

# The dynamical analysis of fitness landscapes

Matteo Smerlak<sup>1</sup>

<sup>1</sup>Max Planck Institute for Mathematics in the Sciences, Leipzig, Germany

June 4, 2020

## Abstract

Growing efforts to measure fitness landscapes in molecular and microbial systems aim to enlighten, and eventually predict, evolutionary trajectories. As in other instances of non-equilibrium dynamics, this task is complicated by the lack of a general optimization principle: depending on their mutation rate, Darwinian populations can alternatively climb the closest fitness peak (survival of the fittest), settle in lower regions with higher mutational robustness (survival of the flattest), or fail to adapt altogether (error catastrophes). Here I establish an equivalence between selection-mutation dynamics in infinite populations and a certain driven diffusion process in type space, from which I derive (i) a general prescription to identify metastable evolutionary states in a complex fitness landscape, as local minima of the effective potential, (ii) a predictive coarse-graining of evolutionary dynamics, based on their basins of attractions and saddles between them, and (iii) a natural evolutionary Lyapunov function. These results apply to any model of evolutionary dynamics, including Eigen’s “quasispecies” and Crow and Kimura’s “paramuse” models. Because the effective potential is computed from the ground state of a quantum Hamiltonian, my approach could stimulate fruitful interactions between evolutionary dynamics, non-equilibrium statistical mechanics and quantum many-body theory.

## Introduction

Darwinian evolution is the motion of populations in the space of all possible heritable types graded by their reproductive value, the fitness landscape (Stadler, 2002; Orr, 2009; Fragata et al., 2019). In Wright’s vivid words, the interaction of selection and variation enables populations to “continually find their way from lower to higher peaks” (Wright, 1932), thereby providing a universal mechanism for open-ended evolution (de Vladar et al., 2017). Thanks to the explosive development of sequencing technologies, fitness landscapes have now been measured in a variety of real molecular (Blanco et al., 2019), viral (Dolan et al., 2018) or microbial (de Visser and Krug, 2014) systems. As a result, the goal of *predicting* evolution no longer appears wholly out of reach (Weinreich, 2006; Lobkovsky and Koonin, 2012; de Visser and Krug, 2014; Lässig et al., 2017; de Visser et al., 2018).

In essence, if we know the topography of the fitness landscape—its peaks, valleys, ridges, etc.—we should be able to compute where a population is likely to move next. Making such predictions from high-resolution fitness assays is a central challenge of quantitative evolutionary theory.

In keeping with Wright’s description of evolution as a hill climbing process, quantitative analysis of empirical fitness landscapes (McCandlish, 2011; Szendro et al., 2013) has so far focused on the distribution of fitness maxima and the length of adaptive (fitness-increasing) walks in genotype space (Kauffman and Levin, 1987; Franke et al., 2011). What these fitness-centric measures fail to capture, however, is the fact that *populations with different mutation rates experience the same fitness landscape differently*. This is already clear if we consider the rate of fitness valley crossings, which strongly depends on the mutation rate (van Nimwegen and Crutchfield, 2000; Weissman et al., 2009) and therefore cannot be computed from topographic data alone. But Eigen’s quasispecies theory (Eigen, 1971)—an infinite-population formalism relevant to molecular and viral evolution (Domingo and Schuster, 2015)—showed that varying mutation rates can also have a *qualitative* effect on evolutionary trajectories, potentially leading to error catastrophes and the loss of adaptation. More subtly, mutational robustness has been shown to evolve neutrally (van Nimwegen et al., 1999) and to sometimes outweigh reproductive rate as a determinant of evolutionary success (“survival of the flattest”) (Wilke et al., 2001; Codoñer et al., 2006). These evolutionary bifurcations are not mere theoretical curiosities: lethal mutagenesis—an effort to push a population beyond its error threshold—is a promising therapeutic strategy against certain viral pathogens (Eigen, 2002; Domingo and Perales, 2019) and perhaps cancer (Solé and Deisboeck, 2004).

These results raise fundamental questions regarding the *dynamical* analysis of fitness landscapes: When is flatter better than fitter? Where are the evolutionary attractors in a given landscape with ruggedness and/or neutrality? What quantity do evolving populations optimize? Can we estimate the time scale before another attractor is visited? More simply, can we predict the future trajectory of an evolving population from its current location, the topography of its landscape, and the mutation rate?

In this paper I outline a mathematical framework to address these questions in large, asexual populations, for both genotypic (discrete, high-dimensional) and phenotypic (continuous, low-dimensional) fitness landscapes. Inspired by Nelson’s stochastic reformulation of quantum dynamics (Nelson, 1966; Yasue, 1978), I show that the selection-mutation process can be understood as a random walk or diffusion in an effective potential—the same kind of dynamics as, say, protein folding kinetics (Bryngelson et al., 1995). This representation reduces the *a priori* difficult problem of identifying evolutionary attractors and dominant trajectories in a complex fitness landscape to the much more familiar problem of Markovian metastability (Hänggi et al., 1990). In contrast with another classical Markovian model of evolution, Gillespie’s adaptive walk model (Gillespie, 1983; Kauffman and Levin, 1987; Sella and Hirsh, 2005), my approach is not restricted to the SSWM

regime and fully accommodates genotypic and/or phenotypic heterogeneity in evolving populations (Gerrish and Lenski, 1998; Park and Krug, 2007). Moreover, because the effective potential integrates fitness and mutational robustness in a single function on the space of types, it is also more suited to analyze—and eventually predict—the dynamics of a population than the bare fitness landscape from which it derives.

## Results

### Selection-mutation dynamics

Consider a fitness landscape  $\Phi = (X, \Delta, \phi)$ , consisting of a space of types  $X$ , a mutation operator  $\Delta$  on  $X$  and a (Malthusian) fitness function  $\phi : X \rightarrow \mathbb{R}$ . The nature of the landscape is left unspecified:  $\Phi$  could be a genotypic landscape, in which case  $X$  will be a finite graph (usually a hypercube or some more general Hamming graph), and  $\Delta$  its Laplacian matrix; or  $\Phi$  could be a “quantitative trait”, phenotypic landscape, and then  $X$  will be a domain of  $\mathbb{R}^d$  and  $\Delta$  a differential operator thereon, usually the Laplacian (if mutational effects are sufficiently small and frequent). We further assume a large asexual population evolving on this landscape according to the continuous-time Crow-Kimura (Crow and Kimura, 1970) selection-mutation equation, which can be linearized to

$$\frac{\partial f_t(x)}{\partial t} = \phi(x)f_t(x) + \mu\Delta f_t(x) + \mathcal{O}(1/N), \quad (1)$$

where  $f_t(x)$  is the (unnormalized) distribution of types  $x \in X$  at time  $t$  and  $\mu$  the mutation rate per individual per unit time. In contrast with previous analytical works which focused on finding exact solutions to (1) (Baake and Wagner, 2001), our goal is to understand the motion of the distribution  $p_t(x)$  in the landscape without making restrictive assumptions on its topography. This is necessary for the predictive analysis of real fitness landscapes, which do not have the symmetries of soluble models. Note that (1) assumes that mutations occur independently of replication events. The results in this paper do not depend on this assumption: we could equally well consider Eigen’s quasispecies model (Eigen et al., 1989), where mutations only arise as replication errors, or indeed any evolutionary model of the form  $\partial_t f_t = A f_t$  with  $A$  an essentially positive operator (i.e. one that preserves the positivity of  $f_t$ ). Finally, the  $\mathcal{O}(1/N)$  term refers to the stochastic effect of genetic drift, which can be neglected when the population size  $N$  is larger than the number of accessible genotypes. The applicability of deterministic models has been discussed extensively in the literature (Eigen et al., 1989; Wilke, 2005), including from an experimental perspective (Domingo and Schuster, 2015).

