Breathing Life into Biology

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By

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GENERAL INTRODUCTION

This is a book about the state of biology in contemporary Western society. Its leitmotif is beautifully expressed by some lines from the Portuguese poet Fernando Pessoa:

What we see
Is not what we see
But what we are

More prosaically, this means that a body of knowledge (and this includes scientific knowledge) tells us as much if not more about the knower than about the known. Consequently, this book falls into two parts. In the first part A, we will look at the *content* of biological science (i.e. the known); in the second part B, we will look at the human society that has elaborated this knowledge (i.e. the knower). A natural link between the two parts is provided by the fact that we humans are ourselves the product of biological evolution, prolonged by the processes of hominization and then the "entry into history".

Before getting down to details, I would like to highlight an issue which is one of the major motivations for this book. As a point of entry, I will take a quotation from a respected molecular biologist, François Jacob. In *La logique du vivant*, he writes "Life is no longer an object of study in the laboratory" (Jacob 1970, pp. 320-321; my translation[1]). And Henri Atlan (Atlan & Bousquet 1994, pp. 43-44) drives the point home: "Life as such does not exist; no-one has ever seen such a thing... The name 'life' has no meaning, because no such thing exists... This means that biology studies an object, the object of its science, which is not life! The object of biology is physico-chemical. From the moment that one does biochemistry and biophysics, and one understands the physico-chemical mechanisms which account for the properties of living beings, life evaporates! Today, a molecular biologist has no use, in his work, for the word 'life'."

At first sight (and indeed, as I will argue, at third sight after deeper reflexion) this statement "Life does not exist" is surprising, indeed

[1] In the original : « On n'interroge plus la vie aujourd'hui dans les laboratoires ».

outrageous. But before judging (which I will get around to), it is important to try and *understand*. Of course, when they are being normal human beings in the course of their daily life, Jacob and Atlan know full well that life exists: they know that a dog is alive whereas a stone is not; they know that murder is a serious crime. It is when they put on their hats as scientists that life "evaporates". And when we look closer, suspending judgement, we can see that "*'Though this be madness, yet there's method in't*". The method, here, lies in the fact that epistemologically speaking, all major scientific objects are not derived by transposition from empirical common-sense; they are constituted *in theory* (Popper 1962; Kuhn 1962). This being so, there is nothing wrong with the fact that scientific objects are often, indeed characteristically, an affront to common sense. To take just one example: a basic tenet in Newtonian mechanics is the theoretical principle that a material particle, if left to itself, will continue moving at constant velocity in a straight line. What a ridiculous idea! – no-one (in their right mind) has ever seen or heard of such a thing. And yet scientifically, this theoretical postulate has proven immensely successful and richly productive.

Coming back to biology, the fact is that at the present time, the central epistemologically well-founded scientific object is not "life", but "the gene". I will not enter into fine technical details here (see Stewart 2004 for a more substantial presentation). I will just make the point that basic Mendelian genetics (at the root of the scientific concept of "the gene") is constitutively *blind* to any character that is invariant in a species. And since autopoïesis – the process by which living organisms continually *produce themselves* – is radically invariant (not only to a single organism, nor even to a single species, but to all living organisms) it is in a way "normal" that a gene-centred biology should be blind to "life" (of which autopoïesis is a central ingredient). This blindness has actually been made worse – contemporary biologists do not see that they cannot see – by the discovery that genes are physically located in chromosomes, and that in terms of molecular "biology"[2] the key component of chromosomes is DNA. This has led to the widespread but fatally misguided illusion that by sequencing DNA, one can approach "the secret of life". The reason why genetics has become such a dominant force lies in the supposition that genes constitute a "genetic program" that determines the near-totality of every living organism. To show that this is no exaggeration, we shall cite again from François Jacob (1970), who is indeed one of the most respected theoreticians of molecular biology:

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[2] The scare-quotes around the term molecular « biology » are irresistible.

> "Heredity is described nowadays in terms of information, messages, and codes. An organism's reproduction has become the reproduction of the molecules that compose it. This is not because every chemical species has the ability to produce copies of itself; but because the structure of macromolecules is determined, down to the smallest detail, by sequences of four chemical radicals contained in the genetic inheritance. What is transmitted from generation to generation are "instructions" that specify molecular structures, the architectural plans of the future organism, and also the means of putting these plans into practice and of coordinating the system's activities. Each egg contains, therefore, in the chromosomes that it has received from its parents, all of its own future, the stages of its development, the form and properties of the being that will emerge from it. The organism thus becomes the realization of a program prescribed by heredity."

These considerations may help to *understand* how it has come about that in contemporary biology, "Life is no longer an object of study in the laboratory". However, to understand is not (necessarily) to approve.

Why do I consider that the eviction of "life" as an authentic object of biology is a cultural and political disaster? Basically, it is a question of values and respect; what scientific knowledge tells us about the knower. If we were to take it lying down, if we were to accept the eviction of "life" from biology as a definitively accomplished fact, if we were to consider that there is no going back on what is after all a choice, this would mean quite profoundly that we no longer accord any real *value* to life. Going further into this question would bring up existential and political issues that I do not propose to develop explicitly in this introduction – although in truth they are implicit throughout, and are indeed the very *raison d'être* for this book, and they will come closer to the surface in Part B. More modestly, I will simply say that a major aim of this book will be to show that, if only we really want to, it is eminently feasible to constitute "life" as an authentic object of biology. Thus, in part A, I will aim to sketch the outlines of a theory of living organisms: to lay the groundwork for a fully-fledged, epistemologically and scientifically respectable theory of *life as such.* To the extent that I am successful, this will mean that we do have a real *choice* as to the sort of biology that our society will produce. We could have a gene-centered biology, as at present; or (although a lot of work remains to be done), we could develop an organism-centered biology that accords a *value* to life.

