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An asymptotic maximum principle for essentially linear evolution models

Abstract. Recent work on mutation-selection models has revealed that, under specific assumptions on the fitness function and the mutation rates, asymptotic estimates for the leading eigenvalue of the mutation-reproduction matrix may be obtained through a low-dimensional maximum principle in the limit $N \to \infty$ (where N is the number of types). In order to extend this variational principle to a larger class of models, we consider here a family of reversible $N \times N$ matrices and identify conditions under which the high-dimensional Rayleigh-Ritz variational problem may be reduced to a low-dimensional one that yields the leading eigenvalue up to an error term of order $1/N$. For a large class of mutation-selection models, this implies estimates for the mean fitness, as well as a concentration result for the ancestral distribution of types.

1. Introduction

Many systems of population biology or reaction kinetics may be cast into a form where individuals (or particles) of different types reproduce and change type independently of each other in continuous time. If the types come from a finite set S and the population is so large that random fluctuations may be neglected, one is led to a linear system of differential equations of the form

$$\dot{y} = yH \tag{1}$$

with initial condition $y(0)$. Here, $y = (y_i)_{i\in S} \in \mathbb{R}_{\geqslant 0}^{|S|}$ holds the abundance of the various types; $H = (H_{ij})_{i,j\in S}$ is an $|S|\times|S|$ matrix, which represents a linear oper-

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ator on $\mathbb{R}^{|S|}$. The main application we have in mind here is in population genetics, where types are alleles, so that Equation (1) is a haploid mutation-reproduction model; but one may also think of a compartment model, where types are locations of a certain chemical. Important examples of the analogous discrete-time dynamics include models of age-structured populations, which are often referred to as matrix population models, see Caswell's monograph [13]. In line with large parts of the population genetics, and most of the stochastics, literature, we will use the convention that y is a row vector to which H is applied from the right, so that H_{ij} ($i \neq j$) is the coefficient for the change from i to j.

We will assume throughout that the linear operator H generates a positive semigroup, $\{\exp(tH) \mid t \geqslant 0\}$. Since S is finite, this is equivalent to $H_{ij} \geqslant 0$ for $i \neq j$. The flow so generated leaves $\mathbb{R}^{|S|}_{\geqslant 0}$ invariant. We will further assume that H is irreducible (i.e., if $G(H)$ is the directed graph with an edge from i to j if $i \neq j$ and $H_{ij} > 0$, then there is a directed path from any vertex to any other vertex).

We will often use the decomposition

$$H = M + R \tag{2}$$

into a Markov generator M and a diagonal matrix R. More precisely, we have $M = (M_{ij})_{i,j\in S}$ with $M_{ij} := H_{ij}$ for $i \neq j$, $M_{ii} := -\sum_{j\in S\setminus\{i\}} M_{ij}$ (so that $\sum_{j\in S} M_{ij} = 0$), and $R = \mathrm{diag}\{R_i \mid i \in S\}$ with $R_i := H_{ii} - M_{ii}$. Clearly, the decomposition in (2) is unique, and M is irreducible iff H is, because $G(M) = G(H)$. M_{ij} is the rate at which an i-individual produces j-offspring ($j \neq i$), and R_i is the net rate at which individuals of type i reproduce themselves; this may also include death terms and thus be negative.

Solutions of (1) cannot vanish altogether (unless $y(0) = 0$), since $\mathrm{tr}(H)$ is finite, hence $\det\big(\exp(tH)\big) = \exp(t\,\mathrm{tr}(H)) > 0$ and $\ker\big(\exp(tH)\big) = \{0\}$, for all $t \geqslant 0$. Therefore, we may also consider the corresponding normalized equation for the proportions $p_i := y_i/(\sum_{j\in S} y_j)$, which is often more relevant. Clearly,

$$\dot{p}_i = \sum_{j\in S} p_j M_{ji} + \big(R_i - \sum_{j\in S} R_j p_j\big) p_i \,. \tag{3}$$

In the population genetics context, this is the mutation-selection equation for a haploid population, or a diploid one without dominance; for a comprehensive review of this class of models, see [10]. It is well known, and easy to verify, that the way back from (3) to (1) is achieved through the transformation [46]

$$y(t) := p(t) \exp\Big(\sum_{j\in S} R_j \int_0^t p_j(\tau) d\tau\Big) \,.$$

This substitution can thus be viewed as a global linearization transformation and explains why (3) is an 'essentially linear' equation. In fact, Eq. (3) appears in a variety of contexts. In particular, its discrete-time relative may be used to describe the dynamics of the age structure of a population, compare [11, Ch. 4]. Due to its

frequent appearance, a better understanding of Eq. (3) and its solutions is the main motivation for the present work.

Clearly, the solution of (3) is obtained from that of (1) through normalization:

$$y(t) = y(0)\exp(tH), \quad p(t) = \frac{y(t)}{\sum_i y_i(t)}\,.$$

Of course, proportions of types in a population that grows without restriction (which is biologically reasonable only over short time scales) do not represent the only way in which (3) may arise. Actually, the same equation for p results if (1) is replaced by

$$\dot{y} = y\big(H - \gamma(t)\big)\,,$$

where $\gamma(t)$ is some scalar (possibly nonlinear) function which describes the elimination of individuals by population regulation. This is obvious from the invariance of (3) under $R_i \to R_i + \gamma(t)$ if performed simultaneously for all i. The function $\gamma(t)$ may, for example, describe an additional death term caused by crowding, which may depend on t through y, but acts on all types in the same way.

Eq. (3) may be read in two ways (cf. [28]). If mutation and reproduction go on independently of each other, the parallel (or decoupled) version is adequate. Here, every i-individual gives birth to offspring of its own type at rate B_i, dies at rate D_i, and mutates to j at rate M_{ij} ($j \neq i$). Then $R_i := B_i - D_i$ is the net reproduction rate or Malthusian fitness [15, Ch. 5.3], and Eq. (3) is immediate. If, however, mutation is a side effect of reproduction (through copying errors of the replication process, for example), the coupled version is more relevant [1, 25]. When an i-individual reproduces (which it does, as before, at rate B_i, while it dies at rate D_i), the offspring is of type j with probability V_{ij} ($\sum_j V_{ij} = 1$). This leads to

$$\dot{p}_i = \Big(\sum_{j\in S} p_j B_j V_{ji}\Big) - \Big(D_i + \sum_{j\in S} R_j p_j\Big)p_i\,, \tag{4}$$

where, again, $R_i = B_i - D_i$. But if we set $M_{ij} := B_i(V_{ij} - \delta_{ij})$, we arrive again at Eq. (3). In both cases, $\sum_j R_j p_j$ is the mean fitness of the population. Obviously, a mixture of both the parallel and the coupled mutation mechanisms can be tackled in a similar way. Furthermore, the decoupled model arises as the weak-selection weak-mutation limit of the coupled one [28], or of the corresponding model in discrete time [10, p. 98].

The model (4) also arises in the infinite population limit of the well-known Moran model with selection and mutation, see [19, Ch. 3] or [16, p. 126]. This is a *stochastic* model where, in a population of m individuals, every individual of type i reproduces at rate B_i, and the offspring, which is of type j with probability V_{ij}, replaces a randomly chosen individual in the population (possibly its own parent). To describe the entire population, let $Z_i(t)$ be the random variable that gives the number of i-individuals at time t, and $Z(t) = \big(Z_i(t)\big)_{i\in S}$. Hence, if $Z(t) = z$, and $j \neq k$, we can have transitions from z to $z + e_j - e_k$, where e_j denotes the unit vector corresponding to j. Such a transition occurs at rate $\sum_i B_i V_{ij} z_i z_k/m$. Let us look at the influence of increasing m, whence we write $Z^{(m)}(t)$ to indicate dependence on system size. As $m \to \infty$, the sequence of random processes

$Z^{(m)}(t)/m$ converges pointwise almost surely, and even uniformly for every finite interval $[0,t]$, to the solution of the differential equation (4) with $D_i \equiv 0$, and initial condition $Z^{(m)}(0)/m$ (resp. its limit as $m \to \infty$), compare [18, Thm. 11.2.1].

The linear equation (1) has a more direct stochastic interpretation in terms of a continuous-time multitype branching process. After an exponential waiting time with expectation τ_i, an individual of type i produces a random offspring with a finite expectation of b_{ij} children of type j (we will not specify the distribution explicitly since we will not fully develop the stochastic picture here). The matrix H with $H_{ij} = (b_{ij} - \delta_{ij})/\tau_i$ then is the generator of the first-moment matrix. That is, if $Z_j(t)$ is again the (random) number of individuals of type j at time t, and $\mathbb{E}^i$ the associated expectation in a population started by a single i individual at time 0, then

$$\mathbb{E}^i(Z_j(t)) = \big(\exp(tH)\big)_{ij}. \tag{5}$$

Furthermore, with the identification $y_i(t) = \mathbb{E}\big(Z_i(t)\big)$, Equation (1) then simply is the forward equation for the expectations. (See [2] or [32] for the general context of multitype branching processes, and [26] for the application to mutation-selection models.)

Important first questions concern the asymptotic properties of the systems discussed. A key to these properties is the leading eigenvalue, $\lambda_{\max}$, of H (i.e., the real eigenvalue exceeding the real parts of all other eigenvalues). If, on short time scales, unrestricted growth according to (1) is relevant, then $\lambda_{\max}$ is the asymptotic growth rate of the population (and is related to the chance of ultimate survival). The stationary distribution of types in (3) is given by the left eigenvector of H corresponding to $\lambda_{\max}$. We will call it the *present distribution* of types, as opposed to the (less well-known, but equally important) *ancestral distribution* that is obtained by picking individuals from the present distribution and following their ancestry backward in time until a new stationary state is reached. This ancestral distribution is given by the elementwise product of the left and right eigenvectors of H corresponding to $\lambda_{\max}$, with proper normalization [29,30]. The knowledge of $\lambda_{\max}$ is a prerequisite for the calculation of these eigenvectors. In the population genetics context, the present distribution is often referred to as mutation-selection balance, with $\lambda_{\max}$ as the mean fitness. Finally, and perhaps most importantly, the dependence of $\lambda_{\max}$ on certain model parameters is of great interest. For example, a lot of research has been directed towards the question of how the mean fitness changes when the mutation rate increases (i.e., when M is varied by some nonnegative scalar factor), and interesting effects have been observed, for example so-called error thresholds. They may be defined as non-analytical changes of $\lambda_{\max}$ that occur when the mutation rate surpasses a critical value, in analogy with a phase transition in physics. This is accompanied by a discontinuous change in the ancestral distribution, as well as pronounced changes in the present distribution of types; see [10, Ch. III] and [17] for general reviews, [26] for recent results and a classification of the various threshold phenomena that may occur, and [24] for a recent application to the evolution of regulatory DNA motifs.

In general, exact expressions for eigenvalues are hard to obtain if $|S|$ is large but fixed. In recent work on mutation-selection models, however, scalar or low-dimensional maximum principles for the leading eigenvalue have been identified for certain examples in a suitable continuous limit as $|S| \to \infty$, see [26,21]. It is the purpose of this paper to generalize these results to a large class of operators. We will do so under the general assumption that the Markov generator M is reversible, which means that the equilibrium flux from state i to state j is the same as that from j to i. This entails that the mutation process is the same in the forward and backward direction of time, and covers many of the frequently-used models in classical population genetics, for example, the house-of-cards model, and the random-walk mutation model with Gaussian mutant distribution (see [10, Ch. 3] for its definition, [42] for the reversibility aspect, and a more general class of reversible random-walk mutation models). Also, practically all models of nucleotide evolution that are in use in molecular population genetics, like the Jukes-Cantor, Kimura, Felsenstein, and HKY models, cf. [44] or [20, Ch. 13], are reversible. This property is particularly important in phylogenetic inference, where one relies on looking back from the present into the past.

