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Systems biology of evolution: the involvement of metal ions

R.J. P. Williams

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Abstract This article outlines a novel way of looking at the relevance of metal ions in organisms to the whole of life as part of an ecosystem bringing together the environment and cellular life. It does so by examining the evolution of the environment due to the ''waste'', mainly oxygen, from cell metabolism which back reacts with the cells themselves. The oxygen generates a progressive change in the metal ions in the environment. The resultant change is buffered by ferrous iron and sulfide and is therefore slow so that there is a gradual adaptation of life to utilisation of elements in a time sequence. In order to appreciate this, systems (biological) evolution, it is necessary to describe the very nature of a thermodynamic flow system of which life is an example.

Keywords Evolution: metal ions in · Ecosystems · Metal ion evolution · Prokaryote metals · Eukaryote metals · Organisation and order

Introduction to systems

There is a general awakening of interest in Systems Biology to lie beside the more familiar Molecular Biology. Systems can generate shape due to energised activity but do not need *ordered* structure, as in DNA/RNA, to persist or recur. Such shape arises from material flow under boundary constraints of either external fields or physical restrictions due to the continuous absorption of energy, which the material degrades. We shall call such a system organised (not ordered). The simplest example is in the formation of rain clouds. A cloud has dynamic shape, roughly constant, created by energised water (vapour and droplets) moving in a directed, not chaotic, flow due to the environmental field gradients of temperature, gravity and pressure. Clouds can be classified in explicable ''types'', e.g. cumulus, stratus etc. due to the variety of gradients in which they form. The types can be explained but the variety within each type is too complicated to be rationalised. Ultimately water on Earth just cycles in a larger organised system from sea, to land, to sea, via clouds in large part. All such systems, Fig. 1, are entropy driven (material) cycles since degradation of energy by them produces an increased number of quanta and resulting disorder. One quantum of sunlight is approximately equal to twenty quanta of thermal energy (heat) at ambient temperature (1 hv $\rightarrow$ 20 kT). Similar energy degradation occurs in the energised ozone layer where oxygen cycles to and from ozone, giving a *chemical* flow pattern. The layer

R.J.P. Williams (✉)
Inorganic Chemistry Laboratory, University of Oxford, South Parks Road, Oxford OX1, 3QR, UK
e-mail: bob.williams@chem.ox.ac.uk

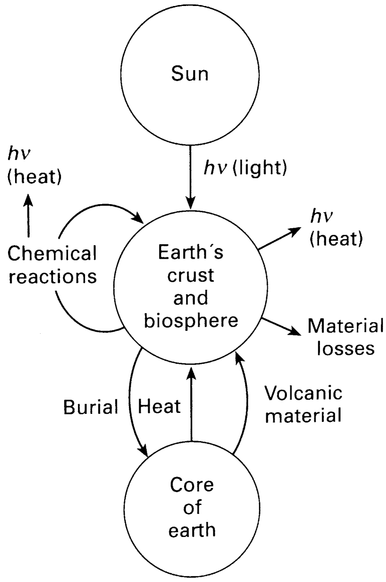


Fig. 1 The flow system of chemical elements (in compounds) from the environment to inorganic and organic systems under the influence of energy and their cycling on decay. This is our ecosystem

has persistent depth, shape. Addition of other chemicals to a system, such as freons to the ozone layer, alters the steady state and its shape. A significant point is that each system has an optimum steady state condition associated with optimal energy capture. A system of energy and material can therefore also generate temporary ordered structures, e.g., O_3, in energised molecules as well as gradients. A combined dynamics of organised flow along gradients and temporary structure is the essence of a biological cell system to which we turn next. (For a more detailed description of systems see Williams and Fraústo da Silva, 2006 and the references in Chapters 2–4.)

Cell systems

All of a cell's components are energised either in their chemical covalent bonding giving ordered structure (organic chemicals, compare ozone) and/or in their concentration within the cell where a gradient exists across a cell membrane. To create the simplest energised *organised* flow, which probably predated a living cell, there is no need for a *coded* ordered molecule but there is need for at least temporary confinement, an energy source, e.g. the sun, and an environmental supply of material, (Fig. 1). Let us assume that a cellular membrane structure of lipids was formed very early, say 4×10^9 years ago, as an energised persistent unit. Diffusion in and out and internal synthesis, both affected by radiation, in what is often called a protocell, could occur so that gradients of ions and sets of unstable molecules were formed. Here any internally created large persistent molecules form new flow restrictions. If such protocells started in the sea rejection of Na^+, Cl^- and Ca^{2+} (Mn^{2+}?) would have been necessary for kinetic, physical and organic chemical, stability (kinetic persistence) and all cells to this day reject these ions. This protocell has a selected chemical nature—it is a *chemotype*. We shall see how these rejected ions (initially poisons) became an essential ingredient in evolution of organisms over billions of years.

