

The dynamical analysis of fitness landscapes

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1 **Abstract**

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

15 **Introduction**

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

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

28 In keeping with Wright’s description of evolution as a hill climbing process, quantitative analysis
29 of empirical fitness landscapes (McCandlish, 2011; Szendro et al., 2013) has so far focused on the
30 distribution of fitness maxima and the length of adaptive (fitness-increasing) walks in genotype
31 space (Kauffman and Levin, 1987; Franke et al., 2011). What these fitness-centric measures fail
32 to capture, however, is the fact that *populations with different mutation rates experience the same*
33 *fitness landscape differently*. This is already clear if we consider the rate of fitness valley crossings,
34 which strongly depends on the mutation rate (van Nimwegen and Crutchfield, 2000; Weissman et al.,
35 2009) and therefore cannot be computed from topographic data alone. But Eigen’s quasispecies
36 theory (Eigen, 1971)—an infinite-population formalism relevant to molecular and viral evolution
37 (Domingo and Schuster, 2015)—showed that varying mutation rates can also have a *qualitative*
38 effect on evolutionary trajectories, potentially leading to error catastrophes and the loss of adapta-
39 tion. More subtly, mutational robustness has been shown to evolve neutrally (van Nimwegen et al.,
40 1999) and to sometimes outweigh reproductive rate as a determinant of evolutionary success (“sur-
41 vival of the flattest”) (Wilke et al., 2001; Codoñer et al., 2006). These evolutionary bifurcations
42 are not mere theoretical curiosities: lethal mutagenesis—an effort to push a population beyond its
43 error threshold—is a promising therapeutic strategy against certain viral pathogens (Eigen, 2002;
44 Domingo and Perales, 2019) and perhaps cancer (Solé and Deisboeck, 2004).

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

51 In this paper I outline a mathematical framework to address these questions in large, asexual popula-
52 tions, for both genotypic (discrete, high-dimensional) and phenotypic (continuous, low-dimensional)
53 fitness landscapes. Inspired by Nelson’s stochastic reformulation of quantum dynamics (Nelson,
54 1966; Yasue, 1978), I show that the selection-mutation process can be understood as a random
55 walk or diffusion in an effective potential—the same kind of dynamics as, say, protein folding
56 kinetics (Bryngelson et al., 1995). This representation reduces the *a priori* difficult problem of
57 identifying evolutionary attractors and dominant trajectories in a complex fitness landscape to the
58 much more familiar problem of Markovian metastability (Hänggi et al., 1990). In contrast with
59 another classical Markovian model of evolution, Gillespie’s adaptive walk model (Gillespie, 1983;
60 Kauffman and Levin, 1987; Sella and Hirsh, 2005), my approach is not restricted to the SSWM

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

66 Results

67 Selection-mutation dynamics

Consider a fitness landscape $\Phi = (X, \Delta, \phi)$, consisting of a space of types X , a mutation operator Δ on X and a (Malthusian) fitness function $\phi : X \rightarrow \mathbb{R}$. The nature of the landscape is left unspecified: Φ could be a genotypic landscape, in which case X will be a finite graph (usually a hypercube or some more general Hamming graph), and Δ its Laplacian matrix; or Φ could be a “quantitative trait”, phenotypic landscape, and then X will be a domain of \mathbb{R}^d and Δ 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

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

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

82 The linear equation (1) can be solved formally in one of two classical ways—neither of which
83 turns out to be directly useful for the prediction problem. The first approach uses the Feynman-
84 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 Λ , 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 dra-
 matically 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 Δ 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

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

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

117 **Bare vs. effective ruggedness**

118 As already mentioned, a classic approach to the ruggedness of fitness landscapes consists in counting
 119 the number of local fitness maxima (Kauffman and Levin, 1987). For instance, in NK landscapes
 120 the expected density of fitness peaks grows from 2^{-N} (additive or “Mount Fuji” landscape) to
 121 $(N + 1)^{-1}$ (uncorrelated or “house of cards” landscape) as the epistasis parameter K increases
 122 from 0 to $N - 1$, irrespective of the distribution of fitness components. However, the number
 123 of fitness peaks—the *bare* ruggedness of the landscape—is not directly relevant for evolutionary
 124 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 ϕ . 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

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

125 This expression shows that that for x to be a local minimum of U , $\phi(x)$ must be greater than
 126 $\phi(x_*) - \mu$. This condition is typically much more stringent than the requirement that x be a local
 127 fitness maximum; the effective potential landscape is therefore significantly smoother than the
 128 fitness landscape. Thus, the number of Q -maxima of an NK landscape does not actually increase
 129 with K , but does with the skewness of the distribution of fitness components (data not shown).

