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ORIGINAL PAPER

Electronomics

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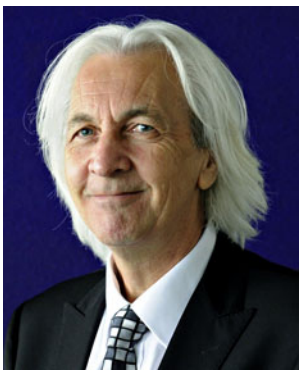

Abstract Recently, the science of comparative genomics has begun to revolutionize our understanding of the biological world. In the light of these developments, a new world view is emerging, more coherent than before, and bringing with it exciting opportunities for electrochemical research. In this essay, the author briefly traces the general outlines of the new landscape. An attempt is also made to set modern developments within a historical context. Strong emphasis is placed on the role of the electron in biology, and the name "electronomics" is suggested for this general field of research.

Keywords Electronomics · Terraformation · Virosphere · Oxidative stress · Neurons · Consciousness

One cannot discover new lands without losing sight of the shore for a very long time.
André Gide

A century ago, electrochemistry was outstandingly successful. By the close of the nineteenth century, it was arguably the central physical science, and all major scientists of that era had some familiarity with it. Einstein studied diffusion, Planck studied liquid junction potentials, and Nernst studied galvanic cells. (Nernst even found time to establish the Institute for Physical Chemistry and Electrochemistry in Göttingen.) However, within a few decades, electrochemistry was toppled from its pedestal. Part of its decline was due to the meteoric rise of quantum theory, and the shift of focus to the sub-atomic world. But another reason for its decline was, paradoxically, its own success at describing the macroscopic world. Electrochemical concepts and theories were rapidly adopted across the whole of the physical and biological sciences, which removed the need for teaching electrochemistry as a specialist subject. Indeed, electrochemistry became so vast and sprawling that it eventually fragmented into numerous sub-disciplines—membrane science, colloid science, electrometallurgy, electrosynthesis, battery technology, redox chemistry, and much else besides—leaving behind a only small core of theoretical electrochemistry that today is in danger of being assimilated into analytical chemistry. To make matters worse, its surviving practitioners are rapidly dwindling in number. In these

Dedication This paper is dedicated to the memory of Lachlan M. D. Cranswick (1968–2010), crystallographer and friend.

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circumstances, it seems reasonable to ask—is theoretical electrochemistry about to become extinct?

Well, I hope not. For one thing, the theory of electron transfer is currently being reformulated in terms of quantum theory, offering powerful new insights into the complex physics of molecular electronic devices, single molecule conduction, tunnel effects, etc. This is vital research if we are ever going to shrink electronic networks to the nanoscale. In addition, knowledge of theoretical electrochemistry has emerged as a necessary adjunct to the twenty-first century materials science. Conducting polymers, carbon nanotubes, and graphene spring to mind immediately. Similarly, redox proteins, ionic liquids, intercalation compounds, and catalysts all require advanced electrochemical knowledge to understand their functioning. Indeed, materials electrochemistry is currently the home of some of the most exciting work taking place in modern science.

Beyond materials electrochemistry, however, there lies an even greater world of opportunity for electrochemists, and that is what I want to talk about in this essay. I refer to biochemistry in general, and genomics in particular. In recent years, advances in genomics have revolutionized our understanding of the history, functions, and inter-relations of major components of the biological world, and uncovered a host of exciting new possibilities. In what follows, I shall try to survey some of the salient features of this emerging landscape, and place them in a historical context.

In 1780, Luigi Galvani discovered that by attaching two different metals to the muscles of a frog he could generate electricity. Shortly thereafter, Alessandro Volta began experimenting with metals alone, and soon found that animal tissue was not needed to produce a detectable current. These famous experiments led to a long and bitter dispute about the difference between "animal electricity" and "metallic electricity"—a controversy that took almost a century to fade away. Although no one today believes that any fundamental difference exists, the socially constructed separation between mainstream electrochemistry and bioelectrochemistry remains as intact as ever. Writing in 2011, it seems absurd to me that such boundaries still survive. Electrochemistry and bioelectrochemistry, like electrons and life, are inextricably mixed on length scales ranging from nanometers to the depths of the oceans, and on time scales ranging from nanoseconds to the age of the Earth, and it is time we viewed them all as one subject.

