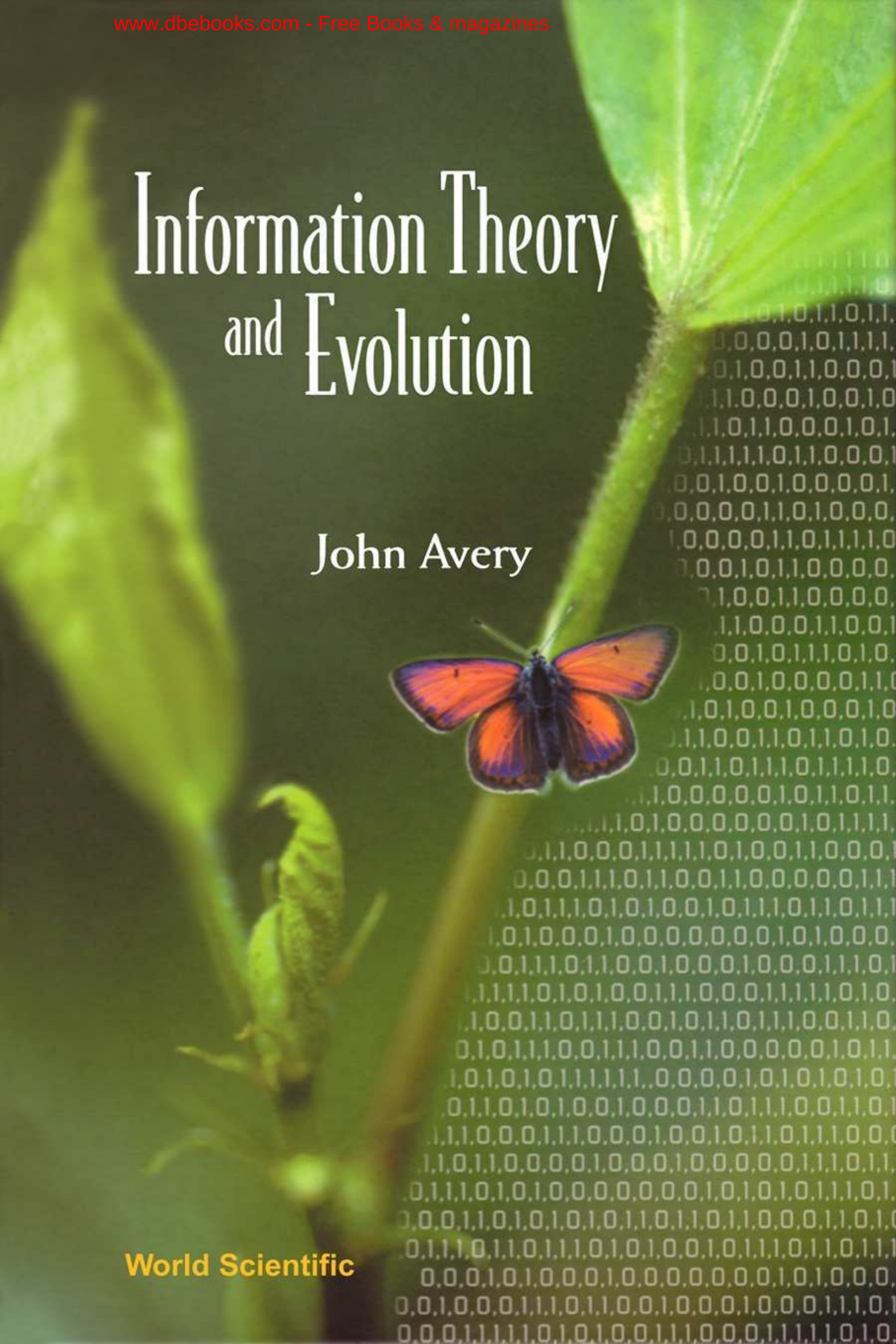

Information Theory and Evolution

John Avery

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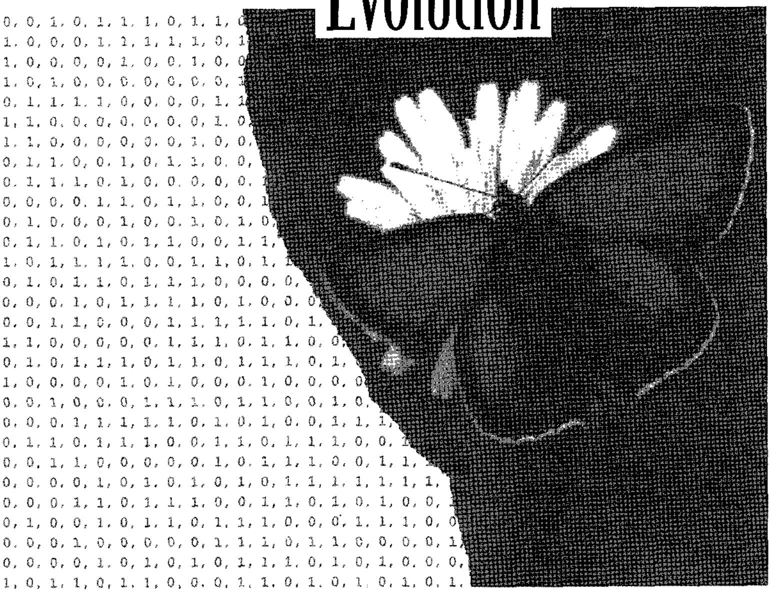

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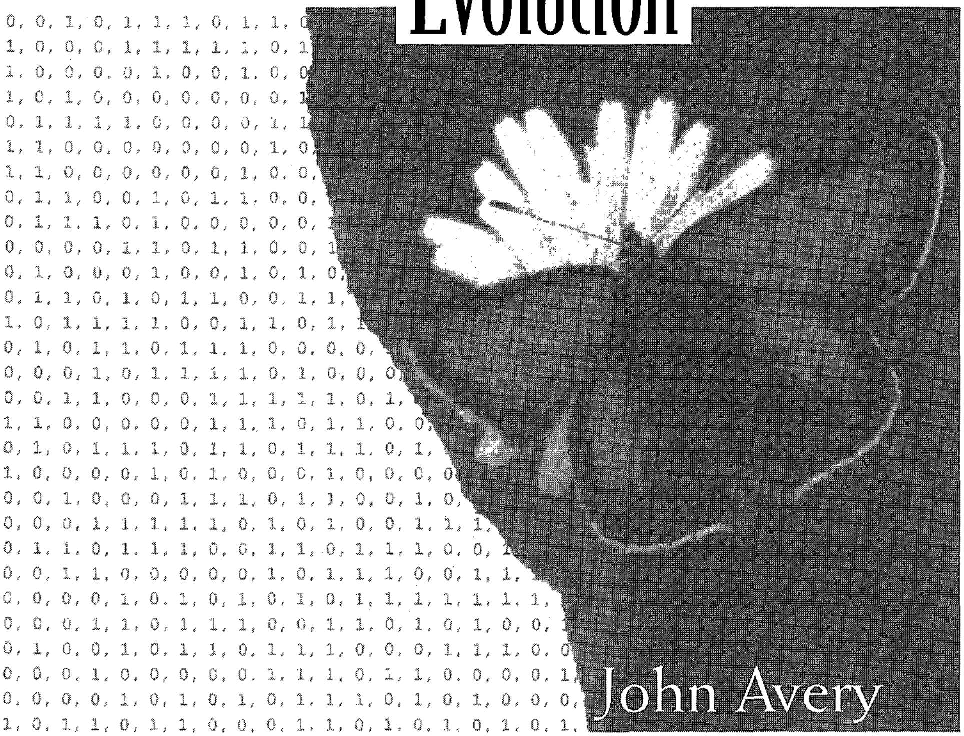

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For James, Larry, Cindy, Anita, and Luis

Preface

The aim of this book is to discuss the phenomenon of life, including its origin and evolution (and also including human cultural evolution) against the background of thermodynamics, statistical mechanics and information theory. The second law of thermodynamics states that the entropy (disorder) of the universe always increases. The seeming contradiction between the second law of thermodynamics and the high degree of order and complexity produced by living organisms will be a central theme of the book. This apparent contradiction has its resolution in the information content of the Gibbs free energy which is constantly entering the biosphere from outside sources, as will be discussed in detail in Chapter 4.

The book begins with a sketch of the history of evolutionary thought and research not only during Charles Darwin's lifetime, but also before and after him. Among the pioneers of evolution whose work will be discussed are Aristotle, Condorcet, Linnæus, Erasmus Darwin, Lamarck, and Lyell. They laid the foundations upon which Charles Darwin built his theory.

After Charles Darwin's death in 1882, the theory of evolution continued to develop and continued to be strengthened by newly discovered facts. Modern molecular biology and DNA technology have allowed us to construct evolutionary family trees in a far more precise way than Darwin and his contemporaries could do on the basis of morphology. Data from comparative sequencing of macromolecules have, on the whole, confirmed the 19th century picture of evolution; but they have also supplied much knowledge which was not available to the early pioneers of evolutionary theory.

Darwin visualized evolution as taking place through natural selection acting on small inheritable variations in the individuals of a species; but we now know that variations can sometimes be sudden and large - through mutations of the type studied by De Vries and Muller, or through the still more drastic mechanism of symbiosis and genetic fusion.

Darwin speculated on the origin of life, but he deliberately omitted discussion of this subject from his publications. However, in the last letter which he is known to have dictated and signed, he wrote: "... the principle of life will hereafter be shown to be a part or consequence of some general law." In our own time, researchers such as A.I. Oparin, Herald Urey, Stanley Miller, Melvin Calvin. Sydney Fox, Leslie Orgel, Carl Sagan, Manfred Eigen, Christian de Duve, Erwin Schrödinger, Claude Shannon, and Stuart Kauffman have begun to uncover this general law.

In the picture that has begun to emerge from the work of these researchers, the earth originally had an atmosphere from which molecular oxygen was almost entirely absent. Energy sources, such as undersea hydrothermal vents, ultraviolet light, volcanism, radioactive decay, lightning flashes, and meteoric impacts, converted the molecules of the earth's primitive ocean and atmosphere into amino acids, nucleotides, and other building blocks of living organisms. Energy-rich molecules, such as H_2S, FeS, H_2, phosphate esters, pyrophosphates, thioesters and HCN were also produced. Since no living organisms were present, and since molecular oxygen was absent from the early atmosphere, the energy-rich molecules were not degraded immediately, and they were present in moderate concentrations in the primitive ocean.

One then visualizes an era of "chemical Darwinism", in which autocatalytic systems competed for the supply of precursors and energy-rich molecules. These autocatalytic systems (i.e. systems of molecules which catalysed the synthesis of themselves) can be thought of as the precursors of life. They not only "ate" the energy-rich molecules present in the early ocean; they also reproduced; and they competed with each other in a completely Darwinian way, random variations in the direction of greater efficiency being selected and propagated.

An extremely interesting aspect of the picture just discussed is the special role of the energy-rich molecules. They play a special role because the process of molecular Darwinism at first sight seems to be violating the second law of thermodynamics - creating order out of disorder, when according to the second law, disorder ought to be continually increasing. If we reflect further along these lines, all forms of life seem at first sight to be creating order out of disorder, in violation of the second law.

Living organisms are able to do this because they are not closed systems. If we look at the "fine print" of the second law of thermodynamics, it says that the entropy (or disorder) of the universe always increases - and of course it does. Living organisms produce order within themselves and their immediate environments by creating disorder in the universe as a whole. The degradation of food into waste products is, in fact, the process through which life creates local order at the expense of global disorder. Life builds amazing displays of local order; but meanwhile, the disorder of the larger system increases. The larger system includes the sun, the earth, and the cold dust clouds of interstellar space.

In the hypothetical picture of the origin of life presented above, the "food" molecules are degraded by the autocatalysts in the process of order-creating molecular evolution. In Chapter 4 of the present book, we will focus on the entropy relationships in this process. The statistical mechanics of Maxwell, Boltzmann and Gibbs will be compared with information theory, as developed by Claude Shannon and others. It will be shown that Gibbs free energy carries a content of information and that the "thermodynamic information" obtained by the autocatalysts from the free-energy-rich molecules in the primitive ocean was the source of the order which developed during the process of chemical evolution.

Today, the earth's greatest source of thermodynamic information is the flood of free energy which reaches us in the form of photons from the sun. In Chapter 4, a quantitative relationship will be derived connecting the energy of an absorbed photon and its information content. Readers who wish to skip the mathematics in Chapter 4 may do so without losing the thread of the argument, provided that they are willing to accept on faith the main result of the derivations - the fact that Gibbs free energy contains the thermodynamic form of information.

It seems probable that thermodynamic information derived from free energy was the driving force behind the origin of life. It is today the driving force behind all forms of life - behind the local order which life is able to produce. This is the "general law" which Darwin guessed might someday be shown to underlie the principle of life. All of the information contained in the complex, beautiful, and statistically unlikely structures which are so characteristic of living organisms can be seen as having been distilled from the enormous flood of thermodynamic information which reaches the earth in the form of sunlight.

Where do humans fit into this picture? Like all other forms of life on earth, humans pass information from one generation to the next, coded into the base sequences of their DNA. However, humans have developed a second, highly effective mode of information transmission - language and culture.

Although language and culture are not unique to our species, the extent to which they are developed is unique on earth. Thus humans are distinguished from other species by having two modes of evolutionary change - genetic evolution, symbolized by the long information-containing DNA molecule, and cultural evolution, which might be symbolized by a book or a computer diskette.

If we compare these two modes of evolution, we can see that genetic evolution is very slow, while cultural evolution is extremely rapid - and accelerating. The human genome has changed very little during the last 40,000 years; but during this period, cultural evolution has altered our way of life beyond recognition. Therefore human nature, formed to fit the way of life of our hunter-gatherer ancestors, is not entirely appropriate for our present way of life. For example, human nature seems to contain an element of what might be called "tribalism", which does not fit well with the modern world's instantaneous communications and increasing interdependence.

Not only does the genetic evolution of humans lag behind their cultural evolution, but also cultural evolution itself has a rapidly-moving component and a slowly-moving component which lags behind, creating tensions. As we enter the 21st century, technology is developing with phenomenal speed, while social and political institutions change far more slowly. The disharmony thus created requires study and thought if human society is not to be shaken to pieces by the rapidity of scientific progress.

Interestingly, information technology and biotechnology, the two most rapidly developing fields, are becoming increasingly linked, each finding inspiration in the other. Biologists have studied the mechanism of self-assembly of supramolecular structures such as cell membranes, viruses, chloroplasts and mitochondria. Researchers in the field of nanoscience are now attempting to use this principle of supramolecular organization, observed in biology, to reach a new degree of miniaturization for the switches and memory devices of information technology. Simulated evolution, modelled after biological evolution, has been used to develop new and unorthodox computer hardware and software. Meanwhile, computers and automation are becoming more and more essential to biotechnology; and in fact many universities now have departments devoted to bioinformatics. Chapter 7 will trace the history of information technology, while Chapter 8 will discuss the ways in which it is merging with biotechnology.

The final chapter of the book looks at the future of the new field, bioinformation technology, attempting to predict what it will achieve during the new century, and discussing how these achievements will affect society.

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Contents

Chapter 1

PIONEERS OF EVOLUTIONARY THOUGHT

Aristotle

Aristotle was born in 381 B.C., the son of the court physician of the king of Macedon, and at the age of seventeen he went to Athens to study. He joined Plato's Academy and worked there for twenty years until Plato died. Aristotle then left the Academy, saying that he disapproved of the emphasis on mathematics and theory and the decline of natural science. After serving as tutor for Alexander of Macedon, he founded a school of his own called the Lyceum. At the Lyceum, he built up a collection of manuscripts which resembled the library of a modern university.

Aristotle was a very great organizer of knowledge, and his writings almost form a one-man encyclopedia. His best work was in biology, where he studied and classified more than five hundred animal species, many of which he also dissected. In Aristotle's classification of living things, he shows an awareness of the interrelatedness of species. This interrelatedness was much later used by Darwin as evidence for the theory of evolution. One cannot really say that Aristotle developed a theory of evolution, but he was groping towards the idea. In his history of animals, he writes:

"Nature proceeds little by little from lifeless things to animal life, so that it is impossible to determine either the exact line of demarcation, or on which side of the line an intermediate form should lie. Thus, next after lifeless things in the upward scale comes the plant. Of plants, one will differ from another as to its apparent amount of vitality. In a word, the whole plant kingdom, whilst devoid of life as compared with the animal, is yet endowed with life as compared with other corporeal entities. Indeed, there is observed in plants a continuous scale of ascent towards the animal."

Aristotle's classification of living things, starting at the bottom of the scale and going upward, is as follows: Inanimate matter, lower plants and sponges, higher plants, jellyfish, zoophytes and ascidians, molluscs, insects, jointed shellfish, octopuses and squids, fish and reptiles, whales, land mammals and man. The acuteness of Aristotle's observation and analysis can be seen from the fact that he classified whales and dolphins as mammals (where they belong) rather than as fish (where they superficially seem to belong, and where many ancient writers placed them).

Among Aristotle's biological writings, there appears a statement that clearly foreshadows the principle of natural selection, later independently discovered by Darwin and Wallace and fully developed by Darwin. Aristotle wrote: "Wheresoever, therefore... all parts of one whole happened like as if they were made for something, these were preserved, having been appropriately constituted by an internal spontaneity; and wheresoever things were not thus constituted, they perished, and still perish".

One of Aristotle's important biological studies was his embryological investigation of the developing chick. Ever since his time, the chick has been the classical object for embryological studies. He also studied the four-chambered stomach of the ruminants and the detailed anatomy of the mammalian reproductive system. He used diagrams to illustrate complex anatomical relationships - an important innovation in teaching technique.

Averröes

During the Middle Ages, Aristotle's evolutionary ideas were revived and extended in the writings of the Islamic philosopher Averröes[1], who lived in Spain from 1126 to 1198. His writings had a great influence on western thought. Averröes shocked both his Moslem and his Christian readers by his thoughtful commentaries on the works of Aristotle, in which he maintained that the world was not created at a definite instant, but that it instead evolved over a long period of time, and is still evolving.

Like Aristotle, Averröes seems to have been groping towards the ideas of evolution which were later developed in geology by Lyell and in biology by Darwin and Wallace. Much of the scholastic philosophy written at the University of Paris during the 13th century was aimed at refuting the doctrines of Averröes; but nevertheless, his ideas survived and helped to shape the modern picture of the world.

The mystery of fossils

During the lifetime of Leonardo da Vinci (1452-1519) the existence of fossil shells in the rocks of high mountain ranges was recognized and discussed.

[1] Abul Walid Mahommed Ibn Achmed, Ibn Mahommed Ibn Rosched

"...the shells in Lombardy are at four levels", Leonardo wrote, "and thus it is everywhere, having been made at various times...The stratified stones of the mountains are all layers of clay, deposited one above the other by the various floods of the rivers." Leonardo had no patience with the explanation given by some of his contemporaries, that the shells had been carried to mountain tops by the deluge described in the Bible. "If the shells had been carried by the muddy waters of the deluge", he wrote, "they would have been mixed up, and separated from each other amidst the mud, and not in regular steps and layers." Nor did Leonardo agree with the opinion that the shells somehow grew within the rocks: "Such an opinion cannot exist in a brain of much reason", he wrote, "because here are the years of their growth, numbered on their shells, and there are large and small ones to be seen, which could not have grown without food, and could not have fed without motion...and here they could not move."

Leonardo believed that the fossil shells were once part of living organisms, that they were buried in strata under water, and much later lifted to the tops of mountains by geological upheavals. However his acute observations had little influence on the opinions of his contemporaries because they appear among the 4000 or so pages of notes which he wrote for himself but never published.

It was left to the Danish scientist Niels Stensen (1638-1686) (usually known by his Latinized name, Steno) to independently rediscover and popularize the correct interpretation of fossils and of rock strata. Steno, who had studied medicine at the University of Leiden, was working in Florence, where his anatomical studies attracted the attention of the Grand Duke of Tuscany, Ferdenand II. When an enormous shark was caught by local fishermen, the Duke ordered that its head be brought to Steno for dissection. The Danish anatomist was struck by shape of the shark's teeth, which reminded him of certain curiously shaped stones called *glossopetrae* that were sometimes found embedded in larger rocks. Steno concluded that the similarity of form was not just a coincidence, and that the *glossopetrae* were in fact the teeth of once-living sharks which had become embedded in the muddy sediments at the bottom of the sea and gradually changed to stone. Steno used the corpuscular theory of matter, a forerunner of atomic theory, to explain how the composition of the fossils could have changed while their form remained constant. Steno also formulated a law of strata, which states that in the deposition of layers of sediment, later converted to rock, the oldest layers are at the bottom.

In England, the brilliant and versatile experimental scientist Robert Hooke (1635-1703) added to Steno's correct interpretation of fossils by noticing that some fossil species are not represented by any living counterparts. He concluded that "there have been many other Species of Creatures in former Ages, of which we can find none at present; and that 'tis not unlikely also but that there may be divers new kinds now, which have not been from the beginning."

Similar observations were made by the French naturalist, Georges-Louis Leclerc, Comte de Buffon (1707-1788), who wrote: "We have monuments taken from the bosom of the Earth, especially from the bottom of coal and slate mines, that demonstrate to us that some of the fish and plants that these materials contain do not belong to species currently existing." Buffon's position as keeper of the Jardin du Roi, the French botanical gardins, allowed him time for writing, and while holding this post he produced a 44-volume encyclopedia of natural history. In this enormous, clearly written, and popular work, Buffon challenged the theological doctrines which maintained that all species were created independently, simultaneously and miraculously, 6000 years ago. As evidence that species change, Buffon pointed to vestigial organs, such as the lateral toes of the pig, which may have had a use for the ancestors of the pig. He thought that the donkey might be a degenerate relative of the horse. Buffon believed the earth to be much older than the 6000 years allowed by the Bible, but his estimate, 75,000 years, greatly underestimated the true age of the earth.

The great Scottish geologist James Hutton (1726-1797) had a far more realistic picture of the true age of the earth. Hutton observed that some rocks seemed to have been produced by the compression of sediments laid down under water, while other rocks appeared to have hardened after previous melting. Thus he classified rocks as being either igneous or else sedimentary. He believed the features of the earth to have been produced by the slow action of wind, rain, earthquakes and other forces which can be observed today, and that these forces never acted with greater speed than they do now. This implied that the earth must be immensely old, and Hutton thought its age to be almost infinite. He believed that the forces which turned sea beds into mountain ranges drew their energy from the heat of the earth's molten core. Together with Steno, Hutton is considered to be one of the fathers of modern geology. His uniformitarian principles, and his belief in the great age of the earth were later given wide circulation by Charles Darwin's friend and mentor, Sir Charles Lyell (1797-1875), and they paved the way for Darwin's application of uniformitarianism to biology. At the time of his death, Hutton was working on a theory of biological evolution through natural selection, but his manuscripts on this subject remained unknown until 1946.

Condorcet

Further contributions to the idea of evolution were made by the French mathematician and social philosopher Marie-Jean-Antoine-Nicolas Caritat, Marquis de Condorcet, who was born in 1743. In 1765, when he was barely 22 years old, Condorcet presented an *Essay on the Integral Calculus* to the Academy of Sciences in Paris. The year 1785 saw the publication of Condorcet's highly original mathematical work, *Essai sur l'application de l'analyse à la probabilité des décisions rendues à la pluralité des voix*[2], in which he pioneered the application of the theory of probability to the social sciences. A later, much enlarged, edition of this book extended the applications to games of chance.

Condorcet had also been occupied, since early childhood, with the idea of human perfectibility. He was convinced that the primary duty of every person is to contribute as much as possible to the development of mankind, and that by making such a contribution, one can also achieve the greatest possible personal happiness. When the French Revolution broke out in 1789, he saw it as an unprecedented opportunity to do his part in the cause of progress; and he entered the arena wholeheartedly, eventually becoming President of the Legislative Assembly, and one of the chief authors of the proclamation which declared France to be a republic. Unfortunately, Condercet became a bitter enemy of the powerful revolutionary politician, Robespierre, and he was forced to go into hiding.

Although Robespierre's agents had been unable to arrest him, Condorcet was sentenced to the guillotine *in absentia*. He knew that in all probability he had only a few weeks or months to live; and he began to write his last thoughts, racing against time. Condorcet returned to a project which he had begun in 1772, a history of the progress of human culture, stretching from the remote past to the distant future. Guessing that he would not have time to complete the full-scale work he had once planned, he began a sketch or outline: *Esquisse d'un tableau historique des progrès de l'esprit humain*[3].

In his *Esquisse*, Condorcet enthusiastically endorsed the idea of infinite human perfectibility which was current among the philosophers of the 18th century; and he anticipated many of the evolutionary ideas which Charles Darwin later put forward. He compared humans with animals, and found many common traits. According to Condorcet, animals are able to think, and even to think rationally, although their thoughts are extremely simple compared with those of humans. Condorcet believed that humans

[2] *Essay on the Application of Analysis to the Probability of Decisions Taken According to a Plurality of Votes*

[3] *Sketch of an Historical Picture of the Progress of the Human Spirit*

historically began their existence on the same level as animals and gradually developed to their present state. Since this evolution took place historically, he reasoned, it is probable, or even inevitable, that a similar evolution in the future will bring mankind to a level of physical, mental and moral development which will be as superior to our own present state as we are now superior to animals.

At the beginning of his manuscript, Condorcet stated his belief "that nature has set no bounds on the improvement of human facilities; that the perfectibility of man is really indefinite; and that its progress is henceforth independent of any power to arrest it, and has no limit except the duration of the globe upon which nature has placed us". He stated also that "the moral goodness of man is a necessary result of his organism; and it is, like all his other facilities, capable of indefinite improvement."

Like the other scientists and philosophers of his period, Condorcet accepted the Newtonian idea of an orderly cosmos ruled by natural laws to which there are no exceptions. He asserted that the same natural laws must govern human evolution, since humans are also part of nature. Again and again, Condorcet stressed the fundamental similarity between humans and animals; and he regarded all living things as belonging to the same great family. (It is perhaps this insight which made Condorcet so sensitive to the feelings of animals that he even avoided killing insects.) To explain the present differences between humans and animals, Condorcet maintained, we need only imagine gradual changes, continuing over an extremely long period of time. These long-continued small changes have very slowly improved human mental abilities and social organization, so that now, at the end of an immense interval of time, large differences have appeared between ourselves and lower forms of life.

Condorcet regarded the family as the original social unit; and in *Esquisse* he called attention to the unusually long period of dependency which characterizes the growth and education of human offspring. This prolonged childhood is unique among living beings. It is needed for the high level of mental development of the human species; but it requires a stable family structure to protect the young during their long upbringing. Thus, according to Condorcet, biological evolution brought into existence a moral precept, the sanctity of the family.

Similarly, Condorcet wrote, larger associations of humans would have been impossible without some degree of altruism and sensitivity to the suffering of others incorporated into human behavior, either as instincts or as moral precepts or both; and thus the evolution of organized society entailed the development of sensibility and morality. Unlike Rousseau, Condorcet did not regard humans in organized civilizations as degraded and corrupt compared to "natural" man; instead he saw civilized humans as more developed than their primitive ancestors.

Believing that ignorance and error are responsible for vice, Condorcet discussed what he believed to be the main mistakes of civilization. Among these he named hereditary transmission of power, inequality between men and women, religious bigotry, disease, war, slavery, economic inequality, and the division of humanity into mutually exclusive linguistic groups.

Regarding disease, Condorcet predicted that the progress of medical science would ultimately abolish it. Also, he maintained that since perfectibility (i.e. evolution) operates throughout the biological world, there is no reason why mankind's physical structure might not gradually improve, with the result that human life in the remote future could be greatly prolonged.

Condorcet believed that the intellectual and moral facilities of man are capable of continuous and steady improvement; and he thought that one of the most important results of this improvement would be the abolition of war. As humans become enlightened in the future (he believed) they will recognize war as an atrocious and unnecessary cause of suffering; and as popular governments replace hereditary ones, wars fought for dynastic reasons will disappear. Next to vanish will be wars fought because of conflicting commercial interests. Finally, the introduction of a universal language throughout the world and the construction of perpetual confederations between nations will eliminate, Condorcet predicted, wars based on ethnic rivalries.

With better laws, social and financial inequalities would tend to become leveled. To make the social conditions of the working class more equal to those of the wealthy, Condorcet advocated a system of insurance (either private or governmental) where the savings of workers would be used to provide pensions and to care for widows and orphans. Also, since social inequality is related to inequality of education, Condorcet advocated a system of universal public education supported by the state.

At the end of his *Esquisse*, Condorcet wrote that any person who has contributed to the best of his ability to the progress of mankind becomes immune to personal disaster and suffering. He knows that human progress is inevitable, and can take comfort and courage from his inner picture of the epic march of mankind, through history, towards a better future.

Eventually Condorcet's hiding-place was discovered. He fled in disguise, but was arrested after a few days; and he died soon afterwards in his prison cell. After Condorcet's death the currents of revolutionary politics shifted direction. Robespierre, the leader of the Terror, was himself soon arrested. The execution of Robespierre took place on July 25, 1794, only a few months after the death of Condorcet.

Condorcet's *Esquisse d'un tableau historique des progrès de l'esprit hu-*

main was published posthumously in 1795. In the post-Thermidor reconstruction, the Convention voted funds to have it printed in a large edition and distributed throughout France, thus adopting the *Esquisse* as its official manifesto. This small but prophetic book is the one for which Condorcet is now chiefly remembered. It was destined to establish the form in which the eighteenth-century idea of progress was incorporated into Western thought, and it provoked Robert Malthus to write *An Essay on the Principle of Population*. Condorcet's ideas are important because he considered the genetic evolution of plants and animals and human cultural evolution to be two parts of a single process.

Linnæus

Meanwhile, during the 17th and 18th centuries, naturalists had been gathering information on thousands of species of plants and animals. This huge, undigested heap of information was put into some order by the great Swedish naturalist, Carl von Linné (1707-1778), who is usually called by his Latin name, Carolus Linnæus.

Linnæus was the son of a Swedish pastor. Even as a young boy, he was fond of botany, and after medical studies at Lund, he became a lecturer in botany at the University of Uppsala, near Stockholm. In 1732, the 25-year-old Linnæus was asked by his university to visit Lapland to study the plants in that remote northern region of Sweden.

Linnæus travelled four thousand six hundred miles in Lapland, and he discovered more than a hundred new plant species. In 1735, he published his famous book, *Systema Naturae*, in which he introduced a method for the classification of all living things.

Linnæus not only arranged closely related species into genera, but he also grouped related genera into classes, and related classes into orders. (Later the French naturalist Cuvier (1769-1832) extended this system by grouping related orders into phyla.) Linnæus introduced the binomial nomenclature, still used today, in which each plant or animal is given a name whose second part denotes the species while the first part denotes the genus.

Although he started a line of study which led inevitably to the theory of evolution, Linnæus himself believed that species are immutable. He adhered to the then-conventional view that each species had been independently and miraculously created six thousand years ago, as described in the Book of Genesis.

Linnæus did not attempt to explain why the different species within a genus resemble each other, nor why certain genera are related and can be grouped into classes, etc. It was not until a century later that these resemblances were understood as true family likenesses, so that the resemblance between a cat and a lion came to be understood in terms of their descent from a common ancestor[4].

Erasmus Darwin

Among the ardent admirers of Linnæus was the brilliant physician-poet, Erasmus Darwin (1731-1802), who was considered by Coleridge to have "...a greater range of knowledge than any other man in Europe". He was also the best English physician of his time, and George III wished to have him as his personal doctor. However, Darwin preferred to live in the north of England rather than in London, and he refused the position.

In 1789, Erasmus Darwin published a book called *The Botanic Garden* or *The Loves of the Plants.* It was a book of botany written in verse, and in the preface Darwin stated that his purpose was "...to inlist imagination under the banner of science.." and to call the reader's attention to "the immortal works of the celebrated Swedish naturalist, Linnæus". This book was immensely popular at the time when it was written, but it was later satirized by Pitt's Foreign Minister, Canning, whose book *The Loves of the Triangles* ridiculed Darwin's poetic style.

In 1796 Erasmus Darwin published another book, entitled *Zoonomia,* in which he proposed a theory of evolution similar to that which his grandson, Charles Darwin, was later to make famous. "...When we think over the great changes introduced into various animals", Darwin wrote, "as in horses, which we have exercised for different purposes of strength and swiftness, carrying burthens or in running races; or in dogs, which have been cultivated for strength and courage, as the bull-dog; or for acuteness of his sense of smell, as in the hound and spaniel; or for the swiftness of his feet, as the greyhound; or for his swimming in the water, or for drawing snow-sledges, as the rough-haired dogs of the north... and add to these the great change of shape and color which we daily see produced in smaller animals from our domestication of them, as rabbits or pigeons;... when we revolve in our minds the great similarity of structure which obtains in all the warm-blooded animals, as well as quadrupeds, birds and amphibious animals, as in mankind, from the mouse and the bat to the elephant and whale; we are led to conclude that they have alike been produced from a

[4]Linnæus was to Darwin what Kepler was to Newton. Kepler accurately described the motions of the solar system, but it remained for Newton to explain the underlying dynamical mechanism. Similarly, Linnæus set forth a descriptive "family tree" of living things, but Darwin discovered the dynamic mechanism that underlies the observations.

similar living filament."

"Would it be too bold", Erasmus Darwin asked, "to imagine that in the great length of time since the earth began to exist, perhaps millions of ages before the commencement of the history of mankind - would it be to bold to imagine that all warm-blooded animals have arisen from one living filament?"

Lamarck

In France, Jean Baptiste Pierre Antoine de Monet, Chevalier de Lamarck (1744-1829), contributed importantly to the development of evolutionary ideas. After a period in the French army, from which he was forced to retire because of illness, Lamarck became botanist to the king, and later Professor of Invertebrate Zoology at the Museum of Natural History in Paris.

Lamarck deserves to be called the father of invertebrate zoology. Linnæus had exhausted his energy on the vertebrates, and he had left the invertebrates in disorder. Their classification is largely due to Lamarck: He differentiated the eight-legged arachnids, such as spiders and scorpions, from six-legged insects; he established the category of crustaceans for crabs, lobsters etc.; and he introduced the category of echinoderms for starfish, sea-urchins etc. Between 1785 and 1822, Lamarck published seven huge volumes of a treatise entitled *Natural History of Invertebrates.* However, it is for his book *Zoological Philosophy*, published in 1809, that the Chevalier de Lamarck is chiefly remembered today.

In his *Zoological Philosophy*, Lamarck stated his belief that the species within a genus owe their similarity to descent from a common ancestor. He was the first prominent biologist since the age of Aristotle to believe that species are not immutable but that they have changed during the long history of the earth.

Although Lamarck deserves much credit as a pioneer of evolutionary thought, he was seriously wrong about the mechanism of change. For example, Lamarck believed that the long neck of the giraffe evolved because each giraffe stretched its neck slightly in an effort to reach the leaves on high trees. He believed that these slightly-stretched necks could be inherited, and thus, in this way, over many generations, the necks of giraffes had grown longer and longer. Although Lamarck was right in his general picture of evolution, he was mistaken in the detailed mechanism which he proposed, since later experiments proved conclusively that, in general, acquired characteristics cannot be inherited. (One must say "in general", because in the case of symbiosis and genetic fusion, acquired characteristics are inherited. Plasmids containing genetic material are also frequently exchanged between bacteria. Furthermore, in human cultural evolution, innovations can be passed on to future generations. We will discuss these Lamarckian mechanisms of evolution in later chapters.)

The debates between Cuvier and Geoffroy St. Hilaire

In 1830, a year after the death of Lamarck, a famous series of debates took place between Georges Léopold Dagobert, Baron Cuvier (1769-1832) and Étienne Geoffroy St. Hilaire (1772-1844). The two men, both professors at the Musée National d'Histoire Naturelle in Paris, were close friends and scientific collaborators. However, they differed in their opinions, especially on the question of whether the form of an animal's parts led to their function, or whether the reverse was true. Cuvier almost singlehandedly founded the discipline of vertebrate paleontology, and he firmly established the fact that extinctions have taken place. However, he did not believe in evolution. In 1828, Cuvier wrote: "If there are resemblances between the organs of fishes and those of other vertebrate classes, it is only insofar as there are resemblances between their functions." In other words, function produces form. Cuvier denied that similarity of form implied descent from a common ancestor.

St. Hilaire, on the other hand, considered all vertebrates to be modifications of a single archetype. He maintained that similar vestigial organs and similarities in embryonic development implied descent from a common ancestor. He was especially interested in homologies, that is, cases where similar structures in two different organisms are used for two different purposes. In 1829, St. Hilaire wrote: "Animals have no habits but those that result from the structure of their organs: if the latter varies, there vary in the same manner all their springs of action, all their facilities, and all their actions."

The opposing viewpoints of the two men led to a famous series of eight public debates, which took place from February to April, 1830. Although Cuvier was thought by most observers to have won the debates, St. Hilaire's belief in evolution continued, as did the friendship between the two naturalists. In 1832 St. Hilaire partially anticipated Darwin's theory of evolution through natural selection: "The external world is all-powerful in alteration of the form of organized bodies...", he wrote, "These [modifications] are inherited, and they influence all the rest of the organization of the animal, because if these modifications lead to injurious effects, the animals which exhibit them perish and are replaced by others of a somewhat different form, a form changed so as to be adapted to the new environment."

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Chapter 2

CHARLES DARWIN'S LIFE AND WORK

Family background and early life

It was Erasmus Darwin's grandson Charles (1809-1882) who finally worked out a detailed and correct theory of evolution and supported it by a massive weight of evidence.

As a boy, Charles Darwin was passionately fond of hunting and collecting beetles, but he was a mediocre student. His father once said to him in exasperation: "You care for nothing but shooting, dogs and rat-catching; and you will be a disgrace to yourself, and to all your family!"

Darwin's father, a wealthy physician, sent him to Edinburgh University to study medicine; but Charles did not enjoy his studies there. "Dr. Duncan's lectures on Materia Medica at 8 o'clock on a winter's morning are something fearful to remember", he wrote later. "I also attended the operating theatre in the hospital at Edinburgh and saw two very bad operations, one on a child, but I rushed away before they were completed. Nor did I ever attend again, for hardly any inducement would have been strong enough to make me do so; this being long before the blessed days of chloroform. The two cases fairly haunted me for many a long year."

The time at Edinburgh was not entirely wasted, however, because several of Darwin's friends at the university were natural philosophers[1], and contact with them helped to develop his interest in natural history. One of the most important of these scientific friends was Dr. R.E. Grant, an expert on marine invertebrate zoology with whom Darwin often collected small sea slugs in the cold waters of the Firth near Edinburgh. On one of these expeditions, Grant suddenly began to praise the evolutionary views of Lamarck, while Darwin listened in silent astonishment. Charles Darwin had previously read his own grandfather's book *Zoonomia* and had greatly admired it; but after a few years he had read it again in a more critical

[1] Today we would call them scientists.

spirit; and after the second reading he had decided that *Zoonomia* was too speculative and contained too few facts. Grant's praise of Lamarck may have helped Darwin to become, later in his life, an advocate of evolution in a different form.

Darwin's father finally gave up the idea of making him into a doctor, and sent him instead to Cambridge to study for the clergy. At Cambridge, Darwin made many friends because of his unfailing good nature, enthusiasm and kindness. A friend from university days remembers that "at breakfast, wine or supper parties he was ever one of the most cheerful, the most popular and the most welcome... He was the most genial, warmhearted, generous and affectionate of friends."

Darwin's best friend during his last two years at Cambridge was the Reverend John Stevens Henslow, Professor of Botany. Darwin was often invited to Henslow's family dinner; and on most days he accompanied the professor on long walks, so that he became known as "the man who walks with Henslow". This friendship did much to develop Darwin's taste for natural history. Henslow's knowledge of botany, zoology and geology was vast; and he transmitted much of it to his enthusiastic young student during their long walks through the beautiful countryside near to the university.

At Cambridge Darwin collected beetles; and the hobby became almost a passion for him. "One day, on tearing off some old bark", he wrote later, "I saw two rare beetles, and seized one in each hand. Then I saw a third kind, which I could not bear to lose, so I popped the one held in my right hand into my mouth. Alas! It ejected some intensely acrid fluid which burnt my tongue, so that I was forced to spit the beetle out, which was lost, as was the third one."

During his last year at Cambridge, Darwin read Alexander von Humboldt's famous *Personal Narrative of Travels to the Equinoctal Regions of South America During the Years 1799-1804*, a book which awakened in him "a burning zeal to add even the most humble contribution to the noble structure of Natural Science". Darwin longed to visit the glorious tropical forests described so vividly by von Humboldt.

Henslow persuaded Darwin to begin to study geology; and during the spring of 1831, Darwin joined the Professor of Geology, Adam Sedgwick, on an expedition to study the ancient rock formations in Wales. This expedition made Darwin realize that "science consists in grouping facts in such a way that general laws or conclusions may be drawn from them."

When Darwin returned from Wales, he found a letter from Professor George Peacock, forwarded by Henslow. "My dear Henslow", Peacock's letter read, "Captain Fitz-Roy is going out to survey the southern coast of Tierra del Fuego, and afterwards to visit many of the South Sea Islands, and to return by the Indian Archipelago... An offer has been made to me to recommend a proper person to go out as a naturalist with the expedition. He will be treated with every consideration. The Captain is a young man of very pleasant manners (a nephew of the Duke of Grafton), of great zeal in his profession and highly spoken of..."

In forwarding this letter to Darwin, Henslow added: "I have stated that I consider you to be the best qualified person I know of who is likely to undertake such a situation... The voyage is to last two years and if you take plenty of books with you, anything you please may be done... In short, I suppose that there never was a finer chance for a young man of zeal and spirit..."

Darwin was beside himself with joy at this chance to follow in the footsteps of his hero, Alexander von Humboldt; but his plans were immediately squelched by the opposition of his father, who considered it "a wild scheme", unsuitable for a future clergyman. "If you can find any man of common sense who advises you to go", his father added, "I will give my consent."

Crushed by his father's refusal, Charles Darwin visited his uncle's family. Darwin's favorite "Uncle Jos" was the son of the famous potter, Josiah Wedgewood, and the nearby Wedgewood estate at Maer was always a more relaxing place for him than his own home - a relief from the overpowering presence of his father. (His uncle's many attractive daughters may also have had something to do with Darwin's fondness for Maer.)

The Wedgewood family didn't seem to think that sailing on the *Beagle* as naturalist would be a "wild scheme", and Darwin's Uncle Jos offered to drive him over to see whether the verdict could be changed. "My father always maintained that my uncle was one of the most sensible men in the world", Darwin wrote later, "and he at once consented in the kindest manner." Darwin had been rather extravagant while at Cambridge, and to console his father he said: "I should be deuced clever to spend more than my allowance whilst on board the *Beagle*." His father answered with a smile: "But they tell me you are very clever."

Aboard the Beagle

Thus it happened that on December 27, 1831, Charles Darwin sailed from Devonport on *H.M.S. Beagle*, a small brig of the British navy. The *Beagle's* commander, Captain FitzRoy, was twenty-seven years old (four years older than Darwin), but he was already an excellent and experienced sailor. He had orders to survey the South American coast and to carry a chain of chronological measurements around the world. It was to be five years before the *Beagle* returned to England.

As the brig plowed through rough winter seas, Darwin lay in his hammock, miserably seasick and homesick, trying bravely to read a new book which Henslow had given to him as a sending-off present: Sir Charles Lyell's *Principles of Geology.* It was an exciting and revolutionary book - so revolutionary, in fact, that Henslow had found it necessary to warn Darwin not to believe Lyell's theories, but only to trust his observations. According to Lyell, "No causes have ever acted (in geology) but those which now are acting, and they have never acted with different degrees of energy from that which they now exert."[2]

Lyell's hypothesis was directly opposed to the Catastrophist school of geology, a school which included deeply religious men like Cuvier, Henslow and Sedgwick, as well as most other naturalists of the time. The Catastrophists admitted that geological evidence shows the earth to be much older than the six thousand years calculated on the basis of the Bible, but they explained this by saying that the Bible describes only the most recent era. Before this, according to the Catastrophists, life on earth had been created many times, and just as many times destroyed by cataclysms like Noah's flood.[3] In this way they explained the fossils embedded in ancient rocks: These they believed were the remains of antediluvian creatures destroyed by the wrath of God. The Swiss naturalist Charles Bonnet (1720-1793) even predicted a future catastrophe after which apes would become men and men would become angels. The Catastrophists believed that periodic cataclysms had created the earth's great mountain ranges, deserts and oceans.

Lyell's book contradicted this whole picture. He believed the earth to be immensely old, and asserted that over thousands of millions of years, the same slow changes which we can still see taking place have accumulated to produce the earth's great geological features. Over long ages, Lyell believed, gradual changes in the level of the land built up even the highest mountain ranges, while the slow action of rain and frost cut the peaks into valleys and planes.

By the time the *Beagle* reached the volcanic island of St. Jago, Darwin had become ardently converted to Lyell's "wonderfully superior method of treating geology"; and after studying the structure of the island, he realized that he could understand it on the basis of Lyell's principles. The realization that he might perhaps write a book on the geology of the various countries visited by the *Beagle* made Darwin's spirits soar; and he was thrilled also by the sight of so many totally new species of birds, insects and flowers.

