REVIEW

A chemical systems approach to evolution

Robert Joseph Paton Williams

Abstract   The paper concerns the chemists way of looking at evolution. It is not based on the DNA but on the chemical elements in The Periodic Table of Mendelev. The first step is the analysis of the element content of organisms as they arose historically. This shows that in keeping with our knowledge of the environment the chemical elements in organisms changed due to the rise in oxygen in the atmosphere. Elements such as copper and zinc were greatly increased in later organism as they were released from their sulfidic ores to the sea. The nature of the changes in the chemical elements available to organisms is then discussed in terms of their functions. It is shown that much though the Darwin perception of evolution is pure chance it is strictly guided by the inevitable chemistry of the elements arising from oxidation of the environment.

Keywords   Environment · Evolution · Chemical elements · Organisms · Prokaryotes · Eukaryotes · Oxygen in atmosphere · DNA/RNA · Messenger systems · Biominerals

Note Concerning this Paper

This paper was given on 29th May 2009 at a meeting of the Accademia Nazionale dei Lincei in order to celebrate the 140th anniversary of the formulation of The Periodic Table by Mendelev. The paper does not concern the chemistry of all the elements in that table but refers only to those of significance in living organisms. However, the functional significance of the elements involved in living processes is a direct reflection of their properties as placed in that table. There are the very different values of the elements in Group I, Na and K; Group II, Mg and Ca; transition metals in Groups III to XI from Sc to Cu; B-subgroup elements such as Zn in Group XII and non-metals from Groups XIII to XVII including B, C, N, O, Cl, Si, P, S, Se and I but as in Mendelev's original table the elements of Group XVIII, the noble gases, do not appear. It is not only mineral but also biological inorganic chemistry that is systematized in the table. Evolution of the environment and organisms are closely related to the inorganic chemistry Mendelev's Table reflects.

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1 Introduction: species and molecular biology

The essence of life is accepted to be the formation of chemically active, spatial enclosures, cells, controlled by genetic information, which have given rise to a huge variety of species. The early recognition of similarities of and differences between organisms in species controlled by reproduction, led to the formulation of them in classes. Similar species were seen to be connected by such properties as structural features including shape, as seen also in fossils, and by behaviour differences. Darwin and his successors proposed that the species appearing at any one time had arisen by chance variation which gave rise to strong survivors whether by effective reproduction or management of life style (Darwin 1859). Biologists were in this way able to draw up evolutionary trees, see Fig. 1. The phrase often used to refer to these ideas concerning species is "survival of the fittest". Now in the last 50 years the essential features of evolutionary trees has been confirmed by organic chemists specialising in analysing and making comparisons of sequences within molecules of individual species and of their pathways of metabolism, and by physical chemists analysing structures of the large biopolymers. The schemes include comparisons of genetic material, DNA/RNA, under the heading of genomes; of proteins, under the heading of the proteomes, and of substrate metabolic paths, under the heading of metabolomes. The studies are often grouped together under the heading of molecular biology and particular stress is then placed on the relationship between biopolymer sequences (genes) and metabolism and the evolution of characteristics of organisms including their shapes, internal structures and behaviours (Maynard-Smith and Szathmáry 2000).

From a simple chemical point of view these studies are not, historically speaking, in keeping with the way in which *chemists* have uncovered the nature and origins of objects and systems in the environment such as of minerals and aqueous solutions, seas, yet it is clear that all organisms have derived their chemicals from the environment. Initially the conventional chemical approach is direct element analysis of an object followed by an effort at understanding its molecular components and their formation using structural, thermodynamic and kinetic considerations. This study led in 1960 to the formulation of the Periodic Table of Mendelev. Here we shall show that using this chemical step-by-step

Fig. 1 A conventional view of evolution. All kinds of organisms develop in time in what is supposed to be a random way without a direction
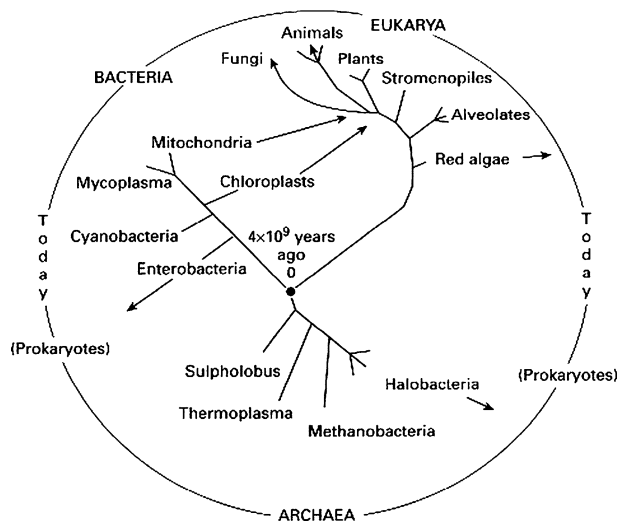
methodology chemists can provide a novel way to analyse and even to understand major features of evolution.

## 2 Chemical systems biology

Ideally, in this approach, thermodynamic concentrations and rates of transformation of all the chemical components of a cell should be studied after obtaining a thorough knowledge of chemical composition. It is immediately obvious that this is an almost impossible task if we have to take into account the great multitude of organic chemical components of cells of a given species. An alternative possibility is to examine first the more basic *quantitative chemical element content of these cells* including not just the elements common to the organic chemicals, that is, C, H, N, O, S and P, but also all the common "inorganic" elements, many of which are found in cells (Fraústo da Silva and Williams 2001), and then to limit enquiry to a selected group of compounds. In such a chemical systems analysis it is necessary to recognise that an organism is linked to its environment in an energised manner. Therefore we must consider the restrictions on the environment of any cell with the ways in which energy is used to accumulate and to incorporate elements in bound cellular components in molecules or to reject them, Fig. 2 (Fraústo da Silva and Williams 2001; Harold 2001). As well as their free element concentrations we wish to characterise as far as possible some of their bound forms in both the environment and in cells and how they have changed with time. In the environment the free concentrations of many metallic inorganic elements are present as simple ions, such as Na^+, K^+ and Cl^-, which, when in the cells, have become what we have called the *free metallome* (Fraústo da Silva and

Fig. 2 The basic diagram of energy input to material in a flowing environment/organism (cells) system
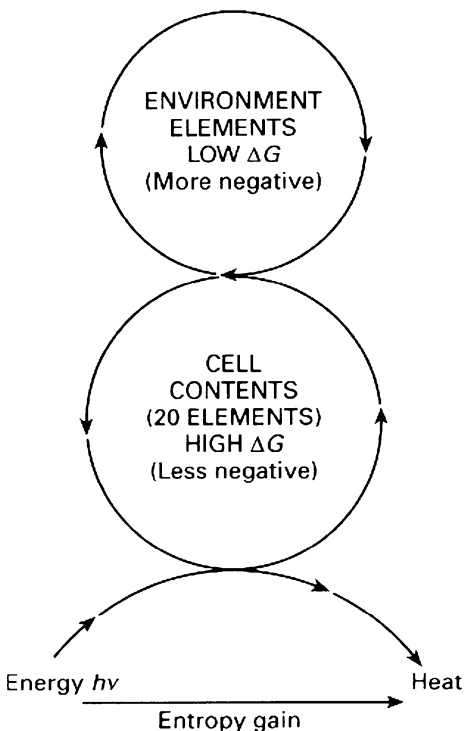
Williams 2001), while the non-metals appear as simple molecules, H_2, O_2, N_2, hydrides, H_2O, H_2S, CH_4 or NH_3 or as small molecules or ions bound to oxygen, CO, CO_2, NO, NO_3^-, HPO_4^{2-}, SO_4^{2-} and so on. These small components are also part of the metabolomes in the cell. It is this limited list of ions and small molecules common to the environment and cells which will engage our attention, but we shall have to restrict our analysis of larger molecules in cells. The organism/environment system then consists in energised exchange of these basic "inorganic" elements together with the cellular synthesis and degradation of their compounds. Instead of looking at differences in genotype we can therefore look at certain chemical characterisation in what we shall call *chemotypes* of cells, thermodynamic systems descriptions, as they have evolved including their interactive environment.

