A stochastic version of the Eigen model

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Abstract

We exhibit a stochastic discrete time model that has exactly the Eigen model [4]as its
deterministic continuous limit. Such model can be divided into two phases: reproduction,
followed by neutral selection. This result suggests that Eigen’s model describes the competition
among individuals differing in terms of fecundity but with the same viability. We explicitly
write down the Markov matrix of the stochastic model in the two species case and compute the
master sequence concentration numerically for various values of the total population. Finally
we compare our results with those obtained with the Eigen model and with the Nowak and
Schuster birth and death model [8].

Keywords: Mutation-selection dynamics, Error threshold, Stochastic model.

1 Introduction

Eigen’s celebrated quasispecies model [4] describes the replication of polynucleotides of fixed length
subject to mutation with the constraint that population size is constant. It consists of a set of
ODEs, each one governing the time evolution of the number (or of the concentration) of a given
polynucleotide template. Thus the process is modelized through a set of deterministic equations.
On the other hand, the process is clearly stochastic, since it involves a mutation probability. The
deterministic model describe the process exactly only in the limit that the total population considered
is infinite. This fact was recognized since when the model was first formulated [4] and a series of
papers [1], [2], [3], [8], [12], have been devoted to extending the model to the case of a finite
population. However, all these models introduce some approximation, deal with particular subcases
or introduce some variation of Eigen’s hypotheses. In the first part of this paper, we describe a
new simple discrete time stochastic model that reproduces the Eigen equations in the continuous
deterministic limit.

The fact that the approximation of the mutation probability with a mutation rate is exact in the
infinite population limit will, in general, imply that the differences between the predictions of the
deterministic model and of a stochastic version of it will become smaller and smaller with increasing
population size. However, the rate of convergence can depend on the parameters of the model. As
we will show (see also [3], for some choices of the mutation probabilities, the rate of convergence is
zero. Hence it is essential to have a reliable stochastic version of the Eigen model to understand for
which choices of the mutation probabilities the finite population corrections can play a relevant role.
In particular, the two species case is very instructive from this point of view. It is simple enough so
that the stochastic model can be treated (almost) exactly, and, since it involves only two mutation
probabilities, the results can be plotted on three dimensional graphs; in this way, the differences
between the Eigen model and the stochastic model can be spotted at a glance. In the second part
of this paper we explicitly write down the transition matrix for our stochastic model in the two
species case and we use it to compute the asymptotic master sequence concentration numerically.
We compare our results with those obtained using the Eigen model and those obtained by Nowak
and Schuster [8] through their birth and death model. The results turns out to be extremely close even for low values of the total population, for almost all choices of the mutation probabilities.

2 The Eigen model

Eigen [4] introduced a model to deal with polynucleotide replication, that we briefly recall here, following the exposition given in Swetina and Schuster [10]. The inspiring idea was to compute the steady state reached by a population of replicating polynucleotides subject to mutation and selection. Let us assume that we have a population of s possible polynucleotide templates \( I_i, j = 1, \ldots, s \); to define the model we have to assign to each \( I_j \) its synthesization rate \( A_j \), its degradation rate \( D_j \), and the probabilities \( Q_{ij} \) of obtaining the polynucleotide \( I_i \) as a result of an inexact replication of a different polynucleotide \( I_j \). The transition probabilities \( Q_{ij} \) have to satisfy the constraint:

\[
\sum_{i=1}^{s} Q_{ij} = 1
\]

meaning that the set of \( s \) polynucleotide templates \( I_i \) is closed under the replication process (that is no new polynucleotides can emerge as a result of an inexact replication). Eigen’s equations are a set of differential equations governing the evolution of the number \( x_i \) of the self-replicating molecule \( I_i \):

\[
\dot{x}_i = \sum_{j=1}^{s} \left( A_j Q_{ij} - D_j \delta_{ij} \right) x_j - \frac{x_i}{N} \sum_{j=1}^{s} (A_j - D_j) x_j
\]

where

\[
N = \sum_{i=1}^{s} x_i
\]

According to [2] the variation of \( x_i \) is composed of a term \( A_i Q_{ii} x_i \) taking into account the successful replication of the polynucleotide \( I_i \), minus a term \( D_i x_i \) due to its degradation rate, plus a term \( \sum_{i \neq j} A_j Q_{ij} x_j \) giving the number of \( I_i \) generated through an inexact replication of other polynucleotides, and finally minus a quadratic selection term that keeps the total population constant. In fact, thanks to this last term Eigen’s equations satisfy

\[
\dot{N} = \sum_{i=1}^{s} \dot{x}_i = 0
\]

Even if equation [2] was developed to model polynucleotides, it is more general and can be applied to any kind of self-replicating entities subject to mutation, under the constraint of constant population. Hence, from now on we will use the more generic term “species” instead of “polynucleotide”.

