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REGULAR ARTICLE

Two Approaches to the Study of the Origin of Life

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Abstract This paper compares two approaches that attempt to explain the origin of life, or biogenesis. The more established approach is one based on chemical principles, whereas a new, yet not widely known approach begins from a physical perspective. According to the first approach, life would have begun with—often organic—compounds. After having developed to a certain level of complexity and mutual dependence within a non-compartmentalised organic soup, they would have assembled into a functioning cell. In contrast, the second, physical type of approach has life developing within tiny compartments from the beginning. It emphasises the importance of redox reactions between inorganic elements and compounds found on two sides of a compartmental boundary. Without this boundary, "life" would not have begun, nor have been maintained; this boundary—and the complex cell membrane that evolved from it—forms the essence of life.

Keywords Biogenesis · Thermodynamics · Periodic system · Element selection · Metals · Hydrogen

1 Introduction

This paper analyses two contrasting approaches of study about how life could have originated. The presently dominating approach to biogenesis I term the chemical approach. It formulates many possible, yet mutually unrelated reaction mechanisms, each leading to one particular compound, the compound of chosen interest. For

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example, Miller's (1953) experiments began from Urey's premise that "organic" compounds, at present essential to life and also commonly found in the universe, could easily have been formed abiotically on Earth as well. Whatever the conditions of their formation in space, here on Earth they would have formed as possible "seeds" of life under the influence of significant energy input, such as by electric charges or "shock waves". Miller, indeed, found simple amino acids among a vast array of reaction products, which would suggest the initial significance of peptides or simple proteins during biogenesis.

Living structures would thus have been preceded by a pre-biotic phase of undirected chemical reactions happening, either in some tar or primordial organic soup, or on the surface of crystals of clay (Cairns-Smith 1982) or minerals (e.g. Wächtershäuser 1992). Such a pre-biotic phase would have been followed by a phase in which these reactions were mysteriously assembled and organised, from then on forming a living system in which they operated in an orchestrated and directed way. However, this leap from a tar or a soup into such an orchestrated system has never been the focus of analysis in the chemical approach; we only possess descriptions of compounds and reaction mechanisms before and after this leap. Moreover, only occasionally are the pre-biotic reactions described in terms of the thermodynamics of the individual reaction mechanism, but never in those of the thermodynamics or the kinetics of the formation and maintenance of physical structures.

But what was the significance of these simple compounds for the formation or breakdown of other compounds in the same environment? Under present conditions, amino acids or peptides form the building blocks of proteins, usually the catalytically inactive, apozymatic part of the catalysing molecule (White 1976, 1982). But in what reactions could they have been involved initially? Where did these reactions lead? What were the exact reaction mechanisms and their thermodynamics; that is, why did a reaction happen at all? In what concentrations did the enzymes occur, and what were their lifetimes and their turnover rates? How, therefore, were the production and turnover of the amino acids or of the polymers they may have formed, along with their products, incorporated later in the biochemistry of a complete cell? In short, what could have constituted their exact role in the early metabolism or replication system? These questions and many others also pertain to the compounds they are supposed to react with, as well as to their reaction products.

The established theories that begin with a primordial organic soup in which living structures would have originated leave five principal questions unanswered. (1) Why and how did a particular set of compounds and no others come together, and why and how were they isolated or encapsulated as an interactive system within some compartment separated from the surrounding environment, a proto-cell? (2) How did the initial metabolism operate, and on which elements or compounds could it have been based? (3) How could this metabolism maintain and replicate these compounds and their interactions? (4) How could this proto-cell generate energy for its operation from scratch? (5) Finally, how did the metabolism and energetics of the cell evolve in conjunction with major changes in the surrounding chemical environment? No theory gives insight into how living structures arose as unique structures separate from their surrounding environment. None of these five

questions has been answered in experiments concerning the formation of individual compounds, certainly not in Miller's (1953) classical ones—so another approach seems apposite.

Alternatively, structures can arise as a result of a flow of energy, and are maintained as long as this flow continues (e.g. Harold 2001). Physical processes of energy extraction, transduction and dissipation are basic to the origin and maintenance of living structures (e.g. Prigogine and Stengers 1984). Physically, living structures are defined as unlikely, dissipative aggregations of interacting molecules. As a process requiring little time is said to be functional to that requiring more (von Bertalanffy 1968), functionality is defined by a difference in time scales of interactive processes. This means that they may obtain a natural order of interdependences resulting from these differences in time scales of their operation.

The key concept in this approach to biogenesis is, therefore, the throughput or transduction of energy through a system of reactions; this energy flow is the sine qua non to life. This flow runs through a thermodynamically open system, which generates energy at some point, and which it eventually dissipates as heat, as waste products, or as both. The generation and maintenance of the energy flow results from an electric charge disequilibrium between inside and outside a membrane surrounding a structure. Once extracted, this charge, in the form of a flow of electrons from the environment into the structure, can be transferred from one compound to the next, with polymerisation as one result. Thus, due to chemical selection, the flow became directed, running through processes that operate in concert. This continuous energy flow leads to the dynamism of the biochemical and morphological processes that we know as organisms.

The question, therefore, is not how particular chemical compounds could have been generated, as the chemical approach assumes, but rather how an energy flow originated. A next question is which chemical pathways and the hierarchical arrangement of their time scales facilitated the course of this flow. It is thereby interesting to know how these pathways maintained, and also how they became more and more specific and more efficient. The underlying physical theory dictates exactly which elements may have been involved in the first and in later biogenetic steps, and why (Williams 1981; Williams and Fraústo da Silva 1996). The view underlying this line of reasoning, emphasising the origin and maintenance of an energy flow, constitutes the physical approach to biogenesis.

2 Analysis of Two Flowcharts

Figure 1 outlines the chemical approach to the study of biogenesis, and Fig. 2 the physical approach. The most striking difference between the two charts is that according to the chemical approach, the pre-biotic phase contains processes that are considered biotic ones in the physical approach (e.g. Bada 2004). For example, according to Fig. 1, polymerisation of simple compounds into carbohydrates, proteins and nucleotides would have occurred in some spatially undifferentiated organic solution, the primordial pre-biotic soup, whereas cellularisation came at a later stage. In contrast, according to the physical approach summarised in Fig. 2,

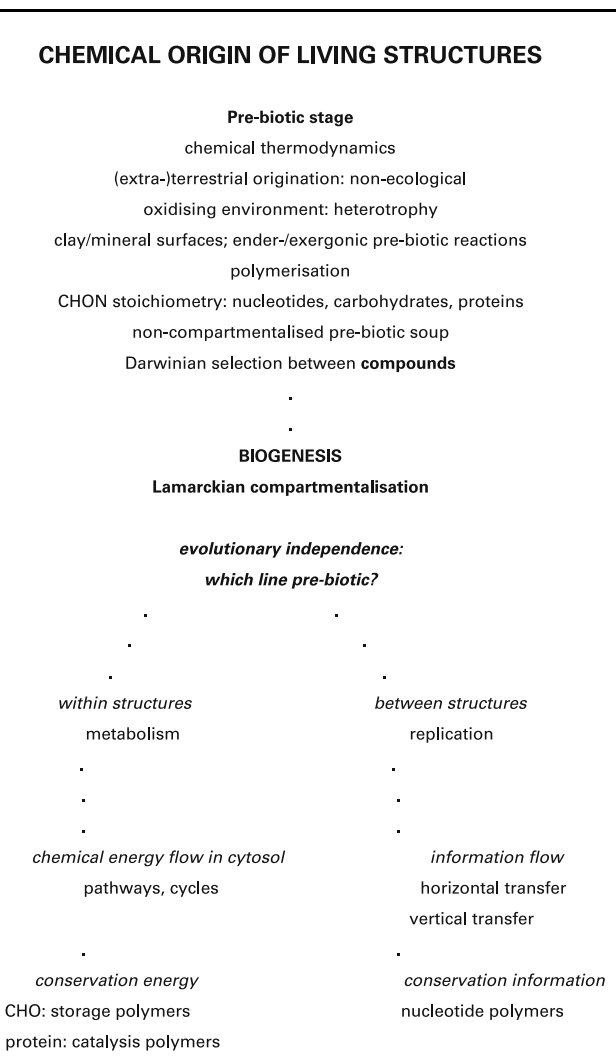

Fig. 1 The beginning of life according to the chemical approach. CHON stands for the elements Carbon, hydrogen, oxygen and nitrogen

processes still basic to the biochemistry of modern life would have absolutely depended on the compartmentalisation of the pre-biotic environment, which led to biogenesis taken place.

2.1 The Chemical Approach

2.1.1 Chemical Aspects

The literature concerning the chemical approach effectively concentrates on pre-biotic processes, trying to understand how, for example, very large or complex

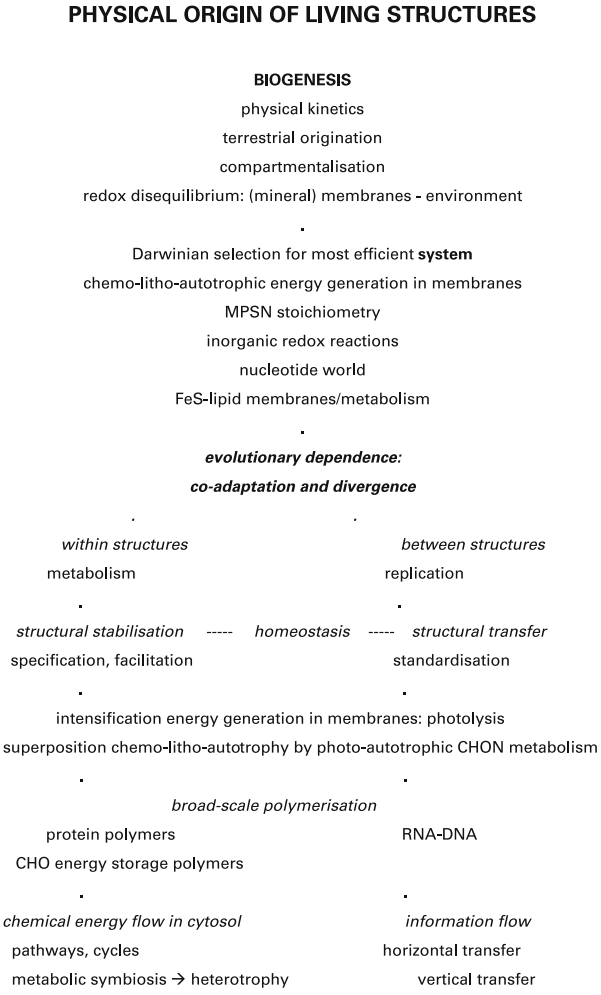

Fig. 2 The beginning of life according to the physical approach. MPSN stands for the elements phosphorus, sulphur and nitrogen; M is a general designation for metals

molecules could have originated outside a living structure (Fig. 1). Such compounds include adenine, ribose, amino acids, peptides, lipids and certain carbohydrates (e.g. Zubay 1996), after biogenesis together forming either a primitive metabolism or a primitive information-replication system (e.g. Eigen and Schuster 1982). They form the very basis of biological systems.

