Interim FAQ:

The Probability of Abiogenesis

[Last Update: April 6, 1995]

I should preface this with the proviso that I do not really exist; I am locked in mortal combat with the evil dragon Tenure (well, Early Tenure) and have long since jettisoned the net as an unproductive drain on my limited mental and temporal resources. Thus, I may disappear for another several months without advance notice.

I would suggest that, in the absence of my long-awaited FAQ, which is still under construction because of my need to get out 'real' publications, that this suffice and be duly entered in the archives. I am happy to spruce this up with references and modifications after input and criticism from the howlers.

That said, I think that Brian Harper (*not* Harmon) has made some excellent points regarding potential problems with abiogenesis scenarios. If I may be so bold as to ignore whatever thread(s) he is participating in, I will try to summarize some of my own thoughts here:

1. The problem of abiogenesis is the problem of self-organization of organic self-replicators. Once there is a sustained process of organic self-replication, natural selection at the molecular level should take over.
2. We don't have good historical clues regarding what the first self-replicators were. Unlike single and multicellular life forms, they left no imprint of their passing. At best, we have metabolic fossils that indicate that the last common ancestor of modern life was preceded by an organism whose biochemistry was based on nucleic acids rather than proteins: the so-called RNA world hypothesis. Unfortunately, this ancestor was itself quite complex and, thus, a distant descendent of the first self-replicator(s).
3. We assume that a transition occurred between the first self-replicators and the RNA world. This assumption is not necessarily valid: for example, earlier life forms may have altered the primordial environment and set the stage for modern life (speculations of this sort have been put forth by folks like Cairns-Smith with regard to inorganic life, and by many prebiotic chemists with regard to pre-nucleic acid-based life). However, the simplest and cleanest assumption is that there is an unbroken lineage between the first replicators and modern replicators.
4. With this assumption, what can we say about the first replicators? That they were in some way based on nucleic acids, much as modern replicators are. Again, this assumption is at least partially borne out by the extensive evidence in favor of the RNA world hypothesis.
5. Therefore, the question, as I see it, is: how easily could self-replicating nucleic acids have self-assembled in one or more variants of the primordial soup? This question can in turn be broken down into three other relevant questions:
    1. What is the probability that nucleotides would have been formed in one or more variants of the primordial soup?

Other Links:

The First Cell

This *Discover magazine* article presents some of the current activities and views of leading scientists studying how cells first came to be.

The Beginnings of Life on Earth

This *American Scientist* article by Christian de Duve discusses the origin of the "RNA World" that may have led to modern biodiversity.

From Primordial Soup to the Prebiotic Beach

In this interview, origin of life pioneer Stanley Miller discusses his views on the origin of life and some of the current research taking place in the field.

2. What is the probability that such nucleotides would have self-assembled into strands?
3. What is the probability that nucleic acid strings would have self-replicated?