Looking next at a self-reproducing living system, it must be very different from a protocell which is just able to re-appear. Self-reproduction is a novel feature of strong persistence but now in daughter chemotypes. They have handed-down *ordered sequences* in *structures*, DNA (RNA), which provide new boundary conditions for flow in the cell directly or due to ordered sequences in proteins. These structures limit the *organisation* of the flowing cell metabolism through chemical fields but are not permanent, (see Fig. 1). The cells came to have a cycling internal cytoplasmic chemical composition of ions and molecules, constantly reacting, to optimalise survival, including controlled concentrations of free metal ions of concentration Mg > Fe > Mn, Co > Ni > Cu < Zn, Fig. 2, easily followed in evolution, Fraústo da Silva and Williams (2001). These ions are as essential as non-metals for catalysts, messenger systems, structure and so on but they were not all introduced into cells activity at the same concentration in the same period of evolution. It is the changing environment which leads to this evolution. This is explained in the sections that follow.

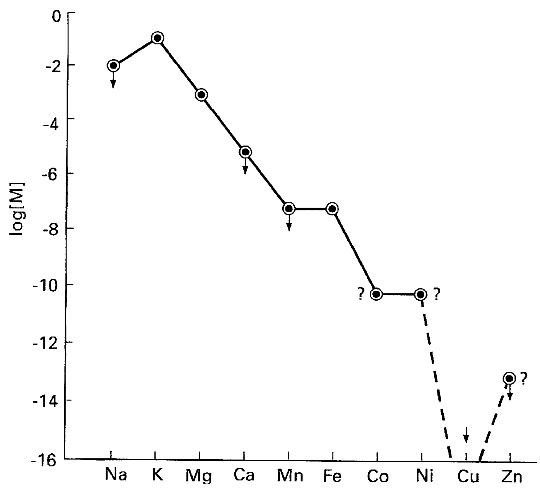
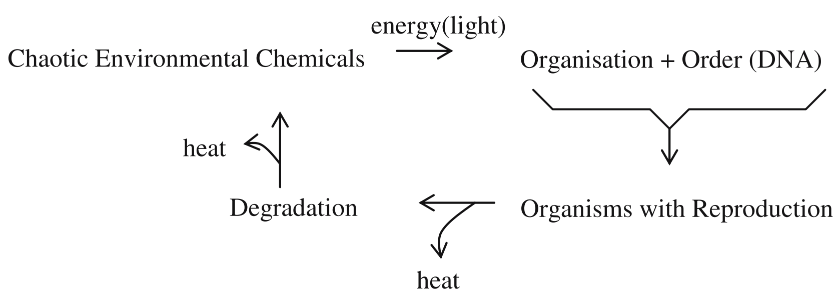


Fig. 2 The homeostatic state of the free metal elements in the cytoplasm which has had to be closely maintained throughout evolution. The metal ions are closely equilibrated with their ligands. Their distribution in cells and organisms generally in evolution is easier to follow than the non-metal elements in multitudes of covalent compounds

Cell cycles and waste

This optimalised system of homeostasis of *the cytoplasm* with DNA/RNA protein instructions, to organic molecule and metal ion flow within a membrane is not fortuitous but comes about through the build-up of energy degradation with time.



Systematic organisation of cell chemicals is as inevitable as formation of clouds or of the ozone layer but self-reproduction has added a huge gain to chemotype persistence. If the above cycle of the most primitive cells had been complete then there would have been no evolution.

The basic chemistry of these and all subsequent organisms had to be the production of *reduced* covalent organic molecules from CO_2 and H_2O and certain gradients of inorganic ions in the cytoplasm. Only *reduced* carbon compounds can make adequately persistent polymers, DNA and proteins, so that early cells rejected *oxidising* chemicals, especially oxygen, as well as Na^+, Cl^- and Ca^{2+} (Mn^{2+}). Cells then had to adapt to this developing oxidised environment, which they themselves had produced, but could only do so slowly. Note the consequent change in groups of species, anaerobes to aerobes, is a forced, self-imposed, change of chemotypes.

