

# Supporting Information

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Here, we present a more self-contained derivation of the fitness-flux theorem and describe the numerical simulations presented in the main text.

**Genotype and Allele Frequencies.** We consider the evolution of a population with  $k$  possible genotypes  $\mathbf{a}_\alpha$  ( $\alpha = 1, \dots, k$ ), in which each genotype is a sequence  $(\mathbf{a}_{\alpha,1}, \dots, \mathbf{a}_{\alpha,L})$  of length  $L$ . This dynamics is defined on the space of genotype frequencies  $x^\alpha$  with the constraints  $x^\alpha \geq 0$  ( $\alpha = 1, \dots, k$ ) and  $\sum_{\alpha=1}^k x^\alpha = 1$ , which is a  $(k-1)$ -dimensional simplex denoted by  $\Sigma_{k-1}$ . Here, we use the set of  $k-1$  linearly independent frequencies  $x = (x^1, \dots, x^{k-1})$  as coordinate system on  $\Sigma_{k-1}$ ; however, most of the equations below do not depend on the choice of any particular coordinate system. Unless otherwise specified, coordinate indices  $\alpha, \beta, \dots$  take the values  $1, \dots, k-1$ , and we use the convention that if the same coordinate appears in a product as upper and lower index, it is summed over, e.g.,  $s_\alpha x^\alpha \equiv \sum_{\alpha=1}^{k-1} s_\alpha x^\alpha$ . The shorthand  $\partial_\alpha \equiv \partial/\partial x^\alpha$  denotes partial derivatives with respect to these coordinates.

The evolutionary dynamics can be projected from genotypes onto allele frequencies  $((x^{1,1}, \dots, x^{1,4}), \dots, (x^{L,1}, \dots, x^{L,4}))$ , where the frequency  $x^{\nu,a}$  of an allele  $a = A, C, G, T$  at locus  $\nu$  is given by

$$x^{\nu,a} = \sum_{\alpha: \mathbf{a}_{\alpha,\nu}=a} x^\alpha. \quad (S1)$$

With the normalization constraints  $\sum_{a=1}^4 x^{\nu,a} = 1$  ( $\nu = 1, \dots, L$ ), the space of allele frequencies has dimension  $3L$ . This projection involves no loss of information if and only if the genotypes in the population are at linkage equilibrium, i.e., if the frequency  $x$  of each sequence  $\mathbf{a}$  is the product of the frequencies of its alleles,

$$x = \prod_{\nu=1}^L x^{\nu, \mathbf{a}_\nu}. \quad (S2)$$

Since most of the following derivations are valid in both spaces, we use the common notation  $x = (x^1, \dots, x^{k-1})$  for the vectors of genotype and allele frequencies. The conditions for linkage equilibrium and the applicability of genotype and allele picture to evolution under selection will be discussed below.

**Selection, Fitness Landscapes and Seascapes.** Selection is given by genotype fitness values  $f_\alpha(x, t)$ , which determine the deterministic change of genotype frequencies in the absence of mutations and genetic drift,

$$\frac{1}{x^\alpha} \frac{dx^\alpha}{dt} = f_\alpha(x, t) - \sum_{\alpha=1}^k x^\alpha f_\alpha(x, t), \quad (S3)$$

for  $\alpha = 1, \dots, k$ . The second term on the right hand side ensures conservation of the constraint  $\sum_{\alpha=1}^k x^\alpha(t) = 1$ . In terms of the linearly independent frequencies  $x = (x^1, \dots, x^{k-1})$ , these evolution equations take the form

$$\frac{dx^\alpha}{dt} = s^\alpha(x, t) \equiv g^{\alpha\beta}(x) s_\beta(x, t) \quad (S4)$$

with selection coefficients

$$s_\beta(x, t) = f_\beta(x, t) - f_k(x, t) \quad (S5)$$

and response coefficients

$$g^{\alpha\beta}(x) = \begin{cases} -x^\alpha x^\beta & \text{if } \alpha \neq \beta \\ x^\alpha(1-x^\alpha) & \text{if } \alpha = \beta. \end{cases} \quad (S6)$$

The inverse of this matrix,  $g_{\alpha\beta} = (g^{\alpha\beta})^{-1}$ , plays the role of a metric on  $\Sigma_{k-1}$ . In writing the continuum evolution equations (S4), it is assumed that the selection coefficients are small on the time scale of a generation and have temporal correlations over much larger times than a generation. By eq. (S5), the selection coefficient  $s_\alpha$  can be expressed as partial change of the mean population fitness in response to a change in the frequency  $x^\alpha$  at constant genotype fitness values,

$$s_\alpha(x, t) = \left[ \frac{\partial}{\partial x^\alpha} \sum_{\beta=1}^k x^\beta f_\beta(y, t) \right]_{y=x}. \quad (S7)$$

A different question is whether the selection coefficients can be expressed as the gradient of a scalar potential function for selection,  $s_\alpha(x, t) = \partial_\alpha F(x, t)$ . Eq. (S7) shows that if the reproductive rates  $f_\alpha$  of all genotypes are constant,  $F$  is time-independent and equals the mean population fitness up to a constant,  $F(x) = \sum_{\alpha=1}^k x^\alpha f_\alpha + F_0$ . In general, however, we have to distinguish mean population fitness and selection potential. The former governs the overall growth rate of population size, the latter depends only on growth rate differences between genotypes, according to eq. (S5). For example, consider a mutant with frequency  $x$  and fitness  $f(x)$  in a resident population of fitness  $f_0(x)$ . If the mutant has a constant competitive advantage  $s = f(x) - f_0(x) = \partial F(x)/\partial x > 0$  over the resident population, the invasion process will lead to an increase  $F(x=1) - F(x=0) = s$ , whereas the mean population fitness  $x f(x) + (1-x) f_0(x)$  may increase or decrease during this process.

Depending on existence and form of a potential function  $F$ , we can distinguish the following types of natural selection acting on genotypes:

1. The selection coefficients  $s_\alpha$  are constant, i.e., the gradient of a linear fitness landscape,

$$s_\alpha = \partial_\alpha F(x) = \partial_\alpha (s_\beta x^\beta). \quad (S8)$$

The function  $F(x)$  is determined up to an arbitrary constant. Such fitness landscapes can capture epistatic interactions between genomic loci; see the discussion in ref. [1].

