LIVES IN BIOLOGY

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INTRODUCTION¹

Human history as cultural history

We need to reform our teaching of history so that the emphasis will be placed on the gradual growth of human culture and knowledge, a growth to which all nations and ethnic groups have contributed.

This book is part of a series on cultural history. Here is a list of the other books in the series that have, until now, been completed:

- Lives of Some Great Novelists
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 $^{^1\}mathrm{This}$ book makes some use of my previously-published book chapters, but much of the material is new.

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Chapter 1

SOME EARLY BIOLOGICAL AND EVOLUTIONARY THINKERS

1.1 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 oneman 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

SOME EARLY BIOLOGISTS



Figure 1.1: Aristotle with a Bust of Homer by Rembrandt.

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.

1.2 Islamic pioneers of the biological sciences

Here ate some quotations from an article entitled *Islamic Scholars and Biology* by Martyn Shuttleworth¹

¹https://explorable.com/islamic-scholars-and-biology

"The Islamic scholar, Al-Dinawari (828 - 896), is one of the leading botanists from this period and his work, *The Book of Plants*, was a landmark book, earning him the epithet, 'The Father of Islamic Botany.' Like the Greeks and Romans before him, he studied and documented at least 637 plants but, importantly, he related plant evolution and related how plant species developed and diversified over time.

"This very important part of botany helped farmers to breed the best and most productive cultivates selectively, a technique that has existed since the dawn of agriculture. He also described the life cycle of plants, including their growth, reproduction and fruiting, making the Book of Plants an excellent reference guide.

"In the 13th Century, the Andalusian Islamic scholar, Abu al-Abbas al-Nabati, took the scientific methods developed by the Muslim thinkers and applied them to botany, concentrating upon medicinal plants. Rather than relying upon trial-and-error and hearsay, Al-Nabati believed that empirical techniques and scientific experimentation should be used to test the effectiveness of medicinal plants. This work certainly began the process of removing anecdotal evidence and superstition from the healing arts.

"The work of Al-Nabati was soon overshadowed by that of his pupil, Ibn Al-Batar, who wrote a book that became the reference work for botanists until well into the 19th Century. His book contained detailed descriptions of over 1400 plant species, many of them essential food sources or of use as drugs. Importantly, at least 300 of these plants were entirely his own discovery.

"Abu Zakariya Yahya Ibn Muhammad Ibn Al-Awwan, a 12th Century Islamic scholar based in Seville, Spain, was one of the most important contributors to the history of biology, namely in the field of agriculture. His Kitab al-Filaha instructed agriculturalists on the care of nearly 600 plant species, including over 50 types of fruit trees. This work discussed the techniques, preferred growing conditions, manure and the diseases and pests afflicting the plants.

"Other Islamic botanists concentrated upon documenting new species of plant, with Ibn-Sauri, Al-Kaiwini and Al-Dinawari producing plant encyclopedias, often with illustrations of plants from as far afield as India and Andalusia.

"The Islamic scholars, as part of their investigations into biology, resurrected the idea of evolutionary theory first hinted at by Anaximander. The most important contributor to Islamic evolutionary theory, and a leading scholar of zoology, was Al-Jahiz, (781 CE - 868/869CE). He wrote a detailed treatise, Kitab al-Hayawan (Book of Animals), which became one of the most important works in the history of biology.

"This book contained detailed descriptions of over 350 species of animal, interwoven with poetic descriptions and well-known proverbs. Al-Jahiz was the first scholar to realize the importance of the environment upon animals, and he understood that the environment would determine the likelihood of an animal surviving. As a result, he proposed a theory called the 'Struggle for Existence,' the forerunner of Darwin's 'Survival of the Fittest'."

1.3 Averröes

During the Middle Ages, Aristotle's evolutionary ideas were revived and extended in the writings of the Islamic philosopher Averröes², who lived in Spain from 1126 to 1198. His writings had a great influence on western thought. Averroes 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 Averroes; but nevertheless, his ideas survived and helped to shape the modern picture of the world.

1.4 Leonardo's anatomical drawings

The universal genius Leonardo da Vinci (1452-1519) was a close observer of human anatomy. Although it was forbidden to do so at the time, he dissected a number of human corpses, and made detailed drawings of his findings in his voluminous notebooks, none of which he published. Had he published his notebooks, his impact on the history of science would have been far greater.

 $^{^{2}}$ Abul Walid Mahommed Ibn Achmed, Ibn Mahommed Ibn Rosched





1.4. LEONARDO'S ANATOMICAL DRAWINGS





1.4. LEONARDO'S ANATOMICAL DRAWINGS















1.4. LEONARDO'S ANATOMICAL DRAWINGS



1.5 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. "...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, Ferdinand 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 gardens, 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

1.6 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 decisions rendues à la pluralité des voix*³, 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.

³ Essay on the Application of Analysis to the Probability of Decisions Taken According to a Plurality of Votes

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, Condorcet 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 humain⁴.

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 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, con-

⁴ Sketch of an Historical Picture of the Progress of the Human Spirit

1.6. CONDORCET

tinuing 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 h 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.

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Chapter 2

CLASSICAL GENETICS

2.1 Gregor Mendel

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 paper¹. 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.

2.2 Hugo de Vries

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.

2.3 Chromosones

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

 $^{^1}$ Mendel sent a copy of his paper to Darwin; but Darwin, whose German was weak, seems not to have read it.

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.

2.4 Thomas Hunt Morgan

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.

2.5 Hermann J. Muller

This work had been taken a step further by Hermannn 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.

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Chapter 3

PIONEERS OF MICROSCOPY

3.1 Antonie van Leeuwenhoek, the founder of microbiology

"The father of microbiology"

Antonie Philips van Leeuwenhoek (1632-1723) was a Dutch businessman, who became interested in lenses. He designed and built his own single-lens microscope. Using it, he became the first person to observe microorganisms, such as bacteria. Because of this achievement, he has been called "the father of microbiology".

How van Leeuwenhoek made his best lenses

Antonie van Leeuwenhoek's best lenses were very tiny indeed, and they were not made by grinding. Instead, van Leeuwenhoek drew a melted rod of glass out into two very long and thin fibers. Then he inserted one of these into a flame. The result was that it threw off a tiny sphere of glass, which he used as a lens. With such a lens he could magnify objects about 500 times. However, he did not reveal his methods to the public, and instead encouraged people to believe that he made all his lenses by grinding.

Some of van Leeuwenhoek's observations

Wikipedia states that

"Using single-lensed microscopes of his own design and make, van Leeuwenhoek was the first to observe and to experiment with microbes, which he originally referred to as dierkens, diertgens or diertjes (Dutch for "small animals" [translated into English as animalcules, from Latin animalculum = "tiny animal"]).[8] He was the first to relatively determine their size. Most of the 'animalcules' are now referred to as unicellular organisms, although he observed



Figure 3.1: Portrait of Antonie van Leeuwenhoek (1632-1723). He has been called "the father of microbiology". As a scientist he was largely self-taught.



Figure 3.2: A microscopic section of a one-year-old ash tree microscopic section of a one-year-old ash tree. The drawing was made by Antonie van Leeuwenhoek.

PIONEERS OF MICROSCOPY



Figure 3.3: A replica of a microscope by van Leeuwenhoek. The single-lens microscopes of van Leeuwenhoek were relatively small devices, the largest being about 5 cm long. They are used by placing the lens very close in front of the eye, while looking in the direction of the sun. The other side of the microscope had a pin, where the sample was attached in order to stay close to the lens. There were also three screws to move the pin and the sample along three axes: one axis to change the focus, and the two other axes to navigate through the sample.
multicellular organisms in pond water. He was also the first to document microscopic observations of muscle fibers, bacteria, spermatozoa, red blood cells, crystals in gouty tophi, and among the first to see blood flow in capillaries. Although van Leeuwenhoek did not write any books, he described his discoveries in letters to the Royal Society, which published many of his letters, and to persons in several European countries"

Letters to England's Royal Society

The Dutch physician, Reinier de Graaf, wrote to Henry Oldenberg, the editor of *Philosophical Transactions of the Royal Society* saying that van Leeuwenhoek's microscopes "far surpassed those which we hitherto have seen". As a result, Oldenberg and van Leeuwenhoek began to exchange letters, which Oldenberg translated and published. Van Leeuwenhoek's discoveries captured the attention of the Royal Society, which elected him to membership in 1680.

Scientific fame

Wikipedia states that

"By the end of the seventeenth century, van Leeuwenhoek had a virtual monopoly on microscopic study and discovery. His contemporary Robert Hooke, an early microscope pioneer, bemoaned that the field had come to rest entirely on one man's shoulders. He was visited over the years by many notable individuals, such as the Russian Tsar Peter the Great. To the disappointment of his guests, van Leeuwenhoek refused to reveal the cutting-edge microscopes he relied on for his discoveries, instead showing visitors a collection of average-quality lenses.

"Van Leeuwenhoek was visited by Leibniz, William III of Orange and his wife, Mary II of England, and the burgemeester (mayor) Johan Huydecoper of Amsterdam, the latter being very interested in collecting and growing plants for the Hortus Botanicus Amsterdam, and all gazed at the tiny creatures. In 1698, van Leeuwenhoek was invited to visit the Tsar Peter the Great on his boat. On this occasion van Leeuwenhoek presented the Tsar with an 'eel-viewer', so Peter could study blood circulation whenever he wanted."

3.2 Robert Hooke's Micrographia

Robert Hooke, FRS (1635-1703) was so universally talented that he has been called "England's Leonardo". Although he was initially poor, he soon achieved both wealth and recognition as a surveyor of London after the Great Fire (1666). In this work, he collaborated with Sir Christoper Wren. Hooke's scientific and engineering work included contributions



Figure 3.4: Microscope manufactured by Christopher White of London for Robert Hooke. Hooke is believed to have used this microscope for the observations that formed the basis of *Micrographia*.



Figure 3.5: Hooke's drawing of a louse.



Figure 3.6: Hooke's drawing of a flea.



Figure 3.7: Hooke's microscope.



Figure 3.8: Hooke was the first to apply the word "cell" to biological objects: Cork.



Figure 3.9: Hooke's drawing of a gnat.



Figure 3.10: Hooke's drawing of a blue fly.

3.2. ROBERT HOOKE'S MICROGRAPHIA

to astronomy and the laws of gravitation, which brought him into conflict with Isaac Newton over questions of priority. Hooke went to Oxford University with Robert Boyle. He assisted Boyle by construction the air pump which Boyle used in his experiments. Hooke also contributed to our knowledge of the laws of elasticity ("Hooke Law). Hooke was one of the founding members of the Royal Society.

Here we will focus on Hooke's book, *Micrographia*, which became a popular best-seller. It opened up a new world to its readers. Below are quotations from one subsection of the book.

Observ. XLIX. Of an Ant or Pismire.

This was a creature, more troublesome to be drawn, then any of the rest, for I could not, for a good while, think of a way to make it suffer its body to ly quiet in a natural posture; but whil'st it was alive, if its feet were fetter'd in Wax or Glew, it would so twist and wind its body, that I could not any wayes get a good view of it; and if I killed it, its body was so little, that I did often spoil the shape of it, before I could throughly view it: for this is the nature of these minute Bodies, that as soon, almost, as ever their life is destroy'd, their parts immediately shrivel, and lose their beauty; and so is it also with small Plants, as I instanced before, in the description of Moss. And thence also is the reason of the variations in the beards of wild Oats, and in those of Musk-grass seed, that their bodies, being exceeding small, those small variations which are made in the surfaces of all bodies, almost upon every change of Air, especially if the body be porous, do here become sensible, where the whole body is so small, that it is almost nothing but surface; for as in vegetable substances, I see no great reason to think, that the moisture of the Aire (that, sticking to a wreath'd beard, does make it untwist) should evaporate, or exhale away, any faster then the moisture of other bodies, but rather that the avolation from, or access of moisture to, the surfaces of bodies being much the same, those bodies become most sensible of it, which have the least proportion of body to their surface. So is it also with Animal substances; the dead body of an Ant, or such little creature, does almost instantly shrivel and dry, and your object shall be quite another thing, before you can half delineate it, which proceeds not from the extraordinary exhaution, but from the small proportion of body and juices, to the usual drying of bodies in the Air, especially if warm. For which inconvenience, where I could not otherwise remove it, I thought of this expedient.

I took the creature, I had design'd to delineate, and put it into a drop of very well rectified spirit of Wine, this I found would presently dispatch, as it were, the Animal, and being taken out of it, and lay'd on a paper, the spirit of Wine would immediately fly away, and leave the Animal dry, in its natural posture, or at least, in a constitution, that it might easily with a pin be plac'd, in what posture you desired to draw it, and the limbs would so remain, without either moving, or shriveling. And thus I dealt with this Ant, which I have here delineated, which was one of many, of a very large kind, that inhabited under the Roots of a Tree, from whence they would sally out in great parties, and make most grievous havock of the Flowers and Fruits, in the ambient Garden, and return back again very expertly, by the same wayes and paths they went.

It was more then half the bigness of an Earwig, of a dark brown, or reddish colour, with long legs, on the hinder of which it would stand up, and raise its head as high as it could above the ground, that it might stare the further about it, just after the same manner as I have also observ'd a hunting Spider to do: and putting my finger towards them, they have at first all run towards it, till almost at it; and then they would stand round about it, at a certain distance, and smell, as it were, and consider whether they should any of them venture any further, till one more bold then the rest venturing to climb it, all the rest, if I would have suffered them, would have immediately followed: many such other seemingly rational actions I have observ'd in this little Vermine with much pleasure, which would be too long to be here related; those that desire more of them may satisfie their curiosity in Ligons History of the Barbadoes. Having insnar'd several of these into a small Box, I made choice of the tallest grown among them, and separating it from the rest, I gave it a Gill of Brandy, or Spirit of Wine, which after a while e'en knock'd him down dead drunk, so that he became moveless, though at first putting in he struggled for a pretty while very much, till at last, certain bubbles issuing out of its mouth, it ceased to move; this (because I had before found them quickly to recover again, if they were taken out presently) I suffered to lye above an hour in the Spirit; and after I had taken it out, and put its body and legs into a natural posture, remained moveless about an hour; but then, upon a sudden, as if it had been awaken out of a drunken sleep, it suddenly reviv'd and ran away; being caught, and serv'd as before, he for a while continued struggling and striving, till at last there issued several bubbles out of its mouth, and then, tanguam animam expirasset, he remained moveless for a good while; but at length again recovering, it was again redipt, and suffered to lye some hours in the Spirit; notwithstanding which, after it had layen dry some three or four hours, it again recovered life and motion: Which kind of Experiments, if prosecuted, which they highly deserve, seem to me of no inconsiderable use towards the invention of the Latent Scheme, (as the Noble Verulam calls it) or the hidden, unknown Texture of Bodies.

Of what Figure this Creature appear'd through the Microscope, the 32. Scheme (though not so carefully graven as it ought) will represent to the eye, namely, That it had a large head AA, at the upper end of which were two protuberant eyes, pearl'd like those of a Fly, but smaller BB; out of the Nose, or foremost part, issued two horns CC, of a shape sufficiently differing from those of a blew Fly, though indeed they seem to be both the same kind of Organ, and to serve for a kind of smelling; beyond these were two indented jaws DD, which he open'd side-wayes, and was able to gape them asunder very wide; and the ends of them being armed with teeth, which meeting went between each other, it was able to grasp and hold a heavy body, three or four times the bulk and weight of its own body: It had only six legs, shap'd like those of a Fly, which, as I shewed before, is an Argument that it is a winged Insect, and though I could not perceive any sign of them in the middle part of its body (which seem'd to consist of three joints or pieces EFG, out of which sprung two legs), yet 'tis known that there are of them that have long wings, and fly up and down in the air.

The third and last part of its body III was bigger and larger than the other two, unto which it was joyn'd by a very small middle, and had a kind of loose shell, or another

3.2. ROBERT HOOKE'S MICROGRAPHIA

distinct part of its body H, which seem'd to be interpos'd, and to keep the thorax and belly from touching.

The whole body was cas'd over with a very strong armour, and the belly III was covered likewise with multitudes of small white shining brisles; the legs, horns, head, and middle parts of its body were bestuck with hairs also, but smaller and darker.

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Chapter 4 EVOLUTION

4.1 Linnaeus, Lamarck and Erasmus Darwin

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 Linnaeus.

Linnaeus 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 Linnaeus was asked by his university to visit Lapland to study the plants in that remote northern region of Sweden.



Figure 4.1: The great Swedish naturalist Carolus Linnaeus developed a language which is now universally used for biological classification.

4.2 The language of Linnean classification

Linnaeus 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.

Linnaeus 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.) Linnaeus 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.

Linneaus proposed three kingdoms, which were divided into classes. From classes, the groups were further divided into orders, families, genera (singular: genus), and species. An additional rank beneath species distinguished between highly similar organisms. While his system of classifying minerals has been discarded, a modified version of the Linnaean classification system is still used to identify and categorize animals and plants.

Although he started a line of study which led inevitably to the theory of evolution, Linnaeus 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.

Linnaeus 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 ancestor¹.

¹ Linnaeus 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, Linnaeus set forth a descriptive "family tree" of living things, but Darwin discovered the dynamic mechanism that underlies the observations.



Figure 4.2: The branching decision-trees in the Linnean language of classification resembles the decision-trees in package-address systems such as postal systems of the Internet. Similar decision-trees are found when an animal finds its way through forest or maze.



Figure 4.3: Within the Animal kingdom, the polar bear belongs to the phylum Chordata, the class Mammalian, the order Carnivore, the family Ursidia, the genus Ursus, and the species Ursus arctus.



Figure 4.4: The three-domain system currently used to classify living organisms. Within each domain, the classification becomes progressively finer: From classes, the groups were further divided into orders, families, genera (singular: genus), and species. An additional rank beneath species distinguished between highly similar organisms. While his system of classifying minerals has been discarded, a modified version of the Linnaean classification system is still used to identify and categorize animals and plants.

Kingdoms and classes

Animals

- 1. Mammalian (mammals)
- 2. Aves (birds)
- 3. Amphibia (amphibians)
- 4. Pisces (fish)
- 5. Insecta (insects)
- 6. Vermes (worms)

Plants

- 1. Monandria: flowers with 1 stamen
- 2. Diandria: flowers with 2 stamens
- 3. Triandria: flowers with 3 stamens
- 4. Tetrandria: flowers with 4 stamens
- 5. Pentandria: flowers with 5 stamens
- 6. Hexandria: flowers with 6 stamens
- 7. Heptandria: flowers with 7 stamens
- 8. Octandria: flowers with 8 stamens
- 9. Enneandria: flowers with 9 stamens
- 10. Decandria: flowers with 10 stamens
- 11. Dodecandria: flowers with 12 stamens
- 12. Icosandria: flowers with 20 (or more) stamens
- 13. Polyandria: flowers with many stamens
- 14. Didynamia: flowers with 4 stamens, 2 long and 2 short
- 15. Tetradynamia: flowers with 6 stamens, 4 long and 2 short
- 16. Monadelphia; flowers with the anthers separate, but the filaments united at the base
- 17. Diadelphia; flowers with the stamens united in two groups

- 18. Polyadelphia; flowers with the stamens united in several groups
- 19. Syngenesia; flowers with 5 stamens having anthers united at the edges
- 20. Gynandria; flowers having stamens united to the pistils
- 21. Monoecia: monoecious plants
- 22. Dioecia: dioecious plants
- 23. Polygamia: polygamodioecious plants
- 24. Cryptogamia: organisms that resemble plants but don't have flowers, which included fungi, algae, ferns, and bryophytes

In France, the Chevalier J.B. de Lamarck (1744-1829), was struck by the close relationships between various animal species; and in 1809 he published a book entitled *Philosophie Zoologique*, in which he tried to explain this interrelatedness in terms of a theory of evolution. Lamarck explained the close similarity of the species within a genus by supposing these species to have evolved from a common ancestor. However, the mechanism of evolution which he postulated was seriously wrong, since he believed that acquired characteristics could be inherited.

Lamarck believed, for example, that giraffes stretched their necks slightly by reaching upward to eat the leaves of high trees. He believed that these slightly-stretched necks could be inherited; and in this way, Lamarck thought, the necks of giraffes have gradually become longer over many generations. Although his belief in the inheritability of acquired characteristics was a serious mistake, Lamarck deserves much credit for correctly maintaining that the close similarity between the species of a genus is due to their descent from a common ancestral species.

Meanwhile, in England, 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", had published *The Botanic Garden* and *Zoonomia* (1794). Darwin's first book, *The Botanic Garden*, was written in verse, and in the preface he 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, Linnaeus". This book was immensely popular during Darwin's lifetime, but modern readers might find themselves wishing that he had used prose instead of poetry.

Darwin's second book, *Zoonomia*, is more interesting, since it contains a clear statement of the theory of evolution:

"...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 colour 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 anphibious 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 similar living filament."

Erasmus Darwin's son, Robert, married Suzannah Wedgwood, the pretty and talented daughter of the famous potter, Josiah Wedgwood; and in 1809, (the same year in which Lamarck published his *Philosophie Zoologique*), she became the mother of Charles Darwin.

4.3 Charles Darwin

As a boy, Charles Darwin was fond of collecting and hunting, but he showed no special ability in school. His father, disappointed by his mediocre performance, once said to him: "You care for nothing but shooting, dogs and rat-catching; and you will be a disgrace to yourself, and to all your family."