[2]This is the famous Principle of Uniformitarianism first formulated by Hutton and later developed in detail by Lyell.

[3]One group of Catastrophists, the Neptunists, believed that gigantic floods shaped the earth's features. A rival group, the Plutonists, attributed most geological features to volcanic action, rather than flood.

"It has been a glorious day", he wrote, "like giving a blind man eyes: He is overwhelmed by what he sees and cannot easily comprehend it."

Later, when the *Beagle* reached Brazil, Darwin was greatly moved by the experience of standing for the first time among the cathedral-like arches of a tropical rain forest. "My mind has been, since leaving England, in a perfect hurricane of delight and astonishment", he wrote, "The glorious pleasure of walking amongst such flowers and such trees cannot be comprehended by those who have not experienced it... Here (the naturalist) suffers a pleasant nuisance of being fairly tied to the spot by some new and wondrous creature... twiners entwining twiners - tresses like hair - beautiful Lepidoptera - silence - hosanna... I am at present fitted for nothing but to read Humboldt: He is like another sun, illuminating all that I behold."

While Captain FitzRoy sailed the *Beagle* slowly southward towards Tierra del Fuego, Darwin followed the ship on horseback, studying the geology of the Argentine Pampas and collecting specimens to send back to Cambridge. Darwin's companions on these expeditions were gauchos, wild Argentine horsemen, expert at throwing the lazo and bolas while galloping at full speed. On one of his rides across the Pampas, Darwin came across the bones of an enormous animal, half buried in a bank of mud and ancient seashells. In a state of great excitement he dug in the surrounding area, and in a few days he succeeded in unearthing the remains of nine huge extinct animals. He was struck by the fact that the bones resembled those of various living South American animals, except for their colossal size. Among them was a guanaco (a wild llama) as big as a camel, a huge armadillo-like creature and a giant sloth-like animal, both as big as elephants. What was the relationship between these extinct animals and living South American species? This problem was to haunt Darwin for many years.

On its way to Tierra del Fuego, the *Beagle* stopped at the Falkland Islands, and Darwin was fascinated by the strange flightless "steamer" ducks found there. He noted that their wings were too small and weak to allow flight. The ducks seemed to paddle with their right and left wings alternately in swimming along the surface of the water; and in this way they were able to move very fast. Darwin reflected that in the South American region there were three species of birds which used their wings for purposes other than flight: the steamer ducks used their wings as paddles, penguins used them as fins, and ostriches used them as sails. Did the ancestors of these birds use their wings for flying? Had the function of the wings changed over a period of time?

On the Falkland Islands, Darwin also noticed that the wild horses had become much smaller than their ancestors, the European horses released there almost three centuries earlier. If the Falkland horses had become noticeably smaller during only a few centuries, then perhaps, over millions of years, the giant armadillo and sloth could have shrunk from the monstrous size of the bones discovered by Darwin to their present size. Perhaps also the wings of the steamer duck, the penguin and the ostrich had become smaller, so that the birds had lost the power of flight. Recalling Lyell's belief in the immense age of the earth, Darwin began to wonder whether small changes, continued over long periods of time, could ultimately produce large changes in living things as well as in geology.

The *Beagle* rounded Cape Horn, lashed by freezing waves so huge that it almost foundered. After the storm, when the brig was anchored safely in the channel of Tierra del Fuego, Darwin noticed how a Fuegian woman stood for hours and watched the ship, while sleet fell and melted on her naked breast, and on the new-born baby she was nursing. He was struck by the remarkable degree to which the Fuegians had adapted to their frigid environment, so that they were able to survive with almost no shelter, and with no clothes except a few stiff, untanned animal skins, which hardly covered them, in weather which would have killed ordinary people.

In 1835, as the *Beagle* made its way slowly northward, Darwin had many chances to explore the Chilean coast - a spectacularly beautiful country, shadowed by towering ranges of the Andes. On January 15, the watch on the *Beagle* noticed something resembling a large star, which gradually increased in size and brilliance. Looking through their telescope, the officers of the *Beagle* could see that the volcano of Osorno was erupting. Darwin was later surprised to learn that on the same night several other volcanos, spread along three thousand miles of coast, had simultaneously erupted.

On February 20, Darwin felt the shock of a severe earthquake, which totally destroyed the towns of Talcahuano and Concepcion. Near the Bay of Concepcion, he could see that the level of the land had been raised three feet by the earthquake; and on the nearby island of St. Maria, Captain FitzRoy found banks of decaying mussel-shells on rocks ten feet above the water line. After the earthquake, it was easy for Darwin to visualize the process by which, over millions of years, the Andes had been raised from the ocean. The sea shells which he found high in the mountains showed that even the highest peaks had once been under the Pacific. Later, high in the Andes, Darwin observed the opposing process - the process by which mountain ranges are torn down. Beside a rushing torrent he stood listening to the rattling noise of stones carried downward by the water. "The sound spoke eloquently to the geologist", he wrote, "The thousands and thousands of stones, which striking against each other made one dull uniform sound, were all hurrying in one direction. It was like thinking on time... As often as I have seen beds of mud, sand and shingles, accumulated to the thickness of many thousands of feet, I have felt inclined to exclaim that causes such as present rivers and present beaches could never have ground down and produced such masses. But on the other hand, while listening to the rattling noise of these torrents and calling to mind that whole races of animals have passed away from the face of the earth, and that during this whole period, night and day, these stones have gone rattling in their course, I have thought to myself, can any mountains, any continent, withstand such a waste?"

After charting the Chilian coast, the *Beagle* sailed westward into the Pacific; and on September 15, 1835, the brig arrived at the Galàpagos Archipelago, a group of strange volcanic islands about 500 miles from the mainland. Most of the species of plants, birds and animals which Darwin found on these islands were aboriginal species, found nowhere else in the world; yet in studying them he was continually reminded of species which he had seen on the South American continent. For example, a group of aboriginal finches which Darwin found on the Galàpagos Islands were related to South American finches. The Galàpagos finches were later shown to belong to thirteen separate species, all closely similar to each other, but differing in their habits and in the structure of their beaks.[4]

The geology of the islands showed that they had been pushed up from the bed of the sea by volcanic action in fairly recent times. Originally each island must have been completely bare of plants and animals. How had it been populated? The fact that the Galàpagos species resembled those of the South American mainland made it seem probable to Darwin that the islands had become the home of chance wanderers from the continent. Seeds had perhaps drifted onto the shore and germinated, or perhaps they had been brought to the islands in the stomachs of birds. Land birds, like the Galàpagos finches, could have been blown there by storms. Perhaps a flock of a single species of finch had arrived, storm-driven, on the black volcanic shores of the islands. Over the centuries, as the finches multiplied, their beaks could have become adapted to the various forms of food available.

"The most curious fact", Darwin wrote later,"is the perfect gradation in the size of the beaks in the various species... Seeing this gradation and diversity in one small, intimately related group of birds, one might really fancy that from an original paucity of birds in this archipelago, one species had been taken and modified for different ends.. Here... we seem to be brought somewhat near to that great fact - that mystery of mysteries - the first appearance of new beings on this earth".

The idea of the gradual modification of species could also explain the fact, observed by Darwin, that the fossil animals of South America were more closely related to African and Eurasian animals than were the living South American species. In other words, the fossil animals of South

[4]Darwin was not even aware at the time that they were finches. It was on his return to London that an ornithologist friend identified them, noted their close relationship to an Equadorian finch, and Darwin came to understand their significance.

America formed a link between the living South American species and the corresponding animals of Europe, Asia and Africa. The most likely explanation for this was that the animals had crossed to America on a land bridge which had since been lost, and that they had afterwards been modified.

The Beagle continued its voyage westward, and Darwin had a chance to study the plants and animals of the Pacific Islands. He noticed that there were no mammals on these islands, except bats and a few mammals brought by sailors. It seemed likely to Darwin that all the species of the Pacific Islands had reached them by crossing large stretches of water after the volcanic islands had risen from the ocean floor; and this accounted for the fact that so many classes were missing. The fact that each group of islands had its own particular species, found nowhere else in the world, seemed to Darwin to be strong evidence that the species had been modified after their arrival. The strange marsupials of the isolated Australian continent also made a deep impression on Darwin.

Work in London and Down

The *Beagle* was now on its way home, and Darwin impatiently counted the days and miles which separated him from his family and friends. To his sisters he wrote: "I feel inclined to write about nothing else but to tell you, over and over again, how I long to be quietly seated among you"; and in a letter to Henslow he exclaimed: "Oh the degree to which I long to be living quietly, without one single novel object near me! No one can imagine it until he has been whirled around the world, during five long years, in a Ten Gun Brig."

Professor Sedgwick had told Darwin's father that he believed that Charles would take his place among the leading scientific men of England. This encouraging news from home reached Darwin on Ascension Island. "After reading this letter", Darwin wrote, "I clambered over the mountains with a bounding step and made the rocks resound under my geological hammer."

On October 2, 1836, the *Beagle* docked at Falmouth, and Darwin, "giddy with joy and confusion", took the first available coach to The Mount, his family's home in Shrewsbury. After a joyful reunion with his family, he visited the Wedgwood estate at Maer, where his Uncle Jos and his pretty cousins were equally impatient to see him. To Henslow he wrote: "I am in the clouds, and neither know what to do or where to go... My chief puzzle is about the geological specimens - who will have the charity to help me in describing their mineralogical nature?"

Soon Darwin found a collaborator and close friend in none other than

Sir Charles Lyell, the great geologist whose book had so inspired him. One of Lyell's best characteristics was his warmth in encouraging promising young scientists. Darwin's theory of the formation of coral barrier reefs and atolls had supplanted Lyell's own theory, but far from being offended, Lyell welcomed Darwin's ideas with enthusiasm. According to Lyell's earlier theory, coral atolls are circular in shape because they are based on the circular rims of submerged volcanos. However, Darwin showed that any island gradually sinking beneath the surface of a tropical ocean can develop into an atoll. He showed that the reef-building organisms of the coral are poisoned by the stagnant water of the central lagoon, but they flourish on the perimeter, where new water is constantly brought in by the waves. Darwin was able to use the presence of coral atolls to map whole regions of the Pacific which are gradually sinking. He pointed out that in the subsiding regions there are no active volcanos, while in regions where the land is rising, there is much volcanic activity.

The years between 1836 and 1839 were busy ones for Darwin. He found lodgings in London, and he worked there with Lyell on his geological collection. During these years he edited a five-volume book on the zoological discoveries of the voyage; and in 1839 his *Journal of Researches into the Geology and Natural History of Various Countries Visited by the H.M.S. Beagle* was published. Originally Darwin's journal formed part of a multivolume work edited by Captain FitzRoy, but the publisher, John Murray, recognized the unusual interest of Darwin's contribution, bought up the copyright, and republished the journal. It immediately became a best-seller, making Darwin famous. Under the shortened title, *The Voyage of the Beagle*, Darwin's journal has been reprinted more than a hundred times.

In 1839 Darwin married his pretty cousin, Emma Wedgwood, the youngest daughter of his much-admired Uncle Jos. She was a charming and light-hearted girl who has studied piano under Chopin. Emma and Charles Darwin were to have ten children together (of whom three were knighted for their contributions to science[5]) and thirty years later he wrote of her: "I can declare that in my whole life I have not heard her utter one word which had rather had been left unsaid."

Darwin was beginning to show signs of the ill health which was to remain with him for the rest of his life, and to escape from the social life of the capital, he moved to the small country town of Down, about 16 miles south of London. Darwin's illness was probably due to a chronic infection - perhaps Chagas disease- , picked up in South America. For the remainder of his life, his strength was very limited, and his daily routine at Down fol-

[5]Among Darwin's grandchildren were Sir Charles Galton Darwin, a pioneer of relativistic quantum theory, and the artist and author, Gwen Raverat. One of his grandnephews was the composer, Ralph Vaughn Williams.

lowed an unvarying pattern which allowed him to work as much as possible within the limits imposed by his illness. The early mornings were devoted to writing (even Sunday mornings) while correspondence and experimental work were done in the afternoons and scientific reading in the evenings.

The Origin of Species

In 1837 Darwin had begun a notebook on *Transmutation of Species*. During the voyage of the *Beagle* he had been deeply impressed by the great fossil animals which he had discovered, so like existing South American species except for their gigantic size. Also, as the *Beagle* had sailed southward, he had noticed the way in which animals were replaced by closely allied species. On the Galàpagos Islands, he had been struck by the South American character of the unique species found there, and by the way in which they differed slightly on each island.

It seemed to Darwin that these facts, as well as many other observations which he had made on the voyage, could only be explained by assuming that species gradually became modified. The subject haunted him, but he was unable to find the exact mechanism by which species changed. Therefore he resolved to follow the Baconian method, which his friend Sir Charles Lyell had used so successfully in geology. He hoped that by the wholesale collection of all facts related in any way to the variation of animals and plants under domestication and in nature, he might be able to throw some light on the subject. He soon saw that in agriculture, the key to success in breeding new varieties was selection; but how could selection be applied to organisms living in a state of nature?

In October 1838, 15 months after beginning his systematic enquiry, Darwin happened to read Malthus' book on population.[6] After his many years as a naturalist, carefully observing animals and plants, Darwin was very familiar with the struggle for existence which goes on everywhere in nature; and it struck him immediately that under the harsh conditions of this struggle, favorable variations would tend to survive while unfavorable ones would perish. The result would be the formation of new species!

Darwin had at last got a theory on which to work, but he was so anxious to avoid prejudice that he did not write it down. He continued to collect facts, and it was not until 1842 that he allowed himself to write a 35-page sketch of his theory. In 1844 he enlarged this sketch to 230 pages, and showed it to his friend Sir Joseph Hooker, the Director of Kew Botanical

[6] *An Essay on the Principle of Population, or, A View of its Past and Present Effects, with an Inquiry into our Prospects Respecting its Future Removal or Mitigation of the Evils which it Occasions*, 2nd edn, Johnson, London (1803).

Gardens. However, Darwin did not publish his 1844 sketch. Probably he foresaw the storm of bitter hostility which his heretical theory was to arouse. In England at that time, Lamarckian ideas from France were regarded as both scientifically unrespectable and politically subversive. The hierarchal English establishment was being attacked by the Chartist movement, and troops had been called out to suppress large scale riots and to ward off revolution. Heretical ideas which might undermine society were regarded as extremely dangerous. Darwin himself was a respected member of the establishment, and he was married to a conservative and devout wife, whose feelings he wished to spare. So he kept his work on species private, confiding his ideas only to Hooker and Lyell.

Instead of publishing his views on evolution, Darwin began an enormous technical study of barnacles, which took him eight years to finish. Hooker had told him that no one had the right to write on the question of the origin of species without first having gone through the detailed work of studying a particular species. Also, barnacles were extremely interesting to Darwin: They are in fact more closely related to shrimps and crabs than to molluscs.

Finally, in 1854, Darwin cleared away the last of his barnacles and began to work in earnest on the transmutation of species through natural selection, arranging the mountainous piles of notes on the subject which he had accumulated over the years. By 1858 he had completed the first part of a monumental work on evolution. If he had continued writing on the same scale, he would ultimately have produced a gigantic, unreadable multivolume opus. Fortunately this was prevented: A young naturalist named Alfred Russell Wallace, while ill with a fever in Malaya, also read Malthus on *Population*; and in a fit of inspiration he arrived at a theory of evolution through natural selection which was identical with Darwin's! Wallace wrote out his ideas in a short paper with the title: *On the Tendency of Varieties to Depart Indefinitely from the Original Type.* He sent this paper to Darwin with the request that if Darwin thought the paper good, he should forward it to Lyell.

Lyell had for years been urging Darwin to publish his own work on natural selection, telling him that if he delayed, someone else would reach the same conclusions. Now Lyell's warning had come true with a vengeance, and Darwin's first impulse was to suppress all his own work in favor of Wallace. In a letter to Lyell, Darwin wrote: "I would far rather burn my whole book than that he or any other man should think that I had behaved in a paltry spirit." Darwin's two good friends, Lyell and Hooker, firmly prevented this however; and through their intervention a fair compromise was reached: Wallace's paper, together with an extract from Darwin's 1844 sketch on natural selection, were read jointly to the Linnean Society (which listened in stunned silence).

At the urging of Lyell and Hooker, Darwin now began an abstract of his enormous unfinished book. This abstract, entitled *On The Origin of Species by Means of Natural Selection, or The Preservation of Favoured Races in the Struggle for Life*, was published in 1859. It ranks with Newton's *Principia* as one of the two greatest scientific books ever written.

Darwin's *Origin of Species* can still be read with enjoyment and fascination by a modern reader. His style is vivid and easy to read, and almost all of his conclusions are still believed to be true. Darwin begins his great book with a history of evolutionary ideas. He starts with a quotation from Aristotle, who was groping towards the idea of natural selection: "Wheresoever, therefore... all the parts of one whole happened like as if they were made for something, these were preserved, having been appropriately constituted by an internal spontaneity; and wheresoever things were not thus constituted, they perished, and still perish." Darwin lists many others who contributed to evolutionary thought, including the Chevalier de Lamarck, Geoffroy Saint-Hillaire, Alfred Russell Wallace, and his own grandfather, Erasmus Darwin.

Next, Darwin reminds us of the way in which mankind has produced useful races of domestic animals and plants by selecting from each generation those individuals which show any slight favorable variation, and by using these as parents for the next generation. A closely similar process occurs in nature, Darwin tells us: Wild animals and plants exhibit slight variations, and in nature there is always a struggle for existence. This struggle follows from the fact that every living creature produces offspring at a rate which would soon entirely fill up the world if no check ever fell on the growth of population. We often have difficulty in seeing the exact nature of these checks, since living organisms are related to each other and to their environment in extremely complex ways, but the checks must always be present.

Accidental variations which increase an organism's chance of survival are more likely to be propagated to subsequent generations than are harmful variations. By this mechanism, which Darwin called "natural selection", changes in plants and animals occur in nature just as they do under the artificial selection exercised by breeders.

If we imagine a volcanic island, pushed up from the ocean floor and completely uninhabited, we can ask what will happen as plants and animals begin to arrive. Suppose, for example, that a single species of bird arrives on the island. The population will first increase until the environment cannot support larger numbers, and it will then remain constant at this level. Over a long period of time, however, variations may accidentally occur in the bird population which allow the variant individuals to make use of new types of food; and thus, through variation, the population may be further increased.

In this way, a single species "radiates" into a number of sub-species which fill every available ecological niche. The new species produced in this way will be similar to the original ancestor species, although they may be greatly modified in features which are related to their new diet and habits. Thus, for example, whales, otters and seals retain the general structure of land-going mammals, although they are greatly modified in features which are related to their aquatic way of life. This is the reason, according to Darwin, why vestigial organs are so useful in the classification of plant and animal species.

The classification of species is seen by Darwin as a genealogical classification. All living organisms are seen, in his theory, as branches of a single family tree. This is a truly remarkable assertion, since the common ancestors of all living things must have been extremely simple and primitive; and it follows that the marvellous structures of the higher animals and plants, whose complexity and elegance utterly surpasses the products of human intelligence, were all produced, over thousands of millions of years, by random variation and natural selection!

Each structure and attribute of a living creature can therefore be seen as having a long history; and a knowledge of the evolutionary history of the organs and attributes of living creatures can contribute much to our understanding of them. For instance, studies of the evolutionary history of the brain and of instincts can contribute greatly to our understanding of psychology, as Darwin pointed out.

Darwin then discusses the complex networks of relationships between living organisms[7]. For example, he discusses the way in which a certain kind of fly prevents horses, cattle and dogs from becoming feral (i.e. thriving as wild animals) in Paraguay. The fly lays its eggs in the navels of these animals when they are born. If the infestations are untreated, fewer of the newborns survive. In other parts of South America, to the north and south of Paraguay, the flies are less numerous, probably because of the presence of parasitic insects. Hence, Darwin concludes, if insect-eating birds were to decrease in Paraguay, the parasitic insects would increase, and this would lessen the number of navel-frequenting flies. Then cattle and horses would become feral, and this would alter the vegetation, which would affect the insects, and so on in ever-increasing circles of complexity.

Another interesting chain of ecological relationships involves clover, bumble-bees, mice, cats and cat-loving people: Red clover is much more common near to towns than elsewhere. Why should this be so? Darwin's explanation is that this type of clover can only be pollinated by bumble-bees. The underground nests of bumble-bees are often destroyed by mice;

[7]Here we can see Darwin as the founder of the modern discipline of ecology.

but near to towns mice are kept in check by cats. Hence, Darwin notes, the presence of cats in a district might determine, through the intervention first of mice and then of bees, the frequency of certain flowers in that district.

Among the many striking observations presented by Darwin to support his theory, are facts related to morphology and embryology. For example, Darwin includes a quotation from the naturalist, von Baer, who stated that he had in his possession two embryos preserved in alcohol, which he had forgotten to label. Von Baer was completely unable to tell by looking at them whether they were embryos of lizards, birds or mammals, since all these species are so similar at an early stage of development.

Darwin also quotes the following passage from G.H. Lewis: "The tadpole of the common Salamander has gills, and passes its existence in the water; but the *Salamandra atra*, which lives high up in the mountains, brings forth its young full-formed. This animal never lives in the water. Yet if we open a gravid female, we find tadpoles inside her with exquisitely feathered gills; and when placed in water, they swim about like the tadpoles of the common Salamander or water-newt. Obviously this aquatic organization has no reference to the future life of the animal, nor has it any adaptation to its embryonic condition; it has solely reference to ancestral adaptations; it repeats a phase in the development of its progenitors."

Darwin points out that, "...As the embryo often shows us more or less plainly the structure of the less modified and ancient progenitor of the group, we can see why ancient and extinct forms so often resemble in their adult state the embryos of existing species."

Darwin sets forth another line of argument in support of evolution based on "serial homologies", - cases where symmetrically repeated parts of an ancient progenitor have been modified for special purposes in their descendants. For example, the bones which fit together to form the brain case in reptiles, birds and mammals can be seen in fossil sequences to be modified vertebrae of an ancient progenitor. After discussing many examples, Darwin exclaims, "How inexplicable are these cases of serial homologies on the ordinary view of creation! Why should the brain be enclosed in a box composed of such numerous and extraordinarily-shaped pieces of bone?... Why should similar bones have been created to form the wing and leg of a bat, used as they are for totally different purposes, namely walking and flying? Why should one crustacean, which has an extremely complex mouth, formed of many parts, consequently have fewer legs; or conversely, those with many legs have simpler mouths? Why should the sepals, petals, stamens and pistils in each flower, though fitted for such distinct purposes, be all constructed on the same pattern?... On the theory of natural selection we can, to a certain extent, answer these questions.... An indefinite repetition of the same part is the common characteristic of all low or little-specialized forms... We have already seen that parts many times repeated are eminently liable to vary... Consequently such parts, being already present in considerable numbers, and being highly variable, would naturally afford materials for adaption to the most different purposes."

No abstract of Darwin's book can do justice to it. One must read it in the original. He brings forward an overwhelming body of evidence to support his theory of evolution through natural selection; and he closes with the following words:

"It is interesting to contemplate a tangled bank, clothed with many plants of many different kinds, with birds singing on the bushes, with various insects flitting about, and with worms crawling through the damp earth, and to reflect that these elaborately constructed forms, so different from each other, and dependent upon each other in so complex a manner, have all been produced by laws acting around us... There is grandeur in this view of life, with its several powers, having been originally breathed by the Creator into a few forms or into one; and that whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning, endless forms most beautiful and wonderful have been and are being evolved."

The Descent of Man

Darwin's *Origin of Species*, published in 1859, was both an immediate success and an immediate scandal. Darwin had sent an advance copy of his book to *The Times* to be reviewed; and because of the illness of the usual reviewer, T.H. Huxley (1825-1895) was asked to comment on the book. Huxley, who was one of the most brilliant zoologists of the period, immediately recognized the validity and importance of Darwin's work and exclaimed: "How exceedingly stupid not to have thought of that!" He wrote a long and favorable review for *The Times*, and partly as a result of this review, the first edition of *The Origin of Species* (1200 copies) was sold out on the day of publication. A second edition, published six weeks later, also sold out quickly; and new editions, reprintings and translations have been published ever since in a steady stream.

Darwin had avoided emphasizing the emotionally-charged subject of man's ancestry, but he did not think that it would be honest to conceal his belief that the human race belongs to the same great family which includes all other living organisms on earth. As a compromise, he predicted in a single sentence that through studies of evolution "light would be thrown on the origin of man and his history". This single sentence, and the obvious implications of Darwin's book, were enough to create a storm of furious opposition. One newspaper commented that "society must fall to pieces if Darwinism be true."

The storm of scandalized opposition was still growing in June 1860, when three anti-Darwinian papers were scheduled for reading at an open meeting of the British Association for the Advancement of Science at Oxford. The meeting hall was packed with 700 people as Samuel Wilberforce, Bishop of Oxford, took the floor to "smash Darwin". Darwin himself was too ill (or too diffident) to be present, but T.H. Huxley had been persuaded to attend the meeting to defend Darwin's ideas. After savagely attacking Darwin for half an hour, the bishop turned to Huxley and asked sneeringly, "Is it through your grandfather or your grandmother that you claim to be descended from an ape?"

Huxley, who was 35 at the time and at the height of his powers, rose to answer the bishop. He first gave scientific answers, point by point, to the objections which had been made to the theory of evolution. Finally, regarding the bishop's question about his ancestry, Huxley said: "If I had to choose between a poor ape for an ancestor and a man, highly endowed by nature and of great influence, who used those gifts to introduce ridicule into a scientific discussion and to discredit humble seekers after truth, I would affirm my preference for the ape." Huxley later recalled: "My retort caused inextinguishable laughter among the people."

Pandemonium broke out in the hall. Lady Brewster fainted, and Admiral FitzRoy, the former captain of the *Beagle*, rose to his feet, lifting a Bible in his hand, exclaiming that the Scriptures are the only reliable authority. Had he known Darwin's true nature, FitzRoy said, he would never have allowed him to sail on board the *Beagle*. As *Macmillan's Magazine* reported later, "Looks of bitter hatred were directed to those who were on Darwin's side." However, later that evening, in the discussions of the events of the day which took place in the Oxford colleges, Darwin's ideas were given a surprisingly fair hearing.

The debate at Oxford marked the turning-point in the battle over evolution. After that, Huxley and Hooker defended Darwin's theories with increasing success in England, while in Germany most of the prominent biologists, led by Professor Ernst Haeckel, were soon on Darwin's side. In America the theory of evolution was quickly accepted by almost all of the younger scientists, despite the opposition of the aging "creationist" Louis Agassiz. However, opposition from religious fundamentalists continued in most parts of America, and in Tennessee a school teacher named John T. Scopes was brought to trial for teaching the theory of evolution. He was prosecuted by the orator and three-time presidential candidate William Jennings Bryan, and defended by the brilliant Chicago lawyer Clarence Darrow. In this famous "Monkey Trial", Scopes was let off with a small fine, but the anti-evolution laws remained in force. It was only in 1968 that the State Legislature of Tennessee repealed its laws against the teaching of evolution[8].

In 1863 Huxley, who was not afraid of controversy, published a book entitled *Evidences of Man's Place in Nature*, and this was followed in 1871 by Darwin's book *The Descent of Man.* Huxley and Darwin brought forward a great deal of evidence to show that human beings are probably descended from an early ape-like primate which is now extinct. Darwin believed that the early stages of human evolution took place in Africa[9]. In order to show that men and apes represent closely-related branches of the same family tree, Darwin and Huxley stressed the many points of similarity - resemblances in structure, reproduction, development, psychology and behavior, as well as susceptibility to the same parasites and diseases.

The Expression of Emotions in Man and Animals; ethology

In *The Origin of Species*, Charles Darwin devoted a chapter to the evolution of instincts, and he later published a separate book on *The Expression of Emotion in Man and Animals.* Because of these pioneering studies, Darwin is considered to be the founder of the science of ethology - the study of inherited behavior patterns.

Behind Darwin's work in ethology is the observation that instinctive behavior patterns are just as reliably inherited as morphological characteristics. Darwin was also impressed by the fact that within a given species, behavior patterns have some degree of uniformity, and the fact that the different species within a family are related by similarities of instinctive behavior, just as they are related by similarities of bodily form. For example, certain elements of cat-like behavior can be found among all members of the cat family; and certain elements of dog-like or wolf-like behavior can be found among all members of the dog family. On the other hand, there are small variations in instinct among the members of a given species. For example, not all domestic dogs behave in the same way.

"Let us look at the familiar case of breeds of dogs", Darwin wrote in *The Origin of Species*, "It cannot be doubted that young pointers will sometimes point and even back other dogs the very first time they are taken out; retrieving is certainly in some degree inherited by retrievers;

[8]In 1999, the Kansas State School Board removed biological evolution from the curriculum followed by students within the state. Furthermore, cosmology was also removed from the curriculum because it presents evidence that the earth is extremely old, thus supporting evolution. Fortunately, the 1999 decision has now been reversed.

[9]This guess has been confirmed by the recent discoveries of Broom, Dart and the Leakey family, among many others.

and a tendency to run round, instead of at, a flock of sheep by shepherd dogs. I cannot see that these actions, performed without experience by the young, and in nearly the same manner by each individual, and without the end being known - for the young pointer can no more know that he points to aid his master than the white butterfly knows why she lays her eggs on the leaf of the cabbage - I cannot see that these actions differ essentially from true instincts..."

"How strongly these domestic instincts habits and dispositions are inherited, and how curiously they become mingled, is well shown when different breeds of dogs are crossed. Thus it is known that a cross with a bulldog has affected for many generations the courage and obstinacy of greyhounds; and a cross with a greyhound has given to a whole family of shepherd dogs a tendency to hunt hares..."

Darwin believed that in nature, desirable variations of instinct are propagated by natural selection, just as in the domestication of animals, favorable variations of instinct are selected and propagated by kennelmen and stock breeders. In this way, according to Darwin, complex and highly developed instincts, such as the comb-making instinct of honey-bees, have evolved by natural selection from simpler instincts, such as the instinct by which bumble bees use their old cocoons to hold honey and sometimes add a short wax tube.

The study of inherited behavior patterns in animals was continued in the 20th century by such researchers as Nikolaas Tinbergen, Konrad Lorenz and Karl von Frisch, three scientists who shared the first Nobel Prize ever awarded in the field of ethology. Among the achievements for which Tinbergen is famous are his classic studies of instinct in herring gulls. He noticed that the newly-hatched chick of a herring gull pecks at the beak of its parent, and this signal causes the parent gull to regurgitate food into the gaping beak of the chick. Tinbergen wondered what signal causes the chick to initiate this response by pecking at the beak of the parent gull. Therefore he constructed a series of models of the parent in which certain features of the adult gull were realistically represented while other features were crudely represented or left out entirely. He found by trial and error that the essential signal to which the chick responds is the red spot on the tip of its parent's beak. Models which lacked the red spot produced almost no response from the young chick, although in other respects they were realistic models; and the red spot on an otherwise crude model would make the chick peck with great regularity.

Tinbergen called this type of signal a "sign stimulus". He found by further studies that he could produce an even more frantic response from the young chick by replacing the red spot by several concentric black circles on a white background, a sign stimulus which he called "super-normal"

In his 1978 book on *Animal Behavior*, Tinbergen pointed out that the features of baby animals, with their large foreheads, round cheeks, and round eyes, all have a characteristic "baby" look. This, Tinbergen wrote, is a sign stimulus which draws a protective response from adults; and he calls attention to the exaggerated "baby" look of some of Walt Disney's animals as an example of a super-normal sign stimulus. Another example of a super-normal sign stimulus, Tinbergen wrote, is the red lipstick and dark eye makeup sometimes used by women.

In the case of a newly-hatched herring gull chick pecking at the red spot on the beak of its parent, the program in the chick's brain must be entirely genetically determined, without any environmental component at all. Learning cannot play a part in this behavioral pattern, since the pattern is present in the young chick from the very moment when it breaks out of the egg. On the other hand (Tinbergen pointed out) many behavioral patterns in animals and in man have both an hereditary component and an environmental component. Learning is often very important, but learning seems to be built on a foundation of genetic predisposition.

To illustrate this point, Tinbergen called attention to the case of sheep-dogs, whose remote ancestors were wolves. These dogs, Tinbergen tells us, can easily be trained to drive a flock of sheep towards the shepherd. However, it is difficult to train them to drive the sheep away from their master. Tinbergen explained this by saying that the sheep-dogs regard the shepherd as their "pack leader"; and since driving the prey towards the pack leader is part of the hunting instinct of wolves, it is easy to teach the dogs this maneuver. However, driving the prey away from the pack leader would not make sense for wolves hunting in a pack; it is not part of the instinctive makeup of wolves, nor is it a natural pattern of behavior for their remote descendants, the sheep-dogs.

Tinbergen also tells us that a Welsh shepherd who wishes to discipline his dog often bites it in the ear; and this is an extremely effective method of enforcing discipline with dogs. To explain the effectiveness of the ear bite, Tinbergen reminds his readers that the leader of a pack of wolves disciplines his subordinates by biting their ears.

As a further example of the fact that learning is usually built on a foundation of genetic predisposition, Tinbergen mentions the ease with which human babies learn languages. The language learned is determined by the baby's environment; but astonishing ease with which a human baby learns to speak and understand implies a large degree of genetic predisposition.

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Chapter 3

MOLECULAR BIOLOGY AND EVOLUTION

Classical genetics

Charles Darwin postulated that natural selection acts on small inheritable variations in the individual members of a species. His opponents objected that these slight variations would be averaged away by interbreeding. Darwin groped after an answer to this objection, but he did not have one. However, unknown to Darwin, the answer had been uncovered several years earlier by an obscure Augustinian monk, Gregor Mendel, who was born in Silesia in 1822, and who died in Bohemia in 1884.

Mendel loved both botany and mathematics, and he combined these two interests in his hobby of breeding peas in the monastery garden. Mendel carefully self-pollinated his pea plants, and then wrapped the flowers to prevent pollination by insects. He kept records of the characteristics of the plants and their offspring, and he found that dwarf peas always breed true - they invariably produce other dwarf plants. The tall variety of pea plants, pollinated with themselves, did not always breed true, but Mendel succeeded in isolating a strain of true-breeding tall plants which he inbred over many generations.

Next he crossed his true-breeding tall plants with the dwarf variety and produced a generation of hybrids. All of the hybrids produced in this way were tall. Finally Mendel self-pollinated the hybrids and recorded the characteristics of the next generation. Roughly one quarter of the plants in this new generation were true-breeding tall plants, one quarter were true-breeding dwarfs, and one half were tall but not true-breeding.

Gregor Mendel had in fact discovered the existence of dominant and recessive genes. In peas, dwarfism is a recessive characteristic, while tallness is dominant. Each plant has two sets of genes, one from each parent. Whenever the gene for tallness is present, the plant is tall, regardless of whether it also has a gene for dwarfism. When Mendel crossed the pure-breeding dwarf plants with pure-breeding tall ones, the hybrids received one type of gene from each parent. Each hybrid had a tall gene and a dwarf gene; but the tall gene was dominant, and therefore all the hybrids were tall. When the hybrids were self-pollinated or crossed with each other, a genetic lottery took place. In the next generation, through the laws of chance, a quarter of the plants had two dwarf genes, a quarter had two tall genes, and half had one of each kind.

Mendel published his results in the *Transactions of the Brünn Natural History Society* in 1865, and no one noticed his paper[1]. At that time, Austria was being overrun by the Prussians, and people had other things to think about. Mendel was elected Abbot of his monastery; he grew too old and fat to bend over and cultivate his pea plants; his work on heredity was completely forgotten, and he died never knowing that he would one day be considered to be the founder of modern genetics.

In 1900 the Dutch botanist named Hugo de Vries, working on evening primroses, independently rediscovered Mendel's laws. Before publishing, he looked through the literature to see whether anyone else had worked on the subject, and to his amazement he found that Mendel had anticipated his great discovery by 35 years. De Vries could easily have published his own work without mentioning Mendel, but his honesty was such that he gave Mendel full credit and mentioned his own work only as a confirmation of Mendel's laws. Astonishingly, the same story was twice repeated elsewhere in Europe during the same year. In 1900, two other botanists (Correns in Berlin and Tschermak in Vienna) independently rediscovered Mendel's laws, looked through the literature, found Mendel's 1865 paper, and gave him full credit for the discovery.

Besides rediscovering the Mendelian laws for the inheritance of dominant and recessive characteristics, de Vries made another very important discovery: He discovered genetic mutations - sudden unexplained changes of form which can be inherited by subsequent generations. In growing evening primroses, de Vries found that sometimes, but very rarely, a completely new variety would suddenly appear, and he found that the variation could be propagated to the following generations. Actually, mutations had been observed before the time of de Vries. For example, a short-legged mutant sheep had suddenly appeared during the 18th century; and stock-breeders had taken advantage of this mutation to breed sheep that could not jump over walls. However, de Vries was the first scientist to study and describe mutations. He noticed that most mutations are harmful, but that a very few are beneficial, and those few tend in nature to be propagated to future generations.

[1]Mendel sent a copy of his paper to Darwin; but Darwin, whose German was weak, seems not to have read it.

After the rediscovery of Mendel's work by de Vries, many scientists began to suspect that chromosomes might be the carriers of genetic information. The word "chromosome" had been invented by the German physiologist, Walther Flemming, to describe the long, threadlike bodies which could be seen when cells were stained and examined through the microscope during the process of division. It had been found that when an ordinary cell divides, the chromosomes also divide, so that each daughter cell has a full set of chromosomes.

The Belgian cytologist, Edouard van Benedin, had shown that in the formation of sperm and egg cells, the sperm and egg receive only half of the full number of chromosomes. It had been found that when the sperm of the father combines with the egg of the mother in sexual reproduction, the fertilized egg again has a full set of chromosomes, half coming from the mother and half from the father. This was so consistent with the genetic lottery studied by Mendel, de Vries and others, that it seemed almost certain that chromosomes were the carriers of genetic information.

The number of chromosomes was observed to be small (for example, each normal cell of a human has 46 chromosomes); and this made it obvious that each chromosome must contain thousands of genes. It seemed likely that all of the genes on a particular chromosome would stay together as they passed through the genetic lottery; and therefore certain characteristics should always be inherited together.

This problem had been taken up by Thomas Hunt Morgan, a professor of experimental zoology working at Colombia University. He found it convenient to work with fruit flies, since they breed with lightning-like speed and since they have only four pairs of chromosomes.

Morgan found that he could raise enormous numbers of these tiny insects with almost no effort by keeping them in gauze-covered glass milk bottles, in the bottom of which he placed mashed bananas. In 1910, Morgan found a mutant white-eyed male fly in one of his milk-bottle incubators. He bred this fly with a normal red-eyed female, and produced hundreds of red-eyed hybrids. When he crossed the red-eyed hybrids with each other, half of the next generation were red-eyed females, a quarter were red-eyed males, and a quarter were white-eyed males. There was not one single white-eyed female! This indicated that the mutant gene for white eyes was on the same chromosome as the gene for the male sex.

As Morgan continued his studies of genetic linkages, however, it became clear that the linkages were not absolute. There was a tendency for all the genes on the same chromosome to be inherited together; but on rare occasions there were "crosses", where apparently a pair of chromosomes broke at some point and exchanged segments. By studying these crosses statistically, Morgan and his "fly squad" were able to find the relative positions of genes on the chromosomes. They reasoned that the probability for a cross to separate two genes should be proportional to the distance between the two genes on the chromosome. In this way, after 17 years of work and millions of fruit flies, Thomas Hunt Morgan and his coworkers were able to make maps of the fruit fly chromosomes showing the positions of the genes.

This work had been taken a step further by Hermann J. Muller, a member of Morgan's "fly squad", who exposed hundreds of fruit flies to X-rays. The result was a spectacular outbreak of man-made mutations in the next generation.

"They were a motley throng", recalled Muller. Some of the mutant flies had almost no wings, others bulging eyes, and still others brown, yellow or purple eyes; some had no bristles, and others curly bristles. Muller's experiments indicated that mutations can be produced by radiation-induced physical damage; and he guessed that such damage alters the chemical structure of genes.

In spite of the brilliant work by Morgan and his collaborators, no one had any idea of what a gene really was.

The structure of DNA

Until 1944, most scientists had guessed that the genetic message was carried by the proteins of the chromosome. In 1944, however, O.T. Avery and his co-workers at the laboratory of the Rockefeller Institute in New York performed a critical experiment, which proved that the material which carries genetic information is not protein, but deoxyribonucleic acid (DNA) - a giant chainlike molecule which had been isolated from cell nuclei by the Swiss chemist, Friedrich Miescher.

Avery had been studying two different strains of pneumococci, the bacteria which cause pneumonia. One of these strains, the S-type, had a smooth coat, while the other strain, the R-type, lacked an enzyme needed for the manufacture of a smooth carbohydrate coat. Hence, R-type pneumococci had a rough appearance under the microscope. Avery and his co-workers were able to show that an extract from heat-killed S-type pneumococci could convert the living R-type species permanently into S-type; and they also showed that this extract consisted of pure DNA.

In 1947, the Austrian-American biochemist, Erwin Chargaff, began to study the long, chainlike DNA molecules. It had already been shown by Levine and Todd that chains of DNA are built up of four bases: adenine (A), thymine (T), guanine (G) and cytosine (C), held together by a sugar-phosphate backbone. Chargaff discovered that in DNA from the nuclei of living cells, the amount of A always equals the amount of T; and the amount of G always equals the amount of C.

When Chargaff made this discovery, neither he nor anyone else understood its meaning. However, in 1953, the mystery was completely solved by Rosalind Franklin and Maurice Wilkins at Kings College, London, together with James Watson and Francis Crick at Cambridge University. By means of X-ray diffraction techniques, Wilkins and Franklin obtained crystallographic information about the structure of DNA. Using this information, together with Linus Pauling's model-building methods, Crick and Watson proposed a detailed structure for the giant DNA molecule.

The discovery of the molecular structure of DNA was an event of enormous importance for genetics, and for biology in general. The structure was a revelation! The giant, helical DNA molecule was like a twisted ladder: Two long, twisted sugar-phosphate backbones formed the outside of the ladder, while the rungs were formed by the base pairs, A, T, G and C.

The base adenine (A) could only be paired with thymine (T), while guanine (G) fit only with cytosine (C). Each base pair was weakly joined in the center by hydrogen bonds - in other words, there was a weak point in the center of each rung of the ladder - but the bases were strongly attached to the sugar-phosphate backbone. In their 1953 paper, Crick and Watson wrote:

"It has not escaped our notice that the specific pairing we have postulated suggests a possible copying mechanism for genetic material". Indeed, a sudden blaze of understanding illuminated the inner workings of heredity, and of life itself.

If the weak hydrogen bonds in the center of each rung were broken, the ladderlike DNA macromolecule could split down the center and divide into two single strands. Each single strand would then become a template for the formation of a new double-stranded molecule.

Because of the specific pairing of the bases in the Watson-Crick model of DNA, the two strands had to be complementary. T had to be paired with A, and G with C. Therefore, if the sequence of bases on one strand was (for example) TTTGCTAAAGGTGAACCA... , then the other strand necessarily had to have the sequence AAACGATTTCCACTTGGT...

The Watson-Crick model of DNA made it seem certain that all the genetic information needed for producing a new individual is coded into the long, thin, double-stranded DNA molecule of the cell nucleus, written in a four-letter language whose letters are the bases, adenine, thymine, guanine and cytosine.

The solution of the DNA structure in 1953 initiated a new kind of biology - molecular biology. This new discipline made use of recently-discovered physical techniques - X-ray diffraction, electron microscopy, electrophoresis, chromatography, ultracentrifugation, radioac tracer techniques, autoradiography, electron spin resonance, nuclear magnetic resonance and ultraviolet spectroscopy. In the 1960's and 1970's, molecular biology became the most exciting and rapidly-growing branch of science.

Protein structure

In England, J.D. Bernal and Dorothy Crowfoot Hodgkin pioneered the application of X-ray diffraction methods to the study of complex biological molecules. In 1949, Hodgkin determined the structure of penicillin; and in 1955, she followed this with the structure of vitamin B12.

In 1960, Max Perutz and John C. Kendrew obtained the structures of the blood proteins myoglobin and hemoglobin. This was an impressive achievement for the Cambridge crystallographers, since the hemoglobin molecule contains roughly 12,000 atoms.

The structure obtained by Perutz and Kendrew showed that hemoglobin is a long chain of amino acids, folded into a globular shape, like a small, crumpled ball of yarn. They found that the amino acids with an affinity for water were on the outside of the globular molecule; while the amino acids for which contact with water was energetically unfavorable were hidden on the inside. Perutz and Kendrew deduced that the conformation of the protein - the way in which the chain of amino acids folded into a 3-dimensional structure - was determined by the sequence of amino acids in the chain.

In 1966, D.C. Phillips and his co-workers at the Royal Institution in London found the crystallographic structure of the enzyme lysozyme (an egg-white protein which breaks down the cell walls of certain bacteria). Again, the structure showed a long chain of amino acids, folded into a roughly globular shape. The amino acids with hydrophilic groups were on the outside, in contact with water, while those with hydrophobic groups were on the inside. The structure of lysozyme exhibited clearly an active site, where sugar molecules of bacterial cell walls were drawn into a mouth-like opening and stressed by electrostatic forces, so that bonds between the sugars could easily be broken.

