Biological Evolution in a Multidimensional Fitness Landscape

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We considered a multi-block molecular model of biological evolution, in which fitness is a function of the mean types of alleles located at different parts (blocks) of the genome. We formulated an infinite population model with selection and mutation, and calculated the mean fitness. For the case of recombination, we formulated a model with a multidimensional fitness landscape the dimension of the space is equal to the number of blocks) and derived a theorem about the dynamics of initially narrow distribution. We also considered the case of lethal mutations. We also formulated the finite population version of the model in the case of lethal mutations. Our models, derived for the virus evolution, are interesting also for the statistical mechanics and the Hamilton-Jacobi equation as well.

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I. INTRODUCTION

The investigation of biological evolution models [1–5] is one of the most fruitful applications of statistical mechanics or theoretical physics to biological problems [6, 7]-[23]. To solve the evolution models, one can apply the whole machinery of modern theoretical physics: spin-glass physics methods [11], quantum statistical mechanics [12, 15–18], quantum field theory [15, 18], Hamilton-Jacobi equation (optimal control) [19–21].

The genome, a collection of genes with different types, could be considered as a particular spin configuration of a statistical system, where the fitness (the rate to produce off-springs of the given genome) is equivalent to the Hamiltonian of the spin system. In evolution theory, the notion of fitness is central in defining the general features of evolution or in modeling a concrete experiment. Fitness is a complicated function of gene content (types of genes) of the genome in sequence space; this function is assumed to have a mean-field like behavior. Most of the investigations have been devoted to the symmetric fitness case, when there is a master (reference) sequence, and fitness (energy) is a simple function of the Hamming distance from that sequence [2]. In [18], a generalization of symmetric fitness landscape was considered, when there are some $K$ reference sequences, and the fitness was a function of $K$ Hamming distances from these reference sequences. In [24–26], there were suggested evolution models where the genome consisted of different blocks and the fitness is a function of the mean types at different blocks. In the current article, we follow the idea of [24], considering an infinitely long genome, a collection of a finite number of blocks, defining mean "magnetizations" at any such block and the fitness as a function of block magnetizations. We then use the Hamilton-Jacobi equation [19] to solve the equation. This new approach is technically easier than that used in [18]. Thus in the present paper, we can calculate the mean fitness of a recombination model in a multidimensional fitness landscape.

Recombination is one of the key factors in evolution. The mathematical aspects of recombination were analyzed in [27–29]. Recently, there was good progress in the statics of recombination [22, 23] and there was some advance in the dynamics [30]. We will formulate the recombination model in a multidimensional fitness landscape for many-loci haploid model with two alleles (type of gene) at any locus (position of a gene in the genome).

The rest of the paper is organized as follows: In section II, we formulate and solve (calculate the mean fitness) the evolution model with selection and mutation in a multidimensional fitness landscape, including the case of lethal mutations [31, 32]. We consider 2 block models for the lethal mutations and an asymmetric initial distribution. In section III, we formulate the recombination model in a multidimensional space. While we could not calculate the mean fitness, we derive a general result regarding the dynamics of population for the initial narrow distribution. In Sec. IV, we summarize our results and discuss problems for further research.

II. THE MULTIDIMENSIONAL MODEL

A. The Model

We identify the alleles as spins and consider the genome as a collection of $L$ spins taking the values $±1$. In the peak configuration, all spins take value $+1$. Our model is a simple generalization of the Crow-Kimura model [4, 12]. The genome is a collection of $H$ pieces (blocks), with the length $L_n$, $1 \leq n \leq H$, such that $\sum_{n=1}^{H} L_n = L$.

Any sequence is characterized by $l_1, \ldots, L_H$, the number of "-" (negative) spins in the blocks. We introduce the "magnetization" $m_n$, defined as

$$m_n = 1 - \frac{2l_n}{L_n}, \quad (1)$$

at the $n$-th piece of genome for all of $n$ with $1 \leq n \leq H$. 

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Our fitness $r$ is a function of $(l_1, \ldots, l_H)$. Thus, we define $r_{l_1 \ldots l_H} = LF(m_1, \ldots, m_H)$. The discrete variables $l_n$ are defined in the interval $[0, L_n]$, while the magnetizations $m_n$ are becoming continuous at the limit $N \to \infty$ and $-1 \leq m_n \leq 1$. We define the function $f(m_1, \ldots, m_H)$ as a fitness function.