130 **Reduced evolutionary dynamics**

Next, the Markovian reformulation immediately suggests a coarse-grained (reduced) representation of evolutionary dynamics, as follows. For each local minimum x_α of U we can consider the set of types X_α from which x_α 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 π spans the directed paths connecting X_α to X_β . According to the standard Arrhenius-Kramers law for the transition time between minima of a potential landscape (Hänggi et al., 1990), the basin X_α with frequency $\sum_{x \in X_\alpha} p_t(x)$ is *metastable* if

$$\min_{\beta} B_{\alpha \rightarrow \beta} \gg 1. \tag{5}$$

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

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

140 **An evolutionary Lyapunov function**

141 Finally, the Markovian reformulation provides a novel Lyapunov function for selection-mutation
142 dynamics. An evolutionary Lyapunov function (ELF) traditionally refers to one of two distinct
143 concepts. The first notion of ELF is a monotonic functional of distributions over type space X ;
144 examples include Fisher’s variance functional in the pure selection regime (Fisher, 1930) or for
145 type-independent mutation rates (Hofbauer and Sigmund, 1998), or Sella and Hirsh’s free fitness
146 functional in the SSWM regime (Sella and Hirsh, 2005) (see also (Jones, 1978)). The second kind
147 of ELF is a monotonic functional of distributions over distributions over type space X (*i.e.* over
148 allele frequency distributions); Iwasa’s (Iwasa, 1988) and Mustonen and Lässig’s (Mustonen and
149 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) $D[\cdot \parallel \cdot]$ with respect to its equilibrium distribution $\propto e^{-U} = Q^2$

must decrease monotonically in time. This means that

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

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

155 Examples

156 To illustrate the predictive value of the Markovian formulation of selection-mutation dynamics we
157 now consider two simulated fitness landscapes, chosen such that evolutionary attractors are not
158 easily read off the landscape itself. For further biologically motivated examples see Ref. (Smerlak,
159 2020), where an interesting link with a Markov process known as the maximal entropy random
160 walk (Burda et al., 2009) is explored.

161 Two-dimensional lattice

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

167 Predicting the evolution of an initially monomorphic population directly from the topography of ϕ is
168 clearly a difficult proposition. By contrast, examination of the effective potential $U = -2 \log Q$ (Fig.
169 1C) immediately reveals the preferred directions for its evolution: the population will go downhill
170 in the potential U , potentially getting transiently trapped in the basins of its local minima and
171 making transitions to other basins along the lowest saddles separating them. This is indeed the
172 behavior of numerical solutions of the Crow-Kimura equation (Fig. 1C).

173 Binary sequences with neutrality

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

¹Phenotypic 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.