6. Question 5.1, above, can be further broken down into four additional questions:
    1. What is the probability that ribose would have formed in the primordial soup from simpler components?
    2. What is the probability that nucleotide bases would have formed in the primordial soup from simpler components?
    3. What is the probability that ribose and bases would have assembled into nucleosides or nucleotides?
    4. What is the probability that nucleosides would have been appropriately activated for polymerization?
7. Many of these sub-questions cannot be adequately answered as of yet. However, I will try to sketch the one best piece of evidence for or against each.
    1. The probability that ribose would have formed is good. The one carbon compound formaldehyde is easily generated by a wide variety of prebiotic routes and can be readily transformed into complex sugars by the mechanistically simple 'formose reaction.' Unfortunately, the 'formose reaction' yields multiple, different sugars ("the prebiotic equivalent of tar"). Because of this, Shapiro has extensively criticized the role of ribose-based polymers in abiogenesis: the efficiency of ribose synthesis by the formose reaction is less than 1%. However, Eschenmoser has recently come up with a plausible prebiotic synthesis of ribose in which the yield is upwards of 30%.
    2. The probability that nucleotide bases would have formed is good. The one carbon compound cyanide is easily generated by a wide variety of prebiotic routes and can be readily transformed into purine bases such as adenine.
    3. Unfortunately, the conditions that lead to the synthesis of sugars would poison the synthesis of purines, and vice versa. Because of this, authors have speculated that the syntheses of the two compounds were separated in space or time. While this may strike you as an ad hoc requirement, there is an excellent chemical rationale for it: if the early Earth had a neutral, as opposed to reducing, atmosphere (the current best guess) then formaldehyde (and hence sugars) may have readily formed, but cyanide would have been quickly scavenged into other forms unsuitable for purine biosynthesis. However, cyanide (and purines) would likely have entered the prebiotic environment in two other ways: first, from comets, which have been shown to be rich in cyanide(s). A huge amount of organic material, possibly as much as was created by atmospheric chemistry, was delivered to the Earth during the time preceding abiogenesis. It is likely that the kinetic energy of comet entry would have led to the synthesis of a variety of compounds, including purines, from stored cyanide. Second, besides the atmosphere and comets, the other primary center for the synthesis organic compounds was deep sea hydrothermal vents. Here the chemistry was likely much more suitable for the synthesis of purines from cyanide than in the atmosphere. Thus, we have the synthesis of sugars in the atmosphere and upper reaches of the ocean, and the synthesis of purines during the impact of comets and in the lower reaches of the ocean: as hypothesized, separation in space and time.
    4. The probability that ribose and bases would have assembled into nucleosides is currently poor. Under the conditions that

have so far been tested, assembly is on the order of 2% of starting materials. While this could very well have resulted in the synthesis of literally tons of nucleosides, I think that for a plausible case for abiogenesis via RNA to be made a higher yield reaction must be found. Remember, all of the reactive compounds I have mentioned were frequently involved in making other molecules as well, so a low yield for one reaction would have meant dilution of that product by the fruits of the higher yield reactions. Until self-assembly and self-replication (see (1), above) occurred, there were not necessarily good ways to reinforce the synthesis of particular compound in a heterogenous environment.

5. The probability of activating nucleosides to nucleotides is good. It is unlikely that triphosphates such as those found today would have been made, but phosphoramidate activation via imadizole groups has been shown to be plausible and is much more effective for prebiotic polymerization reactions (see below).

8. As to question 5.2, the chemistry for the synthesis of short oligonucleotides is good. Ferris and his co-workers have coaxed trimers to pentadecamers (15-mers) from prebiotically-activated nucleotides. The major objections to such molecules being 'the first templates' would be:
    1. Was the concentration of activated nucleotides sufficient to allow realistic levels of condensation for further molecular evolution? If the reader will allow me, I would like to deal with this question in its own right, below.
    2. How was the regiochemistry of condensation controlled? That is, even if we have primarily ribonucleotides, as opposed to arabino-, gluco-, xylo- and multiple others, there are still several different ways that phosphodiester bonds could have formed between the sugars: 5' to 5', 5' to 3', 3' to 3', 3' to 5', 2' to 5', and so forth. Different linkages would have (and do, in reconstructions) lead to different types of oligomers. This would have further diluted the likelihood of any one of these oligomers being somehow replicable.
    3. Moreover, the presence of non-ribonucleotides or oligonucleotides along with ribotides would have led to the 'enantiomeric poisoning' of early replicators. That is, once a 'good' strand got started, it could easily join with a 'bad' monomer or strand, and replication would have halted [this is one of many places where pictures on the WWW page will come in handy some day]. As we will see, though, this problem will likely solve itself in the next point.
9. As to question 5.3, the chemistry for self-replication is excellent. This is what I work on, at least when I'm not trying to invent anti-viral drugs. However, I tread lightly in the footsteps of giants.
    1. Leslie Orgel has shown that template strands of nucleic acids can be replicated using monomers as substrates: that is, poly(G) stretches can be copied by appropriately activated cytidine monomers. Unfortunately, these experiments are most 'vulnerable' to the problem listed in 8.3, above: enantiomeric poisoning by, say, an arabino-nucleotide. Because of this many prebiotic chemists have been searching for the 'Nucleotide Grail:' a compound similar to a nucleotide that would not be subject to its regiochemical frailties. For example, acyclo sugars have been considered to be a strong contender for a replicator that preceded those more directly linked to modern life (see (3), above). I am perhaps in the minority of biochemists in thinking this unnecessary because:
    2. Gunter von Kiedrowski has done exceptional work showing

