

Quasispecies on class–dependent fitness landscapes

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Abstract

We study Eigen’s quasispecies model in the asymptotic regime where the length of the genotypes goes to ∞ and the mutation probability goes to 0. We give several explicit formulas for the stationary solutions of the limiting system of differential equations.

1 Introduction

Manfred Eigen introduced the quasispecies model in his 1971 celebrated article about the first stages of life on Earth [7]. As a part of his article, Eigen constructed a model in order to explain the evolution of a population of macromolecules subject to selection and mutation forces. Given a set of genotypes \mathcal{G} , a fitness function $A : \mathcal{G} \rightarrow [0, \infty[$ and a mutation kernel $M : \mathcal{G} \times \mathcal{G} \rightarrow [0, 1]$, Eigen’s model states that the concentration x_v of the genotype $v \in \mathcal{G}$ evolves according to the differential equation

$$x'_v(t) = \sum_{u \in \mathcal{G}} x_u(t) A(u) M(u, v) - x_v(t) \sum_{u \in \mathcal{G}} x_u(t) A(u).$$

The first term accounts for the production of individuals having genotype v , production due to erroneous replication of other genotypes as well as faithful replication of itself. The negative term accounts for the loss of individuals having genotype v , and keeps the total concentration of individuals constant. Instead of studying the model in all its generality, Eigen considered the following simplified setting:

Genotypes. They are sequences of fixed length $\ell \geq 1$ over a finite alphabet \mathcal{A} of cardinality κ . The set of genotypes is then \mathcal{A}^ℓ .

Selection. It is given by the *sharp peak landscape*, i.e., there is a genotype $w^* \in \mathcal{A}^\ell$, called the master sequence, having fitness $\sigma > 1$, while all the other genotypes have fitness 1. The fitness function $A : \mathcal{A}^\ell \rightarrow [0, \infty[$ is thus given by

$$\forall u \in \mathcal{A}^\ell \quad A(u) = \begin{cases} \sigma & \text{if } u = w^*, \\ 1 & \text{if } u \neq w^*. \end{cases}$$

Mutations. They happen during reproduction, independently at random over each site of the sequence, with probability $q \in [0, 1]$. When a mutation happens, the letter is replaced by another one, chosen uniformly at random over the $\kappa - 1$ other letters of the alphabet. The mutation kernel is thus given by

$$\forall u, v \in \mathcal{A}^\ell \quad M(u, v) = \left(\frac{q}{\kappa - 1} \right)^{d(u, v)} (1 - q)^{\ell - d(u, v)},$$

where d is the Hamming distance, i.e., the number of different digits between two sequences:

$$\forall u, v \in \mathcal{A}^\ell \quad d(u, v) = \text{card}\{l \in \{1, \dots, \ell\} : u(l) \neq v(l)\}.$$

Eigen drew two main conclusions from the study of this simplified model: there is an error threshold phenomenon for the mutation probability and a so-called quasispecies regime for subcritical mutation probabilities. Indeed, when the length of the sequences goes to ∞ , an error threshold phenomenon arises: there exists a critical mutation probability, separating two totally different regimes. For supercritical mutation probabilities the population at equilibrium is totally random, whereas for subcritical mutation probabilities the population at equilibrium is distributed as a quasispecies, i.e., there is a positive fraction of the master sequence present in the population along with a cloud of mutants that closely resemble the master sequence.

After Eigen's proposal of the quasispecies model, many other authors have investigated it, both in the simple setting we have just presented and in more general settings. Eigen, McCaskill and Schuster [8] studied the model in great detail. As pointed out by them, one of the main challenges related to Eigen's model is to find the distribution of the quasispecies: the concentration of the master sequence and the concentrations of the different mutants in the population at equilibrium. It is generally impossible to give explicit formulas for these concentrations. Jones, Enns and Rangnekar [10] and Thompson and McBride [25] give an exact solution of the quasispecies by linearising Eigen's system of differential equations. In the same spirit, Swetina and Schuster [24] use this linearisation to characterise the stationary distribution

of the quasispecies as the eigenvector corresponding to the highest eigenvalue of the linearised system matrix. Saakian and Hu [18] derive exact solutions for the quasispecies model by assuming a certain ansatz; Saakian [16] and Saakian, Biebricher and Hu [17] derive the distribution for several different fitness landscapes, in particular for smooth landscapes. Novozhilov and Semenov [21, 22] and Bratus, Novozhilov and Semenov [2, 20] obtain more concrete results for the quasispecies distribution for several special cases of the mutation kernel and the fitness function.

The aim of this article is to present a scheme in order to obtain explicit formulas. The key ingredients to this scheme are twofold: we break the space of genotypes into Hamming classes and we study the asymptotic regime where the length of the chains ℓ goes to ∞ , the mutation probability goes to 0 and ℓq goes to $a \in]0, \infty[$. The idea comes from the articles [4, 5], where the authors consider a Moran model in order to recover the error threshold phenomenon as well as the quasispecies for a finite-population stochastic model. The Moran model is studied in the setting we have just introduced: genotypes given by \mathcal{A}^ℓ , sharp peak landscape and independent mutations per locus. Eigen's model is recovered in the infinite population limit [6], the error threshold phenomenon is also recovered, and an explicit formula is obtained for the distribution of the quasispecies. We illustrate now how the two ingredients mentioned above make possible to obtain such a formula, by applying our scheme directly to Eigen's model.

Hamming classes. The genotype space \mathcal{A}^ℓ is broken into Hamming classes with respect to the master sequence. To this end we define the mapping $H : \mathcal{A}^\ell \longrightarrow \{0, \dots, \ell\}$ by setting

$$\forall u \in \mathcal{A}^\ell \quad H(u) = d(u, w^*).$$

The mapping H induces a fitness function $A_H : \{0, \dots, \ell\} \longrightarrow [0, \infty[$ on the Hamming classes, which is given by:

$$\forall l \in \{0, \dots, \ell\} \quad A_H(l) = \begin{cases} \sigma & \text{if } l = 0, \\ 1 & \text{if } 1 \leq l \leq \ell. \end{cases}$$

Likewise, the mapping H induces a mutation kernel M_H over the Hamming classes: for all $b, c \in \{0, \dots, \ell\}$,

$$M_H(b, c) = \sum_{\substack{0 \leq k \leq \ell - b \\ 0 \leq l \leq b \\ k - l = c - b}} \binom{\ell - b}{k} \binom{b}{l} q^k (1 - q)^{\ell - b - k} \left(\frac{q}{\kappa - 1}\right)^l \left(1 - \frac{q}{\kappa - 1}\right)^{b - l}.$$

This formula has been given first in [24] and later in a slightly different form in [15]. For $k \in \{0, \dots, \ell\}$, let us denote by x_k the concentration of individuals in the Hamming class k . According to Eigen's model, the evolution of the concentrations is driven by the following system of differential equations:

$$x'_k(t) = \sum_{j=0}^{\ell} x_j(t) A_H(j) M_H(j, k) - x_k(t) \sum_{j=0}^{\ell} x_j(t) A_H(j), \quad 0 \leq k \leq \ell.$$

Asymptotic regime. We make the length of the chains go to ∞ and the mutation probability go to 0 in the following way:

$$\ell \longrightarrow \infty, \quad q \longrightarrow 0, \quad \ell q \longrightarrow a \in]0, \infty[.$$

In this asymptotic regime we obtain a limiting mutation kernel M_∞ given by: for all $j, k \geq 0$,

$$M_\infty(j, k) = \begin{cases} e^{-a} \frac{a^{k-j}}{(k-j)!} & \text{if } j \leq k, \\ 0 & \text{if } j > k. \end{cases}$$

We can now write the limiting system of differential equations:

$$x'_k(t) = \sum_{j=0}^k x_j(t) A_H(j) e^{-a} \frac{a^{k-j}}{(k-j)!} - x_k(t) \sum_{j=0}^{\infty} x_j(t) A_H(j), \quad k \geq 0.$$

The distribution of the quasispecies is the only positive stationary solution of the above system, which exists for values of a such that $\sigma e^{-a} > 1$, and is given by the formula

$$\rho_k = (\sigma e^{-a} - 1) \frac{a^k}{k!} \sum_{j=1}^{\infty} \frac{j^k}{\sigma^j}, \quad k \geq 0.$$

Our objective is to generalise this formula to fitness functions $f : \mathbb{N} \longrightarrow [0, \infty[$ others than the sharp peak landscape fitness function.

