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# Genetics of adaptation and fitness landscapes: From toy models to testable quantitative predictions

Thomas Bataillon,<sup>1,2,3,4,5</sup>  Thomas H. G. Ezard,<sup>1</sup> Michael Kopp,<sup>2</sup> and Joanna Masel<sup>3</sup> 

<sup>1</sup>School of Ocean and Earth Science, National Oceanography Centre, University of Southampton Waterfront Campus, Southampton SO14 3ZH, United Kingdom

<sup>2</sup>Aix-Marseille University, CNRS, I2M, Marseille 13331, France

<sup>3</sup>Department of Ecology and Evolutionary Biology, University of Arizona, Tucson, Arizona 85721

<sup>4</sup>Bioinformatics Research Center, Aarhus University, Aarhus 8000, DK

<sup>5</sup>E-mail: [tbata@birc.au.dk](mailto:tbata@birc.au.dk)

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## Background

The “Fitness landscape” metaphor is central to our ability to conceptualize how mutations generate new phenotypes and, in turn, variation in fitness. This metaphor has been instrumental in shaping collective mental pictures of how evolution proceeds, where the limits to innovation lie, and how adaptation emerges as a consequence of natural selection acting on phenotypic differences that are at least partly heritable.

Fitness landscapes, also sometimes termed adaptive landscapes and originally introduced by Wright, “show up” for a variety of topics. The journal *Evolution* has been at the forefront: from the early 50s (Wright, 1948) onward, many seminal papers (Wright, 1982) were published in *Evolution* (and now also in *Evolution Letters*).

- \*Wright, S. 1982. Character change, speciation, and the higher taxa. *Evolution* 36:427–443.

Interestingly, what started out as a concept that could arguably be dismissed as nothing more than a vague metaphor quickly evolved into formal models of the evolutionary process and, especially in the last two decades, motivated theoretical, experimental, and other empirical evolution research aimed at “measuring/quantifying fitness landscapes” (Fig. 1).

All authors contributed equally and are listed alphabetically.

Here, we focus on two lines of descent that represent two connected research programs:

- Gillespie’s Molecular landscape and similar models relying on the “strong selection weak mutation” regime, which capture the joint impact of mutation and selection on evolutionary trajectories within a discrete genotype space.
- Fisher’s geometric model of mutational impact in high-dimensional continuous phenotype spaces, and its uses for predicting the distribution of fitness effects of new mutations, the joint fitness effects of mutations across environments, and so on.

This themed mini issue does not cover other aspects that are also intimately linked to the original fitness landscape metaphors. For instance, the concept of selection (or fitness) gradients in phenotype space, which also goes back to Wright, lies at the heart of evolutionary quantitative genetics (i.e., the Lande equation; Lande 1976), and has yielded methods for empirical estimation of linear and quadratic selection gradients acting on quantitative traits in natural populations (starting with the seminal paper by Lande and Arnold 1983).

Below, we provide a quick context for theoretical and empirical studies that have advanced our understanding by either deriving properties of new mutations—using both Gillespie’s molecular landscape and Fisher’s geometric model—or measured the effect of mutations and related these empirical measures to predictions of the above theory.

Fitness landscapes : a non exhaustive bestiary

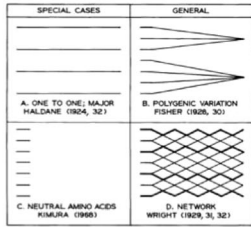


FIG. 1. Four assumptions on the relationship of genotype (left) to phenotype (right).