2. The selection coefficients  $s_\alpha(x)$  are the gradient of a generic fitness landscape [2],

$$s_\alpha(x) = \partial_\alpha F(x), \quad (S9)$$

which describes frequency-dependent selection.

3. The selection coefficients  $s_\alpha(x, t)$  are the gradient of a time-dependent fitness seascape [3],

$$s_\alpha(x, t) = \partial_\alpha F(x, t). \quad (S10)$$

4. The selection coefficients  $s_\alpha(x, t)$  are given by a non-gradient fitness seascape (which may also depend on time),

$$s_\alpha(x, t) = \partial_\alpha F(x, t) + \check{s}_\alpha(x, t) \quad (S11)$$

with  $\partial_\beta \check{s}_\alpha(x, t) - \partial_\alpha \check{s}_\beta(x, t) \neq 0$ . Non-gradient selection coefficients  $\check{s}_\alpha$  describe, for example, cyclic selective advantage between three or more genotypes [4].

We will show below that the time-independent gradient form (S9) is related to the existence of an evolutionary equilibrium under selection, mutations, and genetic drift. This equilibrium no longer exists in a (time-dependent or non-gradient) fitness seascape (S10) or (S11).

Formulae analogous to (S3 - S11) hold in allele frequency space. Assuming linkage equilibrium, the response coefficients (S6) for allele frequencies factorize between loci,

$$g^{\alpha\beta}(x) = \prod_{\nu=1}^L g_\nu^{ab}(x^\nu), \quad (S12)$$

and the same is true for the metric  $g_{\alpha\beta}(x)$ . Epistatic interactions between loci, i.e., selection coefficients  $\partial F/\partial x^{\nu_1}$  depending on the allele frequencies  $x^{\nu_2}$  at another locus, now appear as nonlinearities of the fitness landscape.

**Mutations.** In the absence of selection and genetic drift, the allele frequency change due to mutations takes the form

$$\frac{dx^\alpha}{dt} = m^\alpha(x) = \sum_{\beta=1}^k \mu_\beta^\alpha x^\beta - \left( \sum_{\beta=1}^k \mu_\alpha^\beta \right) x^\alpha \quad (\text{S13})$$

given by the mutation rates  $\mu_\alpha^\beta \equiv \mu(\mathbf{a}_\alpha \rightarrow \mathbf{a}_\beta)$  between genotypes  $(\alpha, \beta = 1, \dots, k)$ , which we assume to be time-independent over the interval of observation. We can rewrite the rate  $m^\alpha(x)$  in terms of the linearly independent frequencies  $x = (x^1, \dots, x^{k-1})$ ,

$$m^\alpha(x) = \hat{\mu}_\beta^\alpha x^\beta + \mu_k^\alpha \quad (\text{S14})$$

with

$$\hat{\mu}_\beta^\alpha = \begin{cases} \mu_\beta^\alpha - \mu_k^\alpha & (\alpha \neq \beta) \\ -\sum_{\gamma=1}^k \mu_\alpha^\gamma - \mu_k^\alpha & (\alpha = \beta). \end{cases} \quad (\text{S15})$$

The ‘‘covariant’’ rates  $m_\alpha(x) = g_{\alpha\beta} m^\beta(x)$  are defined in analogy to (S4). We assume the evolutionary process is in the low mutation regime  $\mu N \ll 1$  (where  $N$  is the effective population size) and the substitution rates  $\mu_\alpha^\beta$  satisfy the detailed balance conditions

$$\frac{\mu_\alpha^\beta}{\mu_\beta^\alpha} = \frac{p_0^\beta}{p_0^\alpha} \quad (\text{S16})$$

for  $\alpha, \beta = 1, \dots, k$ . These conditions, which are fulfilled in all standard models of nucleotide mutation rates, imply that the neutral substitution dynamics in the discrete space of genotypes  $\mathbf{a}_1, \dots, \mathbf{a}_k$  has an equilibrium probability distribution  $p_0^\alpha$ . It is then straightforward to show that the rates  $m_\alpha(x)$  are asymptotically of gradient form,

$$m_\alpha(x) = \partial_\alpha M(x) + O(\mu^2 NL). \quad (\text{S17})$$

The gradient property is tied to the existence of an evolutionary equilibrium under mutations and genetic drift, which is a technical assumption for the proof of the fitness-flux theorem. The equilibrium frequency distribution  $P_0(x)$  turns out to be simply related to the mutation potential  $M(x)$ ; see eq. (S47) below. Deviations from the form (S17) arise only from multiple simultaneous mutations and are negligible for compact genomic units ( $\mu NL \ll 1$ ) such as transcription factor binding sites. For longer sequences, we will turn to a description of population states in terms of allele frequencies. In this case, the asymptotic gradient form  $m_{\nu,a}(x^\nu) = \partial M_\nu(x^\nu)/\partial x^\nu + O(\mu^2 N)$  holds at each locus (no summation over  $\nu$ ) and, assuming linkage equilibrium, the mutation potential for an arbitrary number of loci is given by

$$M(x) = \sum_{\nu=1}^L M_\nu(x^\nu). \quad (\text{S18})$$

If the detailed balance conditions (S16) are replaced by the more restrictive conditions  $\mu_\alpha^\beta = \mu^\beta$ , the rates  $m_\alpha$  are of exact gradient form for arbitrary values of  $\mu N$  and the mutation potential is known exactly [5],

$$M(x) = \sum_{\alpha=1}^k \mu^\alpha \log(x^\alpha). \quad (\text{S19})$$

**Recombination.** In sexually reproducing populations, two genotypes  $\alpha$  and  $\beta$  can recombine and produce a new genotype  $\gamma$ . The genotype frequency changes due to recombination are described by additional terms in eq. (S13). It is possible to include recombination

into a genotype-based flux theorem, but the derivation is technically involved and will be postponed to a later publication. The contribution of recombination vanishes in the projection (S1) of the neutral dynamics from genotypes to the allele frequencies at individual genomic loci. Recombination counteracts linkage disequilibrium generated by epistasis. The projection onto allele frequencies is appropriate to describe evolution under selection and fitness flux as long as simultaneous substitutions at different genomic loci that are coupled by epistasis and linkage disequilibrium are rare. This condition does not preclude linkage disequilibrium between genomic loci under selection and adjacent neutral loci, which gives rise to hitchhiking but is irrelevant for fitness flux. Linkage equilibrium between selected loci emerges if the rate of beneficial substitutions,  $u_+$ , and the recombination rate  $\rho$  satisfy the inequality  $u_+/\rho \ll 1$ , which we assume in the following analysis.

