Reply to reviewers:

Line numbers (LXXX) refer to the original manuscript.

Associate Editor

1. It is true that the fraction of mutation-free AB in the MSB is *N e-U/s (u/s)2*. However, This additional factor, *e-U/s*, is expected to be large (*U*=0.0004, *s*=0.05 -> *e-U/s*=0.99, *U*=0.003, *s*=0.01 -> *e-U/s*=0.74) and therefore doesn't have a significant effect on the constraints on the population size N. Omitting it makes for a simpler argument. Note that this factor e-U/s does appear in our actual model and analysis.
2. Eq. 1 doesn't ignore selection. We use the MSB frequencies of *ab*, *Ab*, and *Ab*, which already include the effect of selection – e-U/s and *µ/s e-U/s.*
3. Figure 3 explicitly defines adaptedness as the mean fitness of the population at the MSB. We added the definitions of adaptedness and adaptability to the legend of figure 4.

Reviewer 1 – NOT DONE YET

1. We separated the evidence of evolution of mutator alleles into empirical and theoretical results. Also, we marked references to reviews as such (Sniegowski et al. 2000, de Visser 2002, Denamur & Matic 2006
2. We added more references and clarified the section on evidence of SIM.
3. We emphasized the main question of the manuscript in the introduction: how does SIM affect complex adaptation? Also, we added a recap of our previous results on the evolution of SIM (Ram & Hadany 2012) to the introduction and expanded on them in the discussion. We also added results of direct competitions between the different mutation strategies that suggest that SIM is favored by selection.
4. We have revised the section defining how mutation operates in our model in order to clarify that individuals are defined by the alleles they have in the focus loci (*A/a* and *B/b*) together with the number of deleterious mutations they have in the non-specific loci. Also, we clarified that stress is determined by fitness which is determined by all loci, not only by the specific focus loci.
5. We emphasized that our model is strictly asexual without recombination or segregation and discuss this limitation in the discussion.
6. Appendix 1: we added a comment about the assumptions made on the model parameters; added the missing factor of 2 to the LHS of the first equation in L407; added missing << in L414; added an explicit sH<<1 note in L432; added a comment at L111 that all the simplifications can be found in the appendix and a reference to Fig. S1 that shows a comparison of the analytic results and the simulation results.
7. We added the number of bootstrap samples and the number of simulation replicates in the legends of Fig 2, Fig. S1 and Fig. S2; we added the number of simulations per parameter set in the methods at the end of section 2.5.
8. We expanded on Fig. 3 in the text, at the beginning of section 3.2, and added a note in L182 about the source of the small advantage of SIM in adaptedness.
9. We checked and fixed formatting issues in the supporting information.
10. We added a note about the difference between Agrawal 2002 and Shaw & Baer 2011 in L50.
11. We revised L133 to complete the sentence on what the simulations were used for.
12. We replaced "see below" with a reference to section 3.3 in L 121 and L160.
13. Indeed, all mutations have the same effect on fitness. We added a note on L65 to avoid confusion.
14. We included more details on citations of proposed solutions to the "adaptive peak shifts" problem; We rephrased the last sentence of the paragraph to explain which problem SIM may help resolve.
15. We removed the β=0 note to avoid confusion.
16. Table 1: …
17. Lilach's email was indeed missing an 'a' after the 'd'.
18. We fixed typos and grammar in L40, L41, L75, L78, L108, L126-127. We didn't change L52 because we prefer the active voice rather than the passive one. We left 'constraints' in L101.