The paper is organized as follows. In Section 2, we will apply the Rayleigh-Ritz maximum principle to our class of matrices. This leads to a high-dimensional problem, which is hard to solve in practice. An example of how the problem may be reduced to a scalar one is given in Section 3. The main results are presented in Section 4. Here, we identify fairly general conditions under which the high-dimensional problem may be reduced to a low-dimensional variational problem that yields the leading eigenvalue up to an error term of order $1/N$, in the limit $N = |S| \to \infty$. Sections 5 and 6 are devoted to the lumping procedure. They show that a large class of models on a type space S arises, in a natural way, from models defined on a 'larger' space $\mathfrak{S}$, by combining several types in $\mathfrak{S}$ into a single one in S. The general framework is set out in Section 5, and in Section 6, we apply it to the important case where $\mathfrak{S}$ is the space of all sequences of fixed length over a given alphabet. Section 7 makes the connection back to the maximum principle and shows how the lumping procedure may lead to 'effective' models (on S) to which our asymptotic results may then be applied. The Hopfield fitness function, along with sequence space mutation, emerges as an example. In Setion 8, we summarize our findings and discuss them informally, and in a more biological context.

2. The general maximum principle for reversible generators

Let us first fix our assumptions and notation. Since we assume M to be an irreducible Markov generator, Perron-Frobenius theory, cf. [31, Appendix], tells us that it has a leading eigenvalue 0 which exceeds the real parts of all other eigenvalues, and an associated strictly positive left eigenvector π. This will be normalized s.t. $\sum_i \pi_i = 1$; then, π is the stationary distribution of the Markov semigroup generated by M.

We will assume that M is reversible, i.e.,

$$\pi_i M_{ij} = \pi_j M_{ji} \tag{6}$$

for all i and j, which also entails $\pi_i H_{ij} = \pi_j H_{ji}$ since R is diagonal. Likewise, due to irreducibility, the leading eigenvalue, $\lambda_{\max}$, of H is simple; we will encounter the corresponding eigenvectors in due course.

Let us note in passing that, due to reversibility combined with irreducibility, the equilibrium distribution π of M is available explicitly as follows [34, p. 35]. Let $(v_1, v_2, \ldots, v_{|S|})$ be the vertices of the directed graph $G(M)$ (with (v_i, v_j) a directed edge iff $M_{ij} > 0$). Since $\pi_i > 0$ for all $i \in S$, (v_j, v_i) is an edge iff (v_i, v_j) is, as a consequence of (6). Now, set $\tilde{\pi}_1 = 1$ and consider any $2 \leqslant \ell \leqslant |S|$. By irreducibility, there is a directed path along $v_1 = v_{k_0}, v_{k_1}, \ldots, v_{k_m} = v_\ell$, which also exists as a path in reverse direction. If we now set

$$\tilde{\pi}_{k_\ell} = \prod_{j=1}^{m} \frac{M_{k_{j-1},k_j}}{M_{k_j,k_{j-1}}}\,, \tag{7}$$

$\pi_i = \tilde{\pi}_i / (\sum_{j\in S} \tilde{\pi}_j)$ is the stationary probability distribution of the Markov generator M. This reflects the path independence of reversible Markov chains [34, p. 35]: For any path with an arbitrary number $m+1$ of vertices $(k_0, k_1, \ldots, k_m)$ in our graph $G(M)$, the product $\prod_{j=1}^{m} (M_{k_{j-1},k_j} / M_{k_j,k_{j-1}})$ only depends on the initial and final vertices, k_0 and k_m, not on the path connecting them. Note that, if $G(M)$ admits a Hamiltonian path, the calculation in (7) can be further simplified by following such a path edge by edge.

It is well-known that reversibility has important consequences for eigenvalues and eigenvectors of a Markov generator. An excellent exposition for the closely-related discrete-time case is Chapter 2.1 of [8]. Following these lines, we now define, for $i \neq j$,

$$F_{ij} \;:=\; \sqrt{\pi_i}\, M_{ij}\, \frac{1}{\sqrt{\pi_j}} \;=\; F_{ji}\,, \tag{8}$$

where the symmetry follows from the reversibility of M. Clearly, $F_{ij} \geqslant 0$ and $F_{ij} = (F_{ij}F_{ji})^{1/2} = (M_{ij}M_{ji})^{1/2}$. As a consequence, the matrix

$$\tilde{H} := \mathit{\Pi}^{1/2} H \mathit{\Pi}^{-1/2} \tag{9}$$

with $\mathit{\Pi} := \mathrm{diag}\{\pi_i \,|\, i \in S\}$ has off-diagonal entries F_{ij}, is symmetric and has real spectrum identical to that of H, with correspondingly transformed eigenvectors. We now decompose $\tilde{H}$ in the same way as we did with H in (2), namely into a Markov generator F plus a diagonal matrix E. To this end, let $F = (F_{ij})_{i,j\in S}$ with F_{ij} as in (8) for $i \neq j$, and complete this by $F_{ii} := -\sum_{j\in S\setminus\{i\}} F_{ij}$. With

$$E_i := R_i + M_{ii} - F_{ii} = R_i + \sum_{\substack{j\in S\\ j>i}} \bigl(2\sqrt{M_{ij}M_{ji}} - (M_{ij} + M_{ji})\bigr),$$

one now has $\tilde{H}_{ij} = F_{ij} + E_i\delta_{ij}$ for all $i, j \in S$, i.e.,

$$\tilde{H} = F + E \tag{10}$$

with F a Markov generator and $E = \mathrm{diag}\{E_i \mid i \in S\}$.

This now allows us to formulate a suitable variant of the Rayleigh-Ritz (or Courant-Fisher) maximum principle for the leading eigenvalue of $\tilde{H}$, compare [41, Thm. 19.4]. Clearly,

$$\begin{aligned}\lambda_{\max} &= \sup_{v:\sum_{\ell\in S} v_\ell^2=1} \sum_{i,j\in S} v_i \tilde{H}_{ij} v_j \\ &= \sup_{v:\sum_{\ell\in S} v_\ell^2=1} \Big(\sum_{i,j\in S} v_i F_{ij} v_j + \sum_{k\in S} E_k v_k^2 \Big) , \end{aligned} \tag{11}$$

where we have used the decomposition (10) in the second step. Note that the supremum is, indeed, assumed, since the space of probability measures on S is compact. The maximizer, i.e., the normalized principal eigenvector of $\tilde{H}$, is unique and strictly positive (since the same holds for the corresponding eigenvector of H), so that the above may also be read as an L^1 variant through the substitution $\nu_i := v_i^2$.

Note that, since F is a Markov generator, the quadratic form $\sum_{i,j\in S} v_i F_{ij} v_j$ is negative semidefinite with maximum 0, which is assumed for the stationary distribution of F (since F is symmetric and irreducible, this is the equidistribution, and unique). We thus have a simple upper bound on $\lambda_{\max}$:

$$\lambda_{\max} \leqslant \sup_{v:\sum_{\ell\in S} v_\ell^2=1} \sum_{k\in S} E_k v_k^2 = \max_{k\in S} E_k \, , \tag{12}$$

while we can obtain a lower bound for any $v \geqslant 0$ with $\sum_\ell v_\ell^2 = 1$ via

$$\sum_{i,j\in S} v_i F_{ij} v_j + \sum_{k\in S} E_k v_k^2 \leqslant \lambda_{\max} \, . \tag{13}$$

Even though each step of the above derivation is elementary, it is worthwhile to summarize the findings as follows.

Proposition 1. *Let S be a finite set, and let H be an $|S|\times|S|$-matrix with decomposition $H = M + R$ into an irreducible and reversible Markov generator M and a diagonal matrix R. If π is the stationary distribution of M, H can be symmetrized to $\tilde{H} = \Pi^{1/2} H \Pi^{-1/2}$ with $\Pi = \operatorname{diag}\{\pi_i \mid i \in S\}$. The matrices H and $\tilde{H}$ are isospectral, and their leading eigenvalue $\lambda_{\max}$ is given by the maximum principle* (11). *Furthermore, simple upper and lower bounds for $\lambda_{\max}$ are provided by Eqns.* (12) *and* (13). □

It is our aim to identify conditions under which the inequality (12) becomes an equality, at least asymptotically as $|S| \to \infty$.

As a first step, consider the maximizer of (11), i.e., the principal eigenvector w of $\tilde{H}$, normalized via $\sum_{i\in S} w_i^2 = 1$. Since $\tilde{H}$ is a symmetric matrix, we have $w\tilde{H} = \lambda_{\max} w$ and, simultaneously, $\tilde{H} w^T = \lambda_{\max} w^T$. Hence,

$$z^T := c_z \Pi^{-1/2} w^T \quad \text{and} \quad h := c_h w \Pi^{1/2} \tag{14}$$

are the principal right and left eigenvectors of $H = \Pi^{-1/2} \tilde{H} \Pi^{1/2}$. We will adjust the constants c_h and c_z s.t. $\sum_i h_i = \sum_i h_i z_i = 1$; clearly, this implies $c_z \cdot c_h = 1$.

The vector h gives the stationary distribution of types in Equation (3). Furthermore, it is well-known that, for irreducible H and $t \to \infty$, the matrix $\exp(t(H - \lambda_{\max}\mathbf{1}))$ becomes a projector onto h, with matrix elements $z_i h_j$ (compare [31, Appendix]). Therefore,

$$\lim_{t\to\infty} \frac{\sum_{j\in S} \bigl(\exp(tH)\bigr)_{ij}}{\sum_{k,\ell\in S} h_k \bigl(\exp(tH)\bigr)_{k\ell}} = \frac{\sum_{j\in S} z_i h_j}{\sum_{\ell\in S} h_\ell} = z_i \,. \tag{15}$$

With (5) in mind, z_i may therefore be understood as the asymptotic offspring expectation of an i individual, relative to the mean offspring expectation of an equilibrium population. If $R = C\mathbf{1}$ for some constant C, we have $z_i \equiv 1$, in line with the fact that $H - C\mathbf{1}$ is then a Markov generator.

From (14), along with the normalization of h and z, the relations

$$h_i = \frac{\pi_i z_i}{\sum_{j\in S} \pi_j z_j} \quad \text{and} \quad w_i^2 = h_i z_i \tag{16}$$

are obvious. In particular, with

$$a_i := w_i^2 = h_i z_i > 0 \,, \tag{17}$$

we obtain the corresponding L^1-maximizer of (11).

To arrive at another interpretation of a, consider the Markov generator Q with elements

$$Q_{ij} = z_i^{-1}(H_{ij} - \lambda_{\max}\delta_{ij})z_j \,. \tag{18}$$

It is easily confirmed that Q is indeed a Markov generator (i.e., $Q_{ij} \geqslant 0$ for $i \neq j$, and $\sum_j Q_{ij} = 0$). Using (16) and reversibility, one observes that Q may also be written as

$$Q_{ij} = h_i^{-1}(H_{ji} - \lambda_{\max}\delta_{ij})h_j \,. \tag{19}$$

In this form, Q is the generator of the backward process on the stationary distribution as described in [30, Corollary 1] for general multitype branching processes, and used in [26] in the context of mutation-selection models. Loosely speaking, Q describes the Markov chain which results from picking individuals randomly from the stationary distribution h and following their lines of descent backward in time. Eq. (18) is the corresponding forward version as used in [29] and [23]. It is immediately verified that Q has principal left eigenvector (i.e., stationary distribution) a. This is known as the *ancestral distribution* of types (as mentioned in the Introduction); its properties are analyzed in [23]. Let us summarize this as follows.

