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Background Notions, Histories, and Fundamental Issues in Physics and Biophysics

There is nothing quite as frightening as someone who knows they are right.

Michael Faraday

Interactions are the basis of life. For a thermodynamically "ideal" system, there is no interaction among constituents, beyond point-like elastic collisions. It is only through interaction of constituents, which is the basis of "nonideal" behavior, that phase behavior and cooperativity arise, and hence life. Nonideality manifests itself at basic levels; water freezes and boils, molten metals cool into crystals, and at advanced levels, where complex mixtures of chemicals stimulated with energy can self-organize into living structures.

1.1 The Evolution of Scientific Thought

The luminiferous aether has definite mechanical properties.

John Tyndall

Nature is reluctant to reveal her secrets. The history of science is a running drama of misconceptions seized upon as correct and final, often for centuries, before a new clarification results, itself subject to the relentless experimental tests upon which continued, provisional acceptance of scientific knowledge is based. Some of the great misconceptions in science include the geocentric theory, heat conceived as a substance called "phlogiston," later replaced with the erroneous idea it was a fluid termed "caloric," spontaneous generation of life, the crystalline spheres of the heavens, the luminiferous aether, absolute determinism, and many more.… One person's theory is another's laughingstock.

On the other hand, an imperfect theory is often perfectly adequate for some purposes and is erroneous only when pushed beyond the limits of approximation in which its validity holds. Newtonian mechanics is one of the best-known such cases, where it is valid for computing terrestrial ballistics and the greater part of planetary motion but fails dramatically on the subnanometer scale, near the speed of light, and in strong gravitational fields.

In this sense, scientific theories are maps onto physical reality, useful constructs with predictive, calculational, and manipulative power within their domain of application. While the claim is frequently made that all observable phenomena in the universe are linked to fundamental properties of matter, the existence of the living state is currently not predictable from these properties. In analogy to maps, actual map makers do not refer to distant, or even all-encompassing maps in their endeavors; making a local topographic map does not require a map of the known universe, nor could the latter predict the former. Hence, those studying chemical and biochemical reactions have no need for the current standard model of particle physics in their endeavors, nor are they stymied by our lack of understanding of cosmic dark energy and matter, even though the phenomena they study may ultimately emerge from these fundamentals.

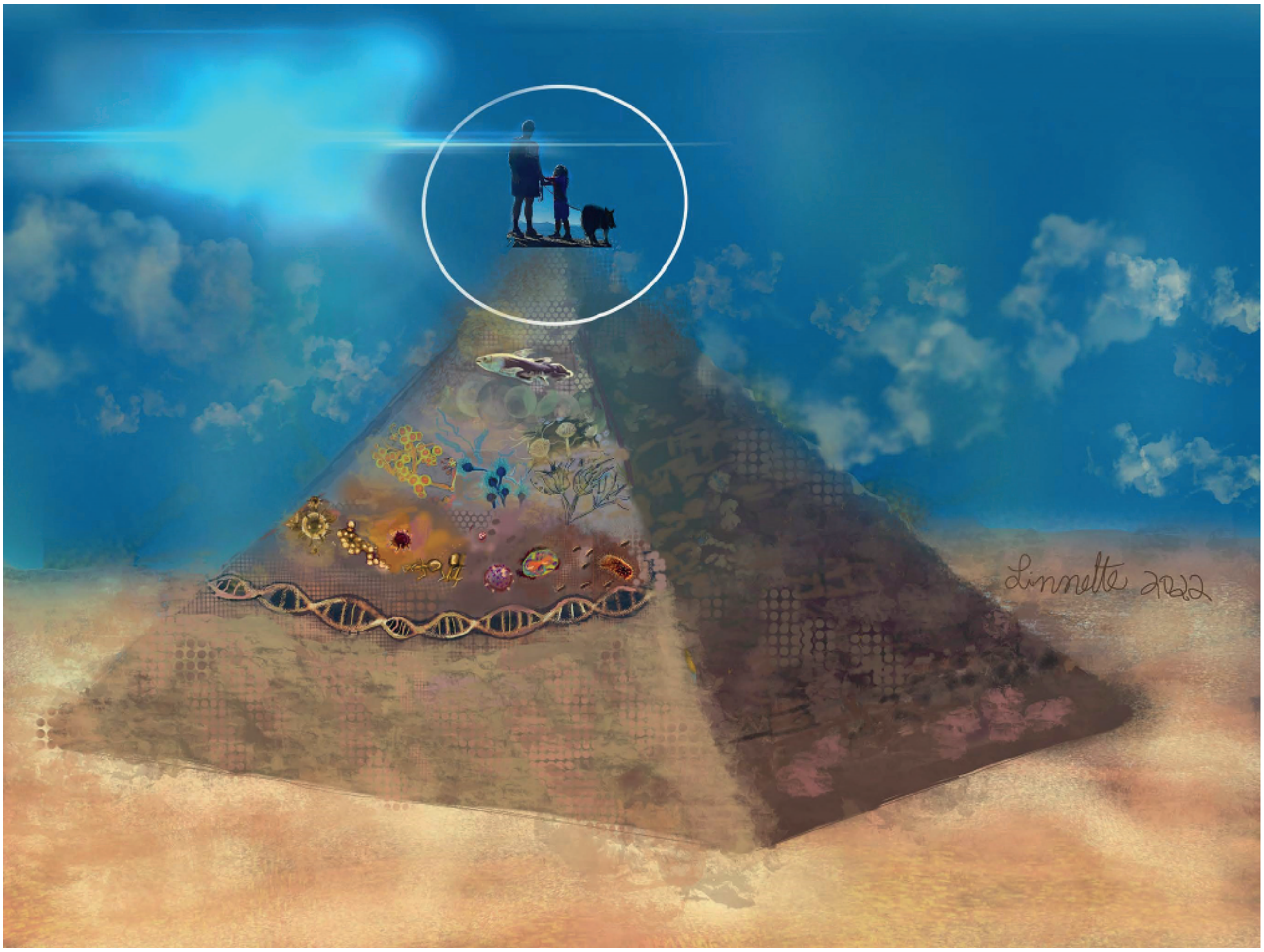
Living state physics emerges from the fundamental properties of matter, but its manifestations seem much further removed from these fundamentals than, say, the quantum mechanical description of a molecular reaction. A current three-way split in thought (and there are more than these three) is (1) life may be viewed as perched upon a pyramid of vanishingly small thermodynamic probabilities and hence is likely quite rare throughout the universe, and (2) the opposing notion that life is actually *inevitable* if the right abundance of matter and energy is present under the right thermodynamic

Biophysics: Physical Processes Underlying the Living State, First Edition. Wayne F. Reed.

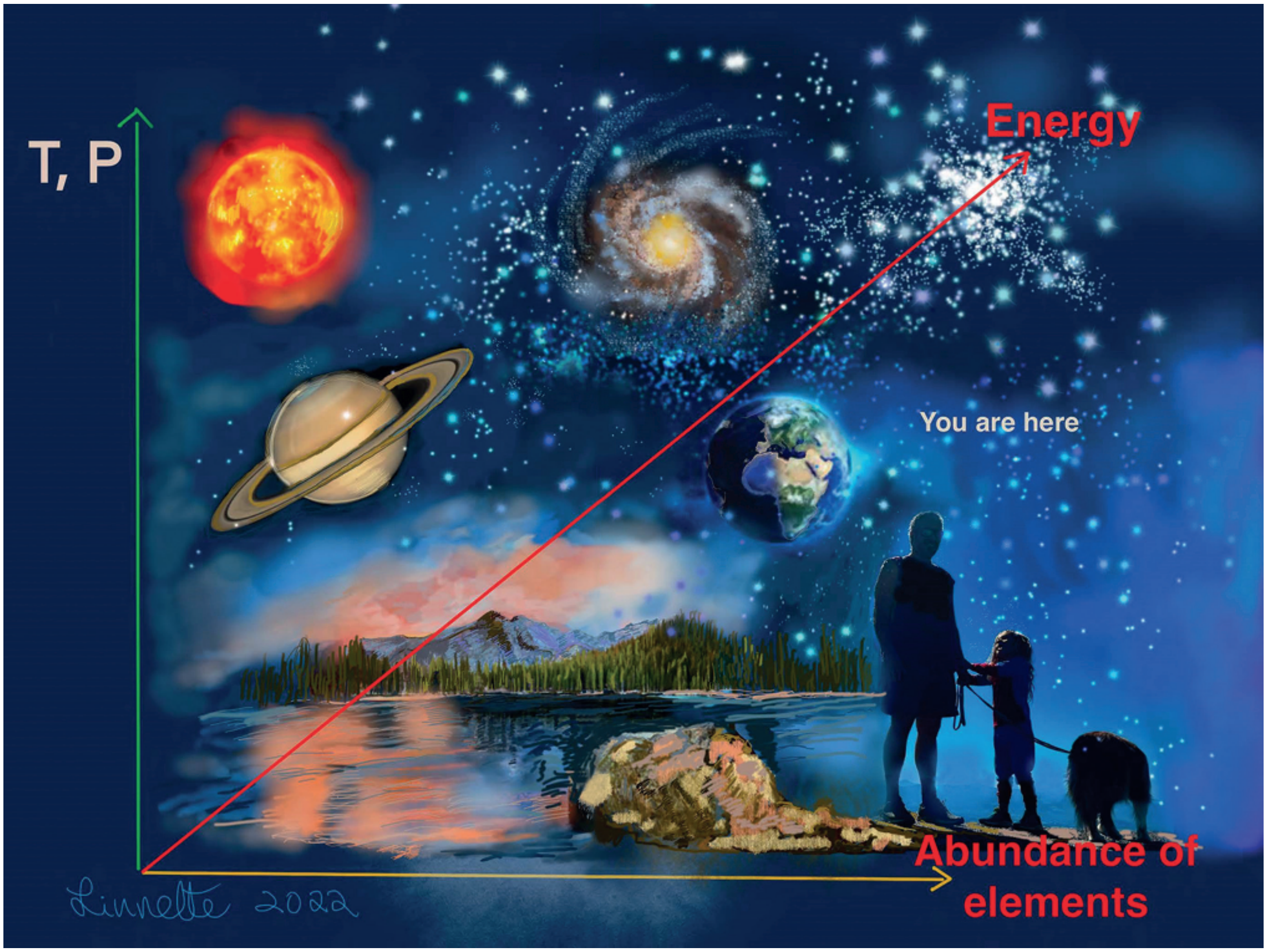
Companion website: www.wiley.com/go/Reed/BiophysicsandMacromolecules

conditions; in this sense, there are "living state portions" of the greater multicomponent phase diagram, in which life will arise and subsequently evolve. This view derives from the ubiquity of self-organization of matter, such as inorganic crystals and spontaneous micellization of surfactants in solution, and from the fact that even on a tiny planet, such as Earth, millions of vastly different life forms exist. It is probable that there are principles of self-organization yet to be discovered. Time may tell. Meanwhile, phase diagrams that predict the existence of life-facilitating atmospheres and liquid water on exoplanets (those planets orbiting a star other than the Sun) are being constructed by astronomers and astrobiologists, using both the latest detection instruments, modeling, and theory (Chapter 15.4).

Then, there is perspective (3) that the information content of physical laws is much smaller than the information content of even the simplest living entity so that the living state cannot be predicted from the physical laws. Hubert Yockey (United States, 1916–2016), who helped pioneer the information-theoretic basis of the genetic code and associated proteins, takes the argument of (3) even a step further and claims that the genetic code must be taken as axiomatic, a given, and that the existence of its coding is "a-thermodynamic," that is, it does not depend on temperature and pressure, and is unrelated to physical laws, and that it is not "merely a physico-chemical phenomenon," and that no set of physical experiments will ever lead to a paradigm necessary to produce a genetic code. Part of his argument is that, while physics elucidates the principles and workings of the physical world, nobody knows how the matter, energy, and principles arose, and they are taken as a given, and theories must explain the given behavior of matter and energy. Similarly, humans have discovered the way the genetic code works, but there is currently no explanation of how it arose.



The improbable pyramid of the living state on Earth. *At the base there is no life, but eventually random prebiotic evolution gives way to genetically-based life, and evolution, in the face of huge improbabilities, leads to higher organisms, including humans*. (Painting by Linnette F. Reed).



Phase diagram of the living state. *Life will inevitably arise under the right conditions of temperature, pressure, abundance of elements, and energy input.* (Painting by Linnette F. Reed).

The heyday of Classical Science. Learned societies in the nineteenth century. (Painting by Linnette F. Reed).

In the meantime, we will have to make do with the knowledge that exists and which new knowledge we can create. There is controversy in every area of science, and biophysics is no exception. It is riddled with competing views, from its large-picture perspectives down to the minutiae of its many subfields, such as specific enzyme mechanisms, and membrane dynamics. Concepts, models, and methods will continue to be judged by what inductive, analytical, explanatory, and predictive power they bring with them. Meanwhile, almost every new idea and theory is subjected to constant scrutiny and often becomes the object of intense ridicule and schisms in thought, which frequently produce schools with competing ideas.

To add to the tension, scientific ideas almost always derive from a ferment of hot debate involving many individuals, often over several continents and decades or more. Frequently, one individual crystallizes the prevailing debate into a new enlightenment and gets their name associated with the discovery, but the fact remains that the latter has arisen from a human community of thought and experimentation.

Another feature of the fraught progress of science is that many, if not most scientific statements can be challenged for being too sweeping, used out of context, employing notation too specific or arbitrary, contravening a convention, being too vague, for inappropriate use of a specific word(s), and so on. Many a sentence in this book can likewise be called into question, and I apologize in advance for all of the inevitable flaws.

All the misconceptions, mistakes, and flaws, are a constant reminder of the fact that many of our scientific notions are fragile, often broken, and replaced by larger, more fruitful perspectives and concepts. These misconceptions and mistakes highlight the fact that we have not found "perfect theories," and that the scientist best gird himself with a circumspect humility, and be ready for wholly unexpected surprises.

1.1.1 Error in the Laboratory

When you can measure what you're talking about, and express it in numbers, you know something about it.

Lord Kelvin

Scientific inquiry ultimately rests on experimental evidence. If theories and models in a certain field are to be fully accepted, they must be able to explain existing experimental evidence and make predictions about the results other experiments would yield. While wide-ranging conceptual errors have been made throughout the history of science, and are ultimately debunked on the basis of experimental evidence, the experiments themselves are prone to many sources of error. So much so that students in science are instructed from their earliest laboratory experiments to attempt to account for all sources of random and systematic error they can think of, and formal structures for statistical analysis of data and estimating error bars have been developed. Sources of error can include faulty or miscalibrated instrumentation, inherent noise in the instrument, instrumentation utilized outside of its range of sensitivity, validity or response time, bias in data analysis due to inappropriate reduction schemes or theories, etc. Erroneous data can lead to serious problems of interpretation and hinder development of applicable theories and models.

Random error limits the precision of measurements and is often referred to as *noise* in the data. Figure 1.1 shows raw light scattering intensity data for two experiments from solutions containing aggregating proteins at two different concentrations. There is no analytical function that can account for every point in each of the two data sets, although a phenomenological single exponential of the form $A(1 - e^{-\alpha t}) + 1$ fits the general shapes very well, as seen by the solid lines in the figure. The noise in the data can arise from thermal noise that is ubiquitous in every detector, fluctuations in the incident laser intensity, and heterogeneities and fluctuations in the solution itself. The isolated points above the main signal band are due to large particles, such as "dust," drifting through the detected scattering volume. The noise phenomena occur on the time scale of seconds, which was the sampling rate of the data in Figure 1.1. There can also be longer term error in the form of signal drift, which is also often thermal in origin, e.g. heating up or cooling down of instrument components, and changes in ambient temperature. The amplitude of the signal divided by the amplitude of the noise is a measure of the *signal-to-noise ratio*, or S/N, and we attempt to maximize it through instrument design and operation, and experimental conditions and procedures. The signal amplitude runs through the middle of the noise band, as seen in Figure 1.1.

