Health Care in the Information Society

Vol. 1

From Adventure of Ideas to Anarchy of Transition

David Ingram

https://www.openbookpublishers.com

All external links were active at the time of publication unless otherwise stated and have been archived via the Internet Archive Wayback Machine at https://archive.org/web

Digital material and resources associated with this volume are available at https://doi.org/10.11647/OBP.0335#resources

ISBN Paperback: 978-1-80064-952-1
ISBN Hardback: 978-1-80064-953-8
ISBN Digital (PDF): 978-1-80064-954-5
ISBN Digital ebook (EPUB): 978-1-80064-955-2
ISBN XML: 978-1-80064-957-6
ISBN HTML: 978-1-80064-958-3

DOI: 10.11647/OBP.0335

Cover image: D koi, *White H2O Molecules* (27 June 2022), https://unsplash.com/photos/5nI9N2wNcBU
Cover design: Jeevanjot Kaur Nagpal

3. Observation and Measurement–From Cubits to Qubits

The story now moves on to consider observation and measurement, and their relationship to number, symbol, code, logic and ethics. Once again, this chapter starts from a broad historical context, setting the scene for discussion of the connection of life science and clinical practice with science and engineering of the past one hundred and fifty years, and information technology of the past seventy-five years.

The chapter visits large- and small-scale measurement and tells stories of people, devices and systems that have revolutionized science and health care in the computer era. It spans between worlds in which yesterday's largest computers are now exceeded in computational capacity by devices built into a wristwatch or handheld device, monitoring, communicating and advising about vital signs. It describes the growing dependence of scientific enquiry on computer technology and software methods, and the new measurement modalities that have grown from these connections, in support of everyday health care. It reflects on the challenge to computation posed by the orders of magnitude increases in variety, scale and volume of measured data and the curation of care records based on these.

As an example, the chapter tracks a century of research, starting with the story of X-ray diffraction methods for the study of crystals, in piecing together the structures of proteins. It describes how databases of such structures began to be organized and shared in the founding era of bioinformatics. It discusses the juxtaposition of measurements with theoretical models, and computational methods that search databases of known structures, to assist interpretation of data about newly studied protein molecules. The chapter concludes with a reflection on the challenges to balance, continuity and governance of health care services. These challenges arise from the explosion of new methods of observation and measurement in the Information Age, and the numerous, huge and disparate silos of data accumulating–containing data about individual citizens that is often non-coherent, proprietary and increasingly impossible to anonymize.

 https://doi.org/10.11647/OBP.0335.03

> Everything is numbers.
>
> –attributed to Pythagoras (*c.* 570 BCE–490 BCE)

> Men, I still think, ought to be weighed, not counted. Their worth ought to be the final estimate of their value.
>
> –Samuel Taylor Coleridge (1732–1834)[1]

> All things physical are information-theoretic in origin and this is a participatory universe [...] Observer participancy gives rise to information; and information gives rise to physics.
>
> –John Archibald Wheeler (1911–2008)[2]

My Uncle Geoffrey, a casualty surgeon, told me the following joke when I was about ten years old–strange that my brain still remembers and pictures him as he spoke. Question: What is the difference between a physician, a surgeon and a pathologist? Answer: Physicians know everything and do nothing; surgeons know nothing and do everything; and pathologists know everything and do everything… a day too late!

Reminiscent of in-crowd banter among doctors, such jokes about professionals are staple comedy fare; this one is maybe now a bit dated! It does, though, give me a link from Chapter Two and the world of knowledge to the world of observation and measurement, with the pathologists observing down microscopes and measuring in test tubes. Incidentally, a more cerebral and knowledgeable surgeon than my uncle, you could not imagine. He used to visit me when I was a student at the University of Oxford and took me out for dinner at the swish Mitre restaurant. He had long since retired from his work in charge of the Emergency Department of the Whittington Hospital in London and died several years before I arrived to work there. One of the doctors I met and chatted to, remembered him with great affection.

Observation and measurement connect hand in hand with science and technology. They underpin scientific method and are, in turn, underpinned by technologies that determine what and how we can observe and measure in the world. Computer technology and computational science have augmented our senses and provided new eyes, and nowhere more so than in health care. This chapter is a story of this coevolution–about its origins and pioneers and their practical impact.

1 S. T. Coleridge, *Lay Sermons* (London: Edward Moxon, 1852), p. 243.

2 J. A. Wheeler, 'Information, Physics, Quantum: The Search for Links', in *Feynman and Computation*, ed. by A. Hey (Boca Raton, FL: CRC Press, 2018), pp. 309–36, https://doi.org/10.1201/9780429500459-19

The Greeks observed the world, confronted paradox in ways of describing and measuring it, and thought about term and number. John Wheeler, colleague of Niels Bohr (1885–1962) and tutor of Richard Feynman (1918–88), is a doyen of theoretical physics. He confronted measurement in the quantum age and thought about information. Information is to science, today, what number was to science, and to Pythagoras, two and a half thousand years ago–that is, an unfolding enigma! Wheeler might have said that everything is information! Carlo Rovelli might now drop the observer and say that everything is relationship, mirroring, it might appear, Alfred North Whitehead's (1861–1947) process philosophy that we encountered in Chapter Two. In this, he moves from description based on the concept of entity, characterizing 'thing with independent existence', to description based on the concept of relationship, characterizing how 'things are connected, or the state of being connected'. That also sounds to connect with Wheeler's 'participancy' of the observer, as captured in his paradigm changing ideas which he characterized as 'it from bit'!

Electronic care records are to health care today what descriptive narrative was to the emergence of medicine in the times of Hippocrates (*c.* 460 BCE–375 BCE) and Galen (*c.* 130 CE–210 CE)–that is, contentious! Forgetting for a moment that weight is a measure, Coleridge's enjoinder was caution about dependence on metrication as a record of human life–what might now be called 'data-ism'. Pythagoreans believed in the connectedness of body and soul–an early expression of *mens sana in corpore sano* [a healthy mind in a healthy body]. Yuval Noah Harari depicts data-ism as magnifying body and diminishing soul.[3]

Whitehead described the world we observe and measure as one of appearances of reality. These unfold more complexly as the range of scientific enquiry extends over both orderly and disorderly phenomena. Science seeks to crystallize the principles underlying these appearances as simply as possible. The computer is both assisting this endeavour and, at the same time, expanding the range and complexity of what we seek to describe and understand. In his long-ago lecture that I described in the Introduction, Thomas Lincoln (1929–2016) gave an example of how in one branch of medicine before antibiotics, much more was measured when much less could be done for the patient. A kind of hopeful fishing expedition. The computer has cast a net over ever-increasing amounts of inedible fish. I remember a time when the miracle of early data-devouring statistical analysis packages led researchers astray to hunt for supposedly significant statistical correlations in their data, to record as markers of success.

3 Y. N. Harari, *Homo Deus: A Brief History of Tomorrow* (London: Random House, 2016).

The reems of paper circulating in the hospital-based department I worked in during the early years of my career in health informatics bore witness to the huge volume of medical notes and the often-tiny amounts of detail in the surgical notes–for example, 'inguinal hernia, TCI', recording an outpatient consultation and covering a diagnosis and instruction to the clinic secretary to arrange admission of the patient (TCI = to come in) for an operation. What matters is not big or small but appropriate to the task at hand. We easily fall into valuing and rewarding volume of data and in this we mirror the computers' capacity to support us in producing it.

Measurement has a dimension of timeliness. Returning to my uncle's joke, the pathology lab team might once have taken a day or two to collect and test a blood sample or prepare a specimen for detailed microscopic investigation and then report back, during which time an urgent clinical situation might have moved on. As I write, there is a contemporary example of the importance of time in the tracing and tracking of infection from Covid-19. Methods of measurement that detect the presence of the virus in saliva samples, completed within minutes–potentially replacing laboratory analysis of samples collected in nose swabs, analyzed by slower PCR tests, reported back several days later (notwithstanding stories of chaotic logistics in the transport, handling and processing of these samples)–are news items being discussed today (19 August 2021). Rapid testing and tracing of contacts of people who test positive for the virus are seen as key to successful containment of its spread in the population.

Notwithstanding the poetic caution of Coleridge, and the counsel of well-seasoned clinicians–that medicine is art as much as it is science–observation and measurement have become fundamental to health care today. Charles P. Snow (1905–80) described the counterpoint of sciences and arts as the clash of two cultures.[4] The clash has persisted from classical times into the emergence of science from countervailing cultures and beliefs. The modern-day father of the analysis of computational algorithms, Donald Knuth, who I write about in Chapter Five, is widely quoted to have once observed, somewhat narrowly and contentiously, that 'Science is what we understand well enough to explain to a computer. Art is everything else we do'. The programming of computers is a challenge to the articulation of knowledge and reasoning within a framework of engineering discipline. Engineering, as with medicine, operates at the interface that unites science and society. It helps us bridge between Snow's two cultures–think of the artist David Hockney and his iPad art! Eric Topol, more recently, has painted a picture of

4 C. P. Snow, *The Two Cultures and the Scientific Revolution* (Cambridge, UK: Cambridge University Press, 1959).

the engineering of artificial intelligence, as providing a bridge between what he describes as 'shallow' and 'deep' medicine.

As mentioned in Chapter Two, Gilbert Ryle (1900–76) argued against the separation of theory and practice and stated two theses: 1) Knowledge-how cannot be defined in terms of knowledge-that; 2) Knowledge-how is a concept logically prior to knowledge-that. This sounds akin to Albert Einstein's (1879–1955) statement that I quoted in Chapter Two, that the only source of knowledge is experience.

In seeking mental traction with this philosophy, cold towel wrapped around the head, it is good to keep in mind a sense of what is unknown and may never be known, or indeed be knowable through any conceivable experience of the appearances of reality. This is the theme of two of my inukbooks. At the turn of the twenty-first century, John Maddox (1925–2009) retired as editor of the journal *Nature* and published *What Remains to Be Discovered*, visiting the frontiers of science and the unanswered questions being pursued there.[5] In 2016, Marcus du Sautoy published *What We Cannot Know.*[6] They are great, and mentally satisfying reads!

As the Coleridge quotation reminds us, health care is a balance, and services must weigh multiple perspectives when reaching general decisions with and about particular individuals and groups. Lifespan and lifestyle are balances of bodily functions and human and social behaviours. From images of the earliest weighing scales, metaphor of balance has featured in matters of truth and justice. We speak of weighing evidence in deciding what is true. The gold-coloured statue of justice, Britannia, a woman standing tall and holding the scales of justice in one hand and a sword in the other, sits atop the Old Bailey Central Court in London and was visible just one hundred metres from my office window, during my fifteen years working in the Department of Medicine at St Bartholomew's Hospital. Such statues, dating from the ancient mythology of Themis/Justicia, adorn courts of justice across the world.

Datum as 'Omnuscle'

Observation, measurement, mathematics and logic connect with sensors and senses, and ever more closely with machine computation and ethics. When thinking about this chapter, I invented the term 'omnuscle' to capture

5 J. Maddox, *What Remains to Be Discovered: Mapping the Secrets of the Universe, the Origins of Life, and the Future of the Human Race* (New York: Macmillan, 1998).

6 M. du Sautoy, *What We Cannot Know: Explorations at the Edge of Knowledge* (London: Fourth Estate, 2016).

this connected world.[7] It sounded right–omnuscle as datum that embodies observation, measurement, number, symbol, code, logic and ethics as well. A quick search shows that 'phonosemantics' is indeed attested in linguistics! The world of computing is an 'omnuscular' world. *Musculus* in Latin means 'little mouse', perhaps because that is what some muscles look like. I like the idea of 'omnuscle' as small or little data! 'Small data' is a term I long-ago coined in personal correspondence with Martin Severs, as big data started to preen its feathers–it is what big data is composed from, although the 'big' sometimes neglects its 'small' provenance. Ernst Schumacher (1911–77) reminded us that 'small is beautiful'.[8]

As usual, I start by digging back in history. Here were spun, woven together, reasoned with and recorded, 'omnuscular' threads that connect health care with the binary worlds of big science and big data today.[9] They connect from the Epidemics of Hippocrates and the origins of medicine to the Covid-19 pandemic and health care services today. In the Information Age, the 'omnuscular' has stretched the world of appearances in every dimension, on every level and at every scale, changing our lives profoundly. We should remember and keep attached, the 'e' of ethics at the end of 'omnuscle'.

Observation and Measurement

In Chapter Two, ontology and epistemology appeared as co-evolving ways of framing human thought and debate about the nature of reality and the articulation of knowledge–two halves of a whole. Colloquially, we speak of measurements as typically expressed and recorded in numbers, and observations as spoken about and recorded in words and images. Philosophically, such distinctions of meaning are blurred. There is recurrent debate about their nature. They have long been batted to and fro in physics–considered (by physicists, of course!) the hardest of sciences–seeking interpretation and resolution of puzzles arising at the interface of theoretical and experimental quantum physics. It has kept physicists and philosophers enwreathed in scientific puzzles and linguistic knots for almost a century!

Lancelot Hogben (1895–1975) published his much-remembered book, *Man Must Measure* in the mid-1930s, tracing methods of measurement from

7 I should maybe call it an 'omnuscule', by adding 'u', for understanding!

8 E. F. Schumacher, *Small Is Beautiful: A Study of Economics as if People Mattered* (London: Abacus, 1973).

9 I notice that high-scoring words that drop from my invented word, 'omnuscular', in the TV game of Countdown, that I am no longer any good at, are 'unmoral' and 'raucous' as well as a lower scoring, 'normal'!

earliest times. It was where I first encountered the pyramids at Giza.[10] Aimed at children but read by all ages, it was a book my parents bought for me, but is now, sadly, lost. I recall reading there about measurement in classical times. Years earlier, Hogben wrote *Mathematics for the Million*, described by the historian and imaginer of future worlds, H. G. Wells (1866–1946), as a book of first-class importance.[11] He also wrote *Science for the Citizen* (1936)[12] and edited *The Loom of Language* (1943)[13]–language as a tapestry. He was classically well-versed and connected language, and problems of language, with mathematics, science and medicine.

Anyone who has visited Cairo will have marvelled at the skill and force whereby the huge boulders of the Great Pyramids of Giza (*c.* 2580 BCE–2560 BCE) were hewn into shape, manhandled and manoeuvred into position, and made, layer by layer, to rise from a square base to a point summit. The makers had rudimentary measures of length, compasses, observation of the sun and the shadows it cast, rollers, levers, ropes and human labour, at their disposal. Such exploits, combining observation and measurement with making things, led to concepts of shape and volume (γεωμετρία [*geometria*], 'earth measurement'), and calibration of angles by degrees.

Although it was no doubt practised in some shape or form much earlier, medicine was first documented from the fifth century BCE, when descriptive accounts of disease first appeared in the *Epidemics of Hippocrates*.[14] Systems of weights and measures are recorded from the third century BCE, in Egypt and Babylon/Mesopotamia (μέσω ποταμος [*meso potamos*], 'middle river'; the land between the Tigris and Euphrates rivers in modern day Iraq). These were driven locally by the needs of agriculture, trade and construction. The cubit unit of length, about half a metre, used the convenient instrument of the human forearm, from elbow to third finger or wrist. There was local variation in such measure, of course, and over time some convergence towards a common standard across the region. It was not until the eighteenth century, in part prompted by Benjamin Franklin's (1706–90) 'Experiments and Observations on Electricity', that the need for wider standardization took root, and from this the modern-day science of metrology.

Edward Gibbon (1737–94) describes how, in later classical times, the length measure of Rhiyyal, or Hashemite cubit, was calibrated with

10 L. T. Hogben, *Man Must Measure: The Wonderful World of Mathematics* (London: Rathbone Books, 1955).

11 L. T. Hogben, *Mathematics for the Million: A Popular Self Educator*, 2nd ed. (London: Allen and Unwin, 1937).

12 L. T. Hogben, *Science for the Citizen* (London: Allen and Unwin, 1938).

13 L. T. Hogben, *The Loom of Language* (New York: W. W. Norton and Company, 1944).

14 R. Lane Fox, *The Invention of Medicine: From Homer to Hippocrates* (London: Penguin Books, 2020).

astronomical observation (Microsoft Word hears and records cubit as qubit! The Riyal is now the unit of the Saudi Arabian currency).[15] Astronomical tables were compiled from recorded observations:

> They cultivated [...] the sublime science of astronomy which elevates the mind of man to disdain his diminutive planet and momentary existence. The costly instrument of observation was supplied by the Caliph Almamom (786 CE–833 CE), and the land of the Chaldaeans still afforded the same spacious level, the same unclouded horizon. In the Plains of Sinaar, and the second time in those of Cufa, his mathematicians accurately measured the degree of the great circle of the earth and determined at 24,000 miles the entire circumference of our globe.[16]

Relating this to angles and the division of the circumference into 360 degrees, he writes:

> This degree most accurately contains 200,000 Rhiyyals, which Arabia had derived from the sacred and legal practice both of Palestine and Egypt, this ancient cubit is repeated 400 times in each basis of the great pyramid and seems to indicate the primitive and universal measures of the East.[17]

Gibbon further describes how astronomers had to tread cautiously in the 'clash of Greek and Eastern culture and despotism' of the times. The 'Eastern Saracen [...] disdained knowledge of antiquity [...] the heroes of Plutarch and Livy were buried in oblivion [...] Truths of science could be recommended only by ignorance and folly' and 'the astronomer would have been disregarded had he not debased his wisdom or honesty by the vane predictions of astrology'.[18]

Robin Lane Fox describes how medicine in the era of Hippocrates was in part humane and philanthropic service, to be carefully balanced against personal gain for its exponents. Its early medicaments were based on plants. He describes how medicines were prescribed in amounts weighed in balance with several coins. In his forensic appraisal of the documents of the times, he sets out to identify the writers of the Epidemics and the times they were written, making connections with the archaeological record of different systems of coinage and the places where they were used.

