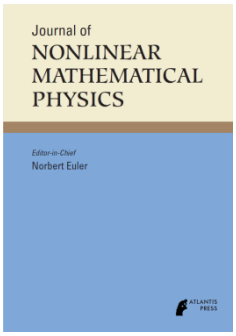

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SOME RIGOROUS RESULTS ON THE EIGEN QUASISPECIES MODEL WITH A PERIODICALLY MOVING SHARP-PEAK LANDSCAPE

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In this paper we prove some results and detail some calculations published in a previous paper by us on the Eigen model with a periodically moving sharp-peak landscape. The model is concerned with evolution of a virus population in a time-dependent environment mimicking interaction of the viruses with the immune system of a host.

Keywords: Perron–Frobenius theorem; Gershgorin theorem; error catastrophe.

2000 Mathematics Subject Classification: 92D15, 15B48, 15A18

1. Introduction

Most applications of Mathematics to real life are based on *models* and applications to biological problems are no exceptions. A model is some kind of simplification of reality hopefully useful to understand reality itself. Two frequent and contrary drawbacks in building mathematical models are oversimplification and overcomplication.

The latter is what happens when the situation is indeed too difficult or else when one is not able to separate its most relevant aspects. In this case, a mathematical model may be useless either because it involves a very large number of equations, or because equations are too complicated to be analyzed by exact or approximate methods, or because the number of parameters in the model is so large that almost any result can be obtained by a suitable choice of them. On the other hand, oversimplification frequently happens when an initially intractable model is so much simplified that it does not describe anymore the situation it was designed for.

This paper is about a more complete version of a model independently proposed and studied by Nilsson and Snoad [11] and by Ronnewinkel *et al.* [16]. Despite its usefulness — it was able of anticipating a new phenomenon — we believe their model was still oversimplified.

Although not yet fully tractable, our own version [10] of that model was simple enough to yield useful numerical results and a richer understanding of the problem.

The real life problem to be analyzed is biological evolution of a virus population in response to a dynamical environment mimicking the immune systems of a population of host organisms. After being infected by a virus strain, the immune system of an organism can usually avoid reinfection by the same strain. In order to survive, viruses are then forced to mutate in order to diguise immune systems.

A model describing a virus population subject to genetic mutations is Eigen's quasispecies model [5]. Since the original paper by M. Eigen in 1971, many more have been written up to now, dealing mainly with static environments. For a good account of the results we suggest any of the following excellent reviews [1, 4, 15]. Studies in the case of a dynamical environment were initiated around year 2000 by Nilsson and Snoad [11–13] and Wilke, Ronnewinkel and Martinetz [16, 18–20]. As we will explain below, Eigen's model is intractable in its full generality. Nonetheless, Eigen himself and many others since then were able to produce useful results by introducing suitable simplifications.

Roughly speaking a quasispecies is a population consisting mostly of individuals having the so-called *wild type* or *master sequence* genome along with mutants at not too distant sites in genome space. Mutants are considered in Genetics as the fundamental stone upon which natural selection can act and evolution result. A quasispecies is then a population whose genomes are *localized*, although not strictly, in genome space.

One important well-known feature of quasispecies models in static environments is the so-called *error catastrophe*. When mutation rates are too large, genetic information of a virus population will be lost by *delocalization* of population in genome space.

In case the environment is dynamical, besides error catastrophe a new catastrophe arises if mutation rates are too low. It was termed *adaptability catastrophe*, because in this case genetic information is lost because the population is not able to mutate rapidly enough to follow environmental changes. Prediction of the new phenomenon of adaptability catastrophe is the main result in [11, 16].

The present work is a consequence of our effort to reproduce results in [11, 16] in a less simplified version of Eigen's model. In [10] we have introduced the model which we are going to treat also here. Our main motivation was trying to rigorously justify some approximations employed in [11, 16]. It turned out that the previous results on the thresholds for the error and adaptability catastrophes were qualitatively, but not quantitatively accurate. This numerical difference could be relevant when considering the use of mutagen drugs as antiviral therapy, as suggested e.g. in [6]. Moreover, our less simplified model added detailed information on the genetic variability of the quasispecies not available in the previous works.

Whereas [10] is directed to a general audience of physicists and dealt mostly with numerical results and how they differ with respect to the previous results by Nilsson and Snoad and Ronnewinkel *et al.*, the present paper is directed to mathematical physicists and mathematical biologists and devoted to providing some mathematical details absent of [10].

Section 2 will concentrate on the initial definitions and notations regarding the Eigen quasispecies model and the static sharp-peak landscape. In Sec. 3 we will introduce the periodically moving sharp-peak landscape to be studied in this paper and the results of the analyses of that model in [11, 16]. In Sec. 4 we define what we mean by a more complete version of the model studied in [11, 16], introduce the matrices which define this model and

prove a theorem characterizing the existence of a quasispecies in our model as the region in which the Perron–Frobenius eigenvalue λ_{PF} of matrix $S^{-1}E_1^\tau$ is larger than 1. Section 5 will then be devoted to estimating this eigenvalue. We close the paper with conclusions in Sec. 6 and an appendix in which we give explicit approximate formulas for the elements of matrix E_1^τ.

Mathematical tools to be used include the Perron–Frobenius [8] and Gershgorin [2, 17] theorems, perturbation theory and an expansion of matrix elements in terms of directed graphs. Explicit approximate formulas for the Perron–Frobenius eingenvalue of $S^{-1}E_1^\tau$ were published without proof in [10]. Derivation of these formulas will be detailed in the present paper.

2. Eigen Quasispecies Model, Simplifications and the Static Sharp-peak Landscape

Let Λ denote the set of all sequences (words) written with ℓ letters chosen from an alphabet with N symbols. Elements in Λ will be thought of as possible *genomes* of individuals in a population of viruses. The alphabet in which genomes are written in nature consists of $N = 4$ letters denoting the DNA or RNA bases, but an usual and inessential simplification is to take $N = 2$, as we will do.

Another simplification we are assuming here is that the *genome length* ℓ is the same for all individuals in our population. Even for very simple individuals such as viruses we have $\ell \sim 10^3$–10^5. We will assume throughout that $\ell \gg 1$. Either using $N = 2$ or $N = 4$ the number of elements N^ℓ in Λ is much larger than any population size, even taking the smallest realistic values for ℓ.

Between elements in Λ, we introduce the *Hamming distance* $d(\sigma, \sigma')$, defined as the minimum number of letter substitutions to be performed in sequence σ to make it coincide with σ'. This is the only distance notion between genomes we will use in this paper. So, when we will later talk about nearest neighbors in genome space of a sequence σ_0, we mean sequences at Hamming distance equal to 1 from σ_0.

We will describe the virus population at time t by giving the number $p_\sigma(t)$ of individuals whose genome is $\sigma \in \Lambda$. We will consider time as discrete, each generation living one unit of time. Individuals reproduce asexually and give birth by the end of their lives to a new generation which replaces present generation. The *fitness* of an individual is the number of offspring it contributes for the next generation. It will be supposed that the population is large enough so that fitnesses can be considered as deterministic rather than random variables. We also suppose that the fitness of an individual is a function of its genome. In this paper we will be specially interested in dynamic situations in which fitnesses also depend explicitly on time. Fitnesses are then described by a *fitness landscape* $f(\sigma, t)$.

In its most general form, Eigen's quasispecies model is described by the system of N^ℓ equations

$$p_\sigma(t+1) = \sum_{\sigma' \in \Lambda} W_{\sigma,\sigma'} f(\sigma', t) p_{\sigma'}(t). \tag{2.1}$$

In the above equation, $W_{\sigma,\sigma'}$ is the probability that an individual of type σ' has offspring of type σ due to mutations. In spite of using the term probability here, we remind readers

that the model is completely deterministic. For an account of quasispecies theories for finite populations, see e.g. [14].