2 Results

Let $f : \mathbb{N} \longrightarrow [0, \infty[$. We consider the system of differential equations

$$x'_k(t) = \sum_{j=0}^k x_j(t) f(j) e^{-a} \frac{a^{k-j}}{(k-j)!} - x_k(t) \sum_{j=0}^{\infty} x_j(t) f(j), \quad k \geq 0,$$

and we look for the stationary solutions of the system, i.e., we want to solve the system of equations

$$(\mathcal{S}) \quad 0 = \sum_{j=0}^k x_j f(j) e^{-a} \frac{a^{k-j}}{(k-j)!} - x_k \Phi, \quad k \geq 0,$$

where $\Phi = \sum_{j \geq 0} x_j f(j)$. Since we think of x_k as the concentration of the Hamming class k in a population, we are only interested in non-negative solutions of the system (\mathcal{S}) . We say that $(x_k)_{k \geq 0}$ is a quasispecies associated to f if it is a non-negative solution of (\mathcal{S}) such that $x_0 > 0$ and $\sum_{k \geq 0} x_k = 1$.

Assumption. We suppose that the fitness of the Hamming class 0 is higher than the fitness of all the other classes, i.e., the fitness function $f : \mathbb{N} \rightarrow [0, \infty[$ satisfies $f(0) > f(k)$, $k \geq 1$.

Note that the hypothesis is coherent with the Hamming class 0 corresponding to the master sequence (the fittest genotype). From now on, every fitness function is assumed to verify this hypothesis. We fix one such fitness function f and we focus ourselves on finding the quasispecies distributions associated to f .

Let us remark that under this assumption, if $(x_k)_{k \geq 0}$ is a quasispecies, then the concentration x_k of the Hamming class k is strictly positive. Indeed, since we assume that $x_0 > 0$,

$$x_k = \frac{\sum_{0 \leq j \leq k} x_j f(j) e^{-a} \frac{a^{k-j}}{(k-j)!}}{\sum_{j \geq 0} x_j f(j)} \geq \frac{x_0 f(0) e^{-a} \frac{a^k}{k!}}{f(0)} > 0.$$

The first of our results expresses the fitnesses as a function of the concentrations of the quasispecies.

Theorem 2.1. *Let us suppose that $(x_k)_{k \geq 0}$ is a quasispecies associated to f . Then,*

$$\forall k \geq 1 \quad f(k) = \frac{f(0)}{x_k} \sum_{j=0}^k (-1)^j \frac{a^j}{j!} x_{k-j}.$$

The interest of this result lies in its potential applications. When performing practical experiments, the concentrations of the different genotypes can be

measured, and one delicate question is to infer the underlying fitness landscape. Recent progresses allow even to sequence in-vivo virus populations, and the quasispecies model is one of the main tools employed in order to infer the fitness landscape from the experimental data [19].

We look now for an inverse formula, in other words, we want to express the concentrations of the different Hamming classes as a function of the fitnesses. let $(x_k)_{k \geq 0}$ be a quasispecies associated to f . The equation for $k = 0$ in the system (\mathcal{S}) is

$$0 = x_0(f(0)e^{-a} - \Phi).$$

Since we suppose that $x_0 > 0$, we have $\Phi = f(0)e^{-a}$. Replacing Φ by $f(0)e^{-a}$ in (\mathcal{S}) we obtain a recurrence relation for $(x_k)_{k \geq 0}$. To begin with, we will try to solve the recurrence relation with initial condition equal to 1, i.e.,

$$(\mathcal{R}) \quad \begin{aligned} y_0 &= 1, \\ y_k &= \frac{1}{f(0) - f(k)} \sum_{j=0}^{k-1} y_j f(j) \frac{a^{k-j}}{(k-j)!}, \quad k \geq 1. \end{aligned}$$

Lemma 2.2. *Let $(y_k)_{k \geq 0}$ be the solution of the recurrence relation (\mathcal{R}) .*

• *If the series associated to $(y_k)_{k \geq 0}$ converges, there exists a unique quasispecies $(x_k)_{k \geq 0}$ associated to f , which is given by:*

$$x_0 = \left(\sum_{k \geq 0} y_k \right)^{-1}, \quad x_k = x_0 y_k, \quad k \geq 1.$$

• *If the series associated to $(y_k)_{k \geq 0}$ diverges, no quasispecies associated to f exists.*

Proof. The first statement of the lemma is obviously true. For the second one, note that if $(x_k)_{k \geq 0}$ is a quasispecies associated to f , then the sequence $(y_k)_{k \geq 0}$ defined by $y_k = x_k/x_0$, $k \geq 0$, satisfies the recurrence relation (\mathcal{R}) , and the series associated to $(y_k)_{k \geq 0}$ converges. \square

Next we give three different explicit formulas for the sequence $(y_k)_{k \geq 0}$. The first of the formulas involves multinomial coefficients.

Theorem 2.3. *For all $k \geq 1$,*

$$y_k = \frac{a^k}{k!} \frac{f(0)}{f(0) - f(k)} \left(1 + \sum_{\substack{1 \leq h < k \\ 1 \leq i_1 < \dots < i_h < k}} \frac{k!}{i_1!(i_2 - i_1)! \dots (k - i_h)!} \prod_{t=1}^h \frac{f(i_t)}{f(0) - f(i_t)} \right).$$

Up-down coefficients. The sequence $(y_k)_{k \geq 0}$ can also be expressed in terms of up-down coefficients. Let us first introduce the up-down numbers or coefficients [23]. Let $n \geq 2$ and let $(q_1, \dots, q_{n-1}) \in \{-1, 1\}^{n-1}$. We say that a permutation $\sigma = (\sigma(1), \dots, \sigma(n))$ of $\{1, \dots, n\}$ has Niven's signature (q_1, \dots, q_{n-1}) if for every $i \in \{1, \dots, n-1\}$, the product $q_i(\sigma(i+1) - \sigma(i))$ is positive [14].

