

Revised version of the MS “When sinks become sources:  
adaptive colonization in asexuals”  
Response to Editor and Reviewers’ comments

## 1 Main modifications

We thank the editor and reviewers for their stimulating comments which helped us improve this manuscript. We have made a point-by-point reply but in order to simplify the review process we have highlighted seven main changes (M1 - M7) made to the manuscript. We hope these changes will answer the main points consistently raised by the reviewers and editor, so we refer to each modification when relevant in the point-by-point reply. All modifications in the text appear in [blue](#).

### **M1) Rewriting a part of the introduction:**

The introduction has been rewritten, and slightly shortened, to hopefully provide a clearer and more to-the-point progression, from the general subject to a short state of the art, to the main working assumptions of our model and summary of the results. In particular, we hope to have clarified what we meant by the absence of gene swamping : it is absent in our system but not in asexuals in general, as our previous formulation erroneously suggested (as pointed out by the editor).

This corresponds to lines 43-47, 50, 52-53 and 63-127.

### **M2) Detailed numerical description of the three phases of invasion (which are now four):**

We now provide detailed illustrations of the phenotypic distribution in the three main phases we had previously identified. We now distinguish four phases, actually: 1/ short initial phase, 2/longer semi-stationary phase, 3/ shift phase and then ultimate 4/ equilibrium. We illustrate them in the new Fig. 3 and comment each of them in a dedicated paragraph, hopefully providing an intuition of what is going on, at least to the best of our ability.

This further shows that the analytical model captures fairly complex dynamics that informal intuition may not have anticipated.

This corresponds to 1.312-339.

### **M3) Generalization + “biological” intuition for the result on the independence of the growth rate dynamics $\bar{r}(t)$ on $d$ :**

Comment 3 of reviewer 1 prompted us to explore whether the independence on  $d$  was indeed a property of the FGM or more general. We find that it is indeed more general, and stems from two key assumptions, ignoring density-dependence and considering an initially empty sink. Apart from that, the result extends to a fairly general set of assumptions on the evolutionary process (mutation and selection terms, see Appendix F). Therefore, the result does not stem from the FGM, but rather from key demographic simplifications, that seem fairly realistic for black-hole sinks.

This generalization also helped us come up with what we hope is clarifying ‘intuitive’ explanation of the result. We had struggled to find it so far, but the analytical generalization now tells us which elements of the model must or must not be invoked.

This is mainly explained lines 340-365 and in Appendix F.

#### **M4.A) Effect of mutation: non-monotonous effect of $U$ on $t_0$**

The initial summary of our results by reviewer 1 (point 4.) pointed us to the fact that our message was not clear regarding  $U$ . Its effect is not to decrease  $t_0$  all the time, it is non-monotonous:  $t_0$  decreases first as  $U$  increases (due to increased source variance) then increases again up to  $U = U_{lethal}$  due to mutation load effects.

We discuss the non-monotonous effects of mutation lines 425-430 and illustrate it in the new results in Fig. 6b, together with simulations showing that our analytical theory accurately captures this pattern.

#### **M4.B) Effect of mutation: $U = 0$ in the sink**

The exploration of the phases (M2) and the remarks of the reviewers on the limits of our results to high mutation rates made us wonder how the model and simulations behaved when  $U = 0$  in the sink. Indeed, the model is also valid, in principle, when mutation is absent in the sink (the WSSM only approximates the mutation term). We thus analyzed a model where  $U = 0$  in the sink (keeping mutation active in the source). This scenario can be meaningful when the environmental change from source to sink affects the mutation rate itself, but it is mostly intended to understand the impact of local mutation on the invasion dynamics. We thus used our analytical model to explore how the invasion time differed between  $U = 0$  and  $U > 0$ . This illustrates the ambivalent effects of mutation.

We discuss these effects of local mutation on the speed of invasion in lines 484-510 and illustrate the new results in Fig. 7 and in a new Appendix J.

**M5) Model + simulations with an intermediate sink:** The editor suggested (point 5.) that we back our discussion of the effect of intermediate sinks with simulations and a model. We thus performed the required simulations and modified our model to explicitly capture this situations. The simulations are in very good agreement with the model, although several simplifying assumptions were relaxed in the simulations (density-dependence in both sinks is implemented and the migration rate from the intermediate sink is proportional to its population size).

This is illustrated in Fig. 6c and discussed lines 441-483.

**M6) Package with Matlab codes** All the Matlab codes to generate individual-based simulations are provided in Supplementary File 1.