Robert Darwin was determined that his son should not turn into an idle, sporting man, as he seemed to be doing, and when Charles was sixteen, he was sent to the University of Edinburgh to study medicine. However, Charles Darwin had such a sensitive and gentle disposition that he could not stand to see operations (performed, in those days, without chloroform). Besides, he had found out that his father planned to leave him enough money to live on comfortably; and consequently he didn't take his medical studies very seriously. However, some of his friends were scientists, and through them, Darwin became interested in geology and zoology.

Robert Darwin realized that his son did not want to become a physician, and, as an alternative, he sent Charles to Cambridge to prepare for the clergy. At Cambridge, Charles Darwin was very popular because of his cheerful, kind and honest character; but he was not a very serious student. Among his many friends, however, there were a few scientists, and they had a strong influence on him. The most important of Darwin's scientific friends were John Stevens Henslow, the Professor of Botany at Cambridge, and Adam Sedgwick, the Professor of Geology.

Remembering the things which influenced him at that time, Darwin wrote:

"During my last year at Cambridge, I read with care and profound interest Humboldt's *Personal Narritive of Travels to the Equinoctal Regions of America*. This work, and Sir J. Hirschel's *Introduction to the Study of Natural Philosophy*, stirred up in me a burning desire to add even the most humble contribution to the noble structure of Natural Science. No one of a dozen books influenced me nearly so much as these. I copied out from Humboldt long passages about Teneriffe, and read them aloud to Henslow, Ramsay and Dawes... and some of the party declared that they would endeavour to go there; but I think they were only half in earnest. I was, however, quite in earnest, and got an introduction to a merchant in London to enquire about ships."

During the summer of 1831, Charles Darwin went to Wales to help Professor Sedgwick,



Figure 4.5: Charles Darwin as a young man. Public domain, Wikimedia Commons

4.4. LYELL'S HYPOTHESIS

who was studying the extremely ancient rock formations found there. When he returned to his father's house after this geological expedition, he found a letter from Henslow. This letter offered Darwin the post of unpaid naturalist on the *Beagle*, a small brig which was being sent by the British government to survey the coast of South America and to carry a chain of chronological measurements around the world.

Darwin was delighted and thrilled by this offer. He had a burning desire both to visit the glorious, almost-unknown regions described by his hero, Alexander von Humboldt, and to "add even the most humble contribution to the noble structure of Natural Science". His hopes and plans were blocked, however, by the opposition of his father, who felt that Charles was once again changing his vocation and drifting towards a life of sport and idleness. "If you can find any man of common sense who advises you to go", Robert Darwin told his son, "I will give my consent".

Deeply depressed by his father's words, Charles Darwin went to visit the estate of his uncle, Josiah Wedgwood, at Maer, where he always felt more comfortable than he did at home. In Darwin's words what happened next was the following:

"...My uncle sent for me, offering to drive me over to Shrewsbury and talk with my father, as my uncle thought that it would be wise in me to accept the offer. My father always maintained that my uncle was one of the most sensible men in the world, and he at once consented in the kindest possible manner. I had been rather extravagant while at Cambridge, and to console my father, I said that 'I should be deuced clever to spend more than my allowance whilst on board the *Beagle*', but he answered with a smile, 'But they tell me you are very clever!'."

Thus, on December 27, 1831, Charles Darwin started on a five-year voyage around the world. Not only was this voyage destined to change Darwin's life, but also, more importantly, it was destined to change man's view of his place in nature.

4.4 Lyell's hypothesis

As the *Beagle* sailed out of Devonport in gloomy winter weather, Darwin lay in his hammock, 22 years old, miserably seasick and homesick, knowing that he would not see his family and friends for many years. To take his mind away from his troubles, Darwin read a new book, which Henslow had recommended: Sir Charles Lyell's *Principles of Geology*. "Read it by all means", Henslow had written, "for it is very interesting; but do not pay any attention to it except in regard to facts, for it is altogether wild as far as theory goes."

Reading Lyell's book with increasing excitement and absorption, Darwin could easily see what Henslow found objectionable: Lyell, a follower of the great Scottish geologist, James Hutton (1726-1797), introduced a revolutionary hypothesis into geology. According to Lyell, "No causes whatever have, from the earliest times to which we can look back, to the present, ever acted, but those now acting; and they have never acted with different degrees of energy from those which they now exert".

This idea seemed dangerous and heretical to deeply religious men like Henslow and Sedgwick. They believed that the earth's geology had been shaped by Noah's flood, and perhaps by other floods and catastrophes which had occurred before the time of Noah. The great geological features of the earth, its mountains, valleys and planes, they viewed as marks left behind by the various catastrophes through which the earth had passed.

All this was now denied by Lyell. He believed the earth to be enormously old - thousands of millions of years old. Over this vast period of time, Lyell believed, the long-continued action of slow forces had produced the geological features of the earth. Great valleys had been carved out by glaciers and by the slow action of rain and frost; and gradual changes in the level of the land, continued over enormous periods of time, had built up towering mountain ranges.

Lyell's belief in the immense age of the earth, based on geological evidence, made the evolutionary theories of Darwin's grandfather suddenly seem more plausible. Given such vast quantities of time, the long-continued action of small forces might produce great changes in biology as well as in geology!

By the time the *Beagle* had reached San Thiago in the Cape Verde Islands, Darwin had thoroughly digested Lyell's book, with its dizzying prospects. Looking at the geology of San Thiago, he realized "the wonderful superiority of Lyell's manner of treating geology". Features of the island which would have been incomprehensible on the basis of the usual Catastrophist theories were clearly understandable on the basis of Lyell's hypothesis.

As the *Beagle* slowly made its way southward along the South American coast, Darwin went on several expeditions to explore the interior. On one of these trips, he discovered some fossil bones in the red mud of a river bed. He carefully excavated the area around them, and found the remains of nine huge extinct quadrupeds. Some of them were as large as elephants, and yet in structure they seemed closely related to living South American species. For example, one of the extinct animals which Darwin discovered resembled an armadillo except for its gigantic size.

The *Beagle* rounded Cape Horn, lashed by freezing waves so huge that it almost floundered. After the storm, when the brig was anchored safely in the channel of Tierra del Fuego, Darwin noticed how a Fuegan 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 Fuegans 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 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. One day, near Concepcion Bay, he experienced the shocks of a severe earthquake.

"It came on suddenly, and lasted two minutes", Darwin wrote, "The town of Concepcion is now nothing more than piles and lines of bricks, tiles and timbers."

Measurements which Darwin made showed him that the shoreline near Concepcion had risen at least three feet during the quake; and thirty miles away, Fitzroy, the captain of the *Beagle*, discovered banks of mussels ten feet above the new high-water mark. This was dramatic confirmation of Lyell's theories! After having seen how much the level of the



Figure 4.6: Plate showing Fuegans from the voyage of the Beagle. Wellcome Images, Wikimedia Commons

land was changed by a single earthquake, it was easy for Darwin to imagine that similar events, in the course of many millions of years, could have raised the huge wall of the Andes mountains.

In September, 1835, the *Beagle* sailed westward to the Galapagos Islands, a group of small rocky volcanic islands off the coast of Peru. On these islands, Darwin found new species of plants and animals which did not exist anywhere else in the world. In fact, he discovered that each of the islands had its own species, similar to the species found on the other islands, but different enough to be classified separately.

The Galapagos Islands contained thirteen species of finches, found nowhere else in the world, all basically alike in appearance, but differing in certain features especially related to their habits and diet. As he turned these facts over in his mind, it seemed to Darwin that the only explanation was that the thirteen species of Galapagos finches were descended from a single species, a few members of which had been carried to the islands by strong winds blowing from the South American mainland.

"Seeing this gradation and diversity of structure in one small, intimately related group of birds", Darwin wrote, "one might really fancy that from an original paucity of birds in this archipelago, one species had been taken and modified for different ends... Facts such as these might well undermine the stability of species."

As Darwin closely examined the plants and animals of the Galapagos Islands, he could see that although they were not quite the same as the corresponding South American species, they were so strongly similar that it seemed most likely that all the Galapagos plants and animals had reached the islands from the South American mainland, and had since been modified to their present form.

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



Figure 4.7: Darwin's finches. Public domain, Wikimedia Commons

animals of South 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.

4.5 The Origin of Species

Darwin had left England on the Beagle in 1831, an immature young man of 22, with no real idea of what he wanted to do with his life. He returned from the five-year voyage in 1836, a mature man, confirmed in his dedication to science, and with formidable powers of observation, deduction and generalization. Writing of the voyage, Darwin says:

"I have always felt that I owe to the voyage the first real education of my mind... Everything about which I thought or read was made to bear directly on what I had seen, or was likely to see, and this habit was continued during the five years of the voyage. I feel sure that it was this training which has enabled me to do whatever I have done in science."

Darwin returned to England convinced by what he had seen on the voyage that plant

and animal species had not been independently and miraculously created, but that they had been gradually modified to their present form over millions of years of geological time.

Darwin was delighted to be home and to see his family and friends once again. To his uncle, Josiah Wedgwood, he wrote:

"My head is quite confused from so much delight, but I cannot allow my sister to tell you first how happy I am to see all my dear friends again... I am most anxious once again to see Maer and all its inhabitants."

In a letter to Henslow, he said:

"My dear Henslow, I do long to see you. You have been the kindest friend to me that ever man possessed. I can write no more, for I am giddy with joy and confusion."

In 1837, Darwin took lodgings at Great Marlborough Street in London, where he could work on his geological and fossil collections. He was helped in his work by Sir Charles Lyell, who became Darwin's close friend. In 1837 Darwin also began a notebook on *Transmutation* of Species. His Journal of researches into the geology and natural history of the various countries visited by the H.M.S. Beagle was published in 1839, and it quickly became a bestseller. It is one of the most interesting travel books ever written, and since its publication it has been reissued more than a hundred times.

These were very productive years for Darwin, but he was homesick, both for his father's home at the Mount and for his uncle's nearby estate at Maer, with its galaxy of attractive daughters. Remembering his many happy visits to Maer, he wrote:

"In the summer, the whole family used often to sit on the steps of the old portico, with the flower-garden in front, and with the steep, wooded bank opposite the house reflected in the lake, with here and there a fish rising, or a water-bird paddling about. Nothing has left a more vivid picture in my mind than these evenings at Maer."

In the summer of 1838, tired of his bachelor life in London, Darwin wrote in his diary:

"My God, it is intolerable to think of spending one's whole life like a neuter bee, working, working, and nothing after all! Imagine living all one's days in smoky, dirty London! Only picture to yourself a nice soft wife on a sofa with a good fire, and books and music perhaps.. Marry! Marry! Marry! Q.E.D."

Having made this decision, Darwin went straight to Maer and proposed to his pretty cousin, Emma Wedgwood, who accepted him at once, to the joy of both families. Charles and Emma Darwin bought a large and pleasant country house at Down, fifteen miles south of London; and there, in December, 1839, the first of their ten children was born.

Darwin chose this somewhat isolated place for his home because he was beginning to show signs of a chronic illness, from which he suffered for the rest of his life. His strength was very limited, and he saved it for his work by avoiding social obligations. His illness was never accurately diagnosed during his own lifetime, but the best guess of modern doctors is that he had Chagas' disease, a trypanasome infection transmitted by the bite of a South American blood-sucking bug.

Darwin was already convinced that species had changed over long periods of time, but what were the forces which caused this change? In 1838 he found the answer:

"I happened to read for amusement Malthus on *Population*", he wrote, "and being well prepared to appreciate the struggle for existence which everywhere goes on from longcontinued observation of the habits of animals and plants, it at once struck me that under these circumstances favorable variations would tend to be preserved, and unfavorable ones destroyed. The result would be the formation of new species"

"Here, then, I had at last got a theory by which to work; but I was so anxious to avoid prejudice that I determined not for some time to write down even the briefest sketch of it. In June, 1842, I first allowed myself the satisfaction of writing a very brief abstract of my theory in pencil in 33 pages; and this was enlarged during the summer of 1844 into one of 230 pages".

All of Darwin's revolutionary ideas were contained in the 1844 abstract, but he did not publish it! Instead, in an incredible Copernicus-like procrastination, he began a massive treatise on barnacles, which took him eight years to finish! Probably Darwin had a premonition of the furious storm of hatred and bigotry which would be caused by the publication of his heretical ideas.

Finally, in 1854, he wrote to his friend, Sir Joseph Hooker (the director of Kew Botanical Gardens), to say that he was at last resuming his work on the origin of species. Both Hooker and Lyell knew of Darwin's work on evolution, and for many years they had been urging him to publish it. By 1835, he had written eleven chapters of a book on the origin of species through natural selection; but he had begun writing on such a vast scale that the book might have run to four or five heavy volumes, which could have taken Darwin the rest of his life to complete.

Fortunately, this was prevented by the arrival at Down House of a bombshell in the form of a letter from a young naturalist named Alfred Russell Wallace. Like Darwin, Wallace had read Malthus' book *On Population*, and in a flash of insight during a period of fever in Malaya, he had arrived at a theory of evolution through natural selection which was precisely the same as the theory on which Darwin had been working for twenty years! Wallace enclosed with his letter a short paper entitled *On the Tendency of Varieties to Depart Indefinitely From the Original Type*. It was a perfect summary of Darwin's theory of evolution!

"I never saw a more striking coincidence", the stunned Darwin wrote to Lyell, "If Wallace had my MS. sketch, written in 1842, he could not have made a better short abstract! Even his terms now stand as heads of my chapters... I should be extremely glad now to publish a sketch of my general views in about a dozen pages or so; but I cannot persuade myself that I can do so honourably... I would far rather burn my whole book than that he or any other man should think that I have behaved in a paltry spirit."

Both Lyell and Hooker acted quickly and firmly to prevent Darwin from suppressing his own work, as he was inclined to do. In the end, they found a happy solution: Wallace's paper was read to the Linnean Society together with a short abstract of Darwin's work, and the two papers were published together in the proceedings of the society. The members of the Society listened in stunned silence. As Hooker wrote to Darwin the next day, the subject was "too novel and too ominous for the old school to enter the lists before armouring."

Lyell and Hooker then persuaded Darwin to write a book of moderate size on evolution through natural selection. As a result, in 1859, he published *The Origin of Species*, which

4.5. THE ORIGIN OF SPECIES

ranks, together with Newton's *Principia* as one of the two greatest scientific books of all time. What Newton did for physics, Darwin did for biology: He discovered the basic theoretical principle which brings together all the experimentally-observed facts and makes them comprehensible; and he showed in detail how this basic principle can account for the facts in a very large number of applications.

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. He begins by discussing the variation of plants and animals under domestication, and he points out that the key to the changes produced by breeders is selection: If we want to breed fast horses, we select the fastest in each generation, and use them as parents for the next generation.

Darwin then points out that a closely similar process occurs in nature: Every plant or animal species produces so many offspring that if all of them survived and reproduced, the population would soon reach astronomical numbers. This cannot happen, since the space and food supply are limited; and therefore, in nature there is always a struggle for survival. 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 domestication.

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 geneological 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



Figure 4.8: Charles Darwin in 1880. The photograph is by Elliott and Fry. Public domain, Wikimedia Commons

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Figure 4.9: "Man is is But a Worm", a cartoon, published in Punch in 1882. Public domain, Wikimedia Commons

of the evolutionary history of the brain and of instincts can contribute greatly to our understanding of psychology, as Darwin pointed out.

Among the many striking observations presented by Darwin to support his theory, are facts related to morphology and embryology. For example, Darwin includes the following quotation from the naturalist, von Baer:

"In my possession are two little embryos in spirit, whose names I have omitted to attach, and at present I am quite unable to say to what class they belong. They may be lizards or small birds, or very young mammalia, so complete is the similarity in the mode of formation of the head and trunk in these animals. The extremities, however, are still absent in these embryos. But even if they had existed in the earliest stage of their development, we should learn nothing, for the feet of lizards and mammals, the wings and feet of birds, no less than the hands and feet of man, all arise from the same fundamental form."

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 adaption 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."

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 dependant 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."

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Chapter 5

MOLECULAR BIOLOGY

5.1 The structure of proteins

X-ray crystallography

In England, J.D. Bernal and Dorothy Crowfoot Hodgkin pioneered the application of Xray 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



Figure 5.1: Dorothy Crowfoot Hodgkin (1910-1994). She and her mentor J.D Bernal were a great pioneers in the application of X-ray crystallogrography to determination of the structure of biological molecules, such as proteins. She was awarded the Nobel Prize in Chemistry in 1964.



Figure 5.2: Linus Pauling (1901-1994). The New Scientist called him one of the 20 most important scientists in history. He was awarded the Nobel Prize in Chemistry in 1954 and the Nobel Peace Prize in 1962.



Figure 5.3: Frederick Sanger (1918-2013) was one of the only two people in history have won two Nobel Prizes in the same field, in his case Chemistry. He won the first on 1958 for his work on the structure of proteins, and the second in 1980 for his method for determining the base sequences of nucleic acids.
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.

Linus Pauling also contributed importantly to our understanding of the structure of proteins. Wikipedia says of his work: "Pauling was one of the founders of the fields of quantum chemistry and molecular biology. His contributions to the theory of the chemical bond include the concept of orbital hybridisation and the first accurate scale of electronegativities of the elements. Pauling also worked on the structures of biological molecules, and showed the importance of the alpha helix and beta sheet in protein secondary structure. Pauling's approach combined methods and results from X-ray crystallography, molecular model building, and quantum chemistry. His discoveries inspired the work of James Watson, Francis Crick, and Rosalind Franklin on the structure of DNA, which in turn made it possible for geneticists to crack the DNA code of all organisms."

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 sub-units 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-....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 onegene-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.

5.2 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 Physics¹ 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. 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..."²

"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

 $^{^{1}}$ with P.A.M. Dirac

² 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".



Figure 5.4: The great Austrian physicist Erwin Schrödinger (1887-1961) was one of the principle founders of quantum theory. He fled from Austria over the mountains to Italy after the Nazis entered his country, and finally found refuge at the Institute for Advanced Studies in Ireland. It was there that he wrote his important book, "What is Life?". Reading Schrödinger's book, Francis Crick was inspired to look for the structure of DNA.

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Figure 5.5: Francis Crick (1916-2004) and James Dewey Watson (born 1928) at the Cavendish Laboratory with their model of DNA. After their discovery of the structure of DNA, it became clear that it was this molecule that carried genetic information between generations.

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.

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. 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 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 informationcontaining 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.

5.3 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



Figure 5.6: Sir Francis Crick (1916-2004). Besides being half of the team that determined the correct structure of DNA, he made many other extremely important contributions to molecular biology and neuroscience. He contributed importantly to the solution of the genetic code, and is known for his "central dogma": Information flows from DNA to RNA, and never backward. RNA codes the synthesis of proteins, and enzymes, which are proteins, catalyze the synthesis of smaller molecules.

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Figure 5.7: James Dewey Watson (born in 1928) Crick's partner in solving the DNA structure. After serving for 35 years as Director and later President of the Cold Springs Harbor Laboratory and greatly expanding it facilities, he joined the US National Institutes of Health, where he has been the driving force behind the Human Genome Project.

5.3. THE STRUCTURE OF DNA



Figure 5.8: Maurice Wilkins (1916-2004). He applied to DNA the X-ray diffraction methods pioneered by Dorothy Hodgkin. It was his work, and that of Rosalind Franklin, together with Linus Pauling's model-building methods, that enabled Crick and Watson to correctly solve the structure of DNA. He shared the 1962 Nobel Prize in Physiology or Medicine with them.



Figure 5.9: Rosalind Franklin (1920-1958). It was one of her high-quality diffraction photographs, taken in Maurice Wilkins' laboratory, that proved to be critical for the DNA structure. She might have shared the Nobel Prize with Wilkins, Crick and Watson, but before this could be considered by the committee, she died of overian cancer.



Figure 5.10: Oswald Theodore Avery (1877-1955). Together with his team at the Rockefeller University Hospital in New York City, he proved experimentally that DNA is the molecule that carries genetic information between generations.



Figure 5.11: The Austro-Hungarian biochemist Erwin Chargaff (1905-2002) found experimentally that in DNA from the nuclei of living cells, the amount of adenine always equals the amount of thiamine; and the amount of guanine always equals the amount of cytosine, but at the time of his discovery, neither he nor anyone else, understood the meaning of this rule.

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, radioactive 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.

5.4 The structure of DNA

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:

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Figure 5.12: Once the structure of DNA was known, it became clear that transgenerational information is transmitted in a chemical language based on a code with four letters, G, T, C and A.

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5.5 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.



Figure 5.13: 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.



Figure 5.14: mRNA passes through the ribosome like a punched computer tape passing through a tape-reader.



Figure 5.15: This figure shows aspartic acid, whose residue (R) is hydrophilic, contrasted with alanine, whose residue is hydrophobic. A protein chain is formed from its constituent amino acids by removal of water so that a direct chain of the form -N-C-C-N-C-C-N-C-C-... is produced. The chain then folds in such a way that the hydrophilic residues are outermost while the hydrophobic residues are on the inside.

5.6 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 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 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, Nirenberg 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 worked out by H. Gobind Khorana of the University of Wisconsin, who used other mRNA sequences (such as GUGUGU..., AAGAA-GAAG... 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.

| 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 | TGC = 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 | CGC=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 | AGC=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 | GGC=Ala | GAG=Glu | GGG=Gly |

Table 5.1: The genetic code

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Chapter 6 THE ORIGIN OF LIFE

6.1 Formation of the Sun and the Earth

Our local star, the Sun, was formed from molecular clouds in interstellar space, which had been produced by the explosion of earlier stars. Our Sun contains mainly hydrogen and a little helium, with very small amounts of heavier elements. The vast amounts of energy produced by the sun come mainly from a nuclear reaction in which hydrogen is converted into helium.