Meanwhile, at Cambridge University, Frederick Sanger developed methods for finding the exact sequence of amino acids in a protein chain. In 1945, he discovered a compound (2,4-dinitrofluorobenzene) which attaches itself preferentially to one end of a chain of amino acids. Sanger then broke down the chain into individual amino acids, and determined which of them was connected to his reagent. By applying this procedure many times to fragments of larger chains, Sanger was able to deduce the sequence of amino acids in complex proteins. In 1953, he published the sequence of insulin.

This led, in 1964, to the synthesis of insulin.

The biological role and structure of proteins which began to emerge was as follows: A mammalian cell produces roughly 10,000 different proteins. All enzymes are proteins; and the majority of proteins are enzymes - that is, they catalyze reactions involving other biological molecules.

All proteins are built from chainlike polymers, whose monomeric subunits are the following twenty amino acids: glycine, aniline, valine, isoleucine, leucine, serine, threonine, proline, aspartic acid, glutamic acid, lysine, arginine, asparagine, glutamine, cysteine, methionine, tryptophan, phenylalanine, tyrosine and histidine. These individual amino acid monomers may be connected together into a polymer (called a polypeptide) in any order - hence the great number of possibilities. In such a polypeptide, the backbone is a chain of carbon and nitrogen atoms showing the pattern ...-C-C-N-C-C-N-C-C-N-...and so on. The -C-C-N- repeating unit is common to all amino acids. Their individuality is derived from differences in the side groups which are attached to the universal -C-C-N- group.

Some proteins, like hemoglobin, contain metal atoms, which may be oxidized or reduced as the protein performs its biological function. Other proteins, like lysozyme, contain no metal atoms, but instead owe their biological activity to an active site on the surface of the protein molecule.

In 1909, the English physician, Archibald Garrod, had proposed a one-gene-one-protein hypothesis. He believed that hereditary diseases are due to the absence of specific enzymes. According to Garrod's hypothesis, damage suffered by a gene results in the faulty synthesis of the corresponding enzyme, and loss of the enzyme ultimately results in the symptoms of the hereditary disease.

In the 1940's, Garrod's hypothesis was confirmed by experiments on the mold, *Neurospora*, performed at Stanford University by George Beadle and Edward Tatum. They demonstrated that mutant strains of the mold would grow normally, provided that specific extra nutrients were added to their diets. The need for these dietary supplements could in every case be traced to the lack of a specific enzyme in the mutant strains. Linus Pauling later extended these ideas to human genetics by showing that the hereditary disease, sickle-cell anemia, is due to a defect in the biosynthesis of hemoglobin.

RNA and ribosomes

Since DNA was known to carry the genetic message, coded into the sequence of the four nucleotide bases, A, T, G and C, and since proteins were known to be composed of specific sequences of the twenty amino acids, it was logical to suppose that the amino acid sequence in a protein was determined by the base sequence of DNA. The information somehow had to be read from the DNA and used in the biosynthesis of the protein.

It was known that, in addition to DNA, cells also contain a similar, but not quite identical, polynucleotide called ribonucleic acid (RNA). The sugar-phosphate backbone of RNA was known to differ slightly from that of DNA; and in RNA, the nucleotide thymine (T) was replaced by a chemically similar nucleotide, uracil (U). Furthermore, while DNA was found only in cell nuclei, RNA was found both in cell nuclei and in the cytoplasm of cells, where protein synthesis takes place. Evidence accumulated indicating that genetic information is first transcribed from DNA to RNA, and afterwards translated from RNA into the amino acid sequence of proteins.

At first, it was thought that RNA might act as a direct template, to which successive amino acids were attached. However, the appropriate chemical complementarity could not be found; and therefore, in 1955, Francis Crick proposed that amino acids are first bound to an adaptor molecule, which is afterward bound to RNA.

In 1956, George Emil Palade of the Rockefeller Institute used electron microscopy to study subcellular particles rich in RNA (ribosomes). Ribosomes were found to consist of two subunits - a smaller subunit, with a molecular weight one million times the weight of a hydrogen atom, and a larger subunit with twice this weight.

It was shown by means of radioactive tracers that a newly synthesized protein molecule is attached temporarily to a ribosome, but neither of the two subunits of the ribosome seemed to act as a template for protein synthesis. Instead, Palade and his coworkers found that genetic information is carried from DNA to the ribosome by a messenger RNA molecule (mRNA).

Electron microscopy revealed that mRNA passes through the ribosome like a punched computer tape passing through a tape-reader. It was found that the adapter molecules, whose existence Crick had postulated, were smaller molecules of RNA; and these were given the name "transfer RNA" (tRNA). It was shown that, as an mRNA molecule passes through a ribosome, amino acids attached to complementary tRNA adaptor molecules are added to the growing protein chain.

The relationship between DNA, RNA, the proteins and the smaller molecules of a cell was thus seen to be hierarchical: The cell's DNA controlled its proteins (through the agency of RNA); and the proteins controlled the synthesis and metabolism of the smaller molecules.

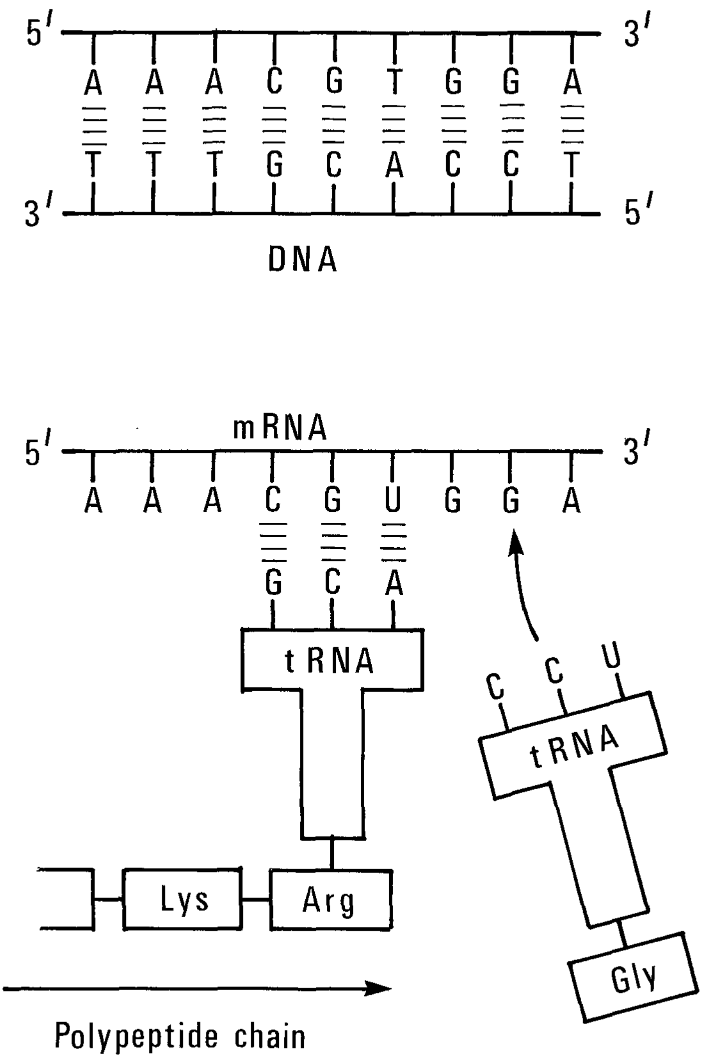


Fig. 3.1 Information coded on DNA molecules in the cell nucleus is transcribed to mRNA molecules. The messenger RNA molecules in turn provide information for the amino acid sequence in protein synthesis.

The genetic code

In 1955, Severo Ochoa, at New York University, isolated a bacterial enzyme (RNA polymerase) which was able join the nucleotides A, G, U and C so

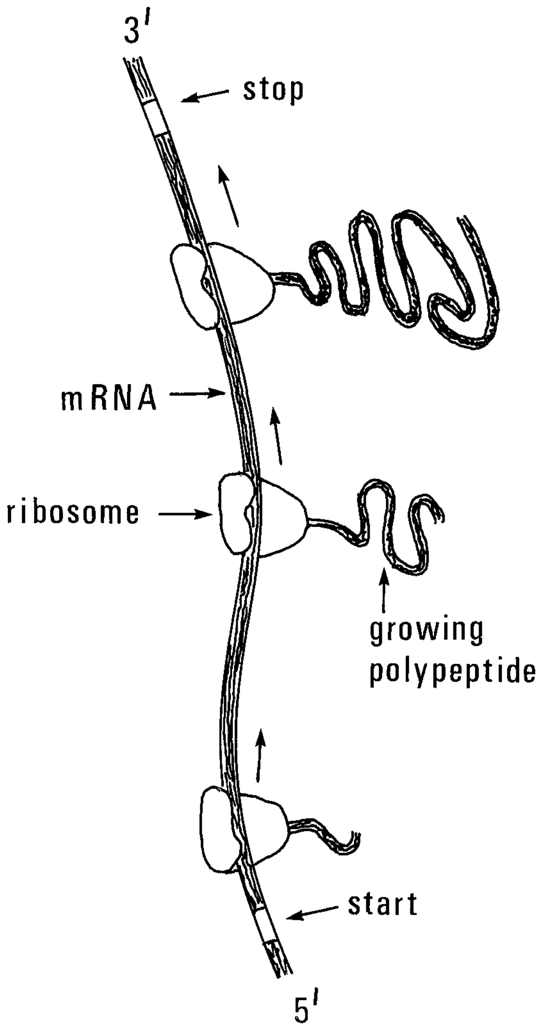
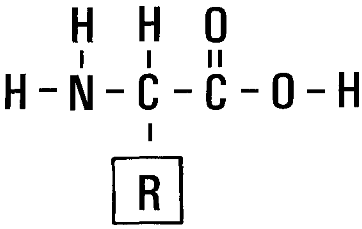


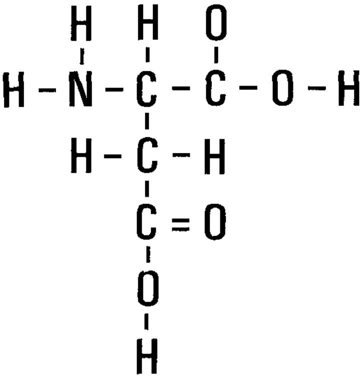
Fig. 3.2 mRNA passes through the ribosome like a punched computer tape passing through a tape-reader.

that they became an RNA strand. One year later, this feat was repeated for DNA by Arthur Kornberg.

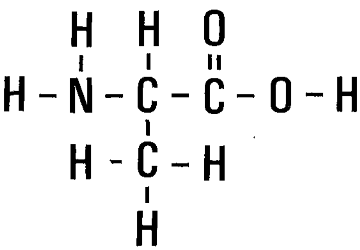
With the help of Ochoa's enzyme, it was possible to make synthetic RNA molecules containing only a single nucleotide - for example, one could join uracil molecules into the ribonucleic acid chain, ...U-U-U-U-U-U-... In



An amino acid



Aspartic acid
(hydrophilic)



Alanine
(hydrophobic)

Fig. 3.3 This figure shows aspartic acid, whose residue (R) is hydrophilic, contrasted with alanine, whose residue is hydrophobic.

1961, Marshall Nirenberg and Heinrich Matthaei used synthetic poly-U as messenger RNA in protein synthesis; and they found that only polyphenylalanine was synthesized. In the same year, Sydney Brenner and Francis Crick reported a series of experiments on mutant strains of the bacteriophage, T4. The experiments of Brenner and Crick showed that whenever a mutation added or deleted either one or two base pairs, the proteins produced by the mutants were highly abnormal and non-functional. However, when the mutation added or subtracted three base pairs, the proteins often were functional. Brenner and Crick concluded that the genetic language has three-letter words (codons). With four different "letters", A, T, G and C, this gives sixty-four possible codons - more than enough to specify the twenty different amino acids.

In the light of the phage experiments of Brenner and Crick, Niernberg and Matthaei concluded that the genetic code for phenylalanine is UUU in RNA and TTT in DNA. The remaining words in the genetic code were

Table 3.1: The genetic code

TTT=Phe	TCT=Ser	TAT=Tyr	TGT=Cys
TTC=Phe	TCC=Ser	TAC=Tyr	TGC=Cys
TTA=Leu	TCA=Ser	TAA=Ter	TGA=Ter
TTG=Leu	TCG=Ser	TAG=Ter	TGG=Trp
CTT=Leu	CCT=Pro	CAT=His	CGT=Arg
CTC=Leu	CCC=Pro	CAC=His	CGC=Arg
CTA=Leu	CCA=Pro	CAA=Gln	CGA=Arg
CTG=Leu	CCG=Pro	CAG=Gln	CGG=Arg
ATT=Ile	ACT=Thr	AAT=Asn	AGT=Ser
ATC=Ile	ACC=Thr	AAC=Asn	AGC=Ser
ATA=Ile	ACA=Thr	AAA=Lys	AGA=Arg
ATG=Met	ACG=Thr	AAG=Lys	AGG=Arg
GTT=Val	GCT=Ala	GAT=Asp	GGT=Gly
GTC=Val	GCC=Ala	GAC=Asp	GGC=Gly
GTA=Val	GCA=Ala	GAA=Glu	GGA=Gly
GTG=Val	GCG=Ala	GAG=Glu	GGG=Gly

worked out by H. Gobind Khorana of the University of Wisconsin, who used other mRNA sequences (such as GUGUGU..., AAGAAGAAG... and GUUGUUGUU...) in protein synthesis.

By 1966, the complete genetic code, specifying amino acids in terms of three-base sequences, was known. The code was found to be the same for all species studied, no matter how widely separated they were in form; and this showed that all life on earth belongs to the same family, as postulated by Darwin.

Genetic engineering

In 1970, Hamilton Smith of Johns Hopkins University observed that when the bacterium *Haemophilus influenzae* is attacked by a bacteriophage (a virus parasitic on bacteria), it can defend itself by breaking down the DNA of the phage. Following up this observation, he introduced DNA from the bacterium *E. coli* into *H. influenzae*. Again the foreign DNA was broken down.

Smith had, in fact, discovered the first of a class of bacterial enzymes which came to be called "restriction enzymes" or "restriction nucleases". Almost a hundred other restriction enzymes were subsequently discovered, and each was found to cut DNA at a specific base sequence. Smith's colleague, Daniel Nathans, used the restriction enzymes *Hin* dII and *Hin* dIII to produce the first "restriction map" of the DNA in a virus.

In 1971 and 1972, Paul Berg, and his co-workers Peter Lobban, Dale Kaiser and David Jackson at Stanford University, developed methods for adding cohesive ends to DNA fragments. Berg and his group used the calf thymus enzyme, terminal transferase, to add short, single-stranded polynucleotide segments to DNA fragments. For example, if they added the single-stranded segment AAAA to one fragment, and TTTT to another, then the two ends joined spontaneously when the fragments were incubated together. In this way Paul Berg and his group made the first recombinant DNA molecules.

The restriction enzyme *Eco* RI, isolated from the bacterium *E. coli*, was found to recognize the pattern, GAATTC, in one strand of a DNA molecule, and the complementary pattern, CTTAAG, in the other strand. Instead of cutting both strands in the middle of the six-base sequence, *Eco* RI was observed to cut both strands between G and A. Thus, each side of the cut was left with a "sticky end" - a five-base single-stranded segment, attached to the remainder of the double-stranded DNA molecule.

In 1972, Janet Mertz and Ron Davis, working at Stanford University, demonstrated that DNA strands cut with *Eco* RI could be rejoined by means of another enzyme - a DNA ligase. More importantly, when DNA strands from two different sources were cut with *Eco* RI, the sticky end of one fragment could form a spontaneous temporary bond with the sticky end of the other fragment. The bond could be made permanent by the addition of DNA ligase, even when the fragments came from different sources. Thus, DNA fragments from different organisms could be joined together.

Bacteria belong to a class of organisms (prokaryotes) whose cells do not have a nucleus. Instead, the DNA of the bacterial chromosome is arranged in a large loop. In the early 1950's, Joshua Lederberg had discovered that bacteria can exchange genetic information. He found that a frequently-exchanged gene, the F-factor (which conferred fertility), was not linked to other bacterial genes; and he deduced that the DNA of the F-factor was not physically a part of the main bacterial chromosome. In 1952, Lederberg coined the word "plasmid" to denote any extrachromosomal genetic system.

In 1959, it was discovered in Japan that genes for resistance to antibiotics can be exchanged between bacteria; and the name "R-factors" was given to these genes. Like the F-factors, the R-factors did not seem to be part of the main loop of bacterial DNA.

Because of the medical implications of this discovery, much attention was focused on the R-factors. It was found that they are plasmids, small loops of DNA existing inside the bacterial cell but not attached to the bacterial chromosome. Further study showed that, in general, between one percent and three percent of bacterial genetic information is carried by plasmids, which can be exchanged freely even between different species of bacteria.

In the words of the microbiologist, Richard Novick, "Appreciation of the role of plasmids has produced a rather dramatic shift in biologists' thinking about genetics. The traditional view was that the genetic makeup of a species was about the same from one cell to another, and was constant over long periods of time. Now a significant proportion of genetic traits are known to be variable (present in some individual cells or strains, absent in others), labile (subject to frequent loss or gain) and mobile - all because those traits are associated with plasmids or other atypical genetic systems."

In 1973, Herbert Boyer, Stanley Cohen and their co-workers at Stanford University and the University of California carried out experiments in which they inserted foreign DNA segments, cut with *Eco* RI, into plasmids (also cut with *Eco* RI). They then resealed the plasmid loops with DNA ligase. Finally, bacteria were infected with the gene-spliced plasmids. The result was a new strain of bacteria, capable of producing an additional protein coded by the foreign DNA segment which had been spliced into the plasmids.

Cohen and Boyer used plasmids containing a gene for resistance to an antibiotic, so that a few gene-spliced bacteria could be selected from a large population by treating the culture with the antibiotic. The selected bacteria, containing both the antibiotic-resistance marker and the foreign DNA, could then be cloned on a large scale; and in this way a foreign gene could be "cloned". The gene-spliced bacteria were chimeras, containing genes from two different species.

The new recombinant DNA techniques of Berg, Cohen and Boyer had revolutionary implications: It became possible to produce many copies of a given DNA segment, so that its base sequence could be determined. With the help of direct DNA-sequencing methods developed by Frederick Sanger and Walter Gilbert, the new cloning techniques could be used for mapping and sequencing genes.

Since new bacterial strains could be created, containing genes from other species, it became possible to produce any protein by cloning the corresponding gene. Proteins of medical importance could be produced on a large scale. Thus, the way was open for the production of human insulin, interferon, serum albumin, clotting factors, vaccines, and protein hormones such as ACTH, human growth factor and leuteinizing hormone.

It also became possible to produce enzymes of industrial and agricultural importance by cloning gene-spliced bacteria. Since enzymes catalyze reactions involving smaller molecules, the production of these substrate molecules through gene-splicing also became possible.

It was soon discovered that the possibility of producing new, transgenic organisms was not limited to bacteria. Gene-splicing was also carried out on higher plants and animals as well as on fungi. It was found that the bacterium *Agrobacterium tumefaciens* contains a tumor-inducing (Ti) plasmid capable of entering plant cells and producing a crown gall. Genes spliced into the Ti plasmid quite frequently became incorporated in the plant chromosome, and afterwards were inherited in a stable, Mendelian fashion.

Transgenic animals were produced by introducing foreign DNA into embryo-derived stem cells (ES cells). The gene-spliced ES cells were then selected, cultured and introduced into a blastocyst, which afterwards was implanted in a foster-mother. The resulting chimeric animals were bred, and stable transgenic lines selected.

Thus, for the first time, humans had achieved direct control over the process of evolution. Selective breeding to produce new plant and animal varieties was not new - it is one of the oldest techniques of civilization. However, the degree, precision, and speed of intervention which recombinant DNA made possible was entirely new. In the 1970's it became possible to mix the genetic repertoires of different species: The genes of mice and men could be spliced together into new, man-made forms of life!

The Polymerase chain reaction

One day in the early 1980's, an American molecular biologist, Kary Mullis, was driving to his mountain cabin with his girl friend. The journey was a long one, and to pass the time, Kary Mullis turned over and over in his mind a problem which had been bothering him: He worked for a California biotechnology firm, and like many other molecular biologists he had been struggling to analyze very small quantities of DNA. Mullis realized that it would be desirable have a highly sensitive way of replicating a given DNA segment - a method much more sensitive than cloning. As he drove through the California mountains, he considered many ways of doing this, rejecting one method after the other as impracticable. Finally a solution came to him; and it seemed so simple that he could hardly believe that he was the first to think of it. He was so excited that he immediately pulled over to the side of the road and woke his sleeping girlfriend to tell her about his idea. Although his girlfriend was not entirely enthusiastic about being wakened from a comfortable sleep to be presented with a lecture on biochemistry, Kary Mullis had in fact invented a technique which was destined to revolutionize DNA technology: the polymerase chain reaction (PCR)[2].

The technique was as follows: Begin with a small sample of the genomic DNA to be analyzed. (The sample may be extremely small - only a few molecules.) Heat the sample to 95 ^oC to separate the double-stranded DNA molecule into single strands. Suppose that on the long DNA molecule there is a target segment which one wishes to amplify. If the target segment begins with a known sequence of bases on one strand, and ends with a known sequence on the complementary strand, then synthetic "primer" oligonucleotides[3] with these known beginning ending sequences are added in excess. The temperature is then lowered to 50-60 ^oC, and at the lowered temperature, the "start" primer attaches itself to one DNA strand at the beginning of the target segment, while the "stop" primer becomes attached to the complementary strand at the other end of the target segment. Polymerase (an enzyme which aids the formation of double-stranded DNA) is then added, together with a supply of nucleotides. On each of the original pieces of single-stranded DNA, a new complementary strand is generated with the help of the polymerase. Then the temperature is again raised to 95 ^oC, so that the double-stranded DNA separates into single strands, and the cycle is repeated.

In the early versions of the PCR technique, the polymerase was destroyed by the high temperature, and new polymerase had to be added for each cycle. However, it was discovered that polymerase from the bacterium Thermus aquaticus would withstand the high temperature. (Thermus aquaticus lives in hot springs.) This discovery greatly simplified the PCR technique. The temperature could merely be cycled between the high and low temperatures, and with each cycle, the population of the target segment doubled, concentrations of primers, deoxynucleotides and polymerase being continuously present.

[2]The flash of insight didn't take long, but at least six months of hard work were needed before Mullis and his colleagues could convert the idea to reality.

[3]Short segments of single-stranded DNA.

After a few cycles of the PCR reaction, copies of copies begin to predominate over copies of the original genomic DNA. These copies of copies have a standard length, always beginning on one strand with the start primer, and ending on that strand with the complement of the stop primer.

Two main variants of the PCR technique are possible, depending on the length of the oligonucleotide primers: If, for example, trinucleotides are used as start and stop primers, they can be expected to match the genomic DNA at many points. In that case, after a number of PCR cycles, populations of many different segments will develop. Within each population, however, the length of the replicated segment will be standardized because of the predominance of copies of copies. When the resulting solution is placed on a damp piece of paper or a gel and subjected to the effects of an electric current (electrophoresis), the populations of different molecular weights become separated, each population appearing as a band. The bands are profiles of the original genomic DNA; and this variant of the PCR technique can be used in evolutionary studies to determine the degree of similarity of the genomic DNA of two species.

On the other hand, if the oligonucleotide primers contain as many as 20 nucleotides, they will be highly specific and will bind only to a particular target sequence of the genomic DNA. The result of the PCR reaction will then be a single population, containing only the chosen target segment. The PCR reaction can be thought of as autocatalytic, and as we shall see in the next section, autocatylitic systems play an important role in modern theories of the origin of life.

Theories of chemical evolution towards the origin of life

The possibility of an era of chemical evolution prior to the origin of life entered the thoughts of Charles Darwin, but he considered the idea to be much too speculative to be included in his published papers and books. However, in February 1871, he wrote a letter to his close friend Sir Joseph Hooker containing the following words:

"It is often said that all the conditions for the first production of a living organism are now present, which could ever have been present. But if (and oh what a big if) we could conceive in some warm little pond with all sorts of ammonia and phosphoric salts, - light, heat, electricity etc. present, that a protein compound was chemically formed, ready to undergo still more complex changes, at the present day such matter would be instantly devoured, or absorbed, which would not have been the case before living creatures were formed."

The last letter which Darwin is known to have dictated and signed before his death in 1882 also shows that he was thinking about this problem: "You have expressed quite correctly my views", Darwin wrote, "where you said that I had intentionally left the question of the Origin of Life uncanvassed as being altogether *ultra vires* in the present state of our knowledge, and that I dealt only with the manner of succession. I have met with no evidence that seems in the least trustworthy, in favor of so-called Spontaneous Generation. (However) I believe that I have somewhere said (but cannot find the passage) that the principle of continuity renders it probable that the principle of life will hereafter be shown to be a part, or consequence, of some general law.."

Modern researchers, picking up the problem where Darwin left it, have begun to throw a little light on the problem of chemical evolution towards the origin of life. In the 1930's J.B.S. Haldane in England and A.I. Oparin in Russia put forward theories of an era of chemical evolution prior to the appearance of living organisms. In 1924 Oparin published a pamphlet on the origin of life. An expanded version of this pamphlet was translated into English and appeared in 1936 as a book entitled *The Origin of Life on Earth.* In this book Oparin pointed out that the time when life originated, conditions on earth were probably considerably different than they are at present: The atmosphere probably contained very little free oxygen, since free oxygen is produced by photosynthesis which did not yet exist. On the other hand, he argued, there were probably large amounts of methane and ammonia in the earth's primitive atmosphere[4]. Thus, before the origin of life, the earth probably had a reducing atmosphere rather than an oxidizing one. Oparin believed that energy-rich molecules could have been formed very slowly by the action of light from the sun. On the present-day earth, bacteria quickly consume energy-rich molecules, but before the origin of life, such molecules could have accumulated, since there were no living organisms to consume them. (This observation is similar to the remark made by Darwin in his 1871 letter to Hooker.)

The first experimental work in this field took place in 1950 in the laboratory of Melvin Calvin at the University of California, Berkeley. Calvin and his co-workers wished to determine experimentally whether the primitive atmosphere of the earth could have been converted into some of the molecules which are the building-blocks of living organisms. The energy needed to perform these conversions they imagined to be supplied by volcanism, radioactive decay, ultraviolet radiation, meteoric impacts, or by lightning strokes.

The earth is thought to be approximately 4.6 billion years old. At the time when Calvin and his co-workers were performing their experiments,

[4]It is now believed that the main constituents of the primordial atmosphere were carbon dioxide, water, nitrogen, and a little methane.

the earth's primitive atmosphere was believed to have consisted primarily of hydrogen, water, ammonia, methane, and carbon monoxide, with a little carbon dioxide. A large quantity of hydrogen was believed to have been initially present in the primitive atmosphere, but it was thought to have been lost gradually over a period of time because the earth's gravitational attraction is too weak to effectively hold such a light and rapidly-moving molecule. However, Calvin and his group assumed sufficient hydrogen to be present to act as a reducing agent. In their 1950 experiments they subjected a mixture of hydrogen and carbon dioxide, with a catalytic amount of Fe^{2+}, to bombardment by fast particles from the Berkeley cyclotron. Their experiments resulted in a good yield of formic acid and a moderate yield of formaldehyde. (The fast particles from the cyclotron were designed to simulate an energy input from radioactive decay on the primitive earth.)

Two years later, Stanley Miller, working in the laboratory of Harold Urey at the University of Chicago, performed a much more refined experiment of the same type. In Miller's experiment, a mixture of the gases methane, ammonia, water and hydrogen was subjected to an energy input from an electric spark. Miller's apparatus was designed so that the gases were continuously circulated, passing first through the spark chamber, then through a water trap which removed the non-volatile water soluble products, and then back again through the spark chamber, and so on. The resulting products are shown as a function of time in Figure 3.5.

The Miller-Urey experiment produced many of the building-blocks of living organisms, including glycine, glycolic acid, sarcosine, alanine, lactic acid, N-methylalanine, β-alanine, succinic acid, aspartic acid, glutamic acid, iminodiacetic acid, iminoacetic-propionic acid, formic acid, acetic acid, propionic acid, urea and N-methyl urea [5]. Another major product was hydrogen cyanide, whose importance as an energy source in chemical evolution was later emphasized by Calvin.

The Miller-Urey experiment was repeated and extended by the Ceylonese-American biochemist Cyril Ponnamperuma and by the American expert in planetary atmospheres, Carl Sagan. They showed that when phosphorus is made available, then in addition to amino acids, the Miller-Urey experiment produces not only nucleic acids of the type that join together to form DNA, but also the energy-rich molecule ATP (adenosine triphosphate). ATP is extremely important in biochemistry, since it is a universal fuel which drives chemical reactions inside present-day living organisms.

Further variations on the Miller-Urey experiment were performed by

[5] The chemical reaction that led to the formation of the amino acids that Miller observed was undoubtedly the Strecker synthesis: $HCN+NH_3+RC{=}O+H_2O \rightarrow RC(NH_2)COOH$.

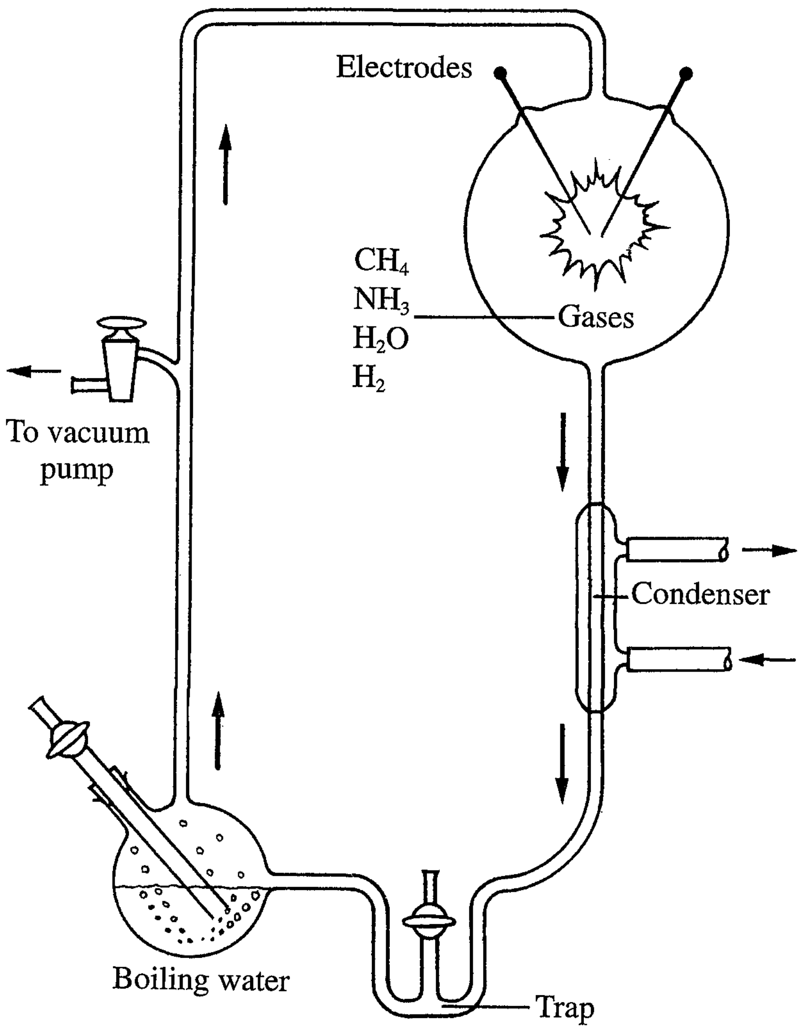


Fig. 3.4 Miller's apparatus

Sydney Fox and his co-workers at the University of Miami. Fox and his group showed that amino acids can be synthesized from a primitive atmosphere by means of a thermal energy input, and that in the presence of phosphate esters, the amino acids can be thermally joined together to form polypeptides. However, some of the peptides produced in this way were cross linked, and hence not of biological interest.

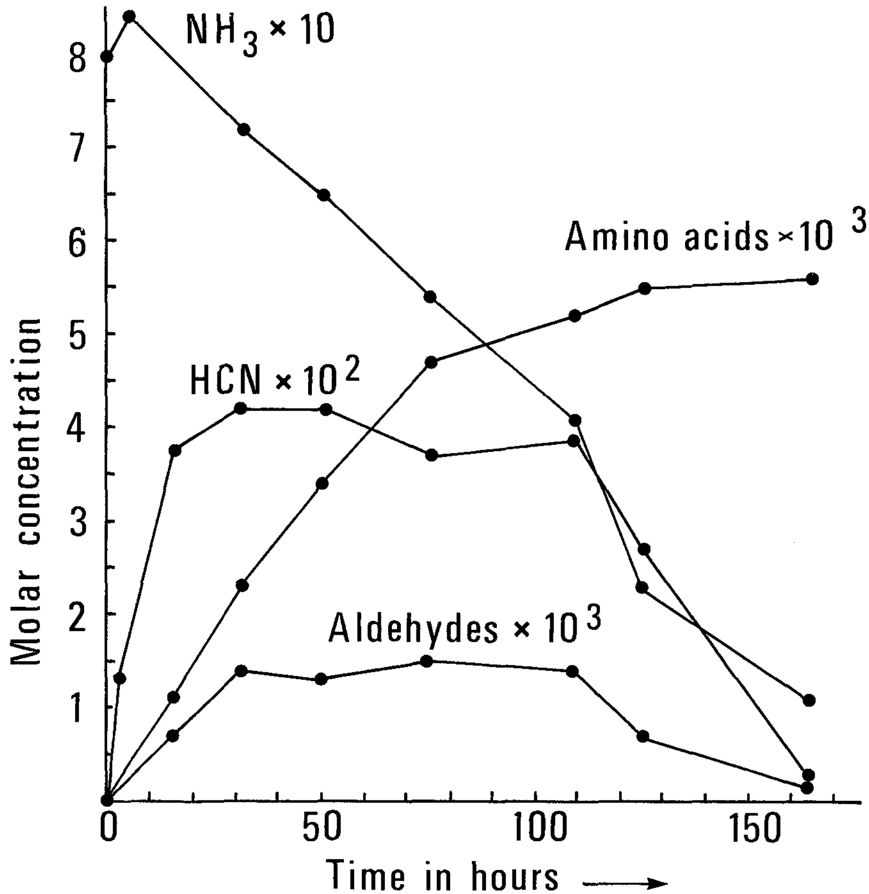


Fig. 3.5 Products as a function of time in the Miller-Urey experiment

In 1969, Melvin Calvin published an important book entitled *Chemical Evolution; Molecular Evolution Towards the Origin of Living Systems on Earth and Elsewhere.* In this book, Calvin reviewed the work of geochemists showing the presence in extremely ancient rock formations of molecules which we usually think of as being produced only by living organisms. He then discussed experiments of the Miller-Urey type - experiments simulating the first step in chemical evolution. According to Calvin, not only amino acids but also the bases adenine, thymine, guanine, cytosine and uracil, as well as various sugars, were probably present in the primitive ocean in moderate concentrations, produced from the primitive atmosphere by the available energy inputs, and not broken down because no organisms were present.

The next steps visualized by Calvin were dehydration reactions in which the building blocks were linked together into peptides, polynucleotides, lipids and porphyrins. Such dehydration reactions are in a thermodynamically uphill direction. In modern organisms, they are driven by a universally-used energy source, the high-energy phosphate bond of adenosine triphosphate (ATP). Searching for a substance present in the primitive ocean which could have driven the dehydrations, Calvin and his coworkers experimented with hydrogen cyanide (HC≡N), and from the results of these experiments they concluded that the energy stored in the carbon-nitrogen triple bond of HC≡N could indeed have driven the dehydration reactions necessary for polymerization of the fundamental building blocks. However, later work made it seem improbable that peptides could be produced from cyanide mixtures.

In *Chemical Evolution*, Calvin introduced the concept of autocatalysis as a mechanism for molecular selection, closely analogous to natural selection in biological evolution. Calvin proposed that there were a few molecules in the ancient oceans which could catalyze the breakdown of the energy-rich molecules present into simpler products. According to Calvin's hypothesis, in a very few of these reactions, the reaction itself produced more of the catalyst. In other words, in certain cases the catalyst not only broke down the energy-rich molecules into simpler products but also catalyzed their own synthesis. These autocatalysts, according to Calvin, were the first systems which might possibly be regarded as living organisms. They not only "ate" the energy-rich molecules but they also reproduced - i.e., they catalyzed the synthesis of molecules identical with themselves.

Autocatalysis leads to a sort of molecular natural selection, in which the precursor molecules and the energy-rich molecules play the role of "food", and the autocatalytic systems compete with each other for the food supply. In Calvin's picture of molecular evolution, the most efficient autocatalytic systems won this competition in a completely Darwinian way. These more efficient autocatalysts reproduced faster and competed more successfully for precursors and for energy-rich molecules. Any random change in the direction of greater efficiency was propagated by natural selection.

What were these early autocatalytic systems, the forerunners of life? Calvin proposed several independent lines of chemical evolution, which later, he argued, joined forces. He visualized the polynucleotides, the polypeptides, and the metallo-porphyrins as originally having independent lines of chemical evolution. Later, he argued, an accidental union of these independent autocatalysts showed itself to be a still more efficient autocatalytic system. He pointed out in his book that "autocatalysis" is perhaps too strong a word. One should perhaps speak instead of "reflexive catalysis", where a molecule does not necessarily catalyze the synthesis of itself, but perhaps only the synthesis of a precursor. Like autocatalysis, reflexive catalysis is capable of exhibiting Darwinian selectivity.

The theoretical biologist, Stuart Kauffman, working at the Santa Fe Institute, has constructed computer models for the way in which the components of complex systems of reflexive catalysts may have been linked together. Kauffman's models exhibit a surprising tendency to produce orderly behavior even when the links are randomly programmed.

In 1967 and 1968, C. Woese, F.H.C. Crick and L.E. Orgel proposed that there may have been a period of chemical evolution involving RNA alone, prior to the era when DNA, RNA and proteins joined together to form complex self-reproducing systems. In the early 1980's, this picture of an "RNA world" was strengthened by the discovery (by Thomas R. Cech and Sydney Altman) of RNA molecules which have catalytic activity.

In connection with autocatalytic systems, it is interesting to think of the polymerase chain reaction, which we discussed above. The target segment of DNA and the polymerase together form an autocatalytic system. The "food" molecules are the individual nucleotides in the solution. In the PCR system, a segment of DNA reproduces itself with an extremely high degree of fidelity. One can perhaps ask whether systems like the PCR system can have been among the forerunners of living organisms. The cyclic changes of temperature needed for the process could have been supplied by the cycling of water through a hydrothermal system. There is indeed evidence that hot springs and undersea hydrothermal vents may have played an important role in chemical evolution towards the origin of life. We will discuss this evidence in the next section.

Throughout this discussion of theories of chemical evolution, and the experiments which have been done to support these theories, energy has played a central role. None of the transformations discussed above could have taken place without an energy source, or to be more precise, they could not have taken place without a source of *free* energy. In Chapter 4 we will discuss in detail the reason why free energy plays a central role, not only in the origin of life but also in life's continuation. We will see that there is a connection between free energy and information, and that information-containing free energy is needed to produce the high degree of order which is characteristic of life.

Molecular evidence establishing family trees in evolution

Starting in the 1970's, the powerful sequencing techniques developed by Sanger and others began to be used to establish evolutionary trees. The evolutionary closeness or distance of two organisms could be estimated from the degree of similarity of the amino acid sequences of their proteins, and also by comparing the base sequences of their DNA and RNA. One of the first studies of this kind was made by R.E. Dickerson and his coworkers, who studied the amino acid sequences in Cytochrome C, a protein of very ancient origin which is involved in the "electron transfer chain" of respiratory metabolism. Some of the results of Dickerson's studies are shown in Figure 3.6.

Comparison of the base sequences of RNA and DNA from various species proved to be even more powerful tool for establishing evolutionary relationships. Figure 3.7 shows the universal phylogenetic tree established in this way by Iwabe, Woese and their coworkers. [6] In Figure 3.7, all presently living organisms are divided into three main kingdoms, Eukaryotes, Eubacteria, and Archaebacteria. Carl Woese, who proposed this classification on the basis of comparative sequencing, wished to call the three kingdoms "Eucarya, Bacteria and Archaea". However, the most widely accepted terms are the ones shown in capital letters on the figure. Before the comparative RNA sequencing work, which was performed on the ribosomes of various species, it had not been realized that there are two types of bacteria, so markedly different from each other that they must be classified as belonging to separate kingdoms. One example of the difference between archaebacteria and eubacteria is that the former have cell membranes which contain ether lipids, while the latter have ester lipids in their cell membranes. Of the three kingdoms, the eubacteria and the archaebacteria are "prokaryotes", that is to say, they are unicellular organisms having no cell nucleus. Most of the eukaryotes, whose cells contain a nucleus, are also unicellular, the exceptions being plants, fungi and animals.

One of the most interesting features of the phylogenetic tree shown in Figure 3.7 is that the deepest branches - the organisms with shortest pedigrees - are all hyperthermophiles, i.e. they live in extremely hot environments such as hot springs or undersea hydrothermal vents. The shortest branches represent the most extreme hyperthermophiles. The group of archaebacteria indicated by (1) in the figure includes **Thermofilum, Thermoproteus, Pyrobaculum, Pyrodictium, Desulfuro-**

[6] "Phylogeny" means "the evolutionary development of a species". "Ontogeny" means "the growth and development an individual, through various stages, for example, from fertilized egg to embryo, and so on." Ernst Haeckel, a 19th century follower of Darwin, observed that, in many cases, "ontogeny recapitulates phylogeny."

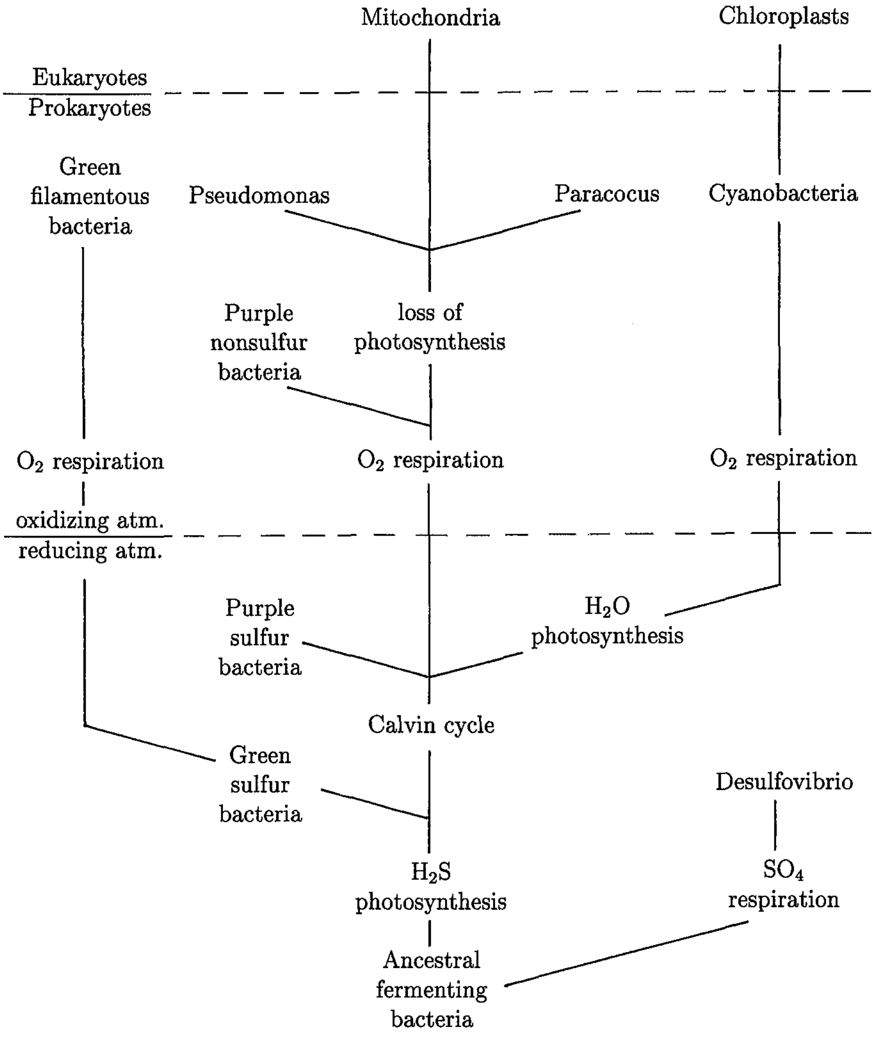


Fig. 3.6 Evolutionary relationships established by Dickerson and coworkers by comparing the amino acid sequences of Cytochrome C from various species.

coccus, and **Sulfolobus** - all hypothermophiles[7]. Among the eubacteria,

[7]Group (2) in Figure 3.7 includes **Methanothermus**, which is hyperthermophilic, and Methanobacterium, which is not. Group (3) includes **Archaeoglobus**, which is hyperthermophilic, and Halococcus, Halobacterium, Methanoplanus, Methanospirilum, and Methanosarcina, which are not.