(a) Wright Evolution 1982

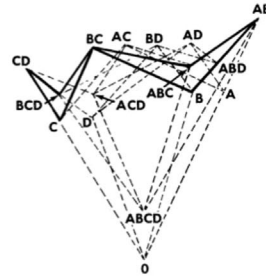
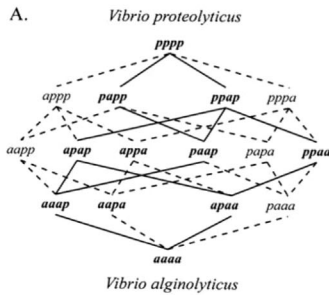
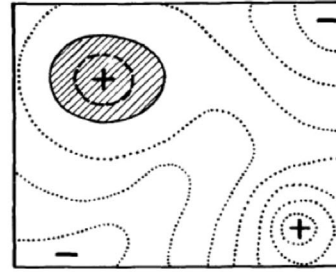
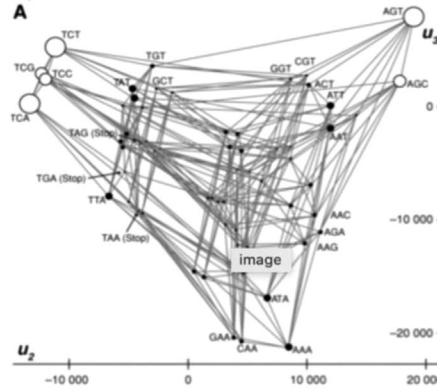


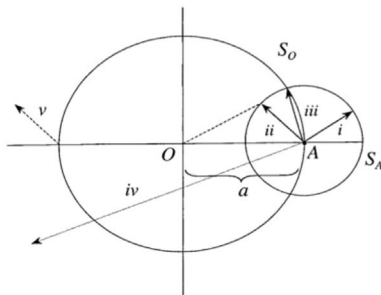
FIG. 3. Total selective values of the 16 homallic genotypes of Fig. 2 according to the contributions indicated there, supplemented by equal semi-dominant pleiotropic effects of genes *A* and *B* (from Wright, 1964b, Fig. 9).



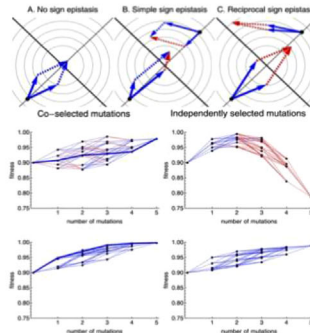
(b) Weinreich et al 2005 Evolution



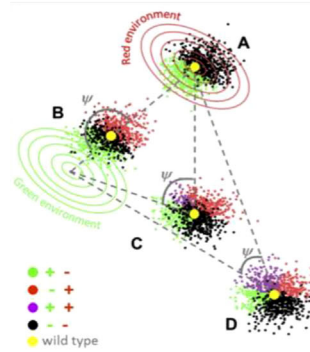
(c) McCandlish 2011 Evolution



(d) Otto & Poon 2000 Evolution



(e) Blanquart et al 2014 Evolution



(f) Martin & Lenormand 2015

**Figure 1.** These are various conceptualizations (and empirical characterization) of fitness landscapes as they appeared in some of the papers listed in this themed virtual issue. (A) Original conceptualization of multilocus genotypes and adaptive landscapes from S. Wright (1982). (B) A four-loci empirical fitness landscape from Weinreich et al. (2005). (C) A projection of a theoretical landscape where distance between genotypes reflects the waiting time for evolutionary transitions, from McCandlish (2011). (D) Conceptual figure illustrating fisher's geometric model, depicting the position of a current genotype (A) at a distance *a* to the fitness optimum (O). Here, fitness is determined by two phenotypic dimensions and mutations are represented as vectors (i, ii, iii, iv). Figure from Otto and Poon (2000). (E) Visualization of sign epistasis by Blanquart et al., using the representation introduced in panel D. Red mutations are deleterious and blue ones beneficial. (F) Clouds of mutations away from four possible wild-type genotypes (yellow dots, A, B, C, D) and their joint fitness in two environments (labelled green and red). Mutations are colored by their joint fitness effects (positive or negative) in both environments. Figure from Martin and Lenormand (2015). Note, all figures are originals from previous *Evolution* issues: © 1982 Sewall Wright. *Evolution* © 1982 The Society for the Study of Evolution. © 2000 Otto and Poon. *Evolution* © 2000 The Society for the Study of Evolution. © 2005 Weinreich et al. *Evolution* © 2005 The Society for the Study of Evolution. © 2011 McCandlish *Evolution* © 2011 The Society for the Study of Evolution. © 2014 Blanquart et al. *Evolution* © 2014 The Society for the Study of Evolution. © 2015 Martin and Lenormand *Evolution* © 2015 The Society for the Study of Evolution.