There were clouds of containing not only hydrogen and helium, but also heavier elements left swirling around the infant Sun. Gradually, over many millions of years, these condensed through a process of collision and accretion, to form the planets. In the four relatively small inner planets, Mercury, Venus, Earth and Mars, heavy elements predominate, while in the giants, Jupiter, Saturn, Uranus and Neptune, we find lighter elements.

The Sun accounts for 99.86% of the solar system's mass, while the four giant planets contain 99% of the remaining mass.

One astronomical unit (1 AU) is, by definition, the average distance of the earth from the sun, i.e. approximately 93 million miles or 150 million kilometers. In terms of this unit, the average distances of the planets from the sun are as follows: Mercury, 0.387 AU; Venus, 0.722 AU; Earth, 1.000 AU; Mars, 1.52 AU; Jupiter, 5.20 AU; Saturn, 9.58 AU; Uranus, 19.2 AU; Neptune, 30.1 AU.

The Solar System also includes the asteroid belt, which lies between the orbits of Mars and Jupiter; the Kuiper belt and scattered disc, which are populations of trans-Neptunian objects; the dwarf planets, Ceres, Pluto and Eris; and the comets. Many of the bodies in the solar system, including six of the planets, have natural satellites or moons. The Earth's moon was produced by collision with a Mars-sized body, soon after the formation of the Earth.

Of the four inner planets, the Earth is the only one that has large amounts of liquid water on its surface. When the Earth cooled sufficiently after the violent collision that gave us our Moon, oceans began to form, and life is believed to have originated in the oceans, approximately 3.8 billion years before the present.



Figure 6.1: Much experimental evidence supports the Standard Model of cosmology, according to which our Universe began in an enormously hot and dense state 15.72 billion years ago, from which it is exploding outward. By 10 billion years before the present it had cooled enough for the first stars to form. Our own local star, the Sun, was formed 4.54 billion years ago from dust clouds left when earlier stars exploded.



Figure 6.2: The Earth was formed 4.54 billion years ago. Life on earth originated approximately 3.8 billion years ago (3.8 BYA).



Figure 6.3: This figure shows the relative sizes of the planets. Closest to the Sun are the relatively small terrestrial planets, Mercury, Venus, Earth and Mars, composed of metals and rock. Farther out are two gas giants, Jupiter and Saturn, which are composed mainly of hydrogen and helium. Still farther out are two ice giants, Uranus and Neptune, which are composed mainly of frozen water, frozen ammonia and frozen methane. The distances of the planets from the Sun shown in this figure are not realistic. The planetary orbits lie in roughly in the same plane, which is called the ecliptic, and all the planets circle the Sun in the same direction.

6.2 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 atmosphere¹. 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.)

¹ It is now believed that the main constituents of the primordial atmosphere were carbon dioxide, water, nitrogen, and a little methane.
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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, 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 urea². 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.

² The chemical reaction that led to the formation of the amino acids that Miller observed was undoubtedly the Strecker synthesis: $HCN + NH_3 + RC=O + H_2O \rightarrow RC(NH_2)COOH$.



Figure 6.4: Miller's apparatus.



Figure 6.5: Products as a function of time in the Miller-Urey experiment.

Further variations on the Miller-Urey experiment were performed by 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.

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 direc-

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tion 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.

Today experiments aimed at throwing light on chemical evolution towards the origin of life are being performed in the laboratory of the Nobel Laureate geneticist Jack Sjostak at Harvard Medical School. The laboratory is trying to build a synthetic cellular system that undergoes Darwinian evolution.

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.



Figure 6.6: Evolutionary relationships established by Dickerson and coworkers by comparing the amino acid sequences of Cytochrome C from various species.

6.3 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 12.6.



Figure 6.7: 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.

Comparison of the base sequences of RNA and DNA from various species proved to be even more powerful tool for establishing evolutionary relationships. Figure 12.7 shows the universal phylogenetic tree established in this way by Iwabe, Woese and their coworkers.³ In Figure 12.7, 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 12.7 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**, **Desulfurococcus**, and **Sulfolobus** - all hypothermophiles⁴. Among the eubacteria, the two shortest branches, Aquifex and Thermatoga are both hyperthermophiles⁵

The phylogenetic evidence for the existence of hyperthermophiles at a very early stage of evolution lends support to a proposal put forward in 1988 by the German biochemist Günter Wächterhäuser. He proposed that the reaction for pyrite formation,

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

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 (FeS₂) 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

³ "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."

⁴ Group (2) in Figure 12.7 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.

⁵ Thermophiles are a subset of the larger group of extremophiles.

surface aided the process. Wächterhäuser further proposed an archaic autocatylitic carbondioxide 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 + H₂S, 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.

A similar picture of the origin of life has been proposed by Michael J. Russell and Alan J. Hall in 1997. In this picture "...(i) life emerged as hot, reduced, alkaline, sulphide-bearing submarine seepage waters interfaced with colder, more oxidized, more acid, $Fe^{2+} >> Fe^{3+}$ -bearing water at deep (*ca.* 4km) floors of the Hadean ocean *ca.* 4 Gyr ago; (ii) the difference in acidity, temperature and redox potential provided a gradient of pH (*ca.* 4 units), temperature (*ca.* 60°C) and redox potential (*ca.* 500 mV) at the interface of those waters that was sustainable over geological time-scales, providing the continuity of conditions conducive to organic chemical reactions needed for the origin of life..." ⁶. Russell, Hall and their coworkers also emphasize the role that may have been played by spontaneously-formed 3-dimensional mineral chambers (bubbles). They visualize these as having prevented the reacting molecules from diffusing away, thus maintaining high concentrations.

Table 12.1 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 ingests only inorganic molecules. The lithoautotrophs use energy from these 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. Multi-cellular 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 12.8, showing branching as a function of time. One very 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.

⁶See W. Martin and M.J. Russell, On the origins of cells: a hypothesis for the evolutionary transitions from abiotic geochemistry to chemoautotrophic prokaryotes, and from prokaryotes to nucleated cells, Philos. Trans. R. Soc. Lond. B Biol. Sci., **358**, 59-85, (2003).



Figure 6.8: Branching of the universal phylogenetic tree as a function of time. "Protists" are unicellular eukaryotes.

| Energy-yielding reaction | Genera |
|---|---|
| $4\mathrm{H}_2\mathrm{+CO}_2 \rightarrow \mathrm{CH}_4\mathrm{+}2\mathrm{H}_2\mathrm{O}$ | Methanopyrus, Methanothermus, Methanococcus |
| $\rm H_2 + S^{\circ} \rightarrow \rm H_2 S$ | Pyrodictium, Thermoproteus, Pyrobaculum, Acidianus, Stygiolobus |
| $4\mathrm{H}_2\mathrm{+H}_2\mathrm{SO}_4 \rightarrow \mathrm{H}_2\mathrm{S}\mathrm{+}4\mathrm{H}_2\mathrm{O}$ | Archaeoglobus |

Table 6.1:Energy-yielding reactions of some lithoautotrophic hyperther-mophiles. (After K.O. Setter)

6.4 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"), Prank 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 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 ex- ample, 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

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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 carbondioxide, 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 large⁷ 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, endoplas-

 $^{^{7}}$ not large in an absolute sense, but large in relation to the prokaryotes

mic 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 their hosts to survive the oxygen crisis. The symbiotic origin of other sub-cellular 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

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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.

6.5 Timeline for the evolution of life on the Earth

The dates shown here are taken from the Wikipedia article entitled *Timeline of the evolutionary history of life.* The unit BYA means "Billion years ago", while MYA means "Million years ago".

- 4.540 BYA. Earliest Earth
- 4.404 BYA, First appearance of water on Earth.
- 4.280 BYA. Earliest appearance of life on Earth.⁸
- 3.900 BYA, Cells resembling prokaryotes appear. These first organisms use CO₂ as a source of carbon, and obtain energy by oxidizing inorganic materials.
- 3.500 BYA, Lifetime of the last universal common ancestor. The split between bacteria and archae occurs.
- 3.000 BYA, Photosynthetic cyanobacteria evolved. They used water as a reducing agent and produced oxygen as a waste product.
- 2.800 BYA, Earliest evidence of microbial life on land.
- 2.500 BYA, Great Oxygenation Event, produced by cyanobacteria's oxogenic photosynthesis.
- 1.850 BYA, Eukaryotic cells appear. They probably evolved from cooperative assemblages of prokaryotes (phagocytosis and symbiosis).
- 1.200 BYA, Sexual reproduction first appears in the fossil records. It may have existed earlier.
- 0.800 BYA, First multicellular organisms.
- 0.600 BYA, The ozone layer is formed, making landbased life more possible.
- 0.580-0.500 BYA, The Cambrian Explosion. Biodiversity quickly increases and most modern phyla of animals appear in the fossil record.
- 0.560 BYA, Fungi appear.
- 0.550 BYA, Comb jellies, sponges, sea anemones and corals evolved.
- 0.530 BYA, The first known fossilized footprints on land.

⁸This date for the first appearance of life on earth is earlier than previously thought possible. It is based on the ratio of carbon isotopes in zircon rocks recently found in Australia.

- 0.485 BYA, Jawless fishes.
- 0.434 BYA, The first primitive plants move onto land, accompanied by fungi which may have helped them.
- 0.420 BYA, Ray-finned fishes, arachnids, and land scorpions.
- 0.410 BYA, First signs of teeth in fish.
- 0.395 BYA, First lichens, stonewarts, harvestmen and springtails. The first known tracks of four-legged animals on land.
- 0.363 BYA, The Carboniferous Period starts. Insects appear on land and soon learn to fly. Seed-bearing plants and forests cover the land.
- 0.360 BYA, First crabs and ferns. Land flora dominated by ferns.
- 0.350 BYA, Large sharks, ratfishes and hagfish.
- 0.320 BYA, The precursors of mammals separate from the precursors to reptiles.
- 0.280 BYA, Earliest beetles, seed plants and conifers diversify.
- 0.2514 BYA, The Permian-Triassic extinction event eliminates 90-95% of marine species, and 70% of terrestrial vertebrates.⁹
- 0.245 BYA, Earliest icthyosaurs (i.e. seagoing dinosaurs).
- 0.225 BYA, Earliest dinosaurs. First mammals.
- 0.220 BYA, Seed-producing forests dominate the land. Herbivours grow to huge sizes. First flies and turtles.
- 0.155 BYA, First bloodsucking insects. Archaeopteryx, a possible ancestor of birds, appears.
- 0.130 BYA, Rise of the flowering plants. Coevolution of plants and their pollinators.
- 0.115 BYA, First monotreme (egg-laying) mammals.
- 0.110 BYA, Toothed diving birds.
- 0.100 BYA, Earliest bees.
- 0.090 BYA, Probable origin of placental mammals. However, the first undisputed fossil evidence is from 0.066 BYA.
- 0.080 BYA, First ants.
- 0.066 BYA, The Cretaceous-Paleogene extinction event wipes out about half of all animal species, including all of the dinosaurs except the birds. Afterwards, mammals become the dominant animal species. Conifers dominate northern forests.
- 0.060 BYA, Earliest true primates. Diversification of large, flightless birds. The ancestors of carnivorous mammals had appeared.
- 0.055 BYA, Diversification of birds. First songbirds, parrots, loons, swifts, and wood-peckers. First whale.
- 0.052 BYA, First bats appear in the fossil record.
- 0.050 BYA, Tapirs, rhinoceroses and camels appear. Diversification of primates.
- 0.040 BYA, Modern-type moths and butterflies were alive.
- 0.035 BYA, Grasses diversify. Many modern mammal groups appear.
- 0.030 BYA, Earliest pigs and cats.

 $^{^{9}}$ Today, there is a danger that human use of fossil fuels will initiate a very similar extinction event. This danger will be discussed in a later chapter.

- 0.025 BYA, First deer.
- 0.020 BYA, Giraffes, hyenas, bears, and giant anteaters appear. Birds increase in diversity.
- 0.015 BYA, First mastodons. Australian megafauna diversify. Kangaroos appear.
- 0.010 BYA, Grasslands and savannahs are established. Major diversification of grassland animals and snakes. Insects diversify, especially ants and termites.
- 0.0095 BYA = 9.50 MYA, Great American Interchange occurs. Armadillos, opossums, hummingbirds, "terror birds", and ground sloths were among the species that migrated from South America to North America after a land bridge formed between the previously isolated continents. Species moving in the opposite direction included horses, tapirs, saber-toothed cats, jaguars, bears, coaties, ferrets, otters, skunks and deer.
- 6.50 MYA, First homanins (our human ancestors diverging from the apes).
- 6.00 MYA, Australopithecines (extinct close relatives of humans after the split with chimpanzees) diversify.
- 5.00 MYA, First tree sloths and hippopotami. Diversification of grazing and carnivorous mammals.
- 4.00 MYA, Diversification of Australopithecines. The first modern elephants, giraffes, zebras, lions, rhinoceros and gazelles.
- 2.80 MYA, Appearance of a species intermediate between the Anthropithecines and Homo Habilis.
- 2.10 MYA, First member of the genus *Homo* appears, Homo habilis.

6.6 Life elsewhere in the universe

On December 18, 2017, scientists from the University of California published an article in *Science News* entitled *Ancient fossil microorganisms indicate that life in the universe is common.* According to the article:

"A new analysis of the oldest known fossil microorganisms provides strong evidence to support an increasingly widespread understanding that life in the universe is common.

"The microorganisms, from Western Australia, are 3.465 billion years old. Scientists from UCLA and the University of Wisconsin-Madison report today in the journal Proceedings of the National Academy of Sciences that two of the species they studied appear to have performed a primitive form of photosynthesis, another apparently produced methane gas, and two others appear to have consumed methane and used it to build their cell walls.

"The evidence that a diverse group of organisms had already evolved extremely early in the Earth's history, combined with scientists' knowledge of the vast number of stars in the universe and the growing understanding that planets orbit so many of them, strengthens the case for life existing elsewhere in the universe because it would be extremely unlikely that life formed quickly on Earth but did not arise anywhere else."

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Chapter 7

HODGKIN, HUXLEY AND ECCLES

7.1 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 resistant¹.

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

¹ 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.

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: 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 catalyze 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

7.2. NERVOUS SYSTEMS

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 multicellular 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.

7.2 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.

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 itself².

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.

7.3 The giant squid axon

The mechanism by which electrical impulses propagate along nerve ax- ons 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 electrical impulse propagating along a nerve is in no way similar to an electrical current in

² 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.



Figure 7.1: Sir Alan Lloyd Hodgkin (1914-1998). He shared the 1963 Nobel Prize in Physiology or Medicine with Andrew Huxley and John Eccles.

7.3. THE GIANT SQUID AXON



Figure 7.2: Sir Andrew Fielding Huxley (1917-2012). He was a member of a famous family that included Thomas Henry Huxley ("Darwin's bulldog"), Aldous Huxley (author of *Brave New World*) and Sir Julian Huxley (a renowned evolutionary biologist, and the first director of UNESCO).



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Figure 7.3: The squid giant axon was large enough to allow Hodgkin and Huxley to perform their experiments demonstrating the mechanism of signal propagation in nerves. The squid giant axon was discovered by John Zachary Young (1907-1997) in the 1930's.
7.3. THE GIANT SQUID AXON



Figure 7.4: Hodgkin and Huxley working together.



Figure 7.5: Intracellular recording of the squid giant axon action potential.



Figure 7.6: A diagram of the Hodgkin-Huxley experiment with the giant squid axon.

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 excitatory 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.

Afterwards, the resting potential is restored by the sodium-potassium ion pump, later discovered by the Danish physiologist Jens Christian Skou. The pump consists of membranebound enzymes that use the energy of ATP to transport the ions across the electrochemical gradient.



Figure 7.7: A schematic diagram of a neuron.

7.4 Chemical synapses

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.

7.5 Neurotransmitters

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Some important neurotransmitters

- Glutamate: This is the most abundant neurotransmitter in humans, used by about half of the neurons in the human brain. It is the primary excitatory transmitter in the central nervous system. One of its functions is to help form memories.
- **GABA**: The name GABA is an acronym for Gamma-aminobutyric acid. GABA is the primary inhibitory transmitter in the vertebrate brain. It helps to control anxiety, and it is sometimes used medically to treat anxiety and the associated sleeplessness.

- **Glycine**: This neurotransmitter is a single amino acid. It is the main inhibitory neurotransmitter in the vertebrate spinal cord. Glycine is important in the central nervous system, especially in the spinal cord, brainstem, and retina.
- Acetylcholine: An ester (the organic analogue of a salt) formed from the reaction between choline and acetic acid, acetylcholine stimulates muscles, functions in the autonomic nervous system and sensory neurons, and is associated with REM sleep. Alzheimer's disease is associated with a significant drop in acetylcholine levels.
- Norepinepherine: Also known as noradrenaline, norepinephorine increases heart rate and blood pressure. It is part of the body's "fight or flight" system. Nore-pinephrine is also needed to form memories. Stress depletes stores of this neuro-transmitter.
- **Dopamine**: Dopamine is also synthesized in plants and most animals. It is an inhibitory transmitter associated with the reward center of the brain. Low dopamine levels are associated with social anxiety and Parkinson's disease, while excess dopamine is related to schizophrenia. The brain includes several distinct dopamine pathways, one of which plays a major role in reward-motivated behavior. Most types of rewards increase the level of dopamine in the brain, and many addictive drugs increase dopamine neuronal activity.
- Serotonin: Biochemically derived from the amino acid tryptophanis, serotonin an inhibitory neurotransmitter involved in mood, emotion, and perception. Low serotonin levels can lead to depression, suicidal tendencies, anger management issues, difficulty sleeping, migraines, and an increased craving for carbohydrates. It's functions include the regulation of mood, appetite, and sleep. Serotonin also has some cognitive functions, including memory and learning.
- Endorphins: The name of this class of neurotransmitters means "a class of a morphine-like substance originating from within the body". are a class of molecules similar to opioids (e.g., morphine, heroin) in terms of structure and function. The word "endorphin" is short for "endogenous morphine." Endorphins are inhibitory transmitters associated with pleasure and pain relief. In other animals, these chemicals slow metabolism and permit hibernation. The treatment of pain by means of acupuncture functions by releasing endorphines.

7.6 Transmission of signals across synapses



Figure 7.8: Sir John Carew Eccles (1903-1997).



Figure 7.9: Jens Christian Skou (1908-2018). He received a Nobel Prize in Chemistry in in 1997 for his discovery of the K^+ -Na⁺ ion pump that uses energy from ATP to transport the ions across membranes against the electrochemical gradient. The photo shows him in 2008. He was born in Lemvig, Denmark.

7.7 Are matter and mind separate?

One could, in principle, supply a computer with an input stream of sensory data, and program the computer to perform actions on the external world. In fact, the computer could be programmed in such a way that the actions taken would depend on the stored memory of previous sensory input. Could the computer then be said to be conscious? This depends on the way in which we define the word "conscious", and so the question is a semantic one, depending on our choice of a definition.

In any case, such a computer arrangement would be very closely analogous to the way in which living organisms experience their environment and act on it. Even the most primitive organisms receive a continuous stream of input data, and, if we choose, we can call this stream an elementary form of consciousness. Living organisms then react to the input stream, and their reactions may be modified by stored information of previous input data. The modification of response on the basis of previous experience is usually called "internuncial" modification, and it will be discussed below.

The pioneering Estonian scientist Jakob von Uexküll, whom we will discuss in detail below, introduced the word "Umwelt", which he defined to be the stream of sensory input data experienced by an organism. For example, speaking of a tick, he wrote: "...this eyeless animal finds the way to her watchpoint [at the top of a tall blade of grass] with the help of only its skin's general sensitivity to light. The approach of her prey becomes apparent to this blind and deaf bandit only through her sense of smell. The odor of butyric acid, which emanates from the sebaceous follicles of all mammals, works on the tick as a signal that causes her to abandon her post (on top of the blade of grass/bush) and fall blindly downward toward her prey. If she is fortunate enough to fall on something warm (which she perceives by means of an organ sensible to a precise temperature) then she has attained her prey, the warm-blooded animal, and thereafter needs only the help of her sense of touch to find the least hairy spot possible and embed herself up to her head..."



Figure 7.10: The French philosopher, mathematician and scientist René Descartes (1596-1650) advocated mind-matter dualism. Descartes thought that nerves bring sensory inputs to the brain, where the data are then transferred to the "soul". After some time, he thought, the soul tells the brain how how the human should respond. Descartes did not discuss the question of whether organisms very low on the evolutionary scale have souls. Darwin visualized a continuous evolutionary progression from lower forms of life to ourselves. At what point did these less developed organisms obtain souls? Everyone must find his or her own opinion on this question.

7.8 Jakob von Uexküll and Umwelt

Jakob Johann, Baron von Uexküll (1864-1944) was born in Estonia, on the estate of his aristocratic parents, Alexander, Baron von Uexküll and Sophie von Hahn. The family lost most of their wealth by expropriation during the Russian Revolution, and Jakob was forced to earn a living. He 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.

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 Hamburg. 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.

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 Umweltforschung offers us the opportunity to explore the phylogenetic evolution of the phenomenon of consciousness.