**M7) New section 3.3** devoted to the range of validity (theoretical and empirical) of the model.

## **2 Point-by-point reply**

Our answers are highlighted in [blue](#).

### **2.1 Editor's comments**

In particular, I share a reviewer's comment about the lack of biological interpretation of the results. In its current version, the manuscript is very much focused on solving equations, obtaining analytical expressions, rather than providing biological interpretations in the context of the model. I feel that the manuscript is currently rather written for a mathematical biology audience, than for an evolutionary biology audience. It is really just a matter of presentation; I do think that the results can be of interest for evolutionary biologists.

[We hope that our modifications have improved the biological comprehension of the main mathematical results. In particular, new figures and text associated with M2, M3, M4 should better illustrate the phases of invasion, what causes them, and how mutation \*vs.\* migration \*vs.\* stress affect the outcomes. M7 should also improve the biologists' insight into the validity / robustness of the results.](#)

In addition to the reviewer's comments, I have a few remarks myself, presented as they appear in the manuscript.

1. 1.42-ff Could be rephrased: as currently written, we expect a description of other types of source-sink systems as well.
2. 1.71-125: I found these two paragraph quite hard to follow; the actual aim of these paragraphs is not clear.
3. 1.84-ff I do not understand this description of "fitness-based" (the "selection on fitness itself" part; fitness is also to be taken into account in the "trait-based" versions, no?)
4. 1.107 I disagree: gene swamping does not only occur in sexuals. See for instance Nagylaki 1975 (PMC1213362).
5. 1.114 Same comment: gene swamping does also occur in asexual populations.

Points 1-5 have been taken into account in the new verions of the Introduction (see M1), we do not refer to fitness based or trait based but to "context-independent" or "context-dependent" models and explain why, we modulated and explained our statements on gene swamping.

6. 1.152-153, 167-168... Unnumbered lines. This is a well-known bug of the lineno package, and there are fixes to ensure that all lines are correctly numbered (e.g. <http://phaseportrait.blogspot.com/2007/08/lineno-and-amsmath-compatibility.html>)

This did not work for us.

7. Unnumbered line above unnumbered equation above 1.153: This should rather read "mean absolute and mean relative fitness". This has been corrected.
8. Also, it is rather odd to call  $m$  a "relative fitness"; usually, the term is used for a fitness divided by the mean(/total) fitness in the population. Please consider using another term (e.g. fitness differential?)

It is fairly classic to use  $m$  for 'Malthusian fitness' in continuous time models in particular but  $m$  is also the log of 'Darwinian fitness'  $m = \log(W)$  in discrete time ( $W$  is only meaningful in discrete time). We have clarified by referring to 'Malthusian fitness' when introducing  $m$  at the beginning of methods and in Table 1.

9. Unnumbered equation above 1.153 Please define notation  $\bar{\phantom{x}}$  This has been corrected. See 1.144.
10. Equation (1) Please define notation  $\prime$  (prime). (sometimes used in population genetics for different equations). This has been corrected. See 1.153.
11. 1.235-236 Moment  $k$  usually depends not just on moment  $k+1$ . This has been corrected. See 1.131.
12. Fig.1  $\bar{r}(0)$  could be identified on the horizontal axis and its value given in the legend. Similarly, the value 0 could be better highlighted. This has been corrected.
13. 1.337 "migrants do not further breed with and genetically "pollute" locally adapted genotypes." I think that this sentence should be re-written to avoid being misused.  
See answer about the definition of gene swamping
14. 1.383ff The LaTeX command for properly typeset " $>>$ " is  $\gg$ . This has been corrected. See 1.352.
15. 1.397ff (and 511-ff) The discussion on the effect of an intermediate sink is interesting, but it would be more impactful if it came with a corresponding figure (and model).  
See M5, we now give both model and simulations.
16. 1.440 There seems to be a problem at the end of the line (missing words). This has been corrected.

## 2.2 Reviewer 1

The authors analyse a model of a population adapting to a harsh sink environment under sustained migration from a source. The fitness landscape is defined by Fisher’s Geometric Model, where the population needs to simultaneously tune a number of phenotypes to their optimal values. They derive a number of analytical results on the dynamics of adaptation under a deterministic approximation that holds when the mutation rate and the migration rate are high.

The main results are the following: 1. The model predicts that successful adaptation to the sink proceeds in three phases: after a short initial phase of rapid increase in fitness, the fitness plateaus for some time then re-accelerates and reaches its equilibrium values 2. The dynamics of adaptation does not depend on the immigration rate 3. When the population adapts to the sink, the migration load is negligible because the sink population becomes very large 4. Above a certain mutation rate, the population may not adapt to the sink. It then suffers from a migration load. 5. Adaptation proceeds faster (lower establishment time) when the mutation rate, the mutational variance, and the maximal growth rate are higher. 6. In harsh environments, the time to establishment increases faster than linearly with the harshness of stress. In those cases, intermediate habitats could greatly speed up adaptation.

