, Erwin, 22
- nervous system, 192–94. *See also* brain; spinal neuronal circuitry
- neural networks, 96–97, 97; attention-based, 102; consciousness and, 214; deep physical (PNNs), 110–11, 221; ensembles of, 108; physics-informed (PINNs), 114; requiring trial and error, 111. *See also* deep learning neural networks; machine learning
- neuromorphic computing, 221–26
- neurons: artificial, 222–23, 224–25, 226; blood supply to brain and, 211; microtubules in, 213–14; in 3D structure of brain sample, 207
- Neuroscience Information Framework, 211
- Newton, Isaac, 41, 42, 264
- Niederer, Steven, 172–73, 182–83
- Nielsen, Paul, 172
- Nievergelt, Jürg, 83
- Nissley, Dwight, 122
- NMR (nuclear magnetic resonance spectroscopy), 101, 104
- Noble, Denis: Connection Machine and, 170, 172, 185; heart cell models, 76–80, 79, 136, 137, 162, 170–73, 190; levels of description and, 159
- Noisy Intermediate Scale Quantum (NISQ) computers, 233
- non-algorithmic processes. *See* noncomputable processes
- noncomputable numbers, 52
- noncomputable processes: consciousness as, 50, 213; in physics, 49–50
- nonhierarchical coupled fluid models, 167
- nonlinear differential equations, 43–44; climate system and, 6
- nonlinear dynamical systems: analogue module of supercomputer and, 238; Hodgkin-Huxley equations and, 222; human complexity and, 215–16
- nonlinearity: abundance of, 18, 44, 109; curve fitting and, 109–10; deep neural

- networks and, 97; deterministic chaos and, 18; difficulty of prediction and, 106; in multiscale, multiphysics modelling, 164; non-Gaussian statistics and, 108; in Turing's model of patterns, 143
- "normal," meaning of, 252, 254
- normal distribution, 107, 107–8
- NP-hard problems, 90–91
- nuclear weapons: fluid dynamics and, 72, 73, 74; simulating the effects of, 86
- nucleotide bases, 26
- Nurse, Paul, 8–9, 16, 37–38, 157–59
- object-oriented programming, in
 - Mycoplasma* model, 147
- Olson, Art, 152
- operons, 154, 158
- optical computers, 219, 220, 221
- optimisation: linear, in *Mycoplasma* model, 148; on smooth landscape, 108–10, 110
- ordinary differential equations, 44; in the biosciences, 8; cellular processes and, 117; in current medical applications, 244; in customised heart twins, 178; in *E. coli* model, 151–52; feedback by nervous system and, 194; in heart cell model, 138, 173; and coupled to PDEs, 162; in HIV simulations, 122–23, 124, 125; in Hodgkin-Huxley, 46; insufficient for Virtual You, 215; in Lorenz simulations, 55; in multicompartmental VCell models, 154–55; *Mycoplasma* models and, 146, 147, 148; in T cell models, 127. *See also* differential equations
- organs and organ systems, 162, 191–95, 193, 215
- osteoporosis, 195, 243
- outliers in data, 106, 108
- overfitting: in machine learning, 106. *See also* curve fitting
- pacemaker, cardiac. *See* sinoatrial node
- pacemaker, gastric, 203–4
- pacemaker implant, 173, 176, 178, 180, 183, 194, 254; Micra model of, 176, 176
- Palmer, Tim, 57–58, 62
- Palsson, Bernhard, 205
- Pan, Jian-Wei, 235
- pancreatic cells, 156
- parallel-in-time methods, 83–84
- parallel processing, 81–82, 83–84, 91–92
- parameters: in *E. coli* model, 151–52; of personalised models, 215. *See also* rate parameters
- parareal algorithm, 84
- Parkinson's disease, 91
- partial differential equations, 44–45; in the biosciences, 8; climate system and, 6; explosive shock waves and, 72; in heart simulations, 169–70; in high-fidelity digital twins, 244; in liver lobule model, 201; to model mitochondria, 155; to model organs and organ systems, 192, 194–95; to model whole human heart, 162, 173; patterns of living things and, 142–43, 145; in VCell, 156; wave equation as, 49–50. *See also* differential equations
- patch clamp, 22, 23
- patents, 36
- patterns in cells, 142–45, 156
- Pendry, John, 218
- Penrose, Roger, 50, 212–14, 233, 235
- periodic attractor, 59
- personal data, 14–19, 34, 247, 252
- personalised medicine, 11, 245–50; in cancer treatment, 135–36; digital twins and, 245–50; drug development for, 129, 132; genetic code and, 25
- personalised models, 215; of brain, 208–10; of heart, 178–83; of lungs, 198–99
- petascale computers, 80, 81, 82, 84
- phase transitions, 74–75, 75
- phenotypes, 27–28
- photonic chip, 219, 221
- photonic quantum computers, 238
- PhysiCell, 160, 161, 162
- physics, noncomputable processes in, 49–50
- physics-based simulations: Big AI and, 96, 112; in high-fidelity digital twins, 244. *See also* multiscale and multiphysics modelling
- physics-informed neural networks (PINNs), 114
- Physiome Project, 11, 171, 190
- PINNs (physics-informed neural networks), 114

