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**Date:** Apr 21, 2014  
**To:** "Lilach Hadany" lilach.hadany@gmail.com,lhadany@post.tau.ac.il  
**From:** "The American Naturalist" amnat@press.uchicago.edu  
**Subject:** Decision on Manuscript 55406

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Dear Dr. Hadany:

The Editorial Board of the *American Naturalist* has reached a decision regarding your article, "Stress-Induced Mutagenesis Breaks the Trade-Off Between Adaptability and Adaptedness." As a matter of journal editorial policy, one or more members of the Editorial Board review each manuscript and decide about its potential interest to readers of the *American Naturalist*. If in our opinion the manuscript does not meet the needs of our journal, we decline it without sending it for external review. I'm afraid your paper falls into this category.

One of our associate editors, Dr. Stephen Proulx, has read your manuscript and his comments are pasted below. After reading your manuscript in detail myself I am in agreement with Dr. Proulx's assessment. I think your analysis of the consequences of different kinds of mutational processes is interesting but I think it is probably better suited to a more specialized journal. The manuscript is framed around the tradeoff between adaptability and adaptation but, as Dr. Proulx says, a great deal of the paper does not actually deal with this question per se. I think the other results you present are interesting and valuable but the main conceptual aspect of work (which is what matters most for a journal like the *American Naturalist*) is the qualitative result that stress-induced mutation can result in there being no tradeoff. Furthermore, while this result is certainly interesting, it is not very surprising and I don't think it constitutes a large enough conceptual advance to be published in a broad, general, journal like Am Nat. Our policy in cases like this one, where there is a good paper that is better suited for another journal than ours, is to return the paper as quickly as possible to the authors so that it may more rapidly be considered elsewhere.

As a result, I cannot accept your manuscript for publication in the *American Naturalist*. Because of space limitations, we can accept only 20% of submissions. We must emphasize the goals of The *American Naturalist*: to publish papers that are of broad interest to the readership, to pose a new and significant problem or introduce a novel subject to the readership, to develop conceptual unification, and to change the way people think about the topic of the manuscript. Unfortunately, this means that we must decline many good manuscripts that are worthy of scientific publication. Declined manuscripts are not eligible for resubmission in a revised form. Thank you for thinking of the *American Naturalist* as an outlet for your work.

Sincerely,

Troy Day  
Editor  
*American Naturalist*

MS #55406  
Author: Yoav Ram; Lilach Hadany

XXX  
ASSOCIATE EDITOR'S RECOMMENDATION

Dear Troy,

I have now thoroughly read this manuscript and found the article to be interesting and the modeling to be generally rigorous and informative. While the area of facultative mutagenesis, adaptation and population fitness is of general interest, the specific content of this article does not rise to the level of broad integration and synthesis that characterize the mission of The American Naturalist. There are two main issues that I think hold the MS back from fitting this format: one is that the results speak to a fairly narrow set of circumstances and the other is that the section on the trade-off

between adaptability and adaptation (the stated goal of the MS) is the weakest part of the paper.

The article is couched in terms of the trade-off between adaptability and adaptation, and in order to get at these the authors first define time until an adaptive state is reached and the mean fitness of populations at equilibrium. These models only consider deleterious mutations. The bulk of the MS deals with calculating the time until adaptation occurs (these are interesting calculations in their own right), and then the trade-off is addressed in section 3.4. Section 3.4 then introduces a new model, one that allows for beneficial mutations, and without any details of the model or its analysis, presents results on this trade-off. The results discussed here are mostly references to the prior work of the authors and the Appendix D, which also mostly refers to prior work by the authors and results from Agrawal (2002). The point that mean fitness is either the same between NM and SIM, or that SIM has somewhat higher mean fitness isn't in itself surprising or new. Novelty isn't the only value of a result, but the section just doesn't seem to give much of a sense of how applicable or useful these results are. For example, figure 4 shows the SIM populations with mutation rates 20-100 times higher than NM, but there is no context for these levels. This is not addressed in the discussion either.

More generally, the MS focuses on the population level effects of facultative mutation rate, but doesn't really address the broader question of how the different aspects of the system could evolve. The appendix F presents some competition results and clearly shows that CM is generally a disfavored strategy, but even with the small set of parameters explored there isn't convincing evidence that SIM will be maintained. Even with 50 fold increases in mutation rate, the SIM populations have only a small increase in frequency following an environmental shift. A full model would incorporate mutation at the loci responsible for SIM and recurrent rounds of environmental shift and environmental stasis. Such a model would include the effect that long periods of stasis would allow for either the loss or maintenance of SIM, and that the short periods of environmental change could augment this. Presumably the ratio of the expected waiting times in each of these regimes (stasis vs. environmental shift) would have an effect on the likelihood that a population is found in a state where SIM is at high frequency.

I also find that the MS lacks any realistic discussion of how differences in fitness would be detected by the microorganismal cells. This relates to the SIM vs. the SIMe model section. Even if the bacteria improve their fitness in the new environment, the machinery that detects stress may still perceive stress, and thus mutation rate would not go down. Since the stress-detection machinery must have evolved over long periods of time in the (perhaps fluctuating) ancestral condition, some discussion is warranted of how this itself would evolve (that is, the detection machinery) and whether mutation rates would really go down as adaptation occurred.

While I am generally convinced of the rigor of the modeling, the MS has a tendency to refer to the validity of approximations in a rather offhand way. I'm afraid that a detailed review of the models would also find objection to this, and a lack of literature review/citation of recent work on valley-crossing models and their general validity. For example, little treatment of the valley crossing (or stochastic tunneling) framework is given. This is potentially important for section 3.1 as SIM could still have an effect when no single mutants are present simple because single mutants could arise and potentially give rise to double mutants before their lineage goes extinct. For example, the work of Weissman et al. (2009) on asexual models of valley crossing details regime shifts that depend on population size and mutation rates, but this work is not even referenced, much less discussed.

Although these criticisms make the MS unsuitable for American Naturalist I do believe that the calculations on the rate of adaptation are of direct interest themselves and would be a valuable contribution to the literature.

Stephen Proulx  
Associate Editor

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