The linear equation (1) can be solved formally in one of two classical ways—neither of which turns out to be directly useful for the prediction problem. The first approach uses the Feynman-Kac formula to write  $f_t(x)$  as a weighted sum over Brownian paths  $X_t$  (Zel’dovich et al., 1987).

85 Unfortunately, these paths cover the whole fitness landscape, *i.e.* they are not by themselves  
 86 predictive. Alternatively, we can decompose  $f_t(x)$  over a basis of normal modes of the operator  
 87  $A = \mu\Delta + \phi$  and consider the evolution of each component independently (Eigen et al., 1989).  
 88 This reduces (1) to a set of uncoupled growth equations, with the eigenvalues of  $A$  as growth  
 89 rates. Accordingly, evolution is seemingly reduced to the natural selection of clouds of genetically  
 90 related mutants, or “clans” (Eigen et al., 1989). The problem with the latter approach is that,  
 91 of all the modes of  $A$ , only one is positive and can therefore be interpreted as a distribution,  
 92 namely eigenfunction of  $A$  with the largest eigenvalue  $\Lambda$ , aka the “quasispecies” distribution  $Q$ .  
 93 For this reason, quasispecies theory is usually understood to be an equilibrium theory: it is useful  
 94 to characterize the asymptotic selection-mutation balance  $Q = \lim_{t \rightarrow \infty} p_t$ , and in particular to  
 95 determine whether this equilibrium is localized (adaptive) or delocalized (error catastrophe), but  
 96 it cannot help us understand the approach to that equilibrium.

## 97 Effective potential landscape

The key observation of this paper is that knowing  $Q$ —a single eigenfunction of  $A$ —to a good accuracy in fact goes a long way toward understanding evolutionary dynamics *far* from selection-mutation equilibrium. This is because from  $Q$  we can perform a change of variable that dramatically simplifies the analysis of evolutionary dynamics, as follows. Consider the function  $g_t(x) = e^{-\Lambda t} Q(x) f_t(x)$ , from which it is straightforward to reconstruct the type distribution  $f_t(x)$  after solving for  $g_t(x)$ . This function evolves according to

$$\frac{\partial g_t(x)}{\partial t} = L g_t(x) \quad \text{with} \quad L = \text{diag}(Q) (A - \Lambda) \text{diag}(Q)^{-1}. \quad (2)$$

It is easy to check that for any essentially non-negative operator  $A$ , (2) is the forward Kolmogorov equation of a reversible *Markov process* with effective potential

$$U(x) = -2 \log Q(x). \quad (3)$$

98 In the case where  $\Delta$  is the Laplacian operator this process is just a biased random walk/Brownian  
 99 motion. Specifically, for discrete types  $L$  generates nearest-neighbor jumps with transition rate  
 100  $L_{x \rightarrow y} = \mu \exp\left(-\frac{U(y) - U(x)}{2}\right)$ ; for continuous types,  $L$  is the Fokker-Planck operator for a diffusion  
 101 in the potential  $U$ , *i.e.*  $Lq = -\nabla \cdot j$  with  $j = \mu(-\nabla q - q\nabla U)$ .

102 Note that the interpretation of the derived Markov process departs from that of the original  
 103 selection-mutation model in two ways. First,  $Q$  is no longer viewed as coding the asymptotic  
 104 equilibrium between selection and mutation, in which all transients are washed out; instead, (two  
 105 times minus) its logarithm acts a potential landscape, whose role is to prescribe the dynamics *away*  
 106 from equilibrium. Second, we are used to thinking of mutations as adding a random component to

the otherwise deterministic flow of natural selection, with  $\mu$  controlling the strength of the noise. Here, by contrast,  $\mu$  plays the role of (i) an (inverse) time scale, and (ii) a parameter of the effective potential  $U$  which directs the evolution of the density in the space of types  $X$ . The noise component of the process itself has *unit* diffusivity.

What is the benefit of replacing the selection-mutation operator  $A$  by the Markov generator  $L$ ? The answer is that the latter has an inbuilt notion of dominant evolutionary trajectory: from a given type  $x$ , the preferred path is the line of steepest descent of the effective potential  $U$ . Moreover, thanks to the smoothing effect of mutations imprinted in the quasispecies distribution, the potential landscape is far simpler—in particular, less rugged—than the fitness landscape itself. We now illustrate these aspects in more detail.

### Bare vs. effective ruggedness

As already mentioned, a classic approach to the ruggedness of fitness landscapes consists in counting the number of local fitness maxima (Kauffman and Levin, 1987). For instance, in  $NK$  landscapes the expected density of fitness peaks grows from  $2^{-N}$  (additive or “Mount Fuji” landscape) to  $(N + 1)^{-1}$  (uncorrelated or “house of cards” landscape) as the epistasis parameter  $K$  increases from 0 to  $N - 1$ , irrespective of the distribution of fitness components. However, the number of fitness peaks—the *bare* ruggedness of the landscape—is not directly relevant for evolutionary trajectories: at finite mutation rates, a low peak can be indistinguishable from no peak.

The reformulation above shows that the true evolutionary attractors are the local maxima of  $Q$  (local minima of  $U$ ), not those of  $\phi$ . But for a type  $x$  to be a local maximum of  $Q$ , it is not enough that its fitness be greater than that of its one-step mutants. Computing  $Q$  in the forward approximation (Pietracaprina et al., 2016), i.e. by summing only the shortest paths from the global fitness maximum  $x_*$ , we find

$$U(x) \underset{\mu \rightarrow 0}{\sim} U(x_*) - 2 \log \sum_{\pi} \prod_{i \in \pi} \frac{\mu}{\phi(x_*) - \phi(\pi_i)}. \quad (4)$$

This expression shows that for  $x$  to be a local minimum of  $U$ ,  $\phi(x)$  must be greater than  $\phi(x_*) - \mu$ . This condition is typically much more stringent than the requirement that  $x$  be a local fitness maximum; the effective potential landscape is therefore significantly smoother than the fitness landscape. Thus, the number of  $Q$ -maxima of an  $NK$  landscape does not actually increase with  $K$ , but does with the skewness of the distribution of fitness components (data not shown).

## Reduced evolutionary dynamics

Next, the Markovian reformulation immediately suggests a coarse-grained (reduced) representation of evolutionary dynamics, as follows. For each local minimum  $x_\alpha$  of  $U$  we can consider the set of types  $X_\alpha$  from which  $x_\alpha$  can be reached along a  $U$ -decreasing path, its basin of attraction. The potential barrier between two adjacent basins is then given by  $B_{\alpha \rightarrow \beta} = \min_\pi \max_{x \in \pi} [U(x) - U(x_\alpha)]$  where  $\pi$  spans the directed paths connecting  $X_\alpha$  to  $X_\beta$ . According to the standard Arrhenius-Kramers law for the transition time between minima of a potential landscape (Hänggi et al., 1990), the basin  $X_\alpha$  with frequency  $\sum_{x \in X_\alpha} p_t(x)$  is *metastable* if

$$\min_{\beta} B_{\alpha \rightarrow \beta} \gg 1. \quad (5)$$

Large deviation theory further indicates that, of all the possible escapes from  $X_\alpha$  to an adjacent basin, the transition to  $\operatorname{argmin}_{\beta} B_{\alpha \rightarrow \beta}$  is exponentially more likely to happen. This reduction in dynamical complexity is the main result of this paper.

The coarse-grained dynamics can be represented using tools usually applied to energy landscapes, such as the basin hopping graphs (BHG) recently developed in the context of RNA folding (Kucharik et al., 2014). In a nutshell, a BHG is obtained by collapsing the local minima  $x_\alpha$  and their basins of attraction  $X_\alpha$  into nodes and connecting them according to adjacency relations between basins, weighted by the barrier height  $B_{\alpha \rightarrow \beta}$ . This representation is useful for visualizing complex fitness landscapes, as illustrated in Fig. 2.