One last remark to close this introduction. In this book, as I have already indicated, I will be severely critical of the "gene-centered" approach which dominates contemporary biology. In this, I am clearly in a tiny minority; but I am not quite alone. Among other references, I would like to cite the book by Kupiec and Sonigo (2000). Our arguments are strongly convergent, in particular in targeting the unfortunate notion of a "genetic programme". Kupiec and Sonigo close their book with these lines (my translation from the French): "DNA certainly exists. But it does not constitute the cause, the determinant, the creator of the organism. The biologists have dreamt of an accessible demi-urge, readable in the world of molecules. The first pages of the catalogue of genomes which extend to infinity, like a tower of Babel reaching to the sky, cry out the necessity of another science. The first generation of those who advocated 'genomics' are now calling for a 'proteomics' to justify a catalogue, after the infinity of DNA, of the infinity of proteins and their specific interactions. The more lucid among them prefer to speak of 'post-genomics'. But while it has failed to reveal the mysteries of life, this '*technolo*-mic' debauchery has tarnished its beauty. Maybe the time has come at last to speak simply of biology." These authors do not themselves follow up on this call for a renewed biology. My hope is that the present book will lay down a few steps in this direction.

PART A

BIOLOGY

I. Conceptual background

As I have already said, major scientific theories do not derive bottom-up from simple empirical observations; on the contrary, as Kant and more recently Kuhn have argued, *a priori* concepts are necessary in the first place for empirical observations to be possible. We will thus start with some conceptual background; for convenience, I have distinguished "philosophical background" in I.1 and "scientific background" in I.2, although of course the two are inextricably intertwined.

I.1. Philosophical background: an ontology of process

If we are seeking to build a theory of "life itself", perhaps the first point to make is that "life" is not a "thing"; it is a *process.* For this reason, it may well be preferable to speak of "the living" (adopting a verbal form) rather than "life" (which, being a noun, has the unfortunate effect of lending itself to a reification)[3].

The second point, following on, is that these processes are not all smooth and continuous; they are punctuated by *events.*

The third point is that a living being (considered as an event-laden process) is not "entire unto itself"; a living organism can only exist in a *relation* with its environment.

These points mean that we need to address fairly and squarely the question of *ontology*. "Ontology" is the branch of philosophy which deals with the fundamental nature of reality, the very nature of that which exists. Ontology has a bad press, particularly among scientists, because it is

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[3] We have an indication here of the importance of *language.* However, in order to avoid getting mixed up by trying to talk about everything at the same time – an excessive attention to reflexivity can obscure the first-level exposition of what we are trying to say – I will defer an explicit discussion of language to Part B.

associated with dogmatic pronouncements that cannot be challenged empirically. Wittgenstein's famous aphorism – "whereof one cannot speak, thereof one must be silent" – is also clearly aimed at unjustifiable ontological claims. And I myself am impatient with idle, unbridled speculation. But the matter is not as simple as it might seem. Kant (1781) noted that theoretical concepts cannot be unequivocally derived from empirical observations; on the contrary it is the other way round, "a priori" concepts are actually necessary *upstream* for empirical observation to be possible at all. Kuhn (1962) has brought this up to date by noting that "normal science" requires a "paradigm", i.e. a set of theoretical concepts and associated empirical methods that cannot be refuted by empirical observation; on the contrary, they are the pre-condition for scientific observation to be possible. If this is true at the epistemological level, it is even more the case when we come to ontology. The very terms in which a theory is formulated *inevitably* presuppose a particular ontological position. Simply ignoring the issue of ontology will not make it go away: the ontological postulates are there anyway, whether or not they are made explicit. The irony is that what renders an ontological postulate dogmatic is the *failure* to make it explicit; because when the ontology is just implicitly assumed it becomes difficult if not impossible to challenge it.

These philosophical considerations are rather abstract and general, and it will be as well to make them more concrete in the case which concerns us here. The great bulk of modern Western natural science is based on an ontology which accords a primacy to *things* (particles); these "things" are what they are independently of any external relations they may or may not have, and only subsequently enter into interactions with other "things" under the influence of various forces (mechanical, gravitational, electro-magnetic…). To give this ontology a convenient label, we may call it "atomistic" or "mechanistic" (in a generic sense). There is nothing demonstrably "wrong" with this mechanistic ontology; on the contrary, it has been the basis for a great deal of very successful science, particularly in classical physics.

However, if we look at the three simple, basic points with which we opened this section, it is immediately apparent that a mechanistic ontology will not be appropriate for our enterprise. What we need is a radically different ontology; one that gives primacy to *processes*, *events* and *relations*. According to Seibt (2016), *process philosophy* opposes "substance metaphysics," the dominant research paradigm in the history of Western philosophy since Aristotle. Substance metaphysics proceeds from the intuition – first formulated by the pre-Socratic Greek philosopher

Parmenides – that “being” should be thought of as basically simple, hence as internally undifferentiated and unchangeable. Substance metaphysicians recast this intuition as the claim that the primary units of reality (called “substances”) must be static – they must simply be what they are at any instant in time. In contrast to the substance-metaphysical snapshot view of reality, with its typical focus on eternalist being and on *what there is*, process philosophers analyze becoming and *what is occurring* as well as *ways* of occurring. In some process accounts, becoming is the mode of being that is common to the many kinds of occurrences or dynamic beings. Other process accounts hold that being is ongoing self-differentiation; on these accounts becoming is both the mode of being of different kinds of dynamic beings *and* the process that generates *different* kinds of dynamic beings. In order to develop a taxonomy of dynamic beings (types and modes of occurrences), processists replace the descriptive concepts of substance metaphysics with a set of new basic categories. Central among these is the notion of a basic entity that is individuated in terms of what it “does”. This type of functionally individuated entity is often labeled “process” in a technical sense of this term that does not completely coincide with our common-sense notion of a process. Some of the “processes” postulated by process philosophers are *temporal developments* that can be analyzed as temporally structured sequences of stages of an occurrence, with each such stage being numerically and qualitatively different from any other; this is in agreement with our common-sense understanding of processes. But some of the “processes” that process philosophers operate with are not temporal developments in this sense: they are, for example, temporal but non-developmental occurrences like activities; or non-spatiotemporal happenings that realize themselves in a developmental fashion and thereby *constitute* the directionality of time. What holds for all dynamic entities labelled “processes”, however, is that they *occur* – that they are somehow or other intimately connected not only to temporal extension but also to the directionality or passage of time.