The description of the mutation process is the principal point in the definition of the model. In order to describe mutations we use the coefficients $x_n \pm (l_n, L_n)$:

$$x_{n+}(l_n, L_n) = \frac{l_n}{L_n}, \quad x_{n-}(l_n, L_n) = \frac{L_n - l_n}{L_n},$$

(2)

where $L_n$ denotes the length of the $n$-th piece, $x_{n+}(l_n, L_n)$ and $x_{n-}(l_n, L_n)$ are the fractions of $-\$ and $+$ spins in the $n$-th piece.

If the initial distribution of the population is symmetric, i.e. all the sequences with the same $l_n$ have the same probability, we describe the system through the $p(l_1, \ldots, l_H, t)$, the probability of all sequences having $l_1, \ldots, l_H$ minus spins in corresponding blocks. Then we write the following system of equations:

$$\frac{dp(l_1, \ldots, l_H, t)}{dt} = (r_{l_1, \ldots, l_H} - LR)p(l_1, \ldots, l_H, t)$$

$$-p(l_1, \ldots, l_H, t)$$

$$+ \sum_{\beta=\pm 1, n} L_n x_{\beta}(l_n, L_n)p(l_1, \ldots, l_n - \beta, \ldots, l_H, t),$$

$$R = \frac{1}{L} \sum_{0 \leq l_n \leq L_n} p(l_1, \ldots, l_H, t)r_{l_1, \ldots, l_H},$$

(3)

The sum over $n$ extends from 1 to $H$ and $R$ and is the mean fitness. We considered mutations independently at all pieces of the genome; thus, in the middle line at the right hand side of Eq. (3) we changed an $l_n$ at the position $n$, where $n$ changes from 1 (first piece of genome) until $H$ (the last piece of genome).

The current configuration $(l_1, \ldots, l_n, \ldots, l_H)$ could be obtained from either $(l_1, \ldots, l_n + 1, \ldots, l_H)$, reversing one of $l_n + 1$ $-\$ spins, or from the $(l_1, \ldots, l_n - 1, \ldots, l_H)$ configuration reversing one of $(L_n - l_n + 1)$ $+\$ spins. There are $(l_n - 1)$ such possibilities for the first case, and $(L_n - l_n + 1)$ for the second case. Dividing by $L$, we derived the coefficients $x_{+}(l_n + 1, L_n)$ and $x_{-}(l_n - 1, L_n)$ in Eq. (3). For $H = 1$, Eq. (3) coincides with the Crow-Kimura model [4, 13, 16].

Let us consider the linear part of the latter equation, and write an equation for $P(m_1, \ldots, m_H, t) = p(l_1, \ldots, l_H, t)$

$$\frac{dP(m_1, \ldots, m_H, t)}{dt} = L(f(m_1, \ldots, m_H) - 1)P(m_1, \ldots, m_H, t)$$

$$+ \sum_{\beta=\pm 1, n \leq H} L_n \left(1 + \frac{\beta m_n}{L_n} + \frac{\beta - 1}{L_n}\right)$$

$$\times P(m_1, \ldots, m_n + 2\beta, \ldots, m_H, t).$$

(4)

Following [33, 34], we define the mean fitness in the steady state of Eq.(3) as the largest eigenvalue of the quadratic matrix on the left hand side of Eq.(4).

Following [19], we assume an anzats:

$$P(m_1, \ldots, m_H, t) = \exp[Lu(m_1, \ldots, m_H, t)].$$

(5)

Then with $1/L$ accuracy we get the following Hamilton-Jacobi equation (HJE):

$$\frac{\partial u(m_1, \ldots, m_H)}{\partial t} = -H(m_1, \ldots, m_H; \frac{\partial u}{\partial m_1}, \ldots, \frac{\partial u}{\partial m_H}),$$

$$-H(m_1, \ldots, m_H; \hat{P}_1, \ldots, \hat{P}_H) = f(m_1, \ldots, m_H)$$

$$-1 + \sum_{1 \leq n \leq H} \frac{L_n}{L} \left(1 + m_n e^{2\hat{P}_n} + \frac{1 - m_n}{2} e^{-2\hat{P}_n}\right),$$

(6)

where we missed $O(1/L)$ terms and introduced the momentums $\hat{P}_n = \partial u/\partial m_n$.