316 INDEX

- Pitts, Walter, 96
 Plank, Gernot, 174, 178, 183, 187
 PNNs (deep physical neural networks), 110–11, 221
 Poincaré, Henri, 44, 65, 99, 163
 populations, virtual, 254, 255
 posits, 54
 Post, Emil, 48–49
 posthuman future, 254
 potassium channel, cardiac, 139
 Pour-El, Marian, 49–50
 power consumption: in Aurora super-computer, 82; by machine learning, 106, 110; by photon-based quantum computers, 237; slashed by analogue computing, 218, 219; by SpiNNaker (spiking neural network architecture) supercomputer, 223; by supercomputers, 82
 precision cardiology, 178–83. *See also* heart twins
 precision medicine: in cancer treatment, 135; genomics-based, 246; limitation of, 248; sepsis and, 160
 predictions: actionable, 88; chaotic systems and, 44; digital twins used for, 250; lacking in evolutionary theory, 66–67; from multiscale, multiphysics models, 189; of *Mycoplasma* model, 150; personalised heart models and, 182; as probabilities, 90; as test of theories, 37, 67; uncertain in Covid-Sim, 88–90; unreliability of machine learning for, 106
 predictive, quantitative biology, 36
 predictive medicine, 244, 245–46, 249
 probe-based confocal laser endomicroscopy, 191
 Project K, 145, 151, 152
 Prometheus, 131
 protein folding problem, 29–32, 100–105
 proteins: binding to candidate drugs, 112; created by ribosomes, 30–32; genetic code and, 26, 28; many from a single gene, 29; in metabolic model, 205; three-dimensional shape of, 29–32, 100–105, 101
 protein universe, 104
 proteome, AlphaFold predictions of, 102–3
 proteomics, 33
 Purkinje fibres, 79
 Pythagoras, 37
 quantum advantage, 234–38
 quantum computers: decoherence in, 232; in hybrid computing solutions, 238; Jiuzhang, 235, 237, 237, 238; rise of, 232–34; theory of, 226–31; for Virtual You, 238
 quantum physics: entanglement and, 230, 231, 232, 234; measurement in, 227–28, 230, 232, 233–34, 235; in multiscale models, 166–67; Penrose theory of consciousness and, 213–14; superposition in, 228, 229, 230, 232; Wolfram's discrete approach to, 264
 qubits, 228, 229, 230, 232–33, 234, 238
 racism, 105, 252
 radiation doses, patient-specific, 190
 radio telescope, world's biggest, 85
 Ralli, Alexis, 233
 Ramakrishnan, Venki, ix, 30
 Ramanujan, Srinivasa, 66
 Randles, Amanda, 186
 random circuit sampling problem, 234–35
 RAS proteins, 122, 165
 rate parameters: for cellular processes, 117–19; for HIV simulations, 122, 124–25; for T cell chemical reactions, 127
 rationalism, 40
 rational numbers, 51, 52. *See also* floating-point numbers
 Razavi, Reza, 178
 reaction-diffusion equations, 143–44
 reality: analogue processing and, 218; mathematics and, 41, 213; Wolfram's model of universe and, 264
 receptors, cellular, 119
 Recon3D, 205
 refractive index: of metamaterials, 218, 219; negative, 218n
 regulators: orthopaedic devices and, 196; turning to digital twins, 180, 189–90
 reproducibility issues, 35, 36, 87–88; with COVID-19 models, 88, 100; with personalised models, 215