One of the foremost process philosophers in our Western tradition is Alfred North Whitehead (1861-1947). A copy of his book *Science and the Modern World* (Whitehead1926) was bequeathed to me by my grandmother; this book is very readable, it has had a major influence on my thought, and I will return to it repeatedly. For our present purposes, however, the major reference is his ‘magnum opus’ *Process and Reality* (Whitehead 1929). Unfortunately this work, although fundamental, is extremely arduous and difficult to summarize. I have however managed to find an extract which is germane to our purpose of building a theory of living organisms (Whitehead 1929, pp 219-220)[4] :

> "The philosophy of organism is a cell-theory of actuality. Each ultimate unit of fact is a cell-complex, not analyzable into components with equivalent completeness of actuality.
>
> The cell can be considered *genetically* and *morphologically*. The genetic theory is considered in this part; the morphological theory is considered [later], under the title of the 'extensive analysis' of an actual entity.
>
> In the genetic theory, the cell is exhibited as appropriating for the foundation of its own existence, the various elements of the universe out of which it arises. Each process of appropriation of a particular element is termed a prehension. The ultimate elements of the universe, thus appropriated, are the already constituted actual entities, and the eternal objects. All the actual entities are positively prehended, but only a selection of the eternal objects. In the course of the integrations of these various prehensions, entities of other categoreal types become relevant; and some new entities of these types, such as novel propositions and generic contrasts, come into existence. These relevant entities of these other types are also prehended into the constitution of the concrescent cell. This genetic process has now to be traced in its main outlines.
>
> An actual entity is a process in the course of which many operations with incomplete subjective unity terminate in a completed unity of operation, termed the 'satisfaction'. The 'satisfaction' is the contentment of the creative urge by the fulfilment of its categoreal demands. The analysis of these categories is one aim of metaphysics.
>
> The process itself is the constitution of the actual entity; in Locke's phrase, it is the 'real internal constitution' of the actual entity. In the older phraseology employed by Descartes, the process is what the actual entity is in itself. The terms 'formal' and 'formally' are here used in this sense.
>
> The terminal unity of operation, here called the 'satisfaction', embodies what the actual entity is beyond itself. In Locke's phraseology, the 'powers' of the actual entity are discovered in the analysis of the satisfaction. In Descartes' phraseology, the satisfaction is the actual entity considered as analyzable in respect to its 'objective' existence. It is the actual entity as a definite, determinate, settled fact, stubborn and with

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[4] Readers who are understandably impatient to "get down to the science" might well want to skim through this passage. It is, however, almost uncannily prescient of what will come later; and it will at least serve to show that our undertaking does have a substantial philosophical basis.

> unavoidable consequences. The actual entity as described by the *morphology* of its satisfaction is the actual entity ‘spatialized’ to use Bergson's term. The actual entity, thus spatialized, is a given individual fact actuated by its own ‘substantial form’. Its own process, which is its own internal existence, has evaporated, worn out and satisfied; but its effects are all to be described in terms of its ‘satisfaction’. The ‘effects’ of an actual entity are its interventions in concrescent processes other than its own. Any entity, thus intervening in processes transcending itself, is said to be functioning as an ‘object’. According to the fourth Category of Explanation it is the one general metaphysical character of all entities of all sorts, that they function as objects. It is this metaphysical character which constitutes the solidarity of the universe. The peculiarity of an actual entity is that it can be considered both ‘objectively’ and ‘formally’. The ‘objective’ aspect is morphological so far as that actual entity is concerned: by this it is meant that the process involved is transcendent relatively to it, so that the *esse* of its satisfaction is *sentiri*. The ‘formal’ aspect is functional so far as that actual entity is concerned: by this it is meant that the process involved is immanent in it. But the objective consideration is pragmatic. It is the consideration of the actual entity in respect to its consequences. In the present chapter the emphasis is laid upon the formal consideration of an actual entity. But this formal consideration of one actual entity requires reference to the objective intervention of other actual entities. This objective intervention of other entities constitutes the creative character which conditions the concrescence in question. The satisfaction of each actual entity is an element in the givenness of the universe: it limits boundless, abstract possibility into the particular real potentiality from which each novel concrescence originates. The ‘boundless, abstract possibility’ means the creativity considered solely in reference to the possibilities of the intervention of eternal objects, and in abstraction from the objective intervention of actual entities belonging to any definite actual world.”

With this we have completed the basic philosophical background.

I.2. Scientific background: some general principles for a theory of biological process

I.2.1. Flows of energy and dissipative structures.

The time has come[5] to cash out these philosophical considerations, and to get down to some science. A living organism is a *process*, we have said.

[5] None too soon, scientifically-minded readers may feel. But I remain unrepentant: “more haste, less speed”. If we had gotten down to the science on the basis of a mechanistic substance ontology, we really would have been wasting our time…

Very well; but what *sort* of process? In an extremely important book, on which I will draw heavily in much of what follows, Nick Lane (2015) gets a very basic point right when he proposes to focus primarily on *energy*; and more precisely on energetics, on *flows* of energy. This means that we situate ourselves immediately in the domain of systems that are far from thermodynamic equilibrium, where there are spontaneous flows of energy (and matter). A key feature of such systems is that they *spontaneously* give rise to the appearance of "dissipative structures". These "structures" are in a state of constant flux; they are the site of a continual flow of matter and energy that runs through them, so that over time there is not a single molecule that is a permanent part of them. A prototype example of a "dissipative structure" is a whirlpool in a river; other natural examples are typhoons and cyclones. A whirlpool intriguingly resists attempts to "pin it down"; there is nothing definite that it is made of, since it has no permanent elements; if one stops it or freezes it to try and get a straight look at it, it just vanishes into nothing; and yet it definitely "exists". Our difficulty in "pinning it down" is a nice illustration of our difficulty in getting our heads round "processes" rather than "things". This point is important enough that it is worth illustrating by another example, this time a phenomenon that can be produced artificially under experimentally controlled conditions: this phenomenon goes by the name of "Bénard cells" (Figure 1). Here, a liquid is enclosed between two horizontal glass plates heated from underneath. At low rates of heating, the heat is dissipated by diffusion; but above a certain rate of heating, convection currents form spontaneously and can be visualized. When observed from above, the rising currents organize themselves into a hexagonal configuration.

