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Understanding the Interface Between Chemistry and Biology: A Foundational Review for Medical and Biomedical Sciences Education

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ABSTRACT

Most theories suggest that life originated from a chemical evolution in the young earth. But how does organic chemistry transform into biology? Are they even completely separate entities or are they just different sides of the same coin? The aim of this work is to identify a new way to fill in the gap between them. Individual living systems can decrease entropy locally, they can reproduce, self-organize and respond to stimuli. However from a strictly biochemical perspective all life is connected to each other in a constant recycling of nutrients. Here we challenge the idea that life can be biochemically separated into individual organisms, thus the entropy of life as a whole increases as in any complex chemical reaction system. We also challenge the idea that reproduction, self organization and response to stimuli can actually differentiate biology from chemistry. We ourselves are the observers of the phenomenon of life and the biochemical events eventually lead to us or to entities that functionally look like us. The fact that part of the results are the observers of the whole event, raises some questions regarding the role of self-organization as a life-defining property. For example, if a river could think, would it perceive the cycle of water in which it participates as self-organizing? If we also consider the stability of DNA molecules with their packaging (e.g. histones, etc), the fact that DNA interactions with other molecules happen due to natural causes even in living systems and the potential of changes in DNA sequences to affect both the natural selection of the biological systems and the natural history of complex organic chemical reactions, it is argued that we cannot rule out the possibility that biological systems and complex chemical reactions are two sides of the same coin.

Keywords: chemical; reactions; organic; biochemistry; life; entropy; evolution.

MANUSCRIPT

Life is the property that distinguishes entities that have biological functions, from those that don't. Various forms of life exist, including bacteria, archaea, protists, fungi, plants and animals. Since there is not a widely accepted definition of life, the criteria can sometimes be ambiguous and include viruses, viroids, or even synthetic life [1, 2, 3].

Living organisms share some common characteristics. They are composed of cells, they maintain homeostasis, they have a metabolism, they reproduce, they adapt to their environment and they respond to stimuli [4].

Life on earth initially appeared 4.28 billion years ago, soon after the formation of the oceans (4.41 billion years) [5]. Several theories have attempted to explain the origin of life on earth. Most theories hypothesize that life arose from non-living material, like simple organic compounds [6]. The transition of non living chemistry to life is widely believed to be a gradual process of increasing complexity rather than a single event [7].

Here we will attempt to perform an in depth analysis of the similarities and key differences between chemistry, particularly complex organic chemistry and biology. What connects them and what separates them? How does chemistry transform into biology? We will also discuss potential misconceptions that we might have as human beings because of limitations in our senses.

The aim is to find a new way to fill in the gap between complex organic chemistry and biology. This will help us get a better insight into the process of abiogenesis.

1) Chemical origin of biological building blocks.

Oparin and Haldane independently proposed that life's building blocks originated from simple abiogenic material in proto-earth [8, 9]. While this doesn't give much details on how these building blocks generate life in the first place, it is important because it predicts that the spontaneous formation of simple building blocks of life from simple elements is possible. The hypothesis of Oparin and Haldane was later validated by the famous Urey-Miller experiment, which introduced heat and electric energy in a chemical mixture of elements that are present in a reducing atmosphere [10]. This resulted, among others, in the formation of some familiar organic compounds (e.g. amino acids) that were somewhat more complex than the initial elements. These results established abiogenesis from a primordial chemical soup as the prevailing theory for the origin of life. Oparin and Haldane further speculated that while these building blocks become more complex, they gradually gain more life-like properties over time, until eventually they become life as we know it. Despite the initial excitement, this hypothesis was later disproved by subsequent experiments.

It has been shown recently that if you mix pyruvate and glyoxylate in iron-rich warm water (mimicking conditions in young earth), the result will be a network of reactions with over 20 known biological intermediates. Some will even have 6 carbon atoms. The scientists also found that the resulting network increased its complexity over time [11].