how oligonucleotides can replicate via ligation, as opposed to monomer addition. That is, a hexamer can template the synthesis of two trimers. This hexamer can in turn template the synthesis of complementary trimers to recreate the original template. This solution to what the first replicators were is elegant for a variety of reasons, chief amongst them the fact that oligos as simple as trimers can be readily constructed from monomers, as described above.

3. In addition, the ligation of oligomers bypasses any problems associated with the heterogeneity of early mixtures. The formation of paired templates occurs best when both strands have the same mix of monomers. Thus, a trimer that contained an arabino-sugar would not bind as well as a trimer that contained all ribo-sugars to a template containing ribo-sugars. There would be natural selection for all and only the correct replicators, those that could properly pair with one another. Thus, the mechanism generally described in (1), above, the selection of functional molecules, would have taken over at this point. This mechanism for self-organization and self-replication should have weeded out a wide variety of chemical heterogeneities from the soup.
4. The synthesis of larger nucleic acids from small is, as we say, academic. While I am sure that most critics will stumble here ("By God even E. coli has 3 million base pairs and you expect us to think it is descended from six???"), the hard parts were really all that I have described above. It is relatively easy to grow the 6 to teens and the teens to hundreds by obvious mechanisms. Once you have teens to hundreds the molecules can in fact fold and catalyze reactions.
5. Random sequence polymers should thus have been present in the primordial soup. Many authors (including myself) have shown how, in defiance of the nonsensical 747 analogy, functional nucleic acids can be selected from random sequence mixes. Given natural selection on a molecular population, one can do literally almost anything: create binding species, anti-virals, new catalysts, new recognition sites for nucleic acid binding proteins ....

10. Concentration is, in my opinion, not an issue for any of the above. If the (huge) quantities of organics were evenly distributed in a primitive ocean, yes, the synthesis of small molecules and oligomers would have been difficult. But it is unlikely that this was the case. Many small molecules and oligomers can be efficiently concentrated on molecular surfaces, such as clays. Moreover, the clays catalyze reactions that take place between the concentrated compounds! For example, the template syntheses described in (8) are much more efficient on the surfaces of certain clays than in solution. The origin of life thus likely occurred on a two-dimensional matrix, rather than in a three-dimensional space. We are borne of slime layers on rocks, not flitting chemicals in an ocean.
11. The problem of perception: Stanley Miller did such awe-inspiring experiments that we are stuck in a particular abiogenetic paradigm: life must have come from amino acids synthesized in the atmosphere and dissolved in a giant pond. This is still roughly the public's perception. However, the community has moved beyond this, albeit slowly. While my meanderings are not the only possible description, I hope that they provide a coherent pathway for those who have not previously considered the challenge in detail. Obviously, there are still great problems: the synthesis of nucleosides, the breakdown of oligomers (not considered here), the synthesis of pyrimidines (not considered, and to some extent not necessary: purines can self-replicate via non-Watson-Crick base pairs). However, other stumbling blocks (the synthesis of ribose, the selection from random strings) have begun to fall.

Perhaps this more or less even-handed treatment of abiogenesis will give comfort to creationists or to those who see intelligent design, but I warn them: to trumpet the barrier today is to eat your words when it falls tomorrow. If you make a proof of Jesus (or Buddha or any supernaturalism) on the back of abiogenesis, be prepared for the disproof as well. Such a disproof is unfair, and not necessarily logically linked, but it will be so perceived.

Non-woof

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