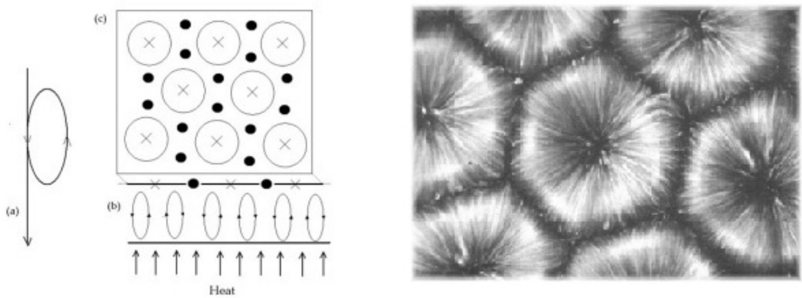

Figure 1. Bénard cells. On the left, a schematic illustration of the principle.
On the right, a micro-photograph of some real Bénard cells.

Now dissipative structures in general, be they natural or experimental, all have a key feature in common: they can arise by *spontaneous generation*, given only the background condition that there is a far-from-equilibrium flow of matter and energy that can "fuel" them. They are *forms* (*dynamic* forms that are not "things" but rather pure processes); however, they do not require any external source of "in-formation" (Oyama 1985), they rather *form themselves* in a radically autonomous manner. This feature is quite fundamental, for the following reason: *in principle* the most basic forms of living organisms *must* be able to arise by spontaneous generation. This might seem to go against a tenet of standard contemporary biology: ever since the classical experiments of Pasteur, it is held that the "spontaneous generation" of life does not and cannot occur. Now it is probably true that under present-day conditions – where all available ecological niches are already fully occupied by more or less highly evolved organisms – the spontaneous generation of novel life-forms does not occur. However, by logical necessity (if we exclude Divine intervention, which would be contrary to the very spirit of scientific explanation[6]), the very first forms of life which existed on the planet Earth *must* have arisen by spontaneous generation. In later sections, we will take a detailed look at specific scenarios for the origin of life; but the more general point is valid independently of the details.

So far so good: living organisms are energetic flows. We now come to the question: flows *of what?* What is the material substrate, the vector for these flows? Living organisms are not flows of water, like the whirlpool or the Bénard cells; rather, they are flows of *chemical* processes. In all extent living organisms on our planet Earth, the chemistry in question centers on carbon-based molecules; it is not for nothing that the branch of chemistry which studies molecules including carbon goes by the name of "*organic* chemistry". Lane's book *The Vital Question* has a significant subtitle: *Why is life the way it is?* (Lane 2015). Lane repeatedly asks whether life could have been different; if there is life on other planets, would we expect it to be similar or different to life on Earth? This is of course a multi-faceted question, and we will come back to it on numerous occasions. At present, the question is this: is life necessarily based on carbon-chemistry? Lane's answer, with which I agree, is basically "yes". The carbon atom, having four valences, has a remarkable capacity to form large, complex molecules

[6] Or, conceivably, by "seeding" from an extra-terrestrial source. But this is (a) extremely unlikely; (b) deeply unsatisfactory anyway, since even if it were correct this would only put the problem back to the origin of *that* extra-terrestrial life. For these reasons I discount it here.

with a backbone of long, branching strings of carbon atoms. The only other atom in the periodic table which even approaches this richness is Silicon – also quadri-valent, but often requiring Si-O bonds (silicates) for minimal stability, which drastically reduces the richness of the possibilities. This conceptual consideration is of course backed up empirically: all forms of life on Earth are indeed based on carbon chemistry.

If we take it as settled that life is indeed based on carbon chemistry, we can come back to the question of energy: what is the specific form of energy that fuels life? In contemporary organisms, these chemical flows are powered by the energy of sunlight – either directly, in the case of plants which are capable of photosynthesis (which is neither more nor less than the formation of large organic molecules using the energy of sunlight), or indirectly in the case of animals (and parasitic micro-organisms and fungi) which feed on the chemical energy from other living organisms. In contemporary organisms, the "chemical whirlpools" involved go collectively by the name of "metabolism". But we should not rush into assuming that the very first forms of proto-metabolism, simple enough to arise by spontaneous generation, were fueled by solar energy. Contemporary photosynthesis, as it occurs in plants, requires chlorophyll, which is a large protein molecule; and the problem is that in order to have any appreciable catalytic activity, proteins have to be synthesized with a very precise sequence of their component amino-acids. In order to achieve this, an elaborate machinery is necessary, involving messenger-RNA templates copied from DNA, transfer-RNAs to match up triplet sequences on the m-RNA with specific amino acids, and structures known as ribosomes holding everything together which is where the protein synthesis actually occurs. It is totally implausible to imagine that anything like this could have been in place at the time when the first proto-metabolism started up.

So: no proteins; and hence, probably no photosynthesis. What then could have been the energy-source for the first proto-metabolism? This is a place to bring in what we may call a "scaffolding" principle. It is a common (and characteristic) feature of living organisms that they have a "circular organisation" in which A depends on B which depends on A… which gives rise to a "chicken-and-egg" type problem when we try to imagine how it could first arise. More generally, there is the situation where there are not just two, but a whole set of processes that are mutually interdependent in the sense that none of them can be sustained without all the others. Cairns-Smith (1985) has proposed the metaphor of an arch (see Figure 2). A conundrum arises because every single stone in the arch only holds in place because of all the others; take any stone away, and the whole structure would crumble. So if we admit that stones can only be added one at a time, how could the arch ever be built?

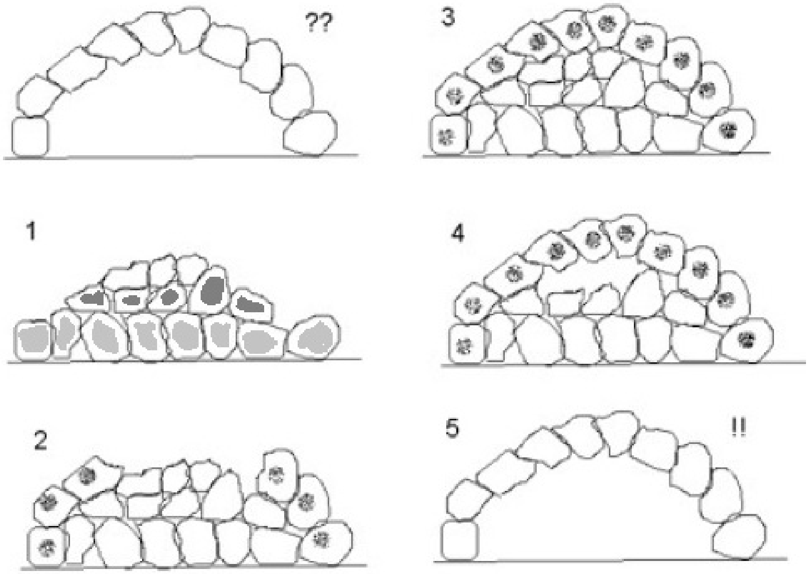

Figure 2. Scaffolding. Taken from Cairns-Smith (1985) [7].