When the data below are analyzed to yield absolute values of protein aggregate masses, systematic errors can also intervene, such as miscalibration of the instrument, "stray" light not from protein scattering that adds to the signal, errors in knowledge of the protein concentration, and in its optical contrast in the solution (differential index of refraction), and extrapolation errors. These systematic errors limit the experimental *accuracy*, while the random errors limit the *precision*.

1.1.2 Error Versus Approximation

"Error" has several meanings. We saw how unsuccessful theories are largely discarded and sometimes invoked as cautionary tales. But we have also seen how error, both systematic and random, is an inevitable part of experimental work using

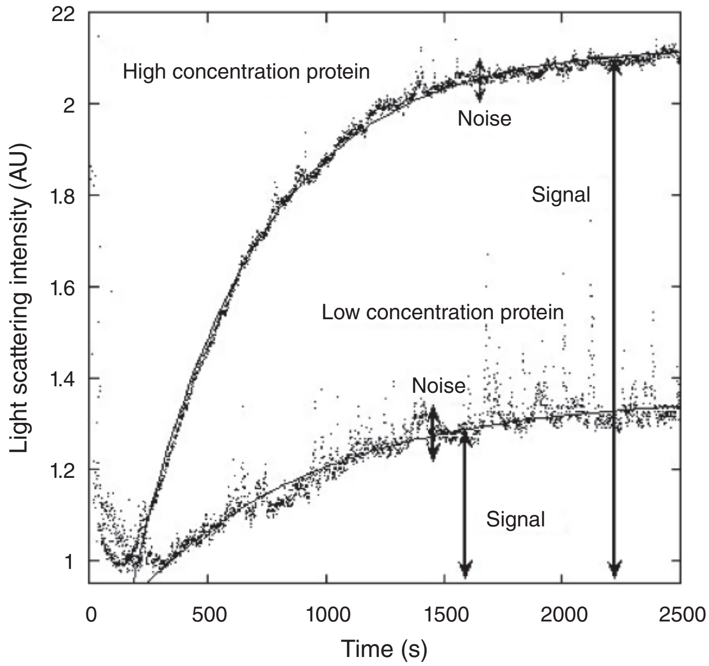


Figure 1.1 Raw light scattering intensity signals for aggregating proteins at high and low concentrations. The noise bands are indicated and isolated points above the bands are due to large scattering impurities drifting through the field of detection. Phenomenological first-order fits are shown by the solid lines. (W.F. Reed unpublished results).

well-accepted instrumental practices within the framework of accepted theory. These types of error cannot be eliminated, but they can be minimized, managed, and accounted for.

Error is implicit as soon as we use the word “approximation” in science. We normally weigh and assess the amount of error that is likely when we choose to simplify a situation with an approximation. Approximations can be quite useful, for example, simplifying an equation such that an analytical solution can be found, rather than a numerical one. While considerable numerical/computational power is abundant and inexpensive nowadays, finding an analytical result usually lends to a more fundamental understanding of a phenomenon, e.g. oscillatory, damped, or asymptotic behavior, electrostatic shielding, and so forth. But it is critical that one remain constantly aware of the assumptions and limits inherent in an approximation, so that the legitimacy and error level due to its use can be assessed.

1.2 Historical Sketch of Atomic Theory and Evolutionary and Genetic Thought

So, how far have we come in our understanding of the natural world, and how did we get here? Before getting into the thick of biophysics and its foundations, we should step back for a few moments and look at some of the history.

1.2.1 Historical Sketch of Atomic Theory

Historically, there was an ongoing argument about whether matter was continuous and infinitely divisible, or was composed of tiny, indivisible particles. Leucippus (Greece, ~500 BC–?) and his student Democritus (Greece, ~460 to ~370 BC) in the fifth century BC proposed an atomistic theory with early glimmerings of molecules built from these. They considered that there were a vast number of types of atoms, that they were indivisible, indestructible, had always existed, and that all things in the universe were composed of atoms and the void. Anaxagoras (Greece, ca. 510–428 BC) conceived of a cosmological evolution of elemental entities under some type of organizational principle, termed “nous” or “mind.”

Even earlier, there arose early atomistic thought in India. Aruni (India eighth century BC), a famous Vedic philosopher in the Hindu tradition, held that “particles too small to see aggregate together into the substances and objects of our experience.”[1] Later, over several centuries, Vaisheshika and Nyaya schools in India formalized ideas about how atoms combine into dyads, triads, and higher structures.

Throughout the Middle Ages, there were schools of atomistic thought in India, Central Asia, and the Middle East, albeit in many different and often conflicting forms. But in medieval Europe atomism was essentially abandoned, largely due to the continuing influence of Aristotle (Greece, 384–322 BC), who considered matter to be infinitely divisible and composed

1 From McEvilley, T. (2012). *The Shape of Ancient Thought: Comparative Studies in Greek and Indian Philosophies*. New York: Constable & Robinson.

of the elements earth, air, fire, and water. Atomistic thought in Europe was slowly rekindled by the likes of Galileo Galilei (Italy, 1564–1642), Francis Bacon (England, 1561–1626), and Thomas Hobbes (England, 1588–1679). Added momentum for atomism came from René Descartes (France, 1596–1650) and Robert Boyle (Ireland/England, United Kingdom, 1627–1691). Robert Boscovich (Croatia/Italy, 1711–1787) produced a mathematical atomic theory based on the laws of Isaac Newton (England, 1643–1727). Daniel Bernoulli (Holland/Switzerland, 1700–1782) in 1738 posited that gases consisted of atoms moving in many directions and that their impact on surfaces caused pressure.

Despite these ancient and early modern insights, atomic science in its modern form did not emerge until the late eighteenth century. Joseph Louis Proust (France, 1754–1826) discovered the law of constant composition in 1794. While greeted skeptically by most scientists[2] at first, John Dalton (England, 1766–1844) developed an atomic theory, which may be considered the springboard to the modern view, and offered five important propositions around 1803:

Dalton's propositions:

1) Matter is made up of indivisible, indestructible atoms
2) All atoms of a given element are identical
3) Atoms of different elements have different weights and chemical properties
4) Atoms of different elements combine in ratios of whole numbers to form compounds
5) Atoms cannot be created, and according to (1) they also cannot be destroyed. Atoms are recovered, unchanged, when a compound decomposes.

One can see that ideas one and five coincide with the ancient ideas of Leucippus and Democritus. Dalton's theory was also greeted with much skepticism throughout the nineteenth century. Amedeo Avogadro (Italy, 1776–1856) strongly bolstered molecular theory by positing in 1811 that equal volumes of gas, under the same pressure and temperature, of different gaseous substances contained the same number of atoms or molecules, even though the mass in the volumes differed. Avogadro's proposition was largely ignored for decades.

Despite persistent skepticism, developments of atomic theory in the nineteenth century were rapid. James Clerk Maxwell (Scotland, United Kingdom, 1831–1879) assumed the existence of atoms and molecules in developing the kinetic theory of gases. Ludwig Boltzmann (Austria, 1844–1906) used the notion of atoms throughout his early development of statistical mechanics.

As the atomic theory was becoming universally accepted in the latter part of the nineteenth century, J.J. Thomson (England, 1856–1940) made a startling discovery. In 1897, using a cathode ray tube with the velocity selector he invented, he discovered that he could dislodge a negative particle – the electron – from any gaseous or metallic material he used. Just when the scientific community was becoming fully adjusted to the atomic theory, Thomson discovered that the atom is not indivisible, after all! This broke with the ancient Greek theory of Leucippus and Democritus and Dalton's first proposition. Naturally, the discovery met with much opposition. But the experiment was widely reproduced and the same electron with the same charge-to-mass ratio, e/m, was found in many different materials. After so much verification the electron rose to the status of the first *subatomic particle* to be discovered. In 1909 Robert Millikan (United States, 1868–1953) in his famous experiment measuring the fall of charged oil droplets found the value of the elementary charge $e = 1.602 \times 10^{-19}$ C, which hence also gave the mass of the electron, $m_{electron} = 9.11 \times 10^{-31}$ kg.

Discovery accelerated rapidly in the late nineteenth and early twentieth centuries. The mass spectrometer allowed elements and their isotopes to be classified by their atomic masses. Henri Becquerel (France, 1852–1908) in 1896 discovered natural radioactivity and was amazed that the radiation was given off from uranium salts without having to put energy into them. Using a mass spectrometer, he discovered that the radiation was deflected, and so could not be the recently discovered X-rays, which are undeflected by magnetic fields.

The radioactive elements thorium, polonium, and radium were discovered by Marie Skłodowska Curie (Poland/France, 1867–1934) and Pierre Curie (France, 1859–1906). Ernest Rutherford (New Zealand/England, 1871–1937) discovered that the positive portion of the atomic charge was contained in a tiny nucleus, 10^{-5} times smaller in diameter than the atom itself. This immediately created the field of nuclear physics, in which a few years later Rutherford both created the first human-made nuclear reaction and discovered another subatomic particle: the proton.

The discovery of the tiny nucleus spurred Niels Bohr (Denmark, 1885–1962), who worked in Rutherford's lab, to develop the first semi-quantum mechanical model of the hydrogen atom, making use of both Planck's constant, h, determined by Max Planck (Germany, 1858–1947) in 1900, and Albert Einstein's (Germany/USA, 1879–1955) 1905 notion of the quantized light particle/wave, later named the *photon*. In 1923, Louis de Broglie (France, 1892–1987) proposed a wave nature of the electron, in addition to its status as a particle. He based this on the success of quantized momentum in the Bohr

2 Until the twentieth century, scientists considered themselves "natural philosophers" and those working in physical science based on mathematics considered themselves "geometers."

atom with its discrete electron energy levels. Furthermore, de Broglie reasoned that in nature one seldom finds physical phenomena with integers attached, the most prominent example being *standing waves*. He conceptualized the quantized energy levels belonging to 3D standing electron waves in the atom. The de Broglie hypothesis was serendipitously confirmed in 1927 by Clinton Davisson (United States, 1881–1958) and Lester Germer (United States, 1896–1971) at Western Electric Company (later Bell Labs). While studying the surface of nickel for practical applications, they unwittingly annealed the nickel into a crystalline lattice and found that electrons were diffracted from the nickel in a manner similar to X-rays, i.e. the electrons were behaving as waves. Using the wave properties of the electron, the first working electron microscope was built in 1931 by Max Knoll (Germany, 1897–1969) and Ernst Ruska (Germany, 1906–1988).

Building on over a century of discoveries, quantum mechanics was essentially born in 1925, with important contributors at that time being Werner Heisenberg (Germany, 1901–1976), Max Born (Poland/Germany, 1882–1970), Pascal Jordan (Germany, 1902–1980), and Erwin Schrödinger (Austria, 1887–1961), among others. Heisenberg is best known for the uncertainty principle, which is a radical break from deterministic classical science, since it states that the position and momentum of a particle at any instant cannot both be exactly known, and hence its future trajectory cannot be computed with certainty. Classical mechanics requires exact knowledge of a particle's position and momentum in order to exactly predict its trajectory under known forces. The ramifications of the uncertainty principle are still being explored today.

Schrödinger is best known for the nonrelativistic quantum mechanical wave equation which bears his name. The Schrödinger wave equation is the "$F = ma$" of quantum mechanics, the starting point for computing a system's properties. The Solvay Conference in Belgium in 1927 brought together the pioneers of quantum mechanics and important conventions, formalisms, and interpretations were agreed upon. At around this time, Paul Dirac (England/United States, 1902–1984) developed a relativistic formulation of the Schrödinger equation, which led to the startling discovery of antimatter. Since then, quantum mechanics has spawned an amazing number of new theories and devices. It led to the invention of lasers and solid-state devices, such as diodes, transistors, and integrated circuits, which revolutionized electronics, and led to computers. Quantum mechanics was immediately incorporated into chemistry by scientists such as Friedrich Hund (Germany, 1896–1997), John C. Slater (United States, 1900–1976), Douglas R. Hartree (England, 1897–1958), Vladimir Aleksandrovich Fock (Russia, 1898–1974), Wolfgang Pauli (Austria/Switzerland, 1900–1958), and Linus Pauling (United States, 1901–1994). Pierre Hohenberg (France/United States, 1934–2017) and Walter Kohn (Austria/United States, 1923–2016) developed a more efficient density functional approach to computation of electronic structure, which has developed rapidly in the past 20 years with advances by John Perdew (United States, 1943–), and others.

1.2.2 Evolutionary Thought

> *Life is not a miracle. It is a natural phenomenon, and can be expected to appear whenever there is a planet whose conditions duplicate those of the Earth.*
>
> Harold Urey

There is an "either/or" character to the historical debate on evolution that parallels the dichotomy of the atomist viewpoint versus the notion of infinite divisibility of matter. The diametric viewpoints were the change and transformation of species versus a timeless, unchanging nature of each species. The former won the long debate and there is no evidence of the latter. At the same time, while evolutionary theory can explain outcomes, it is not well suited for predicting what specific life forms might arise.

The theory of evolution and cell and molecular biology are bedrocks of modern biological science. Concepts of biological evolution existed at least as far back as Anaximander of Miletus (Greece, ~610–546 BC), in sixth century BC, pre-Socratic Greece, who conceived of animals deriving from ancestors living in water in an earlier geological epoch. Empedocles (Greece, ~490–430 BC) held the idea of what resembled a random evolutionary process, where living elements and parts were mixed and joined in embryonic development, hence producing the variety of living forms. Importantly, major philosophers, such as Plato (Greece, ~429–347 BC) and his student, Aristotle, were decidedly anti-evolutionary, maintaining that all living and inanimate things were permanently fixed and of a divine design and purpose. Considering the influence of Aristotle's views in Europe, such as his anti-atomistic thought, this might help explain the late re-appearance of evolutionary thought there. Meanwhile, Chinese philosophers, such as Zhuang Zhou (China, ~369–286 BC) considered that everything was constantly in a state of transformation, including plants and animals, as well as the earth and cosmos themselves. The notion of flux and continuous change also pervades Hindu thought.

While Charles Darwin (England, 1809–1882) is credited with having established the foundation of modern evolutionary theory, there were actually several formulations espoused by earlier scientists and philosophers that contained some of the key elements of Darwin's theory. In the late eighteenth century, George-Louis Leclerc (Compte de Buffon, France, 1707–1788) proposed that what were considered separate species might be descendants of common ancestors, and that a small number of original species might have led to the much greater current variety of species. Denis Diderot (France, 1713–1784) went further and posited that species were constantly changing through essentially trial and error changes, out of which the most fit survived. Interestingly, Charles Darwin's own grandfather, Erasmus Darwin (England, 1731–1802), conjectured that the diversity of modern species might have originated from tiny, primitive organisms.