The idea that biological systems might actually be time-dependent physical systems was first mooted in the late eighteenth century. By the close of the nineteenth century, two major scientific theories had emerged that described the evolution of physical systems over time. Thermodynamics, as formulated by Ludwig Boltzmann, viewed nature as evolving from states of high order to states of low order, ultimately approaching the state of "heat death" in which no flux of matter or energy was possible beyond the merely random. By contrast, Natural Selection, as envisaged by Charles Darwin, saw nature as continually evolving towards states of higher order, in which entropy was actively exported, and fluxes of matter and energy were maintained indefinitely.

The conflicting predictions of these two great theories baffled the Victorian public and continue to baffle the common man to this day, although the explanation is rather obvious to mathematicians. The resolution lies in the fact that the two great scientists assumed different boundary conditions for the systems they were studying. If the boundaries of a system are closed to matter and energy, then the system is *isolated*, and Boltzmann's thermodynamics will, sooner or later, exert their paralyzing effect. But if the boundaries of a system are open to matter and energy, then it may evolve into something much more rich and strange, and that is precisely what has happened to the planet Earth over the past 4.5 billion years. It is an open system, with energy continually pouring through its biosphere. Likewise, every living thing on the surface of the Earth is an open system, and exists in a state of energy flux.

The thermodynamics of open systems are clearly central to an understanding of life, but the relevant theory is not widely known, even among the educated public. For example, there is a widespread misconception that life on Earth somehow requires the *consumption* of energy supplied by the Sun, or that the Earth itself consumes energy. However, a moment's thought shows that this cannot possibly be the case. During the day, heat energy is certainly delivered to the Earth by the Sun, but during the night it all goes back into space again. If this did not happen, the Earth would simply heat up until it boiled! So the Earth cannot possibly be *consuming* energy. What, then, is happening?

In fact, the energy that we get from the Sun during the day is in the form of high-energy photons (yellow light), while the energy that we radiate back into space at night is in the form of low energy photons (infrared radiation). Since there are roughly twice as many photons leaving as arriving, because they have roughly half the energy, it follows that all the chemistry on the surface of the Earth—including life itself—is driven by *the net export of entropy into space*. In the biosphere, plants absorb low-entropy photons by photosynthesis, and then animals eat the plants. By this mechanism, both forms of life compensate for the spontaneous generation of entropy associated with the second law of thermodynamics.

Electrochemical terraformation of the earth

Photosynthesis is an electrochemical process. It is found in many organisms, including plants, algae, and photosynthet-

ic bacteria. Modern genomics has revealed that all of these organisms evolved (in part) from a common ancestor about 2.75 billion years ago. Today, its descendents still utilize sunlight to generate a combination of low-entropy biomass and high-entropy oxygen. The heart of the photosynthetic system is a complex biological structure known as photosystem II. Remarkably, photosystem II produces all of the oxygen on Earth. It also catalyzes the transmembrane transfer of electrons from water to plastoquinone. Four electrons are extracted from an oxygen-evolving complex, and four protons are released in an endergonic reaction of water splitting. The high-entropy product, oxygen, is simply excreted to the atmosphere.

The evolution of photosynthetic organisms on the early Earth (most likely free-living cyanobacteria) was a crucial event in the history of the planet because it led to the oxidation of the entire biosphere, including the oceans and the atmosphere. Globally, Fe(II) was oxidized to Fe(III), and S(−II) was oxidized to S(VI).

Geochemical analysis suggests that oxidation of the Earth's biosphere occurred in two distinct phases (Fig.1). In the first phase, a rise in atmospheric oxygen probably occurred about 2.5 billion years ago, accompanied by the oxygenation of shallow seas. In the second phase, a much larger rise in atmospheric oxygen occurred, probably in the late Neoproterozoic era (800–542 Myr ago), and this led to the oxygenation of the deep ocean. It is remarkable to think that an entire planet was transformed by a single electrochemical process, but that is exactly what happened. Today, 20% of the Earth's atmosphere is oxygen.

It is interesting to compare the history of the Earth with the history of Mars. Geological evidence gathered by various NASA missions has indicated that Mars once had large-scale water coverage, but this disappeared very early.