## An evolutionary Lyapunov function

Finally, the Markovian reformulation provides a novel Lyapunov function for selection-mutation dynamics. An evolutionary Lyapunov function (ELF) traditionally refers to one of two distinct concepts. The first notion of ELF is a monotonic functional of distributions over type space  $X$ ; examples include Fisher’s variance functional in the pure selection regime (Fisher, 1930) or for type-independent mutation rates (Hofbauer and Sigmund, 1998), or Sella and Hirsh’s free fitness functional in the SSWM regime (Sella and Hirsh, 2005) (see also (Jones, 1978)). The second kind of ELF is a monotonic functional of distributions over distributions over type space  $X$  (*i.e.* over allele frequency distributions); Iwasa’s (Iwasa, 1988) and Mustonen and Lässig’s (Mustonen and Lässig, 2010) free fitness functions are of this kind.

Here I introduced a Markovian version of evolutionary dynamics in type space which is not restricted to pure selection or SSWM regimes. Since this Markov processes is reversible, the relative entropy (or Kullback-Leibler divergence)  $D[\cdot \| \cdot]$  with respect to its equilibrium distribution  $\propto e^{-U} = Q^2$

must decrease monotonically in time. This means that

$$F[p_t] = D[\overline{Qp_t} \parallel \overline{Q^2}] \quad (6)$$

is a Lyapunov function for the evolutionary equation (1) for any mutation operator  $\Delta$  and any mutation rate  $\mu$  (Fig. 3). The construction of this ELF follows the same pattern as Iwasa’s and Mustonen and Lässig’s (as a relative entropy), but, unlike theirs but like Fisher’s, results in a functional of distributions over  $X$  and not allele frequency space. Also note that  $F[p_t]$  is not merely an additive correction to mean fitness and thus goes beyond the scope of “free fitness” functions.

## Examples

To illustrate the predictive value of the Markovian formulation of selection-mutation dynamics we now consider two simulated fitness landscapes, chosen such that evolutionary attractors are not easily read off the landscape itself. For further biologically motivated examples see Ref. (Smerlak, 2020), where an interesting link with a Markov process known as the maximal entropy random walk (Burda et al., 2009) is explored.

### Two-dimensional lattice

We begin with a two-dimensional rugged “phenotypic”<sup>1</sup> landscape, generated by sampling values from a Gaussian process with unit correlation length on a  $30 \times 30$  lattice (with periodic boundary conditions). In the realization shown in Fig. 1A, the fitness landscape has a unique global maximum (green dot); this type corresponds to the maximum of the quasispecies  $Q$  for  $\mu \leq 0.02$  (survival of the fittest), but not for higher mutation rates (survival of the flattest), see Fig. 1B.

Predicting the evolution of an initially monomorphic population directly from the topography of  $\phi$  is clearly a difficult proposition. By contrast, examination of the effective potential  $U = -2 \log Q$  (Fig. 1C) immediately reveals the preferred directions for its evolution: the population will go downhill in the potential  $U$ , potentially getting transiently trapped in the basins of its local minima and making transitions to other basins along the lowest saddles separating them. This is indeed the behavior of numerical solutions of the Crow-Kimura equation (Fig. 1C).

### Binary sequences with neutrality

As a simple model of a genotypic landscape with both ruggedness and neutrality, I considered an  $NKp$  landscape (Barnett, 1998) of binary sequences with length  $N = 8$ , epistasis parameter  $K = 6$

---

<sup>1</sup>Phenotypic landscapes are not expected to be rugged the way genotypic landscapes are, at least not in a biological context. I chose this example for the ease of its visualization, as well as for its connection with Anderson localization.



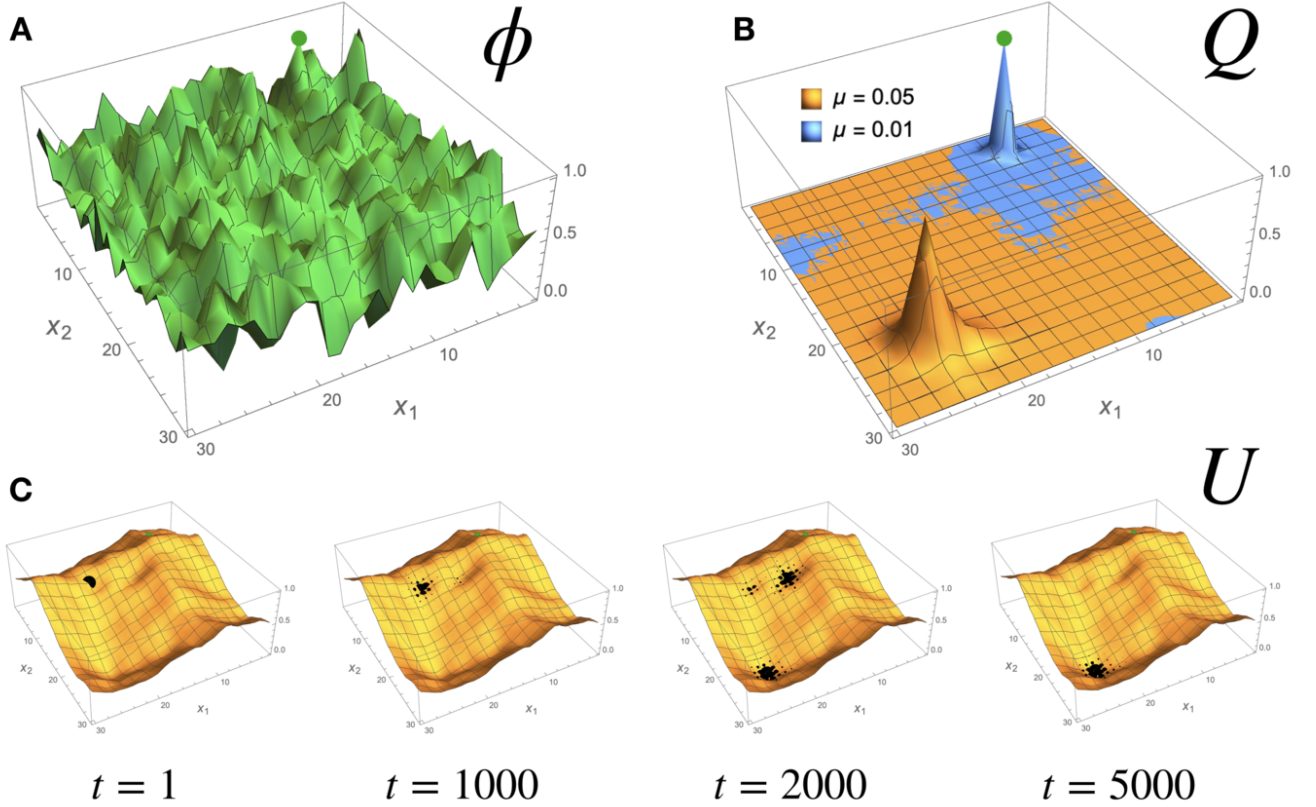


Figure 1: Evolution in a rugged 2d fitness landscape. A: The fitness landscape, obtained by sampling a Gaussian process with unit standard deviation and unit correlation length; the global fitness maximum is indicated by the green dot. It is *a priori* difficult to predict the path taken by a population evolving in this landscape. B: The quasispecies distributions  $Q$  for two different values of the mutation rate  $\mu$ , localized at the fitness peak (low  $\mu$ ) or in some lower but flatter region (high  $\mu$ ). C: The effective potential  $U = -2 \log Q$  for  $\mu = 0.05$  is much smoother than the fitness landscape, with few local minima which act as local attractors for an evolving population (black dots). Note how the population conspicuously moves away from the global fitness maximum.

and neutrality parameter  $p = 0.7$  (details in Methods). The landscape in Fig. 2 has 20 local maxima and an error threshold at  $\mu_c \simeq 0.2$ . Comparing the basin hopping graphs of the fitness landscape  $\phi$  and of the potential landscape  $U$  reveals that most of the complexity of the former is spurious. Moreover, coarse-grained evolutionary trajectories, described by the basin frequencies  $p(X_\alpha)$ , is consistent with the succession of transitions predicated by the basin hopping graph of  $U$ : a population initially concentrated around the genotype 110 (a global fitness maximum) will evolve towards the flatter genotype 179 via the basins of 222 and 95 (Fig. 3A).

