Review of: "Micro- and Macroevolution: A Continuum or Two Distinct Types of Change?"

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Potential competing interests: No potential competing interests to declare.

The work is very interesting and exciting. The following points are just suggestions that I hope will help.

1) P. 2 Before the last line, “we operationalize the mathematical distinction between first- and second-order evolution by identifying **genes and regulatory elements** in the nucleotide code of an **organism as dimensions of its state vector**," it is clear from this sentence that the genetic elements are dimensions. However, throughout the article, I find a difficulty in that dimensions are also understood as the size or length of DNA. The confusion lies perhaps in the fact that intuitively when one speaks of “dimension,” one may think of a “physical” dimension, in this case, the length. So, are "dimensions" the genetic elements or the length of the DNA (or both)?

2) The first two lines on page 3 read "... underlying fundamentally different driving mechanisms advances **our understanding of evolution** and opens new directions for future theoretical and applied research on evolutionary change." To be more precise, I suggest replacing “understanding” with the more focused aim of the paper, namely pointing out an articulation between first- and second-order evolution and its relation with macro- and micro-evolution.

3) Also on page 3, from “…mathematical distinction” to “…characteristic for X,” why not utilize the same symbology (if possible) used just above to clarify the change of vectors between parameters and dimensions rather than add new letters? It would be more usable and intuitive.

4) On page 4, the first few lines where the authors write about changing the space system, I recommend referencing the work of Longo and colleagues, such as Longo and Montévil's *Extended criticality, phase spaces and enablement in biology.*

5) The second line of section 3, p. 4. What is the relation between proprieties and dimensions? Are they synonymous? If yes, I recommend eliminating "property," which only adds a term and does not help understanding. If they are not synonyms, specify in what they differ.

6) Four lines before the end of page 4, some clarifications are needed.

- “… the organism changes only in its parameters.” Although it will be specified later, I suggest mentioning briefly what these parameters correspond to;
- “… the **length of the code** does not change.” Is the length of the code a dimension? If yes, you need to specify it before introducing anything else. Furthermore, there are different dimensions, as you mention right after (“**new**

dimensions are added to the code"). So, the length of the code is only one dimension among others, right? Then why do you choose only that dimension? There is no argument to justify this choice (at the risk of falling into subjectivity that would like to be avoided). More broadly, are DNA length and the genetic elements the **dimensions** that can be added to DNA? It might be my limitation, but sometimes it looks like one, sometimes the other (cf. point 1).

7) First four lines of page 5. The mechanisms specified for "first-order evolution" are heterogeneous with respect to the categories they refer to. "Genetic regulation" and "epigenetic modification" are physiological processes that occur during the development of a certain organism, while "recombination of gene variations" and "selection" seem to refer more to evolutionary time, that is, in a context of different generations. This heterogeneity should at least be mentioned. Furthermore, in the quotation "Gene regulation, epigenetic modification, and recombination of gene variants, followed by selection, are mechanisms that drive first-order evolution, as they **do not expand the length of the nucleotide** code by adding **new dimensions** but only vary the impact of the already existing nucleotide code," what are the new dimensions? Here you are referring only to the length of DNA or the consequences that this change in length can create (new genetic elements, etc.)? Also, are we talking about just one dimension or multiple dimensions? (cf. points 1 and 6).

8) In the section "epigenetic modification," I recommend better stratifying the types of epigenetic modifications by saying what the relationship is between DNA methylation and histone modification. I would also mention other paradigmatic cases of epigenetic modifications such as noncoding RNAs.

9) In the section "recombination of gene variation," page 5, we can read: "Random recombination of alleles by crossover during the production of gametes and the selection of advantageous allele combinations provide additional adaptive potential for **the parameters of the nucleotide code**." What are these parameters? Furthermore, "This mechanism **does not produce new alleles**." But in crossing over during meiosis, actually, there is recombination of homologous chromosomes in the sense that pieces of chromosomes are randomly reassembled. Aren't we talking here about the formation of new alleles? (I could be wrong, though.)

