Mutation model for oligonucleotides fitting a Yule distribution

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Abstract

A spin chain, describing a nucleotides sequence, is identified by the the labels of a vector state of an irreducible representation of $\mathcal{U}_{q=0}(sl_2)$. A master equation for the distribution function is written, where the intensity of the one-spin flip is assumed to depend from the variation of the labels. The numerically computed equilibrium distribution is nicely fitted by a Yule distribution, which is the observed distribution of the ranked short oligonucleotides frequency in DNA

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1 Introduction

Spin chains, both in the classical and quantum version, are extremely important tools to understand various physical situations and, in some cases, provide completely soluble models. An interesting field of applications of these models is the theory of molecular biological evolution. Since 1986, when Leuthäusser [1] put a correspondence between the Eigen model of evolution [2] and a two-dimensional Ising model, many articles have been written representing biological systems as spin models. Recently in [3] it has been shown that the parallel mutation-selection model can be put in correspondence with the Hamiltonian of an Ising quantum chain and in [4] the Eigen model has been mapped into the Hamiltonian of one-dimensional quantum spin chains. In this approach the genetic sequence is specified by a sequence of spin values ±1. DNA is built up a sequence of a four basis or nucleotides which are usually identified by their letter: C, G, T, A (T being replaced by U in RNA), C and U (G and A) belonging to the purine family, denoted by R (respectively to the pyrimidine family, denoted by Y). Therefore in the case of genome sequences each point in the sequence should be identified by an element of a four letter alphabet. As a simplification one identifies each element according to the purine or pyrimidine nature, reducing to a binary value, see [5] for a four-state quantum chain approach. As standard assumption, the strength of the mutation is assumed to depend from the Hamming distance between two sequences, i.e. the number of sites with different labels. Moreover usually it is assumed that the mutation matrix elements are vanishing for Hamming distances larger than 1, i.e. for more than one nucleotide changes. The main aim of the works using this approach, see [6, 7, 8], is to find, in different landscapes, the mean “fitness” and the “biological surplus”, in the framework of biological population evolution. At our knowledge these has been no attempt to apply spin models to obtain the observed equilibrium distribution of oligonucleotides in DNA. Martindale and Konopka [9], indeed, have remarked that the ranked short (ranging from 3 to 10 nucleotides) oligonucleotide frequencies, in both coding and non-coding region of DNA, follow a Yule distribution. We recall that a Yule distribution is given by $f = an^k b^n$, where $n$ is the rank and $a, k < 0$ and $b$ are 3 real parameters. In order to face this problem, in this paper we propose a spin model in which the intensity of the transition matrix depends in some way from the whole distribution of the nucleotides in the sequence. At present we assume that the transition matrix does not vanish only for total spin flip.
equal $\pm 1$.

2 Mutations and Crystal basis

A sequence of $N$ ordered nucleotides, characterized only by the purine or pyrimidine character, that is a string of $N$ binary labels or spin, can be represented as a vector belonging to the $N$-fold tensor product of the fundamental irreducible representation (irrep.) (labelled by $J = 1/2$) of $U_{q=0}(sl_2)$ [10], which is usually called crystal basis representation. This parametrization allows to represent, in a simple way, the mutation of a sequence as a linear transformation between vectors, which can be subjected to selection rules and whose strength depends from the two concerned states. So we identify a $N$-nucleotidic sequence as a vector

$$|J\rangle = |J_3, J^N, \ldots, J^i, \ldots, J^2\rangle$$

where $J^N$ labels the irrep. which the vector belongs to, $J_3$ is the value of the 3rd diagonal generator of $U_{q=0}(sl_2)$ ($2J_3 = n_R - n_Y$, $n_x$ being the number of $x$ elements in the sequence) and $J^i$ ($2 \leq i \leq N-1$) are $N-2$ labels needed to remove the degeneracy of the irreps. in the tensor product, in order to completely identify the state and which can be seen as identifying the irrep. which the sequence truncated to the $i$-th element belongs to. As an example, we consider a trinucleotidic string ($N = 3$) and label the eight different spin chains in the following way($|J_3, J^3, J^2\rangle, R \equiv \frac{1}{2} \equiv \uparrow, Y \equiv -\frac{1}{2} \equiv \downarrow$):