Consider the asymptotic solution:

$$u(m_1, \ldots, m_H, t) = R + u_0(m_1, \ldots, m_H),$$

(7)

we get an equation

$$R = f(m_1, \ldots, m_H) - 1 + \sum_{1 \leq n \leq H} \frac{L_n}{2} \left[1 + m_n e^{2u_0(m_1, \ldots, m_H)} \frac{\partial u_0(m_1, \ldots, m_H)}{\partial m_n}\right]$$

$$+ \sum_{1 \leq n \leq H} \frac{L_n}{2} \left[1 - m_n e^{-2u_0(m_1, \ldots, m_H)} \frac{\partial u_0(m_1, \ldots, m_H)}{\partial m_n}\right].$$

(8)

On the other hand, we have a condition that at any point $m$, our $R$ should be higher than the minimum of the right hand side, considered as a function of momentums $\frac{\partial u_0(m_1, \ldots, m_H)}{\partial m_n}$. We define

$$U(m_1, \ldots, m_H) = \min[f(m_1, \ldots, m_H) - 1$$

$$+ \sum_{1 \leq n \leq H} \left[L_n \left(1 + m_n e^{2u_0(m_1, \ldots, m_H)} \frac{\partial u_0(m_1, \ldots, m_H)}{\partial m_n}\right)$$

$$+ L_n \left(1 - m_n e^{-2u_0(m_1, \ldots, m_H)} \frac{\partial u_0(m_1, \ldots, m_H)}{\partial m_n}\right)\right].$$

(9)

Examining the solution of the minimum problem and looking at different points $m$, we find:

$$R \geq \max[U(m_1, \ldots, m_n)] |_{m_1, \ldots, m_H},$$

$$U(m_1, \ldots, m_H) = f(m_1, \ldots, m_H) - 1$$

$$+ \sum_{1 \leq n \leq H} \frac{L_n}{L} \sqrt{1 - m_n^2}. $$

(10)

In Eq.(9) we take the maximum in the domain $-1 \leq m_n \leq 1$. The function $U(m_1, \ldots, m_H)$ is the equivalent of the potential in classic mechanics.

Following [19], we identify the mean fitness (the maximum eigenvalue of the matrix on the right hand side of Eq.(4)) with the lower bound of Eq.(9),

$$R = \max[U(m_1, \ldots, m_H)] |_{m_1, \ldots, m_H}. $$

(11)
One can calculate the mean fitness $R$ by differentiating the function $U(m_1, \ldots, m_H)$.

Thus, we defined the mean fitness for the general multi-dimensional mean-field like fitness landscape for the evolution model with selection and mutation.

Figure 1 gives the comparison of our analytical result for Eq.(9) with numerics of the 3-dimensional model.

### B. The Multidimensional Model with Lethal Mutations

Let us now consider a model where there exists some probabilities of lethal mutations: the Malthusian fitness $r$ (after $t$ period of time, the population without mutation grows $e^{rt}$) times while in the parallel (Crow-Kimura) model is becoming $\infty$ [30].

At any piece of the genome, we consider the master subsequence, having non-lethal $L_n(1-\lambda)$ neighbors with single mutations, where $0 \leq \lambda < 1$ is a parameter describing the fraction of lethal mutations. When the fitness is a function of the Hamming distance from the reference sequence, we simplify the evolution equations using this symmetry. We define some mutations from the reference sequence as lethal mutations and assume that any sequence having at least one lethal mutation (plus some non lethal mutations) has a $\infty$ fitness. Therefore at the $l$-th Hamming class we have

$$N_{l,\lambda_n} = \frac{L_n(1-\lambda_n)!}{(L_n(1-\lambda_n) - l)!}.$$  

viable $l$ point mutants, and as a maximal $l$, we take $L_n(1-\lambda_n)$. For a small $l \ll L_n$, there is a dilution of the sequence space via a factor $(1-\lambda_n)$, while the total number of viable sequence is:

$$\sum_{l=0}^{L_n(1-\lambda_n)} N_{l,\lambda_n} = 2^{(1-\lambda_n)L_n}.$$  

We define now the fitness function as

$$r_{l_1,\ldots,l_H} \equiv Lf(m_1, \ldots, m_H),$$  

where instead of Eq.(1), we now define

$$l_n = L_n \frac{1 + m_n}{2} (1 - \lambda_n).$$  

Then the calculation is, identical to those in [30], give

$$R = \max_l [f(m_1, \ldots, m_H) - 1 + \sum_n \frac{L_n}{L} (1-\lambda_n) \sqrt{1-m_n^2}].$$  

### C. The Model in Multipeak Fitness Landscape

We formulated the model by Eq.(3) for a rather general case. The multi-peak model, considered in [18], could be derived as a particular case of our solution.