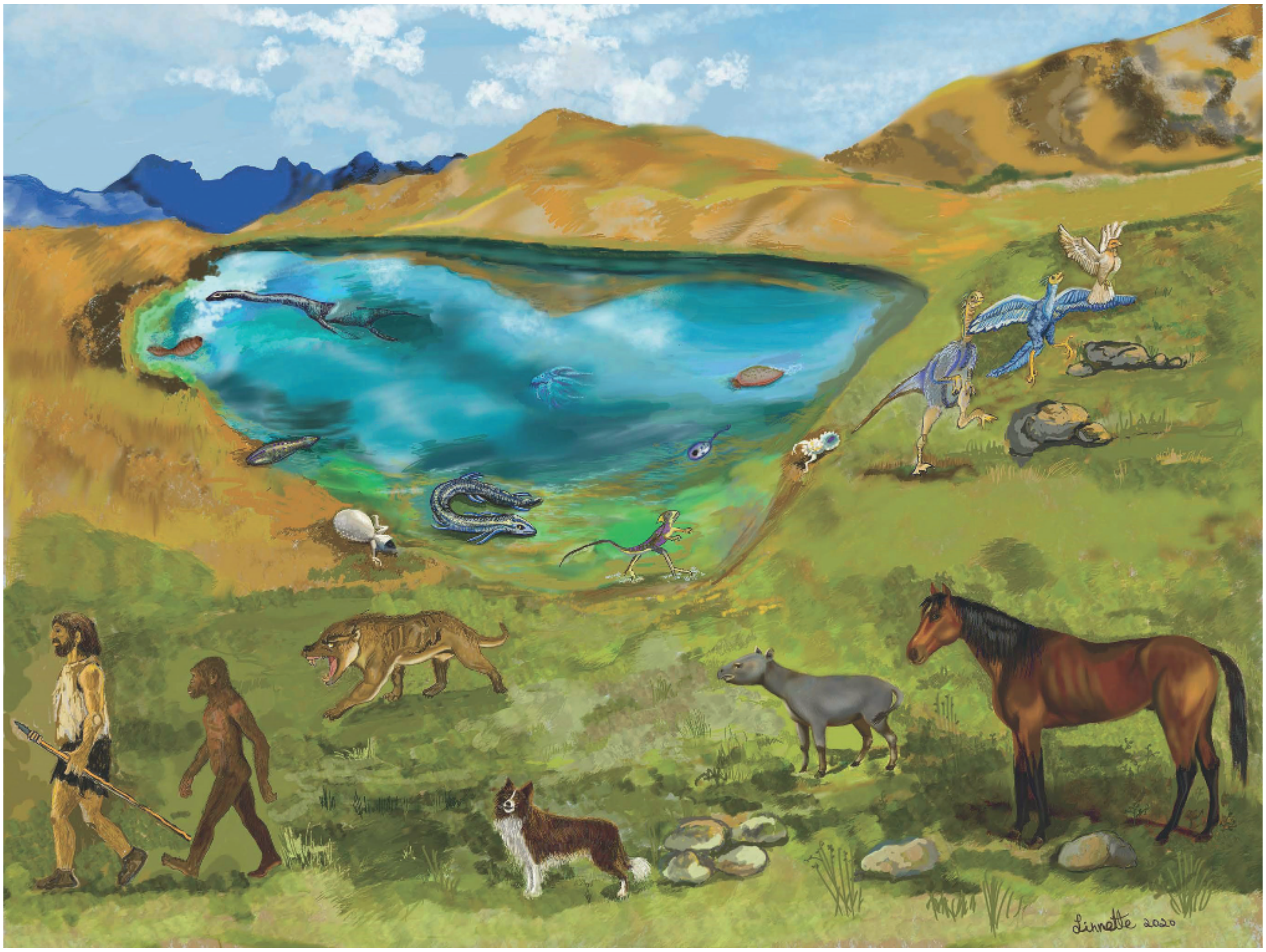
Jean-Baptiste Lamarck (France, 1744–1829) worked out a highly developed theory of evolution starting in 1800. He proposed that evolution was driven by chemical and physical principles of organization of matter toward ever more complex organisms, and that the environment helped shape the changes and adaptations, thus leading to large-scale differentiation among species. While his theory was coherent and detailed, he made what is considered a significant error, which was that characteristics acquired during an individual's life could be transmitted to succeeding generations. This view was discredited in the nineteenth century and carries the unfortunate name of *Lamarkism* or *neo-Lamarckism*. This is unfortunate, because this idea of *inheritance of acquired characteristics* formed, at most, only a minor part of his evolutionary theory and was not his idea in the first place. Darwin also thought that acquired characteristics could be passed on to offspring. There is a resurgence of the notion of certain hereditable phenotypes in the relatively new field of *epigenetics* (see Section 1.2.2.1).

All the ferment in ongoing evolutionary thought came to its most powerful formulation by Darwin. As a young man of 22, he embarked upon a legendary five-year circumnavigation of the globe, which concentrated on South America, and returned to England via Tahiti and Australia. The trip was made on HMS Beagle from 1831 to 1836, and its primary mission was to collect mapping data for the then imperfectly charted portions of South America. The captain, Robert FitzRoy (England, 1805–1865), an English naval officer and an early pioneer of meteorology and earth science, wanted to enrich the mission by having a "gentleman"[3] geologist aboard. Darwin, a son of the rich, dynastic Darwin–Wedgwood family was given the opportunity. Darwin made copious collections of fossils, skeletons, plants, and other specimens and made lengthy notes on his observations, both biological and geological. Specimens and notes were periodically dispatched back to England during the five years. Greeted as a famous geologist and naturalist upon his return, his scientific career exploded and he was introduced into the most prominent scientific circles, in which he met Charles Lyell (Scotland, United Kingdom, 1797–1875). Lyell advanced the theory of the Earth's surface as a gradually changing landscape of oceans, mountains, valleys, and other formations, worked upon over vast stretches of time by natural forces. The ideas of inorganic evolution and vast geological epochs helped stimulate Darwin's thoughts on the evolution of species. Interestingly, Darwin's chief work for 15 years after his return was concentrated in geology, even as he developed his evolutionary ideas alongside these efforts.

In what seems an odd conjuncture, Darwin was spurred in 1838 to the idea of natural selection by the book of Thomas Malthus (England, 1766–1834), *An essay on the principle of population*. Malthus explained that populations should increase exponentially with succeeding generations and hence eventually overrun a habitat. But famine, illness, and want curtail such exponential explosions. Darwin realized that there was continuous selective pressure on populations and that vast numbers of individuals perished prematurely, leaving those best adapted to their environment to survive and procreate. Because environments change there will be a continuous selection of the best adaptations, and hence species evolve over time into other forms. In his view, there was a tree of life, stemming from a single, successful original life form, which then evolved into the many branches of the tree of life. In his theory, a species' variations are spontaneous, gradual, and accidental and survive or perish through natural selection.

Often treated as a footnote to Darwin's work, Alfred Russel Wallace (Wales/England, 1823–1913) independently discovered the notion of natural selection in evolution during a lengthy naturalist expedition to Indonesia. According to Wallace, the idea came to him as he lay sick with a fever and contemplating, no less, Malthus's *An essay on the principle of population*. He and Darwin co-authored the first public summary of the theory of natural selection at the Linnean Society of London on July 1, 1858. Darwin's book "*On the Origin of Species*" followed soon after, in 1859, and had an immediate impact on the scientific community and the popular imagination. Wallace was 14 years Charles Darwin's junior, and Darwin had arrived at his most important notions of evolution at least a decade before Wallace's independent discovery. Darwin was gratified that Wallace had independently come to similar conclusions, based on lengthy fieldwork. The two exchanged their ideas, mutually influencing each other, until Darwin's death. Wallace was a polymath who worked in many fields, including engineering and biological sciences, anthropology, political science, economics, and civics. He published the equivalent of 22 books and 747 essays and other contributions in several of these fields. He had a financially precarious life and railed publicly against nineteenth-century European capitalism and colonialism and was an early voice for nature conservancy.

3 "Gentleman," i.e. someone who could pay their own way on the voyage, as a supernumerary. Darwin's father, Robert Darwin, and his maternal uncle, Josiah Wedgwood II funded Darwin's expenses for the expedition. When Darwin returned to England as a prominent naturalist his father funded his work as a "gentleman scientist."



Ancient notions of evolution. "*For before this I was born once a boy, and a maiden, and a plant, and a bird, and a darting fish in the sea," Empedocles, ca. 400 BC.* (Painting by Linnette F. Reed).

While Darwinian theory is still held as a bedrock of modern biology, progress in the field has been so stunning that many discoveries, unforeseen by Darwin, are still aggregated under this aegis, sometimes also termed *Darwinism*.[4] Darwin was unaware of Gregor Mendel's (Czechia, 1822–1884) groundbreaking work in genetics (Mendel is often considered the "father of genetics"). This latter involved the statistical study of the transmission of hereditable traits, mostly using pea plants, and in crossing different strains he was led to the identification of dominant, and recessive genes. The results were published in 1866 and originally ignored or misunderstood for 35 years, after which the results were rediscovered by several scientists. When finally resurrected, this work became foundational for the field of genetics. In contrast, Darwin had proposed what he termed *pangenesis* to describe transmission of traits. Ironically, this admits to inheritance of acquired characteristics as one of several mechanisms of variations, the notion which was subsequently discarded by Darwinists.

The essential feature of Darwinian theory is that all species arise through natural selection of small, inherited variations that enhance an individual's ability to survive and reproduce. The thinking that developed and became virtually dogmatic for a long period was that random mutations of DNA alone dictated heredity and hence evolution. Developments in epigenetics and horizontal gene transfer, however, provide additional mechanisms for heredity. It is worth briefly considering these here.

1.2.2.1 Epigenetics

While there are historic precedents for notions of *epigenetics* and differences in meaning among different researchers, a consensus definition was formulated by a group of researchers at a meeting in December 2008 at the Cold Spring Harbor

4 A term coined by Thomas Huxley (England, 1825–1895), a prominent biologist, anatomist, and anthropologist, who was a strong supporter of Darwin's theory.

Laboratory: "An epigenetic trait is a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence."[5] This has some deep implications for understanding the development of an organism, including disease conditions, and hence development of this field may positively impact medicine.

Phenotype is defined by the Oxford English Dictionary as "the set of characteristics of a living thing, resulting from its combination of genes and the effect of its environment." *Genotype* is defined as "the combination of genes that a particular living thing carries, some of which may not be noticed from its appearance."

It is remarkable that a heritable phenotype can exist which involves no alteration of an organism's covalent DNA sequence, because heredity has generally been viewed as the passing along of information carried in the DNA code. Thus, epigenetic processes involve how genes are expressed, and this can be controlled in many ways which do not involve any changes in the DNA sequence. Histones, discussed in Chapter 10.6 in relation to DNA superfolding, are proteins intimately involved in regulation of DNA so that changes in histones and their interactions with DNA can cause differences in gene expression. Other processes, such as methylation of DNA, which inserts methyl groups into the groove of the DNA double helix and inhibits transcription, differential action of "silencer" portions of DNA, and many others can cause a wide variety of epigenetic traits.

A stably heritable epigenetic pathway may be triggered by changes in a cell's external environment. The environments and events that trigger the initiation of an epigenetic pathway, which culminate in a modification of a specific *chromatin* location, have been termed the *epigenator*. Triggering events may involve toxins, radiation, hormones, presence of specific nutrients, and many others. An *initiator* translates the epigenator signal into action at a specific *chromatin site*. The initiator may be a protein that can bind to DNA, a special type of noncoding RNA, or some other agent. *Maintainers* then stabilize and perpetuate the modifications to the chromatin site, to the extent that the modifications can be transmitted to offspring. Chromatin is the complex of DNA and proteins that chromosomes are composed of (Chapter 11.4).

Epigenetics is relatively new and has many controversial aspects, among them a possible rethinking of the discarded "inheritance of acquired traits," which has been a particular laughingstock of Darwinists since the nineteenth century. Epigenetic researchers have proposed analogs to all things genetic; hence, the *epigenome*, which is the overall epigenetic constitution of an organism, *epigenomics*, which is the analysis of epigenome characteristics, and the *epigenetic code*.

Epigenetics is fascinating because it suggests almost a type of interactive software atop the hard-wired DNA sequence of an individual, in that it allows the individual to use the genetic DNA hardware in a way that is responsive to environmental factors, producing and inhibiting protein production as conditions warrant. In this sense, the hard-wired DNA sequence is an instrument, whose notes and stanzas are wrung from it, at least partially, by epigenetics. Hence, epigenetic mutations can happen quickly, during an individual's lifetime, whereas change in DNA in offspring is through mutation and hereditary transmission of the altered DNA, a much slower process. The fact that the means in which the genetic hardware is used by an individual, its epigenome, can be heritable still seems astonishing. Some have suggested that what is known as "instinct" in animals, manifestation of unlearned behavior (e.g. a Border Collie's propensity to herd animals), may be partially the result of epigenetic transmission, as well as hardwired behaviors encoded in DNA sequences. It is also thought that epigenetic inheritance lasts fewer generations than hard DNA changes, which makes it a very supple mechanism, responsive to rapidly changing environments.

While there is still much uncertainty about the modes of transmission of epigenetic information, the information likely must be present in germ cells and survive meiosis, which produces the fertilized egg, or zygote. One possibility is that certain parts of the complex chromatin structure involved in DNA dynamics may survive meiosis and be passed on during fertilization. DNA is always associated with proteins and other molecules, including during meiosis, and is never completely free or 'bare'.

1.2.2.2 Horizontal Gene Transfer

This astonishing mechanism leads to the exchange of genes among organisms of different types and species, and even across the three domains of life: eukaryota, bacteria, and archaea (Chapter 14.1.1). It is astonishing because it breaks with the older notion that genes were transmitted "vertically," from parent to offspring. The fact that genes can be transmitted among species, without the need for inheritance, adds a different dimension to evolution. It complicates the tracing of evolution of at least *prokaryote*[6] and single-cell *eukaryote* species and suggests that the "tree of life" for these may be more of a "web of life," with many interconnections among species, and not just branching through selection of inherited genes. It also provides a "shortcut" to the lengthy process of genetic evolution through mutations and generational transfer, by

5 Berger, S. L., Kouzarides, T., Shiekhattar, R., Shilatifard, A. (2009). An operational definition of epigenetics. *Genes and Development*, *23*(7): 781–3.

6 A prokaryote has no cell nucleus, whereas eukaryotes have a distinct cell nucleus containing its genome.

allowing whole genetic functions to "jump" from one organism to a different type and become incorporated in the latter's genome. In this sense, the ever-deepening and expanding field of *genetic engineering* is also a form of horizontal gene transfer, in that humans can take DNA sequences from one organism and incorporate them into the DNA of other organisms, in what is termed *genome editing*. The advent of CRISPR/Cas9[7] has enormously increased the possibilities for inheritable genome editing. Use of this methodology allows engineered changes made to the human germ cells inheritable. This vast new power has naturally stirred many ethical and philosophical concerns.

The number of examples of horizontal gene transfer in nature is large, and several mechanisms have been identified. Viruses, for example, can transfer genetic material among bacteria and horizontal gene transfer is thought to be the origin of antibiotic resistance in bacteria. Other transfers include fungi to plants, bacteria and viruses to plants, and humans to protozoans.