There is today overwhelming evidence supporting the idea that the biological building blocks can originate from simple molecules under specific conditions. Although the experiments do not produce fully functional proteins or actual living systems, it is true that systems of chemical reactions over eons can evolve a lot. A functional protein is immensely complicated, folded, it carries information and it cannot function if it loses its structure even slightly [12]. But functional proteins are not magic bullets and they don't have some sort of "weird" properties. They are chemical molecules like all others. The only difference is that they are able to interact with other functional biomolecules in specific ways. As we will explain later, this points more towards the fact that these molecules share a common origin and evolutionary history.

2)What would the natural history of complex chemical reactions involving very long organic molecules be in the long term?.

Our intuition tells us that a system of chemical reactions, even if it gets external energy, will eventually reach an equilibrium state, but experiments show that this is not always the case [11].

If you start with a large number of initial chemical substrates and they all start reacting with each other bi-directly, then the total number of substrates will increase over time. If equilibrium is avoided and the organic molecules manage to become longer, they will form different stereochemical molecular structures. They will start folding differently in space, creating an ever increasing number of possible 3D configurations. Once the chemical interactions become dependent on the spatial properties and conformations of the molecules, the possibility of reaching a chemical equilibrium in the system, given the addition of external energy, will be greatly diminished. The possible ways of interactions will be way too many and statistics will start not to favor equilibrium.

In addition, every time a complex organic molecule with a complex 3D configuration reacts with other organic or inorganic molecules, such as $CaCO_3$, water, simple amino acids, lipids, etc, there is a high chance that the stereochemical complexity of the system will further increase. The addition of more atoms and especially carbon containing molecules in the spatially complex system can multiply the number of molecules and the 3D complexity of the material available for participation in life's chemical machinery. This will constantly increase the organic stereochemical reservoir.

The natural history of these reactions can in theory lead to the selection of the most stable and sustainable chemical systems among them. As a result of this process, nucleic acids, protein, lipids, sugars, etc will be inevitably formed.

The reactions will eventually favor (and in a way select) the most stable systems. We will try to identify which factors will affect this primordial chemical system.

a) Hydrophobicity.

The formation of hydrophobic bonds can add to the complexity of 3D chemical systems. In addition, it is a critical determinant of the fate of this system. The final result will be that chemical systems will be sequestered and isolated from each other, which will limit and regulate the potential interactions, and create both areas of complexity, but also areas of relative chemical stability.

b) Adhesion.

Another important fate determinant is the capacity of some molecules to strongly adhere to surfaces, membranes or to each other. This creates stability because the systems endure disrupting external or internal events, such as the water flow, currents, wind, etc. Reactions with a “sticky” element will eventually prevail in the long term and form the basis for further chemical complexity and interactions. This will also make the chemical process multifocal rather than diffuse. This will enhance its ability to thrive.

c)Stable systems endure.

In complex systems of organic chemical reactions, eventually nucleic acids and other biological molecules will be formed among others. The systems that are chemically stable will endure more, relative to the unstable ones. Thus, they will be over-represented in the resulting mixture. One example of remarkable stability is the formation of deoxyribonucleic acid molecules and their packaging in histones, etc. The endurance of the structures will contribute to the sustainability and relative expansion of these molecules, as they will be relatively unaffected by the other events that are happening around them. The formation of membranes and the inclusion of these systems inside them will further contribute to their stability.

d) Other factors.

Other factors such as polarity, the speed of some reactions, the abundance of production of metabolites, or small repeatable loops may create systems that can promote their own existence, in a process that resembles a kind of natural selection and survival of the fittest reactions. There are probably other factors that will play a role as well. All these factors will result in the evolution of the systems over time, and cause a step-wise, multifocal natural selection of the most stable compounds and chemical systems.

The above mentioned factors are critical players in real biological systems as well. Stereochemistry is key. It is clear that the structures of organic biological molecules can be extremely long and complicated, characterized by multiple side groups and branched architecture. They frequently have several active sites that interact with other molecules in such a way that one must know their spatial 3D conformation to understand them, because they behave differently in 2D and 3D [13].