When we examine such exchanges of flowing material, we recognise immediately that organisms are separated from the environment in cells by cell membranes. Together the cells give rise to the shapes of all organisms, which as mentioned already, have always been used to aid an ordering of species and their evolution. However, if we are to consider systems of flowing chemicals we must be careful that we do not limit discussion to boundaries formed by cell membranes alone and we must not assume that such shapes are linked to genes alone. That other types of boundary can give rise to shape in the absence of genes will become clear immediately below. Shape is not only due to *ordered structures*, but is due to *restrictions on dynamic flow which we shall call organisation*, Fig. 3. It arises from energisation of material under long-range field constraints. This approach, systems biology (Alon 2006; Corning 2001), therefore has aspects which separate it from molecular biology since molecular biology is concerned overwhelmingly with chemical structures and pathways, order not organisation, and does not consider controlled concentrations or flow. There is certainly a large degree of ordering of chemical elements, e.g. in small molecules and their sequences in polymers, but there is also a high degree of organisation of the flow of the elements and their components in cells. Indeed none of the structures of a cell are permanent and all are part of the flow but some parts are on different timescales
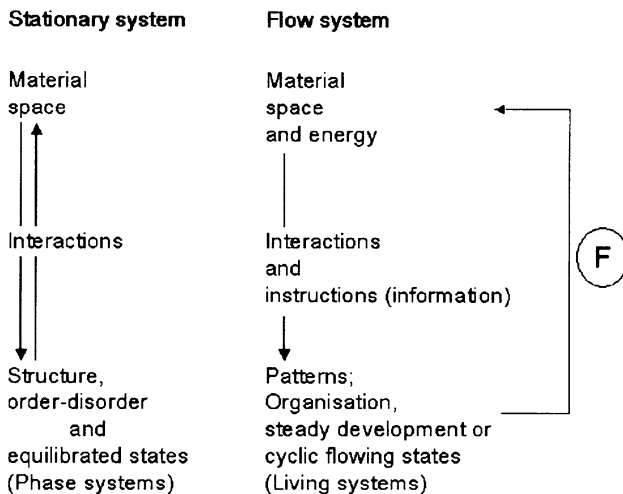
Fig. 3 A generalised distinction between the reversible thermodynamics of equilibrated systems and the irreversible systems of energised flow systems. (F) is feedback of products to reactants which causes the system to evolve.

from others, e.g. DNA, relative to the flows and exchanges of small molecules and ions. The different timescales will be shown to be of extreme importance since they change in evolution as complexity arises. Reverting to molecular biology and indeed the classical biological approach to evolution, Maynard-Smith and Szathmáry (2000) in their important book "The Major Transitions of Evolution", recognise that evolution of species has increased in complexity but they consider that this increase is "neither universal nor inevitable." While this may well be true of the vast diversity of species at any one time we shall show that the general direction of the evolution of the whole energised system of species, considered in chemical types, chemotypes, and not as genotypes, together with the environment is systematic in chemistry and physical complexity. We shall base our conclusion on simple chemical analysis of cell compartments in large part. Let us begin analysis of energised systems of flowing chemicals on planet Earth in the simplest possible way, the case of environmental physical circulation of one chemical, water, and *its contact with minerals*, which reveals the nature of organisation as well as of order, and the different timescales of evolution in parts of it.

3 The simplest physical system, water circulation and erosion, and the simplest chemical system, the ozone layer

We can all recognise that events, such as the seasons and the weather, have features which recur, such as the system of circulation of air with water molecules that brings rain. The rain comes in repeatable cloud patterns. Now, clouds are classified by meteorologists into ten or so shapes which tend to recur at different heights and under different air movement conditions. The cloud shapes persist for considerable times and arise through boundary conditions due to fields, gravity, and energy input from temperature gradients and air movement. There is no physical boundary and no coded (genetic) information. The circulation of liquid water later is from sea to land via rivers where riverbanks now form physical constraints on flow but they too are not permanent although they have much longer time constants than clouds. Over time the rivers move solid material and form novel shapes including deltas. The process of erosion (changing shape) is helped by sea currents and it is the formation of sediments, from the sea and rivers that gives rise to soils, which has allowed life to exist on land. Water circulation, rain, is also essential for organisms on land and internally. Evolution of life is clearly dependent on the physical evolution of the environment, and it too has repeated patterns on different timescales.

A second example of a circulation system, now not physical alone, is the formation and shape of the ozone layer. This layer like any other chemical flow system is affected by the addition of extraneous chemicals that can interact with the circulation. Again there are no physical boundaries, only fields and energy gradients, and no coded information.

In both of these systems of flow we observe that, at any one time, the whole is in a steady state of flux, corresponding to the optimal rate of energy absorption and degradation, and changes in boundaries in their environment give changes in their shapes—a form of evolution. These simple examples show further that material in a gaseous, liquid, or any other condition capable of random motion will have this motion constrained in part into a pattern of directed flow once it is subjected to gradients of energy input and fields, boundaries. The fields can be long range such as gravitational or electrostatic, when we may not see them, or short range repulsive or attractive fields (due to molecular structures for example), where we recognise the boundaries as surfaces, of membranes for example. A further important point to notice is that the treatment of these systems, Fig. 3, cannot be

by thermodynamic equilibria as such systems are "dead"—they do not flow. In a flow the material can be in a steady state but energy is constantly degraded. It is an irreversible system, much though material cycles, see Fig. 2. The major driving force of flow is the transformation of high energy quanta to a greater number of low energy quanta, e.g. light going to heat where light comes from the sun, Fig. 2. A more difficult system to analyse from the two examples given is one that contains many reactive chemicals. We now turn to such a more complicated chemical system, the environment/organism ecosystem, and its evolution. In order to see this evolution of a unique chemical system from its beginning we turn to the initial nature of our environment.

4 The initial condition of the environment

We make the assumption that there is one universe and that chemical elements were formed in it as it cooled from the big Bang in an inevitable *kinetically controlled* sequence (Fraústo da Silva and Williams 2001). The elements are known to have formed in giant stars and the pathway is universal giving the abundance of elements while there are still very considerable amounts of residual H and He. Cooling of heavier elements gave rise to planets in small zones around stars and Earth has a pre-determined resultant abundance of elements which, by the very process of the original element synthesis in the stars, contains much C, N, O and F and lesser amounts of Si, P, S and Cl and then very small amounts of all other non-metals. Note that Li, Be, B are of low abundance due to the nuclear kinetics in the stars. Much free H_2 escaped very early in Earth's history. Amongst metal elements there are large amounts of Na, Mg, Al, Ni and Fe (through special stability of the Ni and Fe nuclei) and small decreasing amounts of K, Ca to Mn and elements following Zn such that all heavier elements are of much lower abundance. The evolution of the abundance of all these elements is well understood. The important quantity for the ecosystem is availability and chemical reactivity of these elements on Earth's surface where life is found, for here evolution of our ecosystem has occurred. The available elements initially as ions or in small molecules were H, C, N, O, (F), P, S, Cl (and Se, which is very important in life, to a smaller degree) amongst non-metals; the metals Na, K, Mg, Ca, in comparable amounts to P and S; and, in strongly decreasing amounts, the transition metal series Mn, Fe, Co, Ni, Zn, and Cu (where Cu was virtually absent) and some W (Mo was virtually absent) amongst the heavier metals. The low initial availabilities of Ni, Co, and especially Zn, Cu and Mo were due to the insolubility of their sulfides since initially H_2S but no O_2 was present (Fraústo da Silva and Williams 2001). These environmental chemical facts are essential to our understanding of the nature of the evolution of chemotypes amongst organisms. The availability of phosphorus is much debated as phosphate has always been of rather low concentration in the sea. The role of mineral iron phosphides has been discussed.

5 The chemical approach to living systems

The two simple properties of cells we have to analyse first, treating them in systems language, are their sources of energy and the concentrations in cellular flow of materials in the form of the available chemical elements transferred to and from the environment. We shall concern ourselves with steady states of flow of the simplest cells over a considerable period of time, the lifetime of an organism, and later with the different chemical steady

states in cells that have arisen historically over different periods of time, that is with the evolution of this environment/organism system. We shall have nothing to say of the origin of life about which we have no definite evidence, but we need to see its nature from the properties of existing organisms in anaerobic environments which we take from fossil evidence to have been present on Earth some 3.5 billion years ago (Corning 2001; Cavalier-Smith et al. 2006). These bacteria and archaea already have one limiting membrane containing a physically continuous cytoplasm and much structure in molecules including genes. In the cytoplasm there is flow but, as there appears to be little grosser structure than that of free biopolymers, we shall assume that in the steady state the major flows maintain an inner homogeneous content due to uptake and external rejection and loss. This requires energised pumping of selected, amongst available, elements of the cytoplasm. These activities are unavoidably linked to the primitive environment of cells, which we take to be the anaerobic sea.