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 Laureate 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. Because of his work on feedback loops in living organisms, von Uexküll can also be thought of as an early pioneer of cybernetics. His work influenced the philosophers Max Scheler, Ernst Cassirer, Martin Heidegger, Maurice Merleau-Ponty, Humberto Maturana, Georges Canguilhem, Michel Foucault, Gilles Deleuze and Félix Guattari.

Interestingly, his grandson, Carl Wolmar Jakob, Baron von Uexküll (born 1944) became a member of the European Parliament and contributed the funds for the Right Livelihood Award, which has been called the "Alternative Nobel Prize". Carl Wolmer Jakob is also the co-founder of the World Future Council and the Other Economic Summit.

Amoebae, slime molds and sponges

Amoebae are eukaryotes that have the ability to alter their shape. Like other eukaryotes they have a cell nucleus and other organelles, such as mitochondria, surrounded by an



Figure 7.11: Jakob Johann, Baron von Uexküll (1864-1944) was the founder of Umwelt research. He was also an early pioneer of Cybernetics and Biosemiotics.

7.8. JAKOB VON UEXKÜLL AND UMWELT



Figure 7.12: Carl Wolmar Jakob, Baron von Uexküll (born 1944) co-founded the World Future Council and the Other Economic Summit, as well as contributing the money needed to fund the Right Livelihood Award.



Figure 7.13: The Copenhagen-Tartu school of biosemiotics is a network of scholars working in the field of biosemiotics at the University of Tartu and the University of Copenhagen. An important member of the group is Center Leader Claus Emmeche of the Niels Bohr Institute (shown here). Other members include Kalevi Kull, Jesper Hoffmeyer, Peeter Torop, Timo Maran and Mikhail Lotman.

7.8. JAKOB VON UEXKÜLL AND UMWELT

outer membrane. Amoebae often eat bacteria by engulfing them.

More than 900 species of slime molds exist in various parts of the world. They are very common on the floors of tropical rain forests, where they perform the valuable service of helping to recycle nutrients.

Slime molds are particularly interesting because they 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

HODGKIN, HUXLEY AND ECCLES



Figure 7.14: Amoebae are eukaryotes, with a nucleus and other organelles, such as mitochondria, contained within a cell membrane. They are able to change their shapes, and often eat bacteria by engulfing them.

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. later section.

The world as seen by a jellyfish

Not all jellyfish are alike. Some species have much more highly-developed sensory perception than others. Jellyfish can swim, and their motions are coordinated by a rudimentary nervous system.

According to Wikipedia, "Jellyfish employ a loose network of nerves, located in the epidermis, which is called a 'nerve net'. Although traditionally thought not to have a central nervous system, nerve net concentration and ganglion-like structures could be considered to constitute one in most species. A jellyfish detects various stimuli including the touch of other animals via this nerve net, which then transmits impulses both throughout the nerve net and around a circular nerve ring, through the rhopalial lappet, located at the rim of

7.8. JAKOB VON UEXKÜLL AND UMWELT



Figure 7.15: The fruiting bodies of a slime mold.



Figure 7.16: Like slime molds, sponges are close to the borderline between singlecelled and multi-cellular organisms.

HODGKIN, HUXLEY AND ECCLES



Figure 7.17: How does a jellyfish experience the world around it?

the jellyfish body, to other nerve cells.

"Some jellyfish have ocelli: light-sensitive organs that do not form images but which can detect light and are used to determine up from down, responding to sunlight shining on the water's surface. These are generally pigment spot ocelli, which have some cells (not all) pigmented.

"Certain species of jellyfish, such as the box jellyfish, have more advanced vision than their counterparts. The box jellyfish has 24 eyes, two of which are capable of seeing color, and four parallel information processing areas or rhopalia that act in competition, supposedly making it one of the few creatures to have a 360-degree view of its environment.

"The eyes are suspended on stalks with heavy crystals on one end, acting like a gyroscope to orient the eyes skyward. They look upward to navigate from roots in mangrove swamps to the open lagoon and back, watching for the mangrove canopy, where they feed."

7.9 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

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 (1864-1944). 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 fur 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 Uexk" ull inspired the later work of the Nobel Laureate 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

 $^{^{3}}$ 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 Umweltforschung offers us the opportunity to explore the phylogenetic evolution of the phenomenon of consciousness.

(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 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."

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Chapter 8

THE CHEMISTRY OF EMOTIONS

8.1 Darwin's book on emotions

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 the Emotions in Man and Animals*. Because of these pioneering studies, Darwin is considered to be the founder of ethology.

Behind Darwin's work in this field 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; 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.

In the introduction of his book, *The Expression of the Emotions in Man and Animals*, Darwin says "I thought it very important to ascertain whether the same expressions and gestures prevail, as has often been asserted without much evidence, with all the races of mankind, especially with those who have associated but little with Europeans. Whenever the same movements of the features or body express the same emotions in several distinct races of man, we may infer with much probability, that such expressions are true ones, that is, are innate or instinctive."

To gather evidence on this point, Darwin sent a printed questionnaire on the expression of human emotions and sent it to missionaries and colonial administrators in many parts of the world. There were 16 questions to be answered:

- 1. Is astonishment expressed by the eyes and mouth being opened wide, and by the eyebrows being raised?
- 2. Does shame excite a blush when the colour of the skin allows it to be visible? and especially how low down on the body does the blush extend?
- 3. When a man is indignant or defiant does he frown, hold his body and head erect, square his shoulders and clench his fists?
- 4. When considering deeply on any subject, or trying to understand any puzzle, does he frown, or wrinkle the skin beneath the lower eyelids?

and so on.

Darwin received 36 replies to his questionnaire, many coming from people who were in contact with extremely distinct and isolated groups of humans. The results convinced him that our emotions and the means by which they are expressed are to a very large extent innate, rather than culturally determined, since the answers to his questionnaire were so uniform and so independent of both culture and race. In preparation for his book, he also closely observed the emotions and their expression in very young babies and children, hoping to see inherited characteristics in subjects too young to have been greatly influenced by culture. Darwin's observations convinced him that in humans, just as in other mammals, the emotions and their expression are to a very large extent inherited universal characteristics of the species.

The study of inherited behavior patterns in animals (and humans) was continued in the 20th century by such researchers as Karl von Frisch (1886-1982), Nikolaas Tinbergen (1907-1988), and Konrad Lorenz (1903-1989), three scientists who shared a Nobel Prize in Medicine and Physiology in 1973.

8.1. DARWIN'S BOOK ON EMOTIONS

Karl von Frisch, the first of the three ethologists who shared the 1973 prize, is famous for his studies of the waggle-dance of honeybees. Bees guide each other to sources of food by a genetically programmed signaling method - the famous waggle dance, deciphered in 1945 by 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 ¹. 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.

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.

In other experiments, Tinbergen explored the response of newly-hatched chicks of the common domestic hen to models representing a hawk. Since the chicks were able to recognize a hawk immediately after hatching, he knew that the response must be genetically programmed. Just as he had done in his experiments with herring gulls, Tinbergen experimented with various models, trying to determine the crucial characteristic that was recognized by the chicks, causing them to run for cover. He discovered that a crude model in the shape of the letter T invariable caused the response if pulled across the sky with the

¹The 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".

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Figure 8.1: Charles Darwin discussed inherited behaviour patterns in *The Origin* of Species. He later published a separate book on this subject entitled *The* Expression of Emotions in Man and Animals.

wings first and tail last. (Pulled backwards, the T shape caused no response.)

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.

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 the astonishing ease with which a human baby learns to speak and understand implies a large degree of genetic predisposition.

8.1. DARWIN'S BOOK ON EMOTIONS



Figure 8.2: A baby crying, one of the illustrations in *The Expression of Emotions in Man and Animals.*

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Figure 8.3: Another illustration in Darwin's book, *The Expression of Emotions in Man and Animals* shows an expression of horror on the face of a man. This expression was induced by an electrical shock, showing the human facial musculature is capable of forming the expression of horror automatically, if properly induced.



Figure 8.4: Another illustration in Darwin's book shows a dog's face expressing threat when confronting an enemy.

8.1. DARWIN'S BOOK ON EMOTIONS



Figure 8.5: An ape expressing affection.



Figure 8.6: The same animal expressing threat. Both drawings are illustrations from Darwin's book.

8.2 Brain chemistry

Emotions in humans and in animals have an extremely long evolutionary history. Chemicals that affect behaviour are present in even the most primitive forms of multicellular organisms, even in slime molds, which are at the exact borderline between single-celled multicellular organisms. Cyclic AMP has been shown to be the molecule that expresses slime mold unhappiness!

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 multicellular 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.

8.3 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.

8.4 Chemical synapses

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 Neuron 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.

8.5 Neurotransmitters

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 fungues 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-aminobutyric acid is an example of an inhibitory neurotransmitter.

Some important neurotransmitters

- **Glutamate**: This is the most abundant neurotransmitter in humans, used by about half of the neurons in the human brain. It is the primary excitatory transmitter in the central nervous system. One of its functions is to help form memories.
- **GABA**: The name GABA is an acronym for Gamma-aminobutyric acid. GABA is the primary inhibitory transmitter in the vertebrate brain. It helps to control anxiety, and it is sometimes used medically to treat anxiety and the associated sleeplessness.
- **Glycine**: This neurotransmitter is a single amino acid. It is the main inhibitory neurotransmitter in the vertebrate spinal cord. Glycine is important in the central nervous system, especially in the spinal cord, brainstem, and retina.
- Acetylcholine: An ester (the organic analogue of a salt) formed from the reaction between choline and acetic acid, acetylcholine stimulates muscles, functions in the autonomic nervous system and sensory neurons, and is associated with REM sleep. Alzheimer's disease is associated with a significant drop in acetylcholine levels.
- Norepinepherine: Also known as noradrenaline, norepinephorine increases heart rate and blood pressure. It is part of the body's "fight or flight" system. Nore-pinephrine is also needed to form memories. Stress depletes stores of this neuro-transmitter.
- **Dopamine**: Dopamine is also synthesized in plants and most animals. It is an inhibitory transmitter associated with the reward center of the brain. Low dopamine levels are associated with social anxiety and Parkinson's disease, while excess dopamine is related to schizophrenia. The brain includes several distinct dopamine pathways, one of which plays a major role in reward-motivated behavior. Most types of rewards increase the level of dopamine in the brain, and many addictive drugs increase dopamine neuronal activity.
- Serotonin: Biochemically derived from the amino acid tryptophanis, serotonin an inhibitory neurotransmitter involved in mood, emotion, and perception. Low serotonin levels can lead to depression, suicidal tendencies, anger management issues, difficulty sleeping, migraines, and an increased craving for carbohydrates. It's functions include the regulation of mood, appetite, and sleep. Serotonin also has some cognitive functions, including memory and learning.
8.6. OXYTOCIN, THE "LOVE HORMONE"

• Endorphins: The name of this class of neurotransmitters means "a class of a morphine-like substance originating from within the body". are a class of molecules similar to opioids (e.g., morphine, heroin) in terms of structure and function. The word "endorphin" is short for "endogenous morphine." Endorphins are inhibitory transmitters associated with pleasure and pain relief. In other animals, these chemicals slow metabolism and permit hibernation. The treatment of pain by means of acupuncture functions by releasing endorphines.

Pleasure versus happiness

Pleasure is fleeting. Happiness lasts. Pleasure is addictive, but happiness is not. Pleasure craves more and more of everything. Happiness can be content with very little. These characteristics make happiness a better goal than pleasure. Interestingly, the neurotransmitter dopamine is associated with pleasure, while serotonin is associated with happiness.²

8.6 Oxytocin, the "love hormone"

Besides discovering acetylcholine, Sir Henry Dale also discovered, in 1906. the peptide hormone Oxytocin, which has sometimes been called the "love hormone". Oxytocin plays a role in social bonding and sexual reproduction in both sexes. During childbirth, Oxytocin is released into the bloodstream of women in response to stretching of the curvex and uterus during labour, and also in response to breastfeeding. The hormone then facilitates the bonding between mother and child. Oxytocin is also present in men and its concentration in their bloodstream increases in response to romantic attachments and social bonding.

A very similar hormone, with similar functions, is also present in other mammals besides humans.

²See, for example, https://gobeyondlifestyle.com/happiness-vs-pleasure-root-addiction/



Figure 8.7: An artist's impression of the structure of oxytocin

8.7 Mother love and rage

We can recognize many of our own emotions in other mammals. Among these are mother love and rage. Interestingly these two emotions are associated respectively with oxytocin and testosterone.

One of the most beautiful emotions is the love that women exhibit towards their children. We must all be grateful that women are willing to undergo the danger and pain of childbirth. We must be grateful for the devotion that they show to their children and families.

Both humans and most other animals compete for dominance and mating rights. In humans, mating displays and struggles for dominance lead to what the economist Thorstein Veblen called "conspicuous consumption". Overconsumption in industrialized nations is one of the factors driving the world towards an ecological catastrophe.



Figure 8.8: Mother love: One of the most beautiful emotions.



Figure 8.9: Mother love.



Figure 8.10: Mother love



Figure 8.11: Mother love:

8.7. MOTHER LOVE AND RAGE



Figure 8.12: Mother love



Figure 8.13: Mother love

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Figure 8.14: Mother love



Figure 8.15: Mother love: Although we recognize the emotions of mammals most clearly as being similar to our own, animals less closely related to ourselves also exhibit emotions that we can recognize. For example, birds are devoted to their young and make great sacrifices to help and protect them.

8.7. MOTHER LOVE AND RAGE



Figure 8.16: Male animals fighting for dominance and mating rights



Figure 8.17: Testosterone is a hormone present in large quantities in males and much smaller amounts in females. It is involved in rank-determining fights and mating.



Figure 8.18: Male lions fighting for dominance and mating rights.



Figure 8.19: In Shakespeare's poetic tragedy, *Romeo and Juliet*, we see many human emotions on display: males fighting for dominance and mating rights (testosterone), romantic attachment (oxytocin), and tribalism (Montagues versus Capulets). The dangers of tribalism in an age of genocidal and potentially omnicidal thermonuclear weapons will be discussed in another chapter.

8.8 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.

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The mechanism by which electrical impulses propagate along nerve ax- ons 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 electrical 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 excitatory 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,



Figure 8.20: A schematic diagram of a neuron.

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 they respond to a line in a particular direction, even when it is displaced parallel to itself³.

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.

³ 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.

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THE CHEMISTRY OF EMOTIONS

Chapter 9

THE EVOLUTION OF COOPERATION

9.1 Introduction

The success of humans as a species is due to our genius for cooperation. Cultural evolution, a new form of evolution, in which information is passed between generations in the form of linguistic symbols rather than genetically, has been the key to human success. Cultural evolution depends on the sharing of knowledge, and humans have developed remarkable linguistic and cooperative abilities.

At the same time, human nature also has a darker side, inherited from our ancestors who were hunter-gatherers, living in small genetically homogeneous tribes, competing for territory, on the grasslands of Africa. The pattern of intra-tribal altruism and inter-tribal aggression, which humans have inherited from their remote ancestors, has been explained by the theories of population genetics and group selection put forward in the 1930's by R.A. Fischer and J.B.S Haldane, and discussed more recently by W.D. Hamilton and E.O. Wilson. In this picture, the tribe itself, rather than the individual, is the unit on which evolutionary forces acted.

This essay will try to show that symbiosis and cooperation have been responsible for all of the great upward steps in evolution, including the development of the first prokareotic cells, the first eukareotes, the first multi-cellular organisms, and the first cooperative groups of multicellular organisms. The views of T.H. Huxley, who stressed competition as an evolutionary force, will be contrasted with the ideas of Charles Darwin, Peter Kropotkin and Lynn Margulis and others, who fully understood the importance of symbiosis and cooperation in evolution.

9.2 The explosion of human knowledge

Cultural evolution depends on the non-genetic storage, transmission, diffusion and utilization of information. The development of human speech, the invention of writing, the development of paper and printing, and finally in modern times, mass media, computers and the Internet - all these have been crucial steps in society's explosive accumulation of information and knowledge. Human cultural evolution proceeds at a constantly-accelerating speed, so great in fact that it threatens to shake society to pieces.

Every species changes gradually through genetic evolution; but with humans, cultural evolution has rushed ahead with such a speed that it has completely outstripped the slow rate of genetic change. Genetically we are quite similar to 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 constantlyaccelerating rate of cultural change, our bodies and emotions (as Malthus put it, the "passions of mankind") are not completely adapted to our new way of life. They still reflect the way of life of our hunter-gatherer ancestors.

Within rapidly-moving cultural evolution, we can observe that technical change now moves with such astonishing rapidity that neither social institutions, nor political structures, nor education, nor public opinion can keep pace. The lightning-like pace of technical progress has made many of our ideas and institutions obsolete. For example, the absolutely-sovereign nation-state and the institution of war have both become dangerous anachronisms in an era of instantaneous communication, global interdependence and alldestroying weapons.

In many respects, human cultural evolution can be regarded as an enormous success. However, at the start of the 21st century, most thoughtful observers agree that civilization is entering a period of crisis. As all curves move exponentially upward - population, production, consumption, rates of scientific discovery, and so on - one can observe signs of increasing environmental stress, while the continued existence and spread of nuclear weapons threatens civilization with destruction. Thus while the explosive growth of knowledge has brought many benefits, the problem of achieving a stable, peaceful and sustainable world remains serious, challenging and unsolved.

9.3 Tribal emotions and nationalism

In discussing conflicts, we must be very careful to distinguish between two distinct types of aggression exhibited by both humans and animals. The first is intra-group aggression, which is often seen in rank-determining struggles, for example when two wolves fight for pack leadership, or when males fight for the privilege of mating with females. Another, completely different, type of aggression is seen when a group is threatened by outsiders. Most animals, including humans, then exhibit a communal defense response - self-sacrificing and heroic combat against whatever is perceived to be an external threat. It is this second type of aggression that makes war possible.

Arthur Koestler has described inter-group aggression in an essay entitled The Urge to

Self-Destruction¹, where he writes: "Even a cursory glance at history should convince one that individual crimes, committed for selfish motives, play a quite insignificant role in the human tragedy compared with the numbers massacred in unselfish love of one's tribe, nation, dynasty, church or ideology... Wars are not fought for personal gain, but out of loyalty and devotion to king, country or cause..."

"We have seen on the screen the radiant love of the Führer on the faces of the Hitler Youth... They are transfixed with love, like monks in ecstasy on religious paintings. The sound of the nation's anthem, the sight of its proud flag, makes you feel part of a wonderfully loving community. The fanatic is prepared to lay down his life for the object of his worship, as the lover is prepared to die for his idol. He is, alas, also prepared to kill anybody who represents a supposed threat to the idol."

Members of tribe-like groups are bound together by strong bonds of altruism and loyalty. Echos of these bonds can be seen in present-day family groups, in team sports, in the fellowship of religious congregations, and in the bonds that link soldiers to their army comrades and to their nation.

Warfare involves not only a high degree of aggression, but also an extremely high degree of altruism. Soldiers kill, but they also sacrifice their own lives. Thus patriotism and duty are as essential to war as the willingness to kill.

Tribalism involves passionate attachment to one's own group, self-sacrifice for the sake of the group, willingness both to die and to kill if necessary to defend the group from its enemies, and belief that in case of a conflict, one's own group is always in the right. Unfortunately these emotions make war possible; and today a Third World War might lead to the destruction of civilization.

9.4 The mystery of self-sacrifice in war

At first sight, the willingness of humans to die defending their social groups seems hard to explain from the standpoint of Darwinian natural selection. After the heroic death of such a human, he or she will be unable to produce more children, or to care for those already born. Therefore one might at first suppose that natural selection would work strongly to eliminate the trait of self-sacrifice from human nature. However, the theory of population genetics and group selection can explain both the willingness of humans to sacrifice themselves for their own group, and also the terrible aggression that they sometimes exhibit towards competing groups. It can explain both intra-group altruism and inter-group aggression.

¹in The Place of Value in a World of Facts, A. Tiselius and S. Nielsson editors, Wiley, New York, (1970)

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Figure 9.1: A photo of the statistician R.A. Fischer, who proposed the idea of group selection in the 1930's, together with J.B.S. Haldane. Group selection explains the profile of tribal altruism and inter-tribal aggression that we observe in humans. Public domain, Wikimedia Commons

9.5 Fisher, Haldane and Hamilton

The idea of group selection in evolution was proposed in the 1930's by J.B.S. Haldane and R.A. Fischer, and more recently it has been discussed by W.D. Hamilton.

If we examine altruism and aggression in humans, we notice that members of our species exhibit great altruism towards their own children. Kindness towards close relatives is also characteristic of human behavior, and the closer the biological relationship is between two humans, the greater is the altruism they tend to show towards each other. This profile of altruism is easy to explain on the basis of Darwinian natural selection since two closely related individuals share many genes and, if they cooperate, the genes will be more effectively propagated.

To explain from an evolutionary point of view the communal defense mechanism - the willingness of humans to kill and be killed in defense of their communities - we have only to

imagine that our ancestors lived in small tribes and that marriage was likely to take place within a tribe rather than across tribal boundaries. Under these circumstances, each tribe would tend to consist of genetically similar individuals. The tribe itself, rather than the individual, would be the unit on which the evolutionary forces of natural selection would act.