**Evolution of Finite Populations: Mutation-Selection-Drift dynamics.** The stochastic evolution of finite populations is described by a time-dependent probability distribution of genotype or allele frequencies,  $P(x, t)$ . Genotype space and allele frequency space for multiple genomic loci are very high-dimensional and are always undersampled, but appropriate marginal distributions and averages of  $P(x, t)$  (such as allele frequencies at single loci, linkage disequilibrium, or fitness flux) can be compared with observations.

The evolution of  $P(x, t)$  can be described by a Kimura-Ohta evolution equation of the form [6]

$$\partial_t P(x, t) = \partial_\alpha \left[ \frac{1}{N} \partial_\beta g^{\alpha\beta}(x) - v^\alpha(x, t) \right] P(x, t), \quad (\text{S20})$$

where  $N$  is the effective population size,  $g^{\alpha\beta}$  are the metric coefficients (S6), and  $v^\alpha(x, t)$  are the total rates of frequency change due to selection and mutations as given by eqs. (S5) and (S14),

$$v^\alpha(x, t) = s^\alpha(x, t) + m^\alpha(x). \quad (\text{S21})$$

The diffusion equation (S20) expresses the temporal change of  $P(x, t)$  as the divergence of a probability current. For later convenience we rewrite this equation in a different operator ordering [7],

$$\partial_t P(x, t) = \partial_\alpha \left[ \frac{1}{N} g^{\alpha\beta}(x) \partial_\beta - \tilde{v}^\alpha(x, t) \right] P(x, t), \quad (\text{S22})$$

where

$$\tilde{v}^\alpha = v^\alpha - \frac{1}{N} g^{\alpha\beta}(x) \partial_\beta \Omega_g(x) \quad (\text{S23})$$

and

$$\Omega_g(x) = \log \det(g_{\alpha\beta}). \quad (\text{S24})$$

**Evolution as Sum over Population Histories.** Consider first the evolution of an ensemble of populations described by discrete genotype or allele frequencies  $x^\alpha(t)$  observed over a time interval of  $n$  discrete generations,  $t_i = t_0 + i\delta$  ( $i = 0, \dots, n$ ) with generation time  $\delta$ . This process has a finite set of population histories

$$\mathbf{x} = (x_0, x_1, \dots, x_n). \quad (\text{S25})$$

Evolution by mutations, selection, and genetic drift dynamics generates a probability distribution  $\mathcal{P}(\mathbf{x})$  over these population histories. The frequency distribution  $P(x, t)$  at the final time  $t = t_n$  is a marginal distribution of  $\mathcal{P}(\mathbf{x})$ ,

$$P(x, t) = \sum_{\mathbf{x}} \mathcal{P}(\mathbf{x}) \delta_{x(t)-x}. \quad (\text{S26})$$

To equate this sum over population histories to the solution of the Kimura-Ohta evolution equation (S20), we first take a continuum limit for the allele frequencies  $x^\alpha$ . The history probability distribution  $\mathcal{P}(\mathbf{x})$  is now a so-called path integral [8], which is a density with the measure

$$\mathcal{D}\mathbf{x} \equiv dx_n \prod_{i=0}^{n-1} dx_i \sqrt{\frac{g(x_i)}{(2\pi(t-t_0)/n)^{k-1}}} \quad (\text{S27})$$

and the normalization

$$\int \mathcal{D}\mathbf{x} \mathcal{P}(\mathbf{x}) = 1. \quad (\text{S28})$$

The frequency distribution  $P(x, t)$  is again the marginal distribution

$$P(x, t) = \int \mathcal{D}\mathbf{x} \mathcal{P}(\mathbf{x}) \delta(x(t) - x). \quad (\text{S29})$$

For large populations, where the mean square allele frequency change per generation is small,

$$\epsilon \equiv \langle \Delta x_i^\alpha g_{\alpha\beta}(x_i) \Delta x_i^\beta \rangle \ll 1 \quad (\text{S30})$$

with  $\Delta x_i \equiv x_{i+1} - x_i$ , the distribution  $\mathcal{P}(\mathbf{x})$  takes the form

$$\mathcal{P}(\mathbf{x}) = P(x_0, t_0) e^{-NS(\mathbf{x})} \quad (\text{S31})$$

with the weight function (action)

$$S(\mathbf{x}) = \frac{\delta}{4} \sum_{i=0}^{n-1} \left[ \frac{\Delta x_i^\alpha}{\delta} - v^\alpha(x_i, t_i) \right] \times g_{\alpha\beta}(x_i, t_i) \left[ \frac{\Delta x_i^\beta}{\delta} - v^\beta(x_i, t_i) \right]. \quad (\text{S32})$$

It can be shown that this path integral has a well defined limit for  $n \rightarrow \infty$  and  $\delta \sim \epsilon \sim 1/n \rightarrow 0$ : for any sufficiently smooth function  $f(\mathbf{x})$ , the average over population histories

$$\langle f(\mathbf{x}) \rangle_\epsilon \equiv \int \mathcal{D}\mathbf{x} f(\mathbf{x}) \mathcal{P}(\mathbf{x}) \quad (\text{S33})$$

converges to  $\langle f(\mathbf{x}) \rangle = \lim_{\epsilon \rightarrow 0} \langle f(\mathbf{x}) \rangle_\epsilon$ , and

$$\langle f(\mathbf{x}) \rangle_\epsilon = \langle f(\mathbf{x}) \rangle + O(\epsilon^{1/2}). \quad (\text{S34})$$