Definition 2.4. Let $n \geq 2$, $0 \leq h < n$ and $0 = i_0 < i_1 < \dots < i_h < n$. The up-down coefficient

$$\left\{ \begin{matrix} n \\ i_0, \dots, i_h \end{matrix} \right\}$$

is defined as the number of permutations of $\{1, \dots, n\}$ having Niven's signature (q_1, \dots, q_{n-1}) given by

$$\forall i \in \{1, \dots, n-1\} \quad q_i = \begin{cases} 1 & \text{if } i \in \{i_1, \dots, i_h\}, \\ -1 & \text{otherwise.} \end{cases}$$

Theorem 2.5. For all $k \geq 1$

$$y_k = \frac{a^k}{k!} \left(\prod_{j=1}^k \frac{f(0)}{f(0) - f(j)} \right) \sum_{\substack{0 \leq h < k \\ 0 = i_0 < \dots < i_h < k}} \left\{ \begin{matrix} k \\ i_0, \dots, i_h \end{matrix} \right\} \prod_{t=0}^h \frac{f(i_t)}{f(0)}.$$

Our last result concerns fitness functions that are eventually constant. For such functions we can express the concentrations $(y_k)_{k \geq 0}$ in terms of the concentrations $(q_k)_{k \geq 0}$ of the quasispecies associated to the sharp peak landscape fitness function. Let f be a fitness function which is eventually constant equal to $c > 0$. Define $(q_k)_{k \geq 0}$ as the solution to the recurrence relation (\mathcal{R}) with fitness function $(f(0), c, c, \dots)$, i.e.,

$$q_k = (f(0)/c - 1) \frac{a^k}{k!} \sum_{i \geq 1} \frac{i^k}{(f(0)/c)^i}.$$

Theorem 2.6. Let $N \geq 0$ be such that

$$f(N) \neq c \quad \text{and} \quad \forall k > N \quad f(k) = c.$$

Then, for all $k > N$,

$$y_k = q_k + \sum_{j=1}^N \frac{a^j}{j!} q_{k-j} \left(\frac{f(j)}{f(0) - f(j)} - \frac{c}{f(0) - c} \right) \\ \times \left(1 + \sum_{h=1}^{j-1} \sum_{0 = i_0 < \dots < i_h < j} \prod_{t=1}^h \binom{j - i_{t-1}}{j - i_t} \frac{f(i_t)}{f(0) - f(i_t)} \right).$$

Finally we give a condition guaranteeing the existence of a quasispecies associated to f . Let us recall that $(x_k)_{k \geq 0}$ is a quasispecies associated to f if it is a non negative solution of (\mathcal{S}) , $x_0 > 0$ and the sum of the x_k s is 1.

Corollary 2.7. *We have:*

- *If $f(0)e^{-a} > \limsup_{n \rightarrow \infty} f(n)$, the series associated to $(y_k)_{k \geq 0}$ converges and there exists a unique quasispecies associated to f .*
- *If $f(0)e^{-a} < \liminf_{n \rightarrow \infty} f(n)$, the series associated to $(y_k)_{k \geq 0}$ diverges and no quasispecies associated to f exists.*

We remark that for fitness functions f (verifying our assumption), the above corollary corresponds to the error threshold phenomenon observed by Eigen. Moreover, the error threshold depends only on a , $f(0)$, and the limiting behaviour of the fitness function f .

To finish this section, we discuss the motivations for making the assumption $f(0) > f(k)$, $k \geq 1$, and why we are mainly interested in solutions $(x_k)_{k \geq 0}$ of (\mathcal{S}) satisfying $x_0 > 0$. Let $K \geq 0$, we call $(x_k)_{k \geq 0}$ a *quasispecies distribution around K associated to f* , if it is a non negative solution of (\mathcal{S}) such that

$$x_0 = \cdots = x_{K-1} = 0 < x_K \quad \text{and} \quad \sum_{k \geq K} x_k = 1.$$

Lemma 2.8. *Let $K \geq 0$, and define the mapping $g : \mathbb{N} \rightarrow [0, \infty[$ by*

$$\forall k \geq 0 \quad g(k) = f(K + k).$$

The sequence $(x_k)_{k \geq 0}$ is a quasispecies distribution around K associated to f if and only if the sequence $(x_{K+i})_{i \geq 0}$ is a quasispecies distribution around 0 associated to g .

Proof. Let the sequence $(x_k)_{k \geq 0}$ be a quasispecies distribution around K associated to f . Since $x_0 = \cdots = x_{K-1} = 0$, for all $k \geq K$ we have

$$0 = \sum_{j=K}^k x_j f(j) e^{-a} \frac{a^{k-j}}{(k-j)!} - x_k \sum_{j \geq K} x_j f(j).$$

We set $i = k - K$ and $h = j - K$ in the above formula and we see that for

all $i \geq 0$,

$$\begin{aligned} 0 &= \sum_{h=0}^i x_{K+h} f(K+h) e^{-a} \frac{a^{i-h}}{(i-h)!} - x_{K+i} \sum_{h \geq 0} x_{K+h} f(K+h) \\ &= \sum_{h=0}^i x_{K+h} g(h) e^{-a} \frac{a^{i-h}}{(i-h)!} - x_{K+i} \sum_{h \geq 0} x_{K+h} g(h). \end{aligned}$$

Therefore, the sequence $(x_{K+i})_{i \geq 0}$ is a quasispecies distribution around 0 associated to g . The converse implication is proved similarly. \square

Lemma 2.9. *Suppose there exists $K \geq 1$ such that $f(K) > \max_{0 \leq k < K} f(k)$. Then, for $k \in \{0, \dots, K-1\}$, no quasispecies distribution around k associated to f exists.*

Proof. Let us suppose that the sequence $(x_k)_{k \geq 0}$ is a solution of (\mathcal{S}) . Let $k \in \{0, \dots, K-1\}$ and let us suppose further that $x_0 = \dots = x_{k-1} = 0$ and $x_k \neq 0$. We will show that if $x_k > 0, \dots, x_{K-1} > 0$, then necessarily $x_K < 0$. On one hand, writing down the K -th equation of (\mathcal{S}) we see that

$$x_K = \frac{1}{\Phi - f(K)e^{-a}} \sum_{j=k}^{K-1} x_j f(j) e^{-a} \frac{a^{K-j}}{(K-j)!}.$$

On the other hand, writing down the k -th equation of (\mathcal{S}) , since $x_0 = \dots = x_{k-1} = 0$ and $x_k > 0$, we conclude that $\Phi = f(k)e^{-a}$. Since $f(k) < f(K)$, if $x_k > 0, \dots, x_{K-1} > 0$, necessarily $x_K < 0$. This implies that no quasispecies distribution around k associated to f exists. \square

The above lemmas justify the hypothesis on the fitness function f , as well as the search for quasispecies distribution around 0 associated to f . From now onwards, if $(x_k)_{k \geq 0}$ is quasispecies distribution around 0 associated to f , and when there is no confusion, we will simply say that $(x_k)_{k \geq 0}$ is a quasispecies.