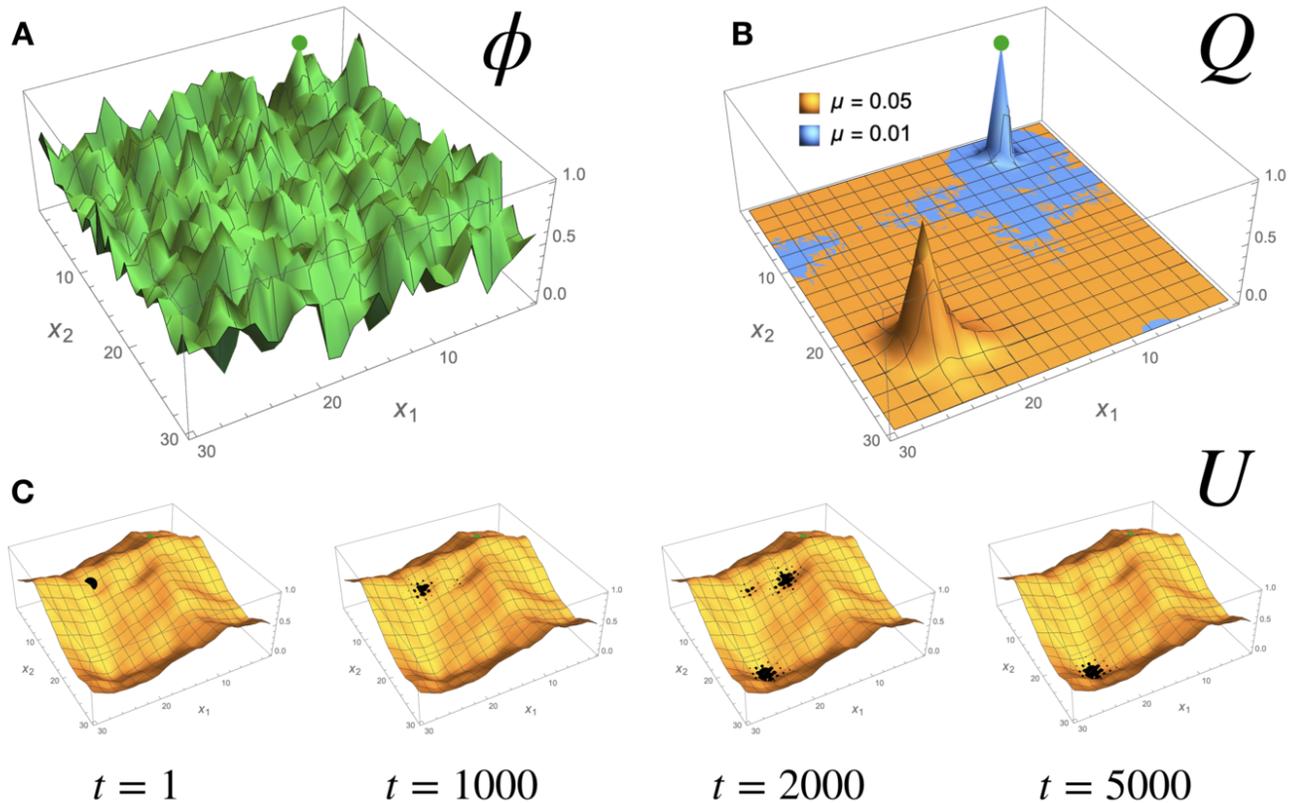


Figure 1: Evolution in a rugged 2d fitness landscape. A: The fitness landscape, obtained by sampling a Gaussian process with unit standard deviation and unit correlation length; the global fitness maximum is indicated by the green dot. It is *a priori* difficult to predict the path taken by a population evolving in this landscape. B: The quasispecies distributions Q for two different values of the mutation rate μ , localized at the fitness peak (low μ) or in some lower but flatter region (high μ). 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.

176 and neutrality parameter $p = 0.7$ (details in Methods). The landscape in Fig. 2 has 20 local
 177 maxima and an error threshold at $\mu_c \simeq 0.2$. Comparing the basin hopping graphs of the fitness
 178 landscape ϕ and of the potential landscape U reveals that most of the complexity of the former
 179 is spurious. Moreover, coarse-grained evolutionary trajectories, described by the basin frequencies
 180 $p(X_\alpha)$, is consistent with the succession of transitions predicated by the basin hopping graph of U :
 181 a population initially concentrated around the genotype 110 (a global fitness maximum) will evolve
 182 towards the flatter genotype 179 via the basins of 222 and 95 (Fig. 3A).

183 One also checks that the Lyapunov function (6) decreases monotonically also when the mean fitness
 184 $\langle \phi \rangle_t$ does not (Fig. 3A) and when the basin frequencies have strongly non-monotonic behavior (Fig.

3B).