Let us choose $H = 2K^{-1}$ and consider $K$ reference sequences with our $s_i^\nu$ spins, $1 \leq i \leq L$, $1 \leq \nu \leq H$. At any position $i$ along the genome, we are looking at the alignment of spins in our $K$ reference sequences. We have chosen the first configuration with all $s_i^\nu$ spins and define the alignment of spin along the $i$-th reference sequence at the $n$-th piece of genome as $\alpha_{i,n}$. We group together the configurations $s_i^\nu = \alpha_{i,n}$ and $s_i^\nu = -\alpha_{i,n}$, where $\alpha_{i,n} = \pm 1$ and these two cases have a joint probability $L_n/L$. The magnetization of the $i$-th sequence $M_i$ is defined through our $m_n$ as:

$$M_i = \sum_{n=1}^{H} \frac{L_n}{L} \alpha_{i,n} m_n.$$  

We then take a fitness which is a function of our $H$ reference sequences. Thus, we should find the maximum of

$$F(M_1, \ldots, M_K) = 1 + \sum_{1 \leq n \leq H} \frac{L_n}{L} \sqrt{1-m_n^2} + \sum_i h_i [-M_i + \frac{H}{L} \alpha_{i,n} m_n]$$  

where we introduced the auxiliary variables $h_i$. The maximum condition gives

$$h_i = \frac{\partial F(M_1, \ldots, M_K)}{\partial M_i},$$  

$$\sum_i h_i \alpha_{i,n} = \frac{m_n}{\sqrt{1-m_n^2}}.$$  


FIG. 1: The comparison of analytical result (smooth line) with the numerics (dots) for the 3-d model with $L_1 = L_2 = L_3 = 20$. The whole genome mutation rate is 1. The first part of the genome has a fitness $f_1(m_1) = km_1^2/2$. In the second part all the mutations are lethal. For the fitness contribution from this part, we have $f_2 = 0$ for other subsequences. Part three is described by a single peak fitness landscape with fitness $J = 3$ for the peak subsequence and zero for other subsequences. Thus, the fitness function is defined as

$$f(m_1, m_2, m_3) = \frac{km_1^2}{2} - \frac{[1 - \delta(m_2 - 1)]}{\infty} + \delta(m_3 - 1),$$  

where the discrete $\delta(x)$ function is equal to 1 at zero and is equal to 0 otherwise. The mean fitness is given as $k(1 - 1/(3k))^2/2 + 3 - 2/3$. 

\[ \frac{km_1^2}{2} - \frac{[1 - \delta(m_2 - 1)]}{\infty} + \delta(m_3 - 1), \]

\[ \frac{km_1^2}{2} - \frac{[1 - \delta(m_2 - 1)]}{\infty} + \delta(m_3 - 1), \]
The last system of equations coincides with the one derived in [18] with the mapping:

\[ m_n = \frac{1}{1 + (\sum_{i=1}^{K} \alpha_{n,i} H_i)} \]  \hspace{1cm} (18)

where \( H_i \) are the fields, conjugate to the \( M_i \) in Eq.(10) of [18]. A single difference: in [18] we defined \( L_n/L \) for \( 2^K \) situations (misprints in Eqs.(9) and (24) of [18], in which \( 2^K \) should be replaced by \( 2^{K-1} \), instead of \( 2^{K-1} \) in the current article.

D. The 2-dimensional case

The definition of the model. Let us consider the 2 dimensional case. We have a system of equations:

\[ \frac{dp(l_1, l_2, t)}{dt} = (r_1, l_2 - L - LR)p(l_1, l_2, t) \]
\[ + \sum_{\beta = \pm 1} L_1 x_\beta(l_1, L_1)p(l_1 - \beta, l_2, t) + L_2 x_\beta(l_2, L_2)p(l_1, l_2 - \beta, t), \]
\[ R = \frac{1}{L} \sum_{0 \leq l_2 \leq L_n} p(l_1, l_2, t)r_{1, l_2}, \]  \hspace{1cm} (19)

We have a HJE for this case:

\[ \frac{\partial u(m_1, m_2)}{\partial t} = -H(m_1, m_2; \partial u / \partial m_1, \partial u / \partial m_2), \]
\[ -H(m_1, m_2; \hat{P}_1, \hat{P}_2) = f(m_1, m_2) \]
\[ -1 + \sum_{1 \leq n \leq 2} \frac{L_n}{L} \left( \frac{1 + m_n}{2} e^{2P_n} + \frac{1 - m_n}{2} e^{-2P_n} \right) \]  \hspace{1cm} (20)