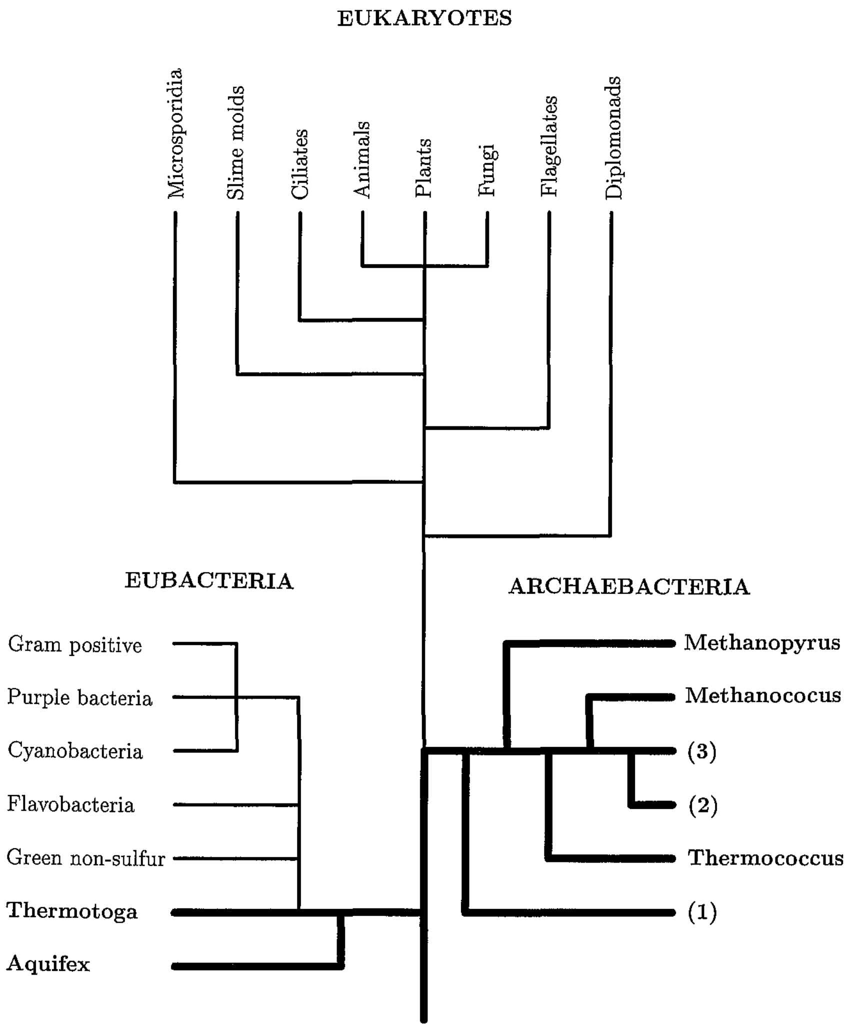


Fig. 3.7 This figure shows the universal phylogenetic tree, established by the work of Woese, Iwabe et al. Hyperthermophiles are indicated by bold lines and by bold type.

the two shortest branches, **Aquifex** and **Thermatoga** are both hyperthermophiles[8].

The phylogenetic evidence for the existence of hyperthermophiles at a very early stage of evolution lends support to a proposal put forward in

[8]Thermophiles are a subset of the larger group of extremophiles.

1988 by the German biochemist Günter Wächterhäuser. He proposed that the reaction for pyrite formation,

$$FeS+H_2S \rightarrow FeS_2+2H^++2e^-$$

which takes place spontaneously at high temperatures, supplied the energy needed to drive the first stages of chemical evolution towards the origin of life. Wächterhäuser pointed out that the surface of the mineral pyrite (FeS_2) is positively charged, and he proposed that, since the immediate products of carbon-dioxide fixation are negatively charged, they would be attracted to the pyrite surface. Thus, in Wächterhäuser's model, pyrite formation not only supplied the reducing agent needed for carbon-dioxide fixation, but also the pyrite surface aided the process. Wächterhäuser further proposed an archaic autocatylitic carbon-dioxide fixation cycle, which he visualized as resembling the reductive citric acid cycle found in present-day organisms, but with all reducing agents replaced by $FeS+H_2S$, with thioester activation replaced by thioacid activation, and carbonyl groups replaced by thioenol groups. The interested reader can find the details of Wächterhäuser's proposals in his papers, which are listed at the end of this chapter.

Table 3.2 shows the energy-yielding reactions which drive the metabolisms of some organisms which are of very ancient evolutionary origin. All the reactions shown in the table make use of H_2, which could have been supplied by pyrite formation at the time when the organisms evolved. All these organisms are lithoautotrophic, a word which requires some explanation: A *heterotrophic* organism is one which lives by ingesting energy-rich organic molecules which are present in its environment. By contrast, an *autotrophic* organism is able to get along without energy-rich organic molecules as food. The *lithoautotrophs* use energy from inorganic molecules, while the metabolisms of *photoautotrophs* are driven by energy from sunlight.

Evidence from layered rock formations called "stromatolites", produced by colonies of photosynthetic bacteria, show that photoautotrophs (or phototrophs) appeared on earth at least 3.5 billion years ago. The geological record also supplies approximate dates for other events in evolution. For example, the date at which molecular oxygen started to become abundant in the earth's atmosphere is believed to have been 2.0 billion years ago, with equilibrium finally being established 1.5 billion years in the past. Multicellular organisms appeared very late on the evolutionary and geological time-scale - only 600 million years ago. By collecting such evidence, the Belgian cytologist Christian de Duve has constructed the phylogenetic tree shown in Figure 3.8, showing branching as a function of time. One very

Table 3.2: Energy-yielding reactions of some lithoautotrophic hyperthermophiles. (After K.O. Setter)

Energy-yielding reaction	Genera
$4H_2+CO_2 \rightarrow CH_4+2H_2O$	Methanopyrus, Methanothermus, Methanococcus
$H_2+S^0 \rightarrow H_2S$	Pyrodictium, Thermoproteus, Pyrobaculum, Acidianus, Stygiolobus
$4H_2+H_2SO_4 \rightarrow H_2S+4H_2O$	Archaeoglobus

interesting feature of this tree is the arrow indicating the transfer of "endosymbionts" from the eubacteria to the eukaryotes. In the next section, we will look in more detail at this important event, which took place about 1.8 billion years ago.

Symbiosis

The word "symbiosis" is derived from Greek roots meaning "living together". It was coined in 1877 by the German botanist Albert Bernard Frank. By that date, it had become clear that lichens are composite organisms involving a fungus and an alga; but there was controversy concerning whether the relationship was a parasitic one. Was the alga held captive and exploited by the fungus? Or did the alga and the fungus help each other, the former performing photosynthesis, and the latter leeching minerals from the lichen's environment? In introducing the word "symbiosis" (in German, "Symbiotismus"), Frank remarked that "We must bring all the cases where two different species live on or in one another under a comprehensive concept which does not consider the role which the two individuals play but is based on the mere coexistence, and for which the term symbiosis

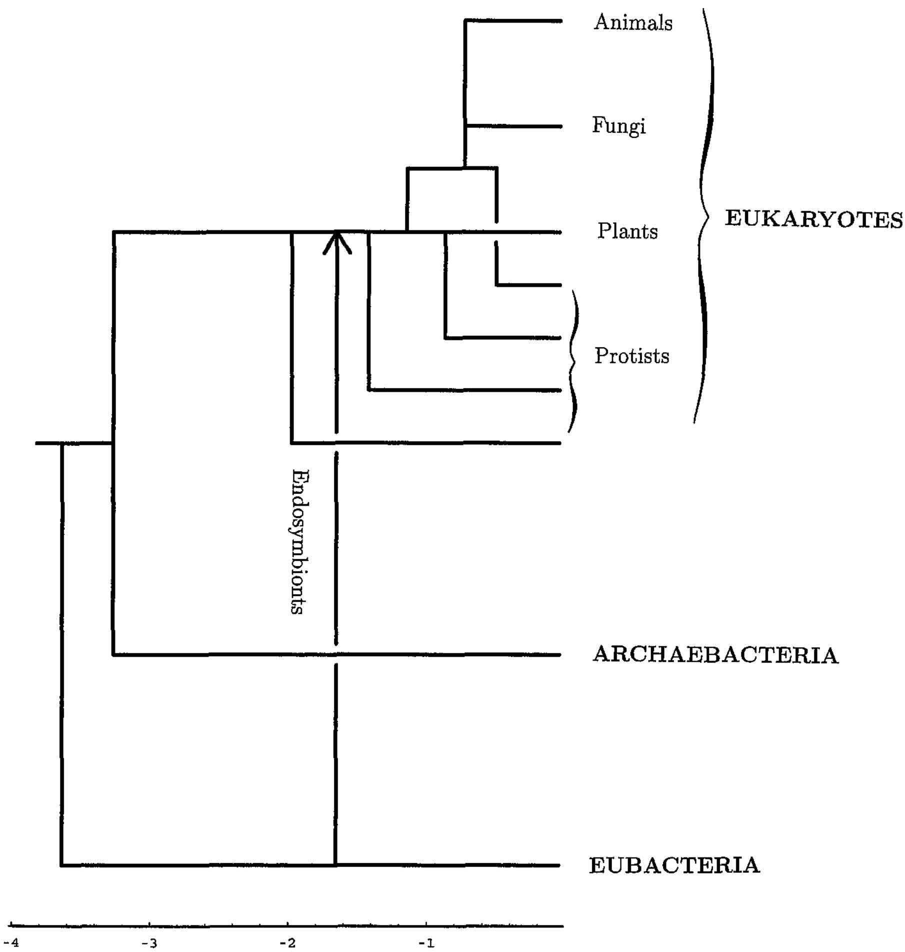


Fig. 3.8 Branching of the universal phylogenetic tree as a function of time. "Protists" are unicellular eukaryotes.

is to be recommended." Thus the concept of symbiosis, as defined by Frank, included all intimate relationships between two or more species, including parasitism at one extreme and "mutualism" at the other. However, as the word is used today, it usually refers to relationships which are mutually beneficial.

Charles Darwin himself had been acutely aware of close and mutually beneficial relationships between organisms of different species. For example, in his work on the fertilization of flowers, he had demonstrated the way in which insects and plants can become exquisitely adapted to each other's needs. However, T.H. Huxley, "Darwin's bulldog", emphasized competition as the predominant force in evolution. "The animal world is on about the same level as a gladiator's show", Huxley wrote in 1888, "The creatures are fairly well treated and set to fight - whereby the strongest, the swiftest and the cunningest live to fight another day. The spectator has no need to turn his thumbs down, as no quarter is given." The view of nature as a sort of "gladiator's contest" dominated the mainstream of evolutionary thought far into the 20th century; but there was also a growing body of opinion which held that symbiosis could be an extremely important mechanism for the generation of new species. Among the examples of symbiosis studied by Frank were the nitrogen-fixing bacteria living in nodules on the roots of legumes, and the mycorrhizal fungi which live on the roots of forest trees such as oaks, beech and conifers. Frank believed that the mycorrhizal fungi aid in the absorption of nutrients. He distinguished between "ectotrophic" fungi, which form sheaths around the root fibers, and "endotrophic" fungi, which penetrate the root cells. Other examples of symbiosis studied in the 19th century included borderline cases between plants and animals, for example, paramecia, sponges, hydra, planarian worms and sea anemones, all of which frequently contain green bodies capable of performing photosynthesis.

Writing in 1897, the American lichenologist Albert Schneider prophesied that "future studies may demonstrate that.., plasmic bodies (within the eukaryote cell), such as chlorophyll granules, leucoplastids, chromoplastids, chromosomes, centrosomes, nucleoli, etc., are perhaps symbionts comparable to those in less highly specialized symbiosis. Reinke expresses the opinion that it is not wholly unreasonable to suppose that some highly skilled scientist of the future may succeed in cultivating chlorophyll-bodies in artificial media."

19th century cytologists such as Robert Altman, Andreas Schimper and A. Benda focused attention on the chlorophyll-bodies of plants, which Schimper named *chloroplasts*, and on another type of subcellular granule, present in large numbers in all plant and animal cells, which Benda named *mitochondria*, deriving the name from the Greek roots *mitos* (thread) and *chrondos* (granule). They observed that these bodies seemed to reproduce themselves within the cell in very much the manner that might be expected if they were independent organisms. Schimper suggested that chloroplasts are symbionts, and that green plants owe their origin to a union of a colorless unicellular organism with a smaller chlorophyll-containing species.

The role of symbiosis in evolution continued to be debated in the 20th century. Mitochondria were shown to be centers of respiratory metabolism; and it was discovered that both mitochondria and chloroplasts contain their own DNA. However, opponents of their symbiotic origin pointed out that mitochondria alone cannot synthesize all their own proteins: Some mitochondrial proteins require information from nuclear DNA. The debate was finally settled in the 1970's, when comparative sequencing of ribosomal RNA in the laboratories of Carl Woese, W. Ford Doolittle and Michael Gray showed conclusively that both chloroplasts and mitochondria were originally endosymbionts. The ribosomal RNA sequences showed that chloroplasts had their evolutionary root in the cyanobacteria, a species of eubacteria, while mitochondria were traced to a group of eubacteria called the alpha-proteobacteria. Thus the evolutionary arrow leading from the eubacteria to the eukaryotes can today be drawn with confidence, as in Figure 3.8.

Cyanobacteria are bluish photosynthetic bacteria which often become linked to one another so as to form long chains. They can be found today growing in large colonies on seacoasts in many parts of the world, for example in Baja California on the Mexican coast. The top layer of such colonies consists of the phototrophic cyanobacteria, while the organisms in underlying layers are heterotrophs living off the decaying remains of the cyanobacteria. In the course of time, these layered colonies can become fosilized, and they are the source of the layered rock formations called stromatolites (discussed above). Geological dating of ancient stromatolites has shown that cyanobacteria must have originated at least 3.5 billion years ago.

Cyanobacteria contain two photosystems, each making use of a different type of chlorophyll. Photosystem I, which is thought to have evolved first, uses the energy of light to draw electrons from inorganic compounds, and sometimes also from organic compounds (but never from water). Photosystem II, which evolved later, draws electrons from water. Hydrogen derived from the water is used to produce organic compounds from carbon-dioxide, and molecular oxygen is released into the atmosphere. Photosystem II never appears alone. In all organisms which possess it, Photosystem II is coupled to Photosystem I, and together the two systems raise electrons to energy levels that are high enough to drive all the processes of metabolism.

Dating of ancient stromatolites makes it probable that cyanobacteria began to release molecular oxygen into the earth's atmosphere at least 3.5 billion years ago; yet from other geological evidence we know that it was only 2 billion years ago that the concentration of molecular oxygen began to rise, equilibrium being reached 1.5 billion years ago. It is believed that ferrous iron, which at one time was very abundant, initially absorbed the photosynthetically produced oxygen. This resulted in the time-lag, as well as the ferrous-ferric mixture of iron which is found in the mineral magnetite.

When the concentrations of molecular oxygen began to rise in earnest, most of the unicellular microorganisms living at the time found themselves in deep trouble, faced with extinction, because for them oxygen was a deadly poison; and very many species undoubtedly perished. However, some of the archaebacteria retreated to isolated anaerobic niches where we find them today, while others found ways of detoxifying the poisonous oxygen. Among the eubacteria, the ancestors of the alpha-proteobacteria were particularly good at dealing with oxygen and even turning it to advantage: They developed the biochemical machinery needed for respiratory metabolism.

Meanwhile, during the period between 3.5 and 2.0 billion years before the present, an extremely important evolutionary development had taken place: Branching from the archaebacteria, a line of large[9] heterotrophic unicellular organisms had evolved. They lacked rigid cell walls, and they could surround smaller organisms with their flexible outer membrane, drawing the victims into their interiors to be digested. These new heterotrophs were the ancestors of present-day eukaryotes, and thus they were the ancestors of all multicellular organisms.

Not only are the cells of present-day eukaryotes very much larger than the cells of archaebacteria and eubacteria; their complexity is also astonishing. Every eukaryote cell contains numerous intricate structures: a nucleus, cytoskeleton, Golgi apparatus, endoplasmic reticulum, mitochondria, peroxisomes, chromosomes, the complex structures needed for mitotic cell division, and so on. Furthermore, the genomes of eykaryotes contain very much more information than those of prokaryotes. How did this huge and relatively sudden increase in complexity and information content take place? According to a growing body of opinion, symbiosis played an important role in this development.

The ancestors of the eukaryotes were in the habit of drawing the smaller prokaryotes into their interiors to be digested. It seems likely that in a few cases the swallowed prokaryotes resisted digestion, multiplied within the host, were transmitted to future generations when the host divided, and conferred an evolutionary advantage, so that the result was a symbiotic relationship. In particular, both mitochondria and chloroplasts have definitely been proved to have originated as endosymbionts. It is easy to understand how the photosynthetic abilities of the chloroplasts (derived from cyanobacteria) could have conferred an advantage to their hosts, and how mitochondria (derived from alpha-proteobacteria) could have helped

[9] not large in an absolute sense, but large in relation to the prokaryotes

their hosts to survive the oxygen crisis. The symbiotic origin of other subcellular organelles is less well understood and is currently under intense investigation.

If we stretch the definition of symbiosis a little, we can make the concept include cooperative relationships between organisms of the same species. For example, cyanobacteria join together to form long chains, and they live together in large colonies which later turn into stromatolites. Also, some eubacteria have a mechanism for sensing how many of their species are present, so that they know, like a wolf pack, when it is prudent to attack a larger organism. This mechanism, called "quorum sensing", has recently attracted much attention among medical researchers.

The cooperative behavior of a genus of unicellular eukaryotes called slime molds is particularly interesting because it gives us a glimpse of how multicellular organisms may have originated. The name of the slime molds is misleading, since they are not fungi, but heterotrophic protists similar to amoebae. Under ordinary circumstances, the individual cells wander about independently searching for food, which they draw into their interiors and digest, a process called "phagocytosis". However, when food is scarce, they send out a chemical signal of distress. Researchers have analyzed the molecule which expresses slime mold unhappiness, and they have found it to be cyclic adenosine monophosphate (cAMP). At this signal, the cells congregate and the mass of cells begins to crawl, leaving a slimy trail. At it crawls, the community of cells gradually develops into a tall stalk, surmounted by a sphere - the "fruiting body". Inside the sphere, spores are produced by a sexual process. If a small animal, for example a mouse, passes by, the spores may adhere to its coat; and in this way they may be transported to another part of the forest where food is more plentiful.

Thus slime molds represent a sort of missing link between unicellular and multicellular or organisms. Normally the cells behave as individualists, wandering about independently, but when challenged by a shortage of food, the slime mold cells join together into an entity which closely resembles a multicellular organism. The cells even seem to exhibit altruism, since those forming the stalk have little chance of survival, and yet they are willing to perform their duty, holding up the sphere at the top so that the spores will survive and carry the genes of the community into the future. We should especially notice the fact that the cooperative behavior of the slime mold cells is coordinated by chemical signals.

Sponges are also close to the borderline which separates unicellular eukaryotes (protists) from multicellular organisms, but they are just on the other side of the border. Normally the sponge cells live together in a multicellular community, filtering food from water. However, if a living sponge is forced through a very fine cloth, it is possible to separate the cells from each other. The sponge cells can live independently for some time; but if many of them are left near to one another, they gradually join together and form themselves into a new sponge, guided by chemical signals. In a refinement of this experiment, one can take two living sponges of different species, separate the cells by passing the sponges through a fine cloth, and afterwards mix all the separated cells together. What happens next is amazing: The two types of sponge cells sort themselves out and become organized once more into two sponges - one of each species.

Slime molds and sponges hint at the genesis of multicellular organisms, whose evolution began approximately 600 million years ago. Looking at the slime molds and sponges, we can imagine how it happened. Some unicellular organisms must have experienced an enhanced probability of survival when they lived as colonies. Cooperative behavior and division of labor within the colonies were rewarded by the forces of natural selection, with the selective force acting on the entire colony of cells, rather than on the individual cell. This resulted in the formation of cellular societies and the evolution of mechanisms for cell differentiation. The division of labor within cellular societies (i.e., differentiation) came to be coordinated by chemical signals which affected the transcription of genetic information and the synthesis of proteins. Each cell within a society of cells possessed the entire genome characteristic of the colony, but once a cell had been assigned its specific role in the economy of the society, part of the information became blocked - that is, it was not expressed in the function of that particular cell. As multicellular organisms evolved, the chemical language of intercellular communication became very much more complex and refined. We will discuss the language of intercellular communication in more detail in a later section.

Geneticists have become increasingly aware that symbiosis has probably played a major role in the evolution of multicellular organisms. We mentioned above that, by means of genetic engineering techniques, transgenic plants and animals can be produced. In these chimeras, genetic material from a foreign species is incorporated into the chromosomes, so that it is inherited in a stable, Mendelian fashion. J.A. Shapiro, one of whose articles is referenced at the end of this chapter, believes that this process also occurs in nature, so that the conventional picture of evolutionary family trees needs to be corrected. Shapiro believes that instead of evolutionary trees, we should perhaps think of webs or networks.

For example, it is tempting to guess that symbiosis may have played a role in the development of the visual system of vertebrates. One of the archaebacteria, the purple halobacterium halobium (recently renamed halobacterium salinarum), is able to perform photosynthesis by means of a protein called bacterial rhodopsin, which transports hydrogen ions across the bacterial membrane. This protein is a near chemical relative of rhodopsin, which combines with a carotinoid to form the "visual purple" used in the vertebrate eye. It is tempting to think that the close similarity of the two molecules is not just a coincidence, and that vertebrate vision originated in a symbiotic relationship between the photosynthetic halobacterium and an aquatic ancestor of the vertebrates, the host being able to sense when the halobacterium was exposed to light and therefore transporting hydrogen ions across its cell membrane.

In this chapter, we have looked at the flow of energy and information in the origin and evolution of life on earth. We have seen how energy-rich molecules were needed to drive the first steps in the origin of life, and how during the evolutionary process, information was preserved, transmitted, and shared between increasingly complex organisms, the whole process being driven by an input of energy. In the next chapter, we will look closely at the relationships between energy and information.

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Chapter 4

STATISTICAL MECHANICS AND INFORMATION

The second law of thermodynamics

In this chapter, we discuss the origin and evolution of living organisms from the standpoint of thermodynamics, statistical mechanics and information theory. In particular, we discuss the work of Maxwell, Boltzmann, Gibbs, Szilard, and Shannon. Their research established the fact that free [1] energy contains information, and that it can thus be seen as the source of the order and complexity of living systems. The reader who prefers to avoid mathematics may jump quickly over the equations in this chapter without losing the thread of the argument, provided that he or she is willing to accept this conclusion.

Our starting point is the second law of thermodynamics, which was discovered by Nicolas Léonard Sadi Carnot (1796-1832) and elaborated by Rudolf Clausius (1822-1888) and William Thomson (later Lord Kelvin, 1824-1907). Carnot came from a family of distinguished French politicians and military men, but instead of following a political career, he studied engineering. In 1824, his only scientific publication appeared - a book with the title *Reflections on the Motive Power of Fire.* Although it was ignored for the first few years after its publication, this single book was enough to secure Carnot a place in history as the founder of the science of thermodynamics. In his book, Carnot introduced a scientific definition of work which we still use today - "weight lifted through a height"; in other words, force times distance. At the time when Carnot was writing, much attention was being given to improving the efficiency of steam engines. Although James Watt's steam engines were far more efficient than previous models, they still could only convert between 5 % and 7 % of the heat energy of their fuels into useful work. Carnot tried to calculate the theoretical maximum of the efficiency of steam engines, and he was able to show that an engine

[1] i.e. energy from which work can be derived

operating between the temperatures T_1 and T_2 could at most attain

$$\text{maximum efficiency} = \frac{T_1 - T_2}{T_1} \tag{4.1}$$

Here T_1 is the temperature of the input steam, and T_2 is the temperature of the cooling water. Both these temperatures are absolute temperatures, i.e., temperatures proportional to the volume of a given quantity of gas at constant pressure.

Carnot died of cholera at the age of 36. Fifteen years after his death, the concept of absolute temperature was further clarified by Lord Kelvin (1824-1907), who also helped to bring Carnot's work to the attention of the scientific community.

Building on the work of Carnot, the German theoretical physicist Rudolph Clausius was able to deduce an extremely general law. He discovered that the ratio of the heat content of a closed system to its absolute temperature always increases in any process. He called this ratio the *entropy* of the system. In the notation of modern thermodynamics, the change in entropy dS when a small amount of heat dq is transferred to a system is given by

$$dS = \frac{dq}{T} \tag{4.2}$$

Let us imagine a closed system consisting of two parts, one at temperature T_1, and the other part at a lower temperature T_2. If a small amount of heat dq flows from the warmer part to the cooler one, the small resulting change in entropy of the total system will be

$$dS = \frac{dq}{T_2} - \frac{dq}{T_1} > 0 \tag{4.3}$$

According to Clausius, since heat never flows spontaneously from a colder object to a warmer one, the entropy of a closed system always increases; that is to say, dS is always positive. As heat continues to flow from the warmer part of the system to the cooler part, the system's energy becomes less and less available for doing work. Finally, when the two parts have reached the same temperature, no work can be obtained. When the parts differed in temperature, a heat engine could in principle be run between them, making use of the temperature difference; but when the two parts have reached the same temperature, this possibility no longer exists. The law stating that the entropy of a closed system always increases is called the second law of thermodynamics.

Maxwell's demon

In England, the brilliant Scottish theoretical physicist, James Clerk Maxwell (1831-1879) invented a thought experiment which demonstrated that the second law of thermodynamics is statistical in nature and that there is a relationship between entropy and information. It should be mentioned that at the time when Clausius and Maxwell were living, not all scientists agreed about the nature of heat, but Maxwell, like Kelvin, believed heat to be due to the rapid motions of atoms or molecules. The more rapid the motion, the greater the temperature.

In a discussion of the ideas of Carnot and Clausius, Maxwell introduced a model system consisting of a gas-filled box divided into two parts by a wall; and in this wall, Maxwell imagined a small weightless door operated by a "demon". Initially, Maxwell let the temperature and pressure in both parts of the box be equal. However, he made his demon operate the door in such a way as to sort the gas particles: Whenever a rapidly-moving particle approaches from the left, Maxwell's demon opens the door; but when a slowly moving particle approaches from the left, the demon closes it. The demon has the opposite policy for particles approaching from the right, allowing the slow particles to pass, but turning back the fast ones. At the end of Maxwell's thought experiment, the particles are sorted, with the slow ones to the left of the barrier, and the fast ones to the right. Although initially, the temperature was uniform throughout the box, at the end a temperature difference has been established, the entropy of the total system is *decreased* and the second law of thermodynamics is violated.

In 1871, Maxwell expressed these ideas in the following words: "If we conceive of a being whose faculties are so sharpened that he can follow every molecule in its course, such a being, whose attributes are still finite as our own, would be able to do what is at present impossible to us. For we have seen that the molecules in a vessel full of air are moving at velocities by no means uniform... Now let us suppose that such a vessel full of air at a uniform temperature is divided into two portions, A and B, by a division in which there is a small hole, and that a being who can see individual molecules, opens and closes swifter molecules to pass from A to B, and only slower ones to pass from B to A. He will thus, without the expenditure of work, raise the temperature of B and lower that of A, in contradiction to the second law of thermodynamics." Of course Maxwell admitted that demons and weightless doors do not exist. However, he pointed out, one could certainly imagine a small hole in the partition between the two halves of the box. The sorting could happen by chance (although the probability of its happening decreases rapidly as the number of gas particles becomes large). By this argument, Maxwell demonstrated that the second law of thermodynamics is a statistical law.

An extremely interesting aspect of Maxwell's thought experiment is that his demon uses information to perform the sorting. The demon needs information about whether an approaching particle is fast or slow in order to know whether or not to open the door.

Finally, after the particles have been sorted, we can imagine that the partition is taken away so that the hot gas is mixed with the cold gas. During this mixing, the entropy of the system will increase, and information (about where to find fast particles and where to find slow ones) will be lost. Entropy is thus seen to be a measure of disorder or lack of information. To decrease the entropy of a system, and to increase its order, Maxwell's demon needs information. In the opposite process, the mixing process, where entropy increases and where disorder increases, information is lost.

Statistical mechanics

Besides inventing an interesting demon (and besides his monumental contributions to electromagnetic theory), Maxwell also helped to lay the foundations of statistical mechanics. In this enterprise, he was joined by the Austrian physicist Ludwig Boltzmann (1844-1906) and by an American, Josiah Willard Gibbs, whom we will discuss later. Maxwell and Boltzmann worked independently and reached similar conclusions, for which they share the credit. Like Maxwell, Boltzmann also interpreted an increase in entropy as an increase in disorder; and like Maxwell he was a firm believer in atomism at a time when this belief was by no means universal. For example, Ostwald and Mach, both important figure in German science at that time, refused to believe in the existence of atoms, in spite of the fact that Dalton's atomic ideas had proved to be so useful in chemistry. Towards the end of his life, Boltzmann suffered from periods of severe depression, perhaps because of attacks on his scientific work by Ostwald and others. In 1906, while on vacation near Trieste, he committed suicide - ironically, just a year before the French physicist J.B. Perrin produced irrefutable evidence of the existence of atoms.

Maxwell and Boltzmann made use of the concept of "phase space", a $6N$-dimensional space whose coordinates are the position and momentum coordinates of each of N particles. However, in discussing statistical mechanics we will use a more modern point of view, the point of view of quantum theory, according to which a system may be in one or another of a set of discrete states, $i = 1, 2, 3, ...$ with energies ϵ_i. Let us consider a set of N identical, weakly-interacting systems; and let us denote the number of the systems which occupy a particular state by n_i, as shown in equation

(4.4):

$$\begin{array}{llllllll} \text{State number} & 1 & 2 & 3 & \ldots & i & \ldots & \\ \text{Energy} & \epsilon_1 & \epsilon_2 & \epsilon_3 & \ldots & \epsilon_i & \ldots & \\ \text{Occupation number} & n_1 & n_2 & n_3 & \ldots & n_i & \ldots & \end{array} \tag{4.4}$$

A "macrostate" of the N identical systems can be specified by writing down the energy levels and their occupation numbers. This macrostate can be constructed in many ways, and each of these ways is called a "microstate": For example, the first of the N identical systems may be in state 1 and the second in state 2; or the reverse may be the case; and the two situations correspond to different microstates. From combinatorial analysis it is possible to show that the number of microstates corresponding to a given macrostate is given by:

$$W = \frac{N!}{n_1!n_2!n_3!...n_i!...} \tag{4.5}$$

Boltzmann was able to show that the entropy S_N of the N identical systems is related to the quantity W by the equation

$$S_N = k \ln W \tag{4.6}$$

where k is the constant which appears in the empirical law relating the pressure, volume and absolute temperature of an ideal gas;

$$PV = NkT \tag{4.7}$$

This constant,

$$k = 1.38062 \times 10^{-23} \ \frac{\text{joule}}{\text{kelvin}} \tag{4.8}$$

is called *Boltzmann's constant* in his honor. Boltzmann's famous equation relating entropy to missing information, equation (4.6), is engraved on his tombstone. A more detailed discussion of Boltzmann's statistical mechanics is given in Appendix 1.

Information theory; Shannon's formula

We have seen that Maxwell's demon needed information to sort gas particles and thus decrease entropy; and we have seen that when fast and slow particles are mixed so that entropy increases, information is lost. The relationship between entropy and lost or missing information was made quantitative by the Hungarian-American physicist Leo Szilard (1898-1964) and by the American mathematician Claude Shannon (1916-2001). In 1929, Szilard published an important article in Zeitschrift für Physik in which he analyzed Maxwell's demon. In this famous article, Szilard emphasized the connection between entropy and missing information. He was able to show that the entropy associated with a unit of information is $k \ln 2$, where k is Boltzmann's constant. We will discuss this relationship in more detail below.

Claude Shannon is usually considered to be the "father of information theory". Shannon graduated from the University of Michigan in 1936, and he later obtained a Ph.D. in mathematics from the Massachusetts Institute of Technology. He worked at the Bell Telephone Laboratories, and later became a professor at MIT. In 1949, motivated by the need of AT&T to quantify the amount of information that could be transmitted over a given line, Shannon published a pioneering study of information as applied to communication and computers. Shannon first examined the question of how many binary digits are needed to express a given integer Ω. In the decimal system we express an integer by telling how many 1's it contains, how many 10's, how many 100's, how many 1000's, and so on. Thus, for example, in the decimal system,

$$105 = 1 \times 10^2 + 0 \times 10^1 + 5 \times 10^0 \tag{4.9}$$

Any integer greater than or equal to 100 but less than 1000 can be expressed with 3 decimal digits; any number greater than or equal to 1000 but less than 10,000 requires 4, and so on.

The natural language of computers is the binary system; and therefore Shannon asked himself how many binary digits are needed to express an integer of a given size. In the binary system, a number is specified by telling how many of the various powers of 2 it contains. Thus, the decimal integer 105, expressed in the binary system, is

$$1101001 \equiv 1 \times 2^6 + 1 \times 2^5 + 0 \times 2^4 + 1 \times 2^3 + 0 \times 2^2 + 0 \times 2^1 + 1 \times 2^0 \tag{4.10}$$

In the many early computers, numbers and commands were read in on punched paper tape, which could either have a hole in a given position, or else no hole. Shannon wished to know how long a strip of punched tape is needed to express a number of a given size - how many binary digits are needed? If the number happens to be an exact power of 2, then the answer is easy: To express the integer

$$\Omega = 2^n \tag{4.11}$$

one needs $n + 1$ binary digits. The first binary digit, which is 1, gives the highest power of 2, and the subsequent digits, all of them 0, specify that the lower powers of 2 are absent. Shannon introduced the word "bit" as an abbreviation of "binary digit". He generalized this result to integers which are not equal to exact powers of 2: Any integer greater than or equal to 2^{n-1}, but less than 2^n, requires n binary digits or "bits". In Shannon's theory, the bit became the unit of information. He defined the quantity of information needed to express an arbitrary integer Ω as

$$I = \log_2 \Omega \text{ bits} = \frac{\ln \Omega}{\ln 2} \text{ bits} = 1.442695 \ \ln \Omega \text{ bits} \tag{4.12}$$

or

$$I = K \ln \Omega \qquad\qquad K \equiv 1.442695 \text{ bits} \tag{4.13}$$

Of course the information function I, as defined by equation (4.13), is in general not an integer, but if one wishes to find the exact number of binary digits required to express a given integer Ω, one can calculate I and round upwards[2].

Shannon went on to consider quantitatively the amount of information which is missing before we perform an experiment, the result of which we are unable to predict with certainty. (For example, the "experiment" might be flipping a coin or throwing a pair of dice.) Shannon first calculated the missing information, I_N, not for a single performance of the experiment but for N independent performances. Suppose that in a single performance, the probability that a particular result i will occur is given by P_i. If the experiment is performed N times, then as N becomes very large, the fraction of times that the result i occurs becomes more and more exactly equal to P_i. For example, if a coin is flipped N times, then as N becomes extremely large, the fraction of "heads" among the results becomes more and more nearly equal to 1/2. However, some information is still missing because we still do not know the sequence of the results. Shannon was able to show from combinatorial analysis, that this missing information about the sequence of the results is given by

$$I_N = K \ln \Omega \tag{4.14}$$

where

$$\Omega = \frac{N!}{n_1!n_2!n_3!...n_i!...} \qquad\qquad n_i \equiv NP_i \tag{4.15}$$

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[2]Similar considerations can also be found in the work of the statistician R.A. Fisher

or

$$I_N = K \ln \Omega = K \left[\ln(N!) - \sum_i \ln(n_i!) \right] \tag{4.16}$$

Shannon then used Sterling's approximation, $\ln(n_i) \approx n_i(\ln n_i - 1)$, to rewrite (4.16) in the form

$$I_N = -KN \sum_i P_i \ln P_i \tag{4.17}$$

Finally, dividing by N, he obtained the missing information prior to the performance of a single experiment:

$$I = -K \sum_i P_i \ln P_i = -K \langle \ln P \rangle \tag{4.18}$$

For example, in the case of flipping a coin, Shannon's equation, (4.18), tells us that the missing information is

$$I = -K \left[\frac{1}{2} \ln \left(\frac{1}{2} \right) + \frac{1}{2} \ln \left(\frac{1}{2} \right) \right] = 1 \text{ bit} \tag{4.19}$$

As a second example, we might think of an "experiment" where we write the letters of the English alphabet on 26 small pieces of paper. We then place them in a hat and draw out one at random. In this second example,

$$P_a = P_b = ... = P_z = \frac{1}{26} \tag{4.20}$$

and from Shannon's equation we can calculate that before the experiment is performed, the missing information is

$$I = -K \left[\frac{1}{26} \ln \left(\frac{1}{26} \right) + \frac{1}{26} \ln \left(\frac{1}{26} \right) + ... \right] = 4.70.. \text{ bits} \tag{4.21}$$

If we had instead picked a letter at random out of an English book, the letters would not occur with equal probability. From a statistical analysis of the frequency of the letters, we would know in advance that

$$P_a = 0.078, \qquad P_b = 0.013, ... \qquad P_z = 0.001 \tag{4.22}$$

Shannon's equation would then give us a slightly reduced value for the missing information:

$$I = -K \left[0.078 \ln(0.078) + 0.013 \ln(0.013) + ... \right] = 4.15.. \text{ bits} \tag{4.23}$$

Less information is missing when we know the frequencies of the letters, and Shannon's formula tells us exactly how much less information is missing.

When Shannon had been working on his equations for some time, he happened to visit the mathematician John von Neumann, who asked him how he was getting on with his theory of missing information. Shannon replied that the theory was in excellent shape, except that he needed a good name for "missing information". "Why don't you call it entropy?", von Neumann suggested. "In the first place, a mathematical development very much like yours already exists in Boltzmann's statistical mechanics, and in the second place, no one understands entropy very well, so in any discussion you will be in a position of advantage!" Like Leo Szilard, von Neumann was a Hungarian-American, and the two scientists were close friends. Thus von Neumann was very much aware of Szilard's paper on Maxwell's demon, with its analysis of the relationship between entropy and missing information. Shannon took von Neumann's advice, and used the word "entropy" in his pioneering paper on information theory. Missing information in general cases has come to be known as "Shannon entropy". But Shannon's ideas can also be applied to thermodynamics.

Entropy expressed as missing information

From the standpoint of information theory, the thermodynamic entropy S_N of an ensemble of N identical weakly-interacting systems in a given macrostate can be interpreted as the missing information which we would need in order to specify the state of each system, i.e. the microstate of the ensemble. Shannon's formula allows this missing information to be measured quantitatively. Applying Shannon's formula, equation (4.13), to the missing information in Boltzmann's problem we can identify W with Ω, S_N with I_N, and k with K:

$$W \to \Omega \qquad S_N \to I_N \qquad k \to K = \frac{1}{\ln 2} \text{ bits} \tag{4.24}$$

so that

$$k \ln 2 = 1 \text{ bit} = 0.95697 \times 10^{-23} \frac{\text{joule}}{\text{kelvin}} \tag{4.25}$$

and

$$k = 1.442695 \text{ bits} \tag{4.26}$$

This implies that temperature has the dimension energy/bit:

$$1 \text{ degree Kelvin} = 0.95697 \times 10^{-23} \frac{\text{joule}}{\text{bit}} \tag{4.27}$$

From this it follows that

$$1 \ \frac{\text{joule}}{\text{kelvin}} = 1.04496 \times 10^{23} \text{ bits} \tag{4.28}$$

If we divide equation (4.28) by Avogadro's number we have

$$1 \ \frac{\text{joule}}{\text{kelvin mol}} = \frac{1.04496 \times 10^{23} \text{ bits/mol}}{6.02217 \times 10^{23} \text{ molecule/mol}} = 0.17352 \ \frac{\text{bits}}{\text{molecule}} \tag{4.29}$$

Figure 4.1 shows the experimentally-determined entropy of ammonia, NH_3, as a function of the temperature, measured in kelvins. It is usual to express entropy in joule/kelvin-mol; but it follows from equation (4.29) that entropy can also be expressed in bits/molecule, as is shown in the figure.

Since

$$1 \text{ electron volt} = 1.6023 \times 10^{-19} \text{ joule} \tag{4.30}$$

it also follows from equation (4.29) that

$$1 \ \frac{\text{electron volt}}{\text{kelvin}} = 1.6743 \times 10^{4} \text{ bits} \tag{4.31}$$

Thus, one electron-volt of energy, converted into heat at room temperature, T =298.15 kelvin, will produce an entropy change of

$$\frac{1 \text{ electron volt}}{298.15 \text{ kelvin}} = 56.157 \text{ bits} \tag{4.32}$$

When a system is in thermodynamic equilibrium, its entropy has reached a maximum; but if it is not in equilibrium, its entropy has a lower value. For example, let us think of the case which was studied by Clausius when he introduced the concept of entropy: Clausius imagined an isolated system, divided into two parts, one of which has a temperature T_1, and the other a lower temperature, T_2. When heat is transferred from the hot part to the cold part, the entropy of the system increases; and when equilibrium is finally established at some uniform intermediate temperature, the entropy has reached a maximum. The difference in entropy between the initial state of Clausius' system and its final state is a measure of how far away from thermodynamic equilibrium it was initially. From the discussion given above, we can see that it is also possible to interpret this entropy difference as the system's initial content of thermodynamic information.

Similarly, when a photon from the sun reaches (for example) a drop of water on the earth, the initial entropy of the system consisting of the photon plus the drop of water is smaller than at a later stage, when the photon's energy has been absorbed and shared among the water molecules, with a resulting very slight increase in the temperature of the water. This entropy

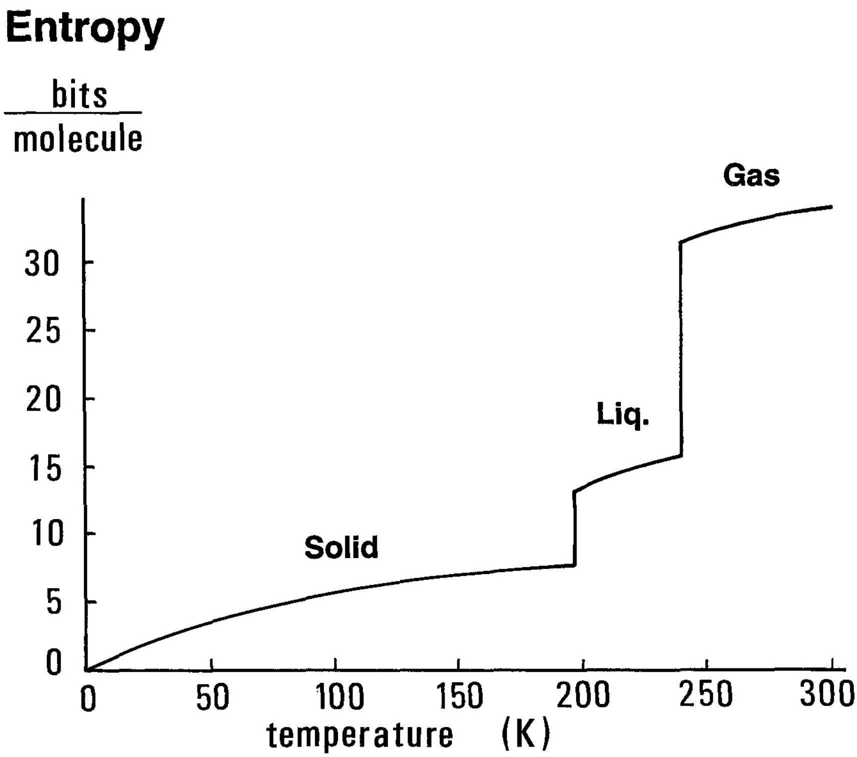

Fig. 4.1 This figure shows the entropy of ammonia as a function of temperature. It is usual to express entropy in joule/kelvin-mol, but it can also be expressed in bits/molecule.

difference can be interpreted as the quantity of thermodynamic information which was initially contained in the photon-drop system, but which was lost when the photon's free energy was degraded into heat. Equation (4.32) allows us to express this entropy difference in terms of bits. For example, if the photon energy is 2 electron-volts, and if the water drop is at a temperature of 298.15 degrees Kelvin, then $\Delta S = 112.31$ bits; and this amount of thermodynamic information is available in the initial state of the system. In our example, the information is lost; but if the photon had instead reached the leaf of a plant, part of its energy, instead of being immediately degraded, might have been stabilized in the form of high-energy chemical bonds. When a part of the photon energy is thus stabilized, not all of the thermodynamic information which it contains is lost; a part is conserved and can be converted into other forms of information.

The information content of Gibbs free energy

At the beginning of this chapter, we mentioned that the American physicist Josiah Willard Gibbs (1839-1903) made many contributions to thermodynamics and statistical mechanics. In 1863, Gibbs received from Yale the first Ph.D. in engineering granted in America, and after a period of further study in France and Germany, he became a professor of mathematical physics at Yale in 1871, a position which he held as long as he lived. During the period between 1876 and 1878, he published a series of papers in the *Transactions of the Connecticut Academy of Sciences.* In these papers, about 400 pages in all, Gibbs applied thermodynamics to chemical reactions. (The editors of the *Transactions of the Connecticut Academy of Sciences* did not really understand Gibbs' work, but, as they said later, "We knew Gibbs, and we took his papers on faith".)

Because the journal was an obscure one, and because Gibbs' work was so highly mathematical, it remained almost unknown to European scientists for a long period. However, in 1892 Gibbs' papers were translated into German by Ostwald, and in 1899 they were translated into French by Le Chatelier; and then the magnitude of Gibbs' contribution was finally recognized. One of his most important innovations was the definition of a quantity which we now call "Gibbs free energy". This quantity allows one to determine whether or not a chemical reaction will take place spontaneously.