In this paper we will consider in detail the case of two species \( s = 2 \), so that we recall some results coming from equation [2] in this case. In the two species case we can write the Eigen equations in terms of the “quality factors” \( Q_{11} \) and \( Q_{22} \) only. Posing \( Q_{11} = Q_1 \), \( Q_{21} = 1 - Q_1 \), \( Q_{22} = Q_2 \), \( Q_{12} = 1 - Q_2 \), equations [2] read:

\[
\begin{align*}
\dot{x}_1 & = (A_1 Q_1 - D_1) x_1 + A_2 (1 - Q_2) x_2 - \frac{x_1}{N} \left[ (A_1 - D_1) x_1 + (A_2 - D_2) x_2 \right] \\
\dot{x}_2 & = A_1 (1 - Q_1) x_1 + (A_2 Q_2 - D_2) x_2 - \frac{x_2}{N} \left[ (A_1 - D_1) x_1 + (A_2 - D_2) x_2 \right]
\end{align*}
\]

We will assume that \( A_1 - D_1 > A_2 - D_2 \), so that \( x_1 \) represents the number of individuals with the highest reproductive capability. Such individuals are usually said to belong to the “master sequence” (because they correspond to the best polynucleotides sequence) or also to the “wild type” (because for low choices of the mutation probabilities they represent the most common type inside the population).
The system \(3, 4\) can be linearized through the following time dependent change of variables (see \(11, 6, 7\)):

\[
x_1(t) = \exp\left(-\frac{1}{N} \int_0^t (A_1 - D_1)x_1(\tau) + (A_2 - D_2)x_2(\tau)d\tau \right) z_1(t)
\]

\[
x_2(t) = \exp\left(-\frac{1}{N} \int_0^t (A_1 - D_1)x_1(\tau) + (A_2 - D_2)x_2(\tau)d\tau \right) z_2(t)
\]

in the new variables equations \(3, 4\) become:

\[
\dot{z}_1 = (A_1 Q_1 - D_1) z_1 + A_2 (1 - Q_2) z_2
\]

\[
\dot{z}_2 = A_1 (1 - Q_1) z_1 + (A_2 Q_2 - D_2) z_2
\]

We are interested in the asymptotic master sequence concentration, that is in the steady state \(\bar{\xi}_E\) of the ratio \(x_1(t)/(x_1(t) + x_2(t))\). It can be determined by finding the eigenvalues and eigenvectors of the matrix:

\[
W = \begin{pmatrix} A_1 Q_1 - D_1 & A_2 (1 - Q_2) \\ A_1 (1 - Q_1) & A_2 Q_2 - D_2 \end{pmatrix}
\]

and is given explicitely by:

\[
\bar{\xi}_E = \lim_{t \to \infty} \frac{x_1(t)}{x_1(t) + x_2(t)} = \lim_{t \to \infty} \frac{z_1(t)}{z_1(t) + z_2(t)}
\]

\[
= \begin{cases} 
\frac{W_{12}}{W_{12} + \lambda_+ - W_{11}} & \text{if } \lambda_+ \geq \lambda_- \iff W_{11} \geq W_{22} \\
\frac{\lambda_- - W_{22}}{W_{21} + \lambda_- - W_{22}} & \text{if } \lambda_+ < \lambda_- \iff W_{11} < W_{22}
\end{cases}
\]

where \(\lambda_{\pm}\) are the eigenvalues of the matrix \(W\):

\[
\lambda_{\pm} = \frac{1}{2} \left[ (W_{11} + W_{22}) \pm \sqrt{(W_{11} - W_{22})^2 + 4W_{12}W_{21}} \right]
\]

In figure \(11\) we plot \(\bar{\xi}_E(Q_1, Q_2)\) for \(A_2 = 1, D_1 = 1, D_2 = 1\) and two choices of \(A_1\): \(A_1 = 4\) and \(A_1 = 10\).

We notice that the denominators in formula \(11\) vanish respectively when \(W_{21} = 0\) and when \(W_{12} = 0\). In the first case we will have \(Q_1 = 1\) from which it follows \(\lambda_+ = W_{11} = A_1 - D_1 > A_2 Q_2 - D_2 = \lambda_-\).