When we turn to the central chemistry of these, the most primitive (Cavalier-Smith et al. 2006; Thauer and Shima 2006; Woese 1998), and in fact all later cells we must note that the cytoplasm of all cells has to be more reducing even than the initial environment and this reduced state is fixed even to today. This follows from the very nature of the biopolymers and lipids that are the bedrock of cellular life. Cells have to reduce these non-metal elements to low oxidation states, that is carbon to or below the level of –CHOH–, nitrogen to NH_3, sulfur to H_2S, and selenium to H_2Se, and the cytoplasm must be free from reactive oxidising agents such as peroxides, superoxide, NO, and NO_2^-. The redox potential of the cytoplasm then forces metal oxidation states to low values, that is Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^+, Zn^{2+} and Mo and W to oxidation state IV, where Cu, Zn and Mo were virtually absent since they were nearly unavailable (Fraústo da Silva and Williams 2001). They, like alkali metal ions, also bind, through Lewis-acid properties, in rapid or quite rapid exchange with organic molecules relative to a cell life-time in a systematic manner (Fraústo da Silva and Williams 2001). The control of the metal oxidation states and the presence of reduced sulfur (H_2S) helped to keep the limit of free ion concentrations in the cytoplasm of all cells in harmony with the conditions of the initial anaerobic environment, see Fig. 4. In fact, we know from analytical data that these concentrations are closely those even of today since internally the low cell redox potential has been maintained. The selective binding in cells is matched to ligand (protein) and to in/out pump production so that even for tightly bound ions both the very low concentrations of free ions and of their compounds are fixed. The selectivity is that commonly seen in model complex ion formation constants, for example in the Irving-Williams order, and is known to be the same for the proteins of transcription factors, many enzymes and pumps. We have discussed this selectivity in detail elsewhere (Fraústo da Silva and Williams 2001) and it is based largely on equilibrium principles in cells (and in the environment). It is a very interesting chemical systems (thermodynamic) restriction on evolution of the ecosystem very different from those of genetic and abundance considerations.

Now there are some combinations of metal ions and molecules or proteins based on a different way of achieving selectivity. Here kinetic control of insertion in a site follows from equilibrium binding to a protein in a first step. This protein has been called (Fraústo da Silva and Williams 2001; Outten and O'Halloran 2001), a carrier, a chelatase or mostly recently a chaperone. The protein has a specific shape generated by the selected metal and this shape is recognised by a second binding agent, a molecule or a protein. The second agent receives the selected metal almost irreversibly. This process allows a metal to be put into a site for which it may have low affinity e.g. Mg^{2+} in chlorophyll. It is common to the synthesis of all porphyrin complexes of Fe, Co, and Ni. It is also used in the synthesis of
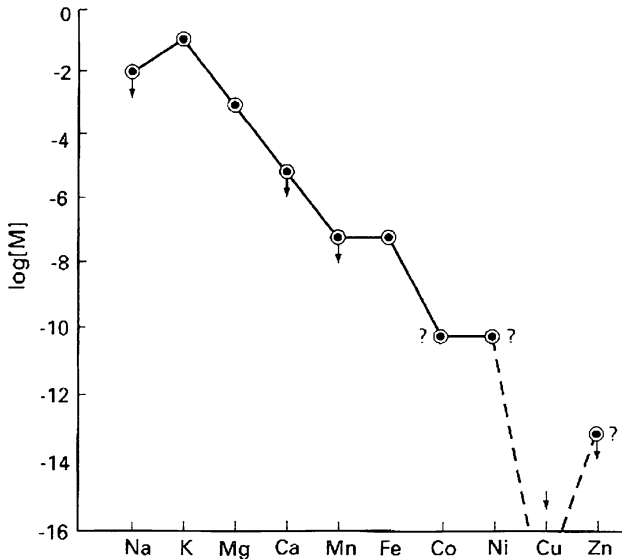
Fig. 4 A plot of the logarithm of the free metal ion concentrations in the cytoplasm of all cells for a range of metal ions. The plot arises from the reductive character of the cytoplasm and in essence is the same as that for elements in the sulfide rich sea except for Na and Ca. The downward arrows represent a small downward trend during more recent aeons. The series is one of equilibria in cells and is also well-known in complex ion chemistry

some strongly bound special sites of certain proteins for a given metal such as copper and in the controlled transport of ions such as calcium.

Now a primitive cell had problems other than those of the internal synthesis of *reduced* organic biopolymers and of limiting ions and their compounds. To maintain survival it had to reduce the *ionic* concentration below that of the sea for otherwise the osmotic strength of ions plus the cells' organic molecules would have burst cells. This is true to this day (except in fresh water) so that cells in general pump out Na^+ and Cl^- continuously. To maintain electrical neutrality approximately, K^+ is allowed into the cell together with Mg^{2+}. Clearly there is always an electrostatic field as well as a strong concentration gradient across all cell membranes and note that fields can affect shape but shape of bacterial cells is limited by a hard outer membrane. At least one other cation had to be rejected, Ca^{2+}, perhaps also Mn^{2+}, since at the concentration in the sea it readily precipitates many anions essential for the metabolome. Calcium binds in a very different way from Mg^{2+} and acts as a strong cross-linking agent. Ca^{2+} was and is pumped out of all cells to a level of $<10^{-6}$ M against an external concentration of $>10^{-3}$ M. We shall see how all these initial necessary ionic gradients have an essential role in later evolution.

To summarize it is the nature of all cellular life that the cytoplasm is strongly reducing and that it has a fixed concentration of free ions while it rejects certain initially "poisonous" ions. Systematic changes with time of biologically created and modified redox gradients and electrical/concentration gradients, between the cytoplasm and the environment gave evolution a direction as we shall see. Observe that chemical elements in primitive cells were used so as to optimise their chemical value, Table 1, given their availabilities.

Table 1 The essential primitive roles of metal ions

| Metal ion	Some roles
Mg^{2+}	Glycolytic pathway (enolase)
	All kinases and NTP reactions[a]
	Signalling (transcription factors)
	DNA/RNA structures
	Light capture
Fe^{2+}	Reverse citric acid cycle
	CO_2 incorporation
	Signalling (transcription factors)
	Control of protein synthesis (deformylation)
	Light capture
W(Mo)	O-atom transfer at low potential
Mn	O_2-release
Ni/Co	H_2, CH_3-metabolism
Na^+, K^+	Osmotic/electrolyte balance
Ca^{2+}	Stabilising membrane and wall, some signalling?

[a] Almost all synthesis pathways

$K^+/Ma^+/Cl^-$ control of osmotic and charge balance while Ca^{2+}, Zn^{2+}, Cu have very little role

6 Energy capture

Before we turn to the oxidation of the environment we must examine not just the requirements of the environment/organism system for flow of material but also those for energy capture and its transduction by the cell. We do not know how energy capture began but we can reasonably believe that energy from some source could create gradients of ions across membranes. How that led to the formation of pyrophosphate in the form of adenosine triphosphate, ATP, from a proton gradient we do not know either but we do know that these are the initial steps of the major mechanisms of energy transduction (Harold 2001; Williams 1961). These steps are the basis of photo-energy transfer, which also produces reduced organic chemicals, and later of oxidative phosphorylation. We can hypothesise other possible early steps for the generation of ion gradients, for example, from unstable chemicals, e.g. iron sulfide (Wachtershauer 1988) or other metal transformations, but the main route became by absorption of light, at first by carotenoids and then by chlorophyll pigments, the general route today. The very nature of most large molecules automatically increases light absorption. Very early in evolution there was an increase not only in useful pigments, but of many co-enzymes—several containing metal ions—all used to this day. This overall advance was in accord with the idea that the steady state of flow will adjust toward optimal energy utilisation through a search. We shall see that in evolution the rate of energy absorption and degradation increases, as does the flux of material. The system heads for a steady state but there are factors preventing its rapid realisation.