In fact, both the molecules concerned, and the processes in which they were involved, seem to have been highly complex and energy demanding from the beginning. Certainly, if all this were to work after cellularisation, many things would have had to happen nearly simultaneously and rapidly (Lazcano and Miller 1994). The mechanism of this sudden transition of several independent and undirected processes into a spatially and temporally structured, viable system of

processes, however, remains itself completely unexplained. Yet, finding out about this mechanism is exactly the point of the biogenetic problem. Not knowing this mechanism is a major stumbling block in our understanding of life's origin according to the chemical approach.

Several questions arise. (1) What caused this transition, and how did it happen? (2) Did the molecules form according to the same reaction mechanisms we observe today, or were those conditions, such as the chemical purity of the initial solutions, different, neither containing nor forming tars, as in some experimental results (Miller 1953; Decker et al. 1982)? (3) Had they previously been forming initial pathways already, despite the absence of a membranous envelope, (4) what would the lack of that capsule have meant to their minimum and relative concentrations and, hence, to the operation of these mechanisms? (5) Or were those pathways, instead, initiated with or even after the formation of the membrane?

But what did that membrane itself, once formed, imply to the production, the operation, the concentrations, or the diffusion of the compounds encapsulated? Obviously, preventing compounds from diffusing away into the environment may imply that, as a result of the capsule, the concentrations increased. When and how strongly, too, did osmosis, resulting from these high concentrations, begin to influence metabolic processes? Did the membrane consist of lipids only, or were pumps included right from the beginning, regulating material exchange and osmosis? And why did this encapsulation happen at all; what exactly could have been its chemical or energetic advantages? Was it the reduction of diffusion rates, or obtaining the right relative concentration and reaction rates? And what if those rates differed? How did this advantage show up: reaction and diffusion rates of unbounded and dispersed sets of individual compounds, for example, surely cannot possibly undergo Darwinian selection relative to an organised set united by a capsule? Which compounds and processes were included in Darwinian selection and how, and which ones not? And so on.

Concerning the genesis of the information system, Eigen et al. (1981) and Eigen and Schuster (1982) assumed that encapsulation came after the coupled origin of the transcription and translation processes. Again, how did this work, putting those processes next into a new, also spatially confined context? What functions did they obtain within that context, and what functions did they have before? They could not have had pre-biotic informational functions prior to metabolism or to reproduction happening, or could they? Were all processes involved in those informational functions already there, only the cell membrane missing?

2.1.2 Energetic Aspects

The occurrence of the presumed initial chemical processes would have required energy, the origin of which is unclear in the chemical approach. At present, energy generation is exclusively restricted to exergonic redox reactions in the membranes of bacteria, or in eukaryotes to those of chloroplasts and mitochondria. But how did these systems build up, and how and when did this way of energy retrieval fit in with pre-biotic process networks?

According to the chemical approach, the pre-biotic processes would consist of exergonic reactions of fermentation, or would have depended on external energy supplied by electric discharges, as in Miller's (1953) experiments, for example. Thus, life could have begun with heterotrophic chemical relationships, i.e. the consumption—and therefore breaking down or oxidation—of organic polymers in the environment as energy sources, such as carbohydrates (e.g. Broda 1975) or amino acids (e.g. Cunchillos and Lecointre 2002). This obviously assumes a reasonably large store of such polymers present and to be maintained abiotically in the environment, apart from those generated and released by the initial processes themselves. However, at present, all organic polymers are generated and broken down with the help of specific enzymes, which we assume worked that way in the past as well. Where did these specific enzymes come from, and how were they put and kept in context? Despite the need for enzymes facilitating the formation and breakdown of polymers, energy is still required in order for the reactions to take place, as well as for generating, maintaining and breaking down the enzymes themselves. Already in the pre-biotic stage, enzymes thus require yet another set of enzymes for their own formation and break down, and so on, thus duplicating the interactive system of formation and destruction of, for example, carbohydrates.

According to the chemical thermodynamics of enzymatic catalysis, the reactions concerned would have involved carbon, hydrogen, oxygen and nitrogen (CHON, or CHONSP elements when we also take sulphur and phosphorus into account), the bulk ingredients of carbohydrates, proteins and nucleotide polymers. In these polymers, many bonds are covalent and endergonic, requiring significant amounts of energy for their formation. In fact, the covalent bond of carbohydrates is so strong that, under a diurnally or seasonally fluctuating energy supply, they primarily store energy, released by their breakdown when energy thus stored is required. Yet, in pre-biotic times, and during the early stages of cellular life, energy may have been scarce. If generated, it would have been poorly available, simply because enzymes to speed up and facilitate reactions were still lacking. Also, the local mineral supply would have been dispersed, and would have depended on simple diffusion, on currents, or on turbulence. However, as chemical energy, its supply may have been statistically constant rather than fluctuating, requiring a limited storage capacity only, possibly found in amino acids, phosphates, or thiols, for example, that are inefficient in this respect. Therefore, although the mineral energy sources may not have been permanently within reach, the resulting need for them may not have been too severe as long as their use was still limited. This may all have changed only with the development of photosynthesis through the extension of an already existing, primitive carbohydrate metabolism.

The same applies to the formation and maintenance of those polymers constituting the genetic system. Cairns-Smith (1982) (see also Bernal 1967) suggested that clay surfaces facilitated the specific formation of such polymers, an idea Wächtershäuser (1998) adopted later within a catalytic context only for minerals like pyrite. Yet, it is beyond imagination how non-stoichiometric crystal configurations, such as clays, could repeatedly give rise exactly to sequences in nucleotides or amino acids that could subsequently build RNA and proteins, etc.

Moreover, the same molecules should have formed later in the cytosol without the help of such crystals, but by completely different biochemical mechanisms.

Thus, in the chemical approach, the energetics of the various reactions is usually studied in isolation from potential reactions. Similar to the switch in the retrieval and flow of matter, it remains unexplained how the switch in energy generation and flow occurred from pre-biotic, individual reactions in a non-compartmentalised environment to those within the interactive complexity of a cell.

2.2 The Physical Approach

The physical approach differs completely from the chemical one. According to the physical approach, the energy flow keeping the life processes going starts with the formation of compartments in the environment, prior to that of macromolecules, or even to that of their building blocks. Similar to a chemical garden, the mineral membrane may have formed as an FeS or FeNiS crust at the interface of an alkaline trickle from a basalt seafloor into the water of a slightly acidulous and reducing, metal-rich sea (Russell and Hall 1997). As in a battery, the charge difference between the two sides of this crust would have initiated a flux of energy from the seawater into space by means of a transfer of electrons and protons. The flow of the latter formed the initial proton-motive force (Mitchell 1961, 1967; Hinkle and McCarty 1978), basic to all energy metabolism. The early stages of metabolism would probably have depended on exergonic redox reactions between inorganic elements or compounds in the membranes, the energy of which is transferred, first, by phosphates and then by ATP to endergonic reactions within the cell volume. This is still the ultimate basis of energy generation and transfer across and from the membranes, although supplemented in some taxa by energy from photolysis or respiration. Apart from this, the small amount of available energy may initially have been used up immediately and not stored for later use.

Russell also made suggestions about the minerals involved, such as mackinawite (FeS) and greigite (Fe_3S_4) (Russell and Hall 1997; Boyce et al. 1983), about their specific properties, the conditions under which they reacted, and about what compounds they could have formed in turn. The initial chemical combinations or stoichiometry depended, therefore, on the availability of metals and hydrogen as electron donors outside the FeS crust and on that of non-metals as electron acceptors, such as phosphorus, sulphur and nitrogen inside it. The reactions occurring at this stage were mainly low-energy redox reactions involving inorganic elements and compounds in which electrons or protons were interchanged. Quantum tunnelling (e.g. Ball 2004; Dutton et al. 2006) may even have reduced the amount of energy required for the acid-base reactions. (N.B. Due to its wave character, a charged particle, an electron or a proton, forming part of molecule A, has a certain chance of forming part of molecule B, where it can stay subsequently, which is known as quantum tunnelling. This implies that, in principle, the particle is transferred without energy cost.)

Thus, the physical approach tries to answer many of the questions left open by the chemical approach, thereby skipping the phase of pre-biotic chemical development (Fig. 2). Russell and Hall's (1997) membrane does not only contain

the very processes that constitute life, but it primarily serves the energy-generation of the proto-cell, as well as that of all cells ever since. The membrane itself constitutes the mechanism of life, rather than simply being a means of encapsulating it (e.g. Harold 1986). All molecular and morphological structures and processes within the cytosol depend on the energy it generates; thermodynamically, they are derivatives, eddies around the energy flow originating at the membrane. As the initial, most primitive metabolic system was chemo-litho-autotrophic, the evolutionary origin and development of the membrane as an energy-generating mechanism is of prime importance; the compounds and processes within the cell volume can only be understood as the result of its origin, operation and evolution.