According to the group selection model, a tribe whose members showed altruism towards each other would be more likely to survive than a tribe whose members cooperated less effectively. Since several tribes might be in competition for the same territory, successful aggression against a neighboring group could increase the chances for survival of one's own tribe. Thus, on the basis of the group selection model, one would expect humans to be kind and cooperative towards members of their own group, but at the same time to sometimes exhibit aggression towards members of other groups, especially in conflicts over territory. One would also expect intergroup conflicts to be most severe in cases where the boundaries between groups are sharpest - where marriage is forbidden across the boundaries.

9.6 Language, religion and tribal markings

In biology, a species is defined to be a group of mutually fertile organisms. Thus all humans form a single species, since mixed marriages between all known races will produce children, and subsequent generations in mixed marriages are also fertile. However, although there is never a biological barrier to marriages across ethnic and racial boundaries, there are often very severe cultural barriers.

Irenäus Eibl-Eibesfeldt, a student of Konrad Lorenz, introduced the word *pseudospeciation* to denote cases where cultural barriers between two groups of humans are so strongly marked that marriages across the boundary are difficult and infrequent. In such cases, he pointed out, the two groups function as though they were separate species, although from a biological standpoint this is nonsense. When two such groups are competing for the same land, the same water, the same resources, and the same jobs, the conflicts between them can become very bitter indeed. Each group regards the other as being "not truly human".

In his book *The Biology of War and Peace*, Eibl-Eibesfeldt discusses the "tribal markings" used by groups of humans to underline their own identity and to clearly mark the boundary between themselves and other groups. One of the illustrations in his book shows the marks left by ritual scarification on the faces of the members of certain African tribes. These scars would be hard to counterfeit, and they help to establish and strengthen tribal identity. Seeing a photograph of the marks left by ritual scarification on the faces of African tribesmen, it is impossible not to be reminded of the dueling scars that Prussian army officers once used to distinguish their caste from outsiders.

Surveying the human scene, one can find endless examples of signs that mark the bearer as a member of a particular group - signs that can be thought of as "tribal markings": tattoos; piercing; bones through the nose or ears; elongated necks or ears; filed teeth; Chinese binding of feet; circumcision, both male and female; unique hair styles; decorations of the tongue, nose, or naval; peculiarities of dress, kilts, tartans, school ties, veils, chadors, and headdresses; caste markings in India; use or nonuse of perfumes; codes of honor and value systems; traditions of hospitality and manners; peculiarities of diet (certain foods forbidden, others preferred); giving traditional names to children; knowledge of dances and songs; knowledge of recipes; knowledge of common stories, literature, myths, poetry or common history; festivals, ceremonies, and rituals; burial customs, treatment of the dead and ancestor worship; methods of building and decorating homes; games and sports peculiar to a culture; relationship to animals, knowledge of horses and ability to ride; nonrational systems of belief. Even a baseball hat worn backwards or the professed ability to enjoy atonal music can mark a person as a member of a special "tribe".

By far the most important mark of ethnic identity is language, and within a particular language, dialect and accent. If the only purpose of language were communication, it would be logical for the people of a small country like Denmark to stop speaking Danish and go over to a more universally-understood international language such as English. However, language has another function in addition to communication: It is also a mark of identity. It establishes the boundary of the group.

Next after language, the most important "tribal marking" is religion. It seems probable that in the early history of our hunter-gatherer ancestors, religion evolved as a mechanism for perpetuating tribal traditions and culture. Like language, and like the innate facial expressions studied by Darwin, religion is a universal characteristic of all human societies. All known races and cultures practice some sort of religion. Thus a tendency to be religious seems to be built into human nature.

9.7 Formation of group identity

Although humans originally lived in small, genetically homogeneous tribes, the social and political groups of the modern world are much larger, and are often multiracial and multiethnic.

There are a number of large countries that are remarkable for their diversity, for example Brazil, Argentina and the United States. Nevertheless it has been possible to establish social cohesion and group identity within each of these enormous nations. India and China too, are mosaics of diverse peoples, but nevertheless, they function as coherent societies. Thus we see that group identity is a social construction, in which artificial "tribal markings" define the boundaries of the group.

As an example of the use of tribal markings to establish social cohesion over a large group of genetically dissimilar humans, one can think of the role of baseball and football in the United States. Affection for these sports and knowledge of their intricacies is able to establish social bonds that transcend racial and religious barriers.

One gains hope for the future by observing how it has been possible to produce both internal peace and social cohesion over very large areas of the globe - areas that contain extremely diverse populations. The difference between making large, ethnically diverse countries function as coherent sociopolitical units and making the entire world function as a unit is not very great.

Since group identity is a social construction, it is not an impossible goal to think of enlarging the already-large groups of the modern world to include all of humanity.

9.8 The social insects

The social insects, ants, bees, wasps and termites, exhibit nearly perfect altruism towards members of their own group. This extreme form of altruism towards near relations (kin altruism) is closely connected with the peculiar method of reproduction of the social insects. The workers are sterile or nearly sterile, while the queen is the only reproductive female. The result of this special method of reproduction is that very nearly perfect altruism is possible within a hive or nest, since genetic changes favoring antisocial behavior would be detrimental to the hive or nest as a whole. The hive or nest can, in some sense, be regarded as a superorganism, with the individuals cooperating totally in much the same way that cells cooperate within a multicellular organism. The social insects exhibit aggression towards members of their own species from other hives or nests, and can be said to engage in wars. Interestingly a similar method of reproduction, associated with extreme intragroup altruism has evolved among mammals, but is represented by only two species: the naked mole rat and Damaraland mole rat.

9.9 From Thomas Huxley to Lynn Margulis and symbiosis

Charles Darwin (1809-1882) was acutely aware of close and mutually beneficial relationships between organisms. For example, in his work on the fertilization of flowers, he studied the ways in which insects and plants can become exquisitely adapted to each other's needs.

On the other hand Thomas Henry Huxley (1825-1895), although he was a strong supporter of Darwin, saw competition as the main mechanism of evolution. In his essay *Struggle for Existence and its Bearing Upon Man* Huxley wrote: "From the point of view of the moralist, the animal world is about on the same level as a gladiators' show. The creatures are fairly well treated and set to fight; hereby 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 granted."

Prince Peter Kropotkin (1842-1921) argued strongly against Huxley's point of view in his book *Mutual Aid; A Factor of Evolution*. "If we ask Nature", Kropotkin wrote, "who are the fittest: those who are continually at war with each other, or those who support one another?', we at once see that those animals that acquire habits of mutual aid are undoubtedly the fittest. They have more chances to survive, and they attain, in their respective classes, the highest development of intelligence and bodily organization."

Today, the insights of modern biology show that although competition plays an important role, most of the great upward steps in evolution have involved cooperation. The biologist Lynn Margulis (1938-2011) has been one of the pioneers of the modern viewpoint which recognizes symbiosis as a central mechanism in evolution.



Figure 9.2: The biologist Lynn Margulis (1938-2011), who contributed importantly to our modern understanding of symbiosis as a central mechanism of evolution. Source: LynnMargulis.jpg, [CC BY-SA 2.5], Wikimedia Commons

9.10 One-celled organisms seen as examples of cooperation

The first bacterial cells (prokaryotic cells) can be thought of as cooperative communities in which autocatalytic molecules thrived better together than they had previously done separately.

The next great upward step in evolution, the development of large and complex (eukaryotic) cells, also involved cooperation: Many of their components, for example mitochondria (small granular structures that are needed for respiration) and chloroplasts (the photosynthetic units of higher plants) are believed to have begun their existence as freeliving prokaryotic cells. They now have become components of complex cells, cooperating biochemically with the other subcellular structures. Both mitochondria and chloroplasts possess their own DNA, which shows that they were once free-living bacteria-like organisms, but they have survived better in a cooperative relationship.

9.11 Cooperation between cells; multicellular organisms

Multicellular organisms evolved from cooperative communities of eukaryotic cells. Some insights into how this happened can be gained from examples which are just on the borderline between the multicellular organisms and single-celled ones. 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 are similar to amoebae.

Under ordinary circumstances, the individual cells wander about independently searching for food, which they draw into their interiors and digest. 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.) 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.

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. Multicellular organisms often live in a symbiotic relationship with other species. For example, in both animals and humans, bacteria are essential for the digestion of food. Fungi on the roots of plants aid their absorption of water and nutrients. Communities of bacteria and other organisms living in the soil are essential for the recycling of nutrients. Insects are essential to many plants for pollination.

9.12 Cooperation in groups of animals and human groups

The social behavior of groups of animals, flocks of birds and communities of social insects involves cooperation as well as rudimentary forms of language. Various forms of language, including chemical signals, postures and vocal signals, are important tools for orchestrating cooperative behavior.

The highly developed language of humans made possible an entirely new form of evolution. In cultural evolution (as opposed to genetic evolution), information is passed between generations not in the form of a genetic code, but in the form of linguistic symbols. With the invention of writing, and later the invention of printing, the speed of human cultural evolution greatly increased. Cooperation is central to this new form of evolution. Cultural advances can be shared by all humans.

9.13 Trading in primitive societies

Although primitive societies engaged in frequent wars, they also cooperated through trade. Peter Watson, an English historian of ideas, believes that long-distance trade took place as early as 150,000 before the present. There is evidence that extensive trade in obsidian and flint took place during the stone age. Evidence for wide ranging prehistoric obsidian and flint trading networks has been found in North America. Ancient burial sites in Southeast Asia show that there too, prehistoric trading took place across very large distances. Analysis of jade jewelry from the Phillipines, Thailand, Maylasia and Viet Nam shows that the jade originated in Taiwan.



Figure 9.3: The invention of writing was prompted by the necessities of trade. Public domain, Wikimedia Commons

The invention of writing was prompted by the necessities of trade. In prehistoric Mesopotamia, clay tokens marked with simple symbols were used for accounting as early as 8,000 BC. Often these tokens were kept in clay jars, and symbols on the outside of the jars indicated the contents. About 3,500 BC, the use of such tokens and markings led to the development of pictographic writing in Mesopotamia, and this was soon followed by the cuneiform script, still using soft clay as a medium. The clay tablets were later dried and baked to ensure permanency. The invention of writing led to a great acceleration of human cultural evolution. Since ideas could now be exchanged and preserved with great ease through writing, new advances in technique could be shared by an ever larger cooperating community of humans. Our species became more and more successful as its genius for cooperation developed.

9.14 Gracilization and decreasing sexual dimorphism

Early ancestors of modern humans had a relatively heavy (robust) bone structure in relation to their height. This robust bone structure seems to have been favored by frequent combat. During their evolution, modern humans became less robust and more gracile. In other words, their skeletons became lighter in relation to their height. Simultaneously the height and weight of males became less different from the height and weight of females. These trends are generally interpreted as indicating that combat became less important as present-day humans evolved.

9.15 Ethics and growth of the social unit

Early religions tended to be centered on particular tribes, and the ethics associated with them were usually tribal in nature. However, the more cosmopolitan societies that began to form after the Neolithic agricultural revolution required a more universal code of ethics. It is interesting to notice that many of the great ethical teachers of human history, for example Moses, Socrates, Plato, Aristotle, Lao Tzu, Confucius, Buddha, and Jesus, lived at the time when the change to larger social units was taking place. Tribalism was no longer appropriate. A wider ethic was needed.

Today the size of the social unit is again being enlarged, this time enlarged to include the entire world. Narrow loyalties have become inappropriate and there is an urgent need for a new ethic - a global ethic. Loyalty to one's nation needs to be supplemented by a higher loyalty to humanity as a whole.

9.16 Interdependence in modern human society

All of the great upward steps in the evolution of life on earth have involved cooperation: Prokaryotes, the first living cells, can be thought of as cooperative communities of

9.17. TWO SIDES OF HUMAN NATURE

autocatylists; large, complex eukaryote cells are now believed to have evolved as cooperative communities of prokaryotes; multicellular organisms are cooperative communities of eukaryotes; multicellular organisms cooperate to form societies; and different species cooperate to form ecosystems. Indeed, James Lovelock has pointed out that the earth as a whole is a complex interacting system that can be regarded as a huge organism.

The enormous success of humans as a species is due to their genius for cooperation. The success of humans is a success of cultural evolution, a new form of evolution in which information is passed between generations, not in the form of DNA sequences but in the form of speech, writing, printing and finally electronic signals. Cultural evolution is built on cooperation, and has reached great heights of success as the cooperating community has become larger and larger, ultimately including the entire world.

Without large-scale cooperation, modern science would never have evolved. It developed as a consequence of the invention of printing, which allowed painfully gained detailed knowledge to be widely shared. Science derives its great power from concentration. Attention and resources are brought to bear on a limited problem until all aspects of it are understood. It would make no sense to proceed in this way if knowledge were not permanent, and if the results of scientific research were not widely shared. But today the printed word and the electronic word spread the results of research freely to the entire world. The whole human community is the repository of shared knowledge.

The achievements of modern society are achievements of cooperation. We can fly, but no one builds an airplane alone. We can cure diseases, but only through the cooperative efforts of researchers, doctors and medicinal firms. We can photograph and understand distant galaxies, but the ability to do so is built on the efforts of many cooperating individuals.

An isolated sponge cell can survive, but an isolated human could hardly do so. Like an isolated bee, a human would quickly die without the support of the community. The comfort and well-being that we experience depends on far-away friendly hands and minds, since trade is global, and the exchange of ideas is also global.

Finally, we should be conscious of our cooperative relationships with other species. We could not live without the bacteria that help us to digest our food. We could not live without the complex communities of organisms in the soil that convert dead plant matter into fertile topsoil. We could not live without plants at the base of the food chain, but plants require pollination, and pollination frequently requires insects. An intricate cooperative network of inter-species relationships is necessary for human life, and indeed necessary for all life. Competition plays a role in evolution, but the role of cooperation is greater.

9.17 Two sides of human nature

Looking at human nature, both from the standpoint of evolution and from that of everyday experience, we see the two faces of Janus; one face shines radiantly; the other is dark and menacing. Two souls occupy the human breast, one warm and friendly, the other murderous. Humans have developed a genius for cooperation, the basis for culture and civilization; but they are also capable of genocide; they were capable of massacres during the Crusades, capable of genocidal wars against the Amerinds, capable of the Holocaust, of Hiroshima, of the killing-fields of Cambodia, of Rwanda, and of Darfur

As an example of the two sides of human nature, we can think of Scandinavia. The Vikings were once feared throughout Europe. The Book of Common Prayer in England contains the phrase "Protect us from the fury of the Northmen!". Today the same people are so peaceful and law-abiding that they can be taken as an example for how we would like a future world to look. Human nature has the possibility for both kinds of behavior depending on the circumstances. This being so, there are strong reasons to enlist the help of education and religion to make the bright side of human nature win over the dark side. Today, the mass media are an important component of education, and thus the mass media have a great responsibility for encouraging the cooperative and constructive side of human nature rather than the dark and destructive side.

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Chapter 10 PATHFINDING

10.1 The 2014 Nobel Prize in Physiology or Medicine

Some excerpts from Edvard L. Moser's Nobel lecture

All three 2014 Nobel Prize winners in Physiology or Medicine stand on the shoulders of E.C. Tolman. Based on experiments on rats running in various types of mazes, Tolman suggested from the 1930s to the 1950s that animals form internal maps of the external environment. He referred to such maps as cognitive maps and considered them as mental knowledge structures in which information was stored according to its position in the environment (Tolman, 1948). In this sense, Tolman was not only one of the first cognitive psychologists but he also directly set the stage for studies of how space is represented in the brain. Tolman himself avoided any reference to neural structures and neural activity in his theories, which was understandable at a time when neither concepts nor methods had been developed for investigations at the brain-behaviour



Figure 10.1: The three winners of the 2014 Nobel Prize in Physiology or Medicine



Figure 10.2: Edward Chace Tolman (1886-1959). He founded a branch of psychology known as *perposive behaviourism*.

interface. However, at the end of his life he expressed strong hopes for a neuroscience of behaviour. In 1958, after the death of Lashley, he wrote the following in a letter to Donald O. Hebb when Hebb asked him about his view of physiological explanations of behaviour in the early days of behaviourism: "I certainly was an anti-physiologist at that time and am glad to be considered as one then. Today, however, I believe that this ('physiologising') is where the great new break-throughs are coming."

The psychology-physiology boundary was broken from the other side by two pioneers of physiology, David Hubel and Torsten Wiesel, who in the late 1950s bravely started to record activity from single neurons in the cortex, the origin of most of our intellectual activity. Inserting electrodes into the primary visual cortex of awake animals, they discovered how activity of individual neurons could be related to specific elements of the visual image. This work set the stage for decades of investigation of the neural basis for vision and helped the emergence of a new field of cortical computation. Their insights at the low levels of the visual cortex provided a window into how the cortex might work. As a result of Hubel and Wiesel's work, parts of the coding mechanism for vision are now understood, almost 60 years after they started their investigations...

The potential for understanding a higher brain function brought May-Britt and me to John O'Keefe's lab in 1996. During a period of three months, John generously taught us everything about place cells and how they were studied and we then went back to Norway, to Trondheim, to set up our own new lab. One of our hopes was to find out how the place signal was generated.

In this overview, I will first review the events that led up to the discovery of grid cells and the organisation of a grid cell-based map of space in the medial



Figure 10.3: Tolmen's experiments with animals learning to run through a maze form the foundation on which the work of John O'Keefe, May-Britt Moser and Edvard Moser was built.



Figure 10.4: David H. Hubel and Torsten N. Wiesel broke the physiologypsychology boundary from the physiology side. By identifying the elementary neural components of the visual image at low levels of the visual cortex, they showed that psychological concepts, such as sensation and perception, could be understood through elementary interactions between cells with specific functions.



Figure 10.5: A photo of John O'Keefe, who discovered place cells in the hippocampus. Place cells are cells that fire specifically when an animal is at a certain location in its local environment.

entorhinal cortex. Then, in the second part, I will present recent work on the interactions between grid cells and the geometry of the external environment, the topography of the grid-cell map, and the mechanisms underlying the hexagonal symmetry of the grid cells.

To determine if place fields were formed in the intrahippocampal circuit, we worked together with neuroanatomist Menno Witter, then at the Free University of Amsterdam...

In 2005, with our students Torkel Hafting, Marianne Fyhn and Sturla Molden, we were able to describe the structure of the firing pattern. Using larger environments than in the past, we could clearly see that the firing pattern was periodic. The multiple firing fields of the cell formed a hexagonal grid that tiled the entire surface space available to the animal, much like the holes in a bee hive or a Chinese checkerboard. Many entorhinal cells fired like this, and we named them grid cells. We were excited about the grid-like firing pattern, both because nothing like it exists in the sensory inputs to the animal, suggesting that the pattern is generated intrinsically in the entorhinal cortex or neighbouring structures, and because such a regular pattern provides a metric to the brain's spatial map, a metric that had been missing in the place map of the hippocampus.


Figure 10.6: Location of recording electrode and lesion in the experiment that led us to move out of the hippocampus, to the entorhinal cortex.



Figure 10.7: Firing pattern of grid cells. (a) Spatially periodic firing pattern of an entorhinal grid cell during 30 min of foraging in a 220 cm wide square enclosure. The trajectory of the rat is shown in grey, individual spike locations in black. (b) Firing pattern of a grid cell in a 1 m wide enclosure. Symbols as in (a) but with red lines superimposed to indicate the hexagonal structure of the grid. Modified from Stensola et al. (2012) and Hafting et al. (2005), respectively.



Figure 10.8: Topographical organisation of grid scale. The figure shows a sagittal brain section with medial entorhinal cortex indicated in red. Firing maps are shown for three grid cells recorded at successive dorso-ventral levels in medial entorhinal cortex. Note change from small scale to large scale along the dorso-ventral axis. Modified from Stensola et al. (2012).

10.2 Paths in cell differentiation

In animals, the fertilized egg cell divides a number of times to form the blastula. At this stage of development, the cells are unspecialized. However, as they continue to divide, the cells become increasingly specialized. First they are totipotent, then pluripotent, then multipotent, then oligopotent and finally unipotent. The increasingly specialized differentiation of cells is closely analogous to the increasingly specialized classification of destinations in package address systems, which will be discussed in the next section.

10.3 Paths in package address systems

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 0 and we asked 'Do you see the 0?' '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,¹ and it is about to overtake voice communication in the volume of information transferred.

In March, 2011, there were more than two billion Internet users in the world. In North America they amounted to 78.3 % of the total population, in Europe 58.3 % and worldwide, 30.2 %. Another index that can give us an impression of the rate of growth of digital data generation and exchange is the "digital universe", which is defined to be the total volume of digital information that human information technology creates and duplicates in a year. In 2011 the digital universe reached 1.2 zettabytes, and it is projected to quadruple by 2015. A zettabyte is 10^{21} bytes, an almost unimaginable number, equivalent to the information contained in a thousand trillion books, enough books to make a pile that would stretch twenty billion kilometers.

Postal addresses

A second example of package address systems can be found in postal addresses. Here the coarsest category is country. Within a particular country the city or town is the next part of the address. Next, the street is specified; then the street number, and finally (in some cases), the number labeling the room or flat within a building. This progression from course categorization to progressively finer specification of the address can be seen in all types of classification.

 $^{^{1}}$ In the period 1995-1996, the rate of increase was even faster - a doubling every four months

10.4 Paths in the organization of computer memories

Most of us use directories to organize the data on our computers. For example, on my own PC, the address of the file on which I am working at the moment is "home/work/books/languages". There is a directory called "home". Within "home" there are many sub-directories, one of which is called "work". Suppose that we click on "work". We find within this sub-directory many sub-sub-directories, one of which is called "books". If, among the many options, we click on "books", we find that it contains many sub-sub-directories, one of which is called "languages".