One also checks that the Lyapunov function (6) decreases monotonically also when the mean fitness  $\langle \phi \rangle_t$  does not (Fig. 3A) and when the basin frequencies have strongly non-monotonic behavior (Fig.



3B).

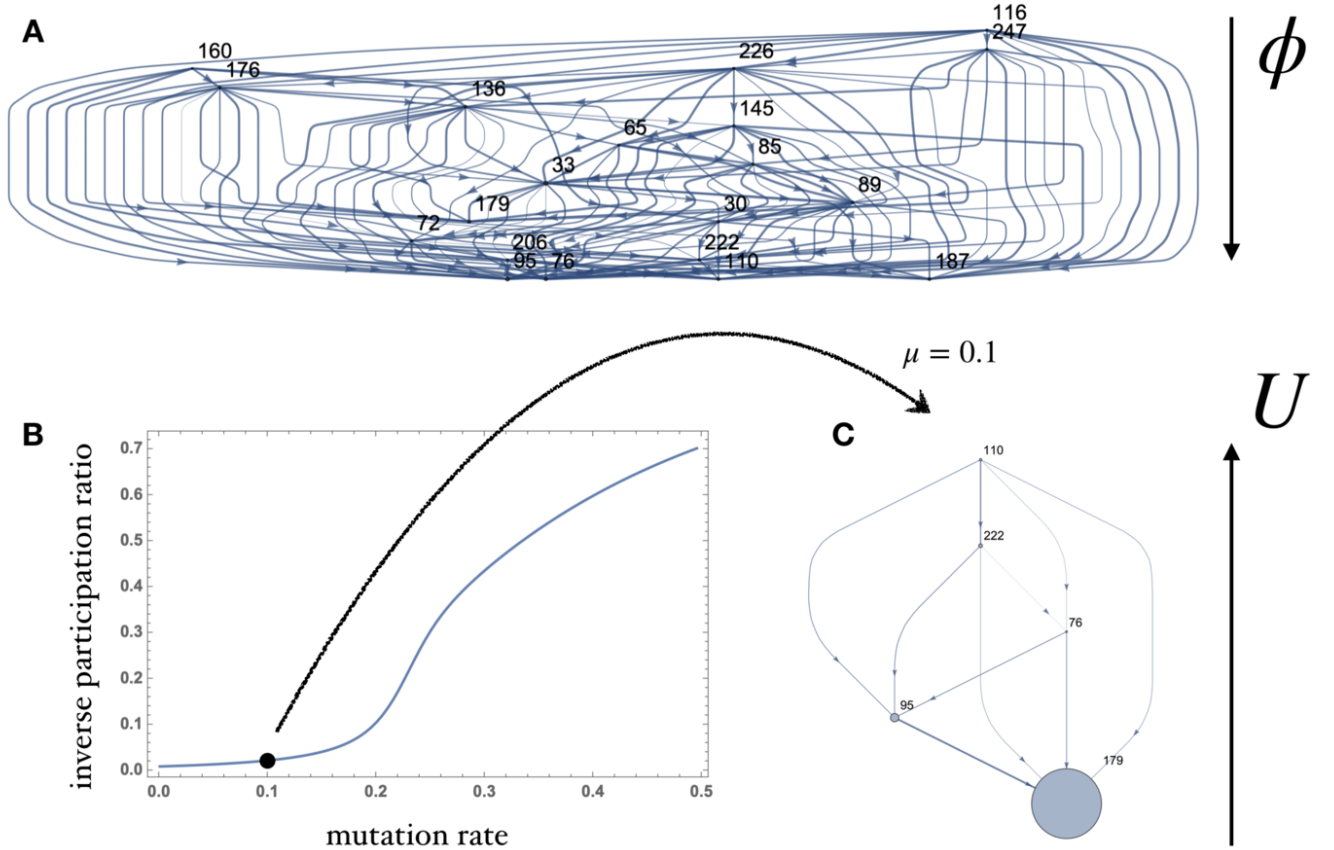


Figure 2: Evolution in an  $NKp$  genotypic landscape with  $2^8 = 256$  types. A: The fitness landscape has 20 local fitness maxima and many saddles between them, making visualization and evolutionary prediction challenging. Here the landscape is represented as a basin hopping graph (BHG), in which nodes are basins of attractions of fitness maxima and edges adjacency relations between basins weighted by the barrier height. B: As the mutation rate passes a threshold at  $\mu \simeq 0.2$  (in units of the maximal fitness difference), the quasispecies distribution delocalizes, as signalled by the inverse participation ratio  $(\sum_x Q(x)^2)^{-1}/|X|$ . C: The BHG for the effective potential (here for  $\mu = 0.1$ ) is much simpler—and immediately predictive, see Fig. 3.