$$
\begin{align*}
\uparrow\uparrow\downarrow &= | -\frac{1}{2}, \frac{1}{2}, 0\rangle & \uparrow\downarrow\uparrow &= | \frac{1}{2}, \frac{1}{2}, 0\rangle \\
\uparrow\downarrow\downarrow &= | -\frac{1}{2}, \frac{1}{2}, 1\rangle & \uparrow\uparrow\downarrow &= | \frac{1}{2}, \frac{1}{2}, 1\rangle \\
\downarrow\downarrow\downarrow &= | -\frac{3}{2}, \frac{3}{2}, 1\rangle & \downarrow\uparrow\uparrow &= | -\frac{1}{2}, \frac{3}{2}, 1\rangle \\
\downarrow\uparrow\uparrow &= | \frac{1}{2}, \frac{3}{2}, 1\rangle & \downarrow\uparrow\uparrow &= | \frac{3}{2}, \frac{3}{2}, 1\rangle. 
\end{align*}
$$

At this stage the crystal basis provides an alternative way of labelling any finite spin sequence, mapping any sequence in a vector state of an irrep., but we know that in physics and mathematics the choice of appropriate variables is of primary importance to face a problem. Indeed we argue that these variables are suitable to partially describe non local events which affect the mutations. Flipping the total spin by $\pm 1$ ($\Delta J_3 = \pm 1$) can induce a transition to a vector belonging or not belonging to the irrep. of the original sequence. One can easily realize that to identify a nucleotidic sequence as
a vector of an irrep. requires to fix the number of RY “contracted couples” occurring in the considered sequence (contraction should be understood in the same sense of contraction of creation-annihilation operators in the Wick expansion). Therefore flipping a spin implies or the creation or the deletion of a RY contracted couple, corresponding respectively to a variation of -1 or +1 of the value of the \( J^N \) and, possibly, of some others \( J^i \) (\( 2 \leq i \leq N-1 \)), or to leave unmodified the number of contracted couples (so that \( \Delta J^N = 0 \), but \( \Delta J^i \neq 0 \) for some values of \( i \)). Note that alternatively one can identify \( 1/2 \equiv (C, G) \) and \( -1/2 \equiv (T, A) \). Below we give phenomenological arguments for our choice.

### 3 Transition operators

Let us consider a \( N \)-nucleotidic string and classify the different transitions on the string labels \( J_3, J^N, \ldots, J^2 \). We can distinguish different string configurations around the \( i \)-th position, so that a single nucleotide mutation in the \( i \)-th position can correspond to different variations in the string labels. We call left (right) side free the nucleotides on the left (right) of \( i \)-th position and not contracted with another one on the same side. Let \( R_L \) be the initial (before mutation) number of the left side free purines and \( Y_r \) the initial number of the right side free pyrimidines. We want to count the total number of contracted RY couples (before and after mutation) in the string, so we call \( R_{in} (R_{fi}) \) the number, in the initial (final) state, of R preceding some Y and not contracted with any Y on their side. In the same way, with \( Y_{in} (Y_{fi}) \) we refer to the number of Y following some R and not contracted with any R on their side. If a \( R \rightarrow Y \) mutation (\( \Delta J_3 = -1 \)) occurs in \( i \)-th position, then \( R_{in} = R_{fi} + 1 \) and \( Y_{in} = Y_{fi} - 1 \), where \( R_{in} = R_{i} + 1 \) and \( Y_{in} = Y_{r} \). We are interested in finding the stationary or equilibrium configuration of the \( 2^N \) different possible sequence. Writing \( p_J(t) \) the probability distribution at time \( t \) of the sequence identified by the vector \( |J\rangle \), a decoupled version of selection mutation equation (see \cite{11} for an exhaustive review), for a haploid organism, can be written as

\[
\frac{d}{dt} p_J(t) = p_J(t) \left( R_J - \sum_K R_K p_K(t) \right) + \sum_K M_{J,K} p_K(t)
\]  

where \( R_K \) is the Malthusian fitness of the sequence corresponding to the vector \( |K\rangle \) and \( M_{J,K} \) are the entries of a mutation matrix \( M \) which satisfies
\[ M_{J,J} = - \sum_{K \neq J} M_{J,K} \quad (3) \]

The equation (2) is reduced to
\[ \frac{d}{dt} x_J(t) = \sum_K (H + M)_{J,K} \times x_K(t) \quad (4) \]

where
\[ x_J(t) = p_J(t) \exp \left( \sum_K R_K \int_0^t p_K(\tau) d\tau \right) \quad (5) \]

and \( H \) is a diagonal matrix, with fitness as entries.