Actually,  $t_0$  is a convex non-monotonous function of the mutation term  $\mu$ : the reviewer describes the initial decrease in invasion time as  $\mu$  increases, which we stated behaves like  $t_0 = c/\mu$ , but the invasion time increases again when  $\mu$  gets larger. This was not put forward enough in our previous version, so (see M4.A), we now give a rigorous demonstration of this behaviour (in Appendix H) and added a third panel in Fig. 6 (6b) to illustrate how  $t_0$  varies with  $\mu$  (with simulation checks).

Generally, I enjoyed reading this interesting manuscript. However, as a biologist, I would have liked the analytical results to be interpreted in biological terms more often. This is particularly critical for some of the main results that are not biologically interpreted: the existence of three phases, the fact that adaptation does not depend on the immigration rate, the fact that the time to establishment increases faster than linearly with harshness of the sink. It is difficult to assess whether these results emerge generally from source-sink dynamics, are properties of the specific patterns of epistasis or GxE imposed by Fisher’s Geometric Model, or of the specific high migration / high mutation regime investigated here.

Hopefully this should be improved by modifications M2 (four phases), M3 (independence on  $d$ ), M4 (effect of mutation rate).

It is important that the authors delineate better the range of applicability of these results.

This is the aim of M7. In the previous version the paragraph (lines 377-396) devoted to the conditions that make our approximation accurate, was probably not enough in focus or detailed. We now devote a dedicated section (3.3) on the ‘range of validity of the model’, that contains this former paragraph, plus further details. In particular we extended significantly our simulations to produce the new Fig. 6b, which shows that the results on  $t_0$  are robust way below  $U = U_c$ , at least for the mean invasion time. The Fig. 6a and the Appendix I already showed the range of validity depending on  $d$  and  $m_D$ . We also quickly discuss in Section 3.3 the issues of empirical estimates.

See lines 511-557.

Along the same lines of conveying an intuition for when the results work, it would be interesting to develop the types of biological systems where these results could apply. The authors mention pathogens. Indeed many pathogens are clonal and present high diversity, but the transmission rate (immigration rate) is not necessarily high, so within-host diversity may not be as high as that investigated by the authors. Maybe (just speculating here!) bacteria in water environments would correspond to that regime.

The question of when an analytical model quantitatively “works” or “fails” is obviously crucial, but can be difficult to answer until an experiment is designed to test this particular model and estimate the relevant parameters. Given the thresholds we obtain (now better in focus see M7) for the validity of the model: (i)  $U < U_c$  and (ii)  $-dU/r_D \gg 1$ , what existing data could allow one to claim that, in any given species x environment, the present model should apply or not ?

Criterion (i) can be roughly discussed based on existing data on random mutants in *E. coli*, for example: we now mention this lines 530-534. However, this is fairly limited.

To evaluate criterion (ii), one needs estimates, in the same source-sink system of  $d, U, r_D$ , in the same time units. We could not find any such estimate (source-sink experiments being themselves fairly scarce), so the claim that this model (and probably many alternative ones) applies or does not apply to a given biological system is difficult to make right now. We hope this paper will motivate future experiments in this direction, by pointing which parameters could be jointly estimated.

This issue is now discussed in the new Section 3.3 (M7).

Lastly, it would be interesting to draw a figure with the evolving distribution of fitness in the sink. I am imagining that it initially resembles the distribution shown on figure 1, then it progressively shifts to the right until it reaches a positive mean growth rate. Such a figure would also show why classical mathematical approaches (for example constant variance) fail.

We thank the reviewer for this remark, indeed such a figure was missing. We chose to show the phenotypic distribution (along the dimension where the optimum is shifted) because it allows a much more clarifying picture (see modif. M2)

## Major comments along these lines

1. Is the  $(n/2) * z$  term in mutation? Is the effect of migration to make  $C_t(z)$  resemble  $\phi(z)$  ?

Indeed, this is now done below eq. 9, but only to some extent (i.e. explaining what each term does). Detailing why the particular form in the equation is  $\partial_z C_t(z) - \partial_z C_t(0)$  or  $(n/2)z$  seems long and not necessarily clarifying. We refer to the original paper for these aspects. See 1.252-259.