3 Related results

We have given three different explicit formulas for the stationary solutions of the system:

$$x'_k(t) = \sum_{j=0}^k x_j(t) f(j) e^{-a} \frac{a^{k-j}}{(k-j)!} - x_k(t) \sum_{j=0}^{\infty} x_j(t) f(j), \quad k \geq 0,$$

As we have pointed out in the introduction, this infinite system of differential equations arises from Eigen's system of differential equations:

$$x'_k(t) = \sum_{j=0}^{\ell} x_j(t) f(j) M_H(j, k) - x_k(t) \sum_{j=0}^{\ell} x_j(t) f(j), \quad 0 \leq k \leq \ell,$$

when considering the asymptotic regime

$$\ell \longrightarrow \infty, \quad q \longrightarrow 0, \quad \ell q \longrightarrow a \in [0, \infty[.$$

Eigen's system of differential equations might be defined with greater generality: given an at most countable set of types \mathcal{G} , a non negative fitness function f on \mathcal{G} , and a stochastic matrix $M = (M(u, v), u, v \in \mathcal{G})$, Eigen's model becomes

$$(*) \quad x'_v(t) = \sum_{u \in \mathcal{G}} x_u(t) f(u) M(u, v) - x_v(t) \sum_{u \in \mathcal{G}} x_u(t) f(u), \quad u \in \mathcal{G}.$$

Define the matrix W by setting

$$\forall u, v \in \mathcal{G}, \quad W(u, v) = f(u) M(u, v).$$

For a finite state space \mathcal{G} and under the hypothesis that the matrix W is irreducible, an application of the Perron–Frobenius theorem for positive matrices shows that the system $(*)$ has a unique stationary solution which is globally stable [1, 9, 10, 25]. A similar result was proven by Moran [12] for a discrete–time version of this model:

$$(**) \quad x_v(n+1) = \frac{\sum_{u \in \mathcal{G}} x_u(n) f(u) M(u, v)}{\sum_{u \in \mathcal{G}} x_u(n) f(u)}, \quad u \in \mathcal{G}.$$

Once again, an application of the Perron–Frobenius theorem shows that the dynamical system $(**)$ has a unique fixed point, which is globally stable. Of course, the stationary solution of the continuous dynamical system and the fixed point of the discrete dynamical system are the same. Moran also extended this result [12, 13] to the case where $\mathcal{G} = \mathbb{Z}$ and mutations only happen between nearest neighbours, i.e., for $q \in]0, 1/2[$ and $i \in \mathbb{Z}$, the mutation matrix M is defined by:

$$M(i, j) = \begin{cases} q & \text{if } j = i \pm 1, \\ 1 - 2q & \text{if } j = i, \\ 0 & \text{otherwise.} \end{cases}$$

Kingman [11] further generalises Moran's result. Let $\mathcal{G} = \mathbb{N}$ and make the following assumptions:

- The fitness function is positive and bounded, i.e., there exists a constant $C > 0$ such that

$$\forall k \geq 0, \quad 0 < f(k) < C.$$

- The mutation matrix M is irreducible and aperiodic.

Let λ be the spectral radius of the matrix W . Kingman then shows that if

$$\limsup_{k \rightarrow \infty} f(k) < \lambda,$$

then there exists a unique positive fixed point of (**) having 1 as the sum of its components. Moreover, this fixed point is globally stable. Kingman's result generalises the first statement of our corollary 2.7. Indeed, in our setting σe^{-a} corresponds to the spectral radius λ . Our result, however, does not follow directly from Kingman's result, for he assumes the matrix W to be recurrent, which is not verified in our case. Kingman's proof, which is based on an infinite dimensional version of the Perron–Frobenius theorem, could be extended to show the existence of a quasispecies, but not the uniqueness. We have therefore chosen to exploit the obtained explicit formulas to derive an analogous of Kingman's result directly. This procedure has not only allowed us to retrieve Kingman's result in our particular setting, but also to give a similar condition under which a quasispecies cannot be formed.

4 Proof of theorems 2.1, 2.3 and 2.5

Proof of theorem 2.1. Let us suppose that $(x_k)_{k \geq 0}$ is a quasispecies. Let us show that, for all $k \geq 1$,

$$f(k) = \frac{f(0)}{x_k} \sum_{j=0}^k (-1)^j \frac{a^j}{j!} x_{k-j}.$$

We will make the proof by induction. The sequence $(x_k)_{k \geq 0}$ is a quasispecies, in particular, $x_0 > 0$ and $\Phi = f(0)e^{-a}$. Replacing Φ by $f(0)e^{-a}$ in (S) and arranging the terms gives

$$f(k) = \frac{1}{x_k} \left(x_k f(0) - \sum_{j=0}^{k-1} x_j f(j) \frac{a^{k-j}}{(k-j)!} \right), \quad k \geq 1.$$

In particular, for $k = 1$,

$$f(1) = \frac{f(0)}{x_1}(x_1 - ax_0).$$

So the result holds for $k = 1$. We fix now $k > 1$ and we suppose that the result holds up to $k - 1$. We replace the values of $f(1), \dots, f(k - 1)$ in the above formula and we obtain

$$f(k) = \frac{f(0)}{x_k} \left(x_k - \sum_{j=0}^{k-1} \sum_{h=0}^j (-1)^h x_{j-h} \frac{a^h}{h!} \frac{a^{k-j}}{(k-j)!} \right).$$

Let us fix $i \in \{1, \dots, k\}$ and let us look for the coefficient of x_{k-i} in the above expression, this coefficient is

$$- \sum_{\substack{0 \leq h \leq j < k \\ j-h=k-i}} (-1)^h \frac{a^h}{h!} \frac{a^{k-j}}{(k-j)!} = - \sum_{0 \leq h < i} (-1)^h \frac{a^h}{h!} \frac{a^{i-h}}{(i-h)!} = (-1)^i \frac{a^i}{i!},$$

which concludes the proof of the theorem. \square

Proof of theorem 2.3. We show that, for all $k \geq 1$,

$$y_k = \frac{a^k}{k!} \frac{f(0)}{f(0) - f(k)} \left(1 + \sum_{\substack{1 \leq h < k \\ 1 \leq i_1 < \dots < i_h < k}} \frac{k!}{i_1!(i_2 - i_1)! \dots (k - i_h)!} \prod_{t=1}^h \frac{f(i_t)}{f(0) - f(i_t)} \right).$$

Arranging the terms in (\mathcal{R}) gives:

$$y_k(f(0) - f(k)) = \sum_{j=0}^{k-1} y_j f(j) \frac{a^{k-j}}{(k-j)!}, \quad k \geq 1.$$

We make the following changes of variables:

$$\begin{aligned} z_0 &= y_0, & g(0) &= f(0), \\ z_j &= \frac{y_j}{a^j} (f(0) - f(j)), & g(j) &= \frac{f(j)}{f(0) - f(j)}, \quad j \geq 1. \end{aligned}$$

With these changes of variables, the recurrence relation becomes

$$z_k = \sum_{j=0}^{k-1} z_j \frac{g(j)}{(k-j)!}, \quad k \geq 1.$$

We iterate this formula and we obtain, for all $k \geq 1$,

$$z_k = z_0 g(0) \left(\frac{1}{k!} + \sum_{h=1}^{k-1} \sum_{1 \leq i_1 < \dots < i_h < k} \frac{1}{i_1!(i_2 - i_1)! \dots (k - i_h)!} \prod_{t=1}^h g(i_t) \right).$$

We replace z_0, z_k and $g(0), \dots, g(k-1)$ by their respective values and we obtain the desired result. \square

Proof of theorem 2.5. We show that, for all $k \geq 1$,

$$y_k = \frac{a^k}{k!} \left(\prod_{j=1}^k \frac{f(0)}{f(0) - f(j)} \right) \sum_{\substack{0 \leq h < k \\ 0 = i_0 < \dots < i_h < k}} \left\{ \begin{matrix} k \\ i_0, \dots, i_h \end{matrix} \right\} \prod_{t=0}^h \frac{f(i_t)}{f(0)}.$$