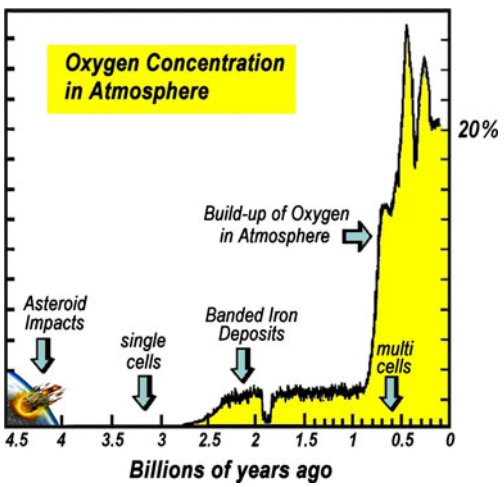

Fig. 1 A rough guide to biospheric oxidation. The early atmosphere was dominated by volcanism; the later atmosphere was dominated by photosynthesis

The reason was the solidification of Mars' interior. This caused the collapse of its magnetic field, and so the electrically charged solar wind was able to penetrate its magnetosphere and strip away its gaseous atmosphere. As the atmospheric pressure dropped, the surface water evaporated, and this too was carried away by the solar wind. Today, the atmosphere of Mars is highly rarefied, with a surface pressure less than 1% of the Earth's. It consists of 95% carbon dioxide, 3% nitrogen, and 1.6% argon and contains only traces of oxygen and water. The atmosphere is also dusty, containing fine particles that give the Martian sky a characteristic red/orange color. The particles are thought to be a mixture of anhydrous iron (III) oxide (hematite, Fe_2O_3) and hydrous iron(III) oxide (goethite, FeO(OH). In addition, there are deposits of minerals that can only have been produced by interaction with water, such as carbonates, hydrothermal silicates, and jarosite (a type of hydrated iron sulfate) which support the hypothesis of ancient water. However, so far as we know, photosynthetic organisms never evolved on Mars.

Despite the terrestrial importance of photosynthesis, many unsolved problems related to its mechanism still confront scientists. A lack of theoretical understanding is also hindering the development of artificial photosynthesis for solar energy conversion. Chief among the unsolved problems is understanding how photosynthetic organisms avoid the wasteful recombination reactions that plague synthetic devices. In photosystem II, there is a factor of 50 or more between the forward rate constants for electron transfer and the backward rate constants for electron transfer, yet the bionic engineering principles that nature uses are far from understood. Another deep question concerns the modeling of electron transfer rates in different dielectric environments, such as inside membranes, inside proteins, and inside nerves cells. The standard theories of electron transfer appear inadequate to this task. Marcus theory, for example, predicts that rate constants for electron transfer should be greater in non-polar environments than in polar environments, and at least one scientist (me!) thinks that is questionable.

Photosynthesis is the paradigmatic process for the interaction of electrons with living matter, but of course it is not the only process. More than 10% of the structurally characterized proteins in the Protein Data Bank are redox proteins, i.e., proteins that participate in, or catalyze, electron transfer. Indeed, electrochemistry plays a major role in all forms of life, from viruses to human beings, but as yet the "design principles" of biological "wiring" remain completely obscure. This is particularly unfortunate because the great historical goal of the biological sciences—the explanation of human consciousness—surely lies at the intersection of electrochemistry and neuroscience.

According to the "central dogma" of molecular biology, genes code for proteins, and proteins provide the scaffold-

ing for electron transport in living systems. Since the study of genes is called genomics, and the study of proteins is called proteomics, it seems natural to complete the series and call the study of electrons in biological systems *electronomics*.

Of course, the importance of electricity to biochemistry and physiology has been recognized since the time of Galvani, but in recent times it has been eclipsed by the brilliant developments in genomics and proteomics. Nevertheless, there are some fine scientific journals devoted to photosynthesis, respiration, biosensors, and bionics, as well as to bioelectrochemistry generally, and the field continues to attract major talent.

