Review of: "Darwin, Gödel, Luria, Delbrück: Biomedical, Mathematical, and Metamathematical Perspectives on Attributes and Consequences of Random Somatic Mutations Subject to Selection"

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In this paper, the Authors aim to extend the concept of heritability to include “non-standard” sources of phenotypic variation such as those coming from the co-evolving organisms (i.e. extended phenotype), germ-line and somatic-line mutations. Their main supporting arguments come from biomedical examples. They also try to establish a formal analogy between the mutational theses of S. Luria and the Godel’s incompleteness theorems.

Yet the aim of the paper is laudable (trying to bridge apparent distant concepts and research sub-fields in a fruitful way), I feel that the manuscript fails completely to achieve this. **Therefore, I cannot recommend the acceptation of the paper on its current state**. Indeed, I think that much work and substantial rewriting remain to be done in the MS to be published in top scientific journal (I suspect that this MS was originally intended to be a sort of invited article in a low-impact journal).

Specific comments:

As the lines are not numbered, I will only provide general comments that support the rejection, but I hope they will help to improve the scientific quality of the manuscript.

1. The title promises way too much considering the MS content.

2. Many sentences are too informal and add nothing to the scientific idea, just two examples: “At this point, mathematicians focused on biology may be forgiven…” or “you will likely be anticipating that the answer is...”

3. There are many sentences whose content should be more explicit, but are dispatched as “in a relatively precise and technical sense”, or “one can imagine conceivable pathways…”, Which meaning? which pathways?

4. When the chemical randomness is discussed, the mutational biases among nucleotides might be explained better and

with some references, as it seems that the only “bias” is the impossibility of a mutation “to itself”.

5. The “news” article in Science is a news article, not a research paper, and it might be insufficient to justify the confusion they point to.

6. I bet many more people than “Physicians and biomedical scientists” have recognized the potential of mutations in somatic cells (e.g. developmental biologists).

7. Plasmodium example may work better with a schematic panel.

8. In pag.5, “At least two mathematical challenges can be identified. One can create a model ...”. WHAT MODEL do the authors refer to? There are dozens of mathematical models in evolutionary and developmental biology, GRN-network based, vertex models, potts models, SEM models, multi-linear models, G-matrix models… Each one is a different world, with a lot of pros and cons and a large body of knowledge related to them. Talking about the challenges of “models” in abstracto is too vague to be scientifically useful.

9. Although it is clear that the Authors belong to the biomedical research subfield, they should (for the sake of generality), frame the discussion in the widely recognized concept of Genotype-Phenotype-Map (GPM), which establishes a relationship between genetic and phenotypic changes. Again, there are literally thousands of research papers devoted to the GPM concept. This needs to be mentioned and properly discussed. Ideally, the Authors should show what their approach can reveal that the GPM cannot.

10. There are several claims through the text calling the attention of “inspired mathematicians” to solve the battery of questions that they propose along the paper. But I think this is not what a scientific paper is about: in a paper, the authors should answer their questions. Even a single, positive answer to a well defined question would make the paper worthwhile; but if they only raise questions to be hopefully answered by someone else, then the paper is useless.

11. Extended phenotype is normally understood (at least in evolutionary biology) as the genetically determined processes and structures that occur “outside the body” (e.g. a spiderweb or a beaver´s dim). The way they use the term is not standard, and seems something more related to phenotypic plasticity (another commonly used here that is not mentioned here). I suggest to the authors the next reading to help them connecting their ideas within a more general evolutionary framework: Chiu, Lynn. *Extended Evolutionary Synthesis: A Review of the Latest Scientific Research* John Templeton Foundation, 2022.

12. The parallelism between mutational context and mutational effects with distant fields such as the axiomatic logic is not solid enough, and remains as a vague analogy. What would be the heuristic potential of this analogy? Is there any formal idea that can be extracted from the analogy even at conceptual level?

13. Something similar occurs in the “extended” version of heritability. If they add more terms, they should clearly show (without expecting others to do the job) how this extension can be used, the new coefficients calculated, which new kinds of prediction that may entail and, overall, why and when it should be better than the standard formulation.

As a positive note, the text is well written and it reads smoothly.