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Letter to the Editor

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In response to: McIntosh, A.C., Information and entropy – top-down or bottom-up development in living system? *International Journal of Design & Nature and Ecodynamics*, **4(4)**, pp. 351–385, 2009.

From: Royal Truman, *Mannheim, Germany.*

Sir,

In a recent article [1], McIntosh drew attention to some issues, which indeed merit close attention. A very bold challenge was posed to those holding to a naturalistic origin of life: "*At the molecular level, the laws of thermodynamics do not permit step changes in the biochemical machinery set up for a particular function performed by the cells of living organisms. Thus, random mutations always have the effect of increasing the disorder (or what can be defined as logical entropy) of any particular system, and consequently decreasing the information content*" [2]. His challenge applies at two levels (A and B):

A. The need for specialized machines to initiate an evolutionary process. Three essential molecular machines were mentioned: DNA polymerase (p. 364), ribosome (p. 365) and enzymes, which excise incorrect nucleotides (p. 375). This is an important observation and stimulates to examine other indispensable machines.

1. *Amino acid (AA) building blocks*. Chemical examination of the biomolecules used by cells reveals that of the vast variety of chemical alternatives that could be generated from the simplest molecules, only a miniscule subset must be allowed to be produced. Life would not be possible if the necessary chemical structures (proteins, carbohydrates, etc.) were surrounded by an 'ocean' of random alternatives. The solution was to first reliably create some key AAs as building blocks; to react these together; and then modify afterwards portions of the resulting polypeptides chemically.

This requires several molecular machines, which must work together in tandem to synthesize optically pure AAs.

2. *Only the peptide-creating bonds must be permitted*. Other chemicals must be kept away from the proteins being created; the side chain functional groups must not react with the amino or carboxylic acid ends; and the favoured cyclic reaction between the ends of the polypeptide chains must be prevented. This requires a machine (the ribosome), which forces only the correct chemistry to occur and prevents the wrong side-reactions.

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3. *The entire polypeptide must be created*. An average, protein consists of about 300 AAs. An organism could not survive if each of the kinds of proteins were to be accompanied by polypeptide chains ranging from one to several hundred AAs. The solution required a considerably more complex ribosome, which would know where to start and where to terminate polymerisation. Incomplete polymers would not be released.
4. *The AAs must react in the correct order*. Since any of 20 AAs could react at each of n positions in a protein, then 20^n different chains could be created, where for an average protein n is around 300. All the above machines could be in place, but unless carefully controlled to prevent random reactions of AAs, all cells which ever lived would never have generated the same polypeptide twice in the history of the universe. Chaos would result in the cell, because there is no preference for chaining any AA over another.

The solution was to generate mRNAs that communicate the correct order for each protein. Each codon on mRNA, consisting of three nucleotides, codes for the order an AA to be used. An adaptor molecule, tRNA, brings the AA and codon together. Now two more series of machines have become necessary. One to synthesize the tRNAs, and the far greater challenge to produce all the aminoacyl tRNA synthetase enzymes [3], which attach precisely the right AA to the appropriate tRNA, and in a high energy (activated) state to facility reaction with other AAs later at the ribosome.

5. *The mRNA must be forced through the ribosome*. Forcing $n - 1$ peptide bonds to form requires exposing each codon position on the mRNA, one after the other, to the 'adaptor' tRNA molecules. The mRNA and growing polypeptide must be held in an exact position, to an atom level of precision, until the peptide bond has formed. Then, a judicious input of the correct energy amount at exactly the right time, precisely at the correct location in the ribosome, must force the mRNA forward exactly another codon position. This adds more design requirements to the ribosome, plus a whole new series of machines to create the energy packets (ATP molecules).
6. *mRNA copies from genes are needed*. DNA provides the details of which order AAs are to react together but the huge chromosome cannot be processed by the message decoder (the ribosome). A much shorter copy of only relevant parts of the DNA message must be made. The resulting mRNA can be then be reused many times. This requires new, extremely complex machines, RNA polymerases.
7. *Genes must be replicated*. The DNA template for mRNA must be replicated and made available for the next generation. Other molecular machines become necessary, DNA polymerases. Additional machines are necessary to cause cell division and to control the details involved.
8. *The correct sugars for nucleic acids are needed*. Using the same raw materials, a huge number of different sugars and their isomers can also be created. The cell must synthesize the correct, optically pure monomers used to construct RNA and DNA, which requires not only a large number of new machines, but also the presence of pure AAs. Note that the molecular machines needed to metabolise AAs are based on instructions coded using DNA and RNA chains, but at the same time, these nucleic acids require some of the same AAs to be themselves synthesized. These mutual requirements cannot realistically be developed sequentially.
9. *Multiple other molecular machines are needed*. The earlier examples serve to illustrate some of the machines needed to permit the genetic code to function. Many additional machines, which are indispensable to survive and reproduce will not be mentioned, such as the tools to produce the biochemicals needed to generate membrane walls; the pores to transfer materials in and out; and dozens of additional enzymes for other key services such as processing nutrients. This explains why the number of genes necessary to permit the simplest form of autonomous life has been estimated at around 300.

McIntosh has done us a major service by reminding us that energy processing in useful manners requires specialized machines. Effects such as gravity or temperature to modify entropy locally, at the expense of the environment, miss the point entirely.

B. The difficulty of increasing complexity or information via mutations in living systems. It is often claimed that mutations provide potential improvements and then natural selection decides which to favour. In the words of Dawkins, "*Mutation is not an increase in true information content, rather the reverse, for mutation in the Shannon analogy, contributes to increasing the prior uncertainty... In every generation, natural selection removes the less successful genes from the gene pool, so the remaining gene pool is a narrower subset. The narrowing is non-random, in the direction of improvement, where improvement is defined, in the Darwinian way, as improvement in fitness to survive and reproduce.*" [4].