Hydrophobicity is also important in biology. The formation of biological and other membranes is a result of hydrophobic properties of some molecules. Cellular membranes, organelle membranes, pore formation, vessel formation, etc are some examples [14].

Adhesive capacity is also an important property of life. For example, if you place living and dead cells inside a flask and you add media, then you can easily sort them out after a while, because only the living cells will adhere to the flask [15].

Sponges are good examples that shows the importance of stickiness in biological systems. Recent studies suggest that they were among the first organisms on earth. At a first glance, they are unique, as they look like something in between living beings and simple chemical systems. The strong adhesions among its molecules (together with other factors) make the biochemical systems in sponges sustainable over time [16].

Polarity, loops, speed of interactions and other factors we talked about are also important players in biology as well [17, 18].

Despite the similarities, the above mentioned chemical systems that we discussed, are still not even close to match the requirements to be considered as life, according to the definitions. These spontaneous systems of reactions will most likely result in increasingly chaotic chemical systems, that will lack the ability to self-organize, reproduce, respond to stimuli, etc. How do these reactions make the leap to bridge chemistry with biology?

4)The fact that we are the observers of the whole phenomenon of life gives us a specific viewpoint, which can be sometimes deceiving.

When we study the phenomenon of life, we come across a very unique and interesting fact. We are not only the observers of the phenomenon, but we are also the results, or at least a part of the results. By studying life, we study all the processes that lead to us and enable us to continue to exist. It’s like someone trying to observe his eyes by using his own eyes.

The organ responsible for our cognition is our nervous system. We have a sense of ourselves as cognitive and logical beings, and we also have a vague sense of our own body and its functions (interoception) [19]. The process of thinking is based on the function of neurons which is based on chemical and electrical events. There is little doubt that our perception has some limitations. The question following question is important. What we understand about life is all that is there, or are we missing some critical facts?

Some limitations of us being the observers of the phenomenon of life are the following:

a)We don’t realize the unfathomable number of chemical interactions and events that happen every second, even inside a tiny bit of living material.

Even when we look through microscopes, we don’t see plain chemical reactions. We see for example organelles, such as mitochondria, lysosomes, flagella, ribosomes, etc. If we had ways to directly observe biochemistry at the molecular level we would be simply mind blown. The underlying chemical complexity is so vast, that it is just beyond our intuition. This is not without consequences. For example we tend to forget that every chemical reaction in life happens for a natural reason. During replication, adenine and thymine interact by forming chemical bonds due to natural reasons. If we were able to see the events in a tiny scale, we would understand that these events have no purpose, at least locally.

We also don’t get a direct feeling of the dramatic chemical decline that an individual organism faces from the moment this individual gets born. A human being at birth is a biological system that can live around 80 years from that moment, while at 20 years he becomes a system that can live approximately 60 years. Our understanding is that a living organism self-organizes and constantly replenishes itself, recovering the order inside its cells. This is partly true however, because if there is not an abrupt major catastrophic event or catastrophic external factor, the body slowly ages over the course of the years. Here is an oversimplification. If hypothetically after 80 years the composition of the body is 95% the same from a chemical perspective, one can understand that due to our inability to comprehend large numbers, we don't realize that if initially there were 10 trillion chemical interactions, there is a major irreversible alteration in almost 18 million reactions every day on average.

In conclusion, although everyone is aware of the fact that living systems can be reduced down to complex chemical reactions, almost no one takes it into consideration in everyday life.

b)Life from a strictly biochemical perspective is a sum of chemical systems that interact. From a biochemical standpoint, there is not such a thing as an individual organism.

Our brain needs to organize the information it gets through external stimuli. This is crucial in order for the brain to understand the world and not get overwhelmed by the complexity of the events that happen every second in front of its eyes. But does this separation make sense from a biochemical perspective?