Over the past century, some pioneering work has been performed at the interface between electrochemistry and biochemistry. The 1937 Nobel Prize in Physiology or Medicine was awarded to Albert Szent-Györgyi for his discoveries "in connection with the biological combustion processes, with special reference to vitamin C." Similarly, the 1953 Nobel Prize was awarded to Hans Adolf Krebs "for his discovery of the citric acid cycle." Among Krebs' many publications was a remarkable survey of energy transformations in living matter, published in 1957, in collaboration with H. L. Kornberg, which discussed the complex chemical processes which provide living organisms with high-energy phosphate by way of what is now known as the *Krebs Cycle*. Also, the 1963 Nobel Prize was awarded jointly to John Eccles, Alan Hodgkin, and Andrew Huxley "for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane." Later, the 1970 Nobel Prize in Physiology or Medicine was awarded jointly to Bernard Katz, Ulf von Euler, and Julius Axelrod for their discoveries relating to chemical transmission of nerve impulses. The analysis of electric currents through nerves remains an area of active interest to this day, particularly "action" potentials which ensure that nerves act in synchrony. Finally, in 1991, the Nobel Prize in Physiology or Medicine was awarded jointly to Erwin Neher and Bert Sakmann "for their discoveries concerning the function of single ion channels in cells." These authors conclusively demonstrated that ion channels existed in biological membranes, and succeeded in measuring the picoamp currents that flow through them. Remarkably, some of the channels open as a result of *single molecule* events—the world's first example of single molecule electrochemistry.

Earlier, in 1978, the Nobel Prize in Chemistry was awarded to Peter Mitchell for his discoveries concerning energy transfer across membranes. Activities, such as muscle contraction, nerve conduction, and sperm motility, cannot take place without an adequate supply of energy. But how is that energy stored and transported in living cells? In 1961, Mitchell proposed a remarkable mechanism for the coupling of electron transfer to the synthesis of adenosine triphosphate (ATP). He suggested that the flow of electrons through membranes creates a gradient of electrochemical potential, which consists of two components: a gradient of hydrogen ion concentration (pH) and a gradient of electric potential. It turns out that the biosynthesis of ATP is then driven by the gradient of electrochemical potential. Mitchell's theory is now well established and has successfully been extended to intracellular transport, the uptake of nutrients by bacterial cells, etc. Later, in 2003, another Nobel Prize in Chemistry was awarded to Roderick MacKinnon "for structural and mechanistic studies of ion channels." Potassium ion channels exhibit a counterintuitive property: they allow large potassium ions to pass through, but prevent small sodium ions from doing so. Before MacKinnon's work, the detailed molecular architecture of potassium ion channels was unknown, and the mechanism by which they worked was speculative. MacKinnon showed that selectivity was achieved by modifying the solvation shell of each ion.

In more recent times, researchers have begun to explore the size and diversity of the viral world, or "virosphere," by collecting samples from many different places and analyzing their genomes. The emerging picture is that viruses from very diverse environments share some features in common. For example, Dennis Bamford of the University of Helsinki has identified surprising similarities between viruses infecting hosts in completely different domains of life, such as the adenovirus in humans and the PRD1 virus in bacteria. This argues for a common origin of both viruses early in Earth's history, before cellular life diverged. Further, it now seems likely that the entire virosphere may be descended from a small number of virus lineages that evolved very early in the history of the planet. If this is the case, then modern viruses may be targetable by a new generation of "broad spectrum" antiviral drugs. One plausible candidate is LJ001, a rhodanine derivative recently patented by UCLA, which shows activity against a wide range of enveloped viruses, including HIV-1 and influenza A.

The virosphere

The virosphere refers to all those places where viruses thrive. Some viruses live inside bacteria, some parasitize eukaryotes, and some have adapted to soil and water. We therefore live on a planet where the virosphere permeates almost everything, from the top of the highest mountains to the bottom of the Earth's crust. In recent years, scientists have come to realize that viruses are not the fringe dwellers that we previously thought, but a central part of the living

world. Indeed, they dominate the planet in terms of (a) the number of individuals, (b) the diversity of species, and (c) the speed at which they evolve. In short, the biological world is mostly viral, yet the electrochemistry of viruses remains virtually unknown.

Since the development of genomics, the extent of virus diversity has astounded biochemists. There are more than five thousand species of virus, most of which reproduce at prodigious rates. For example, within a few hours of introducing a single T7 bacteriophage virus into a colony of ten billion *Escherichia coli* cells, more than 9.9 billion of the bacteria are dead and more than a trillion viruses are alive. Indeed, the dominant predator–prey relationship on the planet turns out to be between viruses and bacteria. A conservative estimate is that viruses mount $>10^{28}$ attacks on bacteria per day.

Viruses mutate with startling rapidity, and exchange their genes with other viruses (and with other species) promiscuously. Even the human genome contains a significant amount of DNA that is of viral origin; estimates range from 3% to 8%. Indeed, it is beginning to look as though the ability of viruses to transfer genetic material "horizontally" between species may have been crucial in the evolution of life, creating many mutant organisms as fodder for Darwinian selection.