We take the formula from theorem 2.3 and we set $\prod_{j=1}^k (f(0) - f(j))$ as a common denominator, we get

$$\begin{aligned} y_k &= \frac{a^k}{k!} \frac{f(0)}{\prod_{1 \leq j \leq k} (f(0) - f(j))} \left(\prod_{1 \leq j < k} (f(0) - f(j)) \right. \\ &+ \left. \sum_{h=1}^{k-1} \sum_{1 \leq i_1 < \dots < i_h < k} \frac{k!}{i_1!(i_2 - i_1)! \dots (k - i_h)!} \prod_{t=1}^h f(i_t) \prod_{\substack{1 \leq j < k \\ j \neq i_1, \dots, i_h}} (f(0) - f(j)) \right). \end{aligned}$$

The expression in the large parenthesis is an homogeneous polynomial of degree $k-1$ in the variables $f(0), \dots, f(k-1)$. For each $h \in \{1, \dots, k-1\}$ and $1 \leq i_1 < \dots < i_h < k$, we get a monomial of the form $f(0)^{k-1-h} f(i_1) \dots f(i_h)$. We calculate the coefficient of each of these monomials and we conclude that

$$\begin{aligned} y_k &= \frac{a^k}{k!} \frac{f(0)}{\prod_{1 \leq j \leq k} (f(0) - f(j))} \left(f(0)^{k-1} + \sum_{h=1}^{k-1} \sum_{1 \leq i_1 < \dots < i_h < k} f(0)^{k-1-h} \prod_{t=1}^h f(i_t) \right. \\ &\times \left. \left((-1)^h + \sum_{t=1}^h \sum_{1 \leq j_1 < \dots < j_t \leq h} (-1)^{h-t} \frac{k!}{i_{j_1}!(i_{j_2} - i_{j_1})! \dots (k - i_{j_t})!} \right) \right). \end{aligned}$$

We know from [3] that

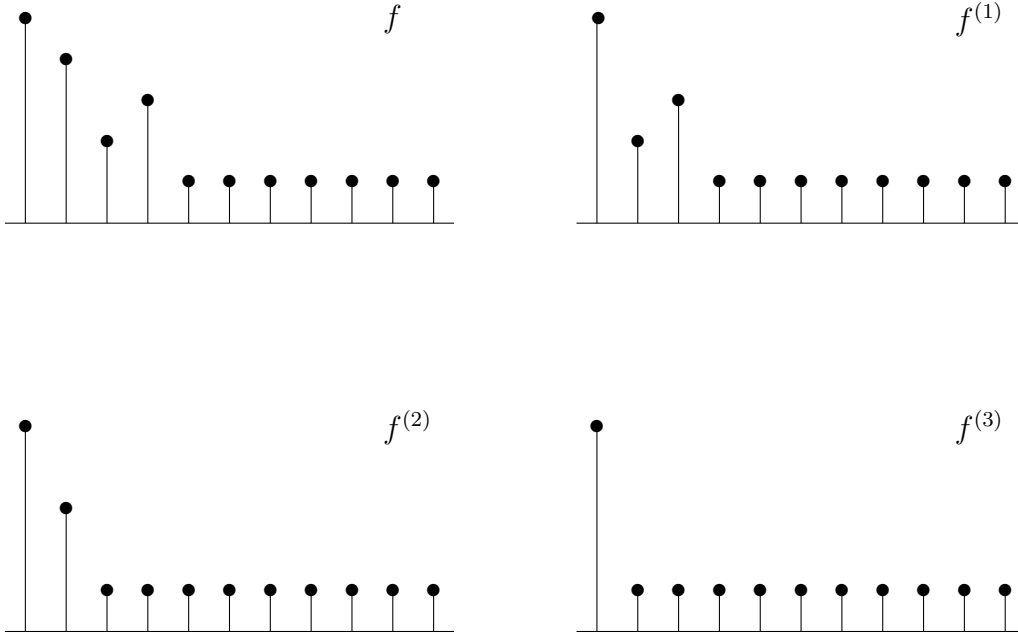
$$\left\{ \begin{matrix} k \\ 0, i_1, \dots, i_h \end{matrix} \right\} = (-1)^h + \sum_{t=1}^h \sum_{1 \leq j_1 < \dots < j_t \leq h} (-1)^{h-t} \frac{k!}{i_{j_1}!(i_{j_2} - i_{j_1})! \dots (k - i_{j_t})!},$$

which implies the desired result. \square

5 Proof of theorem 2.6

Let us introduce some notation before jumping into the proof of the theorem. For a fitness landscape f and $k \geq 0$, we define the fitness landscape $f^{(k)}$ obtained by shifting k places to the left the fitnesses of the different classes and keeping the fitness of the class 0, that is,

$$\forall j \geq 0 \quad f^{(k)}(j) = \begin{cases} f(0) & \text{if } j = 0, \\ f(j+k) & \text{if } j \geq 1. \end{cases}$$



For a fitness landscape f , we denote by $(y_k(f))_{k \geq 1}$ the solution to the recurrence (\mathcal{R}) corresponding to the fitness landscape f . We start by establishing the following lemma, which expresses the value of $y_k(f)$ as a function of $y_{k-1}(f^{(1)}), \dots, y_1(f^{(k-1)})$.

Lemma 5.1. *For all $k \geq 2$, we have*

$$y_k(f) = \frac{a^k}{k!} \frac{f(0)}{f(0) - f(k)} + \sum_{j=1}^{k-1} \frac{a^j}{j!} \frac{f(j)}{f(0) - f(j)} y_{k-j}(f^{(j)}).$$

Proof. Consider the identity of theorem 2.3,

$$y_k(f) = \frac{a^k}{k!} \frac{f(0)}{f(0) - f(k)} \left(1 + \sum_{\substack{1 \leq h < k \\ 1 \leq i_1 < \dots < i_h < k}} \frac{k!}{i_1!(i_2 - i_1)! \dots (k - i_h)!} \prod_{t=1}^h \frac{f(i_t)}{f(0) - f(i_t)} \right),$$

and decompose the above sum according to the value of the first index:

$$\begin{aligned} & \sum_{\substack{1 \leq h < k \\ 1 \leq i_1 < \dots < i_h < k}} \frac{k!}{i_1!(i_2 - i_1)! \dots (k - i_h)!} \prod_{t=1}^h \frac{f(i_t)}{f(0) - f(i_t)} = \sum_{i_1=1}^{k-1} \frac{f(i_1)}{f(0) - f(i_1)} \\ & \times \left(\frac{k!}{i_1!(k - i_1)!} + \sum_{\substack{2 \leq h \leq k - i_1 \\ i_1 < i_2 < \dots < i_h < k}} \frac{k!}{i_1!(i_2 - i_1)! \dots (k - i_h)!} \prod_{t=2}^h \frac{f(i_t)}{f(0) - f(i_t)} \right). \end{aligned}$$

We make the following changes of variables:

$$\begin{aligned} j &= i_1, & h' &= h - 1, & t' &= t - 1, \\ i'_1 &= i_2 - i_1, & \dots, & & i'_{h'} &= i_h - i_1. \end{aligned}$$

Note that in particular we have $f(i_{t'}) = f(i'_{t'} + i_1) = f^{(j)}(i'_{t'})$. The previous expression becomes:

$$\begin{aligned} & \sum_{j=1}^{k-1} \frac{k!}{j!(k-j)!} \frac{f(j)}{f(0) - f(j)} \\ & \times \left(1 + \sum_{\substack{1 \leq h' < k-j \\ 1 \leq i'_1 < \dots < i'_{h'} < k-j}} \frac{(k-j)!}{i'_1!(i'_2 - i'_1)! \dots (k-j - i'_{h'})!} \prod_{t'=1}^{h'} \frac{f^{(j)}(i'_{t'})}{f^{(j)}(0) - f^{(j)}(i'_{t'})} \right). \end{aligned}$$