2. line 290 those three phases are one the most important result, yet the authors do not explain what phenomena occur in these three phases. What is the initial brief increase in fitness followed by a plateau ? Why is fitness accelerating again? These seems to depend on harshness of the environment  $m_D$  (line 291) but we do not have more information. Is this due to the curvature of the FGM? Or is it a more general phenomenon relevant to a larger class of models of adaptation to a sink environment?

M2 should provide some intuitive insight.

3. line 305 the authors could add an interpretation for the interesting lack of effect of  $d$  on evolutionary dynamics. Essentially (if my understanding is correct) this is because the local population size in the sink is directly proportional to the influx of migrants  $d$ , so the fraction of migrants in the sink is constant regardless of  $d$ . This effect is expected to be true for any source-black hole sink dynamics, is there mention of this in previous literature ? Maybe the Gomulkiewicz et al 1999 ?

M3 should deal with this issue.

4. line 346 the duration of "phase 1" is more variable when the mutation rate  $\mu$  is decreased. But again it would be interesting to have an interpretation of this phase 1, and what phenomenon occurs when phase 2 starts.

M2 should provide some insight. The comments on Fig 6 and M7 should also give the reader some idea on what makes the trajectories more or less variable across replicates.

5. line 398 any intuition for why there is such a threshold for the harshness of stress beyond which adaptation does not occur? What features of the model does it depend on?

Indeed this threshold emerges from the relationship between the harshness of stress and the distribution of mutation effects on fitness in the FGM. We added some details in the text (1.445-454) and a reference to a paper focused on the impact of such a relationship on evolutionary rescue.

## Other comments

1. line 13-14 "stress induced by migration" is misleading. Maybe "stress induced by the sink environment"? likewise lines 150 [This has been corrected.](#)
2. line 24 phaseS  
[This has been corrected.](#)
3. line 54 The conjunction "As such" does not connect well with the paragraph above  
[This paragraph and the following one have been rearranged to improve the clarity and the logical connections between ideas.](#)
4. line 80 "no model, be it mathematical or simulation-based, can tackle all these various factors together" Maybe specify, e.g. "a model with all these various factors would be too complex to be intelligible" if this is what the authors mean.  
[This has been corrected.](#)
5. line 91 I think that epistasis and GxE interactions for fitness can be incorporated into a fitness-based model. Perhaps say something more specific, like the distribution of epistasis and GxE interaction generated by FGM match empirical data well.  
[Rephrased to 'context-independent' for the models that, by definition, do not have epistasis or GxE.](#)
6. line 122-123 the infinitesimal model makes assumptions on the genetic architecture of traits. These assumptions can be used for clonal species as well as sexual ones.  
[We do not understand or agree with this point: the infinitesimal model requires independence between many loci, more precisely, it converges as  \$\sqrt{L}\$  where  \$L\$  is the number of independent loci \(see Barton, Etheridge, Veber 2017 Theor. Pop. Biol., 118:50-73\). In asexuals,  \$L = 1\$  by definition.](#)  
Likewise, is the constant genetic variance assumption always breaking down in asexuals? I would say it might work when the mutation rate is high compared to selection, even in clonal species.  
[The reviewer is right: the constant phenotypic variance assumption can also 'work' with asexuals facing a new environment, provided  \$U \gg s\$  \(actually when  \$U \gg U\_c\$ , see Martin and Roques 2016\), but only after first reaching some equilibrium variance, and in an isolated large population of constant size. Source-sinks \(which is discussed in this part of the introduction\) deal with non-equilibrium demographic and evolutionary dynamics and in the presence of migration.](#)
7. Table 1 the use of  $z$  as the variable of the cumulant generating function is confusing as this is also the name of the phenotype vector. Use  $x$ ?  
[This has been corrected.](#)
8. after line 167, "in average" -> "on average"  
[This has been corrected.](#)
9. line 192 rephrase 'the decay rate, in the sink, of an optimal phenotype'. This is the decay rate of a population composed of individuals with the optimal phenotype only.  
[This has been corrected.](#)
10. line 202 could you please comment on the distribution of effects of mutations in FGM? For example say that its mean is  $-\lambda / 2 * n$ , also specify its variance  
[We added a reference to a review on this model for simplicity and stated the mean result. See l.196.](#)

11. line 215 please define the notation  $\Gamma$ . It would be nice to interpret this distribution further. What is the mean fitness, the variance of fitness

We defined the gamma notation. The rest is detailed in the reference given and the distribution is already illustrated in Fig. 1. See 1.208-209.