One of the possible origins of viruses is the ancient "RNA world," i.e., the biosphere that preceded the modern "DNA world." Most evolutionary theorists now agree that our modern DNA world evolved from an earlier RNA world, in which RNA played the role of both genetic material and catalyst. Thus, in the RNA world, information storage and protein synthesis were both accomplished by RNA, with no help from DNA.

The top half of Fig. 2 is meant to illustrate the "central dogma" of molecular biology. The original idea was first articulated by Francis Crick in 1958. Until then, everyone thought that DNA made its own proteins. It was a major shock to realize that DNA transferred its genetic information to RNA, which then transferred the information to the ribosome. Finally, it was the ribosome that "read" the information and used it for protein synthesis. Today, we can get a crude understanding of this system by comparing it with a desktop computer. Just as hard disks evolved before memory sticks, biologists eventually came to realize that RNA evolved before DNA. This scenario is known as the "RNA world," and it existed on the planet Earth about 4 billion years ago. Those long-lost RNA organisms were low-information entities, chemically unstable, but very rapidly evolving. By contrast, DNA organisms were high-information entities, chemically stable, and slowly evolving. Unfortunately, DNA has been massively oversold to the public as the "molecule of life," which has given them the impression (still current) that you cannot have life without it. But you can. RNA-based viruses are a good example.

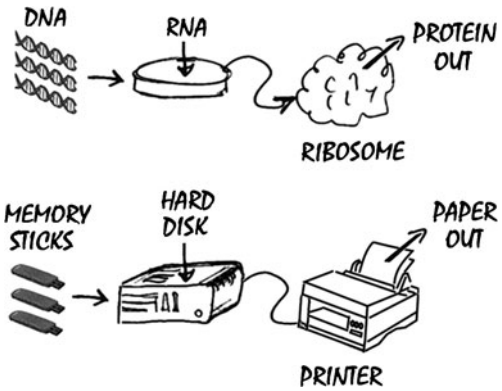

Fig. 2 A rough guide to information flow in DNA-based life

The bottom half of Fig. 2 is meant to illustrate information flow in DNA-based life. While helpful as a mental construct, it does have one serious defect. In the computer world, hard disks are very reliable, and memory sticks are comparatively unreliable. In living things, it is just the opposite. RNA is the unreliable component and DNA is the pinnacle of information storage. So early life, which used poor old RNA, was restricted to very small virus-like organisms that mutated at a very high rate indeed, possibly hundreds of times faster than DNA organisms. This had some advantages (rapid evolution) and some disadvantages (restriction to very small life forms). The eventual evolution of DNA allowed larger, more complex life forms to evolve (though still single celled), because they could store the necessary amounts of information securely. Today, it is a serious intellectual possibility that RNA-based viruses evolved before the first cellular organisms and perhaps helped to create the DNA world. Modern RNA viruses might even be direct descendents of the first life forms on Earth.

Oxidative stress

On planet Earth today, almost all organisms that have cell nuclei use oxygen to power phosphorylation. *Oxidative phosphorylation* is a metabolic pathway that uses energy from the oxidation of nutrients to produce ATP, which then transports energy around the cell. This pathway is more efficient than competing anaerobic pathways, such as the transformation of glucose to pyruvate. However, an unwanted side effect of oxidative phosphorylation is that it generates reactive metabolites of oxygen which can attack various cell components. These metabolites include superoxide ($O_2^{\bullet -}$) and hydrogen peroxide (H_2O_2). In the presence of transition metal ions, even more damaging species such as hydroxyl radicals (OH•) may also be formed. Taken together, these species are collectively known as "reactive oxygen species."

Over geological time, many enzymes have evolved to protect higher organisms from reactive oxygen species. Examples include superoxide dismutase (which reduces $O_2\bullet^-$ to H_2O_2), glutathione peroxidase (which reduces lipid hydroperoxides to alcohols), and catalase (which is one of the most efficient enzymes known, and which decomposes H_2O_2 to H_2O). However, the condition known as "oxidative stress" still occurs when an organism's defensive enzymes are overwhelmed. It is now thought that oxidative stress is implicated in a wide range of degenerative illnesses in man, including atherosclerosis, pulmonary fibrosis, rheumatoid arthritis, and some forms of cancer. Indeed, we might reasonably refer to these as "electronomic illnesses."