The process mechanisms constituting the cell contents or cytosol did not develop in the pre-biotic soup, nor could they be generated de novo within the membrane at the moment this was formed. Instead, they built up step by step and in concert with the development of the cell membrane, with that of the environment, and with that of the carriers transferring the energy from the membrane into the cell volume. A large part of ATP, the most abundant and fastest energy carrier, is recharged continually by the exergonic processes in the cell membrane and discharges again at the endergonic ones in the cell volume. This stepwise evolutionary development of the membrane, in conjunction with that of a suite of transfer and reaction mechanisms that constitute the cytosol, was subject to Darwinian selection. The selection criterion is the efficiency with which energy is channelled through the system; systems differ in efficiency and can be selected for their efficiency.

Hypotheses about all these processes are explicit and can be tested, if they are not known already from biophysics and biochemistry. However, so far, the possibility to formulate explicit and testable hypotheses about the pivotal biogenetic steps reaches farther than the physical and chemical technology and methodology involved.

2.2.1 From Phosphates to Nucleosides

Inside this mineral membrane, pyrophosphates could initially have received electrons and protons, thus forming diphosphate and triphosphate oligomers by condensation; subsequently, they released them again through hydrolysis within the "cell" volume, away from the membrane. It was this initial reaction mechanism, based on electron and proton transfer by phosphate oligomers, that is preserved today, from its beginning evolving and differentiating in a multitude of ways. It thus gave rise, first, to nucleotides and nucleotide coenzymes, and eventually to nucleic acids (White 1976, 1982). One step along this evolutionary line was the addition of heterocyclic ligands to the oligophosphates as charge stabilisers, first by ribose sugar, followed by one of the nucleoside bases adenine, guanine, cytosine, uracil, or thymine, each of them facilitating the condensation-hydrolysation cycle (Pullman 1972). When fused with ribose and adenine, a triphosphate forms, ATP. Yet, the ATP molecule does not exist in an extended form as it is usually depicted, but it is folded so that the nucleoside base is close to the phosphate component, with the terminal phosphate group in close proximity to the 6–amino group of the adenine ring. Moreover, it chelates with several divalent metals, particularly magnesium, which keeps it in this configuration (Bock 1960), and which facilitates its continual

fusion and fission in connection with acid-base reactions of polycondensation (polymerisation) processes (e.g. Williams and Fraústo da Silva 2006).

However, ATP does not operate directly as a general, primary energy supplier, condensing all sorts of compounds directly, but it operates specifically through other nucleoside triphosphate—or NTP—intermediates specific for particular types of compounds (Lehninger 1965, 1971). The transfer of the terminal phosphate group from ATP to nucleoside diphosphates or NDPs happens with nucleoside diphosphokinases as catalysts. These other nucleosides differ among themselves only in their purine or pyrimidine components, transforming ATP into UTP, CTP, or GTP, or adenosinediphosphate, ADP, into UDP, CDP, or GDP, etc. Of these, uridine triphosphate, UTP, constitutes the specific intermediate energy donor for the synthesis of carbohydrates after having received UDP as a phosphate group from ATP. Cytidine triphosphate, CTP, in turn, is the intermediate for the biosynthesis of lipids. Guanosine triphosphate, GTP, participates in this way in the formation of proteins. Adenosine monophosphate, AMP, participates in forming peptide chains. One point of interest here is that the evolution of energy transfer apparently went along different, specific routes according to the compounds concerned. The evolution of these routes may have been independent of each other, and could therefore in principle have happened at different evolutionary times.

The energy transfer from ATP, or from NTP in general, goes via intermediate compounds, one phosphate after detaching from ATP forming an intermediate compound with the molecule to which it is going to transfer energy (Ho 1995). Given the ubiquity of energy transfers from ATP to all sorts of compounds, this means that the biochemical system is highly consistent to allow for the formation of intermediates in all cases.

2.2.2 The Growth of the Information System

As probably the first and most primitive, as well as most ubiquitous of these nucleotides, ATP still accepts electrons at the membrane, subsequently handing them over to the coenzymes NAD or NADP, which, apparently as duplicate structures, would have evolved later. Here, as in the case of the coenzyme CoA, the phosphates do not form the active part any more. Moreover, the phosphate strings as the initial electron carriers eventually developed into nucleotide coenzymes and protein cofactors as well as into a great variety of metabolically active RNA's (see also de Duve 1991), where the bases form hydrogen bridges between the two strands of RNA and DNA. The phosphates themselves form the backbone of the molecule, where, in an abstract way, the sequence of the bases is relevant as information carrier. Thus, the evolutionarily later addition of ribose and a base set into motion a development away from the original function of the phosphates, so that this function can hardly be recognised any more, if at all.

In electron transport, group transport, co-enzymatic activity, and metabolic activity, a multitude of forms of RNA originated from a common root. To allow a fine-tuning of all these more and more complex activities, standardisation of the various metabolic reactions may have taken place, possibly again by some early form of RNA. Eventually, this resulted in the genetic function of RNA—and its

later, more stable form DNA—with respect to the standardised transfer of metabolic functions during replication. Moreover, the operation of RNA as an enzyme could have been facilitated and been made more specific by attaching an apozymatic protein part to it. Similarly, catalytically active metals remained the active prosthetic part of metalloproteins (see Bayman et al. 2003). This would mean that metabolic and genetic functions developed in dependence on each other within a metabolic context, and only later diverged and specialised to some extent. First RNA and then DNA obtained a function in both metabolic and replication standardisation. Later, DNA also obtained the additional, regulatory function in the cell cycle of prokaryotes and eukaryotes, and in the ontogeny of multicellular organisms. Metabolism neither needed to have preceded genetic functions, nor the other way round (compare Dyson 1999); they can have developed in concert, diverging gradually over time.

During the first, integrated period, the tuning of the metabolic processes represented the system information (compare Elsasser 1987). Only when a certain level of complexity was reached, was information stored in a specialised standardisation structure, the genome. As a part of the eukaryotisation process, the genome became encapsulated within the cytosol as the cell nucleus, its operation thus being separated from the metabolic processes. Step by step, the specificity and significance of the genetic component increased, so that we now view the function of DNA to be the storage of information in relation to replication, or eventually to reproduction, possibly even with an independent origin before metabolism developed pre-biotically. Our emphasis on replication and reproduction criteria for defining life according to information-first theories may indeed be putting the cart before the horse. Yet, much of the genome is still a participant in metabolic process standardisation and facilitation through feedback mechanisms (see Keller 2000; Oyama 1985). Stripping life processes from teleological interpretations, as is done in the physical approach, may, in fact, lead to an overall view of the genetic system in terms of standardisation of homeostatic processes, rather than in those of information storage and repair.

It is not clear at what level of complexity the genome added a replication component to that of regulating metabolism. Although in the more ancient non-photosynthetic bacterial taxa DNA is already responsible for replication distinct from metabolic functions, the development of a genome with two distinct functions became compulsory when photosynthesis began to operate.

2.2.3 Photolysis

The electrons donated by the nucleotide coenzymes could have been received by thiols that at later evolutionary stages may have esterified fatty acids necessary for lipid formation (de Duve 1991, 2005). Thus, a nucleotide-thiol world would have originated from which another, carbohydrate-protein-DNA world developed subsequently. This later evolutionary development gained prominence when the charge disequilibrium around the membrane decreased at the time the initial reducing environment changed into an oxidising one (see Anbar and Knoll 2002). In the green and purple sulphur bacteria, light instead of minerals became an important

source of energy for restoring the charge disequilibrium, first through photolysis of hydrogen sulphide, H_2S, and later by that of water, H_2O, thereby freeing electrons. The final result was the Z-scheme of photosynthesis (Hill and Bendall 1960; Blankenship 2002) in which photosystem II elevates the redox potential from positive values to a slightly negative one, after which it becomes slightly positive again. From here, the more primitive photosystem I lifts the potential to a value presumably comparable to the ancient ocean, ca. –0.8 V, from where ATP picks up the electrons, transferring them into the cytosol.

In fact, the evolutionary sequence may have been exactly the reverse of the modern biochemical one: photosystem I is the older and less efficient of the two, based on photolysis of the less energy-rich H_2S, whereas the more recent photosystem II is the most efficient, being able to split the energy-rich molecule of H_2O. The starting redox value of the electron flow of the more ancient bacteria, presumably having lived under less oxidising conditions, ca. 0.20 V for *Heliobacterium*, ca. 0.25 V for green sulphur bacteria, and ca. 0.40 V for purple bacteria, is lower than that for green plants, where this value is ca. 0.3 V for the more ancient photosystem I and ca. 1.0 V for photosystem II (e.g. Madigan et al. 2000). Their age, use of compound, efficiency, and their sequence in the redox-based reaction mechanism of the Z-scheme, at present daily happening billions of times in a single leaf, may therefore reflect not only their own evolutionary history, but also that of their chemical environment to which life responded.

Possibly long before photosynthesis evolved, though, several other mechanisms—metabolic pathways and cycles—had evolved independently in different bacterial taxa operating anabolically under the prevailing anaerobic conditions. Later, these mechanisms—often running counter to those operating under anaerobic conditions—merged through successive symbiosis events (Kooijman and Hengeveld 2005), which may also have happened to the two photosynthetic systems (Blankenship 1992). Because of photosynthesis, so much energy became available that, initially, part of it was expelled as oligosugars. This is still obvious from the sheaths of the first life forms to have both photosystems operating in series, but with a restricted storage capacity, the cyanobacteria. Therefore, with the abundant availability of energy, a storage and retrieval metabolism with respect to carbohydrates evolved as a buffering system against diurnal fluctuations in light—the dark reaction of photosynthesis. Also, the biochemical use of all the energy required the development of enzymes specific for the formation of each of the carbohydrates. Many of the previous enzymes based on nucleotides or metals may at that point have received or extended their apozymatic proteinaceous parts allowing for reaction specification and facilitation. This, in turn, required further stabilisation of DNA as a macromolecule, for example by histones and by the highly intricate repair machinery.

Of great importance is the pivotal role of the energy generation of the cell membrane within the energetics of its metabolism. Ultimately, this evolved from a primitive energy generation in an FeS crust into a highly developed one, thereby retaining its way of operation. In fact, the FeS cubanes of the ferredoxins as possible remnants of the ancient crust (Cammack 1983) still occupy a central place in the process mechanism, the acceptance of electrons from the photosystems on one side,

and their donation via ATP to NAD and NADP to reactions in the cytosol on the other.