Chemical reactions usually take place at constant pressure and constant temperature. If a reaction produces a gas as one of its products, the gas must push against the pressure of the earth's atmosphere to make a place for itself. In order to take into account the work done against external pressure in energy relationships, the German physiologist and physicist Hermann von Helmholtz introduced a quantity (which we now call *heat content* or *enthalpy*) defined by

$$H = U + PV \tag{4.33}$$

where U is the internal energy of a system, P is the pressure, and V is the system's volume.

Gibbs went one step further than Helmholtz, and defined a quantity which would also take into account the fact that when a chemical reaction takes place, heat is exchanged with the surroundings. Gibbs defined his free energy by the relation

$$G = U + PV - TS \tag{4.34}$$

or

$$G = H - TS \tag{4.35}$$

where S is the entropy of a system, H is its enthalpy, and T is its temperature.

Gibbs' reason for introducing the quantity G is as follows: The second law of thermodynamics states that in any spontaneous process, the entropy of the universe increases. Gibbs invented a simple model of the universe, consisting of the system (which might, for example, be a beaker within which a chemical reaction takes place) in contact with a large thermal reservoir at constant temperature. The thermal reservoir could, for example, be a water bath so large that whatever happens in the chemical reaction, the temperature of the bath will remain essentially unaltered.

In Gibbs' simplified model, the entropy change of the universe produced by the chemical reaction can be split into two components:

$$\Delta S_{universe} = \Delta S_{system} + \Delta S_{bath} \tag{4.36}$$

Now suppose that the reaction is endothermic (i.e. it absorbs heat). Then the reaction beaker will absorb an amount of heat ΔH_{system} from the bath, and the entropy change of the bath will be

$$\Delta S_{bath} = -\frac{\Delta H_{system}}{T} \tag{4.37}$$

Combining (4.36) and (4.37) with the condition requiring the entropy of the universe to increase, Gibbs obtained the relationship

$$\Delta S_{universe} = \Delta S_{system} - \frac{\Delta H_{system}}{T} > 0 \tag{4.38}$$

The same relationship also holds for exothermic reactions, where heat is transferred in the opposite direction. Combining equations (4.38) and (4.35) yields

$$\Delta G_{system} = -T\Delta S_{universe} < 0 \tag{4.39}$$

Thus, the Gibbs free energy for a system must decrease in any spontaneous chemical reaction or process which takes place at constant temperature and pressure. We can also see from equation (4.39) that Gibbs free energy is a measure of a system's content of thermodynamic information. If the available free energy is converted into heat, the quantity of information

$\Delta S_{universe} = -\Delta G_{system}/T$ is lost, and we can deduce that in the initial state of the system, this quantity of information was available. Under some circumstances the available thermodynamic information can be partially conserved. In living organisms, chemical reactions are coupled together, and Gibbs free energy, with its content of thermodynamic information, can be transferred from one compound to another, and ultimately converted into other forms of information.

Measured values of the "Gibbs free energy of formation", ΔG_f^0, are available for many molecules. To construct tables of these values, the change in Gibbs free energy is measured when the molecules are formed from their constituent elements. The most stable states of the elements at room temperature and atmospheric pressure are taken as zero points. For example, water in the gas phase has a Gibbs free energy of formation

$$\Delta G_f^0(H_2O) = -228.59 \ \frac{\text{kJ}}{\text{mol}} \tag{4.40}$$

This means that when the reaction

$$H_2(g) + \frac{1}{2}O_2(g) \to H_2O(g) \tag{4.41}$$

takes place under standard conditions, there is a change in Gibbs free energy of $\Delta G^0 = -228.59$ kJ/mol[3]. The elements hydrogen and oxygen in their most stable states at room temperature and atmospheric pressure are taken as the zero points for Gibbs free energy of formation. Since ΔG^0 is negative for the reaction shown in equation (4.41), the reaction is spontaneous. In general, the change in Gibbs free energy in a chemical reaction is given by

$$\Delta G^0 = \sum_{products} \Delta G_f^0 - \sum_{reactants} \Delta G_f^0 \tag{4.42}$$

where ΔG_f^0 denotes the Gibbs free energy of formation.

As a second example, we can consider the reaction in which glucose is burned:

$$C_6H_{12}O_6(s) + 6O_2(g) \to 6CO_2(g) + 6H_2O(g) \qquad \Delta G^0 = -2870 \ \frac{\text{kJ}}{\text{mol}} \tag{4.43}$$

From equation (4.29) it follows that in this reaction,

$$-\frac{\Delta G^0}{T} = 1670 \ \frac{\text{bits}}{\text{molecule}} \tag{4.44}$$

[3]The superscript ^{0} means "under standard conditions", while kJ is an abbreviation for joule$\times 10^3$.

If the glucose is simply burned, this amount of information is lost; but in a living organism, the oxidation of glucose is usually coupled with other reactions in which a part of the available thermodynamic information is stored, or utilized to do work, or perhaps converted into other forms of information.

The oxidation of glucose illustrates the importance of enzymes and specific coupling mechanisms in biology. A lump of glucose can sit for years on a laboratory table, fully exposed to the air. Nothing will happen. Even though the oxidation of glucose is a spontaneous process - even though the change in Gibbs free energy produced by the reaction would be negative - even though the state of the universe after the reaction would be much more probable than the initial state, the reaction does not take place, or at least we would have to wait an enormously long time to see the glucose oxidized, because the reaction pathway is blocked by potential barriers.

Now suppose that the lump of glucose is instead eaten by a girl working in the laboratory. (She likes sweet things, and can't resist eating a lump of sugar when she sees one.) In her body, the glucose will be oxidized almost immediately, because enzymes will lower the potential barriers along the reaction path. However, only part of the available free energy, with its content of thermodynamic information, will be degraded into heat. A large part will be coupled to the synthesis of ATP in the girl's mitochondria. The high-energy phosphate bonds of the ATP molecules will carry the available thermodynamic information further. In the end, a large part of the free energy made available by the glucose oxidation will be used to drive molecular machinery and to build up the statistically unlikely (information-containing) structures of the girl's body.

What is life?

What is Life? That was the title of a small book published by the physicist Erwin Schrödinger in 1944. Schrödinger (1887-1961) was born and educated in Austria. In 1926 he shared the Nobel Prize in Physics[4] for his contributions to quantum theory (wave mechanics). Schrödinger's famous wave equation is as fundamental to modern physics as Newton's equations of motion are to classical physics.

When the Nazis entered Austria in 1938, Schrödinger opposed them, at the risk of his life. To escape arrest, he crossed the Alps on foot, arriving in Italy with no possessions except his knapsack and the clothes which he was wearing. He traveled to England; and in 1940 he obtained a position in Ireland as Senior Professor at the Dublin Institute for Advanced Studies.

[4] with P.A.M. Dirac

There he gave a series of public lectures upon which his small book is based.

In his book, *What is Life?*, Schrödinger developed the idea that a gene is a very large information-containing molecule which might be compared to an aperiodic crystal. He also examined in detail the hypothesis (due to Max Delbrück) that X-ray induced mutations of the type studied by Hermann Muller can be thought of as photo-induced transitions from one isomeric conformation of the genetic molecule to another. Schrödinger's book has great historic importance, because Francis Crick (whose education was in physics) was one of the many people who became interested in biology as a result of reading it. Besides discussing what a gene might be in a way which excited the curiosity and enthusiasm of Crick, Schrödinger devoted a chapter to the relationship between entropy and life.

"What is that precious something contained in our food which keeps us from death? That is easily answered," Schrödinger wrote, "Every process, event, happening - call it what you will; in a word, everything that is going on in Nature means an increase of the entropy of the part of the world where it is going on. Thus a living organism continually increases its entropy - or, as you may say, produces positive entropy, which is death. It can only keep aloof from it, i.e., alive, by continually drawing from its environment negative entropy - which is something very positive as we shall immediately see. What an organism feeds upon is negative entropy. Or, to put it less paradoxically, the essential thing in metabolism is that the organism succeeds in freeing itself from all the entropy it cannot help producing while alive..."[5]

"Entropy, taken with a negative sign, is itself a measure of order. Thus the device by which an organism maintains itself stationary at a fairly high level of orderliness (= fairly low level of entropy) really consists in continually sucking orderliness from its environment. This conclusion is less paradoxical than it appears at first sight. Rather it could be blamed for triviality. Indeed, in the case of higher animals we know the kind of orderliness they feed upon well enough, viz. the extremely well-ordered state of matter state in more or less complicated organic compounds which serve them as foodstuffs. After utilizing it, they return it in a very much degraded form - not entirely degraded, however, for plants can still make use of it. (These, of course, have their most powerful source of 'negative entropy' in the sunlight.)" At the end of the chapter, Schrödinger added a note in which he said that if he had been writing for physicists, he would have made use of the concept of free energy; but he judged that this concept might be difficult or confusing for a general audience.

[5]The Hungarian-American biochemist Albert Szent-Györgyi, who won a Nobel prize for isolating vitamin C, and who was a pioneer of bioenergetics, expressed the same idea in the following words: "We need energy to fight against entropy".

In the paragraphs which we have quoted, Schrödinger focused on exactly the aspect of life which is the main theme of the present book: All living organisms draw a supply of thermodynamic information from their environment, and they use it to "keep aloof" from the disorder which constantly threatens them. In the case of animals, the information-containing free energy comes in the form of food. In the case of green plants, it comes primarily from sunlight. The thermodynamic information thus gained by living organisms is used by them to create configurations of matter which are so complex and orderly that the chance that they could have arisen in a random way is infinitesimally small.

John von Neumann invented a thought experiment which illustrates the role which free energy plays in creating statistically unlikely configurations of matter. Von Neumann imagined a robot or automaton, made of wires, electrical motors, batteries, etc., constructed in such a way that when floating on a lake stocked with its component parts, it will reproduce itself.[6] The important point about von Neumann's automaton is that it requires a source of free energy (i.e., a source of energy from which work can be obtained) in order to function. We can imagine that the free energy comes from electric batteries which the automaton finds in its environment. (These are analogous to the food eaten by animals.) Alternatively we can imagine that the automaton is equipped with photocells, so that it can use sunlight as a source of free energy, but it is impossible to imagine the automaton reproducing itself without some energy source from which work can be obtained to drive its reproductive machinery. If it could be constructed, would von Neumann's automaton be alive? Few people would say yes. But if such a self-reproducing automaton could be constructed, it would have some of the properties which we associate with living organisms.

The autocatalysts which are believed to have participated in molecular evolution had some of the properties of life. They used "food" (i.e., energy-rich molecules in their environments) to reproduce themselves, and they evolved, following the principle of natural selection. The autocatalysts were certainly precursors of life, approaching the borderline between non-life and life.

Is a virus alive? We know, for example, that the tobacco mosaic virus can be taken to pieces. The proteins and RNA of which it is composed can be separated, purified, and stored in bottles on a laboratory shelf. At a much later date, the bottles containing the separate components of the virus can be taken down from the shelf and incubated together, with the result that the components assemble themselves in the correct way, guided by steric and electrostatic complementarity. New virus particles are

[6]In Chapter 8 we will return to von Neumann's self-replicating automaton and describe it in more detail.

formed by this process of autoassembly, and when placed on a tobacco leaf, the new particles are capable of reproducing themselves. In principle, the stage where the virus proteins and RNA are purified and placed in bottles could be taken one step further: The amino acid sequences of the proteins and the base sequence of the RNA could be determined and written down. Later, using this information, the parts of the virus could be synthesized from amino acids and nucleotides. Would we then be creating life? Another question also presents itself: At a certain stage in the process just described, the virus seems to exist only in the form of information - the base sequence of the RNA and the amino acid sequence of the proteins. Can this information be thought of as the *idea* of the virus in the Platonic sense? (Pythagoras would have called it the "soul" of the virus.)

Is a computer virus alive? Certainly it is not so much alive as a tobacco mosaic virus. But a computer virus can use thermodynamic information (supplied by an electric current) to reproduce itself, and it has a complicated structure, containing much cybernetic information.

Under certain circumstances, many bacteria form spores, which do not metabolize, and which are able to exist without nourishment for very long periods - in fact for millions of years. When placed in a medium containing nutrients, the spores can grow into actively reproducing bacteria. There are examples of bacterial spores existing in a dormant state for many millions of years, after which they have been revived into living bacteria. Is a dormant bacterial spore alive?

Clearly there are many borderline cases between non-life and life; and Aristotle seems to have been right when he said, "Nature proceeds little by little from lifeless things to animal life, so that it is impossible to determine either the exact line of demarcation, or on which side of the line an intermediate form should lie." However, one theme seems to characterize life: It is able to convert the thermodynamic information contained in food or in sunlight into complex and statistically unlikely configurations of matter.

A flood of information-containing free energy reaches the earth's biosphere in the form of sunlight. Passing through the metabolic pathways of living organisms, this information keeps the organisms far away from thermodynamic equilibrium ("which is death"). As the thermodynamic information flows through the biosphere, much of it is degraded into heat, but part is converted into cybernetic information and preserved in the intricate structures which are characteristic of life. The principle of natural selection ensures that as this happens, the configurations of matter in living organisms constantly increase in complexity, refinement and statistical improbability. This is the process which we call evolution, or in the case of human society, progress.

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Chapter 5

INFORMATION FLOW IN BIOLOGY

Cybernetic (or semiotic) information; codes and languages

As we have seen in Chapter 4, the evolutionary process is driven by an enormous flow of thermodynamic information passing through the earth's biosphere. Most of it is lost - degraded into heat - but a tiny fraction of the flow is stabilized and preserved as cybernetic information[1]. This second form of information, which is associated with the sending and receiving of signals, with communication, with codes or languages, and with biological or cultural complexity, will be the theme of the remaining chapters of this book [2]. In addition to the flow of Gibbs free energy (i.e. thermodynamic information) through living organisms and ecosystems, there is also a flow of cybernetic (or semiotic) information.

The language of molecular complementarity

In living (and even non-living) systems, signals can be written and read at the molecular level. The language of molecular signals is a language of complementarity. The first scientist to call attention to complementarity and pattern recognition at the molecular level was Paul Ehrlich, who was born in 1854 in Upper Silesia (now a part of Poland). Ehrlich was not an especially good student, but his originality attracted the attention of his teacher, Professor Waldeyer, under whom he studied chemistry at the University of Strasbourg. Waldeyer encouraged him to do independent experiments with the newly-discovered aniline dyes; and on his own initiative,

[1]The polymerase chain reaction discussed in Chapter 3 can be thought of as a process in which thermodynamic information is converted into cybernetic information. A second example is Spiegelman's experiment, discussed at the end of Chapter 8.

[2]Sometimes information associated with signs is alternatively called "semiotic information" as is discussed in Appendix 2.

Ehrlich began to use these dyes to stain bacteria. He was still staining cells with aniline dyes a few years later (by this time he had become a medical student at the University of Breslau) when the great bacteriologist Robert Koch visited the laboratory. "This is young Ehrlich, who is very good at staining, but will never pass his examinations", Koch was told. Nevertheless, Ehrlich did pass his examinations, and he went on to become a doctor of medicine at the University of Leipzig at the age of 24. His doctoral thesis dealt with the specificity of the aniline dyes: Each dye stained a special class of cell and left all other cells unstained.

Paul Ehrlich had discovered what might be called "the language of molecular complementarity": He had noticed that each of his aniline dyes stained only a particular type of tissue or a particular species of bacteria. For example, when he injected one of his blue dyes into the ear of a rabbit, he found to his astonishment that the dye molecules attached themselves selectively to the nerve endings. Similarly, each of the three types of phagocytes could be stained with its own particular dye, which left the other two kinds unstained[3]. Ehrlich believed that this specificity came about because the side chains on his dye molecules contained groupings of atoms which were complementary to groups of atoms on the surfaces of the cells or bacteria which they selectively stained. In other words, he believed that biological specificity results from a sort of lock and key mechanism: He visualized a dye molecule as moving about in solution until it finds a binding site which exactly fits the pattern of atoms in one of its side chains. Modern research has completely confirmed this picture, with the added insight that we now know that the complementarity of the "lock" and "key" is electrostatic as well as spatial.

Two molecules in a biological system may fit together because the contours of one are complementary to the contours of the other. This is how Paul Ehrlich visualized the fit - a spatial (steric) complementarity, like that of a lock and key. However, we now know that for maximum affinity, the patterns of excess charges on the surfaces of the two molecules must also be complementary. Regions of positive excess charge on the surface of one molecule must fit closely with regions of negative excess charge on the other if the two are to bind maximally. Thus the language of molecules is not only a language of contours, but also a language of charge distributions.

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[3]The specificity which Ehrlich observed in his staining studies made him hope that it might be possible to find chemicals which would attach themselves selectively to pathogenic bacteria in the blood stream and kill the bacteria without harming normal body cells. He later discovered safe cures for both sleeping sickness and syphilis, thus becoming the father of chemotherapy in medicine. He had already received the Nobel Prize for his studies of the mechanism of immunity, but after his discovery of a cure for syphilis, a street in Frankfurt was named after him!

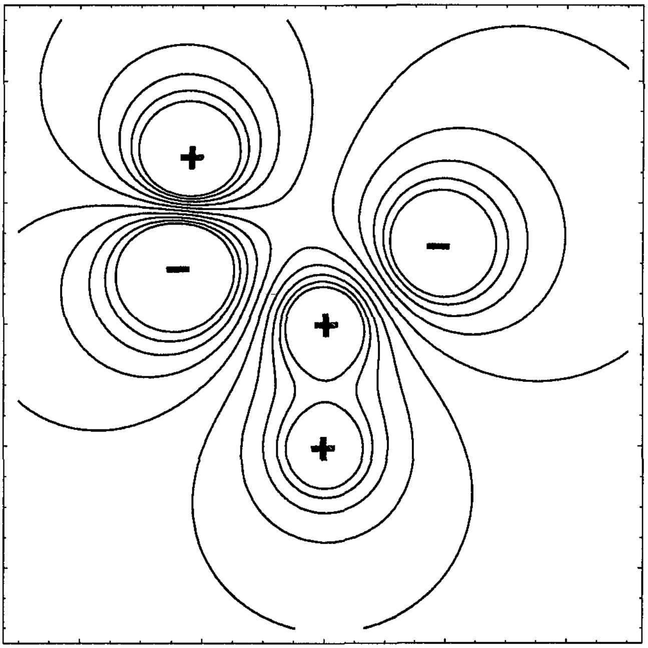

Fig. 5.1 This figure shows the excess charges and the resulting electrostatic potential on a molecule of formic acid, HCOOH. The two oxygens in the carboxyl group are negatively charged, while the carbon and the two hydrogens have positive excess charges. Molecular recognition involves not only steric complementarity, but also complementarity of charge patterns.

The flow of information between and within cells

Information is transferred between cells in several ways. Among bacteria, in addition to the chronologically vertical transfer of genetic information directly from a single parent to its two daughter cells on cell division, there are mechanisms for the sharing of genetic information in a chronologically horizontal way, between cells of the same generation. These horizontal genetic information transfers can be thought of as being analogous to sex, as will be seen more clearly from some examples.

In the most primitive mechanism of horizontal information transfer, a bacterium releases DNA into its surroundings, and the DNA is later absorbed by another bacterium, not necessarily of the same species. For example, a loop or plasmid of DNA conferring resistance to an antibiotic (an "R-factor") can be released by a resistant bacterium and later absorbed by a bacterium of another species, which then becomes resistant[4].

A second mechanism for horizontal information transfer involves infection of a bacterium by a virus. As the virus reproduces itself inside the bacterium, some of the host's DNA can chance to be incorporated in the new virus particles, which then carry the extra DNA to other bacteria.

Finally, there is a third mechanism (discovered by J. Lederberg) in which two bacteria come together and construct a conjugal bridge across which genetic information can flow.

Almost all multicellular animals and plants reproduce sexually. In the case of sexual reproduction the genetic information of both parents is thrown into a lottery by means of special cells, the gametes. Gametes of each parent contain only half the genetic information of the parent, and the exact composition of that half is determined by chance. Thus, when the gametes from two sexes fuse to form a new individual, the chances for variability are extremely large. This variability is highly valuable to multicellular organisms which reproduce sexually, not only because variability is the raw material of evolutionary adaption to changes in the environment, but also because the great variability of sexually-reproducing organisms makes them less likely to succumb to parasites. Infecting bacteria might otherwise deceive the immune systems of their hosts by developing cell-surface antigens which resemble those of the host, but when they infect sexually-reproducing organisms where each individual is unique, this is much less likely.

Within the cells of all organisms living today, there is a flow of information from polynucleotides (DNA and RNA) to proteins. As messenger RNA passes through a ribosome, like punched tape passing through a computer tapereader, the sequence of nucleotides in the mRNA is translated into the sequence of nucleic acids in the growing protein. The molecular mechanism of the reading and writing in this process involves not only spatial complementarity, but also complementarity of charge distributions.

As a protein grows, one amino acid at a time, it begins to fold. The way in which it folds (the "tertiary conformation") is determined both by spatial complementarity and by complementarity of charge distributions:

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[4]The fact that this can happen is a strong reason for using antibiotics with great caution in agriculture. Resistance to antibiotics can be transferred from the bacteria commonly found in farm animals to bacteria which are dangerous for humans. Microbiologists have repeatedly warned farmers, drug companies and politicians of this danger, but the warnings have usually been ignored. Unfortunately there are now several instances of antibiotic-resistant human pathogens that have been produced by indiscriminate use of antibiotics in agriculture.

Those amino acids which have highly polar groups, i.e., where several atoms have large positive or negative excess charges - "hydrophilic" amino acids - tend to be placed on the outside of the growing protein, while amino acids lacking large excess charges - "hydrophobic" amino acids - tend to be on the inside, away from water. Hydrophilic amino acids form hydrogen bonds with water molecules. Whenever there is a large negative charge on an atom of an amino acid, it attracts a positively-charged hydrogen from water, while positively-charged hydrogens on nucleic acids are attracted to negatively charged oxygens of water. Meanwhile, in the interior of the growing protein, non-polar amino acids are attracted to each other by so-called van der Waals forces, which do not require large excess charges, but only close proximity.

When a protein is complete, it is ready to participate in the activities of the cell, perhaps as a structural element or perhaps as an enzyme. Enzymes catalyse the processes by which carbohydrates, and other molecules used by the cell, are synthesized. Often an enzyme has an "active site", where such a process takes place. Not only the spatial conformation of the active site but also its pattern of excess charges must be right if the catalysis is to be effective. An enzyme sometimes acts by binding two smaller molecules to its active site in a proper orientation to allow a reaction between them to take place. In other cases, substrate molecules are stressed and distorted by electrostatic forces as they are pulled into the active site, and the activation energy for a reaction is lowered.

Thus, information is transferred first from DNA and RNA to proteins, and then from proteins to (for example) carbohydrates. Sometimes the carbohydrates then become part of surface of a cell. The information which these surface carbohydrates ("cell surface antigens") contain may be transmitted to other cells. In this entire information transfer process, the "reading" and "writing" depend on steric complementarity and on complementarity of molecular charge distributions.

Not only do cells communicate by touching each other and recognizing each other's cell surface antigens - they also communicate by secreting and absorbing transmitter molecules. For example, the group behavior of slime mold cells is coordinated by the cyclic adenosine monophosphate molecules, which the cells secrete when distressed.

Within most multicellular organisms, cooperative behavior of cells is coordinated by molecules such as hormones - chemical messengers. These are recognized by "receptors", the mechanism of recognition once again depending on complementarity of charge distributions and shape. Receptors on the surfaces of cells are often membrane-bound proteins which reach from the exterior of the membrane to the interior. When an external transmitter molecule is bound to a receptor site on the outside part of the protein, it causes a conformational change which releases a bound molecule of a different type from a site on the inside part of the protein, thus carrying the signal to the cell's interior. In other cases the messenger molecule passes through the cell membrane.

In this way the individual cell in a society of cells (a multicellular organism) is told when to divide and when to stop dividing, and what its special role will be in the economy of the cell society (differentiation). For example, in humans, follicle-stimulating hormone, lutenizing hormone, prolactin, estrogen and progesterone are among the chemical messengers which cause the cell differentiation needed to create the secondary sexual characteristics of females.

Another role of chemical messengers in multicullular organisms is to maintain a reasonably constant internal environment in spite of drastic changes in the external environment of individual cells or of the organism as a whole (homeostasis). An example of such a homeostatic chemical messenger is the hormone insulin, which is found in humans and other mammals. The rate of its release by secretory cells in the pancreas is increased by high concentrations of glucose in the blood. Insulin carries the news of high glucose levels to target cells in the liver, where the glucose is converted to glycogen, and to other target cells in the muscles, where the glucose is burned.

Nervous systems

Hormones require a considerable amount of time to diffuse from the cells where they originate to their target cells; but animals often need to act very quickly, in fractions of seconds, to avoid danger or to obtain food. Because of the need for quick responses, a second system of communication has evolved - the system of neurons.

Neurons have a cell bodies, nuclei, mitochondria and other usual features of eukaryotic cells, but in addition they possess extremely long and thin tubelike extensions called axons and dendrites. The axons function as informational output channels, while the dendrites are inputs. These very long extensions of neurons connect them with other neurons which can be at distant sites, to which they are able to transmit electrical signals. The complex network of neurons within a multicellular organism, its nervous system, is divided into three parts. A sensory or input part brings in signals from the organism's interior or from its external environment. An effector or output part produces a response to the input signal, for example by initiating muscular contraction. Between the sensory and effector parts of the nervous system is a message-processing (internuncial) part, whose complexity is not great in the jellyfish or the leech. However, the complexity of the internuncial part of the nervous system increases dramatically as one goes upward in the evolutionary order of animals, and in humans it is truly astonishing.

The small button-like connections between neurons are called synapses. When an electrical signal propagating along an axon reaches a synapse, it releases a chemical transmitter substance into the tiny volume between the synapse and the next neuron (the post-synaptic cleft). Depending on the nature of the synapse, this chemical messenger may either cause the next neuron to "fire" (i.e., to produce an electrical pulse along its axon) or it may inhibit the firing of the neuron. Furthermore, the question of whether a neuron will or will not fire depends on the past history of its synapses. Because of this feature, the internuncial part of an animal's nervous system is able to learn. There many kinds of synapses and many kinds of neurotransmitters, and the response of synapses is sensitive to the concentration of various molecules in the blood, a fact which helps to give the nervous systems of higher animals extraordinary subtlety and complexity.

The first known neurotransmitter molecule, acetylcholine, was discovered jointly by Sir Henry Dale in England and by Otto Loewi in Germany. In 1921 Loewi was able to show that nerve endings transmit information to muscles by means of this substance. The idea for the critical experiment occurred to him in a dream at 3 am. Otto Loewi woke up and wrote down the idea; but in the morning he could not read what he had written. Luckily he had the same dream the following night. This time he took no chances. He got up, drank some coffee, and spent the whole night working in his laboratory. By morning he had shown that nerve cells separated from the muscle of a frog's heart secrete a chemical substance when stimulated, and that this substance is able to cause contractions of the heart of another frog. Sir Henry Dale later showed that Otto Loewi's transmitter molecule was identical to acetylcholine, which Dale had isolated from the ergot fungus in 1910. The two men shared a Nobel Prize in 1936. Since that time, a large variety of neurotransmitter molecules have been isolated. Among the excitatory neurotransmitters (in addition to acetylcholine) are noradrenalin, norepinephrine, serotonin, dopamine, and glutamate, while gamma-amino-butyric acid is an example of an inhibitory neurotransmitter.

The mechanism by which electrical impulses propagate along nerve axons was clarified by the English physiologists Alan Lloyd Hodgkin and Andrew Fielding Huxley (a grandson of Darwin's defender, Thomas Henry Huxley). In 1952, working with the giant axon of the squid (which can be as large as a millimeter in diameter), they demonstrated that the electri-

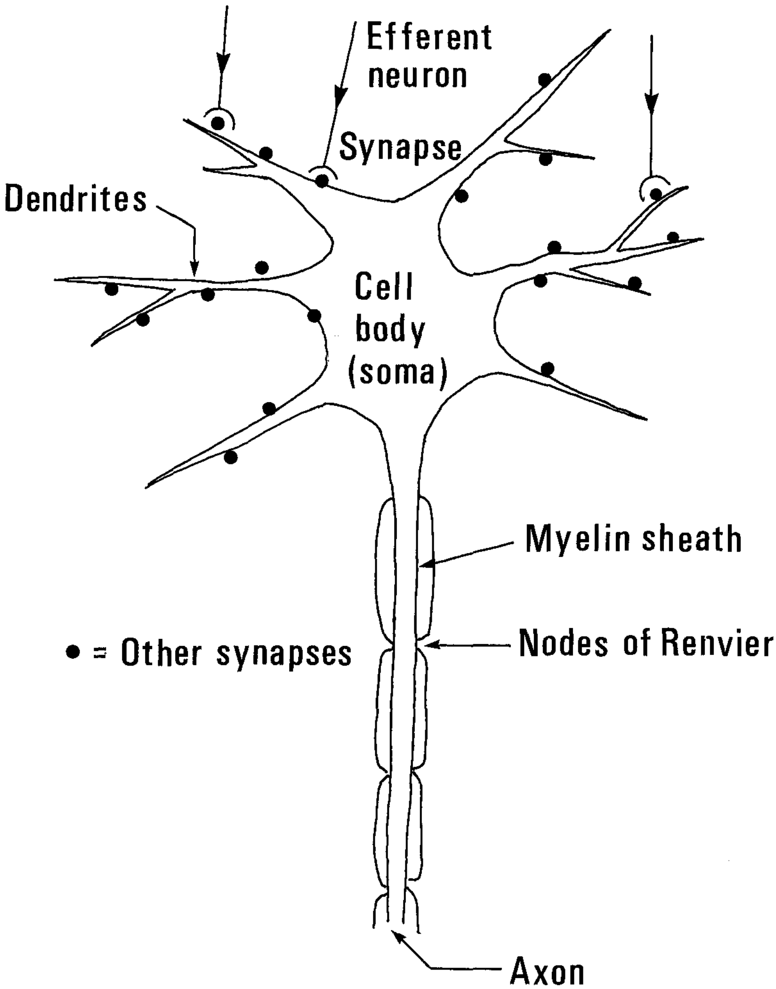

Fig. 5.2 A schematic diagram of a neuron.

cal impulse propagating along a nerve is in no way similar to an electrical current in a conducting wire, but is more closely analogous to a row of dominoes knocking each other down. The nerve fiber, they showed, is like a long thin tube, within which there is a fluid containing K^+, and Na^+ ions, as well as anions. Inside a resting nerve, the concentration of K^+ is higher than in the normal body fluids outside, and the concentration of

Na^+ is lower. These abnormal concentrations are maintained by an "ion pump", which uses the Gibbs free energy of adenosine triphosphate (ATP) to bring potassium ions into the nerve and to expel sodium ions.

The membrane surrounding the neural axon is more permeable to potassium ions than to sodium, and the positively charged potassium ions tend to leak out of the resting nerve, producing a small difference in potential between the inside and outside. This "resting potential" helps to hold the molecules of the membrane in an orderly layer, so that the membrane's permeability to ions is low.

Hodgkin and Huxley showed that when a neuron fires, the whole situation changes dramatically. Triggered by the effects of exitatory neurotransmitter molecules, sodium ions begin to flow into the axon, destroying the electrical potential which maintained order in the membrane. A wave of depolarization passes along the axon. Like a row of dominoes falling, the disturbance propagates from one section to the next: Sodium ions flow in, the order-maintaining electrical potential disappears, the next small section of the nerve membrane becomes permeable, and so on. Thus, Hodgkin and Huxley showed that when a neuron fires, a quick pulse-like electrical and chemical disturbance is transmitted along the axon.

In 1953, Stephen W. Kuffler, working at Johns Hopkins University, made a series of discoveries which yielded much insight into the mechanisms by which the internuncial part of mammalian nervous systems processes information. Kuffler's studies showed that some degree of abstraction of patterns already takes place in the retina of the mammalian eye, before signals are passed on through the optic nerve to the visual cortex of the brain.

In the mammalian retina, about 100 million light-sensitive primary light-receptor cells are connected through bipolar neurons to approximately a million retinal neurons of another type, called ganglions. Kuffler's first discovery (made using microelectrodes) was that even in total darkness, the retinal ganglions continue to fire steadily at the rate of about thirty pulses per second. He also found that diffuse light illuminating the entire retina does not change this steady rate of firing.

Kuffler's next discovery was that each ganglion is connected to an array of about 100 primary receptor cells, arranged in an inner circle surrounded by an outer ring. Kuffler found the arrays to be of two types, which he called "on center arrays" and "off center arrays". In the "on center arrays", a tiny spot of light, illuminating only the inner circle, produces a burst of frequent firing of the associated ganglion, provided that cells in the outer ring of the array remain in darkness. However, if the cells in the outer ring are also illuminated, there is a cancellation, and there is no net effect. Exactly the opposite proved to be the case for the "off center arrays". As before, uniform illumination of both the inner circle and outer ring of these arrays produces a cancellation and hence no net effect on the steady background rate of ganglion firing. However, if the central circle by itself is illuminated by a tiny spot of light, the ganglion firing is inhibited, whereas if the outer ring alone is illuminated, the firing is enhanced. Thus Kuffler found that both types of arrays give no response to uniform illumination, and that both types of arrays measure, in different ways, the degree of contrast in the light falling on closely neighboring regions of the retina.

Kuffler's research was continued by his two associates, David H. Hubel and Torsten N. Wessel, at the Harvard Medical School, to which Kuffler had moved. In the late 1950's, they found that when the signals sent through the optic nerves reach the visual cortex of the brain, a further abstraction of patterns takes place through the arrangement of connections between two successive layers of neurons. Hubbel and Wessel called the cells in these two pattern-abstracting layers "simple" and "complex". The retinal ganglions were found to be connected to the "simple" neurons in such a way that a "simple" cell responds to a line of contrasting illumination of the retina. For such a cell to respond, the line has to be at a particular position and has to have a particular direction. However, the "complex" cells in the next layer were found to be connected to the "simple" cells in such a way that they respond to a line in a particular direction, even when it is displaced parallel to itself [5].

In analyzing their results, Kuffler, Hubel and Wessel concluded that pattern abstraction in the mammalian retina and visual cortex takes place through the selective destruction of information. This conclusion agrees with what we know in general about abstractions: They are always simpler than the thing which they represent.

Animal languages

Communication between two or more multicellular organism often takes place through the medium of signal molecules, which are recognized by receptors. For example, the perfume of flowers is recognized by insects (and by us). Insect pheromones are among the most powerful signal molecules. The language of ants depends predominantly on chemical signals. In most mammals too, the sense of smell plays a large role in mating, maternal

[5] Interestingly, at about the same time, the English physiologist J.Z. Young came to closely analogous conclusions regarding the mechanism of pattern abstraction in the visual cortex of the octopus brain. However, the similarity between the image-forming eye of the octopus and the image-forming vertebrate eye and the rough similarity between the mechanisms for pattern abstraction in the two cases must both be regarded as instances of convergent evolution, since the mollusc eye and the vertebrate eye have evolved independently.

behavior, and group organization.[6] Anyone who has owned a pet cat or dog knows what an important role the sense of smell plays in their social lives.

Pheromones are defined as chemical compounds that are exchanged as signals between members of the same species, and very many of these substances have now been isolated and studied. Pheromones often play a role in reproduction. For example, females of the silkworm moth species Bombyx mori emit an alcohol, *trans*-10-*cis*-12-hexadecadienol, from a gland in tip of their their abdomens. The simplified name of this alcohol is "bombykol", after the name of the moth. The male moth is equipped with feathery antennae, the hairs of which are sensitive to the pheromone - so sensitive in fact that a receptor on one of the hairs is able to register the presence of a single bombykol molecule! Arroused by even a very modest concentration of bombykol, the male finds himself compelled by the inherited programs of his brain to follow the path of increasing concentration until he finds the female and mates with her.

The pheromone *trans*-9-keto-2-decanoic acid, the "queen substance", plays a somewhat more complex role in the social organization of the honeybee. This pheromone, which is emitted by the queen's mandibular glands, has several functions. Workers lick the queen's body and regurgitate the substance back and forth to each other, so that it is spread throughout the hive. When they do so, their ovaries fail to develop, and they are also restrained from raising larvae in such a way that the young bees could become queens. Thus, as long as the reigning queen is alive and producing the pheromone, she has no rivals. Another function of *trans*-9-keto-2-decanoic acid is to guide a husband to the queen on her nuptial flight and to promote the consummation of their marriage.

Worker bees cannot recognize each other as individuals, but each hive has a distinctive scent, shared by all its members. Foreign bees, with a different nest scent, are aggressively repelled. Like bees, their close relatives the ants also have a distinctive nest scent by which members of a colony recognize each other and repel foreigners.

Ants use chemical trails to guide each other to sources of food. An ant which has found an open jam jar marks the trail to it with a signalling substance, and other ants following this pheromone trail increase the intensity of the marking. However, the signal molecules continually evaporate. Eventually the trails disappear, and the ants are freed to explore other sources of food.

Bees guide each other to sources of food by another genetically programmed signaling method - the famous waggle dance, deciphered in 1945

[6]Puppies up to the age of 7 weeks or so have a distinctive odor which is attractive to humans as well as to dogs.

by Karl von Frisch. When a worker bee has found a promising food source, she returns to the hive and performs a complex dance, the pattern of which indicates both the direction and distance of the food. The dancer moves repeatedly in a pattern resembling the Greek letter Θ. If the food-discoverer is able to perform her dance on a horizontal flat surface in view of the sun, the line in the center of the pattern points in the direction of the food. However, if the dance is performed in the interior of the hive on a vertical surface, gravity takes the place of the sun, and the angle between the central line and the vertical represents the angle between the food source and the sun.

The central part of the dance is, in a way, a re-enactment of the excited forager's flight to the food. As she traverses the central portion of the pattern, she buzzes her wings and waggles her abdomen rapidly, the number of waggles indicating the approximate distance to the food [7]. After this central portion of the dance, she turns alternately to the left or to the right, following one or the other of the semicircles, and repeats the performance. Studies of the accuracy with which her hive-mates follow these instructions show that the waggle dance is able to convey approximately 7 bits of information - 3 bits concerning distance and 4 bits concerning direction. After making his initial discovery of the meaning of the dance, von Frisch studied the waggle dance in many species of bees. He was able to distinguish species-specific dialects, and to establish a plausible explanation for the evolution of the dance.

Like bees, most mammals have communication systems which utilize not only scent, but also other displays and signals. For example, galagos or bushbabies, small furry primates found in the rainforests of Africa, have scent glands on their faces, chests, arms, elbows, palms, and soles, and they also scent-mark their surroundings and each other with saliva and urine. In fact, galagos bathe themselves in urine, standing on one foot and using their hands and feet as cups. This scent-repertoire is used by the bushbabies to communicate reproductive and social information. However, in addition, they also communicate through a variety of calls. They croak, chirp, click, whistle and bark, and the mating call of the Greater Galago sounds exactly like the crying of a baby - whence the name.

The communication of animals (and humans) through visual displays was discussed by Charles Darwin in his book *The Expression of the Emotions in Man and Animals.* For example, he discussed the way in which the emotions of a dog are expressed as visual signs: "When a dog approaches a strange dog or man in a savage or hostile frame of mind", Darwin wrote, "he walks very stiffly; his head is slightly raised, or not much lowered; the

[7] The number of waggles is largest when the source of food is near, and for extremely nearby food, the bees use another dance, the "round dance".

tail is held erect and quite rigid; the hairs bristle, especially along the neck and back; the pricked ears are directed forwards, and the eyes have a fixed stare... Let it now be supposed that the dog suddenly discovers that the man he is approaching is not a stranger, but his master; and let it be observed how completely and instantaneously his whole bearing is reversed. Instead of walking upright, the body sinks downwards or even crouches, and is thrown into flexuous movements; the tail, instead of being held stiff and upright, is lowered and wagged from side to side; his hair instantly becomes smooth; his ears are depressed and drawn backwards, but not closely to the head, and his lips hang loosely. From the drawing back of the ears, the eyelids become elongated, and the eyes no longer appear round and staring."

A wide variety of animals express hostility by making themselves seem larger than they really are: Cats arch their backs, and the hairs on their necks and backs are involuntarily raised; birds ruffle their feathers and spread their wings; lizards raise their crests and lower their dewlaps; and even some species of fish show hostility by making themselves seem larger, by spreading their fins or extending their gill covers. Konrad Lorenz has noted, in his book *On Aggression*, that the "holy shiver" experienced by humans about to perform an heroic act in defense of their community is closely related to the bristling hair on the neck and back of a cat or dog when facing an enemy.

Human language has its roots in the nonverbal signs by which our evolutionary predecessors communicated, and traces of early human language can be seen in the laughter, tears, screams, groans, grins, winks, frowns, sneers, smiles, and explanatory gestures which we use even today to clarify and emphasize our words.

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Chapter 6

CULTURAL EVOLUTION AND INFORMATION

The coevolution of human language, culture, and intelligence

The prehistoric genetic evolution of modern humans, as well as their more recent cultural evolution can be understood in terms of a single theme - information. The explosively rapid development of our species can be thought of as a continually accelerating accumulation of information, as this chapter will try to demonstrate.

In his *Systema Naturae*, published in 1735, Carolus Linnæus correctly classified humans as mammals associated with the anthropoid apes. However, illustrations of possible ancestors of humans in a later book by Linnæus, showed one with a manlike head on top of a long-haired body, and another with a tail. A century later, in 1856, light was thrown on human ancestry by the discovery of some remarkable bones in a limestone cave in the valley of Neander, near Düsseldorf - a skullcap and some associated long bones. The skullcap was clearly manlike, but the forehead was low and thick, with massive ridges over the eyes. The famous pathologist Rudolf Virchow dismissed the find as a relatively recent pathological idiot. Other authorities thought that it was "one of the Cossacks who came from Russia in 1814". Darwin knew of the "Neanderthal man", but he was too ill to travel to Germany and examine the bones. However, Thomas Huxley examined them, and in his 1873 book, *Zoological Evidences of Man's Place in Nature*, he wrote: "Under whatever aspect we view this cranium... we meet with apelike characteristics, stamping it as the most pithecoid (apelike) of human crania yet discovered."

"In some older strata," Huxley continued, "do the fossilized bones of an ape more anthropoid, or a man more pithecoid, than any yet known await the researches of some unborn palaeontologist?" Huxley's question obsessed Eugene Dubois, a young Dutch physician, who reasoned that such a find would be most likely in Africa, the home of chimpanzees and gorillas, or in the East Indies, where orang-outangs live. He was therefore happy to be appointed to a post in Sumatra in 1887. While there, Dubois heard of a site in Java where the local people had discovered many ancient fossil bones, and at this site, after much searching, he uncovered a cranium which was much too low and flat to have belonged to a modern human. On the other hand it had features which proved that it could not have belonged to an ape. Near the cranium, Dubois found a leg bone which clearly indicated upright locomotion, and which he (mistakenly) believed to belong to the same creature. In announcing his find in 1894, Dubois proposed the provocative name "Pithecanthropus erectus", i.e. "upright-walking ape-man"

Instead of being praised for this discovery, Dubois was denounced. His attackers included not only the clergy, but also many scientists (who had expected that an early ancestor of man would have an enlarged brain associated with an apelike body, rather than apelike head associated with upright locomotion). He patiently exhibited the fossil bones at scientific meetings throughout Europe, and gave full accounts of the details of the site where he had unearthed them. When the attacks nevertheless continued, Dubois became disheartened, and locked the fossils in a strongbox, out of public view, for the next 28 years. In 1923, however, he released a cast of the skull, which showed that the brain volume was about 900 cm^3 - well above the range of apes, but below the 1200-1600 cm^3 range which characterizes modern man. Thereafter he again began to exhibit the bones at scientific meetings.

The fossil bones of about 1000 hominids, intermediate between apes and humans, have now been discovered. The oldest remains have been found in Africa. Many of these were discovered by Raymond Dart and Robert Broom, who worked in South Africa, and by Louis and Mary Leaky and their son Richard, who made their discoveries at the Olduvai Gorge in Tanzania and at Lake Rudolph in Kenya. Table 6.1 shows some of the more important species and their approximate dates.

One can deduce from biochemical evidence that the most recent common ancestor of the anthropoid apes and of humans lived in Africa between 5 and 10 million years before the present. Although the community of palaeoanthropologists is by no means unanimous, there is reasonably general agreement that while A. africanus is probably an ancestor of H. habilis and of humans, the "robust" species, A. aethiopicus, A. robustus and A. boisei[1] represent a sidebranch which finally died out. "Pithecanthropus erectus", found by Dubois, is now classified as a variety of Homo erectus, as is "Sinanthropus pekinensis" ("Peking man"), discovered in 1929 near

[1] A. boisei was originally called "Zinjanthropus boisei" by Mary and Louis Leakey who discovered the fossil remains at the Olduvai Gorge. Charles Boise helped to finance the Leakey's expedition.