Proposition 2. *Let the assumptions be as in Proposition* 1. *Then, the principal eigenvector w of $\tilde{H}$ gives the principal left and right eigenvectors of H and their mutual relations through Eqns.* (14) *and* (16). *The L^1-maximizer $a = (a_i)_{i\in S}$ of* (11) *admits the interpretation of an ancestral distribution as the stationary state of the backward Markov generator Q of* (18) *and* (19). □

3. A scalar maximum principle: An example

The maximum principle (11) is not very useful in practice if $|S|$ is large but fixed, since maximization is then over a large space. In [26], this high-dimensional maximization could be reduced to a scalar one for special choices of M and R. We will re-derive this result here in a simplified way, which will also serve as an introduction to the more general methods and results we are aiming at. Let $S = \{0, 1, \ldots, N\}$ with the following mutation scheme:

$$\boxed{0} \underset{U_1^-}{\overset{U_0^+}{\rightleftarrows}} \boxed{1} \underset{U_2^-}{\overset{U_1^+}{\rightleftarrows}} \boxed{2} \quad \cdots \quad \underset{U_{i+1}^-}{\overset{U_i^+}{\rightleftarrows}} \quad \cdots \quad \boxed{N\text{–}1} \underset{U_N^-}{\overset{U_{N-1}^+}{\rightleftarrows}} \boxed{N}$$

Suppressing the (relevant!) dependence on N in the notation, we then have

$$M_{i,i+1} = U_i^+, \quad M_{i,i-1} = U_i^- \tag{20}$$

for $i \in S$, where we set $U_N^+ = U_0^- = 0$. This is a variant of the so-called single-step mutation model of population genetics [10, Ch. III.4]. It emerges if sequences of sites (nuceotide sites or loci) are considered, and the 'type' is identified with the number of sites at which the sequence differs from a given reference sequence or wildtype; see [43] for a recent application. If fitness is a function of this number only, and if mutations occur independently of each other in continuous time, we are in the setting of the single-step mutation model.

Hence, for all $i \in S$, we have

$$F_{i,i+1} = (M_{i,i+1}M_{i+1,i})^{1/2} = (U_i^+ U_{i+1}^-)^{1/2} = F_{i+1,i} \tag{21}$$

with the obvious meaning for $i = 0$ and $i = N$; also, $F_{ij} := 0$ whenever either i or j is not in S, or if $|i - j| > 1$. In order to evaluate the lower bound in (13), let N be large, $1 \leqslant L \ll N$, and $\ell \in S$. We will use the simple test function $\nu := (\nu_0, \nu_1, \ldots, \nu_N)$ defined through

$$\nu_i = c_\ell \cdot \begin{cases} 0, & i \notin \big(\ell + [-L, L]\big) \cap S \\ 1, & i \in \big(\ell + [-L, L]\big) \cap S \end{cases}$$

with $[-L, L] := \{-L, -L+1, \ldots, L-1, L\}$, and the constant c_ℓ chosen so that $\sum_i \nu_i = 1$. That is, ν is a normalized step function around ℓ, which does not extend beyond 0 or N. If $\ell + [-L, L] \subset S$, one always has $c_\ell = 1/(2L+1)$; a short calculation shows that, in any case,

$$\frac{1}{2L+1} \leqslant c_\ell \leqslant \frac{1}{L+1}\,,$$

due to $L \ll N$. With $\nu_i = v_i^2$, the quadratic form in (11) and (13) reduces to

$$\sum_{i,j \in S} v_i F_{ij} v_j = c_\ell \sum_{i,j \in \ell + [-L,L]} F_{ij} = -c_\ell (F_{\ell-L,\ell-L-1} + F_{\ell+L,\ell+L+1})\,,$$

due to the tridiagonal nature of the Markov generator F. Since

$$\frac{1}{2}(F_{\ell-L,\ell-L-1} + F_{\ell+L,\ell+L+1}) \leqslant \max_{i\in S} F_{i,i+1} = \max_{i,j\in S} F_{ij} =: F_{\max},$$

one has

$$\Big| \sum_{i,j\in S} v_i F_{ij} v_j \Big| \leqslant \frac{2F_{\max}}{L+1}\,. \tag{22}$$

On the other hand, the second term in (11) resp. (13) (to be called the 'diagonal part' in what follows) becomes

$$\sum_{i\in S} E_i v_i^2 = c_\ell \sum_{i=\ell-L}^{\ell+L} \Big(R_i - U_i^+ - U_i^- + \sqrt{U_i^+ U_{i+1}^-} + \sqrt{U_i^- U_{i-1}^+} \Big)\,, \tag{23}$$

where $U_i^\pm := 0$ is implied whenever $i \notin S$.

Employing Landau's $\mathcal{O}$-notation [9, Ch. 1], we now assume that

$$U_i^\pm = u^\pm(x_i) + \mathcal{O}(1/N) \quad \text{and} \quad R_i = r(x_i) + \mathcal{O}(1/N) \tag{24}$$

with continuous functions u^+, u^-, and r on [0,1], and the new 'type variable' $x_i = i/N$; it is further implied that the constant in the $\mathcal{O}(1/N)$ bound is uniform for all i. (Eq. (24) differs from the scaling in [26] by a global factor of N, which means nothing but a change of the time scale.)

Define $g(x) := u^+(x) + u^-(x) - 2\sqrt{u^+(x)u^-(x)}$, let x^* be a point at which $r(x) - g(x)$ assumes its supremum, and choose $\ell := \lfloor Nx^* \rfloor$. With an appropriate scaling of L (such as $L \sim \sqrt{N}$, to be specific), the right-hand side of (22) is $\mathcal{O}(1/\sqrt{N})$. In (23), the sum has $\mathcal{O}(\sqrt{N})$ terms, which is balanced by $c_\ell = \mathcal{O}(1/\sqrt{N})$; together with (24), this turns the right-hand side of (23) into $r(x^*) - g(x^*) + \mathcal{O}(1/N)$. At the same time, the upper bound in (12) also behaves like $r(x^*) - g(x^*) + \mathcal{O}(1/N)$. Thus, the right-hand side of (22) contributes the largest error term, so that we obtain the asymptotic maximum principle

$$\lambda_{\max} = \sup_{x\in[0,1]} \big(r(x) - g(x) \big) \tag{25}$$

up to $\mathcal{O}(1/\sqrt{N})$, as $N \to \infty$.

Finally, recall from Section 2 that, for finite N, the maximizer of (11) is unique and given by the ancestral distribution $a = (h_i z_i)_{i\in S}$. However, in the limit as $N \to \infty$, uniqueness may be lost, which is also reflected by the fact that the supremum in (25) may be assumed at more than one point. It is these degenerate situations where error thresholds may occur [26].

Remark 1. The maximum principle (25) also holds for functions r and $u^\pm$ with a finite number of jumps [26]. This can be dealt with in the current framework with slightly more effort, but we avoid this here to keep the example as transparent as possible.

Remark 2. With a more careful choice for the scaling of L, one gets the quadratic form (defined by the matrix F) down to $\mathcal{O}(1/N^{1-\varepsilon})$ for arbitrary $\varepsilon > 0$, but $\mathcal{O}(1/N)$ is only obtained with the help of better (smooth) test functions. This will now be done.

4. An asymptotic maximum principle: the general case

The maximum principle allows for an asymptotic estimation of the leading eigenvalue when the Markov generator F can be considered as 'small' in a suitable sense, in comparison to the derived effective 'diagonal' part as defined by E. Before stating precise conditions and results, let us briefly discuss the heuristics behind this. Due to the symmetry of F, we can rewrite Eq. (11) as

$$\lambda_{\max} = \sup_{v:\sum_{\ell\in S} v_\ell^2=1} \Big(-\frac{1}{2}\sum_{i,j\in S} F_{ij}(v_i - v_j)^2 + \sum_{k\in S} E_k v_k^2 \Big) . \qquad (26)$$

Thus, it is obvious that the F-term favours constant v while the diagonal E-part favours v that are concentrated on the points k where E_k is maximal. Clearly, the outcome of this competition depends on some concentration and smoothness properties of the matrices involved.

For simplicity, let us now assume that our set S consists of integers or, more generally, d-tuples of integers. So, $S \subset \mathbb{Z}^d$, with $|S| < \infty$. (It will become apparent later that this is not the most general choice possible, but a relevant and convenient one, with obvious extensions.) We will now look more closely into the situation where $|S| \nearrow \infty$. Consider a family of sets

$$S = S(N), \quad S \subset \mathbb{Z}^d, \quad \text{so that} \quad |S| \sim N^d \quad \text{as } N \to \infty, \qquad (27)$$

where we suppress once again the dependence of S on N. A reasonable setup is then obtained if $\frac{1}{N}\cdot S \subset D$, where D is a compact domain in $\mathbb{R}^d$, $\frac{1}{N}\cdot S$ becomes dense in D for $N \to \infty$, and there exist functions E and f_k from $C_b^2(D,\mathbb{R})$ (i.e., twice continuously differentiable with bounded second derivatives) with

$$E_i = E\Big(\frac{i}{N}\Big) + \mathcal{O}\Big(\frac{1}{N}\Big) \qquad (28)$$

and

$$F_{ij} = f_k\Big(\frac{i}{N}\Big) + \mathcal{O}\Big(\frac{1}{N}\Big) , \qquad (29)$$

where $k = j - i$, and the constant in the $\mathcal{O}(1/N)$ bound is uniform for all i and j. More generally, one can replace $\mathcal{O}(1/N)$ in (28) and (29) by $\mathcal{O}(1/\eta(N))$ for some function $\eta(N)$ that grows with N, if that better suits the individual situation. (Note that our notation is slightly abusive in that E denotes both the matrix defined by (10), and the function approximating its elements; however, the meaning is always obvious from the context.)

Our main result will be the following theorem. For $S \subset \mathbb{Z}^d$, we will use throughout the shorthand notation $S - i := \{j - i \mid j \in S\}$.

Theorem 1. *Assume that E_i and F_{ij} are as in Eqns.* (28) *and* (29) *. Assume further that the $C_b^2(D,\mathbb{R})$ function E assumes its absolute maximum in $\mathrm{int}(D)$, and that f satisfies*

$$\sum_{k\in S-i} f_k\Big(\frac{i}{N}\Big)|k_\ell|k_m^2 \leqslant C \qquad (30)$$

for some constant C, uniformly for all $i \in S$, and $1 \leqslant \ell, m \leqslant d$. Then, there exist constants $0 \leqslant C', C'' < \infty$ such that

$$E(x^*) - \frac{C'}{N} \leqslant \lambda_{\max} \leqslant E(x^*) + \frac{C''}{N}, \tag{31}$$

where x^* is a point where $E(x)$ assumes its maximum.

Remark 3. It will become clear when we proceed that the condition on the derivatives of $E(x)$ and the $f_k(x)$ may be relaxed; it is indeed sufficient that these functions be continuous and *locally* C_b^2, in a neighbourhood of x^*.

Note that the upper bound is clear in view of Eqns. (28) and (12) (recall that the quadratic form defined by F is negative semidefinite); it can be made sharper if the order of the approximation in (28) and (29) is improved. It remains to prove the lower bound (which cannot be improved by sharpening the $\mathcal{O}(1/N)$ in (28) and (29)). We will do so by evaluating the quadratic form in (26) for a sequence of test functions of Gaussian type centred around x^* in the interior of D (and approaching a Dirac measure located at x^* with increasing N). Specifically, we will use throughout

$$v_i := c\mathrm{e}^{-\alpha N|i/N - x^*|^2} \quad \text{with } c = c(N) \quad \text{s.t.} \quad \sum_{i \in S} v_i^2 = 1, \tag{32}$$

where $\alpha > 0$ is a positive real number independent of N.