The mean fitness \( R \) is defined through the equations

\[ R = f(m_1, m_2) - 1 + \sum_{1 \leq n \leq 2} \frac{L_n}{L} \sqrt{1 - m_n^2}, \]
\[ f'_1(m_1, m_2) = \frac{L_1}{L} \frac{m_1}{\sqrt{1 - m_1^2}}, \]
\[ f'_2(m_1, m_2) = \frac{L_2}{L} \frac{m_2}{\sqrt{1 - m_2^2}} \]  \hspace{1cm} (21)

The two-block model with lethal mutations. In Fig. 2 we compare the analytical results with the numerics for the two-block model, where one part has the length \( (L - n) \) with a lethal mutation (all the spin configurations of the block besides the one have \(-\infty\) fitness), and the other block has the length \( n \) and a fitness \( f(m_1) = km_1^2/2 \). We obtain the mean fitness of this model as

\[ R = \frac{k}{2} \left( 1 - \frac{n}{k(n + m)} \right)^2 = \frac{m}{n + m} \]  \hspace{1cm} (22)

The asymmetric original distribution. We consider the original distribution \( m(0) = 0.6 \) for the symmetric distribution, only considering the 1-d (Crow-Kimura) model:

\[ f(m) = \frac{k}{2} m^2 \]  \hspace{1cm} (23)

Later we take the simplest asymmetric distribution, where the part \( L_1 \) spins have \( l_1 \) minus spins and original narrow distribution with \( m_1 = 1 - 2l_1/L_1 \). Another part has \( l_2 \) minus spins have original narrow distribution around \( m_2 = 1 - 2l_2/L_2 \). We consider the model by Eq.(19) with the fitness

\[ f(m_1, m_2) = \frac{k}{2} m^2, \]
\[ m = (m_1 L_1 + m_2 L_2)/L \]  \hspace{1cm} (24)

Fig 3 gives the results of the dynamics for \( m, m_1, m_2 \).
TABLE I: Mean fitness for the 2-d model by Eq. (25). \( L_1 = L_2 = L/2, k_2 = k_3 \)

<table>
<thead>
<tr>
<th>( L )</th>
<th>100</th>
<th>100</th>
<th>100</th>
<th>100</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k_1 )</td>
<td>4</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>( k_3 )</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>( R_{\text{theor}} )</td>
<td>7.0312</td>
<td>9.025</td>
<td>8.0277</td>
<td>9.025</td>
<td>9.025</td>
</tr>
<tr>
<td>( R_{\text{num}} )</td>
<td>7.0315</td>
<td>9.0251</td>
<td>8.0280</td>
<td>9.025</td>
<td>9.025</td>
</tr>
</tbody>
</table>

Assuming an ansatz

\[
A_{ij} = k_1, A_{22} = k_2, A_{12} = k_3 \tag{25}
\]

we obtain for the correlation:

\[
P(x) = \frac{\pi L \sqrt{\det(G)}}{2} \exp[-L < x|G|x >^2]
\]

\[
u(x) = -< x|G|x >/2, \tilde{x} = \tilde{m} - \tilde{s}
\]

We investigate the population distribution. We consider a fitness

\[
f(m_1, m_2) = \frac{1}{2} \sum_{ij} A_{ij} m_i m_j,
\]

Assuming an ansatz

\[
A_{11} = k_1, A_{22} = k_2, A_{12} = k_3
\]

we obtain the correlation:

\[
K_{ij} \equiv \int dx \frac{p_i(x)p_j(x)}{p(x)} = \sum_{l,n} G_{ln} G_{nj} < x_i x_n > = G_{ij}
\]

Differentiating the HJE Eq.(20) for the steady state by \( x_1, x_2 \), and putting \( p_1 = 0, p_2 = 0, \) we obtain:

\[
A_{ij} s_j - G_{ij} s_j
\]

For the symmetric fitness case

\[
G_{11} = 2G_{22} = G_{12} = G_{33},
\]

\[
s_1 = s_2 \text{ and Eq.(28) gives:}
\]

\[
k_1 + k_3 = g_1 + g_3
\]

We verified the validity of Eq.(30) by the numerics in Table 1.