We remind also that most of the literature on quasispecies models is written using a continuous-time version of the above equation, leading thus to a system of ordinary differential equations. We regard the choice between continuous or discrete time as an inessential question of taste. In particular, papers [11, 16], upon which we based for proposing the model to be investigated here, adopt different choices and obtain similar results. We also quote that a slightly different quasispecies model was proposed by Crow and Kimura [3], also known as ParaMuSe model. Although the Eigen and ParaMuSe models are technically different [9], results are similar.

Many fitness landscapes have been studied, mostly in static situations. Among those we have the sharp-peak, Fujiyama and random landscapes [15]. The simplest landscape is the *sharp-peak* landscape (SPL) defined by

$$f(\sigma,t)=\begin{cases}1+k, & \text{if } \sigma=\sigma_0(t)\\ 1, & \text{if } \sigma\neq\sigma_0(t)\end{cases}, \tag{2.2}$$

where $\sigma_0(t)$ denotes the *wild type* or *master* sequence at time t. We remind here that most sequences in Λ will be unpopulated not only because it is a huge set, but also because life is very organized. We cannot hope that many genomes in Λ describe viable organisms. In fact, we should hope that most individuals in a population will have genomes equal to or close to a genome with optimal fitness, which is the master sequence. This is the motivation behind the above defined SPL. As we will also explore it further, it is useful having in mind that the wild type or master sequence may depend on time.

Parameter $k>0$ in (2.2) is the *selective advantage* of the master sequence with respect to all other sequences. Due to the linearity of (2.1), it is obvious that multiplying all fitnesses by the same constant has the trivial effect of multiplying all populations by the same constant. Thus, choice of 1 as the fitness of all nonmaster sequences in (2.2) is just a matter of convenience. Although simplistic, we will see that the SPL is already complex enough to produce interesting results.

The final ingredient necessary to fully specify evolution of the population through (2.1) is the *mutation matrix* $W_{\sigma,\sigma'}$. It is common here to assume that the mutation probability is the same at any site in a sequence, whichever symbol is present at the site. If μ denotes the *mutation rate per base*, then the above assumption implies $W_{\sigma,\sigma'}=\mu^{d(\sigma,\sigma')}(1-\mu)^{\ell-d(\sigma,\sigma')}$.

A further simplification, considering that the observed values of μ for living organisms are of order 10^{-7}–10^{-11}, is to neglect powers of μ with exponent larger than 1 in the mutation matrix. The result is

$$W_{\sigma\sigma'}=\begin{cases}1-\beta, & \text{if } \ d(\sigma,\sigma')=0\\ \mu, & \text{if } \ d(\sigma,\sigma')=1\\ 0, & \text{if } \ d(\sigma,\sigma')>1\end{cases}, \tag{2.3}$$

where we also took the opportunity to introduce the *mutation rate per genome* denoted as β and defined as

$$\beta=\mu\ell. \tag{2.4}$$

Although we will not use that solution in this paper, it must be noted that the Eigen model with the static SPL, i.e. σ_0 does not depend on time, and the mutation matrix (2.3) is exactly solvable [7].

Before we go on to explore the above described situation, let us spend some time describing some general results on the static SPL, which will be helpful later.

The Eigen model with the simple static SPL and the simplified mutation matrix (2.3) are still difficult to manage becuase (2.1) is a system of N^ℓ equations. In order to reduce the number of equations to deal with and uncouple them, it is useful to consider *error classes*. Error class Γ_k, $k = 0, 1, 2, \ldots, \ell$ is the union of all sequences in Λ at distance k from the master sequence. If $X_0(t)$ denotes the population at Γ_0, i.e. at the master sequence, and $X_1(t)$ the population at the remaining error classes $\Gamma_1, \Gamma_2, \ldots, \Gamma_\ell$ all taken together, then we obtain

$$\begin{cases} X_0(t+1) = (1-\beta)(1+k)X_0(t) \\ X_1(t+1) = \beta(1+k)X_0(t) + X_1(t) \end{cases}. \tag{2.5}$$

In deriving the above equations we have used a further approximation known as *no back-mutations* approximation. In fact it should be hoped that some of the mutating offspring of individuals in Γ_1 at time t would contribute to $X_0(t+1)$. As there are $\ell-1$ nearest neighbors of a sequence in Γ_1 in Γ_2 and only one in Γ_0, then almost all mutations of an individual in Γ_1 will result in an individual in Γ_2. As a consequence in the first of (2.5) we have neglected a contribution to $X_0(t+1)$ coming from individuals in Γ_1. This approximation makes (2.5) very easy to handle, because its first equation is independent of the second.

Start by noticing that the whole population is given by $N(t) = X_0(t) + X_1(t)$ and (2.5) implies that

$$N(t+1) = N(t) + kX_0(t), \tag{2.6}$$

showing that the population size is not constant. In order to be able to define a quasispecies as some equilibrium composition for the population, then we must not base on population numbers, but rather on *frequencies*. Denoting

$$x_j(t) = \frac{X_j(t)}{N(t)}, \tag{2.7}$$

$j = 0, 1$ the frequencies corresponding to X_0 and X_1, then (2.5) may be written in terms of frequencies as

$$\begin{cases} x_0(t+1) = \dfrac{(1-\beta)(1+k)\,x_0(t)}{1+kx_0(t)} \\ x_1(t+1) = \dfrac{\beta(1+k)\,x_0(t) + x_1(t)}{1+kx_0(t)} \end{cases}, \tag{2.8}$$

which are now nonlinear.

From the above equations it is easy to obtain the limiting behavior of the frequencies as $t \to \infty$. There are two fixed points for x_0 under the evolution (2.8): $x_0 = 0$ and $x_0 = x_0^* \equiv 1 - \beta - \beta/k$. Whereas the former always exists, the latter is biologically relevant only

if $0 < x_0^* \leq 1$, which amounts to

$$1 - \beta - \frac{\beta}{k} > 0. \tag{2.9}$$

It is easy to see that 0 is an attractive fixed point when x_0^* is not relevant and repulsive when it is relevant. On the other hand, x_0^* is always attractive whenever it is relevant. It follows that when (2.9) holds, then the limiting frequencies are $(x_0^*, 1 - x_0^*)$, and when it does not hold the limiting frequencies are $(0, 1)$.

We have a kind of "phase transition" in which the ordered phase determined by (2.9) is such that a positive fraction of the population remains in the master class. The disordered phase is such that the master sequence becomes unpopulated, even individuals with the master sequence being fitter than all others. This phenomenon, in which natural selection becomes uneffective when mutation rates β are too large or the selective advantage k is too small, was called *error catastrophe*. The error threshold separating the two phases is, by (2.9),

$$\beta_u^{\text{static}} = \frac{k}{1+k}. \tag{2.10}$$

The ordered phase will be called *quasispecies* phase.

3. The Periodically Moving SPL

The situation we want to explore in this paper is a certain dynamical version of the SPL. At a time in which a large part of a host population has been infected by — and thus acquired immunity against — viruses with a certain master sequence, it is conceivable that mutant viruses will have more chance of infecting the hosts. This situation may be modelled by considering (2.2) with a time-dependent σ_0. More concretely we assume that σ_0 remains constant for a period of τ generations and then it is *shifted* to another sequence among its ℓ nearest neighbors in Λ, which will be master for the following period of τ generations, after which another shift follows and so on.

This situation was considered by Nilsson and Snoad in [11] and by Ronnewinkel *et al.* in [16]. A slight difference between the two works is that whereas Nilsson and Snoad take a random new master sequence among all nearest neighbors of the previous one, Ronnewinkel *et al.* concentrate on a deterministic motion of the master sequence along a long path in Λ in which each successive master sequence is a nearest neighbor of the preceding one. In [10] we commented more on this difference. It turns out that taking a long deterministic path or a random path will make no difference in calculating the regions for existence of a quasispecies in the present model.