If this scenario of an early nucleotide-thiol world, followed by a carbohydrate-protein-DNA world, is correct, it explains why the demands for carbon and nitrogen increased considerably. Yet, this new part of biochemistry was superimposed on an earlier one based on nucleotides and thiols, possibly not completely integrating with it. To a large extent, the former metabolism underneath kept operating as it did before. The increased demand for carbon and nitrogen often required symbiotic relationships between one partner supplying carbon compounds and receiving ones based on nitrogen, and another operating the other way round (Kooijman and Hengeveld 2005).

2.3 The Physical Versus the Chemical Approach

2.3.1 Two Problems: The Congruence Principle and Chemical Lamarckism

Unlike in the physical approach, in the chemical one there are two problems with regard to the congruence of pre-biotic chemical processes and those happening within the cell. Firstly, according to de Duve's (1995) Congruence Principle, there should be a similarity between processes during the pre-biotic phase and those during the subsequent biotic one in the (proto-) cells. Yet, Miller and Orgel (1974) are of the opinion that "in general they do not correspond at all." This means that so far all the efforts to understand the beginning of life in terms of processes happening in the pre-biotic organic soup have been in vain. For example, while it is possible to form certain amino acids under pre-biotic conditions, the mechanism of strong electric discharges bears no relationship with biotic syntheses in cellular conditions. Therefore, it is not sufficient to know whether or not a particular compound can be formed abiotically; instead, we need to know the origin of the biotic reaction mechanism under cellular conditions. Not the process result per se, but the process mechanism is our concern.

The second problem faced by the chemical approach concerns the biogenetic transition from pre-biotic processes to biotic ones: what transition mechanism would have transformed pre-biotic reaction mechanisms into biotic ones? The problem with evolutionary explanations on this point is that they are Lamarckian: the exact mechanism of transformation cannot be given. Similarly, according to Miller and Orgel (1974), biogenetic studies do not describe this mechanism of transformation explicitly. For example, Cairns-Smith's (1982) book "*Genetic Takeover*", as indicated by its title, specifically concerned this problem, but it does not give an explicit mechanism of this takeover. However, typical for Lamarckian solutions, it referred to, for example, clay matrices, molecules, or genes, operating as pre-biotic scaffoldings with the help of which functioning systems could be built subsequently, after which these scaffoldings could be discarded (Cairns-Smith 1985). The compounds that were formed following cellularisation, would have been able to constitute the initial, working metabolic or genetic system right away; they only waited to be encapsulated. With or without some scaffolding, this means that their later biological function would have been prepared in the pre-biotic,

biologically non-functional phase. Moreover, the processes and selection criteria before encapsulation and those favouring this later remain unclear.

These two problems of pre-biotic relative to biotic congruence and of chemical Lamarckism apply (1) to metabolic processes of thioester or carbohydrate formation; (2) to genetic ones concerning the formation of nucleotides and RNA; (3) to the formation of amino acids and peptides and proteins connected with the information system; and (4) to the energetics involved. All these reactions concern polymerisations, processes involving endergonic condensation reactions of the removal of water. In order for this to happen in an aqueous environment, these endergonic reactions have to be coupled to exergonic ones in the form of ATP, together with other nucleotides (see above) delivering the energy needed. Once formed, it also costs energy to maintain the polymers by counteracting continual hydrolysation. Where did this energy come from initially, as ATP? How was its flow organised, and was the pre-biotic concentration and supply of the phosphates, ribose and adenine enough to form sufficient ATP? Also, their concentrations will have been low due to their small yield during their formation and their high decay rates (Shapiro 1988, 1995). Moreover, when formed in free solution, their diffusion rates will have been high in the non-compartmentalised environment, lowering their concentration and disordering any possible organised reaction systems. Apart from energy, nucleosides are also required as intermediates between ATP and the various polymers to be formed, such as lipids, carbohydrates, proteins and RNA, together with their specific nucleotide enzymes (see above).

Therefore, what applies to reactions between chemical compounds equally applies to their energy supply: knowingly or not, the kinetic energetics relies on a Lamarckian argument. In the chemical scenario, pre-biotic forces would all have depended on bulk reactions involving many atoms or molecules, whereas reactions in living structures involve interactions between individual atoms and molecules organised within reaction systems and resulting from their quantum mechanical properties (compare Fraústo da Silva and Williams 1991). The bulk forces concern uncoupled energy sources external to the endergonic, physical processes, such as sunlight, UV radiation, electric discharges, and shock waves, freezing, drying and heating, or chemical ones as chemical upheavals or fermentation of existing carbohydrates (e.g. Miller and Orgel 1974), the latter supposedly having rained down from space. Interestingly, all these energy sources are those in use by man, whereas life processes utilise electrochemical energy which we cannot handle (Lehninger 1965). In contrast to processes utilised by man, those in living systems do not thermalise energy, but the energy is stored for later use. In fact, this causes serious problems of interpretation of experimental results. For example, how does a reaction thought to operate by a shock wave (e.g. Hazen 2005) translate during the biogenetic encapsulation process into some exergonic electrochemical reaction from then on happening within a membrane or in a reaction chain in the cytosol? These external forces, after all, had to be replaced by different, internal ones once the cell membrane had formed, for which it is compulsory to know the replacement or transformation mechanism.

In all cases, the Lamarckian reasoning rests on an interpretation of the past in terms of the present: we know how the system works at present, and we cannot

imagine it to have operated differently before, during and immediately after the biogenetic event. As our present biochemical systems are thought to depend on CHONSP elements as well as on carbohydrates, proteins and DNA, we search for the building blocks of the latter, or for primitive forms of them, to be found somewhere in the universe (e.g. Ehrenfreund and Charnley 2000) or during ancient, pre-biotic times on Earth. Thus, we construct a pre-biotic world in terms of compounds and processes prevalent and functioning today, but which, during pre-biotic times would have operated in isolation from each other; all that was needed was that a selection of compounds be enclosed together in a capsule to make a working, organised biological system. This uniformitarian approach works to some extent in geology, but it does not in biological systems the mechanisms of operation of which change evolutionarily.

In summary, we need to know the exact transformation mechanisms for the proposed energetic takeover, the metabolic takeover, and for the genetic takeover, but for none of them have suggestions been made. This lack of mechanistic insight in the pre-biotic processes transforming into biotic ones makes the chemical approach Lamarckian. Also, the uncoupling of functions from structures violates von Bertalanffy's (1968) conception of their distinction in terms of time scales of operation of two or more processes relative to each other. The resulting Lamarckian reasoning cannot, therefore, be tested. What we need instead is a testable, and hence, Darwinian mechanism of biogenesis.

2.3.2 Darwinian Elements in the Physical Approach

The physical approach considers the energy flow compulsory to any organisation of compounds and reaction mechanisms. Initially, energy transducers themselves, like the phosphates and the ultimate nucleotide coenzymes, could in principle have been different, and could have formed simpler energy transfer and reaction systems. The point is to find an energy processing mechanism, generating and transducing energy uninterruptedly from its evolutionary beginning to the present. This mechanism must consist of initially abundantly available elements with specific properties to generate and transfer energy from exergonic reactions to endergonic ones. As in a battery, the charge difference at both sides of the $(FeS)_n$ crust could have generated the energy, which could have been transferred inside by electrons and protons. The electron carriers could have been differentiated evolutionarily into the metabolic and genetic parts still in operation today.

Here, the functioning of the mechanism develops as an evolutionary adaptive process along with the compounds constituting it, rather than requiring their uncoupling as in Lamarckism. This stepwise evolutionary molecular and structural refinement and tuning, as well as spatial and temporal differentiation into form and function from the initial phases to the most complex ones, all follow Darwinian principles.

This Darwinian view accords with that of, for example, von Bertalanffy (1968), Morowitz (1968), Prigogine and Stengers (1984), Wicken (1987), or of Fraústo da Silva and Williams (1991) on open, dynamic systems. As mentioned, basically, there is no distinction between form and function (von Bertalanffy 1968): what we

conceive as a form is a process happening at a lower rate than that of a function. To this temporal differentiation, spatial compartmentalisation can be added, as in the environmental compartmentalisation leading to biogenesis, and any further compartmentalisation of the initial "cell" into the eukaryotic cell, etc. (e.g. de Duve 1984; Hengeveld and Fedonkin 2004; Martin and Russell 2003). When these processes and compartments have their own processing rates, they lead to a function when they connect with another, slower or faster process, or with that of another compartment. What is essential is that, through the development of ever more elaborated interaction rules, living systems evolve from the ultimate beginning. This cannot happen from loose bits and pieces, later to be united into a system of reaction mechanisms by adding interaction rules, only then attaining their biological relevance relative to each other. In the latter case, it remains unexplained when and how which of these rules were added, how, according to which criteria, they were subjected to selection, and so on. In the first case following the physical approach, interaction rules form the biochemical heart of the mechanisms of biogenetic process; these rules were subject to selection right from the beginning, directly shaping all subsequent life processes. This difference in emphasis results in qualitative differences in research outcomes. A similar point is made in Russell et al. (2003).

2.3.3 The Ecological Side of Life

One further difference between the physical and chemical approaches concerns the possibility of life originating outside the Earthly realm according to the latter, that is as ready-to-use chemical compounds raining down from other planets, meteorites or dust clouds (e.g. Ehrenfreund and Charnley 2000), or as complete organisms from another planet (e.g. Hoyle and Wickramasinghe 1978). As in the pre-biotic organic soup, they would have originated and existed outside the environmental or organismic context on Earth, within which they had to operate subsequently. This approach is non-ecological, both at the molecular, and at the organismic level. Consequently, according to this approach, cell membranes would only prevent compounds and pathways from diffusing away into the environment, thereby isolating them from the outside world. Life processes are therefore not seen as a direct consequence of the continued existence of a charge disequilibrium between inside and outside the cell keeping the essential energy flux going. But just because of this disequilibrium generating the energy flux, cells are part and parcel of the environment and cannot be isolated from it. Cells are compartments of the general environment.