12. Below equation 7, it would be nice to have an interpretation of the  $-\mu * n/2$  term (mutation load). And a comment on the fact that it depends on dimensionality (is it the so-called 'cost of complexity'?)

We detailed a bit: we think this is not a 'mutation load' per se as we are measuring fitness outside of the environment where the mutation selection balance sets (we allude to a 'variance load'), although the outcome is the same (because of the quadratic fitness function, same effect that makes  $\mathbb{E}[s]$ , the mean effect of mutations on fitness, be constant across environments). Allusion to a 'cost of complexity' could be confusing here: the cost of complexity is more apparent in proportions of beneficial mutations decreasing with  $n$ ; this load is proportional to  $n$  simply because  $\mu$  is the equilibrium per trait variance.

See 1.220-222.

13. figure 1 would be helpful to place the  $r_{max}$  on the x-axis

This has been corrected.

14. line 300 at this point it was not clear why large  $d$  is needed.

The sentence has been removed.

15. equation (11) perhaps the result on the asymptotic value of  $\bar{r}$  can be compared with the result on the equilibrium  $m_{source}$  (line 215), that has the same mean.

We thought that this might be repeating what is stated in the paragraph below this equation, where we state that when  $U < U_{lethal}$  a new mutation selection balance establishes with the same load as in an isolated population.

16. line 370 if I understand correctly, higher  $r_{max}$  means faster adaptation both because it slows the decay of the sink population and increases the proportion of migrants that have positive growth in the sink. The sentence gives the impression that it is not fully resolved why increasing  $r_{max}$  allows faster adaptation, perhaps rephrase.

Indeed: we rephrased.

17. line 374 would be helpful to refer to figure 1 here.

We apologize but did not see where figure 1 was relevant in this line.

18. figure 6, could you please approximately place the  $m_D$  beyond which adaptation in the sink does not occur for these parameters?

We considered that adaptation does not occur when  $t_0 > 5 \cdot 10^3$ , corresponding here to  $m_D \approx 0.5$ . This cannot be clearly rendered in Fig. 6. However, this is visible in Fig. 10 (Appendix I).

19. line 434 again would be nice to have a biological interpretation of these three phases

M2 now does it, we felt it would be repetitive to repeat this interpretation at this point, especially as we have limited resolution in the data to claim a strong agreement with our theory (four time points). we have toned down this particular part accordingly.

20. line 497 would be a good place to refer to fig. 4.

This has been corrected.

21. line 533 anisotropic version, very well, but I guess in that case the analysis becomes MUCH harder because the fitness effect of mutation depends not only on the fitness of the parental genotype but also on the exact position in the phenotypic space (the  $z_i$ ).

We now note that the model is more complex, and propose two options to overcome the difficulty (one done in a current in prep manuscript). See 1.695-697.

## 2.3 Reviewer 2

The authors tackle here an interesting biological question: how a new population, of asexual organisms, can survive in a hostile environment, “the sink”, through the constant immigration of new individuals from a self-sustaining population, “the source”. Using Fisher Geometric Model and building upon their own previous work (Martin & Lenormand 2015, Martin & Roques 2016), they analytically tracked the distribution of fitness of the individuals forming the sink population, as well as the population size in “the sink”. Here, the authors focus on the deterministic dynamics of the system as opposed to Débarre et al 2013 who characterize the long-term equilibria of a similar two populations systems. In addition, they simulated Wright Fisher population to confirm the analytical results.

The authors were able to provide an analytical solution to ODE-PDE system, allowing them to characterize both the mean fitness as well as the demographics of the population. Successful trajectories can be described in terms of three phases, matching some previous experimental works. One of the most striking results is that immigration does not affect the evolutionary dynamics of the population. In addition, the authors also derived the time it takes for a population to become self sufficient (defined as surviving even in the absence of immigration), as whether establishment happens rapidly or very slowly has quite distinct biological implication. Lastly, the authors discuss their results in regards to classical measure to prevent and limit infections or pest invasions. In particular, this analytical approach allows to compare the relative effectiveness of various method, ranging from quarantine, prophylaxis or mutagenesis. Interestingly, their analytical expression captures that mutagen drugs can be more harmful than helpful when used at wrong concentrations.

## General comments

1. Regarding figures 2-5: The various panels are quite small, with the axes label and ticks barely readable. Distinguishing between solid, dashed-dotted and dotted lines require to zoom up to 400% to be able to see which line is which. The panels themselves are quite clear but they definitely need to be larger. Note also that the black line is sometimes hard to distinguish against the red ones.

The panels have been enlarged, the font sizes have been increased and the lines have been thickened to improve readability of the figures.