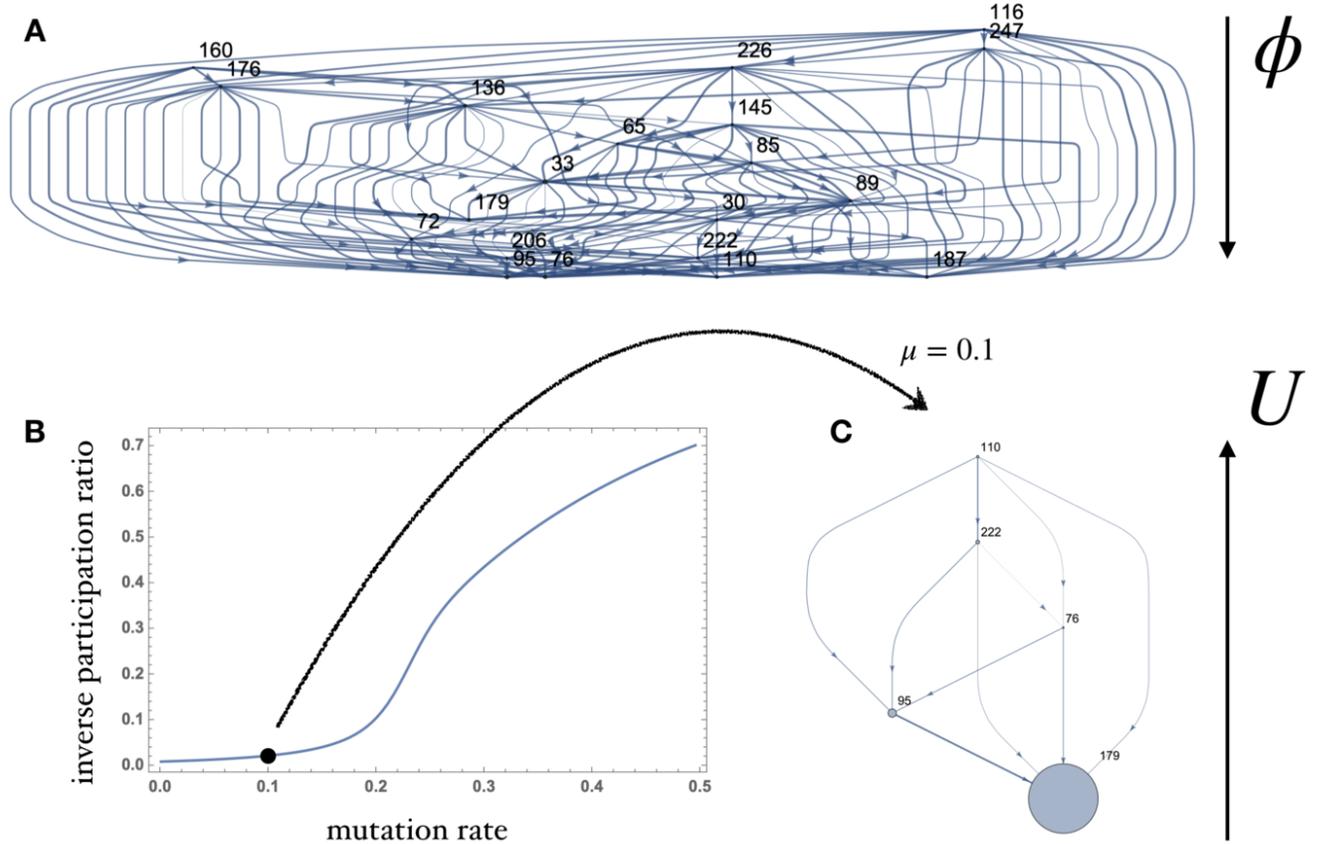


Figure 2: Evolution in an NKp genotypic landscape with $2^8 = 256$ types. A: The fitness landscape has 20 local fitness maxima and many saddles between them, making visualization and evolutionary prediction challenging. Here the landscape is represented as a basin hopping graph (BHG), in which nodes 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.

