Review of: "The evolution of E. coli is NOT driven by genetic variance but by thermodynamics."

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The fundamental processes governing biological evolution have not been sufficiently unveiled so far. In fact, the intimate mechanisms explaining the cellular functionality, the adaptive transformations, and the diversification of species are under widespread scientific research. An increasing number of these new findings have provided solid evidence questioning the Standard Theory of Evolution, (also termed Neo-Darwinism, evolutive synthesis, synthetic theory, modern synthesis, or modern evolutive synthesis).

Aside from postulating key advances to better understand the fundamental mechanisms of evolution, such studies, indeed, are crucial to understand essential aspects related to the origin and organization of the functional complexity of the cell.

In this specific context, Drs. Baverstock and Annila point in their last work two relevant conclusions: I) “Genetic variation does not drive evolution”, and II) “Thermodynamics is the driver of evolution”.

I) The Richard Lenski’s experiments on long-term evolution of *E. coli* (LTEE) show that although mutations are inherited, they do not seem to be determinant factors, in terms of adaptation, in the evolution of *E. coli*. More specifically, the adaptive dynamics of this microorganism, observed since 1988, do not correlate with the accumulated mutations. These findings seem to indicate that *E. coli* evolves independently of the accumulated mutations.

On the light of a detailed analysis of these experiments, Drs. Baverstock and Annila consistently conclude that the evolution of *E. coli* is not governed by genetic variability. This assertion contradicts the Genetic Theory of Natural Selection of Fisher on which the current Standard Evolution Theory is based.

II) The second relevant conclusion of Drs. Baverstock and Annila is that thermodynamics acts as the engine of the biological evolution.

There is no doubt that thermodynamics is crucial to understand important functional aspects of the cellular life. Even more, some of the fundamental principles of thermodynamics have decisive implications in processes governing the evolution of living beings.

The Nobel Prize Laureate in Chemistry Ilya Prigogine explained in 1977 the conceptual bases of molecular self-organization through energy dissipation in open systems operating far from thermodynamic equilibrium. In fact, self-organization is the main source of molecular order in cells. Detailed studies over the last four decades have demonstrated that self-organization is central to understand enzymes activities (the fundamental molecular machinery of life), the functional coordination between enzymatic reactions, the emergence of dissipative enzymatic networks, and the molecular rhythms. In addition to self-organization, molecular information processing arises in unicellular organisms. Both main sources of molecular order (self-organization and molecular information processing) generate global functional behaviors and, as a consequence, complex systemic properties (directional motility, integral growth, reproduction, sensitivity to the external medium, adaptive responses, and evolution) emerge in cellular organisms. Essentially, cells are open systems that operate far from thermodynamic equilibrium and exchange energy-matter with the environment. This way, during cellular adaptation new enzymatic self-organized processes increase cell information and structural-functional complexity. Thus, evolution represents an increase in the self-organizing efficiency of adaptive metabolic-molecular processes towards complexity. Therefore, many functional processes in the cell are clearly governed by fundamental thermodynamic principles (more detailed in: De la Fuente et al., 2021)

Connected with these aspects of Statistic Mechanics, Drs. Baverstock and Annila go beyond the postulates of the dissipative self-organization proposed by Prigogine and conclude that Thermodynamics acts as the essential engine of biological evolution itself.

However, despite the extensive body of their own previous publications on this topic, the relationship between the principles and concepts of thermodynamics and Evolution is not sufficiently explained in his paper. For example, the statement that "*the power law characteristic fitness is the universal signature of the principle of least action. Synonymous with the Second Law of Thermodynamics, it governs the evolution of natural systems*" should be furtherly justified. As Authors well know, it is not obvious that all biological phenomena exhibiting a power law have to be necessarily driven by thermodynamics. In my opinion, a broader and more detailed summary of some of the main studies published by themselves on this relevant issue should have been made. For example, in Sharma and Annila (2007) they address how evolution is given by the principle of increasing entropy.

Another interesting point is their mention of the relationship between the principle of least action and evolution, which has not been clearly outlined in conclusion #2. Here, the Authors should have provided more explanatory details going deeper into the question, especially because they analyzed such points previously. In this sense, in addition to the reference to (Makela and Annila 2010) provided in the paper, the reference to Kaila and Annila (2008) can be included to give more information.

I would also like to acknowledge the work carried out by Dr. Jeremy England (England, 2003, 2010, 2015) on the importance of some principles of thermodynamics to explain how life-like behaviors could emerge from an inert collection of chemicals (hypothesis called "dissipation-driven adaptation"). Dr. England provides a very interesting explanation of why self-replicating structures arise in physical systems. So, random groups of molecules can self-organize to absorb and dissipate heat more efficiently from the environment. The decrease in entropy makes possible evolving molecular structures to stay in a "non-equilibrium state" and, as a consequence, the process leads, under certain circumstances, to the possibility of the emergence of life; because the law of increasing entropy drives matter to dissipate energy acquiring life-like physical properties. Therefore, the origin and subsequent evolution of life come from fundamental principles of thermodynamics. Unfortunately, a quantitative correlation between the amount of energy dissipated and the adaptation rates is lacking in these research works so far.

Last but not least, I would like to comment that some readers of Drs. Baverstock and Annila's paper may consider that their concept of gene refers exclusively to the first period of the Neo-Darwinist synthesis. The modern synthesis definition of gene has evolved to accommodate novel experimental evidences (Moon et a., 2015, Schwartz et al., 2014; Acuña et al., 2012). However, other relevant scientists such as Dr. Denis Noble (Noble 2016) have already discussed the vagueness and inconsistency of these new concepts in its relation to evolution. Besides, it should be mentioned that the Standard Evolution Theory, despite the successive updates of the concept of gene and their incorporation to the concept of gen regulatory networks, has not reached to explain with coherence the origin of the huge amount of molecular information contained in the cell as, for instance, the information enclosed in the epigenetic patterns and in the regulation of the alternative splicing and the mechanisms of its inheritance. The Standard Theory of Evolution has neither been able to develop an appropriate interpretation of the role of these processes in the biological adaptation and evolution.

Drs. Baverstock and Annila's arguments are strongly exposed in their work and represent a solid challenge to Standard Evolution Theory. These arguments are essential to reconsider the fundamental postulates of evolution in the face of growing criticism related to the lack of coherence to interpret biological facts, and ultimately, to overcome the limitations and inconsistencies of the neo-Darwinian synthesis.

This work represents a valuable contribution to the creation of a new framework to replace Standard Evolutionary Theory.

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