We can visualize the process of starting in the home directory and finally reaching the sub-sub-directory "languages" as a process of pathfinding. At each point where the paths branch, we make a choice, just as an animal does when finding its way through a forest or maze. At each choice, the destination reached becomes more specific; the classification of destinations becomes more refined.

One is reminded of the postal address system, within which the destination of a letter becomes more refined at each branch: First the country is specified, then the city or town, then the street, then the house number, and finally (in some cases) the apartment or room. Here too, the destination becomes progressively more refined as one progresses through a set of choices.

One may even be reminded of the existentialist philosophy of Jean-Paul Sartre and others, which has the motto "existence is prior to essence". As we progress through life, we make choices, and within each choice, we make sub-choices which define more and more specifically our final destination, i.e. our destiny or "essence".

10.5 Pattern abstraction

Pattern abstraction in the octopus brain

J.Z. Young lectures to the Wells Society at Imperial College

I vividly remember a lecture that Prof. J.Z. Young delivered to the Wells Society² of London's Imperial College of Science and Technology. It was during the early 1960's, and at that time I was writing my Ph.D. thesis in theoretical chemistry.

Professor Young told us of his research on the visual cortex of the octopus. Being a mollusc, the octopus is lucky to have eyes at all, but in fact its eyes are very similar to our own, a striking example of convergent evolution. Young's research combined microscopic examination of extremely thin slices of the octopus brain with experiments on the extent to which the octopus is able to learn, and to profit from past experience.

Each image on the retina of the octopus eye is directly mapped in a one to one manner onto the outer layer of the animal's visual cortex. But as the signal propagated inwards towards the center of the visual cortex, the arrangement of dendrites and axons insures

 $^{^2\}mathrm{H.G.}$ Wells had once been a student at Imperial College, London. and the Wells Society was named after him.

that synapses would only fire if activated by a specific pattern. The specificity of the pattern becomes progressively more refined as it propagates more deeply into the cortex.

Finally a "grandmother's face cell" is reached, a cell which can only be activated by a specific pattern. At this point in the visual cortex of the octopus, neural pathways to to parts of the brain controlling muscular actions are activated. The paths branched, with one leading towards an attack response and the other towards retreat. There is a bias towards the attack pathway, so that initially, any pattern observed by the eyes of the animal will produce an attack.

Professor Young told us that he could actually see the arrangements of dendrites and axons in his histological studies of the visual cortex of the octopus. These histological studies were supplemented by behavioral experiments, in which the octopus was either rewarded for the attack, or else punished with a mild electric shock. If rewarded, the animal would continue to attack when again presented with the same pattern. If punished, the animal would always retreat when presented with the same stimulus. Prof. Young explained this behaviour by postulating the existence of a feedback neural circuit which blocked the attack pathway if the animal was punished. When the signal subsequently passed the "grandmother's face cell", only the retreat pathway remained. The octopus had learned.



Figure 10.9: Prof. John Zachary Young, FRS, in 1978. He has been described as "one of the most influential biologists of the 20th century". His studies of pattern abstraction in the visual cortex of the octopus combined examination of histological microsections with experimental studies of octopus learning.



Figure 10.10: The octopus eye, like the human eye, has an image-forming lens and a retina. This similarity is a striking example of convergent evolution. The common ancestor of humans and molluscs had no eye at all.

10.6 Abstraction of concepts and natural laws

Can two contradictory statements both be true? The physicist Niels Bohr thought that this could happen, and he called such an occurrence "complementarity". I think that I understand what Niels Bohr meant: Whenever we make a statement about the real world we are making a model which is simpler than what it is supposed to represent. Therefore every statement must to some extent be false because it is an oversimplification. In fact, a model of the world is an abstraction, and it is possible to make two conflicting abstractions, starting with the same real object.

If you say, "The eye is like a camera", you are making an abstraction by concentrating on the way that the eye works and the way that a camera works. Both use a lens to form an image. If you say "The eye is like a small onion", you are again making an abstraction, but this time concentrating the size and texture of the eye. It is somewhat round, elastic and damp. If you drop it on a stone floor, it will bounce rather than breaking. Both these abstractions have a certain degree of truth, although they are contradictory.

Similarly, science and ethics are both abstractions, and both oversimplify the real world, which is much more complex than either of them. Which abstraction we should use depends on the problem that we wish to discuss. If we are talking about atomic spectra, then Schrödinger and Dirac should be our guides. But if the lecture is on how to achieve peace in the world, I would far rather hear it from Mahatma Gandhi than from either Schrödinger or Dirac.

In his autobiography, Charles Darwin says that "Science consists in arranging facts in such a way that general conclusions may be drawn from them". At the lowest level of abstraction, we have a very large number of individual observations. A number of these observations may be gathered together to form a low-level generalization. The low-level generalizations may in turn be coordinated into a somewhat more general law, and so on. Today one hears that physicists are aiming at a "theory of everything", which, if could ever be achieved, would coordinate all individual observations of every kind.

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CLASSIFICATION AND LANGUAGES

Chapter 11

BIOENERGETICS

11.1 Summer work at Szent-Györgyi's laboratory

During the summers of 1960 and 1961, while I was still a postgraduate student in theoretical physics at the University of Chicago, I had the privilege of spending two summers working in the laboratory of the great Hungarian-American physiologist and biochemist, Albert Szent-Györgyi. He was famous for isolating vitamin C and for discovering the molecular mechanism of muscle contraction. But more importantly, he founded a new field of study: Bioenergetics.

Szent-Györgyi wondered how the chemical energy from food is harnessed to do mechanical work or to drive our metabolisms. He reasoned that there must be structures in living organisms which are analogous to the structures of engines. If you pour gasoline onto the street and set fire to it, no useful work results, only heat But if you burn it inside an engine, the chemical energy of the gasoline can be converted into useful mechanical work.

Following this line of thought, Szent-Györgyi looked for energy-transducing structures in the tissues of living organisms. Among the structures that caught Szent-Györgyi's attention were mitochondria, which power the metabolism of all animals, and he also studied the microscopic photosynthetic unit (thylakoids) in plants. After some years of work, he became convinced that quantum theory was needed in order to gain a complete understanding of how these microscopic engines work. Therefore he spent a year at the Institute for Advanced Study in Princeton, where he learned quite a lot of quantum theory.

Although he knew enough quantum theory to understand what physicists were talking about, he nevertheless thought that for the research which he wanted to undertake, he needed to collaborate with people whose whole education was in that field, and he brought some theoretical physicists (including me) to his laboratory. During the time that I was there, we worked to obtain a quantum theoretical understanding of the mechanism of the primary process in photosynthesis, where the energy of a photon is stabilized and trapped, ready to drive the synthesis of sugars.

I had heard about Albert Szent-Györgyi before the opportunity to work in his labora-

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Figure 11.1: Albert Szent-Györgyi in Italy in 1917.



Figure 11.2: Albert Szent-Györgyi in 1937, when he won the Nobel Prize in Physiology or Medicine. The prize was awarded partly for his work on the biochemistry of respiration, and partly for his isolation of vitamin C.

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Figure 11.3: Szent-Györgyi working in his laboratory.

tory presented itself. My brother Gordon had worked at the Woods Hole Marine Biological Laboratory during a previous summer and had told me that he considered Szent-Györgyi to be a great genius. Also, a University of Chicago classmate, David Freifelder, had said to me "You absolutely must read Szent-Györgyi's book, 'Bioenergetics'!"

11.2 Muscle contraction

Here are some excerpts from an article by Jack A. Roll, entitled *Generation of life in a test tube: Albert Szent-Györgyi, Bruno Straub, and the discovery of actin.* The article was published on 20 April, 2918 in Advances in Physiology Education¹- Bruno Straub was Szent-Györgyi's student, with whom he collaborated on the work.

"Albert Szent-Györgyi, at 44 years of age, won the Nobel Prize in 1937 for his work on vitamin C and the establishment of the groundwork of the citric acid cycle. He now wanted to investigate one of the fundamental aspects of life and settled on the study of muscle contraction. The Szent-Györgyi laboratory in Hungary during World War II demonstrated that contraction could be reproduced in vitro by threads consisting of just two proteins, myosin and the newly discovered protein by Bruno Straub that they called actin. Szent-Györgyi called seeing the contraction of these threads, which occurred in the presence of ATP and ions, "the most thrilling moment" of his scientific life.

This major discovery of the generation of "life" in a test tube was totally unknown for years by the rest of the world because of the war. When the discovery was finally communicated to the world, it was not immediately accepted by all as being relevant to the physiology of muscle contraction.

11.3 Mitochondria

Mitochondria are believed to be descended from free-living bacteria. According to one theory for their evolution, they were engulfed and eaten by an ancient eukariotic cell, i.e. a large amoeba-like cell containing a nucleus and many organelles. The free-living bacteria thus eaten somehow escaped complete digestion and an endosymbiotic relationship was formed. This event may have occurred when the atmosphere of the earth changed from being reducing to oxidizing, because of the oxygen produced by plants. The benefit conferred by the symbiosis was the ability to perform oxidative phosphorolation, i.e. the synthesize ATP in an oxidizing atmosphere. Since that time, eukaryotes have contained mitochondria.

¹https://www.physiology.org/doi/full/10.1152/advan.00189.2017



Figure 11.4: The adinosine triphosphate (ATP) molecule acts as a universal fuel for both muscle contraction and metabolic processes within our bodies. Mitochondria use the stored chemical energy of sugars to synthesize ATP.



Figure 11.5: Mitochondria contain membrane-bound enzymes that use the chemical energy of sugars to produce the high-energy phosphate bonds of adinosine triphosphate (ATP).

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Figure 11.6: Mitochondria are thought to be descended from free-living organisms, as is shown in Figure 12.6, and they have their own DNA.

11.4 The photosynthetic unit

Like mitochondria, the chloroplasts that contain the photosynthetic unit of plants are thought to he the descendents of free-living cyanaobacteria, as is shown in Figure 12.6. Inside the chloroplasts are pocket-like structures called *thylakoids*. The membrane of thylakoids is like a sandwich. The middle part of this sandwich consists of pigment molecules, for example chloraphyl, which absorb the light, and produce an electron-hole pair. The outer layer of the thylakoid membrane sandwich consists of charge donor molecules, i.e. molecules whose highest filled molecular orbital is relatively high in energy, while the innermost layer consists of charge acceptor molecules, that is, molecules whose lowest empty orbital is quite low in energy. After a ohoton has been absorbed, the electron migrates to the charge.acceptors, while the hole migrates to the electron-donor molecules on the outside. Thus the electron and hole are rapidly separated, and the back-reaction is prevented. The mechanism is similar to the separation of the charge and hole in a silicon solar cell.

The Calvin cycle (the dark reaction)

After the primary process of photon absorption and charge-hole separation has taken place in the thylakoid, the available energy is stabilized in a dark reaction studies by Melvin Calvin (1911-1997) and his co.workers at the University of California, Berkeley. In the dark reaction, which is known as the *Calvin cycle*, the energy originally derived from absorption of a photon is further stabilized by being converted into the chemical energy of sugars. Calvin also contributed importantly to theories of the origin of life, and he is the author of a book entitles *Chemical Evolution Towards the Origin of Life On Earth and Elsewhere*. He was awarded the Nobel Prize for Chemistry in 1961.



Figure 11.7: The donor-pigment-acceptor triad needed for charge-hole separation.



Figure 11.8: Like mitochondria, chloroplasts were once free-living organisms, as is shown in Figure 12.6. Both chloroplasts and cyanobacteria have a double membrane, DNA, ribosomes, and thylakoids. Both the chloroplast and cyanobacterium depicted are idealized versions (the chloroplast is that of a higher plant) - a lot of diversity exists among chloroplasts and cyanobacteria.



Figure 11.9: Bacterial rhodopsin is interesting because it is a single molecule which is embedded in the membrane of the salt-loving bacterium *halobacterium halobium*, and which is capable of using the energy of sunlight to pump H^+ ions across the membrane against the electrochemical gradient. The molecule is almost identical to rhodopsin that occurs in our eyes. Perhaps, when our remote ancestors lived in the sea, they had a symbiotic relationship with halobacteria which led to the evolution of the vertebrate eye.

11.5 Some of Albert Szent-Györgyi's personal reflections

On my Mother's side, I am the fourth generation of scientists. My Father was interested only in farming and so my Mother's influence prevailed. Music filled the house and the conversation at the table roamed about the intellectual achievements of the entire world. Politics and finance had no place in our thoughts. I am a scientist, myself, because at an early age I learned that only intellectual values were worth striving for, artistic or scientific creation being the highest aim. I strongly believe that we establish the coordinates of our evaluation at a very early age. What we do later depends on this scale of values which mostly cannot be changed later.

I wanted to understand life but found the complexity of physiology overA whelming. So I shifted to pharmacology where, at least, one of the partners, the drug, was simple. This, I found, did not relieve the difficulty. So, I went into bacteriology, but found bacteria too complex, too. I shifted on, to physicochemistry and then to chemistry, that is, to molecules, the smallest units in those days. Ten years ago I found molecules too complex and shifted to electrons, hoping to have reached bottom. But Nature has no bottom: its most basic principle is "organization." If Nature puts two things together she produces something new with new qualities, which cannot be expr essed in terms of qualities of the components. When going from electrons and protons to atoms, from here to molecules, molecular aggregates, etc., up to the cell or the whole animal, at every level we find something new, a new breathtaking vista. Whenever we separate two things, we lose something, something which may have been the most essential feature. So now, at 68, I am to work my way up again following electrons in their motion through more extensive systems, hoping to arrive, someday, at an understanding of the cellular level of organization. So the internal course of my life made a smooth sinusoid curve; not so the external course.

Lost in the 20th Century

Here are a few quotations from Albert Szent-Györgyi's autobiographical book, *Lost in the* 20th Century:

Overlooking my case history, I find a complete dichotomy. On the one hand, my inner story is exceedingly simple, if not indeed dull: my life has been devoted to science and my only real ambition has been to contribute to it and live up to its standards. In complete contradiction to this, the external course has been rather bumpy. I finished school in feudal Hungary as the son of a wealthy landowner and I had no worries about my future. A few years later I find myself working in Hamburg, Germany, with a slight hunger edema. In 1942 I find myself in Istanbul, involved in secret diplomatic activA ity with a setting fit for a cheap and exciting spy story. Shortly after, I get a warning that Hitler had ordered the Governor of Hungary to appear before him, screaming my name at the top of his voice and demanding my delivery. Arrest warrants were passed out even against members of my family. In my pocket I find a Swedish passport, having been made a full Swedish citizen on the order of the King of Sweden-I am "Mr. Swenson," my wife, "M rs. Swenson." Sometime later I find myself in Moscow, treated in the most royal fashion by the Government (with caviar three times a day), but it does not take long before I am declared "a traitor of the people" and I play the role of the villain on the stages of Budapest. At the same time, I am refused entrance to the USA for my Soviet sympathies. Eventually, I find peace at Woods Hole, Massachusetts, working in a solitary corner of the Marine Biological Laboratory. After some nerve-racking complications, due to McCarthy, things straightened out, but the internal struggle is not comA pletely over . I am troubled by grave doubts about the usefulness of scientific endeavor and have a whole drawer filled with treatises on politics and their relation to science, written for myself with the sole purpose of clarifying my mind, and finding an answer to the question: will science lead to the elevation or destruction of man, and has my scientific endeavor any sense? All this, in itself, would have no interest. There are many who did more for science, were braver, suffered more agony and even paid the penalty of death. What may lend interest to my story is that it reflects the turbulence of our days.

A fearless advocate of peace and rationality

Albert Szent-Györgyi spoke and wrote fearlessly against the institution of war. Here is a quotation from his writing:

The story of man consists of two parts, divided by the appearance of modern science... In the first period, man lived in the world in which his species was born and to which his senses were adapted. In the second, man stepped into a new, cosmic world to which he was a complete stranger... The forces at man's disposal were no longer terrestrial forces, of human dimension, but were cosmic forces, the forces which shaped the universe. The few hundred Fahrenheit degrees of our flimsy terrestrial fires were exchanged for the ten million degrees of the atomic reactions which heat the sun.

This is but a beginning, with endless possibilities in both directions; a building of a human life of undreamt of wealth and dignity, or a sudden end in utmost misery. Man lives in a new cosmic world for which he was not made. His survival depends on how well and how fast he can adapt himself to it, rebuilding all his ideas, all his social and political institutions. ...Modern science has abolished time and distance as factors separating nations. On our shrunken globe today, there is room for one group only: the family of man.

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Chapter 12

WATER AND BIOLOGICAL SPECIFICITY

12.1 Hydrogen bonds in water

In the water molecule, there is a small positive excess charge, $+\delta$, on each of the hydrogens, and a small negative excess charge, -2δ , on the oxygen. Hydrogen bonds in water and ice are formed by Coulomb attractions between these positive and negative charges. In the figure shown below, the hydrogen bonds are represented by dotted lines. The insolubility of nonpolar molecules is due to the fact that they break up the hydrogen bonds in water, and it thus costs energy to incorporate them into water.

Polar molecules, on the other hand, can fit into the hydrogen bonding system of water by forming their own hydrogen bonds with water molecules, and thus they are water-soluble.

Soaps and detergents have a polar end, attached to a long nonpolar tail. They allow groups of nonpolar molecules to become water-soluble by forming a layer with the polar ends pointing outward to the water, while the long non-polar ends point inwards.



Figure 12.1: In the water molecule, there is a small positive excess charge, $+\delta$, on each of the hydrogens, and a small negative excess charge, -2δ , on the oxygen. Hydrogen bonds in water and ice are formed by Coulomb attractions between these positive and negative charges. In this figure, the hydrogen bonds are represented by dotted lines. The insolubility of nonpolar molecules is due to the fact that they break up the hydrogen bonds in water, and it thus costs energy to incorporate them into water.
12.2 Water and the folding of proteins

When I worked at the Imperial College of Science and Technology in London, during the 1960's, I was a member of the Royal Institution of Great Britain, where Michael Faraday was once the director, and where Faraday gave lectures on science that were attended by Queen Victoria's husband, Prince Albert and his sons.

The tradition of polished and entertaining lectures initiated by Faraday is continued today. I vividly remember attending a lecture on the structure of the protein, lysozyme.

Lysozyme was the first antibacterial agent discovered by Alexander Fleming. He was disappointed to find that the pathogenic bacteria against which it is effective are not associated with very serious diseases. In fact, these diseases are not serious because the human body produces the enzyme lysozyme. We have it, for example, in our nasal mucus.

But back to the Royal Institution lecture on the structure of lysozyme, which had been determined by the use of X-ray crystallography. As in Faraday's day, the lecture was given with much style. The lecturer was the person responsible for solving the structure, David Chilton Phillips (1925-1999), who was later made a Life Peer, Baron Phillips of Ellesmere.

Hanging from the ceiling of the lecture room was a long chain model of the amino acid sequence of the lysozyme macro-molecule, before folding. D.C. Phillips explained all the difficulties of obtaining good crystals and performing the X-ray diffraction experiments. Then he said "Finally, after much work, and a little prayer, we obtained a structure", and he gazed upward, as if to heaven. Then dramatically, a model of the folded protein was lowered downward towards us from its previously unseen position at the top of the room.

Phillips flipped a switch, and we saw on the linear model, the positions of the hydrophilic amino acids and the hydrophobic ones, indicated respectively by green and red lights, Then flipping another switch, he showed us their positions on the folded molecule. The hydrophilic amino acids were all on the outside, while the hydrophobic ones were on the inside. The surrounding water had determined the way in which the protein had folded (its tertiary structure) as well as its enzymatic activity. We could see clearly the active site of lysozyme, its "mouth", where it bit into the cell walls of bacteria.

The case of lysozyme is surely not an isolated one. It seems logical to generalize from this case, and to think that the tertiary structure and enzymatic activity of all watersoluble proteins is determined by the interaction of hydrophilic and hydrophobic amino acids with the surrounding water.

12.3 The second law of thermodynamics

The second law of thermodynamics was discovered by Nicolas Leonard 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 operating between the temperatures T_1 and T_2 could at most attain

maximum efficiency =
$$\frac{T_1 - T_2}{T_1}$$
 (12.1)

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

$$dS = \frac{dq}{dT} \tag{12.2}$$

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

$$dS = \frac{dq}{T_1} - \frac{dq}{T_2} > 0$$
 (12.3)

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.

12.4 Statistical mechanics

Besides his monumental contributions to electromagnetic theory, the English physicist James Clerk Maxwell (1831-1879) 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.

As a young student, Boltzmann read Maxwell's paper on the velocity distributions of molecules in a gas, and he spent the remainder of his life developing these Maxwell's initiative into the science of statistical mechanics. Boltzmann was able to derive the following equation hold for the particles in a perfect (non-interacting) gas:

$$\frac{n_i}{N} = \frac{e^{-\epsilon_i/kT}}{\sum_i e^{-\epsilon_i/kT}}$$
(12.4)

Here n_i represents the number of particles in a state with energy ϵ_l , while N is the total number of particles. T is the absolute temperature, and k, which is called *Boltzmann's* constant, has a dimension such that the dimension of kT is energy.

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.

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_i , 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.



Figure 12.2: The English physicist James Clerk Maxwell (1931-1879). Together with Ludwig Boltzmann, he was one of the founders of statistical mechanics. Maxwell took the first step in a paper on the velocity distributions of molecules in a gas.