### III. RECOMBINATION IN A MULTI-DIMENSIONAL FITNESS LANDSCAPE

#### A. The Model

In order to describe the recombination (horizontal gene transfer), we follow [22, 23]. We consider the following system of equations:

\[
dp(l_1, \ldots, l_H, t) = (r_1, \ldots, r_H - LR)p(l_1, \ldots, l_H)
\]

\[-Lp(l_1, \ldots, l_H, t) + \sum_{\beta = \pm 1, n} L_n x_\beta(l_n - \beta, L_n)p(l_1, \ldots, l_n - \beta, \ldots, l_H, t)
\]

\[+ c(\sum_{\beta = \pm 1, n} L_n x_\beta(l_n - \beta, L_n) - 1)p(l_1, \ldots, l_H, t)
\]

\[+ \sum_{\beta = \pm 1, n} L_n x_\beta(l_n - \beta, L_n) + 2\beta s_n
\]

\[×p(l_1, \ldots, l_n + \beta, \ldots, l_H, t)]
\]

where the sum over \( n \) extends from 1 to \( H \), and

\[
s_n = \sum_{l_1, \ldots, l_H} p(l_1, \ldots, l_H, t) L_n - 2\beta_n
\]

is the equivalent of surplus or "surface" magnetization. For the simple symmetric fitness landscape (\( K = 1 \)) which has one surplus parameter, but now there are \( H \) parameters.

The term \(-Lp(l_\ldots l_K, t)\) describes the mutations of the whole genome with a rate 1 per allele; the following line describes the mutation. Using a coefficient \( c \), we define the diagonal recombination terms: \(-c\) is the total rate of changing the given sequence, and \( x_\beta(l_n, L_n)\) describes the recombination event when we replace a spin from our current sequence with the same kind of spin from the pool of spins at the same position in population. In the second term inside "[\ldots]", we define the recombination terms as the change in the current configuration: we replace a spin with an opposite spin from the spin pool.

Let us derive the Hamilton-Jacobi equation. We used the same anznats, Eq. (5), as before; the simple derivations give:

\[
\frac{\partial u}{\partial t} = H(m_1, \ldots, m_K; s_1, \ldots, s_H; u_{1'}, \ldots, u_{l'})
\]

\[-H = f(m_1, \ldots, m_H) - f(s_1, \ldots, s_H) - 1 - c
\]

\[+ \sum_{\beta = \pm 1, \text{1} \leq n < H} L_n \left( 2\beta + m_n e^{2u_n} + \frac{1 - m_n e^{-2u_n}}{2} \right)
\]

\[+ c(\sum_{n} L_n \left( 2\beta + m_n e^{2u_n} + \frac{1 - m_n e^{-2u_n}}{2} \right) - 1)
\]

\[+ \sum_{n} L_n \left( 2\beta + m_n e^{2u_n} + \frac{1 - m_n e^{-2u_n}}{2} \right)
\]

where we denote \( u_n = \frac{\partial u(m_1, \ldots, m_n}; t) \). The function \( u(m_1, \ldots, m_H, t) \) has the maximum at the point \( (m_1, \ldots, m_H) = (s_1, \ldots, s_H) \).

We don’t see a simple way to calculate the asymptotic solution of the last equation.
B. An Approximate Solution of Recombination Dynamics

Let us consider the dynamics of the initial normal distribution,

\[ P(m_1, \ldots, m_H, 0) = \exp[-L \sum_m \frac{y_{ln}^2}{2} (m_l - s_l(0))(m_n - s_n(0))]. \]  

Equation (34) describes a narrow distribution around some Hamming classes.

We assume that for some not too large periods of time, we have a similar solution,

\[ P(m_1, \ldots, m_H, t) = \exp[-L \sum_m \frac{y_{ln}^2}{2} (m_l - s_l(t))(m_n - s_n(t))]. \]  

where \( y_{ln} \) describes the normal distribution.