So using equation \(11\) we get:

\[
\bar{\xi}_E = 1 \quad \text{for } Q_1 = 1
\]

In the second case we will have \(Q_2 = 1\) from which it follows \(W_{11} = \lambda_+ = A_1 Q_1 - D_1, \lambda_- = A_2 - D_2\) and substituting into equation \(11\)

\[
\bar{\xi}_E = \begin{cases} 
\frac{W_{11} - W_{22}}{W_{21} + W_{11}} & \text{if } Q_1 \geq \frac{A_2 - D_2 + D_1}{A_1} \\
0 & \text{if } Q_1 < \frac{A_2 - D_2 + D_1}{A_1}
\end{cases} \quad \text{for } Q_2 = 1
\]

This last case is of particular interest. Indeed, \(Q_2 = 1\) means that the probability of back mutation from mutants to wild-type is zero and this means, in turn, that the state in which the population is formed of only mutants is an absorbing state for the process; that is, once it is reached it cannot be left. If we think of mutation as a probabilistic process instead of a deterministic one, then, if the population is finite, there is always a finite (possibly very small) probability to reach the absorbing state by the simultaneous mutation of all wild type individuals. Since a finite probability event will always happen provided we wait long enough, the only possible steady state when \(Q_2 = 1\) and population is finite should be \(\bar{\xi}_E = 0\). From a more biological point of view, this is due to the fact that there is no genetic drift in the deterministic model. Any stochastic version of the Eigen model
will introduce the genetic drift in the process, and the drift will always push the system in its only stable state, that is the extinction of the master sequence. In conclusion, the difference between the asymptotic master sequence concentration calculated through the Eigen model and through any stochastic version of it will always be

\[
\frac{W_{11} - W_{22}}{W_{21} + W_{11}} \quad \text{if} \quad Q_1 > \frac{A_2 - D_2 + D_1}{A_1}, \quad Q_2 = 1
\]

independent of the population size. Despite of this fact the Eigen equations are frequently used also in this case (see [9] for example). The fact that the deterministic nature of the Eigen model makes it unfit to correctly predict the asymptotic master sequence concentration is of particular evidence in the case we just illustrated and it was already noticed in [3] and by Eigen himself [4]. However, this observation raise the natural question of whether there exist other choices of the mutation probabilities such that the deterministic nature of the Eigen model leads to wrong predictions. To answer this question a possible strategy consists in:

- developing a reliable stochastic version of Eigen model (given in section 3),
- using it to compute the asymptotic master sequence concentrations for a large number of possible choices of the mutation probabilities (we explain how this is done for the two species case in section 4 and 5).
- comparing the Eigen model and the stochastic model predictions (that is done in section 5).

### 3 A stochastic version of the Eigen model

In this section we define a discrete time stochastic model of replication with mutation subject to the constraint that the population is constant and having the Eigen model as its deterministic continuous time limit. Let \( h \) denote the time step; at each time step two stochastic processes occur: reproduction and selection. We introduce two variables sets \( x^{(i)} \) and \( y^{(i)} \), \( i = 1, \ldots, s \) to describe the two processes. \( x^{(i)}_{n} \) denotes the number of \( I^{(i)} \) individuals at the beginning of the \( n \)-th time step before reproduction and selection, while \( y^{(i)}_{n} \) denotes the number of \( I^{(i)} \) individuals at the \( n \)-th time step after reproduction but before selection. In the following we explain in detail the two processes, while a graphical sketch of them is given in figure 2. First each specie undergoes reproduction and degradation with synthesization and degradation rate \( A_i \) and \( D_i \) respectively. Each \( I^{(i)} \) individual from the parent generation has a probability \( hD_i \) of being removed from the population, while each of the newly synthesized \( I^{(i)} \) can mutate into the specie \( I^{(j)} \) with a probability \( Q_{ij} \). Hence, at time step \( n \), the probability that \( k \) of the \( hA_i x^{(j)}_{n} \) (assuming \( hA_i x^{(j)}_{n} \) being an integer number) newly synthesized \( I^{(j)} \) templates mutate into \( I^{(i)} \) ones is given by:

\[
P[I^{(j)} \rightarrow I^{(i)}] = \left( \frac{hA_i x^{(j)}_{n}}{k} \right) Q_{ij}^k (1 - Q_{ij})^{hA_i x^{(j)}_{n} - k}
\]

The deterministic limit (that is, the limit of infinite population) of this process is obtained by considering the evolution of the expectation value instead of the probability distribution. Let us denote this expectation value by \( \bar{y}^{(i)}_{n} \); then:

\[
\bar{y}^{(i)}_{n} = x^{(i)}_{n} + hD_i x^{(i)}_{n} + \sum_{j=1}^{s} \sum_{k=0}^{\lfloor hA_j x^{(j)}_{n} \rfloor} \left( \frac{hA_j x^{(j)}_{n}}{k} \right) Q_{ij}^k (1 - Q_{ij})^{hA_j x^{(j)}_{n} - k} = x^{(i)}_{n} + h \sum_{j=1}^{s} (A_j Q_{ij} - D_i \delta_{ij}) x^{(j)}_{n}
\]