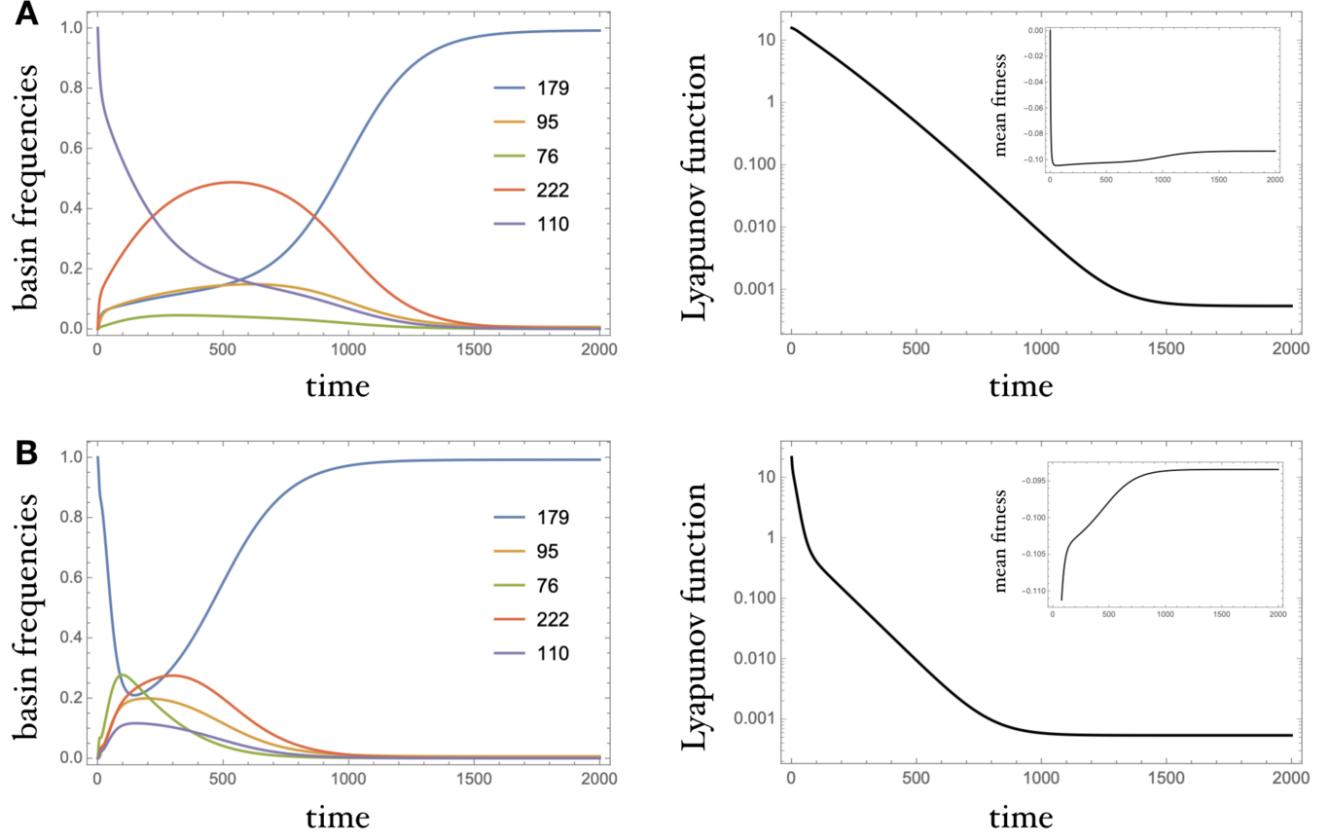


Figure 3: Evolutionary trajectories in the landscape of Fig. 2A, obtained by integration of the Crow-Kimura equation. A: A population initially concentrated in basin 110 moves towards basin 179 through basins 222 and 95, as suggested by the BHG in Fig. 2C. This happens in spite of the fact that 110 is a global fitness maximum and mean fitness decreases in time. B: Here the population starts off concentrated at type 179 and spreads in other basins under the effect of mutations, before returning to the basin of 179 as  $t \rightarrow \infty$ . This non-monotonic behavior of the basin frequency does not prevent the evolutionary Lyapunov function to decrease monotonically.

## Discussion

Evolutionary theory has long benefited from analogies with statistical physics—the other field of science dealing with large, evolving populations—, see *e.g.* (Sella and Hirsh, 2005; Mustonen and Lassig, 2010; de Vladar and Barton, 2011; Smerlak, 2017). More recently, Leuthäusser (Leuthäusser, 1986) and others (Baake et al., 1997; Saakian and Hu, 2004) have highlighted a parallel between evolutionary models in genotype space and certain *quantum* spin systems, which can be leveraged to compute the quasispecies distribution  $Q$  for some special fitness landscapes (Baake and Wagner, 2001). But the scope of the analogy between evolution and non-equilibrium physics is, in fact, much broader: the interplay between selection and mutation is typical of *localization phenomena* in

195 *disordered systems* (Stollmann, 2001), be them classical or quantum. The linearized Crow-Kimura  
 196 equation 1, for instance, is formally identical to the parabolic Anderson model (Zel'dovich et al.,  
 197 1987; Carmona and Molchanov, 1994; König, 2016), a simple model of intermittency in random  
 198 fluid flows; the linearized Eigen model in turn resembles the Bouchaud trap model (Bouchaud,  
 199 1992), a classical model of slow dynamics and ageing in glassy systems. These physical phenomena  
 200 have obvious evolutionary counterparts: the Anderson localization transition corresponds to the  
 201 error threshold; intermittency to epochal or punctuated evolution; tunnelling instantons to fitness  
 202 valley crossings; and ageing to diminishing-return epistasis. The generalization of Nelson's mapping  
 203 of the Schrödinger equation to a diffusion process presented in this paper implies that all are in fact  
 204 unified under the familiar umbrella of Markovian metastability.

205 The value of such analogies is twofold. On the one hand, they bring the large repertoire of results  
 206 and techniques derived in condensed matter and nonequilibrium physics to bear on evolutionary  
 207 dynamics; an example is the forward approximation 4. Conversely, the link between evolution and  
 208 the physics of disordered media can stimulate new work in physics and mathematics. As already  
 209 mentioned, the generator of selection-diffusion dynamics is not always Hermitian (it is not in Eigen's  
 210 model). This suggests that some of the results usually derived for random Schrödinger operators  
 211 can likely be generalized for more general classes of operators, as already emphasized by  
 Altenberg (Altenberg, 2012).

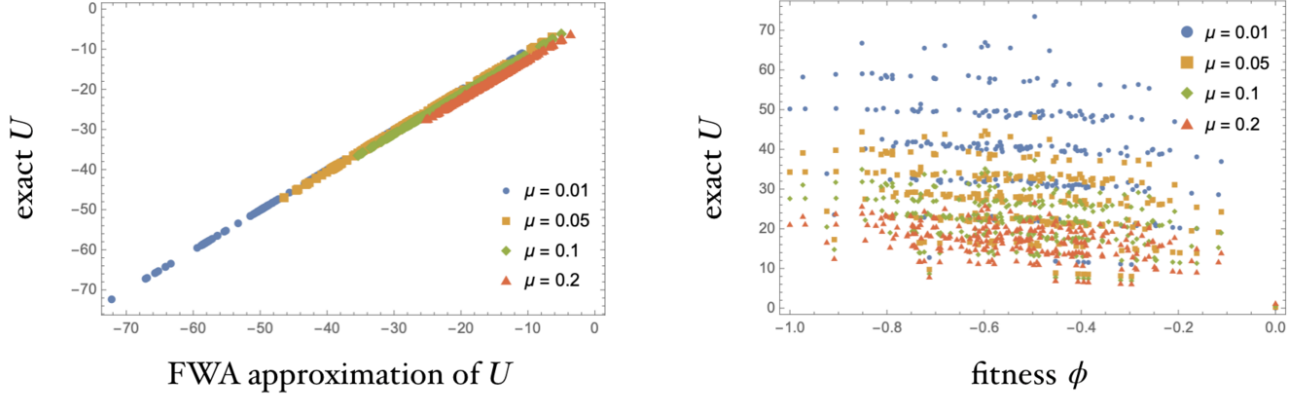


Figure 4: Effective potential for a non-degenerate NK landscape with  $N = 8$  and  $K = 6$ . The FWA approximation familiar from Anderson localization theory gives excellent results, including at large mutation rates (left). By contrast, the bare fitness values  $\phi$  are poorly correlated with the effective potential  $U$  (right). Here mutation rates are given in units such that  $\phi$  ranges from  $-1$  to  $0$ . -

212

## Conclusion

A widely shared understanding of the role of mutations in evolution has them feeding raw material to the fitness-maximizing sieve of natural selection. But when mutation rates are high, as they are in *e.g.* RNA viruses (Drake and Holland, 1999) and likely were in early life (Eigen et al., 1989), evolutionary success requires more than the discovery of a high-fitness mutant genotype: the mutants of the new mutant must also have relatively high fitness, *i.e.* the mutant type must be mutationally robust. The effective potential  $U$  introduced in this paper combines fitness and flatness into a single evolutionary potential—should we call it “fitness”?—which directly determines evolutionary trajectories across the spectrum of mutation rates. I argue that instead of the fitness landscape itself, it is this effective potential that we should analyze, coarse-grain, etc. if we are to predict evolution.

On a conceptual level, the effective potential  $U$  addresses two longstanding questions in evolution: (i) On what time scale (individual generation, infinite lineage) should “fitness” be defined (Rosenberg and Bouchard, 2015)? and (ii) What quantity does evolution optimize (Smith, 1978)? My proposed answers are, respectively: (i) It is fine to define the fitness  $\phi(g)$  of a type  $g$  as reproductive success over one generation, which makes it directly measurable, but one should keep in mind that  $\phi(g)$  is not necessarily a good predictor for the success of a lineage descending from  $g$ —this role is played by the effective potential  $U(g)$ ; and (ii) like other dissipative processes, evolution through selection and mutations minimizes the statistical divergence to its Markovian equilibrium. There is an arrow of time in micro-evolution—just not one that points towards maximal fitness.