We get the following system of equations for \( ds_n(t)/dt \) using our Hamiltonian form Eq.(33)

\[ \sum_n y_{ln} \frac{ds_n}{dt} = - \frac{dH(s_1, \ldots, s_H; s_1, \ldots, s_H; 0, \ldots, 0)}{dm_l} + \sum_n \frac{dH(s_1, \ldots, s_H; s_1, \ldots, s_H; 0, \ldots, 0)}{dp_n} y_{ln}. \]  

(36)

Let us prove that the last two terms do not depend on \( c \). From the first line we obtain:

\[ \frac{dH(s_1, \ldots, s_H; s_1, \ldots, s_H; 0, \ldots, 0)}{dm_l} = \frac{\partial f(m_1, \ldots, m_H)}{\partial m_l}. \]  

(37)

For the rest we derive:

\[ -2 \sum_l \frac{L_l u_l}{L} y_{ln}. \]  

(38)

Eventually, putting the results of Eqs.(37),(38) into Eq.(36), we derive:

\[ \sum_n y_{ln} \frac{ds_n}{dt} = f'_{ln}(s_1, \ldots, s_H) - 2 \sum_n \frac{L_l u_l}{L} s_l y_{ln}. \]  

(39)

Thus for the initially narrow distribution of population by Eq. (34) and mean-field like fitness landscape, the recombination does not have any impact on the relaxation dynamics for some period of time \( T \). If the number of mutations and recombination per genome per replication is in the order of \( 1 \), then we have the following condition for this time period: \( 1 \ll T \ll L \).

C. Asymmetric Recombination.

The theorem from the previous section is not valid for the asymmetric recombination, since we have different recombination rates for the allele changes to up and down. Consider the simple case of a one dimensional fitness landscape.

\[ \frac{dP_l}{dt} = [(r_2 - LR)] P_1 + (l + 1) P_{l+1} + (1 - (l - 1)) P_{l-1} - L[c_1(1 - \frac{l}{L}) L_{l+1} + c_2(1 - \frac{l}{L}) P_{l-1}] + L[c_1(1 - \frac{l}{L}) P_{l+1} + c_2(1 - \frac{l}{L}) L_{l-1}], \]  

(40)

where \( c_1, c_2 \) describe the recombination rates to the up and down directions in Hamming classes and \( l = \sum_i P_i \).

Using an ansatz \( P_l = \exp[Lu(m, t)] \), we derive the following HJE

\[ \frac{du}{dt} = f(m) - f(s) - c_1 \frac{(1 + m)(1 - s)}{4} - c_2 \frac{(1 - m)(1 + s)}{4} + e^{2u} \frac{1 + m}{2} \frac{1 + s}{2} c_2 - 1 \]

\[ + e^{-2u} \frac{1 - m}{2} \frac{1 + s}{2} c_1. \]  

(41)

Now we take \( u(t) = -y(m - s(t))^2/2 \) and get an equation

\[ y \frac{ds}{dt} = f'(s) - 2y s(t) - \frac{(c_1 - c_2)}{2} (1 - s(t))^2 y. \]  

(42)

We see that the recombination immediately starts to change the distribution, see Fig.4 for the illustration.

D. The Recombination Model with Lethal Mutations

In order to describe the lethal mutations, we consider the genome which consists of two parts with the length \( L_1 = \lambda L \)

![Figure 4](image-url)
and $L(1 - \lambda)$. In the first piece, there is only one sequence with the fitness 0, and any mutation in this part gives a lethal sequence with the $-\infty$ fitness.

We can investigate the situation using our model by Eq.(40). Previously we used the mutation rate $\lambda$. Now we introduce the mutation rate $\mu_0$ per nucleotide and $c$ as a recombination rate per nucleotide.

We just write the equations for $p(0,l) \equiv p_l$, identifying also $r_l(0,l) \equiv r_l$:

$$\frac{dp_l}{dt} = r_l p_l - p_l \mu_0 L + \bar{L} [\mu_0 (L - 1 - p_{l+1} + \bar{L} - l + 1 - p_{l-1}) + c \frac{l - 1 - s_n}{2} + \frac{L - l + 1 - s_n}{2} - 1] p_l + c \frac{l - 1 - s_n}{2} p_{l-1} + \frac{L - l + 1 + s_n}{2} (p_{l+1})],$$

where we denoted the length of the genome without lethal mutations as $\bar{L} = L(1 - \lambda)$. While in the previous models we took $\mu_0 = 1$, now we write formulas for general $\mu_0$.

