Exact solution of the Eigen model with general fitness functions and degradation rates

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We present an exact solution of Eigen’s quasispecies model with a general degradation rate and fitness functions, including a square root decrease of fitness with increasing Hamming distance from the wild type. The found behavior of the model with a degradation rate is analogous to a viral quasispecies under attack by the immune system of the host. Our exact solutions also revise the known results of neutral networks in quasispecies theory. To explain the existence of mutants with large Hamming distances from the wild type, we propose three different modifications of the Eigen model: mutation landscape, multiple adjacent mutations, and frequency-dependent fitness in which the steady-state solution shows a multicenter behavior.

Quasispecies | virus evolution | error threshold

Molecular models of biological evolution have attracted much attention in recent decades (1–15). Among them, Eigen’s concept of quasispecies plays a fundamental role (1, 2). It describes the evolution of a population consisting of a wild type accompanied by a large number of mutant types in sequence space by a large system of ordinary differential equations. The Eigen model has been found to describe quite well the evolution of viral populations (3) and has deeply changed our view of the process of evolution: adaptation does not wait for better adapted mutants to arise but starts with the selection of the better adapted mutants and then explores by mutation the surrounding sequence space for even better mutants. When the mutation rate surpasses an error threshold, the population gets genetically unstable, and it could be shown that indeed virus populations can be driven to extinction when the error rate is artificially raised beyond the error threshold.

To describe the population precisely, we should know the fitness value of each type and the mutation rates to go from one type to another. The experimental efforts to do so are immense. During the last three decades, the model has been investigated numerically as well as analytically for a simple fitness function. Although this sort of data reduction does allow a view on a large population, the fitness functions chosen are too simplistic to explain realistic cases such as a population of RNA virus. In this work, we solve the system of differential equations exactly, assuming uniform degradation rates and fitness functions including a square root decrease of fitness with increasing Hamming distance (HD) from the wild type. Our exact solutions also revise the known theoretical results of neutral networks in quasispecies theory (2). To explain biological systems more realistically (16), we propose three different modifications of the Eigen model: mutation landscape, multiple adjacent mutations, and frequency-dependent fitness in which the steady-state solution shows a multicenter behavior.

Model

Several excellent reviews (2–5) emphasize the merits of the quasispecies model for the interpretation of virological studies. Let us give a brief description of the quasispecies model as we use it in this work: a sequence type of length N is specified by a sequence of N spin values $s_k = \pm 1$, $1 \leq k \leq N$ (1, 2). In reality the spins can take four values corresponding to the natural nucleotide types, but a two-value spin model already catches the essential features and can be studied more easily. Two-value spin models also have been used to study long-range correlations in DNA sequences (17) and DNA unzipping (18, 19), and valuable results have been obtained. A generalization of our results for the four-value spin case is presented in the Supporting Text, which is published as supporting information on the PNAS website. However, such results include more cumbersome formulae, and from now on we will only consider the two-value spin model.

Let $s_i = +1$ represent purines (R) and $s_i = -1$ pyrimidines (Y). Type i is then specified by $S_i = (s_i^0, s_i^1, \ldots, s_i^L)$. The model describes replicating molecules under control of variation and natural selection with Eq. 1, to be defined below. The rate coefficients of replication and mutation are assumed to be independent of the concentration of the types. The model describes the exponential growth phase of virus evolution, in which there are enough nutrients and low virus concentration. The multistep cross-catalytic reactions are replaced by an autocatalytic one. Here the evolution picture is rather simple, compared with the linear growth phase in the case of strong saturation effects.

Selection is on a genotype level: fitness is a function of $S_i$. The variation is assumed to be produced only by point mutations. Eigen made a deterministic approach with kinetic rate equations that requires an infinite population, whereas classical population genetics uses probabilistic equations. We denote the probability for the appearance of $S_i$ at time $t$ by $p_{S_i}(t)$ and define fitness $r_{i,j}$ of $S_j$ as the average number of offsprings produced per unit time and degradation rate $D_i$ of $S_i$ as an inverse mean longevity. The chosen $r_{i,j}$ and $D_i$ are functions in genome sequence space $S_i$, i.e., $r_{i,j}(S_i)$ and $D_i(S_i)$.

The mutation matrix element $Q_{ij}$ is the probability that an offspring produced by state $j$ changes to state $i$, and the evolution is given by the set of equations for $2^N$ probabilities $p_i$ (2, 6)

$$\frac{dp_i}{dt} = 2^N \sum_{j=1}^{2^N} (Q_{ij} - \delta_{ij} D_i) p_j - p_i \left( \sum_{j=1}^{2^N} (r_{j,i} - D_j) p_j \right)$$

[1]

Here $p_i$ satisfies $\sum_{i=1}^{2^N} p_i = 1$ and $Q_{ij} = q^{N-d(i,j)} (1 - q)^{d(i,j)}$ with $q$ being the mean nucleotide incorporation fidelity, and $d(i,j) = (N - \sum_{k=1}^{L} \min(s_i^k, s_j^k)) / 2$ being the HD between $S_i$ and $S_j$. $N = 2, 1, 2$; $d(i,j)$ represents the total number of different spin values in $S_i$ and $S_j$.

