Review of: "Numeric Structure of Genetic Code in Natural Evolution: Energy Grounds"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

First of all, I intend to mark that the presented manuscript is devoted to an extremely interesting and complex issue - the origin of life on Earth. For this I want to thank the Authors.

I have to note that, as for a non-physicist, the article did not seem clear enough to me. Of course, there is a lack of my knowledge here, however, if the work is intended not only for physicists, it is worth reconsidering the style of the manuscript towards a more friendly for biologists, especially since biologists are probably the main target audience.

First, despite the Authors` note that they do not touch on biochemical issues in this article, it seems to me that full-fledged discussion about the origin of the genetic code is hardly possible without reasoning on the molecular mechanisms and, most importantly, theories of the origin of the genetic code. Perhaps a good solution would be to try to apply the presented physical or "pre-biophysical" model to the existing biochemical hypotheses of the origin of the code. It is even possible that the Authors could put forward arguments in favor of any of them, based on their model. The Authors touched on this issue only superficially, which, in my opinion, is extremely insufficient.

It should also be noticed that there are some inaccuracies in the manuscript. For example, when discussing “magic numbers”, it is worth dwelling on an important question: “are there only 20 encodings in mRNA?” Yes, but only positive ones. However, in this case, we ignore the stop codons.

Energy metabolism in the article refers to the reactions of substrate phosphorylation, oxidative phosphorylation and photosynthesis. However, energy metabolism in biological objects is not limited to these three pathways. Numerous variants of the metabolism of chemotrophic or chemolithotrophic organisms are ignored. The Authors probably had a reason for this, but it is not entirely clear from the text.

The Authors calls the modern genetic code the "winner", that is, the variant of the code that kicked the rest out. However, from the text one gets the feeling that the Authors hint that it survived precisely because it is as adaptive as possible. However, this is a highly debatable issue. In particular, I recommend finding interesting ideas on adaptive landscapes in the following paper:

Novozhilov, A. S., Wolf, Y. I., and Koonin, E. V. (2007). Evolution of the genetic code: partial optimization of a random code for robustness to translation error in a rugged fitness landscape. Biology direct, 2(1), 24.

, where such a conclusion is called into very reasonable doubt.

However, it is possible that the Authors did not put it in, but in this case, it should be clearly stated, since the general construction of the text causes just such an idea.

Another argument against the idea that the current genetic code is the most adaptive of all possible is the presence of code variations in different organisms and even in our own mitochondria. Moreover, going back to the “magic number” of

20, variants of the genetic code can contain 21 or even 22 codon responses; pyrrolysine even has its own aaRS.

I would also like to say that the abbreviation GC for designating the genetic code is hardly successful, because in such a complex text, GC from the first time I personally always read like guanine-cytosine.

I believe that for an adequate assessment of the manuscript, it is necessary, first of all, to apply the put forward hypothesis more closely to molecular models - as if to say, to make the article a little more “practical”. Reconsidering the paper stile into a more friendly one for non- physicist also would be of a great upgrade. Probably, after this, the text will become more understandable, and the contribution of the manuscript will become easier to assess.

I hope my comments are of some use. I wish the Authors success in finalizing and publishing the article!