## Acknowledgements

I am indebted to M. Kenmoe, A. Klimek, M. Lässig, O. Rivoire and D. Saakian for discussions and feedback. Funding for this work was provided by the Alexander von Humboldt Foundation in the framework of the Sofja Kovalevskaja Award endowed by the German Federal Ministry of Education and Research.

## Methods

### From positive to Markov semigroups

The main result of this paper is best formulated in terms of positive operator semigroups (Bátkai et al., 2017). A positive operator semigroup  $(P_t)_{t \geq 0}$  is one that preserves the positivity of distributions on a space  $X$ , but not their normalization. This is the case of the linear flow  $(P_t) = (e^{At})$  if the

non-diagonal elements of its generator  $A$  are all non-negative (i.e.  $A$  is “essentially non-negative”). Up to the addition of a multiple of the identity, we may further assume that the diagonal elements are also non-negative, i.e.  $A$  is a non-negative operator.

The Perron-Frobenius theorem states that  $A$  has a left eigenvector  $Q$  with simple eigenvalue  $\Lambda$  whose components are all positive in each irreducible component; moreover  $P_t = e^{At}$  converges to the projection operator on  $Q$  as  $t \rightarrow \infty$ . Now, under the conditions above, the operator

$$L = \text{diag}(Q) (A - \Lambda) \text{diag}(Q)^{-1} \quad (7)$$

is the infinitesimal generator of a reversible Markov process on  $X$  with equilibrium distribution  $\propto e^{-U}$  with  $U = -2 \log Q$ . This is easily proved as follows.

If  $X$  is a discrete space (genotypic landscape), we must check that  $L$  satisfies the conditions for a transition rates matrix, namely that  $L$  has non-negative off-diagonal elements and  $\sum_i L_{ij} = 0$ . The former follows from the same property for  $A$  because  $L_{ij} = Q_i A_{ij} Q_j^{-1}$  for  $i \neq j$ . The latter follows from  $Q$  being a left eigenvector of  $A$  with eigenvalue  $\Lambda$ :

$$\sum_i L_{ij} = \sum_i Q_i A_{ij} Q_j^{-1} - \Lambda = \Lambda - \Lambda = 0. \quad (8)$$

Note that, when  $A = \mu \Delta + \phi$  with  $\Delta$  the Laplacian on a graph (such that  $\Delta_{ij} = 1$  when  $i$  and  $j$  are adjacent and zero if  $d(i, j) > 1$ ), then  $L$  generates nearest-neighbor jumps with rate  $L_{j \rightarrow i} = L_{ij} = \mu Q_i Q_j^{-1} = \mu \exp[(U_i - U_j)/2]$ , as stated in the main text.

For the continuous case, consider a domain of  $\mathbb{R}^d$  and assume for simplicity that the mutation operator  $\Delta = \nabla^2$  is the Laplacian in that domain, generating a standard  $d$ -dimensional Brownian motion. In this way  $A$  is a self-adjoint Schrödinger operator. Let  $g_t = Q f_t^\Lambda$ , where  $\partial_t f_t^\Lambda = (A - \Lambda) f_t^\Lambda$ . An explicit computation then shows that  $g_t$  satisfies the continuity equation  $\partial_t g_t = -\nabla \cdot j_t$  with the reversible flux  $j_t = -\mu(\nabla g_t + g_t \nabla U)$ . This is the Fokker-Planck equation for a diffusion process with unit diffusivity and potential  $U$ .

## Model landscapes

The Gaussian process landscape of Fig. 1 is obtained by sampling a vector from the multivariate Gaussian distribution with zero mean and  $L^2 \times L^2$  covariance matrix  $G_{x,y} = e^{-d(x,y)}$  where  $d$  denotes the distance function on the two-dimensional periodic lattice  $\mathbb{Z}_L \times \mathbb{Z}_L$ .

The  $NKp$  fitness landscape over the hypercube  $\{0,1\}^N$  with epistasis (or ruggedness) parameter  $K$ , neutrality parameter  $p$  and component distribution  $\mathcal{D}$  is defined by the formula  $\phi(x) = -\frac{1}{N} \sum_{i=1}^N f_i(x_i, x_{i+1}, \dots, x_{i+K}) b_i(x_i, x_{i+1}, \dots, x_{i+K})$  where the components of the binary string  $x$  are identified cyclically and the values of functions  $f_i, b_i : \{0,1\}^{K+1} \rightarrow \mathbb{R}$  are i.i.d.

samples from  $\mathcal{D}$  and Bernoulli( $1 - p$ ), respectively. Unless specified otherwise it is customary to take  $\mathcal{D} = \text{Uniform}(0, 1)$ . The  $NK$  model is the special case when  $p = 0$ , *i.e.* without neutrality.

## References

- L. Altenberg. Resolvent positive linear operators exhibit the reduction phenomenon. *Proceedings of the National Academy of Sciences*, 109(10):3705–3710, feb 2012. doi: 10.1073/pnas.1113833109. URL <https://doi.org/10.1073/pnas.1113833109>.
- E. Baake, M. Baake, and H. Wagner. Ising Quantum Chain is Equivalent to a Model of Biological Evolution. *Physical Review Letters*, 78(3):559–562, jan 1997. doi: 10.1103/physrevlett.78.559. URL <https://doi.org/10.1103/physrevlett.78.559>.
- Ellen Baake and Holger Wagner. Mutation-selection models solved exactly with methods of statistical mechanics. *Genetical Research*, 78(1):93–117, aug 2001. doi: 10.1017/s0016672301005110. URL <https://doi.org/10.1017/s0016672301005110>.
- Lionel Barnett. Ruggedness and neutrality—the NKp family of fitness landscapes. In *ALIFE Proceedings of the sixth international conference on Artificial life*. MIT Press Cambridge, MA, USA, 1998.
- Celia Blanco, Evan Janzen, Abe Pressman, Ranajay Saha, and Irene A. Chen. Molecular Fitness Landscapes from High-Coverage Sequence Profiling. *Annual Review of Biophysics*, 48(1):1–18, may 2019. doi: 10.1146/annurev-biophys-052118-115333. URL <https://doi.org/10.1146/annurev-biophys-052118-115333>.
- J. P. Bouchaud. Weak ergodicity breaking and aging in disordered systems. *Journal de Physique I*, 2(9):1705–1713, sep 1992. doi: 10.1051/jp1:1992238. URL <https://doi.org/10.1051/jp1:1992238>.
- Joseph D. Bryngelson, José Nelson Onuchic, Nicholas D. Socci, and Peter G. Wolynes. Funnel pathways, and the energy landscape of protein folding: A synthesis. *Proteins: Structure, Function, and Genetics*, 21(3):167–195, mar 1995. doi: 10.1002/prot.340210302. URL <https://doi.org/10.1002/prot.340210302>.
- Z. Burda, J. Duda, J. M. Luck, and B. Waclaw. Localization of the Maximal Entropy Random Walk. *Physical Review Letters*, 102(16), apr 2009. doi: 10.1103/physrevlett.102.160602. URL <https://doi.org/10.1103/physrevlett.102.160602>.
- András Bátkai, Marjeta Kramar Fijavž, and Abdelaziz Rhandi. *Positive Operator Semigroups*. Birkhäuser, 2017.