As mentioned already energy capture giving material flux has to be coupled to reduction of especially CO and CO_2 in order for polymerisation to produce kinetically stable organic chemicals. It is this reduction that causes release of oxidising equivalents to the environment. In the next section, we shall consider the ecosystem evolving through these unavoidable oxidative changes of the environment, Fig. 5 (Williams and Fraústo da Silva
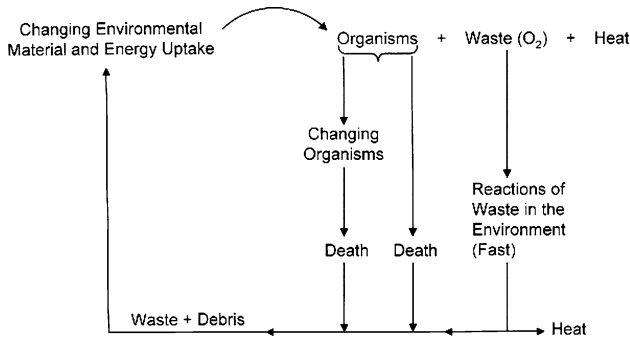
Fig. 5 The cycle of material through the environment/organism ecosystem which is driven by the generation of heat largely from light

2006). The search for an understanding of evolution is clearly most easily uncovered by following simultaneously changes in inorganic element chemistry in the environment/organism ecosystem and not just by changes in synthesised organic chemicals only present in cells.

7 The effect of cellular waste oxygen upon the environment

Today's cycles of water and ozone described earlier produce virtually no new chemicals in the environment although the water cycle did and does cause slow physical erosion and so the whole water cycle changed physically in time. We also mentioned that the addition of chemicals such as freons to the ozone layer altered the ozone flow and its zone shape. When we turn to environment/cellular activity the material flow is not cyclic. While cells removed certain elements such as H, C, N, P and S, and incorporated them, and took in some ions, they rejected others including Na^+, Ca^{2+}, Cl^- with some heavy metal ions. At the same time they rejected O_2 to the environment (Castling 2005). O_2 was and is quite rapidly reactive in the environment and became the source of many major element changes, which were pollutants for the initial anaerobes (Saito et al. 2003). Amongst non-metal elements it converted CO and CH_4 to CO_2, NH_3 to N_2, H_2S to SO_4^{2-}, and H_2Se to SeO_4^{2-} quite quickly and of the metal elements it oxidised their sulfides to more soluble oxides rather slowly hence increasing to more poisonous levels many metal ions of Co, Ni, Cu, Zn, and Cd in the sea while it released molybdenum as molybdate from MoS_2. One metal ion was lost to a large degree, Fe^{2+}, converted to Fe^{3+} and precipitated. We can follow many of these changes in the sedimentary rocks (Williams 1961), Fig. 6, or in element isotope ratio changes (Cavalier-Smith et al. 2006). Now the quantitative genera-tion of O_2 at any time was small so that it took two to three billion years to oxidise all the iron and sulfur in the sea (Alon 2006). To a first approximation the sequence (evolution) of other environmental changes is therefore governed by the buffering of the rising oxygen redox potential, see Fig. 7 (Fraústo da Silva and Williams 2001; Williams and Fraústo da Silva 2006). It must be stressed that these sequences of chemical oxidation changes of the environment were close to equilibrium and were inevitable given the demands for reduction of elements taken from the environment by organisms. There is a need for energy input to generate this change and all the available evidence suggests that over the period of 4×10^9 years the energy input to the surface of Earth has not changed greatly from
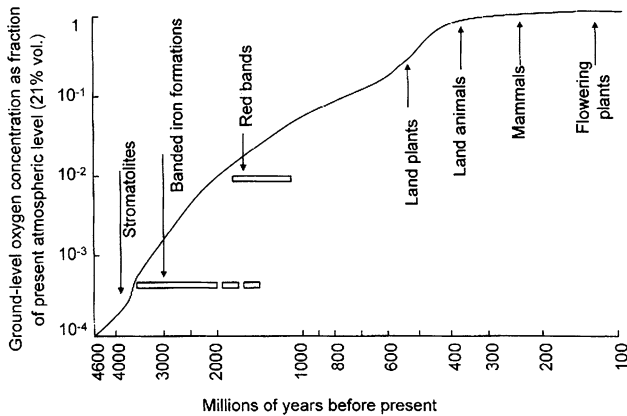
Fig. 6 The evolution of organism types with the rise in oxygen, which can be followed by the formation of minerals, such as iron bands. The appearance of complex organisms eukaryotes began about 2000 million years ago
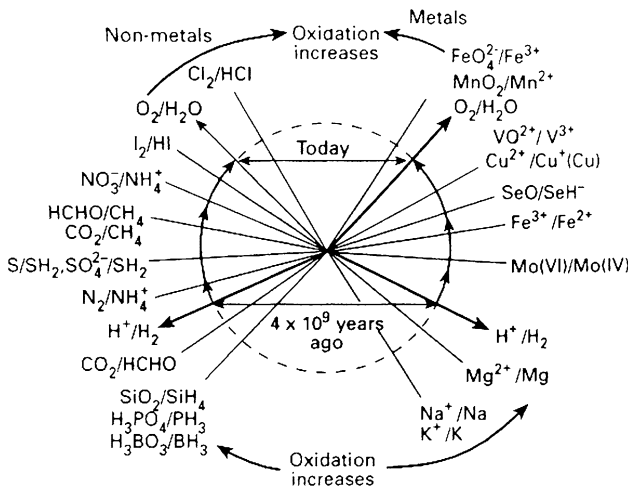
Fig. 7 The standard redox potentials of the elements most involved in organisms at pH = 7.0. Note redox potential could not be lower than the H^+/H_2 potential (-0.4 volts) initially and the probable crude average potential of several non-equilibrated redox pairs was higher—around (-0.2 volts). The swing to today is toward the redox potential of O_2/H_2O ($+0.8$ volts) but this is above the crude average of the non-equilibrated total system. The order of appearance of changes in the ecosystem is taken to follow the series indicated

today's global average which maintains a surface temperature of around 300 K although there have been considerable fluctuations (Corning 2001). The fluctuations have not affected the general direction of chemical change much though they have varied its rate considerably due to the consequent upsurges and downturns in oxygen generation by organisms and the variation in numbers of organisms. The gradual build up toward the present day steady state of oxygen concentration in the atmosphere, which may have been reached 500 million years ago (Williams 1961), does not mean that changes in the sea and

land have also ceased yet. There is still a vast reserve of reduced material, especially note sulfides, on or near the surface of Earth. We can expect trace element concentrations to change for millions of years to come but note that these changes can be affected too by volcanoes and by the novel impact of mankind's industry, see below.

There is one further environmental change, which has only been appreciable in the last 2 billion years, that is the appearance of an ozone layer. This layer protects the land from high-energy radiation and has been a major factor in organism evolution.

We turn next to the effect these environmental changes, always close to equilibrium, had upon organisms which are the second part of the ecosystem. They themselves generated the changes of the environment but then they had to adapt inevitably to the new environmental conditions since their survival was dependent on mastery of the released "poisons"—both non-metals and metals. All organisms are far from equilibrium of course and cannot adapt quickly—they are conservative.

## 8 The first stages of evolution: prokaryotes (Leach et al. 2006)

Apart from improvements of energy capture from light and of metabolism utilising coenzymes the subsequent development in prokaryotes was to put to use the production in the environment of poisonous O_2, SO_4^{2-}, Fe^{3+}, NO_3^- and inert N_2. These chemicals from outside cells, were not just sources of S, Fe and N but, with O_2, could yield energy, ATP, in novel ways when reacted across membranes with the reduced debris from cell death which was taken into the cells. This advance, the use of so-called oxidative phosphorylation to give ATP, gave rise to organisms independent from energy from non-equilibrated sulfides or from light. The new energy capture activity led ultimately to animals and fungi, as opposed to plants, the plants being the source of reduced compounds. The distinction often made between aerobes (able to use O_2) and anaerobes (not using O_2) is not a logical one. The true distinction is between anaerobes, using non-biological energy sources, minerals or light, and organisms utilising *oxidising agents* and reduced chemicals from organic debris, only some of which also use light.