Prokaryote evolution

We all consider that the earliest cells were anaerobic and they could not use the full panoply of available elements today as the atmosphere had considerable amounts of H_2S. In this environment the precipitation of sulfides is in the order of limitation of the ion concentration

$$Cu < Zn < Ni < Co < Fe < Mn \text{ and } Mo < W$$

Hence strict anaerobes even today are very low in especially Cu, Zn and Mo. There is little Ni and Co but the ions Fe^{2+} and Mn^{2+} with Mg^{2+} were available at 10^{-6} M or thereabouts and were plentiful in cells. We find anaerobes use some Ni and Co (B_{12}) as reducing catalysts and much Fe as the prominent electron transfer agent while Mg ions are used in weak acid catalysis. It appears that Mn ions were largely rejected. The first considerable development was that of aerobic bacteria which could now utilise Mo not W and Cu, due to the oxidation of sulfides. The copper ions were not used in the cytoplasm but outside its membrane in the periplasmic space acting on novel substrates produced by oxygen, e.g., NO_2^-. In all these prokaryote cells we know there was a large role of Mg and Fe ions as internal control messengers to transcription factors and between metabolic pathways but Zn, Cu and Ca ions were not involved (Fraústo da Silva and Williams 2001 and references therein).

Eukaryote evolution

By two billion years ago the environment, part of the ecosystem, had changed to be largely oxidising Fig. 3. The change was so slow as O_2 was removed at first by the ferrous and sulfide in the sea. The need was for organisms to adapt to the new environment and they did so by the development of a multi-compartment larger, slow-reproducing, cellular system, the eukaryotes, side by side with the fast-reproducing prokaryotes. The great advantage of extra compartments is that they allow oxidative chemical reactions to be isolated from the required reductive activity of the cytoplasm and the storage of ions, not allowed in the cytoplasm in vesicles. These larger cells also incorporated aerobic bacteria, organelles, (*symbiotic compartments*) and had filaments, and a flexible membrane. A necessary and advantageous change of messenger communication was now required between the now-flexible compartments to give homeostasis and from the environment to give a much increased sensitivity to cellular surrounds. The main messenger was based on the Ca^{2+} ion gradient generated by the rejection of this ion (Carafoli and Klee 1999).

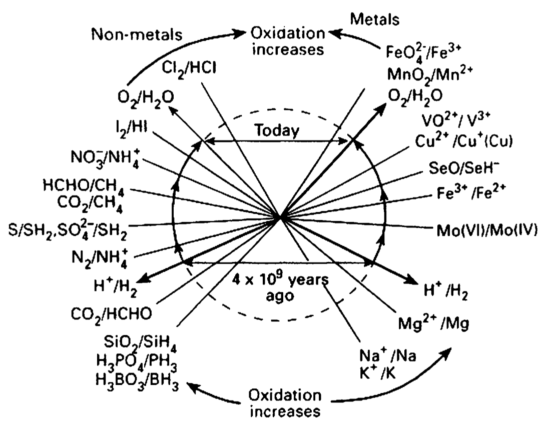


Fig. 3 The systematic, directed, changes of oxidation state of the elements due to the continuous and accelerating increase of O_2–production.The environment was forced to change and it could change quickly. Survival of organisms then had to follow a series of chemotypes which could manage the environment where the total ecosystem gradually increased its energy flux—a thermodynamic system driving force

A novel feature therefore is that the eukaryote responds quickly to the environment without involving DNA or protein sequences. The cell can change its shape and metabolism, its *system* organisation, in a millisecond but these changes are neither persistent nor exactly reproducible. The fast response is now of organisation, still involving restricting order, but the ordered units (DNA etc.) do not alter, the gradients (the organisation) do. Gradients are *extensive thermodynamic* system properties dependent on continuously variable concentration and are unlike ordered units for boundary constraints (DNA) which have *intensive properties*. Once this fast action of coordinated internal responses developed evolution advanced not just by slow structural order and reproductive intensive changes, but by utilising more and more fast changing flow characteristics, extensive properties, quickly sensitive to the environment, for example, using senses. We also know that zinc ions now become used in transcription factors and that copper ions become more generally used in vesicles. Zinc and copper were now more available due to the partial oxidation of their sulfides.

Multi-cellular eukaryotes

By about one billion years ago the oxidative chemical changes of the environment part of the ecosystem were complete, see Fig. 3, including much higher concentrations of zinc and copper ions in the environment. The parallel change, later in time, of the evolution of organisms was the appearance of multi-cellular eukaryotes, groups of cells held together by now extracellular, connective tissue, cross-linked by Cu enzymes, with a further novel communication system of mainly oxidised organic transmitter (produced by Cu enzymes) and hormonal chemicals acting from cell to cell through controlled extracellular fluids Fig. 4. The hormones acted on zinc-containing transcription factors. This system's development