- René A. Carmona and S. A. Molchanov. Parabolic Anderson problem and intermittency. *Memoirs of the American Mathematical Society*, 108(518):0–0, 1994. doi: 10.1090/memo/0518. URL <https://doi.org/10.1090%2Fmemo%2F0518>.
- Francisco M. Codoñer, José-Antonio Darós, Ricard V. Solé, and Santiago F. Elena. The Fittest versus the Flattest: Experimental Confirmation of the Quasispecies Effect with Subviral Pathogens. *PLoS Pathogens*, 2(12):e136, 2006. doi: 10.1371/journal.ppat.0020136. URL <https://doi.org/10.1371%2Fjournal.ppat.0020136>.
- James F. Crow and Motoo Kimura. *An Introduction to Population Genetics Theory*. Harper and Row, New York, 1970.
- J. Arjan G. M. de Visser, Santiago F. Elena, Inês Fragata, and Sebastian Matuszewski. The utility of fitness landscapes and big data for predicting evolution. *Heredity*, 121(5):401–405, aug 2018. doi: 10.1038/s41437-018-0128-4. URL <https://doi.org/10.1038%2Fs41437-018-0128-4>.
- J. Arjan G.M. de Visser and Joachim Krug. Empirical fitness landscapes and the predictability of evolution. *Nature Reviews Genetics*, 15(7):480–490, jun 2014. doi: 10.1038/nrg3744. URL <https://doi.org/10.1038%2Fnrg3744>.
- Harold P. de Vladar and Nicholas H. Barton. The contribution of statistical physics to evolutionary biology. *Trends in Ecology & Evolution*, 26(8):424–432, aug 2011. doi: 10.1016/j.tree.2011.04.002. URL <https://doi.org/10.1016%2Fj.tree.2011.04.002>.
- Harold P. de Vladar, Mauro Santos, and Eörs Szathmáry. Grand Views of Evolution. *Trends in Ecology & Evolution*, 32(5):324–334, may 2017. doi: 10.1016/j.tree.2017.01.008. URL <https://doi.org/10.1016%2Fj.tree.2017.01.008>.
- Patrick T. Dolan, Zachary J. Whitfield, and Raul Andino. Mapping the Evolutionary Potential of RNA Viruses. *Cell Host & Microbe*, 23(4):435–446, apr 2018. doi: 10.1016/j.chom.2018.03.012. URL <https://doi.org/10.1016%2Fj.chom.2018.03.012>.
- Esteban Domingo and Celia Perales. Viral quasispecies. *PLOS Genetics*, 15(10):e1008271, oct 2019. doi: 10.1371/journal.pgen.1008271. URL <https://doi.org/10.1371%2Fjournal.pgen.1008271>.
- Esteban Domingo and Peter Schuster. What Is a Quasispecies? Historical Origins and Current Scope. In *Current Topics in Microbiology and Immunology*, pages 1–22. Springer International Publishing, 2015. doi: 10.1007/82\_2015\_453. URL [https://doi.org/10.1007%2F82\\_2015\\_453](https://doi.org/10.1007%2F82_2015_453).
- J. W. Drake and J. J. Holland. Mutation rates among RNA viruses. *Proceedings of the National Academy of Sciences*, 96(24):13910–13913, nov 1999. doi: 10.1073/pnas.96.24.13910. URL <https://doi.org/10.1073%2Fpnas.96.24.13910>.



- M. Eigen. Error catastrophe and antiviral strategy. *Proceedings of the National Academy of Sciences*, 99(21):13374–13376, oct 2002. doi: 10.1073/pnas.212514799. URL <https://doi.org/10.1073/pnas.212514799>.
- Manfred Eigen. Selforganization of matter and the evolution of biological macromolecules. *Die Naturwissenschaften*, 58(10):465–523, oct 1971. doi: 10.1007/bf00623322. URL <https://doi.org/10.1007/bf00623322>.
- Manfred Eigen, John McCaskill, and Peter Schuster. The Molecular Quasi-Species. *Advances in Chemical Physics*, 75:149–263, mar 1989. doi: 10.1002/9780470141243.ch4. URL <https://doi.org/10.1002/9780470141243.ch4>.
- Ronald Aylmer Fisher. *The genetical theory of natural selection*. Clarendon Press, 1930. doi: 10.5962/bhl.title.27468. URL <https://doi.org/10.5962/bhl.title.27468>.
- Inês Fragata, Alexandre Blanckaert, Marco António Dias Louro, David A. Liberles, and Claudia Bank. Evolution in the light of fitness landscape theory. *Trends in Ecology & Evolution*, 34(1): 69–82, jan 2019. doi: 10.1016/j.tree.2018.10.009. URL <https://doi.org/10.1016/j.tree.2018.10.009>.
- Jasper Franke, Alexander Klözer, J. Arjan G. M. de Visser, and Joachim Krug. Evolutionary Accessibility of Mutational Pathways. *PLoS Computational Biology*, 7(8):e1002134, aug 2011. doi: 10.1371/journal.pcbi.1002134. URL <https://doi.org/10.1371/journal.pcbi.1002134>.
- Philip J. Gerrish and Richard E. Lenski. The fate of competing beneficial mutations in an asexual population. In *Mutation and Evolution*, pages 127–144. Springer Netherlands, 1998. doi: 10.1007/978-94-011-5210-5\_12. URL [https://doi.org/10.1007/978-94-011-5210-5\\_12](https://doi.org/10.1007/978-94-011-5210-5_12).
- John H. Gillespie. A simple stochastic gene substitution model. *Theoretical Population Biology*, 23(2):202–215, apr 1983. doi: 10.1016/0040-5809(83)90014-x. URL [https://doi.org/10.1016/0040-5809\(83\)90014-x](https://doi.org/10.1016/0040-5809(83)90014-x).
- Josef Hofbauer and Karl Sigmund. *Evolutionary Games and Population Dynamics*. Cambridge University Press, 1998.
- Peter Hänggi, Peter Talkner, and Michal Borkovec. Reaction-rate theory: fifty years after Kramers. *Reviews of Modern Physics*, 62(2):251–341, apr 1990. doi: 10.1103/revmodphys.62.251. URL <https://doi.org/10.1103/revmodphys.62.251>.
- Yoh Iwasa. Free fitness that always increases in evolution. *Journal of Theoretical Biology*, 135(3):265–281, dec 1988. doi: 10.1016/s0022-5193(88)80243-1. URL [https://doi.org/10.1016/s0022-5193\(88\)80243-1](https://doi.org/10.1016/s0022-5193(88)80243-1).
- B. L. Jones. Some principles governing selection in self-reproducing macromolecular systems.