The above cited works are interesting both because their authors were the pioneers in considering dynamic fitness landscapes and also because they anticipated a new phenomenon — the *adaptability catastrophe* — connected to a second threshold β_l. We have already seen that in the static SPL a quasispecies may cease to exist because of a large mutation rate $\beta > \beta_u^{\text{static}}$. The adaptability catastrophe, absent from the static SPL, occurs when the mutation rate is too small, i.e. $\beta < \beta_l$. In this case the population is not able to adapt itself rapidly enough to the periodic shift of the master sequence. A dynamic version β_u of the static threshold β_u^{static} will also exist in the dynamic SPL. More concretely, it was

shown both in [11] and [16] that for some choices of k and τ *two* thresholds β_l and β_u will exist such that a quasispecies will exist for $\beta \in (\beta_l, \beta_u)$ and not exist outside this interval.

Both [11] and [16] use the no-back mutations approximation and describe the complete population by a vector $p_{NS}(t) = (A(t), B(t), C(t))$ in $\mathbb{R}^3$, where $A(t)$ is the number of individuals in error class $\Gamma_0(t)$, $B(t)$ is the number of individuals in the specific genome in $\Gamma_1(t)$ which will become master sequence after the next genome shift and $C(t)$ is the number of individuals in all other sequences. By using the same simplifications as in (2.5), we find that for any instants of time between successive shifts of the master sequence we have

$$p_{\mathrm{NS}}(t+1) = E_{\mathrm{NS}}\, p_{\mathrm{NS}}(t), \tag{3.1}$$

with

$$E_{\mathrm{NS}} = \begin{pmatrix} (1-\beta)(1+k) & 0 & 0 \\ \dfrac{\beta}{\ell}(1+k) & 1-\beta & 0 \\ \dfrac{\beta(\ell-1)}{\ell}(1+k) & \beta & 1 \end{pmatrix}. \tag{3.2}$$

The population evolution before the first master sequence shift is then given by $p_{\mathrm{NS}}(\tau_-) \equiv E^{\tau}_{\mathrm{NS}} p_{\mathrm{NS}}(0)$.

The effect of the master sequence shift, as in the analyses of [11, 16], is to instantly replace the population vector at time $p_{\mathrm{NS}}(\tau_-)$ by $p_{\mathrm{NS}}(\tau_+)$, which components are

$$(A(\tau_+), B(\tau_+), C(\tau_+)) = (B(\tau_-), 0, C(\tau_-) + A(\tau_-) + (\ell-1)B(\tau_-)). \tag{3.3}$$

We take then $p_{\mathrm{NS}}(\tau_+)$ as initial condition, use again (3.1) for the next cycle and so on.

In deriving (3.3) there are two new assumptions: one is that all ℓ sequences in $\Gamma_1(t)$ are equally populated with population $B(t)$ and the other is that sequences in $\Gamma_2(t)$ are so scarcely populated that we may neglect their populations.

We showed in [10] that the results in [11, 16] may be obtained from the preceding equations by exactly diagonalizing a 3×3 matrix. Because we thought the two assumptions hidden in (3.3) were too drastic we decided in the above mentioned work to propose and analyze a less simplified model for the same situation.

4. A More Complete Model for the Periodically Moving SPL

We begin by considering sequences $\sigma_1, \sigma_2, \ldots, \sigma_M$ in Λ such that $d(\sigma_i, \sigma_{i+1}) = 1$, $i = 1, 2, \ldots, M$, where we also take periodic boundary conditions identifying $\sigma_{M+1} \equiv \sigma_1$. Without loss of generality we may think of these sequences as the successive master sequences in the dynamic SPL model described above. We shall also suppose, with the obvious exceptions stated above when $i = 1$ and $j = M$ or vice-versa, that $d(\sigma_i, \sigma_j) \geq 2$ if $|i - j| \geq 2$. This last simplifying assumption means that in using approximation (2.3), individuals with genome σ_i will have offspring only with genomes σ_j where $j = i$ or $j = i \pm 1$. Such a deterministic path of master sequences in Λ is similar to what was denoted in [16] as a *regular motion* of the master sequence.

Parameter M is the number of shifts of the master sequence it takes until the first master sequence σ_1 becomes again master. In case the master sequence is shifted to a

random nearest neighbor, as in [11], then M is of order 2^ℓ with large probability of order $1-1/\ell$. Of course, having to deal with such huge matrices would not be feasible, but it will turn out that results are rather independent of M provided it is sufficiently large.

We will adopt here the deterministic point of view of [16]. In case of a random path as in [11], then condition that $d(\sigma_i,\sigma_j)\geq 2$ if $|i-j|\geq 2$ will be violated in average at each ℓ generations, thus many times during a time of $M\tau$ generations. But, as noticed in [16] and justified in [10], these violations will not change results in the random case with respect to the deterministic one.

Let $p_i(t)$ denote the number of individuals with genome σ_i at time t, $p(t)$ be the vector $(p_1(t),p_2(t),\ldots,p_M(t))$ in $\mathbb{R}^M$ and $q(t)$ be the total number of individuals in all other sequences in Λ which are not components of $p(t)$. Vector $p(t)$ will be called *relevant population* and $q(t)$ will be called *background population*. We will also consider $\hat{p}(t)=(p(t),q(t))\in\mathbb{R}^{M+1}$ and call it *complete population*.

For the first τ generations, σ_1 will be the master sequence. During this time, i.e. for $0\leq t\leq\tau-1$, Eigen's equation (2.1) with the SPL (2.2) and mutation matrix (2.3) can be written in vector form as

$$\hat{p}(t+1)=\hat{E}_1\,\hat{p}(t), \tag{4.1}$$

with $\hat{E}_1$ being the $(M+1)\times(M+1)$ matrix given in block form as

$$\hat{E}_1=\begin{pmatrix} & & & 0\\ & E_1 & & 0\\ & & & 0\\ & & & \vdots\\ & & & 0\\ \left(1-\frac{2}{\ell}\right)\beta(1+k) & \left(1-\frac{2}{\ell}\right)\beta & \cdots & \left(1-\frac{2}{\ell}\right)\beta & 1 \end{pmatrix} \tag{4.2}$$

and E_1 is the $M\times M$ matrix for evolution only of the first M components of $\hat{p}(t)$, i.e. $p(t+1)=E_1p(t)$. It is explicitly given by

$$E_1=\begin{pmatrix} (1-\beta)(1+k) & \frac{\beta}{\ell} & 0 & 0 & \cdots & 0 & \frac{\beta}{\ell}\\ \frac{\beta}{\ell}(1+k) & 1-\beta & \frac{\beta}{\ell} & 0 & \cdots & 0 & 0\\ 0 & \frac{\beta}{\ell} & 1-\beta & \frac{\beta}{\ell} & \cdots & 0 & 0\\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots\\ \frac{\beta}{\ell}(1+k) & 0 & 0 & 0 & \cdots & \frac{\beta}{\ell} & 1-\beta \end{pmatrix}. \tag{4.3}$$

More generally, for $(j-1)\tau\leq t\leq j\tau-1$ we will have

$$\hat{p}(t+1)=\hat{E}_j\,\hat{p}(t), \tag{4.4}$$

with

$$\hat{E}_j=\hat{S}^{j-1}\,\hat{E}_1\,(\hat{S}^{-1})^{j-1},$$

where the $(M+1)\times(M+1)$ matrix $\hat{S}$ in the above equation implements the master sequence shift by right-shifting (taking into account the periodic boundary condition) the first M components of the complete population vector and leaving fixed the background population

$$\hat{S} = \begin{pmatrix} 0 & 0 & \cdots & 0 & 1 & 0 \\ 1 & 0 & \cdots & 0 & 0 & 0 \\ 0 & 1 & \cdots & 0 & 0 & 0 \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ 0 & 0 & \cdots & 1 & 0 & 0 \\ 0 & 0 & \cdots & 0 & 0 & 1 \end{pmatrix}. \tag{4.5}$$

As we will also need it, we define an $M \times M$ matrix S which is simply $\hat{S}$ with the last row and the last column deleted, i.e. the restriction of $\hat{S}$ to the relevant population subspace.