The most destructive components of reactive oxygen species are the free radicals. Small free radicals are unstable and tend to react indiscriminately with any molecule in their vicinity. Most commonly, single-electron reduction of oxygen occurs by the leakage of electrons from defective electron pathways, yielding superoxide:

$$O_2 + e^- \rightarrow O_2\bullet^-$$

Much recent work on free radical destruction has focused on dietary antioxidants such as vitamin C (ascorbate), vitamin E (tocopherol), beta-carotene, and polyphenols. Vitamins C and E, like beta-carotene, have been widely studied, but less is known about the polyphenols. These interesting compounds include flavonoids such as quercetin (apple), catechins (tea), anthocyanins (berries), and hesperitin derivatives (citrus fruits). At present, very little is understood about their electrochemistry or their role in human diet. All chemical antioxidant molecules act by donating an electron to a free radical, thereby neutralizing it. However, during this process, the antioxidant may itself turn into a free radical, and it would be very desirable to know what happens to it.

A third defensive mechanism against reactive oxygen species is, remarkably, a solid state one. This involves the brown-black pigment melanin. Melanin is a co-polymer of many smaller components, with differing proportions and bonding patterns in different biological species. Melanins are found in parts of the body where there is intense electrical signaling, e.g., in the iris of the eye, in the inner ear, and in the brain. In the brain, special melanins protect the medulla, the brainstem, and the *substantia nigra*. (Parkinson's disease is caused by the death of dopaminergic neurons in the *substantia nigra*.) Again, very little is known about the electrochemistry of melanin.

Neurons

Neurons are electrically excitable cells that process and transmit information by electrical and chemical signaling. They are the core components of the nervous system and are found in the brain, the spinal cord, and the peripheral ganglia. Superficially, a typical neuron consists of a cell body called the soma, a set of filaments called dendrites, and a long protuberance called an axon. Besides the cell nucleus, the soma also contains ribosomes, mitochondria, and various organelles. In other words, the soma appears like an ordinary cell. Extending from the soma membrane, however, is a remarkable system of dendrites that carry electrical signals. If a cell receives a strong enough electrical signal from a neighboring cell, the resting potential of its membrane becomes depolarized, and an electrical impulse is transmitted along the axon. This impulse is called an *action potential*. To speed the transmission of action potentials, axons are sheathed by a special membrane substance called myelin.

Myelin is composed of multiple layers that are wound radially around the long axis of the axon. Diffraction studies have shown that the layers have a protein–lipid–protein structure. The lipid layers are composed of glycolipid, phospholipid, and cholesterol in an approximately 2:3:4 ratio. The glycolipid and cholesterol are mainly located in the outer part of the membrane, where they interact with water. By contrast, the phospholipid is mainly located in the inner part of the membrane and is hydrophobic. The area between them consists of hydrocarbon chains (fatty acids). More than 50% of the hydrocarbon chains contain one or more double bonds, which introduce kinks into otherwise straight molecules. The kinks prevent tight packing of the lipid molecules and are thought to enhance the flexibility of the membrane. Significantly, the loss of myelin occurs in many neurodegenerative diseases, most notably multiple sclerosis. As demyelination proceeds, the speed that nerve signals move down the axons decreases to about one tenth of its former value. It seems likely that raising the dielectric constant of nerves is responsible for raising their *RC* time constant, but no one is certain. The long-term effect of ingesting the "wrong" dietary fatty acids on myelin formation is also unknown.

Between the terminus of each axon and the beginning of a neighboring cell lies a special gap called a *synapse*. A synapse is a small fluid-filled region about 20 nm wide. Astonishingly, there are more than 10^{12} synapses in the human brain. Generally speaking, there are two types of synapse: chemical synapses and electrical synapses. In human beings, the chemical synapses predominate, although many electrical synapses are found in the eye. At a chemical synapse, the pre-synaptic neuron releases a chemical agent called a *neurotransmitter* which then diffuses to special receptors on the membrane of the post-synaptic neuron. The arrival of the neurotransmitter induces an electrical response in the receiving cell, usually the

depolarization of its cell membrane. However, the overall process is "slow" (~0.5 ms).

Biochemists have discovered many remarkable features of the neurotransmission system. For example, the neurotransmitter molecules are pre-packaged in vesicles, so that when an action potential arrives, they are ready to be released. In addition, many neurotransmitters are highly specific for the type of information they must convey. For this reason, different neurotransmitters are concentrated in different parts of the brain.