Table 6.1: Hominid species

genus and species	years before present	brain volume
Ardipithecus ramidus	5.8 to 4.4 million	
Australopithecus anamensis	4.2 to 3.9 million	
Australopithecus afarensis	3.9 to 3.0 million	375 to 550 cm^3
Australopithecus africanus	3 to 2 million	420 to 500 cm^3
Australopithecus aethiopicus	2.6 to 2.3 million	410 cm^3
Australopithecus robustus	2 to 1.5 million	530 cm^3
Australopithecus boisei	2.1 to 1.1 million	530 cm^3
Homo habilis	2.4 to 1.5 million	500 to 800 cm^3
Homo erectus	1.8 to 0.3 million	750 to 1225 cm^3
Homo sapiens (archaic)	0.5 to 0.2 million	1200 cm^3
Homo sapiens neand.	0.23 to 0.03 million	1450 cm^3
Homo sapiens sapiens	0.12 mil. to present	1350 cm^3

Beijing, China.

Footprints 3.7 million years old showing upright locomotion have been discovered near Laetoli in Tanzania. The Laetoli footprints are believed to have been made by A. afarensis, which was definitely bipedal, but upright locomotion is thought to have started much earlier. There is even indirect evidence which suggests that A. ramidus may have been bipedal.

Homo habilis was discovered by Mary and Louis Leakey at the Olduvai

Gorge, among beds of extremely numerous pebble tools. The Leakey's gave this name (meaning "handy man") to their discovery in order to call special attention to his use of tools. The brain of H. habilis is more human than that of A. africanus, and in particular, the bulge of Broca's area, essential for speech, can be seen on one of the skull casts. This makes it seem likely that H. habilis was capable of at least rudimentary speech.

Homo erectus was the first species of hominid to leave Africa, and his remains are found not only there, but also in Europe and Asia. "Peking man", who belonged to this species, probably used fire. The stone tools of H. erectus were more advanced than those of H. habilis; and there is no sharp line of demarcation between the most evolved examples of H. erectus and early fossils of archaic H. sapiens.

Homo sapiens neanderthalensis lived side by side with Homo sapiens sapiens (modern man) for a hundred thousand years; but in relatively recent times, only 30,000 years ago, Neanderthal man disappeared. Did modern man outcompete him? Do present-day humans carry any Neanderthal genes? To what extent was modern man influenced by Neanderthal cultural achievements? Future research may tell us the answers to these questions, but for the moment they are mysteries.

The hominid species shown in Table 6.1 show an overall progression in various characteristics: Their body size and brain size grew. They began to mature more slowly and to live longer. Their tools and weapons increased in sophistication. Meanwhile their teeth became smaller, and their skeletons more gracile - less heavy in proportion to their size. What were the evolutionary forces which produced these changes? How were they rewarded by a better chance of survival?

Our ancestors moved from a forest habitat to the savannas of Africa. They changed from a vegetarian diet to an omnivorous one, becoming hunter-gatherers. The primate hand, evolved for grasping branches in a forest environment, found new uses. Branches and stones became weapons and tools - essential to hunters whose bodies lacked powerful claws and teeth. With a premium on skill in making tools, brain size increased. The beginnings of language helped to make hunts successful, and also helped in transmitting cultural skills, such as toolmaking and weaponmaking, from one generation to the next.

From the time scale shown in Tables 6.1 and 6.2, we can see that the coevolution of language, culture and intelligence took place over a period of several million years. As the cultures of the hominids became more complex, efficient transmission of skills and knowledge between generations required an increasingly complex language. This in turn required increased brain size and slow maturation, features which are built into the genomes of modern humans. A stable family structure and tribal social structure were also needed to protect the helpless offspring of our species as they slowly matured.

A modern human baby is almost entirely helpless. Compared with offspring of grazing animals, which are able to stand up and follow the herd immediately after birth, a human baby's development is almost ludicrously slow. However, there is nothing slow about the rate at which a young member of our species learns languages. Between the ages of one and four, young humans develop astonishing linguistic skills, far surpassing those of any other animal on earth. In the learning of languages by human children there is an interplay between genes and culture: The language learned is culturally determined, but the predisposition to learn some form of speech seems to be an inherited characteristic. For example, human babies of all nationalities have a tendency to "babble" - to produce random sounds. The sounds which they make are the same in all parts of the world, and they may include many sounds which are not used in the languages which the babies ultimately learn.

In his book, *Descent of Man* (John Murray, London, 1871) Charles Darwin wrote: "Man has an instinctive tendency to speak, as we see in the babble of young children, while no child has an instinctive tendency to bake, brew or write." Thus Darwin was aware of the genetic component of learning of speech by babies.[2]

When our ancestors began to evolve a complex language and culture, it marked the start of an entirely new phase in the evolution of life on earth.

[2]Interestingly, a gene which seems to be closely associated with human speech has recently been located and mapped by C.S.L. Lai *et al*, who reported their results in Nature, **413**, 2001. These authors studied three generations of the "KE" family, 15 members of which are afflicted with a severe speech disorder. In all of the afflicted family members, a gene called FOXP2 on chromosome 7 is defective. In another unrelated individual, "CS", with a strikingly similar speech defect, the abnormality was produced by chromosomal translocation, the breakpoint coinciding exactly with the location of the FOXP2 gene. A still more recent study of the FOXP2 gene was published online in Nature AOP on August 14, 2002. The authors (Wolfgang Enard, Molly Przeworski, Cecilia S.L. Lai, Victor Wiebe, Takashi Kitano, Anthony P. Monaco, and Svante Pääbo) sequenced the FOXP2 gene and protein in the chimpanzee, gorilla, orang-utan, rhesus macaque and mouse, comparing the results with sequences of human FOXP2. They found that in the line from the common ancestor of mouse and man to the point where the human genome branches away from that of the chimp, there are many nucleotide substitutions, but *all* are silent, i.e. they have no effect at all on the FOXP2 protein. The even more numerous non-silent DNA mutations which must have taken place during this period seem to have been rejected by natural selection because of the importance of conserving the form of the protein. However, in the human line after the human-chimp fork, something dramatic happens: There are only two base changes, but *both* of them affect the protein! This circumstance suggests to Enard *et al* that the two alterations in the human FOXP2 protein conferred a strong evolutionary advantage, and they speculate that this advantage may have been an improved capacity for language.

In all terrestrial organisms, information is transmitted between generations by means of the genetic code; and genetic evolution takes place through natural selection acting on modifications of this code. In human cultural evolution, information is also transmitted between generations by means of language. This second mode of evolution gave our species enormous adaptive advantages. While genetic changes are random and slow, cultural changes are purposeful and rapid. For example, when our ancestors moved out of Africa and spread over Europe and Asia, they did not adapt to the colder climate by growing long fur, but instead invented clothing. Table 6.2 shows some of the important palaeolithic cultures, together with their dates and characteristics.

An acceleration of human cultural development seems to have begun approximately 40,000 years ago. The first art objects date from that period, as do migrations which ultimately took modern man across the Bering Strait to the western hemisphere. A land bridge extending from Siberia to Alaska is thought to have been formed approximately 70,000 years ago, disappearing again roughly 10,000 years before the present. Cultural and genetic studies indicate that migrations from Asia to North America took place during this period. Shamanism,[3] which is found both in Asia and the new world, as well as among the Sami (Lapps) of northern Scandanavia, is an example of the cultural links between the hunting societies of these regions.

In the caves of Spain and southern France are the remains of vigorous hunting cultures which flourished between 30,000 and 10,000 years ago. The people of these upper palaeolithic cultures lived on the abundant cold-weather game which roamed the southern edge of the ice sheets during the Wurm glacial period: huge herds of reindeer, horses and wild cattle, as well as mammoths and wooly rhinos. The paintings found in the Dordogne region of France, for example, combine decorative and representational elements in a manner which contemporary artists might envy. Sometimes among the paintings are stylized symbols which can be thought of as the first steps towards writing.

In this period, not only painting, but also tool-making and weapon-making were highly developed arts. For example, the Solutrian culture, which flourished in Spain and southern France about 20,000 years ago, produced beautifully worked stone lance points in the shape of laurel leaves and willow leaves. The appeal of these exquisitely pressure-flaked blades must have been aesthetic as well as functional. The people of the Solutrian culture had fine bone needles with eyes, bone and ivory pendants, beads

[3] A shaman is a special member of a hunting society who, while in a trance, is thought to be able to pass between the upper world, the present world, and the lower world, to cure illnesses, and to insure the success of a hunt.

Table 6.2: Palaeolithic cultures

name	years before present	characteristics
Oldowan	2.4 to 1.5 million	Africa, flaked pebble tools
Choukoutien	1.2 to 0.5 million	chopper tool culture of east Asia
Abbevillian	500,000 to 450,000	crude stone handaxes Africa, Europe, northeast Asia
Acheulian	400,000 to 200,000	skillfully shaped stone handaxes, some use of fire
Clactonian	450,000 to 250,000	fully developed flake tools
Mousterian	70,000 to 20,000	produced by Neanderthal man, retouched core and flake tools, wooden, spears, fire, burial of dead
Aurignacian	50,000 to 20,000	western Europe, fine stone blades, pins and awls of bone, fire, cave art
Solutrian	20,000 to 17,000	France and central Europe, long, pressure-flaked bifacial blades
Magdalenian	17,000 to 10,000	western Europe, reindeer hunting awls and needles of bone and antler

and bracelets, and long bone pins with notches for arranging the hair. They also had red, yellow and black pigments for painting their bodies.

The Solutrian culture lasted for 4,000 years. It ended in about 17,000 B.C. when it was succeeded by the Magdalenian culture. Whether the Solutrian people were conquered by another migrating group of hunters, or whether they themselves developed the Magdalenian culture we do not know.

Beginning about 10,000 B.C., the way of life of the hunters was swept aside by a great cutural revolution: the invention of agriculture. The earth had entered a period of unusual climatic stability, and this may have helped to make agriculture possible. The first agricultural villages date from this time, as well as the earliest examples of pottery. Dogs and reindeer were domesticated, and later, sheep and goats.

Radio-carbon dating shows that by 8,500 B.C., people living in the caves of Shanidar in the foothills of the Zagros mountains in Iran had domesticated sheep. By 7,000 B.C., the village farming community at Jarmo in Iraq had domesticated goats, together with barley and two different kinds of wheat.

Starting about 8000 B.C., rice came under cultivation in East Asia. This may represent an independent invention of agriculture, and agriculture may also have been invented independently in the western hemisphere, made possible by the earth's unusually stable climate during this period.

At Jericho, in the Dead Sea valley, excavations have revealed a prepottery neolithic settlement surrounded by an impressive stone wall, six feet wide and twelve feet high. Radiocarbon dating shows that the defenses of the town were built about 7,000 B.C. Probably they represent the attempts of a settled agricultural people to defend themselves from the plundering raids of less advanced nomadic tribes.

Starting in western Asia, the neolithic agricultural revolution swept westward into Europe, and eastward into the regions that are now Iran and India. By 4,300 B.C., the agricultural revolution had spread southwest to the Nile valley, where excavations along the shore of Lake Fayum have revealed the remains of grain bins and silos. The Nile carried farming and stock-breeding techniques slowly southward, and wherever they arrived, they swept away the hunting and food-gathering cultures. By 3,200 B.C. the agricultural revolution had reached the Hyrax Hill site in Kenya. At this point the southward movement of agriculture was stopped by the swamps at the headwaters of the Nile. Meanwhile, the Meriterranean Sea and the Danube carried the revolution westward into Europe. Between 4,500 and 2,000 B.C. it spread across Europe as far as the British Isles and Scandinavia.

Early forms of writing

In Mesopotamia (which in Greek means "between the rivers"), the settled agricultural people of the Tigris and Euphraties valleys evolved a form of writing. The practical Mesopotamians seem to have invented writing as a means of keeping accounts.

Small clay and pebble counting tokens symbolizing items of trade began to be used in the Middle East about 9000 B.C., and they were widely used in the region until 1500 B.C. These tokens had various shapes, depending on the ware which they symbolized, and when made of clay they were often marked with parallel lines or crosses, which made their meaning more precise. In all, about 500 types of tokens have been found at various sites. Their use extended as far to the west as Khartoum in present-day Sudan, and as far to the east as the region which is now Pakistan. Often the tokens were kept in clay containers which were marked to indicate their contents. The markings on the containers, and the tokens themselves, evolved into true writing.

Among the earliest Mesopotamian writings are a set of clay tablets found at Tepe Yahya in southern Iran, the site of an ancient Elamite trading community halfway between Mesopotamia and India. The Elamite trade supplied the Sumerian civilization of Mesopotamia with silver, copper, tin, lead, precious gems, horses, timber, obsidian, alabaster and soapstone.

The tablets found at Tepe Yahya are inscribed in proto-Elamite, and radiocarbon dating of organic remains associated with the tablets shows them to be from about 3,600 B.C. The inscriptions on these tablets were made by pressing the blunt and sharp ends of a stylus into soft clay. Similar tablets have been found at the Sumerian city of Susa at the head of the Tigris River.

In about 3,100 B.C. the cuneiform script was developed, and later Mesopotamian tablets are written in cuneiform, a phonetic script in which the symbols stand for syllables.

The Egyptian hieroglyphic (priest writing) system began its development in about 4,000 B.C. At that time, it was pictorial rather than phonetic. However, the Egyptians were in contact with the Sumerian civilization of Mesopotamia, and when the Sumerians developed a phonetic system of writing in about 3,100 B.C., the Egyptians were quick to adopt the idea. In the cuneiform writing of the Sumerians, a character stood for a syllable. In the Egyptian adaptation of this idea, some of the symbols stood for syllables or numbers, or were determinative symbols, which helped to make the meaning of a word more precise. However, some of the hieroglyphs were purely alphabetic, i.e. they stood for sounds which we would now represent by a single letter. This was important from the standpoint of cultural history, since it suggested to the Phoenicians the idea of an alphabet of the modern type.

In Sumer, the pictorial quality of the symbols was lost at a very early stage, so that in the cuneiform script the symbols are completely abstract.

By contrast, the Egyptian system of writing was designed to decorate monuments and to be impressive even to an illiterate viewer; and this purpose was best served by retaining the elaborate pictographic form of the symbols.

Besides the impressive and beautiful hieroglyphic writing which decorated their monuments, the Egyptians used a more rapidly-written script called Hieratic, which also existed in a shorthand version called Demotic (the "people's script"). During the Ptolemaic period[4], the Coptic language was spoken by part of the population of Egypt. This language was closely related to Egyptian, but was written using the Greek alphabet, an alphabet which developed from that of the Phoenecians. Knowledge of Coptic was one of the keys which helped Egyptologists to decipher the Rosetta stone, and hence the hieroglyphs.[5]

Starting with the neolithic agricultural revolution and the invention of writing, human culture began to develop with explosive speed. Agriculture led to a settled way of life, with leisure for manufacturing complex artifacts, and for invention and experimentation. Writing allowed the cultural achievements of individuals or small groups to become widespread, and to be passed efficiently from one generation to the next.

Compared with the rate of ordinary genetic evolution, the speed with which the information-driven cultural evolution of Homo sapiens sapiens began to develop is truly astonishing. 12,000 years before the present, our ancestors were decorating the walls of their caves with drawings of mammoths. Only 10,000 years later, they were speculating about the existence of atoms! New methods for the conservation and utilization of information were the driving forces behind the explosively accelerating evolution of human culture.

This remarkably rapid growth of human culture was not accompanied by very great genetic changes in our species. It took place instead because of a revolutionary leap in the efficiency with which information could be conserved and transmitted between generations, not in the code of DNA, but in the codes of Mesopotamian cuneiform, Egyptian hieroglyphics, Chinese ideograms, Mayan glyphs, and the Phoenecian and Greek alphabets.

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[4]The first ruler in the Ptolomeic dynasty was one of the generals of Alexander the Great. The last in the line was the famous queen, Cleopatra, a contemporary (and lover) of Julius Caesar.

[5]It was the English physician, physicist and egyptologist Thomas Young who first argued that ancient Egyptian might be similar to Coptic. He was the first to decipher the Demotic script on the Rosetta stone, and he later compiled the first dictionary of Demotic Egyptian. He thus laid the foundation for Champollion's decoding of hieroglyphics in 1823.

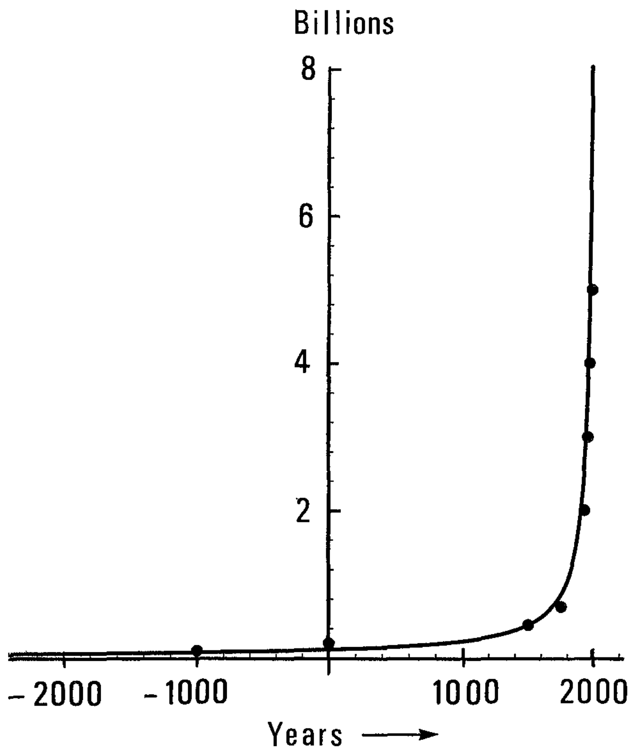

Fig. 6.1 Starting with the neolithic agricultural revolution and the invention of writing, human culture began to develop with explosive speed. This figure shows the estimated human population as a function of time during the last 4,000 years. The dots are population estimates in billions, while the solid curve is the hyperbola $p = c/(2020 - y)$, where p is the global human population y is the year, and $c = 234000$. The curve reflects an explosively accelerating accumulation of information. Culturally transmitted techniques of agriculture allowed a much greater density of population than was possible for hunter-gatherers. The growth of population was further accelerated by the invention of printing and by the industrial and scientific developments which followed from this invention.

The invention of paper, ink, and printing

The ancient Egyptians were the first to make books. As early as 4,000 B.C., they began to make books in the form of scrolls by cutting papyrus reeds into thin strips and pasting them into sheets of double thickness. The sheets were glued together end to end, so that they formed a long roll. The rolls were sometimes very long indeed. For example, one roll, which is now in the British Museum, is 37 centimeters wide and 41 meters long.

The world's first great public library was established in Alexandria, Egypt, at the start of the Hellenistic Era (323 B.C. - 146 B.C.). Ptolemy I, who ruled Egypt after the dissolution of the empire of Alexander of Macedon, built a great library for the preservation of important manuscripts. The library at Alexandria was open to the general public, and at its height it was said to contain 750,000 volumes. Besides preserving important manuscripts, the library became a center for copying and distributing books[6].

The material which the Alexandrian scribes used for making books was papyrus, which was relatively inexpensive. The Ptolemys were anxious that Egypt should keep its near-monopoly on book production, and they refused to permit the export of papyrus. Pergamum, a rival Hellenistic city in Asia Minor, also boasted a library second in size only to the great library at Alexandria. The scribes at Pergamum, unable to obtain papyrus from Egypt, tried to improve the preparation of the skins traditionally used for writing in Asia. The resulting material was called *Membranum pergamentum*, and in English, this name has become "parchment".

Paper of the type which we use today was not invented until 105 A.D. According to tradition, this enormously important invention was made by a Chinese eunuch named Tsai Lun. The kind of paper invented by Tsai Lun could be made from many things - for example, bark, hemp, rags, etc. The starting material was made into a pulp, mixed together with water and binder, spread out on a cloth to partially dry, and finally heated and pressed into thin sheets.

The Chinese later made another invention of immense importance to the cultural evolution of mankind. This was the invention of printing. Together with writing, printing is one of the key inventions which form the basis of human cultural evolution. The exact date of the invention of woodblock printing is uncertain, but indirect evidence makes it seem likely that the technique was first used in the Sui dynasty (581 A.D. - 618 A.D.). Woodblock printing became popular during the T'ang period (618 A.D. - 906 A.D.), and it was much used by Buddhist monks who were interested in producing many copies of the sacred texts which they had translated from Sanskrit. The act of reproducing prayers was also considered to be meritorious by the Buddhists.

Chinese administrators had for a long time followed the custom of brushing engraved official seals with ink and using them to stamp documents. The type of ink which they used was made from lampblack, water and

[6]Unfortunately this great library was destroyed. Much damage was done in 145 B.C. by riots and civil war. According to some accounts, the destruction was completed in 47 B.C. when Julius Caesar's fleet set fire to the Egyptian fleet, and the fire spread to the city of Alexandria.

binder. In fact, it was what we now call "India ink". However, in spite of its name, India ink is a Chinese invention, which later spread to India and from there to Europe.

We mentioned that paper of the type which we now use was invented in China in the first century A.D. Thus, the Buddhist monks of China had all the elements which they needed to make printing practical: They had good ink, cheap, smooth paper, and the tradition of stamping documents with ink-covered engraved seals. The first surviving block prints which they produced date from the 8th century A.D. They were made by carving a block of wood the size of a printed page so that raised characters remained, brushing ink onto the block, and pressing this onto a sheet of paper.

The oldest known printed book, the "Diamond Sutra", is dated 868 A.D., and it consists of only six printed pages. It was discovered in 1907 by an English scholar who obtained permission from Buddhist monks in Chinese Turkistan to open some walled-up monastery rooms, which were said to have been sealed for 900 years. The rooms were found to contain a library of about 15,000 manuscripts, among which was the Diamond Sutra.

Block printing spread quickly throughout China, and also reached Japan, where woodblock printing ultimately reached great heights in the work of such artists as Hiroshige and Hokusai.

The invention of block printing during the T'ang dynasty had an enormously stimulating effect on literature, and the T'ang period is regarded as the golden age of Chinese lyric poetry. A collection of T'ang poetry, compiled in the 18th century, contains 48,900 poems by more than 2,000 poets.

About 1041-1048 A.D., a Chinese alchemist named Pi Sheng invented movable type, made from a mixture of clay and glue, and hardened by baking. He assembled the type into a text on an iron tray covered with a mixture of resin, wax and paper ash. He then gently heated the tray, and allowed it to cool, so that the type became firmly fixed in place. After printing as many copies of the text as he desired, Pi Sheng reheated the iron tray and reused the characters.

In 1313 a Chinese magistrate named Wang Chen initiated a large-scale printing project using movable type. He is said to have ordered craftsmen to carve 60,000 characters on movable wooden blocks. These were used to print a book on the history of technology. However, in spite of the efforts of Pi Sheng and Wang Chen, movable type never became very popular in China, because the Chinese written language contains 10,000 characters. However, printing with movable type was highly successful in Korea as early as the 15th century A.D., perhaps because a phonetic writing system existed in Korea, with symbols for syllables.

The unsuitability of the Chinese written language for the use of movable type was one of the greatest tragedies of Chinese civilization. Writing had been developed at a very early stage in Chinese history, but the system remained a pictographic system, with a different character for each word. A phonetic system of writing was never developed.

The failure to develop a phonetic system of writing had its roots in the Chinese imperial system of government. The Chinese empire formed a vast area in which many different languages were spoken. It was necessary to have a universal language of some kind in order to govern such an empire. The Chinese written language solved this problem admirably.

Suppose that the emperor sent identical letters to two officials in different districts. Reading the letters aloud, the officials might use entirely different words, although the characters in the letters were the same. Thus the Chinese written language was a sort of "Esperanto" which allowed communication between various language groups, and its usefulness as such prevented its replacement by a phonetic system.

The disadvantages of the Chinese system of writing were twofold: First, it was difficult to learn to read and write, and therefore literacy was confined to a small social class whose members could afford a prolonged education. The system of civil-service examinations made participation in the government dependent on a high degree of literacy, and hence the old, established scholar-gentry families maintained a long-term monopoly on power, wealth and education. Social mobility was possible in theory, since the civil service examinations were open to all, but in practice it was nearly unattainable.

The second great disadvantage of the Chinese system of writing was that it was unsuitable for printing with movable type. An "information explosion" occurred in the West following the introduction of printing with movable type, but this never occurred in China. It is ironical that although both paper and printing were invented by the Chinese, the full effect of these immensely important inventions bypassed China and instead revolutionized the west.

The information explosion

Like the process of silk manufacture, the art of papermaking remained for a long time a Chinese secret, but paper made in China (like silk) was traded with the Arab world along caravan routes. Finally, in 751, Chinese prisoners taken at the battle of Talas, near Samarkand, revealed the secret of papermaking to the Arabs. Between the 8th century and the 13th century, paper was extensively manufactured and used throughout the Islamic world, which stretched from the Middle East through North Africa to Spain. It seems strange that Chinese techniques of printing were not also transmitted during this period to the highly advanced Islamic civilization. Some historians believe that methods of printing were known to the Arabs in the 8th-13th centuries, but for religious reasons not used, the Koran being considered too holy to be reproduced by mechanical means. A further factor may have been the fact that the highly decorative classical Arabic script was not very well adapted to printing with movable type. Even in modern, simplified Arabic, each letter has many forms, whose use depends on the position in the word and on the neighboring letters.

Much of the knowledge achieved by the ancient civilizations of western Asia and the Meriterranean regions had been lost with the destruction of the great library of Alexandria. However, a few of the books of the classical and Hellenistic authors had survived in the eastern part of the Roman Empire at Byzantium.

The Byzantine empire included many Syriac-speaking subjects; and in fact, beginning in the 3rd century A.D., Syriac replaced Greek as the major language of western Asia. In the 5th century, there was a split in the Christian church of Byzantium, and the Nestorian church separated from the official Byzantine church. The Nestorians were bitterly persecuted, and therefore they migrated, first to Mesopotamia, and later to southwest Persia.

During the early Middle Ages, the Nestorian capital of Gondasapur was a great center of intellectual activity. The works of Plato, Aristotle, Hippocrates, Euclid, Archimedes, Ptolemy, Hero and Galen were translated into Syriac by Nestorian scholars, who had brought these books with them from Byzantium.

Among the most distinguished of the Nestorian translators were members of a family called Bukht-Yishu (meaning "Jesus hath delivered"), which produced seven generations of outstanding scholars. Members of this family were fluent not only in Greek and Syriac, but also in Arabic and Persian.

In the 7th century, the Islamic religion suddenly emerged as a conquering and proselytizing force. The Arabs and their converts quickly conquered western Asia, northern Africa and Spain. After a short initial period of fanaticism which was often hostile to learning, the attitude of the Islamic conquerers changed to an appreciation of ancient cultures; and during the middle ages, the Islamic world reached a very high level of civilization.[7] Thus, while the century from 750 to 850 was primarily a period of translation from Greek into Syriac, the century from 850 to 950 was a period of translation from Syriac to Arabic.

The skill of the physicians of the Bukht-Yishu family convinced the

[7]There were, however, oscillations between periods of liberal fostering of intellectual efforts, and periods of puritanical suppression.

Caliphs of Baghdad of the value of Greek learning, and in this way the family played an important role in the preservation of the classical cultures. Soon Baghdad replaced Gondisapur as a center of learning and translation.

Islamic scholars not only preserved our heritage from the ancient classical cultures but also added much to it. Chemistry, medicine, physics, astronomy and mathematics all owe much to the highly cultured Islamic world of the Middle Ages. The magnitude of this contribution can be judged from the many modern scientific words which have an Arabic origin. For example, the English words for chemistry is derived from the Arabic word "*al-chimia*, meaning "the changing". The word "*al-kali*", which appears in the writings of the Persian chemist Rahzes (860-950), means "the calcined" in Arabic. It is the source of our word "alkali" as well as of the symbol K for potassium. In mathematics, one of the most outstanding Arabic writers was al-Khwarismi (780-850). The title of his book, *Ilm al-jabr wa'd muqabalah*, is the source of the English word "algebra". In Arabic, *al-jabr* means "the equating". Al-Khwarizmi's name has also become an English word, "algorism", the old word for arithmetic.

Towards the end of the Middle Ages, Europe began to be influenced by the advanced Islamic civilization. European scholars were anxious to learn, but there was an "iron curtain" of religious intolerance which made travel in the Islamic countries difficult and dangerous for Christians. However, in the 12th century, parts of Spain, including the city of Toledo, were reconquered by the Christians. Toledo had been an Islamic cultural center, and many Moslem and Jewish scholars, together with their manuscripts, remained in the city when it passed into Christian hands. Thus Toledo became a center for the exchange of ideas between east and west; and it was in this city that many of the books of the classical Greek and Hellenistic philosophers were translated from Arabic into Latin.[8]

Another bridge between east and west was established by the Crusades. Crusaders returning from the Middle East brought paper with them to Europe, and from 1275 onwards the manufacture of paper became common in Italy, contributing importantly to the Italian Renaissance. In the 14th century, the manufacture of paper spread to France and Germany. Woodblock printing came into use in Europe during the last quarter of the 14th century. When the use of paper became common, it was noticed that the smooth and absorbent surface of paper was much more suitable for receiving a printed impression than was the surface of parchment, besides

[8]Very often, the train of translations was very indirect, e.g., from Greek to Arabic to Hebrew to Spanish to Latin. For this reason, some of the earliest classical Greek texts made available to the Christian world were very incomplete. Added to this was the fact that translators and scribes felt quite free to edit, amend, and add to the texts on which they were working.

being far less expensive. In the 15th century, European artists such as Albrecht Dürer began to produce woodblock prints of great beauty. At the same time, woodblock printing was used to produce small books with a few pages of script, for example religious works and Latin grammars. Some experiments with movable wooden type seem to have been made in Holland, but the results were disappointing because when the letters were made as small as was desirable, they were not sufficiently durable.

Starting in approximately 1430, European craftsmen from the medieval guilds, who had a knowledge of the use of metal dies, began to apply this technique to printing. In the first step of this process, a set of dies, one for each letter of the alphabet, was engraved in brass or bronze. The dies were then used to produce a mold, over which lead was poured. When the lead plate was removed from the mold, the letters stood out in raised form. This method of metallographic printing was used in Holland and in the Rhineland, and in the period 1434-1439, Johannes Gutenberg used it in what is now Strasbourg France.

Gutenberg is generally credited with the simultaneous development (in 1450) of movable metal type and the printing press. He was a silversmith whose knowledge of metallurgy was undoubtedly useful to him when he designed the machinery and type for printing. His partner in the book-producing enterprise was a businessman named Johann Fust. In 1509, there was a lawsuit in which Fust's grandson, Johann Schöffer, claimed that Fust alone was the inventor of the new printing method. However, in 1505, Schöffer had already written in a preface to an edition of Livy, "..the admirable art of typography was invented by the ingenious Johan Gutenberg at Mainz in 1450." One is more inclined to believe Schöffer's statement of 1505 than his later testimony in the 1509 lawsuit, which seems to have been motivated by the hope of financial gain.

The printing press invented by Gutenberg was a modification of the press which already used in Europe for binding books. The bed was fixed, and the movable upper platen (or level surface) was driven by a bar attached to a worm screw. The type letters were cast by pouring a molten alloy of lead, tin and antimony into moulds produced from dies. The letters were arranged into lines of type on wooden composing sticks held in the hand of the typographer, and each line was then justified (i.e. all the lines were made to have equal length) by the insertion of small blank lead spacers. After the printing of a page, each line was taken to pieces by hand, and the letters were returned to their containers.

Paper alone had an enormously stimulating effect on European culture when its manufacture and use became common at the end of the 13th century; but when paper was combined with Gutenberg's improved printing techniques in the 15th century, the combination produced an explosive accumulation of information. The combination of paper and improved printing resulted in the scientific and industrial revolutions, and in short the modern world.

One must add that it was not only paper and printing which combined to produce the information explosion, but also fragments from the writings of the classical ancient civilizations which had been translated first into Syriac, then from Syriac into Arabic, and finally from Arabic into Latin, and which thus, by a roundabout route, drifted into the consciousness of the west.

The career of Leonardo da Vinci illustrates the first phase of the information explosion: Inexpensive paper was being manufactured in Europe, and it formed the medium for Leonardo's thousands of pages of notes. His notes and sketches would never have been possible if he had been forced to use expensive parchment as a medium. On the other hand, the full force of Leonardo's genius and diligence was never felt because his notes were not printed. (In fact, fearing persecution for his radical ideas, Leonardo kept his notebooks secret.) Copernicus, who was a younger contemporary of Leonardo, had a much greater effect on the history of ideas because his work was published. Thus while paper alone made a large contribution to the information explosion, it was printing combined with paper which had an absolutely decisive and revolutionary impact: The modern scientific era began with the introduction of printing.

The development of printing in Europe and the rapid spread of books and knowledge produced a brilliant chainlike series of scientific discoveries - the sun-centered system of Copernicus, Kepler's three laws of planetary motion, Descartes' invention of analytic geometry, Gilbert's studies of magnetism, Galileo's discoveries in experimental physics and astronomy, the microscopy of Hooke and Leeuwenhoek, Newton's universal laws of motion and gravitation, the differential and integral calculus of Newton and Leibniz, the medical discoveries of Harvey, Jenner, Pasteur, Koch, Semmelweis and Lister, and the chemical discoveries of Boyle, Dalton, Priestly, Lavoisier and Berzelius.

The rapid accumulation of scientific knowledge made possible by paper and printing was quickly converted into the practical inventions of the industrial revolution. In the space of a few centuries, the information explosion changed Europe from a backward region into a society of an entirely new type, driven by scientific and technological innovation and by the diffusion and accumulation of knowledge.

Information-driven human cultural evolution as part of biological evolution

In thinking about human cultural evolution, one has a tendency to put it into a compartment by itself, separated from the evolution of microorganisms, animals, and plants. We feel that culture is not a subject for biologists but rather the domain of humanists. There is indeed a sharp qualitative discontinuity which marks the change from information transfer through the medium of DNA, RNA and proteins, to information transfer and accumulation through the medium of the spoken, written and printed word. Nevertheless it is important to remember that our species is a part of the biosphere, and that all our activities are fundamentally biological phenomena.

In Chapter 1 we discussed the ideas of Condorcet, one of the pioneers of evolutionary thought. He regarded genetic evolution (the process by which humans evolved from lower animals) and cultural evolution (the process by which civilized humans evolved from primitive man) as being two parts of a larger phenomenon which he called "progress". Although cultural evolution seems to differ qualitatively from genetic evolution, Condorcet regarded the two as being aspects of the same overall process.

Sharp qualitative discontinuities have occurred several times before during the earth's 4-billion year evolutionary history: A dramatic change occurred when autocatalytic systems first became surrounded by a cell membrane. Another sharp transition occurred when photosynthesis evolved, and a third when the enormously more complex eukaryotic cells developed from the prokaryotes. The evolution of multicellular organisms also represents a sharp qualitative change. Undoubtedly the change from molecular information transfer to cultural information transfer is an even more dramatic shift to a higher mode of evolution than the four sudden evolutionary gear-shifts just mentioned. Human cultural evolution began only an instant ago on the time-scale of genetic evolution. Already it has completely changed the planet. We have no idea where it will lead.

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Chapter 7

INFORMATION TECHNOLOGY

The first computers

If civilization survives, historians in the distant future will undoubtedly regard the invention of computers as one of the most important steps in human cultural evolution - as important as the invention of writing or the invention of printing. The possibilities of artificial intelligence have barely begun to be explored, but already the impact of computers on society is enormous.

The first programmable universal computers were completed in the mid-1940's; but they had their roots in the much earlier ideas of Blaise Pascal (1623-1662), Gottfried Wilhelm Leibniz (1646-1716), Joseph Marie Jacquard (1752-1834) and Charles Babbage (1791-1871).

In 1642, the distinguished French mathematician and philosopher Blaise Pascal completed a working model of a machine for adding and subtracting. According to tradition, the idea for his "calculating box" came to Pascal when, as a young man of 17, he sat thinking of ways to help his father (who was a tax collector). In describing his machine, Pascal wrote:

"I submit to the public a small machine of my own invention, by means of which you alone may, without any effort, perform all the operations of arithmetic, and may be relieved of the work which has often times fatigued your spirit when you have worked with the counters or with the pen."

Pascal's machine worked by means of toothed wheels. It was much improved by Leibniz, who constructed a mechanical calculator which, besides adding and subtracting, could also multiply and divide. His first machine was completed in 1671; and Leibniz' description of it, written in Latin, is preserved in the Royal Library at Hanover:

"There are two parts of the machine, one designed for addition (and subtraction), and the other designed for multiplication (and division); and they should fit together. The adding (and subtracting) machine coincides completely with the calculating box of Pascal. Something, however, must be added for the sake of multiplication..."

"The wheels which represent the multiplicand are all of the same size, equal to that of the wheels of addition, and are also provided with ten teeth which, however, are movable so that at one time there should protrude 5, at another 6 teeth, etc., according to whether the multiplicand is to be represented five times or six times, etc."

"For example, the multiplicand 365 consists of three digits, 3, 6, and 5. Hence the same number of wheels is to be used. On these wheels, the multiplicand will be set if from the right wheel there protrude 5 teeth, from the middle wheel 6, and from the left wheel 3."

By 1810, calculating machines based on Leibniz' design were being manufactured commercially; and mechanical calculators of a similar (if much improved) design could be found in laboratories and offices until the 1960's.

The idea of a programmable universal computer is due to the English mathematician, Charles Babbage, who was the Lucasian Professor of Mathematics at Cambridge University. (In the 17th century, Isaac Newton held this post, and in the 20th century, P.A.M. Dirac and Stephen Hawking also held it.)

In 1812, Babbage conceived the idea of constructing a machine which could automatically produce tables of functions, provided that the functions could be approximated by polynomials. He constructed a small machine, which was able to calculate tables of quadratic functions to eight decimal places, and in 1832 he demonstrated this machine to the Royal Society and to representatives of the British government.

The demonstration was so successful that Babbage secured financial support for the construction of a large machine which would tabulate sixth-order polynomials to twenty decimal places. The large machine was never completed, and twenty years later, after having spent seventeen thousand pounds on the project, the British government withdrew its support. The reason why Babbage's large machine was never finished can be understood from the following account by Lord Moulton of a visit to the mathematician's laboratory:

"One of the sad memories of my life is a visit to the celebrated mathematician and inventor, Mr. Babbage. He was far advanced in age, but his mind was still as vigorous as ever. He took me through his workrooms."

"In the first room I saw the parts of the original Calculating Machine, which had been shown in an incomplete state many years before, and had even been put to some use. I asked him about its present form. 'I have not finished it, because in working at it, I came on the idea of my Analytical Machine, which would do all that it was capable of doing, and much more. Indeed, the idea was so much simpler that it would have taken more work to complete the Calculating Machine than to design and construct the other in its entirety; so I turned my attention to the Analytical Machine.'"

"After a few minutes talk, we went into the next workroom, where he showed me the working of the elements of the Analytical Machine. I asked if I could see it. 'I have never completed it,' he said, 'because I hit upon the idea of doing the same thing by a different and far more effective method, and this rendered it useless to proceed on the old lines.'"

"Then we went into a third room. There lay scattered bits of mechanism, but I saw no trace of any working machine. Very cautiously I approached the subject, and received the dreaded answer: 'It is not constructed yet, but I am working at it, and will take less time to construct it altogether than it would have taken to complete the Analytical Machine from the stage in which I left it.' I took leave of the old man with a heavy heart."

Babbage's first calculating machine was a special-purpose mechanical computer, designed to tabulate polynomial functions; and he abandoned this design because he had hit on the idea of a universal programmable computer. Several years earlier, the French inventor Joseph Marie Jacquard had constructed an automatic loom in which large wooden "punched cards" were used to control the warp threads. Inspired by Jacquard's invention, Babbage planned to use punched cards to program his universal computer. (Jacquard's looms could be programmed to weave extremely complex patterns: A portrait of the inventor, woven on one of his looms in Lyon, hung in Babbage's drawing room.)

One of Babbage's frequent visitors was Augusta Ada[1], Countess of Lovelace (1815-1852), the daughter of Lord and Lady Byron. She was a mathematician of considerable ability, and it is through her lucid descriptions that we know how Babbage's never-completed Analytical Machine was to have worked.

The next step towards modern computers was taken by Hermann Hollerith, a statistician working for the United States Bureau of the Census. He invented electromechanical machines for reading and sorting data punched onto cards. Hollerith's machines were used to analyze the data from the 1890 United States Census. Because the Census Bureau was a very limited market, Hollerith branched out and began to manufacture similar machines for use in business and administration. His company was later bought out by Thomas J. Watson, who changed its name to International Business Machines.

In 1937, Howard Aiken, of Harvard University, became interested in combining Babbage's ideas with some of the techniques which had developed from Hollerith's punched card machines. He approached the Interna-

[1]The programming language ADA is named after her.

tional Business Machine Corporation, the largest manufacturer of punched card equipment, with a proposal for the construction of a large, automatic, programmable calculating machine.

Aiken's machine, the Automatic Sequence Controlled Calculator (ASCC), was completed in 1944 and presented to Harvard University. Based on geared wheels, in the Pascal-Leibniz-Babbage tradition, ASCC had more than three quarters of a million parts and used 500 miles of wire. ASCC was unbelievably slow by modern standards - it took three-tenths of a second to perform an addition - but it was one of the first programmable general-purpose digital computers ever completed. It remained in continuous use, day and night, for fifteen years.

In the ASCC, binary numbers were represented by relays, which could be either on or off. The on position represented 1, while the off position represented 0, these being the only two digits required to represent numbers in the binary (base 2) system. Electromechanical calculators similar to ASCC were developed independently by Konrad Zuse in Germany and by George R. Stibitz at the Bell Telephone Laboratory.

Electronic digital computers

In 1937, the English mathematician A.M. Turing published an important article in the Proceedings of the London Mathematical Society in which envisioned a type of calculating machine consisting of a long row of cells (the "tape"), a reading and writing head, and a set of instructions specifying the way in which the head should move the tape and modify the state and "color" of the cells on the tape. According to a hypothesis which came to be known as the "Church-Turing hypothesis", the type of computer proposed by Turing was capable of performing every possible type of calculation. In other words, the Turing machine could function as a universal computer.

In 1943, a group of English engineers, inspired by the ideas of Alan Turing and those of the mathematician M.H.A. Newman, completed the electronic digital computer Colossus. Colossus was the first large-scale electronic computer. It was used to break the German Enigma code; and it thus affected the course of World War II.

In 1946, ENIAC (Electronic Numerical Integrator and Calculator) became operational. This general-purpose computer, designed by J.P. Eckert and J.W. Mauchley of the University of Pennsylvania, contained 18,000 vacuum tubes, one or another of which was often out of order. However, during the periods when all its vacuum tubes were working, an electronic computer like Colossus or ENIAC could shoot ahead of an electromechanical machine (such as ASCC) like a hare outdistancing a tortoise.

During the summer of 1946, a course on "The Theory and Techniques of Electronic Digital Computers" was given at the University of Pennsylvania. The ideas put forward in this course had been worked out by a group of mathematicians and engineers headed by J.P. Eckert, J.W. Mauchley and John von Neumann, and these ideas very much influenced all subsequent computer design.

Cybernetics

The word "Cybernetics", was coined by the American mathematician Norbert Wiener (1894-1964) and his colleagues, who defined it as "the entire field of control and communication theory, whether in the machine or in the animal". Wiener derived the word from the Greek term for "steersman".

Norbert Wiener began life as a child prodigy: He entered Tufts University at the age of 11 and received his Ph.D. from Harvard at 19. He later became a professor of mathematics at the Massachusetts Institute of Technology. In 1940, with war on the horizon, Wiener sent a memorandum to Vannevar Bush, another MIT professor who had done pioneering work with analogue computers, and had afterwards become the chairman of the U.S. National Defense Research Committee. Wiener's memorandum urged the American government to support the design and construction of electronic digital computers, which would make use of binary numbers, vacuum tubes, and rapid memories. In such machines, the memorandum emphasized, no human intervention should be required except when data was to be read into or out of the machine.

Like Leo Szilard, John von Neumann, Claude Shannon and Erwin Schrödinger, Norbert Wiener was aware of the relation between information and entropy. In his 1948 book *Cybernetics* he wrote: "...we had to develop a statistical theory of the *amount of information*, in which the unit amount of information was that transmitted by a single decision between equally probable alternatives. This idea occurred at about the same time to several writers, among them the statistician R.A. Fisher, Dr. Shannon of Bell Telephone Laboratories, and the author. Fisher's motive in studying this subject is to be found in classical statistical theory; that of Shannon in the problem of coding information; and that of the author in the problem of noise and message in electrical filters... The notion of the amount of information attaches itself very naturally to a classical notion in statistical mechanics: that of *entropy*. Just as the amount of information in a system is a measure of its degree of organization, so the entropy of a system is a measure of its degree of disorganization; and the one is simply the negative of the other."

During World War II, Norbert Wiener developed automatic systems for control of anti-aircraft guns. His systems made use of feedback loops closely analogous to those with which animals coordinate their movements. In the early 1940's, he was invited to attend a series of monthly dinner parties organized by Arturo Rosenblueth, a professor of physiology at Harvard University. The purpose of these dinners was to promote discussions and collaborations between scientists belonging to different disciplines. The discussions which took place at these dinners made both Wiener and Rosenblueth aware of the relatedness of a set of problems that included homeostasis and feedback in biology, communication and control mechanisms in neurophysiology, social communication among animals (or humans), and control and communication involving machines.