Cairns-Smith's solution to the conundrum is illustrated by the stages labelled 1 to 5 in the Figure. Stage 1: one starts by laying down a layer of stones (light-grey), followed by a second layer (dark-grey), and finally a third layer (unmarked). One can then start laying down, one-by-one, the stones that will form the arch (stages 2 and 3). Once all the arch-stones are in place (stage 3), they can if necessary be cemented together. This sets the scene for stage 4; one can now start *taking away* the "scaffolding" stones that were laid down in stage 1. There is no problem in removing these stones, one-by-one, until they are all removed; and so we arrive at 5, the

[7] It is important not to be misled here by the fact that the unit elements of the scheme are represented here by stones, which are static, substantial "things"; there is no problem in considering that they actually stand for processes. Cairns-Smith himself used this story in the context of a gene-centred approach; but I am allowing myself the luxury of a "take-over" operation since the scheme applies equally well to metabolic processes.

arch which now has no need of any scaffolding; all the tell-tale traces of the way it was done have been removed, so the result looks "miraculous" – as indicated by the double exclamation-marks "!!".

We may now apply this "scaffolding" metaphor to the case of the primitive energy-source for living organisms. The hypothesis is that the first proto-metabolism, the one that arose by spontaneous generation, had a different energy source and a somewhat different composition to contemporary metabolism; that this was enough to get things off the ground; and that later on (see below for subsequent developments), this primitive form of metabolism could be replaced with the more modern form, and thereupon disappear more or less without trace.

So if not sunlight, what *was* the energy-source for basic, primitive life? We will get to the concrete empirical details in good time; and indeed the whole point of the science is to *get* to the concrete empirical details; but we are again in a "more haste less speed" situation, and it is important to get the theoretical orientation right before grasping at the details. Lane (2015) notes that, in principle, life could have been driven by thermal or mechanical energy, or UV radiation; the imagination is the limit. But as it turns out, empirically, all life on Earth is driven by redox chemistry, via remarkably similar respiratory chains; the common feature is the formation of ATP by the intermediary of proton gradients across thin membranes. Lane calls this "the most counterintuitive idea since Darwin"; and characteristically, he goes on to ask: *could this be the only way possible?* And at this point he brings in the work of Peter Mitchell (1957) on the chemi-osmotic gradient. Lane asks: "Why were Mitchell's ideas so hard to accept? Equations that nobody could understand, declaring that respiration was not about chemistry at all, that the reactive intermediate which everyone had been searching for did not even exist, and that the mechanism coupling electron flow to ATP synthesis was actually a gradient of protons across and impermeable membrane, the proton-motive force. No wonder he made people cross! This is the stuff of legend… that's ironic because Mitchell arrived at his radical view of bioenergetics not by thinking about the detailed mechanism of respiration itself, but a much simpler and more profound question – how do cells (he had bacteria in mind) keep the insides different from the outside? From the very beginning, he saw *organisms and their environment as intimately and inextricably linked through membranes*[8], a view which is central to this

[8] I have underlined this key phrase; we are in an ontology of processes, but also of *relations.*

whole book". Lane cites Mitchell: "I cannot consider the organism without its environment… From a formal point of view the two may be regarded as equivalent phases between which dynamic contact is maintained by the membranes that separate and link them." Lane continues: "This line of Mitchell's thinking is more philosophical than the nuts and bolts of the chemiosmotic theory which grew from it, but I think it is equally prescient. Our modern focus of molecular biology means we have all but forgotten Mitchell's preoccupation with membranes as a necessary link between inside and outside, with what Mitchell called 'vectorial chemistry' – chemistry with a direction in space, where position and structure matter. Not test-tube chemistry, where everything is mixed in solution. Essentially all life uses redox chemistry to generate a gradient of protons across a membrane. Why on earth do we do that? … Why electrons, and why protons?

Life is all about electrons. A 'formula' for life is CH_20. Given the starting point of carbon dioxide, then life must involve the transfer of electrons and protons from something like hydrogen (H_2) on to CO_2. It doesn't matter where the electrons come from – they could be snatched from water (H_20 or… or…). The point is they are transferred on to CO_2, and all such transfers are redox chemistry. Could life have used something other than carbon? Answer: no – potential complexity of organic chemistry is essential]. The loophole of great reactivity pent up behind kinetic barriers [… resides in the fact that] many electron donors and acceptors are both soluble and stable, entering and exiting cells without much ado. [Hence] the reactive environment required by thermodynamics can be brought safely inside, right into those critical membranes. That makes redox chemistry much easier to deal with than heat or mechanical energy, or UV radiation or lightning. Respiration is also the basis of photosynthesis […] tapping into the energy of the sun changed the world, but in molecular terms all it did was set electrons flowing faster down respiratory chains.

All these factors mean that redox chemistry should be important for life elsewhere in the universe too. But […] the actual mechanism of respiration, proton gradients over membranes, is another matter altogether. Why proton gradients and chemiosmotic coupling?"

With this long quotation from Lane (2015), I come to the end of what I have to say at a general theoretical level about energetics. However it is interesting to note that these considerations have led us, quite naturally, to the question of *cells*. We may also recall that Whitehead (1929) himself stated that "The philosophy of organism is a cell-theory of actuality". In order to complete our conceptual “tool-kit”, it will therefore be useful to consider the question of cells.

I.2.2. Cells and membranes: autopoïesis.