With the above definitions, it is easy to see that by the end of the first cycle of τ generations, i.e. by the end of the time in which σ_1 is the master sequence, the population vector is given by $\hat{p}(\tau) = \hat{E}_1^\tau p(0)$. As the total population is not necessarily constant, then any equilibrium compositions of the population may be expected only by considering frequencies, as in the static SPL. Instead of dividing by total population and getting nonlinear equations, as in the passage from (2.5) to (2.8), we will introduce a factor to take into account a possible growth of the total population. An equilibrium population will thus be some vector $\hat{v} \in \mathbb{R}^{M+1}$ with nonnegative components in which the frequencies of the master sequence and all other considered sequences repeat themselves *with a right-shift* after τ generations, i.e.

$$\hat{E}_1^\tau \hat{v} = \hat{\lambda}\, \hat{S} \hat{v}, \tag{4.6}$$

where $\hat{\lambda}$ is the growth factor for the whole population in the time of τ generations.

Matrices and vectors having all of their components nonnegative are called *nonnegative* [8]. A special case is when all components are positive and then we will call these matrices and vectors *positive*.

In spite of $\hat{v}$ in (4.6) not being a steady-state population, but a vector of steady-state frequencies, we will still call it a *steady-state population*. By (4.6) we see that the steady-state population is an eigenvector of $\hat{S}^{-1}\hat{E}_1^\tau$ and $\hat{\lambda}$ is the corresponding eigenvalue. Of course identification of an eigenvector with a population will be possible only if $\hat{v}$ is a nonnegative vector and $\hat{\lambda} > 0$. It is clear that $\hat{v} = (0, \ldots, 0, 1)$ is always a steady-state population with $\hat{\lambda} = 1$, in which all individuals are in the background.

As matrices E_1, $\hat{E}_1$, S and $\hat{S}$ are nonnegative, then also E_1^τ, $S^{-1}E_1^\tau$, $\hat{E}_1^\tau$ and $\hat{S}^{-1}\hat{E}_1^\tau$ are all nonnegative. The Perron–Frobenius (PF) theorem, see Theorem 4.2 in Chap. I of [8], guarantees that for any nonnegative matrix G there exists $r > 0$ such that all eigenvalues $\lambda \in \mathbb{C}$ of G are such that $|\lambda| \leq r$, that r is itself an eigenvalue of G and its corresponding eigenvector can be taken nonnegative.

By using the PF theorem we guarantee existence of a nonnegative eigenvector v_{PF} with eigenvalue λ_{PF} for $S^{-1}E_1^\tau$ and similarly $\hat{v}_{\mathrm{PF}}$ and $\hat{\lambda}_{\mathrm{PF}}$ for $\hat{S}^{-1}\hat{E}_1^\tau$.

We may then prove the following

Theorem 4.1.

(i) *$\lambda_{\rm PF}$ is a simple root of the characteristic polynomial of $S^{-1}E_1^\tau$ and all other eigenvalues of this matrix have absolute value strictly smaller than $\lambda_{\rm PF}$. Furthermore $v_{\rm PF}$ has strictly positive components and positive multiples of $v_{\rm PF}$ are the only nonnegative eigenvectors of $S^{-1}E_1^\tau$.*

(ii)

$$\hat\lambda_{\rm PF} = \max\{\lambda_{\rm PF}, 1\}. \tag{4.7}$$

(iii) *If $\lambda_{\rm PF} < 1$, the only eigenvectors of $\hat S^{-1}\hat E_1^\tau$ with eigenvalue $\hat\lambda_{\rm PF} = 1$ are the multiples of the trivial $\hat v_{\rm PF} \equiv (0,\dots,0,1)$. If $\lambda_{\rm PF} > 1$, the only nonnegative eigenvectors of $\hat S^{-1}\hat E_1^\tau$ are multiples of $(0,\dots,0,1)$ and of a positive vector $\hat v_{\rm PF}$*

$$\hat v_{\rm PF} = \left(v_{\rm PF}, \frac{v_{\rm PF}\cdot w}{\lambda_{\rm PF}-1}\right), \tag{4.8}$$

where w is the vector in $\mathbb{R}^M$ whose components are $w_j = (\hat E_1^\tau)_{M+1,j}$.

Proof. Besides being nonnegative, Theorem 3.2 in Chap. IV of [8] guarantees that $S^{-1}E_1^\tau$ is also *irreducible*. Some claims in (i) follow from irreducibility by various theorems in chapter I of [8]: Theorem 4.3 ensures that $\lambda_{\rm PF}$ is a simple root, Corollary 4.2 guarantees that $v_{\rm PF}$ is *positive* and Theorem 4.4 makes sure its positive multiples are the only nonnegative eigenvectors of $S^{-1}E_1^\tau$. The claim that all other eigenvalues of $S^{-1}E_1^\tau$ have absolute value strictly smaller than $\lambda_{\rm PF}$ is due to *primitivity* of this matrix, guaranteed by Corollary 1.1 in Chap. III of [8].

By the peculiar form (4.2) it can be seen that

$$\hat E_1{}^\tau = \begin{pmatrix} E_1^\tau & 0_M \\ w & 1 \end{pmatrix}, \tag{4.9}$$

where 0_M stands for a column vector with M zeros and w is a positive line vector with M components. It follows that if $\lambda_{\rm PF} \neq 1$, we may construct from the eigenvector $v_{\rm PF}$ of $S^{-1}E_1^\tau$ an eigenvector $\hat v$ for $\hat S^{-1}\hat E_1^\tau$ with the same eigenvalue $\lambda_{\rm PF}$ in the form $\hat v = (v_{\rm PF}, v_{M+1})$, where

$$v_{M+1} = \frac{w\cdot v_{\rm PF}}{\lambda_{\rm PF}-1}.$$

This will be referred to in this proof as *augmentation construction*. Furthermore, $\hat v$ will be positive if $\lambda_{\rm PF} > 1$.

Vice-versa, if the vector v obtained by deleting the last component in an eigenvector $\hat v$ of $\hat S^{-1}\hat E_1{}^\tau$ is not the zero vector, then it is an eigenvector of $S^{-1}E_1^\tau$ with the same eigenvalue. This will be called the *deletion construction*.

As $\hat S^{-1}\hat E_1^\tau$ is reducible, we must use more indirect arguments in proving (ii) and (iii). Begin by noticing that by the deletion construction, if $\hat v_{\rm PF}$ is not parallel to $(0,\dots,0,1)$, then we may obtain a nonnegative eigenvector of $S^{-1}E_1^\tau$ with eigenvalue $\hat\lambda_{\rm PF}$. By the uniqueness property for $v_{\rm PF}$ in (i), we must have either $\lambda_{\rm PF} = \hat\lambda_{\rm PF}$ or $\hat v_{\rm PF} = (0,\dots,0,1)$.

If $\lambda_{\mathrm{PF}} > 1$ the augmentation construction produces a positive eigenvector for $\hat{S}^{-1}\hat{E}_1{}^{\tau}$ with eigenvalue λ_{PF}. It follows then that $\hat{\lambda}_{\mathrm{PF}} \geq \lambda_{\mathrm{PF}} > 1$ and hence $\hat{v}_{\mathrm{PF}} \neq (0, \ldots, 0, 1)$. In this case, the argument in the preceding paragraph forces that $\hat{\lambda}_{\mathrm{PF}} = \lambda_{\mathrm{PF}}$. Moreover, $\hat{v}_{\mathrm{PF}}$ must be given by (4.8) or else, using the deletion construction, uniqueness of v_{PF} would be violated.