In our model the mutation matrix is written as the sum of the following partial mutation matrices (T means transposition):

- If \( R_l = Y_r \) we distinguish two subcases:
  
  1. \( R_l = Y_r \neq 0 \)
      
      \[ M_1 = \sum_{i=2}^{N-1} \sum_{k=i+1}^N \alpha_{ik} \left( A_{i,k} J_+ + J_+ A_{i,k}^T \right) \quad (6) \]
  
  2. \( R_l = Y_r = 0 \)
      
      \[ M_2 = \alpha_2 \left( J_+ + J_+ \right) \quad (7) \]

- If \( R_l > Y_r \), we distinguish two subcases:
  
  1. \( Y_r = 0 \)
      
      \[ M_3 = \sum_{i=2}^{N} \alpha_3 \left( A_i J_+ + J_+ A_i^T \right) \quad (8) \]
  
  2. \( Y_r \neq 0 \)
      
      \[ M_4 = \sum_{i=3}^{N-1} \alpha_4 \left( A_i J_+ + J_+ A_i^T \right) \quad (9) \]

- If \( R_l < Y_r \), we distinguish two subcases:
1. $R_l = 0$

$$M_5 = \sum_{m=2}^{N} \alpha_5^m (J_- A_m^T + A_m J_+)$$  \hspace{1cm} (10)

2. $R_l \neq 0$ ($2 \leq N - 2; i + 1 \leq k \leq N - 1$).

$$M_6 = \sum_{i=2}^{N-2} \sum_{k=i+1}^{N-1} \alpha_6^{ik} (A_{i,k}^T J_- A_{k+1}^T + A_{i,k} J_{k+1}^T J_+)$$  \hspace{1cm} (11)

where $J_+$ and $J_-$ are the step operators (to save space we do not write their explicit form) defined by Kashiwara [10], acting on the states of an irrep. with highest weight $J^N$, i.e. inducing a mutation $\Delta J_i = 0$, $\forall i \neq N$,

$$J_{\pm} | J \rangle = | J_3 \pm 1, J^N, ..., J^k, ..., J^2 \rangle$$  \hspace{1cm} (12)

and

$$A_{i,k} | J \rangle = | J_3, J^N, ..., J^k, J^{k-1} - 1, ..., J^i - 1, J^{i-1}, ..., J^2 \rangle$$  \hspace{1cm} \hspace{1cm} (13) 

$$A_i | J \rangle = | J_3, J^N - 1, ..., J^i - 1, J^{i-1}, ..., J^2 \rangle$$  \hspace{1cm} \hspace{1cm} (14)

Therefore $A_{i,k}^T$ is the operator which connects vectors differing by $+1$ in the value of $J^i$, for $k - 1 \leq l \leq i$. A few words to comment on the above equations. Let us consider a mutation $R \rightarrow Y$, which involves a transition $\Delta J_N = -1$ (case $R_l > Y_r$) and entails $\Delta J_3 = -1$, we have to apply the operator $J_-$, as well as the operator $A_i$. Of course, first we have to lower by 1 the value of $J_3$, then to modify $J^N$, otherwise the initial state may eventually be annihilated, even if the transition is allowed (in the case $J^N - 1 < J_3$).

Likewise, in correspondence of a transition $Y \rightarrow R$ ($\Delta J_3 = +1$), first the change $J^N \rightarrow J^N + 1$ has to be performed, then $J_3 \rightarrow J_3 + 1$. Clearly in eq.(12), assuming equal rates for mutations and for back mutations, we have to sum the operator, which gives rise to the transition $Y \rightarrow R$ with that one which leads to $R \rightarrow Y$, that is

$$A_i J_- + J_+ A_i^T$$  \hspace{1cm} (15)

5
This operator leads to the mutation $Y \rightarrow R$ or $R \rightarrow Y$ for a nucleotide in $i$-th position, in a string with $R_l > Y_r$. If the mutation $R \rightarrow Y$ corresponds to a rising of $J^N$ (i.e. a transition with $\Delta J_N = 1$, $\Delta J_3 = -1$, case $R_l < Y_r$), first $J^N$ has to be modified, then $J_3$; therefore we write

$$J_+ A^T_{m} + A_m J_+$$  \hspace{1cm} (16)$$

The above operator gives rise to mutations $R \rightarrow Y$ and $Y \rightarrow R$ for a nucleotide in $i$-th position, preceding the $m$-th one, in the case $R_l = 0$, $Y_r \neq 0$.