One of the great moments in the history of biology was the discovery that living organisms are composed of cells. The first discovery of biological cells is generally credited to Robert Hooke (1667). In an observation from very thin slices of bottle cork, he discovered a multitude of tiny pores that he named "cells". However, Hooke himself did not fully appreciate the full import of his observation; he did not consider that the “cellulae” were alive. A more significant advance was made shortly afterwards by Anton van Leeuwenhoek. Using a microscope with a greatly improved lens that could magnify objects 270-fold, he found motile objects. In a letter to the Royal Society on October 9, 1676, he stated that motility is a quality of life and therefore these were living organisms. Over time, Leeuwenhoek wrote many more papers; in particular, he described many specific forms of micro-organisms, that he himself called “animalcules”. The significance of this is that since free-living single cells are possible and exist, they represent the very simplest forms of living organisms.

What is a cell? Deliberately reducing it to the bare essentials, a biological cell has two components: a membrane, and a metabolism. Both components are essential. A mere membrane – a more-or-less spherical husk that is hollow – is not alive (actually, it would be rather like one of the “pores” observed by Hooke; he was quite right in considering that they were pretty much inert, and not alive). On the other hand, a metabolism just by itself – the sorts of “chemical whirlpools” we envisaged in the previous section – is pretty ephemeral and does not have the same sort of identity as a proper cell. In fact, these two components are *functionally* necessary to each other: without a membrane the elements in a fully-blown metabolism will end up diffusing away, and the metabolism will collapse; and conversely a membrane, if it is not continually repaired by an enclosed metabolism, will end up disintegrating. This latter point may help to correct a potentially misleading impression: in spite of what one might think at first sight, a membrane is not a static “thing”, but is indeed a process. Given this reciprocal, circular dependency between metabolism and membrane, the question arises as to how a cell as a whole first arose. Without already having a membrane, it is difficult to sustain a fully-fledged metabolism; but without already having a metabolism, the same goes for a membrane.

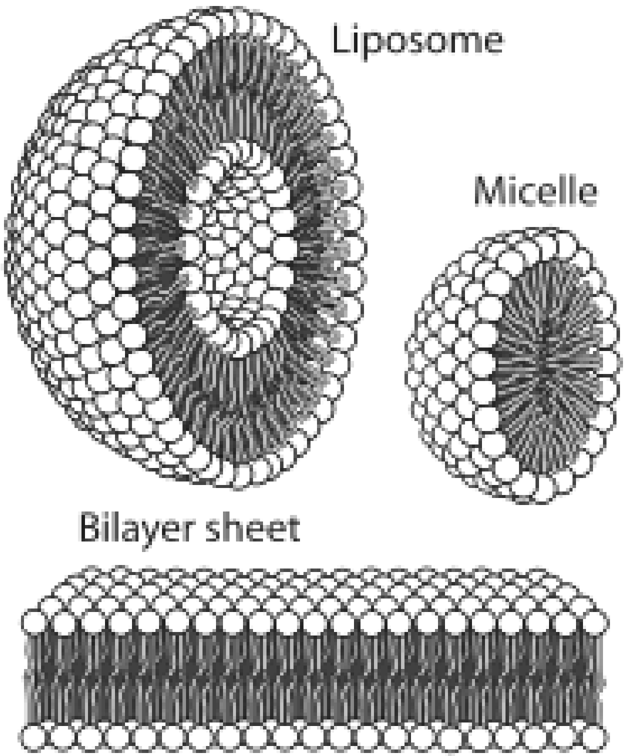

Figure 3. Lipid membrane formation

It seems plausible to suppose that what occurred is a form of "coupling". This requires that the two components should be able to arise, in a first instance, in simplified forms which are independent of each other. We have already seen, in II.1, how a "proto-metabolism" might arise. What then about a "proto-membrane"? A suggestion along these lines has indeed been made in the literature (Segré et al., 2001), who evoke a "lipid world". As illustrated in Figure 3, the key observation is that phospholipid molecules, in aqueous solution, *self-assemble* quite spontaneously, without any need for external help, to form bi-layer sheets; and, even more interestingly for our present purposes, *liposomes* which are hollow spheres of exactly the sort required for a cell membrane. Phospholipid molecules as such were not present on early Earth, but other amphiphilic long-chain organic molecules also form membranes. A possible intermediate step may have centered on *hydrogels.* In simulated ancient seawater, clay forms a hydrogel -- a mass of microscopic spaces capable of soaking up liquids like a sponge. Clay hydrogels could have confined and protected primordial metabolic processes until the membrane that surrounds living cells developed. The scenario, then, is this: that a form of proto-metabolism progressively entered into a *coupling* relationship with a form of proto-membrane, giving rise to the appearance of the first *cells.*

Why is the advent of cells such a momentous event, to the extent that it may be considered as a veritable landmark in the origin of living organisms? There are several ways to appreciate the significance of this event. The first stems from considering that proto-metabolisms, and proto-membranes, each taken on their own, were highly ephemeral and sporadic. We have likened a proto-metabolism to a sort of "chemical whirlpool" or eddy-current; like an eddy-current, it readily arises spontaneously, which we have emphasized as a key feature of the beginnings of living organisms; but the flip-side to this is that it just as easily disappears again without trace. In a word, a proto-metabolism as we have envisaged it is intrinsically *ephemeral.* As for proto-*membranes*, it is not too implausible to suppose that a number of long-chain amphiphilic of the requisite type may have been formed; but their appearance would have been intrinsically *sporadic.* What changes when a proto-metabolism couples with a proto-membrane is that the resultant cell is now a *systemic* entity which has overcome the ephemeral, sporadic nature of its components taken separately. Once they get going, cells *produce themselves* and thus represent a much more vigorous *dynamic attractor.*

Another way of appreciating the significance of cells comes from more conceptual considerations. In Maturana & Varela (1980), the Chilean biologist Humberto Maturana recounts that from his childhood onwards, he had asked himself over and again the same question: "What is the *essential* characteristic of living organisms? What kind of systems are living systems that they may die?" The usual approach to this type of question consists in starting from a common-sense definition – i.e. to consider that, after all, we already know enough about what a living organism is, at least enough to be able to tell without hesitation that a dog is a living thing while a stone is not – and to examine "empirically" the properties that are common to all entities categorized as "living" in this way. But that approach is not sufficient. Maturana recalls how, at a certain stage of his quest (and particularly when trying to answer questions from his students) he was forced to accept that one could recognize living systems when one encountered them, but without being able to say what they were:

> "I could enumerate features of living systems such as reproduction, heredity, growth, irritability, and so on; but how long a list was necessary? When would the list be completed? In order to know when the list was completed, I had to know what a living system was, which was, in fact, the question that I wanted to answer in the first place by producing such a list. I could speak about adaptation and evolution, development and differentiation, and show how all these phenomena were tied together by the phenomenon of natural selection; but the question: 'What was the invariant feature of living systems around which natural selection operated?' remained unanswered. Every approach that I could attempt and that I did attempt left me at the starting point." (Maturana & Varela 1980, p. xiii).