1.2.2.3 Debate Continues Concerning Purpose or Direction in Nature, or Lack Thereof

The notion that there is purpose in nature is termed *teleology*,[8] and Aristotle is often considered its founder. Some gasp at this word as heretical, others find it an inevitable or fundamental part of nature. This is not a settled debate, and we won't wade into it here. A *teleologist* might say that an eye evolved *in order* to take advantage of the light in the environment and allow perception of objects, their qualities, dimensions, and distances in 3D. A *reductionist* insists that phenomena can be decomposed into, and built up from, simpler parts and principles. In this debate, a reductionist might maintain that the eye arose through random mutation and selection and led to perception of objects, but the eye did not arise "on purpose," or "for a purpose," or "in order" to do anything. The reductionist might similarly maintain that the totality of a mental process, such as adding numbers or sensing fear, is explained entirely by the corresponding neural electrochemical events in the brain. The teleologist might argue that the neural electrochemical events are necessary but not sufficient to fully characterize the mental process. A prominent reductionist argument against purpose is that it requires *design*, and then design can lead to the notion of a designer, which tends to correspond to the God notion, which then tends to transcend the current bounds of the scientific method. The teleologist might refuse to be called a teleologist and defend against this argument by maintaining there are as yet unknown principles immanent in nature, especially those involving self-organization of matter, that lead to what seem purposeful biological features in an organism, but don't require any notion of design, a designer, or a prior contemplation of a feature or a blueprint; e.g. that there is possibly a biased random walk in evolution leading toward optimal use of energetic resources in the environment. The teleologist might further insist that complex biological features cannot arise through random mutation and selection, simply because a few billion years and the limited material available on the outer crust of our small planet are insufficient to test and select enough mutations to arrive at the sophisticated functions found in organisms. At which point the reductionist might claim that, yes indeed, it is highly improbable that life arose randomly, but it beat the odds and *did* arise randomly. We are now back to the earlier mentioned divide of life being *improbable* versus life being *inevitable* when certain conditions of elemental abundance and energy availability are met.

1.2.3 Genetics and Molecular Biology

The aim of this book is to interweave discoveries and methods from different fields, rather than to divide natural phenomena and practical applications into rigid subfields. Nevertheless, the areas of biochemistry, genetics, and molecular biology overlap greatly and are underpinned by evolutionary theory, and yet they parcel themselves out as distinct fields with different goals and methods. While Darwin is considered the "father of modern evolutionary theory," Mendel is usually considered the "father of genetics." But neither of them were involved in the underlying chemistry of evolution and heredity.

The search for the molecular basis of living state processes began in the eighteenth century and encompasses many very different research questions using very different approaches. Just a few examples: Antoine Lavoisier (France, 1743–1794) worked on the chemistry of respiration and fermentation, the discovery of the first enzyme was by Anselme Payen (France, 1795–1871); in 1833, the first abiotic synthesis of a living state molecule, urea, by Friedrich Wöhler (Germany, 1800–1882); in 1828, the discovery of the citric acid cycle by Hans Krebs (Germany/England, 1900–1981); and the naming of the distinct field "biochemistry" by modern contributors Carl Neuberg (Germany/United States, 1877–1956) and Franz Hofmeister (Czechia, 1850–1922). Arguably, two of the strongest areas in biochemistry are metabolism and enzymology, but biochemistry overlaps with just about every other life science area, including biomacromolecules, cell biology, genetics, immunology, and structural biology.

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7 CRISPR = clustered regularly interspaced short palindromic repeats. Palindrome = a word which is the same when spelled backward. Cas9 is a bacterial defense protein which can cut DNA.

8 Teleology is the study of the purpose or design of natural occurrences, not to be confused with "theology."

In 1871, Friedrich Miescher (Switzerland, 1844–1895) published his discovery of phosphate-rich nucleic acids isolated from white blood cells. This established the foundation of the chemical origin of genes, even though Miescher and others did not recognize its genetic role at the time, and the theory that proteins were the origin of heredity generally prevailed. However, the discovery of nucleic acids added an entirely new class of biochemical to the ones already known at that time: lipids, polysaccharides, and proteins.

Chromosomes were discovered as subcellular structures by Karl Wilhelm von Nägeli (Switzerland, 1817–1891) in 1842, without realizing their role. Edouard van Beneden (Belgium, 1846–1910) found that the chromosomes of parents' organisms don't fuse together, but remain as distinct entities after fertilization. This connects directly to Mendel's genetic laws, but it wasn't realized at the time. In 1903, Theodor Boveri (Germany, 1862–1915) and Walter Sutton (United States, 1877–1916) independently demonstrated that the chromosome was the basic hereditary unit. Hugo DeVries (Holland, 1848–1935) crystallized many previous notions about mutations in his book *Species and Varieties: Their Origin by Mutation*, published in 1905. DeVries's theory of mutation held that variations could arise in a single mutational step, related to changes in genes, and manifested according to Mendel's laws, and not gradually over many generations, as Darwin had thought. This discovery fell midway in the period of the *eclipse of Darwinism*, which lasted for a few decades in the late nineteenth and early twentieth centuries, as certain erroneous Darwinian ideas of gradual variations and inheritance of acquired characteristics were shed. This continued until various discoveries illuminated relationships among genes, proteins, and evolution. The *modern synthesis* reconciled Darwin's evolutionary theory with Mendel's genetic laws. Thomas Hunt Morgan (United States, 1866–1945) discovered that genes reside on specific locations in chromosomes, and that mutations involved physical changes in genes.

Because chromosomes contain both nucleic acids and proteins it was widely held until 1941 that proteins carried genetic information. A series of discoveries by several researchers led to the definitive conclusion in 1944 that a nucleic acid, deoxyribose nucleic acid (DNA, see Chapter 11), is the genetic material, and that genes code for proteins. Using the X-ray diffraction patterns of DNA captured by Rosalind Franklin (England, 1920–1958), James Watson (United States, 1928–) and Francis Crick (England, 1916–2004) elucidated the double helical form of the DNA molecule in 1953, and it was discovered that there were complementary pairings of just four base pairs involved in the protein coding.

The biochemistry and biophysics of DNA, and associated genetics, went through explosive developments after the discovery of the DNA double helix. A well-known nuclear physicist, George Gamow (Soviet Union/United States, 1906–1968), postulated that there were three pairings of bases to produce $4^3 = 64$ *codons*, the sequence of three nucleotides that specify an amino acid. He also postulated that since there are only 20 amino acids (AA) used in living organisms there was *degeneracy* in the code, such that more than one codon could specify the same amino acid. Crick and colleagues found the codon for phenyl alanine, and Severo Ochoa (Spain/United States, 1905–1993) found the codes for the amino acids lysine and cytosine. Finally, after contributions by many researchers, Har Gobind Khorana (India/United States, 1922–2011) completed the table of the *genetic code* (Chapter 11.2) and was also the first to synthesize *oligonucleotides*, a polymer with a small number of *nucleotides*, which are the basic structural units of RNA and DNA.

There were many researchers involved in the development of protein and nucleic acid sequencing. Frederic Sanger (England, 1918–2013) was seminal in both fields. He coupled chromatography in one dimension with electrophoresis in a second dimension and separated and identified hydrolyzed fragments of the insulin molecule, and then puzzled them back together to obtain the entire sequence. He succeeded in sequencing the amino acids in bovine insulins in 1951–1952 and proved that proteins have a defined amino acid sequence, and hence a defined chemical composition. The group of Robert Holley (United States, 1922–1993) at Cornell University sequenced tRNA from yeast in 1964. Sanger's group had sequenced tRNA from *Escherichia coli* bacteria by 1967. Many researchers were involved in the next step, the sequencing of DNA. Ray Wu (China/United States, 1928–2008) and colleagues developed methods based on nucleotide labeling and DNA polymerization over 1970–1973. The first full *genome*, the entire genetic content of an organism, was sequenced in 1977. This latter was for a *bacteriophage*, a virus that attacks bacteria. Since then, sequencing has become commonplace and rapid. The *human genome project* was an ambitious international project whose goal was to sequence all the genes in the human genome. It was started in 1990 and completed in 2003. It was the largest international biological cooperative project in history.

Genetic engineering has undergone exponential growth since the late twentieth century and into the twenty-first. Two main methods are used. One is the *recombinant DNA method*, which, as mentioned, is a humanmade horizontal gene transfer, where desired sequences of DNA are taken from one organism and allowed to recombine with DNA from another organism, which then expresses the desired protein. The second method, even more powerful, is direct *de novo* synthesis of any desired nucleotide sequence. Genetic engineering is used to create novel organisms and characteristics to produce new medicines, fermentation products, and plant species resistant to herbicides and insecticides. Cloning, the creation of identical copies of an organism by taking and expressing its genetic material, has unleashed both tremendous possibilities and huge ethical challenges and controversies. It has furnished the fuel for many science fiction novels and movies.

1.3 Historical Developments in Biophysics

Because biophysics is interpreted in many different ways it is worth starting by revisiting the opening remarks in the Preface. Biophysics is not a canonical, unitary field, but all would agree that biophysics involves both physics and biology, but then perspectives diverge after that. It is appealing to attempt to establish the "living state" of matter as a phase unified by fundamental principles: living state physics.

Because of its interdisciplinarity and these various interpretations it is hard to discern a continuous thread of development in biophysics.

From the point of view that biophysics is the transfer of devices from physics to biology, Antonie van Leeuwenhoek (Holland, 1632–1723) invented the first practical, high-power, single lens microscopes, a milestone in optics, which is traditionally a part of physics. His microscopes revealed the existence of microbes, a discovery which shook the scientific world and led Leeuwenhoek to be considered the "father of microbiology."

1.3.1 Electrophysiology

Luigi Galvani (Italy, 1737–1798) discovered that the legs of a dead frog could be induced to move by shocking them with an electrically charged object. This gave rise to the concept that animal motion was coupled to electrical phenomena, and this might be considered the beginning of *electrophysiology*. John Walsh (England, 1726–1795) in 1773 published his extensive studies of the properties of electrical fish, including conduction of their electricity through water, metals, and people with joined hands. Carlo Matteucci (Italy, 1811–1868) made continuous contributions to bioelectricity and even constructed a battery based on frog legs in series, and demonstrated that the currents summed up in the same way as the inorganic piles (batteries) of Alessandro Volta (Italy, 1745–1827).

Electrophysiology grew rapidly throughout the late nineteenth and the entire twentieth centuries. Augustus Waller (France/England, 1856–1922) created the first *electrocardiogram* of the human heart in 1887. Willem Einthoven (Holland, 1860–1921) produced the first high-quality electrocardiogram, ECG or EKG, in the 1890s, and spent the rest of his life improving and standardizing the method, including interpretation of the signals and relation to normal and disease conditions. The oscilloscope was a foundational instrument in this field, and the first one using a cathode ray tube was invented by Karl Ferdinand Braun (Germany, 1850–1918).

While researchers were devising means to detect electrical processes in the heart, others were fascinated by electrical activity in the brain and this led to the field of *electroencephalography*. The use of electrodes to probe bioelectricity was increasing in refinement and applications in the nineteenth century. Using electrodes placed directly on the brain surfaces of dogs and rabbits Adolf Beck (Poland, 1863–1942) discovered rhythmic electrical oscillations in the brains, or *brain waves* in 1890–1891. The first animal *electroencephalogram* (EEG), a recording of brain electrical activity was published in 1912 by Vladimir Vladimirovich Pravdich-Neminsky (Russia, 1879–1952). Through an invention of Hans Berger (Germany, 1873–1941), the first human EEG was recorded in 1924. Encephalography as a research field and clinical tool rapidly grew out of this. EEGs are used clinically to detect epilepsy, brain tumors, strokes, and other brain injuries. In research, they are important in neuroscience and cognitive science.

Electrical phenomena associated with nerve conduction were studied both theoretically and experimentally throughout the nineteenth century. Julius Bernstein (Germany, 1839–1917) invented the differential rheotome and was able to measure nerve impulses with it. He developed a remarkable hypothesis in which the impulses are caused by membranes of nerve cells having a process involving differential permeability to K^+ and other ions, thus changing electrical potential across the membrane, which could travel as a pulse along axons. This fruitful idea powered intense experimental activity right up to WWII. After WWII, in the late 1940s to early 1950s, Alan Hodgkin (England, 1914–1998) and Andrew Huxley (England, 1917–2012) made their breakthrough series of experiments, and corresponding mathematical interpretation, that put nerve impulse propagation on a modern electrochemical and quantitative basis (Chapter 13).

1.3.2 Hermann von Helmholtz

Hermann von Helmholtz (Germany, 1821–1894) was something of a latter-day Renaissance Man. A physicist, physician, physical psychologist, inventor, musician, and philosopher, he contributed to the understanding of visual and auditory perception, the physics of the eye, formulation of the principle of conservation of energy, and made landmark discoveries in electrodynamics, fluid dynamics, and chemical thermodynamics. While the conservation of energy is usually thought of as a bedrock principle of physics, his insight into energy conservation actually came from the study of muscle movement, and his philosophical intent to rid physiology of *vitalism* (Section 1.7). He unified the notion of energy having manifestations in mechanical, thermal, light, and magnetic energies.[9] His biophysical inventions included the *opthalmoscope*, which allows the inside structure of the human eye to be viewed, a galvanometer so sensitive he made the first measurements of the speed of nerve conduction (ca. 30 m/s, Chapter 13), and the *Helmholtz resonator*, which isolates selected frequencies from complex sounds, such as music, and can be used for mechanical Fourier analysis of sound. Among Helmholtz's many doctoral students: Max Planck; Albert Michelson (Germany/United States, 1852–1938) who accurately measured the speed of light using interferometric principles and could find no difference in the speed due to the Earth's motion, which both preceded and corroborated Einstein's special theory of relativity; and Heinrich Hertz (Germany, 1857–1894), known for the first demonstration of electromagnetic waves and the discovery of the photoelectric effect.

1.3.3 Osmosis and Diffusion

Two other entry points to biophysics were osmotic pressure (Chapter 4.8) and diffusion (Chapter 6.8). Jean-Antoine Nollet (France, 1700–1770) discovered osmotic flow through natural membranes in 1748. The semipermeable membranes used for succeeding osmotic studies were also from natural membranes. Nollet also deduced that electricity flows at very high speed, using the curious experiment of having hundreds of monks connecting their hands in a circle thousands of feet in circumference via pieces of iron, then discharging a battery of Leyden jars,[10] and observing that all the monks reacted painfully to the shock at the same time. This also further proved that electricity could flow both through biological organisms and inorganic metals in the same circuit. The flurry of activity involving osmotic flow led quickly to notions of diffusion. Adolf Fick

Nollet shocks his monks. (Painting by Linnette F. Reed).

9 The term "energy" came later, Helmholtz referred to these linked phenomena with the word Kraft (German for "force").

10 Leyden jars accumulate large amounts of electrical charge between metals on the inside and outside of a jar, a capacitor in essence. The charge can be released when the inside and outside oppositely charged metals are joined by a conducting path.

(Germany, 1829–1901), who had been formally trained in mathematics, physics, and medicine, published the basic laws of diffusion in 1856 in a text on medical physics (*Die medizinische Physik*), which is perhaps the first in biophysics.

Work on osmosis and diffusion gave the impetus for the field of *physical chemistry*. The latter is immediately relevant to the living state, because its purview includes reaction kinetics, thermodynamics and electrochemistry in solutions and on surfaces, and intermolecular forces. It was recognized as a field by two of its founders, Jacobus van't Hoff (Holland, 1852–1911) and Wilhelm Ostwald (Latvia/Germany, 1853–1932), with the founding in 1887 of *Zeitschrift für physikalische Chemie*.