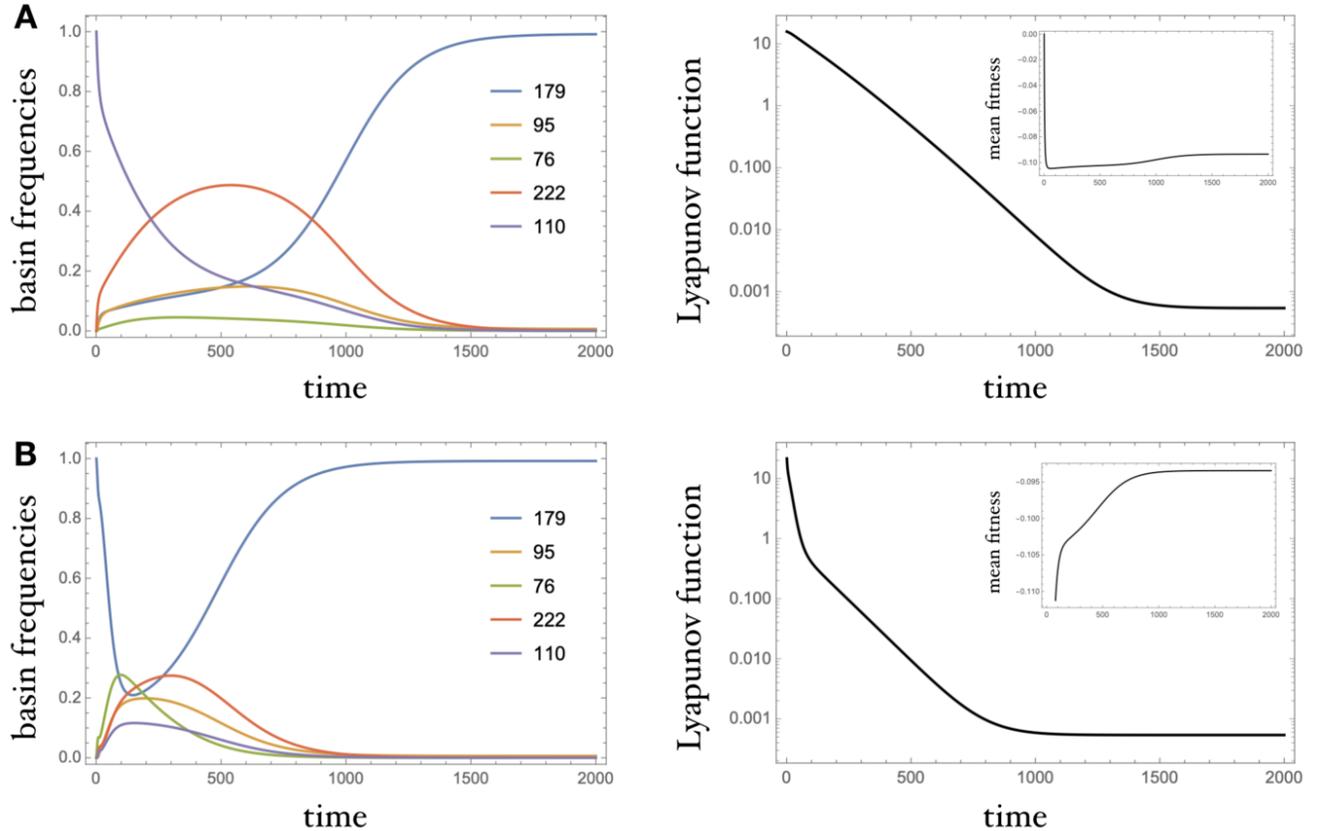


Figure 3: Evolutionary trajectories in the landscape of Fig. 2A, obtained by integration of the Crow-Kimura equation. A: A population initially concentrated in basin 110 moves towards basin 179 through basins 222 and 95, as suggested by the BHG in Fig. 2C. This happens in spite of the fact that 110 is 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.

186 Discussion

187 Evolutionary theory has long benefited from analogies with statistical physics—the other field of
 188 science dealing with large, evolving populations—, see *e.g.* (Sella and Hirsh, 2005; Mustonen and
 189 Lassig, 2010; de Vladar and Barton, 2011; Smerlak, 2017). More recently, Leuthäusser (Leuthäusser,
 190 1986) and others (Baake et al., 1997; Saakian and Hu, 2004) have highlighted a parallel between
 191 evolutionary models in genotype space and certain *quantum* spin systems, which can be leveraged
 192 to compute the quasispecies distribution Q for some special fitness landscapes (Baake and Wagner,
 193 2001). But the scope of the analogy between evolution and non-equilibrium physics is, in fact,
 194 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 classes of operators, as already emphasized by
 Altenberg (Altenberg, 2012).