Also while mentioning that figures share the same legend is a good idea, please rewrite the legend in addition to “same legend as in figure 2”.

This cannot be done unless we reduce the size of the figures. We decided to keep the legends as such.

2. In figure 1 legend, individuals with fitness between  $\bar{r}(0)$  and 0 are called selected. This name is a bit confusing as these individuals are doomed to extinction. I’m assuming that the authors called them because in the absence of migration they will initially increases in frequency in the shrinking population.

This has been modified: these individuals are now called “Selected, not growing”.

3. It would be nice to discuss the new results with respect to Orr & Unckless (2008)<sup>1</sup> and Orr & Unckless (2014)<sup>2</sup>. In particular, it would be nice to mention how the results for an isolated system compared to a source-sink system.

Indeed, we have now introduced a new paragraph in discussion connecting sink invasion and evolutionary rescue (in Orr & Unckless and our recent corresponding work on the rescue in the FGM). We believe it brings an interesting distinction between the time at which a sink becomes a source ( $t_0$ ), and the time at which a sink has given probability to ultimately become a source, but later on, even if migration was stopped (which can be computed from rescue theory). This has also substantially modified our discussion of the effect of propagule pressure on emergence risk vs emergence time.

See 1.614-635.

4. I also would like if the authors could discuss the role of compartmentalisation within a host as discussed in the following paper: Moreno-Gamez et al 2015<sup>3</sup>.

We thank the reviewer for pointing us to this reference which did not know of. A link with our discussion is that it deals with the invasion of a metapopulation with different stresses, by mutation, selection, migration, in an asexual. However, the assumptions in this model, as we understood them, differ widely with those of our model, so that we fear that a detailed comparison of these results with ours might confuse the reader.

More precisely, our understanding of the model is the following:

This is a 'context-independent' model with three alleles: wild type, resistant to drug 1, resistant to drug 2 and a genotype carrying both. It is context independent in that the effects of mutations on fitness are additive (no epistasis) and there is no GxE in the sense that (i) the fitness of the resistant mutant to drug  $i$  is unaffected by drug  $i$  (it is the same with or without the drug) and (ii) there is not a continuous measure of stress level (our  $m_D$ ) that would affect the fitness effect of mutations. This is very different from our model with infinitely many alleles with different effects across all environments, with epistatic interaction, and GxE. Our discussion is on the effect of an intermediate  $m_I$  providing a springboard to invade a higher  $m_D$  depending on the particular values of  $m_I$  and  $m_D$ . We cannot compare this to the proposed reference, or we do not know how to do so at least.

5. In addition to the case of lethal mutagenesis, it would be interesting if the authors could also discuss the potential dynamics of mutational meltdown (Lynch & Gabriel 1990<sup>4</sup>, Matuszewski et al 2017<sup>5</sup>) and whether their analytical results can inform us on the effectiveness of such approach.

Mutational meltdown, as formulated initially by Lynch & Gabriel 1990 (at least as we understand it from the original article), refers to a positive feedback between Muller's ratchet and the resulting decreases in population size due to the recurrent loss of the fittest class. This process takes place at different orders of magnitude of time from lethal mutagenesis (discussed in Martin & Roques 2016 for ex.), and is anyhow ineffective in any model where compensatory evolution is allowed (as is the case with the FGM): compensatory evolution allows fitter classes to be recreated by beneficial mutations from a lower fitness class, (a process pervasively observed in experimental evolution): the ratchet does not "click" then (see Poon & Otto 2000 Evolution) and mutational meltdown should be ineffective.

---

<sup>1</sup><https://www.journals.uchicago.edu/doi/10.1086/589460>

<sup>2</sup><https://doi.org/10.1371/journal.pgen.1004551>

<sup>3</sup><https://doi.org/10.1073/pnas.1424184112>

<sup>4</sup> <https://doi.org/10.1111/j.1558-5646.1990.tb05244.x>

<sup>5</sup><https://doi.org/10.1093/ve/vex004>

We thus believe that this is really a different thing, and not applicable to the FGM considered here (or indeed to any model with beneficial mutations from less fit genotypes) so we do not think it is relevant here.