10) Before the last line of page 5, we read: "if they differ in length," do you mean that length is a dimension?

12) First lines of page 6: "In contrast to digital codes, where the dimensions – program modules – can only be switched on or off, the dimensions of nucleotide codes can have many gradations between being **silent and fully expressed**, resulting in a broad spectrum of effects." Do you mean here the degree of expression of the new gene elements of DNA?

13) First lines of section 3.2, page 6: "Second-order changes of a biological system are present if **new dimensions** – protein-coding genes or regulatory elements – are added to its nucleotide code, resulting in the expansion of the length of the nucleotide code." Thus, the dimensions are not the elongation of the DNA but the types of elements that are added to the DNA. This dimension/length/genetic elements relationship is not clear as the text unfolds (cf. 1, 6, 7).

13) Molecular evolution is the only process that we can recognize in macroevolution? What about species sorting, extinction, branching, development of new patterns? On this point, see works by Derek Turner such as *Philosophy of Paleontology: A Philosophical Introduction*.

14) First lines page 7: “This operationalization allows the substitution of the research of evolution based on a **subjective analysis** of the phenotype of organisms by a genotype-based analysis, supported by standard DNA analysis technology that can reveal whether the expansion of the state vector into new dimensions has occurred or only a change in its parameters.” There is no explicit argument that genotype-based analysis is free from subjective insidiousness. For example, the decision to take as a reference dimension of the DNA length (and all its consequences in terms of the addition of genes and regulatory genes) could very well be understood as a choice, and as such, “subjective” in the sense that other dimensions could be chosen. Also, why the focus is only on some mechanisms (macro and micro) instead of others? In light of this, saying that all the work is “objective guided" seems like too strong a statement. Perhaps one could rather speak of a pragmatic and/or operational approach?

15) In the middle of page 7: “Second-order changes are driven by the accumulation of **unrepaired code-expanding mutations of the DNA**.” So is it considered a macroevolutionary process only when a mutation results in the expansion of DNA length? It seems to me that mutations are transversal concerning the first/second-order evolution distinction. If second order involves only mutations that cause DNA elongation, we can say that we are talking about mutations such as insertion. But then, are mutations that do not change DNA length (e.g., point mutations such as substitution; translocations) part of the first-order evolution, namely microevolution? In addition, where do we place the mutations that decrease DNA length, such as deletions?

16) Section 4 is not so comprehensible to the layperson. If the authors want to reach a wide audience, I suggest making it more pedagogical.

17) Second paragraph page 12: “Therefore, first-order evolution is identical with microevolution.” A very strong statement. Considering the supposed transversality of kinds of mutations (see point 15), it is difficult to think of first and second order as categories that clearly separate macro and micro. If one wants to embrace this clear-cut position between first-order evolution/macroevolution and second-order evolution/microevolution, further arguments are needed.

18) Second paragraph section 5 page 15: “Does the response to rapid environmental changes come from first- or second-order evolution, or from both?.” But does not macroevolution occur at deep times? In what sense could it be a “rapid” response to the environment?

19) “We operationalized this distinction based on the genotype of an organism, which allows the substitution of a **subjective phenotype-based approach** of evolution with a genotype-based approach supported by DNA analysis technology.” Two points on this topic are missing. First, it would be necessary to argue why the phenotype approach can be framed as subjective. Second, justify why gene-based analysis is instead objective (cf. 14).

20) Four lines before the end: “The articulation of the concept of evolution by distinguishing first-order and second-order evolution, as well as their specific underlying driving processes, **makes it possible to answer one of the major unanswered questions in evolutionary biology**.” This statement is very strong, and it seems that with this analysis really all questions with respect to macro and micro are resolved, but perhaps this is not the case. It is therefore advisable to make the statement less absolute by saying that this work can be regarded as an important contribution to the debate.

I hope that some of these points will be helpful to writers. I apologise in advance if some of my suggestions suffer from a lack of thorough understanding of your work. Thank you for allowing me to read and reflect on this proposal.