Report on second revision of Random genetic drift sets an upper limit on mRNA splicing accuracy in metazoans

by Florian Bénitière, Anamaria Necsulea, Laurent Duret

I had two main points of criticism in the previous round of review: the clarity of the presentation of the results and the utility of the mathematical model. In this second revision, the authors have greatly improved the readability of the manuscript by updating Fig. 2. This helps the reader a lot to focus on the analyses and satisfactorily resolves my first main point.

Regarding the model, I now understand, based on the authors' response to my initial comment, that it is meant to illustrate the drift-barrier hypothesis. I agree that the described model can serve this purpose. However, if the purpose of the model is the illustration of the verbal hypothesis, it is misplaced in the manuscript in my opinion. As it is, the model is introduced early in the discussion. This, in my opinion, is too late to illustrate the verbally formulated drift-barrier hypothesis. By that point, the reader will likely have understood the hypothesis and its implications: low N_e results in relaxed purifying selection and thus more lowly expressed splice variants. Instead, I would suggest to introduce the model early in the results section (maybe even as the first subsection, e.g. "Modeling the drift-barrier hypothesis"). Introduced that early, it would then also simplify the presentation of the empirical results because it can serve as a baseline for qualitative comparison. Therefore, I think that describing the model early in the results would make better use of the model compared to the current version and by that improve the manuscript. However, I admit that following this suggestion would imply a relatively big reshuffling of the manuscript. Ultimately the decision lies with the recommender and the authors (but I personally would still strongly favor a restructured manuscript).

Besides this question of manuscript organization, I am supporting this great and extensive work. The manuscript is well written and the results shed new light on alternative splicing and the emergence of splice variants and therefore merits recommendation.