In the later centuries described by Gibbon, medicine was already a profession. He records that that there were '860 physicians licensed to pursue their lucrative profession in Baghdad'. This later era paralleled

15 E. Gibbon, *The History of the Decline and Fall of the Roman Empire* (London: Strahan and Cadell, 1788).
16 Ibid., pp. 982–83.
17 Ibid., footnote on p. 983.
18 Ibid., p. 983.

the emergence of chemistry, converting 'alkalis and acids, and poisonous mineral to soft and salutary medicines', alongside the quest to transmute metals and find the 'elixir of health'. He describes a world in which 'reason and fortune of thousands were evaporated in the crucibles of alchemy, promoted by mystery, fable and superstition'.[19]

From ancient times and over many millennia, the recording of time employed sun and sundial, flow of water and sand, and burning of candles. Escapement mechanisms arrived in third century BCE Greece, to assist calibration of elapsed time, although the human body as a system, yet alone heart rate as a thing, was not yet imagined. Escapements started with water and evolved over centuries into wheels and gears, and portable clocks and watches regulated by springs. Pendulum clocks arrived in 1656, to calibrate Gottfried Wilhelm Leibniz's (1646–1716) day. These set the standard of time until the electronic era took over, bringing quartz oscillators in the 1930s and atomic clocks at the start of my songline in 1945. My uncle Geoffrey collected clocks and we have the two-hundred-and-fifty-year-old family longcase pendulum clock calibrating our day now. This clock started ticking as the world moved from the Enlightenment into the Industrial Age, leaving behind its agrarian landscape. It ticks today as the world clicks on in its transition into the Information Society.

Number and Logic

Logical reasoning with and about numbers sprung to life in Greece of the fifth century BCE, the era of Parmenides (born *c.* 515 BCE) and his student and colleague Zeno (*c.* 495 BCE–430 BCE), living in what is now Southwest Italy. There were likely similar awakenings in those times in China, as discussed by the historian Joseph Needham (1900–95), although the record of these has been largely lost. The study of paradox (παράδοξο [paradox], 'beyond or outside of thinking; contrary to expectations'), immortalized in such as Zeno's paradoxes of dichotomy–Achilles racing a tortoise, and arrow in flight –were central to debate about concepts of number, space and time, in context of observation and measurement.

Paradoxes are thought experiments–ways of exploring thinking, and how we think about thinking. The debaters contest one another's assumptions and reasonings about the paradox, whereby wrong or seemingly implausible conclusions are reached (travel over any finite distance can neither be started nor completed; the fast runner can never overtake the slower runner; the arrow is stationary) to defend and refute different understandings about

19 Ibid.

the nature of space and time. These thought experiments were a testbed of ideas of their times, just as the real experiments of psychologists like Kahneman are advancing thinking about thinking today.[20]

Discussion of paradox shaped widening philosophical and scientific debate in the eras of Pythagoras (*c.* 570 BCE–490 BCE), Socrates (470 BCE–399 BCE), Plato (*c.* 428 BCE–348 BCE), Aristotle (384 BCE–322 BCE) and Archimedes (*c.* 287 BCE–212 BCE). 'Common sense' ideas about number, based on experience acquired in observation and measurement of the world, were found wanting in the quest for abstract underlying concepts. This opened the way to new thinking about numbers and counting. In these debates, ways of expressing and defending reasoning–resting on stated assumptions and defined rules and methods of logical argument, thereby open to scrutiny–came to the fore. Disagreements about ways of reasoning revealed in discussion of paradox, and attempts to understand and unravel them, led to new concepts of number: of zero and infinity, of point in space and time, of strange properties of numbers–such as irrational numbers that appeared neither odd nor even. Many centuries later, the calculus of Isaac Newton (1643–1727) and Leibniz in the seventeenth century arose from experimental and observational science of that time–such as in describing the orbits of the planets. It introduced new mathematical methods for describing and integrating infinitesimal change. Two centuries later, paradox of self-reference in logical statements triggered and shaped advance in theory of number and its relationship to theory of computation in the twentieth century.

Paradox also played a part in discussion of natural language, relating to fuzzy definitions of words used. One such example concerned the term baldness. As the number of hairs on the head increases from zero, at what precise event of addition of a single hair does a subject being described change from being bald to not being bald? Can one hair make the difference? We recognize the term, and it somehow relates to number, but the relationship is unclear. Similarly, as one throws logs together, one at a time, at what addition of a single log does the assembly of logs become a pile?

Such debate shaped the interplay of number and logic with experimental observation and measurement, and with philosophy and belief.

Symbol and Code

20 D. Kahneman, *Thinking, Fast and Slow* (New York: Macmillan, 2011); D. Kahneman, O. Sibony and C. R. Sunstein, *Noise: A Flaw in Human Judgment* (New York: Little, Brown Spark, 2021).

Chapter Two introduced the representation of knowledge expressed in terms of symbol and code. The S and C of 'omnuscle' reflect these attributes of data-processing in the Information Age. George Boole (1815–64), Augustus De Morgan (1806–71) and John Venn (1834–1923) took logic into the realm of symbolic logic and computation, where these symbols lie at the heart of how computers work, and how observation and measurement become integral with models of reality programmed in software.

In *I Am a Strange Loop*,[21] Douglas Hofstadter described human reasoning as enacted in the brain on the level of symbols. In Chapter Six, I introduce this as one of my inukbooks on the themes of What is Life? and What is Information? It might have been seen as a mixture of speculative, incomprehensible or whacky, by many cognitive neuroscientists, but his earlier classic book, *Gödel, Escher, Bach*,[22] which showed his immense knowledge of patterns and symbols in mathematics, art and music, gave him the right to be read respectfully. His book describes the brain as 'a chaotic seething soup of particles, on a higher level it is a jungle of neurons, and on a yet higher level it is a network of abstractions that we call symbols'.[23] Eminent molecular biologists, such as Paul Nurse, now speak in the language of information circuits as integrative mechanisms of biology. Hofstadter talks of 'a high-level picture of information-manipulating processes alone'.[24]

That said, and as I describe further in Chapter Six, Feynman cautioned against thinking that the computer needs to be, in any way, brain-like in how it tackles the same tasks that humans do. The emerging field of neuromorphic computing, pursuing implementation of now much more fully understood neuron- and brain-like features, with which to cast and solve computational problems, might now somewhat temper that advice.

Ethics

Incrementally through the Information Age, as the granularity and ease of dissemination and dispersion of data became ever more magnified by the computer, the ownership and governance of data came under ever greater scrutiny. What is personal to be kept private and secure and what is public to be freely shared? What should and must be shared with governments and in the context of professional relationships within health care services? Ethical concepts and considerations framed discussion of ownership and sharing

21 D. R. Hofstadter, *I Am a Strange Loop* (New York: Basic Books, 2007).

22 D. R. Hofstadter, *Gödel, Escher, Bach: An Eternal Golden Braid* (New York: Basic Books, 1979).

23 Hofstadter, *I Am a Strange Loop*, cover text.

24 Ibid., p. 174.

of personal data and became embodied in law. Demonstrated conformance to the legal rights of the data subject, whose permissions regarding use of their data were required to be obtained and recorded through a process of informed consent, became a key attribute of personal data. This extended to the safeguards that must operate when using the data, including potentially difficult and onerous obligations on those handling it, to anonymize the identity of the data subject and correct any propagation of errors seen to have occurred when computing with their data. These requirements became central to how computer systems represent, work with and manage personal health records. The need for this to be done in a demonstrably rigorous, coherent and regulated manner became a significant driver of standardization of such systems.

The ‘e’ at the end of ‘omnuscle’ became a long tail (and tale!), sometimes wagging the dog a bit too hard, perhaps. Humans have proven cavalier in how they behave in, and care about, the sharing of their data, with and by computers–such as through their Google, Facebook and Twitter accounts–while trenchantly protective about how official and professional bodies they consult and engage with are allowed to share it. Big Brother is now having an identity crisis, and lawyers, administrators and politicians, a field day. After first framing intractable law married to intractable computational assumptions, they have switched to prosecuting and defending inevitable defaulters through the courts. Zobaczymy [we will see]![25]

Philosophy and Natural Science

And what of philosophy in relation to observation and measurement? René Descartes (1596–1650) differentiated body and mind–he of Cartesian dualism and the Cartesian coordinate axes of graphs. Modern science seeks to integrate and make whole. The nervous system and brain integrate functions of the body. Bodily homeostasis is regulated lower down in the brainstem and is largely subconscious. Conscious thought and sensation and control of bodily movement reside higher up in the cerebral cortex and cerebellum. Observation, originating through the sensory nervous system–hands, eyes, ears, nose, tongue and touch, all included–travels upwards. Thoughts and actions travel down–the two lines connect. Does what we see, hear and feel echo what our mind is set on seeing, hearing and feeling? There are subtle and subtly manipulable echo chambers in our interactions with and through computers, too. And, as discussed in Chapter Two, philosophy of mind has sought, and some think failed, to distinguish

25 On this Polish expression, see Preface.

intelligence–'knowledge that'–from the application of intelligence through action–'knowledge how'. Philosophy of mind interacts with psychology and neuroscience in clarifying debate about consciousness, thought, intelligence, and now also artificial intelligence (AI).

Observation and measurement intricately interconnect with theory and experimental method of science. Theory provides concept and framework around which to structure knowledge and understanding. Observation and measurement, and tools for analyzing and reasoning with them, anchor detail, rigour, utility and sustainability of that knowledge. And the experimenter is an observer, with potential to interfere and introduce bias throughout.

In twenty-first-century physics, these connections remain unclear. The quantum theory describes reality in terms of wave functions and probabilities. Newtonian classical mechanics embodies a deterministic model of space and time relationships. Somewhere and somehow, they connect. Both have rested on experimental data that verified their predictions, within their respective domains of observation and measurement. There are different schools of thought and substantial continuing experiment at the interface of quantum and classical descriptions. One has it that the act of observation changes (collapses) the uncertain quantum state of the system being observed, as described by its wave function, thereby aligning it with the certain state of the classical description. But what exactly is the nature of observation associated with collapse of quantum wave function probabilities? And how can we characterize transition between a system, like a balding head acquiring hairs, that changes from a quantum system to a classical system, such as a carbon buckyball of incrementally increasing size. And what about entanglement, action at a distance, and John Stewart Bell's (1928–90) inequality–the mood music sometimes seems to change by the week?

Quantum theory has brought to the surface modern-day paradoxes of observation and measurement. It is deep stuff at the level of the meaning of existence and relationship. Erwin Schrödinger's (1887–1961) both dead and alive cat is perhaps among the best known. The Quantum Zeno paradox also now reflects on the meaning ascribed to observation and measurement. My 2019 inukbook, *What Is Real*? seeks to summarize this confusion.[26] It is already out of date. Non-local action–seemingly instantaneous communication of signal between entangled quantum entities–required by quantum theory and with plausible experimental evidence in support, yet seemingly defying tenets of relativity theory which constrain such transmission to the speed of

26 A. Becker, *What Is Real?: The Unfinished Quest for the Meaning of Quantum Physics* (London: John Murray, 2018).

light, defies satisfactory resolution. There are libraries of books descriptive of this state of unknowing. No one knows–maybe there is a Gödel-like theorem of mathematics lurking, making it an ill-formed question or an unknowable truth! Or, as Rovelli maintains, is physics barking up the wrong tree and should better envisage reality in terms of relationship rather than entity? Some, such as Wheeler, have sought an explanation based on information; in his case the idea of 'it from bit'.

Unfortunately, 'I don't know how to solve the equations' is not a highly prized answer in a theoretical physics exam paper, notwithstanding that no one knows what they mean. Students are still expected to show they can do the maths. Neither would I have gained good marks in my final exams, fifty plus years ago, for explaining the elusive neutrino other than as a zero-mass particle, and I would have had next to nothing to say about the mathematical basis today of quantum field theory and quantum gravity.

If physics is in this sort of quandary about observation and measurement, what hope is there for the highly variable domains of biology and medicine, and health care? They have different problems to deal with. I emphasize their different characteristics in the following sections, but not intending complete separation of domains. Words describing observations and measurements and how we reason with them, that have shared and generally accepted, if somewhat fuzzy, colloquial usages (such as object, class, type, quantity and attribute), have acquired narrower meaning within specific contexts of discipline–such as with these same terms in computer science. Even within disciplines, debate focuses on different ways of narrowing these definitions still further. Between disciplines, debates focus on whether there can exist a sound basis for mutually meaningful exchange of information and ideas. Linguistic, scientific and clinical ambiguities surface frequently along the evolutionary timeline of the systems of terminology described in Chapter Two, seeking to standardize the language of health care records.

Biological Variability

There is an important difference of methods tuned to the study of the biological and physical worlds. The search for useful generalization targets simplification of the complexity of observed reality, to an essence that enables reasoning with and about it. In the biological world, there is naturally occurring and 'normal' variability. Healthy people exhibit wide-ranging blood pressure. It varies with age, circumstance, time of day and in many other such contexts. It needs to be adaptable like this, for the organism to survive. And experiment seeking to understand blood pressure in health and disease must accommodate that reality. It can be mitigated by standardizing posture and method when making measurements, but there remains a distribution of results that pertain, when seeking to test hypotheses about cause and effect–does this drug usefully control blood pressure in this clinical situation? The general classification of clinical conditions encountered is similarly impacted by the immense variety of people and environments being surveyed and grouped together.

Characteristically high biological variabilities, known about in general, and widespread particularities (special cases), encountered in practice, limit the scope for useful simplification. This is not to say that simple principles cannot provide useful insights into the nature of complex systems–why they are as they are, in general–and useful ways to reason about and cope with their complexity. When faced with a particular individual phenotype, in practice, it can be difficult to relate such simplification to the presenting case and circumstance, unambiguously, and base useful action upon it.

Methods that can be made to work in a pilot and experimentally constrained context, are liable to falter or fail when pitted against unconstrained, real-life situations, at scale. And in systems devised to categorize and classify the highly variable and contextualized appearances of the biological world, to organize and manage its variety and guide related actions, the handling of special cases that arise is liable to lead to increased complexity of those systems. This might be attempted either with increased complexity of the rules used in making a classification or with expansion of the number of different categories recognized as a basis for classification, and thereby a smaller sample space for each. Such are the arts of analysis and statistics!

In the physical world, scientific method is targeting a different situation. Experience supports the hypothesis that general laws apply, and that we can learn about them experimentally and apply them usefully. Such experiment can more feasibly be conducted within defined and controlled settings. There is thus created a common ground that makes possible reliably testable and sharable answers to the questions the experiment is designed to probe, in the search for principles and laws that underpin the measured reality. Implementation of the experiment will often still pose considerable engineering challenge: to control the environment in which experiment is conducted, measure relevant properties reliably and distinguish the signal looked for from associated contextual noise generated in the experimental process and apparatus.

In the physical sciences, scientists hone their model of a system and analyze and compute the precision with which it describes the modelled data. They focus on minimizing experimental variability, making it possible to ascribe difference between measurement and model prediction to either experimental error or inadequacy of the model. They set a high bar for recognizing new discovery. Five sigma is a level of significance test that requires a one in thirty-three million chance that the signal observed is simply due to background noise (leaving aside, here, the finer points of clarification about the applicability of one- or two-tailed statistical tests). There can then be a virtuous circle, with continuing improvement of both theory and experiment. Biology and medicine feel lucky just to be able to track the difference between the experimental and control group, reliably, let alone discriminate among alternative theories as to how that difference might have arisen.

Notwithstanding the intrinsically fragmented landscape of methods of observation and measurement, analysis, inference and action in the biological and clinical domains, working with what we have is a powerful imperative. One way or another, a rampant tumour must be combatted, now, or a life may be lost. The nature, quality, meaning and impact of data, weighed in individual and population human context, now threads throughout health care.

Clinical Measurement

> The foundation of reality upon which appearance rests can never be neglected in the evaluation of appearance.[27]

> Appearances are finally controlled by the functionings of the animal body. These functionings and the happenings within the contemporary regions are both derived from a common past, highly relevant to both.[28]

Taken together, these two quotations serve to emphasize the dual importance of theory and context in weighing evidence. In clinical medicine, observation and measurement arise and play out within complex personal and practical contexts. The balance of theory and practice is difficult to achieve and navigate in clinical practice. It is like holding and adjusting a course when sailing a dinghy–you know and apply the theory but capsize and dowsing is an ever-present risk in gusting winds!