Consider now $\lambda_{\mathrm{PF}} \leq 1$. We cannot have $\hat{\lambda}_{\mathrm{PF}} > 1$, otherwise we would obtain by the deletion construction an eigenvector for $S^{-1}E_1^{\tau}$ with eigenvalue larger than λ_{PF}. We cannot have $\hat{\lambda}_{\mathrm{PF}} < 1$, either, because we already know of an eigenvector for $\hat{S}^{-1}\hat{E}_1{}^{\tau}$ with eigenvalue 1. Then $\hat{\lambda}_{\mathrm{PF}} = 1$. Finally, if $\lambda_{\mathrm{PF}} < 1$ then $\hat{v}_{\mathrm{PF}} = (0, \ldots, 0, 1)$. Otherwise, we could apply the deletion construction and obtain a nonnegative eigenvector for $S^{-1}E_1^{\tau}$ with eigenvalue 1. □

The above results imply that the Jordan block of $S^{-1}E_1^{\tau}$ associated with eigenvalue λ_{PF} is a 1×1 matrix and all other Jordan blocks are associated with eigenvalues strictly smaller than λ_{PF} in absolute value. Thus, for large enough $m \in \mathbb{N}$, almost any (in the sense of Lebesgue measure in $\mathbb{R}^M$) initial relevant population vector $p(0)$ will become after m cycles of τ generations approximately equal to $\lambda_{\mathrm{PF}}^m S^m v_{\mathrm{PF}}$. The exceptional initial relevant populations, if any, would be the ones having a zero component in the direction of v_{PF}. We were not able to determine whether there exist any nonnegative vectors having zero component in the direction of v_{PF}, but if they do exist, they are not biologically relevant because the set of these vectors has 0 Lebesgue measure.

Thus, if $\lambda_{\mathrm{PF}} < 1$, the evolution of almost any initial nonnegative complete population vector $\hat{p}(0)$ will tend to be parallel to the trivial $(0, \ldots, 0, 1)$ as the number m of cycles of τ generations goes to ∞.

If $\lambda_{\mathrm{PF}} > 1$, then almost any initial nonnegative population vector will not tend to $(0, \ldots, 0, 1)$ and will be asymptotically parallel to $\hat{v}_{\mathrm{PF}}$ as $m \to \infty$. In this case the population is not asymptotically scattered to the background sequences.

In other words, almost any initial population will preserve some genetic structure given by $\hat{v}_{\mathrm{PF}}$ if $\lambda_{\mathrm{PF}} > 1$ and lose it if $\lambda_{\mathrm{PF}} < 1$. A quasispecies will exist then if $\lambda_{\mathrm{PF}} > 1$ and not exist if $\lambda_{\mathrm{PF}} < 1$.

Knowing now that the transition between a quasispecies phase and the disordered phase is governed by λ_{PF}, we proceed to estimating this eigenvalue.

5. Estimation of λ_{PF}

5.1. *Heat analogy*

One immediate difficulty we encounter on trying to find the eigenvalues of $S^{-1}E_1^{\tau}$ is the fact that, although E_1 is rather simple, raising it to power τ complicates things. A simple analogy will be useful in understanding matrix E_1^{τ}.

Consider the diffusion equation with losses

$$\frac{\partial u}{\partial t} - D\,\frac{\partial^2 u}{\partial x^2} + \gamma\, u(x,t) = 0, \tag{5.1}$$

where D and γ are positive costants, along with the periodic boundary condition $u(0,t) = u(M,t)$. If we think of $u(x,t)$ as the temperature at point x and time t, then the equation above describes the evolution of temperatures $u(x,t)$ in a thin circular rod of length M

made of a heat-conducting material, which, due to the last term in the right-hand side, also exchanges heat with an environment at temperature 0. D is the heat conductivity and γ a coefficient describing the effectiveness of heat transfer to the environment. If the initial temperatures $u(x,0)$ are all positive, then heat is always lost to the environment.

By replacing $u(x,t)$ by a uniform mesh discretization $u(i\Delta x, j\Delta t) \equiv u_{i,j}$ and approximating the partial derivatives by their simplest discretizations, (5.1) becomes

$$u_{i,j+1} = \left(1 - \frac{2D\Delta t}{(\Delta x)^2} - \gamma\Delta t\right) u_{i,j} + \frac{D\Delta t}{(\Delta x)^2}\,(u_{i+1,j} + u_{i-1,j}). \tag{5.2}$$

The reader may see without difficulty that if the selective advantage k in (2.2) is zero, then the evolution equation $p(t+1) = E_1 p(t)$ written in components becomes exactly (5.2) if we choose $\Delta t = \Delta x = 1$ and take $D = \mu = \beta/\ell$, $\gamma = \beta(1 - 2/\ell)$.

This means that if there is no selective advantage, i.e. all genomes have the same fitness, then any initial relevant population $p(0)$ will diffuse and also be lost to the environment, to be identified here with the background population q. Notice also that as $\ell \gg 1$, then $\gamma \approx \beta \gg \mu = D$, which means that the loss of population to the background is much more relevant than the diffusion of population to nearest sites.

The effect of taking $k > 0$ is to introduce a heat source at $x = 0$. But, as heat loss dominates diffusion largely, heat produced at $x = 0$ will have almost no effect on temperatures even at points more or less close to the source. Of course E_1^τ will be analogous to the evolution operator of temperatures for τ time units.

5.2. *Directed graph calculation of* E_1^τ

Matrix E_1 is rather sparse. Its only nonzero elements are the ones in the main diagonal, in its upper and lower neighbor diagonals and, due to the periodic boundary condition, the last elements in the first row and column. This property helps simplifying the calculation of E_1^τ, as we now explain.

Let A be any $n \times n$ matrix with elements $a_{i,j}$ and m a positive integer. By using the definition of matrix product it is easy to be convinced that the matrix A^m has elements given by the graphical representation

$$(A^m)_{i,j} = \sum_{g \in \mathcal{G}_m^{(i,j)}} \prod_{e=1}^{m} a_{i_e(g), j_e(g)}. \tag{5.3}$$

In the above equation, $\mathcal{G}_m^{(i,j)}$ is the set of all directed graphs with vertices in the set $\{1, 2, \ldots, n\}$ and m edges $(i_1(g), j_1(g)), \ldots, (i_m(g), j_m(g))$ connecting vertex i to vertex j, i.e. with $i_1(g) = i$, $j_m(g) = j$ and $i_{e+1}(g) = j_e(g)$, $e = 1, 2, \ldots, m-1$.

For general matrices, the sum in (5.3) has a very large number of terms. But due to sparseness of E_1, the number of nonzero graphs contributing to the sum is much smaller if $A = E_1$. Moreover, as E_1 is nonnegative, any sum over a subset of $\mathcal{G}_\tau^{(i,j)}$ is a lower bound to the exact $(E_1^\tau)_{i,j}$. Another advantage is that nonzero elements in E_1 are of 3 possible sizes: some are equal to β/ℓ, thus much smaller than 1, some are equal to $1 - \beta$, thus $O(1)$, and finally some may be large if k is large. It is thus possible to devise approximation schemes by neglecting suitably small nonzero terms in the sum (5.3). This is done in Appendix A.

5.3. *A lower bound and an approximate formula for the PF eigenvalue*

In order to find a lower bound to the PF eigenvalue of any *irreducible* nonnegative matrix, we will use the proof method in [8] of the version of the PF theorem for irreducible matrices. For any $n \times n$ matrix A, the *Collatz–Wielandt function* f_A is defined as

$$f_A(x) = \min_{x_i \neq 0} \frac{(Ax)_i}{x_i}, \tag{5.4}$$

where x are vectors in $\mathbb{R}^n$, $(Ax)_i$ and x_i are the i-th components of the vectors Ax and x and the minimum is taken over all the indices i such that $x_i \neq 0$. A proof of the PF theorem for irreducible matrices, see e.g. [8], goes through showing that f_A attains a maximum over the set $\mathbb{P}^n$ of nonnegative vectors in $\mathbb{R}^n$, this maximum is exactly the PF eigenvalue and the vector x which maximizes f_A is the corresponding eigenvector. Then for any $x \in \mathbb{P}^n$, the PF eigenvalue r of A is such that $r \geq f_A(x)$.