The new prokaryotes which adapted to the oxidising chemicals + debris are called variously sulfate-bacteria, nitro-bacteria, ferri-bacteria and aerobes. (Some are classified with anaerobes but the environment is no longer strictly anaerobic.) We need to note that they had to acquire a battery of new enzymes on the *external* surface of the cytoplasmic membrane, since the compounds are poisons in the cytoplasm. Many of these enzymes are found in an extra-cellular space, the bacterial periplasm. (Very interestingly the new uses of molybdenum (available after removal of much sulfide) are in NO_3^- reduction in this space. However, non-toxic N_2 is reduced in the cytoplasm by low valent molybdenum.) This is a major advance since it introduces a complexity associated with an extra reaction space (Maynard-Smith and Szathmáry 2000; Williams and Fraústo da Silva 2006), an additional compartment which utilises reagents not permitted in the cytoplasm. In particular some copper enzymes are now found in the periplasm. Copper was made available by oxidation of its sulfide. These cells therefore evolved, adapted, through use of "poisons", rejected chemicals from the cytoplasm of cells (Williams and Fraústo da Silva 2006), and their products. We shall observe this mode of evolution many times in our account.

Before leaving the prokaryotes observe that there are cells with different capacities for the handling of different oxidised chemicals. This specialisation, compartmental division of labour, here random in space, led to a cooperative ecosystem which increases in cooperativity continuously amongst later organisms.

9 The evolution of eukaryotes (Maynard-Smith and Szathmáry 2000; Cavalier-Smith et al. 2006)

Eukaryotes are large cells with many compartments and much internal structure. There is no satisfactory explanation from genetics for the appearance of them some two billion years ago but much can be deduced from their protein content assessed from their DNA (Dupont et al. 2006; Morgan et al. 2004). By then there had been a further change in the chemistry of the environment. This is the time when the sea came to have sulfate and almost no sulfide, very little free iron, only ferric at 10^{-17} M, and oxygen in the atmosphere, say at 1% of present levels, Fig. 8 (Cavalier-Smith et al. 2006). At this time cobalt, nickel and especially zinc and copper sulfides had begun to be oxidised although this process remains slow as these minerals were largely buried. All these changes were damaging to early prokaryotes although, as we have described above, they adapted quite well by using reactions outside the cytoplasm and by a lose cooperation between many species. An alternative possible new cellular construction, which underlies the evolution of eukaryotes, was the use of a much greater number of divisions of space inside one cell so that incompatible reactions could be carried out in separate internally trapped, organised compartments protected from one another instead of haphazardly, Fig. 9 (Maynard-Smith and Szathmáry 2000; Williams and Fraústo da Silva 2006). To achieve this evolution needed a much larger cell with a longer lifetime, a more complicated genome, internal filaments holding vesicles in place, greater protection from damage, and clearly a more effective way of recognising and utilising its environment would assist it. As these cells were slow to reproduce it is not surprising that the pre-existing prokaryotes did not
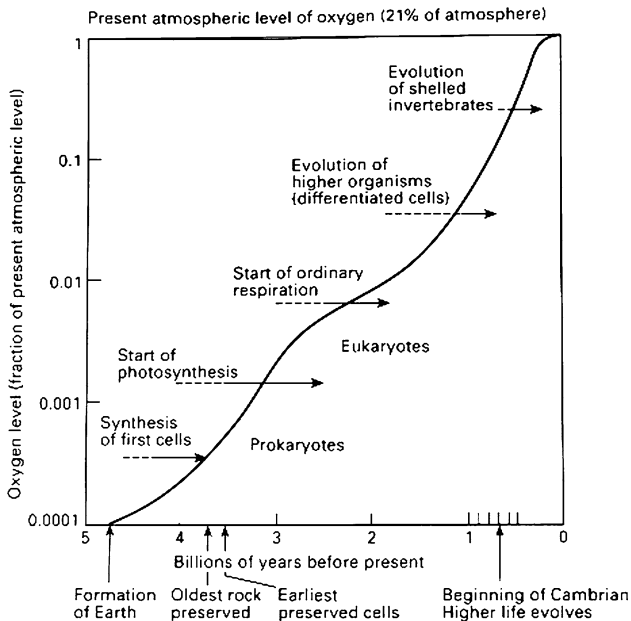
Fig. 8 The rise in oxygen in the atmosphere gave rise to the evolution of different types of organism correlated with the introduction or use of novel elements from the environment and increasing numbers of compartments
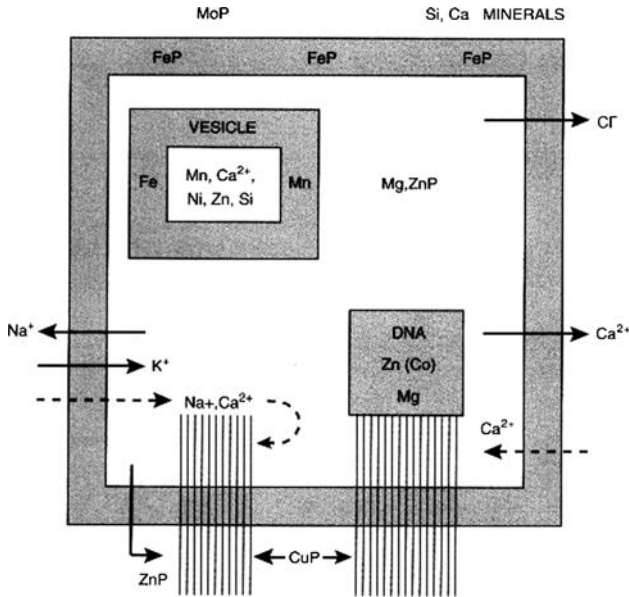
Fig. 9 The outline distribution of ions in a eukaryotic cell showing the different distribution in vesicles and the use of Cu and Zn proteins outside cells

disappear but co-existed with eukaryotes and as we shall see in certain ways the prokaryotes even assisted the eukaryotes.

Now let us look at the internal chemical changes, particularly due to oxidation, which underlie the evolution of eukaryotes (Dupont et al. 2006). The most obvious is the change of the contents of the outer membrane based on an *oxidised* molecule, cholesterol (Cavalier-Smith et al. 2006). This membrane, with no outer membrane, is now flexible so that it can sense, using fields or direct contact, obstacles and change shape. It could also swallow large particles including whole prokaryotes. In addition to using them as a source of food the eukaryotes found a way to incorporate virtually whole bacteria as functional units. These "bacteria" (Margulis 1998), chloroplasts and mitochondria, became the major sources of *compartmentalised energy generation within the eukaryotes*. This is the first example of internal symbiosis. Note that this use of internal small "organisms", much modified today as organelles, mitochondria and chloroplasts, separated the formation of proton gradients essential in energy transduction (Williams 1961), from the main cytoplasm, which is held at a constant pH for good metabolic reasons. The organelles use considerably more manganese (chloroplasts) and the newly released copper (both organelles) than elsewhere inside the cell. These two elements could be quite damaging to the long-lasting DNA of the eukaryote but are less damaging to prokaryotes for which fast mutation can be an advantage. Note also the new copper/zinc superoxide dismutase in the eukaryote cytoplasm and contrast the iron or manganese enzymes of prokaryotes. The Cu/Zn enzyme does not exchange ions while the Fe and Mn enzymes can and are more dangerous to DNA. The increased use of zinc in eukaryotes is further associated with its functioning in DNA transcription factors, zinc fingers, opposite the genes for some novel functions required by eukaryotes (Fraústo da Silva and Williams 2001; Outten and O'Halloran 2001).

Other advantages of novel compartments inside the cell is that they permitted reactions such as degradative digestive hydrolysis (in *acidic* vesicles called lysozymes), peroxide

reactions (in vesicles called peroxyzomes), selective precipitation and crystallisation (in high Ca vesicles) eventually for external mineral production, e.g. $CaCO_3$, and selective formation of enzymes and other polymers for export (in the vesicles called the endoplasmic reticulum and Golgi apparatus) and so placed them away from the cytoplasm where their activities would be damaging. In these vesicles high acidity, high concentrations of bound Cu and Mn for oxidation and high concentrations of Ca and sulfate are variously created.

