Revision round #2

Decision for round #2 : ***Revision needed***

Dear authors,

Thank you once again for submitting the revised version of your manuscript, “A gene-regulatory network model for density-dependent and sex-biased dispersal evolution during range expansions,” for consideration at PCI Evol Biol. I appreciate the significant effort you’ve put into addressing the feedback from the previous review round. The improvements—particularly the rewritten introduction, new figures, and supplementary material—have certainly made the manuscript clearer.

After reviewing the revised manuscript and your responses, I decided to send it back to Reviewer 3, as I felt that some of their comments weren’t fully addressed. Their detailed feedback highlights several points that need further attention before we can move forward with a recommendation.

Reviewer 3 continues to find the comparison between the GRN and RN models difficult to interpret, and I agree. First, the way the two models are presented—RN as a solid line and GRN as a "cloud" of individual lines—makes it hard to directly compare them. They suggest using a more consistent format for both models (like showing average ± standard deviation or quartiles) to make things clearer.

The second concern, which I also share, is about the differences in mutational effects between the GRN and RN models. Supplementary figures (S4 and S8) show how mutation affects the reaction norms differently, but the reviewer mentions that these differences might come from the arbitrary settings of mutation effects, rather than being inherent to the GRN architecture. What needs to be clarified here is whether the larger standing genetic variation in the GRN model is truly a feature of its architecture or is influenced by parameter choices. Reviewer 3 suggests reducing the mutation size in the GRN model to bring it closer to the RN model, but you may have other ideas for how to address this.

There’s also a question about the apparent discrepancy between equilibrium dispersal rates and range expansion dynamics. In Figure 5A, dispersal is greater under the GRN model right from the first generation, but in Figure 3, the equilibrium dispersal rates between the two models seem pretty similar. Why don’t both models start at the same dispersal rate and then diverge over time as expected? Please clarify this point.

Please revise your manuscript to address these issues, along with the other points raised by Reviewer 3, which you’ll find in the detailed feedback below.

When you’re ready, please submit a revised manuscript along with a detailed, point-by-point response. Once these revisions are made, I’ll be able to continue with the evaluation and move toward a final decision.

Our response: Dear Dr. Mullon, thank you very much. Your comments and those of the referees have once more helped us improve our manuscript. Most importantly, we have now included an additional sensitivity analysis concerning mutation effects and discuss these new results in the manuscript. Please find our detailed answers below.

Best regards,

Jhelam Deshpande

Best regards,

Charles Mullon.

by ***Charles Mullon****, 29 Sep 2024 08:37*
Manuscript: **https://doi.org/10.1101/2023.07.18.549508**
version: 3

Review by Arnaud Le Rouzic, 24 Sep 2024 15:39

Review of "A gene-regulatory network model for density-dependent and sex-biased dispersal evolution during range expansions" by JN Deshpande and EA Fronhofer, PCI-EvolBiol-749.

This is a revised version of a ms submitted to PCI in December 2023. The ms has been read by three reviewers, which evaluation was (as far as I can tell) rather consistent. All three reviewers found some scientific merit to the manuscript and considered it to deserve publication; all also noticed some shortcomings that should be addressed.

The manuscript has been substantially re-written (up to the point that the "revision tracking" version is hard to follow). Large-scale changes (including new paragraphs, deleted paragraphs, and text restructuration) have been perfomed in all sections. Figure 1 has been added, and figures 2 and 3 have been redrawn with different colors and style. A series of supplementary figures have been added to address some of the reviewers' concerns.

I had 5 major comments on the previous version: 1) the introduction was lacking focus, 2) the rationale for contrasting with "first principle" predictions was unclear, 3) Model comparison was difficult from the figures (and I was unsure that both models were calibrated in terms of mutations), 4) Patterns from the range expansion figures did not seem to match the equilibrium dispersion values, 5) The population genetics of range expansion was not considered (e.g. selection/gene flow balance between the central and expanding patches). Some of these issues (especially 1 and 3) largely overlapped with other reviewers' concerns.

My concern #1 has been addressed for the most part. The authors have deeply rewritten the introduction, and I felt that is it now more to the point. It also refers more precisely to the relevant literature, and I think this concern has been mostly addressed.

My concern #2 has also been addressed. The authors have reframed the results so that the RN model is more clearly associated with a "reference" model, which is fine. Commenting more precisely on the parameter space in which the GRN model departs from the RN model (for instance in paragraph 221) convincingly clarifies the purpose of model comparison.