- Reynolds number, 84
rheumatoid arthritis, 194
ribosomes, 30–32, 31
Richards, Graham, 129
Richards, Ian, 49–50
Richardson, Lewis Fry, 5
Ritter, Petra, 208
RNA, 26, 30, 31
Rodriguez, Blanca, 137–38, 173
Röntgen, Wilhelm, 21–22
RoseTTAFold, 104
rounding errors, 55, 60, 61–62, 63; butterfly effect and, 65; machine learning and, 107; stochastic rounding and, 64
Rudy, Yoram, 138, 173, 174
Ruelle, David, 59
Russell, Bertrand, 67
- Sadiq, Kashif, 122
Sagar, Mark, 191
Sakmann, Bert, 22
Samuel, Arthur L., 96
Sanger, Fred, 23, 26
Sanghvi, Jayodita, 149–50
sarcomeres, 168–69, 181
SARS-CoV-2: cryo-electron microscopy of, 121; drugs to inhibit protease of, 113–14; model of immune responses to, 162; origin in animals, 120; unpredictable mutants of, 120. *See also* COVID-19
Sauer, Tim, 63
Scafell Pike, 131
Schemmel, Johannes, 224–26
Schrödinger, Erwin, 228
Schrödinger’s cat, 228, 229
scientific method, 19, 39–41, 96
scoliosis, 183, 196
sea-level rise, 86
Segal, Eran, 247
sepsis, 160
Serrano, Luis, 154
Shahriyari, Leili, 92
Shelley, Mary, 45, 187
Shi, Luping, 226
shooting method, 84
Shor, Peter, 229
Shuler, Michael, 146
sick sinus syndrome, 159
signal transduction, cellular, 119
sign bit, 52–53, 53
significand, 52–53
simulated annealing, 109
simulation science, origins of, 71–75
single precision floating-point numbers, 53, 54; Bernoulli map and, 60–63; Lorenz 96 and, 63; machine learning and, 107; stochastic rounding and, 64
sinoatrial node, 159, 168, 172
skeleton. *See* musculoskeletal models
Sloot, Peter, 16, 132
Smaill, Bruce, 172
small intestine and stomach, models of, 203–4
smartphones: cardiac dynamics simulations on, 182; in diagnosis, 245; gathering patient data, 33–34
smell, sense of, 211–12, 214
Smith, Ham, 27
Smith, Nic, 172
Solodkin, Ana, 210
Solovyova, Olga, 178
Solvay, Ernest, 163
Solvay Conferences, 163–64
spinal neuronal circuitry, 207–8
SpiNNaker (spiking neural network architecture), 223–24, 224
Square Kilometre Array (SKA), 85
squid giant axon, 22, 45, 76
Stahlberg, Eric, 92, 113
statistical mechanics, 56, 166
Steen, S. W. P., 212
Steitz, Thomas, 30
stents: for brain aneurysms, 184, 186; coronary, 179, 180
Stevens, Rick, 82, 113–14
stochastic differential equations, 117, 151–52. *See also* differential equations
stochastic rounding, 64
Stokes, George Gabriel, 45
stomach and small intestine, models of, 203–4
strange (chaotic) attractors, 58, 59; turbulence and, 84
Streitz, Fred, 122

318 INDEX

- stroke, 181, 196, 210, 211
- structured data, 33, 34
- sudden cardiac death, 177
- Summit, 131
- supercomputers, 80–84; codesign for, 83; cosmological simulations and, 261; in drug development, 131; heterogeneous architectures of, 216; neuromorphic, 223–24, 224; next generation of, 238; power consumption by, 82. *See also* exascale computers
- SuperMUC-NG, 1–2, 131
- Suresh, Vinod, 192
- surrogate models, 99, 167, 195
- Sycamore quantum computer, 234–35, 236, 237
- synapses, 207; artificial, 224–25, 226; imagery of tissue samples and, 92
- synthetic cells, 150, 151
- synthetic neurons. *See* artificial neurons

- tachycardia, prediction of, 178
- Takahashi, Koichi, 147
- Takens, Floris, 59
- Tanghai, Merryn, 198–99
- T cells: agent-based models, 160; cancer and, 128–29; dendritic cells and, 160; foreign antigens and, 124–25, 127; nerves in spleen and, 193–94; ODE models showing activation of, 127–28; in SARS-CoV-2 infection, 162; viral peptides and, 125; virtual T cells, 126–29
- theory in medicine and biology: compared to physical sciences, ix, 6, 8, 112; diagnosis and, 248–49; Francis Bacon, 40–41; information flow and, 158–59; laws of nature and, 8–9, 37; to make sense of data, 36–38; to make sense of experiments, 9, 36–37, 67; need for more of, 38, 66–68, 246. *See also* mathematics
- Thiele, Ines, 205–6
- Thomas, Randall, 184
- Thompson, D’Arcy, 143
- Thompson, Silvanus, 42
- thumb, in primates, 197
- Tianjic chip, 226
- tissues, models of, 162, 214–15