## Minor comments

1. l 14-15: define briefly what establishment means: formation of a self-sufficient population in the sink [This has been corrected](#).
2. l 18: the fitness optimum in the sink and that of the source [This has been corrected](#).
3. l 23 and l 26: “beyond some mutation rate threshold” is written twice to describe different outcomes. On line 314, you describe the first behaviour as below some threshold. I assume you mean below on line 23. [This has been corrected](#).
4. l 25 : trajectory of [the] mean fitness [This has been corrected](#).
5. l 78 : define GxE [This has been corrected](#).
6. l 167 (+2) : [on] average [This has been corrected](#).
7. l 181: at  $\rightarrow$  of [This has been corrected](#).
8. l 291: is larger  $\rightarrow$  increases [This has been corrected](#).
9. l 293: For consistency, “the mean” should also be capitalized [This has been corrected](#).
10. Figure 2: plain lines  $\rightarrow$  solid lines, dash-dot line  $\rightarrow$  dashed-dotted lines  
“theory given by”  $\rightarrow$  “analytical predictions given by” [This has been corrected](#).
11. Figure 3: remove clearly. [This has been corrected](#).
12. Figure 4: plain  $\rightarrow$  solid, dash-dot  $\rightarrow$  dashed-dotted [This has been corrected](#).
13. l 348: Please rephrase. I’m confused by “when U is not too small, even far from the WSSM regime”. I don’t know what the authors are trying to convey: the results hold both for medium and low values of U or only for one of the two regimes. [This has been corrected](#).

## 2.4 Reviewer 3

The authors investigate the possible adaptation of a population to a “sink” environment where it is initially maladapted. The initial population is arriving in the sink by a constant immigration from a source where it is well-fit and at equilibrium at a different fitness optimum. By using Fisher’s Geometric Model (FGM) and a Weak Selection Strong Mutation (WSSM) assumption, the authors develop estimates on the cumulant generating function of the distribution of population in the sink, which lead to analytic formulae and a precise description of the transient and long-time behaviour of the latter population. Particularly, the authors obtain an explicit formula for the mean fitness of the population in the sink at time  $t > 0$ ; this formula allows the prediction of the eventual adaptation of the population (i.e. the mean fitness becomes positive in finite time) and, in the case where establishment happens, an expression of the time to adaptation. The analysis is also supported by individual-based stochastic simulations which help testing the robustness of the predictions in a slightly different, presumably more realistic, context.

I found the paper very well written and well-documented. The framework is fairly simple (quadratic fitness function) and somehow restrictive due to the WSSM assumption, but the fact the population dynamics can be fully understood gives a high relevance to the study as it constitutes a solid basis

on which theories can be constructed or tested. Additionally, the existence of explicit formulae is sufficiently rare to be noticed. However there are a couple of details that need to be further checked or explained before I can fully recommend the paper. I would be happy to review the paper again once the authors have replied to the following comments.

## Major comments

1. The authors present simulation results and describe the algorithm used for the actual computations, but do not present the precise implementation of the computer code used to do the simulations. If the publication of the latter code is not restricted because of industrial or strategic interests (which I doubt), I suggest the authors to publish their code and to advertise it in the paper, as it builds trust in their results.

The code used to do the simulations of the individual-based model is now available as [Supplementary Information 1](#).

2. Some choices in the algorithm could be discussed in more details; in particular, the stopping criterion for the source population : where does the  $20/\sqrt{\mu}$  generations come from (l. 271)? The given reference (Martin and Roques, 2016) containing a lot of results, which one is targeted by the reference?

The stopping criterion  $t = 20/\sqrt{\mu}$  for the computation of the equilibrium source population is now explained in more details, and with a precise reference to the corresponding result in (Martin and Roques, 2016).

See l. 275-278.

And, similarly, to what does the criterion  $t > 5 \cdot 10^3$  correspond (l. 282)?

This choice is “conservative” and *ad hoc*: in the WSSM regime, with our choice of parameter values (Figs. 2 and 4), the equilibrium for  $\bar{r}(t)$  is reached at times  $t \ll 5 \cdot 10^3$ . It is however useful to carry out the simulations until  $t = 5 \cdot 10^3$  to observe successful establishments for smaller mutation rates (thus, outside of the WSSM regime) corresponding to the parameter values in Fig. 8. When  $m_D$  is increased,  $t_0$  increases, as described in Fig. 6. With our choice of parameter values, the trajectory of  $t_0(m_D)$  becomes superlinear before  $t$  reaches  $5 \cdot 10^3$  (see Fig. 10 in Appendix I). As the trajectory  $t_0(m_D)$  rapidly increases in this superlinear regime, increasing the stopping criterion (while keeping reasonable computation times) would not change the results (no more establishment would be observed) and therefore seems unnecessary.