Another feature of the eukaryotes was the ability to recognise advantageous or deleterious environmental circumstances by sensing of the environment in two ways. Thus the exposed external and flexible membrane carried an electrostatic field gradient which could sense neighbouring fields and change shape (compare cloud formation). The major new response of the eukaryote cell, however, was utilising its calcium gradient in signalling to its cytoplasm (Ca^{2+} concentration 10^{-7} M) by in-flow from the environment (10^{-3} M) Ca^{2+} (Carafoli and Klee 1999). (The gradient was created to assist all life by removing poisonous calcium from the beginning of life.) Environmental changes affecting a cell now caused Ca^{2+} ions to enter the eukaryote cytoplasm momentarily via activated channels. Ca^{2+} there activated many *coordinated fast cytoplasmic physical and metabolic changes* including contraction or expansion of the membrane via its network of filaments and the switching on of extra energy transduction in organelles. The calcium message was amplified by calcium-release from internal ER vesicles. Calcium was rapidly removed back to vesicles and the environment by pumps to avoid poisoning. The resultant responses to the environment are part of the knitting together of the two parts of the ecosystem, environment/organisms, which has increased greatly to today.

Now great disadvantages of eukaryotes were the vulnerability of a long life, and complexity. Complexity was reduced by dropping some pathways essential for all life, e.g. N_2-fixation, energy transduction, and certain coenzyme syntheses, including heme and Fe/S complexes, while obtaining all of them from bacteria. The organelles have their own DNA. Note how all this symbiosis reduces the "load" on the eukaryote DNA. Let us see next how organisms progressed further as the oxygen levels rose and increasing quantities of "poisons" entered the environment. The systematic development of the use of the "poisons" of compartments and symbiosis will be clear, see Table 2.

10 The multi-cellular eukaryotes (Maynard-Smith and Szathmáry 2000; Dupont et al. 2006)

Subsequent evolution depended largely on increase in the number of compartments now of differentiated cells (and organs) in the large multi-cellular eukaryotes, we see all around us with use of increasingly available novel elements. Once again note the increased systems efficiency of combining together internally, compartments, now cells of different capability in different organs, as opposed to that of the previously disorganised sets of different single cell classes separated in space. This development itself required the positioning of many cells (organs) held within a single body by external connective tissue. This tissue was cross-linked via the oxidative action of newly released *copper* in enzymes and hydrolysed periodically to allow growth by the increase of *zinc* hydrolytic enzymes (Williams and Fraústo da Silva 2006). As stated copper and zinc had gradually increased in the environment by oxidation of sulfide to sulfate some 1 billion years ago. It is surely this change of the environment which enables evolution of multi-cellular eukaryotes. As we have pointed out elsewhere it is difficult for organisms to use other elements in the functions which copper and zinc supply (Fraústo da Silva and Williams 2001; Williams and Fraústo

Table 2 Involvement of elements in homeostasis during evolution

Primitive anaerobic prokaryotes	Early (anaerobic) single-cell eukaryotes	Later (single-cell) and multi-cellular eukaryotes (aerobic)
H, C, N, O, P, S, Se substrates and polymers	⟶	
H^+, Na^+, Mg^{2+}, Cl^-, K^+, Ca^{2+} exchangers	⟶	
Ca^{2+} structural	⟶	
H^+, P, S, Fe signals	⟶	
W enzymes ⟶		
Mn, Fe, Mo, low potential enzymes	⟶	high potential enzymes
Ni enzymes (H_2.CO) ⟶		
Ni (urease) ⟶	………… ⟶	plants only
Co(B_{12}) ⟶	………… ⟶	animals only
Ca^{2+} ATP-ases ⟶		
(Zn enzymes) ⟶ ? ⟶	Zn enzymes ⟶	in vesicles and extra-cellular
		⟶ Zn signalling (DNA)
Ca^{2+} rejected ⟶	Ca^{2+} in vesicles and filaments and inner signalling ⟶	Calmodulin, annexin
Na^+, K^+ osmotic and charge balance ⟶		Outer filaments and signalling Na^+/K^+ between cells, Na^+/K^+ ATP-ase
		Organic hormones Iodine hormones
	⟶	Cu enzymes

da Silva 2006). The novelty of separate cells (later organs) in one organism demanded novel communication through the inter-cell (inter-organ) extracellular fluid contained now within a total organism of many linked cells (organs). To maintain the homeostasis of cells, this fluid came to have a fixed ionic composition of Na^+, K^+, Cl^-, Mg^{2+} and Ca^{2+} ions, not too unlike the sea. Now these ions cannot act as messengers between cells as they are too highly concentrated in the extracellular fluids and hence are not open to variation there. The new communication system which evolved was that of novel organic molecules, often released from vesicles in a donor cell and which activated distant receptor cells. The messengers, named transmitters (fast acting) and hormones (slow acting), are mainly oxidised organic molecules. The oxidised transmitters, e.g. adrenalin and amidated peptides, in vesicles are often synthesised using copper enzymes. The release mechanism from vesicles due to an external event at the donor cell relies, as before, on calcium input to this cell while the activation of the receptor cell relies on the organic transmitter messenger causing opening of *calcium channels* of this second cell (Morgan et al. 2004; Carafoli and
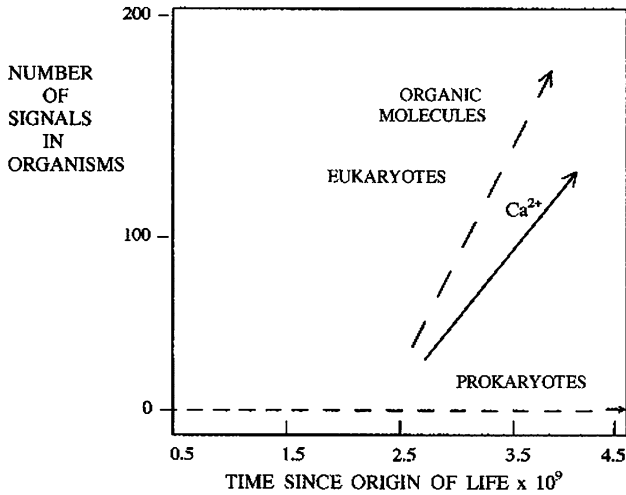
Fig. 10 The increasing use of calcium as a messenger between the environment and all eukaryote cells followed by that of organic molecules as messengers between cells in one organism. The two cooperate

Klee 1999). This is the basis of much relatively fast chemical communication and its evolution is shown in Fig. 10 and Tables 3 and 4 (Fraústo da Silva and Williams 2001; Wachtershauer 1988). Now complex cell (organ) organisation has to undergo continuous modification during growth from a single cell and long-lasting hormones act as controls as, for the most part, they undergo only slow changes in circulating fluids, e.g. sterols, Fig. 11. These hydrophobic hormones are synthesised in cells by localised protected oxidation by iron enzymes (P-450) and they then pass through membranes. They act mostly as long-term homeostatic agents but on change of concentration they cause changes in growth patterns. These oxidised organic molecules such as steroids, thyroxine and retinoic acid act at DNA via zinc finger receptor proteins, present in ever-increasing numbers which are readily recognised in DNA sequences. (Note thyroxine is a compound of iodine produced by oxidation.) We consider that zinc acts as a slow coordinating messenger for these

Table 3 Some classes of calcium proteins in eukaryotes (Morgan et al. 2004; Carafoli and Klee 1999)

Protein	Location and function
Calmodulin[a]	Cytoplasm, trigger of kinases etc.
Calcineurin[a]	Cytoplasm, trigger of phosphatases
Annexins	Internal associated with lipids, trigger
C-2 domains	Part of several membrane-link enzymes
S-100[a]	Internal and external: buffer, messenger, trigger
EGF-domains	External growth factor but general protein assembly control e.g. fibrillin
GLA-domains	External, associated with bone
Cadherins	Cell–cell adhesion
Calsequestin	Calcium store in reticula
ATP-ases	Calcium pumps

[a] EF-hand proteins

Table 4 Distribution of different Ca^{2+} binding protein motifs in organisms

	Binding proteins					
	Excalibur	EF-hand	C-2	Annexins	Calreticulum	S-100
Archaea	–	6[a]	–	–	–	–
Bacteria	17	68[a]	–	–	–	–
Yeasts	–	38	27	1	4	–
Fungi	–	116	51	4	6	–
Plants	–	499	242	45	40	–
Animals	–	2,540	762	160	69	107

The table is based on the total number of all proteins in the DNA sequences available in 2004. The activities calcium proteins are indicated in Table 3

[a] These proteins have single EF-hands and are not signalling proteins, all the remainder are for signalling. From Morgan et al. 2004

hormones and hence for metamorphosis and growth, contrast calcium, which acts to give fast coordinated response.

