**Author response**

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"Stress-Induced Mutagenesis and Complex Adaptation"

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We are grateful to the editors and reviewers for their thorough consideration of our manuscript and constructive recommendations for revision.

In response to the comments raised by the editor and the reviewers we have made major changes to the manuscript. Briefly, we discuss model assumptions which were not discussed before: the use of a threshold relationship between fitness and mutation rate; the possible effect of single mutants having intermediate fitness; the plausibility that low fitness can induce mutagenesis. We also compare our results with those of other authors that studied the trade-off between *adaptability* and *adaptedness*.

Following is the review, complete with our responses to each of the issues (line numbers in the form of L# refer to the original manuscript, the form M# refer to the revised manuscript):

**Response to Editor comments:**

*First, I'd like to see one or two sentences outlining that it is reasonable to consider low fitness -- arising from a maladapted genotype (in reality, aren't almost all genotypes maladapted?) rather than a potentially mutagenic environmental stress like starvation -- as a stress that might induce SIM. I see one reference on this point, but it would be nice to note explicitly any evidence that comes from a bacterial system.*

We added a few sentences to the model section (**LXXX**). We note that in bacteria, stress responses are expected to be triggered when deleterious mutations reduce fitness by impairing the ability of the cell to perform vital functions. As an example, we point to the classical Lac assay experiments in which a *lac-* mutant starves on lactose and in response to starvation increases the mutation rate.

*Second, and related, I'd like to see some justification for modeling SIM as 'all or nothing' rather than as a function of a genotype's fitness decrement from the optimum. Lenski's group recently published a paper predicting that fitness may never be reached, even during adaptation to a simple constant environment (Wiser, M. J., N. Ribeck, and R. E. Lenski. 2013. Long-term dynamics of adaptation in asexual populations. Science 342:1364–1367). If this result is at all general, does it mean we should think that SIM will always be induced?*

We had already treated this criticism in Appendix E in which we model SIM as a continuous relationship between fitness and mutation rate. Unfortunately, we forgot to refer to Appendix E in the main text. To correct this mistake and because this issue may be interesting to other readers, we added Fig. 2B (previously Fig. E2 in Appendix E) which shows the adaptation rate of continuous SIM and compares it to threshold SIM (the main SIM strategy in this manuscript). The figure shows that threshold SIM is a good approximation for continuous SIM, because the main factors determining the adaptation rate are the mutation rates of wild-type and single mutant individuals. We added a paragraph which describes this result to section 3.3 (**LXXX**).

We revised the text based on all minor comments:

* Refs in numbers in L50 and L31
* Changed to "…simulation results…" in L228
* Fig. 1 legend: note on x-axis jitter
* Fig. 1 x-label: changed to "Number of mutations"
* Figs. 2,3: fixed typo in x-label

**Response to Reviewer II comments:**

*\* What happens in the case where s<0 (that is, the intermediate mutant has a slight fitness advantage)? This interesting case can be quite different and should be discussed separately.*

We added a discussion of a scenario in which single mutants have intermediate fitness (*sH*<s<0) to the Discussion section (**LXXX**). This is indeed a different scenario than the one we studied in this manuscript, and we have previously shown (Ram & Hadany 2012) that SIM is favored by selection on smooth fitness landscapes. We plan to explore SIM's effect on the adaptation rate smooth landscapes in future work.

*\* The questions of the tradeoff between adaptability and adaptedness were discussed in Komarova, Wodarz. "The optimal rate of chromosome loss for the inactivation of tumor suppressor genes in cancer." PNAS 101.18 (2004): 7017-7021, and also Komarova, Sadovsky, and Wan. "Selective pressures for and against genetic instability in cancer: a time-dependent problem." Journal of The Royal Society Interface 5.18 (2008): 105-121. It can be interesting to compare the approach of the authors with the approach and the results of these papers.*

Our many thanks to reviewer II for pointing out the very interesting work by Komarova and colleagues. We added a new paragraph to the discussion section (**LXXX**) which discusses these papers, along with other models that optimize mutation rates to balance the trade-off between *adaptability* and *adaptedness*. We conclude that SIM can be seen as a strategy to break this trade-off rather than to optimally balance the trade-off.

*\* How do the results fit into the debate about the role of mutations (and genetic instabiliy) in carcinogenesis (see papers by Loeb on the one hand, and by Bodmer and Tomlinson, on the other)?*

We included references to both Tomlinson's and Loeb's views on the effect of mutation on carcinogenesis. We prefer not to put more emphasis on this subject because we are not certain that it fits the scope of this paper, which focuses on microorganisms, rugged landscapes, and long-term evolution.

**Unsolicited changes:**

* Added ref to Karpinets et al. 2006 regarding role of SIM in cancer in Section 3.5.
* Corrected Figure in Appendix D to Fig. D1
* Changed reference to "Appendix 2" to "Appendix B" in Appendix C

We hope that our response will meet your approval.

Sincerely,

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