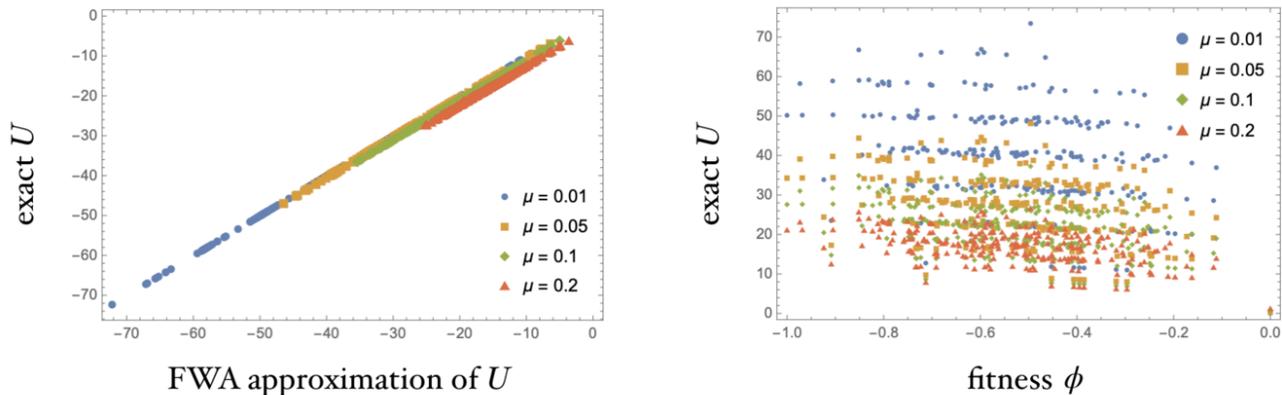


Figure 4: Effective potential for a non-degenerate NK landscape with $N = 8$ and $K = 6$. The FWA approximation familiar from Anderson localization theory gives excellent results, including at large mutation rates (left). By contrast, the bare fitness values ϕ are poorly correlated with the effective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

212

213 Conclusion

214 A widely shared understanding of the role of mutations in evolution has them feeding raw ma-
215 terial to the fitness-maximizing sieve of natural selection. But when mutation rates are high, as
216 they are in *e.g.* RNA viruses (Drake and Holland, 1999) and likely were in early life (Eigen et al.,
217 1989), evolutionary success requires more than the discovery of a high-fitness mutant genotype: the
218 mutants of the new mutant must also have relatively high fitness, *i.e.* the mutant type must be
219 mutationally robust. The effective potential U introduced in this paper combines fitness and flat-
220 ness into a single evolutionary potential—should we call it “fitness”?—which directly determines
221 evolutionary trajectories across the spectrum of mutation rates. I argue that instead of the fitness
222 landscape itself, it is this effective potential that we should analyze, coarse-grain, etc. if we are to
223 predict evolution.

224 On a conceptual level, the effective potential U addresses two longstanding questions in evo-
225 lution: (i) On what time scale (individual generation, infinite lineage) should “fitness” be de-
226 fined (Rosenberg and Bouchard, 2015)? and (ii) What quantity does evolution optimize (Smith,
227 1978)? My proposed answers are, respectively: (i) It is fine to define the fitness $\phi(g)$ of a type g as
228 reproductive success over one generation, which makes it directly measurable, but one should keep
229 in mind that $\phi(g)$ is not necessarily a good predictor for the success of a lineage descending from g —
230 this role is played by the effective potential $U(g)$; and (ii) like other dissipative processes, evolution
231 through selection and mutations minimizes the statistical divergence to its Markovian equilibrium.
232 There is an arrow of time in micro-evolution—just not one that points towards maximal fitness.

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237 and Research.

238 Methods

239 From positive to Markov semigroups

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

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

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

246 is the infinitesimal generator of a reversible Markov process on X with equilibrium distribution
 247 $\propto e^{-U}$ 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 Λ :

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

248 Note that, when $A = \mu\Delta + \phi$ with Δ the Laplacian on a graph (such that $\Delta_{ij} = 1$ when i
 249 and j are adjacent and zero if $d(i, j) > 1$), then L generates nearest-neighbor jumps with rate
 250 $L_{j \rightarrow i} = L_{ij} = \mu Q_i Q_j^{-1} = \mu \exp[(U_i - U_j)/2]$, as stated in the main text.

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

257 Model landscapes

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

261 The NKp fitness landscape over the hypercube $\{0, 1\}^N$ with epistasis (or ruggedness) para-
 262 meter K , neutrality parameter p and component distribution \mathcal{D} is defined by the formula
 263 $\phi(x) = -\frac{1}{N} \sum_{i=1}^N f_i(x_i, x_{i+1}, \dots, x_{i+K}) b_i(x_i, x_{i+1}, \dots, x_{i+K})$ where the components of the bi-
 264 nary 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.

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

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