In ref. 1 the concept of an error threshold is introduced, and the error threshold has been quantified by a formula. For the calculation of the error threshold, the selection values and mutation rates of all types would be required, which is still not

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Abbreviations: AS, antiselective; FM, ferromagnetic; HD, Hamming distance; PM, paramagnetic.

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feasible. For data reduction, several fitness functions (landscapes) have been considered (2). The simplest one has a single peak (2) in a flat landscape. Without loss of generality we set the peak to \( S_1 = (1, 1, \ldots, 1) \), i.e., the state with all spin up, and have

\[
f(S_1) = A > 1, \quad \text{and} \quad f(S_i) = 1 \quad \text{for} \quad S_i \neq S_1,
\]

for which Eigen error threshold formula (equation II-45 in ref. 1) gives an exact result

\[
A e^{-\gamma} > 1,
\]

for successful selection (p, 180 in ref. 2). The parameter \( \gamma = N(1-q) \) describes the mutation efficiency. When the inequality is satisfied, a mutant distribution is built around the peak configuration in the steady state. Otherwise the distribution is flat in the infinite genome length limit, i.e., no sequence is

\[
\text{In statistical mechanics this case corresponds to mean-field-like interaction, which is exactly solvable} (20). \text{ We can write} f(S_i) \text{ and} D(S_i) \text{ as}
\]

\[
f(S_i) = f_0 \left( \sum_{i=1}^{N} s_i^{(0)} \right), \quad D(S_i) = d_0 \left( \sum_{i=1}^{N} s_i^{(0)} / N \right),
\]

where \( f_0(k) \) and \( d_0(k) \) with \( k = \sum_{i=1}^{N} s_i^{(0)} / N \) are polynomials. It is easy to show that \( k = 1 - 2d_1 / N \), where \( d_1 \) is the HD between \( S_1 \) and \( S_i \). Following ref. 13, in Supporting Text we exactly reformulate the solution of the system (Eq. 1) as a problem of statistical mechanics of quantum spins with some non-Hermitian Hamiltonian \( H \). Error threshold corresponds to singularity in the phase structure of Eq. 1. The same singularity exists also in the partition function \( Z = Tr \exp[-H] \) at the limit \( \beta \to \infty \); here \( \beta \), the inverse temperature in statistical mechanics model, corresponds to the time in Eq. 1. In Supporting Text, we show that, when \( \beta \to \infty \), the dominant contributions to \( \ln Z / \beta \) come from spin configurations with a particular \( k \) resulting in

\[
\ln Z / \beta = [e^{-\gamma(1-\sqrt{1-k^2})} f_0(k) - d_0(k)].
\]

The mean growth rate \( \sum (r_i - D_i) p_i \) is given as the maximum of Eq. 5 at \( -1 \leq k \leq 1 \), where nonzero \( k \) means a successful selection. We also show that for the steady-state distribution \( p_i \) the surplus production \( s = \sum_{i=1}^{N} p_i \sum_{i=1}^{N} s_i / N \) satisfy the equation

\[
e^{-\gamma(1-\sqrt{1-k^2})} f_0(k) - d_0(k) = f_0(s) - d_0(s),
\]

where \( k \) gives the maximum of Eq. 5. The surplus \( s \) has a direct biological meaning about how the population is grouped around the peak configuration. The difference between \( s \) and \( k \) has been discussed carefully in ref. 12.

**Error Thresholds**

Now we use Eq. 5 to study error thresholds for the following cases.

**Case 1: Single Peak Fitness Function Without Degradation.** Let us first disregard the degradation \( d_0(k) = 0 \), and take \( f_0(k) = 1 + (A - 1)k^0 \) at the limit \( p \to \infty \). There is a simple nonsel ective “paramagnetic” (PM) phase with \( k = 0 \) and \( \ln Z = \beta \). At high values of \( A \) there is a selective “ferromagnetic” (FM) phase with \( k = 1 \) and \( \ln Z = \beta A e^{-\gamma} \). The system chooses the phase with the highest \( Z \), and the Eigen error threshold formula of Eq. 3 is obtained. Eigen introduced \( A e^{-\gamma} \) as a “selective value” of the peak (equation II-31 in ref. 1). In case of several isolated peaks the system chooses the one with the maximal selective value.