The second phase consists in the random extraction without replacement of \( N \) specimens from the total population, so that, after this step, the total population will always be composed of \( N \)
The probability of extracting \( k \) individuals out of the \( y_{nh}^{(i)} \) of species \( I^{(i)} \) is given by the hypergeometric distribution:

\[
P[x_{(n+1)h}^{(i)} = k] = \binom{N}{k} \left( \sum_{j=1}^{s} \frac{y_{nh}^{(j)}}{y_{nh}^{(i)}} - N \right) / \left( \sum_{j=1}^{s} \frac{y_{nh}^{(j)}}{y_{nh}^{(i)}} \right)
\]

that has mean:

\[
\bar{x}_{(n+1)h}^{(i)} = \sum_{k=0}^{y_{nh}^{(i)}} k P[x_{(n+1)h}^{(i)} = k] = N \frac{y_{nh}^{(i)}}{\sum_{j=1}^{s} y_{nh}^{(j)}}
\]

The last equality states the intuitive fact that the random extraction of \( N \) specimens, on the average, does not change the relative concentration of the templates:

\[
\frac{\bar{x}_{(n+1)h}^{(i)}}{\sum_{j=1}^{s} x_{(n+1)h}^{(j)}} = \frac{\bar{x}_{(n+1)h}^{(i)}}{N} = \frac{y_{nh}^{(i)}}{\sum_{j=1}^{s} y_{nh}^{(j)}}
\]

Obviously from equation (7) it follows at once that

\[
\sum_{i=1}^{s} \bar{x}_{(n+1)h}^{(i)} = N
\]

Hence, in the deterministic limit, the model is described by the following discrete equation:

\[
x_{(n+1)h}^{(i)} = \frac{x_{nh}^{(i)} + h \sum_{j=1}^{s} (A_j Q_{ij} - D_i \delta_{ij}) x_{nh}^{(j)}}{1 + \frac{h}{N} \sum_{j=1}^{s} (A_j - D_j) x_{nh}^{(j)}} = \left( x_{nh}^{(i)} + h \sum_{j=1}^{s} (A_j Q_{ij} - D_i \delta_{ij}) x_{nh}^{(j)} \right) \left( 1 - \frac{h}{N} \sum_{j=1}^{s} (A_j - D_j) x_{nh}^{(j)} + O(h^2) \right)
\]

\[
\Rightarrow x_{(n+1)h}^{(i)} = \frac{x_{nh}^{(i)} - x_{nh}^{(i)} h}{h} = \sum_{j=1}^{s} (A_j Q_{ij} - D_i \delta_{ij}) x_{nh}^{(j)} - x_{nh}^{(i)} \frac{
\sum_{j=1}^{s} (A_j - D_j) x_{nh}^{(j)} + O(h)}{N}
\]

and taking the limit \( h \to 0 \) we recover the Eigen equations (2).

## 4 Transition matrix for the two species case

In this section we write down the transition matrix for our Markov Chain model in the case of two species, \( s = 2 \). For a simple treatment of Markov Chains and transition matrices we refer the reader to the book by Grimstead and Snell [5].

The choice of the time step \( h \) is completely arbitrary, however, since we are interested in an asymptotic quantity, in this limit its value should not be particularly relevant, so we fix it to be 1 here. We also restrict to the case \( D_1 = D_2 = 1 \), that is the case when parents never pass to the following generation. This case is much simpler to treat since we have only a stochastic process in the reproductive phase instead of two. Furthermore, we assume \( A_1 > A_2 \), so that specie \( I^{(1)} \) is the master sequence. Let us write a transition matrix for the reproductive step as described in section 3. It will be a matrix \( P \) of dimension \((N+1) \times (A_1 N + 1)\), the \( P_{ij} \) entries gives the probability that

\[
x_1^1 = N - i + 1 \quad \Rightarrow \quad y_1^1 = A_1 (N - i + 1) + A_2 (i + 1) - j + 1
\]

Under the assumptions that we made the entries of \( P \) will read:

\[
P_{r+1,k+1} = \sum_{l=0}^{A_1 N} Q_1 A_1^{(N-r)-l} (1 - Q_1)^l \left( A_1 (N - r) \right) Q_2^{(k-l)} (1 - Q_2) (A_2 r - k + l) \left( \frac{A_2 r}{k - l} \right)
\]
Indeed, if there would be no mutation, starting from the initial state

\[ x_n^1 = N - r \quad x_n^2 = r \]

we would end up with the state

\[ y_n^1 = A_1(N - r) \quad y_n^2 = A_2r \]

The first three factors on the right hand side of (8) give the probability that \( l \) among the \( I^{(1)} \) individuals mutate into \( I^{(2)} \) individuals, meaning that

\[ y_n^1 \xrightarrow{Q_l} A_1(N - r) - l \quad y_n^2 \xrightarrow{Q_l} A_2r + l \]

