The Origin of Life II: How did it begin?

PAUL DAVIES

The problem of how a mixture of chemicals can spontaneously transform themselves into even a simple living organism remains one of the great outstanding challenges to science. Various primordial soup theories have been proposed in which chemical self-organization brings about the required level of complexity. Major conceptual obstacles remain, however, such as the emergence of the genetic code, and the "chicken-and-egg" problem concerning which came first: nucleic acids or proteins. Currently fashionable is the so-called RNA world theory, which casts RNA in the role of both chicken and egg. Other theories assume that protein chemistry and even clay crystal life came before nucleic acids. To be fully successful, a theory of biogenesis has to explain not merely the emergence of molecular replication and chemical complexity, but the crucial information content and information processing capabilities of the living cell.

Introduction

In paper I, I considered recent developments in the problem of when and where life began. I argued that a favourable setting was the deep subsurface on either Earth or Mars, some 4 billion years ago, with Mars being somewhat favoured. However, I said almost nothing about what actually took place to bring life into being. In this paper I shall

discuss the problem of how life originated, which remains one of the great outstanding challenges to science.

The central difficulty is easy to grasp. How can undirected physical forces produce a state of such immense complexity and specificity as a living organism? The simplest autonomous organisms contain millions of large specialised molecules. The living cell consists of an elaborate web of inter-dependent chemical substances, many of which aren't found anywhere except in living systems. If we want to understand how life came to exist from nonliving substances, we cannot appeal to the prior existence of molecules that are only created by life.

In the nineteenth century it was widely supposed that life was some sort of "magic matter," often called protoplasm, and that the formation of life resembled baking a cake – a question of mixing the right ingredients in the right proportions and the right order. Today we know that the cell is made of perfectly ordinary substances, the essential elements being carbon, hydrogen, nitrogen, oxygen, phosphorus, and sulphur, although the term "organic chemistry" remains as a hang-over from the time when it was believed that life obeyed different physical laws from inanimate matter.

The revolution in the biological sciences, particularly in molecular biology and genetics, has revealed not only that the cell is far more complex than hitherto supposed, but that the secret of the cell lies not so much with its ingredients as with its extraordinary information storing and processing abilities. In effect, the cell is less magic matter, more

supercomputer. In paper I, I mentioned the genetic code as one example of the computational prowess of the cell. Life performs its amazing feats not because of a special form of chemistry, but because organisms can harness chemical processes and subordinate them to an agenda encoded in DNA. So any successful theory of biogenesis has to account not only for the stuff of life – the myriad customised molecules that are vital to its operation – but also for its informational aspects.

The living cell is so complex that it clearly didn't spring into being all in one go, as a result of a single amazing chemical reaction. There must have been a long sequence of physical processes leading up to the first microbe. There seem to be three distinct aspects of life that must be explained on the way: reproduction, metabolism and cellular structure. Organisms must be able to replicate, i.e. pass on genetic information. But without metabolism, they wouldn't be able to do anything (including replicate). And because Darwinian evolution depends on a competition between individuals, it is hard to see how life could evolve without cells. But researchers cannot even agree on the sequence of these major features. Some argue that cellular structures formed first, others that the road to life started with self-replicating molecules, and yet others that complex energy-harnessing chemical cycles preceded both.

The role of chance

Given that the origin of life occurred a long time ago and may have been a unique event, we may never know for sure what actually happened. Even if we could make some sort

of life in the laboratory, we may be left in the dark about the precise historical sequence of events that caused it to happen in nature. Even so, it may still be possible to answer the most pressing question: Is life very likely or very unlikely, given suitable conditions? Jacques Monod[1] has stressed that physical systems are shaped by two factors – chance and law (or 'necessity' as he called it). The origin of life lies somewhere on a line between pure chance and pure law, but where exactly?