The two most common neurotransmitters in the human brain are glutamate and gamma-aminobutyric acid. Serotonergic neurons release serotonin (5-hydroxytryptamine) which is involved with the regulation of mood and (amazingly) digestion. Likewise, dopaminergic neurons release dopamine, which is implicated in motivation, attention, emotion, and sleep. It is well-known that psychoactive drugs such as cocaine and amphetamines inhibit the re-uptake of dopamine, thus increasing its local concentration. However, the biochemical mechanisms by which dopamine affects the brain remain poorly understood.

The vital role of neurotransmitters in brain functioning means that any departures from their normal concentrations may have serious clinical implications for an individual. Parkinson's disease, Alzheimer's disease, and schizophrenia are all associated with the disruption of electrical signals at synapses. The ultimate causes of these terrible diseases lie shrouded in mystery, but electrochemistry might one day shed light on them. One way forward was indicated by Ralph Adams in the 1970s, when he showed that it was possible to record in vivo electrochemistry of biogenic amines. Since that time, several neurotransmitters have been studied in vivo by electrochemists, including dopamine, norepinephrine, serotonin, and various metabolites. The ascorbate ion (vitamin C) has also attracted wide attention. While not a neurotransmitter, the levels of ascorbate in the human brain range from 200 to 400 μM, suggesting a very important role. However, its full range of functions is far from clear.

Consciousness

For centuries, human beings have struggled in vain to understand consciousness. However, consciousness is our only reality. Through it, we perceive ourselves and the world, we implement our intentions, and we learn. Since the early twentieth century, the subject of consciousness has gradually migrated from philosophy to psychology, and finally, to bioelectrochemistry and neuroscience, where it remains largely stalled. Among the many unsolved problems associated with consciousness are the "what?" question and the "how?" question. The "what?" question refers to the definition of what consciousness actually is. Brain scans have revealed that consciousness is a dynamic process, involving the temporal dynamics of information flow in the brain. But the subjective nature of the phenomenon remains elusive. The "how?" question, which seeks a physical explanation of consciousness, is equally problematic. Today, most scientists are convinced that consciousness somehow emerges from the *concerted* actions of millions of neurons, but neither the bioelectrochemical structures nor the physical mechanisms that allow this have been identified.

Even the most elementary brain functions involve vast numbers of neurons for their correct functioning. Since the response time of an individual neuron is about 0.5 ms, it follows that neurons-in-series would be far too slow to generate consciousness. Consequently, some sort of neurons-in-parallel mechanism must be involved. Some authors have suggested that the superposition of quantum states may be implicated, so that the brain is—in effect—a quantum computer. However, the lack of a detailed model has prevented progress in this area. Nevertheless, it appears that the problem of consciousness may indeed be connected in some way with quantum phenomena. This idea has received strong support from Roger Penrose, who has asserted that some higher brain functions are beyond the power of digital computers (or even "perfect" Turing machines).

A familiar feature of consciousness is that it is *unique*. There is only one conscious self, despite the multitude of neuronal inputs to the brain. Typically, we receive multiple kinds of data from our senses (visual, thermal, audible, tactile, olfactory…) yet we experience reality as a single integrated phenomenon. The parallel processing in the brain is clearly immense.

If the brain does indeed function as a massively parallel quantum computer, there must be at least one quantum effect involved, most likely the superposition of quantum states. However, at the present state of knowledge, it is difficult to imagine how superposed quantum states could last more than a few femtoseconds in the thermally fluctuating aqueous environment of the brain. How might the brain achieve that? We simply do not know.

Summary

Electrochemistry is a vast subject which has had a profound influence on human society. Its impact has been deep and wide, from the extraction of metals and minerals to biosensing in the human brain. However, despite its historical success, it remains very difficult to identify new and potentially rewarding pathways to the future. In my view, much will depend on how the field of comparative

genomics unfolds. If all goes well, what I foresee over the next two decades is a thorough reformulation of electrochemical theory in terms of quantum theory, and the application of the resulting hybrid theory to biochemical problems. This will create a new field of endeavor which I have here termed "electronomics." Even if this does not occur, it is clear that 4.5 billion years of evolution have created electronic bio-circuits that are beyond anything yet dreamed of by mankind… one of our primary tasks must therefore be to identify the basic components of these bio-circuits and deduce how they work. The bio-nano-transistor is hiding just out of view. Let us find it!