Wiener and Rosenblueth therefore tried to bring together workers in the relevant fields to try to develop common terminology and methods. Among the many people whom they contacted were the anthropologists Gregory Bateson and Margaret Mead, Howard Aiken (the designer of the Automatic Sequence Controlled Calculator), and the mathematician John von Neumann. The Josiah Macy Jr. Foundation sponsored a series of ten yearly meetings, which continued until 1949 and which established cybernetics as a new research discipline. It united areas of mathematics, engineering, biology, and sociology which had previously been considered unrelated. Among the most important participants (in addition to Wiener, Rosenblueth, Bateson, Mead, and von Neumann) were Heinz von Foerster, Kurt Lewin, Warren McCulluch and Walter Pitts. The Macy conferences were small and informal, with an emphasis on discussion as opposed to the presentation of formal papers. A stenographic record of the last five conferences has been published, edited by von Foerster. Transcripts of the discussions give a vivid picture of the enthusiastic and creative atmosphere of the meetings. The participants at the Macy Conferences perceived Cybernetics as a much-needed bridge between the natural sciences and the humanities. Hence their enthusiasm. Weiner's feedback loops and von Neumann's theory of games were used by anthropologists Mead and Bateson to explain many aspects of human behavior.

Microelectronics

The problem of unreliable vacuum tubes was solved in 1948 by John Bardeen, William Shockley and Walter Brattain of the Bell Telephone Laboratories. Application of quantum theory to solids had led to an understanding of the electronic properties of crystals. Like atoms, crystals were found to have allowed and forbidden energy levels.

The allowed energy levels for an electron in a crystal were known to form bands; i.e., some energy ranges with a quasi-continuum of allowed states (allowed bands), and other energy ranges with none (forbidden bands). The lowest allowed bands were occupied by electrons, while higher bands were empty. The highest filled band was called the *valence band*, and the lowest empty band was called the *conduction band.*

According to quantum theory, whenever the valence band of a crystal is only partly filled, the crystal is a conductor of electricity; but if the valence band is completely filled with electrons, the crystal is an electrical insulator. (A completely filled band is analogous to a room so packed with people that none of them can move.)

In addition to explaining conductors and insulators, quantum theory yielded an understanding of semiconductors - crystals where the valence band is completely filled with electrons, but where the energy gap between the conduction band and the valence band is relatively small. For example, crystals of the elements silicon and germanium are semiconductors. For such a crystal, thermal energy is sometimes enough to lift an electron from the valence band to the conduction band.

Bardeen, Shockley and Brattain found ways to control the conductivity of germanium crystals by injecting electrons into the conduction band, or alternatively by removing electrons from the valence band. They could do this by forming junctions between crystals "doped" with appropriate impurities, and by injecting electrons with a special electrode. The semiconducting crystals whose conductivity was controlled in this way could be used as electronic valves, in place of vacuum tubes.

By the 1960's, replacement of vacuum tubes by transistors in electronic computers had led not only to an enormous increase in reliability and a great reduction in cost, but also to an enormous increase in speed. It was found that the limiting factor in computer speed was the time needed for an electrical signal to propagate from one part of the central processing unit to another. Since electrical impulses propagate with the speed of light, this time is extremely small; but nevertheless, it is the limiting factor in the speed of electronic computers.

In order to reduce the propagation time, computer designers tried to make the central processing units very small; and the result was the development of integrated circuits and microelectronics. (Another motive for miniaturization of electronics came from the requirements of space exploration.)

Integrated circuits were developed, in which single circuit elements were not manufactured separately, but instead the whole circuit was made at one time. An integrated circuit is a multilayer sandwich-like structure, with conducting, resisting and insulating layers interspersed with layers of germanium or silicon, "doped " with appropriate impurities. At the start of the manufacturing process, an engineer makes a large drawing of each layer. For example, the drawing of a conducting layer would contain pathways which fill the role played by wires in a conventional circuit, while the remainder of the layer would consist of areas destined to be etched away by acid.

The next step is to reduce the size of the drawing and to multiply it photographically. The pattern of the layer is thus repeated many times, like the design on a piece of wallpaper. The multiplied and reduced drawing is then focused through a reversed microscope onto the surface to be etched.

Successive layers are built up by evaporating or depositing thin films of the appropriate substances onto the surface of a silicon or germanium wafer. If the layer being made is to be conducting, the surface might consist of an extremely thin layer of copper, covered with a photosensitive layer called a "photoresist". On those portions of the surface receiving light from the pattern, the photoresist becomes insoluble, while on those areas not receiving light, the photoresist can be washed away.

The surface is then etched with acid, which removes the copper from those areas not protected by photoresist. Each successive layer of a wafer is made in this way, and finally the wafer is cut into tiny "chips", each of which corresponds to one unit of the wallpaper-like pattern. Although the area of a chip may be much smaller than a square centimeter, the chip can contain an extremely complex circuit.

In 1965, only four years after the first integrated circuits had been produced, Dr. Gordon E. Moore, one of the founders of Intel, made a famous prediction which has come to be known as "Moore's Law". He predicted that the number of transistors per integrated circuit would double every 18 months, and that this trend would continue through 1975. In fact, the general trend predicted by Moore has continued for a much longer time. Although the number of transistors per unit area has not continued to double every 18 months, the logic density (bits per unit area) has done so, and thus a modified version of Moore's law still holds today. How much longer the trend can continue remains to be seen. Physical limits to miniaturization of transistors of the present type will soon be reached; but there is hope that further miniaturization can be achieved through "quantum dot" technology, molecular switches, and autoassembly, as will be discussed in Chapter 8.

A typical programmable minicomputer or "microprocessor", manufactured in the 1970's, could have 30,000 circuit elements, all of which were contained on a single chip. By 1989, more than a million transistors were being placed on a single chip; and by 2000, the number reached 42,000,000.

Table 7.1: Worldwide hard disk drive market (from an AT&T Labs Research Report by K.G. Coffman and A.M. Odlyzko). 1 terabyte = 10^{12} bytes.

year	$ revenues (billions)	storage capacity (terabytes)
1995	21.6	76,243
1996	24.6	147,200
1997	27.3	334,791
1998	27.0	695,140
1999	29.1	1,463,109
2000	32.5	3,222,153
2001	36.2	7,239,972
2002	40.7	15,424,824

As a result of miniaturization and parallelization, the speed of computers rose exponentially. In 1960, the fastest computers could perform a hundred thousand elementary operations in a second. By 1970, the fastest computers took less than a second to perform a million such operations. In 1987, a massively parallel computer, with 566 parallel processors, called GF11 was designed to perform 11 billion floating-point operations per second (flops). By 2002 the fastest computer performed 40 at teraflops, making use of 5120 parallel CPU's.

Computer disk storage has also undergone a remarkable development. In 1987, the magnetic disk storage being produced could store 20 million bits of information per square inch; and even higher densities could be achieved by optical storage devices. Storage density has until followed a law similar to Moore's law. The storage available for a constant price has doubled every 18 months, as is illustrated in Table 7.1.

In the 1970's and 1980's, computer networks were set up linking machines in various parts of the world. It became possible (for example) for a scientist in Europe to perform a calculation interactively on a computer in the United States just as though the distant machine were in the same room; and two or more computers could be linked for performing large calculations. It also became possible to exchange programs, data, letters and manuscripts very rapidly through the computer networks.

The exchange of large quantities of information through computer networks was made easier by the introduction of fiber optics cables. By 1986, 250,000 miles of such cables had been installed in the United States. If a ray of light, propagating in a medium with a large refractive index, strikes the surface of the medium at a grazing angle, then the ray undergoes total internal reflection. This phenomenon is utilized in fiber optics: A light signal can propagate through a long, hairlike glass fiber, following the bends of the fiber without losing intensity because of total internal reflection. However, before fiber optics could be used for information transmission over long distances, a technological breakthrough in glass manufacture was needed, since the clearest glass available in 1940 was opaque in lengths more than 10 m. Through studies of the microscopic properties of glasses, the problem of absorption was overcome. By 1987, devices were being manufactured commercially that were capable of transmitting information through fiber-optic cables at the rate of 1.7 billion bits per second.

The history of the Internet and World Wide Web

The history of the Internet began in 1961, when Leonard Kleinrock, a student at MIT, submitted a proposal for Ph.D. thesis entitled "Information Flow in Large Communication Nets". In his statement of the problem, Kleinrock wrote: "The nets under consideration consist of nodes, connected to each other by links. The nodes receive, sort, store, and transmit messages that enter and leave via the links. The links consist of one-way channels, with fixed capacities. Among the typical systems which fit this description are the Post Office System, telegraph systems, and satellite communication systems." Kleinrock's theoretical treatment of package switching systems anticipated the construction of computer networks which would function on a principle analogous to a post office rather than a telephone exchange: In a telephone system, there is a direct connection between the sender and receiver of information. But in a package switching system, there is no such connection - only the addresses of the sender and receiver on the package of information, which makes its way from node to node until it reaches its destination.

Further contributions to the concept of package switching systems and distributed communications networks were made by J.C.R. Licklider and W. Clark of MIT in 1962, and by Paul Baran of the RAND corporation in 1964. Licklider visualized what he called a "Galactic Network", a globally interconnected network of computers which would allow social interactions and interchange of data and software throughout the world. The distributed computer communication network proposed by Baran was motivated by the desire to have a communication system that could survive a nuclear war. The Cold War had also provoked the foundation (in 1957) of the Advanced Research Projects Agency (ARPA) by the U.S. government as a response to the successful Russian satellite "Sputnik".

In 1969, a 4-node network was tested by ARPA. It connected computers at the University of California divisions at Los Angeles and Santa Barbara with computers at the Stanford Research Institute and the University of Utah. Describing this event, Leonard Kleinrock said in an interview: "We set up a telephone connection between us and the guys at SRI. We typed the L and we asked on the phone 'Do you see the L?' 'Yes we see the L', came the response. We typed the O and we asked 'Do you see the O?' 'Yes we see the O.' Then we typed the G and the system crashed." The ARPANET (with 40 nodes) performed much better in 1972 at the Washington Hilton Hotel where the participants at a Conference on Computer Communications were invited to test it.

Although the creators of ARPANET visualized it as being used for long-distance computations involving several computers, they soon discovered that social interactions over the internet would become equally important if not more so. An electronic mail system was introduced in the early 1970's, and in 1976 Queen Elizabeth II of the United Kingdom became one of the increasing number of e-mail users.

In September, 1973, Robert F. Kahn and Vinton Cerf presented the basic ideas of the Internet at a meeting of the International Network Working Group at the University Sussex in Brighton, England. Among these principles was the rule that the networks to be connected should not be changed internally. Another rule was that if a packet did not arrive at its destination, it would be retransmitted from its original source. No information was to be retained by the gateways used to connect networks; and finally there was to be no global control of the Internet at the operations level.

Computer networks devoted to academic applications were introduced in the 1970's and 1980's, both in England, the United States and Japan. The Joint Academic Network (JANET) in the U.K. had its counterpart in the National Science Foundation's network (NSFNET) in America and Japan's JUNET (Japan Unix Network). Internet traffic is approximately doubling each year[2], and it is about to overtake voice communication in the volume of information transferred.

Self-reenforcing information accumulation

Humans have been living on the earth for roughly two million years (more or less, depending on where one draws the line between our human and pre-

[2]In the period 1995-1996, the rate of increase was even faster - a doubling every four months

Table 7.2: Estimated traffic on Internet backbones in U.S. (after K.G. Coffman and A.M. Odlyzko, AT&T Labs Res. Rept, 2001)

year	terabytes per month
1990	1.0
1991	2.0
1992	4.4
1993	8.3
1994	16.3
1995	?
1996	1,500
1997	2,500-4,000
1998	5,000-8,000
1999	10,000-16,000
2000	20,000-35,000

human ancestors, Table 6.1). During almost all of this time, our ancestors lived by hunting and food-gathering. They were not at all numerous, and did not stand out conspicuously from other animals. Then, suddenly, during the brief space of ten thousand years, our species exploded in numbers from a few million to more than six billion (Figure 6.1), populating all parts of the earth, and even setting foot on the moon. This population explosion, which is still going on, has been the result of dramatic cultural changes. Genetically we are almost identical with our hunter-gatherer ancestors, who lived ten thousand years ago, but cultural evolution has changed our way of life beyond recognition.

Beginning with the development of speech, human cultural evolution began to accelerate. It started to move faster with the agricultural revolution, and faster still with the invention of writing and printing. Finally, modern science has accelerated the rate of social and cultural change to a completely unprecedented speed.

The growth of modern science is accelerating because knowledge feeds on itself. A new idea or a new development may lead to several other innovations, which can in turn start an avalanche of change. For example, the quantum theory of atomic structure led to the invention of transistors, which made high-speed digital computers possible. Computers have not only produced further developments in quantum theory; they have also revolutionized many other fields.

The self-reenforcing accumulation of knowledge - the information explosion - which characterizes modern human society is reflected not only in an explosively-growing global population, but also in the number of scientific articles published, which doubles roughly every ten years. Another example is Moore's law - the doubling of the information density of integrated circuits every eighteen months. Yet another example is the explosive growth of internet traffic shown in Table 7.2.

The internet itself is the culmination of a trend towards increasing societal information exchange - the formation of a collective human consciousness. This collective consciousness preserves the observations of millions of eyes, the experiments of millions of hands, the thoughts of millions of brains; and it does not die when the individual dies.

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Chapter 8

BIO-INFORMATION TECHNOLOGY

The merging of information technology and biotechnology

Information technology and biology are today the two most rapidly developing fields of science. Interestingly, these two fields seem to be merging, each gaining inspiration and help from the other. For example, computer scientists designing both hardware and software are gaining inspiration from physiological studies of the mechanism of the brain; and conversely, neurophysiologists are aided by insights from the field of artificial intelligence.

Designers of integrated circuits wish to prolong the period of validity of Moore's law; but they are rapidly approaching physical barriers which will set limits to the miniaturization of conventional transistors and integrated circuits. They gain inspiration from biology, where the language of molecular complementarity and the principle of autoassembly seem to offer hope that molecular switches and self-assembled integrated circuits may one day be constructed.

Geneticists, molecular biologists, biochemists and crystallographers have now obtained so much information about the amino acid sequences and structures of proteins and about the nucleotide sequences in genomes that the full power of modern information technology is needed to store and to analyze this information. Computer scientists, for their part, turn to evolutionary genetics for new and radical methods of developing both software and hardware - genetic algorithms and simulated evolution.

Self-assembly of supramolecular structures; Nanoscience

In previous chapters, we saw that the language of molecular complementarity (the "lock and key" fitting discovered by Paul Ehrlich) is the chief mechanism by which information is stored and transferred in biological systems. Biological molecules have physical shapes and patterns of excess charge[1] which are recognized by complementary molecules because they fit together, just as a key fits the shape of a lock. Examples of biological "lock and key" fitting are the fit between the substrate of an enzyme and the enzyme's active site, the recognition of an antigen by its specific antibody, the specificity of base pairs in DNA and RNA, and the autoassembly of structures such as viruses and subcellular organelles.

One of the best studied examples of autoassembly through the mechanism of molecular complementarity is the tobacco mosaic virus. The assembled virus has a cylindrical form about 300 nm long (1 nm = 1 nanometer = 10^{-9} meters = 10 Ångstroms), with a width of 18 nm. The cylindrically shaped virus is formed from about 2000 identical protein molecules. These form a package around an RNA molecule with a length of approximately 6400 nucleotides. The tobacco mosaic virus can be decomposed into its constituent molecules *in vitro*, and the protein and RNA can be separated and put into separate bottles, as was discussed in Chapter 4.

If, at a later time, one mixes the protein and RNA molecules together in solution, they spontaneously assemble themselves into new infective tobacco mosaic virus particles. The mechanism for this spontaneous autoassembly is a random motion of the molecules through the solvent until they approach each other in such a way that a fit is formed. When two molecules fit closely together, with their physical contours matching, and with complementary patterns of excess charge also matching, the Gibbs free energy of the total system is minimized. Thus the self-assembly of matching components proceeds spontaneously, just as every other chemical reaction proceeds spontaneously when the difference in Gibbs free energy between the products and reactants is negative. The process of autoassembly is analogous to crystallization, except that the structure formed is more complex than an ordinary crystal.

A second very well-studied example of biological autoassembly is the spontaneous formation of bilayer membranes when phospholipid molecules are shaken together in water. Each phospholipid molecule has a small polar (hydrophilic) head, and a long nonpolar (hydrophobic) tail. The polar head is hydrophilic - water-loving - because it has large excess charges with which water can form hydrogen bonds. By contrast, the non-polar tail of a phospholipid molecule has no appreciable excess charges. The tail is hydrophobic - it hates water - because to fit into the water structure it has to break many hydrogen bonds to make a hole for itself, but it cannot pay for these broken bonds by forming new hydrogen bonds with water.

There is a special configuration of the system of water and phospholipid molecules which has a very low Gibbs free energy - the lipid bilayer. In

[1] They also have patterns of polarizable groups and reactive groups, and these patterns can also play a role in recognition.

this configuration, all the hydrophilic polar heads are in contact with water, while the hydrophobic nonpolar tails are in the interior of the double membrane, away from the water, and in close contact with each other, thus maximizing their mutual Van der Waals attractions. (The basic structure of biological membranes is the lipid bilayer just described, but there are also other components, such as membrane-bound proteins, caveolae, and ion pores.)

The mechanism of self-organization of supramolecular structures is one of the most important universal mechanisms of biology. Chemical reactions take place spontaneously when the change in Gibbs free energy produced by the reaction is negative, i.e., chemical reactions take place in such a direction that the entropy of the universe increases. When spontaneous chemical reactions take place, the universe moves from a less probable configuration to a more probable one. The same principle controls the motion of larger systems, where molecules arrange themselves spontaneously to form supramolecular structures. Self-assembling collections of molecules move in such a way as to minimize their Gibbs free energy, thus maximizing the entropy of the universe.

Biological structures of all kinds are formed spontaneously from their components because assembly information is written onto their joining surfaces in the form of complementary surface contours and complementary patterns of excess charge[2]. Matching pieces fit together, and the Gibbs free energy of the system is minimized. Virtually every structure observed in biology is formed in this way - by a process analogous to crystallization, except that biological structures can be far more complex than ordinary crystals.

Researchers in microelectronics, inspired by the self-assembly of biological structures, dream of using the same principles to generate self-organizing integrated circuits with features so small as to approach molecular dimensions. As we mentioned in Chapter 7, the speed of a computing operation is limited by the time that it takes an electrical signal (moving at approximately the speed of light) to traverse a processing unit. The desire to produce ever greater computation speeds as well as ever greater memory densities, motivates the computer industry's drive towards ultraminiaturization.

Currently the fineness of detail in integrated circuits is limited by diffraction effects caused by the finite wavelength of the light used to project an image of the circuit onto a layer of photoresist covering the chip where the circuit is being built up. For this reason, there is now very active research on photolithography using light sources with extremely short wavelengths,

[2]Patterns of reactive or polarizable groups also play a role.

in the deep ultraviolet, or even X-ray sources, synchrotron radiation, or electron beams. The aim of this research is to produce integrated circuits whose feature size is in the nanometer range - smaller than 100 nm.

In addition to these efforts to create nanocircuits by "top down" methods, intensive research is also being conducted on "bottom up" synthesis, using principles inspired by biological self-assembly. The hope to make use of "the spontaneous association of molecules, under equilibrium conditions, into stable, structurally well-defined aggregates, joined by non-covalent bonds"[3].

The Nobel Laureate Belgian chemist J.-M. Lehn pioneered the field of supramolecular chemistry by showing that it is possible to build nanoscale structures of his own design. Lehn and his coworkers at the University of Strasbourg used positively-charged metal ions as a kind of glue to join larger structural units at points where the large units exhibited excess negative charges. Lehn predicts that the supramolecular chemistry of the future will follow the same principles of self-organization which underlie the growth of biological structures, but with a greatly expanded repertory, making use of elements (such as silicon) that are not common in carbon-based biological systems.

Other workers in nanotechnology have concentrated on the self-assembly of two-dimensional structures at water-air interfaces. For example, Thomas Bjørnholm, working at the University of Copenhagen, has shown that a nanoscale wire can be assembled spontaneously at a water-air interface, using metal atoms complexed with DNA and a DNA template. The use of a two-dimensional template to reproduce a nanostructure can be thought of as "microprinting". One can also think of self-assembly at surfaces as the two-dimensional version of the one-dimensional copying process by which a new DNA or RNA strand assembles itself spontaneously, guided by the complementary strand.

In 1981, Gerd Binning and Heinrich Rohrer of IBM's Research Center in Switzerland announced their invention of the scanning tunneling microscope. The new microscope's resolution was so great that single atoms could be observed. The scanning tunneling microscope consists of a supersharp conducting tip, which is brought near enough to a surface so that quantum mechanical tunneling of electrons can take place between tip and surface when a small voltage is applied. The distance between the supersharp tip and the surface is controlled by means of a piezoelectric crystal. As the tip is moved along the surface, its distance from the surface (and hence the tunneling current) is kept constant by applying a voltage to the piezoelectric crystal, and this voltage as a function of position gives an image of the

[3]G.M. Whiteside et al., Science, **254**, 1312-1314, (1991).

surface.

Variations on the scanning tunneling microscope allow single atoms to be deposited or manipulated on a surface. Thus there is a hope that nanoscale circuit templates can be constructed by direct manipulation of atoms and molecules, and that the circuits can afterwards be reproduced using autoassembly mechanisms.

The scanning tunneling microscope makes use of a quantum mechanical effect: Electrons exhibit wavelike properties, and can tunnel small distances into regions of negative kinetic energy - regions which would be forbidden to them by classical mechanics. In general it is true that for circuit elements with feature sizes in the nanometer range, quantum effects become important. For conventional integrated circuits, the quantum effects which are associated with this size-range would be a nuisance, but workers in nanotechnology hope to design integrated circuits which specifically make use of these quantum effects.

Molecular switches; bacteriorhodopsin

The purple, salt-loving archaebacterium *Halobacterium halobium* (recently renamed *Halobacterium salinarum*) possesses one of the simplest structures that is able to perform photosynthesis. The purple membrane subfraction of this bacterium's cytoplasmic membrane contains only two kinds of molecules - lipids and bacteriorhodopsin. Nevertheless, this simple structure is able to trap the energy of a photon from the sun and to convert it into chemical energy.

The remarkable purple membrane of *Halobacterium* has been studied in detail by Walter Stoeckenius, D. Osterhelt [4], Lajos Keszthelyi and others. It can be decomposed into its constituent molecules. The lipids from the membrane and the bacteriorhodopsin can be separated from each other and put into different bottles. At a later time, the two bottles can be taken from the laboratory shelf, and their contents can be shaken together in water. The result is the spontaneous formation of tiny vessicles of purple membrane.

In the self-organized two-component vessicles, the membrane-bound protein bacteriorhodopsin is always correctly oriented, just as it would be in the purple membrane of a living *Halobacterium*. When the vessicles are illuminated, bacteriorhodopsin absorbs H^+ ions from the water on the inside, and releases them outside.

[4] D. Osterhelt and Walter Stoeckenius, Nature New Biol. **233**, 149-152 (1971); D. Osterhelt et al., Quart. Rev. Biophys. **24**, 425-478 (1991); W. Stoeckenius and R. Bogomolni, Ann. Rev. Biochem. **52**, 587-616 (1982).

Bacteriorhodopsin consists of a chain of 224 amino acids, linked to the retinal chromophore. The amino acids are arranged in 7 helical segments, each of which spans the purple membrane, and these are joined on the membrane surface by short nonhelical segments of the chain. The chromophore is in the middle of the membrane, surrounded by α-helical segments. When the chromophore is illuminated, its color is temporarily bleached, and it undergoes a cis-trans isomerization which disrupts the hydrogen-bonding network of the protein. The result is that a proton is released on the outside of the membrane. Later, a proton is absorbed from the water in the interior of the membrane vessicle, the hydrogen-bonding system of the protein is reestablished, and both the protein and the chromophore return to their original conformations. In this way, bacteriorhodopsin functions as a proton pump. It uses the energy of photons to transport H^+ ions across the membrane, from the inside to the outside, against the electrochemical gradient. In the living *Halobacterium*, this H^+ concentration difference would be used to drive the synthesis of the high-energy phosphate bond of adenosine triphosphate (ATP), the inward passage of H^+ through other parts of the cytoplasmic membrane being coupled to the reaction ADP + $P_i \rightarrow$ ATP by membrane-bound reversible ATPase.

Bacteriorhodopsin is interesting as a component of one of the simplest known photosynthetic systems, and because of its possible relationship to the evolution of the eye (as was discussed in Chapter 3). In addition, researchers like Lajos Keszthelyi at the Institute of Biophysics of the Hungarian Academy of Sciences in Szeged are excited about the possible use of bacteriorhodopsin in optical computer memories[5]. Arrays of oriented and partially dehydrated bacteriorhodopsin molecules in a plastic matrix can be used to construct both 2-dimensional and 3-dimensional optical memories using the reversible color changes of the molecule. J. Chen and coworkers[6] have recently constructed a prototype 3-dimensional optical memory by orienting the proteins and afterwards polymerizing the solvent into a solid polyacrylamide matrix. Bacteriorhodopsin has extraordinary stability, and can tolerate as many as a million optical switching operations without damage.

Neural networks, biological and artificial

In 1943, W. McCulloch and W. Pitts published a paper entitled *A Logical Calculus of the Ideas Immanent in Nervous Activity.* In this pioneering

[5]A. Dér and L. Keszthelyi, editors, *Bioelectronic Applications of Photochromic Pigments*, IOS Press, Amsterdam, Netherlands, (2001).

[6]J. Chen et al., Biosystems **35**, 145-151 (1995).

paper, they proposed the idea of a Threshold Logic Unit (TLU), which they visualized not only as a model of the way in which neurons function in the brain but also as a possible subunit for artificial systems which might be constructed to perform learning and pattern-recognition tasks. Problems involving learning, generalization, pattern recognition and noisy data are easily handled by the brains of humans and animals, but computers of the conventional von Neumann type find such tasks especially difficult.

Conventional computers consist of a memory and one or more central processing units (CPUs). Data and instructions are repeatedly transferred from the memory to the CPUs, where the data is processed and returned to the memory. The repeated performance of many such cycles requires a long and detailed program, as well as high-quality data. Thus conventional computers, despite their great speed and power, lack the robustness, intuition, learning powers and powers of generalization which characterize biological neural networks. In the 1950's, following the suggestions of McCulloch and Pitts, and inspired by the growing knowledge of brain structure and function which was being gathered by histologists and neurophysiologists, computer scientists began to construct artificial neural networks - massively parallel arrays of TLU's.

The analogy between a TLU and a neuron can be seen by comparing Figure 5.2, which shows a neuron, with Figure 8.1, which shows a TLU. As we saw in Chapter 5, a neuron is a specialized cell consisting of a cell body (*soma*) from which an extremely long, tubelike fiber called an *axon* grows. The axon is analogous to the output channel of a TLU. From the soma, a number of slightly shorter, rootlike extensions called *dendrites* also grow. The dendrites are analogous to the input channels of a TLU.

In a biological neural network, branches from the axon of a neuron are connected to the dendrites of many other neurons; and at the points of connection there are small, knoblike structures called *synapses*. As was discussed in Chapter 5, the "firing" of a neuron sends a wave of depolarization out along its axon. When the pulselike electrical and chemical disturbance associated with the wave of depolarization (the *action potential*) reaches a synapse, where the axon is connected with another neuron, transmitter molecules are released into the *post-synaptic cleft*. The neurotransmitter molecules travel across the post-synaptic cleft to receptors on a dendrite of the next neuron in the net, where they are bound to receptors. There are many kinds of neurotransmitter molecules, some of which tend to make the firing of the next neuron more probable, and others which tend to inhibit its firing. When the neurotransmitter molecules are bound to the receptors, they cause a change in the dendritic membrane potential, either increasing or decreasing its polarization. The *post-synaptic potentials* from the dendrites are propagated to the soma; and if their sum exceeds a threshold

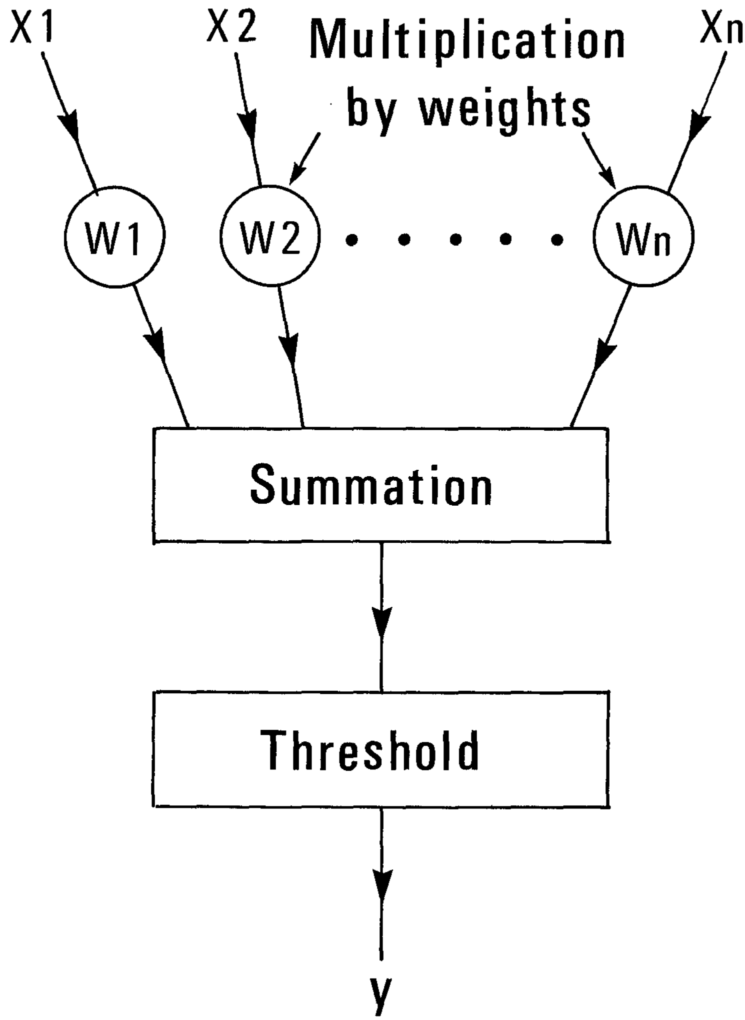

Fig. 8.1 A Threshold Logic Unit (TLU) of the type proposed by McCulloch and Pitts.

value, the neuron fires. The subtlety of biological neural networks derives from the fact that there are many kinds of neurotransmitters and synapses, and from the fact that synapses are modified by their past history.

Turning to Figure 8.1, we can compare the biological neuron with the Threshold Logic Unit of McCulloch and Pitts. Like the neuron, the TLU has many input channels. To each of the N channels there is assigned a

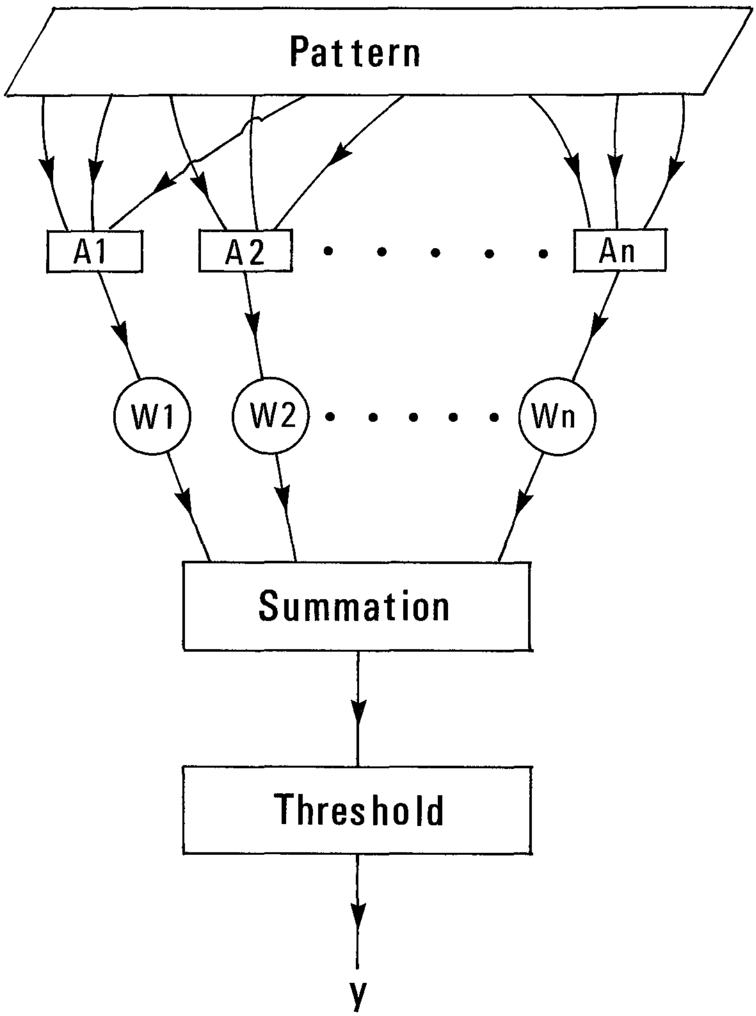

Fig. 8.2 A perceptron, introduced by Rosenblatt in 1962. The perceptron is similar to a TLU, but its input is preprocessed by a set of *association units* (A-units). The A-units are not trained, but are assigned a fixed Boolean functionality.

weight, $w_1, w_2, ..., w_N$. The weights can be changed; and the set of weights gives the TLU its memory and learning capabilities. Modification of weights in the TLU is analogous to the modification of synapses in a neuron, depending on their history. In the most simple type of TLU, the input signals are either 0 or 1. These signals, multiplied by their appropriate weights, are summed, and if the sum exceeds a threshold value, θ the TLU "fires", i.e. a pulse of voltage is transmitted through the output channel to the next TLU in the artificial neural network.

Let us imagine that the input signals, $x_1, x_2, ..., x_N$ can take on the values 0 or 1. The weighted sum of the input signals will then be given by

$$a = \sum_{j=1}^{N} w_j x_j \tag{8.1}$$

The quantity a, is called the *activation*. If the activation exceeds the threshold θ, the unit "fires", i.e. it produces an output y given by

$$y = \begin{cases} 1 \text{ if } a \geq \theta \\ 0 \text{ if } a < \theta \end{cases} \tag{8.2}$$

The decisions taken by a TLU can be given a geometrical interpretation: The input signals can be thought of as forming the components of a vector, $\mathbf{x} = \{x_1, x_2, ..., x_N\}$, in an N-dimensional space called *pattern space*. The weights also form a vector, $\mathbf{w} = \{w_1, w_2, ..., w_N\}$, in the same space. If we write an equation setting the scalar product of these two vectors equal to some constant,

$$\mathbf{w} \cdot \mathbf{x} \equiv \sum_{j=1}^{N} w_j x_j = \theta \tag{8.3}$$

then this equation defines a hyperplane in pattern space, called the *decision hyperplane*. The decision hyperplane divides pattern space into two parts - (1) input pulse patterns which will produce firing of the TLU, and (2) patterns which will not cause firing.

The position and orientation of the decision hyperplane can be changed by altering the weight vector $\mathbf{w}$ and/or the threshold θ. Therefore it is convenient to put the threshold and the weights on the same footing by introducing an augmented weight vector,

$$\mathbf{W} = \{w_1, w_2, ..., w_N, \theta\} \tag{8.4}$$

and an augmented input pattern vector,

$$\mathbf{X} = \{x_1, x_2, ..., x_N, -1\} \tag{8.5}$$

In the N+1-dimensional augmented pattern space, the decision hyperplane now passes through the origin, and equation (8.3) can be rewritten in the form

$$\mathbf{W} \cdot \mathbf{X} \equiv \sum_{j=1}^{N+1} W_j X_j = 0 \tag{8.6}$$

Those input patterns for which the scalar product $\mathbf{W} \cdot \mathbf{X}$ is positive or zero will cause the unit to fire, but if the scalar product is negative, there will be no response.

If we wish to "teach" a TLU to fire when presented with a particular pattern vector $\mathbf{X}$, we can evaluate its scalar product with the current augmented weight vector $\mathbf{W}$. If this scalar product is negative, the TLU will not fire, and therefore we know that the weight vector needs to be changed. If we replace the weight vector by

$$\mathbf{W}' = \mathbf{W} + \gamma \mathbf{X} \tag{8.7}$$

where γ is a small positive number, then the new augmented weight vector $\mathbf{W}'$ will point in a direction more nearly the same as the direction of $\mathbf{X}$. This change will be a small step in the direction of making the scalar product positive, i.e. a small step in the right direction.

Why not take a large step instead of a small one? A small step is best because there may be a whole class of input patterns to which we would like the TLU to respond by firing. If we make a large change in weights to help a particular input pattern, it may undo previous learning with respect to other patterns.

It is also possible to teach a TLU to remain silent when presented with a particular input pattern vector. To do so we evaluate the augmented scalar product $\mathbf{W} \cdot \mathbf{X}$ as before, but now, when we desire silence rather than firing, we wish the scalar product to be negative, and if it is positive, we know that the weight vector must be changed. In changing the weight vector, we can again make use of equation (8.7), but now γ must be a small negative number rather than a small positive one.

Two sets of input patterns, A and B, are said to be *linearly separable* if they can be separated by some decision hyperplane in pattern space. Now suppose that the four sets, A, B, C, and D, can be separated by two decision hyperplanes. We can then construct a two-layer network which will identify the class of an input signal belonging to any one of the sets, as is illustrated in Figure 8.2.

The first layer consists of two TLU's. The first TLU in this layer is taught to fire if the input pattern belongs to A or B, and to be silent if the input belongs to C or D. The second TLU is taught to fire if the input pattern belongs to A or D, and to be silent if it belongs to B or C. The second layer of the network consists of four output units which are not taught, but which are assigned a fixed Boolean functionality. The first output unit fires if the signals from the first layer are given by the vector $\mathbf{y} = \{0, 0\}$ (class A); the second fires if $\mathbf{y} = \{0, 1\}$ (class B), the third if $\mathbf{y} = \{1, 0\}$ (class C), and the fourth if $\mathbf{y} = \{1, 1\}$ (class D). Thus the simple two-layer network shown in Figure 8.2 functions as a *classifier*. The output units in the second layer are analogous to the "grandmother's face cells" whose existence in the visual cortex is postulated by neurophysiologists. These cells will fire if and only if the retina is stimulated with a particular class of patterns.

This very brief glance at artificial neural networks does not do justice to the high degree of sophistication which network architecture and training algorithms have achieved during the last two decades. However, the suggestions for further reading at the end of this chapter may help to give the reader an impression of the wide range of problems to which these networks are now being applied.

Besides being useful for computations requiring pattern recognition, learning, generalization, intuition, and robustness in the face of noisy data, artificial neural networks are important because of the light which they throw on the mechanism of brain function. For example, one can compare the classifier network shown in Figure 8.2 with the discoveries of Kuffler, Hubel and Wessel concerning pattern abstraction in the mammalian retina and visual cortex (Chapter 5).

Genetic algorithms

Genetic algorithms represent a second approach to machine learning and to computational problems involving optimization. Like neural network computation, this alternative approach has been inspired by biology, and it has also been inspired by the Darwinian concept of natural selection. In a genetic algorithm, the hardware is that of a conventional computer; but the software creates a population and allows it to evolve in a manner closely analogous to biological evolution.

One of the most important pioneers of genetic algorithms was John Henry Holland (1929-). After attending MIT, where he was influenced by Norbert Wiener, Holland worked for IBM, helping to develop the 701. He then continued his studies at the University of Michigan, obtaining the first Ph.D. in computer science ever granted in America. Between 1962 and 1965, Holland taught a graduate course at Michigan called "Theory of Adaptive Systems". His pioneering course became almost a cult, and together with his enthusiastic students he applied the genetic algorithm approach to a great variety of computational problems. One of Holland's students, David Goldberg, even applied a genetic algorithm program to the problem of allocating natural gas resources.

The programs developed by Holland and his students were modelled after the natural biological processes of reproduction, mutation, selection and evolution. In biology, the information passed between generations is contained in chromosomes - long strands of DNA where the genetic message is written in a four-letter language, the letters being adenine, thymine, guanine and cytosine. Analogously, in a genetic algorithm, the information is coded in a long string, but instead of a four-letter language, the code is binary: The chromosome-analogue is a long string of 0's and 1's, i.e., a long binary string. One starts with a population that has sufficient diversity so that natural selection can act.

The genotypes are then translated into phenotypes. In other words, the information contained in the long binary string (analogous to the genotype of each individual) corresponds to an entity, the phenotype, whose fitness for survival can be evaluated. The mapping from genotype to phenotype must be such that very small changes in the binary string will not produce radically different phenotypes. From the initial population, the most promising individuals are selected to be the parents of the next generation, and of these, the fittest are allowed produce the largest number of offspring. Before reproduction takes place, however, random mutations and chromosome crossing can occur. For example, in chromosome crossing, the chromosomes of two individuals are broken after the nth binary digit, and two new chromosomes are formed, one with the head of the first old chromosome and the tail of the second, and another with the head of the second and the tail of the first. This process is analogous to the biological crossings which allowed Thomas Hunt Morgan and his "fly squad" to map the positions of genes on the chromosomes of fruit flies, while the mutations are analogous to those studied by Hugo de Vries and Hermann J. Muller.

After the new generation has been produced, the genetic algorithm advances the time parameter by a step, and the whole process is repeated: The phenotypes of the new generation are evaluated and the fittest selected to be parents of the next generation; mutation and crossings occur; and then fitness-proportional reproduction. Like neural networks, genetic algorithms are the subject of intensive research, and evolutionary computation is a rapidly growing field.

Evolutionary methods have been applied not only to software, but also to hardware. Some of the circuits designed in this way defy analysis using conventional techniques - and yet they work astonishingly well.

Artificial life

As Aristotle pointed out, it is difficult to define the precise border between life and nonlife. It is equally difficult to give a precise definition of artificial life. Of course the term means "life produced by humans rather than by nature", but what is life? Is self-replication the only criterion? The phrase "produced by humans" also presents difficulties. Humans have played a role in creating domestic species of animals and plants. Can cows, dogs, and high-yield wheat varieties be called "artificial life"? In one sense, they can. These species and varieties certainly would not have existed without human intervention.

We come nearer to what most people might call "artificial life" when we take parts of existing organisms and recombine them in novel ways, using the techniques of biotechnology. For example, Steen Willadsen[7], working at the Animal Research Station, Cambridge England, was able to construct chimeras by operating under a microscope on embryos at the eight-cell stage. The *zona pelucida* is a transparent shell that surrounds the cells of the embryo. Willadsen was able to cut open the *zona pelucida*, to remove the cells inside, and to insert a cell from a sheep embryo together with one from a goat embryo. The chimeras which he made in this way were able to grow to be adults, and when examined, their cells proved to be a mosaic, some cells carrying the sheep genome while others carried the genome of a goat. By the way, Willadsen did not create his chimeras in order to produce better animals for agriculture. He was interested in the scientifically exciting problem of morphogenesis: How is the information of the genome translated into the morphology of the growing embryo?

Human genes are now routinely introduced into embryos of farm animals, such as pigs or sheep. The genes are introduced into regulatory sequences which cause expression in mammary tissues, and the adult animals produce milk containing human proteins. Many medically valuable proteins are made in this way. Examples include human blood-clotting factors, interleukin-2 (a protein which stimulates T-lymphocytes), collagen and fibrinogen (used to treat burns), human fertility hormones, human hemoglobin, and human serum albumin.

Transgenic plants and animals in which the genes of two or more species are inherited in a stable Mendelian way have become commonplace in modern laboratory environments, and, for better or for worse, they are also becoming increasingly common in the external global environment. These new species might, with some justification, be called "artificial life".

In discussing the origin of life in Chapter 3, we mentioned that a long

[7]Willadsen is famous for having made the first verified and reproducible clone of a mammal. In 1984 he made two genetically identical lambs from early sheep embryo cells.

period of molecular evolution probably preceded the evolution of cells. In the early 1970's, S. Spiegelman performed a series of experiments in which he demonstrated that artificial molecular evolution can be made to take place *in vitro*. Spiegelman prepared a large number of test tubes in which RNA replication could take place. The aqueous solution in each of the test tubes consisted of RNA replicase, ATP, UTP (uracil triphosphate), GTP (guanine triphosphate), CTP (cytosine triphosphate) and buffer. He then introduced RNA from a bacteriophage into the first test tube. After a predetermined interval of time, during which replication took place, Spiegelman transferred a drop of solution from the first test tube to a new tube, uncontaminated with RNA. Once again, replication began and after an interval a drop was transferred to a third test tube. Spiegelman repeated this procedure several hundred times, and at the end he was able to demonstrate that the RNA in the final tube differed from the initial sample, and that it replicated faster than the initial sample. The RNA had evolved by the classical Darwinian mechanisms of mutation and natural selection. Mistakes in copying had produced mutant RNA strands which competed for the supply of energy-rich precursor molecules (ATP, UTP, GTP and CTP). The most rapidly-reproducing mutants survived. Was Spiegelman's experiment merely a simulation of an early stage of biological evolution? Or was evolution of an extremely primitive life-form actually taking place in his test tubes?

