

# Report on the manuscript “When does gene flow facilitate evolutionary rescue?” by Tomasini and Peischl, 2019

In their work, Tomasini and Peischl present a model for evolutionary rescue of two separated populations which interact through migration. Their main goal is to show that, under certain conditions, gene flow can favour evolutionary rescue in endangered species. Both the populations are threaten by environmental changes at two different times. The so-deteriorated environments are no longer suitable for the wild-type individuals, which are so doomed to the extinction. Their model, through a deterministic approach, describes the probability of evolutionary rescue of the endangered populations, as a function of the migration of individuals between the two regions. Their main achievement is to able to derive mathematical conditions under which the gene flow is beneficial to evolutionary rescue.

The authors give a nice introduction to the topic, explaining motivations and, through a clear description of the state of art, they nicely illustrate the open problem underlying their work, motivating the study in a satisfactory way. Throughout their manuscript, they address the research questions proposed in the introduction, starting from the simplest case, which is described by symmetry in migration and carrying capacities, to more general cases with asymmetries in migration rates and carrying capacities.

In general, I find the bulk of this work interesting and I think it has potential to be recommended in the community. However I have some questions and comments which I hope could be stimulating and improve the quality of the manuscript. Before starting with the specific comments, in general, while reading the manuscript, I often had the feeling that evolution theory is used as a primary explanation for the behaviour of the model. I would have find the manuscript easier to understand if the primary explanation was based on the mathematics. Trying to be more clear: since the solutions of the model depend on the equations, their behaviour can be explained only through mathematical analysis. On the other side, I appreciate the references to previous known results, which clearly support the consistency of the model. The following comments are often extension of what just said.

## Comments

1. Table 1: Is there a particular reason for choosing  $u = 1/K_{\text{tot}}$ ? This value used in the simulations, however, as a matter of generality, why not leaving it general, as done for example with the other parameters reported in the table?
2. (a) In section *Population dynamics* (page 6) the authors present the equations describing the evolution of the population size. I think it might be worth to stress out that  $N_i(t)$  is not the overall population size, but represents only the size of the wild-type population. Also, I think it would be beneficial to the reader to have the initial conditions  $N_1(0) = k_1$ ,  $N_2(0) = k_2$  stated in this section, for example after equation (10).  
(b) I think it might be worth to highlight the fact that the evolution of the mutant populations is never explicitly considered. Initially this was not very clear to me. For example, in line 229 the sentence “...high migration to be too efficient in removing mutations from deme 1” might be a bit misleading, and instead of “removing mutations” I would use “preventing establishment of mutations”.
- (c) Still regarding the modelling of the population sizes, I have a question for the authors:

I understand  $k_1$  and  $k_2$  are the maximal number of individuals “allowed” in each deme. Hence, let us assume that one mutant appears, for instance, in deme 2 during phase 1 (when the population is constantly kept at  $k_2$  wt individuals): does this not break the “carrying capacity rule”? Or is the carrying capacity meant to hold only for wild type individuals?

3. I think it would be helpful if the authors could spend few more words on equation (1), regarding the probability of rescue (it would be enough to do it in the supplementary material).

(a) In particular, regarding the time limits  $(-\infty, +\infty)$ : I have the feeling that evolutionary rescue would have sense only if it happens in a finite time  $T < \infty$ . I would like if the authors can clarify this point, explaining why the product in (1) is until  $t = +\infty$ .

(b) From equation (2) it seems that

$$\prod_{t=-\infty}^0 (1 - uN(t)p(t)) = 1 - P_{sgv} \quad \text{and} \quad \prod_{t=0}^{\infty} (1 - uN(t)p(t)) = 1 - P_{dn}.$$

I think it would be clearer to split (2), stating explicitly these two equations. I also would spend few more words about  $\prod_{t=-\infty}^0 (1 - uN(t)p(t))$ . For instance, equation (5) describes  $P_{sgv}$  as a function of  $p^{(1)}$  and  $p^{(2)}$ . But  $P_{sgv}$  in (2) seems to depend on  $t \in (-\infty, 0)$ , while  $p^{(1)}$  and  $p^{(2)}$  are defined only for positive time.

4. (a) The formulas (3) and (4) of the probability of establishment of the mutation depend on  $m$  for  $t \in [0, \theta]$ . However  $m$  has not been previously defined. Later  $m$  is used when  $m_{12} = m_{21}$ , as  $m = 2m_{12} = 2m_{21}$ , so I imagine this is its meaning. I think it would be useful to state this before equations (3)-(4).

(b) Moreover, how are (3) and (4) defined when  $m_{12} \neq m_{21}$ ?