Now while these evolutionary changes came about utilising the increase in otherwise poisonous copper and zinc, and note also calcium, all three in several functions, there was also a marked reduction in the use of nickel and cobalt which had been of value in the earlier reducing environment (Thauer and Shima 2006). In fact higher plant cells do not use coenzyme B_{12} (Co) and man has no nickel enzymes in his genome and cobalt is in vitamin B_{12}. Again while these multi-cellular organisms gained in efficiency in collecting light (plants) or scavenging (animals and fungi) they became increasingly complex and they became more and more chemically dependent on "lower" species (which still used cobalt and nickel) actually bound to or in them. The whole ecosystem of chemotypes became a unity with hostility only between similar species—but observe that species are not important in systems evolution. Plants became dependent on fungi for minerals and on bacteria for nitrogen while animals became dependent on plants for all elements but on symbiotic organisms for many synthesised chemicals (vitamins). Plants and animals give carbon food to symbionts. Notice how systems efficiency has increased as organisms live together and share chemicals so that each DNA carries a reduced load. At the apex of complex growth is man, the poorest chemical factory, dependent on hundreds of symbiotic organisms, unable to make many essential coenzymes, vitamins, amino acids and sugars. Where is the sense of survival of the chemically fittest but in the system as a whole, dependent on (and driven along by) the environment existing at a given time. While all novel organisms developed complexity in response to systematic environmental change this very complexity made it advantageous to rely on simpler organisms for chemicals necessary for all organisms.

We must stress that the large size of plants enabled greatly increased capture of light and synthesis while the great capacity of animals together with earlier organisms to digest made for a greater and greater rate of degradation of material. Energy was increasingly degraded by this cycle—a large factor in evolution is this increasing rate of entropy production.

11 The fossil evidence

We can follow some parts of evolution directly in fossils. For the period between 3.5 and 1.0 billion years ago the only evidence is of the imprints of soft-bodied organisms. There is
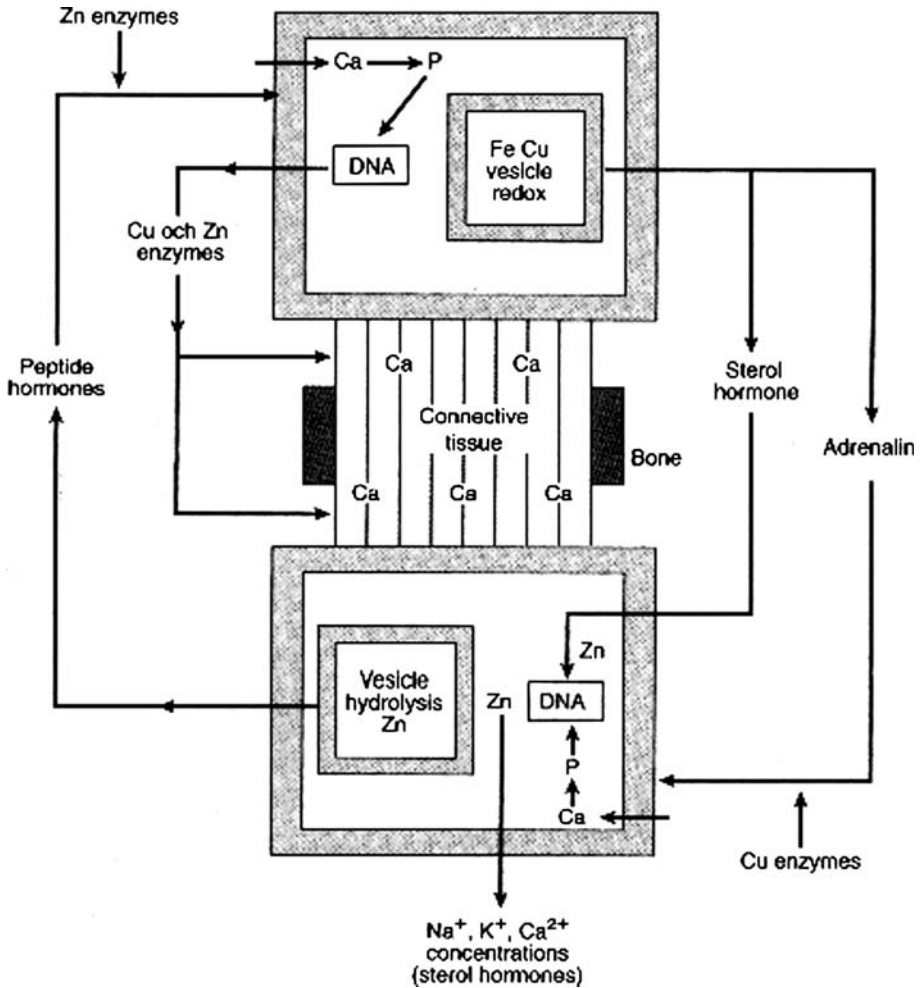
Fig. 11 The introduction of mainly oxidised organic molecules as transmitters, e.g. adrenaline, and hormones, e.g. sterols, as well as connective tissue in the new multi-cellular organisms. Note the connection with increased copper and zinc in the environment and the novel functions of calcium, see text

no certain evidence of the development of eukaryotes from prokaryotes but some images, together with DNA extrapolation from the variety of existing organisms, suggest that single cell eukaryotes arose between 2 and 1 billion years ago. Between 1 billion and 0.55 billion years ago the fossil evidence began to change as a few hard bodies were discovered. It is probably in this period that multi-cellular structures evolved. However it is very clear that after 0.54 billion years ago, the Cambrian explosion, and quite quickly, a very large variety of multi-cellular invertebrate organisms arose and many had hard shells. From then on the fossil record is very rich. By close to 0.5 billion years ago the vertebrates evolved. By that time complexity including nerve and other message systems and the primitive beginnings of a brain had appeared. In about half a billion years the variety and numbers of living organisms developed dramatically following the changes to the

environment. This description of the link between the environment, organisms and fossil evidence will be published shortly with R.E.M. Rickaby.

12 Nerves and brains (Williams and Fraústo da Silva 2006)

This is an immense topic and the evolution of the brain has no simple explanation. The demand on animals is that they scavenge instead of waiting for chance to gain sustenance. Efficient scavenging depends upon sensing and collecting. Now the large animal organisms, which evolved because of internal efficiency of specialised organs, have differently localised sensing and dynamic organs, separated by a large distance, and therefore need the fastest possible communication network to survive. (Motionless plants do not require such sensing except to light (leaves) and gravity (roots) which are generalised units separated by space fields where shape arises as in clouds!!) Clearly what was then needed in animals was connectivity between sensing and mobility equipment that was located differently in space, e.g. senses. Senses, except smell, are not very useful near the ground, but some muscles must contact the ground. The solution found was the evolution of a fast long-range communication between the two by long axons of nerve cells using physical electrostatic switching of ion gradients. The most mobile, fastest, ions and of adequate free concentrations for this purpose are Na^+, K^+ and Cl^- and they were adapted. Observe that all cells from the beginning of evolution had produced gradients of these ions, Fig. 12, through the need to protect against osmotic instability, Na^+ and Cl^- are environmental "poisons". Unfortunately these ions cannot stimulate chemical change at a target, as they do not bind. Hence at axon/axon (synapses) and nerve/muscle junctions of two cells the communication network frequently utilises the already devised Ca^{2+} influx often followed by stimulated organic molecule exiting to link cell to cell, as in earlier eukaryotes. Notice how the use of elements evolves so that gradually the available poisonous elements for primitive life are functional, e.g. Cu, Ca, Na, Cl.