**Case 2: Single Peak Fitness Function with Degradation.** Consider nonzero degradation \( d_0(k) = c + ak \), where the positive number \( a > 0 \) is the degradation parameter, and the same fitness function as in case 1. Physically, \( d_0(k) \) should be always positive for any value of \( k \) and we take \( c > \alpha \). Because of symmetry of Eigen’s equations under the transformation \( D_i \to D_i + C \) with \( C \) being a constant, we can simply choose \( d_0(k) = \alpha k \), which will be used in the following discussion. Now we have the PM phase with \( k = 0 \) and \( \ln Z / \beta = 1 = W_{PM} \), the FM phase with \( k = 1 \) and

\[
\ln Z / \beta = A e^{-\gamma} - \alpha = W_{FS}(k).
\]

Besides these phases, we also have the antiselective (AS) phase, which can be located by finding the maximum of

\[
\ln Z / \beta = [e^{-\gamma(1-\sqrt{1-k^2})} - \alpha k] = W_{AS}(k),
\]

in the interval \( -1 \leq k \leq 1 \). To find the maximum we should take the value of Eq. 8 either at the border with \( k = -1 \) or at the local maximum point. The derivative of \( W_{AS}(k) \) with respect to \( k \) gives

\[
W_{AS}'(k) = -\gamma k e^{-\gamma(1-\sqrt{1-k^2})} / \sqrt{1-k^2} - \alpha.
\]

The solution of

\[
W_{AS}(k_0) = 0,
\]

gives a negative value of \( k_0 \), which means that most spin values of the spin state with \( k = k_0 \) are different from those of the peak configuration \( S_1 \); hence, we call the spin state AS phase. At \( k = 0 \), \( W_{AS}(k) \) of Eq. 8 coincides with \( W_{PM} \) and \( W_{AS}(k) = -\alpha < 0 \); \( W_{AS}(k) \) decreases in the interval \([0, 1]\). As \( k \) moves from 0 to the negative \( k_0 \) of Eq. 9, \( W_{AS}(k) \) moves from \( -\alpha \) to 0. Thus, \( W_{AS}(k) \) monotonically decreases at the interval \([k_0, 0]\), and it is larger than \( W_{PM} \) at the interval \([k_0, 0]\). In case of several solutions of Eq. 9, we should choose the one that gives the maximal \( W_{AS} \) and compare such \( W_{AS} \) with the border value \( e^{-\gamma} + \alpha \) at \( k = -1 \) to determine the maximal weight \( W_{AS}^M \) for the AS phase

\[
W_{AS}^M = \max\{e^{-\gamma(1-\sqrt{1-k_0^2})} - ak_0, \ e^{-\gamma} + \alpha \}.
\]

There are two possible stable phases, AS and FM, in the model. For given \( \alpha, A, \) and \( \gamma \), we can compare \( W_{PM} \) and \( W_{AS}^M \) to determine which phase dominates. The error threshold (phase boundary) is given by

\[
A e^{-\gamma} - \alpha > W_{AS}^M.
\]

For a nonzero degradation rate, ref. 2 gives the formula: \( A e^{-\gamma} > 1 + D_0 - (D_i) \) (see equations III.4 and III.5 in ref. 2), where \( D_0 \) is the degradation rate of the master type and \( D_i \) is the average degradation rate of all other types. The majority of types groups around \( k = 0 \), therefore \( (D_i) = 0 \) and the error threshold condition of ref. 2 is

\[
A e^{-\gamma} - \alpha > 1.
\]

This error threshold deviates from Eq. 11 because the AS phase was not considered in ref. 2. This AS phase can represent a virus quasispecies under attack by the immune system (21).
**Case 3: Flat Fitness Functions.** During the last decade the importance of extended or flat fitness landscapes for the biological evolution (22–29) has been recognized. We first consider a simple mesa-type mount in the fitness landscape

\[
    f_0(k) = A, \quad k_0 \leq k \leq 1, \quad f_0(k) = 1, \quad 0 < k < k_0,
\]

where \(k\) is the overlap of the points on the mesa with the configuration with all up spins \(s_1^i; 1 - k_0\) defines the broadness of the mesa. For the fitness function of Eq. 13 and zero degradation, again a PM solution with \(k = 0\) is found. In the FM phase Eq. 5 takes a maximum value at the border \(k = k_0\), and we derive an error threshold

\[
    Ae^{-\sqrt{\frac{1}{k_0^2} - \frac{k_0}{k}}} > 1.
\]

If there are several mesa mounts with different \(A\) and \(k_0\), the system chooses the one with the maximal left expression of Eq. 14, and we call this expression the selective value of the mesa. We see that increasing the extension of the mesa increases its selective ability.