In particular, the allele frequency distribution (S29) converges to the solution of (S20) in this limit. The initial-point (Itô) discretization of the functions  $g_{\alpha\beta}(x, t)$  and  $v^\alpha(x, t)$  exactly reproduces the operator ordering in (S20) and explicitly displays the normalization (S28) of the partition function [7]. An equivalent history probability distribution

$$\mathcal{P}(\mathbf{x}) = P(x_0, t_0) e^{-N\tilde{S}(\mathbf{x})} \quad (\text{S35})$$

can be defined with a measure

$$\mathcal{D}\mathbf{x} \equiv dx_n \prod_{i=0}^{n-1} dx_i \sqrt{\frac{g(\tilde{x}_i)}{(2\pi(t-t_0)/n)^{k-1}}} \quad (\text{S36})$$

and a weight function in midpoint (Stratonovich) discretization,

$$\tilde{S}(\mathbf{x}) = \frac{\delta}{4} \sum_{i=0}^{n-1} \left[ \frac{\Delta x_i^\alpha}{\delta} - \tilde{v}^\alpha(\tilde{x}_i, \tilde{t}_i) \right] \times \times g_{\alpha\beta}(\tilde{x}_i, \tilde{t}_i) \left[ \frac{\Delta x_i^\beta}{\delta} - \tilde{v}^\beta(\tilde{x}_i, \tilde{t}_i) \right] + \tilde{c}(\tilde{x}_i, \tilde{t}_i) \quad (\text{S37})$$

where  $\tilde{x}_i \equiv (x_i + x_{i+1})/2$ ,  $\tilde{t}_i \equiv (t_i + t_{i+1})/2$ , the allele frequency change field  $\tilde{v}(x, t)$  is given by (S23) up to a negligible correction term of order  $\epsilon$  arising from (S36), coefficients  $g_{\alpha\beta}$  are given by the matrix inverse of  $(g^{\alpha\beta})$  and  $\tilde{c}(x, t)$  is a scalar function which guarantees the normalization (S28). For the quadratic term  $\Delta x_i^\alpha g_{\alpha\beta} \Delta x_i^\beta / \delta$ , this discretization corresponds to the operator ordering in (S22). The two densities (S31) and (S35) define the same continuum limit (S34). We emphasize that in population genetics, unlike in other applications of the path integral, there are natural discrete scales of time and allele frequencies, and the continuum formalism is merely a convenient choice for computing probabilities in ensembles of population

histories, which displays the equivalence of discrete-generation models in large populations. A different application of the path integral as an ensemble of histories of individuals within one population has recently been used to describe the micro-evolution of structured populations [9].

**Equilibrium Frequency Distributions.** An equilibrium state of the evolution process (S20) is defined as a stationary frequency distribution  $P_{\text{eq}}(x)$  with vanishing probability current,

$$\left[ \frac{1}{N} g^{\alpha\beta}(x) \partial_\beta - \tilde{v}^\alpha(x, t) \right] P_{\text{eq}}(x) = 0. \quad (\text{S38})$$

As shown by inspection of this equation, the neutral process given by eqs. (S20) and (S21) with  $v^\alpha(x, t) = m^\alpha(x)$  has an equilibrium distribution  $P_0(x)$  if and only if the rates  $m_\alpha(x)$  are of gradient form,  $m_\alpha(x) = \nabla_\alpha M(x)$ . This condition defines the mutation potential  $M(x)$  in eq. (S17). The equilibrium frequency distribution takes the simple form [7]

$$P_0(x) = e^{\Omega_0(x)} = Z_0^{-1} e^{NM(x) + \Omega_g(x)} \quad (\text{S39})$$

with  $\Omega_g(x)$  given by (S24). A well-known special case of this relation is Kimura's U-shaped equilibrium distribution for a single locus that has two alleles  $a, b$  [10] with frequencies  $x \equiv x^b = 1 - x^a$ . The equilibrium frequency distribution  $P_0^u(x, \mu_a^b, \mu_b^a)$  under neutrality is of the form (S39) with

$$\Omega_0(x) = -\log[x(1-x)], \quad (\text{S40})$$

$$M(x) = \mu_a^b \log x + \mu_b^a \log(1-x), \quad (\text{S41})$$

and the normalization factor

$$Z_0^u = \Gamma(N\mu_a^b) \Gamma(N\mu_b^a) / \Gamma(N\mu_a^b + N\mu_b^a). \quad (\text{S42})$$

The mutation potential determines the rate  $m^1 = g^{11} \partial_x M(x) = \mu_a^b(1-x) - \mu_b^a x$  with  $g^{11} = x(1-x)$ . It is straightforward to generalize this form to a space of  $k$  genotypes if the detailed balance conditions (S16) are fulfilled and at most two genotypes coexist at any point in time, which is a good approximation for  $\mu NL \ll 1$ . The asymptotic equilibrium distribution  $P_0(x)$  is defined on the edges of the simplex  $\Sigma_{k-1}$  and has the form  $P_0^u(x, \mu_\alpha^\beta, \mu_\beta^\alpha)$  for each pair of coexisting genotypes  $\alpha, \beta$  linked by mutations. Specifically, we obtain

$$P_0(x) = Z_0^{-1} \left[ \sum_{\alpha=1}^k p_0^\alpha \delta(x^\alpha - 1) + \frac{1}{2} \sum_{\alpha, \beta=1}^k \frac{p_0^\alpha}{p_u(\mu_\alpha^\beta, \mu_\beta^\alpha)} P_0^u(x^\beta - x^\alpha, \mu_\alpha^\beta, \mu_\beta^\alpha) \times \chi(x^\alpha - x^\beta) \delta(x^\alpha + x^\beta - 1) \right] \quad (\text{S43})$$

with the normalization

$$Z_0 = 1 + \frac{1}{2} \sum_{\alpha, \beta=1}^k \frac{p_0^\alpha}{p_u(\mu_\alpha^\beta, \mu_\beta^\alpha)} [1 - p_u(\mu_\alpha^\beta, \mu_\beta^\alpha) - p_u(\mu_\beta^\alpha, \mu_\alpha^\beta)], \quad (\text{S44})$$

where  $p_0^\alpha$  is the equilibrium distribution of fixed phenotypes given by (S16),  $\chi(x) = 1$  if  $1/N \leq x < 1 - 1/N$  and 0 otherwise, and

$$p_u(\mu_\alpha^\beta, \mu_\beta^\alpha) = \frac{1}{\mu_\alpha^\beta N Z_0^u} \left( \frac{1}{N} \right)^{\mu_\alpha^\beta N} \quad (\text{S45})$$

is the probability of the fixed state  $\alpha$  given by the distribution  $P_0^u(\mu_\alpha^\beta, \mu_\beta^\alpha)$ . In allele frequency space, the asymptotic equilibrium