- Titan, 131
- Tomita, Masaru, 146
- Torvalds, Linus, 183
- Townsend-Nicholson, Andrea, 34
- transcranial electromagnetic stimulation (TMS), 208
- transfer RNA, 30, 31
- travelling salesman problem, 91
- Trayanova, Natalia, 182
- trust in simulations, 87–90; CovidSim pandemic simulations and, 88–90; government policies and, 253; personalised models and, 215
- trust in use of data, 251–52
- Tsien, Dick, 79
- turbulence: in breathing, 198; in cloud formation, 7; on hexagonal lattice, 263; machine learning and, 106–7; non-Gaussian statistics in, 108; parallel-in-time method and, 84; periodic orbits of, 59
- Turing, Alan: on limits of computation, 48–49, 51, 213, 229; on pattern formation, 143–45, 156

- Ulam, Stanislaw, 44, 73–74, 118, 261
- uncertainty quantification, 88, 89
- UNIVAC, 74
- unstable periodic orbits, 59, 61, 62
- unstructured data, 33–34
- unum (universal number) format, 54
- urban planning, application of exascale machines to, 86

- vaccines: for COVID-19, 247; for hepatitis B, 120; opposition to, 87
- vagus nerve, 193
- Vázquez, Mariano, 138, 174–75, 200–201
- variational quantum eigensolver (VQE), 238
- Vaughan-Jones, Richard, 170
- VCell, 155–57
- Venter, Craig, 27, 146, 147–48, 150, 245, 246, 247
- ventricular arrhythmias, 177
- ventricular cell model, 79
- ventricular model, 162
- Vesalius, Andreas, 20, 20, 189
- Viceconti, Marco, 195

- Vickers, John, 3–4
 Vigmond, Edward, 182, 187
 viral peptides, 123, 124, 125
 viral quasi-species reconstruction problem, 223
 Virtual Brain, The, 206–12, 209
 virtual human, global enterprise to create, 10–12
Virtual Humans (film), 1–3, 2, 174, 195, 200–201, 242
 Virtual You: analogue processors in, 238–39; ancient quest for, 240–42; enhancement and, 254; experimental treatments on, 254; five steps in creation of, 11–12, 189, 243, 244; hybrid quantum-classical machines and, 238–39; limitations of current models and, 215–16; long path to, 244; multiple versions of, 250–51, 251; new issues prompted by, 251–55; quantum computing and, 229–31; representation of the world and, 242–43; trust in, 87–88; twenty-first century medicine and, 245–49; ultimate aim of, 3, 39. *See also* digital twins
 virus simulations, 119–21. *See also* HIV simulations
 voltage clamp, 22, 76
 von Heijne, Gunnar, 32
 von Neumann, John, 73, 102, 261
 von Neumann bottleneck, 83
 Vorobyov, Igor, 139
 VVUQ (validation, verification, uncertainty quantification), 88
 Waage, Peter, 118
 Wainwright, Thomas, 74–75
 Wakefield, Andrew, 87
 Waldmann, Herman, 126
 wall clock time, 76
 Wan, Shunzhou, 60
 Wang, Hongyan, 60, 61
 Wang, Ziwen, 221, 222
 Warshel, Arieh, 166
 Watson, James, 40–41, 145
 wave equation, noncomputable solutions to, 49–50
 wave function, 227–28; collapse of, 213, 228, 233–34, 237; quantum computer and, 230
 weather forecasting, 5–7, 74, 154, 165, 175; ensembles in, 57, 57–58; nuclear war simulation and, 86
 Weinberg, Wilhelm, 67
 Wild, Jim, 199
 Willcox, Karen E., 88
 will.i.am, 105
 Williams, Michael, 233
 Williams, Stan, 221–23
 Winslow, Rai, 170, 171, 172
 Wolfram, Stephen, 262–64
 Workman, Paul, 104–5
 X-ray diffraction, 22; of DNA, 40–41; of proteins, 100, 101, 104, 106; of ribosome, 30; of viruses, 120
 X-rays, 14, 17, 21–22, 25, 40, 49, 100
 Yonath, Ada, 30
 Yoon-sun, 184–86, 185, 190
 yottascale computers, 81
 Zerial, Marino, 202–3
 zettascale computers, 81, 216
 Zhang, Henggui, 159
 Zhang, Pan, 235
 Zhao, Jichao, 177