To clarify this point, compare the formation of salt crystals, clouds and snowflakes. The structure of salt crystals is more or less completely determined by the laws of physics (specifically their geometrical symmetries). Given an appropriate solution, the formation of a specific crystalline structure is assured and inevitable. By contrast, the structure of a cloud is almost all at the mercy of chance. You would be hard-pressed to predict the shape or even the moment of formation of a specific cloud from knowledge of climatic conditions and the laws of fluid mechanics. In between these extremes lies the example of the snowflake. Its general hexagonal symmetry is a consequence of the laws of physics, but the specific filigree structure is a result of happenstance. So is biogenesis like crystallisation – inevitable once the right substances and conditions are present? Or is it analogous to the snowflake, where the central features of life are written into the laws of physics, but some fortuitous circumstances are needed to make it actually happen? Or might it be a stupendous fluke, a result of pure chance, like shuffling a pack of cards into suit and numerical order by sheer luck?

Among the experts opinions differ greatly. Sidney Fox[2] argued that life is built into the basic laws of physics and chemistry, so that its emergence is in some sense pre-ordained, and resembles crystallisation. By contrast, Monod[1] believed that the laws of nature are not in the least bio-friendly, and that life formed by blind chance alone - a chemical fluke unique in the universe. Christian de Duve[3] considers that life is a "cosmic imperative," more or less bound to occur under earthlike conditions, although, like the snowflake, the details are left to chance. During the past couple of decades there has been a marked shift in favour of the point of view that life is to a certain extent expected and widespread in the universe, but as far as I can tell there is no clear-cut scientific reason for this fashionable belief; it is more a matter of sentiment and fashion.

A complicating factor in these arguments is that "life" is usually left undefined. Whilst I do not wish to provide a comprehensive definition of life here, it is helpful to distinguish between the following possibilities:

1. The only possible life is "life as we know it," based on nucleic acids and proteins, perhaps with alternative genetic codes, but with the same basic biochemistry. There is only one route to life from one starting point.

2. Life exists only in the basic form we know, but there are many routes to attaining it, from many different starting points. That is, "life" acts rather like an attractor in dynamical systems theory, or the end point of convergent chemical evolution, making it an almost inevitable end state from a wide range of pre-biotic initial conditions.

3. There are many alternative forms of life based on many possible biochemical schemes, perhaps involving molecules other than nucleic acids and proteins, or even elements other than carbon. Similar initial conditions may lead to very different forms of life.

4. There are many alternative forms of life, each of which requires a different route, so across the universe, various initial conditions give rise to various forms of life.

Alternative 1 is consistent with life on Earth being a unique quirk of fate in a universe that is not especially bio-friendly. Alternative 2 implies that the laws of physics and chemistry ingeniously fast-track matter to life, so that a very specific form of life is written into the laws of nature in a fundamental way. This idea seems highly teleological to the point of conspiracy (and reminiscent of supernatural design), although it is obviously logically possible. Alternative 3 implies that life is in some sense not very remarkable or special - almost like an additional state of matter. Alternative 4, beloved of science fiction writers, is the most speculative. It requires that nature is inherently strongly bio-friendly, with the necessary logical architecture not only built in at a basic level, but transcending the specifics of physics and chemistry. It should be mentioned that the subject of Artificial Life[4], in which lifelike objects are created in computers and allowed to evolve according to simple mathematical rules, also proceeds from the assumption that life is a quasi-universal phenomenon dependent only on an appropriate logical structure, and largely independent of physics and chemistry. We might say in this

case that life is not so much written into the laws of physics, as built into the logic of the universe.

In what follows I shall restrict my remarks to 1 and 2 only, since it is hard enough to explain life as we know it, without speculating about the origin of life as we don't know it.