The traditional picture has been of the clinician as the observer and measurer and the patient as the one being observed and measured. Patients experience and observe their maladies, and how these are treated and cared for, in and through their own bodies and minds. Clinicians experience and observe their patients in and through *their* own bodies and minds, too. The two observe and experience one another, and how they interact and

27 A. N. Whitehead, *Adventures of Ideas* (New York: Macmillan, 1933), p. 293.
28 Ibid., p. 241.

collaborate matters. The connectedness does not end there. It extends within the clinical team and community, to the patient's family and community, and across countries. Clinical practice, and the outcomes it achieves, plays out across all these levels, and therein lie the art and science of health and healing–they do not work well as divided or clashing cultures. The dynamic between clinician and patient has evolved from the invention of medicine in classical times and continues to evolve in the Information Age.

According to surviving documentary records and art from the times of Hippocrates and Galen, medicine as a practice started to emerge in a noticeable way in Greece, in the five centuries BCE and the early centuries CE. Its invention as science and early evolution as a profession is traced meticulously in Lane Fox's recent account. In the sixteenth century, specific gravity of urine was measured accurately and imbued with many diagnostic and curative meanings. Galen had taught that urine came directly from the *vena cava* and thus directly reflected the state of the patient's blood. Until about 1800, reliance on measurement in treating disease was still widely thought of as quackery. Doctors were dismissive of the taking of a temperature or a pulse and it took thirty years for the stethoscope to be accepted into clinical practice, around 1845.[29] With the increasing metrication of patient state, arose the ideas of normal status and wellbeing. As we saw in Chapter Two, the term 'norm' was first used to designate things conformant to a common type, then usual state or condition, of people as well as things. By 1900, norms and standards had become central to diagnosis and treatment of disease. Ease was wellbeing and dis-ease was pathology, and in Ivan Illich's (1926–2002) apocalyptic view, as discussed in Chapter Seven, this was evidence that 'society has become a clinic, and all citizens have become patients'. He saw the way ahead diverging into two alternative paths: increasing 'sickening medicalization of health care' or 'demedicalization of the concept of disease'.[30]

The science and technology of measurements available for the practice of medicine, to characterize and illuminate problems and to enable and guide treatments, have advanced beyond recognition over the past century. The capture of images displaying body state and function now involves a substantial assembly of measurement devices and computations. Theory of measurement (metrology) became established, and in 1944 a professional Institute of Measurement and Control was formed, now based close to University College London (UCL). It brings together engineers and scientists interested in measurement, automation and control systems. The

29 For a review of this period, see I. Illich, *Limits to Medicine: Medical Nemesis: The Expropriation of Health* (London: Boyars, 1995).

30 Ibid., p. 116.

initial focus was on national utilities, industrial infrastructure and logistics. This has broadened in the digital age, to cover sensors linked with machine intelligence, the Internet of Things and personal health monitoring devices. Measurement theory now covers many dimensions. The frequency and breadth of usage of the term 'dimension' increased manifold to an asymptote over the century.

Measurements sample the state of the measured system. Measurement is performed by some measuring agent or device–such as a thermometer measuring temperature within the human body or a human counting the number of blood cells in a specimen slide observed under a microscope. The measuring device exhibits a state that couples to the state of the system it is being used to measure–with increasing temperature, the mercury of early thermometers expands along a tube and the degree of expansion reflects the temperature of the measured system. In this simple and dated example (toxic mercury no more!), a human then sees and records the temperature exhibited along a scale set out to calibrate the expanding mercury column in the device.

Brought together in this simplest of examples is the scientific knowledge embodied in the device (knowledge about the expansion of mercury with temperature), the design engineering expertise that ensures it can sample the state of the measured system (a bulb with suitable thermal conductivity such that heat can flow and temperature can equilibrate quickly between body and device, without unduly disturbing the body), and a suitable volume of mercury that can be heated quickly enough and at the same time exhibit an accurately readable expansion, given the range of temperatures it will be exposed to in normal use.

What is measured, the state of the system that this measurement relates to, the properties of the materials used in the device to probe this state of the system, the signal generated as the device responds to the state of the measured system (in the body thermometer example, this is the movement of the expanding column of mercury, but most devices now generate and record electrical signals and their digitizations, in some shape or form), the means whereby this signal is captured, shaped, communicated and recorded, the quality of signal propagated and accumulated along the way, the faithfulness and interpretation of the final recording made–all these contribute to theory of measurement. Scientific advance in physics, chemistry and biology, engineering advance in materials and methods, electronics and electrical circuit design, mathematical and computational methods for processing signals, ranging from single numbers or sets of numbers to arrays of numbers in multidimensional arrays or images–all of these are specialisms of science and engineering, and of mathematics and computation.

The handling of bias and error requires that any method of measurement be systematically validated and calibrated. The tuning of device characteristics is a compromise to achieve a signal that faithfully (and without bias) reflects the state or function of the system that it is designed to sample, while minimizing extraneous signal arising due to perturbing factors within the system or in the measuring device and measurement process. What we want to see is spoken of as measurement signal. What we want to peer through, and that may obfuscate what we want to see, is spoken of as measurement noise. The design of the system is a compromise between signal and noise. Efforts to tune out noise may also reduce the useful signal. Efforts to amplify the useful signal may increase the associated noise. Design mitigations seek to eliminate bias and improve signal to noise ratio.

The interpretation of measurement connects with the knowledge, skills and experience of the measurer, be they human or embodied in machine and algorithm. This draws on knowledge of the form and function of the measured system and the context within which the measurement is being made. In the simple example of body temperature, has the subject just drunk a hot cup of tea, for example? That is important to know, of course, but, more seriously, where in the body was temperature measured and what aspects of the state of the body system are exhibited at this location. In the context of a blood pressure measurement taken by a human with a sphygmomanometer, was the patient calm, and what was their posture, and how skilled the operator? What does the measurement tell us about the state of the patient's cardiovascular system? How relevant and significant is this kind of measurement, in this particular context, when reasoning about the patient's state and deciding on any actions needed?

To a trained and knowledgeable ear, a stethoscope reveals much more than is heard by a lay person listening in, to whom Korotkov sounds–Nikolai Sergeyevich Korotkov (1874–1920)–might go largely unremarked, if remarked on at all. Even drawing fully on the skills of a highly trained human operator, the desired goals of the measurement may only be achieved by extensive computational analysis of the recorded data. Buried within the signal measured may lie unseen or unsuspectedly useful further information about the state of the system probed, perhaps treated as noise–for example, the tell-tale chance observation of the oscillating radio signature of the first observed quasar (pulsar), discovered by Jocelyn Bell Burnell during a night-time stint at the astronomical observatory where she was conducting her PhD research, lurking in an astronomical chart record being collected for another purpose.

The usefulness of a device or method is often characterized by the specificity and sensitivity of the measurements made with it, in relation to the question that has motivated them. Is this person Covid positive, for example? Sensitivity (true positive rate) characterizes how well the actually positive (true positive, TP) cases are detected, avoiding false negative (FN) results. Specificity (true negative rate) characterizes how well the actually negative cases (true negative, TN) are detected, avoiding false positive (FP) results.[31] It is always possible to detect all the positive cases simply by declaring every case to be positive–this requires no measurement! Though absurd, that method is sensitive, in that it succeeds in identifying all the positive cases that exist. The approach lacks specificity, however, in that all the negative cases would be misidentified as positive–the measurement thus not providing useful information for specifying the separation into the groups of true positive and true negative cases. How the sensitivity and specificity of measurements are weighed, depends on context–of the characteristics of the population sampled (its actual distribution of positive and negative cases) and the clinical importance of correct decision–is it so important that actual positives be detected that the impact of the associated number of false positives results can be tolerated?

Medicine today is practised as a combination of skilled observation, measurement, reasoning and action, its observations potentially combining all sensory awareness–of sight, touch, hearing, taste and smell. The relative importance of these and the need for skilful practice in their enactment (reliable, consistent and reproducible, as well as being handled well with the person being cared for), varies according to time and context. The nature of these different clinical roles embodied in observing and measuring requires a high degree of awareness on the part of the practitioner. Interpretations made, actions taken and outcomes monitored are, likewise, contextual.

Clinical observation–feeling a pulse, listening to a chest or voice–is a human skill. Different clinicians within a single specialty will evolve these skills differently, according to their experience and capabilities. My late and beloved Polish father-in-law, with a lifetime of clinical experience in his combination of hospital and home-based practice, decided the time had come to hang up his stethoscope when he felt he no longer had the sense of touch and hearing on which he had built his diagnostic skills, practised with only rudimentary machine-based imaging and laboratory chemistry available.[32] The diagnostic skills in different specialties are tuned

31 On true positive rates and true negative rates, see further Wikipedia contributors, 'Sensitivity and Specificity', *Wikipedia, The Free Encyclopedia* (16 June 2023), https://en.wikipedia.org/wiki/Sensitivity_and_specificity

32 This was when he was in his mid-eighties and he still had devoted and dependent patients of many years standing, who he charged very little, and who he continued to visit at their homes. My wife tells me that the local chamber of doctors, where he still attended regular professional events, had suggested that he would have to be disbarred if he didn't put up his fees!

to interpret different kinds of observations, measurements and contexts. There are yet wider and more important subtleties! A sense of timeliness is also important. Situations evolve and clarify–timely action or inaction, timely pauses for observation and reflection, times requiring immediate response, whether prompted by urgent instinctive reasoning or in adhering to mandated protocol.

Dialogue and storytelling feature strongly in clinical communication. Dialogue with patients and their family and friends, and within clinical teams, serves to unravel presenting problems and their contexts. Dialogue with others further afield, including from different specialty domains, helps to guide decision and action. Capturing human observations in words and drawings, calibrating, scaling and quantifying them, and relating them to measurements, is a complex and sensitive matter.[33]

Diagnosis of clinical problems and decisions about treatments, based on observation and measurement, can be viewed as an intrinsically experimental method–ideas (hypotheses) crystallize, and actions are taken to test them. The Greek etymology of the word 'diagnosis' attests to reasoning or understanding arrived at through or based on knowledge. Sometimes that knowledge was of mythology or scripture. Diagnostic process attests to a situation where the boundaries of the system being investigated are well defined and the available means for stimulating it and observing a response are well encapsulated in terms of both theory and practice. In clinical medicine, such boundaries are highly permeable, leaking noisy information into the melting pot. An experimental testbed approach to measurement, combined with practical experience of it, that enables patterns of malfunction to be spotted and recognized, based on intuition

33 To take a rather extreme example, the observation and recording of colour is a well-trodden field. Universalists would take the view that the human biology of the eye is the same and the frequency spectrum of a light source is the same, independent of the context in which it is being seen by the human eye. Thus, they argue, a colour terminology must have universal constraints. Relativists are interested in cultural and geographical factors impinging on perception of colour, which lead to many diverse manners of expression—some recognize only very few basic colours, others many more, with different regions of the spectrum attracting different amounts of attention. The complexity and range of words used in the Arctic to describe colour, as described in M. Fortescue, 'The Colours of the Arctic', *AMERINDIA*, 38 (2016), 25–46, illustrates how elusive any attempt would be to calibrate such observation within a clinical context, other than in the broadest of terms, or to generalize among different regions of the world where the emphasis and range of colour terms varies from minutely detailed, to very much more broad brush. I recount this example to give context to the reality that the computer has brought qualitatively different contexts to the scale and range of all manner of sensing devices that are now feasible, well beyond what the human brain will ever be able to handle and reason with.

and observation, are two sides of a coin. They play together in sorting out a malfunctioning car engine or electronic circuit board, escalating in some sequence towards a decision that may be to repair or discard and replace. The situation is of a different nature with living systems, where boundaries and interdependencies between component parts are more amorphous, and experiment is typically conducted within a context of uncontrolled influences and behaviours. Causes and effects inter-react through feedback, and replacing or discarding parts of body systems is not often lightly or easily undertaken!

If a train of thought leads to elicitation of confirmatory evidence, a plan of action is decided on and implemented. The clinician may suspect diabetes and decide on conducting a glucose tolerance test. This test challenges the body with fasting or injection of a bolus of glucose and measures the effect this has on glucose metabolism over the ensuing hours. The details of the measurements may vary but all are directed at inferring something about the state of health of the presenting patient and deciding among options for future management of the disorder they may exemplify. The record kept is, in a sense, a laboratory notebook. With growth of experience comes the skill to recognize and anticipate patterns of illness and their optimum management. In some situations, such as emergency medicine, immediate action is imperative to mitigate harm. Thinking and action designed to tackle underlying damage must wait. In such situations, where time is of the essence and pause for thought a sharply limited possibility, a protocol such as ATLS (Advanced Trauma Life Support, developed by the American College of Surgeons) is best followed–going by the book, where evidence shows this is, in general, the most effective strategy in the interests of the patient. Connecting the best of investigative practice with effective treatment protocol is a key challenge and opportunity of the Information Age, drawing on accurate, reliable and reproducible measurement in support.

In everyday medicine, there is a natural tendency and wish to respond to need by doing something. This is tempered by caution, encapsulated by the exhortation attributed to Hippocrates–probably erroneously, according to Lane Fox–to do no harm and to palliate intractable disease. 'Wait and see' is a common heuristic employed to deal with such uncertainty. Clinicians can work only with the understanding and tools of their times, and risk reputation in straying unwisely into untried or untested territory. What can in principle and in practice be done, what should be done and what is done, reflect different facets of the art and science of medicine and its human context more broadly. As ever, there is also an economic balance of choices to be made. How these are weighed, and how well, depends heavily on the quality of information and the tools and resources available. The art of medicine is, like politics, the art of the possible.

Weighing the costs and benefits of the multiply expanding and expensive dimensions of clinical measurement and observation, coupled with the similar explosion in feasible prevention and treatment of disease, has proven an ever more ambiguous and contentious quest. It sometimes feels that as we come to expect greater vitality in living longer, we somehow come to fear our inevitable mortality more! One wonders what AI will make of these challenges. Perhaps, it will throw up its metaphorical hands–post an emoji and decide not to bother, treading instead a different, perhaps more limited, purely presenting-data-driven pathway of diagnosis and treatment of disease. For sure, from the human perspective, there will need to be a caring and careful balance.

Measurement and Professional Practice

Bodily disorder can be very hard to pin down and manage within the lexicon of known and treatable conditions and situations, as can reasoning about the probable outcome of clinical action or inaction in addressing the disorder. In professional practice, recognition of patterns of disorder, based on clinician experience, is relied on heavily to sort out signal and noise in the welter of data from multiple observations and measurements, that may present.

Machines may in time prove more reliable and effective in finding patterns in this data, which is useful in determining and effecting successful action. In a sense, the machine is learning over time, discovering what works, experimentally, by progressively aggregating and structuring the data from records of clinical practice, to discover an optimal subset that is effective when deciding the best route forward, prospectively, for newly presenting cases. This algorithmic contribution to the diagnosis and management of disorder needs to fit, in an understandable way, with the human needs and goals set in caring for the individual patient. The marriage of machines and humans in this endeavour is a key challenge for AI in health care.

In the previous chapter, the potentially harmful impact on human communication, arising from the delegation of translation between natural languages to machine translators or natural language generators, raised its head as a concern. Here, the potential impact arising from delegation of clinical decision making to machines, is similarly uncertain. In some areas, clinical practice has already long done this and adapted beneficially and with ease. For example, computerized radiotherapy treatment planning has relegated to a distant memory the bench-based graphical methods that were used, during my early career in medical physics, for deciding the radiation beam timings and alignments. But what about choices among heavily impactful diagnostic procedures imposed on the weakest and most distressed of patients? I vividly recall being alongside my wife as she was turned back–lying on a stretcher and inside the radiology department, having been wheeled through long subterranean corridors for a much-needed MRI scan. She was a critical care patient and proved too prone to sickness and too weak to safely undergo the lengthy constraint within the narrow scanning chamber of the machine. These are heart-wrenching moments of clinical decision and not likely well-addressed by 'computer says yes, or no'.

Medical and life science have evolved pervasive new interfaces with mathematics, physics, chemistry and computation. Clinical practice has evolved a correspondingly immense menu of measurements and actions, and a burgeoning lexicon of associated terms used, classifications ascribed and observations, measurements and reasoning recorded. As biological and clinical science advance, so the ensemble of such datasets multiplies, with the potential to illuminate, confuse and contradict, to varying degrees. Just look at the immense and complex detail that must be mastered in the clinical polypharmacy encompassed by state-of-the-art treatment protocols for combatting all manner of different cancers today.

Feynman cautioned against undue digging in matters of scientific enquiry. 'If we look at a glass of wine closely enough, we see the entire universe [...] if our small minds for some convenience divide this glass of wine, this universe, into parts–physics, biology, geology, astronomy, psychology, and so on–remember that nature does not know it!'[34] Investigating clinical professionals also know more than nature knows and may be both well and badly informed. The way they become informed, how well and to what end they are informed, become key issues as the book extends to information utility, from Chapter Eight. At the centre of enquiry in clinical practice, there are diverse individual patients, their diverse families and friends, communities, cultures and populations, and constraining contexts of present need, available resource and potential action. Noise and bias multiply in scale and lead to misinformation alongside information explosion. I have sat and discussed with highly trained and experienced intensive care unit (ICU) staff, who proved right after having said and acted on saying 'I am going to ignore this, this, this and this because of this, which matters more'. Such combined human and scientific insight in interpreting

34 R. P. Feynman, R. B. Leighton and M. Sands, *The Feynman Lectures on Physics* (Beijing: Beijing World Publishing Corporation, 2004), I, 3–10. Also illustrated audio recording at Be Smart, 'Universe in a Glass of Wine (Richard Feynman Remixed)', online video recording, *YouTube* (31 December 2013), https://www.youtube.com/watch?v=b3_n7TDL7lc

clinical observation and measurement is a very high bar to rise to at the level of machine learning. Adaptive machine learning along a timeline of clinical measurement is different from interpretation of a static situation at a particular moment in time.