This view forms the ecological heart of the physical approach: life processes and their evolution cannot be seen separate from environmental conditions surrounding them (Williams and Fraústo da Silva 2006), neither in space nor over time; they happen in dependence on them and at their mercy. Living systems are energetically and materially open compartments of the environment, organised in such a way that the transduction of energy eventually dissipates from them, resulting in entropic decay. They distinguish themselves from other processes in the environment by

their higher rates of energy transduction and dissipation; they differ, but quantitatively only.

2.3.4 Why Retain Unnecessary Problems?

Why bend over backwards, pushing all biotic processes into the pre-biotic phase, and, in effect, have life recommence the biotic phase? Would it not be better if all phases of biogenesis were to occur under biotic conditions? Despite Miller's experiments and the more recent observations in space, would it not be better to avoid the pre-biotic theorising? Skipping the pre-biotic phase, during which all sorts of pre-adapted compounds, some un-encapsulated, may have been formed in the "primordial soup", would amount to avoiding search for the answers to insurmountable problems. Moreover, these problems seem unnecessary: because of their incongruence with pre-biotic ones, it still remains necessary to explain the origin of the mechanism of biotic processes within the context of the cell. After all, do we really know that extra-terrestrial or pre-biotic processes actually existed? And do we know which transformation mechanisms existed between the two phases? Or do we have indications of the past existence of such mechanisms from present biochemical processes? All considered, it seems that the "soup" phase is unnecessary for understanding the origin and evolution of life. It serves only as a distraction.

3 Discussion

3.1 Methodological Aspects

Perception of the past leads to risks of misinterpretation in terms of the present. Yet, in biogenetic studies, we may have fallen into the methodological trap of adducing a pre-biotic role to modern carbohydrates, amino acids, peptides and proteins, or of adenine, ribose and information-containing strings of nucleotides, and so on. The same holds for CHON elements, dominating present-day biochemistry, rather than a whole suite of inorganic ones (e.g. Williams and Fraústo da Silva 1996; Hengeveld and Fedonkin 2007, this issue).

3.1.1 Biochemical Aspects

The emphasis on reproduction—replication and propagation—as one of many criteria for defining life (e.g. Hengeveld and Fedonkin 2004) led to investigations of the pre-biotic formation of nucleotide bases, and of their sequence in RNA and DNA. Together with amino acids, peptides and proteins, RNA and DNA are considered in isolation from other processes such as those of metabolism, implicitly or explicitly expressing the information-first view of biogenesis. This approach assumes that genes are independent and active, and that RNA and DNA are primarily connected with replication. According to, for example, Keller (2000), however, recent developments in genetics show that "DNA, RNA and protein

components function alternatively as instructions and as data", and form a dynamic, distributed programme. Gene activity is replaced by gene activation, expressing its interactive, dynamic nature, which also holds for the genome as a whole, and for the developmental programme (Oyama 1985). Software memory, in Elsasser's (1987) terms, merges into hardware memory. Genes, when activated, can be spliced in sometimes hundreds of different ways, and can perform widely different functions. This also applies to proteins; after translation, different proteins can be spliced from the same information (e.g. Miklos and Campbell 1994). Moreover, the same protein can function differently under different cellular conditions. Therefore, given their essentially interactive nature, an independent origin during the pre-biotic phase seems unlikely; their origin, evolutionary development and elaboration, and functioning must have fallen entirely within the biotic phase. Similarly, their role and specifics in relation to replication must have been attained as one of the consequences of the developing biochemistry of the early cells. To a large extent, evolution concerns changes in organisation of basic modules, rather than changes in their number or identity; this holds from nucleotides and amino acids upwards to RNA and DNA and to proteins, respectively, and possibly to even higher levels or organisation.

As another example, adenine could either have rained from space onto the Earthly surface, or have polymerised in ancient terrestrial environments from hydrogen cyanide and cyanide (Oro 1960). However, how much adenine should have rained down or have been formed in concentrations high enough for reactions to take place, let alone for their pre-biotic role? Also, how stable is it under Earthly conditions (see Shapiro 1988, 1995), and is it formed among other reaction products (Decker et al. 1982), and in what percentage? In Miller's (1953) experiment, the yield of adenine was ca. 0.5%, and that of ribose, less than 0.1%. And what about the other bases as mediators between ATP and further reactions (see above)? Historically, the emphasis in experiments and the literature on the origin of the five bases is that they may have resulted from base sequences in RNA and DNA where phosphate and ribose play the negligible role of backbone; they only connect the bases which, alone and in their sequence, allow for the information as a higher-order, newly emerging, abstract trait of life. However, it is inconceivable that life would have begun with an abstract trait as information, laid down in an equally abstract sequence of bases, and this independent of concrete metabolic or replicative functions for interpreting this sequence, which would have been added on later. As long as a pre-biotic information system, developed previous to a metabolic system, lacks a reading and interpretation mechanism, it would occur in a biochemical vacuum, awaiting the evolution of a mechanism that fits. What else can their evolution to such abstract, functionless structures have been other than Lamarckistic?

In contrast, the physical approach considers the phosphates as phylogenetically pivotal, whereas the ribose and base rings, together with the topology of the various parts of the molecule, play the part of charge buffers (Pullman 1972). These will have been added secondarily. A secondary evolution of the other bases as reaction mediators also fits this scheme; they developed when the formation of other compounds, such as proteins, came to the fore. This gives the papers of, for

example, Baltcheffsky and Baltcheffsky (1974) or Westheimer (1987) on the primary evolutionary role of phosphates more prominence.

As yet another example of adducing a historically primary role to compounds with a central role in recent biochemistries concerns the evolution of amino acids. Amino acids as building blocks of proteins have received much interest, although they usually form the inactive, apozymatic part of the enzyme, with a nucleotide or a metal as the active prosthetic part (White 1976, 1982; Bayman et al. 2003). Yet, the latter are designated as cofactors. The emphasis is not on the prosthetic group and its origin, the operation of which can be activated or facilitated, or be made specific by the apozymatic part, possibly added secondarily. Similarly, the operation of the ribosome has been misinterpreted until recently: the protein part rather than that of RNA was thought to have been the enzymatically significant part. However, the protein part appears to "buttress" the enzymatically active RNA, facilitating and directing its operation (Cech 2000). RNA has a similar, active role in spliceosomes, the proteinaceous part being enzymatically inactive (Reanney 1979). Here too, the evolutionary significance of nucleotides received too little attention relative to that of proteins. This does not mean that proteins are insignificant, but to understand the biochemical evolution of life, we need to know which protein evolved when and in what biochemical context, what functions and relative roles it and its descendants may have had, and what the evolution and function of its prosthetic part are. Recently, a suite of RNAs with widely different functions is being disclosed, together forming an ancient form of, still active, biochemistry (e.g. Gesteland et al. 2006).

As in nucleotides, peptides and proteins, terrestrial processes are often invoked to explain the possible pre-biotic formation of carbohydrates. Alternatively, their main development as energy-storing molecules may have had to await the evolution of photosynthesis. Also, discussion of the origin of pre-biotic carbohydrates concentrates on extra-terrestrial carbohydrates on meteorites, or in interstellar dust clouds, etc. (e.g. Chelnikier and Trân Thanh Vân 2003), where several hundreds of compounds have been identified (Ehrenfreund and Charnley 2000). They range from simple to complex, and are often found in present-day organisms. However, their significant role in the modern cell metabolism and in their biotic use may have led biogenetic research into their biochemical origin astray.

Thermodynamically, water, although a main constituent of present-day life, could have been the curse of early, pre-biotic polymers, hydrolysing them soon after their formation (Ferris 2002), if they could have formed at all (e.g. Van Holden 1980). Yet, as water is, for various reasons, essential in living structures, the first search for the feasibility of life on other planets is always after the availability of water (e.g. Lunine 1999). In this context, the solubility of many compounds in water, and, hence, its relevance for nutrient transport, are often mentioned as important properties. Other arguments are that the Earthly temperature range of water is also favourable for carbon metabolism, or that it is bipolar, and that, because of this, it can form hydrogen bridges keeping large molecules, such as DNA or proteins, together. And so on. Special mechanisms have therefore been invoked explaining how living structures may have evaded problems of hydrolysation (e.g. Black 2000; Ferris 2002).

Biochemically, though, its principal importance is that of an alternation of condensation and hydrolysis underlying the formation and breakdown of most polymers, the pivotal processes of cell metabolism. This continuous alternation allows for the transport and temporary storage of energy by means of electrons and protons from the early phosphates onwards. From the upstart of life, though, it could also have been the continual source of protons, which kept their pivotal role in the energetics of life ever since.

Physically too, the significance of the cell membrane as the seat of life has also largely been missed, possibly because it is inactive in the eukaryotic cell. Yet, as the thermodynamist Harold (1986) put it: "In the beginning was the membrane." This could have been cured by the rediscovery of the symbiotic nature of the eukaryotic cell (Margulis 1970, 1993), giving the activity of the membranes of mitochondria and chloroplasts a pivotal role in the energy supply of this cell type. However, they are treated as cell organelles only, although without their membrane activity, eukaryotic life would not exist. The emphasis remained on the metabolic and informational processes in the cytosol, rather than on the indispensable role of membranes for the energetics of the cell from biogenesis onward. Despite the significance of its role in the compulsory energy generation of the cell, the study of the evolution of the cell membrane from the FeS crust onward has not been given central place. Without understanding its origin and evolution, in conjunction with that of the chemical environment and of the biochemistry of the cytosol, we cannot explain the evolution of life on Earth.

Emphasizing the biochemistry of carbohydrate metabolism obscures the physics underlying biogenesis and the maintenance of subsequent living structures. In contrast, the question is how exactly the entropy of the "environment" decreased locally, and what mechanisms evolved lowering it even more. Life evolved from an initial compartmentalisation of the environment. Yet, although it grew independent in some respects, overall it is still a low-entropy compartment of the environment. In its analysis, redox reactions in inorganic mechanisms were undervalued as prime biogenetic initiators (e.g. Fraústo da Silva and Williams 1991; Williams 1981; Williams and Fraústo da Silva 1996, 1999; Russell and Hall 1997; Anbar and Knoll 2002; Hengeveld and Fedonkin 2004, in preparation), and also in the modern, highly evolved systems, keeping their energy flow going. Moreover, redox values dictate which reactions will happen, and which compounds either become stable or lose their previous stability. It is the physics of the process that dictates all aspects of the chemistry of life, and from which all chemical and biological structures, functions and behaviour follow. As, for example, the possible evolution of the Z-scheme of photosynthesis suggests, it is of prime importance for its biological understanding to study the elemental changes in the environment through geological time, together with altering redox values accompanying these changes. Not to take account of this by concentrating exclusively on the evolutionary unfolding of carbohydrates, proteins and DNA in metabolic and information systems leads to confusion and to a misrepresentation of the physical factors ultimately responsible for the ecological and chemical evolution of living systems.