3. Is there a realistic scenario in which  $U_c > U_{lethal}$ ?

We have  $U_c = n^2\lambda/4$  so that  $\mu_C = \sqrt{U_C \lambda} = n/2 \lambda = \mathbb{E}[s]$  (the mean effect of mutations on fitness). The maximal  $\mu$  for lethal mutagenesis is such that  $r_{max} - n/2 \mu = 0$ , hence  $\mu_{lethal} = 2r_{max}/n$ . We would thus need to know if  $\mu_{lethal} < \mu_C$ , i.e. if  $r_{max} < \mathbb{E}[s] n/2$  is ‘realistic’. This is another empirical issue difficult to set, but let us give it a try. Estimates of mutation effects in microbes are often given scaled by the growth rate of the parent. If we consider the parent well adapted to the lab environment, its growth rate is close to an  $r_{max}$  (albeit not in a ‘sink’) so that  $\mathbb{E}[s] = x r_{max}$ , and typically  $x \in [0.001, 0.1]$  in the few strains/microbes where it has been measured this way. We would thus require  $1 < x n/2$  hence  $n \in [20, 2000]$ . Estimates of  $n$  are of course difficult too, but under the isotropic FGM they should be given by the shape of a gamma DFE in optimal conditions (Martin & Lenormand 2006), which is inconsistent with  $n \in [20, 2000]$  ( $n < 10$  in the few such estimates, as DFEs are typically skewed).

We do not believe that a rigorous review of the relevant mutational and demographic parameters, in the few species where it has been estimated, is in the scope of this article. In the absence of such a review with proper confidence interval an actual useful answer to the reviewer’s question is impossible. We let the editor decide whether we should do otherwise.

See l. 530-540.

4. Appendix C, p.32, before 1.677, after “ $v(t)$  is given by”: I agree with the computation if  $N(0) = N_0 > 0$  but there are sanity checks to do when  $N(0) = 0(1/N(t) \rightarrow \infty$  as  $t \rightarrow 0$ ,  $N'(s)/N(s)$  is not integrable on  $(0, t), \dots$ ). This remark especially concerns the “The above expression can be simplified to ...” statement.

These computations have been clarified. In particular, we first compute  $v(t)$  by integrating the expressions over intervals of the form  $(\varepsilon, t)$ , with  $\varepsilon > 0$ , and we pass to the limit  $\varepsilon \rightarrow 0$ . See p.39.

5. Appendix D, Case (iii), p.35, from 9 lines before line 694, the end of the computation is not so clear. If the sign of  $\varepsilon$  is the only thing that matters here, then it would be nice to have a simple argument rather than a series expansion which is painful to check and the validity of which is not clear to me (I couldn’t get rid of the dependency in  $m_D$  and  $r_{max}$ , has the hidden dependency in  $\mu$  of  $X$  been taken into account?) It would also be nice to be recalled of the aim of the computation at this point.

These computations have been clarified. In particular, the series expansion is now explained in more (but not painful) details, and the aim of the computation has been recalled. See p.46 (Appendix G).

Finally, there is a discussion about the valid values of  $\alpha$ ; it seems to me that, with  $\alpha$  small enough, then one does not need to worry about dimension (any  $n$  satisfies the inequality before line 694). Maybe the authors should comment on the interest of taking larger values of  $\alpha$ ?

This is true that for  $\alpha$  small enough, the condition on the dimension is always satisfied. However, the result becomes more accurate for larger values of  $\alpha$ . We have added some comments about this. See p.46.

6. Appendix E: between line 706 and 707, I think a few more lines would greatly ease the understanding for some readers (the computation is not really explained in the present version).

We have added several details to fully explain the computation, see Appendix H, 1.906-914.

## Minor comments

1. 1.220 p.9, there is no real “need” to know the moment generating function, this is rather the particular method you chose to solve the problem.

This has been corrected.

2. Note that this is a matter of taste and I will not require this to be changed, but I find the choice  $C_t(z)$  to denote the value of the cumulant generating function at time  $t$  rather disturbing: the “underscore  $t$ ”  $\square_t$  notation being frequently used in some other context to denote the time derivative.

This is true, but this notation is consistent with the previous work (Martin and Roques, 2016), and leads to shorter expressions.

3. p. 12 Section 3.1, lines 285-287: the sentence is a little ambiguous, and the indentation is wrong.

This has been corrected.

4. Appendix A, p. 28, I don’t understand the notation  $\mathbb{E}_{m_{source}}$  [...] which appears in the computation of  $M_{migr}$ , as it is the standard expectation.

This has been corrected.  $\mathbb{E}_{m_{source}}$  has been replaced by  $\mathbb{E}$ .

5. Appendix C: maybe recall that  $m(t) = \partial_z C_t(0)$  before or immediately after Equation (15). This has been corrected.