## *Gillespie's Legacy: A Clever Heuristic that Integrates Mutation and Selection*

In Gillespie's mutational landscape, there is no phenotype but just an abstract mutation-to-fitness mapping. By treating evolution as a Markov chain describing successive fixation events, these models facilitate our understanding of complex evolutionary trajectories. Evolutionary accessibility is a property of an entire network of genotypes linked by possible mutational steps between them. The choice between alternative transitions at each step depends both on relative mutation rates and on fixation probabilities, where the latter combine selection coefficients with effective population size.

- Gillespie, J. H. 1984. Molecular evolution over the mutational landscape. *Evolution* 38:1116–1129.
- Gillespie, J. H. 2001. Is the population size of a species relevant to its evolution? *Evolution* 11;55:2161–2169.
- Weinreich, D. M., R. A. Watson, and L. Chao. 2005. Perspective: sign epistasis and genetic constraint on evolutionary trajectories. *Evolution* 59:1165–1174.
- McCandlish, D. M. 2011. Visualizing fitness landscapes. *Evolution* 65:1544–1558.
- Orr, H. A. 2002. The population genetics of adaptation: the adaptation of DNA sequences. *Evolution* 56:1317–1330.
- Bertram, J., K. Gomez, and J. Masel. 2017. Predicting patterns of long-term adaptation and extinction with population genetics. *Evolution* 71:204–214.

## *A Rediscovery/Revival of Fisher's Geometric Model of Adaptation*

Fisher's original model of stabilizing selection on a set of multivariate phenotypes was proposed over 90 years ago (Fisher 1930). It was probably intended as a rhetorical toy: a purely theoretical construct to champion the idea that adaptation of organisms should be seen as "fine tuning" of phenotypes in many dimensions. The model predicts that only mutations of small effects have a sizable probability of being beneficial, and that the number of phenotypic dimensions drastically limits the amount of beneficial mutations (i.e., the more traits a pleiotropic mutation affects, the less likely it is to be beneficial). This toy model was dormant for many years before it was briefly taken up by Kimura who argued that very small mutations were comparatively more likely to be lost early on by drift. Over the last two decades, Fisher's model has been back on the forefront and extensively explored theoretically. This renewal can be traced back to two papers by Orr (1998) and Otto and Poon (2000), which were soon

picked up others. Many of these contributions were published in *Evolution*.

- Orr, H. A. 1998. The population genetics of adaptation: the distribution of factors fixed during adaptive evolution. *Evolution* 52:935–949.
- Poon, A., and S. P. Otto. 2000. Compensating for our load of mutations: freezing the meltdown of small populations. *Evolution* 54:1467–1479.
- Orr, H. A. 2000. Adaptation and the cost of complexity. *Evolution* 54:13–20.
- Martin, G., and T. Lenormand. 2006. A general multivariate extension of Fisher's geometrical model and the distribution of mutation fitness effects across species. *Evolution* 60:893–907.
- Chevin, L. M., G. Martin, and T. Lenormand. 2010. Fisher's model and the genomics of adaptation: restricted pleiotropy, heterogeneous mutation, and parallel evolution. *Evolution* 64:3213–3231.
- Lourenço, J., N. Galtier, and S. Glémin. 2011. Complexity, pleiotropy, and the fitness effect of mutations. *Evolution* 65:1559–1571.
- Blanquart, F., G. Achaz, T. Bataillon, and O. Tenaillon. 2014. Properties of selected mutations and genotypic landscapes under Fisher's geometric model. *Evolution* 68:3537–3554.