The chicken and egg problem

A major obstacle in understanding how life originated is sometimes known as the chicken-and-egg problem. Known life is based on an accommodation between two very different classes of molecule – nucleic acids and proteins. DNA and RNA contain the genetic data, that is, they are informational molecules, while proteins act as enzymes to make the necessary reactions go, and also to provide the building material for most of the structures within the cell. Thus nucleic acid serves the role of egg, while proteins are analogous to the chicken. (More scientifically, biologists use the term genotype to refer to the inherited characteristics of an organism, and phenotype to refer to the specific organism itself. Using this analogy, nucleic acids are identified with the genotype and proteins with the phenotype.) Since life as we know it is impossible without both classes of molecule, there is an obvious problem of which came first, "chicken" or "egg"? Without nucleic acids to encode the manufacturing instructions, proteins don't get made, but without proteins, nucleic acids cannot replicate. Each needs the other. However, both are exceedingly elaborate, specific and delicate forms of molecule. It is hard enough to

imagine one of them forming by chance, but to suppose both nucleic acids and proteins were happy chemical accidents occurring at the same time and place stretches credulity.

Attempts to solve the chicken-and-egg problem divide into three: egg-first, chicken-first and neither-first. I shall review each in turn. All three suppose that there was an extended phase of pre-biotic chemical evolution leading up to life as we know it. It is assumed that known life is a result of successive evolutionary refinements – a sort of high-tech end product of much fine-tuning and adaptation. Life surely began from fumbling low-tech beginnings, limping along with crudely adapted molecules until, over the aeons, more and more improvements were discovered and incorporated. By the time life reached its present form, using nucleic acids and proteins, much, perhaps all, trace of its low-tech origins were obliterated, making it hard for us to discover how life achieved its present ingenious arrangement, and making its existence seem almost a miracle. Cairns-Smith[5] has used the helpful analogy of a stone arch, which is a self-supporting structure. This too would seem to be a inexplicable state of matter, because every stone depends on every other stone for the arch to hold itself up. The explanation for this seemingly impossible structure lies in the existence of an initial scaffold that is employed to support the stones during the building operation. Once the last stone has been put in place, the scaffold can be removed. The problem in the case of life is to identify the primitive ancient scaffold on which the high-fidelity self-supporting form of life we know today was put together.

Two distinct approaches have been followed in an attempt to discover this “scaffold.” One is to examine the biochemistry of extant organisms for molecular relics of an

ancient, more primitive phase of life. This may provide clues about the earliest stages. The other approach is to start at the bottom and try to synthesise some of the smaller molecules that life uses from chemical mixtures. The ultimate goal of these experiments would be to create some sort of life from scratch in a test tube. Of course, even if this were successful, it would still leave open the question of how life originated in nature, without specialist equipment and trained organic chemists on hand to design delicate procedures. But it would certainly be a start. Unfortunately biochemists are still a very long way from being able to produce *de novo* anything resembling known life.

Biosynthesis experiments

Most of the biosynthesis experiments have concentrated on trying to make only the basic building blocks of life, such as amino acids and nucleotides, from simple chemical mixtures. This programme draws its inspiration from Darwin's original "warm little pond" conjecture[6]. In the 1920s, Haldane[7] and Oparin[8] elaborated the idea that an ever-richer brew of chemicals might have formed on the early Earth, either in a lake or in the oceans, from which life was eventually incubated by some as-yet unknown chemical reaction. This became known as the primordial soup theory, and it has had many variations. What all researchers agree on is the crucial importance of liquid water, so whatever the setting and the nature of the chemical brew, an aqueous medium of some sort is essential.

In 1953, in a pioneering experiment, Miller and Urey[9] set out to re-create a version of the primordial soup in the laboratory. They sealed a mixture of methane, ammonia, hydrogen and water in a flask, and passed an electric spark through it for a week. The experiment was an attempt to simulate what the researchers believed were the conditions that prevailed on the early Earth. At the end of the week, the flask contained many amino acids. Other biochemists have subsequently experimented with their own brands of primordial soup, with varying degrees of success[10].