**Case 4: Fitness Decreases Slowly with the HD d from the Peak.** We now consider a landscape with a mount that has shallow slopes from the peak till \(d_m\)

\[
    f(d) = A[1 - a \sqrt{d/N}], \quad 0 \leq d \leq d_m,
\]

and \(f(d) = 1\), for \(d > d_m\). We consider the case \(d_m \ll N\). Eqs. 5 and 15 with \(d_0 = 0\) and small \((1 - k) = 2d/N\) gives an optimization problem for \(Ay^2(1 + (y - a) \sqrt{d/N})\). For \(y < a\) the population groups closely around the master type, whereas for \(y > a\) the distribution becomes wider. Therefore, such a simple mechanism could describe an extensive genomic change. As in ref. 30, the population landscape has a narrow steep peak at lower mutation rates but a wide shallow hill at high mutation rates.

**Neutral Selective Value**

When flat fitness function of Eq. 13 exists only for a fraction \(\nu \quad (0 < \nu < 1)\) of \(N\) spins, then fitness \(f_0(k_1, k_2)\) is a function of two groups of spins with \(\nu N\) and \((1 - \nu)N\) spins, respectively

\[
    f_0(k_1, k_2) = A \quad \text{for} \quad k_0 \leq k \leq 1, \quad f_0(k_1, k_2) = 1, \quad \text{otherwise},
\]

where \(k_1 = \Sigma_{i=1}^{\nu N} s_i/((\nu N))\) corresponds to “flat fitness” spin group, and \(k_2 = \Sigma_{i=1+\nu N}^{N} s_i/((1 - \nu)N)\) the remainder spins. In Section II of Supporting Text, for the partition \(Z = Tr \exp[-\beta H]\) we obtain

\[
    \frac{\ln Z}{\beta} = e^{-\gamma^2 m} f_0(k_1, k_2) - hm - \nu \alpha k_1 - (1 - \nu) x k_2 + \nu \sqrt{h^2 + x^2} + (1 - \nu) \sqrt{h^2 + x^2},
\]

where \(m\) is a transverse magnetization (related to quantum spin operator \(\sigma^z\)) for both groups of spins, and \(k_1, k_2\) are longitudinal magnetization (related to quantum spin operator \(\sigma^x\)) for the first and second groups; \(h, x_1, x_2\) are Lagrange multipliers corresponding to \(m, k_1\), and \(k_2\), respectively. Setting the derivatives of \(\ln Z/\beta\) with respect to \(h, x_1, \) and \(x_2\) to 0, we obtain

\[
    \frac{\ln Z}{\beta} = e^{-\gamma^2 m} f_0(k_1, k_2),
\]

with \(m = v \sqrt{1 - k_0^2} + (1 - \nu) \sqrt{1 - k_0^2} \) and \(-1 \leq k_1 \leq 1, -1 \leq k_2 \leq 1\). The maximum is at \(k_2 = 1\) and \(k_1 = 0\). The error threshold condition is

\[
    Ae^{-\gamma^2 m} f_0(k_1, k_2) > 1.
\]

The right-hand side is the selective value in the considered case. The neutral selective value has a factor \(\nu \sqrt{1 - k_0^2}\) in the exponent, which is a product of two factors: the “width” \(\nu\) and the “length” \(\sqrt{1 - k_0^2}\).

In refs. 25 (equation 4) and 27 (equation 2), \(Ay^2(1 - \nu)\) has been considered as a neutral selective value, and a similar expression has been given in ref. 29. They defined \(\nu\) as the average number of neutral neighbors. If we consider small HD from the peak, \(N(1 - k_0) \ll \sqrt{N}\), then the mean neutrality coincides with \(\nu\) in our fitness landscape. We see that in the formula of refs. 25 and 27 the factor \(\sqrt{1 - k_0^2}\) (length of neutrality) is missed. To define neutral selective value, we should take exact copying probability \(q^N\) plus the probability of all neutral mutations. We should differentiate neutrality for single mutation from neutrality for multiple ones; the latter makes major contribution for selective ability, which is the origin of small cutoff factor \(\sqrt{1 - k_0^2}\). Even if there are neutral paths with a large HD (31) of length 40, their contributions to the mean fitness and error threshold might still be negligible due to small \(\nu\) (width of neutrality).