One of the most interesting properties of life is that it can utilize simple elements and biosynthesize complex biomolecules. Thus, it can reverse entropy locally. For example plants or photosynthetic bacteria can use simple elements and energy in order to form their building blocks [20]. So this local entropy decrease is a major difference between living systems and ordinary complex chemical systems. But is this actually the case?

Imagine that you place one bacterial cell inside a flask and you add growth medium so it can grow. After a while the cell will use the energy and the resources in the medium to create new bacterial cells, hence locally producing order. But life does not exist in isolation. The studied bacteria perform their activity because there is a complex template already existing inside them. Bacteria don’t come out of nowhere. They exist because of all the other life that exists or pre-existed. Every reaction in the flask happens because of the template and follows natural laws. A chaos of both anabolic and catabolic reactions are happening, but overall the bacteria will leave a mess inside the flask (the dirty colour of the medium and the smell when you open the flask are convincing). What happens in real life is that all the by-products of metabolism (gasses, waste, etc) become food and thus ingredients for other organisms in a constant recycling of nutrients. So even the waste products cannot be excluded from the chemical cycle of life. All life is connected to each other and from a strictly biochemical standpoint, there is not such a thing as an individual organism.

Lets see how life as a whole operates from a pure biochemical perspective. Contrary to what people think, entropy is very strictly defined by the number of microstates that are consistent with the macroscopic quantities of the system. Photosynthetic bacteria and plants use energy to form complex organic macromolecules (biomass) from simple molecules. However, they consume energy to achieve that. They also perform respiration, they produce gasses and odors, they produce some heat, they perform some movement inside them, like all living beings [21]. Eventually, all plants and photosynthetic bacteria die and their biomass gets degraded. Only 10% of the biomass will produce new biomass, while 90% will produce energy, heat, respiration, motion, etc. Then these consumers will also eventually die and their biomass will be utilized by other consumers, while again 10% will lead to biomass formation, and so on [22, 23].

In other words, decreases of entropy are not the norm in biological systems. Collectively, there is a constant recycling of carbon-based macromolecules, which constantly assemble and then degrade. But life is mostly all the disorder what happens during or aside this form of carbon recycling (e.g. motion, respiration, etc). We don’t see it this way because we tend to “cherry-pick” reactions, by considering individual organisms or systems that look like us as independent functional units, while we overlook the rest of the interactions.

To make an analogy, imagine that you have a flask full of some hypothetical molecules that move randomly and you add external energy. Also assume that the molecules are a little bit “sticky” and adhere to each other but only for a while. What you will mostly observe is areas of clumps and dead space, because this is how disorder looks like. Now suppose that the observer is a group of clumps himself. The observer might think that the purpose of this environment is to create clumps like him, and that the clump formation decreases entropy locally. The observer would have a hard time to explain this entropy decrease because one would expect production of disorder instead, given the initial ingredients of the experiment and the external conditions.

In conclusion, life overall is a disordered biochemical system and in that sense it does not differ from any spontaneously occurring complex organic chemical reaction system.

c)Does life really self-organize?

All chemical reactions of life individually happen due to natural reasons, but collectively they seem to serve an ultimate purpose that enables self-organization. This is considered one of the major properties that separates living from non-living systems.

However, we already mentioned that we ourselves are the observers of the phenomenon of life. All the biochemical events lead to us and to systems that functionally look like us (e.g. we share large amounts of the same genetic material with corn, Universal code, Krebs cycle, reproduction, etc). The fact that a part of the results of a process is the observer of the whole event, automatically puts into question the epicness of self-organization. If a river could think, would it perceive the cycle of water in which it participates itself as self-organizing? Although an oversimplification, imagine you have a series of events: A->B->C->D->……X->Y->Z->A->B->...etc and the observer is (N+O+P). The observer will think that the system self-organizes. But it's not that the system self-organizes. It is that similar systems under the same laws of nature produce similar results all the time.