3.1.2 Ecological Aspects: Elemental and Redox Evolution of the Environment

There have been major changes in redox values of the chemical environment in which life took place, partly as a result of life. These broad environmental changes concerned a transfer of electrons and protons from donor to acceptor elements and compounds, and will inevitably have led to adaptations of the life processes to the new conditions. As these shifts in the local chemical environment followed a general environmental thermodynamic decay, processes other than those caused by living systems may have added to the latter, if they did not predominate. The consequence, though, was that the living structures had to adapt to the new redox potentials and mineral availability in the environment (e.g. Williams and Fraústo da Silva 1999, 2003, 2006; Anbar and Knoll 2002; Hengeveld and Fedonkin in preparation). Once more, oxygen evolution through the Z-scheme of photosynthesis is but one expression of this trend.

Presumably, the redox potential of the seawater in which biogenesis took place was in the order of –4.0 Eh. But if we assume conservatively that the pH was around 6 (CO_2 atmosphere), and that it was buffered around H_2S/SO_4^{2-}, then the redox would approximate –175 mV, whereas at present it is positive, up to general values of 4.0 Eh (Russell et al. 2003). This means that, successively, different elements became involved in the biochemistry of the membranes, as well as in that of the cytosol (Anbar and Knoll 2002; Williams and Fraústo da Silva 2003; Hengeveld and Fedonkin in preparation). However, they could have replaced each other to some extent, but never completely. For example, we saw already that photosystem I, which evolved before photosystem II, splits molecules of H_2S which were biologically accessible earlier than those of H_2O, which is the energy source of the latter system. H_2S is still used as electron donor in the more primitive photosynthetic green and purple sulphur bacteria as well. The same may have been true for the thiols being replaced by alcohols, etc. (de Duve 1991), or for the most ancient of all, the FeS crust presumably having evolved into ferredoxins.

It is well known that, with the advent of oxygenic photosynthesis, oxygen and hydrogen were released, whereas the oxygen content built up in the sea and the atmosphere, in which, because of its small weight, hydrogen was either fixed, or from which it escaped into space. Oxygen first oxidised sulphides into sulphates, which precipitated out (Anbar and Knoll 2002) when the seawater has a salinity of 12wt%. After this, iron oxide also precipitated out, forming vast and thick layers of banded iron, found all over the world (e.g. Cloud 1988). Towards the end of the Precambrian, the same happened to phosphorus (Lambert et al. 1983), during which time it also formed the mineral of the first fossilised animals. Oxygen first appeared in the atmosphere during the early Proterozoic (e.g. Bekker et al. 2004), and then in the oceans during the late Precambrian (Canfield and Teske 1996). Up to now since the Precambrian, calcium carbonate precipitated out extra-cellularly, and, by adsorbing on collagen filaments, forming shells and skeletons which, in turn, formed thick layers of rock. This also happened to carbon during the Palaeozoic, accumulating mainly from plant debris. With the fossil accumulation of carbon during the Carboniferous, atmospheric oxygen concentrations also rose considerably, decreasing again after carbon began to be recycled. After the Carboniferous,

plant growth reduced (Beerling et al. 2001) and animals and fungi increased so much that carbon and oxygen were recycled (Beerling et al. 2001). These two, relatively recently evolved taxa, animals and fungi, are specialised in breaking down live and dead biological material, respectively, thereby using oxygen and releasing CO_2, and nitrogen, for example, thus starting biospherical nutrient cycles (Sterner and Elser 2002). Their activity retarded further global accumulation of the greenhouse gases carbon dioxide, CO_2, and methane, CH_4, as well as oxygen, at times stopping this altogether. In this way, history may have repeated itself on a higher organismic level after the evolution of oxidative phosphorylation leading to the evolution of mitochondria.

As mentioned, sulphur from H_2S was replaced biochemically by oxygen from H_2O in photolysis in the two successive photosystems. Similarly, towards the end of the Precambrian, newly available metals replaced nickel, selenium, vanadium and tungsten, found in ancient life forms, and magnesium and copper replaced iron in haem groups of plants as well as in some animal taxa, respectively (Williams and Fraústo da Silva 1999). Initially, ultraviolet light reduced Fe^{3+} to Fe^{2+}, but this process became insufficient after an ozone shield formed in the stratosphere. Further, under aerobic conditions, the supply of other elements, such as sulphur, iron, nitrogen and phosphorus ran into short supply, nitrogen becoming biologically unavailable. Because of its reduced availability and of its increased biochemical use, the balance between nitrogen and carbon uptake was broken. This necessitated representatives of many animal and plant taxa to form symbiotic relationships with those of other taxa, either for their carbohydrate supply or for that of nitrogen, lichens being the best known of them all (e.g. Kooijman and Hengeveld 2005).

Thus, as the chemical evolution of the environment followed a broad-scale process of thermodynamic decay, conditions changing from reducing to oxidising, a large fund of electrons and protons moved from metals to non-metals. This shift may have been retarded, if not halted altogether, by the influx of energy from a new, effectively unlimited extraterrestrial source, light (but see Ward and Brownlee 2002), which may be basic to global recycling instead of nutrient exhaustion. This lead to the formation of nutrient cycles in the biosphere, either alone (e.g. Sterner and Elser 2002), or by their combination. The input of external energy began with the evolution of photoautotrophs and the nutrient cycles with that of heterotrophs, animals and fungi, the latter closing cycles of the main elements during biogenesis, iron, sulphur, carbon, oxygen, nitrogen, calcium and phosphorus.

3.1.3 Chemical Specificity

Following the chemical approach, Miller and Orgel (1974), Zubay (1996) and Mason (1991) among many others, selectively give specific reactions individually, and this without reference to their thermodynamic background. Without this background, it remains unclear why they happen, and what other reactions and reaction products may have also occurred under pre-biotic field conditions. This, in turn, makes it impossible to reconstruct biogenetic processes. Kaufmann (1993, 2000) completely dropped the physical and chemical identity of the elements and compounds concerned, reducing the build up of chemical networks to a decrease in

the number of degrees of freedom of their permutations, a position which many chemists will doubtless not wish to adopt.

The physical approach considers the physical and chemical properties of elements and compounds taking part in a reaction or reaction chain to be essential. Thus, Ponnamperuma (1972), for example, explained why, contrary to carbon, silicon did not become pivotal to life: when silicon combines with oxygen, its unpaired electrons link up with neighbouring oxygen atoms, thus giving huge super-molecules of a silicon dioxide, this removing silicon from circulation. Furthermore, the outer shells of the larger silicon atom give a weaker bonding than carbon, making it susceptible to attack by, for example, water or ammonia (Wald 1962). In contrast to the smaller carbon atom, it therefore cannot form large, linear macromolecules as carbon does.

Westheimer (1987) and Lane (2002) similarly explained why phosphorus and oxygen, respectively, are important in biological systems. Fraústo da Silva and Williams (1991), more rigorously, described the properties of many elements in relation to life (see also Williams 1981), and Williams and Fraústo da Silva (1996) analysed the natural selection of elements by living structures. Similarly, the atomic configuration within molecules such as ATP (e.g. Pullman 1972), or proteins (e.g. Pauling and Corey 1951), or the transfer of electrons and protons, have been described quantum mechanically, thus explaining their specific structure and behaviour. Those and many other studies show the importance of the physical and chemical specificity of elements and compounds within energy transduction systems.

As to biogenesis, we cannot dispense with the properties of individual atoms, or of the still simple and small molecules. These entities carried the energy into and through the cavity, and allowed its flow following its generation in the FeS crust. The strength of this flow depended, apart from the channelling efficiency within the cytosol, on the size of the charge disequilibrium, which itself depended on the chemical composition of the fluid inside the cavity relative to that of the seawater outside.

Therefore, everything centres on the energy flow entering into and flowing through the system, eventually dissipating from it as heat or fixed in waste products. The elements and compounds taking part in the reactions determine the strength of the energy flow, the chemical equilibria of the reactions, their rates and products, the stability and longevity of these products as determined by the retention time of the energy in the molecules and their capacity of storing energy, and the length of the biochemical pathways and cycles. The flow of energy and mass define the marginal conditions for living structures, and thus select the elements and compounds constituting the processes of life.

When physical or chemical conditions change, the structures have to adapt, either by shielding them off as happened by cysteine strands in ferredoxins, by extending or duplicating the mechanism as in the photosynthetic system, or by substituting a particular element by another, such as iron by copper or magnesium in haem. In all these cases, existing mechanisms remained intact, enabling the continuity of the energy flow running through them to be ensured.

As the energy flow is the primary process in the operation of living systems, it sets constraints to the properties of the chemical elements and compounds taking part in the biochemistry of a living system, and, hence, to their identity. Therefore, a physical perspective gives a straightforward understanding of the kinetics of biogenesis using a reconstructive, bottom-up approach.

3.1.4 Empirical Versus Deductive Approaches

Overall, the chemical approach views biogenesis in hindsight; knowledge of the molecular and biochemical structure and functioning of modern living systems should give clues to their biogenetic past. However, applying knowledge about modern structures and processes is useful, but should not be taken too far. Extrapolating modern structures and processes to the time when, or even before, life began in order to reconstruct biogenesis constitutes an empirical, top-down approach. However, this retrospective, top-down approach easily leads to erroneous results when these structures and processes are more recent than the biogenetic event. It often throws up unjustified similarities, rather than mechanistic insight into the evolutionary process.