Let us remark that eq.(9) is included in eq.(8), if the coupling constants $\alpha$ are assumed equal; in eq.(11), only the writing order for $A_{k+1}$ (and its transposed) and $J_\pm$ has to be respected. Assuming now that the coupling constants do not depend on $i$, $k$, $m$, we can write the mutation matrix $M$ as

$$M = \mu_1(M_3 + M_5) + \mu_2 M_1 + \mu_3 M_2 + \mu_4 M_6 + M_D$$  \hspace{1cm} (17)$$

where $M_D$ is the diagonal part of the mutation matrix defined by eq.(3). The scale of the values of the coupling constants of $M$ is suggested by the phenomenogy. We want to write an interaction term which makes the mutation in alternating purinic/pyrimidinic tracts less likely than polipurinic or polipyrimidinic ones. We mean as a single nucleotide mutation in a polipurinic (polypyrimidinic) tract, a mutation inside a string with all nucleotides $R$ ($Y$), i.e. a highest (lowest) weight state. Such a transition corresponds to the selection rules $\Delta J_N = -1$, $\Delta J_3 = \pm 1$, i.e. a transition generated by the action of $M_3$ and $M_5$. In the mutation matrix $M$, we give them a coupling constant smaller than the We introduce, for $\Delta J_3 = \pm 1$, only four different mutation parameters $\mu_i$ ($i = 1, 2, 3, 4$), with $\mu_1 < \mu_k \, k > 1$.

1. $\mu_1$ for mutations which change the irrep., $\Delta J^N = \pm 1$, and include the spin flip inside a highest or lowest weight vector;

2. $\mu_2$ for mutations which do not change the irrep., $\Delta J^N = 0$, but modify other values of $J^k$, $\Delta J^k = \pm 1$ ($2 \leq k \leq N - 1$);

3. $\mu_3$ for mutations which do neither change the irrep., $\Delta J^N = 0$, nor the other values of $J^k$, $\Delta J^k = 0$, ($2 \leq k \leq N - 1$);

4. $\mu_4$ for mutations which change the irrep., $\Delta J = \pm 1$, but only in a string with $0 \neq R_l < Y_r$.

We do not introduce another parameter, for mutations generated by $M_4$, i.e. $i$-th nucleotide mutation in a string with $R_l > Y_r \neq 0$, to not distinguish, in a polipurinic string, a mutation according to its position.
4 Results

The evolution equation of the model for the probabilities will be written in terms of the matrix $H = H + M + \lambda \mathbf{1}$, where the fitness can be $H = J_3$ (purely additive fitness) and $\lambda$ is chosen in such a way to guarantee $H$ is positive. Being $H + M$ irreducible, the composition of equilibrium population is given by

$$p_J = \frac{\tilde{x}_J}{\sum_K \tilde{x}_K}$$

where $\tilde{x}_J$ is the Perron-Frobenius eigenvector \cite{12} of $H$. We look for a numerical solution, with a suitable choice of the value of the parameters, for $N = 3, 4, 6$. Before solving numerically the model, we point out explicitly its main features. $M$ describes an interaction on the $i$-th spin neither depending on the position nor on the nature of the closest neighbours, but which takes into account, at least partially, the effects on the transition in the $i$-th site of the distribution of all the spins, that is non local effects. Indeed it depends on the “ordered” spin orientation surplus on the left and on the right of the $i$-th position. Should it not depend on the order, it may be considered as a mean-field like effect. Moreover $\Delta J_3 = \pm 1$ transitions are allowed, which, e.g. for $N = 4$, can be considered or as the flip of a spin combined with an exchange of the two, oppositely oriented, previous or following spins or as the collective flip of particular three spin systems, containing a two spin system with opposite spin orientations (see example below). Biologically, the transition depends in some way on the "ordered" purine surplus on the left and on the right of the mutant position. Let us briefly comment on the physical-biological meaning of the “ordered” spin sequence. Our aim is to study finite oligonucleotide sequence in which a beginning and an end are defined. This implies we can neither make a thermodynamic limit on $N$ nor define periodic conditions on the spin chain. So we have to take into account the “edge” or “boundary” conditions on the finite sequence. An analogous problem appears in determining thermodynamic properties of short oligomers and, in this framework, in \cite{13} the concept of fictitious nucleotide pairs E and E' has been introduced, in order to mimick the edge effects. The ordered couple of RY takes into account in some way the different interactions of R and Y with the edges. For example, the transition matrix, on the above basis (for $N = 3$) is the following one, up to a multiplicative dimensional
factor $\mu_0$