Since $f(0) = f^{(j)}(0)$ and $f(k) = f^{(j)}(k-j)$ for all $j \in \{1, \dots, k-1\}$, taking away the ' from the indexes, we see that

$$\begin{aligned} y_k(f) &= \frac{a^k}{k!} \frac{f(0)}{f(0) - f(k)} + \sum_{j=1}^{k-1} \frac{a^j}{j!} \frac{f(j)}{f(0) - f(j)} \times \frac{a^{k-j}}{(k-j)!} \frac{f^{(j)}(0)}{f^{(j)}(0) - f^{(j)}(k-j)} \\ & \times \left(1 + \sum_{\substack{1 \leq h < k-j \\ 1 \leq i_1 < \dots < i_h < k-j}} \frac{(k-j)!}{i_1!(i_2 - i_1)! \dots (k-j - i_h)!} \prod_{t=1}^h \frac{f^{(j)}(i_t)}{f^{(j)}(0) - f^{(j)}(i_t)} \right). \end{aligned}$$

Yet, by theorem 2.3,

$$y_{k-j}(f^{(j)}) = \frac{a^{k-j}}{(k-j)!} \frac{f^{(j)}(0)}{f^{(j)}(0) - f^{(j)}(k-j)} \times \left(1 + \sum_{h=1}^{k-j} \sum_{1 \leq i_1 < \dots < i_h < k-j} \frac{(k-j)!}{i_1!(i_2 - i_1)! \dots (k-j - i_h)!} \prod_{t=1}^h \frac{f^{(j)}(i_t)}{f^{(j)}(0) - f^{(j)}(i_t)} \right).$$

We replace in the previous formula and we conclude. \square

Let $f : \mathbb{N} \rightarrow [0, \infty[$ be a fitness function which is eventually constant, i.e., there exist $N \geq 0$ and a positive constant c such that

$$f(N) \neq c \quad \text{et} \quad \forall k > N \quad f(k) = c.$$

Let $(y_k(f))_{k \geq 0}$ be the solution to the recurrence relation (\mathcal{R}) for the fitness function f . We want to show that, for all $k > N$,

$$y_k(f) = q_k + \sum_{j=1}^N \frac{a^j}{j!} q_{k-j} \left(\frac{f(j)}{f(0) - f(j)} - \frac{c}{f(0) - c} \right) \times \left(1 + \sum_{h=1}^{j-1} \sum_{0=i_0 < \dots < i_h < j} \prod_{t=1}^h \binom{j - i_{t-1}}{j - i_t} \frac{f(i_t)}{f(0) - f(i_t)} \right),$$

where $(q_k)_{k \geq 0}$ is the solution to the relation of recurrence (\mathcal{R}) for the sharp peak fitness landscape $(f(0), c, c, \dots)$, i.e.,

$$q_k = (f(0)/c - 1) \frac{a^k}{k!} \sum_{i \geq 1} \frac{i^k}{(f(0)/c)^i}, \quad k \geq 1.$$

Before proceeding to the proof of the theorem 2.6, we introduce the following notation in order to simplify the expression of the formula we want to prove. For a fitness function f and $l \geq 1$, we set

$$C_l(f) = 1 + \sum_{h=1}^{l-1} \sum_{0=i_0 < i_1 < \dots < i_h < l} \prod_{t=1}^h \binom{l - i_{t-1}}{l - i_t} \frac{f(i_t)}{f(0) - f(i_t)}.$$

Lemma 5.2. *The coefficients C_i , $i \geq 2$, satisfy the recurrence relation*

$$C_i(f) = 1 + \sum_{j=1}^{i-1} \binom{i}{j} \frac{f(j)}{f(0) - f(j)} C_{i-j}(f^{(j)}).$$

Proof. Let $i \geq 2$. For $j \in \{1, \dots, i-1\}$,

$$C_{i-j}(f^{(j)}) = 1 + \sum_{h=1}^{i-j-1} \sum_{0=l_0 < l_1 < \dots < l_h < i-j} \prod_{t=1}^h \binom{i-j-l_{t-1}}{i-j-l_t} \frac{f(j+l_t)}{f(0)-f(j+l_t)}.$$

We replace $C_{i-1}(f^{(1)}), \dots, C_1(f^{(i-1)})$ in the above formula, and we change the indexes in the following way:

$$h' = h + 1, \quad j = i_1, \quad j + l_1 = i_2, \quad \dots, \quad j + l_h = i_{h'}.$$

Exchanging the order of the sums gives the desired formula for $C_i(f)$. \square

Proof of theorem 2.6. We show the result by induction on N . Let us suppose first that $N = 1$ and let $k \geq 2$. Then all the fitness functions $f^{(j)}$, $j \geq 1$, are equal to the sharp peak landscape fitness function. Applying lemma 5.1 gives:

$$y_k(f) = \frac{a^k}{k!} \frac{f(0)}{f(0)-c} q_0 + a \frac{f(1)}{f(0)-f(1)} q_{k-1} + \sum_{j=2}^{k-1} \frac{a^j}{j!} \frac{c}{f(0)-c} q_{k-j}.$$

Yet, the sequence $(q_k)_{k \geq 0}$ satisfies the recurrence relation (\mathcal{R}) for the fitness function $(f(0), c, c, \dots)$, i.e.,

$$\forall k \geq 1 \quad q_k = \frac{1}{f(0)-c} \left(\frac{a^k}{k!} f(0) + c \sum_{j=1}^{k-1} \frac{a^j}{j!} q_{k-j} \right).$$

It follows that

$$y_k(f) = q_k + a \left(\frac{f(1)}{f(0)-f(1)} - \frac{c}{f(0)-c} \right) q_{k-1}.$$

The base case $N = 1$ is thus settled. Let now $N \geq 2$ and let us suppose that the result of theorem 2.6 holds up to $N-1$. Let $k > N$. On one hand, for all $j \geq N$, the fitness function $f^{(j)}$ is equal to the sharp peak landscape fitness function, therefore $y_{k-j}(f^{(j)}) = q_{k-j}$ for all $j \in \{1, \dots, N\}$. On the other

hand, $f(N+1) = \dots = f(k) = c$. Thus, applying lemma 5.1 gives

$$\begin{aligned}
y_k(f) &= \frac{a^k}{k!} \frac{f(0)}{f(0) - f(k)} + \sum_{j=1}^{k-1} \frac{a^j}{j!} \frac{f(j)}{f(0) - f(j)} y_{k-j}(f^{(j)}) \\
&= \frac{1}{f(0) - c} \left(\frac{a^k}{k!} f(0) + c \sum_{j=1}^{k-1} \frac{a^j}{j!} q_{k-j} \right) - \frac{c}{f(0) - c} \sum_{j=1}^N \frac{a^j}{j!} q_{k-j} \\
&\quad + \sum_{j=1}^N \frac{a^j}{j!} \frac{f(j)}{f(0) - f(j)} y_{k-j}(f^{(j)}) \\
&= q_k - \frac{c}{f(0) - c} \sum_{j=1}^N \frac{a^j}{j!} q_{k-j} + \sum_{j=1}^N \frac{a^j}{j!} \frac{f(j)}{f(0) - f(j)} y_{k-j}(f^{(j)}).
\end{aligned}$$