For example, finding amino acids in present-day living structures, as well as in Miller's (1953) experimental results or in cosmic dust clouds, still does not show how some pre-biotic chemical network would have operated, from which living structures might be derived. We do not know what place they had in such early networks, nor what particularly these acids would have been selected for at the time. What were the selection criteria: were they different from their present biochemical place and operation? The fact that pre-biotic and biotic processes are incongruent suggests that, if certain amino acids were in existence at the time, their origin and maintenance, together with their dynamic place among other compounds, was different. What use is it then to study them in a biogenetic context? Those experiments or astronomic observations merely show that they are easily formed abiotically, and therefore presumably biotically as well. They do not give mechanistic insight into the evolutionary formation and biochemical diversification of living systems.

The alternative, deductive, bottom-up approach of physical kinetics also uses data on recent structures and processes, but then they are checks on our reasoning rather than starting points for modelling ancient processes. Thus, the physical approach starts from first principles from which some biogenetic structures or processes are deduced. It attempts to reconstruct the initiation and progression of biogenetic processes. The first principles define the selection criteria of the chemical elements and compounds best fitting the kinetic processes at hand. The choice of first principles results from insight into basic process requirements of system formation, whereas information on present molecular and biochemical structures and processes checks this insight. Thus, we check if similar structures or processes exist in modern metabolisms as possible remnants of ancient ones. As checks, these comparisons constitute the continual testing of the reasoning developed.

For example, as for any structure, the first principles concerning the origin and operation of living structures imply in the first place the need for a continuous

energy flux, and that this flux runs a course of least resistance. The resulting processes run as long as this flux exists. It appears that this flux can indeed be generated efficiently at a steep gradient at a membrane. According to Russell and Hall's (1997) model, initially there would have been a thin mineral crust of $(Fe(Ni)S)_n$ generating a charge disequilibrium between the two sides and, hence, an energy flow from the environment outside and the tiny volume inside. Geochemical observations (e.g. Anbar and Knoll 2002; Williams and Fraústo da Silva 2003) indicate that the required elements were available at the time, but also that, over time, they gradually became exhausted, forcing the system to adapt in a predictive way (Williams and Fraústo da Silva 2006). Also, energy from a stronger UV radiation generated by an active young Sun, in the absence of a filtering ozone layer continually oxidized ferrous iron, Fe^{3+}, to ferric iron, Fe^{2+} (Braterman et al. 1983). This photolytic ferric iron can then accept electrons in the crust, reducing Fe^{3+} to Fe^{2+}, which in a next step can be transferred into the cavity. Biochemically, $(FeS)_n$ cubanes of the ancient (e.g. Cammack 1983; Eck and Dayhoff 1966) ferredoxins as possible remnants of this iron sulphide crust are still essential for the energy transfer in active membranes, which serves as a check for Russell and Hall's (1997) model. Other steps that may have been taken during the early chemical evolution of life can similarly be checked.

Thus, the chemical approach is based on an empirical, top-down methodology generating hypotheses that cannot be tested, whereas the physical approach is based on a bottom-up one, deducing and testing models of biogenetic processes from first principles.

3.2 General Principles

3.2.1 Systems Theoretical Aspects

So far, this paper has emphasised kinetic principles underlying biogenesis, which, in turn, require systems-theoretical ones (e.g. von Bertalanffy 1968; Morowitz 1992; Williams and Fraústo da Silva 2006). This section concerns ideas on steps that may have been taken in the initiation of life.

The Second Law of thermodynamics applies to closed systems where, with an initial increase in disorder, a state of entropic equilibrium will eventually be reached. Such equilibria are attained when no matter is interchanged between the system and its surroundings, making it closed. Only energy can be exchanged. The processes the chemical approach assumes to have happened in the primordial organic soup, or on crystal or clay surfaces, accord with this condition. However, in order for the entropy to decrease for system maintenance and during the evolutionary development of living structures, a continuous energy transduction is required, such that the system remains forever in a state of disequilibrium relative to its environment. Instead of an equilibrium state, a dynamic or stationary state is found in modern systems in which minerals and other compounds are continually added to and removed from the system, so that the overall composition either remains the same or alters gradually during biological development. The resulting steady state must perpetually keep at a certain distance from chemical equilibrium,

which means that, with the continual addition and removal of matter, and therefore of chemical energy, the process keeps running. This continual addition and removal of chemical energy and matter maintains the organisation of the structure of the system, and may increase its complexity, thereby reducing its entropic value.

Russell and Hall's (1997) model of tiny, hollow mineral pores and bubbles as initial compartments from which life would have developed meets this condition. Next, some rules evolved following from the system conditions according to the transduction of energy. Thus, the reaction outcomes are not slavishly defined by the initial conditions, as in closed systems, but by the system conditions themselves, with the result that any disturbance can be compensated for, maintaining the same overall outcome. Only when over billions of years the input of not only mineral supplies but also of solar energy became exhausted, some meta-equilibrium state will eventually be reached, implying that life on Earth dies off inevitably (Ward and Brownlee 2002).

Overall, the energy flow running through a living system can be linear: the energy and minerals crossing the—mineral—membrane leave the system as heat, as waste products, or as a new replicate structure. However, although the process as a whole can be linear, it contains internal, homeostatic chemical interactions. For example, within the membrane, UV radiation recharges Fe^{3+} into Fe^{2+}, which loses the added electron again in the cytosol. This happens when this electron oxidises ADP, thereby forming ATP, which carries it off into the cell volume. Here, it loses the electron, forming ADP and inorganic phosphate, which can receive a new electron, reconstituting ATP, and so on. Physically, this constitutes the iron cycle (de Duve 1991). Chemically, this means that ADP and inorganic phosphate condense into ATP by losing a molecule of water, whereas, with the uptake of water, ATP hydrolyses in the cytosol by releasing this molecule again under the formation of ADP and phosphate. Thus, a most primitive metabolic cycle could have originated in the cavity, being energised by the flow of energy-rich electrons generated in the crust or membrane. Therefore, during this initial stage, the reactions in the cavity operate according to a closed system without interchange of matter by continually alternating the direction of this reaction: from condensation to hydrolysation to condensation, etc. In this process, energy degrades, entering the system as large, high-energy quanta and leaving it as up to 30 times more numerous, low-energy, small ones (Williams and Fraústo da Silva 1999). This cycle came to form the basis of the overall form of biochemical energy flow and degradation in which the ATP–ADP cycle also became inserted in reaction chains in the cytosol. Biochemical evolution could thus have occurred by an extension of and an increase in complexity of this form of energy flow. Thus, the biochemical role of water may be found in this energy degradation through the condensation-hydrolysation chain having operated from early on.

Indeed, Morowitz (1968, 1992) suggested that the origin and extension of biochemical pathways and cycles follows kinetic rules of least resistance of the energy flow into and within the cavity. According to Morowitz (1968), ever more complex pathways and cycles could have begun, reined in by homeostatic reactions (see also Gánti 2003). Thus, the electrons involved in the condensation-hydrolysation cycles can oligomerise molecules against the chemical thermodynamic

disequilibrium caused by the presence of water, thereby elongating the chain of cycles step by step. This resulted in the formation and breakdown of thioesters, nucleic acids, lipids, carbohydrates and proteins. At some point in this process, the crusty, mineral membrane became more permeable to matter and a more open system evolved in terms of material interchange. All this could happen, not in spite of water but just because of its presence, continually being added and subtracted in a growing chain of successive reactions. Rather than being a curse to the chemistry of life, it is exactly because of this basic mechanism that water forms life's essential ingredient. The continual degradation of energy maintained the thermodynamic disequilibrium, and this, in turn, kept the energy flow running. This basic cycle thus formed the thermodynamic drive of life.

With the increasing complexity of the interactions, material standards were set by standardising macromolecules and tuning them to each other within the overall homeostasis of the cell, resulting, first in the polymerisation of RNA and then in that of DNA. Next, various metabolic pathways and cycles, and later whole organisms, fused symbiotically into one single, compound system (Margulis 1970; Martin and Muller 1998; Hengeveld and Fedonkin 2004; Kooijman and Hengeveld 2005). Overall, the system became open, with the addition of solar energy and the consequent addition of oxygen to create metabolisms developing ever further away from equilibrium. This kept entropic decay running, and this at increasing rates. Yet, within the systems, compartments separated out, all operating as black boxes relative to each other (Kooijman 2000) and following their own rules.

One basic condition for the system to keep the operations between the various components fine-tuned must have been that it operated at the same optimal temperatures right from the beginning, that is at the present ones between ca. 30°C and 40°C. For higher temperatures, special adjustments are found, as in the hyperthermophiles (Jaenicke 1996; Rice et al. 1996). This constancy of temperature is conditional on the operation of a highly organised, dynamic system and is therefore basic to a systems approach to biogenesis.

3.2.2 Emergent Properties and Living Structures

A single molecule of water can neither freeze, nor boil; these are properties of many molecules together. Reactions among single molecules can be understood in quantum mechanical terms, those amongst many molecules, through physical or chemical mass equations. Often, as in the case of water, a new phenomenon, such as freezing or boiling, emerges that, although rooted in the idiosyncratic properties of the individual atoms or molecules, is linked through their interactions. It is the characteristics of these interactions, which define the newly emerged phenomenon. The biogenetic emergence of life can be one such phenomenon. The question is, therefore, can we understand life from atomic and molecular properties defining these interactions and, if so, at what stage does it become too complex?

Above, I emphasised the behaviour of individual elements in the formation of an initial crust and of the formation of nucleotides and nucleotide coenzymes, thereby avoiding the question as to which reactions in the cytosol were supplied by the energy released. There are two reasons for this, (1) which reactions can take place

depends on other elements and compounds present in the proto-cytosol as well as on physical conditions, and (2) given our present knowledge about, for example, energy generation, it is too risky to go into great detail as to what may follow. Concerning the first point, differences in the chemical composition of the alkaline trickle from a porous basalt seafloor can, in principle, be substantial. We therefore need geochemical information about likely compositions. Moreover, redox reactions are sensitive to the exact values of pH and temperature (e.g. de Duve 1991), two factors about which there is still much discussion. Concerning the second point, I have adopted Russell and Hall's (1997) model for the initial crust formation as the presently most likely one, realising there may be more than this one only, although so far there is no hint in any other direction.