We will first consider the diagonal part and show

Proposition 3. *Let E_i be as in* (28)*, and let x^* be a point in the interior of D where $E(x)$ assumes its maximum. Let the v_i be as in Eq.* (32)*. Then,*

$$\sum_{i \in S} E_i v_i^2 = E(x^*) + \mathcal{O}\Big(\frac{1}{N}\Big)\,.$$

The upper bound in the proposition being immediate, we only need to prove the lower bound. We will use the following

Lemma 1. *Let $g\colon \mathbb{R}^d \longrightarrow \mathbb{R}_{\geqslant 0}$ be a non-negative, continuous, integrable function with $g(x) \leqslant C/(1+|x|)^{d+\varepsilon}$ for all x, and (fixed) positive constants C and ε. Then, for any $x^* \in \mathbb{R}^d$,*

$$\lim_{n \to \infty} \frac{1}{n^d} \sum_{i \in \mathbb{Z}^d} g\Big(\frac{i}{n} - nx^*\Big) = \int_{\mathbb{R}^d} g(x)\,\mathrm{d}x\,. \tag{33}$$

Proof. Note first that the sum in (33) exists for arbitrary, but fixed n due to the assumed decay condition for g. Let $b_n := \bigtimes_{k=1}^{d} (-1/2n, 1/2n]$. Then, one has $\mathbb{R}^d = \dot{\bigcup}_{i \in \mathbb{Z}^d} (i/n + b_n)$, and, for all x, there is a (unique) element γ of $\mathbb{Z}^d/n$ with $x \in (\gamma + b_n)$; this will be called $\gamma_n(x)$. We now define

$$g_n^+(x) := \sup_{z \in (\gamma_n(x) + b_n)} g(z), \quad g_n^-(x) := \inf_{z \in (\gamma_n(x) + b_n)} g(z)\,. \tag{34}$$

Since integration over $\mathbb{R}^d$ is invariant under a shift of argument, and $g_n^\pm$ are step functions, we have

$$\begin{aligned}\int_{\mathbb{R}^d} g_n^-(x)\,\mathrm{d}x &= \int_{\mathbb{R}^d} g_n^-(x-nx^*)\,\mathrm{d}x = \frac{1}{n^d}\sum_{i\in\mathbb{Z}^d} g_n^-(i/n-nx^*)\\ &\leqslant \frac{1}{n^d}\sum_{i\in\mathbb{Z}^d} g(i/n-nx^*) \leqslant \frac{1}{n^d}\sum_{i\in\mathbb{Z}^d} g_n^+(i/n-nx^*) \qquad (35)\\ &= \int_{\mathbb{R}^d} g_n^+(x-nx^*)\,\mathrm{d}x = \int_{\mathbb{R}^d} g_n^+(x)\,\mathrm{d}x\,.\end{aligned}$$

Both g_n^+ and g_n^- converge to g pointwise (since g is continuous). Furthermore, $g_n^\pm(x)$ are both bounded from above due to the properties of the assumed majorizing function, and hence $\int_{\mathbb{R}^d} g_n^-(x)\,\mathrm{d}x$ and $\int_{\mathbb{R}^d} g_n^+(x)\,\mathrm{d}x$ both converge to $\int_{\mathbb{R}^d} g(x)\,\mathrm{d}x$ as $n\to\infty$ by the dominated convergence theorem. But then, the same must be true of the sum in (35), which proves the assertion. □

Corollary 1. *For any non-negative integer k, and any $\alpha>0$*

$$\lim_{N\to\infty} N^{(k-d)/2}\sum_{i\in\mathbb{Z}^d}\Big|\frac{i}{N}-x^*\Big|^k e^{-\alpha N|i/N-x^*|^2} = \int_{\mathbb{R}^d}|x|^k e^{-\alpha|x|^2}\,\mathrm{d}x\,. \qquad (36)$$

Proof. Use Lemma 1 with $n=\sqrt{N}$ and $g(x)=|x|^k e^{-\alpha|x|^2}$. □

Lemma 2. *For any $A\subset\mathbb{Z}^d$, $\delta>0$ and $k\in\mathbb{N}$,*

$$N^{(k-d)/2}\sum_{\substack{i\in A\\ |i/N-x^*|\geqslant\delta}}\Big|\frac{i}{N}-x^*\Big|^k e^{-2\alpha N|i/N-x^*|^2} = \mathcal{O}\big(e^{-\alpha N\delta^2}\big)\,. \qquad (37)$$

Proof. Just note that

$$\begin{aligned}N^{(k-d)/2}&\sum_{\substack{i\in A\\ |i/N-x^*|\geqslant\delta}}\Big|\frac{i}{N}-x^*\Big|^k e^{-2\alpha N|i/N-x^*|^2}\\ &\leqslant e^{-\alpha N\delta^2} N^{(k-d)/2}\sum_{i\in\mathbb{Z}^d}\Big|\frac{i}{N}-x^*\Big|^k e^{-\alpha N|i/N-x^*|^2} \qquad (38)\end{aligned}$$

and apply Corollary 1 to the last expression to get the assertion. □

Corollary 2. *Corollary 1 holds true with $\mathbb{Z}^d$ replaced by $S(N)$ of* (27)*.*

Proof. Since $x^*\in\mathrm{int}(D)$, we may choose a $\delta>0$ so that $\mathbb{Z}^d\setminus S(N)\subset\{i\in\mathbb{Z}^d : |i/N-x^*|\geqslant\delta\}$. Then, the difference in the sum in (36) is $\mathcal{O}(e^{-\alpha N\delta^2})$, according to Lemma 2, with $A=S(N)$. □

Proof (of Proposition 3). Since we may write

$$\Big|\frac{i}{N}-x^*\Big|^k v_i^2 = \frac{1}{N^{k/2}}\frac{N^{(k-d)/2}|i/N-x^*|^k e^{-2\alpha N|i/N-x^*|^2}}{N^{d/2}\sum_{j\in S} e^{-2\alpha N|i/N-x^*|^2}}\,,$$

Lemma 2 and Corollary 2 entail that, for $k>0$,

$$\sum_{\substack{i\in S(N)\\ |i/N-x^*|\geqslant\delta}} \Big|\frac{i}{N}-x^*\Big|^k v_i^2 = \mathcal{O}(e^{-\alpha N\delta^2}) \tag{39}$$

and

$$\sum_{\substack{i\in S(N)\\ |i/N-x^*|<\delta}} \Big|\frac{i}{N}-x^*\Big|^k v_i^2 = \mathcal{O}\Big(\frac{1}{N^{k/2}}\Big)\,. \tag{40}$$

So far, we have only used that x^* is in $\mathrm{int}(D)$. But x^* is also a point where $E(x)$ assumes its maximum, and $E(x)$ is twice differentiable in a neighbourhood of x^*. Hence, there exist $\delta>0$ and $0\leqslant C<\infty$, such that, for all $|x-x^*|<\delta$, $E(x)\geqslant E(x^*)-C|x-x^*|^2$. Therefore,

$$\begin{aligned}\sum_{i\in S} v_i^2E_i &= \mathcal{O}\Big(\frac{1}{N}\Big)+\sum_{\substack{i\in S\\ |i/N-x^*|<\delta}} E\Big(\frac{i}{N}\Big)v_i^2+\sum_{\substack{i\in S\\ |i/N-x^*|\geqslant\delta}} E\Big(\frac{i}{N}\Big)v_i^2\\ &\geqslant E(x^*)\big(1+\mathcal{O}(e^{-\alpha N\delta^2})\big)-C\sum_{\substack{i\in S\\ |i/N-x^*|<\delta}}\Big|\frac{i}{N}-x^*\Big|^2 v_i^2\\ &\quad+\mathcal{O}\Big(\frac{1}{N}\Big)+\inf_{x\in D}\big(E(x)\big)\sum_{\substack{i\in S\\ |i/N-x^*|\geqslant\delta}} v_i^2\\ &= E(x^*)+\mathcal{O}\Big(\frac{1}{N}\Big),\end{aligned}$$

where we have used (28) along with normalization in the first, (39) in the second, and (39) and (40) in the last step. This proves the assertion of Proposition 3. □

After dealing with the diagonal part, we are now ready to embark on the quadratic form.

Proposition 4. *Let F_{ij} be as in* (29)*, and assume that f satisfies condition* (30) *of Theorem 1. Then,*

$$\sum_{i,j\in S} v_iF_{ij}v_j = \mathcal{O}\Big(\frac{1}{N}\Big)\,.$$

Proof. Evaluating the difference between $|i/N-x^*|^2=\langle i/N-x^*,i/N-x^*\rangle$ and $|j/N-x^*|^2=\langle j/N-x^*,j/N-x^*\rangle$, we first note that $|j/N-x^*|^2-|i/N-x^*|^2=\langle (i+j)/N-2x^*,(j-i)/N\rangle$ (here, $\langle .\,,.\rangle$ denotes the scalar product). In view of $v_i=ce^{-\alpha N\langle i/N-x^*,i/N-x^*\rangle}$, and with $j=i+k$,

$$v_i>v_{i+k}\iff \eta(i,k):=\Big\langle\frac{2i+k}{N}-2x^*,\frac{k}{N}\Big\rangle>0$$

(note that $\eta(i,0)=0$). Using $F_{ij}=F_{ji}$ (see (8)), $(v_i-v_j)^2=(v_j-v_i)^2$, and $F_{i,i+k}=f_k(i/N)+\mathcal{O}(1/N)$ (see (29)), we can rewrite the quadratic form as

$$\begin{aligned}\sum_{i,j\in S} v_iF_{ij}v_j &= -\frac{1}{2}\sum_{i\in S}\sum_{k\in S-i} F_{i,i+k}(v_i-v_{i+k})^2\\ &= -\sum_{i\in S}\sum_{\substack{k\in S-i\\ \eta(i,k)>0}} F_{i,i+k}(v_i-v_{i+k})^2\\ &= -\sum_{i\in S}\sum_{\substack{k\in S-i\\ \eta(i,k)>0}} \Big(f_k\Big(\frac{i}{N}\Big)+\mathcal{O}\Big(\frac{1}{N}\Big)\Big)(v_i-v_{i+k})^2\,.\end{aligned}$$

We have thus achieved that the summation includes only terms where $v_i>v_{i+k}$, which entails that

$$v_i-v_{i+k}=ce^{-\alpha N|i/N-x^*|^2}(1-e^{-\alpha N\eta(i,k)})\leqslant c\alpha N e^{-\alpha N|i/N-x^*|^2}\eta(i,k)\,,$$

since $1-e^{-x}\leqslant\min(x,1)\leqslant x$ for $x\geqslant 0$ (of which we only use the latter inequality). Together with the fact that the quadratic form is negative semidefinite, this gives

$$\begin{aligned}0 &\geqslant -\frac{1}{2}\sum_{i\in S}\sum_{k\in S-i} F_{i,i+k}(v_i-v_{i+k})^2\\ &\geqslant -\alpha^2N^2\sum_{i\in S}v_i^2\sum_{\substack{k\in S-i\\ \eta(i,k)>0}}\Big(f_k\Big(\frac{i}{N}\Big)+\mathcal{O}\Big(\frac{1}{N}\Big)\Big)\big(\eta(i,k)\big)^2\\ &\geqslant -\alpha^2N^2\sum_{i\in S}v_i^2\sum_{k\in S-i}\Big(f_k\Big(\frac{i}{N}\Big)+\mathcal{O}\Big(\frac{1}{N}\Big)\Big)\big(\eta(i,k)\big)^2\,. \qquad (41)\end{aligned}$$

In the last step, the constraint on the sum could be removed since we added to the sum nonnegative terms only: $f_k(i/N)\geqslant 0$ for $k\neq 0$ (up to $\mathcal{O}(1/N)$), and $\big(\eta(i,k)\big)^2\geqslant 0$ with equality for $k=0$.