We may then easily obtain useful lower bounds for r by taking suitable vectors x and calculating $f_A(x)$. An example is given in the following

Theorem 5.1. *Let A be an irreducible $n \times n$ nonnegative matrix and i, j be indices with $1 \leq i < j \leq n$. Then the PF eigenvalue r of A is bounded below by*

$$r_{i,j} = a_{j,j} + \frac{\delta_{i,j}}{1 - \delta_{i,j}} a_{j,i}, \tag{5.5}$$

where

$$\delta_{i,j} = \frac{a_{i,i} - a_{j,j} - 2a_{i,j} + \sqrt{(a_{i,i} - a_{j,j})^2 + 4a_{i,j}a_{j,i}}}{2[(a_{i,i} - a_{j,j}) + (a_{j,i} - a_{i,j})]}. \tag{5.6}$$

Proof. We take, for any pair i, j of indices with $i < j$, vectors of the form $x_{i,j}(\delta) = \delta e_i + (1 - \delta)e_j$, where $\delta \in [0, 1]$ and e_k is the k-th vector in the canonical basis of $\mathbb{R}^n$. As $x_{i,j}(\delta)$ has only two nonzero components, it is straightforward to calculate the value of δ so that $f_A(x_{i,j}(\delta))$ is maximized. The result is $\delta = \delta_{i,j}$, where $\delta_{i,j}$ is given by (5.6) and the maximum value is $r_{i,j}$ given by (5.5). □

In the concrete case of $A = S^{-1}E_1^\tau$ the lower bound in (5.5) with $i = 1$ and $j = M$ is also an excellent approximation for λ_{PF} if μ is not too small, as illustrated in Fig. 1 of [10]. Although we do not have any rigorous results on how good an approximation the lower bound is, we do have an interesting argument using ideas from Gershgorin's theorem [2, 17] explaining why it is a reasonable approximation.

Let A be any $n \times n$ matrix, not necessarily nonnegative, and i be an element in $\{1, 2 \ldots, n\}$. The i-th *Gershgorin disk* is the region

$$\mathcal{D}_i = \left\{ z \in \mathbb{C}\,; |z - a_{i,i}| \leq \sum_{\substack{j=1 \\ j \neq i}}^{n} |a_{i,j}| \right\}.$$

Gershgorin's theorem states that all eigenvalues of A are in $\mathcal{D} \equiv \bigcup_{i=1}^n \mathcal{D}_i$. Although this is usually not emphasized, Gershgorin's theorem follows as a simple corollary of the following

Lemma 5.1. *Let A be any square matrix. If λ is an eigenvalue of A with eigenvector v and the largest component of v in absolute value is the i-th, then $\lambda \in \mathcal{D}_i$.*

Proof. The i-th component of equation $(A - \lambda I)v = 0$ is

$$(a_{i,i} - \lambda)v_i + \sum_{j \neq i} a_{i,j} v_j = 0.$$

Thus

$$|(a_{i,i} - \lambda)v_i| \leq \sum_{j \neq i} |a_{i,j}|\,|v_j|,$$

where we have used the triangle inequality. Using now in the above inequality the fact that $|v_j| \leq |v_i|$ for all j, we prove that $\lambda \in \mathcal{D}_i$. □

We may now use the above lemma in conjunction with an enhanced form of Gershgorin's theorem enunciated and proved at page 977 in [2]. This enhanced form says that if A is an $n \times n$ matrix, the union $\mathcal{D}$ of all Gershgorin disks of A is $\mathcal{D} = \mathcal{C}_1 \cup \mathcal{C}_2$, where $\mathcal{C}_1$ is the union of j Gershgorin disks, $\mathcal{C}_2$ is the union of the remaining $n - j$ Gershgorin disks and $\mathcal{C}_1 \cap \mathcal{C}_2 = \varnothing$, then $\mathcal{C}_1$ contains exactly j eigenvalues of A and $\mathcal{C}_2$ contains all the remaining $n-j$ eigenvalues. This form implies of course that if $\mathcal{D}_i$ and $\cup_{j \neq i} \mathcal{D}_j$ are disjoint, then exactly one eigenvalue of A must lie in $\mathcal{D}_i$. We can then prove the following

Proposition 5.1. *If $k > 4\mu/(1 - \mu\ell - \mu)$, the largest component in absolute value of the PF eigenvector of E_1 is the first.*

Proof. By looking at the Gershgorin disks of E_1, it can be seen immediately that if $k > 0$ then $\mathcal{D}_2 = \mathcal{D}_M \supset \mathcal{D}_i$ for $3 \leq i \leq M-1$. If $k > 4\mu/(1-\mu\ell-\mu)$, $\mathcal{D}_1$ will be disjoint of the union of the other disks and any point in $\mathcal{D}_1$ will be farther from the origin of the complex plane than any point in $\cup_{j \neq 1} \mathcal{D}_j$. By the above quoted enhanced form of Gershgorin's theorem, it follows that if $k > 4\mu/(1 - \mu\ell - \mu)$, then the eigenvalue of E_1 lying in $\mathcal{D}_1$ is the PF eigenvalue.

Moreover, by Lemma 5.1 the largest component in absolute value of the PF eigenvector of E_1 must be the first. In fact, if some other component $j \neq 1$ were the largest, then the PF eigenvalue would lie in $\mathcal{D}_j$. This is absurd because $\mathcal{D}_1 \cap \mathcal{D}_j = \varnothing$ if $j \neq 1$. □

We now start the argument showing that λ_{PF} should be well approximated by $r_{1,M}$ in (5.5). Suppose then $k > 4\mu/(1 - \mu\ell - \mu)$ and also that τ is large. Dominance of the PF eigenvalue implies that $E_1^\tau v$ will point approximately in the direction of the PF eigenvector of E_1 for almost any nonnegative vector v. Thus, for almost any nonnegative v the largest component of $E_1^\tau v$ will be the first if $k > 4\mu/(1 - \mu\ell - \mu)$ and τ is large enough. Taking now $v = v_{\mathrm{PF}}$, the PF eigenvector of $S^{-1}E_1^\tau$, we see that the largest component of Sv_{PF} must be the first, because it is parallel to $E_1^\tau v_{\mathrm{PF}}$. As the first component of Sv_{PF} is the last component of v_{PF}, we obtain that for $k > 4\mu/(1 - \mu\ell - \mu)$ and τ large enough v_{PF} is a vector having its last component as the largest.

If we want to obtain the largest possible lower bounds for λ_{PF} of the form (5.5), we must choose the values of i and j according to the columns of $S^{-1}E_1^\tau$ with the largest elements. Notice first that the elements of a column of $S^{-1}E_1^\tau$ are the elements of the same column in E_1^τ in a different order. By the heat analogy or, more exactly, by the estimates

in Appendix A, elements in column 1 of E_1^τ are the largest and elements in columns 2 and M in E_1^τ are equal and larger among elements in all columns other than the first.

Thus, in order to obtain large values for $r_{i,j}$ we must take $i = 1$. The choice $j = M$ comes from the fact proved above that the M-th component of $v_{\rm PF}$ is the largest, so a vector of the form $\delta e_1 + (1-\delta)e_j$ with $j = M$ should approximate $v_{\rm PF}$ better than a vector of the same form with $j = 2$.

Although not completely rigorous, this is the argument we have for justifying that for $A = S^{-1}E_1^\tau$ lower bound (5.5) with $i = 1$, $j = M$ is a good approximation for $\lambda_{\rm PF}$. This will be the case if k and τ are large enough and also μ is not too small. The last requirement is due to the fact that if μ is too small, then the j-th components of $v_{\rm PF}$ with $j < M$ but close to M are not negligible. As can be seen in Fig. 1 of [10], the approximation indeed fails for very small μ.