- Journal of Mathematical Biology*, 6(2):169–175, jul 1978. doi: 10.1007/bf02450787. URL <https://doi.org/10.1007%2Fbf02450787>.
- Stuart Kauffman and Simon Levin. Towards a general theory of adaptive walks on rugged landscapes. *Journal of Theoretical Biology*, 128(1):11–45, sep 1987. doi: 10.1016/s0022-5193(87)80029-2. URL <https://doi.org/10.1016%2Fs0022-5193%2887%2980029-2>.
- Marcel Kucharič, Ivo L. Hofacker, Peter F. Stadler, and Jing Qin. Basin Hopping Graph: a computational framework to characterize RNA folding landscapes. *Bioinformatics*, 30(14):2009–2017, mar 2014. doi: 10.1093/bioinformatics/btu156. URL <https://doi.org/10.1093%2Fbioinformatics%2Fbtu156>.
- Wolfgang König. *The Parabolic Anderson Model*. Springer International Publishing, 2016. doi: 10.1007/978-3-319-33596-4. URL <https://doi.org/10.1007%2F978-3-319-33596-4>.
- Ira Leuthäusser. An exact correspondence between Eigen’s evolution model and a two-dimensional Ising system. *The Journal of Chemical Physics*, 84(3):1884–1885, feb 1986. doi: 10.1063/1.450436. URL <https://doi.org/10.1063%2F1.450436>.
- Alexander E. Lobkovsky and Eugene V. Koonin. Replaying the Tape of Life: Quantification of the Predictability of Evolution. *Frontiers in Genetics*, 3, 2012. doi: 10.3389/fgene.2012.00246. URL <https://doi.org/10.3389%2Ffgene.2012.00246>.
- Michael Lässig, Ville Mustonen, and Aleksandra M. Walczak. Predicting evolution. *Nature Ecology & Evolution*, 1(3), feb 2017. doi: 10.1038/s41559-017-0077. URL <https://doi.org/10.1038%2Fs41559-017-0077>.
- David M. McCandlish. Visualizing fitness landscapes. *Evolution*, 65(6):1544–1558, mar 2011. doi: 10.1111/j.1558-5646.2011.01236.x. URL <https://doi.org/10.1111%2Fj.1558-5646.2011.01236.x>.
- V. Mustonen and M. Lässig. Fitness flux and ubiquity of adaptive evolution. *Proceedings of the National Academy of Sciences*, 107(9):4248–4253, feb 2010. doi: 10.1073/pnas.0907953107. URL <https://doi.org/10.1073%2Fpnas.0907953107>.
- Edward Nelson. Derivation of the Schrödinger Equation from Newtonian Mechanics. *Physical Review*, 150(4):1079–1085, oct 1966. doi: 10.1103/physrev.150.1079. URL <https://doi.org/10.1103%2Fphysrev.150.1079>.
- H. Allen Orr. Fitness and its role in evolutionary genetics. *Nature Reviews Genetics*, 10(8):531–539, aug 2009. doi: 10.1038/nrg2603. URL <https://doi.org/10.1038%2Fnrg2603>.
- S.-C. Park and J. Krug. Clonal interference in large populations. *Proceedings of the National*

- Academy of Sciences*, 104(46):18135–18140, nov 2007. doi: 10.1073/pnas.0705778104. URL <https://doi.org/10.1073%2Fpnas.0705778104>.
- Francesca Pietracaprina, Valentina Ros, and Antonello Scardicchio. Forward approximation as a mean-field approximation for the Anderson and many-body localization transitions. *Physical Review B*, 93(5), feb 2016. doi: 10.1103/physrevb.93.054201. URL <https://doi.org/10.1103%2Fphysrevb.93.054201>.
- Alexander Rosenberg and Frederic Bouchard. Fitness. In *The Stanford Encyclopedia of Philosophy*. Edward N. Zalta (ed.), 2015.
- David Saakian and Chin-Kun Hu. Eigen model as a quantum spin chain: Exact dynamics. *Physical Review E*, 69(2), feb 2004. doi: 10.1103/physreve.69.021913. URL <https://doi.org/10.1103%2Fphysreve.69.021913>.
- G. Sella and A. E. Hirsh. The application of statistical physics to evolutionary biology. *Proceedings of the National Academy of Sciences*, 102(27):9541–9546, jun 2005. doi: 10.1073/pnas.0501865102. URL <https://doi.org/10.1073%2Fpnas.0501865102>.
- Matteo Smerlak. Natural Selection as Coarsening. *Journal of Statistical Physics*, 172(1):105–113, nov 2017. doi: 10.1007/s10955-017-1925-5. URL <https://doi.org/10.1007%2Fs10955-017-1925-5>.
- Matteo Smerlak. Localization of neutral evolution: selection for mutational robustness and the maximal entropy random walk. jan 2020. doi: 10.1101/2020.01.28.922831. URL <https://doi.org/10.1101%2F2020.01.28.922831>.
- J M Smith. Optimization Theory in Evolution. *Annual Review of Ecology and Systematics*, 9(1): 31–56, nov 1978. doi: 10.1146/annurev.es.09.110178.000335. URL <https://doi.org/10.1146%2Fannurev.es.09.110178.000335>.
- Ricard V. Solé and Thomas S. Deisboeck. An error catastrophe in cancer? *Journal of Theoretical Biology*, 228(1):47–54, may 2004. doi: 10.1016/j.jtbi.2003.08.018. URL <https://doi.org/10.1016%2Fj.jtbi.2003.08.018>.
- Peter F. Stadler. Fitness landscapes. In *Biological Evolution and Statistical Physics*, pages 183–204. Springer Berlin Heidelberg, 2002. doi: 10.1007/3-540-45692-9\_10. URL [https://doi.org/10.1007%2F3-540-45692-9\\_10](https://doi.org/10.1007%2F3-540-45692-9_10).
- Peter Stollmann. *Caught by Disorder*. Birkhäuser Boston, 2001. doi: 10.1007/978-1-4612-0169-4. URL <https://doi.org/10.1007%2F978-1-4612-0169-4>.
- Ivan G Szendro, Martijn F Schenk, Jasper Franke, Joachim Krug, and J Arjan G M de Visser. Quantitative analyses of empirical fitness landscapes. *Journal of Statistical Mechanics: Theory*

- and *Experiment*, 2013(01):P01005, jan 2013. doi: 10.1088/1742-5468/2013/01/p01005. URL <https://doi.org/10.1088/2F1742-5468/2F2013/2F01/2Fp01005>.
- E van Nimwegen and J Crutchfield. Metastable Evolutionary Dynamics: Crossing Fitness Barriers or Escaping via Neutral Paths? *Bulletin of Mathematical Biology*, 62(5):799–848, sep 2000. doi: 10.1006/bulm.2000.0180. URL <https://doi.org/10.1006/2Fbulm.2000.0180>.
- E. van Nimwegen, J. P. Crutchfield, and M. Huynen. Neutral evolution of mutational robustness. *Proceedings of the National Academy of Sciences*, 96(17):9716–9720, aug 1999. doi: 10.1073/pnas.96.17.9716. URL <https://doi.org/10.1073/2Fpnas.96.17.9716>.
- D. M. Weinreich. Darwinian Evolution Can Follow Only Very Few Mutational Paths to Fitter Proteins. *Science*, 312(5770):111–114, apr 2006. doi: 10.1126/science.1123539. URL <https://doi.org/10.1126/2Fscience.1123539>.
- Daniel B. Weissman, Michael M. Desai, Daniel S. Fisher, and Marcus W. Feldman. The rate at which asexual populations cross fitness valleys. *Theoretical Population Biology*, 75(4):286–300, jun 2009. doi: 10.1016/j.tpb.2009.02.006. URL <https://doi.org/10.1016/2Fj.tpb.2009.02.006>.
- Claus O Wilke. Quasispecies theory in the context of population genetics. *BMC Evolutionary Biology*, 5(1):44, 2005. doi: 10.1186/1471-2148-5-44. URL <https://doi.org/10.1186/2F1471-2148-5-44>.
- Claus O. Wilke, Jia Lan Wang, Charles Ofria, Richard E. Lenski, and Christoph Adami. Evolution of digital organisms at high mutation rates leads to survival of the flattest. *Nature*, 412(6844):331–333, jul 2001. doi: 10.1038/35085569. URL <https://doi.org/10.1038/2F35085569>.
- Sewal Wright. The roles of mutation, inbreeding, crossbreeding and selection in evolution. *Proceedings of the Sixth International Congress on Genetics*, 1:356–366, 1932.
- Kunio Yasue. Detailed Time-Dependent Description of Tunneling Phenomena Arising from Stochastic Quantization. *Physical Review Letters*, 40(11):665–667, mar 1978. doi: 10.1103/physrevlett.40.665. URL <https://doi.org/10.1103/2Fphysrevlett.40.665>.
- Ya B Zel'dovich, S A Molchanov, A A Ruzmaïkin, and Dmitrii D Sokolov. Intermittency in random media. *Soviet Physics Uspekhi*, 30(5):353–369, may 1987. doi: 10.1070/pu1987v030n05abeh002867. URL <https://doi.org/10.1070/2Fpu1987v030n05abeh002867>.