We now note that (30) entails that, for $1\leqslant\ell,m\leqslant d$,

$$\sum_{k\in S-i} f_k\Big(\frac{i}{N}\Big)k_\ell k_m,\quad \sum_{k\in S-i} f_k\Big(\frac{i}{N}\Big)k_\ell k_m^2,\quad\text{and}\quad \sum_{k\in S-i} f_k\Big(\frac{i}{N}\Big)k_\ell^2k_m^2/N \qquad (42)$$

are all bounded from above by a positive constant C (the latter case relies on $S/N\subset D$ with compact D). Writing

$$\begin{aligned}\big(\eta(i,k)\big)^2 &= \Big\langle 2\Big(\frac{i}{N}-x^*\Big)+\frac{k}{N},\frac{k}{N}\Big\rangle^2\\ &= \frac{1}{N^2}\sum_{\ell,m=1}^{d}k_\ell k_m\Big[4\Big(\frac{i_\ell}{N}-x_\ell^*\Big)\Big(\frac{i_m}{N}-x_m^*\Big)+4\Big(\frac{i_\ell}{N}-x_\ell^*\Big)\frac{k_m}{N}+\frac{k_mk_\ell}{N^2}\Big]\end{aligned}$$

allows us to bound the various parts of the sum in (41) as follows:

$$-4\sum_{i\in S} v_i^2 \sum_{k\in S-i} f_k\Big(\frac{i}{N}\Big) \sum_{\ell,m=1}^{d} k_\ell k_m \Big(\frac{i_\ell}{N}-x_\ell^*\Big)\Big(\frac{i_m}{N}-x_m^*\Big)$$
$$\geqslant -4Cd \sum_{m=1}^{d}\sum_{i\in S}\Big(\frac{i_m}{N}-x_m^*\Big)^2 v_i^2 = \mathcal{O}\Big(\frac{1}{N}\Big)\,, \quad (43)$$

where we used the Cauchy-Schwarz inequality for

$$\sum_{\ell,m=1}^{d} k_\ell k_m \Big(\frac{i_\ell}{N}-x_\ell^*\Big)\Big(\frac{i_m}{N}-x_m^*\Big) \leqslant \sum_{\ell=1}^{d} k_\ell^2 \sum_{m=1}^{d}\Big(\frac{i_m}{N}-x_m^*\Big)^2,$$

(42) in the first, and (39) and (40) in the last step.

Again, with (42), (39), and (40), we obtain

$$-4\sum_{i\in S} v_i^2 \sum_{\ell,m=1}^{d}\sum_{k\in S-i} f_k\Big(\frac{i}{N}\Big)\frac{k_\ell k_m^2}{N}\Big(\frac{i_\ell}{N}-x_\ell^*\Big)$$
$$\geqslant -4\frac{Cd}{N}\sum_{i\in S} v_i^2 \sum_{l=1}^{d}\Big|\frac{i_\ell}{N}-x_\ell^*\Big| = \mathcal{O}\Big(\frac{1}{N^{3/2}}\Big)\,, \quad (44)$$

where we further used that $\sum_{\ell=1}^{d}|i_\ell/N - x_\ell^*| \leqslant c|i/N - x^*|$ for some positive constant c. Finally, (42) also gives that

$$\sum_{i\in S} v_i^2 \sum_{\ell,m=1}^{d}\sum_{k\in S-i} f_k\Big(\frac{i}{N}\Big)\frac{k_\ell^2 k_m^2}{N^2} = \mathcal{O}\Big(\frac{1}{N}\Big). \quad (45)$$

Combining (43), (44), and (45), we arrive at the assertion. □

Remark 4. Eq. (45) is the reason that the lower bound in (31) cannot be improved by better approximations in (28) and (29).

Remark 5. We have, so far, assumed that x^* is in the interior of D. If x^* is on the boundary of D, a similar approach may be taken with a one-sided, exponentially decaying test function. The error in the approximation will, however, be larger than in the case tackled here.

So far, we have used the Rayleigh-Ritz variational principle (11) to obtain results on the leading eigenvalue of H, but said nothing about the maximizer (note that the latter need *not* coincide with the test function v). Recall from Section 2 that, for finite N, the maximizer is unique and – in its L^1 version – given by the ancestral distribution $a = (h_i z_i)_{i\in S}$. Actually, from the bounds above, we can also conclude that a is concentrated in a neighbourhood of x^*, where the width of the neighbourhood depends on the behaviour of E near its maximum. In the generic case of a quadratic maximum, a is concentrated in a region with a width of order $1/\sqrt{N}$. More precisely, we have:

Theorem 2. *Let E_i and F_{ij} satisfy the assumptions of Theorem 1. Assume that E assumes its maximum at a unique point $x^* \in \mathrm{int}(D)$, and that the Hessian of E at x^* is negative definite.*

Then, there is a $\rho > 0$ independent of N, so that, for every $0 < \beta \leqslant 1$ and N large enough:

$$\sum_{\substack{i \in S \\ |i/N - x^*| \geqslant \sqrt{\rho/\beta N}}} a_i \leqslant \beta \,,$$

where a is the ancestral distribution (of (17) and Prop. 2).

Proof. Recall first that the (L^2) maximizer of (11) is given by $w = (\sqrt{a_i})_{i \in S}$ (cf. (17)). Hence, by Theorem 1, the negative semidefiniteness of F, and (28), we have

$$\begin{aligned} E(x^*) - \frac{C'}{N} \leqslant \lambda_{\max} &= \sum_{i,j \in S} w_i F_{ij} w_j + \sum_{i \in S} E_i w_i^2 \\ &\leqslant \sum_{i \in S} E_i w_i^2 \leqslant \max_{i \in S} E_i = E(x^*) + \mathcal{O}\Big(\frac{1}{N}\Big) \,. \end{aligned} \tag{46}$$

Now, consider $E(x)$ in a neighbourhood of x^*. Since the Hessian at x^* is negative definite, we have $E(x) \leqslant E(x^*) - C|x - x^*|^2$ for some $C > 0$ in a neighbourhood of x^*, this being independent of N. For ε small enough and $\delta(\varepsilon) := \sqrt{\varepsilon/C}$, therefore,

$$E(x) \leqslant \begin{cases} E(x^*), & |x - x^*| < \delta(\varepsilon) \\ E(x^*) - \varepsilon, & |x - x^*| \geqslant \delta(\varepsilon). \end{cases}$$

Together with (28) and (46), this implies

$$\begin{aligned} E(x^*) + \mathcal{O}\Big(\frac{1}{N}\Big) = \sum_{i \in S} E_i w_i^2 &\leqslant E(x^*) - \varepsilon \sum_{\substack{i \in S \\ |i/N - x^*| \geqslant \delta(\varepsilon)}} w_i^2 + \mathcal{O}\Big(\frac{1}{N}\Big) \\ &\leqslant E(x^*) + \mathcal{O}\Big(\frac{1}{N}\Big) \,. \end{aligned}$$

Hence, for some positive constant γ,

$$0 \leqslant \varepsilon \sum_{\substack{i \in S \\ |i/N - x^*| \geqslant \sqrt{\varepsilon/C}}} w_i^2 \leqslant \gamma/N$$

for all sufficiently small ε. Choosing $\varepsilon = \gamma/\beta N$ and $\rho = \gamma/C$ gives the assertion. □

Remark 6. For notational simplicity, we have assumed above that $E(x)$ assumes its (absolute) maximum at a unique point x^*, which is the generic case. It is obvious from the proof, however, that an analogous result holds if the maximum is assumed at a finite number of points (each with a negative definite Hessian). Then, the ancestral distribution is concentrated on the union of the corresponding neighbourhoods of these points (or a subset thereof), again with widths of order $1/\sqrt{N}$.

Let us return to the case where $E(x)$ assumes its (absolute) maximum at a unique point x^*. We have seen that the ancestral distribution concentrates around x^* for $N \to \infty$, in the sense that any given fixed fraction $1-\beta$ (or even more) of the distribution's mass is contained in a region whose width decreases with $1/\sqrt{N}$. From this, we can further conclude that the *mean ancestral type* (in proper scaling), $(\sum_i i a_i)/N$, converges to x^*, which adds some interpretation to the maximum principle in Theorem 1. More precisely, we have

Corollary 3. *Under the assumptions of Theorem 2, we have*

$$\sum_{i\in S} \frac{i}{N} a_i = x^* + \mathcal{O}\Big(\frac{1}{N^{1/3}}\Big)\,,$$

as $N \to \infty$.

Proof. By the triangle inequality, and with a constant ρ as in Theorem 2, we have

$$\begin{aligned}\Big|\sum_{i\in S} \frac{i}{N} a_i - x^*\Big| &= \Big|\sum_{i\in S} \Big(\frac{i}{N} - x^*\Big) a_i\Big| \leqslant \sum_{i\in S} \Big|\frac{i}{N} - x^*\Big| a_i \\ &= \sum_{\substack{i\in S \\ |x^*-i/N|<\sqrt{\rho/\beta N}}} \Big|\frac{i}{N} - x^*\Big| a_i + \sum_{\substack{i\in S \\ |x^*-i/N|\geqslant\sqrt{\rho/\beta N}}} \Big|\frac{i}{N} - x^*\Big| a_i\end{aligned}$$

for all $0 < \beta \leqslant 1$. The first term is bounded by $\sqrt{\rho/\beta N}$ by construction. Due to Theorem 2 and the fact that $S/N \subset D$ with compact D, the second term is bounded by $C\beta$ for some positive constant C. Thus,

$$\Big|\sum_{i\in S} \frac{i}{N} a_i - x^*\Big| \leqslant \sqrt{\frac{\rho}{\beta N}} + C\beta$$

for all $0 < \beta \leqslant 1$ and N large enough. Choosing $\beta = \beta(N) = 1/N^{1/3}$ gives the assertion. □

Remark 7. So far, we have only considered the leading eigenvalue and the corresponding eigenvector, in 'crudest' approximation order $1/N$. Using more advanced techniques from perturbation theory [33], it would be possible to obtain results on further eigenvalues and eigenvectors, as well as higher-order error terms.

5. Lumping

Let us now drop the specific assumptions of the previous section, return to the general situation in the Introduction, and reflect on the type space S, which has, so far, remained unspecified. In the example of Section 3, the types were defined in terms of some intermediate genetic level that could be derived from a more detailed picture. In this Section, we will show that a large class of models on some type space S can be derived, in a natural way, from models defined on a 'larger' space $\mathfrak{S}$ (to be called genotype space) if the branching and mutation rates satisfy certain symmetry or compatibility conditions. The idea rests on the common assumption

that fitness depends on the genotype through an intermediate level of 'effective' parameters (which may, for example, be 'phenotypes', or 'genetic values' in quantitative genetics), and the mapping from the genotype to this intermediate level is multiple-to-one. One will therefore try and combine several of the genotypes into a single effective type; if this is also compatible with the mutation scheme, a reduction of the number of dimensions is possible. In the theory of Markov chains, this approach is known as *lumping* [35, Ch. VI]. We will proceed in two steps: First, the lumping procedure will be described in an abstract setting, with arbitrary genotype and type spaces $\mathfrak{S}$ and S, respectively. In a second step, we will specialize to the concrete sequence (or multi-locus) picture.

For the first step, let $\mathfrak{S}$ be a possibly large, but finite set. In analogy with (1), consider the dynamics

$$\dot{\rho} = \rho(\mathcal{M} + \mathcal{R}) \tag{47}$$

on $\mathbb{R}^{|\mathfrak{S}|}$, with $\mathcal{M}$ a Markov generator and $\mathcal{R} = \mathrm{diag}\{\mathcal{R}_\sigma \mid \sigma \in \mathfrak{S}\}$. For this discussion, $\mathcal{M}$ need neither be irreducible nor reversible.

Consider a mapping

$$\varphi : \mathfrak{S} \longrightarrow S = \mathrm{im}(\varphi) \tag{48}$$

so that $\mathfrak{S}$ may be understood as the disjoint union of fibres Φ_m:

$$\mathfrak{S} = \dot{\bigcup}_{m\in S} \Phi_m\,, \quad \text{with} \quad \Phi_m := \{\sigma \in \mathfrak{S} \mid \varphi(\sigma) = m\} = \varphi^{-1}(m)\,.$$

We will now give conditions under which the dynamics (47) may be reduced to a dynamics on S. The following result is a variant of a theorem by Burke and Rosenblatt [12], see also [35, Chapter VI]. The setting is illustrated in Figure 5.