1.3.4 X-rays

Radioactivity and X-rays were both discovered at the end of the nineteenth century. Wilhelm Röntgen (Germany 1845–1923) discovered X-rays in 1895. He serendipitously discovered the rays while using a Crooke's tube[11] and realized it was a new form of radiation, to which he gave the name X-rays (X-Strahlen), the "X" being a place holder for the unknown rays until they could be identified. The name stuck, although within days it was suggested that they be called *Röntgenstrahlen*, the name still used in the German-speaking world. Others had observed the glows coming from Crooke's tubes, but Röntgen was the first to systematically study their properties, in particular their penetrating power through various materials. He made the first X-ray photograph, or simply "X-ray," of his own hand, and then of his wife's, Figure 1.2. When she saw it she declared "Ich habe meinen Tod gesehen" (I have seen my death).

Within a year, by 1896, X-rays were already being used clinically in Europe, the United States, and Japan, in what was probably the nineteenth century's most rapid major technology transfer from laboratory discovery to practical use. X-ray technology developed throughout the twentieth century and culminated in the invention in 1972 of *computed axial tomography scans* (CAT scans, or simply CT scan), which involve taking X-ray images at many different angles and combining them computationally into a 3D image. Many other types of *tomography*[12] exist, using gamma rays, visible light, infrared, electrical resistivity and capacitance, neutrons, and even muons, as well as antimatter.

There were arguments over the nature of X-rays for over a decade after the 1895 discovery, until it became clear that they exhibited polarization and other properties of electromagnetic waves and were hence a part of the electromagnetic wave spectrum. The polarization of X-rays was demonstrated in 1906 by Charles Barkla (England/Scotland, 1877–1944).

Max von Laue (Germany, 1879–1960) and his assistants performed the first experiment in X-ray diffraction in 1912,[13] obtaining an X-ray diffraction pattern from copper sulfate crystals. The father and son team of William Henry Bragg (England, 1862–1942) and William Lawrence Bragg (Australia/England, 1890–1971) was inspired by Laue's results, confirmed them, and then focused much of their career on the growing field of X-ray diffraction and crystallography. The methods came quickly into use in many countries. The structures of large numbers of crystals were determined, and increasingly sophisticated methods of data interpretation developed, including the use of Fourier transforms in the late 1920s. The work had immediate impact in physics, chemistry, and materials science. The detailed structure of different alloys could quickly be determined, greatly advancing metallurgy. Working with Lawrence Bragg, Max Perutz (Austria/England, 1914–2002) turned efforts toward the difficult task of determining the structure of biological macromolecules. His laboratory attracted Watson and Crick and their famed DNA experiments. In 1953, he invented a method of substituting a heavy metal (mercury) into a crystal of the protein hemoglobin and used X-ray diffraction for the world's first determination of the 3D structure of a protein. Since then, X-ray diffraction of proteins has become a mainstay of both molecular biology and pharmaceutical science, and the structures of thousands of proteins are now determined each year.

Figure 1.2 The famous X-ray of Röntgen's wife's hand, made by Röntgen in 1895. (Courtesy of Science History Images / Alamy Stock Photo).

In addition to X-ray crystallography, *X-ray spectroscopy* became a major tool shortly after Röntgen's discovery and is a major component of modern chemical analysis. Using the principle of X-ray diffraction with crystal lattices of known

11 A tube with low-pressure gas inside across which a high-voltage discharge is made. High-energy electrons (KeV) striking the end of the tube, typically a metal target, cause X-ray emission through breaking radiation (Bremsstrahlung) and inner electron ionization of the target atoms. This stands in contrast to a cathode ray tube which uses a heated filament and thermionic emission of low energy electrons (eV) which strike a phosphor that emits light.

12 Greek τομοζ "tomos," a "slice" or "section," and γραφω, "grapho," to write or describe.

13 Max von Laue and the discovery of x-ray diffraction in 1912. *Annals of Physics (Berlin)* 2012, *524* (5): A83–5. doi:10.1002/andp.201200724.

atomic spacing a spectrometer can be made that determines the wavelength of X-rays produced in a process. X-ray absorption spectroscopy measures the wavelength of X-rays associated with energy transitions from electron ground states in elements to higher excited states, whereas X-ray emission spectroscopy measures the wavelength of X-rays corresponding to energy released when an electron falls from a highly excited state to a lower one. It quickly became a method for identifying elements.

In 1913, Henry Moseley (England, 1887–1915) discovered that X-ray spectra from one element to the next massive one followed a very regular pattern, and from this deduced the notion of *atomic number*, which was later understood to correspond to the number of protons in an element's nucleus. This led to a modification of the periodic table according to atomic number rather than atomic mass, as had first been systematized by Dmitri Mendeleev (Russia, 1834–1907). Moseley, seeing gaps in his periodic table, also predicted four missing elements, which were subsequently found. These had atomic numbers 43 (technetium), 61 (promethium), 72 (hafnium), and 75 (rhenium). Moseley left his research at Oxford to volunteer as a telecommunications officer. He was killed in action in WWI in 1915, in the ghastly and devastating battle of Gallipoli, Turkey.[14]

1.3.5 Imaging Methods

Besides X-ray CT imaging, some other major imaging methods in modern medicine trace back to developments in physics. Nuclear magnetic resonance (NMR) was first demonstrated by Isidor Rabi (United States, 1898–1988) and colleagues in 1937. They measured the magnetic moment of the proton and of several lithium compounds. The method quickly expanded to become one of the greatest workhorses of modern chemistry and materials science. It has advanced by the availability of ever higher magnetic fields, and use of radio frequency waves to interrogate the spin states of nuclei. Because it uses no high-energy radiation, such as X-rays, it is biologically benign and it has been adapted to 3D imaging of whole organs in patients in *nuclear magnetic resonance imaging*, or MRI, where "nuclear" has been dropped, presumably so as not to frighten patients.

Positron emission tomography (PET) is used to pinpoint tumors or infections. It relies on the annihilation of electrons and their antiparticle, the positron, which produces two gamma rays which can then be traced back to their location of annihilation in tissues (Chapter 9.17). As mentioned above, antimatter was discovered from Dirac's formulation of the relativistic quantum mechanical wave equation.

1.3.6 Radiation Biophysics

The effects of radiation on living organisms, cells, biological tissues, and biological macromolecules is the traditional purview of *radiation biophysics*, sometimes also termed *radiobiology*. Research on biological effects of radiation began soon after the discovery of X-rays, gamma rays (electromagnetic waves with wavelengths on the order of 10^{-11} m and less), and alpha (ionized helium nuclei) and beta particle (electrons and positrons) radiation.

Several early radioactivity researchers and their assistants lost their hair, sustained skin injuries, or suffered worse fates. Marie Curie and her daughter, Irène Joliot-Curie (France, 1897–1956), herself a Nobel-prize-winning chemist, both died of leukemia, likely due to their long exposure to radioactive substances. Pierre Curie found that exposing tadpoles to radiation from radium caused developmental abnormalities. Thomas Edison (United States, 1847–1931) became a major force in improving and commercializing medical X-ray technology, via the General Electric Co. He observed that some assistants fell gravely ill from working with X-rays.

Hermann Heineke (Germany, 1873–1922) made the first published studies on the effect of radiation on animals and internal organs, starting in 1902. Heinrich Albers-Schönberg (Germany, 1865–1921) reported the sexual sterilization of guinea pigs due to prolonged exposure to radiation in 1903. Efim Simenovic London (Lithuania/Russia, 1869–1939) subjected guinea pigs to prolonged exposure of radium and reported in 1903 that this led to loss of appetite, lethargy, weakness of response to stimuli, and death in four to five days. Friedrich Dessauer (German/Switzerland, 1881–1963) made one of the first quantitative radiation studies, establishing statistical relationships between doses and responses in 1925. Radiation biophysics blossomed after WWII. Methods for producing cloned cell lines of mammalian tissue, and for creating mutations, were developed in the 1950s. With these new tools, it was soon realized that chromosomes could be severed by X-rays.

14 The Gallipoli campaign lasted eight months, and pitted allies Britain, France, and Russia against the Ottoman Empire, which was allied with Germany. One of the main goals was for the Western allies to control the Suez Canal and secure routes through to the Black Sea. There were over 500,000 casualties in the conflict!

1.4 Subfields in Biophysics

Biophysics can be divided into subfields along a number of different axes. Most subfields connect to other fields and subfields in biological and medical sciences, such as neuroscience, electrophysiology, enzymology, cell and molecular biology, and genetics. Below, some of the most often used designations for biophysical subfields are outlined.

1.4.1 Molecular Biophysics

Molecular biophysics involves the physical structure and properties of nucleic acids, proteins, lipids, carbohydrates, hormones, and many other molecules. Molecular biophysics seeks the physical origins of their biofunctionality. The large molecules are examples of *polymers*, also termed *macromolecules*. Macromolecules are central to genetics, and to biochemistry and its explanations of processes such as metabolic cycles. Macromolecules, whether biological or human-made, share many fundamental properties and many of the same characterization methods. We shall see, however, that the functionality and capabilities of biological macromolecules are mind-bogglingly more sophisticated than any that humans have created to-date.

Macromolecules are sometimes viewed as a branch of *soft matter physics*, which is itself a subfield of *condensed matter physics*. Many features of the living state fall into focus areas of soft matter physics. Among other phenomena soft matter physics involves mesoscopic structures – larger than the component atoms and molecules, but much smaller than the entire system – and their sensitivity to mechanical, thermal, optical, electromechanical, and other stresses. Other soft matter examples besides macromolecules include liquids, foams, colloids, gels, and many biological materials, such as cartilage and membranes.

The largest single focus in this book is on macromolecules, both biological and synthetic, the properties common to both types, and the experimental and theoretical approaches to understanding them. Chapters 7 and 8 are concerned exclusively with macromolecules, while Chapter 9 introduces scattering and cognate methods used to characterize them. Selected properties and phenomena involving the main classes of biomacromolecules are treated in Chapters 10–13.

1.4.2 Cellular Level and Integrative Biophysics

Macromolecules, small molecules, ions, and water come together to create functional entities. These include specific subcellular structures, such as mitochondria, the Golgi complex, and lysosomes, as well as whole-cell organisms, such as prokaryotic and eukaryotic microbes. Many specific processes are enabled at the cellular level. Some examples include cell and membrane structures which support nerve impulses and propagation, as well as active and passive transport of molecules and structures. Highly specialized cell types also lead to muscular contraction, photosynthesis, vision, tactility, olfaction, gustation, and acoustic perception. Also of major importance is how cells interact and integrate with each other, including regulatory and feedback mechanisms. We will touch on some of these topics in several of the chapters in Part IV.

1.4.3 Macroscopic Biophysics

This generally deals with large-scale aspects of higher organisms. Biomechanics involves locomotion, stresses and strains, muscular–skeletal systems, and mechanics and rheological properties of biofluids, bone, wood, and other biomaterials. It also deals with systems such as fluid transport in plants, blood circulation in animals, and gas/liquid exchange processes.

1.4.4 Theoretical Biophysics

This is a vast area and often is meant to include theoretical biology, in general, where many topics are dealt with mathematically; population dynamics, symbiotic and ecological models, entire biomes, and the interaction between living organisms and geology, the oceans, and the atmosphere. Some of its organizing principles come from thermodynamic concepts such as autocatalysis, stability, irreversibility, nonequilibrium processes, self-assembly, dynamic order, synergetics, and phase transitions. Other fundamentals come from fluid mechanics: viscosity, diffusion, electrophoresis, laminar and turbulent flow, and heat and mass transport.

Other areas that make use of principles more akin to engineering and computer science include network and information theory, and negative and positive feedback control theory.

Modeling and computational efforts are often subsumed under theoretical biophysics. Many simulations have been developed to test theories on the prebiotic origins of life (Chapter 15.1). Importantly, there is no universal consensus on how life arose. Among many other applications, computer simulations are also used to predict mutations, to understand how proteins fold, and to explore embryonic and development pathways. Simulations are sometimes termed *in silico experiments*.

The beginnings of *quantum biophysics* or *quantum biology* were hinted at by the founders of quantum physics, including Schrödinger, Delbrück, and Bohr. Emerging areas in the field include energy transfer and charge separation in photosynthesis, tunneling in enzyme catalysis, and roles in sensing processes, such as magnetoreception and olfaction, and possible quantum mechanical roles in cognition and the origin of life. There is a short treatment of some of these in Chapter 15.

1.4.5 Instrumental and Medical Biophysics

Section 1.3.6 introduced some of the central concerns of radiation and medical biophysics. Instrumental biophysics involves the large-scale adaptation of the experimental tools of physics to biophysical and medical research and practice. Instruments frequently invented in physics laboratories to probe the underlying structure of matter have become the bedrock of many disciplines.

1.5 Interdisciplinarity

Until just the last few centuries scientific inquiry was an open field, and thinkers typically expounded their ideas in many different areas, such as philosophy, history, political science, and the physical and life sciences. Many of the most famous Greek philosophers were multidisciplinary, and during the European Renaissance, from the fourteenth to seventeenth century, there was a tremendous rediscovery of classical art, architecture, literature, philosophy, and science. The term "Renaissance man" denotes someone talented in many different fields, e.g. Leonardo da Vinci (Italy, 1452–1519). In Renaissance Italy, the term was *uomo universale*, or universal man, someone educated and productive in many areas. In that era, knowledge was so sparse that a vigorous thinker could wade into several fields, find its boundaries and make contributions. As more knowledge accrued it became more and more difficult to be in the lead of any given area of inquiry, and so specialization inevitably set in. The modern Ph.D., or doctor of philosophy (*Philosophiae Doctor* in Latin), with its emphasis on original research in a particular field didn't arise until the early nineteenth century in Germany, spearheaded by Wilhelm von Humboldt (Germany, 1767–1835). It spread to the United States by the mid-nineteenth century, as well as to other countries.

While there is much current emphasis on "interdisciplinarity" in modern research and teaching, scientific fields became disciplinary for a very good reason; the set of phenomena and the methods used to understand and structure them have traditionally been very different. Disciplinary journals are the norm rather than the exception. The traditional and current departmental structure of universities in North America and elsewhere strongly embodies this disciplinarity, and there are frequently very high barriers to communication and cooperation between such departments.

Nonetheless, there are some areas of inquiry which require so many different perspectives and approaches that they have necessarily become interdisciplinary endeavors, gathering from physics, chemistry, life sciences, medicine, the engineering disciplines, and physiological psychology. Examples include programs and departments in biophysics, materials science and engineering, neuroscience, polymer science and engineering, and planetary science.