For a while following the Miller-Urey experiment there arose a feeling that "cooking up" life was just a matter of doing more of the same – sustaining something like those experimental conditions while ever more complex biochemical molecules were produced. Optimists regarded the Miller-Urey experiment as the first step on a road to life, down which a chemical mixture is inexorably conveyed by the passage of time. However, that view now seems misconceived. First, Earth's primitive atmosphere almost certainly did not have the mix of gases that Miller and Urey used. Life is rich in carbon and hydrogen, but relatively poor in oxygen. Oxygen, in spite of its vital role in advanced life, is a corrosive poison for many organisms, especially many of the archaea and bacteria associated with ancient life. Free oxygen did not build up on Earth until about two billion years ago, a product of extended photosynthesis. Miller and Urey introduced hydrogen directly, and via both methane and ammonia. This formed what chemists term a reducing atmosphere (as opposed to oxidising). Geologists, however, believe that the early Earth had a neutral rather than reducing atmosphere (plentiful carbon dioxide and nitrogen, but little hydrogen). This objection is certainly a problem for traditional primordial soup

theories. However, if life began in a volcanic setting, or deep underground, as I argued in Paper I, reducing conditions are not problematic. Even today, the Earth's crust exudes in certain geothermally active locations reducing gases such as hydrogen, hydrogen sulphide, methane and ammonia.

A more serious objection to the significance of Miller-Urey type experiments is that their principal products – amino acids – are not hard to form anyway. They have since been discovered inside meteorites[11], and are being sought by astronomers in comet tails and interstellar clouds, which are known to be rich in organics[12,13]. They could have been delivered to the Earth (and Mars) in copious quantities by comet and asteroid impacts, rather than being manufactured in situ. The ease of formation of amino acids (and other organic building blocks) has a ready thermodynamic explanation, for creating them from inorganic gases like methane and ammonia is, thermodynamically speaking, a "downhill" process (i.e. strongly favoured, with energy emitted). However, the next step – linking the amino acids together to form long chains (called peptides), the precursors of proteins – is thermodynamically "uphill," at least in a watery medium. Energy is needed to drive it. In living organisms the necessary energy is provided by carefully customised molecules manufactured by cells. But in a pre-biotic setting, these handy molecules would be absent. There was no lack of available energy sources to drive chemical reactions – for example, sunshine and volcanic heat – but the problem is that heat energy, like most natural sources of energy, is chaotic (unlike the precision of a specialised energised molecule). Since a protein is a delicate, elaborate and highly specific molecule, it is unlikely to form if energy is simply thrown at a mixture of amino acids willy-nilly. The

difficulty can be compared to building a house. Even if a simple process can be used to make the bricks, the bricks must then be assembled into an elaborate and highly specific structure. Heating a collection of amino acids is rather like putting a stick of dynamite under a pile of bricks and hoping that a house results.

The problem is actually far worse than described. A typical small protein contains about a hundred amino acids, strung together in a specific order as instructed by the genome. If the order is changed even slightly, the protein's function may be compromised or rendered totally ineffective. Of the 10^{130} ways in which 100 amino acids of 20 varieties can be arranged, only an exceedingly tiny subset of combinations will be biologically functional. The situation is analogous to the content of a book. If the words of a novel are jumbled up, nonsense is very likely to result. Only a minute fraction of all possible word combinations makes literary sense. Similarly, only a minute fraction of amino acid combinations makes biological sense. Clearly, the chances of hitting the right combination of 100 amino acids by random molecular shuffling are infinitesimal. Since a functioning cell requires thousands of different proteins, it is not credible to suppose they formed by chance alone, even if the entire volume of the observable universe were filled with primordial soup.

On top of all this, there is the problem of chirality[14]. Amino acids (and many other organic molecules) possess a definite handedness, that is, they differ structurally from their mirror images. Although left- and right-handed amino acids are chemically equally favoured, life on Earth uses only the left-handed forms. A soup of amino acids would be

expected to contain equal numbers of left and right forms; the odds against a substantial quantity of primordial soup containing only one variety by chance is infinitesimal. Although physical mechanisms are known[15] that can induce a small chiral excess in a chemical mixture, the way in which this might be translated into a fully homochiral living state is unclear.