Theorem 3. *Let $\mathfrak{S}$ and S be finite, let φ be the mapping of* (48)*, and assume that there are matrices $M = (M_{nm})_{n,m\in S}$ and $R = \mathrm{diag}\{R_i \mid i \in S\}$ with*

$$\mathcal{R}_\sigma = R_{\varphi(\sigma)}, \qquad \textit{for all } \sigma \in \mathfrak{S}, \tag{49}$$

$$\sum_{\tau\in\Phi_m} \mathcal{M}_{\sigma,\tau} = M_{\varphi(\sigma),m}, \quad \textit{for all } \sigma \in \mathfrak{S},\ m \in S\,, \tag{50}$$

where $\mathcal{M}$ is the Markov generator of Eq. (47)*. Then, M is a Markov generator on $\mathbb{R}^{|S|}$. If ρ solves* (47)*, then*

$$y_m := \sum_{\sigma\in\Phi_m} \rho_\sigma \tag{51}$$

satisfies the differential equation (1)*, i.e., $\dot{y}_m = \sum_n y_n(M_{nm} + R_n\delta_{nm})$. If $\mathcal{M}$ has stationary distribution $\tilde{\pi} = (\tilde{\pi}_\sigma)_{\sigma\in\mathfrak{S}}$, M has stationary distribution $\pi = (\pi_m)_{m\in S}$, where $\pi_m = \sum_{\sigma\in\Phi_m} \tilde{\pi}_\sigma$; reversibility of $\mathcal{M}$ with respect to $\tilde{\pi}$ implies that of M with respect to π. If $\mathcal{M} + \mathcal{R}$ has principal left eigenvector $\tilde{h}$, $M + R$ has principal left eigenvector h with $h_m = \sum_{\sigma\in\Phi_m} \tilde{h}_\sigma$.*

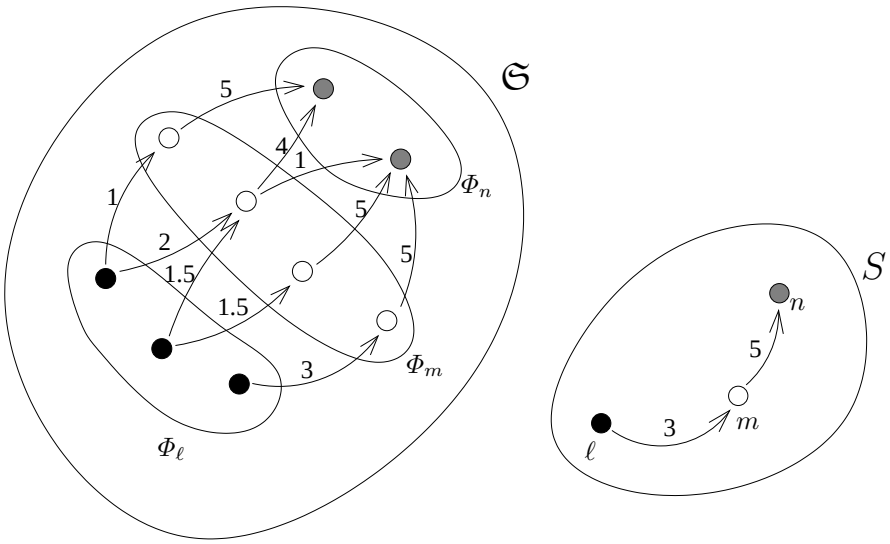

Fig. 1. The lumping procedure. The 'large' space $\mathfrak{S}$ is partitioned so that all elements in a given subset, say Φ_m, have the same reproduction rate R_m (Eq. (49)), and the same total mutation rate, $\sum_{\tau\in\Phi_n}\mathcal{M}_{\sigma,\tau}$, to elements in any other given subset Φ_n (Eq. (50)). Then, each subset may be represented by a single element in a smaller space S, and the induced 'effective' model on S is again a linear mutation-reproduction model.

Proof. The proof is a straightforward verification. Note first that M is a Markov generator (on $\mathbb{R}^{|S|}$), because, for any $\sigma\in\Phi_m$,

$$\sum_{n\in S} M_{mn} = \sum_{n\in S}\sum_{\tau\in\Phi_n}\mathcal{M}_{\sigma\tau} = \sum_{\tau\in\mathfrak{S}}\mathcal{M}_{\sigma\tau} \;=\; 0\,,$$

since $\mathcal{M}$ is a Markov generator.

Starting now from (51) and (47), we find

$$\begin{aligned}\dot{y}_m &= \sum_{\sigma\in\Phi_m}\dot{\rho}_\sigma = \sum_{\sigma\in\Phi_m}\sum_{\tau\in\mathfrak{S}}\rho_\tau(\mathcal{M}_{\tau\sigma}+\mathcal{R}_\tau\delta_{\tau\sigma})\\ &= \sum_{n\in S}\sum_{\tau\in\Phi_n}\rho_\tau\big(M_{\varphi(\tau),m}+R_{\varphi(\tau)}\delta_{\varphi(\tau),m}\big)\\ &= \sum_{n\in S} y_n(M_{nm}+R_n\delta_{nm})\,,\end{aligned}$$

where we have used (49) and (50) in the second step, and (51) in the last, together with the fact that both $M_{\varphi(\tau),m}$ and $R_{\varphi(\tau)}\delta_{\varphi(\tau),m}$ are constant on every fibre Φ_n.

Finally, the assertions on stationary distributions and reversibility are direct verifications in the same spirit. □

6. From sequence space to type space

In this Section, we will be more explicit and start from sequence space. The natural scheme that will emerge involves the grouping of sites together with a 'coarse-grained' dependence on some 'genetic distance'. Many of the frequently-used

models fall into this scheme. Related results appear in statistical physics, compare [7,6], from where we will borrow some techniques.

Let us begin with the general setup for a mutation-reproduction model on sequence space. We will assume that the type σ of an individual is characterized by a (DNA, RNA) sequence which we take to be an element of the space $\mathfrak{S} := \Sigma^N$ with $\Sigma = \{1, \dots, q\}$; we write $\sigma = (\sigma_1, \dots, \sigma_N)$. For generality, we let q be an integer $\geqslant 2$; if $q = 2$, the alternative choice $\Sigma = \{-1, 1\}$ is often more convenient. Consider now a partition of the set of sites $\Lambda = \{1, \dots, N\}$ into K disjoint subsets Λ_k, i.e.,

$$\Lambda = \dot{\bigcup}_{1 \leqslant k \leqslant K} \Lambda_k. \tag{52}$$

Let $\mathcal{P}(\Sigma) = \{(\mu_1, \dots, \mu_q) \mid \mu_\ell \geqslant 0, \sum_\ell \mu_\ell = 1\}$ denote the simplex of probability measures (or vectors) on Σ. Set, with obvious meaning,

$$\mathcal{P}_{\Lambda_k}(\Sigma) := \mathcal{P}(\Sigma) \cap \Big\{0, \frac{1}{|\Lambda_k|}, \frac{2}{|\Lambda_k|}, \dots, 1 - \frac{1}{|\Lambda_k|}, 1\Big\}^q$$

and

$$\mathcal{P}_{(\Lambda_1, \dots, \Lambda_K)}(\Sigma) = \bigotimes_{k=1}^{K} \mathcal{P}_{\Lambda_k}(\Sigma)\,. \tag{53}$$

That is, $\mathcal{P}_{(\Lambda_1, \dots, \Lambda_K)}(\Sigma)$ is the set of product measures with values restricted to certain rationals induced by the partition.

Consider now the mapping (which will take the role of φ from the previous section)

$$\mathfrak{m}:\ \Sigma^N \longrightarrow \mathbb{Q}^{Kq}, \quad \sigma \mapsto \mathfrak{m}(\sigma) \tag{54}$$

with $\mathfrak{m}(\sigma) = \big(\mathfrak{m}_k^\ell(\sigma)\big)_{1 \leqslant k \leqslant K}^{1 \leqslant \ell \leqslant q}$ and

$$\mathfrak{m}_k^\ell(\sigma) := \frac{1}{|\Lambda_k|} \sum_{s \in \Lambda_k} \delta_{\ell, \sigma_s} = \frac{1}{|\Lambda_k|} \big|\{s \mid s \in \Lambda_k, \sigma_s = \ell\}\big|\,. \tag{55}$$

So, $\mathfrak{m}_k^\ell(\sigma)$ is the fraction of the sites in Λ_k which are in state $\ell \in \Sigma$. Note that $\sum_{\ell=1}^q \mathfrak{m}_k^\ell(\sigma) = 1$, i.e., for each k, $\mathfrak{m}_k(\sigma) := \big(\mathfrak{m}_k^1(\sigma), \dots, \mathfrak{m}_k^q(\sigma)\big)$ defines a probability measure on Σ, with $\mathfrak{m}_k \in \mathcal{P}_{\Lambda_k}(\Sigma)$.

Describing the system in terms of these lumped quantities will only lead to a simplification if a suitable symmetry is available. In our case, this is given by those permutations of the sites that are compatible with the chosen partition.

Let Γ_Λ be the permutation group on $\Lambda = \{1, \dots, N\}$, i.e.,

$$\Gamma_\Lambda := \{\gamma \mid \gamma:\ \Lambda \to \Lambda \text{ is a bijection}\}\,,$$

and $\Gamma_{(\Lambda_1, \dots, \Lambda_K)}$ the subgroup compatible with the partition (52), i.e.,

$$\Gamma_{(\Lambda_1, \dots, \Lambda_K)} = \big\{\gamma \in \Gamma_\Lambda \mid \gamma(\Lambda_k) = \Lambda_k, 1 \leqslant k \leqslant K\big\} \simeq \Gamma_{\Lambda_1} \times \cdots \times \Gamma_{\Lambda_K}\,.$$

We introduce the canonical action of the permutation group on Σ^N through the inverse permutation of sites, i.e., $(\gamma\sigma)_j = \sigma_{\gamma^{-1}(j)}$. We are now ready for

Theorem 4. *Let $\Sigma^N = \{1,\dots,q\}^N$, and matrices $\mathcal{M} = (\mathcal{M}_{\sigma,\tau})_{\sigma,\tau\in\Sigma^N}$ and $\mathcal{R} = \mathrm{diag}\{\mathcal{R}_\sigma \mid \sigma \in \Sigma^N\}$ be given, with $\mathcal{M}$ a Markov generator. Let ρ solve $\dot\rho = \rho(\mathcal{M}+\mathcal{R})$. Furthermore, let $\mathfrak{m}$ be as in* (54)*, and $\hat S := \mathfrak{m}(\Sigma^N) \subset \mathbb{Q}^{Kq}$. Assume that there exist a function $g\colon\ \Sigma^N \times \Sigma^N \longrightarrow \mathbb{R}_{\geqslant 0}$, and matrices $\hat M = (\hat M_{mn})_{m,n\in\hat S}$ and $R = \mathrm{diag}\{R_n \mid n\in\hat S\}$, so that the following conditions are satisfied:*

(a) $g(\gamma\tau,\gamma\sigma) = g(\tau,\sigma)$, *for all* $\gamma \in \Gamma_{(\Lambda_1,\dots,\Lambda_K)}$;
(b) $\mathcal{M}_{\sigma\tau} = \hat M_{\mathfrak{m}(\sigma),\mathfrak{m}(\tau)}\, g(\sigma,\tau)$, *for all* $\sigma,\tau\in\Sigma^N$;
(c) $\mathcal{R}_\sigma = R_{\mathfrak{m}(\sigma)}$, *for all* $\sigma\in\Sigma^N$.

Then, $y_m := \sum_{\sigma\in\Phi_m}\rho_\sigma$ solves the differential equation $\dot y = y(M+R)$, where

$$M_{nm} = \hat M_{nm}\sum_{\tau\in\Phi_m} g(\sigma,\tau)$$

is independent of the choice of $\sigma\in\Phi_n$. Moreover, M is a Markov generator. If $\mathcal{M}$ has stationary distribution $\tilde\pi = (\tilde\pi_\sigma)_{\sigma\in\mathfrak{S}}$, M has stationary distribution $\pi = (\pi_m)_{m\in S}$, where $\pi_m = \sum_{\sigma\in\Phi_m}\tilde\pi_\sigma$; reversibility of $\mathcal{M}$ with respect to $\tilde\pi$ implies that of M with respect to π. If $\mathcal{M}+\mathcal{R}$ has principal left eigenvector $\tilde h = (\tilde h_\sigma)_{\sigma\in\mathfrak{S}}$, then $M+R$ has stationary distribution $h = (h_m)_{m\in\hat S}$ with $h_m = \sum_{\sigma\in\Phi_m}\tilde h_\sigma$.

