

Proceedings of National Academy of Sciences USA

Review of:

Title: A generalized model of mutation-selection balance with applications to aging.

Authors: David Steinsaltz, Steven Evans, and Kenneth Wachter
First author affiliation: Dept Demography, UC Berkeley.

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1. Is the overall quality of this paper suitable for this journal?
"Yes" implies that the paper is in the top 10% of its field.

No. I also believe that it would not be publishable in its present form in a top-ranking journal in applied probability or demography.

2. Is this contribution of sufficient general interest to justify publication in PNAS rather than a specialty journal?

No.

3. Does the evidence justify the conclusions drawn?

Yes.

4. Is this paper clearly written for a diverse audience of scientists?

Yes, although the ``diverse audience'' could be misled by an inadequate review of the literature.

5. Are the procedures described sufficiently well that the work can be repeated?

Yes, in the sense that the proofs given are complete.

6. If there is supplemental material, does it make a substantive contribution that warrants deposition in PNAS Online?

COMMENTS FOR THE EDITOR / AUTHORS

The authors consider integer-valued discrete measures $g(dx)$ on a state space M as a model of genome-wide mutational change. The state space M could, for example, be bases at different nucleotide positions, so that $g=0$ is pure ``wild type''. Two dynamical processes are considered: Nonrecurrent mutation (which is modeled as an immigration process into M) and selection against mutant (``non-wild-type'') forms that are already present. Deleterious selection is emphasized but the models can handle positive selection as well. The authors' dynamical equation is not rigorously derived (``Our dynamic equation for P_t is...'') but seems quite plausible.

Two cases are considered: The ``non-epistatic'' or linear case in which selection acts additively on genomes $g(dx)$ (or multiplicatively in terms of fitnesses) and a more general ``epistatic'' case in which selection

$S(g)$ can act in an arbitrary manner.

Most of the exposition is devoted to the more easily-analyzed non-epistatic case, but the authors do not appear aware of related older work. Among the more relevant is Sawyer (1976, *Advances in Applied Probability*), which not only handles mutation-as-immigration and selection in the same way as in the authors' model, but also includes Markov motion in type space and branching-process multiplication as well. Explicit limiting distributions are derived that are similar to the authors' results.

As a historical antecedent, the authors might also mention Kingman's "house of cards" model (Kingman 1980, *The Mathematics of Genetic Diversity*, CBMS-NSF Regional Conf. series). This handles a deterministic version of the authors' linear model in such a way as to make long-term evolution with positive selection easy to analyze.

In regards to the evolution of measure-valued processes in the presence of selection and mutation, the authors should also refer to related work of Ethier, Dawson, and Kurtz.

The authors' work with nonlinear ("epistatic") selection is potentially more interesting. However, relatively little is accomplished other than to show that the force of selection can, in some cases, be removed by an application of the Feynman-Kac formula.

The aim of the paper appears to be questions related to age-structured selective effects and the evolution of senescence. The paper begins with a brief but interesting review of work in this area. The final section has suggestive comments about applications to demography, but details (including precise results) are "to be spelled out in later work."

Minor comments:

(1) There are several references to an imprecisely-described theorem in what is essentially a textbook by R. Durrett ([6]). Even though this book is on my desk (I purchased it recently), I was not able to find the theorem described. Many journals require page numbers for references to books. This would have been a good idea here.

(2) The type-space of the process is described as "a complete, separable metric space of mutations M ". While identifying "mutation" (which means "change") with the product of the mutation may seem natural to do, it is inherently confusing since (among other things) it leaves open the question of whether the authors want to distinguish different mutations that produce the same end result. Many biology journals strongly recommend that authors restrict the use of the word "mutation" to the process itself and not use it as a synonym for the end product.