1.5.1 A Simplified Net of Scientific Knowledge

Caminante no hay camino, se hace el camino al andar.[15]

Antonio Machado

Figure 1.3 is a simplified attempt to capture the evolution of scientific thought. In the early period – ancient Greece, China, and India – the thread of knowledge is quite thin. Knowledge was limited enough for philosophers to contribute in many

15 A loose translation "Traveler, there is no trail, you make the trail as you go forth."

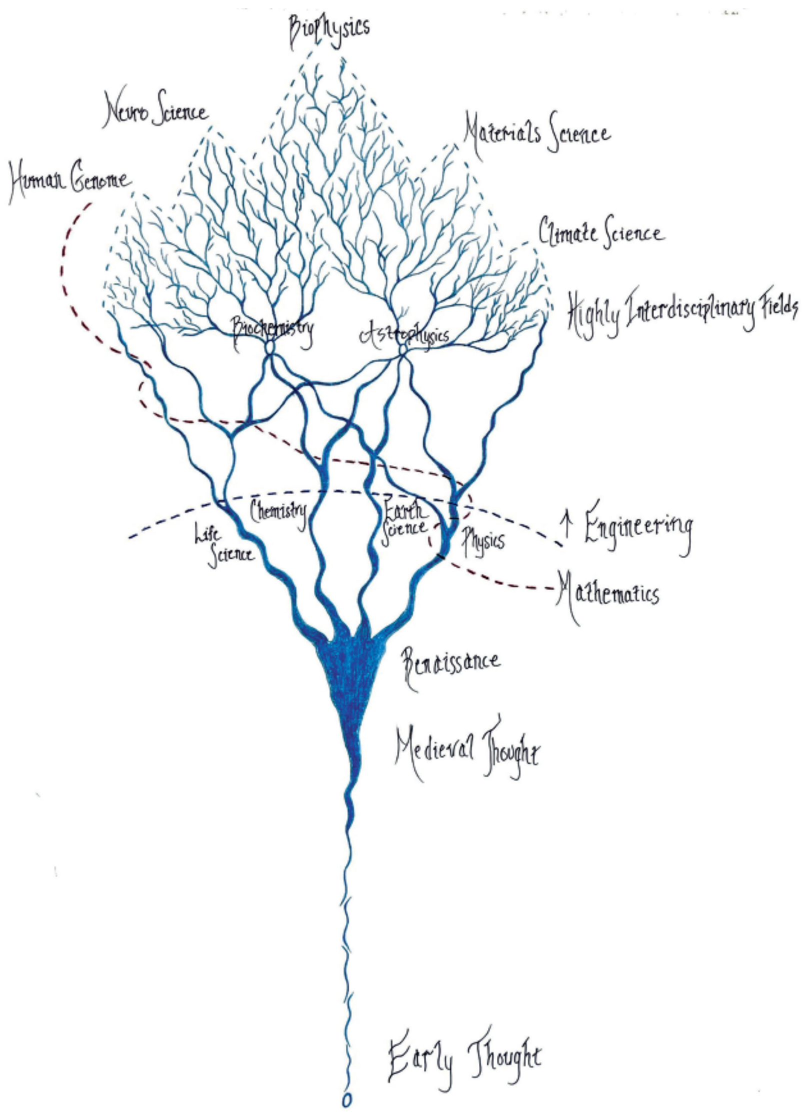

Figure 1.3 Artist's depiction of a web of science. Expansion of science from early thought to highly branched and specialized fields, gathering into complex interdisciplinary fields. (Drawing by Cynthia Satzinger).

very different fields over a lifetime. The rise of the Roman Empire, which imported much learning from Greece, and even used enslaved Greek philosophers as tutors for the ruling class, had different priorities. It was natural to emphasize applied science, in the form of great civil engineering projects, of roads, dams, and aqueducts, of improving means of terrestrial and ocean-going transport and communication, of weaponry and the machines of war; in short, engineering. Meanwhile, it was critical to develop civil and political mechanisms to administer a vast empire with up to 70 million people from radically different customs, languages, and cultures.

It is no surprise that the thread of knowledge stays thin and even diminishes in the West through the European middle ages, as ancient knowledge was often lost. The torch was passed during this time to the burgeoning Islamic world, which made fundamental advances in mathematics, astronomy, chemistry, geophysics, and medicine during the *Islamic Golden Age*, from the 8th to 14th centuries. The net of knowledge in Figure 1.3 thickens during this period. The Islamic civilization also had classical Arabic translations of the ancient works from Greece, India, Persia, and China. In Spain, the Toledo School of Translators (*Escuela de Traductores de Toledo*) was a meeting place of Islamic, Jewish, and Christian scholars, who translated the ancient texts into Classical Arabic, Latin, and early forms of Castilian (the root of modern Spanish). Scholars from medieval northern Europe frequently traveled to Toledo to gain access to ancient knowledge.

There is no doubt that the advent of the printing press in 1439 by Johannes Gutenberg (Germany, ~1400–1468) was one of the key inventions of the modern world and enhanced the vigor of the European Renaissance. With the advent of the Renaissance not only were the best legacies of the ancient world rediscovered and expanded upon, but a new wave of critical thinking and experimentation arose starting in the sixteenth century. Nicolaus Copernicus (Poland/Prussia, 1473–1543) resurrected the heliocentric theory of Aristarchus of Samos (Greece, ~310 to ~230 BC) and underpinned it with his astronomical observations and mathematical calculations. Once again, Aristotle's influence, which maintained the false geocentric theory, predominated in Europe. Copernicus's book *De revolutionibus orbium coelestium* (*On the Revolutions of the Celestial Spheres*) was published in 1543, shortly before his death. It is thought that Copernicus feared both scientific and theological ostracism from this radical theory. In fact, the book unleashed a torrent of criticism from both areas.

Famously, the consummate Renaissance man, Galileo, strongly supported the Copernican theory and fell into conflict with the Catholic Inquisition, which accused and convicted him of heresy, forced him to publicly recant his support, and condemned him to house arrest for the rest of his life.[16] His major contributions to physics, astronomy, mathematics, and engineering are too numerous to begin listing, but a major feature of his work was his mathematical description of phenomena, and his belief that mathematics could describe natural phenomena. This was a major step in separating natural science from theology and speculative philosophy.

Francis Bacon (England, 1561–1626) was influential in advocating for observation, hypothesis, inductive thinking, and objective testing of nature, rather than relying on ancient authority. This type of skeptical empiricism still underlies most of modern science.

It is notable that all these Renaissance men worked in several very different fields during their lifetime, and so the thread of knowledge in Figure 1.3 is now becoming a trunk, but still does not branch. Moving out of the Renaissance there are two distinct tendencies; Figure 1.3 shows mathematics beginning to permeate the sciences around the seventeenth century, and remains intertwined thereafter, with the strongest vine encircling physics, but growing into chemistry and earth sciences, and much later into biological sciences. Second, the separate disciplines of life and physical sciences become defined in their own right, and the physical sciences become subdivided into physics and chemistry, while earth sciences draw from all the other fields. Branching and specialization have begun.

Isaac Newton is the towering figure that powered centuries of discovery and applications in physics and mathematics. His 1687 book *Philosophia Naturalis Principia Mathematica (Mathematical Principles of Natural Philosophy)* provided the first quantitative theory of gravitation and founded classical mechanics. He developed calculus in order to elaborate his mechanical theories. In his 1704 book, *Opticks*, he gave the first detailed theory of light as tiny particles, which foreshadowed Einstein's photon theory presented in 1905, and he also invented the first known reflecting telescope.

Increasingly, in the seventeenth and eighteenth centuries, many scientists were simultaneously physicists and mathematicians. Johannes Kepler (Germany, 1571–1630) derived mathematical laws for the motion of planets, based on the observations of Tycho Brahe (Denmark/Sweden/Czechia, 1546–1601), which supported the heliocentric theory of Copernicus. Pierre de Fermat (France, 1601–1665) foreshadowed calculus and established an important extremalization principle for how light travels. Blaise Pascal (France, 1623–1662) was a pioneer in probability and number theory, contributed to the theory of hydraulics and gases, insisted on the reality of the vacuum, invented the hydraulic press and several mechanical calculators, and was also an eminent philosopher of mathematics and science, and an eloquent prose writer. Leonhard Euler (Switzerland/Russia/Germany, 1707–1783) contributed to almost every branch of physics and is often considered the most prolific mathematician in history. Carl Friedrich Gauss (Germany, 1777–1855) made wide-ranging contributions in mathematics, including non-Euclidean geometry and probability theory, as well as in astronomy and electromagnetic theory. Daniel Bernoulli (Holland/Switzerland, 1700–1782) made enduring contributions in pure math, statistics, and fluid mechanics, including his equation which predicts the principle of aerodynamic lift, eventually leading to the airplane.

Throughout the nineteenth century, the various disciplines begin to subdivide, e.g. physical chemistry, organic chemistry, biochemistry, electrophysiology, physical psychology, fluid mechanics, acoustics, thermodynamics, and optics. At the same time, some of their mutual interests make them link up to each other, forming a web of science: organic chemistry, biochemistry, and physiology find shared areas of inquiry. Electrochemistry and electrophysiology join in the quest to understand nerve conduction.

In the twentieth century and into the twenty-first century, there is ever-increasing specialization, sometimes so deep that practitioners in one specialty have little or no knowledge of even proximate fields. At the same time, philosophical musings have been eradicated from the goals and expression of mainstream scientific research and literature. But, starting roughly in the twentieth century, research areas were becoming too complex to be approached by a single specialty. Materials science, polymer science, neuroscience, genetic engineering, and other areas increasingly required knowledge and methods from previously disjoint specialties. Figure 1.3 shows several areas and how they reconvene the disconnected specialties and bring them to bear.

In Figure 1.3, there is a wave propagating outwards with the development of science: practical applications which shape entire civilizations. This is engineering, and virtually every field and subfield has an engineering component

16 Galileo is said to have uttered "Eppur si muove," upon his sentencing to house arrest by the Inquisition, meaning "yet it moves," referring to the Earth moving in space and not being the stationary focal point of the solar system (or of the entire universe, as was often thought!).

associated with it. Civil engineering, one of the oldest applied sciences, gathers together mechanics, earth science, materials science, and others to create structures appropriate for their designated functions and environments. Mechanical engineering arguably begins with bows and arrows, works through the innovations of the ancient Greek and other civilizations, and makes a huge leap after the establishment of Newtonian mechanics and its consequences. Chemical engineering combines chemistry, fluid mechanics, thermodynamics, metallurgy, and a host of uniquely industrial process, operational, and control concepts to enable production of modern products. Biomolecular engineering emerges from the latter, where the engineering now focuses on the creation of biologically derived molecules and products. Electrical engineering fleshes out the innumerable inventions deriving from classical electromagnetic theory and has harnessed quantum physics to produce the diodes, transistors, and integrated circuits underlying modern computers and a vast number of other devices. Biomedical engineering combines modern concepts from electrical, chemical, and mechanical engineering, fuses them with neuroscience, cardiology, and other fields of medicine to develop complex, effective new devices. The list goes on.

1.5.2 Engineering Vis-à-vis Science

The American Engineers' Council for Professional Development (ECPD, the predecessor of ABET, the Accreditation Board for Engineering and Technology) has defined "engineering" as:

> The creative application of scientific principles to design or develop structures, machines, apparatus, or manufacturing processes, or works utilizing them singly or in combination; or to construct or operate the same with full cognizance of their design; or to forecast their behavior under specific operating conditions; all as respects an intended function, economics of operation or safety to life and property.

Most people have this notion of engineering: reducing scientific concepts, theories, and mathematical representations to practice and applications. The notion that engineering traditionally stands apart from the sciences can again be seen in the departmental and college structure of North American and other universities. Frequently, a college of engineering is separate from the sciences and is considered a "professional school," producing graduates equipped for immediate employment in the traditional sectors of chemical, civil, electrical, and mechanical engineering, as well as more recent fields of biomolecular, environmental, computer, and software engineering. In the sciences, in contrast, graduates serious about practicing as researchers in their profession are invariably oriented toward multiyear Ph.D. programs, which are largely research apprenticeships.

A certain blurring between science and engineering has also occurred with the recognition that "engineering science" is a discernible aspect of engineering, different from practice. This can be seen in the nature of research in engineering schools, and publication of work from many academic engineers in traditionally scientific rather than engineering journals.

1.6 Disciplinary Physics

A common rejoinder to the question "What is physics?" is "It's what physicists do." Through the last centuries, physics was implicitly "not biological." In fact, so separate did life seem to earlier scientists that the question of ultimate explanation in terms of physical principles raged for centuries, as briefly discussed above.

Physics describes the structure, properties, interactions, and transformations of mass–energy in the arena of space-time. This includes

- Unified theory of fundamental forces: gravitational, electromagnetic, strong, and weak.
- Structure and transformation of matter at the level of elementary particles (hadrons/quarks, leptons, photons, etc.): the Standard Model.
- Mechanics, whether classical or quantum mechanical, of the motion of two or more objects under the influence of other objects and fields.
- Average behavior and distributions of ensembles of particles: statistical mechanics/thermodynamics.
- Applications of fundamental theories to particular systems, including nuclei, atoms, molecules, macromolecules, hard and soft solids, liquids, gases, plasmas, ballistics, celestial mechanics, optics, and more.
- Astrophysics, the application of physical principles to the interpretation of astronomical data on stars, galaxies, and other celestial objects.
- Cosmology, the origin, structure, and evolution of the universe (or multiverse).

1.6.1 Fundamental Forces

Physics to-date has recognized four fundamental forces: gravitational, electromagnetic, strong, and weak. Gravitational and electromagnetic forces share an inverse square distance law between interacting particles and proportionality to the product of masses and charges, respectively. The forces are mediated by gravitons and photons, respectively. The gravitational force is exclusively attractive and cannot be "canceled" out. As such, its reach is cosmic and it is responsible for the formation of planets, solar systems, galaxies, and galactic clusters. The electromagnetic force is responsible for the binding of electrons to nuclei to form atoms and molecules. It is hence the most important of the fundamental forces in chemical and biological processes. The electromagnetic force is enormously stronger than gravitation; the electrostatic attraction between electron and proton is on the order of 2.3×10^{39} times greater than that of their mutual gravitational attraction, and hence the latter force has no discernible role in atomic and molecular structure. On the other hand, because positive and negative charges can neutralize or "cancel" electromagnetic effects, and there is a general, overall electroneutrality of objects, the electromagnetic force does not normally compete with gravity on celestial and cosmic scales. In fact, barring specific instances such as atmospheric accumulation of charge leading to lightning discharge, possible net charge in the ionosphere, and other effects, the Earth is essentially electroneutral everywhere, although there is debate over whether and how much net charge the Earth may have. Compared to the number of elementary charges in and on the earth, any net charge would be an exceedingly tiny fraction of this number. You can easily compute how little net charge it would take on the Earth and, say, Mars to rip each other out of their gravitational orbits about the sun.

The electrostatic attraction between the atomic nucleus and atomic electrons is responsible for the atom's existence. Size scales for atoms and small molecules are on the order of 0.1 nm, and the energy levels for electrons are on the order of 1–10 eV. The Pauli exclusion principle for fermions, electrons in the atomic case, forbids electrons from sharing the same set of quantum numbers. This results in electrons pairing with opposite spins, yielding the atomic energy level structure of the periodic table, $1s^2 2s^2 2p^6$.... Without the exclusion principle electrons would merely fall into the 1s energy ground state for all elements and chemistry as we know it would not exist.

The strong force, or *strong interaction*, mediated by *gluons*, whose range is on the order of 10^{-15} m, binds *quarks* together into the *baryons* called neutrons and protons, also termed *nucleons*, as well as a menagerie of more massive, unstable baryons. All free baryons, including the neutron, will decay into protons. A "residual" of the short-range strong force leads to nuclear structure, with binding energies on the order of 8 MeV/nucleon,[17] mediated by mesons. The stabilization of the neutron in nuclei, leads, together with protons, to the existence of the chemical elements. The short-range nature of the strong force puts a limit on the size of stable nuclei. Bismuth, atomic number 83, is the most massive stable element.[18] All of the isotopes of the next element, Polonium, number 84, are unstable, with relatively short half-lives.

The weak force has an even shorter range than the strong force, on the order of 10^{-18} m. It is responsible for the transformation of many elementary particles into each other. For example, the change of an up quark to a down quark is responsible for beta-decay of the neutron into a proton, with release of an electron and electron anti-neutrino. The force is mediated by the Z and W bosons. This leads to the current picture of the Standard Model.

1.6.2 The Standard Model

There are two major classes of matter; the quarks and the leptons. Each of these classes has particles falling into three generations. All particles have a corresponding *antiparticle*. The photon, and several other electrically neutral particles, such as the Z and Higgs bosons, and neutral mesons are their own antiparticles.