$P_{0,\nu}(x^\nu)$  is of this form, and the distribution for an arbitrary number of loci at linkage equilibrium is given by

$$P_0(x) = \prod_{\nu=1}^L P_{0,\nu}(x^\nu). \quad (\text{S46})$$

Given a neutral (approximate) equilibrium and selection coefficients of time-independent gradient form,  $s_\alpha(x) = \partial_\alpha F(x)$ , the full evolution process of eq. (S20) has an (approximate) equilibrium state of the form

$$P_{\text{eq}}(x) = e^{\Omega_{\text{eq}}(x)} = Z^{-1} e^{\Omega_0(x) + NF(x)}. \quad (\text{S47})$$

For example, Kimuras U-shaped equilibrium for a two-allele locus under directional selection of strength  $s$  is given by eqs. (S39 - S41, S47) with

$$F(x) = sx. \quad (\text{S48})$$

The relation corresponding to (S47) for the equilibrium distributions of fixed genotypes,

$$p_{\text{eq}}^\alpha = Z^{-1} p_0^\alpha e^{NF_\alpha}, \quad (\text{S49})$$

with  $F_\alpha = F(x^\beta = \delta_{\alpha,\beta})$  has been derived in ref. [11].

**Entropy of Population States.** The local entropy of the population state  $x(t)$  with respect to the normalized time-dependent solution  $P(x, t)$  of the diffusion equation (S20) can be defined as [14]

$$\Omega(x, t) = -\log P(x, t). \quad (\text{S50})$$

This name is justified since the average of  $\Omega(x, t)$  is the entropy of the distribution  $P(t)$ ,

$$\langle \Omega \rangle(t) = -\int dx P(x, t) \log P(x, t) \equiv \Omega(P(t)). \quad (\text{S51})$$

It will prove convenient to decompose the local entropy,

$$\Omega(x, t) = \Omega_0(x) - \mathcal{H}(x, t), \quad (\text{S52})$$

into the contribution  $\Omega_0(x, t) = -\log P_0(x)$  of the neutral equilibrium distribution  $P_0$  given by (S39) and the relative log likelihood

$$\mathcal{H}(x, t) = \log \frac{P(x, t)}{P_0(x)}. \quad (\text{S53})$$

The average

$$\langle \mathcal{H} \rangle(t) = \int dx P(x, t) \log \frac{P(x, t)}{P_0(x)} \equiv H(P(t)|P_0) \quad (\text{S54})$$

is the relative entropy of the time-dependent distribution  $P(t)$  of the full process with respect to the neutral equilibrium  $P_0$ . If the full process is also at equilibrium,  $P(x, t) = P_{\text{eq}}(x)$ , this relative log likelihood equals the fitness up to an additive constant,

$$H_{\text{eq}}(x) = NF(x) - \log Z, \quad (\text{S55})$$

as shown by eq. (S47).

**Fluxes of Population Histories.** For a given population history  $\mathbf{x}$  with initial frequencies  $x_0$  and final frequencies  $x$  in the time interval  $(t_0, t)$ , we define the total cumulative flux

$$\Theta(\mathbf{x}) \equiv \sum_{i=0}^{n-1} \Delta x_i^\alpha \tilde{v}_\alpha(\tilde{x}_i, \tilde{t}_i), \quad (\text{S56})$$

which is shown here in midpoint discretization. In this and the following expressions, we assume the continuum limit  $n \rightarrow \infty$  to be

taken. Using eqs. (S21) and (S23), we can decompose this flux into the contributions of genetic drift, mutations, and selection,

$$\Theta(\mathbf{x}) = \Theta_g(\mathbf{x}) + \Theta_m(\mathbf{x}) + \Phi(\mathbf{x}) \quad (\text{S57})$$

with

$$\begin{aligned} \Theta_g(\mathbf{x}) &\equiv \frac{1}{N} \sum_{i=0}^{n-1} \Delta x_i^\alpha \partial_\alpha \Omega_g(\tilde{x}_i) \\ &= \frac{1}{N} [\Omega_g(x) - \Omega_g(x_0)], \end{aligned} \quad (\text{S58})$$

$$\begin{aligned} \Theta_m(\mathbf{x}) &\equiv \sum_{i=0}^{n-1} \Delta x_i^\alpha m_\alpha(\tilde{x}_i) \\ &= M(x) - M(x_0), \end{aligned} \quad (\text{S59})$$

$$\begin{aligned} \Phi(\mathbf{x}) &\equiv \sum_{i=0}^{n-1} \Delta x_i^\alpha s_\alpha(\tilde{x}_i, \tilde{t}_i) \\ &= \sum_{i=0}^{n-1} \Delta x_i^\alpha [\partial_\alpha F(\tilde{x}_i, \tilde{t}_i) + \check{s}_\alpha(\tilde{x}_i, \tilde{t}_i)]. \end{aligned} \quad (\text{S60})$$

Comparison with eqs. (S39), (S47) shows that the cumulative fluxes of any population history  $\mathbf{x}$  at equilibrium are proportional to differences in the corresponding local entropies between its end point and its initial point,

$$N[\Theta_g(\mathbf{x}) + \Theta_m(\mathbf{x})] = \Omega_0(x) - \Omega_0(x_0), \quad (\text{S61})$$

$$N\Phi(\mathbf{x}) = N[F(x) - F(x_0)] = H_{\text{eq}}(x) - H_{\text{eq}}(x_0), \quad (\text{S62})$$

$$N\Theta(\mathbf{x}) = \Omega_{\text{eq}}(x) - \Omega_{\text{eq}}(x_0). \quad (\text{S63})$$

The last equation implies the relation

$$e^{-N\Theta(\mathbf{x}) + \Omega_{\text{eq}}(x) - \Omega_{\text{eq}}(x_0)} = 1, \quad (\text{S64})$$

which expresses detailed balance at equilibrium (this will become clear from the proof of the fitness-flux theorem). We now generalize the relation between flux and entropy to nonequilibrium processes.