Proof. For $\gamma\in\Gamma_{(\Lambda_1,\dots,\Lambda_K)}$, we have

$$\mathfrak{m}(\gamma\sigma) = \mathfrak{m}(\sigma) \quad\text{and}\quad \gamma(\Sigma^N) = \Sigma^N\,, \tag{56}$$

where the first identity is obvious from (55). Equation (56) entails that

$$\gamma(\Phi_m) = \Phi_m, \tag{57}$$

i.e., $\Gamma_{(\Lambda_1,\dots,\Lambda_K)}$ acts transitively on Φ_m.

In order to apply Theorem 1, we have to check assumption (50). Consider therefore $\sum_{\tau\in\Phi_m}\mathcal{M}_{\sigma\tau} = \hat M_{\mathfrak{m}(\sigma),m}\sum_{\tau\in\Phi_m} g(\sigma,\tau)$. For arbitrary $\gamma\in\Gamma_{(\Lambda_1,\dots,\Lambda_K)}$, assumption (a) and Eq. (57) give

$$\begin{aligned}\psi(\sigma) &:= \sum_{\tau\in\Phi_m} g(\sigma,\tau) = \sum_{\tau\in\Phi_m} g(\gamma\sigma,\gamma\tau)\\ &= \sum_{\tau'\in\gamma(\Phi_m)} g(\gamma\sigma,\tau') = \sum_{\tau'\in\Phi_m} g(\gamma\sigma,\tau') = \psi(\gamma\sigma)\,.\end{aligned}$$

Due to the transitivity of $\Gamma_{(\Lambda_1,\dots,\Lambda_K)}$ on Φ_m, $\psi(\sigma)$ is constant on the fibres $\Phi_{\mathfrak{m}(\sigma)}$. Assumption (50) is therefore valid, and an application of Theorem 1 then gives the desired result. □

Remark 8. The connection with the situation in Section 4 is made by setting $d = Kq$, and observing that $\tilde S/N \subset [0,1]^d =: \tilde D$. Obviously, $\tilde S$ and $\tilde D$ must take the roles of S and D. If $|\Lambda_k| \sim \alpha_k N$ with positive constants α_k, $1\le k\le K$, and $\sum_k\alpha_k = 1$, then $\tilde S$ becomes dense in $\tilde D$ as $N\to\infty$. The corresponding D is a parallelepiped with edge lengths α_k.

Examples of particular relevance emerge if g is a $\Gamma_{(\Lambda_1,\ldots,\Lambda_K)}$-invariant *distance*, such as the Hamming distance (i.e., the number of sites at which two sequences differ). A very simple case was implicit in Section 3, where the single-step mutation model on $S = \{0, 1, \ldots, N\}$ was interpreted in terms of a model on $\{-1, 1\}^N$. Here, a site in state $+1$ or -1 corresponds to a site whose state does or does not coincide with the respective state in a reference sequence (sometimes called the 'wildtype'). If the reproduction and mutation rates only depend on the Hamming distance from the reference sequence, we are in a setting with $K = 1$, $q = 2$ and hence $d = 2$, which further boils down to $d = 1$ if the restriction $\mathfrak{m}_1^1 + \mathfrak{m}_1^2 = 1$ is used (see also below). In such a simple case, the lumped model is immediate. More elaborate examples will be discussed in the next Section.

7. Towards Applications

In many examples of sequence space models, the lumping construction as described in the previous sections leads to an effective model to which the maximum principle of Section 4 may then be applied. In particular, a given example will be a case for Theorem 1 if it has the following properties:

(P1) The partition $\{\Lambda_k\}_{k=1}^K$ in (52) is relatively uniform, in the sense that there exist constants $0 < c \leqslant C < 1$ such that

$$c \leqslant \inf_{1\leqslant k\leqslant K} \frac{|\Lambda_k|}{N} \leqslant \sup_{1\leqslant k\leqslant K} \frac{|\Lambda_k|}{N} \leqslant C$$

uniformly in N. (Alternatively, this may be replaced by the single, and slightly weaker, condition $\liminf_{N\to\infty} \inf_{1\leqslant k\leqslant K} \frac{|\Lambda_k|}{N} > 0$; note that $\sum_k |\Lambda_k| = N$ by construction.) This condition ensures that $x_i = i/N$ will become a meaningful continuous type variable for $N \to \infty$.

For the next two properties, a suitable enumeration of the elements of S is required to ensure an appropriate representation of the matrices M and R.

(P2) The function g that occurs in the sequence space mutation matrix and that is required in the lumping procedure (see Theorem 4) decreases sufficiently fast away from the diagonal. Note that under condition (P1), for any σ, τ we have that

$$d_{\mathrm{H}}(\sigma, \tau) \geqslant \frac{N}{C} \, \|\mathfrak{m}(\sigma) - \mathfrak{m}(\tau)\|_1 \, ,$$

where d_{H} is the Hamming distance. Thus, if g has compact support independent of N (as in the example in Section 3), or if it decays sufficiently fast (e.g., exponentially) with d_{H}, this entails the decay condition on f in Theorem 1.

(P3) After lumping, the effective reproduction and mutation matrices R and M lend themselves to a continuous approximation. That is, $R_m = r(m) + \mathcal{O}(1/N)$ and $M_{mn} = s\big(m, n\big) + \mathcal{O}(1/N)$ with functions r and s that are $C_2^b(D, \mathbb{R})$, where the implied constant in the $\mathcal{O}(1/N)$ bound is uniform for all m and n. This entails the approximation condition on E and F in (28) and (29) that is also required for Theorem 1.

Clearly, (P2) and (P3) stipulate that the enumeration of the types is adapted to the problem. The right choice is often intuitively clear, as in the examples in Section 3, and in [21]. But sometimes more thought is required, as will be illustrated by means of a few examples and special cases below.

(E1) Some simplifications arise in the case $q = 2$, where we now use $\Sigma = \{-1, 1\}$ rather than $\{1, 2\}$. Here, the constraint $\mathfrak{m}_k^1 + \mathfrak{m}_k^2 = 1$ can be used to reduce the number of variables per subset to one. It is convenient to set $b_k \equiv \mathfrak{m}_k^1 - \mathfrak{m}_k^2$. Eq. (53) is then replaced by

$$\mathcal{P}_{(\Lambda_1,\ldots,\Lambda_K)}(\Sigma) = \bigotimes_{k=1}^{K} \{-1, -1 + \frac{2}{|\Lambda_k|}, \ldots, 1 - \frac{2}{|\Lambda_k|}, 1\}\,,$$

and we obtain the simple formula

$$b_k(\sigma) = \frac{1}{|\Lambda_k|} \sum_{s\in\Lambda_k} \sigma_s\,.$$

(E2) The case $d = 1$ (and hence $S \subset \mathbb{Z}$) corresponds to so-called 'mean field models'. They have been studied in the case where $g(\sigma, \tau) = 0$ for $d_{\mathrm{H}}(\sigma, \tau) \geqslant 1$, i.e., mutation is restricted to neighbours in sequence space (see [3,4,47,5, 26] for $q = 2$, and [27,21] for $q = 4$).

(E3) A special type of models that falls into the above class is related to fitness landscapes based on Hopfield Hamiltonians. These are special cases of spin-glass models [39] that were originally motivated by neural networks, then became prototype models for random interactions in statistical physics, and were later also used as tunably rugged fitness landscapes in biology [38,45].
Let us consider the case $q = 2$, with sequence space $\mathfrak{S} = \Sigma^N = \{-1, 1\}^N$. A Hopfield Hamiltonian then is a function that assigns to every $\sigma \in \mathfrak{S}$ an energy $\mathcal{H}_N(\sigma)$ in the following way: M elements $\xi^1, \ldots, \xi^M$ of Σ^N (known as *patterns*) are specified (usually by independent random draws from Σ^N). Given these, one defines

$$\mathcal{H}_N(\sigma) := \frac{1}{N} \sum_{\mu=1}^{M} \sum_{s,t=1}^{N} \sigma_s \sigma_t \xi_s^\mu \xi_t^\mu = N \sum_{\mu=1}^{M} \big(\omega_\mu(\sigma)\big)^2, \tag{58}$$

where

$$\omega_\mu(\sigma) := \frac{1}{N} \sum_{s=1}^{N} \sigma_s \xi_s^\mu = \frac{1}{N} \langle \sigma, \xi^\mu \rangle\,, \tag{59}$$

i.e., a sequence is assigned an energy by sitewise comparison of the sequence with all patterns (see Fig. 2). The properties (in particular, the ruggedness) of the energy landscape so defined (and to be used to assign fitness, see below) depends on the number and the particular choice of the patterns.
Let us now explain the lumping procedure for $\mathcal{H}_N(\sigma)$, as adopted from [6] and illustrated in Fig. 2 (the more general setting with $q > 2$ can be found in [22]). To this end, we associate with the collection of row vectors ξ^μ the

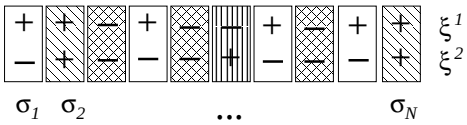

Fig. 2. Lumping in a Hopfield model with $M = 2$. Here, $\xi^1, \xi^2 \in \{-1, 1\}^N$ are two reference sequences ('patterns'). Fitness is assigned to a sequence $\sigma = (\sigma_1, \sigma_2, \ldots, \sigma_N) \in \{-1, 1\}^N$ by sitewise comparison with both patterns (Eqs. (58), (59), and (61)). This defines four subsets of sites (indicated by different shadings) so that the sites in each subset are equivalent with respect to both ξ^1 and ξ^2 and may thus be permuted without a change of fitness.

$M \times N$ matrix $\xi = (\xi_s^\mu)_{1 \leqslant s \leqslant N}^{1 \leqslant \mu \leqslant M}$. We denote by ξ^μ the rows and by ξ_s the columns of this matrix. A partition $\Lambda_1, \ldots, \Lambda_K$ with $K \leq 2^M$ is now obtained as follows. Let $e_1, \ldots, e_{2^M}$ $\left(e_k = (e_k^\mu)^{1 \leqslant \mu \leqslant M}\right)$ denote an enumeration of all M-dimensional column vectors with entries ± 1. Then we set

$$\Lambda_k := \{s \in \Lambda \mid \xi_s = e_k\} .$$

If all the Λ_k are non-empty, $K = 2^M$; otherwise, empty subsets may be omitted, and $K < 2^M$. We then have

$$\omega_\mu(\sigma) = \frac{1}{N} \sum_{k=1}^{K} e_k^\mu \sum_{s \in \Lambda_k} \sigma_s = \frac{1}{N} \sum_{k=1}^{K} |\Lambda_k| e_k^\mu b_k(\sigma) ,$$

and so

$$\mathcal{H}_N(\sigma) = N \sum_{\mu=1}^{M} \sum_{k,\ell=1}^{K} e_k^\mu e_\ell^\mu |\Lambda_k||\Lambda_\ell| b_k(\sigma) b_\ell(\sigma)$$

is a function of the $b_k(\sigma)$. Thus, if we consider reproduction and mutation rates of the form

$$\mathcal{M}_{\sigma\tau} = \alpha\big(\mathcal{H}_N(\sigma), \mathcal{H}_N(\tau)\big)\, g(\sigma, \tau) , \tag{60}$$

$$\mathcal{R}_\sigma = \beta\big(\mathcal{H}_N(\sigma)\big) , \tag{61}$$

with a nonnegative function α and any real function β, we may apply Theorem 4 to derive the effective dynamics with lumping according to the values of $b_k(\sigma)$. In particular, the choice $\beta(x) = x$ gives the familiar Hopfield fitness landscape, and $\alpha(x) \equiv 1$ along with $g(\sigma, \tau) = \mu$ for $d_H(\sigma, \tau) = 1$, $g(\sigma, \tau) = 0$ for $d_H(\sigma, \tau) > 1$, and $g(\sigma, \sigma) = -2N\mu$ yields the decoupled sequence space mutation model where every site mutates independently and at the same rate μ (e.g., [5]). It may be considered as the decoupled variant of the quasispecies model [17]; the latter may be constructed in a similar way. Both are mutation-selection models in a molecular setting and well known for their error thresholds that may occur when μ surpasses a critical value. A preliminary analysis of sequence space mutation-selection models with Hopfield fitness has been given in [38,45] and shows a rich behaviour, with various error thresholds, depending on the specific choice of patterns.