The leptons include the *electron*, the *muon*, and the *tau-lepton*, in increasing order of mass. The electron is the only stable one of these three, and the other two will spontaneously decay into electrons and corresponding *neutrinos*, an electrically neutral particle with extremely low mass. There is a neutrino type for each of these – electron, muon, and tau neutrinos – although the neutrino is found to oscillate between these forms as it propagates through space. Lepton interactions are mediated by photons.

The *hadrons* are composed of quarks. There are three generations of quarks, each with two quark members; the *up and down quarks*, the *strange and charm quarks*, and the *bottom and top quarks*, in increasing order of mass. Baryons are composed of three quarks and, as mentioned, the proton, two up and one down quark (uud), is the only stable one. The higher baryons such as the *sigma particles* and *hyperons*, to name just two, all decay down to the proton, principally via the weak force. The majority of detectable matter in the universe is baryonic. *Mesons* are the other family of hadrons. They are composed of quark/anti-quark pairs and are hence unstable.

17 MeV = megaelectron volt, that is, 10^6 eV.

18 Its isotope ^{209}Bi has a half-life over 10^{19} years, i.e. much longer than the age of the known universe.

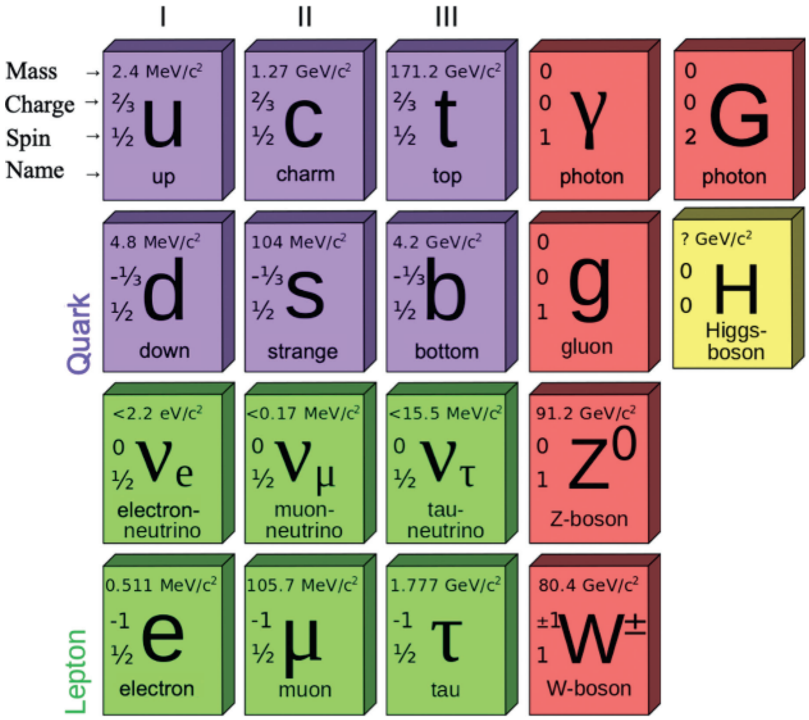

Figure 1.4 The Standard Model. (Wikimedia Commons (2013) / Licensed under CC BY-SA 3.0).

All the mediating (force-carrying) particles are *bosons*. Figure 1.4 summarizes the basic particles of the standard model. The *Higgs boson* responsible for the specific masses of particles in the standard model has recently been detected at CERN's Large Hadron Collider. The mass of the Higgs Boson is around 125 GeV/c^2 .

A very simplistic view on elementary particle stability is to consider Einstein's iconic equation $E_0 = m_0c^2$, which assigns a rest mass energy, E_0, to any given particle of rest mass m_0. Given nature's propensity to seek the lowest energy level, this drives particles in a given family to decay toward the less massive particles in their family. The proton is the least massive baryon and the only stable form. Even the neutron, which is only slightly more massive than the proton, will decay into a proton (and electron and electron antineutrino) when removed from a stable nucleus, with a half-life of about ten minutes. Similarly, the electron is the only stable lepton. The muon is a couple hundred times more massive than an electron, and decays to an electron (and electron anti-neutrino and muon neutrino) in its own reference frame with a half-life of a couple microseconds.

The elementary particles are locked into the structure of atoms and molecules, and hence into the fabric of the living state. In this sense, the properties of the living state could be "reduced" through a long chain of time and length scales to the properties and interactions of elementary particles, but this would likely be unrevealing of the living state properties themselves. Once the elementary particle properties are locked into atoms and molecules, then chemistry, and hence biochemistry and the living state, no longer need any recourse to their detailed properties. This is analogous to the construction of a house; it is unnecessary to know the microscopic details of wood fiber in beams or of the atomic metallic lattice structure in nails and screws in order to produce a macroscopic house whose shape, properties, and functions are unrelated to these microscopic and atomic details.

The reverse challenge is even more extreme and virtually impossible: Could the existence of the living state and its properties be induced starting from the properties of elementary particles? From the information point of view, this is impossible, because the amount of information contained in the standard model is far less than the information contained in even the simplest living organism. As discussed in Chapter 4.19, complete information can only flow from a system with higher information to lower information, and not vice versa. *Crick's Central Dogma*, presented in Chapter 4.19.4 is an example of this; complete information can only flow from DNA and RNA (with a 64-letter alphabet from the genetic code) to proteins (with only 20 amino acids that can be specified), but not vice versa.

1.6.3 Cosmology

The sky is the daily bread of the eyes.

Ralph Waldo Emerson

Before discussing conjectures on the prebiotic origins of life (Chapter 15.1) one might ask about the origins of the known universe itself. While much progress in understanding has been made in cosmology there are many daunting mysteries and there is no definitive cosmology that successfully deals with many of the open issues. When one considers that it is less than 400 years since Galileo was found heretical in his support of the solar-centered Copernican system, which ran afoul of then-prevailing religious dogma in much of Europe, the results of modern astrophysics have catapulted human understanding of the cosmos far beyond anything conceivable just a short time ago.

It was long surmised that stars were similar to our Sun, and such was suggested to some by the work of Copernicus. Giordano Bruno (Italy, 1548–1600) and René Descartes were likely the first to assert that the Sun is just one of countless stars. By the eighteenth century, there was strong astronomical evidence to support this, and the discovery of nebulae, star clusters, and other celestial objects eventually led to the idea of galaxies, which became firmly established in the late nineteenth century. At that time, a "steady state universe" was conceived, in which stars and planets could be born and die, but in which an overall average state was maintained. This notion was so ingrained that Einstein famously added a "cosmological term" to his gravitational equations in order to ensure a steady universe that neither expanded nor contracted. When the Astronomer Edwin Hubble (United States, 1889–1953) discovered, via the red-shift of light from distant galaxies, that the universe was expanding, Einstein declared that the cosmological term might have been his greatest blunder. In light of recent astrophysical evidence of the outward acceleration of the known universe, it might not have been a blunder.

1.6.3.1 The Big Bang Theory

In the early twentieth century, Hubble and others, using the best telescopes and spectrometers of the day, found that spectral lines from hydrogen and other elements emanating from galaxies were *red-shifted*.[19] This was found to be generally the case and that the farther away the galaxy, the greater the redshift. Einstein's relativistic Doppler shift equation[20] could be used to compute the speed of galactic recession with respect to earthbound observers, and it was found, within the limits of celestial distance measurements available, that the speed of recession was proportional to the distance of the galaxy away from earth. The constant of proportionality is *Hubble's constant*, and its reciprocal is the age of the known universe from the time of the presumed Big Bang; approximately 13.8 billion years.

The term "Big Bang" was coined sardonically by astronomer Fred Hoyle (England, 1915–2001), who maintained the Steady State universe to be a more accurate cosmology. The evidence for the Big Bang comes from several sources; the Hubble redshift just mentioned, the ubiquitous *2.7 K cosmic microwave background*, the abundance of light nuclei, and the formation and structure of galaxies. It is also linked to several unsolved quandaries; because several leading theories predict equal abundances of baryonic matter and antimatter, there is no compelling reason that the visible universe is now dominated by matter. Then there is *dark matter*, thought to be responsible for celestial motion for which the quantity of visible matter is insufficient. Visible baryonic matter is thought to be only a small amount of the actual matter, the rest being dark. It is not known what form(s) the dark matter may exist in, though there are several hypotheses, e.g. MACHOS (massively compact halo objects, such as nonluminous brown dwarf stars), WIMPS (weakly interacting massive particles, which carry large mass but don't interact with other matter except gravitationally), possible huge amount of neutrino mass, even though the rest mass energy of the neutrino is thought to be less than 1 eV, *axions*, and several other conjectures. Finally, *dark energy* is conjectured to be behind the observed acceleration of the expanding universe. The nature of dark energy is also currently unknown. The latest estimates are that 68% of the universe is dark energy, 27% dark matter, and only 5% "normal matter." If these estimates are even approximately true, it suggests that we know pitifully little about our universe. On the other hand, the existence of dark energy and matter may result from flaws in our current best theories, especially gravitational theory.

Further uncertainties include the notion that the ongoing expansion of space leads to a cosmic horizon[21], in which we would perceive ever less and less of the visible universe around us, leading to a sort of "island universe." Another dimension to this is the possibility of the "multi-verse," that many, perhaps an uncountable number of universes exist and we are the inhabitants of just one of them, i.e. the big bang may not be so "big" after all. Because there is no current means of experimentally testing the multiverse idea, it is often treated as metaphysical, even though its proponents can elaborate thought-provoking ideas, theories, and equations.

With these caveats, a thumbnail sketch of the Big Bang follows. Extrapolation of the measured expansion of the known universe implies an initial gravitational singularity, a point at which density and temperature are infinite, around 13.8 billion years ago. Taken less literally, it may have been extreme but finite density and temperature over a small region. In either case, nobody knows where this mass/energy may have come from, but the idea is that it exploded and then rapidly expanded,

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19 Red-shifted light is measured to have a longer wavelength than is measured in the rest-frame of the light source.

20 The Doppler shift derived in special relativity does not take account of the expansion of space-time itself. While reasonably accurate at explaining redshifts from galaxies at short cosmological distances, it begins to diverge at large distance from the *cosmological redshift*, which uses general relativity and the expansion of spacetime.

21 Cosmic horizon is defined as 'the maximum distance from which light from particles could have traveled to the observer in the age of the universe. It represents the boundary between the observable and the unobservable regions of the universe, so its distance at the present epoch defines the size of the observable universe.

reducing density and temperature as the matter/energy expanded outwards, *creating* space in the process. All four forces – gravitational, electromagnetic, electroweak, and strong nuclear – were unified initially, but at around 10^{-43} s into the expansion, the temperature reduced enough for gravity to split off from the other forces. It is postulated that at around 10^{-37} s, there was *cosmic inflation*, in which space, the universe, expanded rapidly at greater than light speeds.[22] The theory then posits that quantum fluctuations in density, due to the Heisenberg uncertainty principle, were quickly magnified to macroscopic dimensions due to this inflation, setting the stage for local inhomogeneity in the macro-universe, and the subsequent formation of galaxies, and the stars within them. During this period the strong nuclear force split off from the electromagnetic and weak nuclear forces. The universe's volume may have expanded by a factor of 10^{78}, or more, during this inflationary period.

Inflation stopped after about 10^{-32} s, and the universe was still exceedingly hot and could sustain *quark-gluon plasmas*. These latter occur when the temperature reaches the *Hagedorn temperature* of about 2×10^{12} K. Baryons, especially protons and neutrons have so much internal energy at this temperature that they essentially "boil" and "evaporate" into a plasma of their constituent quarks and mediating particles, the gluons. There was a huge density of photons which scattered strongly from all the free, charged particles. Atoms did not yet exist. Only as the universe continued to expand and the temperature dropped sufficiently was it possible for a proton to combine with a neutron to form a deuteron, the deuterium nucleus, and for two neutrons and a proton to form a triton, the tritium nucleus, and for two protons and two neutrons to form the alpha particle, the helium nucleus. The measured abundance of these and other light isotopes add support to the Big Bang theory. They are thought to be the only nuclei formed outside of nucleosynthesis inside stars. Nonetheless, the majority of the baryonic matter continued to be in the form of protons.

As expansion and cooling continued electrons could be captured by the protons to form hydrogen atoms, and the light nuclei formed helium and an isotope of lithium, about 400,000 years after the Big Bang. These neutral atoms are dramatically less efficient at scattering light than charged particles[23] so that, with the formation of atoms, the universe became "transparent." The photons from the previous epoch, no longer scattered and absorbed so intensely as before the formation of atoms, expanded with the rest of the universe as a remnant of the Big Bang. Due to the *cosmological Doppler redshift* this remnant's wavelength lengthened extremely and became the *cosmic microwave background radiation*, discovered serendipitously in 1964 at Bell Telephone Laboratories by Robert Wilson (United States, 1936–) and Arno Penzias (Germany/United States, 1933–). This added major strength to the Big Bang theory. In 1989, the United States National Aeronautics and Space Administration (NASA) launched the Cosmic Background Explorer (COBE), which confirmed that the background radiation conformed within experimental error to a perfect black body at $T = 2.7$ K. Additionally, slight anisotropies in the radiation were found throughout the entire cosmic field mapped, which strengthened the idea that the rapid expansion of space due to inflation had magnified primordial quantum fluctuations.

Once hydrogen atoms were formed, "the rest is history." The universe continued to expand and the gas density inhomogeneities became nucleation sites for proto-galaxies, where portions of the pervasive hydrogen gas condensed locally under gravitation. Within the protogalaxies, further anisotropies caused the gravitational condensation of hydrogen gas into proto-stars. In a protostar, the gravitational collapse led to heating of the gas, reaching the minimum temperature for nuclear fusion reactions to begin at above 10^7 K, at which point, the collapsing hydrogen mass lit up with thermal radiation and became a star. There is a fascinating ancestry to stars. Those formed early began to generate heavy elements in their exceedingly hot cores. When these stars exploded they sent heavy elements throughout their galaxy, causing "second generation stars," such as our Sun, to have small amounts of heavier nuclei, in addition to the preponderant hydrogen and helium. These heavy elements ejected by the massive stars may also have led to the formation of "iron" planets, such as the Earth, as well as gas giants, such as Jupiter, and ice giants, such as Neptune (see Chapter 15.5).

While cosmology is still a speculative and unsettled subject, the results of astrophysics are very well established. Hence, such celestial issues as the life cycle of stars and their various fates as red giants, white dwarves, neutron stars, and black holes are well described theoretically and backed by massive and increasing observational data. *Gravitational lensing*, detection of extrasolar planets, origins of *quasars*,[24] and more, are active and substantial areas of research.

22 Special Relativity shows why matter cannot exceed the speed of light in "flat" spacetime. But if space itself is growing – think of a spatial grid expanding equally in all directions – its rate of growth is unrelated to the relative motion of matter through the grid, i.e. particles at rest in the grid will move away from each other due to the grid's expansion, which is not matter and not constrained by the speed of light.

23 Think of the charged particles as "mirrors," analogous to free electrons in a metal, and the neutral atoms as a gas of dielectric particles. Light reflects intensely in every which direction as it bounces off the charged particles, but scatters weakly from the gas, and mostly just passes through the gas undeflected.

24 Quasars=quasi stellar sources of radiation, are supermassive black holes presumed to be *galactic nuclei*. Gas pulled into a quasar accelerates and emits enormous amounts of electromagnetic radiation.