Let us define

$$m = \frac{2l - \bar{L}}{L},$$
$$r_l = f(m) \bar{L}$$

then we can use the results of [23] to calculate the mean fitness. If we define the potential $U(m,s)$:

$$U(m,s) = f(m) + \sqrt{(1 - m^2)}C + \frac{cm^2}{2} - \frac{c}{2},$$
$$C = [(\mu_0 + \frac{c}{2})^2 - \frac{c^2 s^2}{4}]$$

then the mean fitness of the genome is defined as

$$\max[U(m,s) - L\mu_0],$$
$$LR = Lf(s)(1 - \lambda).$$

E. The finite population version of the model with lethal mutations.

In the case of HIV, there are highly variable parts of the genome with about 100 nucleotides [35]. In [35] the use of an evolution model with shorter effective genome length to describe the virus evolution in such a case has been suggested; latter this idea was applied in [36]. We assume that the usage of an effective genome length is reasonable for the zero epistasis case, while in the case of lethal mutations as well, we can not use an ordinary model with the short genome length.

Extending the ideas in [37], we suggest the following finite population versions of the model. The genome consists of two parts. The first part has a length $L\lambda$ where all the mutations are lethal, while the $n$ mutations from the part with the length $\bar{L}(1 - \lambda)$ give a mutant with the fitness function $r_n$. The population is described via $L - n$ viable sequences and the $n$ lethal ones, and the total population size $N$ is fixed. We describe the population via the number of viruses $n_l$ in the $l$-th Hamming class, $0 \leq l \leq L$ and $\bar{n}$. We have a conserved population size, $n + \sum_{l=0}^{L} n_l = N$.

During the time period $\delta t$, there are $\mu\delta t(1 - \lambda)$ non-lethal mutations and $\mu\delta t\lambda$ lethal mutations.

We consider the following steps during the evolution:

a. A birth of $\delta n$ new lethal mutants which is a binomial random process with the probability parameter $\delta t\lambda$ and $(N - \bar{n})$ trials.

b. A birth of $\delta n_l$ new viruses in the $l$-th class, which is a binomial random process with $n_l$ trials and a probability parameter $r_l(1 - \lambda)$.

c. Forward non-lethal mutations $f_l$, which are described via binomial random process with a probability parameter $\delta t\lambda$ and $n_l$ trials.

d. Backward non-lethal mutations $b_l$, which are described via binomial random process with probability parameter $\delta t\lambda$ and $n_l$ trials.

Thus after these mutation processes, $n_l \rightarrow n_l + f_l - b_l$, $n_{l+1} = n_{l+1} + f_l$, $n_{l+1} = n_{l+1} + b_l$, $n_{l+1} = n_{l+1} + f_l$.

d. The dilution of the model, where we reduce the virus population via $\bar{n} + \sum_{l=0}^{L} \delta n_l$ numbers, uniformly distributed via $L + 2$ classes.

IV. CONCLUSION

We formulated and solved the evolution model on the multidimensional fitness space, where we considered the genome as a collection of several pieces and the total fitness as the function of the allele type fractions of the pieces. Such a model is more general and more realistic than the multi-point fitness landscape, considered in [18]. The numerics confirmed our analytical results well.

We calculated the mean fitness of this model, including the case of lethal mutations and found a simple way of deriving the results of the multi-peak fitness models.

We formulated the recombination model in the multidimensional fitness space. While we could not calculate the mean fitness, we derived the Hamiltonian-Jacobi equation for the dynamics of the population and deduced an important theorem about the dynamics. For the initially narrow initial distribution and mean-field fitness landscape, the recombination dynamics does not affect the dynamics of the population for a rather long period of times (see Fig.2). This theorem is not valid in the case of asymmetric recombination.

We formulated the finite population version of the model with lethal mutations. Our results could be applied to model virus experiments, prescribing to different parts of the genome either lethal mutations or negative or positive selection. For example, we can apply our model in the case of the Dengue virus, where 95% of the genome is epistasis free while there are strong correlations between the gene contributions of the reminder 5% [38].

The main open mathematical problem in the investigation of multi-dimensional evolution is the calculation of the surplus and the distribution around the peak of distribution.
While we calculated the mean fitness, we failed to calculate the surplus. In classical mechanics, one can easily define the ground state energy and the position of the interacting particles, looking for the minimum of potential energy. Now, for our Hamiltonian by Eqs. (20), the situation is highly non-trivial. One should consider the asymptotic solution for the characteristics (the solutions of Hamilton equation), looking for the steady states. Another problem, which is important for applications, is to define the quadratic expansion of the solution $u(m_1, m_2)$ near the maximum of distribution. Again, the situation is highly non-trivial, and different statistical physics phases are possible like the phases in [39]. While we found some relations, Eqs. (28), (30), we failed to find the complete solution of distribution. We hope that it is possible to succeed using the advanced methods of HJE, to address this open problem.

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[38] R. Griffey, Private information.