5. In section *Simulation model* (page 6), stochastic simulations are proposed for testing the model given in equations (2)-(10).

(a) It does not look very clear to me in which way the simulations reduce the population size in the deteriorated demes. From lines 171-172: “Individuals in each deme reproduced, mutated and migrated, followed by density regulation”. I have the feeling that the authors forgot to state that there is also a mortality rate (in that sentence, the only possible reduction I see is given by the mutation of wild-type individuals, since migration does not reduce the overall population between the 2 demes).

(b) With respect to these simulations, the proposed equations (9)-(10) seem to describe an opposite behaviour, as no birth rate is present and both the populations decline exponentially in phase 2, as it comes out by calculating  $N'_1(t) + N'_2(t)$  using (10).

(c) The simulations are used to validate the analytical findings of the continuous model (line 166) and, indeed, the solutions of the two are always compared. However I do not understand for which reasons we should trust the simulations more than the continuous model. If simulations of this kind are well-established in literature, some references should be provided. Otherwise one could also argue that the model (2)-(10) should be used to validate the discrete simulations and not the other way round. I think a clarification about this is necessary.

(d) One or two plots describing the stochastic evolution of the populations would be nice to see.

6. (a) In line 13 of Supplemental Material,  $s$  is reported to be negative, while in the main text,  $s \in (0, 1)$ . The authors should keep the consistency with the main text.

(b) In page 4, the authors do not specify the range in which  $r$  and  $z$  can vary: they seem to be both positive (this is clearly truth for  $r$ ), but is there a maximum value they can reach? If not, I think reporting  $r > 0$ ,  $z > 0$  and  $0 < s < 1$  in table 1 would give more clarity to the text.

7. Lines 195-200, from “The existence of... ”:

(a) the explanation of the reasons behind the existence of a critical migration rate is very nice, but I think it might be helpful to first explain it using the mathematics (this could also be done only in the supplementary material) and then give the biological interpretation. Indeed, solving equation (9) one gets the explicit solution (S4), which can be rewritten as

$$N_1(t) = \left( k_1 - \frac{m_{21}k_2}{r + m_{12}} \right) e^{-(r+m_{12})t} + \frac{m_{21}k_2}{r + m_{12}}.$$

If one considers  $m_{12} = m_{21} = m/2$  and  $\theta = 500$ , then for big times  $t < \theta$  one could approximate

$$N_1(t) \approx \frac{m}{2r + m} k_2.$$

Therefore the number of wild-type individuals in the deteriorated deme increases as a function of the migration rate.

(b) On the other hand, I had to spend some time for understanding the sentence “ too much migration between demes prevents rescue mutations from establishing despite being positively selected in one of the two demes, a process called gene swamping” (lines 198-200). Surely I think that this sentence should be used as a confirmation of the consistency of the model with respect to the evolutionary theories. However, the solutions of the model should be explained using the mathematics. Indeed, using the parameters  $z = 0.02$  and  $s = 1.0$  reported in the caption of Figure 1, during phase 1 the function  $p^{(2)}$  is always zero for any  $m > 0$  (and this is consistent with the fact that the mutation is lethal in the old environment), and the function  $p^{(1)}$  is non-zero only for very small values of  $m$ . Therefore, from (7), for bigger values of  $m$ , one gets  $\pi_{dn} = 0$ . This is the reason why “for large migration rates, rescue can only occur during phase 2” (line 201). I think it might be helpful to remark this, and it might be enough to just plot  $p^{(1)}$  versus the migration rate.

8. Figure 1B, page 7: Is the probability of rescue represented with filled dots calculated as (number of rescues) / (number of total simulations), where number of total simulations = 2000?

9. In section “When does intermediate migration favors rescue?” (page 8) (and also in Appendix B), the condition under which intermediate migration is beneficial to evolutionary rescue is proposed (and derived). This is done by showing that  $P_{rescue} = P_{rescue}(m)$ , seen as a function of  $m$ , increases at  $m = 0$ . This means that even a very small migration would have a more beneficial effect as compared to the no migration case. However, in principle, this does not necessarily imply that intermediate migration has a better impact with respect to the maximal migration case. Indeed, in order to prove that  $P_{rescue}$  is maximal if migration is intermediate, I would either check if there is a maximum in  $(0, 2)$  or, checking continuity of  $P_{rescue}(m)$ , it would also be enough to see that  $P'_{rescue}(0) > 0$

and  $P'_{rescue}(2) < 0$ . However, if I am missing something, I would like the authors to explain this part with more details, as it concerns the main result of their work.