1.7 Are Currently Known Physical Laws Adequate for Understanding Living State Phenomena?

There are currently no known biological phenomena that disobey physical laws and principles. However, this is not to say that there are not necessarily other physical principles, as yet undiscovered. For example, an automobile is built entirely on physical principles, but knowledge of all those principles does not allow one to deduce the existence of an automobile. This is not to introduce an "intelligent design" substrate into the discussion, and this book will remain uninvolved concerning current debates and controversies in this area. But the automobile analogy at least leaves the door open to the likelihood that we have not yet discovered all the principles involved in the self-organization of matter into the living state. After all, the history of science is replete with incidences when people thought that all the major principles were known, only to be entirely controverted by new insights and principles, e.g. the famous fall from ultimate glory of nineteenth-century physical science, with its great achievements in electromagnetism, mechanics, and thermodynamics, was a particularly poignant era of hubris, which was humbled by special and general relativity, quantum mechanics, and quantum statistical physics. Nonlinearity in systems, often previously avoided as intractable, has been shown to lead both to chaotic behavior, as well as to the formation of far-from-equilibrium structures.

Concerning the issue of whether physical laws, whether known or not yet known, are an adequate basis for understanding the living state, many ventured that biology has its own set of principles. This was a long-held view, often termed *vitalism*, and there were many attempts to find the "spark of life," or the "élan vital." It was often assumed that this distinct "life force" is foreign or even contradictory to physics. Niels Bohr in his reflections on the nature of life extended his notion of wave/particle complementarity to life, conjecturing that the principles of life stand in complementary relationship to those of physics. Bohr incorporated a "yin and yang" symbol into his coat of arms to show the central meaning that complementarity had for him. Vitalism reigned for millennia until certain facts began to reveal that biomolecules and biological processes obey physical laws.

Luigi Galvani appears to be the first to discover bioelectricity while producing kicking motion of dead frog legs with electrical currents. He initially thought of it as "animal electricity" and that living tissue was needed to transmit electricity. Volta, a rival, soon demonstrated that metals and other inorganic substances could conduct electricity and so the distinction between "inanimate" electricity and "bioelectricity" disappeared.

It was widely believed that the molecules of life were distinct from those found in nonliving entities. As mentioned, in 1828 Friedrich Wöhler found that urea, a byproduct of living organisms, could be synthesized without the use of any biological precursor molecules, using silver cyanate and ammonium chloride.

Spontaneous generation was first formulated by Aristotle and held that life could arise spontaneously where a suitable nutrient source existed, e.g. maggots could appear spontaneously around rotted food. Louis Pasteur (France, 1822–1895) disproved this idea in his famous sterilization experiments. Yet Pasteur himself held that fermentation was a "vital function" that could only occur via living organisms. Eduard Buchner (Germany, 1860–1917) found that sugar could be fermented from yeast extract free of any living cells. Numerous abiological synthetic routes to end products of fermentation have since been found. Yet, two more examples of absolute concepts are overturned by careful experimentation and analysis.

In 1967, Francis Crick, the codiscoverer of the structure of DNA, stated "And so to those of you who may be vitalists I would make this prophecy: what everyone believed yesterday, and you believe today, only cranks will believe tomorrow."[25]

The prevailing "mainstream" scientific view is that biological and biochemical phenomena can be traced to underlying physical laws. Another controversy, of course, is whether we currently understand physical laws well enough to describe biology. One school of thought holds that quantum mechanics and relativity are final theories which ultimately span all possible physical phenomena, and hence it is only a matter of finding the right ways of applying them in order to explain any physically perceivable phenomenon. Another school of thought exists that says that throughout human history new theories have always arisen that have shrunken or falsified existing theories and that to claim that we have finally reached conclusive, all-encompassing theories is to merely continue the vanity of bygone eras when similar pronouncements of universality were made concerning the state of erstwhile, often debunked knowledge.

The view that biology is ultimately explainable by physics does not imply that biology "reduces" to physics, only that the hierarchy of complex phenomena are based on physical principles. Still, are biological, and hence physical laws an adequate basis for understanding the phenomenon of consciousness? Whereas vitalism is almost extinct as a school of thought there is still at least philosophical controversy about the reducibility of consciousness to physical mechanisms,

25 Francis Crick In 'The Prospect Before Us', of Molecules and Men (1969), 99.

and to whether we do or do not have free will. Some of the unsettled issues of biophysics of consciousness are introduced in Chapter 15.3.

Neurological activity, electrochemical processes, is exhibited in all activities of the brain, including emotions, thought, etc. Hence, it is accepted that "conscious phenomena," such as emotions and thinking, depend on neurophysiology for their existence, and that consciousness as we know it ceases when the corresponding neurophysiological processes cease.

What is still controversial is whether or not the neurophysiological processes which are necessary for consciousness are sufficient to explain what consciousness actually is. For example, are the physiological processes merely a projection onto the subspace of spacetime/matter for a process occurring in a greater space which would have corresponding projections into other spaces besides spacetime that would yield different characterizations of consciousness? The projection of any 3D shape onto a single axis is a line, but no one would declare that the line *is* the 3D object, or to be a complete description of it. At this point, such conjectures are metaphysical because there is currently no knowledge of what the other dimensions of consciousness might be nor how they could be measured. "Holistic" approaches might maintain that the other dimensions of consciousness can in fact be experienced by proper meditative and other self-regulating approaches.

Finally, no matter how triumphant anyone proclaims evolutionary or any other reigning theory to be, we still run into the hard fact that nobody knows the ultimate origin of the universe, of matter/energy, of the laws that imbue it, or of what, if anything, lies beyond our own particular physically detectable universe.

This is also where "modern science" as it is currently practiced diverges from its earlier forms of "natural philosophy," in which scientists and mathematicians (e.g. Newton, Descartes, Pascal) expounded on their philosophic and even religious views in addition to their concrete scientific advances. Modern science seeks to discover underlying principles in nature, to formulate them mathematically or symbolically, and to use them for greater unified understanding of phenomena and for technological manipulation. But science is not required to answer where the principles come from, or if there is any "meaning" to them beyond what they represent for understanding and manipulation. A practicing scientist can successfully apply the principles of quantum mechanics and statistical mechanics, without ever questioning whence they come or if there is any "intent" in these principles.

Extremalization principles, such as Fermat's principle, and Lagrangian and Hamiltonian mechanics, provide tremendously successful scientific workhorses, as does minimization of Gibbs free energy in chemistry. It has long been debated whether these principles imply an "intent" of nature or are just "the way things are" with no additional explanations needed. Moreau de Maupertuis (France/Switzerland, 1698–1759), who formulated a least action principle actually interpreted it theologically, as the "wisdom of God" in following the "thriftiest" of paths in nature's processes.

The applications of least action principles are vast indeed, encompassing huge swaths of optics, mechanics, chemistry, biophysics, and more. And the sweep of these principles is stunning. Biochemistry makes excellent predictions based on them. Couple the exclusion principle for fermions to the least energy principle and one arrives at the notion of electronic structure in the periodic table, the seat of all chemistry. Apply least energy and exclusion to electrons in a metal and you get enormously high electron speeds, even at absolute zero. Take away exclusion from this and you get things like superconductivity and superfluidity. Add the directionality of superposed quantum mechanical electron states and you get the self-organizational principles involved in crystallization of substances. One wonders what as yet undiscovered self-organizational principles may exist that insert into the least energy and other principles that may impel biological self-organization and evolution.

1.8 Unifying Characteristics of the Living State

There was a time when it was thought that life could be characterized by a few simple qualitative attributes, such as reproduction, irritability, consumption and excretion, etc. Biophysics tends to define these and other living state characteristics based on physical principles. Despite the vast variety and extraordinary complexity of living organisms, there are nonetheless unifying properties common to all life forms. Some of these are:

- Proteins are made of 20 main amino acids, all of which have L-chirality, except glycine, which is achiral (Chapter 3.1).
- All DNA is made of four nucleotides (Chapter 3.2). Virtually unlimited combinations are possible.
- The nucleotide adenosine triphoshpate (ATP) is a universal source of free energy. This may be derived from sources such as sunlight, inorganic chemical reactions, or use of organic materials produced by other organisms.
- All organisms reproduce copies or new versions of themselves.
- The genetic code is carried by DNA in all organisms (some viruses use RNA), and, with few variations, mediates the accumulation and transmission of biological information; all organisms produce proteins using the genetic code.

- All biomolecules and processes are the result of evolutionary adaptation of organisms to their environment, primarily through natural selection.
- Biochemical processes and structures are defined by very precise compositions, conformations and interactions. Life shows extreme sensitivity to small chemical differences and minor changes can have drastic biological effects, e.g. methanol is toxic, ethanol far less so.
- Life is stereoselective and can process only a specific chirality type for given families of biomolecules.
- Organisms are compartmentalized by membranes or other structures that mediate matter and energy exchange with the environment.
- The biological milieu is aqueous; most biopolymers are charged for solubility, and are *polyelectrolytes*.
- Biological molecules are built of light atoms: C, H, O, N, P, S ions Na^+, K^+, Ca^{2+}, Mg^{2+}, and a small amount of heavier atoms, such as Fe, Co, and Mn.
- Life represents far from equilibrium, open systems. Equilibrium = Death.
- Life entails highly organized structures that are maintained far from equilibrium due to a flow of energy from a source (e.g. sunlight or food), through the organism, which maintains its organization and excretes waste heat and chemical byproducts.
- The highly organized state of life is due to accumulated, high information content in genetic material.
- Living state processes involve low energies, typically in the 0.01–5 eV range.
- Living organisms are self-regulating and feedback controlled.
- Reproduction involves conservation and transmission of accumulated information.
- Large numbers of molecules are involved ($>10^9$ even in the smallest bacterium). Large numbers act as a buffer against random thermal fluctuations.
- Life involves great material heterogeneity; there is a very wide variety of molecules involved in life, including many types of small molecules and an amazing sweep of biopolymers.
- Nonergodicity: In statistical mechanics the averages pertaining to a large ensemble of systems will yield the same values as the long-term average of a single particle's trajectory through phase space (Ergodic theorem). As an example of nonergodicity; the response of a collection of neurons in a neural structure will not yield the same result as a single neuron stimulated many times.

The so-called *central dogma of molecular biology* should be mentioned.[26] This principle states that information flows in a single direction from DNA to proteins, mediated by RNA, but the reverse does not occur; information does not pass back from proteins to DNA.[27]

Another important observation is that developmental strategies are conserved in evolution, e.g. human hand, bat wing, bird wing. Dinosaur bone structural motifs are similar to modern bones.

1.9 Summary

Scientific discovery over the ages has been a growing activity, launched in antiquity and burgeoning in modern times. Its path has been strewn with countless wrong turns and misconceptions, but it corrects itself through experimental verification and new, more comprehensive theories which subsume or replace older ones. Everything in science can be questioned, although some things more than others, e.g. the certainty of the electron mass, charge, and spin versus the uncertainty of precisely how a huge number of interacting components, effects, and principles affect the Earth's climate. Disciplinary specialization was needed over the past centuries because the growing depth of knowledge in all fields required concentration on a huge amount of information in any given field to make progress. Biophysics represents one of the areas which requires a multidisciplinary approach, where the disparate strands of biology, physics, chemistry, physiology, and many others, need be woven together to approach the mind-boggling complexities of the living state. The living state is highly organized, maybe even optimized in many instances, and it is not known yet whether this order arises from purely random events, out of nonlinear chaos, or from informational and self-organizational principles of matter we haven't yet discovered ... and perhaps may never discover.

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26 The use of the word "dogma" in this is unfortunate, since it implies something that is incontrovertible and provided by a higher authority. While the principle is well established, it is risky in any field of science to declare something "incontrovertible," since the essence of science is falsifiability; all laws and principles in science are always open to upset and modification, should there be evidence to falsify or reduce the sweep of a law.

27 *Retroviruses* use the enzyme *reverse transcriptase*, which turns its RNA into DNA, which becomes inserted and active in the host's genome via the enzyme *integrase*.

For this author, science is not a belief system. I don't "believe" in science, physics, evolution, the Big Bang. Science is just the best map currently available to make sense of the bewildering phenomena we experience and are a part of. But it does not contain the central element necessary for an ideological or religious belief system, which posit unquestionable, untestable dogma and concepts as their basis. If what was considered to be a "law of science" is found to actually not be universal, scientists do not typically murder the discoverers, commit suicide, or reject the entire scientific method. Rather, they pour heavy skepticism on the new findings and work exhaustively to test their experimental veracity, and then just move with excitement to the next phase of discovery.

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Problems: Review of Basic Physics

These elementary problems are diagnostic in nature. They are a reminder of the type of physics problems you will have solved in earlier courses.

1 A singly ionized CH_4 molecule in a vacuum is accelerated across a potential of 5×10^4 V.
  a) Compute the time it takes to traverse a 50 cm straight line path after exiting the acceleration stage.
  b) The ion enters a uniform magnetic field B, at right angles in which it undergoes a circular orbit of radius $R = 5$cm. Compute the magnitude of the magnetic field.
  c) If the ion is allowed to continue to circulate in the above orbit, find the frequency (Hz) and angular frequency (radians/s) of the orbit.
  d) If the ion enters the B field at 45° to a B field of 3 T, find the radius of its orbit.
  e) Describe the trajectory of the ion in part (e).

2 The energy levels in a hydrogen atom are given by

$$E_n = -\frac{13.6(\text{eV})}{n^2}$$

a) Find the wavelength of light emitted when an electron makes a transition from $n = 3$ to $n = 1$.
b) Find the fraction of H atoms in the $n = 2$ level at $T = 300$ K.
c) Consider the emission spectrum of a gas consisting of H atoms and H ions, and an H-atom gas at room temperature through which a light containing continuous ultraviolet and visible wavelengths shines. Does the emission spectrum of the former have more, less, or the same number of lines as the absorption spectrum of the latter? Explain.

3 a) A proton is in a 2-T magnetic field. Find the frequency of electromagnetic radiation that will drive it between the spin-up and spin-down states in this field. (This is NMR.)
b) Consider an electron in the same field. Find the frequency of electromagnetic radiation that will drive it between the spin-up and spin-down states in this field. (This is electron spin resonance, ESR.)

4 The spacing between atoms in a certain metal crystal is $d = 0.12$ nm. If X-rays incident at 45° to the normal to the face of the crystal reflect and create a first-order maximum ($m = 1$), what is the energy of the X-rays?

5 Say the Earth and Mars have equal and opposite net charge, what net charge at their distance of closest approach would be enough to overcome the gravitational attraction between the Earth and the Sun?

6 Particles of α-, β-, and γ-radiation all have energy of 700 keV and enter a uniform magnetic field of 3 T. Find the speed of each particle and make a diagram to show the trajectory of each when in the B field.

7 ${}_6C^{14}$ has a half-life of 5730 years. In radioactive dating, the standard used is that there are 14 disintegrations per minute per gram of "fresh" carbon (i.e. carbon on the earth's surface participating in the carbon cycle, and not buried in the earth).
a) Compute the fraction of ${}_6C^{14}$ isotopes in fresh carbon according to this disintegration standard
b) If a 300-g archeological (buried) carbon specimen is unearthed and found to yield 1200 disintegrations per second, estimate the age of the specimen.

8 Air rushes past an airfoil of 30 m^2, going over the airfoil at 150 m/s and below the airfoil at 80 m/s. Find the maximum load this airfoil can lift up.

9 An electron and positron moving directly toward each other have 800 keV kinetic energy in the lab frame just before they annihilate. Two gamma rays are produced in the annihilation. Compute the energy of each.