We must therefore conclude that not only is the assembly of amino acids into proteins thermodynamically unfavourable, there is also a negligible probability of functional proteins resulting from undirected chemical bonding in a random mixture. Amino acids left to react on their own will never make the specific polypeptide chains that life needs. This makes the "chicken first" theory look decidedly shaky. But proteins are only half the story. What about the "egg" – the nucleic acids?

The RNA world and other theories

Is it possible that nucleic acids preceded proteins and somehow managed to get along without them? In the 1980s, this theory was given a fillip with the discovery[16] that RNA can sometimes act as a weak enzyme, catalysing some reactions between other strands of RNA. This has led to the so-called RNA world scenario[17,18], according to which RNA (being chemically more potent than DNA) originally served as both chicken and egg – phenotype and genotype - promoting vital reactions and at the same time storing genetic information. At some stage, the theory goes, the RNA world co-opted polypetide chains to improve the efficiency of replication. Darwinian selection would then have favoured

the more efficient replicators, and in that manner the close partnership between nucleic acids and proteins gradually became forged. The step from RNA to the more familiar DNA, and thus to life as we know it, would then have been comparatively straightforward.

The RNA world theory is not without its problems, however. It has to be explained where the RNA came from in the first place. Nucleic acids are, if anything, harder to synthesise than proteins. They are also rather delicate molecules. In living cells, RNA strands typically contain thousands of building blocks (called nucleotides). It is inconceivable that such large molecules would form naturally in a primordial soup. On the other hand, the RNA world might have formed an intermediate stage in the development of life. Perhaps a completely different chemical system preceded the RNA world and manufactured it as a by-product, eventually being displaced by it?

A theory of this sort has been proposed by Cairns-Smith[5]. According to his scheme, the first steps on the road to life were taken by clay crystals. Crystals are, of course, adept replicators, but in their pure form they contain almost no information (a crystal is a regular array of atoms). However, impurities in the crystalline structure could be used to encode information. To serve as a crude genome, an impure crystal would have to grow and fragment in such a way as to preserve the impurity sequences. Cairns-Smith has suggested certain mineral structures that might do this. The transition from clay life to nucleic acid life remains largely conjectural in this theory.

Ghadiri and his collegues[19] have turned the RNA world theory on its head, and claimed that proteins could also serve as both chicken and egg, that is, some proteins are able to replicate and pass on information. Other researchers have been of the opinion that solving the problem of replication should take second place after accounting for metabolism, and have sought models of chemical cycles that might act to harness energy and drive a chemical soup to greater and greater complexity. Kauffman[20] has developed a theory of autocatalytic networks, in which a set of molecules react in such a way that some molecules catalyse their own formation, producing a complex web of interactions that serves to bring about increasingly elaborate molecular self-organisation. Dyson[21] has produced a theory in which a collection of protein-like molecules can undergo a crude form of reproduction en masse. Morowitz[22] has tried to identify the core chemical cycle within primitive organisms to see how it may have come into existence spontaneously in a pre-biotic phase.

All theories of biogenesis face additional challenges to explain how the chemical schemes being proposed became incorporated into cells with membranes having the right physical and chemical properties, and to identify the precise setting in which the key reactions took place. Oparin[8] was impressed by the way that a mixture of oil and water can form a so-called coacervate in which the oil retreats into tiny cell-like droplets, and was convinced that the cellular structure came first, and the complex organic chemistry then took place within this natural "test tube". But there are other possibilities too. There are distinct advantages to moving the setting from the traditional location - a primordial soup on the Earth's surface - to a hot, deep place, such as near a volcanic vent, or beneath

the ocean floor, where seawater percolates through the porous basalt and brings up dissolved gases and minerals by convection. I have already mentioned the desirable reducing conditions that are normal there. But there are other chemical advantages too. The tiny pores of rock can serve as rudimentary cells, while their surfaces act as powerful catalysts promoting the synthesis of complex organic molecules. Also, as mentioned in Paper I, there is good evidence that early life dwelt in this subsurface region, so it is an obvious location to consider for biogenesis. Such a location is a natural setting for the theory of Wächterhäuser[23], who believes that the surface of the common mineral iron pyrites (fool's gold, which forms from hydrogen sulphide and iron) will catalyse the polymerisation of amino acids, and perhaps generate more complex organic structures too, including replicating molecules.