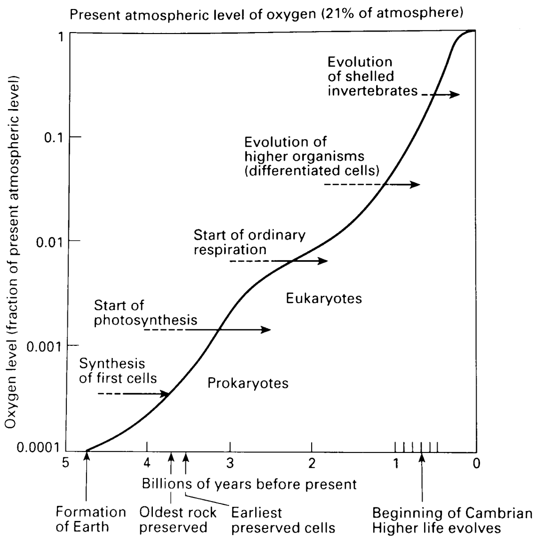


Fig. 4 The parallel development of complexity of organisms arising from the increase in the oxidation of the environment, see Fig. 3. This gave advantage to compartmentalised organisms which could utilise oxidised chemicals more effectively but were disadvantaged by the difficulties of complexity and became more and more dependent on lowly organisms for chemicals

was linked to many uses of inorganic elements further released from sulfides (Zn, Cu especially), and of oxidised organic structures especially in extracellular fluids and vesicles. These organisms have slow reproduction, they are new chemotypes but are dependent on external symbiosis, including assistance from prokaryote chemistry for vitamins, e.g. vitamin B_{12} (Co), but also, as with all eukaryotes, by internal cell symbiosis by mitochondria which produced heme and Fe_n S_n cofactors. At the same time we observe a decreasing use of Ni and Co since the substrates upon which they acted in anaerobes were no longer in the environment, e.g., methane.

With multi-cellular organisation the organisms also become users of increasing energy (large plants) and better, faster scavengers (animals). These gains belong again to a driven ecosystem of symbiotic co-operators avoiding waste. The *chemotype* system development is not random, much though that of species is but, with the environment, is part of an inevitable evolving ecosystem. There was no other possible evolutionary route than to employ more and more energy utilisation the more and more opportunities that were produced by the enforced oxidation changes of the environment.

Higher animals

As advanced animals increased in numbers sizes of their compartments the need for more sensitive rapid response to the environment grew. They needed faster long-range communication for scavenging and protection as the distance between their mobile parts, muscles, and their sensors, eyes and ears, increased. The development came about through the introduction of a *physical*, as opposed to a chemical, very fast messenger system—an electrochemical depolarisation wave in an extended projection of the cell—the nerve axons. The chemicals employed were the very ions rejected by prokaryotes (or even by protocells), Na^+ and Cl^-, stored now in extracellular fluids. These ions have virtually no chemistry. Once again a new chemotype evolved in a systematic sequence. The Na^+ and Cl^- nerve messages required a coupled chemical act to be effective–they used the earlier messengers, Ca^{2+} and organic transmitters, at cell termini. Note that the use of new gradients in a new chemotype, allows quite novel organisation, activity, not linked directly to order (structure). The DNA and the proteins do not change but the gradients of ions do.

Brains and mankind

By connecting the nerves to central units, the brain, in which there was storage of messenger chemicals dependent on nerve messages received, a final possibility of the development of the environment/organism/energy ecosystem arose, that of stored (i.e. persistent) gradients holding images of the external world. The brain could learn and could be taught to manipulate as well as respond to the environment so that the organisms, finally in the form of man, no longer changed the environment by accident but did so by introspective reasoning dependent not on DNA changes, i.e. by thinking based on stores not molecular structures. The elements of the environment now available are not those in the sea but all of those in the Periodic Table. Looking back the route to man is clear in all of the evolution of organised systems starting from single cells. We may say it was inevitable due to the staged release of especially metal ions. Genes (ordered structures) are no longer dominant in the behaviour of man but this release from DNA control began with the fast signalling by calcium ions in the earliest eukaryotes. The brain has allowed the environment to be more rapidly integrated with, not just recognised by an organism. How man manages the system is now a critical feature of evolution not due in any way to random change of internal molecular structure. Finally for our own benefit we must ask what is the optimal condition of this system and those of us interested in metal ions must look carefully at all novel distributions in the environment. This article aims to show that a considerable effort is needed in the study of metal ions in compartments. This knowledge may lead to an understanding of cell evolution together with that of our environment, which cannot be followed by the study of the organic chemistry of cells.

To read this view of systematic evolution in detail may I refer to Williams and Fraústo da Silva (2006). The origin and details of the various ideas concerning systems are given there. More specific references to the biological chemistries and their separate evolution are Maret (2001); Birch (1993); Williams and Fraústo da Silva (2002); Beinert et al (1997); Hill et al (1998); Stryer (1981); and Williams (2003).

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