Here is a hypothetical example: There are some chemical reactions in the surface of a moon of Jupiter. If somebody analyzes the chemistry in the surface of this moon now and in 50 years, most likely the results will be similar, because the reactions produce similar results all the time. Similarly the composition of the biochemistry of life on earth today will be similar as it will be in 50 years from now . We will still see trees, animals, bacteria, etc. However, both in the case of chemistry on Jupiter's moon and biochemistry on earth, if you look carefully, you will find some small differences.

Imagine that we cultivate some chemical reactions with the help of external energy in a small tube. Let's say that the system becomes extremely complex and we get to a point where we see nothing else but combinations of colors and shapes. Consider that a system (structure) inside this complicated mixture is the observer of the whole system, which means that he sees the events from inside, where he lives. For that observer, he exists because the chemical reactions continue until the initial ingredients or the external energy cease to exist. In reality, if things were different, he wouldn't have any problem, but only in the case in which he was that different result himself. He would have been perfectly adapted in that case too. He would simply perceive the catalogue of the chemical reactions that create him as a self-organizing mechanism, because everything that happens contribute to him being there as he is.

Can this hypothetical system be compared to life on earth, and can this fictional observer have some similarities with us? Life itself seems to be the sum of biochemical reactions on earth. If we were some really weird forms of aliens and we were observing earth from the outer space, then it is very possible that we would only see a very complicated network of reactions. Similar systems under same laws will produce similar results all the time. We don't know if the aliens would separate into individual organisms. For such aliens that don't separate, DNA molecules are likely just a part of this chemical soup (albeit a relatively stable one) and participate in some interactions that happen for natural reasons. Other nucleic acid bases form bonds with DNA molecules in a way that other DNA molecules are being formed, and so on. Mutations and other genetic or epigenetic changes will ultimately determine the fate of the system. Changes in DNA sequences that sometimes enhance the sustainability of the system would be selected. Darwinian natural selection would still be at play. The hypothetical aliens would see the same things that we see now when we observe life, but from a different perspective. From our point of view, DNA molecules are a kind of code that carries information. Both our viewpoint and the aliens viewpoint would be valid because we observe the same phenomenon. It's like the two different sides of the same coin. The only difference is that the aliens would never ask about how life originated on earth, because the answer would be obvious. Life always was and still is about the natural history of complex organic chemical reactions in any order.

d)There is nothing more tricky than to attempt to understand human cognition and logic by using human cognition.

How can chemical systems evolve into beings with capability to think and have logic? This question can be reduced down into the following dilemma. Is cognition a homeostatic tool like all other properties of biochemistry, or is it something different?

All our thoughts, regardless of how deep they are or complex, can be reduced down to simple chemical processes. There are absolutely no exceptions. Reason is driven by what we perceive as integral tendencies that are pleasure-seeking, as well as internal forces and instincts (reproduction, survival, etc). If you are hungry for days, you are gonna be constantly thinking of ways to feed yourself. You can deliberately fast, but this is because you decided that this will give you even more pleasure (e.g religious views) than eating.

Logic is also driven by self and other parties interests and aims. Brain function builds upon and uses the existing synaptic background that originates from nervous synapses that have been already developed. Based on the evolutionary history written in the DNA molecules and what they have learned so far, they seek to find solutions or develop strategies to fulfill their interests and aims. They do so, because this will result in pleasure and they will avoid pain. In other words, logic and cognition are tools that nature uses to serve its purposes. They are homeostasis tools, no different than the liver, the lungs, the kidneys, etc on that sense.

DISCUSSION

Life on earth probably originated from plain chemistry, but we are still looking for the mechanisms the bridged chemistry with biology. Plain chemical reactions can only theoretically go so far. However, we have shown here that a more careful and rigorous look suggests that biological systems might in fact not be that different if we take our perspective into consideration. There are probably several mechanisms that enabled life to emerge, but the main difference between biology and chemistry might have been the fact that we ourselves are the observers.

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CONFLICT OF INTERESTS

The author reports no conflict of interest.

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