How does Illich's diagnosis stand up fifty years on in the Information Age? Is medicine heading further towards the factory production line nemesis that he luridly foresaw? Or will health care, rather, become 'demedicalized', as he believed essential, making room for greater personal stewardship of health care needs and choices? In his critique of two different schools of philosophy, Bertrand Russell (1872–1970) believed that truth resided somewhere in between. In this case, might we find a middle course, characterized in a balance of two halves, which I designate in Chapter Seven, in a simplistic way, as a balance of lifestyle and lifespan? This balance, and how it will play out in the Information Society, is the integrative theme I explore further in Chapter Eight. In this chapter, I will continue to explore how observation and measurement are evolving in Information Age medicine, continuously reshaping the art of the possible, alongside changing patterns of health and disease in society.

Measurement and Personal Health Care

In many countries, lifespan is increasing; people are living longer in good health and living longer with chronic illness. Whereas an ideal life for all might be wished to be long, able, active, fulfilled and healthy, these attributes may alternatively be short, disabled, inactive, unfulfilled and unhealthy. All binary compositions of these are possible, and vary over time in the opening, active and closing phases of a life. Different needs and priorities pertain, different organization of health care services are needed to meet and support them, and, thereby, there are also different information needs. It is a continuing characteristic of our age that variation across the spectrum of healthy lifespan and fulfilled lifestyle show marked inequalities, within and between countries. These reflect the natural and social environments lived in, as well as availability and access to health care systems and services.

Chronic illness–illness that does not immediately threaten life, that can in the main be controlled and managed away from hospitals but does not dissipate–has become more common as medicine has succeeded in offering a healthy lifespan and postponing the inevitability of its closure. Nowadays, ageing itself is approached as akin to an illness that can be treated. Staying fit and able into old age has become a more achievable goal, seen to be dependent on choices and control of a healthy and fulfilled lifestyle, as much as through medicine that prolongs lifespan.

Life has evolved to defend itself for survival against odds. The human body is resilient in self-defence and self-repair. And humankind has evolved to cope with, adapt to and help care for the adversities of ill health, both personally and for other people, where personal resource and capability is lacking, or lapses. And where a human body and human society is unable to fulfil those roles, medical science and health care services have acquired a huge repertoire of supportive and corrective interventions. Science has atomized disease to reveal function and dysfunction of the human body and enable intervention at ever greater depth and detail. All this is now better understood and communicated, including in scientific terms.

The past century has witnessed considerable change on all these fronts, and this has accelerated in the Information Age. But some earlier defences have weakened. Families have scattered more widely, not close enough to provide mutual support in coping with challenging events and stages of life. Generally more affluent lifestyles have highlighted the inequalities experienced by the less fortunate. The burden of managing an unhealthy lifespan has increased in duration and volume. It is perhaps not without significance that the first half of the twentieth century, culminating in the early decades of the NHS, saw the 'upswing' decades of politics, care and community in America, and the second half, coinciding with advent of the Information Age, were 'downswing' decades, pivoted to in the 1960s. This inverted U-shaped curve was characterized as 'we-to I, I-to-we', by Robert Putnam in his 2020 book, *The Upswing*, with its forensic data analysis of societal change over the twentieth century in the USA.[35] He did not correlate any of his charts with the rise of information technology, but there looks to have been a crossing of straight lines, forming the letter X–a descending line from community cohesion into a more selfish individualism and a rising line, in counterpoint, of the growth of IT and virtual reality. Putnam is convinced that the coming decades will bounce back towards greater respect for community values and cohesion, to tackle societal failings in stewardship of environment and economy and address concern for equality in matters of race and gender. In this scenario, information as utility could grow in line with this upswing, to help put right the societal failings that unbridled information technology has amplified and brought to a head in the Information Age.

New requirements and methods have emerged. There are many more ways open for the individual to monitor, manage and control their health care needs and for health services to prevent and pre-empt their disease progression. Just as hospitals emerged and grew some centuries ago,

35 R. D. Putnam, *The Upswing: How America Came Together a Century Ago and How We Can Do It Again* (London: Simon and Schuster, 2020).

and primary care services multiplied over the past century, 'personalized medicine' has brought new options and possibilities for cost-effective and safe individual self-care, and hospital at home. There is again a confusion of terminology, here. For the patient, personalized medicine has come to mean an increasing array of options for managing on their own, at home or with their family and immediate carers. For the disease specialist, personalized medicine has come to mean the more precise calibration of professional interventions, drawing on knowledge of the situation and characteristics of each individual patient.

Simple-to-use and quite small devices can enable a patient, or someone attending them at home, to monitor their blood chemistry and vital signs, alerting them to initiate prescribed interventions to control and manage their disorder. Diabetic patients can follow their blood glucose levels at home, on demand, from a pricked sample of blood. Sales of pulse oximeters have mushroomed during the Covid epidemic, based on infrared light shone onto the skin by a finger-clipped sensor. Much more will be possible as sensor biophysics and cellular biology and biochemistry advance, and their technologies are miniaturized and become nanotechnologies. Some will piggyback on the mainframe of yesteryear scale of computational capacity now embodied in a smartphone. For acute, but perhaps only intermittently expressed, conditions that require specialist oversight (such as cardiac arrhythmias), continuous and wearable monitoring devices, active throughout daily life, may offer safer, more effective and more achievable options for management of those conditions. These devices are monitored from wireless domestic networks, linked to specialist centres, thereby avoiding or minimizing the necessity to be hospitalized.

In these ways, advances in device technology are bringing a new balance of personal and professional care, combining new means of measurement and treatment with more detailed computation and analysis of data collected. While this can form the basis of useful information and guidance for both citizen and professional, about actions they can and should take, it risks increasing the fragmentation and incoherence of associated records, impacting adversely on continuity of care. If the diabetic patient can manage the monitoring of their glycaemic state at home, and adjust diet and behaviour, accordingly, how will professional surveillance in the wider context of health and disease be maintained, when there is less personal contact with clinicians trained to look for and detect the unexpected. There are new issues of governance, too, as sharing of data spreads ever more widely, centred more on the wishes and discretion of the individual citizen, and less on that of the professionals who serve them.

And in areas of acute illness and specialism, a treatment for breast cancer, for example, traditionally managed through treatment protocols extending to all patients, can now be customized to individual patients, based on knowledge of individual genotype and sensitivity and specificity of available treatments, relative to known genotypes. A drug that has hitherto shown limited efficacy for the whole group of breast cancer patients may prove highly effective for a defined, genome-characterized subgroup, and relatively ineffective for others. Huge and growing archives of time-series connected clinical and genomics data–uniquely identifiable with individuals, and on into their families–are extending from research into utility in support of everyday practice. This is an active area of research in multinational teams, such as those I have worked with over the past two decades.[36]

Science and Computation

Much of the measurement involved at the leading edge of scientific discovery and professional practice today is intimately integrated with computation. Quantum theory and device physics have transformed chemistry and opened the door to computational chemistry. This, in turn, has transformed computational biology and computational medicine. New concepts of information and information technology have permeated physics, chemistry, biology and medicine, horizontally across disciplines and increasingly over time. As Walther Ch. Zimmerli wrote, information technology is a 'horizontal technology'.[37] Horizontal technology has evolved into horizontal and citizen science. This trend has led to the reshaping of academic endeavour away from siloed domains of discipline and towards a more collaborative focus, grouped in hybrid disciplines to tackle 'Grand Challenge'. At UCL, new academic institutes have drawn together researchers from different disciplines, such as in the CoMPLEX Institute, which stands for Computation, Mathematics and Physics in the Life Sciences and Experimental Biology.

Some years ago, I represented the UK Medical Research Council on the national body overviewing research on what was termed eScience, and as a member of an advisory board of the Council for the Central Laboratory of the UK Research Councils (CCLRC), drawn from across disciplines. CCLRC is based at Harwell, near Oxford, the home base and coordinating centre for large-scale research facilities such as a high energy laser source,

36 The Advancing Clinico-Genomic Trials on Cancer (ACGT) and P(ersonalized)-Medicine initiatives of the European Union (EU) Framework Programme.

37 W. C. Zimmerli, 'Who Has the Right to Know the Genetic Constitution of a Particular Person?', *Ciba Foundation Symposium*, 149.93 (1990), 93–110, https://doi.org/10.1002/9780470513903.ch8

synchrotron light source, neutron pile and telescope observatory. These committee memberships included people responsible for major physics facilities at the Culham Centre for Fusion Energy (CCFE) and the Conseil Européen pour la Recherche Nucléaire (CERN).

Such facilities are stretching the limits of capability of both device and computation, in the scale of measurements of space and time, from the smallest to the largest, and volumes of data collected and analyzed. This evolution has gone hand in hand with the extension of computer processor power, memory size, dynamic and archived storage capacity and network connectivity. Some of the devices themselves are engineering masterpieces–the particle accelerators, telescopes, satellites, lasers and fusion devices are extraordinarily impressive human constructions of our era. It was a privilege to see them and have them explained by their international teams of expert scientists, engineers and operators, at close hand.

It was at Harwell, in 1932, that John Cockcroft (1897–1967)[38] and Ernest Walton (1903–95) first demonstrated nuclear fission, by firing protons at high speed into a metal target. This landmark achievement followed three decades of extraordinary advance in experimental physics: experiments at the University of Cambridge conducted by Joseph John Thomson (1856–1940), moving the image created in cathode ray tubes in applied electric and magnetic fields, and by Ernest Rutherford (1871–1937), firing alpha particles at a thin metal foil and observing back scattering, also at Cambridge, leading to the discovery of the electron and nucleus of the atom. Observing the huge power consumption required by the machine used by Cockcroft and Walton, and the small amount of fission energy released in the experiment, the accomplished and illustrious Lord Rutherford said, in an address to the British Association in 1933:

> These transformations of the atom are of extraordinary interest to scientists, but we cannot control atomic energy to an extent which would be of any value commercially, and I believe we are not likely ever to be able to do so [...] Our interest in the matter is purely scientific, and the experiments which are being carried out will help us to a better understanding of the structure of matter.[39]

38 I had a connection with the Cockcroft family in the 1950s, through their daughter, Elizabeth, who came for a while to work on the staff of the children's home in Hampshire run by my parents.

39 Quoted from A. S. Eve, *Rutherford–Being the Life and Letters of the Rt. Hon. Lord Rutherford* (Cambridge, UK: Macmillan, 1939), p. 374.

A very different future was created than the one he, one of its most luminary progenitors, had predicted![40]

Knowing this historical background, the experience of touring the Harwell and Culham devices of today is breathtaking. We were given conducted tours during the construction of the Diamond Light Source, an electron synchrotron to probe structure and function of materials at the molecular level. The multiple beam lines for mounting experiments on small samples of material, probing them with pulses of X-rays radiating from the electrons accelerated near to the speed of light, are finely tuned in frequency and sensitive to the tiniest amounts and structural properties of the material being studied. The five hundred and sixty-two-metre storage ring is engineered to millimetre precision and held stable on foundations drilled into the chalk substrate of the land on which it is built. The data centre nearby, with row upon row of high-performance computers, is networked with researchers studying subjects arising widely around the circle of knowledge, and around the world.

The nearby Culham Laboratory has been the European research centre for fusion research. A robotic arm sealed away inside the spherical tokamak achieves pinpoint precision in lifting, moving and fitting the panels that line and insulate its wall. The highly skilled and athletic operator activates its movement with hand-operated equipment in the control centre. It looks like a fitness machine in a gymnasium. Five or more technical staff work nearby at screens, to supervise. Vastly more computational resources are deployed to land a small panel in its desired position in the tokamak wall than was used to land the lunar lander from Apollo 11. Jokingly, our guide said they look on the fusion reactor as a peripheral device of the robotic arm, so great is the functioning reactor dependent on it, and so great have been the engineering and computational challenges faced in making it work. Similar challenges posed by the robotic devices employed in the current Mars lander mission,

40 The advancing wave of science eludes the predictions of the most eminent of its progenitors. Richard Feynman, the physics icon of my earlier years, buoyed by the then recent discovery of the predicted omega-minus particle in 1964, completing a group of symmetry in the standard model, predicted that particle physics would be a done deal fifty years hence! Incidentally, this was the year that I arrived at the University of Oxford after reading Volume I of his Freshman Lectures in Physics to students at the California Institute of Technology (Caltech). Fifty years must have seemed a safely long interval—no one would remember! Waiting for a unified field theory of forces and elementary particles to be strung together is a bit like Ionescu's *Waiting for Godot*, if not for the God particle (the Peter Higgs boson), which has now declared its existence! The predicted date of arrival of practical nuclear fusion reactors has been thirty years hence, for many years! During the writing of this book, net release of energy has been demonstrated in experimental prototypes of future fusion reactors.

to drill for and analyze samples of materials to be brought back to earth, are described to be as great as those of getting safely to and from the planet.

On my visits over more recent years, back to old haunts in the Physics Department at the University of Oxford, I have listened to researchers who are working on new devices and technologies of quantum computation, a level of computational resource that may break the secrecy of technologies on which systems of cryptography currently depend. These are outstanding advances to be admired–sadly, well beyond my brain power now! They involve huge new investments, while at the same time contributing to attrition of previous investments, as the devices and infrastructure of the facilities, and the skills in ways of working with them, are often quickly superseded, and made obsolete.

This overview of science and computation may seem rather far-removed from the everyday realities of health care, and no doubt in large part it is. But in the Information Age, science and instrumentation created at the leading edge of scientific endeavour have often evolved and connected extraordinarily quickly into the everyday devices used in laboratories and services, in universities, hospitals, industry and at home. As solid-state physics, molecular science and nanotechnology have advanced, much measurement previously restricted to high-end and expensive laboratories, can now be customized within small and easily handled devices. These can be operated by smart phones, wrapped around with software to analyze and chart information collected during our everyday lives–about the environment around us, what we are doing and how our body is functioning.

Nearly sixty years ago, the physics of nuclear magnetic resonance (NMR) was taught to me as a mix of experimental and theoretical physics, where problems involving the Felix Bloch (1905–83) equations were used to tease our mathematical skills. NMR is now the basis of magnetic resonance imaging (MRI) scanning, a central tool of clinical imaging, and NMR spectroscopy is used routinely in the life sciences to probe the chemistry of life. From electrons revealing themselves to Thomson as what he described as 'corpuscles', to electrons accelerated in synchrotrons and emitted X-rays tuned to probe materials at femto-levels of sensitivity–all within one hundred years! From demonstrating fission of the nucleus to nuclear powered electricity generators, first in Russia and then in the UK, in just over twenty years, and, more soberingly, to the destructive potential of nuclear weapons in less than ten years. From the establishment of paper and thin film chromatography as a method of separating, identifying and measuring amounts of different molecules in a prepared biological sample, starting with Mikhail Tsvet (1872–1919) in Russia around 1900, to the gas and liquid chromatography of today and the flow techniques for rapid detection of Covid-19 virus.

The life science of genetics and molecular biology moved from discovery of the double helix structure and molecular coding of DNA, seventy years ago, building on X-ray crystallography of earlier decades, to the unravelling of its human sequence in a collaborative international research partnership of the 1990s, to new measurement devices that mirrored such results within days, hours and increasingly minutes, and to scientific databanks and population-wide clinical biobanks that aggregate and curate sequences and structures, measured and computed in populations, over lifetimes, throughout the world.

Such measurements and capabilities and the related science and informatics of genome and proteome have reframed genetics research and clinical genetics services. They have enhanced and accelerated discovery and refinement of pharmaceuticals, through new capability to visualize drug action–matching chemical attachment of candidate molecule to target cellular receptor. This imagery has been displayed to illustrate daily news about the Covid virus infection. And in December 2020, AlphaFold has shown that machine learning can succeed in accurate prediction of the three-dimensional folding structure of proteins, working only from the measured sequence data and the already known structures and properties of other proteins.

All these ideas, from the largest to the smallest scales of endeavour, have been made real in a new era of computational physics, chemistry and biology. It is a triumph of computational science and device engineering. It is an inspiring world of science and the appliance and appliances of science. But we must not lose sight of the many problems it poses for creating and sustaining balance, continuity and governance of citizen-centred health care services appropriate to an emerging Information Society. These have loomed on several fronts. First, in overreliance on and overinterpretation of poor-quality data, relating to how we view and value health care services, and based on sometimes highly conjectural abstract models of the real-world. Second, in the additional burden that non-coherent experimentation and implementation place on already overburdened health care services, which struggle to keep abreast of more basic needs. And third, in the business models underpinning health care information systems at large, which are based, in the main, on closed source and proprietary software, lacking adequate and rigorously defined and shared common ground with other software, in their semantic foundations. Lack of this common ground renders coherent overview, from dual professional and citizen perspective, and fruitful collaboration and mutual participation in health care related endeavours, increasingly difficult and burdensome to achieve, if not impossibly so.

