Review of: "Mutational selection: fragile sites, replicative stress, and genome evolution"

Paco Majic[1]

1 Swiss Federal Institute of Technology, Zurich

Potential competing interests: No potential competing interests to declare.

In this mansucript, Haig revisits the idea that the first selective barrier mutations must overcome is the context in which they arise. This is, in my opinion, a central question in evolutionary biology that is severely understudied. In this particular manuscript, Haig discusses developmental selection on new mutations from the point of view of how such selection might influence the evolution of the mutational fragility of genes and other genomic features.

As a first comment, I would suggest a change in terminology. Haig describes the selective process within organisms as “mutational selection”. Because the concept is not new, I would recommend the use of “developmental selection” instead. This is the term originally employed by Buchholz (1922) to refer to competition between various individuals at embryonic stages, but also to gametes and cells in the germline. This is also the terminology more recently employed by Cruzan et al (2022) to refer to the culling of mutations during development and by myself to describe how competition between cells in a mosaic organisms could lead to mutation rate biases (Majic & Payne, 2023). I prefer “developmental selection” over “mutational selection” because of the historical precedent, but also because the object of selection is the cell lineage in which a mutation happens in its developemntal context. Note that “intra-organismal” selection has also been employed to refer to this. I emphasize this because I think it important to standardize terminology, especially in relation to a concept that might be major in evolution and yet surprisingly understudied. The diversity in terminology might give the impression of a more scattered conceptual framework. Given this conviction, I will further refer to what Haig calls mutational selection as developmental selection.

I think the main contribution of this paper is to suggest that developmental selection can lead to the retention of alleles that are fragile, rather than robust to mutations. This is a really interesting idea, but it took me a couple of reads to understand that this was the main point of the paper. Although Haig mentions a few examples of how this could happen, I feel the overall argument could be imporved. FIrstly, I think the main idea only becomes apparent as examples are presented. An explicit description of the main thesis in the first section of the paper would greatly imporve the communication of the paper's main points. Secodnly, the sections of the paper explaining how different genetic and genomic features might be affected by developemntal selection feel disconnected (and sometimes the paragraphs within each section as well), to the point that I found myself forgetting what each section and the argumentative thread of the paper were about.

Overall, Haig raises interesting points concerning developmental selection from the perspective of selfish genes. What I find especially appealing about such view, is that my view on the matter is partly antithetical to it, as I tend to see developemntal selection as a proof of the agency of organisms and developemnt over their own evolution and that of their

genes (see Majic et al, 2022, Majic 2022, Majic & Payne 2023). As this line of research moves forward, it will be interesting to see how instrumental developmental selection may be to gene-ceneterd evolution and/or to organism-centered evolution.

Buchholz, J. T. (1922). Developmental selection in vascular plants.*Botanical Gazette*, *73*(4), 249-286.

Cruzan, M. B., Streisfeld, M. A., & Schwoch, J. A. (2022). Fitness effects of somatic mutations accumulating during vegetative growth. *Evolutionary Ecology*, *36*(5), 767-785.

Majic, P., & Payne, J. L. (2023). Developmental selection and the perception of mutation bias.*Molecular Biology and Evolution*, *40*(8), msad179.

Majic, P., Erten, E. Y., & Payne, J. L. (2022). The adaptive potential of nonheritable somatic mutations.*The American Naturalist*, *200*(6), 755-772.

Majic, P. (2022). The Molecular Scaffolds of the élan vital.*Parrhesia: A Journal of Critical Philosophy*, (36).