\[
M = \begin{pmatrix}
x & \delta & 0 & \gamma & \epsilon & 0 & \epsilon & 0 \\
\delta & x & 0 & 0 & \epsilon & 0 & \epsilon & 0 \\
0 & 0 & x & \delta & \epsilon & 0 & \epsilon & 0 \\
\gamma & 0 & \delta & x & 0 & \epsilon & 0 & \epsilon \\
\epsilon & 0 & \epsilon & 0 & x & \delta & 0 & 0 \\
0 & \epsilon & 0 & \epsilon & \delta & x & \delta & 0 \\
\epsilon & 0 & \epsilon & 0 & 0 & \delta & x & \delta \\
0 & \epsilon & 0 & \epsilon & 0 & 0 & \delta & x
\end{pmatrix}
\quad (19)
\]

where the diagonal entries are not explicitly written, and are given by $\left( \right)$. Note that the above matrix depends only on three coupling constants due to the very short length of the chain. For $N \geq 4$ the 4th coupling constant (denoted in the following by $\eta$) will appear. Let us emphasize that the mutation matrix $M$ (19) does not only connect states at unitary Hamming distance. As an example, we write explicitly the transitions from $|1,1,0\rangle$ ($\uparrow\downarrow\uparrow$) and from $|1,1,0\rangle$ ($\uparrow\uparrow\downarrow$)

\[
\begin{align*}
\uparrow\uparrow\uparrow & \rightarrow \begin{cases} \uparrow\uparrow\uparrow \\ \down\down\uparrow \\ \up\up\down \end{cases} \\
\down\down\up & \rightarrow \begin{cases} \up\down\down \\ \up\up\down \\ \up\up\up \end{cases}
\end{align*}
\]

For lack of space, we do not explicitly write the mutation matrix, which allows transitions only between chains at Hamming distance equal to one, with coupling constant $\beta$. Notice however that such a (Hamming) matrix is not obtained by eq.(19) putting $\delta = \gamma = \epsilon = \beta$. If we order (in a decreasing way) the equilibrium probabilities, we obtain, using the mutation matrix with Hamming distance, a rank ordered distribution of transition probability like that in fig\(^1\) for $N = 4$. Its shape does not depend on the value of $\beta$. The rank-ordered distribution of the probabilities shows a plateau structure: every plateau contains spin sequences at the same Hamming distance from the sequence with the highest value of the fitness. Using the mutation matrix (19), the rank ordered probabilities distribution does not show a plateau structure, but its shape is well fitted by a Yule distribution (fig\(^2\)), like the observed frequency distribution of oligonucleotide in the strings of nucleic acids [9]. Let us observe that we obtain a Yule distribution (and not a plateau structure) even if all parameters in (19) are tuned at the same value, which means that the distribution is the outcome of the model and
not of the choice of the values of the coupling constants. Analogous resultes
are obtained for $N = 6$ (fig.3). Let us point out that:

i) our model is not equivalent to a model where the intensity depends on
the site undergoing the transition, or from the nature of the closest neigh-
bours or the number of the $R$ and $Y$ labels of the sequence; indeed essentially
the intensity depends on distribution in the sequence of the $R$ and $Y$;

ii) the ranked distribution of the probabilities follows a Yule distribution
law, but as the value of the parameter $b$ is close to the unity, the distribution
is equally well fitted by a Zipf law $(f = a n^k)$, in agreement with the remark
of [9].

In conclusion we are far from claiming that our simple model is the only
model able to explain the observed oligonucleotides distribution, for several
obvious reasons, but that the standard approach using the Hamming distance
does not give a Yule or Zipf distribution. One may correctly argue that the
comparison between the Hamming model, depending on only one parameter
and taking into account only one site spin flip, with our model, which depends
on four parameters and takes into account spin flip of more than one site,
is not meaningful. So we have computed the stationary distribution with a
mutation matrix not vanishing for Hamming distance larger than one and
allowing the same number of mutations as our model. The result reported
in fig.4 shows that the plateaux structure is always the dominant feature.