In order to write an expression for the lower bound and approximate eigenvalue $r_{1,M}$ in terms of the parameters of the model, we must be able to calculate elements of matrix E_1^τ. This is done in Appendix A by using the directed graph expansion. By noticing that $(S^{-1}E_1^\tau)_{i,j} = (E_1^\tau)_{i+1,j} \equiv t_{i+1,j}$, where an index with value $M+1$ is interpreted as being equal to 1 due to the periodic boundary conditions, then (5.5, 5.6) become

$$r_{1,M} = t_{1,M} + \frac{\delta_{1,M}}{1-\delta_{1,M}}\, t_{1,1},$$

with

$$\delta_{1,M} = \frac{t_{2,1} - t_{1,M} - 2t_{2,M} + \sqrt{(t_{2,1}-t_{1,M})^2 + 4t_{2,M}t_{1,1}}}{2[(t_{2,1}-t_{1,M}) + (t_{1,1}-t_{2,M})]}.$$

and approximate expressions for the matrix elements are given by formulae (A.1, A.3, A.4, A.8).

In the numerator of the expression for $\delta_{1,M}$ we may neglect $t_{2,M}$ with respect to other terms to which it is summed outside the square root, but not inside it, in which it is multiplied by the large $t_{1,1}$. In the denominator we neglect $t_{2,1}$, $t_{1,M}$ and $t_{2,M}$ which are order μ or μ^2 when summed to the much larger $t_{1,1}$. Neglecting also terms of order k summed to terms of order $(1+k)^\tau$, we obtain

$$\delta_{1,M} \approx \frac{t_{2,1} - t_{1,M} + \sqrt{(t_{2,1}-t_{1,M})^2 + 4t_{2,M}t_{1,1}}}{2t_{1,1}} \approx \frac{(1+k)\mu}{k(1-\beta)}. \tag{5.7}$$

By this result, we are now justified in approximating $\delta_{1,M}/(1-\delta_{1,M}) \approx \delta_{1,M}$ in the expression for $r_{1,M}$. Putting it together with (A.1, A.3) and using $\mu = \beta/\ell$, we finally obtain

$$\lambda_{\rm PF} \;\approx\; r_{1,M} \approx \frac{\beta(1-\beta)^{\tau-1}(1+k)^\tau(2+k)}{k\,\ell}. \tag{5.8}$$

The above approximation was used in [10] to obtain good approximations for the phase diagram of the periodically moving SPL. It is interesting to notice that it does not depend on M, because the approximate formulas for elements $t_{i,j}$ used in deriving it are independent of M. This is in its turn a consequence of the heat analogy, in which the loss term dominates over the diffusion term.

To complete the study of the phase diagram, we should also study the behavior of $\lambda_{\rm PF}$ for very small values of μ, for which the approximation above is not good. This is done in the following subsection.

5.4. *Perturbative calculation of* $\boldsymbol{\lambda_{\rm PF}}$

By looking at (4.3) it can be seen that E_1 becomes diagonal in case we take limits $\ell \to \infty$ and $\mu \to 0$ such that $\beta = \mu\ell$ is constant. Furthermore, by a simple cofactor expansion of the determinant, we find that it is possible to exactly diagonalize $S^{-1}E_1^\tau$ in this limit. The eigenvalues of $S^{-1}E_1^\tau$ in this case are

$$\lambda_j(0) = e^{i\theta_j}\alpha\,(1-\beta)^\tau, \tag{5.9}$$

where

$$\alpha = (1+k)^{\tau/M}, \tag{5.10}$$

$$\theta_j = \frac{2\pi j}{M} \tag{5.11}$$

and $j = 0, 1, 2, \ldots, M-1$. Of course the PF eigenvalue is obtained if $j = 0$. The corresponding eigenvectors are

$$v_j(0) = \frac{1}{\alpha^M}\,(\alpha e^{i\theta_j}, \alpha^2 e^{i2\theta_j}, \ldots, \alpha^M). \tag{5.12}$$

We are now going to take $\epsilon = \ell^{-1}$ as a perturbative parameter and calculate the correction at first order in ϵ to the PF eigenvalue $\lambda_{\rm PF} \equiv \lambda_0(\epsilon)$. Let then

$$S^{-1}E_1^\tau \equiv T_0 + \epsilon T_1 + O(\epsilon^2).$$

Using the directed graph expansion we may calculate the $O(\epsilon)$ terms in E_1^τ, from which it follows that

$$T_1 = \begin{pmatrix} (1+k)\beta(1-\beta)^{\tau-1}\sigma_\tau & 0 & \tau\beta(1-\beta)^{\tau-1} & \cdots & 0 & 0 \\ 0 & \tau\beta(1-\beta)^{\tau-1} & 0 & \cdots & 0 & 0 \\ 0 & 0 & \tau\beta(1-\beta)^{\tau-1} & \cdots & 0 & 0 \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ (1+k)\beta(1-\beta)^{\tau-1}\sigma_\tau & 0 & 0 & \cdots & \tau\beta(1-\beta)^{\tau-1} & 0 \\ 0 & \beta(1-\beta)^{\tau-1}\sigma_\tau & 0 & \cdots & 0 & \beta(1-\beta)^{\tau-1}\sigma_\tau \end{pmatrix}, \tag{5.13}$$

where we have abbreviated

$$\sigma_\tau = \sum_{j=0}^{\tau-1}(1+k)^j = \frac{(1+k)^\tau - 1}{k}. \tag{5.14}$$

Writing

$$\lambda_{\rm PF} = \lambda_0(\epsilon) = \lambda_0(0) + \epsilon\lambda_{01},$$

$$v_0(\epsilon) = v_0(0) + \epsilon v_{01},$$

expanding

$$T v_0(\epsilon) = \lambda_0(\epsilon)\, v_0(\epsilon)$$

in powers of ϵ and neglecting terms $O(\epsilon^2)$ or higher we obtain

$$T_1 v_0(0) + T_0 v_{01} = \lambda_{01} v_0(0) + \lambda_0(0) v_{01}. \tag{5.15}$$

We can also calculate $v_0^*(0)$, the left-eigenvector of T_0 with eigenvalue $\lambda_0(0)$, or equivalently, the eigenvector of the transpose of T_0 with eigenvalue $\lambda_0(0)$. We find

$$v_0^*(0) = \frac{1}{M}\,(\alpha^{M-1}, \alpha^{M-2}, \cdots, \alpha, 1),$$

where the normalization was chosen such that

$$\langle\, v_0^*(0), v_0(0)\,\rangle = 1.$$

Taking then the scalar product of (5.15) at left with $v_0^*(0)$, using the above normalization and noticing that

$$\langle\, v_0^*(0), T_0 v_{01}\,\rangle = \lambda_0(0) \langle\, v_0^*(0), v_{01}\,\rangle$$

we obtain

$$\lambda_{01} = \langle v_0^*(0), T_1 v_0(0)\rangle.$$

Now, after calculating a tedious matrix product and simplifying, the result is

$$\lambda_{01} = \beta(1-\beta)^{\tau-1}\left\{\tau\left(1-\frac{2}{M}\right)[1+(1+k)^{\frac{2\tau}{M}}] + \frac{k+2}{Mk}[(1+k)^{\tau} - (1+k)^{-\tau}]\right\}. \tag{5.16}$$

Notice that despite (5.8) does not depend on M, both the 0-th order term (5.9) and the above first order correction do depend on M. In the comparison with numerically calculated $\lambda_{\rm PF}$, both the dependence on M for small β and the (almost) independence for larger β were illustrated in Fig. 1 of [10], which shows good agreement between the estimates and the numerical values in both regions. Notice also that our perturbative result has a limit when $M \to \infty$

$$\lambda_{\rm PF} = (1-\beta)^{\tau}\left(1 + \frac{2\tau\beta}{\ell(1-\beta)}\right) + O(\frac{1}{\ell^2}). \tag{5.17}$$

This should be thought as the relevant approximation for $\lambda_{\rm PF}$ at the small β region, because with large probability $M = O(2^{\ell})$, a huge number.