**Fitness-Flux Theorem.** The theorem states that for any evolutionary dynamics governed by time-dependent selection, mutations, and genetic drift as given by eq. (S20), or equivalently by eqs. (S29) and (S32), the following identity holds:

$$\langle e^{-N\Theta + \Delta\Omega} \rangle = 1. \quad (\text{S65})$$

Here,  $\Theta(\mathbf{x})$  is the total cumulative flux (S56) in an arbitrary time interval  $(t_0, t)$ , and  $\Delta\Omega(\mathbf{x}) \equiv \Omega(x, t) - \Omega(x_0, t_0)$  is the change in local entropy for a given population history  $\mathbf{x}$ , which depends only on its initial point  $(x_0, t_0)$  and its end point  $(x, t)$ . The angular brackets denote an average over population histories in the interval  $(t_0, t)$ ,

$$\begin{aligned} \langle e^{-N\Theta + \Delta\Omega} \rangle &\equiv \int \mathcal{D}\mathbf{x} \mathcal{P}(\mathbf{x}) e^{-N\Theta(\mathbf{x}) + \Delta\Omega(\mathbf{x})} \\ &= \int \mathcal{D}\mathbf{x} P(x_0, t_0) e^{-N\Theta(\mathbf{x}) + \Delta\Omega(\mathbf{x}) - N\check{S}(\mathbf{x})}. \end{aligned} \quad (\text{S66})$$

For convenience, this path integral is written in a midpoint discretization rule with the measure (S36) and the weight function (S37). Assuming that the neutral evolution process in the time interval  $(t_0, t)$  has an equilibrium frequency distribution  $P_0(x)$ , we can use the decomposition (S52), (S57) with (S61) to write the identity (S65) in the form

$$\langle e^{-N\Phi + \Delta\mathcal{H}} \rangle = 1. \quad (\text{S67})$$

An immediate consequence of this theorem is the inequality

$$N\langle \Phi \rangle \geq \Delta H \quad (\text{S68})$$

at constant population size  $N$ . We note that the assumption of a neutral equilibrium is not crucial. If the neutral process is not at equilibrium, the flux identity (S65) still holds, but alternative assumptions are needed for its decomposition into contributions of mutational flux and fitness flux.

**Proof of the Theorem.** The theorem is proved using a set of identities called integral fluctuation theorems, which have been developed in nonequilibrium thermodynamics over recent years [12, 13, 14, 15]. The following proof uses a generalization of Crooks' formalism [13] to continuous-time path integrals [15]. For every population history (S25), we define the time-reversed history

$$\mathbf{x}^T \equiv (x_0^T, x_1^T, \dots, x_n^T) = (x_n, x_{n-1}, \dots, x_0), \quad (\text{S69})$$

and the time-reversed fitness seascape

$$F^T(x, t_i) = F(x, t - t_i + t_0), \quad (\text{S70})$$

which determines selection coefficients

$$s^T(x, t_i) = s(x, t - t_i + t_0). \quad (\text{S71})$$

Hence, the reverse history evolves under selection coefficients

$$s^T(\tilde{x}_i^T, \tilde{t}_i) = s(\tilde{x}_{n-i}, t - \tilde{t}_i + t_0). \quad (\text{S72})$$

Eqs. (S71) and (S72) define the time-reversed selection, even for non-gradient seascapes of the form (S11). With the frequency transitions  $\Delta x_i^T = -\Delta x_{n-i}$ , we obtain the weight function

$$\tilde{S}^T(\mathbf{x}^T) = \tilde{S}(\mathbf{x}) + \Theta(\mathbf{x}) \quad (\text{S73})$$

and the conditional probabilities

$$G^T(\mathbf{x}^T) = e^{\tilde{S}^T(\mathbf{x}^T)} = e^{-N\Theta(\mathbf{x})} G(\mathbf{x}) \quad (\text{S74})$$

of the time-reversed process. The transformations (S73) and (S74) involve the total cumulative flux (S56) of the forward process in a time-reversal symmetric discretization rule. We can also relate the initial distributions of the forward and backward process,

$$P(x_0^T, t_0) = P(x, t) = P(x_0, t_0) e^{\Delta\Omega(\mathbf{x})} \quad (\text{S75})$$

and the integration measures,

$$D\mathbf{x} = D\mathbf{x}^T. \quad (\text{S76})$$

Eqs. (S74) and (S75) together relate the probability densities of population histories in both processes,

$$\begin{aligned} \mathcal{P}(\mathbf{x}^T) &= \mathcal{P}(\mathbf{x}) e^{-N\Theta(\mathbf{x}) + \Delta\Omega(\mathbf{x})} \\ &= \mathcal{P}(\mathbf{x}) e^{-N\Phi(\mathbf{x}) + \Delta\mathcal{H}(\mathbf{x})}, \end{aligned} \quad (\text{S77})$$

and with (S76), we recognize (S67) as the normalized partition function of the backward process,

$$\langle e^{-N\Theta(\mathbf{x}) + \Delta\Omega(\mathbf{x})} \rangle = \int D\mathbf{x}^T \mathcal{P}(\mathbf{x}^T) = 1. \quad (\text{S78})$$

Specifically at evolutionary equilibrium, the flux relation (S65) holds not only as an average in an ensemble of population histories, but for each population history, see (S64). Eq. (S77) then shows that this is nothing but the statement of detailed balance,

$$P(x, t) e^{-NS(\mathbf{x}^T)} = \mathcal{P}(\mathbf{x}^T) = \mathcal{P}(\mathbf{x}) = P(x_0, t_0) e^{-NS(\mathbf{x})}. \quad (\text{S79})$$