It almost sounds like *Alice Through the Looking Glass*, when Alice keeps trying to reach the top of the hill but finds herself walking back into the house every time! We might add, that not only does the path of the "list" not lead to any solution, but the same problem arises when we try to look closer at any single item on the list. Let us take, for example, the first characteristic on Maturana's list (which is on many other people's list too): "reproduction". First objection: mules, for example, do not reproduce; does that mean they are not living animals? But this objection, after all, is not very serious; it could be "the exception that confirms the rule," and it is indeed true that living organisms that do not reproduce are exceptions. Much more profound is the *same* objection as that which invalidates the list-based approach: unless one *already* knows what a living organism is, the fact that it is an entity that "reproduces itself" does not inform us any better. For example, under certain conditions, crystals – and also, as in the case of the mad cow disease epidemic, prions – do "reproduce themselves"; is that sufficient for them to qualify as "living" beings?

After asking himself these questions over and over again, Maturana realized that he had to change his approach radically. However, unlike Alice, Maturana found that the answer did not come immediately. It was only gradually that he came to think that living systems had to be characterized not by reference to their environment or their context, but with relation to themselves, as *autonomous* entities. In Maturana (1969) he wrote for the first time that living systems were constituted as entities by the *circularity* of the production processes of their own components. Once the idea is stated explicitly, it does seem intuitively obvious. If one asks what *produces* a living organism, clearly it is… the organism itself. Whether in an animal, a plant, or a micro-organism, tissues and organs are the result of an ongoing dynamic process of *production*; the molecules that compose an organism are continually renewed by the metabolism of the organism. And that is true only of living organisms. For example, a machine manufactured by human beings (even a machine tool, or a whole factory) produces something *other* than itself; and it is also produced *by* something other than itself. This "self-referential" circularity, therefore, does seem to be an essential characteristic of living organisms. Maturana, in collaboration with Francisco Varela (1980), looked for a more adequate formulation of the concept of "circular organization" and coined the term "autopoïesis," from the Greek *autos* (self) and *poiein* (to produce). An autopoïetic organism is a system which has its own organization as the fundamental variable which it actively maintains constant.

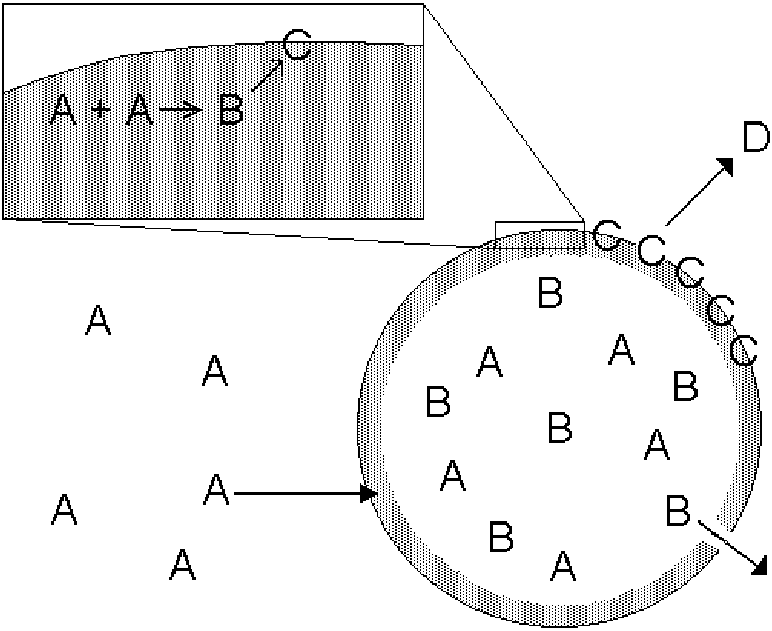

Figure 4. A schematic relation of the circular relationship between metabolism and membrane. Metabolism is represented as the reaction A + A -> B; the elements B migrate to the membrane where they take the form C and serve to repair gaps in the membrane. The membrane continually needs to be repaired because the elements C spontaneously decay to form elements D.

This concept of autopoïesis is highly abstract. This is both a strength and a weakness. It is a strength, because it is both relatively simple, and also very general. However it is also a weakness, because it is not immediately evident how to translate it into concrete terms. Varela himself recognized this, and particularly in his later work took the example, precisely, of a simple cell – a metabolism bounded by a membrane – as a prototypical example of an autopoietic entity as illustrated in Figure 4. Varela he further illustrated this by a simple computer simulation of a "tessellation automaton" (see Bourgine & Stewart 2004). In what follows, we will attempt to make the concept of a biological cell even more detailed and concrete.

With this, our conceptual tool-kit is in place. For the rest of this part A, I will adopt the format of telling the history of life on Earth, from the origin of life up to the present day. Of course, since we do not have a time-machine that would enable us to go back and observe directly what happened, any such history is necessarily a theoretical construction, a *scenario*. However, precisely for this reason, it is appropriate to the task at hand; for in this book I am seeking to present a scientific *theory* in which "life" is the central object. The "scenario" format has the advantage that the various elements involved – and as we shall see, there are a certain number of them – very naturally fall into place in a sequential order. And although we do not have any *direct* observations of what happened, we shall see that on many points there is a very considerable amount of empirical evidence.

Before embarking on the scenario – which will lead us from the origin of life and continuing in Part B up to the present day – there is an issue which it will be as well to put on the table. This is the question of *teleology*. The risk is that of taking the end-point – our current human situation – for granted, and to bias the telling of the story in such a way as to make it appear that the whole process was governed by an inevitable tendency towards this end-point. Since in what follows I will be complaining about the notion of a "genetic programme", it would be ironical if I myself were to fall into the same trap. The objection is a serious one; but I have three replies.