**Steady-State Distribution**

Now we solve the steady-state distribution of the Eigen model with a single peak fitness and \(d_0(k) = 0\). Because of the symmetry of the problem, the probabilities \(p_1\) of Eq. 1 depend only on the HD from the peak configuration \(S_1\) whose probability to appear is \(p_1\). We denote the representatives of other \(N\) classes as configurations \(C_2, \ldots, C_{N+1}\), with corresponding probabilities \(p_2, \ldots, p_{N+1}\). The total probability of the class \(C_l\) is: \(p_l = p_{(N-1)}\). We suggest an ansatz for \(p_1: p_1 \sim 1\) and \(p_l \sim (\gamma/N)^{l-1}\). From Eq. 1 with \(dp_i/dt = 0\), we can derive an expression for \(p_1\) and write \(p_{n+1}\) for \(n \geq 1\) in terms of \(p_1, \ldots, p_n:\n
\[
    p_1 = \frac{e^{-\gamma} A - 1}{A - 1},
\]

\[
    p_{n+1} = \frac{1}{A - 1} \left[ p_1 A \frac{\gamma^n}{N} + \cdots + n^l p_{n-1} \frac{\gamma}{N^{l-1}} \right]
\]

\[
    + \cdots + n^l p_n \frac{\gamma}{N}. \quad [21]
\]

Eq. 20 implies \(L = (A - \Sigma_i p_i) / A = (1 - e^{-\gamma})\), which is a generalization of Haldane result for the mutational load (28, 32) \(L\).

Let us consider the crude picture of the Eigen model’s steady state. There is a central cluster around the peak configuration (with maximal density). The majority of population is concentrated within the HD \(N(1 - s)/2\), where the surplus \(s\) is defined above by Eq. 6. For the further classes the density decreases \(N\) times with every step. The case when fitness is a function of distances from several peaks, again, could be solved and is consistent with the described picture.

**Mutants with a Large HD from the Wild Type**

Rohde, Daum, and Biebricher (16) observed many different mutants at large HDs (up to 9) from the wild type. Eq. 21 implies that mutants with an HD \(d\) from the wild type will appear with a probability of the order of \((\gamma/N)^d\); thus the data in ref. 16 could
not be described by the original Eigen model in any way. We here propose three possible modifications of the Eigen model to explain the experimental data.

The first way is to introduce a nontrivial mutation landscape (33), which perhaps is the case for retroviruses. In this case, $q_j$ depends on the site and the mutation matrix $Q_{ij} = q_j^{N-d(i,j)}(1-q_j)^{d(i,j)}$ is nonsymmetric. When $q_j$ is a function of the HD from the wild configuration, Eq. 5 is modified: \( \gamma \to \gamma(k) \), where \( \gamma(k) = N/(1-q_j) \) for the configuration \( S_j \) having the overlap \( k \) with the wild one. Mutants at large HDs distances can appear, if the mutation rate for those genotypes is small enough to have a selective value \( A \exp[-\gamma(k)] \) close to the wild one.

The second way is to introduce the frequency-dependent fitness (even in exponentially growth phase); such a proposal is supported by experimental data for RNA viruses (34). For example, in Eq. 1 with \( D_y = 0 \) we replace \( r_j \) by \( r_j(1-c_p) \), where \( c \) is a small coefficient, and have

\[
\frac{dp_j}{dt} = \sum_{i=1}^{2^N} Q_{ij}(1-c_p)p_i - p_j \sum_{i=1}^{2^N} r_j(1-c_p)p_i \tag{22}\]

We consider the case of fitness \( r_1 > r_2 > 1 \) and \( r_2 > r_3(1-c) \), \( 1 > c > 0 \). For other configurations again \( r_1 = 1 \). Configuration \( S_2 \) is located in some HD \( d(1,2) \leq 1 \) from the peak configuration \( S_1 \).

When \( e^{-\gamma} < Q_1 \), where \( Q_1 = 1/r_1 \), there is no selection in the system; the steady-state distribution is flat. When \( Q_1 < e^{-\gamma} < Q_2 \), there is macroscopic distribution only around first configuration \( Q_2 \) will be defined later by Eq. 24. When \( e^{-\gamma} > Q_2 \), there are macroscopic probabilities \( 1 \) only at configurations \( S_1 \) and \( S_2 \) with \( p_1 = x \) and \( p_2 = y \). For other configurations \( p_i \sim 1/N^i \), where \( d \) is the shortest HD of the given configuration from \( S_1 \) or \( S_2 \). Then we immediately derive a system of two equations for \( x \) and \( y \)

\[
r_1Q(1-c)x = x[r_1(1-c)x + r_3(1-cy)y + 1 - x - y],
\]

\[
r_2Q(1-c)y = y[r_1(1-c)x + r_3(1-cy)y + 1 - x - y],
\]

where \( Q = q^N \). The system is easy to solve. From the condition \( x > 0 \) and \( y > 0 \), we derive an equation for the threshold \( Q_2 \)

\[
Q_2 = \frac{(r_2-1)(r_1-r_2) + r_2c}{cr_1r_2}. \tag{24}\]

When \( x > 0 \) and \( y > 0 \), the distribution is a sum of two distributions, decreasing quickly with the HDs from the main peak and \( y \) finite at small mutations, whereas in the case of the Eigen model \( c = 0 \) \( y \) disappears as \( (y/N)^{v_1(2)} \).