Apart from these two practical limitations, there is also one concerning interactions leading to new dynamic structures as emergent properties at this level. Although it is possible to reconstruct in hindsight why water freezes or boils at certain temperatures, to predict from scratch its behaviour in bulk is difficult. Concerning biogenesis, we need to know when and at what level of complexity new dynamic properties can emerge, what properties we may expect, and if they lead to a level of new phenomena anyway. The first steps of the formation of types of molecules like individual nucleotides or reaction chains may look simple enough to understand. But even the first steps can be complex.

In the modern cell, for example, ATP is stabilised by divalent metals such as Mg^{2+}, and its hydrolysis therefore is subject to pH and the concentration of Mg^{2+}, apart from the concentration of ATP, ADP and inorganic phosphate. Its standard free energy of hydrolysis at pH 7.0 and 25°C is –7.3 kcal/mol, but in the intact cell it will be closer to –12.5 kcal/mol, a considerable difference in comparison with that of other molecules with which ATP interacts. Also, we saw that ATP does not interact directly with proteins, etc., but indirectly with other NTPs and NDPs as intermediates. Although these interactions will have evolved later, it does show that even the apparently simple electron transfer is in fact embedded in a more intricate network of conditioning and mediating interactions. In other cases, metals, such as Zn^{2+} or Mg^{2+}, and non-metals, as OH^- or SH^-, act as catalysts by increasing the polarity of the potential reactants. This complexity makes it difficult, or impossible, to predict biogenesis in terms of emergent properties. It is even more difficult to say, even in hindsight, in what way it is an emergent phenomenon with physical and chemical properties different from those of the constituent compounds. However, the beginning of the energy flow and the channelling and extension of this flow along lines of least thermodynamic resistance should provide acceptable scenarios. In fact, biogenesis is defined by thermodynamic conditions of the build up and evolutionary development of the biochemical reaction system of living structures. Our future questions will be those of, for thermodynamic reasons, which reactions, reaction chains and constituent molecules might have come first and which later. It is their fitting into this dynamic system that will give insight, rather than individual molecules.

Studying the beginning of the energy flow has several more advantages. Firstly, models deduced from first principles suggest which compounds or process mechanisms fit. Also, the model, being predictable, defines physical, chemical

and geochemical testing criteria as to their functional place within the system proposed, independent of their relevance in modern biochemistry. Insight into the origin of the energy flow is tightly linked to systems theory, which is indispensable for understanding biogenetic events.

3.2.3 Process Rigidity

The more complex and finely tuned a reaction system, the more vulnerable it is to change. To keep operating under changing conditions, ancient reaction networks must therefore be protected rather than changed, making the system as a whole conservative and rigid. To allow a certain flexibility to be maintained, a system developed that consisted of rigid modules operating differently in different combinations and contexts. Thus, living systems contain only four nucleotides and twenty amino acids doing all the genetic and metabolic standardisation work in ever changing and evolving combinations. In itself, the number of proteins, though large, is still small relative to the virtually unlimited number of permutations possible in the tens of thousands of peptides or proteins these twenty kinds constitute. In fact, they consist, again, of protein modules spliced together in various ways, forming composite proteins with specific properties (Miklos and Campbell 1994). This even applies to reaction chains and cycles requiring events of symbiosis (e.g. Kooijman and Hengeveld 2005; Martin and Muller 1998).

Similarly, photosystems I and II, now operating in series, may have evolved at different times and in different taxa under conditions still recognisable from their present properties (Bayman et al. 2001), although Allen (2005) disputed this. The same applies to the ferredoxins which may date back to the initial $(Fe(Ni)S)_n$ crust, or to the nucleotides and the nucleotide coenzymes, reflecting the initial electron transport function of the phosphates, and to RNA and DNA. Thus, as modules, molecular and biochemical processes and structures, reaction chains and cycles can have persisted for billions of years almost unscathed (e.g. Kooijman and Hengeveld 2005), still reflecting ancient adaptations to the conditions at the time. As archives from the far past, they supply checks to our theorising. For example, ancient metals or nucleotides are still functional in proteins (Bayman et al. 2003; White 1976, respectively), and redox values can be reconstructed, supplying checks on the correctness, or at least workability, of hypotheses about the mechanisms possibly generating and processing energy.

Because of its conservatism and rigidity, life broadly follows a bootstrapping process, step-by-step generating ever-new forms of complexity that were once "unheard of" and even "unthinkable", at present retaining much of what was developed before. Yet, we have to find evidence of this bootstrapping process in previous stages of complexity (Hengeveld and Fedonkin in preparation).

3.2.4 The Stochastic Nature of Formative Processes

As mentioned, ATP hydrolyses in the cytosol into ADP and inorganic phosphate, and condenses again, for example at the membrane, into ATP, which forms an

initial homeostatic cycle. How does this process progress at the level of the individual molecules, all moving in Brownian fashion among other molecules?

Whether a molecule reacts will depend on the chance configuration of surrounding molecules with which it interacts. Ideally, step length, and angle of direction between successive movement steps may be assumed to be normally distributed; these determine the chance of interacting with another molecule so that, for example, ADP and inorganic phosphate form ATP. This, together with chemical thermodynamic conditions, determines the retention time of phosphate in the nucleotide in a molecular Markov chain. As this bond is "energy-rich", it determines the retention time of energy in the molecule—and the overall rate of energy degradation in an organism (compare Ho 1995, 1998). As to the energy transfer by ATP, stochastic rules apply in terms of differential retention time of energy in the system: since the energy is used in the formation of bonds in other molecules, the same reasoning holds for whole networks of chemical reactions.

Thus, according to different retention times, a hierarchy of energy retention originates, expressing the dynamic metabolic structure of cells, and this hierarchy will have been formed following a bootstrapping process. One can then differentiate between structures and functions in terms of retention times, the first having the longer and the latter the shorter times. One of the longer retention times developed in the nucleotides of DNA, which thus became metabolic and genetic reaction standards. These molecular structures are kept intact by hydrogen bridges, histones and complex repair systems, and are functional over many generations, often still regulating the formation of ancient molecules or biochemical pathways. Also, depending on reaction equilibria among several compounds, metabolic cycles can originate along these lines. This stochastic approach particularly applies when the number of molecules per unit volume is small, or when the frequency of their interactions is low.

As mentioned, the condensation-hydrolysation cycle could have operated initially as in a thermodynamically closed system, that is, the energy could have gone round and round, and meanwhile have been stored in the constituent molecules as well. Later, systems of fluctuating enzymes can have developed in which energy is released in only minimal amounts, so that energy barriers were levelled completely rather than reduced (see Ho 1995).

3.2.5 Stabilisation and Repair

As the complexity of the interactions increased, an extensive stabilisation and repair system for the genome became essential. Part of this system involved stabilisation and repair sensu stricto, such as by the doubling of the chromonema. This could have stabilised the macromolecule itself, when hydrogen bridges formed between the two. It also enabled mutations in one of them to be recognised, which reduced the chance of mutations to protract. In eukaryotes, doubling of the chromonemata enabled their meiotic reshuffling with another one from a genetically independent cell, which once more reduces the chance of mutations protracting considerably (Bernstein and Bernstein 1997). Similarly, in proteins of particularly hyperthermophile bacteria, ion pairs between glutamates

and amino acids stabilise the molecule against effects of high temperatures (Jaenicke 1996; Rice et al. 1996).

Frequent genetic interchange between cells, though, necessary for preventing genetic material from widely different cells from being inserted, requires a compatibility system that allows cells to recognise each other as conspecifics. This recognition system turned prokaryotic replication into the sexual propagation and meiosis found in eukaryotes, and this, in turn, to species as biological entities (Paterson 1985). Eventually, it took many forms, especially among multicellular organisms, at present ranging from the molecular level to that of ecological and behavioural discrimination. Yet, although these recognition systems cannot stop horizontal gene flow between different life forms altogether, this flow is minimised.

More extensive lateral gene transfer, often by symbiosis, will have happened shortly after biogenesis. It may have begun with the fusion of metabolic pathways (Kooijman and Hengeveld 2005), later followed by the fusion of two photosynthetic systems (Blankenship 1992; Bayman et al. 2001, but not according to Allen 2005, and see Pierson and Olsen 1989), and by that of archaebacteria and eubacteria into eukaryotes (Martin and Muller 1998). In connection with the biochemical balancing of carbon and nitrogen, symbiosis may further have occurred in single-celled eukaryotes (Delwiche and Palmer 1997), in fungi and algae into lichens, among multicellulars (Kooijman and Hengeveld 2005), or indeed, within a single plant (Kooijman personal communication).

In principle, all forms of adaptation and symbiosis restrict the influence of stochastic events. This restriction of chance is basic to all adaptation and, as such, can be seen as a principal characteristic distinguishing life from non-life, although not defining it.

4 Conclusion

Two different, non-overlapping research traditions—paradigms sensu Kuhn (1962)—coexist in biogenetic research. The dominant and oldest of them approaches biogenesis from a chemical viewpoint, whereas the more recent one starts from physics.

The chemical approach leaves several fundamental questions unanswered, such as the kinetics of individual processes in the context of that of the overall cell structure, the transition from the "soup" stage to that of a functioning cell, the origin of energy processing in membranes, the structural origin and evolution of the cell with respect to maintenance and replication, the initial operation and function of the nucleotide-thioester biochemistry of the nucleotide and RNA worlds, and the evolution of the ancient biochemistry in conjunction with that of the environment.

The physical approach answers these questions without introducing evolutionary inconsistencies or Lamarckian constructs. Moreover, it puts problems into the context of systems kinetics of the evolving biological structures, and this, again, in the context of their perpetually changing environments.

Therefore, the physical approach ought to receive detailed attention, whereas at the same time the chemical approach should be examined critically with this

alternative, physical approach in mind. Following this physical approach, the problem of biogenesis ought to be viewed ecologically and historiographically and from a systems theoretical viewpoint, following a "bottom-up" approach as far as possible, rather than a "top-down" one that uses modern biochemistry of the cell as its point of entry.

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