Finally, there is a general point worth mentioning that is often overlooked. Because replication is an exponential process, if life were to form in a finite reservoir of suitable material, it would rapidly use up the available resources, and grind to a halt. Theories that life might form inside comets[24], for example, encounter this problem. Life can evolve beyond the first step only if there is a *throughput* of energy and material. The advantage of a seabed setting (on Earth or Mars) is the existence of a continual flux of convecting fluid coming up from the deeper zone. Since life is unable to penetrate more than a few kilometres into the crust, on account of the fact that the temperature becomes intolerably high, there is no danger that the supply of material will be promptly exhausted by invasion of the first organisms[25].

Outstanding conceptual problems

Most theories of biogenesis have concentrated on the chemistry of life. However, life is more than just complex chemical reactions. The cell is also an information storing, processing and replicating system. We need to explain the origin of this information, and the way in which the information processing machinery came to exist. It is important to realise that a gene is a set of coded instructions for the manufacture of a protein according to a precise recipe. Genetic instructions are not merely information per se (as arises in, for example, thermodynamics and statistical mechanics), but represent a form of *semantic* information, i.e. they have to *mean* something[26]. For a genetic instruction to be successful, there has to be a molecular milieu capable of interpreting the message in the genetic code. The problem of how meaningful or semantic information can emerge spontaneously from a collection of mindless molecules subject to blind and purposeless forces presents a deep conceptual challenge.

Related to this puzzle is the problem of how digital control emerged from analogue processes. The cell uses digital information to communicate between nucleic acids and proteins. The flow of information from DNA and RNA to proteins via a coded information channel is effectively the way engineers use digital control to boost the fidelity of electronic devices. It is well known that digital computation, digital radio, digital data storage, digital cameras, digital television and so on are far more efficient than their analogue counterparts. Life went digital at the dawn of time, by using, not a binary, but a quaternary coding system to store bits of information. So the central process

of life – DNA and RNA instructing proteins – takes place not directly, through “hard-wired” chemical bonds, but via digital software. So another way of looking at the problem of biogenesis is to ask how the molecular hardware wrote its own software. How did this ingenious coded communication system evolve?[18]

What about the origin of the genetic information itself? Where did the specific bits of information stored in the genome of the first living cell come from?[27] After all, information cannot come out of thin air. There is a powerful mechanism for generating information in physical systems, in the form of Darwinian evolution by variation and selection. The information in the human genome, for example, has accumulated by Darwinian processes over billions of years. However, Darwinism cuts in only when life has got going; we cannot appeal to Darwinian evolution to explain how life began.

Some researchers think it is a case of “Darwinism all the way down.” That is, we can define life to be any system capable of replication, variation and selection. It need not amount to anything we would normally recognize as life. It could be simply a set of fairly small molecules that might form by chance in a plausible pre-biotic setting. It is possible to imagine that once such a collection of replicators exists, molecular Darwinism would do the rest[3], evolving ever more complex and sophisticated replicating systems, until something like the RNA world appears.

Unfortunately the identity of these hypothetical simple replicators remains unknown, and the efficacy of molecular Darwinism is largely untested. Nor is it clear to what extent

chemical self-organization may rivalled Darwinism in the early stages of biogenesis. It is even conceivable that quantum mechanical effects may have played a key role[28,29]. A fully satisfactory account of the origin of biological information will probably have to await a better understanding of the nature and dynamics of information, and how it relates to matter. Thus a solution of the problem of biogenesis is likely to involve some profound developments in the conceptual basis of physical science[30].

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