Delving into software designed to support discovery at the limits of science and compare it with software in practical, widescale use in daily support of health care services, is sometimes a sobering and rather shaming experience, as illustrated in the following chapters of this story. There is a reason for this–the science and engineering communities that I have described have shared key knowledge and knowhow that has enabled them to collaborate and integrate across disciplines and nations. Governments have enabled that to happen. The health care world has chosen not to invest in this way, preferring to support industry business models that sustain competitive position through proprietary information models, and the records based on them. Future citizen-centred information utility for health care needs to be drawn together on common ground, to share knowledge and methods whereby the data needed can integrate effectively and facilitate coherent records and continuity of care. Proprietary and legacy information systems cannot keep pace with this changing scene, unless functioning, effectively, as monopolies. This is a key issue for the fundamental reinvention and reform of health care services that is now needed–long evident and now increasingly recognized.

Data

The content of records is covered under the blanket plural term, data. The Latin root of the word is about giving and so a reasonable question might be: What does data give us? Apart from the ruefully obvious answer, a headache, we might be forgiven for thinking that it serves no intrinsic purpose! It just is, and it is up to us to accept it more as a gift, leaving with us what we see in it and get from it. I suppose, as in the Latin saying (but with no offence intended to my wonderful Greek friends, whose culture's gifts to civilization are beyond doubt!), we should be cautious of gifts–*timeo Danaos et dona ferentes* [I fear the Greeks even when they bring gifts]! Diverse in form, fuzzy and uncertain in definition and precision, data that we compute with (computable data) must have a clear and consistent provenance, as with the shelf location of books in the library of Chapter Two, if we are to be able to rely on them when building our own knowledge and basing our decisions and actions safely around them. Each type of data has its qualities and limitations, as do combinations of data collected and shared from disjoint data sources–as another saying goes, data is not the plural of anecdote!

In the immense variety of systems supporting measurement in health care, all manners of data are in play. Numeric variables range through nominal, ordinal, interval and ratio levels of measurement. Numeric, textual and image data and standardized terms and codes are used to record, group and classify data, reflecting the disciplines and contexts in which they arise, and the statistical analysis and algorithms (and now machine learning) used to interpret and reason with them.

Chemistry quantifies interactions of atoms and molecules. It defines units of amount in terms of atoms and molecules. Today, measurements of time and space range over the infinitesimally small and the astronomically large.[41] Scientists experiment with atto-second ($\sim 10^{-18}$) laser pulses, detect femto-mole ($\sim 10^{-15}$) concentrations of material with spectrometers, and peer to distances at the gigaparsec limits of the observable universe. One gigaparsec = 3.26 billion light years = 3.086×10^{13} kilometres. The age of the universe based on observations from the Max Planck satellite observatory, named after the founding father of quantum theory, is 13.82 billion years.[42]

In my 1991 talk at the Royal Society of Medicine (Appendix I),[43] I said that in thinking of these spectacular human accomplishments, I knew of no more powerful balancing reminder, to place such successes in the context of what the biological world achieves, than two facts from the science of human sensory systems: 'The kinetic energy of a pea after free falling for a distance of 5 cm would be sufficient to stimulate the retina of every person

41 The cardinality of sets of things studied involves unimaginably large numbers—this is not new. Avogadro's number, the number of units in one mole of any substance is equal to $6.02214076 \times 10^{23}$ and has been known for one hundred years. We now know that the human body contains billions and trillions of cells, bacteria, nerve synapses or corona virus particles in an infected lung. DNA sequences within the cell extend to some three billion base pairs, within the twenty-three pairs of chromosomes. Astronomers estimate that there are two trillion galaxies in the observable universe and twenty sextillion (10^{21}) planets, a number which far exceeds the number of seconds since the Big Bang, leaving aside quandaries about the nature and relationship of time and gravity at that point! More down to earth, the number of ways that a pack of 52 cards can be arranged (factorial 52, written 52! and meaning 52x51x50x….3x2x1) is a very much bigger number, still.

42 At the other end of time, in the realm of quantum mechanics, the Planck time (tP) proposed by Max Planck (1858–1947), is the unit of time in the system of natural units known as Planck units. A Planck time unit is the time required for light to travel a distance of 1 Planck length in a vacuum, which is a time interval of approximately 1.911×10^{-43} s (Lorentz-Heaviside version) or 5.39×10^{-44} s (Gaussian version). All scientific experiments and human experiences occur over time scales that are many orders of magnitude longer than the Planck time, making any events happening at the Planck scale undetectable with current scientific knowledge. As of November 2016, the smallest time interval uncertainty in direct measurements was on the order of 850 zeptoseconds (8.50×10^{-19} seconds). See Wikipedia contributors, 'Planck Units', *Wikipedia, The Free Encyclopedia* (23 April 2023), https://en.wikipedia.org/wiki/Planck_units for more information.

43 Available at https://www.openbookpublishers.com/books/10.11647/obp.0335#resources

who has ever lived', and 'The average energy carried in the sound of the human voice three hours per day for a lifetime, would be sufficient just to boil one cup of water'–both from Primo Levi (1919–87), in *Other People's Trades*.[44] It does say average and I have not checked the calculations but have a feeling that Levi probably did!

As these numbers are chosen to emphasize, data is pervasive and 'given' in overwhelming amounts. Twenty years along my songline, the amount of data collected and stored in the earliest computer databases and processed within computer programs running on millisecond cycle time computer CPUs, was reckoned in kilobytes and (then 'huge'!) megabytes. The achievements of engineers in that era were, nonetheless, frugally remarkable, in what they achieved with what now seems so little. I celebrate some of these pioneers in Chapter Five and Chapter Eight. The machines I used for my PhD studies in the 1970s were already displayed in museums that I visited, just a few years later! The size of file for a typical digital radiograph today (fifteen megabytes) would occupy ten of the spinning discs of the early 1970s and the file sizes for MRI or CAT scanner studies may extend to five hundred megabytes.

Today, data collected in scientific experiments probing at the limits of these Information Age scales of measurement is at the level of exabytes ($2x10^{60}$ bytes) and beyond. Meteorologists use these information technology-based resources to measure pressure, temperature, humidity, wind, rain, solar radiation, at land and sea, and monitor weather patterns with satellite-based sensors, providing fine detail from throughout the globe. Sonar-powered underwater sensors are being developed to provide an underwater Global Positioning System (GPS), setting the stage for mapping the earth's undersea geography. The UK Biobank project is following a cohort of 500,000 people over time and collecting genotype and phenotype data–now, for example, including functional MRI on 100,000 of the cohort. Life scientists use these resources to create three-dimensional computational models of proteins and drugs and markers of diseased cell surfaces that can be targeted by drugs designed to lock there. They use synchrotrons to generate pulses of X-rays that scatter on impacting material samples of interest, measuring and analyzing the scattered radiation to infer its structure. In this way, foot and mouth disease vaccine was studied and a structural modification designed and tested, to improve its rigidity and increase its natural decay lifetime, enabling it to be used further away from its production facility.[45] PET scanner radioisotopes must be sourced from

44 P. Levi, *Other People's Trades* (London: Sphere Books, 1990), p. 114.

45 R. David, 'New Vaccine Promise', *Nature Reviews Microbiology*, 11.5 (2013), 298, https://doi.org/10.1038/nrmicro3019

close-by cyclotrons. Foot and mouth vaccine cannot be manufactured close to cattle herds throughout the world.

Scientific experiments now employ arrays of computing machinery connected through global networks. Data processing is conducted on linked grids of nanosecond-speed processors and petabyte-scale storage devices. Capacity to tackle currently intractable processing tasks is emerging in quantum computers, based on optically linked arrays of quantum entangled devices, storing qubits of data interacting within multiple quantum states.

A 2008 International Data Corporation (IDC) white paper described the world we live in as awash in digital data: 'An estimated 281 exabytes (2.25×10^{21} bits) in 2007. This is equivalent to 281 trillion digitized novels but less than 1% of Avogadro's number, or the number of atoms in 12 grams of carbon (6.022×10^{23})'.[46] By these estimates, the scale of digital data in our cyberworld will surpass Avogadro's number by 2023. We marvel at these achievements and worry about their energy dissipation, rising rapidly to replace mineral oil consumption with that of snake oil!

Health care brings another scale of measurement to the forefront; that of the size of populations covered, with eight billion, heading towards ten billion, people living in the world today. The investigations incorporated in health records cover data collected throughout a person's lifetime. They contain measurements from many kinds of laboratory tests, many varieties of physical images, many kinds of signals from physiological sensors, all feeding into capturing the data about who did what, when, where, how and why, and with what outcome, of health care services. These are recorded by different practitioners, by patients themselves, and directly from devices making the measurements, at different times, drawing on different knowledge bases and in different individual, discipline, profession and service contexts.

Health and care also bring into focus the importance of following the time course of measurements made. There is natural variation in living systems, from minute to minute, through the day, with eating, physical exercise and rest, and in changing conditions throughout the year. Living systems are dynamic. They are energetic and they move and adjust, maintaining balance and adjusting to context. The measurement of bodily function in the varying contexts of being healthy, becoming ill, and being treated, layers dysfunction over normal function. Onset and recovery from illnesses reveal themselves as a function of time. Single measurements

46 L. Mearian, 'Study: Digital Universe and Its Impact Bigger than We Thought', *Computerworld* (11 March 2008), https://www.computerworld.com/article/2537648/study--digital-universe-and-its-impact-bigger-than-we-thought.html

adjudged to be within a normal healthy range, may, in context of a series of such measurements, or in conjunction with other measurements, be judged as indicators of illness. And the reverse may apply. Dysfunction may also arise sporadically–an abnormal heart rhythm–and require a continuing sequence of 'normal' measurements to detect an abnormality among them.

Record

These many aspects of measurement and relevant context of data impinge on the importance for health care of maintaining appropriate, coherent, consistent, accountable and accessible records over time, for individuals and for populations. This need extends across all levels of care, from tertiary, secondary and primary care into the growing domain of home-based care and self-care, all of which interrelate and must communicate in terms of their meanings and contexts.

The wide-ranging types of clinical data and their personal and confidential character place exacting requirements on acceptable methods for their handling in care records, the potential risks arising from their misuse being especially acutely felt when they are held in electronic form. Record systems must show themselves to be technically rigorous and sustainable, clinically and economically feasible and trusted. Complete and timely records must be securely and confidentially accessible across organizations of health care and connected with patients at home and in their local community. Methods and heuristics employed to reason with and act automatically on these records, usefully and acceptably, must have trusted governance, independent of system supplier and technology employed in their construction. Standardized protocol and procedure must be balanced against limitations of clinical freedom to interpret and prescribe on behalf of the individual patient, and the right of the patient to be involved at all levels. The records are a co-creation and owned by the data subjects–the patients. All professionally and personally involved must have the wherewithal to be involved, as appropriate to their status, and to participate and collaborate.

Experience of inadequate performance of software in systems sitting in oversight of the tripod of clinical measurement, decision and action, may frequently be interpreted as signalling a need for more data, rather than as an indication of a dysfunctional machine or system. This may lead to additional burdening and bending of human activity, to treat and feed the sick machine's disorder, thereby degrading the human quality of care that can be offered to the patient and their disorder.

I have seen and experienced the focus on more, and repetitively poor quality, redundant, or inaccessible data, in years working close to wards, and in months of watching ward level activities, sometimes continuously, in day- and night-times and through dangerously deskilled and understaffed weekends, alongside my very sick wife. I have heard similar stories from informatics colleagues, themselves going through serious illness, lamenting almost unusably archaic computer systems on view to them in hospital wards. Poor data and record discipline adds to uncertainty in clinical decision and action.

This is a deliberately pessimistic perspective, to highlight the audacious challenge to create the future otherwise. The transition from Information Age to Information Society is principally an integrative challenge:

- to support and sustain balance, continuity and governance of health care services, over time, connecting more locally in the homes and communities where people live and are cared for, and more globally in diverse organizations of specialist care;
- to enable personalized medicine, in terms of customization of methods for the care of individual patients and support for their personal autonomy;
- to provide and connect with coherent and trusted curation of care records and open access to and sharing of knowledge, to mutually inform and enable professional teams and citizens, alike;
- to enhance education, research and professional development, again enabling the participation of citizens and professionals, alike.

Care records cannot ever hope and should not pretend to be in any sense complete; the clinical and personal context is highly variable and the pathway ever-changing. There is different perspective and bias naturally arising within communities of people involved and methods employed. Some components of observation and measurement are well-bounded in context and can be rigorously standardized. Some combine reasoned argument, reference to precedent and personal narrative, alongside observation and measurement.

Hundreds of billions of dollars per annum, extending now over the past fifty years to plausibly many trillions, have been spent in seeking to keep pace with, and rationalize, failure in the lucrative but serially underperforming endeavour to computerize health care records. I chart the story of those decades in Chapter Seven. But we should not need to rely on such documentary trail and decades of hand-wringing journalistic accounts of disappointments. Ask friends who have experienced the discontinuity of services across different sectors and regions of care, today. It was a deliberately provocative maxim that I coined for openEHR: that we can now do ten times better, ten times more economically and ten times as fast, if freed from past legacy and sunk cost. The second part of the book focuses on understanding how and why this situation came about, technically, clinically and organizationally, and still continues today. It is a story not without hope for doing much better in the future, as the third part of the book seeks to show. The programme for reform set out there seeks to be audaciously pragmatic, complementing Mervyn King's audacious pessimism and Barack Obama's audacity of hope.

The first twenty years of my professional songline charted my move from physics into medical physics and engineering, life science, and medical informatics. This focused on building computational models of human physiology, based on data and knowledge about bodily systems and their application in education and practice. This is the topic I move on to in the next chapter. At the start of that era along my songline, patient records typically took the form of thirty-centimetre-high stacks of paper in folders; summarized after each clinic attendance, Dictaphone in hand, by hurrying senior registrars. Today, they still sometimes take this form, but more often are partly or wholly captured within digital record systems. Methods for representing and structuring the record and rendering the expanding content such that it can be reliably computable, sustainable and easily accessed, in different contexts of practice, audit and research, have figured greatly over recent decades. This topic, central to my mission of the past thirty years, is centre stage in Part Three, from Chapter Eight of the book.

I move on, here, to describe how new measurement and computation that constitute the clinical data and content of records, have co-evolved over the past century, using examples of key technologies of measurement that have emerged at the interface of science, engineering and computational method in support of health care.

Measurement Sciences, Technologies and Devices

The mathematical advances from the nineteenth century tracked in Chapter Two and the computer science and technology that followed in the twentieth century, were mirrored in the advances in physical science and engineering fifty years later, and in what these have led to in the life, clinical and population sciences today.

These broad domains of science, engineering and practice have mixed and matched with new devices and methods supporting observation and measurement. The computer now captures, records, analyzes and displays the data, and controls the devices, just as it does, and will, with coming generations of space probes and autonomous motor vehicles. In the connections they have made from the science of measurement devices to their practical applications, computer technology and computational method have changed everything. I will give examples of some that I have connected with most closely along my songline.

Over the past one hundred and thirty years, a succession of advances in the physical and life sciences and medicine–many recognized in Nobel Prizes–have underpinned the engineering of new measurement devices fundamental to life science and medicine. Much of today's repertoire of clinical measurement has its scientific origins in physics of the late nineteenth and the first half of the twentieth century, taken further in chemistry and applied within life sciences and medicine in the second half of the twentieth century, and continuing in the molecular biology and bioinformatics of today. Taken together, these have been transformative; their practical potential realized alongside advances in computer science and technology from the middle decades of the century.

Here are some key examples. They link with radiation physics, electromagnetism, optics and photonics, nuclear physics and ultrasound.

X-ray imaging

1890s: Wilhelm Roentgen (1845–1923)–X-rays, 1901 Nobel Prize in Physics–X-ray imaging.

1970s: Godfrey Hounsfield (1919–2004) and Allan Cormack (1924–98)–Computerized Axial Tomography (CAT) scanner, 1979 Nobel Prize in Physiology or Medicine.

Electrocardiography

1901: Willem Einthoven (1860–1927)–electrocardiogram, 1924 Nobel Prize in Physiology or Medicine.

Microscopy

1930s: Ernst Ruska (1906–88) and Max Knoll (1897–1969)–electron microscope, 1986 Ruska awarded half of Nobel Prize in Physics for his work on electron optics.

1930s: Frits Zernike (1888–1966)–phase contrast microscope, 1953 Nobel Prize in Physics.

Magnetic Resonance Imaging

1940s: Edward Purcell (1912–97) and Felix Bloch (1905–83)–Nuclear magnetic resonance, 1952 Nobel Prize in Physics.

1970s: Paul Lauterbur (1929–2007) and Peter Mansfield (1933–2017)–Magnetic resonance imaging (MRI), 2003 Nobel Prize in Physiology or Medicine.

Nuclear Medicine

1950s: Positron Emission Tomography (PET).

1970s: Michael E. Phelps–PET camera and scanner for animals and humans.

Diagnostic Ultrasound

1950s: Ian Donald (1910–87)–ultrasound as tool in obstetrics and gynaecology–1963, the diasonograph.