By the induction hypothesis, for all $j \in \{1, \dots, N\}$, we have

$$\begin{aligned}
y_{k-j}(f^{(j)}) &= q_{k-j} + \sum_{l=1}^{N-j} \frac{a^l}{l!} q_{k-j-l} \left(\frac{f^{(j)}(l)}{f^{(j)}(0) - f^{(j)}(l)} - \frac{c}{f^{(j)}(0) - c} \right) C_l(f^{(j)}) \\
&= q_{k-j} + \sum_{l=1}^{N-j} \frac{a^l}{l!} q_{k-j-l} \left(\frac{f(j+l)}{f(0) - f(j+l)} - \frac{c}{f(0) - c} \right) C_l(f^{(j)}).
\end{aligned}$$

We replace $y_{k-N}(f^{(N)}), \dots, y_{k-1}(f^{(1)})$ in the formula for $y_k(f)$ and we obtain

$$\begin{aligned}
y_k(f) &= q_k - \frac{c}{f(0) - c} \sum_{j=1}^N \frac{a^j}{j!} q_{k-j} + \sum_{j=1}^N \frac{a^j}{j!} \frac{f(j)}{f(0) - f(j)} \\
&\quad \times \left(q_{k-j} + \sum_{l=1}^{N-j} \frac{a^l}{l!} q_{k-j-l} \left(\frac{f(j+l)}{f(0) - f(j+l)} - \frac{c}{f(0) - c} \right) C_l(f^{(j)}) \right).
\end{aligned}$$

Let us fix $i \in \{1, \dots, N\}$. The coefficient of q_{k-i} in the development of $y_k(f)$ is then equal to:

$$\begin{aligned}
&\frac{a^i}{i!} \left(\frac{f(i)}{f(0) - f(i)} - \frac{c}{f(0) - c} \right) \\
&\quad + \sum_{\substack{1 \leq j \leq N \\ 1 \leq l \leq N-j \\ j+l=i}} \frac{a^j}{j!} \frac{f(j)}{f(0) - f(j)} \frac{a^l}{l!} \left(\frac{f(j+l)}{f(0) - f(j+l)} - \frac{c}{f(0) - c} \right) C_l(f^{(j)}) \\
&= \frac{a^i}{i!} \left(\frac{f(i)}{f(0) - f(i)} - \frac{c}{f(0) - c} \right) \left(1 + \sum_{j=1}^{i-1} \binom{i}{j} \frac{f(j)}{f(0) - f(j)} C_{i-j}(f^{(j)}) \right).
\end{aligned}$$

We conclude thanks to lemma 5.2. \square

6 Proof of the corollary

We begin by giving two useful lemmas. For a fitness function $f : \mathbb{N} \rightarrow [0, \infty[$ we denote by $(y_k(f))_{k \geq 0}$ the solution to the recurrence relation (\mathcal{R}) corresponding to the function f .

Lemma 6.1. *Let $f, g : \mathbb{N} \rightarrow [0, \infty[$ be two fitness functions satisfying both $f(0) = g(0)$ and $f(k) \geq g(k)$ for all $k \geq 1$. Then, for all $k \geq 0$, we have $y_k(f) \geq y_k(g)$.*

Proof. The result follows from the inequality

$$\frac{1}{f(0) - f(k)} \sum_{j=0}^{k-1} y_j f(j) \frac{a^{k-j}}{(k-j)!} \geq \frac{1}{g(0) - g(k)} \sum_{j=0}^{k-1} y_j g(j) \frac{a^{k-j}}{(k-j)!},$$

along with an induction argument. \square

Let $N \geq 1$ and $\sigma > c \geq 0$. We define the fitness function $g_N : \mathbb{N} \rightarrow [0, \infty[$ by setting:

$$\forall k \geq 0, \quad g_N(k) = \begin{cases} \sigma & \text{if } k = 0, \\ 0 & \text{if } 1 \leq k \leq N, \\ 1 & \text{if } N + 1 \leq k. \end{cases}$$

Lemma 6.2. *The series associated to $(y_k(g_N))_{k \geq 0}$ converges if and only if $\sigma e^{-a} > c$.*

Proof. We know the result to be true for the sharp peak landscape, i.e. for $N = 0$. By the comparison lemma 6.1, if $\sigma e^{-a} > c$ the series associated to $(y_k(g_N))_{k \geq 0}$ converges. Suppose next that $\sigma e^{-a} \leq c$. By lemma 2.2, the convergence of the series associated to $(y_k(g_N))_{k \geq 0}$ is equivalent to the existence of a quasispecies associated to g_N . We will thus show that such a quasispecies cannot exist if $\sigma e^{-a} \leq 1$. Let us suppose that a quasispecies

$(x_k)_{k \geq 0}$ exists. The sequence $(x_k)_{k \geq 0}$ then verifies:

$$\begin{aligned} x_0 &> 0, \quad \sum_{k \geq 0} x_k = 1, \\ \Phi &= \sigma x_0 + c \sum_{k > N} x_k, \\ 0 &= x_0(\sigma e^{-a} - \Phi), \\ 0 &= x_0 \sigma \frac{a^k}{k!} e^{-a} - x_k \Phi, \quad 1 \leq k \leq N. \end{aligned}$$

In particular $\Phi = \sigma e^{-a}$ and $x_k = x_0 a^k / k!$ for $1 \leq k \leq N$. Thus,

$$\sigma e^{-a} = \Phi = \sigma x_0 + c(1 - (x_0 + \dots + x_N)) = \left(\sigma - c \sum_{k=0}^N \frac{a^k}{k!} \right) x_0 + c.$$

Let

$$t_N(a) = \sum_{k=0}^N \frac{a^k}{k!}.$$

We conclude that x_0 is given by

$$x_0 = \frac{\sigma e^{-a} - c}{\sigma - c t_N(a)}.$$

Denote by a^* the only positive solution to the equation $c t_N(a) = \sigma$. The expression obtained for x_0 is not positive for $a \in [\ln(\sigma/c), a^*]$, so a quasispecies cannot exist for a in this interval. If on the contrary $a \geq a^*$, we have

$$x_0 + \dots + x_N = t_N(a) x_0 = \frac{\sigma e^{-a} t_N(a) - c t_N(a)}{\sigma - c t_N(a)}.$$

However, $t_N(a) < e^a$, which implies that this last expression is strictly larger than 1. Thus, a quasispecies cannot exist if $a \geq a^*$ either. \square

We proceed now to the proof of the corollary. After lemma 2.2, corollary 2.7 will be settled if we manage to show that the series associated to $(y_k)_{k \geq 0}$ converges if $f(0)e^{-a} > \limsup_{n \rightarrow \infty} f(n)$, and diverges if $f(0)e^{-a} < \liminf_{n \rightarrow \infty} f(n)$. Let us start by showing the former. Suppose first that the function is constant equal to $c \geq 0$ from N onwards. We can thus apply theorem 2.6, and obtain

$$\forall k > N, \quad y_k = q_k + \sum_{j=1}^N \frac{a^j}{j!} q_{k-j} \left(\frac{f(j)}{f(0) - f(j)} - \frac{c}{f(0) - c} \right) C_j(f).$$

It follows that

$$\sum_{k \geq 0} y_k = \sum_{k=0}^N y_k + \sum_{k > N} q_k + \sum_{j=1}^N \frac{a^j}{j!} \left(\sum_{k > N} q_{k-j} \right) \left(\frac{f(j)}{f(0) - f(j)} - \frac{c}{f(0) - c} \right) C_j(f).$$