12.4. STATISTICAL MECHANICS



Figure 12.3: The Austrian physicist Ludwig Boltzmann (1844-1906), the cofounder of statistical mechanics. As a young student, Boltzmann read Maxwell's paper on velocity distributions, and he spent the remainder of his life developing these ideas into the science of statistical mechanics.

12.5 Gibbs free energy

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

$$H = U + PV \tag{12.5}$$

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

$$G = U + PV - TS \tag{12.6}$$

or

$$G = H - TS \tag{12.7}$$

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



Figure 12.4: Josiah Willard Gibbs (1839-1903). He found a way to apply thermodynamics to chemistry.

of the universe produced by the chemical reaction can be split into two components:

$$\Delta S_{universe} = \Delta S_{system} + \Delta S_{bath} \tag{12.8}$$

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

$$\Delta S_{bath} = -\frac{\Delta H_{system}}{T} \tag{12.9}$$

Combining (13.8) and (13-9) with the condition requiring the entropy of the universe to increase, Gibbs obtained the relationship

$$\Delta S_{universe} = \Delta S_{system} - \frac{\Delta H_{system}}{T} > 0 \tag{12.10}$$

The same relationship also holds for exothermic reactions, where heat is transferred in the opposite direction. Combining equations (13.38) and (13.35) yields

$$\Delta G_{system} = -T\Delta S_{universe} < 0 \tag{12.11}$$

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.

Measured values of the "Gibbs free energy of formation", ΔG_f° , 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

$$\Delta G_f^{\circ}(H_2 O) = -228.59 \ \frac{\text{kJ}}{\text{mol}}$$
(12.12)

This means that when the reaction

$$H_2(g) + \frac{1}{2}O_2(g) \to H_2O(g)$$
 (12.13)

takes place under standard conditions, there is a change in Gibbs free energy of $\Delta G^{\circ} = -228.59 \text{ kJ/mol}^{-1}$. 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° is negative for the reaction shown in this equation, the reaction is spontaneous. In general, the change in Gibbs free energy in a chemical reaction is given by

$$\Delta G^{\circ} = \sum_{products} \Delta G_f^{\circ} - \sum_{reactants} \Delta G_f^{\circ}$$
(12.14)

where ΔG_f° denotes the Gibbs free energy of formation.

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¹ The superscript $^{\circ}$ means "under standard conditions", while kJ is an abbreviation for joule $\times 10^3$.



Figure 12.5: According to the second law of thermodynamics, the entropy of the universe constantly increases. Increase of entropy corresponds to increase of disorder, and also to in- crease of statistical probability. Living organisms on the earth are able to achieve a high degree of order and highly improbable structures because the earth is not a closed system. It constantly receives free energy (i.e. energy capable of doing work) from the sun, and this free energy can be thought of as carrying thermodynamic information, or "negative entropy".

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

$$C_6 H_{12} O_6(s) + 6 O_2(g) \to 6 C O_2(g) + 6 H_2 O(g) \qquad \Delta G^\circ = -2870 \ \frac{\text{kJ}}{\text{mol}}$$
(12.15)

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.

12.6 Svante Arrhenius

Svante Augustus Arrhenius was born in Wik Castle, Sweden in 1859, the son of Svante Gustav and Carolina Thunberg Arrhenius. He was a child prodigy, who without encouragement from his parents, taught himself to read at the age of 3. As a very young child, he also became an arithmetical prodigy by watching his father add numbers in his account books.

Arrhenius started research at the University of Uppsala, but he was dissatisfied with the instruction in physics and chemistry. In 1881 he moved to the Swedish Academy of Sciences in Stockholm. There he produced a Ph.D. dissertation which focused on conductivity of electrolytes. The dissertation was so contrary to the chemical ideas of the time that it was accepted only grudgingly by the committee judging it, and Ahrrenius was only granted a 4th class degree. Nevertheless, the 56 propositions put forward in the dissertation are universally accepted today, almost entirely without modification, and they won Ahrrenius the 1903 Nobel Prize in Chemistry.

Michael Faraday (1791-1867) had previously shown that charged particles, which he named "ions", could carry an electrical current through a solution. Ahrrenius developed Faraday's concept of ions by demonstrating that when salts are dissolved in water, ions are present even without an electrical current. He also defined acids to be substances which produce solutions in which H^+ ions predominate, while in bases, when dissolved, produce solutions in which OH^- ions predominate.

In chemical reaction theory, Ahrrenius introduced the idea of an activation energy, E_a , which can be thought of as the height of an energy barrier which must be surmounted in order for the reaction to take place. Thus most chemical reactions become more probable when the temperature T is raised, since the rapid motion of the reactants at higher temperatures can supply the energy needed to overcome the reaction barrier E_a . Ahrrenius connected the concept of activation energy with the statistical mechanics of Ludwig



Figure 12.6: Svante Arrhenius (1859-1927) was one of the main founders of physical chemistry and a pioneer of climate science. He was related to climate activist Greta Thunberg, and Greta's father is named after him.

Boltzmann (1844-1906) by means of his famous equation:

$$K = A e^{-E_a/RT}$$

In the Ahrrenius equation, K is the reaction rate, A is a constant proportional to the frequency of reactant collisions with the proper orientation, T is the absolute temperature, and R is the constant that appears in the equation of state of a perfect gas, PV = nRT.

12.7 The role of water in biological specificity

Below is a paper based on a lecture that I gave at a conference in Sorrento, Italy. The lecture discusses the role of water in biological specificity. In 1984 a paper based on the lecture was published in the International Journal of Quantum Chemistry. The paper has also been translated into Czech, and published in the Journal of the Czech Academy of Sciences.

To understand the role of water in biological specificity, let us imagine two opposite electrical charges in an aqueous environment. If the water were not there, the attraction between the two opposite charges would fall off as the square of the distance between them. However, there are water molecules between the two opposite charges, and to find the effective forces, we must consider the Gibbs free energy, G = U + PV - TS, of the total system, including the water. When two opposite electrical charges are in an aqueous

environment, the water molecules separating them become aligned so that their electric dipole moments point in the direction of the electric field. This alignment lowers the entropy of the system and raises its Gibbs free energy. Thus an effective force is produced in a direction that will lower the Gibbs free energy by reducing the volume of polarized water. This force acts strongly over a much larger distance than a simply Coulomb force. Thus the two opposite charges, which might be excess charges on the active site of an enzyme and its substrate, or an antigen and an antibody, are drawn together by the thermodynamic force that seeks to minimize the number of polarized water molecules separating them.

This thermodynamic effective force explains how the important biological processes such as auto-assembly of structures. or enzymatic activity can function so efficiently. It is because the thermodynamic forces function strongly over a much longer range than Coulomb forces, and they draw the complementary charges on the enzyme and substrate molecules, or antigen-antibody molecules, together with efficiency over much longer distances than Coulomb attraction alone could achieve. INTERNATIONAL JOURNAL OF QUANTUM CHEMISTRY, VOL. XXVI, 843-855 (1984)

A Model for Biological Specificity*

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Abstract

The phenomenon of biological specificity is described, and a history of discoveries related to the phenomenon is presented. Aspects of biological specificity described include the mechanism of the immune system, chemotherapy, enzyme-substrate specificity, neurotransmitters, autoassembly of viruses, autoassembly of subcellular organelles, differentiation, and cellular recognition. A model for biological specificity involving both steric and electrostatic complementarity is presented and the role of structured water and hydrophobic forces is also discussed.

During the coming week, the lectures at this meeting will deal with biological topics. Most of us here are quantum chemists or physicists—That is certainly what I am myself. If we wish to apply our methods to biological problems, we are faced with a dilemma: The difficulty is that both quantum chemistry and biology are subjects which require a whole lifetime to learn thoroughly, so that it is impossible for any single person to have a deep knowledge of both fields. So what are we to do? Almost the only possibility available to us is to collaborate with a biologist or a biochemist. In such a partnership, each person has to learn enough of the other's field so that they can talk together. I hope that this lecture will serve as a contribution to the effort which we as quantum chemists must make to learn some biology. We need to make this effort in order to have biologists as friends and collaborators, and in order to appreciate the remarkable things which are happening in their field.

In this lecture, I would like to review the history of discoveries and ideas related to biological specificity. I hope in this way to convince you that the phenomenon of specificity is extremely widespread and fundamental in the operation of biological systems. I hope to show that it is involved not only in the mechanism of the immune system, but also in the mechanism of chemotherapy, in enzyme-substrate specificity, in the mechanism of neurotransmitters, in the autoassembly of viruses, in the autoassembly of subcellular organelles, in differentiation and cellular recognition, in the senses of taste and smell, and in hormone-receptor specificity. Finally, I would like to present a model of biological specificity—a model which involves both steric and electrostatic complementarity; and I will try to discuss briefly the role of structured water and hydrophobic forces.

Let us begin by looking at the history of immunology and chemotherapy. The first important discovery in this field was made by Edward Jenner in the 18th

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century. It had been known for a long time that a person who had once been infected by smallpox and who had recovered was afterwards immune to the disease. In ancient China, a powder was made from dry crusts taken from cases of smallpox, and this powder was sniffed up the nose. The result was usually a mild case of smallpox, and the innoculated person was afterwards immune. The practice of innoculation against smallpox was brought to England in 1717 by Lady Mary Montagu, the wife of the Bristish Ambassador to Turkey. This method was like Russian roulette, because it sometimes produced a fatal case of the disease. However, in 1796, Edward Jenner demonstrated that it was possible to produce immunity to smallpox by innoculation with cowpox, a much milder disease.

The discovery of a safe method of vaccination against smallpox was greeted with enormous enthusiasm everywhere in Europe. The British Parliament voted Jenner a reward of £30,000, his birthday was celebrated as a holiday in Germany, and in Russia, the first child to be vaccinated was named Vaccinov and was educated at the expense of the state.

Jenner's discovery greatly influenced Louis Pasteur. He studied Jenner's papers with extreme care and he speculated continually about how a method of safe vaccination could be found for other diseases besides smallpox. Pasteur finally was able to develop vaccines for several diseases, including anthrax and rabies, and he established general methods for preparing vaccines. We would now explain Pasteur's methods by saying that when bacteria are grown under certain abnormal conditions, a few mutant bacteria are favored by the conditions of growth. The mutants multiply, and the normal bacteria disappear. The mutant bacteria are unable to cause a serious case of the disease, but they nevertheless have antigens on their surfaces which are able to provoke a response of the immune system.

The first real understanding of the mechanism of the immune system was due to the work of Paul Ehrlich and Ilya Mechnikov, and in 1908 they shared a Nobel Prize for this work. Paul Ehrlich can be said to be the discoverer of biological specificity. As a young medical student at the University of Strasbourg, he was fortunate to work under the distinguished chemist Heinrich von Waldeyer, who took a great interest in Ehrlich. Stimulated by Waldeyer, Ehrlich began to do experiments in which he prepared thin slices of various tissues for microscopic examination by staining them with the newly discovered aniline dyes. During the last half of the 19th century, there was a great deal of interest in histological staining. It was during this period that Walther Flemming in Germany discovered chromosomes by staining them with special dyes, and Christian Gram in Denmark showed that bacteria can be classified into two types by staining methods. (We now call these two types "gram positive" and "gram negative"). During this same period, and while he was still a student, Paul Ehrlich made the important discovery that mammalian blood contains three different types of white cells which can be distinguished by staining.

Ehrlich's early work on staining made him famous, and it also gave him a set of theories which led him to his great discoveries in immunology and chemotherapy. According to Ehrlich's ideas, the color of the aniline dyes is due to the aniline ring. However, dyes used commercially must also adhere to fabrics, and this adherence, according to Ehrlich, is due to the specific structure of the side chains. If the pattern of atoms on a side chain is complementary to the pattern of atoms on the binding site, the dye will adhere, but otherwise not. Thus there is a "lock and key" mechanism, and for this reason dyes with specific side chains stain specific types of tissue.

In one of his experiments, Paul Ehrlich injected methylene blue into the ear of a living rabbit, and found that it stained only the nerve endings of the rabbit. Since the rabbit seemed to be unharmed by the treatment, the experiment suggested to Ehrlich that it might be possible to find antibacterial substances which could be safely injected into the bloodstream of a patient suffering from an infectious disease. Ehrlich hoped to find substances which would adhere selectively to the bacteria, while leaving the tissues of the patient untouched.

With the help of a large laboratory especially constructed for him in Frankfurt, the center of the German dye industry, Ehrlich began to screen thousands of modified dyes and other compounds. In this way he discovered trypan red, a chemical treatment for sleeping sickness, and arsphenamine, a drug which would cure syphilis. Ehrlich thus became the father of modern chemotherapy. His success pointed the way to Gerhard Domagk, who discovered the sulphonamide drugs in the 1930s, and to Fleming, Waksman, Dubos and others, who discovered the antibiotics.

Ehrlich believed that in the operation of the immune system, the body produces molecules which have a pattern of atoms complementary to patterns (antigens) on invading bacteria, and that these molecules (antibodies) in the blood stream kill the bacteria by adhering to them. Meanwhile, the Russian naturalist Ilya Mechnikov discovered another mechanism by which the immune system operates. While on vacation in Sicily, Mechnikov was studying the digestive process in starfish larvae. In order to do this, he introduced some particles of carmine into the larvae. The starfish larvae were completely transparent, and thus Mechnikov could look through his microscope and see what happened to the particles. He saw that they were enveloped and apparently digested by wandering amoebalike cells inside the starfish larvae. As he watched this process, it suddenly occurred to Mechnikov that our white cells might similarly envelop and digest bacteria, thus protecting us from infection. Describing this discovery, Mechnikov wrote in his diary: "I suddenly became a pathologist! Feeling that there was in this idea something of surpassing interest, I became so excited that I began striding up and down the room, and even went to the seashore to collect my thoughts."

Mechnikov later named the white cells "phagocytes" (which means "eating cells"). He was able to show experimentally that phagocytosis (i.e., the envelopment and digestion of bacteria by phagocytes) is an important mechanism in immunity. For a number of years, there were bitter arguments between those who thought that the immune system operates through phagocytosis, and those who thought that it operates through antibodies. Finally it was found that both mechanisms play a role. In phagocytosis, the bacterium will not be ingested by the phagocyte unless it is first studded with antibodies. Thus both Mechnikov and Ehrlich were proved to be right.

Early in the 20th century, important work in immunology was done by Karl Landsteiner, who won the 1930 Nobel Prize in medicine and physiology for his discovery of the human blood groups. His book, entitled The Specificity of Serological Reactions, is listed in the references [1]. In 1936, Landsteiner asked Linus Pauling (who was then visiting the Rockefeller Institute for Medical Research), to try to develop a theory which would account for antibody-antigen specificity in the operation of the immune system [2]. The result was a theory by Pauling, in which some features were correct, but others badly wrong. Pauling decided that "... The specific combining region of an antibody molecule is complementary in structure to a portion of the surface of the antigen, with the antigen-antibody bond resulting from the cooperation of weak forces (electronic van der Waals forces, electrostatic interaction of charged groups, and hydrogen bonding) between the complementary structures, over an area sufficiently large that the total binding energy can resist the disrupting influence of thermal agitation." This much of Pauling's 1940 theory is today considered to be correct. However, Pauling also made the hypothesis-and this is where he went wrongthat in the immune system, the antigen serves as a template for the construction of the antibody (in much the same way that a DNA strand serves as a template for the construction of the complementary strand). Once the lymphocytes have "learned" how to produce antibodies fitting a particular antigen, Pauling believed, they continue to produce them, and thus we become immune [3].

Pauling's reason for believing in a template theory of antibody formation was the enormous range of specificities which can be matched. The mammalian immune system can produce antibodies of roughly 10^7 different specificities. It seemed impossible to Pauling that so many different specificities could be genetically coded. However, subsequent research [4–6] has shown that the capability for producing this immense variety of antibodies is, in fact, genetically programmed. Each lymphocyte produces its own specific antibody molecule, and when a lymphocyte divides, the daughter cells continue to produce exactly the same antibody. Animals of a particular species, when challenged with a particular antigen, may be unable to produce an antibody against it, while animals of a slightly different genetic strain, when challenged with the same antigen, can readily produce the appropriate antibody.

Thus, Pauling's template theory of immunity had to be abandoned. It was replaced by the clonal theory of Niels Kai Jerne and Sir Frank MacFarlane Burnet. According to the clonal theory of immunity, which is the currently accepted theory, a few lymphocytes corresponding to each of the 10[°] different specificities are present in a nonimmune individual. When the individual becomes ill with an infection, antigens on the surfaces of the invading microorganisms bind to antibody molecules on the surfaces of just those lymphocytes which have the right specificity. This stimulates the selected lymphocytes to divide rapidly, and after a period of time, a population of lymphocytes capable of producing the correct antibody builds up. When this happens, the infected individual

recovers. Even after recovery, a substantial population of that strain of lymphocyte remains, and if the individual is again invaded by the same type of microorganism, this population of lymphocytes can immediately produce the appropriate antibody. an individual with this capability is immune.

The clonal theory of immunity has an interesting consequence: Because of the fact that when a lymphocyte divides, the daughter cells produce exactly the same antibody as the parent, it follows that if one could culture lymphocytes, one could produce pure antibodies *in vitro*. However, if one tries to culture these cells in a direct way, they die after a few generations. In 1975, Georges Köhler and Cesar Milstein succeeded in culturing lymphocytes by fusing them with myeloma cancer cells. The resulting hybrid cell lines were immortal, and cultures from single cells could be grown indefinitely, producing pure "monoclonal" antibodies [6-15].

The monoclonal antibody technique of Köhler and Milstein allows one to separate mixtures of unknown composition into their components. This is done in the following way: A mouse is immunized with the mixture, and spleen cells from the mouse are fused with myeloma cells. The hybrid cells are spread out into several hundred small culture dishes, one cell to each dish. After a clone has grown from the single cell in each dish, the supernatants are reacted one at a time with the mixture. Each component of the mixture makes an insoluble product with a different supernatant, and thus the mixture is separated into its components.

The monoclonal antibody technique is an extremely powerful tool, which can be used in the purification of proteins, the characterization of viruses, the treatment of cancer, in genetic studies, and in many other applications.

Until now, we have been considering only immunology and chemotherapy as examples of biological specificity. However, specificity is a much more general and fundamental phenomenon in biology. For example, one can see the phenomenon in operation in the autoassembly of viruses and subcellular organelles. Fraenkel-Conrat [16] has shown that by changing the pH, it is possible to take a virus to pieces. When the original pH is restored, the pieces spontaneously reassemble themselves into a virus capable of producing an infection. A similar spontaneous assembly must also occur whenever a virus reproduces itself. After the constituent parts have been manufactured by the ribosomes of the host cell, they must come together spontaneously. This process is analogous to crystallization, but more complicated, since the virus contains molecules of several different kinds. How can the pieces "know" enough to fit themselves together? The answer must be that regions on each constituent molecule of a virus are complementary to regions on the neighboring molecule of the finished structure, so that they bind selectively to the right place, and perhaps are even attracted to the right place. The same kind of spontaneous assembly, analogous to crystallization, must occur in the autoassembly of subcellular organelles, such as chloroplasts and mitochondria.

Specificity is also important in the operation of the central nervous system. A number of different substances are released at synapses (for example, acetylcholine, noradrenalin, serotonin, and dopamine). These neurotransmitter substances can stimulate or inhibit the firing of the next neuron, each substance being specific to a particular type of receptor on the neighboring neuron [17–20].

Cell surface antigens are involved in differentiation during the development of an embryo. For example, the H-Y antigen (a pattern of atoms which is present on the plasma membrane of all male mammalian cells) is known to be a differentiation antigen. The H-Y antigen [21–30] has been shown to be present on the cell surfaces of male mammalian embryos at the eight-cell stage, and it has been shown to be involved in the development of the embryo into a male, long before testosterone is present in the embryo. If the H-Y antigen is absent, the embryo develops into a female. Interestingly, the H-Y antigen seems to play a similar role in birds, reptiles, and amphibians; but in birds, it occurs on the cells of the female, and in amphibians, sometimes on the cells of one sex, and sometimes the other. This irregularity is only superficial, however, since the H-Y antigen is invariably linked to the development of the heterogametic sex. In the case of mammals, the male is heterogametic; in the case of birds, the female is heterogametic; and in the case of amphibians, the heterogametic sex is variable, depending on the species.

Other areas of biology where specificity plays an important role include the senses of taste and smell [31, 32], enzyme-substrate interactions [33-35] and hormone-receptor interactions.

I would like to end this lecture by proposing a model for biological specificity. The model consists of three assertions: (1) The complementarity involved in biological specificity is, in general, both steric and electrostatic. (2) There is a matching of nonpolar regions. (3) The total system, including water molecules, tends to move in such a way that its Gibbs free energy, G = E + PV - TS, decreases.

The last point in the model has been called the "thermodynamic hypothesis" by Anfinsen [36], and he has shown that it holds in the folding of proteins. ("Hypothesis" is almost too modest a name for the rule that the Gibbs free energy of a system tends to decrease, since this rule is one of the main guiding principles of theoretical chemistry.) One can even define a "thermodynamic force," as has been done by Buckingham and McLachlan [37-40]. If the Gibbs free energy G is a function of N coordinates, x_1, x_2, \ldots, x_N (which might represent nuclear coordinates), then the thermodynamic force corresponding to one of the coordinates is given by $\partial G/\partial x_i$. The direction of this force gives the direction in which the system tends to move, according to the thermodynamic hypothesis. However, one should remember that this is not the same kind of force which enters Newton's equations.