Medical devices probe body systems ever more widely, deeply and precisely, interacting with and sensing the state of health. The sciences and technologies on which they are based, combine and overlap. To understand a PET/CT scanner, one might travel through nuclear physics, electromagnetism, radiochemistry, mathematics and computational science, before even starting to think about and marvel at the design engineering and clinical skills on display, that enable everything to be made to work together, to achieve useful and reliable goals in the diagnosis and monitoring of disease.

Sound pressure waves permeate from the anxious voice, through the air, to a human ear, and from the pulsing heart, through the body, to stethoscope diaphragm and human ear. They feature in pulsed measurement of intraocular pressure and ultrasound scans for non-invasive dynamic imaging and measurement of body state and function. Electromagnetic waves–gamma rays, X-rays, light waves and radio waves–propagate everywhere. Science and technology track and tune them throughout the spectral frequencies and wavelengths of radio, infrared, visible and ultraviolet light, and on down in wavelength to X-rays and gamma rays of highest energy, harmfully absorbed within body tissue. Atomic and nuclear physics, electromagnetism, photonics, optics, chemistry, biology and electronics combine to underpin the science of clinical measurement devices. The computer now takes all such modalities of measurement in its stride.

Measurement devices are transmitters, receivers, transducers and processors of signals. Light waves illuminate the microscope and the sample it views. They transmit through and interact with tissue at infrared wavelengths, in pulse oximeters and neonatal brain scanners. Electron microscopes and other probes and sensors extend signal and image resolution beyond what can be achieved with light waves. Radiation and radioisotope physics have made historic contributions in crystallography, clinical imaging, clinical chemistry, nuclear medicine and molecular and cellular biology. Nuclear magnetic resonance has become central to life science and medical imaging. Bioinformatics and health informatics are burgeoning new domains of life science and clinical practice.

The scientists and engineers have a reverence for their hard-won and satisfying creations. Clinicians, in general, have quite limited bandwidth for understanding these levels of scientific and engineering detail–they use the resulting machine rather like a car, sometimes not very sensibly or carefully! I have several in my family and some–well, mostly my wife (she laughs when I write this!)–are not so good at taking care of machines like toasters, radios and cars! Today, it is easy to develop a false sense of security or insecurity, when driving computational machines that are akin to early motor cars, which needed constant checks and adjustments by their drivers, when being driven cautiously on highly variable road surfaces and past startled humans. It is beguilingly easy to use these still early computational machines and applications as if we were Lewis Hamilton in a modern-day Mercedes racing car, but with none of his skills! In virtual worlds, this is especially easy; the gaming industry catapults gamers into the excitement of Forza Horizon 4. In real life, we may find ourselves, marginally rope- and piton-protected on a risky mountain face of computerization, with little computer mountaineering skill or sense of the rock face we are navigating, or the plunge below.

In the following sections, a principal aim has been to paint a picture of the interconnectedness of scientists and engineers and the teams and environments in which they have worked in advancing medicine in health care services. There are also underlying stories of how science before the computer's arrival, connected with science after its arrival, and key personalities and teams that bridged the two eras. It does not claim comprehensiveness or balance. The discovery of the structure of DNA was built, Newton-like, on the work of many shoulders. The happy coincidence of one with eyes to see, and opportunity to observe a chance event, has marked greatness in the scientific lexicon. Bell Burnell is one very famous example, as previously mentioned. Such heady moments of insight and discovery help lift people to a new level. An environment centred on common ground, enabling cross-fertilization of ideas among colleagues in closely connected teams, from different disciplines and areas of research, is an important determinant of their creativity.

X-Rays–Radiation Physics

Imaging

The penetrating and destructive power of X-rays was experimented with and experienced by physicists, long before being understood at the level of particle physics and the quantum theory. The lethal potential of the radiation only slowly imposed itself on those experimenters, told in the stories of Marie Curie (1867–1934) in the late nineteenth century, through to the atomic physicists of the 1930s; some–perhaps many–probably died young as a result.

X-rays found application in metallurgy, to study dislocations of metal structure and check quality of welds that affected its material strength. Holes were cut out from structural members in the fuselage of aircraft, to reduce weight and thus improve fuel efficiency in flight. Metal fatigue led to terrible accidents, such as in the Comet airliner crashes of my childhood. Hidden dangers of this kind are often not easily mitigated. I remember working one summer in a disused aircraft hangar, rearranged for testing new designs of linear accelerator for cancer treatment. It was at South Marston, near Swindon in the UK–subsequently the site of the, now closed, UK Honda car factory. The machine under test was partly shielded by huge concrete blocks, but with probably at most fifty percent of the sphere of emitted radiation covered and no allowance for scattering. Nearby testing of metal welds for defects, based on exposure of X-rays onto photographic gels, was conducted in open areas.

X-ray imaging measured the absorption and scattering of the radiation, as it was transmitted through the body and exposed onto a silver-halide film. It was immediately useful in imaging damaged bones. Barium meals were given to patients, in the form of liquid contrast media that sharpened the X-ray images obtained when the meal entered and passed through the gastro-intestinal tract, improving the ability to localize and observe abnormalities such as stomach ulcers. This sort of investigation has been largely superseded by endoscopic imaging, which passes a camera, sometimes somewhat unpleasantly for the patient, from either end of the body into the tract. It can also enable less invasive surgical interventions, to deal with problems that previously had to be enacted through invasive laparoscopic surgery, opening the abdomen.[47]

47 Notable pioneers of endoscopic investigation, like Christopher Williams, working at St Mark's Hospital in London, and now the lauded author of his landmark early textbook of endoscopy, were my colleagues at Bart's in the 1980s. As were Parveen

X-ray technology is also used to track leakage from gastrointestinal (GI) tract into the peritoneum, occurring in regions that cannot be reached with the endoscopic camera. In other instruments, cardiac catheterization and injection of boluses of contrast-enhancing radiopharmaceuticals create real-time X-ray images of blood flow through coronary blood vessels, revealing potentially life-threatening blockages. Similar methods guide intravascular interventions to excise thrombi and mitigate occlusion of blood vessels by positioning stents.

In the early 1970s, I was working in the medical physics department of University College Hospital in London when the story of the first EMI Company Computerized Axial Tomography (CAT) X-ray scanner started to unfold. There were rather dismissive opinions voiced about the computational method employed, termed Algebraic Reconstruction Technique or ART. The rather snooty and snide title of one article questioning the significance of its pioneering iterative reconstruction method was 'Is ART science?'!

CAT technology constructed a cross-sectional image from a set of scans of the radiation transmitted from X-ray source to detector, through the body, reflecting absorption and scattering of incident X-ray beam by the body tissue through which it passed. This was the computer algorithm central to the measurement made. The set of scans was collected, step by step, at each angle sampled, in a 360-degree circular sweep of the device around the body cross-section of interest. The EMI engineers had created what proved a world-changing innovation for clinical practice, and scientists and clinicians of the day were a mixture of nervously excited and arrogantly dismissive in their opinions of it–a not uncommon story about engineering innovation, as further exemplified in Chapter Five!

The images obtained greatly improved the precision of anatomical localization possible–first demonstrated in brain scans. The computational method remains fundamentally the same today, although optimized and considerably enhanced. The computation now extends to three-dimensional image reconstruction and visualization of the body over time. The range of clinical applications has extended from anatomical into functional imaging studies, able to probe dynamic behaviour of body systems, such as the heart and lungs. The computational methods it pioneered have been taken into other modalities of medical imaging, such as radioisotope, nuclear magnetic resonance and ultrasound scanning. Methods for imaging three-dimensional and four-dimensional (three-dimensional plus time) manifolds of data have cross-fertilized with scientific disciplines beyond medicine. For example, the CAT scanner has been used by archaeologists

---

Kumar and Mike Clark, whose landmark textbook of medicine has now found its way to into a passing mention in the latest series of Netflix's *The Crown*, I noticed!

for study of mummified bodies in museum collections dating from ancient times–a field now referred to as paleoradiology.

The engineering of the devices and their computational methods has continued to evolve. Those forming medical images today, the level of anatomical and functional detail they reveal, the safety of the investigative procedure they enable, and the ways in which the machines capture, record, and communicate the resulting images, are of a completely different order from the early CAT scanner prototypes of the 1970s. They bring new eyesight to clinical investigation and new metrics of quantification and classification of disorder.

Radiotherapy

As with electromagnetic radiation, particle radiation from a radioisotope or linear accelerator source causes destructive harm to tissue it passes through. In medical treatments, radiotherapy harnesses this to target and destroy cancer cells, while avoiding harm to healthy tissue nearby. In my time in medical physics of the 1970s, the targeting was an embryonic art of manual optimization, enacted by radiotherapist and physicist, working with paper charts, and supported by dose-depth calibration curves depicting the absorption of the radiation from the machine in tissue.

The science of radiation physics and biology was unfolded by notable medical physicist researchers of earlier decades. Jack Boag (1911–2007), at the Royal Marsden Hospital, Jack Fowler (1925–2016) at Mount Vernon and Joseph Rotblat (1908–2005) at Bart's, who described himself as a 'Pole with a British passport', were leaders of that era alongside radiation biologists, such as Rotblat's colleague at Bart's and co-organizer with him of the Pugwash Conferences, Patricia Lindop (1930–2018).

Experiments with animals and later with phantoms made from tissue equivalent materials, quantified dose distribution and harm to life, to understand and quantify the interaction of radiation with tissue in clinical imaging devices and radiotherapy, and devise risk management protocols protecting both the patients and the teams operating the machines. Computer-based treatment planning developed rapidly, as further discussed in Chapter Eight, where I describe a team that pioneered innovation within hospital physics at the Royal Marsden Hospital, from the 1960s. Today, such science and engineering are carried forward in product development programmes of the multinational industries of medical technology, exploring and developing new treatment modalities, such as proton beam therapy.

Crystallography

In the early decades of the twentieth century, X-rays were used to reveal the ordered structure of crystalline matter, through the patterns revealed by scattering from successive layers of its structure, captured in images recorded onto film. The wavelength of the incident X-ray radiation matched the regular spacing of atoms aligned within the material, leading to measurable patterns of interference in the image. This image was an average over the scattering from all the molecules aligned in the crystal lattice, thus achieving a usable signal to noise ratio. The physics underlying this process and leading to the interpretation of the patterns it produces, by crystallographers and life scientists, was formalized by William Henry Bragg (1862–1942) and William Lawrence Bragg (1890–1971), the father and son who shared the 1915 Nobel Prize for Physics 'for their services in the analysis of crystal structure by means of X-rays'. They certainly established 'bragging rights' as the founders of this field, which grew and diversified, very rapidly, over the coming decades! Henry Bragg was a UCL physicist, chemist and mathematician. In the following years at UCL, the crystallographer Kathleen Lonsdale (1903–71), his student, further developed the technique in its application to chemistry. A Quaker luminary of the era, she is remembered through the naming of the building where she worked, and which now houses the Physics Department and once housed the Chemistry Department, as well.

X-ray diffraction technology laid the foundations of a step change in study of the biology of the cell. The physicist William Astbury (1898–1961) worked as a student of Lawrence Bragg at UCL and later at Cambridge. He was a pioneer of its application to the study of cell function. This developed into the field of molecular biology, in the 1930s, and from there into the rise of bioinformatics, in later decades, the theme of the next section of this chapter. The chemist Linus Pauling (1901–94) built on Astbury's work and connected it with the atomic physics of the era, in pioneering quantum chemistry. He used ball and rod models to capture the structure of the chemical substances he was studying.[48] With advancing detail of evidence

48 Linus Pauling was one of four scientists to have been awarded two Nobel Prizes, one of his being the Peace Prize. There were two physicists and two chemists: the Polish physicist Marie Curie, recognized for her work on X-rays, and the American, John Bardeen (1908–91), whose prize in 1956 recognized his contribution to the invention of the transistor; the other chemist was Fred Sanger (1918–2013), who laid foundations for key measurement technologies that enabled molecular biology to scale to the level of the first whole genome sequence of an organism, Haemophilus influenzae, in 1995. Peter Pauling (1931–2003), the son of Linus Pauling, was working at UCL, studying protein structure, when I arrived

from crystallographers, notably the biophysicist Maurice Wilkins (1916–2004) and chemist Rosalind Franklin (1920–58), the histories were drawn together in the discovery of the double helix structure of DNA in 1956, by Francis Crick (1916–2004) and James Watson, at Cambridge. Cambridge has continued as a powerhouse of this scientific era.

Another luminary figure of the times was John Bernal (1901–71), who focused the field on mathematical methods for unravelling molecular structures, starting first with study of graphite and bronze, and moving on to viruses. His son, Michael Bernal, taught computer science in the London Institute course I attended in 1969. Like Astbury, John Bernal was also a student of Lawrence Bragg, and Max Perutz (1914–2002) and Dorothy Hodgkin (1910–94) were his students. Crick, in turn, was a student of Perutz–it was a truly remarkable and formidable lineage, that forged formative connections of physical and life science, computer science and engineering, and medicine and health care of the coming decades.

The 1962 Nobel Prize for Chemistry was shared by Perutz and John Kendrew (1917–97), for their work on the structure of haemoglobin and myoglobin molecules. They combined expertise in biochemistry, molecular biology and crystallography but their major advance was described by Perutz as 'pure physics'. He worked for most of his career studying the three-dimensional structure of haemoglobin, the full model of which he published in 1959, and from which he deduced the conformational changes that occur when the molecule loads and unloads oxygen in the human respiratory system.[49] Dorothy Hodgkin was awarded the 1964 Nobel Prize in Chemistry for her work using X-ray crystallography in deducing biochemical structures, including that of the protein hormone, insulin.

---

there in 1969. This was laborious work and the preparation of the experimental material, and its crystallization took many months. I remember meeting and talking to him in the Department, where he would often be found sitting on a stool and looking at pages of X-ray images, laid out in front of him on the floor. He would move the stool around and peer at them from different angles, trying to piece together what he could deduce from them about the atomic composition and structure of the crystal, revealed by the images. He was creating his own mental axial tomography!

49 I once had the pleasure of attending a lecture by Perutz. His was an extraordinary life and his book of essays is beside me as I write (M. F. Perutz, *I Wish I'd Made You Angry Earlier: Essays on Science, Scientists, and Humanity* (Oxford: Oxford University Press, 2002)). He recalls the twenty-two years he devoted to finding the structure of haemoglobin; the three-dimensional model which he published in 1959 is pictured opposite the title page. This he described as being based on 'pure physics', with no assumption of the chemical nature of the protein and no idea of what it would look like.

John Bernal connected teams and environments in London, Oxford and Cambridge. Later in his career, he led research at Birkbeck College (now Birkbeck, University of London), situated a very short distance from the UCL environment pioneered by the Braggs. One of his close colleagues, there, was Andrew Booth (1918–2009), who forged links with the mathematician and pioneer of computer science, John von Neumann (1903–57), at Princeton University, to pioneer early electromechanical computing devices for assisting in crystallographic data analysis.[50] Kathleen Booth (1922–2022), his centenarian wife, was a pioneering computer scientist, mathematician, and researcher at Birkbeck, who wrote one of the earliest books on programming.[51] Her recent obituary records that they left England to embark on a more peaceful, recognized and productive life in Canada–hence, perhaps, her one hundred years!

Franklin also worked in John Bernal's department at Birkbeck College. She obtained some of the first X-ray diffraction images of DNA and was engaged in the quest to understand their meaning for its structure. Crick and Watson used the familiar chemical models of known molecules of the era, in the form of spheres of different sizes representing constituent atoms, connected by rods of different lengths, at different angles, to represent chemical bonds. Working in this way, and armed with crystallographic X-ray images, including Franklin's then unpublished results, they inferred the double helix structure of DNA–a flash of genius for which they were awarded the 1962 Nobel Prize in Physiology or Medicine, jointly with Franklin's former colleague, Wilkins, 'for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material'. Franklin died very young and her team member, Aaron Klug (1926–2018), continued their joint work and was awarded the Nobel Prize for Chemistry in 1982.

Gamma Rays−Nuclear Physics

A radioactive nucleus (radionuclide) is an unstable atomic nucleus that exhibits spontaneous nuclear decay, emitting elementary particles and/or electromagnetic radiation. In *in vivo* medical investigations, tracer

50 For further information on the role played by Booth in the early computer developments in London and the UK from the late 1940s, see R. Johnson, *School of Computer Science and Information Systems: A Short History* (London: Birkbeck, University of London, 2008), https://www.dcs.bbk.ac.uk/site/assets/files/1029/50yearsofcomputing.pdf

51 W. J. Hutchins, ed., *Early Years in Machine Translation: Memoirs and Biographies of Pioneers* (Amsterdam: John Benjamins Publishing, 2000).

substances are used to track and identify bodily function and disease. A radioisotope is an atom with a radioactive nucleus. Radioisotopes that emit gamma radiation are employed as labels attached to these tracer molecules, to enable them to be tracked through the body, by gamma ray detectors. The labelled tracer is injected into the blood stream, to circulate, permeate and attach within the body, to assist discovery of the nature and location of disorder.

Because their radiation causes harm over time, radioisotopes need to be short-lived, present only for the time needed to arrive at their target location in the body and be observed there using detectors positioned to measure the radiation that they emit. Radioisotopes of long duration arise and decay naturally in the world. Short-lived radioisotopes also arise in the interactions involving radiation and particulate matter–medical cyclotrons are used to create these radioactive nuclei. These are then customized with bench chemistry methods to incorporate them within tracer molecules. Such labelling methods were perfected in chemistry laboratories to create highly sensitive radioimmunoassay methods used for measuring the tiny concentrations of molecules that pertain in the chemical reactions of living systems.