Let us comment on the non point mutations which naturally are present in
our model. In literature there is an increasing number of paper that, on the
basis of more accurate data, question both the assumptions that mutations
occur as single nucleotide and as independent point event. In a quite recent
paper Whelan and Goldman [14] have presented a model allowing for single-
nucleotide, doublet and triplet mutation, finding that the model provides
statistically significant improvements in fits with protein coding sequences.
We note that the triplet mutations, for which there is no known inducing
mechanism, but which can possibly be explained by large scale event, called
sequence inversion in [14], are indeed the kind of mutations, above discussed,
that our model naturally describes. Doublet mutations do not appear, due to
the assumed spin flip equal $\pm 1$, but on one side some of these mutations are
hidden by the binary approximation, and on the other side the parameter
ruling such mutations, as computed in [14], is lower than the one ruling
the triplet mutation. In conclusion the Hamming distance does not seem a
suitable measure of the distance in the space of the biological sequences, the
crystal basis, on the contrary, seems a better candidate to parametrize the
elements of such space. Our model makes use of this parametrisation, allows
to modelise some non point mutations and exhibits intriguing and interesting
features, hinting in the right direction, worthwhile to be further investigated.
In the present simple version, the model depends only on 4 parameters for
any N, which are, very likely, not enough to describe sequences longer that
the considered ones. However the model is rather flexible and, besides the
obvious introduction of more coupling constants, allows, e.g., to analyse part
of the sequences containing hot spots in the mutation (using fictitious edge
nucleotides), to take into account doublet mutations (indeed the operator
$A^T_{i,i+1}$ describes a doublet spin flip at position $i,i+1$) and an easy
generalisation to four letter alphabet. Although the very short chain, which
we were interested in, can be studied numerically without any use of the
crystal basis, we propose a general algorithm, which can be applied to chains
of arbitrary length and which can be easily implemented in computers.

References

[1] I. Leuthäusser, J.Chem.Phys. 84 (1986) 1884.
[2] M. Eigen, Naturwissenschaften 58 (1971) 465.
     M. Eigen, J. McCaskill and P. Schuster, Adv.Chem.Phys. 75 (1989) 149.
[3] E. Baake, M. Baake and H. Wagner, Phys.Rev.Lett. 78 (1997) 559.
[4] S. Saakian and Chin-Kun Hu, Phys.Rev. E 69 (2004) 021913.
[5] J. Herisson, H. Wagner and M. Baake, J.Stat.Phys. 102 (2001) 315.
[6] H. Wagner, E. Baake and T.Gerisch, J.Stat.Phys. 92 (1998) 1017.
[7] E. Baake and H. Wagner, Genet.Res.Camb. 78 (2001) 93.
[8] J. Herisson, O. Redner, H. Wagner and E.Baake, Theoretical Population Biology 62 (2002) 9.
[9] C. Martindale and A. K. Konopka, Computers Chem. 20 (1996) 35.
[10] M. Kashiwara, Commun. Math. Phys. 92 (1990) 249.
[11] J. Hofbauer and K. Sigmund, The Theory of Evolution and Dynamical Systems (Cambridge University Press 1988).
[12] Encyclopedic Dictionary of Mathematics, Vol. III, Mit Press (Cambridge, Ma, USA 1987).

[13] Goldstein RF. and Benight A. S., Biopolymers 32 (1992) 1679.

[14] Whelan S. and Goldman N., Genetics 167 (2004) 2027.

Figure 1: Rank ordered distribution of equilibrium population (N=4) obtained for an Hamming transition matrix, with $\beta = 0.60$. 
Figure 2: Rank ordered distribution of equilibrium population (N=4) for a transition matrix $M$ with $\epsilon = 0.25$, $\gamma = \delta = \eta = 0.50$. The distribution was fitted by a Yule function (continuous line) $f = aR^kb^R$ ($R$ is the rank). The parameters was estimated as $a = 0.37$, $b = 1.02$, $k = -1.28$.

Figure 3: Rank ordered distribution of equilibrium population (N=6) for a transition matrix $M$, with $\epsilon = 0.25$, $\gamma = \delta = \eta = 0.50$. The distribution was fitted by a Yule function (continuous line) $f = aR^kb^R$ ($R$ is the rank). The parameters was estimated as $a = 0.26$, $b = 1.00$, $k = -1.11$. 
Figure 4: Rank ordered distribution of equilibrium population (N=4) obtained for a transition matrix allowing the same number of mutations as $M$, between sequences at different Hamming distances.