8. Summary and Discussion

The motivation for this work came from haploid mutation-selection models, or other essentially linear models, which frequently appear in population biology. These are models for relative frequencies of types (genotypes, age classes...) in a population, which turn linear after a suitable transformation to quantities that may be interpreted as the absolute frequencies that would be obtained if growth were unrestricted.

We have been mainly concerned with the leading eigenvalue of the matrix that describes this *linear* dynamics. This leading eigenvalue is the key to the asymptotic properties of the corresponding *essentially linear* model. For example, it directly yields the mutation load in a mutation-selection model. It also provides the key to the stationary distribution of types in the present as well as the ancestral population (the latter is obtained when running the process backward into the past until stationarity is reached). Furthermore, its parameter dependence determines whether error thresholds occur in a given system.

We have considered here the large class of models with a *reversible* mutation part, meaning that, in the (hypothetic) mutation equilibrium π in the absence of reproduction, the mean number of transitions between any pair of types is the same in the forward and the backward direction. This is a standard assumption in many models of population genetics. Note that any *symmetric* mutation generator is automatically reversible (because π is then the equidistribution). Many mutation models of classical population genetics are reversible (like the random-walk mutation model with Gaussian mutant distribution [10, 42]), and the same holds for practically all models of nucleotide evolution, as discussed already in Section 1. At the molecular level, reversibility is a basic assumption on which practically all model-based phylogenetic tree estimation methods rest.

Reversibility implies that the matrix H that governs the linear(ized) dynamics is similar to a symmetric one, which in turn means that its leading eigenvalue may be determined by the Raleigh-Ritz variational principle. But this alone is not very useful in practice if the number of types is large, which is the usual situation in all but a few textbook examples. The main concern of this paper, therefore, was to reduce the number of dimensions to its 'effective' number. This involved two steps: A lumping procedure that leads to an equivalent smaller, still discrete, system; and an approximation that turns the discrete system into a continuous one by replacing the discrete types by a continuous type variable. Let us discuss them in turn.

Lumping: This a kind of coarse-graining that applies if the fitness function and the mutation model on the 'original' (genotype) space $\mathfrak{S}$ have enough symmetries to allow for lumping of several states of $\mathfrak{S}$ into a single one, so that the induced 'effective' model on a smaller space S is again a mutation-reproduction model. As illustrated in Fig. 1, this works if

1. for every state m in S, all states $\sigma \in \mathfrak{S}$ that are lumped into it (i.e., all elements of the fibre Φ_m) must have the same fitness, R_m (Eq. (49)), and
2. for every element $\sigma \in \Phi_m$, the *total* mutation rate to 'target types' in Φ_n, i.e., $\sum_{\tau\in\Phi_n} \mathcal{M}_{\sigma,\tau}$, must be the same; it may depend on n and m, but not on which particular element $\sigma \in \Phi_m$ is considered. Note, however, that only the

total mutation rates are relevant, not how they are distributed across the various types in Φ_n; see Eq. (50) and Fig. 1.

Well-known examples that allow for lumping are evolution models on sequence space Σ^N, the set of possible sequences of length N over an alphabet Σ (e.g., $\Sigma = \{A, G, C, T\}$ or $\Sigma = \{-1, 1\}$), provided all sites mutate independently and according to the same process, and the fitness function is invariant under permutation of sites. Independent mutation is a perfectly natural standard assumption; permutation invariance of fitness is more of a restriction, but still a common assumption. It applies, for example, if fitness only depends on the sequence through the number of mutated positions (i.e., the Hamming distance) relative to the wildtype or some other reference sequence. Specifically, the fitness of regulatory sequences has been modelled as a hyperbolic function of their binding energy to the regulatory protein, which, in a good approximation, depends linearly on the number of mismatches relative to the perfectly matching sequence [24]. Then, $S = \{0, \ldots, N\}^d$ with $d = |\Sigma|$ is the obvious choice, where the elements of S are given by $i = (i_\ell)_{\ell\in\Sigma}$ with i_ℓ denoting the number of sites occupied by letter ℓ. In fact, $d = |\Sigma| - 1$ is also sufficient due to the constraint $\sum_{\ell\in\Sigma} i_\ell = N$. If $\Sigma = \{-1, 1\}$ and if we assume parallel mutation and selection, we arrive at a special case of the single-step mutation model in Section 3. Namely, on Σ^N, the non-diagonal elements of the mutation generator are $\mathcal{M}_{\sigma,\tau} = \mu/N$ if σ and τ differ at exactly one site, while all other elements vanish; on $S = \{0, 1, \ldots, N\}$, we get

$$U_i^+ = \mu\frac{N-i}{N} = M_{i,i+1} \quad \text{and} \quad U_i^- = \mu\frac{i}{N} = M_{i,i-1} \tag{62}$$

as the 'lumped' mutation rates (since $N - i$ and i, respectively, are the number of ways in which a sequence with i mismatches may mutate into one with $i + 1$ or $i - 1$ mismatches in one step).

For simple situations like this one, the above lumping according to the Hamming distance is routinely used, one way or another (see, e.g., [40, 24]). It is also implicit in many multilocus models; here, the original genotype is usually not considered at all, and one entirely relies on some effective model as identified with the number of mutated sites relative to some wild– or optimal type, see [36, 14].

With somewhat more effort, models with a nucleotide alphabet may be treated along the same lines [21], this time, with $d = |\Sigma| - 1 = 3$. What is less obvious is that the procedure also works for more interesting fitness functions like those that arise from Hopfield models. Here, again, $\Sigma = \{-1, 1\}$, but, this time, fitness is assigned according to the sitewise comparison of the sequence with *several* reference sequences (known as patterns). Such fitness functions have multiple peaks, are tunably rugged, and fail to be permutation invariant across all sites. Rather, the set of sites $\Lambda = \{1, 2, \ldots, N\}$ may be partitioned into $d = K$ (disjoint) subsets so that the sites in each subset are equivalent with respect to *all* reference sequences. Consequently, permutation invariance still applies within subsets, and the effective type now is a d-tuple of letter frequencies, each taken over the sites in a given subset. For details, see Section 7, and Fig. 2.

Continuous approximation: Even after lumping, the state space is usually large, typically $S = \{0, 1, \ldots, N\}^d$ with large N and moderate d. In a second simplifi-

cation step (that may, of course, be applied independently if the model was on S in the first place), we now replace the discrete variational problem by a continuous one on a compact domain $D \in \mathbb{R}^d$. As described in Section 4, the discrete type $i \in S$ is replaced by $x_i = i/N$ in S/N, and approximated by a continuous variable x in the limit $N \to \infty$. For the two-state model discussed above, $x \in [0,1]$ is simply the fraction of mutated sites relative to the reference sequence. (In population genetics, the infinite sites limit $N \to \infty$ at constant i (and hence $i/n \to 0$) is more familiar; for a discussion of how this relates to the limiting procedure here, see [26] and [5]). For models with a nucleotide alphabet, $x \in [0,1]^3$ tells us at which fraction of the sites there is a replacement of the reference letter by one of the three other nucleotides (in a suitable encoding). Finally, in the Hopfield model, $x \in [0,1]^d$ holds the fractions of sites that read '$+1$' within the d subsets.

Our *main result*, Theorem 1, now rephrases the variational problem in terms of matrices E and F that result from symmetrization of M, and hence of $M + R$. F is the symmetrized mutation matrix, as far as the non-diagonal elements are concerned; its diagonal elements are arranged so that F is a Markov generator. E is a diagonal matrix that holds both the reproduction rates and contributions from the mutation rates.

Theorem 1 now tells us that, under certain conditions on E and F, a large simplification relative to the discrete problem is obtained: The variational problem boils down to a continuous one on $D \subset \mathbb{R}^d$. If d is small, this can often be solved explicitly. Let us now first discuss these conditions, and then the result, in more detail.

The assumptions on E and F in (28), (29) and (30) appear to be rather special, but they are, in fact, very natural for many models in population genetics. The *continuous approximation of the matrices E and F*, as imposed by (28) and (29), always applies if the reproduction and mutation rates have their own continuous approximations each (i.e., $R_i = r(i/N) + \mathcal{O}(1/N)$ and $M_{ij} = u_k(i/N) + \mathcal{O}(1/N)$ with $C_b^2(D,\mathbb{R})$ functions r and u_k for all i, j, where $k = j - i$) as in the single-step mutation model (Section 3 and Eq. (62)). For lumped versions of sequence space models, the condition on the mutation part is always fulfilled; often, the continuous version is even exact, i.e. without the $\mathcal{O}(1/N)$ term, as we see from (62). As to the reproduction rates, the condition requires that the fitness function becomes locally smooth when the types become continuous (but this does not exclude ruggedness at a larger scale). Many models in population genetics rely on this assumption, in particular, the usual models of quantitative genetics (for review, see [10]).

Furthermore, F must *decay sufficiently fast away from the diagonal* (Eq. (30)). If we have a suitable distance between types and mutation decays fast enough with distance, then, with a suitable indexing, the symmetrized mutation matrix F will be concentrated around its diagonal. In the single-step mutation model, M is tridiagonal, and hence (30) is trivially satisfied. In many other models (such as the random walk mutation model with Gaussian mutant distribution), the decay is exponential and hence even faster than the cubic decay required in (30).

Under the conditions just discussed, it turns out that the remaining variational problem involves only the diagonal term E; F contributes only an 'irrelevant' $\mathcal{O}(1/N)$ term. The maximum of the continuous function $E(x)$ that approximates

the entries of E then yields the leading eigenvalue, or mean fitness, in leading order. For the single-step mutation model ($d = 1$), $E(x)$ is easily seen to be $E(x) = r(x) - g(x)$ (cf. (25)), where r is the (continuous approximation of) the fitness of type x, and $g(x)$ has a plausible interpretation as loss in fitness due to mutation [26]. The explicit expression for $E(x)$ is immediate in this case since the mutation matrix is tridiagonal. In nontrivial examples, however, more work is required to get this function explicitly; examples will be presented in a forthcoming paper.

In the generic case that $E(x)$ has a unique, quadratic maximum, we can further say that the *ancestral distribution* is concentrated around the point x^* at which $E(x)$ assumes its maximum. More precisely, any given fraction of at least $1 - \beta$ of the distribution's mass is contained in an interval centred at x^* whose width decreases as $1/\sqrt{N}$ (Theorem 2). As a consequence, x^* obtains the interpretation of the mean ancestral type, up to an error term of the order of at most $1/N^{1/3}$ (Corollary 3).

Open questions concern the stationary distribution in the *present* population, and quantities associated with it. In the single-step model, the mean type of the present population is available through the inverse function of r evaluated at $\lambda_{\max}$ (if r is monotonic); this also leads the way to other properties of the distribution, in particular, the variance of the present type, and the variance in fitness [26]. This does, however, not carry over to higher dimensions in a simple way – the present seems to be more difficult to deal with than the past! For the same reason, the criteria for the existence of error thresholds given in [26] remain to be generalized.

The motivation for this work came from continuous-time mutation-reproduction (or mutation-selection) models (cf. (1), (3) and (4)), which also set the scene for this discussion. However, it should have become clear that our results are not tied to these specific models. Our main result (Theorem 1) simply yields asymptotic estimates for the leading eigenvalues of large matrices that possess a certain continuous approximation, and whose elements decay sufficiently fast away from the diagonal. These properties are shared by many dynamical systems (in discrete and continuous time); obvious candidates are models with migration and spatially varying growth rate (see [37, Chap. II] for an overview of spatially structured population models).

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