

Resubmission Cover Letter
Evolution

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and Peter Ralph
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To the Editor(s) –

We are writing to submit a revision of our manuscript, “System drift and speciation” (ID 18-0316), for your review. We sincerely apologize for the delayed resubmission but hope that you will find the revised manuscript significantly improved.

We thank you and the two reviewers for providing constructive suggestions and feedback that has helped to improve the manuscript. We have followed the suggestions closely and hope to have fully addressed all the concerns and suggestions as detailed in our point-by-point response below.

In our original submission, we studied the effect of gene regulatory network evolution on speciation, first by applying linear system theory to characterize the large space of phenotypically equivalent network organizations, and second by using quantitative genetics to show that neutral genetic drift on this network space can lead to speciation over plausible timescales.

We agree with the reviewers that the combination of these two approaches, while interesting, was not seamless and that the quantitative genetics section required further development, and thus have followed the recommendation of both the Editor and Associate Editor, by breaking the manuscript into two papers. One paper – the present revision – covers the application of system theory to regulatory networks, and the other (which we plan to resubmit soon) will cover the quantitative genetics. In addition to the revised text, we are submitting as supplementary files, a detailed response to the reviews and a color-coded diff to make it easy to see what has been removed. We are happy with the result – as predicted by the reviewers, the resulting paper stands alone without the quantitative genetics results.

We hope that by focusing this paper on system theory, we have clarified our results, which include a mathematical description of phenotypically equivalent network space and its implications for speciation under neutral genetic drift. These results suggest that the space of phenotypically equivalent network organizations is substantial, and often not reproductively compatible, leaving many opportunities for independently evolving populations to become reproductively incompatible. The linear system framework applied in this manuscript explicitly describes possible molecular pathways and naturally predicts Haldane’s rule.

We would like to note that the previous version of this paper as a preprint has since received 10 citations as well as attracted substantial positive attention as a preprint (e.g., see tweets at <https://www.biorxiv.org/content/10.1101/231209v2>). Furthermore, this paper has been downloaded more than 2,326 times (<https://rxivist.org/papers/24911>), making it the 155th most downloaded evolutionary biology paper available on the *bioRxiv*, as of this writing.

Sincerely,

Joshua Schiffman and Peter Ralph