The diagnostic imaging field of nuclear medicine employs cameras and scanners that detect gamma radiation from decaying radionuclides–the gamma camera is an example. The team I worked in at University College Hospital (UCH) in the early 1970s, experimented with connecting data captured by these devices with early Digital Equipment Corporation computers. The signals generated were used to create and optimize images showing where the administered tracer molecule had become localized within the body, and from this infer details of the body functions it linked with.

Radioactively labelled tracer molecules are used to investigate a wide range of pathologies–for example: brain, respiratory, cardiac and metabolic function, and malignancy. Rather than relying on the transmission of X-rays to highlight regional damage and disorder, this technology uses knowledge of body chemistry and pharmacology to deploy tracers that can home in on specific mechanisms of interest, providing additional information on which to base clinical interpretation–radiolabels of glucose, for example, to target malignancies. There is a trade-off between level of precision achieved in determining anatomical location and detail of bodily function, and safety of what are significantly invasive procedures.

Positron emitting radionuclides were first used in transverse tomography in the 1950s. In Positron Emission Tomography (PET), the detection of the two gamma rays emitted at the same time and in opposite directions, from mutual annihilation of a positron with a nearby electron, requires detectors wired together to detect these two simultaneous events. Labelled positron-emitting radionuclides enable imaging of bodily function–notably enhanced metabolic activity in tumour cells. The method thus gave new insight in checking for secondary cancers anywhere within the scanned region of the body. The anatomical localization achievable was poor by comparison with other imaging modalities but gave additional specific information about presence of malignancy.

In like manner to CT X-ray scanners, advanced PET scanners used a circular ring, or succession of rings, of detectors. Electronic coincidence of detection of emitted gamma rays was used to position the disintegrating nucleus within the cross-section area covered by each ring, thus creating a three-dimensional volume image of where the injected radioisotope had lodged. To implement this detector in electronic circuitry was a complex challenge, quickly handed over to computer-based methods, enabling control by program algorithm rather than electrical circuit logic.

The resolution of the images obtained with PET scanning, seeking to localize abnormality, was still inferior to the CAT machine. But in acute situations, a combination of imaging modalities could be employed, supplementing one another to improve positional and functional resolution, including in time. The hazard imposed and benefits and risks for the patient–immediate and longer term–must be balanced as best possible. In further advanced iterations of these methods, machines delivering both PET scan and CAT scan, in a combined procedure, were developed. These machines, and their extensive supporting infrastructures and teams, form the (extremely expensive) state of the art, today.

There are many such examples, and the ones described here have been chosen principally from those of which I was an eyewitness, to illustrate the thread whereby science, measurement technology, and computation have proceeded hand in hand and towards medical applications. PET/CT scanning draws on physics, chemistry, biology, mathematics and computer science in the images it produces. It is a triumph of its science, engineering and clinical practice pioneers, and can now be safely operated by radiographers–a profession now enhanced to cover far more than X-ray-based modalities alone–supported by teams of clinicians and engineers.

Electrophysiology

Other connections along my songline, with people I encountered working at or linked with UCL from the late 1960s, opened windows for me into new areas of computation in the life sciences. Two such were Andrew Huxley (1917–2012) and John Zachary Young (1907–97).

Huxley, who had previously been awarded the 1963 Nobel Prize for Physiology or Medicine with Alan Hodgkin (1914–1998) and John Eccles (1993–97), was then Head of the UCL Physiology Department. It is difficult to imagine more prestigious intellectual aristocracy of that era than a combination of the Huxley and Hodgkin names. They are remembered for the Hodgkin-Huxley mathematical model of the propagation of the nerve action-potential. Huxley spent a whole summer, before the computer era, working through the solution of these partial differential equations, using a hand-operated mechanical calculator, and becoming expert in optimizing that method. From this field developed that of electrocardiography, as a measurement science, computational analysis and topographical mapping of electrical signals collected from around the chest wall. This topic and its computational aspects are further discussed in Chapter Four on models and simulations.

Young, known for his work characterizing the action-potential in the squid axon, was Professor of Anatomy at around the same time. Young's interest in the integrative properties of the nervous system had followed from that of Charles Sherrington (1857–1992) in the 1920s. Sherrington held the Oxford Waynflete Chair of Physiology at Magdalen College from 1913 and he and Edgar Adrian (1889–1977) were awarded the 1932 Nobel Prize in Physiology or Medicine for their work on the functions of neurons. Young is author of one of my inukbooks, *Programs of the Brain*,[52] which I discuss in Chapter Six. I remember this tousled, grey-headed figure pounding along Gower Street from the Darwin Building of UCL, nearby to my first perch in the Medical School, in about 1971.

Emerging within the life science domain have been new ideas about bioenergetics and bioelectricity, which look poised to help clarify fundamental principles of the development and function of living systems.

Ultrasound

Diagnostic ultrasound measurement was first applied to blood flow measurement, detecting the Doppler effect in sound scattered from the moving blood corpuscles. I remember my late colleague in the UCH Medical Physics Department, Roland Blackwell, studying this and showing me his results; he also worked on its use in imaging methods in obstetrics and gynaecology. Gail ter Haar, the daughter of my Oxford physics tutor, Dirk ter Haar, made her name in ultrasound research at the London Institute of

52 J. Z. Young, *Programs of the Brain: Based on the Gifford Lectures, 1975−7* (Oxford: Oxford University Press, 1978).

Cancer Research, close by to the Royal Marsden Hospital and its tertiary cancer services.

Ultrasound waves are now routinely transmitted, reflected and scattered from different volumes of tissue, and detected in two-dimensional cross sectional images generated by sweeping a directional sensor or array of sensors across the body. They are used to measure distance and build images progressively, showing variation over time. Greater safety in the balance of nature and quality of image achievable with ultrasound, set against implicit risk to embryo, made this of particular interest in scanning the health and growth of a baby, *in utero*.

In the 1970s, my late colleague Jo Milan (1942–2018), at the Royal Marsden Hospital in London, switched his attention from the computerization of radiotherapy treatment planning to diagnostic ultrasound imaging. He obtained his doctorate for work that connected ultrasound probe with computer, producing early two-dimensional digitized diagnostic images. I tell the story of his illustrious contribution to hospital information systems and electronic health care records in Chapter Eight. Diagnostic ultrasound measurements combined with computation now provide a range of mappings of body state and function in gastroenterology and cardiology–probing for abnormal structure and fluid collections in the abdomen and disorders of cardiac anatomy and function, for example.[53] They feature in measurements of corneal thickness in the eye and increasingly in hand-held devices usable beyond hospital settings.

Photonics

Advances in microscopy have spearheaded new methods of life science and clinical measurement and investigation, over several centuries. The optical microscope revolutionized biological science and the electron and scanning electron microscope extended the magnification and resolution of images deep into the living cell. Atomic force microscopy further extended the range of measurements possible and the environments in which these could be made.

The term photonics now brings together an extraordinary range of technologies, devices and applications, drawing signals from widely across

53 My younger son, Tom, is leading a UK national initiative to support continuing professional development and support of echocardiography teams and services, at the coalface of care. This endeavour can now be organized more easily and effectively using the network and image sharing opportunities of the Information Age. It portends a new and more sustainable culture of teamwork, peer review and support for the governance and improvement of services.

the spectrum of electromagnetic waves.[54] These have progressively been combined with electronic devices and computation to advance scientific understanding and clinical capability. For example, advances in fibre optics and cameras have led to new opportunities to investigate the GI tract with endoscopes. The combination of a miniaturized camera, x-ray angiography and machine intelligence software has led to more precise methods of imaging. Optical coherence tomography has been combined with angiography to guide the sizing and positioning of stents used to strengthen damaged blood vessels. Advances in thermal infrared imaging technology have enabled non-invasive monitoring of neonates. And the ever-greater precision and range of time and distance measurement, as, for example, made possible by optical frequency comb technology, is opening yet-wider vistas of the ultra-small and ultra-large. John Lewis Hall and Theodor Wolfgang Hänsch shared half of the 2005 Nobel Prize in Physics 'for their contributions to the development of laser-based precision spectroscopy, including the optical frequency comb technique'.

Nuclear Magnetic Resonance Spectroscopy and Imaging

Nuclear magnetic resonance (NMR) is a physical phenomenon used to probe the perturbed energy levels of atomic nuclei when placed in a strong static magnetic field and subjected to a weak oscillating field probe. The probe is tuned to detect resonance with the perturbed energy levels of the nucleus, which occurs at a frequency dependent on the magnetic properties of the nucleus and the medium in which it is situated. This phenomenon was unfolded in the 1940s and has found worldwide application in magnetic resonance imaging (MRI), now a leading clinical imaging technology. NMR spectroscopy, used in studying the physics of molecules and properties of crystalline and non-crystalline materials, has notably advanced the study of the structure of organic materials, such as proteins. Used to probe body tissue, the technique is relatively non-invasive. It is used to probe the energy levels of protons in the water and carbon nuclei of the tissue being studied.

Studies of protein structure have employed intricate, multilevel combinations of experimental and computational method, to analyze nuclear magnetic resonance (NMR) spectra that probe atom by atom, nucleus by nucleus, through the spine and side chains of protein molecules, over nanometre distances, and detect motions occurring in picosecond time

54 Amiri, I. S., S. R. B. Azzuhri, M. A. Jalil, H. M. Hairi, J. Ali, M. Bunruangses and P. Yupapin, 'Introduction to Photonics: Principles and the Most Recent Applications of Microstructures', *Micromachines*, 9.9 (2018), 452, https://doi.org/10.3390/mi9090452

intervals. Applying NMR spectroscopy in this sort of probe is complex and time consuming. It proceeds systematically, marking different parts of the molecule studied, such that they can be recognized and analyzed, and using the measurements made to infer three-dimensional structure. These intricate laboratory procedures have progressively become automated, just as hospital chemical pathology laboratory tests were automated fifty years ago. X-ray crystallography is still a preferred method, in terms of the positional resolution it can achieve. But purifying samples and growing crystals is a slow process–it does not progress in Internet time! NMR spectroscopy has the advantage of allowing the liquid state to be probed.

X-ray crystallography and NMR spectroscopy have strong and longstanding scientific pedigrees. Devices that enable sequencing of molecular structures of interest have advanced in scale and speed, setting the pace for, and keeping pace with, scientific enquiry. Three-dimensional visualizations are intrinsic to the study of the function of these molecules but obtaining them experimentally, for the hundreds of thousands of molecules for which chemical composition and sequence data are known, is prohibitively costly and time-consuming.

It was at this stage that bioinformatics began to come into its own and take off as basic science. Computational methods have progressively filled the gap in providing new approaches to infer structure, less precise but much faster to implement, based on sequence data alone. Sequencing methods, too, have advanced spectacularly in their speed and cost-effectiveness, now utilizing automated laboratory devices based on nanopore technologies. Libraries of known sequences and their structures are used to piece together candidate structures of other proteins. Many-body problems, such as these, might be thought tractable by applying the methods of quantum mechanics to determine atomic and molecular state. They are hard enough in the abstract realms of theoretical physics and controlled physical experiment, however, let alone in biological context. This was the challenge addressed by Tom Blundell, described in the following section, whose career has spanned Oxford, Cambridge (where he was a student of Dorothy Hodgkin) and London.

Molecular Biology and Bioinformatics

Molecular biology was thought of as completing a circle with biochemistry and genetics, in seeking understanding of the functions of proteins and genes in the living cell.

In its earliest days, Astbury described molecular biology as follows:

> [...] not so much a technique as an approach, an approach from the viewpoint of the so-called basic sciences with the leading idea of searching below the large-scale manifestations of classical biology for the corresponding molecular plan. It is concerned particularly with the *forms* of biological molecules and [...] is predominantly three-dimensional and structural–which does not mean, however, that it is merely a refinement of morphology. It must at the same time inquire into genesis and function.[55]

Leaving aside Astbury's implied disdain for the niceties of what counts as basic or pure science (which somewhat mirrors the ring fence between pure and applied mathematics), this biological quest has drawn in other disciplines, pure and applied, creating a widening mix of bioscience. After biochemistry, have come biophysics and bioengineering, with bioenergetics, as a subdomain of biophysics, and biomechanics as a subdomain of bioengineering. At further levels of abstraction around the Ranganathan circle of knowledge, have come biomathematics and bioinformatics. And bioethics–which must patrol somewhere in the same region as biophilosophy, biolaw and bioreligion–has long been a field and afield! They each grasp, define, measure and describe a different perspective of the one elephant, the living organism, both enriching and complexifying discourse.

Bioinformatics emerged as a science, described as being concerned with measuring and modelling the genome, proteome, transcriptome and metabolome. It provides the central measurement and computational STEM of biology. STEM, here, is a play on words, emphasizing computation as a spine holding together the coherence of the science, technology, engineering and mathematics discipines that the biology draws on. This stem has been described as the central discipline of biology. I once opined to a group of clinical researchers at a departmental seminar at Bart's, that the topic of my talk, which was medical informatics and the GEHR (Good European Health Record Project), in its work towards designing a coherent information architecture for the digital health care record, was, similarly, a computational stem of all the topics they would likely ever have on their agenda! They looked shocked, surprised and unbelieving more than affronted–I surprised myself!

The scientific foundations of the interplay of molecular biology with bioinformatics have rested first on measurement of the biochemistry of the cell, then on its development and evolution through cell and organ lifetimes, and over evolutionary time, seeking to piece together a picture

55 W. Astbury, 'Molecular Biology or Ultrastructural Biology?', *Nature*, 190 (1960), 1124, https://doi.org/10.1038/1901124a0

and model of cell structure and function. This is a subtle and connected series of bioscience stories, way beyond sensible narration by me, but resting on a further set of pivotal and illustrious career contributions, recognized by more Nobel Prizes. There have been many such pioneering prize winners, some of whom I have already touched on. I add further mention, here, of Fred Sanger (1918–2013), Sydney Brenner (1927–2019), John Sulston (1942–2018) and Paul Nurse, who have spanned and led in this era of scientific transition into bioinformatics.

Sanger was born one year after my dad and died one year after him. Their paths crossed and they lived in the same community for several years, in wartime, when, as mentioned in Chapter Two, both were undertaking Quaker relief work. Sanger struggled with maths and physics, taking three years to get past the Part One Cambridge Natural Sciences Tripos. He focused, thereafter, on biochemistry and achieved first class honours. He laid foundations of experimental method for the genomics era, being awarded the 1958 Nobel Prize in Chemistry 'for his work on the structure of proteins, especially that of insulin'. He also shared in the 1980 Nobel Prize in Chemistry, awarded to Paul Berg (1926–2023) 'for his fundamental studies of the biochemistry of nucleic acids, with particular regard to recombinant-DNA', and the other half jointly to him and Walter Gilbert 'for their contributions concerning the determination of base sequences in nucleic acids'. Gilbert was Quaker school and Cambridge physics educated, supervised there by Abdus Salam (1926–96), Nobel Laureate in Physics in 1979 with Sheldon Glashow and Steven Weinberg (1933–2021), for their contributions to the unification of the weak force and electromagnetic interaction between elementary particles. It is interesting to note how the contribution of one who struggled with physics and maths, aligned so fully with one whose insight was tutored from the heart of theoretical physics!

Sulston and Brenner shared the 2002 Nobel Prize in Physiology or Medicine with Robert Horvitz, awarded for their contributions to 'understanding of organ development and programmed cell death'. Brenner was a key figure in piecing together how cells function, working first at Oxford, then at Cambridge and in the USA, puzzling over experiment and theory of the role of DNA and ideas about information flow within biological systems. He created a computer-based matrix that pulled together the relationships, to guide his thinking.

Sulston studied how genes regulate tissue and organ development via a mechanism called programmed cell death. In his Nobel lecture, he remarked that having chosen the right biological organism (the nematode worm) to work on turned out to be as important as having identified the right problems to address. He led the Cambridge arm of the Human Genome Project, from 1990–2003, seeking, successfully and at considerable cost and effort, to be first to map the full sequence and thus be able to ensure that detail of the genetic code would reside on common ground, within the public domain. In this they set out to defeat the competing US efforts led by Craig Venter, who tackled the sequencing with an alternative approach termed 'shot-gun sequencing'. This used computer algorithms that mixed and matched sequences obtained from small fragments of DNA. It had promised faster progress but was thought likely to prove unreliable, given the complexity of the genome that was envisaged to be involved. His controversial approach aimed towards the patenting of genetic sequences, thereby making them proprietary intellectual property. Sulston was a leading campaigner against the patenting of human genetic information.

Paul Nurse pioneered research on the control mechanisms active in the cell. He was awarded the 2001 Nobel Prize in Physiology or Medicine along with Leland Hartwell and Tim Hunt, for their discoveries of protein molecules that control the division of cells in the cell cycle. He has been a doughty advocate and campaigner for science in public life, enacted in leading roles, such as his appointment as the founding head of the Crick Institute, newly built, near to UCL, and recognized in a stellar range of personal awards.