The last three factors giving instead the probability that at the same time \( A_2r - k + l \) of the \( I^{(2)} \) individuals mutate into \( I^{(1)} \) individuals, meaning that

\[ y_n^1 \xrightarrow{Q_l} A_1(N - r) - l \xrightarrow{Q_2} C1(N - r) - l + A_2r - k + l = A_1(N - r) + A_2r - k \]

\[ y_n^2 \xrightarrow{Q_l} A_2r + l \xrightarrow{Q_2} A_2r + l - A_2r + k - l = k \]

To avoid a cumbersome notation we let \( l \) and \( k \) vary from 0 to \( A_1N \), exploiting the fact that the generalized binomial coefficient

\[ \binom{N}{k} = \frac{\Gamma(N + 1)}{\Gamma(k + 1)\Gamma(N - k)} \]

is 0 when \( k < 0 \) or \( k > N \). The real intervals of variation of \( k \) and \( l \) (avoiding factorials of negative numbers) would be:

\[ k = 0, \ldots, A_1(N - r) + A_2r; \quad l = \max(0, k - A_2r), \ldots, \min(k, A_1(N - r)) \]

The transition matrix \( P \) allows one to compute the probabilities of all the possible outcomes of the reproductive phase. For the selection phase, we have to define \( N + 1 \) transition matrices \( R^{(i)} \) of dimensions \((A_1N + 1) \times (N + 1)\). In fact, depending on the state before the reproductive phase, we can have \( N + 1 \) different values \( T_i = A_1(N - i + 1) + A_2(i - 1) \) of the total population before the selection phase. The entries \( R_{jk}^{(i)} \) gives the probabilities that starting from a total population of \( T_i = A_1(N - i + 1) + A_2(i - 1) \) individuals with composition

\[ y_n^1 = A_1(N - i + 1) + A_2(i - 1) - j + 1 \]

\[ y_n^2 = j - 1 \]

we randomly extract a population composed of

\[ x_{n+1}^1 = N - k + 1 \]

\[ x_{n+1}^2 = k - 1 \]

That is, using the hypergeometric distribution:

\[ R_{k+1,r+1}^{(i)} = \binom{T_i - N}{k - r} \binom{N}{r} \binom{T_i}{k} \]

\[ k = 0, \ldots, T_i \quad r = 0, \ldots, N \]

We can now put together the two steps to obtain the transition matrix \( M \) for our stochastic model by simply multiplying properly the matrices \( P \) and \( R^{(i)} \):

\[ M_{ij} = \sum_{k=1}^{A_1N+1} P_{ik} R_{kj}^{(i)}, \quad i, j = 1, \ldots, N + 1 \]

In the appendix we show that, as required for transition matrices, it holds

\[ \sum_{j=1}^{N+1} M_{ij} = 1 \] (9)
5 Results

Depending on the values of $Q_1, Q_2$, the Markov chain model belongs to different classes. For $0 \leq Q_1, Q_2 < 1$ and $(Q_1, Q_2) \neq (0, 0)$ the Markov chain is “ergodic”. In such case, whatever the initial (row) probability vector $v$ be, the system will tend to the unique fixed (row) probability vector of $M$:

$$\lim_{n \to \infty} vM^n = w \quad wM = w$$

(10)

the $i$-th component of $w$ gives the probability that the system will end up in the $i$-th state, that is the probability that

$$x_{\infty}^1 = N - i + 1$$

$$x_{\infty}^2 = i - 1$$

and we can calculate the asymptotic master sequence concentration $\bar{\xi}_M$ by the simple formula

$$\bar{\xi}_M = \frac{\sum_{i=1}^{N+1} (N - i + 1)w_i}{N}$$

(11)

If $Q_1 = 1, Q_2 \neq 1$ then the Markov chain is “absorbing” with $x_1^1 = N$ being its only absorbing state. In such case, whatever the initial state be, the final state will always be the absorbing one. Therefore, we will have $x_{\infty}^1 = N$ and $\bar{\xi}_M = 1$. Analogously, if $Q_1 \neq 1, Q_2 = 1$ the absorbing state will be $x_i^N = 0$ and we will have $\bar{\xi}_M = 0$. In the case $(Q_1, Q_2) = (1, 1)$ the Markov chain will be again absorbing but now with two absorbing states: $x_i^1 = N, x_i^1 = 0$. However, when $A_2 = 1$, as in the cases that we considered, $M$ will be of the form:

$$M = \begin{pmatrix}
1 & 0 & \ldots & 0 \\
\vdots & \ddots & \ddots & \vdots \\
M_{N,1} & \ldots & M_{N,N} & 0 \\
0 & \ldots & 0 & 1
\end{pmatrix}$$

that is the state $x_i^1 = 0$ can be reached only from $x_{i-1}^1 = 0$. Therefore, provided that $x_0^1 \neq 0$, we will have $\bar{\xi}_M = 1$.