Is this true? Mutations can occur throughout the whole genome and the highly random nature of survival in the face of multiple internal and environmental challenges prompt the effectiveness of natural selection to be examined more carefully. Although several well-known claims have been made that mutations + natural selection = new information, none of these are based on detailed studies using real genomes and natural conditions. For example, Dawkins' 'Methinks it is like a weasel' software program [5] has no biological analogy or relevance [6].

Another popular claim is based on work done by Schneider [7], who writes: "*The **ev** model quantitatively addresses the question of how life gains information*". Truman analysed and tested the software [8] extensively and found the claims made unacceptable [9, 10].

Is it not more realistic that random mutations would have the net, average effect of destroying coding instructions for complex processes? McIntosh documents how most mutations are deleterious but located in the near neutral zone. This means that natural selection could not easily identify them and weed them out, *contra* Dawkins' claim earlier.

McIntosh's observations are pertinent, for several reasons.

1. Proteins usually seem to be designed for more robustness than necessary. For example, Axe points out [11, 12] that to maintain the correct folded structure, more features, such as salt bridges and other interactions, are present than needed. Destroying one stabilizing bond often has no, or negligible, effect on the stability or function of the protein. He calls this a 'buffering' effect. Studies show that although various mutations are harmless individually, jointly they wreck the protein. Some authors suggest [13] a multiplicative effect. For example, if an organism has a 90% chance of surviving a single AA change, then for three such events at the same time the chance drops to $0.9 \times 0.9 \times 0.9 = 0.73$. Axe's data show that this is only true for a few mutations in total, or combinations of mutations, and then loss of function is complete [12].
2. Often a large number of genes can be removed from organisms with no visible effect on their viability.
3. Some key processes are redundant, such that deactivation of a key gene has no visible effect since the backup process is activated.

The implication of observations such as these is that many mutations are currently allowed because the genome has been built to withstand such insults. This would reflect what Gitt calls [14] the 'apobetics' portion of the information hierarchy, meaning an intended outcome. Mutations relentlessly weaken the long-term survival ability, but these are not immediately obvious and natural selection would not prevent the universal trend towards degradation. As the whole population

degrades over time, the effects of deleterious mutations would be ever less visible relative to the now weaker alternatives. Therefore, natural selection is not truly able to retain only the pristine versions. With enough time this extra robustness, or information, built in will be exhausted, leading to the genetic meltdown Sanford predicts [15]. At that time, the net effect of mutations plus natural selection will become more apparent.

Does modification of a protein to process a different substrate provide evidence for evolutionary improvement or increases in information in the Shannon sense? McIntosh mentions the case of mutations causing loss of recognition of glucose and use of lactose. He points out that, "*Such conditions are not adding more than that which was there already, since they represent sub-machinery of an existing working machine*" [16].

Such examples of microevolution cannot be extrapolated to explain the origin of the huge molecular machines mentioned above, requiring in some cases dozens of new proteins. But recalling Gitt's concept of 'apobetics' there is another consideration. Sometimes modification of just two or three AAs permits a related function to be carried out, such as degrading and removing another very similar toxin. Resistance to new antibiotics in huge bacterial populations is sometimes suspiciously fast. It is probable that some members already possess variant proteins, in anticipation of difficulties that might occur. When the catastrophic challenge arises, the population does not need to wait for some fortunate mutations but can benefit as a whole immediately from the reserve of predisposed variants.

It is also possible that processes were built-in to enhance biological variety by judicious, non-random mutations. An analogy is the manner useful antibodies are produced via deliberate mutations at specific sites on genes. Although new molecular machines would not be produced in this manner, the coded information plus variety enhancement could permit a narrow range of related functions to be carried out.

As an analogy, a firearm could be designed to shoot a single bullet very precisely, or another design, like a shotgun's, could be used which covers a range of possibilities within a suitable distribution of intended outcomes.

For these and other reasons, it is unlikely that random mutations, plus selection, provide the building material for complex new functions. One class of mutations commonly found is **deletions of portions of DNA**. In simpler prokaryote populations, this would often present an immediate selective advantage: eliminating those genes not immediately needed decreases the energy needs of the organism and decreases the cell replication time significantly (replication of DNA is very time consuming). Realistic calculations [17, 18] suggest that genome truncation would be strongly favoured. And the absence of superfluous genetic material to use in evolving new genes would prevent more complex organisms from evolving.

I applaud the Journal's decision to present these topics for discussion in the scientific community.

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[2] *Ibid*, p. 375.

[3] http://en.wikipedia.org/wiki/Aminoacyl_tRNA_synthetase.

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[6] Once any target sentence is selected, 'mutations' approaching the goal are immediately selected with 100% infallibility. No mutation can ever kill the organism; the order of mutations is not relevant; the number of letters in the target is very small, etc. The software is simply based on a deterministic algorithm which will inevitable converge to any chosen target sequence. The relevance to neo-Darwinian theory is lacking.
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[10] The 'logic functions' and assumptions were not, and cannot not, be calibrated against any real biological data. For example, mutations were not allowed to occur at over 99.9% of the genome, only at the binding sites, which explains why the mutation rate of 1/256 over the whole sequence can be used every generation; a series of complexity-increasing stepping stones are made conveniently available and easily reachable with a few mutations. Under the usual settings, higher logic functions, easily reached, instantly lead to a dramatic increase in their proportion in the population.
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