The first point in the model does not mention dispersion forces. This is not because dispersion forces are always negligibly small, but because it is hard to visualize complementarity with respect to dispersion forces. In cases where dispersion forces are important, it is steric complementarity which allows the two specific combining regions to come close enough to each other so that the dispersion forces are effective. Hydrogen bonds also go unmentioned in the first point of the model, but this is because they are included under the heading of electrostatic complementarity. As Professor Tomasi has emphasized in his lecture, when two molecules approach each other but are not yet in contact, the classical electrostatic interaction between them is often the dominant term in the interaction energy [41]. Alberte and Bernard Pullman have also emphasized the importance of electrostatic interactions [42-45]. Thus, when we visualize the interaction between, for example, an enzyme and its substrate as they approach each other, we should visualize the interaction as being initially primarily electrostatic. Only after the approach has become very close ($\sim 1-2$ Å), will other types of forces become important.

We must now ask what role the solvent water molecules will play. The large variety of ways in which a water molecule can form hydrogen bonds with its neighbors contributes to the entropy of water. When this freedom to form hydrogen bonds in many ways is restricted, the entropy is decreased. If we introduce a nonpolar molecule into water, the water molecules around it become more highly ordered and "icelike," the variety of ways in which they form hydrogen bonds is limited, and thus the entropy is decreased. This is the reason for the well-known insolubility of nonpolar molecules in water [49, 50]. The entropy term in the Gibbs free energy,

$$G = E + PV - TS, \tag{1}$$

favors configurations in which the contact of water with nonpolar molecules or groups is minimized. This hydrophobic effect has the consequence that in biological specificity, nonpolar regions of combining sites tend to come together in order to escape contact with water (point 2 of the model).

The entropy of water is also reduced when the water molecules are aligned by an electric field. Water has a high dielectric constant, which is due to the dipole moment formed by the positively charged hydrogens and the negatively charged oxygen lone pairs [46-62]. When two charges interact with each other in an aqueous medium, the intervening water molecules align themselves with their dipole moments pointing in such a way that the interaction energy of the two charges is reduced. Thus, at first sight, it would seem that the effect of the polarized water between two charges would be to very much reduce their attraction for each other. We should remember, however, that the Gibbs free energy of the system also contains an entropy term, and this term has the opposite effect. When water molecules are aligned in the electric field, their entropy is lowered. If the system tends in its motion towards a state with the lowest possible Gibbs free energy, it will prefer a state where the number of oriented water molecules is reduced. Thus the entropy term in the Gibbs free energy tends to make the "thermodynamic force" between two charges stronger, canceling at least part of the effect of the dielectric constant.

One can easily calculate the entropy of a system of N dipoles in an external field if one makes the simplifying assumption that the dipoles have only two quantum states, one parallel to the applied field, and the other antiparallel, differing by the energy $\Delta E = \mu F$. (F is the effective electric field acting on the dipole, i.e., it is due partly to the external field and partly to the fields of the

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other dipoles in the system.) then using the relation

$$S = \frac{E}{T} + k \ln Q \tag{2}$$

(where k is Boltzmann's constant, T is the temperature, E is the energy of the system, and Q is its partition function) we obtain

$$S = Nk \left(\frac{xe^{-x}}{1 + e^{-x}} + \ln(1 + e^{-x}) \right),$$

$$x = \frac{\Delta E}{kT}$$
(3)

The behavior of this entropy as a function of x is as shown in Figure 1.



Figure 1. The entropy of a system of electric dipoles as a function of the electric field strength, under the simplifying assumption that the dipoles have only two possible quantum states, one parallel and the other antiparallel to the field.

The simple example discussed above cannot give us more than an extremely rough and qualitative picture of how the entropy of water behaves as a function of electric field strength. Some further insight can be obtained by considering the entropy change which takes place when ice Ic is placed in a strong electric field. Ice Ic (cubic ice) is a form of ice in which the oxygen atoms are arranged in a structure isomorphous with the arrangement of carbon in diamond [48].

850

Each oxygen atom in ice Ic is tetrahedrally hydrogen bonded to four other oxygen atoms. The distance between neighboring oxygen atoms is 2.76 Å.

In 1935, Linus Pauling [63, 64] published a paper on the low-temperature entropy of ice in which he argued that the water molecule is essentially intact in ice. In the gas phase, the H—O bond length in water is 0.95 Å. Pauling argued that "the magnitudes of changes in properties from steam to ice are not sufficiently great to permit us to assume that this distance is increased to 1.38 Å." Therefore, Pauling argued, in ice, a hydrogen atom between two oxygens is not placed midway between them, but is nearer to one than to the other. Pauling's hypothesis that the water molecule in ice is essentially intact was later confirmed by neutron diffraction experiments.

In his 1935 paper, Pauling showed that if the water molecules in ice are assumed to be essentially intact, the hydrogen-bonding system of the crystal can be formed in $(\frac{3}{2})^N$ different ways, where N is the number of water molecules in the crystal. He showed that this large variety of possible conformations of the crystal, none of which differs appreciably in energy from the others, gives rise to a residual low-temperature entropy of

$$\Delta S = Nk \ln{(\frac{3}{2})} = 0.805 Nk, \tag{4a}$$

where k is Boltzmann's constant. This calculated residual low-temperature entropy is close to the measured value of 0.87Nk, an agreement which gives strong support to Pauling's theory.

Now let us consider what happens when ice is placed in an electric field which is strong enough to produce total orientation of the dipoles, but which nevertheless leaves the water molecules essentially intact. Can the water molecules reorient themselves in such a way that all the molecules have large components of their dipole moments pointing in the direction of the field, while still maintaining the hydrogen bonding system? From Figure 2, we can see that this is possible, but that there is only one possible configuration in which the dipoles are correctly oriented. In other words, in an electric field which is strong enough to produce total orientation of the water molecules, the residual low temperature entropy drops to zero, and the entropy change produced by applying the field is given by Eq. (4a). for smaller field strengths, the entropy would be difficult to calculate, but presumably it would fall off as a function of field strength in the manner of the entropy of the system of dipoles shown in Figure 1.

The two simple systems discussed above can give us a certain amount of qualitative insight into the behavior of the entropy of water as a function of applied electric field. However, it would be very desirable to have experimental determinations of the entropy and energy of water in strong electric fields. This information would be needed if one were to attempt to calculate the thermodynamic force between two charged particles in an aqueous medium.

If electrostatic forces are important in biological specificity, one might ask how far such forces extend. It might be possible to answer this question experimentally, starting with a knowledge of the diffusion constants of the molecules



Figure 2. The hydrogen bonding system in ice *Ic.* When a strong electric field is applied, the molecules can orient themselves in such a way that each molecule has a large component of its dipole moment pointing in the direction of the field, while still maintaining the hydrogen bonding system. However, there is only one conformation in which this is possible (that shown in the figure); and thus, application of a strong electric field reduces the low-temperature residual entropy to zero.

involved in (for example) antigen-antibody reactions or enzyme-substrate reactions. It might then be possible to calculate the time which would be needed for binding under the assumption that the components had to reach the correct position and orientation by entirely random Brownian motion. The rate of binding could afterwards be calculated under the assumption that electrostatic forces reach out a certain distance into the solution, so that if the components diffuse to within a certain distance of one another, and to within a certain difference from the correct orientation, they will be trapped. In other words, the binding rate would be calculated under the assumption that if the reactants diffused to within a certain critical distance and critical error of orientation from the correct position, they would have very little probability of escaping, and would almost inevitably be drawn in and correctly oriented by electrostatic forces. These two binding rates could be compared with observed rates, and from this comparison, the degree to which electrostatic forces reach out into the solution and draw the components into place could be estimated.

Experiments and calculations might also be aimed at examination of the binding sites responsible for specificity, to determine whether or not electrostatic complementarity is involved. The crystallographic structures of a number of enzymes are known. For example, the structure of lysozyme has been determined by D. C. Phillips and co-workers [65]. As Professor Ricard has pointed out [35], the binding site of an enzyme is more closely complementary to an inhibitor than it is to the equilibrium conformation of its substrate. As the substrate of an

enzyme-mediated reaction approaches the binding site, forces exerted by the site distort the substrate in the direction of the transition state, thus reducing the activation energy for the reaction. Notice that this picture implies the existence of forces which extend some distance out from the site. In cases where two reactants are joined together by an enzyme, such forces may help to guide the reactants together in the proper orientation, a mechanism which Koshland has called "orbital steering" [34].

From x-ray crystallographic data, it is possible to construct the electrostatic potential [66, 67]. To do this, one represents the charge density $\rho(x)$ by a Fourier series of the form:

$$\rho(\mathbf{x}) = \sum_{\mathbf{K}} (\rho)_{\mathbf{K}} e^{i\mathbf{K}\cdot\mathbf{x}}, \qquad (4)$$

where the vectors **K** are reciprocal lattice vectors. Essentially, the Fourier coefficients $(\rho)_{\mathbf{K}}$ are what is measured in an x-ray diffraction experiment. Since the charge density and the electrostatic potential $\phi(\mathbf{x})$ are related through Poisson's equation:

$$\nabla^2 \phi = -4\pi\rho. \tag{5}$$

It follows that if $\phi(\mathbf{x})$ is represented by the Fourier series

$$\phi(\mathbf{x}) = \sum_{\mathbf{K}} (\phi)_{\mathbf{K}} e^{i\mathbf{K}\cdot\mathbf{x}}, \tag{6}$$

the Fourier coefficients are related by

$$(\phi)_{\mathbf{K}} = \frac{4\pi}{K^2} (\rho)_{\mathbf{K}}.$$
(7)

Thus crystallographic measurements of Fourier coefficients of the charge density can be used to construct electrostatic fields. This method could be used to examine the active sites of enzymes to determine the electrostatic potentials near to the sites. Alternatively, it might be possible to calculate the charge distributions and potentials quantum mechanically, using methods such as those described by Professor McWeeny in his lecture [68–74].

I hope that future work in this direction will throw some light onto the phenomenon of biological specificity, one of the most widespread and fundamental phenomena in biology. In the meantime, I would tentatively put forward the view that in biological specificity, the molecules involved do not have to cover the entire distance to their binding sites by random diffusion. Perhaps during the last steps of the journey, they are guided into place by relatively long-range thermodynamic forces involving the entropy and energy of the intervening water molecules.

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LIVES IN BIOLOGY

Chapter 13

SOME MODERN DEVELOPMENTS

13.1 Gene splicing

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.

Further investigation revealed that *H. influenzae* produced an enzyme, later named *Hin* dII, which cut a DNA strand only when it recognized a specific sequence of bases: The DNA was cut only if one strand contained the sequence GTPyPuAC, where Py stands for C or T, while Pu stands for A or G. The other strand, of course, contained the complementary sequence, CAPuPyTG. The enzyme *Hin* dII cut both strands in the middle of the six-base sequence.

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 four-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 were 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 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 was one of the oldest techniques of civilization. However, the degree and speed of intervention which recombinant DNA made possible was entirely new. In the 1970's it became possible to mix the genetic repetoires of different species: The genes of mice and men could be spliced together into new, man-made forms of life!

The Asilomar Conference

In the summer of 1971, Janet Mertz, who was then a student in Paul Berg's laboratory, gave a talk at Cold Spring Harbor. She discussed some proposed experiments applying recombinant techniques to the DNA of the tumor-inducing virus SV40.

This talk worried the cell biologist, Richard Pollack. He was working with SV40 and was already concerned about possible safety hazards in connection with the virus. Pollack telephoned to Berg, and asked whether it might not be dangerous to clone a gene capable of producing human cancer. As a result of this call, Berg decided not to clone genes from tumor-inducing viruses.

Additional concern over the safety of recombinant DNA experiments was expressed at the 1973 Gordon Conference on Nucleic Acids. The scientists attending the conference voted to send a letter to the President of the U.S. National Academy of Sciences:

"...We presently have the technical ability", the letter stated, "to join together, covalently, DNA molecules from diverse sources... This technique could be used, for example, to combine DNA from animal viruses with bacterial DNA... In this way, new kinds of hybrid plasmids or viruses, with biological activity of unpredictable nature, may eventually be created. These experiments offer exciting and interesting potential, both for advancing knowledge of fundamental biological processes, and for alleviation of human health problems."

"Certain such hybrid molecules may prove hazardous to laboratory workers and to the public. Although no hazard has yet been established, prudence suggests that the potential hazard be seriously considered."

"A majority of those attending the Conference voted to communicate their concern in this matter to you, and to the President of the Institute of Medicine... The conferees suggested that the Academies establish a study committee to consider this problem, and to recommend specific actions and guidelines."

As a result of this letter, the National Academy of Sciences set up a Committee on Recombinant DNA, chaired by Paul Berg. The Committee's report, published in July, 1974, contained the following passage:

"...There is serious concern that some of these artificial recombinant DNA molecules could prove biologically hazardous. One potential hazard in current experiments derives from the need to use a bacterium like $E.\ coli$ to clone the recombinant DNA molecules and to amplify their number. Strains of $E.\ coli$ commonly reside in the human intestinal tract, and they are capable of exchanging genetic information with other types of bacteria, some of which are pathogenic to man. Thus, new DNA elements introduced into $E.\ coli$ might possibly become widely disseminated among human, bacterial, plant, or animal populations, with unpredictable effects."

The Committee on Recombinant DNA recommended that scientists throughout the world should join in a voluntary postponement of two types of experiments: Type 1, introduction of antibiotic resistance factors into bacteria not presently carrying the R-factors; and Type 2, cloning of cancer-producing plasmids or viruses.

The Committee recommended caution in experiments linking DNA from animal cells to bacterial DNA, since animal-derived DNA can carry cancer-inducing base sequences. Finally, the Committee recommended that the National Institutes of Health establish a permanent advisory group to supervise experiments with recombinant DNA, and that an international meeting be held to discuss the biohazards of the new techniques.

In February, 1975, more than 100 leading molecular biologists from many parts of the world met at the Asilomar Conference Center near Monterey, California, to discuss safety guidelines for recombinant DNA research. There was an almost unanimous consensus at the meeting that, until more was known about the dangers, experiments involving cloning of DNA should make use of organisms and vectors incapable of living outside a laboratory

13.1. GENE SPLICING

environment.

The Asilomar Conference also recommended that a number of experiments be deferred. These included cloning of recombinant DNA derived from highly pathogenic organisms, or containing toxin genes, as well as large-scale experiments using recombinant DNA able to make products potentially harmful to man, animals or plants.

The Asilomar recommendations were communicated to a special committee appointed by the U.S. National Institutes of Health; and the committee drew up a set of guidelines for recombinant DNA research. The NIH Guidelines went into effect in 1976; and they remained in force until 1979. They were stricter than the Asilomar recommendations regarding cloning of DNA from cancer-producing viruses; and this was effectively forbidden by the NIH until 1979. (Of course, the NIH Guidelines were effective only for research conducted within the United States and funded by the U.S. government.)

In 1976, the first commercial genetic engineering company (Genentech) was founded. In 1980, the initial public offering of Genentech stock set a Wall Street record for the fastest increase of price per share. In 1981, another genetic engineering company (Cetus) set a Wall Street record for the largest amount of money raised in an initial public offering (125 million U.S. dollars). During the same years, Japan's Ministry of International Trade and Technology declared 1981 to be "The Year of Biotechnology"; and England, France and Germany all targeted biotechnology as an area for special development.

A number of genetic-engineering products reached the market in the early 1980's. These included rennin, animal growth hormones, foot and mouth vaccines, hog diarrhea vaccine, amino acids, antibiotics, anabolic steroids, pesticides, pesticide-resistant plants, cloned livestock, improved yeasts, cellulose-digesting bacteria, and a nitrogen-fixation enzyme.

Recently the United States and Japan have initiated large-scale programs whose aim is to map the entire human genome; and the European Economic Community is considering a similar program. The human genome project is expected to make possible prenatal diagnosis of many inherited diseases. For example, the gene for cystic fibrosis has been found; and DNA technology makes it possible to detect the disease prenatally.

The possibility of extensive genetic screening raises ethical problems which require both knowledge and thought on the part of the public. An expectant mother, in an early stage of pregnancy, often has an abortion if the foetus is found to carry a serious genetic defect. But with more knowledge, many more defects will be found. Where should the line be drawn between a serious defect and a minor one?

The cloning of genes for lethal toxins also needs serious thought and public discussion. From 1976 to 1982, this activity was prohibited in the United States under the NIH Guidelines. However, in April, 1982, the restriction was lifted, and by 1983, the toxins being cloned included several aflatoxins, lecithinase, cytochalasins, ochratoxins, sporidesmin, T-2 toxin, ricin and tremogen. Although international conventions exist under which chemical and biological weapons are prohibited, there is a danger that nations will be driven to produce and stockpile such weapons because of fear of what other nations might do.

Finally, the release of new, transgenic species into the environment requires thought and caution. Much benefit can come, for example, from the use of gene-spliced bacteria for nitrogen fixation or for cleaning up oil spills. However, once a gene-spliced microorganism has been released, it is virtually impossible to eradicate it; and thus the change produced by the release of a new organism is permanent. Permanent changes in the environment should not be made on the basis of short-term commercial considerations, nor indeed on the basis of short-term considerations of any kind; nor should such decisions be made unilaterally by single nations, since new organisms can easily cross political boundaries.

The rapid development of biotechnology has given humans enormous power over the fundamental mechanisms of life and evolution. But is society mature enough to use this power wisely and compassionately?

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)¹.

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 °C 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" oligonucleotides² with these known beginning ending sequences are added in excess. The temperature is then lowered to 50-60 °C, 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 °C, so that the double-stranded DNA separates into single strands, and the cycle is repeated.

¹ 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.

 $^{^{2}}$ Short segments of single-stranded DNA.
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.

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.

13.2 Bioinformation technology and artificial life

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 charge³ which are recognized by complementary molecules because

 $^{^3}$ They also have patterns of polarizable groups and reactive groups, and these patterns can also play a role in recognition.

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 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 charge⁴. 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, 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"⁵

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

⁴ Patterns of reactive or polarizable groups also play a role.

⁵ G.M. Whiteside et al., Science, **254**, 1312-1314, (1991).

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 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 subtraction 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. Osterhelt⁶, 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.

⁶ 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).

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 vesicles of purple membrane.

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

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 a-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 vesicle, the hydrogenbonding 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 memories⁷. 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 coworkers⁸ 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 paper, they proposed the idea of a Threshold Logic Unit (TLU), which they visualized not only as a model of the way in

⁷ A. Der and L. Keszthelyi, editors, Bioelectronic Applications of Photochromic Pigments, IOS Press, Amsterdam, Netherlands, (2001).

⁸ J. Chen et al., Biosystems **35**, 145-151 (1995).

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 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 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



Figure 13.1: A Threshold Logic Unit (TLU) of the type proposed by McCulloch and Pitts.



Figure 13.2: 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.

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

$$a = \sum_{j=1}^{N} w_j x_j$$
 (13.1)

The quantity a, is called the *activation*. If the activation exceeds the threshold 9, the unit "fires", i.e. it produces an output y given by

$$y = \begin{cases} 1 & \text{if } a \ge \theta \\ 0 & \text{if } a < \theta \end{cases}$$
(13.2)

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, $x = x_1, x_2, ..., X_N$, in an *N*-dimensional space called pattern space. The weights also form a vector, $w = w_1, w_2, ..., w_N$, in the same space. If we write an equation setting the scalar product of these two vectors equal to some constant,

$$\mathbf{w} \cdot \mathbf{x} \equiv \sum_{j=1}^{N} w_j x_j = \theta \tag{13.3}$$

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 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,

$$\mathbf{W} = w_1, w_2, ..., w_N, \theta \tag{13.4}$$

and an augmented input pattern vector,

$$\mathbf{X} = x_1, x_2, \dots, x_N, -1 \tag{13.5}$$

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

$$\mathbf{W} \cdot \mathbf{X} \equiv \sum_{j=1}^{N+1} W_j X_j = 0 \tag{13.6}$$

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

$$\mathbf{W}' = \mathbf{W} + \gamma \mathbf{X} \tag{13.7}$$

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. Prom 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 Willadsen⁹, 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

⁹ 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.

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 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 1013 to 1015 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 built¹⁰.

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

¹⁰ Von Neumann's kinematic automaton was taken seriously by the Mission IV Group, part of a tenweek 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.

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 semiotics¹¹. 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 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

¹¹ Semiotics is defined as the study of signs (see Appendix 2).

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 field¹².

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 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 messengers¹³. 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

 $^{^{12}}$ As many readers probably know, Stephen Wolfram was also destined to become a millionaire by inventing the elegant symbol-manipulating program system, Mathematica.

¹³ We can recall the case of slime mold cells which signal to each other by means of the chemical messenger, cyclic AMP (Chapter 3).

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.

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 A to characterize various sets of rules according to the type of behavior which they generated. Rule sets with a value near to the optimum (λ = 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 Lindenmayer, 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 Lindenmayer 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 Nasals study to determine whether selfreproducing 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 lifelike 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 selfgenerated 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:¹⁴ "Everything we know about life is based on one example: Life on Earth. Everything we know about

¹⁴ T. Ray, http://www.hip.atr.co.jp/ ray/pubs/html

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"¹⁵ 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". 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.

¹⁵ In this terminology, ordinary biologists are "b-lifers".

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 improbability 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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