The last case we have to consider is $(Q_1, Q_2) = (0, 0)$. In this case $M^2$ defines an absorbing Markov chain with the two absorbing states $x_i^1 = N, x_i^1 = 0$. Since $M$ is of the form

$$M = \begin{pmatrix}
0 & 0 & \ldots & 1 \\
M_{2,1} & M_{2,2} & \ldots & M_{2,N+1} \\
\vdots & \vdots & \ddots & \vdots \\
M_{N,1} & \ldots & M_{N,N} & M_{N,N+1} \\
1 & \ldots & 0 & 0
\end{pmatrix}$$

it will alternate among these two states, so that the two possible outcomes will be (generally with different probabilities):

$$\lim_{n \to \infty} x_{2n}^1 = N \quad \lim_{n \to \infty} x_{2n+1}^1 = 0$$

or

$$\lim_{n \to \infty} x_{2n}^1 = 0 \quad \lim_{n \to \infty} x_{2n+1}^1 = N$$

In this case we decided to set

$$\bar{\xi}_M = \frac{1}{2N} \lim_{n \to \infty} (x_{2n}^1 + x_{2n+1}^1) = \frac{1}{2}$$

In the cases when the Markov chain is ergodic, we found numerically, using formula (10), the fixed probability vector $w$. We report in figure the graphs of the difference among $\bar{\xi}_E(Q_1, Q_2)$ calculated
through Eigen equation and $\bar{\xi}_M(Q_1, Q_2)$ calculated through the Markov chain model for $N = 50$, $A_2 = D_1 = D_2 = 1$ and $Q_1, Q_2$ varying among 0 and 1, for the two choices $A_1 = 4$ (a) and $A_1 = 10$ (b).

From the picture we see that, already for a low choice of $N$ as $N = 50$, the Eigen model and the Markov chain model predictions are in a very good agreement, except near the origin $(Q_1, Q_2) = (0, 0)$ and when $Q_2 = 1$ and $Q_1 > 1/A_1$.

In figure 4 (for $A_1 = 4$) and 5 (for $A_1 = 10$) we report the difference $\bar{\xi}_E - \bar{\xi}_M$ when $Q_1 \in [0.001, 0.999], Q_2 \in [0.001, 0.999]$ for the different population values $N = 2$ (a), $N = 10$ (b), $N = 50$ (c), $N = 100$ (d). Both figures show the same phenomena. We clearly see that the agreement between $\bar{\xi}_E$ and $\bar{\xi}_M$ improves by increasing $N$, and at the same time the maximum difference between $\bar{\xi}_E$ and $\bar{\xi}_M$ for $Q_2 = 0.999$ moves toward the error threshold $Q_1 = 1/A_1$. The difference between $\bar{\xi}_E$ and $\bar{\xi}_M$ near the point $(0, 0)$ decreases more slowly with increasing $N$, however it becomes considerably steeper.

When $Q_2 = 1$ the transition matrix has the only absorbing state $\xi_M = 0$, so that the only possible outcome is the extinction of species 1. In this case it is interesting to calculate the time to absorption, that is the expected number of generations before species 1 becomes extinguished. It can be obtained by the transition matrix through the following procedure. A reduced matrix $S$ is defined from $M$ by removing the last row and last column (corresponding to the only absorbing state). The matrix $I - S$, where $I$ denotes the identity, is invertible. Let $c$ be a column vector of dimension $N$, all of whose entries are 1, then the expected number of generations before the species 1 becomes extinct, when we start by the initial state $x_0^i = N - i + 1$, is given by the $i$–th entry of the column vector

$$t = (I - S)^{-1} c$$

We used these relations to find computationally the expected time of extinction $\tau$ for some choices of the mutation probability $Q_1$ when the initial state is $x_0^1 = N$. We report the results in figure 6 for $A_1 = 2$ (a) and $A_1 = 4$ (b). The choice $A_1 = 10$ was ruled out for computational time reasons. From figure 6 we can see that, in the proximity of the error threshold the expected extinction time starts to grow very fast. Moreover, the steepness of the curve increase by increasing the total population.