The third possible explanation could be multiple (duplicates, triplet . . . ) adjacent mutations (35). We can suggest a simple explanation by assuming triplet adjacent mutations (36). Assuming the existence (besides the simple point mutations) of triplet mutations with per genome per replication mutation probability \( y_1 < 1 \), \( r_1/(r_1-r_2) \approx 10 \), and missing the nonlinearity, we can get a reasonable estimate

\[
\frac{p_1}{p_2} \sim \frac{\gamma_1}{N^p} \sim 0.1, \tag{27}\]

which is of the same order as \( p_{1112}/p_1 \), \( p_{1112} \) being the probability for the appearance of I1112 in figure 4 in ref. 16 (I1112 has adjacent triplet mutations).

**Discussion**

More than 30 years after the first analytical result by Eigen (1), we presented exact formulas (Eqs. 5 and 6) for the mean fitness and surplus production in Eigen’s quasispecies model, using simplified landscapes with fitness values and degradation rates that are functions of the HD from the master type (Eqs. 1 and 4). In addition to the selective and nonselective phases, an AS phase is described at higher degradation rates. Depending on the landscape chosen, the threshold condition reported in ref. 2 had to be modified. The Eigen model immediately produces the notion of selective value (vs. fitness value on Wright’s fitness landscape in zero mutation case); the evolving system is choosing the peak with maximal selective value. For an isolated peak, the selective value is the product of fitness and copying fidelity (ref. 1). We derived a selective value for a general case (Eq. 5), including the neutral phenomenon (mesa with neutral spins) Eq. 19. The fitness function, decreasing from the master type with the square root of the HD, plays a special role. Such fitness allows a radical rearrangement of population. The model with nonzero degradation maybe realistic for the host–parasite interaction (21) and could be useful for the problems of immunology as well (37).

We have proposed three possible modifications of Eigen’s quasispecies model to describe the existence of mutants at large HDs from the wild type. All three mechanisms exist in experimental data (16, 33, 34). From the theoretical point of view the adjacent site mutations are especially interesting, because they can give rapid relaxation in changing environments in realistic case of finite population. Consider the situation, when the adjacent triplet mutations have the same rate as the single-site one, and new wild configuration in changing environments at the
HD $d$ from the current configuration could be achieved by triplet mutations. Let us denote by $\gamma_1$ and $\gamma_2$ the probabilities of single and triplet mutations per genome per replication. In ref. 38 it has been calculated that finite population relaxation period (fitness barrier crossing time) in case of single mutations scales as $t_1 \sim (N/\gamma_1)^d$. A similar estimate for triplet mutations gives $t_3 \sim (N/\gamma_3)^{3d/3}$. If a system needs 1 million replication cycles ($t_3$) to reach the steady state in case of only single-point mutations; a similar system needs only $\approx 100$ replication cycles ($t_3$) to reach approximately the same steady state through adjacent site triplet mutations. Thus, the latter can relax much more quickly.

Although we propose to modify the quasispecies model to explain the experimental data, we agree with the most fundamental idea of the quasispecies theory: the whole collection of the viruses (quasispecies) acts as a target of selection and mutation. Further work should deal with more realistic or interesting situations, such as finite population problems (39, 40), random fitness landscapes, and the role of neutral networks in evolution.

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Supporting Text

I. Derivation of Eqs. 5 and 6 in the Main Text

A. Derivation by Maximum Principle

To derive Eqs. 5 and 6 in the main text, we follow the method of refs. 1 and 2 of this supporting text. Let us consider an eigenvalue problem with the linear part of Eq. 1 in the main text

\[
\sum_{j=1}^{2^N} [Q_{ij} r_j - \delta_{ij} D_j] p_j \equiv \sum_j A_{ij} p_j = \lambda p_i, \quad (S.1)
\]

where \( \lambda \) is an eigenvalue of the matrix \( A_{ij} \). We are interested in the maximal eigenvalue \( \lambda_{\text{max}} \), which can be determined (see equation 51 of ref. 1) as

\[
\lambda_{\text{max}} = \max \frac{\sum_{ij} A_{ij} p_i p_j}{\sum_l p_i^2}, \quad (S.2)
\]

where the maximum is over all distributions of \( p_i \). Following ideas of refs. 1 and 2, we identify \( \lambda_{\text{max}} \) of Eq. S2 with \( \ln Z/\beta \) of Eq. 5 in the main text.