The bioinformatics discipline accelerated from the early 2000s, capitalizing on rapid advances in measurement technology and combining new rapid sequencing methods with computational algorithms for mining and analyzing largescale databanks of known molecular sequences. These were used to explore the structure and function of the macromolecules they code for and how they fit together in the enactment of the machinery of the cell. This still rapidly evolving story is proving considerably more complex than might have been envisaged in the early days of protein chemistry and DNA sequencing.

The network of connections discovered has been compared to the electrical circuits of electronic systems, with their component resistors, capacitors, inductors and transistors, organized into rectifiers, logic gates and switches, filters, amplifiers, and so on. In the cell, the multitudes of macromolecules are organized in a similar pattern of component groupings, responsible for the diverse and linked processes that power and enact the chemistry of life. These synthesize and transport molecules around the cell, across membranes between different compartments, engaging in different roles and reactions, there, and moving material into and out of the cell. At an atomic level, these processes can also be described in terms of the physics of electron and proton gradients, electrochemical forces and energy balances. This evolution in scientific thinking is a synthesis of experimental, mathematical and computational physics, chemistry, biology and medicine. And overarching all of this are predicted to lie certain information networks and mathematical symmetries, yet to be understood, that determine the structures and functions that can exist, and thus constrain what does exist. Chapter Six takes a side journey along this route of discovery in the science of life. Here, I continue to follow the connection from measurement and computation into clinical practice.

The progress made in scaling and speeding up measurement is evidenced by the new reality that the three billion or so base pairs in two metres or so length of DNA in the cell, grouped within the twenty-three chromosomes, can now be quickly sequenced and analyzed for individual subjects. The Sanger Institute and the adjacent European Bioinformatics Institute (EBI) at Cambridge and now the Francis Crick Institute in London, provide a focus for assembling the data and creating the analytical methods of bioinformatics, now central to life science research and its connection with clinical genetics and clinical practice. Much focus, in the near term, is directed towards understanding and potentially treating inherited conditions.

The NHS in England has pioneered the 100,000 genomes project scaling these efforts to population level. Other such biobank initiatives around the world are following a similar pathway. Inherited diseases are highly varied and many extremely rare. Pulling together genotype and phenotype data from affected patients across a country, and across the world, is crucial for both scientific enquiry and effective clinical management, requiring capture of coherent data from investigation and treatment in different centres. This is a significant factor in the push for an open platform of digital care records, as pioneered by openEHR. The openEHR community, led in this aspect by researchers in Sardinia, has played a part in efforts to align phenotype data collected in care records with the evolving new methods and practice of genomics medicine.

As I arrived back at UCL in 1995, the Provost, Derek Roberts (1932–2021), asked me to meet Janet Thornton, and I visited her office in the then Human Biology department, now grouped under the umbrella of UCL Life Sciences. Herself trained as a physicist; she was engaged in research characterizing protein folding. It was she that characterized the then emerging discipline of bioinformatics as the central discipline of biology–an assessment encapsulated in the title of a Royal Society Symposium she organized at that time. Brave words for a physicist, but persuasively evidenced by its subsequent evolution. Janet has gone on to create and lead the European Bioinformatics Institute (EBI) at Cambridge.

In the early days of bioinformatics, life science had to come to grips with the expanding databases of gene sequences assembled from the plant and animal kingdoms, and in clinical research. Algorithms that mined, characterized, searched and analyzed these sequences, mushroomed.

Looking for the codes and patterns governing the structure of genes and gene expression in all stages of the growth and reproduction of an organism is a huge enterprise. There was uncertainty as to how many such genes there were in the human genome and about the role of much of the genetic material that seemed not to be directly connected with them–termed junk DNA or non-coding DNA, but with the suspicion, as with stuff hidden in long-forgotten loft-stores in our houses, that it might hide unknown but important gems!

The mapping of gene sequences to the historic language of genetics, based on breeding experiments, and the study of inherited rare diseases and the susceptibility to them of family members, added further detail and complexity. Computer scientists became active in devising computational methods to go further, mining DNA sequences to look for underlying patterns of gene structure, transcription and expression in the biochemistry of the cell and organism, and in family histories. They extended sequencing methods to the study of the gut flora, assembling a further huge data domain, in what was, by analogy with the genome, termed the gut biome. Study of the hundreds of thousands of proteins expressed by genes within the cell gave rise to a sub-discipline of proteomics. Viral and bacterial DNA and RNA were studied, recasting these fields within the framework of bioinformatics. Bioinformatics extended to characterization of plant biology and ecosystems.

The idea of inferring protein structure from sequence data was attractive in prospect. The jigsaw puzzle-like challenge was first to identify the pieces of the puzzle (the atoms and chemical bonds), as revealed in multiple measurements made, and then fit them together to solve the puzzle and thereby infer a possible three-dimensional structure of the complete protein molecule. This systematic process was gradually supported by computational methods that inferred details of position and connection of component atoms, molecular spine and side chains. Numerical optimization methods were then used to infer ways in which the structure might fold in on itself, to achieve a stable energetic state, thus completing the structure prediction.

The emerging field of structural biology took this world further away from the laboratory bench and into the computational world of bioinformatics. Today, computer databanks house hundreds of thousands of protein sequences. Tom Blundell had explored computational methods for piecing together three-dimensional structures by looking for homology (common pattern, such as in position and structure of components) between sections of the sequence data of a molecule under investigation, and sequences for which structures were already known and recorded in international protein databanks. These databanks were data mined to discover likenesses.

Structural biologists devised software to apply constraints in how the discovered homologues might be combined, stereo-chemically, in terms of bond lengths and angles, and then employed numerical optimization methods to derive a feasible and minimum energy state combination of these, embodying all the protein's known constituents.

And on 2 December 2020, the DeepMind company, based at King's Cross in London, owned now by Google, capped their triumphs in mastery of chess and of the game of Go, with AlphaGo. They announced that their new program, AlphaFold, had succeeded in deriving protein folding structure from the sequence data of a protein to a very high degree of accuracy in placement of its atoms within the structure. It will be fascinating to understand, if we are told and can understand, the process it embodies–step by step, breaking the sequence into sequences of known folding structures, then gradually integrating them together towards a structure of the complete sequence. This story has continued to unfold at a dizzying pace. Equally interesting will be to see what resemblance it may bear to Blundell's strategy for tackling the problem. It is difficult to imagine that it has been able to approach the problem at the level of atomic orbitals, quantum wave functions and energy minimization. In whatever way it has been achieved, it will be at least on the level of achievement of Alan Turing (1912–54) in decoding the ENIGMA messages, which was a triumph of insight in combinatorics combined with knowledge of the physical mechanism of the machine itself. Maybe, one day soon there will be an AlphaEnigma able to replicate Turing's feat.

Academic computer science, a bit dizzy with its unfolding roles and contributions, across science, engineering and society, claimed bioinformatics as a subdomain of its own discipline. It had done this also, for a while, with computational physics and biology, until such subclassifications became rather pointless–rather like making biochemistry, biophysics, biomathematics and biomedicine subdivisions of the discipline of biology. Many such meta disciplines arose, grouping sciences across disciplinary boundaries into more holistic frameworks, and so arose systems biology and systems medicine.

The Science of Systems

The term system crops up everywhere these days. Everything seems either to be a system, or to exist and function within a system. Systems of thought and reasoning (for example, formal logic); systems of measurement (for example, SI units, *Système Internationale*); systems of structure and organization of the natural world (solar system, periodic system of the elements) and of human edifice and activity (Dewey decimal system, health care system). The term is widely appropriated across science, engineering and society. There is systems science, systems engineering and there are social systems. The system has become an all pervading and sometimes disturbing presence and paradigm–we blame the system!

The evolution of the systems approach in science, has reflected situations where measurements of complex natural phenomena exist within, and interrelate with, one another in a defining overarching context. It only makes sense to measure, record and reason with measurement made on the system where this context is considered, too. Measurements of blood pressure, cardiac output and heart rate make sense as a grouping within the context of the human circulatory system. And, depending on the purpose of our measurement, so also will depend how we capture, record and reason with these measured data. There has evolved a branch of science called systems theory, that addresses the issue of how we deal with ensembles of data and record pertaining to measurement and analysis of systems. There is instructive history of how systems theory and systems science have evolved.

Quite early in my reading into the world of mathematical modelling, as discussed in the next chapter, I came across the work of the chemist, Ilya Prigogine (1917–2003), at the Centre for Complex Quantum Systems of the University of Texas, Austin. He studied emergent properties of systems and their connection with the behaviour of living systems. His work on irreversible thermodynamics and the concept of dissipative structures and their role in thermodynamic systems away from an equilibrium state, led to his award of the Nobel Prize for Chemistry in 1977.

From this reading, I became aware of Ludwig von Bertalanffy (1901–72), who is credited with early attempts to draw multiple threads together within a general concept of systems theory. He was a biologist and is said to have coined the term systems biology. He wanted to restrict use of the term to refer to principles common to systems in general, saying:

> There exist models, principles, and laws that apply to generalized systems or their subclasses, irrespective of their particular kind, the nature of their component elements, and the relationships or 'forces' between them. It seems legitimate to ask for a theory, not of systems of a more or less special kind, but of universal principles applying to systems in general.[56]

He believed that systems theory 'should be an important regulative device in science', to guard against superficial analogies that 'are useless in science

56 L. von Bertalanffy, *General System Theory: Foundations, Development* (New York: George Braziller, 1968), p. 32.

and harmful in their practical consequences'.[57] The theory was couched in and drew together some familiar, and some newly coined terms–boundary, homeostasis, adaptation, reciprocal transaction, feedback loop, throughput, microsystem, mesosystem, exosystem, macrosystem, chronosystem.

According to Wikipedia, systems theory is 'a transdisciplinary, interdisciplinary, and multi-perspectival endeavour' that 'emerged in multiple contexts of academia' and 'brings together principles and concepts from ontology, the philosophy of science, physics, computer science, biology and engineering as well as geography, sociology, political science, psychotherapy (especially family systems therapy), and economics'. It 'promotes dialogue between autonomous areas of study as well as within systems science itself'.[58]

This scope is an extremely broad canvas on which to discern a theory of systems and paint a picture–extending over space, time, context, purpose, structure, function and behaviour. I will leave it there, for now, although the term information system, does require more discussion. I delay this until Chapter Five, where the context is of information engineering, and where systems analysis and systems engineering also feature. In scientific method, the term system segues into the domain of models of systems. In the next chapter, I will describe and discuss how mathematical and computational models have evolved over time, and especially during the Information Age, propelled forward by information technology.

A major international initiative pitched at the level of systems physiology and medicine is the Virtual Physiological Human (VPH) Institute, championed by Peter Hunter, Denis Noble and Peter Kohl. The VPH is:

> [...] a methodological and technological framework that, once established, will enable collaborative investigation of the human body as a single complex system. The collective framework will make it possible to share resources and observations formed by institutions and organizations, creating disparate but integrated computer models of the mechanical, physical and biochemical functions of a living human body.[59]

I discuss VPH further as one of my examples of mathematical models in biology and medicine, in Chapter Four.

57 Ibid., p. 81.

58 Wikipedia contributors, 'Systems Theory', *Wikipedia, The Free Encyclopedia* (25 June 2023), https://en.wikipedia.org/wiki/Systems_theory

59 Wikipedia contributors, 'Virtual Physiological Human', *Wikipedia, The Free Encyclopedia* (27 January 2021), https://en.wikipedia.org/wiki/Virtual_Physiological_Human

Parenthesis–Manifold and Balance

In the mathematics of topology, shapes are thought about and grouped within manifolds and their properties explored. Mathematicians continue to search for new manifolds and the rules that define them. In measurement we talk of three- and four-dimensional manifolds of data–capturing and recording events within dimensions of space and space-time. Classifications of disease are akin to manifolds, albeit sometimes rather arbitrary and unruly ones! Oxford Reference describes that 'In the philosophy of Kant, the manifold is the unorganized flux presented to the senses, but not experienced, since experience results from the mind structuring the manifold by means of concepts. The nature of the unstructured manifold is unknowable (transcendental)'.[60]

In both these usages of the term, manifold relates to grouping and classification as a means towards understanding. The Information Age has tested our intelligence and capacity in this regard, to the limits. Observation and measurement have focused over ever greater and ever smaller scales and extents. Academic discourse has ramified fractally, towards smaller distinctions and greater diversifications of theory and practice. Finding reliable and trusted methods for sharing, guiding and containing this boundless inflation of data and meanings, challenges human purposes, values and cultures. It is very confusing.

In times of confusion and anarchy, human societies oscillate unstably, locally and globally, in cycles between opposing limits of victory and defeat, triumph and disaster, boom and bust. Such limit cycles reflect imbalances and inequalities we have created and allowed to emerge. They lead to wars of culture, politics, ideology and criminality, now pursued through manyfold manifolds of information warfare, which have also exploded in range and scale. To be able to come to terms with the destabilizing potential of these new manifolds of the Information Age, and the imbalances, inequalities and inequities they can magnify and disseminate, we need to better understand, and share understanding of what is in play.

The human body has evolved the property of homeostasis, to enable it to balance and navigate the internal and external environments that it contains and encounters, and their perturbations. The Information Age has extended these environments and perturbations, worldwide. The thus connected world society finds itself and its environments increasingly unstable and must evolve quickly to achieve new balance–a more secure, both social and environmental homeostasis that enables humankind to navigate the pace

60 'Manifold', *Oxford Reference* (2023), https://www.oxfordreference.com/display/10.1093/oi/authority.20110803100130846

and impact of machine evolution and social change. What kinds of manifold and balance might that entail for navigating health care? We do not yet have understanding that helps us know, but the history of navigation at sea might provide useful analogy.

The shaping power and impact of new measurements, of global reach, is well illustrated by this history, which was transformed by accurate and feasible measurement of latitude and longitude. From earliest times, estimation of the position of a boat had rested on determination of its direction and speed of travel, relying on astronomical observation, compass, knotted rope and calculation based on the recording of speed and direction of travel. The science and precision of navigation evolved through the creativity and determination of artisan instrument makers of compass, sextant and clock escapement, and mathematical calculation to create complex lunar charts, providing methods that could be feasibly implemented onboard a ship at sea. The sextant stabilized measurement of latitude and the Harrison escapement clock enabled timekeeping, to keep track of elapsed time and thereby the longitude displacement of the boat relative to a common reference meridian–the Greenwich meridian. Pendulum clocks, the former instruments used for measuring time, were of no use on a pitching and yawing boat at sea!

The forces of mercantilism, empire and looting quickly cottoned on to the exploitative potential of these new accurate means for navigation. They sought, for their own interests, to maintain secrecy of the increasingly essential maps and charts that could then be created, to make navigation accurate, detailed and safe. James Poskett's book, *Horizons: A Global History of Science*, has a fascinating historical account of how maps were evolved in this way.[61] Private enclosure of global charts and maps would have served those narrow interests but done nothing for the cooperation and benefit of other travellers. As the challenge of accurate measurement of position on the earth's surface was gradually met, so too came recognition of the importance of new international public institutions that were created to maintain the navigational commons and defend against destabilizing and unbalancing forces. A new manifold and a new balance.

There is a parallel struggle facing software technology today, to defend the common ground underpinning information utility for the Information Society. The Information Age has taken science and society into new and virtual worlds of measurement and modelling of data, along new axes, and manifolds of life science, clinical and population data. The Internet and Cloud technologies on which these operate rest on accomplishments of worldwide

61 J. Poskett, *Horizons: A Global History of Science* (London: Penguin Books, 2022).

science, technology and collaboration. They are products and resources of the modern-day intellectual Commons. The gene sequencing technology of today has grown from similar scientific worldwide collaborations in the Commons as has much of artificial intelligence.

Appropriation of such accomplishment and resource into proprietary software parallels the way in which the Enclosure Acts of 1773 destroyed the culture and enrichment of common land in England. Information enclosure is a symbol and threat of our age, because of its wide-ranging causative power –it extends from life science and clinical science to social media and artificial intelligence. Appropriation of the Commons of intellectual property is cloaked as a free-enterprise good and daggered as an impoverishment and disempowerment of society more widely. Opportunity for shared understanding of the theory and practice of the virtual worlds in which we now model and analyze data, risks becoming stymied by knowledge and know-how sequestered in proprietary domains. Knowledge of the engineering of information systems in which these worlds are enacted, and the vital information about life and wellbeing, on which they rest in supporting the health care services that serve and protect the living, must not be lost to society in this way.

Models and simulations of reality, operating in the virtual domain, are the subject of the next chapter. Engineering, which exists at the interface of science and society, is the subject of Chapter Five–a place where theory and practice contend. It is there that we must look for progress and there that the future will unfold. In all aspects of data capture, management and processing there are escalating engineering challenges of precision, scale and sustainability. There are ethical, social, economic and political implications to be faced, and choices to be made. Lying at the interface of science and society, these choices challenge vested interests and establishments, often remaining poorly understood, resisted or unrecognized, until too late in the day for efficient and effective preventive, mitigatory, or interventional action.

Creating, sustaining and collaborating on common ground is the essence of these challenges that lie ahead. It is central to the quest for good balance, continuity and governance of health care, and the creation of a care information utility to support it, centred on the needs of the individual citizen in the future Information Society, focused on support and delivery of care as locally as possible to their home, and standardized as globally as possible to ensure mutual coherence and cost-effectiveness of services.