I am not sure that my concern #3 has been addressed in the revised version. I think all three reviewers shared the same feeling about the impossibility to compare models from figures 2 and 3. The authors have changed the figure design, but I am afraid that the new version is not better than the former one. The results from the RN model are displayed as a solid line standing for the reaction norm predicted from the median parameters (and interquartile predictions), while the results from the GRN model are individual simulated lines cumulated on the plot. As a result, both representations are so different that it is not possible to eyeball whether the predictions really match, beyond the fact that the purple line seems close to the "cloud" of green lines. The authors proposed to quantify the differences between models in supplementary figures, but as far as I understand, these represent the difference between both models and the mathematical optimum (i.e. not the difference between simulated RN and GRN).

Here, the authors decided to keep a visual representation that seemed to bother all three reviewers, and instead proposed supplementary figures, as if the point was to check some reviewers' concerns. I think it is natural, when the purpose is to comment on differences between model predictions, to propose figures in which models are treated in the same way. Both models predict a stationary distribution of reaction norms at equilibrium, and both could be computed and presented in an equivalent way (average +/- sd, median and quartiles, etc), so that it the difference could be eyeballed directly.

Note that the new fig 3 barely readable in my printed copy (color lines overlap and it seems impossible to eyeball the differences between GRN observations).

Our response: We have changed figures according to your suggestion. We now display the median and quartiles for the GRN model but also add the histograms of population densities so that it is clear to a reader that the match between the two models is greatest at the population densities that are most frequent. This information is important because it is only under these conditions that one can expect our algorithm to optimize efficiently.

There might have also been some misunderstanding about my comment 3c. I totally agree that it is difficult to calibrate mutational effects across models, especially when models are so different. I think I also understand what the authors illustrate with sup figs S4 and S8: mutations not only have different effects in different models, they also affect the reaction norm differentially, so that their effect depends on the population density. In the GRN model, epistasis may also lead to the evolution of mutational effect, and one could thus expect that the effect of mutations may evolve even if the reaction norm is at equilibrium. Yet, this was exactly what I wanted to point out : because it is difficult to calibrate mutations across models, it is also difficult to conclude on potential differences in evolvability and speed of adaptation (standing genetic variation and mutational variance). Setting sigma_m = 1 leads to larger mutation size on dispersal in he GRN that in the RN, and this is arbitrary (the unit of sigma_m is different in both models). Even if I agree that increasing sigma in the RM model might not change the dispersal at low density, decreasing sigma in the GRN is likely to bring both models closer in terms of mutational effect on dispersal. As a consequence, the larger standing genetic variation in GRN simulations might be arbitrary to some extant. My point is that this might not only be a property of the GRN architecture, but rather a property of setting sigma_m to some specific values.

Our response: We have now added simulations that explore lower mutation effects in the GRN. We find that indeed as you suggested the range expansions are the same speed in the GRN and RN models (SI FIg. S13). Interestingly, the GRN model still maintains more variation than the RN at low population densities in equilibrium metapopulation conditions (SI FIg. S2). The conclusion from this analysis is: when dispersal mortality and extinction probability are high, both models maintain similar genetic variation for the smaller and larger per locus per allele mutation effects. However, maintenance of variation at low dispersal mortality and extinction probability critically depends on assumed mutation effects.

My concern #4 might have been unclear. In figures 4 and 5, the slope of the dispersal speed at t=0 is the dispersal rate at equilibrium. In what is now fig 5A (top left panel), the GRN model disperses faster from the first generation. However, in Fig 3 top left, there is not that much of a difference between equilibrium dispersal rates between RN and GRN (as far as I can see, but see comment #3 above about figure readability). I find it paradoxical, is evolution so fast that in fig 5 it is impossible to see that both populations start to disperse at the same rate before diverging?

Our response: Please see the new SI Fig (SI Fig. S12) that shows the dynamics of trait change. Dispersal increases rather rapidly in the cases where there is greater variation maintained in the GRN model

My concern #5 was related to the fact that gene flow may affect adaptation, because the optimal dispersal rate for edge populations might be different than the more central populations. The authors consider that this is not central to the study, and I can hardly contradict them without simulations. From Figures 4 and 5, dispersion does not seem to evolve much (the expansion is rather linear), and gene flow from non-expanding populations could partly explain this observation. This concern #5 was not addressed, but it remains minor.

Our response: Indeed gene flow from the core to the front can prevent adaptation to the conditions of the front (evolution of greater dispersal in our case). But we do see that dispersal evolves to greater values in the range expansion front (see SI Fig. S12)

Minor comments: the authors have addressed most of them satisfactorily.