6 Discussion and conclusions

The standard reference in the literature for the finite population case is the Nowak and Schuster paper. In that paper, the authors introduced a stochastic birth and death model approximating the Eigen model in the single peak landscape case. We have used the Nowak and Schuster birth and death model to compute the asymptotic master sequence concentration $\xi(Q_1, Q_2)$ in the two species case (actually, in the original model the mutation probability $1 - Q_1$ and $1 - Q_2$ are supposed to be equal, however the extension to independent mutation probabilities is trivial). In figures 1 and 2 we plot the differences among $\xi_E$ calculated with Eigen’s model and $\xi_{BD}$ calculated with the Nowak and Schuster model. The choice of the parameters is the same as in figures 4 and 5 respectively. By comparing figures 1 and 2 with figures 4 and 5 we see that both stochastic models deviate from the Eigen model near the line $Q_2 = 1$. The birth and death model deviations, in this region, are slightly larger then those of the Markov chain model. On the other hand, the birth and death model do not evidences any problem near the point $Q_1 = 0, Q_2 = 0$.

We recall that, since the Eigen model formulation, it has always been known that its deterministic nature confined it to threat exactly only the infinite population case. So that, to cope with the finite population case a stochastic version of Eigen model is needed. However, to the best of our knowledge, all the stochastic versions of the Eigen model proposed in the literature contain some simplifying assumptions (11, 12, 13, 14, 15). Let us stress that this is not the case of the stochastic model we have proposed in the present paper.

The fact that, as we have shown, do exist choices of the mutation probabilities such that the Eigen model predictions are not satisfactory, nor for large values of the total population $N$, pushed us to perform a comparison between the two species asymptotic master sequence concentration predicted by the Eigen model and by the one we introduced. The results show that the only critical
regions are those near the point \( Q_1 = 0, Q_2 = 0 \) and near the segment \( E_t < Q_1 < 1, Q_2 = 1 \), where \( E_t \) denotes the error threshold. Far from these critical regions the agreement between the Eigen and the stochastic model is very good also for low values of the total population, despite the fact that the Eigen model is obtained by the stochastic model through two subsequent approximations: the deterministic and the continuous time limit. Let us stress that the two species case with the Eigen model is obtained by the stochastic model through two subsequent approximations: the stochastic model is very good also for low values of the total population, despite the fact that the steepness increase with the total population. Second, the value of \( \tau \) at the error threshold is higher when \( A_1 = 2 \) (figure 5a) than when \( A_1 = 4 \) (figure 5b). This suggest that if \( A_1 \gg A_2 \), the master sequence could go extinct for \( Q_1 > E_t \) in a small number of generations, also for high values of the total population \( N \). Second, the value of \( \tau \) at the error threshold is higher when \( A_1 = 2 \) (figure 5a) than when \( A_1 = 4 \) (figure 5b). This suggest that if \( A_1 \simeq A_2 \), then, even if \( Q_1 < E_t \), a large number of generations could be necessary before the master sequence go extinct, especially if the total population \( N \) is large. So that one has to be quite cautious in using the Eigen model predictions in this limit case.

Finally, we would like to mention that writing the transition matrix of our stochastic model for a given number of species greater than 2 present no conceptual difficulties. However, the number of states appearing in the transition matrix is equal to the number of partitions of \( N + s \) into \( s \) classes. This means that already for \( s = 3 \), for example, the number of states is equal to \((N + 1)(N + 2)/2\) and numerical computation with the transition matrix are affordable only for low values of \( N \). Henceforth, to deal with the \( s > 2 \) case one is forced to introduce some approximation of the kind used in [9]. An alternative approach would be to use computer simulations, and since we have defined a completely discrete model, its implementation for computer simulations is really straightforward. Moreover, simulating our model is computationally more economic than using the computer model introduced by Nowak and Schuster [9].

Appendix

In this appendix we show that equation (9) does indeed hold. Note that the Vandermonde identity implies

\[
\sum_{r=1}^{N+1} R_{k,r}^{(i)} = 1
\]

(12)

Let us now show that it also holds

\[
\sum_{k=0}^{A_1 N} P_{r+1,k+1} = 1
\]

(13)
We have:
\[
\sum_{k=0}^{A_1 N} \sum_{l=0}^{A_1 (N-r)-l} \frac{A_1^l}{Q_1} (1-Q_1)^{l-1} \binom{A_1 (N-r)}{l} Q_2^l (1-Q_2)^{(A_2 r-k+l)} \frac{A_2 r}{k-l} =
\]
\[
= \sum_{l=0}^{A_1 (N-r)-l} (1-Q_1)^{l-1} \binom{A_1 (N-r)}{l} \sum_{k=0}^{A_1 N} Q_2^l (1-Q_2)^{(A_2 r-k+l)} \frac{A_2 r}{k-l} =
\]

Let us consider a fixed value for \( l \) in the second summation. If the sum on \( k \) is such that \( k-l \) spans the interval \( 0, \ldots, A_2 r \), then such sum is equal to 1:
\[
\sum_{k-l=0}^{A_2 r} Q_2^l (1-Q_2)^{(A_2 r-k+l)} \frac{A_2 r}{k-l} = (1-Q_2 + Q_2) A_2 r = 1
\]