Yet, the series associated to $(q_k)_{k \geq 0}$ is convergent for $f(0)e^{-a} > c$. If the function $f : \mathbb{N} \rightarrow [0, \infty[$ is not eventually constant, we set

$$c^\infty = \limsup_{n \rightarrow \infty} f(n).$$

Let $\varepsilon > 0$, pick $N \geq 0$ large enough so that for all $k > N$, $f(k) < c^\infty + \varepsilon$. We define the function $f^N : \mathbb{N} \rightarrow [0, \infty[$ by:

$$\forall k \geq 0 \quad f^N(k) = \begin{cases} f(k) & \text{if } 0 \leq k \leq N, \\ c^\infty + \varepsilon & \text{if } k > N. \end{cases}$$

For ε small enough, $f^N(0)e^{-a} > c^\infty + \varepsilon$. Since f^N is constant equal to $c^\infty + \varepsilon$ from N onwards, the series associated to $(y_k(f^N))_{k \geq 0}$ converges. By the comparison lemma 6.1, the same is true for the series associated to $(y_k(f))_{k \geq 0}$. We prove next that if $f(0)e^{-a} < \liminf_{n \rightarrow \infty} f(n)$, then the series associated to $(y_k)_{k \geq 0}$ diverges. We define the function $f_N : \mathbb{N} \rightarrow [0, \infty[$ by:

$$\forall k \geq 0 \quad f_N(k) = \begin{cases} f(0) & \text{if } k = 0, \\ 0 & \text{if } 1 \leq k \leq N, \\ c^\infty - \varepsilon & \text{if } k > N. \end{cases}$$

For ε small enough, $f_N(0)e^{-a} < c^\infty - \varepsilon$. After lemma 6.2 the series associated to $(y_k(f_N))_{k \geq 0}$ is divergent. By the comparison lemma 6.1, the same is true for the series associated to $(y_k(f))_{k \geq 0}$.

7 Conclusions

We have given several explicit formulas for the stationary solutions of Eigen's quasispecies model in the regime where the length of the genotypes goes to infinity. Theorem 2.1 allows the inference of the fitness landscape from data about the concentrations of the different genotypes, which makes it particularly attractive for applications. The formulas in theorems 2.3 and 2.5 give the concentrations of the different Hamming classes, relative to the master

sequence. For fitness landscapes which are eventually constant, a link is made to the already known distribution of the quasispecies (for the sharp peak landscape [5]) in theorem 2.6. Finally corollary 2.7 generalises the error threshold criterion observed for the sharp peak landscape to fitness landscapes depending on the Hamming class. The main interest of our results lies in their exact nature; the only approximation they rely on is the long chain regime, which even the simplest genomes in nature fall into. The main limitation of our work is the assumption that the fitness of an individual depends on its genome only through the number of point mutations from the master sequence. Nevertheless, we believe that our results provide a first step in finding quasispecies distributions for even more general fitness landscapes.

References

- [1] Chikafusa Bessho and Naoki Kuroda. A note on a more general solution of Eigen’s rate equation for selection. *Bull. Math. Biol.*, 45(1):143–149, 1983.
- [2] Alexander S. Bratus, Artem S. Novozhilov, and Yuri S. Semenov. Linear algebra of the permutation invariant Crow-Kimura model of prebiotic evolution. *Math. Biosci.*, 256:42–57, 2014.
- [3] L. Carlitz. Permutations with prescribed pattern. *Math. Nachr.*, 58:31–53, 1973.
- [4] Raphaël Cerf. *Critical population and error threshold on the sharp peak landscape for a Moran model*. Memoirs of the American Mathematical Society. 2015.
- [5] Raphaël Cerf and Joseba Dalmau. The distribution of the quasispecies for a moran model on the sharp peak landscape. *Stochastic Processes and their Applications*, 126(6):1681 – 1709, 2016.
- [6] Joseba Dalmau. Convergence of a moran model to eigen’s quasispecies model. *arXiv preprint*, 2014.
- [7] Manfred Eigen. Self-organization of matter and the evolution of biological macromolecules. *Naturwissenschaften*, 58(10):465–523, 1971.
- [8] Manfred Eigen, John McCaskill, and Peter Schuster. The molecular quasi-species. *Advances in Chemical Physics*, 75:149–263, 1989.

- [9] B. L. Jones. Analysis of Eigen’s equations for selection of biological molecules with fluctuating mutation rates. *Bull. Math. Biology*, 39(3):311–316, 1977.
- [10] B.L. Jones, R.H. Enns, and S.S. Rangnekar. On the theory of selection of coupled macromolecular systems. *Bulletin of Mathematical Biology*, 38(1):15–28, 1976.
- [11] J. F. C. Kingman. On the properties of bilinear models for the balance between genetic mutation and selection. *Math. Proc. Cambridge Philos. Soc.*, 81(3):443–453, 1977.
- [12] P. A. P. Moran. Global stability of genetic systems governed by mutation and selection. *Math. Proc. Cambridge Philos. Soc.*, 80(2):331–336, 1976.
- [13] P. A. P. Moran. Global stability of genetic systems governed by mutation and selection. II. *Math. Proc. Cambridge Philos. Soc.*, 81(3):435–441, 1977.
- [14] Ivan Niven. A combinatorial problem of finite sequences. *Nieuw Arch. Wisk. (3)*, 16:116–123, 1968.
- [15] Martin Nowak and Peter Schuster. Error thresholds of replication in finite populations mutation frequencies and the onset of muller’s ratchet. *Journal of Theoretical Biology*, 137(4):375 – 395, 1989.
- [16] David B. Saakian. A new method for the solution of models of biological evolution: derivation of exact steady-state distributions. *J. Stat. Phys.*, 128(3):781–798, 2007.
- [17] David B. Saakian, Christof K. Biebricher, and Chin-Kun Hu. Lethal mutants and truncated selection together solve a paradox of the origin of life. *PLoS ONE*, 6(7):1–12, 07 2011.
- [18] David B. Saakian and Chin-Kun Hu. Exact solution of the eigen model with general fitness functions and degradation rates. *Proceedings of the National Academy of Sciences of the United States of America*, 103(13):4935–4939, 2006.
- [19] David Seifert, Francesca Di Giallonardo, Karin J. Metzner, Huldrych F. Günthard, , and Niko Beerenwinkel. A framework for inferring fitness landscapes of patient-derived viruses using quasispecies theory. *Genetics*, 199(1):192–203, 2015.

- [20] Yuri S. Semenov, Alexander S. Bratus, and Artem S. Novozhilov. On the behavior of the leading eigenvalue of Eigen's evolutionary matrices. *Math. Biosci.*, 258:134–147, 2014.
- [21] Yuri S. Semenov and Artem S. Novozhilov. Exact solutions for the selection-mutation equilibrium in the crow-kimura evolutionary model. *ArXiv preprint*, 2015.
- [22] Yuri S. Semenov and Artem S. Novozhilov. On eigen's quasispecies model, two-valued fitness landscapes, and isometry groups acting on finite metric spaces. *ArXiv preprint*, 2015.
- [23] Vladimir Shevelev. Number of permutations with prescribed up-down structure as a function of two variables. *Integers*, 12(4):529–569, 2012.
- [24] J. Swetina and P. Schuster. Self-replication with errors. a model for polynucleotide replication. *Biophys. Chem.*, 16(4):329–45, 1982.
- [25] Colin J. Thompson and John L. McBride. On Eigen's theory of the self-organization of matter and the evolution of biological macromolecules. *Math. Biosci.*, 21:127–142, 1974.