**Generalization to Time-Dependent Population Size.** The evolution of a population of time-dependent effective size  $N(t)$  can be described by a Kimura-Ohta diffusion equation of the form

$$\partial_t P(x, t) = \partial_\alpha \left[ \frac{1}{N(t)} \partial_\beta g^{\alpha\beta}(x) - v^\alpha(x, t) \right] P(x, t), \quad (\text{S80})$$

because relevant changes of the effective population size  $N(t)$  are always small on the time scale of a generation. Parametrizing the population size in terms of a reference size,  $N(t) = \zeta(t)N$ , the temporal variation in population size can be absorbed by a nonlinear rescaling of evolutionary time given by  $d\tau/dt = 1/\zeta(t)$ ,

$$\partial_\tau P(x, \tau) = \partial_\alpha \left[ \frac{1}{N} \partial_\beta g^{\alpha\beta}(x) - \zeta(\tau) v^\alpha(x, \tau) \right] P(x, \tau) \quad (\text{S81})$$

with the substitution  $v^\alpha(x, \tau) \equiv v^\alpha(x, t(\tau))$ . Hence, with appropriate definitions of rescaled mutation flux and fitness flux,

$$N_0 \Theta_m(\mathbf{x}) = \sum_{i=0}^{n-1} N(t) \Delta x_i^\alpha \partial_\alpha M(\tilde{x}_i), \quad (\text{S82})$$

$$N_0 \Phi(\mathbf{x}) = \sum_{i=0}^{n-1} N(t) \Delta x_i^\alpha s_\alpha(\tilde{x}_i, \tilde{t}_i), \quad (\text{S83})$$

the fitness-flux theorem (S65) remains valid and takes the form

$$\langle e^{-N_0 \Phi + \Delta\mathcal{H} - N_0 \Theta_m + \Delta\Omega_m} \rangle = 1. \quad (\text{S84})$$

Compared to the form (S67), there are the two additional terms  $\Delta\Omega_m$  and  $-N\Theta_m$ . In the low-mutation regime  $\mu N \ll 1$ , these terms describe the small change in neutral polymorphism frequency distributions and the associated flux which are induced by a change in effective population size. Both terms are of order  $\mu N_0$  and hence, negligible against the contributions  $-N_0 \Phi$  and  $\Delta\mathcal{H}$ .

**Strong-Selection Limit and Fisher's Theorem.** In the asymptotic regime of strong selection ( $sN \gg 1$ ,  $s/\mu \gg 1$ ), the genotype evolution of a polymorphic population is dominated by its most probable history  $\mathbf{x}_*$ , which is given by the deterministic evolution equation

$$\frac{dx_*^\alpha}{dt} = g^{\alpha\beta}(x_*(t)) s_\beta(x_*(t)). \quad (\text{S85})$$

as a function of final time  $t$ . This form is obtained from the asymptotics of the stochastic evolution equation (S20),

$$\partial_t P(x, t) = \partial_\alpha g^{\alpha\beta}(x) s_\beta(x, t) P(x, t) [1 + O(1/Ns, \mu/s)] \quad (\text{S86})$$

or equivalently by saddle-point analysis of the action (S32) as discussed below. The deterministic approximation is valid for frequencies  $x \gg 1/Ns$ , while the low-frequency statistics of polymorphisms remains governed by genetic drift. The cumulative fitness flux of the deterministic history increases at a rate  $d\Phi(\mathbf{x}_*)/dt = \phi_*(t)$  as a function of final time  $t$ , which equals the fitness variance:

$$\begin{aligned} \phi_*(t) &= \frac{dx_*^\alpha}{dt} s_\alpha(x_*(t)) = s^\alpha(x_*(t)) s_\alpha(x_*(t)) \\ &= \sum_{\alpha=1}^k x_*^\alpha(t) \left[ f_\alpha(x_*(t), t) - \sum_{\beta=1}^k x_*^\beta(t) f_\beta(x_*(t), t) \right]^2 \\ &\equiv \text{Var} f(x_*(t), t), \end{aligned} \quad (\text{S87})$$

as shown by using (S3) and (S4). The counterpart of this identity in allele-frequency space, where the contribution of recombination to the deterministic evolution vanishes even for sexually reproducing populations, is Fisher's theorem [16]. As for the fitness-flux theorem, no additional assumptions on the form of selection are required: the theorem is valid in an arbitrary fitness seascape. We recall, however, that the identity (S87) is not in general a statement about increase of fitness. Only in the particular case of a time-independent fitness landscape, the deterministic flux equals the rate of fitness increase,  $\phi_*(t) = dF(x_*(t))/dt$ . If not only the selection

coefficients, but all genotype growth rates are time-independent constants, this also equals the rate of increase in mean population fitness,  $\phi_*(t) = \sum_{\alpha=1}^k f_{\alpha} dx_{\alpha}^*/dt$ .

The fitness-flux theorem, which is a statement about the fluctuations of  $\Phi$  in a time interval  $\Delta t$ , remains valid at any finite value of  $sN$ . In the strong-selection regime, the scaled cumulative flux of the deterministic history takes large positive values for  $\Delta t \gg 1/(s^2 N)$ ,

$$N\Phi(\mathbf{x}_*) \simeq N \int dt s^{\alpha}(x_*(t)) s_{\alpha}(x_*(t)) \gg 1, \quad (\text{S88})$$

which results in an exponentially small contribution of order  $\exp[-N\Phi(\mathbf{x}_*)]$  to the average over histories in the fitness-flux theorem (S67). The dominant contribution comes from the time-reversed history  $\mathbf{x}_*^T$ ,

$$1 = \langle e^{-N\Phi + \Delta\mathcal{H}} \rangle \simeq e^{-N\Phi(\mathbf{x}_*^T)} \mathcal{P}(\mathbf{x}_*^T) \simeq e^{N\Phi(\mathbf{x}_*)} e^{-N\Phi(\mathbf{x}_*)}. \quad (\text{S89})$$