## *Applications of Fisher's Geometric Model: The Distribution of Mutations in a Heterogeneous World*

Early theoretical and empirical work often assumed that fitness landscapes were constant, which contrasted metaphorical appropriations: in the Modern Synthesis, G. G. Simpson evoked the idea of the adaptive landscape as a dynamic entity, a "choppy sea" with waves, ridges, and troughs rising, falling, merging, and separating in relentless perpetual motion. The idea that fitness landscapes can be dynamic is also consistent with population responses to frequency-dependent selection (in particular, the idea that populations can be trapped at stable fitness minima [Abrams et al. 1993; Geritz et al. 1998]) or the ways in which mutational and selection patterns can interact to alter landscape features without invoking environmental change (reviewed by Arnold et al. 2008 in the context of *G*-matrices).

Considering models where more than one phenotypic optimum may exist across environments, sexes, and/or generations opens up a myriad of interesting predictions. Recent theoretical papers have explored long standing problems inherent to the genetics of adaptation: for example, how can complex organisms adapt to environmental change? Do mutations that confer adaptation to environment A systematically incur a cost in environment B? What are the consequences of sex-specific selection for

adaptation, the maintenance of variation, or even genetics of speciation?

- Matuszewski, S., J. Hermisson, and M. Kopp. 2014. Fisher's geometric model with a moving optimum. *Evolution* 68:2571–2588.
- Connallon, T., and A. G. Clark. 2015. The distribution of fitness effects in an uncertain world. *Evolution* 69:1610–1618.
- Fraïsse, C., P. A. Gunnarsson, D. Roze, N. Bierne, and J. J. Welch. 2016. The genetics of speciation: insights from Fisher's geometric model. *Evolution* 70:1450–1464.
- Martin, G., and T. Lenormand. 2015. The fitness effect of mutations across environments: Fisher's geometrical model with multiple optima. *Evolution* 69:1433–1447.
- Zajitschek, F., and T. Connallon. 2018. Antagonistic pleiotropy in species with separate sexes, and the maintenance of genetic variation in life-history traits and fitness. *Evolution* 72:1306–1316.
- Yamaguchi, R., and S. P. Otto. 2020. Insights from Fisher's geometric model on the likelihood of speciation under different histories of environmental change. *Evolution* 74:1603–1619.

## *Last but Not Least: Confronting Fitness Landscape Model Predictions with Data*

Over the last 15 years, many empirical estimates of the distribution of fitness effects of new mutations have been motivated by predictions borne out of theoretical papers grounded in Fisher's model or Gillespie's molecular landscape heuristics. A more recent emphasis (see above) has been on trying to evaluate how much the distribution of fitness effects can change across environments and the extent to which fitness landscape models can account for patterns in the data.

- Hietpas, R. T., C. Bank, J. D. Jensen, and D. N. A. Bolon. 2013. Shifting fitness landscapes in response to altered environments. *Evolution* 67:3512–3522.
- Perfeito, L., A. Sousa, T. Bataillon, and I. Gordo. 2014. Rates of fitness decline and rebound suggest pervasive epistasis. *Evolution* 68:150–162.

- Simon, A., N. Bierne, and J. J. Welch. 2018. Coadapted genomes and selection on hybrids: Fisher's geometric model explains a variety of empirical patterns. *Evolution Letters*, 2: 472–498.
- Weng, M.-L., J. Ågren, E. Imbert, H. Nottebrock, M. T. Rutter, and C. B. Fenster. 2020. Fitness effects of mutation in natural populations of *Arabidopsis thaliana* reveal a complex influence of local adaptation. *Evolution* 75:330–348.

### DISCLAIMER

The papers listed here were co-opted as important/central within the two rather narrowly defined research programs described above. Geography, gender of authors, study type, or systems were not determining factors in our selection. Empirical studies are to date confined to a narrow range of tractable experimental systems. Further biases inherent to our selection reflect both the current state of these subfields and our own biases as editors. The papers listed here should be seen as a historical snapshot of the field and their representation in the journal *Evolution*, and a possible starting point for thinking more actively on how to redress existing biases.

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- van Nimwegen, E., Crutchfield, J.P., & Huynen, M. (1999) Neutral evolution of mutational robustness. *Proc. Natl. Acad. Sci. USA*, 96, 9716–9720.
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