A small remark: I am using  $m \in [0, 2]$  since  $m/2 = m_{ij}$  and  $m_{ij}$  are probabilities, but I have the feeling that the authors require  $m_{12} + m_{21} = 1$ . If this is the case, please add one line to explain the reason and consider my comment with  $m \in [0, 1]$ .

10. Lines 244-245: “We can see that the chances of survival from standing mutations are maximal in absence of migration (figure 3, also figure S2).” I think the authors refer to figure 2 instead of figure 3. Moreover, in all figures they do not really plot from  $m = 0$  but from  $m = 1e - 04$ . If there a particular reason for this I think it might be worth to state it, otherwise this should be fixed.
11. In Supplemental material, appendix B, equation (S6): the parameters  $\tilde{\beta}$  and  $\tilde{\zeta}$  have not been defined and, even though they can be deduced by equations (16)-(17) of the main text help, I think it might be helpful to add a line for their definition.
12. lines 303-306: as in previous comments, I think it would be clearer to explain the behaviour of the model using the equations. Following comment 7, for big  $\theta$  and big  $t < \theta$ , during phase 1, the population in deme 1 can be approximated with

$$N_1(t) \approx \frac{m_{21}}{r + m_{12}} k_2.$$

This indeed constitutes an approximated initial condition for the population  $N_1$  in phase 2. Now, rewriting the above in terms of  $\zeta$

$$N_1(t) \approx \frac{(1 - \zeta)m}{r + \zeta m} k_2,$$

it is possible to see that this function decreases in  $\zeta$  (and its maximum is achieved at  $\zeta = 0$ ). This explains the effect of the migration asymmetry on the rescue probability.

13. line 346, “the number of individuals of a type  $i$  in the non-deteriorated deme”: I think the authors mean “the number of individuals in the non-deteriorated deme  $i$ ”.
14. Equation (18), page 13:
  - (a) the parameter  $w_i$  at the numerator has not been defined. Should it be  $w_i = w_{wt}^{(o)}$ ?
  - (b) As well, it is not clear what  $N_{tot}(t)$  and  $k$  at the denominator represent. It could be  $N_{tot}(t) = N_1(t) + N_2(t)$  and  $k = K_{tot}$ , but these need to be defined. The same holds for equation (S8).
15. line 52 of Supplemental material, “deme 1 is almost depleted after a few generations”: this would be clearer if the authors are able to show it mathematically. As well, I think that a plot of  $N_2$ , as defined in (S8), would add clarity to the section.
16. lines 423-424: the main positive effect of gene flow occurs during phase 1, but I feel that the reasons should be discussed more deeply. Indeed, phase 2, except for the initial conditions (see comment 7), is not affected by the gene flow. In a certain sense, one could neglect the separation of the two populations, since  $\pi_{dn}(t) = 2zu(N_1(t) + N_2(t))$  and, summing  $N'_1$  and  $N'_2$ , from equation (10) one gets

$$N_1(t) + N_2(t) = (N_1(\theta) + N_2(\theta))e^{-rt}.$$

Hence, in this phase, the migration rates seem to play a role only on the definition of the initial condition  $N_1(\theta) + N_2(\theta)$ .

## Typos

- line 52: “remain” instead of “remains”
- line 55: “form” instead of “from”
- line 88-89: “questions” instead of “question”
- line 114: is  $w_m^{(n)} = 1 + z > 1$ ? Is  $z \in (0, 1)$  as  $s$ ?
- line 133: “Mutations that occur before phase 2 (that is, after all demes are deteriorated)”. I think the authors mean “(that is, before all demes are deteriorated)”.
- line 176 (end): “ $i, j \in \{1, 2\}$ ” instead of “ $i, j \in [1, 2]$ ”.
- line 176: missing space between “migrated,” and “followed”.
- below line 190: “the” repetition in “Figure 1A shows the the total probability of rescue”.
- Figure 1(B) and Figure 5 miss have incomplete x-label (missing “rate” in “migration rate”)
- line 197: “acts” instead of “act”.
- line 221:  $P_{dn}^1$  has not been previously defined. Should it be replaced by  $P_{dn}$ ?
- line 236: capital “i” in “if rescue”.
- line 249:  $m$  instead of m.
- line 352: “rates” instead of “rate”?
- line 363: should “two-model” be “two demes model”?
- line 391: “spatially structured” instead of “spatially structure”
- line 408: “a migration rate” instead of “an migration rate”
- line 423: repetition “during during”
- line 432: “individuals” instead of “individual”
- line 460: “than” instead of “then”.
- line 44 of Supplemental material: “fr the probaility”
- Check the reference list, in particular Carja and Plotkin 2019, Peischl and Kirkpatrick 2012