We recall that the deterministic evolution equation (S85) can be derived from the strong-selection limit of the action (S32) or (S37) written in continuum form

$$S(\mathbf{x}) = \frac{1}{4} \int_{t_0}^t dt [\dot{x}^{\alpha} - s^{\alpha}(x, t)] g_{\alpha\beta}(x) [\dot{x}^{\beta} - s^{\beta}(x, t)] \quad (\text{S90})$$

with  $\dot{x}^{\alpha}(t) \equiv dx^{\alpha}(t)/dt$  (the distinction between discretization rules becomes irrelevant in the deterministic limit). The deterministic history  $\mathbf{x}^*$  defined by (S85) with initial condition  $x^*(t_0) = x_0$  satisfies Hamilton's variational principle: it minimizes the action (S90) over the set of all histories  $\mathbf{x}$  with the same initial point  $x(t_0) = x_0$ . In the special case where selection is given by a fitness landscape,  $s_{\alpha}(x) = \partial_{\alpha} F(x)$ , the deterministic history  $\mathbf{x}^*$  also satisfies a modified variational principle: it minimizes the reduced action

$$\begin{aligned} S'(\mathbf{x}) &= S(\mathbf{x}) + \frac{1}{2} \int_{t_0}^t dt \dot{x}^{\alpha} s_{\alpha}(x) \\ &= \frac{1}{4} \int_{t_0}^t dt [\dot{x}^{\alpha} g_{\alpha\beta}(x) \dot{x}^{\beta} + s_{\alpha}(x) s^{\alpha}(x)] \\ &= \frac{1}{4} \int_{t_0}^t dt [\dot{x}^{\alpha} g_{\alpha\beta}(x) \dot{x}^{\beta} + \text{Var}f(x)] \end{aligned} \quad (\text{S91})$$

over the restricted set of all histories  $\mathbf{x}$  with the same initial point  $x(t_0) = x_0$  and the same endpoint  $x(t_f) = x^*(t_f) \equiv x_f$ , because  $S'(\mathbf{x}) - S(\mathbf{x}) = F(x_f) - F(x_0)$  is a history-independent constant within this set. The latter type of variational calculus is known in the population genetics literature as Svirezhev's principle and its generalizations [18, 19, 20]. However, the reduced action (S91) is not suitable as a basis for the stochastic calculus of evolutionary histories.

**Numerical Simulations.** We consider the substitution dynamics in a system of  $L$  independent two-allele genomic loci under time-dependent selection and population size. A fixed population state  $x = (x^1, \dots, x^L)$  of this system is specified by the allele frequencies  $x^{\nu} \equiv x^{\nu,b} = 1 - x^{\nu,a} = 0, 1$  at individual loci ( $\nu = 1, \dots, L$ ). These alleles have time-dependent fitness values  $f_{\nu,a}(t)$  and  $f_{\nu,b}(t)$ , which determine the selection coefficients

$$s_{\nu}(t) = f_{\nu,b}(t) - f_{\nu,a}(t) \quad (\text{S92})$$

and the additive fitness seascape

$$F(x, t) = \sum_{\nu=1}^L s_{\nu}(t) x^{\nu}(t). \quad (\text{S93})$$

The evolution under mutations, selection, and genetic drift generates substitutions at these loci with Kimura-Ohta rates [21, 22]  $u_{\nu}^{a \rightarrow b} = \mu \psi(\sigma_{\nu}(t))$  and  $u_{\nu}^{b \rightarrow a} = \mu \psi(-\sigma_{\nu}(t))$ , where  $\mu$  is the uniform mutation rate per locus,  $\sigma_{\nu}(t) = N(t) s_{\nu}(t)$  are scaled selection coefficients, and

$$\psi(\sigma) = \frac{\sigma}{1 - e^{-\sigma}}. \quad (\text{S94})$$

An ensemble of populations evolving under this process has a time-dependent distribution of fixed genotypes  $P(x, t) = \prod_{\nu=1}^L p_{\nu}(t)$ , where  $p_{\nu}(t)$  is the probability of allele  $b$  at locus  $\nu$ . An individual population history  $\mathbf{x} = (x_0, x_1, \dots, x_n)$  recorded at times  $(t_0, \dots, t_n)$  has a time-dependent relative entropy

$$\begin{aligned} \mathcal{H}(t_i) &= \\ &= \sum_{\nu=1}^L \left[ x^{\nu}(t_i) \log \frac{p_{\nu}(t_i)}{p_0} + (1 - x^{\nu}(t_i)) \log \frac{1 - p_{\nu}(t_i)}{p_0} \right], \end{aligned} \quad (\text{S95})$$

where  $p_0 = 1/2$  are the neutral equilibrium frequencies of alleles at individual loci, and a scaled cumulative fitness flux

$$N\Phi(t_i) = \sum_{\nu=1}^L \sum_{j=0}^{i-1} [x^{\nu}(t_{j+1}) - x^{\nu}(t_j)] \sigma_{\nu}(t_j), \quad (\text{S96})$$

which is simply the sum of the selection coefficients of all substitutions occurring until the point  $t_i$ .

Simulations are performed for  $L = 12$  loci with scaled selection coefficients  $\sigma_{\nu} = 0.5, 0.5, 0.5, 1, 1, 1, 1, 1.5, 1.5, 1.5, 1.5, 2, 2, 2, 2$  and a uniform mutation rate  $\mu = 0.006$ . We consider three different protocols of sequence evolution (see Fig. 2 of the main text). Histories of populations are recorded at 400 time points in the interval  $(0, 28.8)$  for protocols 1 and 2 and at 800 time points in the interval  $(0, 57.6)$  for protocol 3 (time is measured in units of  $1/\mu L$ ). We generate an ensemble of  $10^5$  population histories for each protocol. The protocols have the following characteristics of demography and selection:

1. Evolutionary equilibrium with constant scaled selection coefficients

$$\sigma_{\nu}(t) = \sigma_{\nu}. \quad (\text{S97})$$

2. Nonequilibrium stationary state with scaled selection coefficients

$$\sigma_{\nu}(t) = \pm \sigma_{\nu} \text{ fluctuating with rate } \gamma = \mu/3 \quad (\text{S98})$$

independently at each locus. Averages over this process are obtained from an ensemble of 100 independent selection histories.

3. Transitions between equilibria under a time-dependent population size  $N(t) = N_0 \zeta(t)$ , which results in time-dependent scaled selection coefficients

$$\sigma_{\nu}(t) = \zeta(t) \sigma_{\nu}. \quad (\text{S99})$$

We use a bottleneck protocol

$$\zeta(t) = \frac{1}{2} + \frac{1}{2} [w(t, 3.6, 5) + w(-t, -28.8, 5)] \quad (\text{S100})$$

with  $w(t, t', \Delta t) = 1/[1 + \exp((t - t')/\Delta t)]$ . Scaled fitness flux is defined by eq. (S83).

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