Since we consider the single-peak fitness function and choose the peak to appear at \( S_1 \equiv (1,1,\ldots,1) \), Eq. 4 of the main text implies that \( f(S_i) \) and \( D(S_i) \) depend only on the Hamming distance between \( S_i \) and \( S_1 \). Thus, we have \( N+1 \) classes of fitness corresponding to Hamming distances from 0 to \( N \), and all \( p_i \) from the same class are equal. The number of configurations in the \( l \)–th class \( C_l \) (whose Hamming distance from \( S_1 \) is \( l \) ) is

\[
N_l \equiv \frac{N!}{l!(N-l)!}. \quad (S.3)
\]

We define \( \hat{p}_l = \sqrt{N_l} p_i \), where configuration \( i \) belongs to the class \( l \). Therefore in the denominator of Eq. S2 we have

\[
\sum_l p_i^2 = \sum_{l=0}^{N} p_l^2.
\]

For the class probability we have \( \sqrt{N_l} \hat{p}_l \). Therefore \( \sum_l \sqrt{N_l} \hat{p}_l = 1 \).

We introduce also \( r_l \equiv f_0(\frac{N-2l}{N}) \), \( D_l = d_0(\frac{N-2l}{N}) \) and a matrix

\[
\hat{A}_{ll} = \sum_j A_{ij} \sqrt{\frac{N_l}{N_l}}, \quad (S.4)
\]
where configuration \( i \) belongs to the class \( l \), and the sum is over the configurations \( j \) from the class \( l' \).

The equation for the eigenvalue \( \lambda \) is (see equation 56 of ref. 1)
\[
\sum_{i} \hat{A}_{l'i'} \hat{p}_{i'} = \lambda \hat{p}_{i},
\] (S.5)
and
\[
\lambda_{\text{max}} = \frac{\sum_{n} \hat{A}_{nl} \hat{p}_{n}}{\sum_{l} \hat{p}_{l}^{2}}.
\] (S.6)

Let us assume that \( \hat{p}_{n} \) has a maximum at \( l = n \), and the width the \( \hat{p}_{n} \) distribution near \( \hat{p}_{n} \) is \( |l - n| \approx N^{\alpha} \), \( \alpha < 1 \). Consider Eq. S.5 for \( l = n \). The principal contribution in the sum via \( l_i \) comes from the neighborhood \( |n - l_i| \ll N^{\alpha} \). Therefore, in the sum, \( \hat{p}_{n} \) could be replaced by \( \hat{p}_{n} \), and Eq. S.5 for \( \hat{p}_{n} \) on the right side gives (with the accuracy \( \sim 1/N^{1-\alpha} \))
\[
\sum_{i} \hat{A}_{nl} = \lambda.
\] (S.7)

We should take also the maximum of the last expression via \( n \), as in Eqs. S.2 and S.6. Therefore, we derive
\[
\lambda_{\text{max}} = \max_{n} \{ \sum_{l} \hat{A}_{nl} \}.
\] (S.8)

In each configuration of class \( C_{n} \), there are \( n \) down spins and \( N - n \) up spins. To perform the sum over \( l \) in Eq. S.8, we choose \( l_1 \) spins from \( n \) down spins and change them to up spins; we also choose \( l_2 \) spins from \( N - n \) up spins and change them to down spins. After these two actions, we have \( n - l_1 + l_2 \) down spins. The sum over \( l \) in Eq. S.8 can be replaced by the sum over \( l_0 \) from 0 to \( N \). For a given \( l_0 \), we consider all possible combinations of \( l_1 \) and \( l_2 \) such that \( l_1 + l_2 = l_0 \). With the replacement \( q^{N} \to e^{-\gamma} \) and \( (1 - q)/q \to \gamma/N \) for small \( (1 - q) \), \( \sum_{l} \hat{A}_{nl} \) in Eq. S.8 can be written as
\[
e^{-\gamma} \sum_{l_0=0}^{N} \sum_{l_1 + l_2 = l_0} \left( \frac{\gamma}{N} \right)^{l_0} \frac{n!}{l_1! l_2!} \sqrt{\frac{N}{N_n}} f_{0}(\frac{N - 2(n - l_1 + l_2)}{N}) - D_{n},
\]
or
\[
e^{-\gamma} \sum_{l_0=0}^{N} \sum_{l_1 + l_2 = l_0} \frac{\gamma^{l_0}}{N^{l_0}} \sqrt{\frac{n!}{(n - n)!}} \frac{n!}{l_1! l_2!} \frac{(N - n)!}{(N - n)!} f_{0}(\frac{N - 2(n - l_1 + l_2)}{N}) - D_{n}.
\] (S.9)

where \( n_{1,2} = n - l_1 + l_2 \). Let us consider the limit \( N \gg l_0, n/N \sim 1 \). From the binomial expansion of \((1 + x)^{l_0}\) with \( x = 1 \), we have
\[
\sum_{l_1 + l_2 = l_0} \frac{1}{l_1! l_2!} = \frac{2^{l_0}}{l_0!}.
\]