G.F. Joyce, D.P. Bartel and others have performed experiments in which strands of RNA with specific catalytic activity (ribozymes) have been made to evolve artificially from randomly coded starting populations of RNA. In these experiments, starting populations of 10^{13} to 10^{15} randomly coded RNA molecules are tested for the desired catalytic activity, and the most successful molecules are then chosen as parents for the next generation. The selected molecules are replicated many times, but errors (mutations) sometimes occur in the replication. The new population is once again tested for catalytic activity, and the process is repeated. The fact that artificial evolution of ribozymes is possible can perhaps be interpreted as supporting the "RNA world" hypothesis, i.e. the hypothesis that RNA preceded DNA and proteins in the early history of terrestrial life.

In Chapter 4 we mentioned that John von Neumann speculated on the possibility of constructing artificial self-reproducing automata. In the early 1940's, a period when there was much discussion of the Universal Turing Machine, he became interested in constructing a mathematical model of the requirements for self-reproduction. Besides the Turing machine, another source of his inspiration was the paper by Warren McCulloch and Walter Pitts entitled *A logical calculus of the ideas immanent in nervous activity*, which von Neumann read in 1943. In his first attempt (the kinematic model), he imagined an extremely large and complex automaton, floating on a lake which contained its component parts.

Von Neumann's imaginary self-reproducing automaton consisted of four units, A, B, C and D. Unit A was a sort of factory, which gathered component parts from the surrounding lake and assembled them according to instructions which it received from other units. Unit B was a copying unit, which reproduced sets of instructions. Unit C was a control apparatus, similar to a computer. Finally D was a long string of instructions, analogous to the "tape" in the Turing machine described in Chapter 7. In von Neumann's kinematic automaton, the instructions were coded as a long binary number. The presence of what he called a "girder" at a given position corresponded to 1, while its absence corresponded to 0. In von Neumann's model, the automaton completed the assembly of its offspring by injecting its progeny with the duplicated instruction tape, thus making the new automaton both functional and fertile.

In presenting his kinematic model at the Hixton Symposium (organized by Linus Pauling in the late 1940's), von Neumann remarked that "...it is clear that the instruction [tape] is roughly effecting the function of a gene. It is also clear that the copying mechanism B performs the fundamental act of reproduction, the duplication of the genetic material, which is clearly the fundamental operation in the multiplication of living cells. It is also easy to see how arbitrary alterations of the system...can exhibit certain traits which appear in connection with mutation, lethality as a rule, but with a possibility of continuing reproduction with a modification of traits."

It is very much to von Neumann's credit that his kinematic model (which he invented several years before Crick and Watson published their DNA structure) was organized in much the same way that we now know the reproductive apparatus of a cell to be organized. Nevertheless he was dissatisfied with the model because his automaton contained too many "black boxes". There were too many parts which were supposed to have certain functions, but for which it seemed very difficult to propose detailed mechanisms by which the functions could be carried out. His kinematic model seemed very far from anything which could actually be built[8].

Von Neumann discussed these problems with his close friend, the Polish-American mathematician Stanislaw Ulam, who had for a long time been

[8]Von Neumann's kinematic automaton was taken seriously by the Mission IV Group, part of a ten-week program sponsored by NASA in 1980 to study the possible use of advanced automation and robotic devices in space exploration. The group, headed by Richard Laing, proposed plans for self-reproducing factories, designed to function on the surface of the moon or the surfaces of other planets. Like von Neumann's kinetic automaton, to which they owed much, these plans seemed very far from anything that could actually be constructed.

interested in the concept of self-replicating automata. When presented with the black box difficulty, Ulam suggested that the whole picture of an automaton floating on a lake containing its parts should be discarded. He proposed instead a model which later came to be known as the Cellular Automaton Model. In Ulam's model, the self-reproducing automaton lives in a very special space. For example, the space might resemble an infinite checkerboard, each square would constitute a multi-state cell. The state of each cell in a particular time interval is governed by the states of its near neighbors in the preceding time interval according to relatively simple laws. The automaton would then consist of a special configuration of cell states, and its reproduction would correspond to production of a similar configuration of cell states in a neighboring region of the cell lattice.

Von Neumann liked Ulam's idea, and he began to work in that direction. However, he wished his self-replicating automaton to be able to function as a universal Turing machine, and therefore the plans which he produced were excessively complicated. In fact, von Neumann believed complexity to be a necessary requirement for self-reproduction. In his model, the cells in the lattice were able to have 29 different states, and the automaton consisted of a configuration involving hundreds of thousands of cells. Von Neumann's manuscript on the subject became longer and longer, and he did not complete it before his early death from prostate cancer in 1957. The name "cellular automaton" was coined by Arthur Burks, who edited von Neumann's posthumous papers on the theory of automata.

Arthur Burks had written a Ph.D. thesis in philosophy on the work of the nineteenth century thinker Charles Sanders Pierce, who is today considered to be one of the founders of semiotics[9]. He then studied electrical engineering at the Moore School in Philadelphia, where he participated in the construction of ENIAC, one of the first general purpose electronic digital computers, and where he also met John von Neumann. He worked with von Neumann on the construction of a new computer, and later Burks became the leader of the Logic of Computers Group at the University of Michigan. One of Burks' students at Michigan was John Holland, the pioneer of genetic algorithms. Another student of Burks, E.F. Codd, was able to design a self-replicating automaton of the von Neumann type using a cellular automaton system with only 8 states (as compared with von Neumann's 29). For many years, enthusiastic graduate students at the Michigan group continued to do important research on the relationships between information, logic, complexity and biology.

Meanwhile, in 1968, the mathematician John Horton Conway, working in England at Cambridge University, invented a simple game which greatly

[9]Semiotics is defined as the study of signs (see Appendix 2).

increased the popularity of the cellular automaton concept. Conway's game, which he called "Life", was played on an infinite checker-board-like lattice of cells, each cell having only two states, "alive" or "dead". The rules which Conway proposed are as follows: "If a cell on the checkerboard is alive, it will survive in the next time step (generation) if there are either two or three neighbors also alive. It will die of overcrowding if there are more than three live neighbors, and it will die of exposure if there are fewer than two. If a cell on the checkerboard is dead, it will remain dead in the next generation unless exactly three of its eight neighbors is alive. In that case, the cell will be 'born' in the next generation".

Originally Conway's Life game was played by himself and by his colleagues at Cambridge University's mathematics department in their common room: At first the game was played on table tops at tea time. Later it spilled over from the tables to the floor, and tea time began to extend far into the afternoons. Finally, wishing to convert a wider audience to his game, Conway submitted it to Martin Gardner, who wrote a popular column on "Mathematical Games" for the Scientific American. In this way Life spread to MIT's Artificial Intelligence Laboratory, where it created such interest that the MIT group designed a small computer specifically dedicated to rapidly implementing Life's rules.

The reason for the excitement about Conway's Life game was that it seemed capable of generating extremely complex patterns, starting from relatively simple configurations and using only its simple rules. Ed Fredkin, the director of MIT's Artificial Intelligence Laboratory, became enthusiastic about cellular automata because they seemed to offer a model for the way in which complex phenomena can emerge from the laws of nature, which are after all very simple. In 1982, Fredkin (who was independently wealthy because of a successful computer company which he had founded) organized a conference on cellular automata on his private island in the Caribbean. The conference is notable because one of the participants was a young mathematical genius named Stephen Wolfram, who was destined to refine the concept of cellular automata and to become one of the leading theoreticians in the field[10].

One of Wolfram's important contributions was to explore exhaustively the possibilities of 1-dimensional cellular automata. No one before him had looked at 1-dimensional CA's, but in fact they had two great advantages: The first of these advantages was simplicity, which allowed Wolfram to explore and classify the possible rule sets. Wolfram classified the rule sets into 4 categories, according to the degree of complexity which they generated. The second advantage was that the configurations of the system

[10]As many readers probably know, Stephen Wolfram was also destined to become a millionaire by inventing the elegant symbol-manipulating program system, Mathematica.

in successive generations could be placed under one another to form an easily-surveyed 2-dimensional visual display. Some of the patterns generated in this way were strongly similar to the patterns of pigmentation on the shells of certain molluscs. The strong resemblance seemed to suggest that Wolfram's 1-dimensional cellular automata might yield insights into the mechanism by which the pigment patterns are generated.

In general, cellular automata seemed to be promising models for gaining insight into the fascinating and highly important biological problem of morphogenesis: How does the fertilized egg translate the information on the genome into the morphology of the growing embryo, ending finally with the enormously complex morphology of a fully developed and fully differentiated multicellular animal? Our understanding of this amazing process is as yet very limited, but there is evidence that as the embryo of a multicellular animal develops, cells change their state in response to the states of neighboring cells. In the growing embryo, the "state" of a cell means the way in which it is differentiated, i.e., which genes are turned on and which off - which information on the genome is available for reading, and which segments are blocked. Neighboring cells signal to each other by means of chemical messengers[11]. Clearly there is a close analogy between the way complex patterns develop in a cellular automaton, as neighboring cells influence each other and change their states according to relatively simple rules, and the way in which the complex morphology of a multicellular animal develops in the growing embryo.

Conway's Life game attracted another very important worker to the field of cellular automata: In 1971, Christopher Langton was working as a computer programmer in the Stanley Cobb Laboratory for Psychiatric Research at Massachusetts General Hospital. When colleagues from MIT brought to the laboratory a program for executing Life, Langton was immediately interested. He recalls "It was the first hint that there was a distinction between the hardware and the behavior which it would support...You had the feeling that there was something very deep here in this little artificial universe and its evolution through time. [At the lab] we had a lot of discussions about whether the program could be open ended - could you have a universe in which life could evolve?"

Later, at the University of Arizona, Langton read a book describing von Neumann's theoretical work on automata. He contacted Arthur Burks, von Neumann's editor, who told him that no self-replicating automaton had actually been implemented, although E.F. Codd had proposed a simplified plan with only 8 states instead of 29. Burks suggested to Langton that he should start by reading Codd's book.

[11]We can recall the case of slime mold cells which signal to each other by means of the chemical messenger, cyclic AMP (Chapter 3).

When Langton studied Codd's work, he realized that part of the problem was that both von Neumann and Codd had demanded that the self-reproducing automaton should be able to function as a universal Turing machine, i.e., as a universal computer. When Langton dropped this demand (which he considered to be more related to mathematics than to biology) he was able to construct a relatively simple self-reproducing configuration in an 8-state 2-dimensional lattice of CA cells. As they reproduced themselves, Langton's loop-like cellular automata filled the lattice of cells in a manner reminiscent of a growing coral reef, with actively reproducing loops on the surface of the filled area, and "dead" (nonreproducing) loops in the center.

Langton continued to work with cellular automata as a graduate student at Arthur Burks' Logic of Computers Group at Michigan. His second important contribution to the field was an extension of Wolfram's classification of rule sets for cellular automata. Langton introduced a parameter λ to characterize various sets of rules according to the type of behavior which they generated. Rule sets with a value near to the optimum ($\lambda = 0.273$) generated complexity similar to that found in biological systems. This value of Langton's λ parameter corresponded to a borderline region between periodicity and chaos.

After obtaining a Ph.D. from Burks' Michigan group, Christopher Langton moved to the Center for Nonlinear Studies at Los Alamos, New Mexico, where in 1987 he organized an "Interdisciplinary Workshop on the Synthesis and Simulation of Living Systems" - the first conference on artificial life ever held. Among the participants were Richard Dawkins, Astrid Lindenmeyer, John Holland, and Richard Laing. The noted Oxford biologist and author Richard Dawkins was interested in the field because he had written a computer program for simulating and teaching evolution. Astrid Lindenmeyer and her coworkers in Holland had written programs capable of simulating the morphogenesis of plants in an astonishingly realistic way. As was mentioned above, John Holland pioneered the development of genetic algorithms, while Richard Laing was the leader of NASA's study to determine whether self-reproducing factories might be feasible.

Langton's announcement for the conference, which appeared in the Scientific American, stated that "Artificial life is the study of artificial systems that exhibit behavior characteristic of natural living systems...The ultimate goal is to extract the logical form of living systems. Microelectronic technology and genetic engineering will soon give us the capability to create new life *in silico* as well as *in vitro*. This capacity will present humanity with the most far-reaching technical, theoretical, and ethical challenges it has ever confronted. The time seems appropriate for a gathering of those involved in attempts to simulate or synthesize aspects of living systems."

In the 1987 workshop on artificial life, a set of ideas which had gradually emerged during the previous decades of work on automata and simulations of living systems became formalized and crystallized: All of the participants agreed that something more than reductionism was needed to understand the phenomenon of life. This belief was not a revival of vitalism; it was instead a conviction that the abstractions of molecular biology are not in themselves sufficient. The type of abstraction found in Darwin's theory of natural selection was felt to be nearer to what was needed. The viewpoints of thermodynamics and statistical mechanics were also helpful. What was needed, it was felt, were insights into the flow of information in complex systems; and computer simulations could give us this insight. The fact that the simulations might take place *in silico* did not detract from their validity. The logic and laws governing complex systems and living systems were felt to be independent of the medium.

As Langton put it, "The ultimate goal of artificial life would be to create 'life' in some other medium, ideally a *virtual* medium where the essence of life has been abstracted from the details of its implementation in any particular model. We would like to build models that are so life-like that they cease to become *models* of life and become *examples* of life themselves."

Most of the participants at the first conference on artificial life had until then been working independently, not aware that many other researchers shared their viewpoint. Their conviction that the logic of a system is largely independent of the medium echoes the viewpoint of the Macy Conferences on cybernetics in the 1940's, where the logic of feedback loops and control systems was studied in a wide variety of contexts, ranging from biology and anthropology to computer systems. A similar viewpoint can also be found in biosemiotics (Appendix 2), where, in the words of the Danish biologist Jesper Hoffmeyer, "the sign, rather than the molecule" is considered to be the starting point for studying life. In other words, the essential ingredient of life is information; and information can be expressed in many ways. The medium is less important than the message.

The conferences on artificial life have been repeated each year since 1987, and European conferences devoted to the new and rapidly growing field have also been organized. Langton himself moved to the Santa Fe Institute, where he became director of the institute's artificial life program and editor of a new journal, *Artificial Life*. The first three issues of the journal have been published as a book by the MIT Press, and the book presents an excellent introduction to the field.

Among the scientists who were attracted to the artificial life conferences was the biologist Thomas Ray, a graduate of Florida State University and Harvard, and an expert in the ecology of tropical rain forests. In the late

1970's, while he was working on his Harvard Ph.D., Ray happened to have a conversation with a computer expert from the MIT Artificial Intelligence Lab, who mentioned to him that computer programs can replicate. To Ray's question "How?", the AI man answered "Oh, it's trivial."

Ray continued to study tropical ecologies, but the chance conversation from his Cambridge days stuck in his mind. By 1989 he had acquired an academic post at the University of Delaware, and by that time he had also become proficient in computer programming. He had followed with interest the history of computer viruses. Were these malicious creations in some sense alive? Could it be possible to make self-replicating computer programs which underwent evolution by natural selection? Ray considered John Holland's genetic algorithms to be analogous to the type of selection imposed by plant and animal breeders in agriculture. He wanted to see what would happen to populations of digital organisms that found their own criteria for natural selection - not humanly imposed goals, but self-generated and open-ended criteria growing naturally out of the requirements for survival.

Although he had a grant to study tropical ecologies, Ray neglected the project and used most of his time at the computer, hoping to generate populations of computer organisms that would evolve in an open-ended and uncontrolled way. Luckily, before starting his work in earnest, Thomas Ray consulted Christopher Langton and his colleague James Farmer at the Center for Nonlinear Studies in New Mexico. Langton and Farmer realized that Ray's project could be a very dangerous one, capable of producing computer viruses or worms far more malignant and difficult to eradicate than any the world had yet seen. They advised Ray to make use of Turing's concept of a virtual computer. Digital organisms created in such a virtual computer would be unable to live outside it. Ray adopted this plan, and began to program a virtual world in which his freely evolving digital organisms could live. He later named the system "Tierra".

Ray's Tierra was not the first computer system to aim at open-ended evolution. Steen Rasmussen, working at the Danish Technical University, had previously produced a system called "VENUS" (Virtual Evolution in a Nonstochastic Universe Simulator) which simulated the very early stages of the evolution of life on earth. However, Ray's aim was not to understand the origin of life, but instead to produce digitally something analogous to the evolutionary explosion of diversity that occurred on earth at the start of the Cambrian era. He programmed an 80-byte self-reproducing digital organism which he called "Ancestor", and placed it in Tierra, his virtual Garden of Eden.

Ray had programmed a mechanism for mutation into his system, but he doubted that he would be able to achieve an evolving population with his first attempt. As it turned out, Ray never had to program another organism. His 80-byte Ancestor reproduced and populated his virtual earth, changing under the action of mutation and natural selection in a way that astonished and delighted him.

In his freely evolving virtual zoo, Ray found parasites, and even hyperparasites, but he also found instances of altruism and symbiosis. Most astonishingly of all, when he turned off the mutations in his Eden, his organisms invented sex (using mechanisms which Ray had introduced to allow for parasitism). They had never been told about sex by their creator, but they seemed to find their own way to the Tree of Knowledge.

Thomas Ray expresses the aims of his artificial life research as follows:[12] "Everything we know about life is based on one example: Life on Earth. Everything we know about intelligence is based on one example: Human intelligence. This limited experience burdens us with preconceptions, and limits our imaginations... How can we go beyond our conceptual limits, find the natural form of intelligent processes in the digital medium, and work with the medium to bring it to its full potential, rather than just imposing the world we know upon it by forcing it to run a simulation of our physics, chemistry and biology?..."

"In the carbon medium it was evolution that explored the possibilities inherent in the medium, and created the human mind. Evolution listens to the medium it is embedded in. It has the advantage of being mindless, and therefore devoid of preconceptions, and not limited by imagination."

"I propose the creation of a digital nature - a system of wildlife reserves in cyberspace in the interstices between human colonizations, feeding off unused CPU-cycles and permitted a share of our bandwidth. This would be a place where evolution can spontaneously generate complex information processes, free from the demands of human engineers and market analysts telling it what the target applications are - a place for a digital Cambrian explosion of diversity and complexity..."

"It is possible that out of this digital nature, there might emerge a digital intelligence, truly rooted in the nature of the medium, rather than brutishly copied from organic nature. It would be a fundamentally alien intelligence, but one that would complement rather than duplicate our talents and abilities."

Have Thomas Ray and other "a-lifers"[13] created artificial living organisms? Or have they only produced simulations that mimic certain aspects of life? Obviously the answer to this question depends on the definition of life, and there is no commonly agreed-upon definition. Does life have to involve carbon chemistry? The a-lifers call such an assertion "carbon chauvinism".

[12] T. Ray, http://www.hip.atr.co.jp/ ray/pubs/pubs.html

[13] In this terminology, ordinary biologists are "b-lifers".

They point out that elsewhere in the universe there may exist forms of life based on other media, and their program is to find medium-independent characteristics which all forms of life must have.

In the present book, especially in Chapter 4, we have looked at the phenomenon of life from the standpoint of thermodynamics, statistical mechanics and information theory. Seen from this viewpoint, a living organism is a complex system produced by an input of thermodynamic information in the form of Gibbs free energy. This incoming information keeps the system very far away from thermodynamic equilibrium, and allows it to achieve a statistically unlikely and complex configuration. The information content of any complex (living) system is a measure of how unlikely it would be to arise by chance. With the passage of time, the entropy of the universe increases, and the almost unimaginably improbable initial configuration of the universe is converted into complex free-energy-using systems that could never have arisen by pure chance. Life maintains itself and evolves by feeding on Gibbs free energy, that is to say, by feeding on the enormous improbability of the initial conditions of the universe.

All of the forms of artificial life that we have discussed derive their complexity from the consumption of free energy. For example, Spiegelman's evolving RNA molecules feed on the Gibbs free energy of the phosphate bonds of their precursors, ATP, GTP, UTP, and CTP. This free energy is the driving force behind artificial evolution which Spiegelman observed. In his experiment, thermodynamic information in the form of high-energy phosphate bonds is converted into cybernetic information.

Similarly, in the polymerase chain reaction, discussed in Chapter 3, the Gibbs free energy of the phosphate bonds in the precursor molecules ATP, TTP, GTP and CTP drives the reaction. With the aid of the enzyme DNA polymerase, the soup of precursors is converted into a highly improbable configuration consisting of identical copies of the original sequence. Despite the high improbablity of the resulting configuration, the entropy of the universe has increased in the copying process. The improbability of the set of copies is less than the improbability of the high energy phosphate bonds of the precursors.

The polymerase chain reaction reflects on a small scale, what happens on a much larger scale in all living organisms. Their complexity is such that they never could have originated by chance, but although their improbability is extremely great, it is less than the still greater improbability of the configurations of matter and energy from which they arose. As complex systems are produced, the entropy of the universe continually increases, i.e., the universe moves from a less probable configuration to a more probable one.

In Thomas Ray's experiments, the source of thermodynamic information is the electrical power needed to run the computer. In an important sense one might say that the digital organisms in Ray's Tierra system are living. This type of experimentation is in its infancy, but since it combines the great power of computers with the even greater power of natural selection, it is hard to see where it might end.

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Chapter 9

LOOKING TOWARDS THE FUTURE

Tensions created by the rapidity of technological change

In human cultural evolution, information transfer and storage through the language of molecular complementarity is supplemented by new forms of biological information flow and conservation - spoken language, writing, printing, and more recently electronic communication. The result has been a shift into a much higher evolutionary gear.

Because of new, self-reenforcing mechanisms of information flow and accumulation, the rate of evolutionary change has increased enormously: It took 3 billion years for the first autocatalytic systems to develop into multicellular organisms. Five hundred million years were required for multicellular organisms to rise from the level of sponges and slime molds to the degree of complexity and organization that characterizes primates and other mammals; but when a branch of the primate family developed a tool-using culture, spoken language, and an enlarged brain, only 40,000 years were required for our ancestors to change from animal-like hunter-gatherers into engineers, poets and astronomers.

During the initial stages of human cultural evolution, the rate of change was slow enough for genetic adaptation to keep pace. The co-evolution of speech, tool use, and an enlarged brain in hominids took place over a period of several million years, and there was ample time for genetic adaptation. The prolonged childhood which characterizes our species, and the behavior patterns of familial and tribal solidarity, were built into the genomes of our ancestors during the era of slow change, when cultural and genetic evolution moved together in equilibrium. However, as the pace of cultural information accumulation quickened, genetic change could no longer keep up.

Genetically we are almost identical with our neolithic ancestors; but their world has been replaced by a world of quantum theory, relativity, supercomputers, antibiotics, genetic engineering and space telescopes - unfortunately also a world of nuclear weapons and nerve gas. Because of the slowness of genetic evolution in comparison to the rapid and constantly-accelerating rate of cultural change, our bodies and minds are not perfectly adapted to our new way of life. They reflect more accurately the way of life of our hunter-gatherer ancestors.

In addition to the contrast between the slow pace of genetic evolution when compared with the rapid and constantly-accelerating rate of cultural evolution, we can also notice a contrast between rapidly- and slowly-moving aspects of cultural change: Social institutions and structures seem to change slowly when compared with the lightning-like pace of scientific and technological innovation. Thus, tensions and instability characterize information-driven society, not only because science and technology change so much more rapidly than institutions, laws, and attitudes, but also because human nature is not completely appropriate to our present way of life. In particular, human nature seems to contain an element of what might be called "tribalism", because our emotions evolved during an era when our ancestors lived in small, mutually hostile tribes, competing with one another for territory on the grasslands of Africa.

Looking towards the future, what can we predict? Detailed predictions are very difficult, but it seems likely that information technology and biotechnology will for some time continue to be the most rapidly-developing branches of science, and that these two fields will merge. We can guess with reasonable certainty that much progress will be made in understanding the mechanism of the brain, and in duplicating its functions artificially. Scientists of the future will undoubtedly achieve greatly increased control over the process of evolution. Thus it seems probable that the rapidity of scientific and technological change will produce ethical dilemmas and social tensions even more acute than those which we experience today. It is likely that the fate of our species (and the fate of the biosphere) will be made precarious by the astonishing speed of scientific and technological change unless this progress is matched by the achievement of far greater ethical and political maturity than we have yet attained.

Science has proved to be double-edged - capable of great good, but also of great harm. Information-driven human cultural evolution is a spectacular success - but can it become stable? Terrestrial life can look back on almost four billion years of unbroken evolutionary progress. Can we say with confidence that an equal period stretches ahead of us?

Can information-driven society achieve stability?

"We are living in a very special time", Murray Gell-Mann[1] remarked in a recent interview, "Historians hate to hear this, because they have heard it so many times before, but we *are* living in a very special time. One symptom of this is the fact that human population has for a long time been increasing according to a hyperbolic curve - a constant divided by 2020 minus the year."

The graph of global human population as a function of time, to which Gell-Mann refers in this quotation, is shown in Figure 6.1. Estimates of population are indicated by dots on the graph, while the smooth curve shows the hyperbola $P = C/(2020 - y)$, P being the population, y, the year, and C a constant. The form of the smooth curve, which matches the dots with reasonable accuracy, is at first surprising. One might have expected it to be an exponential, if the rate of increase were proportional to the population already present. The fact that the curve is instead a hyperbola can be understood in terms of the accumulation of cultural information. New techniques (for example the initial invention of agriculture, the importation of potatoes to Europe, or the introduction of high-yield wheat and rice varieties) make population growth possible. In the absence of new techniques, population is usually held in check by the painful Malthusian forces - famine, disease, and war.

The curve in Figure 6.1 shows an explosive growth of human population, driven by an equally explosive growth of stored cultural information - especially agricultural and medical information, and the information needed for opening new land to agriculture. As Gell-Mann remarks, population cannot continue to increase in this way, because we are rapidly approaching the limits of the earth's carrying capacity. Will human numbers overshoot these limits and afterwards crash disastrously? There is certainly a danger that this will happen.

Besides the challenge of stabilizing global population, the information-driven human society of the future will face another daunting task: Because of the enormously destructive weapons that have already been produced through the misuse of science, and because of the even worse weapons that may be invented in the future, the long-term survival of civilization can only be insured if society is able to eliminate the institution of war. This task will be made more difficult by the fact that human nature seems to contain an element of tribalism.

Humans tend to show great kindness towards close relatives and members of their own group, and are even willing to sacrifice their lives in

[1] Gell-Mann is an American physicist who was awarded a Nobel Prize in 1969 for his contributions to the theory of elementary particles.

battle in defense of their own family, tribe or nation. This tribal altruism is often accompanied by inter-tribal aggression - great cruelty towards the "enemy", i.e. towards members of a foreign group which is perceived to be threatening ones own. The fact that human nature seems to contain a genetically-programmed tendency towards tribalism is the reason why we find football matches entertaining, and the reason why Arthur Koestler once remarked: "We can control the movements of a space-craft orbiting about a distant planet, but we cannot control the situation in Northern Ireland."

How could evolutionary forces have acted to make the pattern of tribal altruism and inter-tribal aggression a part of human nature? To put the same question differently, how could our ancestors have increased the chances for survival of their own genes by dying in battle? The statistician R.A. Fisher and the evolutionary biologist J.B.S. Haldane considered this question in the 1920's[2]. Their solution was the concept of population genetics, in which the genetically homogeneous group as a whole - now sometimes called the "deme" - is taken to be the unit upon which evolutionary forces act.

Haldane and Fisher postulated that the small tribes in which our ancestors lived were genetically homogeneous, since marriage within the tribe was more probable than marriage outside it. This being the case, a patriotic individual who died for the tribe, killing many members of a competing tribe in the process, increased the chance of survival for his or her own genes, which were carried into the future by the surviving members of the hero's group. The tribe as a whole either lived or died; and those with the best "team spirit" survived most frequently.

Because of the extraordinarily bitter and cruel conflicts between ethnic groups which can be found in both ancient and modern history, it is necessary to take the ideas of Haldane and Fischer seriously. This does not mean that the elimination of the institution of war is impossible, but it means that the task will require the full resources and full cooperation of the world's educational systems, religions, and mass media. It will be necessary to educate children throughout the world in such a way that they will think of humanity as a single group - a large family to which all humans belong, and to which they owe their ultimate loyalty.

In addition to educational reform, and reform of the images presented by the mass media, the elimination of war will require the construction of a democratic, just, and humane system of international governance, whose laws will act on individuals rather than on states. The problems involved are very difficult, but they must be solved if the information-driven society

[2]More recently the evolution of tribal altruism and inter-tribal aggression has also been discussed by W.D. Hamilton and Richard Dawkins.

of the future is to achieve stability.

Respect for natural evolution

The avalanche of new techniques in biotechnology and information technology will soon give scientists so much power over evolution that evolutionary ethical problems will become much more acute than they are today. It is already possible to produce chimeras, i.e. transgenic animals and plants incorporating genetic information from two or more species. Will we soon produce hybrids which are partly machines and partly living organisms? What about artificial life? Will humans make themselves obsolete by allowing far more intelligent beings to evolve in cyberspace, as Thomas Ray proposes? What about modification and improvement of our own species? Is there a limit beyond which we ought not to go in constructing new organisms to suit human purposes?

Perhaps one answer to these questions can be found by thinking of the way in which evolution has operated to produce the biosphere. Driven by the flood of Gibbs free energy which the earth receives from the sun, living organisms are generated and tested by life. New generations are randomly modified by the genetic lottery, sometimes for the worse, and sometimes for the better; and the instances of improvement are kept. It would be hard to overestimate the value of this mechanism of design by random modification and empirical testing, with the preservation of what works. The organisms which are living today are all champions! They are distillations of vast quantities of experience, end products of four billion years of solar energy income.

The beautiful and complex living organisms of our planet are exquisitely adapted to survive, to live with each other, and to form harmonious ecological systems. Whatever we do in biotechnology ought to be guided by caution and by profound respect for what evolution has already achieved. We need a sense of evolutionary responsibility, and a non-anthropocentric component in our system of ethics.

Construction versus destruction

It is often said that ethical principles cannot be derived from science - that they must come from somewhere else. Nevertheless, when nature is viewed through the eyes of modern science, we obtain some insights which seem almost ethical in character. Biology at the molecular level has shown us the complexity and beauty of even the most humble living organisms, and the interrelatedness of all life on earth. Looking through the eyes of contemporary biochemistry, we can see that even the single cell of an amoeba is a structure of miraculous complexity and precision, worthy of our respect and wonder.

Knowledge of the second law of thermodynamics - the statistical law favoring disorder over order - reminds us that life is always balanced like a tight-rope walker over an abyss of chaos and destruction. Living organisms distill their order and complexity from the flood of thermodynamic information which reaches the earth from the sun. In this way, they create local order; but life remains a fugitive from the second law of thermodynamics. Disorder, chaos, and destruction remain statistically favored over order, construction, and complexity.

It is easier to burn down a house than to build one, easier to kill a human than to raise and educate one, easier to force a species into extinction than to replace it once it is gone, easier to burn the Great Library of Alexandria than to accumulate the knowledge that once filled it, and easier to destroy a civilization in a thermonuclear war than to rebuild it from the radioactive ashes. Knowing this, scientists can form an almost ethical insight: To be on the side of order, construction, and complexity, is to be on the side of life. To be on the side of destruction, disorder, chaos and war is to be against life, a traitor to life, an ally of death. Knowing the precariousness of life - knowing the statistical laws that favor disorder and chaos, we should resolve to be loyal to the principle of long continued construction upon which life depends.

Suggestions for further reading

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Appendix A

ENTROPY AND INFORMATION

In Chapter 4, we mentioned that Boltzmann was able to establish a relationship between entropy and missing information. In this appendix, we will look in detail at his reasoning.

The reader will remember that Boltzmann's statistical mechanics (seen from a modern point of view) deals with an ensemble of N weakly-interacting identical systems which may be in one or another of a set of discrete states, $i = 1, 2, 3, ...$ with energies ϵ_i, with the number of the systems which occupy a particular state denoted by n_i,

$$\begin{array}{ll} \text{State number} & 1 \;\; 2 \;\; 3 \; ... \; i \; ... \\ \text{Energy} & \epsilon_1 \;\; \epsilon_2 \;\; \epsilon_3 \; ... \; \epsilon_i \; ... \\ \text{Occupation number} & n_1 \;\; n_2 \;\; n_3 \; ... \; n_i \; ... \end{array} \tag{A.1}$$

A "macrostate" of the N identical systems can be specified by writing down the energy levels and their occupation numbers. This macrostate can be constructed in many ways, and each of these ways is called a "microstate". From combinatorial analysis it is possible to show that the number of microstates corresponding to a given macrostate is given by:

$$W = \frac{N!}{n_1!n_2!n_3!...n_i!...} \tag{A.2}$$

Boltzmann assumed that for very large values of N, the most probable macrostate predominates over all others. He also assumed that the amount of energy which is shared by the N identical systems has a constant value, E, so that

$$\sum_i n_i\epsilon_i - E = 0 \tag{A.3}$$

He knew, in addition, that the sum of the occupation numbers must be equal to the number of weakly-interacting identical systems:

$$\sum_i n_i - N = 0 \tag{A.4}$$

It is logical to assume that all microstates which fulfill these two conditions are equally probable, since the N systems are identical. It then follows that the probability of a particular macrostate is proportional to the number of microstates from which it can be constructed, i.e. proportional to W, so that if we wish to find the most probable macrostate, we need to maximize W subject to the constraints (3) and (4). It turns out to be more convenient to maximize $\ln W$ subject to these two constraints, but maximizing $\ln W$ will of course also maximize W. Using the method of undetermined Lagrange multipliers, we look for an absolute maximum of the function

$$\ln W - \lambda\left(\sum_i n_i - N\right) - \beta\left(\sum_i n_i\epsilon_i - E\right) \tag{A.5}$$

Having found this maximum, we can use the conditions (3) and (4) to determine the values of the Lagrangian multipliers λ and β. For the function shown in equation (5) to be a maximum, it is necessary that its partial derivative with respect to each of the occupation numbers shall vanish. This gives us the set of equations

$$\frac{\partial}{\partial n_i}\left[\ln N! - \sum_i \ln(n_i!)\right] - \lambda - \beta\epsilon_i = 0 \tag{A.6}$$

which must hold for all values of i. For very large values of N and n_i, Sterling's approximation,

$$\ln(n_i!) \approx n_i(\ln n_i - 1) \tag{A.7}$$

can be used to simplify the calculation. With the help of Sterling's approximation and the identity

$$\frac{\partial}{\partial n_i}\left[n_i(\ln n_i - 1)\right] = \ln n_i \tag{A.8}$$

we obtain the relationship

$$-\ln n_i - \lambda - \beta\epsilon_i = 0 \tag{A.9}$$

which can be rewritten in the form

$$n_i = e^{-\lambda-\beta\epsilon_i} \tag{A.10}$$

and for the most probable macrostate, this relationship must hold for all values of i. Substituting (10) into (4), we obtain:

$$N = \sum_i n_i = e^{-\lambda} \sum_i e^{-\beta\epsilon_i} \tag{A.11}$$

so that

$$\frac{n_i}{N} = \frac{e^{-\beta\epsilon_i}}{\sum_i e^{-\beta\epsilon_i}} \equiv \frac{e^{-\beta\epsilon_i}}{Z} \tag{A.12}$$

where

$$Z \equiv \sum_i e^{-\beta\epsilon_i} \tag{A.13}$$

The sum Z is called the "partition function" (or in German, Zustandssumme) of a system, and it plays a very central role in statistical mechanics. All of the thermodynamic functions of a system can be derived from it. The factor $e^{-\beta\epsilon_i}$ is called the "Boltzmann factor". Looking at equation (12), we can see that because of the Boltzmann factor, the probability

$$P_i \equiv \frac{n_i}{N} = \frac{e^{-\beta\epsilon_i}}{Z} \tag{A.14}$$

that a particular system will be in a state i is smaller for the states of high energy than it is for those of lower energy.

We mentioned above that the constraints (3) and (4) can be used to find the values of the Lagrangian multipliers λ and β. The condition

$$E = N \sum_i P_i \epsilon_i \tag{A.15}$$

can be used to determine β. By applying his statistical methods to a monatomic gas at low pressure, Boltzmann found that

$$\beta = \frac{1}{kT} \tag{A.16}$$

where T is the absolute temperature and k is the constant which appears in the empirical law relating the pressure, volume and temperature of a perfect gas;

$$pV = NkT \tag{A.17}$$

From experiments on monatomic gases at low pressures, one finds that the "Boltzmann constant" k is given by

$$k = 1.38062 \times 10^{-23} \frac{\text{Joules}}{\text{Kelvin}} \tag{A.18}$$

We mentioned that Boltzmann's equation relating entropy to disorder is carved on his tombstone. With one minor difference, this equation is

$$S_N = k \ln W \tag{A.19}$$

(The minor difference is that on the tombstone, the S lacks a subscript.) How did Boltzmann identify $k \ln W$ with the entropy of Clausius, $dS = dq/T$? In answering this question we will continue to use modern picture of a system with a set of discrete states i, whose energies are ϵ_i. Making use of Sterling's approximation, equation (9), and remembering the definition of W, (2), we can rewrite (19) as

$$\begin{aligned} S_N &= k \ln \left[\frac{N!}{n_1! n_2! n_3! ... n_i! ...} \right] \\ &= k \left[\ln(N!) - \sum_i \ln(n_i!) \right] \approx -kN \sum_i \frac{n_i}{N} \ln \frac{n_i}{N} \end{aligned} \tag{A.20}$$

Equation (20) gives us the entropy of the entire collection of N identical weakly-interacting systems. The entropy of a single system is just this quantity divided by N:

$$S = \frac{S_N}{N} = -k \sum_i P_i \ln P_i = -k \langle \ln P \rangle \tag{A.21}$$

where $P_i = n_i/N$, defined by equation (14), is the probability that the system is in state i. According to equation (14), this probability is just equal to the Boltzmann factor, $e^{-\beta \epsilon_i}$, divided by the partition function, Z, so that

$$S = -k \sum_i \frac{e^{-\beta \epsilon_i}}{Z} \ln \left(\frac{e^{-\beta \epsilon_i}}{Z} \right) = -\frac{k}{Z} \sum_i e^{-\beta \epsilon_i} \left(-\beta \epsilon_i - \ln Z \right) \tag{A.22}$$

or

$$S = k \ln Z + \frac{U}{T} \tag{A.23}$$

where

$$U \equiv \sum_i \epsilon_i P_i \tag{A.24}$$

The quantity U defined in equation (24) is called the "internal energy" of a system. Let us now imagine that a very small change in U is induced by an arbitrary process, which may involve interactions between the system and the outside world. We can express the fact that this infinitesimal alteration in internal energy may be due either to slight changes in the energy levels ϵ_i or to slight changes in the probabilities P_i by writing:

$$dU = \sum_i P_i d\epsilon_i + \sum_i \epsilon_i dP_i \tag{A.25}$$

To the first term on the right-hand side of equation (25) we give the name "dw":

$$dw \equiv \sum_i P_i d\epsilon_i \tag{A.26}$$

while the other term is named "dq".

$$dq \equiv dU - dw = \sum_i \epsilon_i dP_i \tag{A.27}$$

What is the physical interpretation of these two terms? The first term, dw, involves changes in the energy levels of system, and this can only happen if we change the parameters defining the system in some way. For example, if the system is a cylinder filled with gas particles and equipped with a piston, we can push on the piston and decrease the volume available to the gas particles. This action will raise the energy levels, and when we perform it we do work on the system - work in the sense defined by Carnot, force times distance, the force which we apply to the piston multiplied by the distance through which we push it. Thus dw can be interpreted as a small amount of work performed on the system by someone or something on the outside. Another way to change the internal energy of the system is to transfer heat to it; and when a small amount of heat is transferred, the energy levels do not change, but the probabilities P_i must change slightly, as can be seen from equations (13), (14) and (16). Thus the quantity dq in equation (27) can be interpreted as an infinitesimal amount of heat transferred to the system. We have in fact anticipated this interpretation by giving it the same name as the dq of equations (4.2) and (4.3). If the probabilities P_i are changed very slightly, then from equation (21) it follows that the resulting small change in entropy is

$$dS = -k \sum_i [\ln P_i dP_i + dP_i] \tag{A.28}$$

From equations (13) and (14) it follows that

$$\sum_i P_i = 1 \tag{A.29}$$

as we would expect from the fact that P_i is interpreted as the probability that the system is in a particular state i. Therefore

$$\sum_i dP_i = d\sum_i P_i = 0 \tag{A.30}$$

and as a consequence, the second term on the right-hand side of equation (4.31) vanishes. Making use of equation (14) to rewrite $\ln P_i$, we then have:

$$dS = -k\sum_i [(-\beta\epsilon_i - \ln Z)dP_i] \tag{A.31}$$

or

$$dS = \frac{1}{T}\sum_i \epsilon_i dP_i = \frac{dq}{T} \tag{A.32}$$

The somewhat complicated discussion which we have just gone through is a simplified paraphrase of Boltzmann's argument showing that if he defined entropy to be proportional to $\ln W$ (the equation engraved on his tombstone) then the function which he defined in this way must be identical with the entropy of Clausius. (We can perhaps sympathize with Ostwald and Mach, who failed to understand Boltzmann!)

Appendix B

BIOSEMIOTICS

The *Oxford Dictionary of Biochemistry and Molecular Biology* (Oxford University Press, 1997) defines biosemiotics as "the study of signs, of communication, and of information in living organisms". The biologists Claus Emmeche and K. Kull offer another definition of biosemiotics: "biology that interprets living systems as sign systems".

The American philosopher Charles Sanders Peirce (1839-1914) is considered to be one of the founders of semiotics (and hence also of biosemiotics). Peirce studied philosophy and chemistry at Harvard, where his father was a professor of mathematics and astronomy. He wrote extensively on philosophical subjects, and developed a theory of signs and meaning which anticipated many of the principles of modern semiotics. Peirce built his theory on a triad: (1) the sign, which represents (2) something to (3) somebody. For example, the sign might be a broken stick, which represents a trail to a hunter, it might be the arched back of a cat, which represents an aggressive attitude to another cat, it might be the waggle-dance of a honey bee, which represents the coordinates of a source of food to her hive-mates, or it might be a molecule of *trans*-10-*cis*-hexadecadienol, which represents irresistible sexual temptation to a male moth of the species Bombyx mori. The sign might be a sequence of nucleotide bases which represents an amino acid to the ribosome-transfer-RNA system, or it might be a cell-surface antigen which represents self or non-self to the immune system. In information technology, the sign might be the presence or absence of a pulse of voltage, which represents a binary digit to a computer. Semiotics draws our attention to the sign and to its function, and places much less emphasis on the physical object which forms the sign. This characteristic of the semiotic viewpoint has been expressed by the Danish biologist Jesper Hoffmeyer in the following words: "The sign, rather than the molecule, is the basic unit for studying life."

A second important founder of biosemiotics was Jakob von Uexküll

(1894-1944). He was born in Estonia, and studied zoology at the University of Tartu. After graduation, he worked at the Institute of Physiology at the University of Heidelberg, and later at the Zoological Station in Naples. In 1907, he was given an honorary doctorate by Heidelberg for his studies of the physiology of muscles. Among his discoveries in this field was the first recognized instance of negative feedback in an organism. Von Uexküll's later work was concerned with the way in which animals experience the world around them. To describe the animal's subjective perception of its environment he introduced the word *Umwelt*; and in 1926 he founded the Institut für Umweltforschung at the University of Heidelberg. Von Uexküll visualized an animal - for example a mouse - as being surrounded by a world of its own - the world conveyed by its own special senses organs, and processed by its own interpretative systems. Obviously, the Umwelt will differ greatly depending on the organism. For example, bees are able to see polarized light and ultraviolet light; electric eels are able to sense their environment through their electric organs; many insects are extraordinarily sensitive to pheromones; and a dog's Umwelt far richer in smells than that of most other animals. The Umwelt of a jellyfish is very simple, but nevertheless it exists[3]. Von Uexküll's Umwelt concept can even extend to one-celled organisms, which receive chemical and tactile signals from their environment, and which are often sensitive to light. The ideas and research of Jakob von Uexküll inspired the later work of the Nobel Lauriate ethologist Konrad Lorenz, and thus von Uexküll can be thought of as one of the founders of ethology as well as of biosemiotics. Indeed, ethology and biosemiotics are closely related.

Biosemiotics also values the ideas of the American anthropologist Gregory Bateson (1904-1980), who was mentioned in Chapter 7 in connection with cybernetics and with the Macy Conferences. He was married to another celebrated anthropologist, Margaret Mead, and together they applied Norbert Wiener's insights concerning feedback mechanisms to sociology, psychology and anthropology. Bateson was the originator of a famous epigrammatic definition of information: "..a difference which makes a difference". This definition occurs in Chapter 3 of Bateson's book, *Mind and Nature: A Necessary Unity*, Bantam, (1980), and its context is as follows: "To produce news of a difference, *i.e. information*", Bateson wrote, "there must be two entities... such that news of their difference can be represented as a difference inside some information-processing entity, such as a brain or, perhaps, a computer. There is a profound and unanswerable question about

[3]It is interesting to ask to what extent the concept of Umwelt can be equated to that of consciousness. To the extent that these two concepts can be equated, von Uexküll's Umweltforshcung offers us the opportunity to explore the phylogenetic evolution of the phenomenon of consciousness.

the nature of these two entities that between them generate the difference which becomes information by making a difference. Clearly each alone is - for the mind and perception - a non-entity, a non-being... the sound of one hand clapping. The stuff of sensation, then, is a pair of values of some variable, presented over time to a sense organ, whose response depends on the ratio between the members of the pair."

Suggestions for further reading

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