Reviewer 2

1. As specified above (7) we revised the model overview to emphasize that all deleterious mutations (in the *A/a* and *B/b* loci or in the non-specific loci) are equal in regard to their effect both on fitness and on the mutation rate. This is because with SIM, the mutation rate is a function of the fitness and not of the number of deleterious mutations – the mutation rate is *U* if the fitness is ≥ 1 and *τU* otherwise (in section 3.3 it is *U* if fitness is > 1 and *τU* otherwise).
2. We ran simulations in which the mutation rate is a continuous function of the mean fitness. We used the functions suggested by Agrawal (2002): *Ux = τU-(τU - U)ωk* where *k* is a curvature parameter (we used *k*=1/10, 1, 10, and 100), *U* is the baseline mutation rate used in normal mutagenesis, and τ is the maximum fold-increase in mutation rate. We present the results in section 3.4 and Fig. 2B.
3. If SIM is already extinct at the environmental change then it will not achieve adaptation; however, before the environmental change SIM is as likely to reach extinction as NM, because the mutation rate of the fittest individuals is the same as in the case of NM and the population mean fitness is slightly higher. To account for the possibility that a SIM population can go to extinction while waiting for adaption in a non-constant sized population, we ran competitions between NM and SIM in which SIM can suffer from the increased mutation load and lose to NM due to a decrease of the SIM sub-population size. Our simulation results show that SIM is advantageous over NM – see new Fig. 5 and section 3.5. This was also done in our previous work (Ram & Hadany 2012) with a smooth fitness landscape - SIM and NM competed over multiple environmental changes until one of them went to extinction. In that work, SIM was introduced at 5% and was still significantly advantageous over NM and CM.
4. We added the mean of the Poisson distribution to L85.
5. The frequency of individuals with a mutant (uppercase) allele in either the *A/a* or *B/b* locus at the MSB is *µ/s*. assuming independence between the loci, the frequency of a double mutant *ab* is *(µ/s)2*. Multiplied by *N* we get the expected number of double mutants at the MSB, *N(µ/s)2*. The number of mutations per individual is Poisson distributed with mean *U/s*. If we define *g*=*U/*µ, then the frequency of any double mutants is *(U/s)2e-U/s/2*. For some double mutant to be the double mutant *ab* we need both mutations to be at the right locus, with common probability *~1/g2*. So we get (*U/s)2e-U/s/2g2 = (µ/s)2 e-U/s / 2 ≈ (µ/s)2*. The last approximation is discussed above in (1).
6. We added "expected" in L95 and L96.
7. Thank you for finding the mistake Eq. 1 and 2 and in Appendix 1 in the calculation of *q* the appearance probability. We corrected the expressions, which led also to corrections in Eqs. 5-7. We reproduced Figs. 2, 4 and S1. The fit with the simulations results is now slightly better. There is no major change in the conclusions.
8. We added a note about U+2µ≈U because U>>µ to appendix 1. Therefore the frequency of mutation-free *ab* can be written as e-U/s rather then e-(U+2µ)/s. The same goes for the frequency of mutation free *aB* which can be written as *µ/s\*e-U/s* with the additional factor of *(1-µ/s)*.
9. Section 3.3 on SIMe was revised. We hope that the motivation for this extension is clearer now.
10. Figure 4: We changed the axes labels, the legend, and the text so that it would be clearer that the figure axes are relative measures in comparison to NM; added a note about limit the limit on τ (*τU*<<1) to the figure legend – for CM this is equivalent to the constraint *U*<<1 used throughout the manuscript, for SIM this is a constraint that ensures that single mutants don't become rare due to mutational load.
11. We added a paragraph to the introduction and also expanded in the discussion about our former findings (Ram & Hadany 2012) in which we've shown that SIM can be selected for (see also (6) above). Also, we added the results of competitions between the different mutational strategies to show that indeed SIM can be selected for in this model.
12. We added a paragraph on direct fitness costs to the discussion section. In short, we agree that assessing the individual's condition is costly. However, organisms constantly asses their condition for other purposes – bacteria, for example, have a number of stress responses such as the SOS response and the general stress response. Once these mechanisms already exist, they can be recruited to regulate the mutation rate. One doesn't need to consider their cost for SIM because these mechanisms operate in NM and CM and are essential for viable organisms (see Foster 2007 for details on SIM and bacterial stress responses).