Note that \( k-l = 0 \) is for sure in the interval of summation over \( k \), since \( k \) has the same interval of variation of \( l \). On the other hand let us notice that the maximum value for \( l \) is \( A_1 (N-r) \) since for greater values of \( l \) the binomial factor
\[
\binom{A_1 (N-r)}{l}
\]
is always zero. Hence \( k-l = A_2 r \) will be in the interval of summation over \( k \) if \( A_1 N - A_1 (N-r) \geq A_2 r \), but this is granted by the condition \( A_1 > A_2 \). The sum over \( l \) will now give 1 for exactly the same reasons.

From equations (13) and (12) we get:
\[
\sum_{j=1}^{N+1} M_{ij} = \sum_{j=1}^{N+1} \sum_{k=1}^{A_1 N+1} P_{jk} R_{ij}^{(k)} = \sum_{k=1}^{A_1 N+1} P_{ik} \sum_{j=1}^{N+1} R_{kj}^{(i)} = 1
\]

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Figure 1: $\bar{\xi}(Q_1, Q_2)$ for $A_1 = 4, A_2 = D_1 = D_2 = 1$ (a) and $A_1 = 10, A_2 = D_1 = D_2 = 1$ (b)
Figure 2: An example of a time step of the stochastic model defined in section 3 for $s = 3$, $\bullet = I^{(1)}$, $\bigcirc = I^{(2)}$, $\blacktriangle = I^{(3)}$, $hA_1 = 3$, $hA_2 = 1$, $hA_3 = 1$. Each individual $I^{(i)}$ in the parent generation give raise to $hA_i$ new individuals, each of them having a probability $Q_{ji}$ of mutating into an $I^{(j)}$ one. The parent individual has a probability $hD_i$ of degradating before the selection phase. In the selection phase $N$ individuals are extracted at random (without replacement) from the pool of individuals obtained after the reproduction phase. The event probability is associated to each arrow. Notice that the probability of any individual of surviving the selection phase is independent on the specie.
Figure 3: The difference $\bar{\xi}_E - \bar{\xi}_M$ as a function of $(Q_1, Q_2)$, for $N = 50, A_1 = 4, A_2 = D_1 = D_2 = 1$ (a) and for $N = 50, A_1 = 10, A_2 = D_1 = D_2 = 1$ (b).
Figure 4: The difference $\bar{\xi}_E - \bar{\xi}_M$ as a function of $(Q_1, Q_2)$, for $A_1 = 4, A_2 = D_1 = D_2 = 1$ and $N = 2$ ($a$), $N = 10$ ($b$), $N = 50$ ($c$) and $N = 100$ ($d$). The graphs are drawn using a grid of 625 points covering the square $Q_1 \in [0.001, 0.999], Q_2 \in [0.001, 0.999]$. 
Figure 5: The difference $\bar{\xi}_E - \bar{\xi}_M$ as a function of $(Q_1, Q_2)$, for $A_1 = 10, A_2 = D_1 = D_2 = 1$ and $N = 2$ (a), $N = 10$ (b), $N = 50$ (c) and $N = 100$ (d). The graphs are drawn using a grid of 625 points covering the square $Q_1 \in [0.001, 0.999], Q_2 \in [0.001, 0.999]$. 
Figure 6: Logarithm of expected generation of extinction for the master sequence as a function of $Q_1$ when $Q_2 = 1$. The curves given correspond (from right to left) to total population $N = 50$, $N = 100$, $N = 200$, $N = 300$ and $N = 400$. Left graph $A_1 = 2$, right graph $A_1 = 4$. Dashed lines correspond to the Eigen error threshold.
Figure 7: The difference $\bar{\xi}_E - \bar{\xi}_{BD}$ as a function of $(Q_1, Q_2)$, for $A_1 = 4$, $A_2 = D_1 = D_2 = 1$ and $N = 2$ (a), $N = 10$ (b), $N = 50$ (c) and $N = 100$ (d). The graphs are drawn using a grid of 625 points covering the square $Q_1 \in [0.001, 0.999]$, $Q_2 \in [0.001, 0.999]$. 
Figure 8: The difference $\bar{\xi}_E - \bar{\xi}_{BD}$ as a function of $(Q_1, Q_2)$, for $A_1 = 10$, $A_2 = D_1 = D_2 = 1$ and $N = 2$ (a), $N = 10$ (b), $N = 50$ (c) and $N = 100$ (d). The graphs are drawn using a grid of 625 points covering the square $Q_1 \in [0.001, 0.999]$, $Q_2 \in [0.001, 0.999]$. 