From the nerve cells it is a relatively small step to nerve cell organisation so that all senses and dynamic actions work together and can stimulate cooperative organism response including shape and metabolic changes. No coded response system is involved so that now the environment/organism system is in rapid, independent of DNA, response mode. Behaviour is now not just linked to genes but is dependent on chemical/physical field changes (see clouds). At first it remained, even in these two parts, automatic.
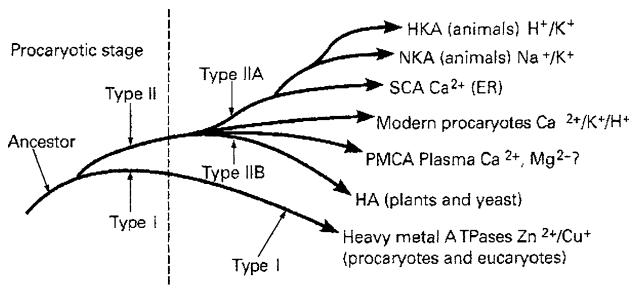
Fig. 12 The development of pumps for ions. Note the two different types. Type II ensured Na^+ and Ca^{2+} removal from cells and later evolved in a multitude of forms associated in part with the nerve cells in animals. Type I removes heavy metal ions such as copper and zinc

13 Memory and mankind

An interesting late feature of this organisation of nerve cells was that they led to memory in the brain in addition to automatic very fast responses. The brain evolved storage of external and internal events in fields (not sequences). These field images, memories, are remarkable and not localised, involving as they do storage of ions, charge, and molecules at many considerably separated but connected brain zones. Thus the image has a shape and a capacity but no molecular structure as in a sequence and it is relatively transient (note again the nature of clouds). The field image, (memory), independent of DNA, is learnt from experience and teaching so that action, response, is no longer automatic or inherited but has a development within the individual organism and in communities and is fast. The images allow self-consciousness in higher animals and then rational thought in man to aid action. Rational thought has given rise to the evolution of man's society without a connection to genes and has allowed action independent from them. The consequence is an ability to manipulate physically and chemically the environment. It is important to see that society evolved very quickly without genetic change. Man was not the first organism to have increased recognition of the environment nor the first able to increase use of it, or to organise to take advantage of it, see single cell eukaryotes. These processes have been gradually introduced and continuously developed in a chemical systematic change of organisms during all of evolution, but man is the first organism to be able to rationalise and manipulate in effect the whole of the physics and chemistry of the environment, of other organisms, and of himself. He does so using chemistry and chemicals external to himself. He is then unique as a species and is a separate chemotype. His dilemma is that he is daring to use this knowledge and ability to gain ascendancy over all other species and also over the chemical environment to some degree with his quite novel chemistry but also with novel waste. There is then the danger of self-indulgent misjudgement of the chemical system. Population increase, over protection of a species, man, and external use of energy/environmental chemicals of all kinds can not go unchecked as genetic change is too slow to compensate. The changes have been made exceedingly fast due to very fast transport and communication network and industrial machines. The whole has the ingredients for causing a breakdown in the environment/organism ecosystem, largely based on genetic controls, on which man depends since organisms have very limited chemical capacity for fast change. Global warming (CO_2 production) is but one chemical result but several others are surely present. In so far as these strictures are correct, a great effort is required by the chemists not just to increase wealth locally and competitively amongst nations through research but to teach the sensitive chemical nature of the environment/organism system which can only be understood through physics and chemistry. Although mankind cannot avoid the consequences of the changes produced already he should be able to develop policies to minimalize their effect and create the best future for himself and the planet.

Finally, we stress that from a systems viewpoint evolution has been chemically consequential and unavoidable given the initial conditions of the environment and cells. Chemotypes appear in a logical order. Species and individuals within chemotypes are a totally different problem, and are probably without explanation being randomly developed. The concentration on internal markers, e.g. biopolymer sequences, and on physical characteristics of organisms can show relationships between species but does not make the essential chemical element connection with the environment.

14 Summary

Evolution has previously been treated as a random succession of organisms seeking survival in a competitive struggle. Emphasis has been on classifying and connecting species and their advantages and how they have arisen mainly through a sequence of random DNA changes. Here we take a quite different physical/chemical systems approach to the evolution of a unity of cell types seeing them as inevitably following and coupled to environmental change, oxidation, which cells themselves forced, Fig. 13. These chemotypes are defined by gross features of chemical element flow, composition and combination, and of physical compartmental diversity and organisation. There is an inevitable progression by adaptation and mutual dependence (symbiosis) and functional chemical complexity. Within chemotypes, random exploration gave rise to species but they are not open to systems analysis. The chemical elements in the chemotypes include organic and some dozen available "inorganic" elements, and the environmental changes in them has been the major cause of evolution, giving it a direction, Table 2. The system is then an ecological unity continuously affected by products from organisms, ejected to create an environment waste, which then back react to force adaptive change on organisms. We see the progression as leading inevitably to the characteristics of the latest chemotype, man, with novel environmental connections and risks as he extends the organism/environment chemistry to include all the elements of the Periodic Table. In no way is man a special creation and he may not be the end-point of chemical systems evolution, Fig. 11. Some two billion years or more ago bacteria caused a parallel environmental switch when they released oxygen and generated a change in the availability of certain elements with dramatic consequences for evolution. Will our waste have a similar effect, see Fig. 5? The whole ecosystem, largely cyclic, was and is driven by energy degradation. *Seeing this perspective opens a huge range of exploration for chemical study*. We are left with a puzzle as to how the changes of the environment could impact directly upon genes

Fig. 13 The systematic introduction of new chemotypes in time with a schematic illustration of the cause behind the introduction of novelty—the slowly increasing oxidation of the environment. This gives evolution a direction in a chemical system. Species can be random within the chemotype classes. The central axis of the cone is time and is associated with the radial axis oxidation (oxygen levels) of the environment, which increases toward the centre. Any chemotype can exist within a newly conical section
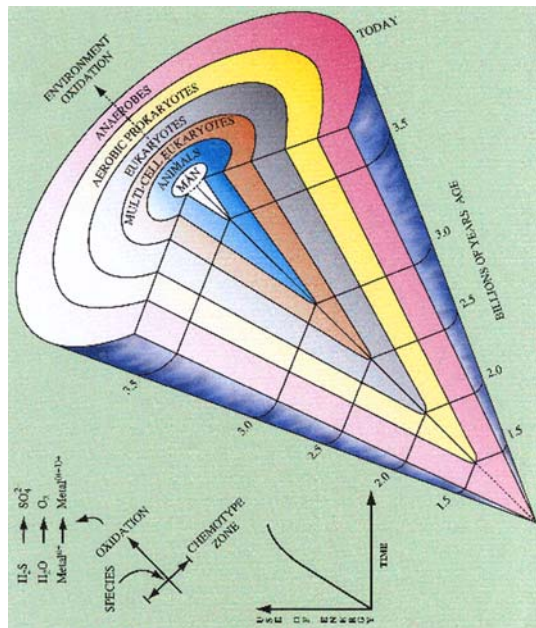
(Williams and Fraústo da Silva 2006) as appears to be the case in some quite particular cases (Janlonka and Lamb 1995; Neuberger et al. 2003). It is fascinating to see the systematize chemical properties which lie behind Mendelev's Table appearing in the uses of the elements in living organisms.

15 A note on Gaia

Lovelock (2000) has advocated for some time that there has been an evolving steady state relationship between the *organic materials* of life and the changing atmosphere which has reached an optimal condition between present day material and the atmospheric gases. The oneness of the steady state is called Gaia. In this article and elsewhere (Fraústo da Silva and Williams 2001; Williams and Fraústo da Silva 2006) we have indicated that such a steady state has never existed. Evolution on the chemical scale is the chemistry of the changing environment, caused by life and affecting organic and inorganic chemicals, which force adaptation of organisms. Organism chemistry of some twenty elements changed but slowly in response to the environmental evolution since organisms are conservative. The system as a whole will attempt to reach a steady state, Gaia, not of chemicals but of energy capture and degradation but the material balance in that final condition is not predictable, involving, as it must, very many elements. Thus "Gaia" now representing present day life is at risk from global warming and many other changes today but they are just the human contribution to environmental change that will lead to further evolution, which we cannot predict. Life has always been forced to change by its own pollution of the surface of Earth.

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Note

Since the material in this survey was published in Maynard-Smith and Szathmáry (2000) and Williams and Fraústo da Silva (2006) several authors have analysed DNA/RNA sequences in greater detail, see C. Andreini, L. Banci, I. Bertini and A. Rosato. J. Proteome Res. 2006, **5**, 3173–3178, J.W. Torrance, M.W. MacArthur and J.M. Thornton, Structure, Function and Bio-information, **71**, 813–830, 2008, and Y. Zhang and V.N. Gladyshev. Chem. Rev. 2009 (May) and the references in these articles. The conclusions strongly re-enforce the connection we have described in this article and previously between the environment changes and the evolution of organisms which has to be via inorganic chemistry changes, principally oxidation.