So, while the perturbative result for finite M gives a finite region close to $\beta = 0$ in which $\lambda_{\rm PF} > 1$, (5.17) shows that this region vanishes when $M \to \infty$, in accordance with the results in [11, 16].

6. Conclusions

Calculating eigenvalues for huge matrices is known to be a hard numerical task. Although there are still rigor gaps to be filled in the present calculations, we feel the results here and in [10] are more logically satisfying than the ones in [11, 16]. The model considered here is more complete and still treatable without having to resort to unjustified approximations.

Using the approximations derived in this paper we could qualitatively justify the conclusions of the above papers regarding the existence of two thresholds for the existence of a quasispecies. But these thresholds are not quantitatively equal to the ones in [11, 16], mainly for small selective advantages k. This was illustrated at Fig. 4 in [10]. This numerical difference might be important if using mutagen drugs as antiviral therapy [6].

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Appendix A. Approximating the elements of E_1^τ

It is necessary to have explicit formulas for the elements of matrix E_1^τ in order to produce both approximations (5.8) and (5.17) for $\lambda_{\rm PF}$. In this appendix we will obtain some of such approximate formulas by using the directed graph expansion outlined in Subsec. 5.2.

Denote then $E_1^\tau \equiv T$, with elements $t_{i,j}$. We start with $t_{1,n}$. In this and other calculations we shall think of the order M of matrix E_1 as very large, $M \gg \tau$. Graphs contributing to $t_{1,n}$ start at vertex 1 and should arrive to vertex n in τ steps; thus $t_{1,n} = 0$ if $\tau+1 < n < M+1-\tau$.

At first, we have

$$t_{1,1} \approx (1+k)^\tau (1-\beta)^\tau, \tag{A.1}$$

which comes from the single graph with τ edges connecting vertex 1 to itself. All other graphs contributing to $t_{1,1}$ are of order at μ^2 and will be neglected.

For $2 \le n \le \tau + 1$, the minimum number of edges in the graph contributing with the smaller elements $(E_1)_{i,i\pm1} = \mu$ is $n-1$. Graphs with larger numbers of such edges are thus depleted with respect to graphs with $n-1$ such edges by a factor of at least μ^2 and will be neglected. Within this approximation we thus have, for $2 \le n \le \tau + 1$,

$$\begin{aligned} t_{1,n} &\approx \mu^{n-1} \sum_{j=0}^{\tau+1-n} c_{n-1,j} [(1+k)(1-\beta)]^{\tau+1-n-j} (1-\beta)^j \\ &= (1-\beta)^{\tau+1-n} \mu^{n-1} \sum_{j=0}^{\tau+1-n} c_{n-1,j} (1+k)^{\tau+1-n-j}, \end{aligned} \tag{A.2}$$

where

$$c_{n-1,j} = \binom{j+n-2}{n-2}$$

is a combinatorial factor giving the number of ways j indistinguishable objects can be put in $n-1$ distinguishable boxes.

Formula (A.2) may be understood by noticing that $c_{n-1,j}$ is the number of graphs contributing to $t_{1,n}$ which have, besides $n-1$ edges of type $(E_1)_{i,i-1}$, $\tau+1-n-j$ edges of type $(E_1)_{1,1} = (1+k)(1-\beta)$ and, consequently, j edges of type $(E_1)_{i,i}$ with $i \geq 2$. Fortunately, summation in (A.2) may be exactly calculated.

The case $n = 2$ is very easy, because $c_{1,j} = 1$ and we only have to sum a finite geometric progression. For $n = 3$, we have $c_{2,j} = j + 1$. Then

$$\sum_{j=0}^{\tau-2} c_{2,j}(1+k)^{\tau-2-j} = \frac{\partial}{\partial x} \sum_{j=0}^{\tau-1} x^j (1+k)^{\tau-1-j} \Bigg|_{x=1}$$

$$= \frac{\partial}{\partial x} \frac{(1+k)^\tau - x^\tau}{1+k-x} \Bigg|_{x=1} = \frac{(1+k)^\tau - (1+\tau k)}{k^2}.$$

The other cases may be handled by taking successive derivatives. In general we get

$$t_{1,n} \approx \begin{cases} \mu^{n-1}(1-\beta)^{\tau+1-n} \dfrac{(1+k)^\tau - \sum_{j=0}^{n-2} \binom{\tau}{j} k^j}{k^{n-1}}, & \text{if } \; n \leq \tau+1 \\ \mu^{M+1-n}(1-\beta)^{\tau+n-M-1} \dfrac{(1+k)^\tau - \sum_{j=0}^{M-n} \binom{\tau}{j} k^j}{k^{M+1-n}}, & \text{if } \; M+1-\tau \leq n \leq M \\ 0, & \text{if } \; \tau+2 \leq n \leq M-\tau \end{cases}, \tag{A.3}$$

where the sum in the first line is interpreted as being 0 if $n = 1$ and the approximate equality means that graphs which are not of the leading order in parameter μ were neglected.

For the terms $t_{n,1}$ with $n \geq 2$ we may notice that graphs contributing to $t_{n,1}$ are exactly the same contributing to $t_{1,n}$ but with all edges reversed. Almost all factors due to edges remain exactly the same with the only modification that in the graphs considered in the above (A.3) there is exactly one edge representing $(E_1)_{1,2} = \mu$ and it will be replaced by $(E_1)_{2,1} = (1+k)\mu$. Thus we may use (A.3) to obtain to leading order in μ

$$t_{n,1} \approx (1+k)\, t_{1,n}, \quad \text{if} \quad n > 1. \tag{A.4}$$

For the diagonal elements $t_{n,n}$ at lines $n \neq 1$, the leading contribution in powers of μ is $(1-\beta)^\tau$. For $n \gg 2$ and $M+1-n \gg 1$, i.e. "central" lines in the matrix, column 1 is too far to influence $t_{n,n}$. By this we mean that, in the heat analogy, heat injected at $x = 0$ has a negligible influence at $x = n$ because losses and diffusion from nearby locations are dominant. Then we may approximate

$$t_{n,n} \approx (1-\beta)^\tau. \tag{A.5}$$

Again in the central lines approximation, we have

$$t_{n,n\pm j} \approx \binom{\tau}{j} \mu^j (1-\beta)^{\tau-j} \quad \text{if} \quad j \leq \tau, \tag{A.6}$$

where the combinatorial coefficient accounts for the number of ways of choosing j factors μ in a product of τ factors and

$$t_{n,n\pm j} = 0 \quad \text{if} \quad j > \tau. \tag{A.7}$$

An important result in deducing (5.8) is an estimate for $t_{2,M}$. The easiest way to get it is a recursive calculation:

$$(E_1^\tau)_{2,M} = \sum_{j=1}^{M} (E_1^{\tau-1})_{2,j}\,(E_1)_{j,M}.$$

The only nonzero terms in the preceding sum are for $j = 1, M-1, M$ and we have

$$(E_1^\tau)_{2,M} = \mu[(E_1^{\tau-1})_{2,1} + (E_1^{\tau-1})_{2,M-1}] + (1-\beta)\,(E_1^{\tau-1})_{2,M}.$$

Neglecting the term with $(E_1^{\tau-1})_{2,M-1}$, which is of larger order in μ, iterating and using (A.4) to approximate $(E_1^j)_{2,1}$ we finally get

$$t_{2,M} \approx \frac{\mu^2(1+k)(1-\beta)^{\tau-2}}{k^2}\,[(1+k)^\tau - (1+k) - k(\tau-1)]. \tag{A.8}$$

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