The first reply is that one of the features that distinguishes biology from physics is that the notion of "final causation". I will take up this question in more detail in section III.3, but I will say a few words here. Teleology consists of treating consequences as though they are causes. For example: saying that the heart exists *in order* to pump blood, the kidneys to excrete urine and thereby purify the blood, the lungs to oxygenate the blood; or to take an example from plants, that the leaves of a tree are there to capture sunlight. Teleology has a bad press in scientific circles, because if it is taken as a *substitute* for genuine efficient causes situated upstream in the causal chain, it is both lazy (shirking the real work of finding efficient causes) and wrong (the consequences are not what *produce* the heart or the leaves). But it is not for nothing that biologists that biologists are loath to renounce final causation, because it is these functions that give meaning to biological organization. I explain in III.3 how this problem can be overcome.

My second reply is to plead guilty as charged; but to argue that it is not a crime. *Of course* the story I am going to tell will lead to me, John Stewart; this is predetermined because it could not be otherwise. Any narration, even if it is pure fiction, creates a "referential impression" (see X.3 and X.5.6 below), gives the impression that it is talking about an independent objective object or process that it is merely faithfully representing. And *of course* this impression is an illusion, constructed through and through by the narrator. But there are two sides to constructivism. On the one hand it can function as "deconstruction", showing that the referential impression is "only" a construction. But on the other hand, this should not lead us to underestimate what is involved a producing a viable construction: narrating a story so as to succeed in producing a referential impression is not done just by snapping the fingers, it is a genuine achievement. A staircase is "only" a construction; but building a staircase on which I will confidently walk is a definite achievement (and if you don't agree, I certainly would not venture on any staircase that *you* constructed). So yes, my narration will be teleological; but by admitting it openly from the start, the reader is forewarned – and I hope it will not be considered a crime. This fits of course with the theme "the knower and the known", which is a leitmotif for this whole book.

My third reply is that I am sure these first two replies do not exhaust the question. So I invite readers, as they go along, to be alert for elements of teleology; and to decide for themselves whether or not this disqualifies what I am trying to say. With this, we may now proceed to the scenario.

II. A scenario for the origin of life

II.1. Introduction

As Humpty-Dumpty said to Alice: "Begin at the beginning; go on until you reach the end; then stop." If we are telling the story of life on Earth, the beginning is the origin of life. It is useful to start by recalling the time-scale of the events involved. The Earth was formed around 4600 million years ago; but it first had to cool down sufficiently for life to be possible, and then there was a heavy meteorite bombardment which would have rendered life impossible; this bombardment ended 4000 million years ago. On the other hand, there is clear evidence that archaebacteria, similar to those still existing now, had made their appearance by 3500 million years ago. There is thus a relatively short window of 500 million years, between 4000 and 3500 million years ago, during which life must have made its appearance. 500 million years is of course quite a long time; but not only is it a maximal estimate (it may have been less), 500 million years is short compared to the age of the Earth, and to the 3500 million years for which life has existed. This gives the impression that "Life" made its appearance quite rapidly, in fact almost as soon as the geo-physical conditions allowed it. Thus, the origin of life is not only a case of spontaneous generation (which it is by definition, if we exclude a miraculous helping hand from God); more than that, there is a real sense in which the origin of life was not a weird accident but rather a highly probable, indeed almost inevitable event. This feature is to be born in mind when considering possible scenarios for the origin of life: the major events must have been such as to be relatively *probable*.

To further get our bearings, another introductory remark will be useful. All the living organisms which now exist can be organized in a "tree of life" (Figure 5).

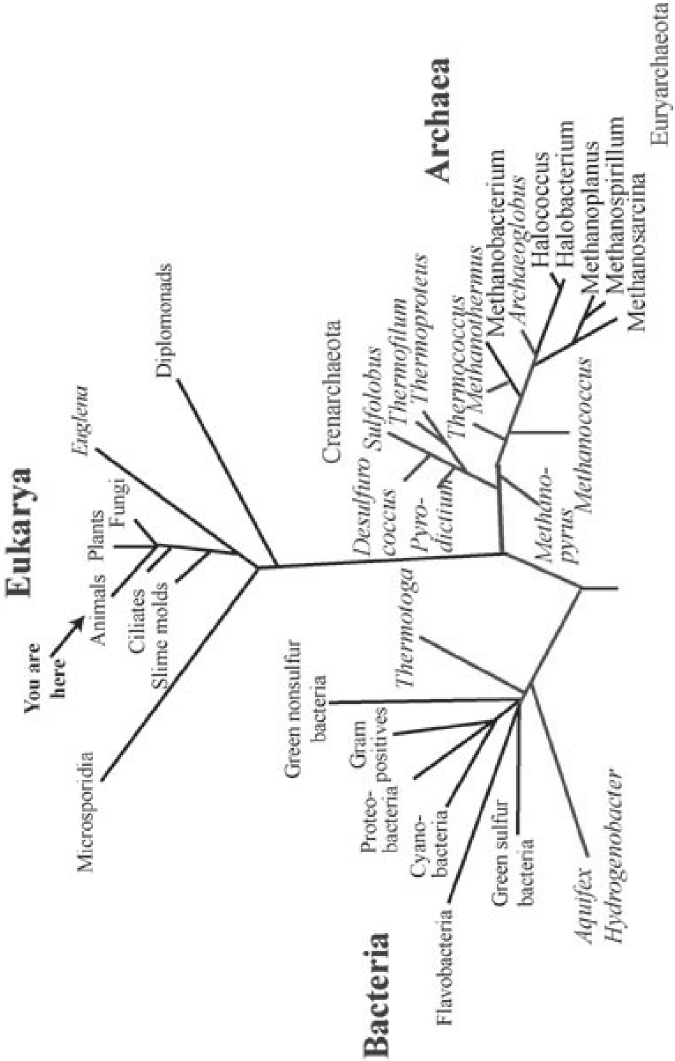

Figure 5. The phylogenetic Tree of Life [9].

[9] From: http://oceanexplorer.noaa.gov/okeanos/explorations/ex1104/background/microbes/media/ microbes_universal_tree.html. It must be noted that the very principle of a "Tree of Life" is not as simple as it may appear, notably due to the phenomenon of