With the accuracy $1/N^{1-\alpha}$ we replace $f_0((N - 2(n - l_1 + l_2))/N) \to f_0((N - 2n)/N)$, $n!/n_{1,2}! \to n!(l_1-l_2)$, $(N - n)!/(N - n_{1,2})! \to (N - n)^{-l_1-l_2}$, $(n^l_{1,2}) \to n^l_{1,2}/l_1!,(N-n)^{l_2} \to (N - n)^{l_2}/l_2!$. Combining all those formulas we derive from Eq. S.8 for the $\ln Z/\beta \equiv \lambda_{\max}$:

$$e^{-\gamma(1-\sqrt{k^2})}f_0(k) - d_0(k) = \lambda_{\max},$$  \hspace{1cm} (S.10)

where $k = (N - 2n)/N$. To find the $\lambda_{\max}$ one should consider the maximum of Eq. S.10. Therefore, we derive Eq. 5 of the main text.

The excess replication rate $R$ is defined as

$$R = \sum_{i=1}^{2N} p_i(r_i - D_i) = \sum_{l=0}^{N} \sqrt{N_l}{\hat{p}_l}(r_l - D_l),$$  \hspace{1cm} (S.11)

and the surplus $s$ as

$$s = \sum_{l=0}^{N} \sqrt{N_l}{\hat{p}_l}(1 - 2l/N).$$

To derive an equation for the surplus $s$, we assume the following picture of the steady state distribution in the considered model. The class probability $\sqrt{N_l}{\hat{p}_l}$ increases till the $l = n_0$, where $\sqrt{N_l}{\hat{p}_l}$ is a maximal one, then $\sqrt{N_l}{\hat{p}_l}$ decreases. In the sum for both $R$ and $s$ the principal contributions come from the neighborhood of $l = n_0$. Therefore, in the last sums with accuracy $1/N^{1-\alpha}$ we can replace $(r_l - D_l) \to (r_{n_0} - D_{n_0})$ and $(1 - 2l/N) \to (1 - 2n_0/N)$. We derive

$$s = (1 - 2n_0/N)$$

and

$$R = f_0(1 - 2n_0/N) - d_0(1 - 2n_0/N).$$

We already derived $R = e^{-\gamma(1-\sqrt{k^2})}f_0(k) - d_0(k)$. Therefore, we derive for the surplus an equation:

$$e^{-\gamma(1-\sqrt{k^2})}f_0(k) - d_0(k) = f_0(s) - d_0(s).$$  \hspace{1cm} (S.12)

**B. Derivation of Mean Fitness by Series Expansion**

Following the method of ref. 3, we can show that solution of system 1 in our main text can be reformulated as a problem of quantum statistical mechanics with Hamiltonian $H$. For a given distribution $p_i(0)$, we can construct vectors $\sum_i p_i(0)|S_i>$ in the Hilbert space.
of $N$ spins, where $|S_i \equiv |s_i^{(i)}\ldots s_N^{(i)}\rangle$ are eigenstates of “longitudinal” Pauli matrices $\sigma_i^z$.

The Hamiltonian $H$ and $p_i(t)$ are, respectively, given by

$$-H = [i e^{-\gamma} + \sum_{l=1} e^{-\gamma} (\frac{1-q}{q})^l \sum_{1 \leq i_1 < i_2 \ldots < i_N \leq N} \sigma_{i_1}^x \ldots \sigma_{i_N}^x] \Phi(\sigma_1^x, \ldots, \sigma_N^x) - d(\sigma_1^x, \ldots, \sigma_N^x),$$

$$p_i(t) = \frac{\sum_j p_j(0) < S_i \exp[-Ht] |S_j \rangle}{\sum_j p_j(0) < S_i \exp[-Ht] |S_j \rangle}. \tag{S.13}$$

Here $e^{-\gamma} = \frac{q}{N}$, $\sigma_n^x$ are “transverse” Pauli matrices, acting on the spin at the site $n$. We consider the case $f(\sigma_1^x, \ldots, \sigma_N^x) = f_0(\sum_{l=1}^N \sigma_l^x/N)$. Actually we have derived Eq. S.13 for the case of $d_0 = 0$ in ref. 3, but the generalization to the nonzero $d_0$ is trivial. With an $O(1/N)$ accuracy it is possible to have the replacement

$$[i e^{-\gamma} + \sum_{l=1} e^{-\gamma} (\frac{\gamma}{N})^l \sum_{1 \leq i_1 < i_2 \ldots < i_N \leq N} \sigma_{i_1}^x \ldots \sigma_{i_N}^x] \rightarrow \exp[-\gamma(1 - \sum_{l=1}^N \frac{\sigma_l^x}{N})]. \tag{S.14}$$

At the left-hand side of the last equation we have used $\gamma/N$ to represent $(1-q)/q$ for small $(1-q)$.

For the moment we consider the series expansion for the model without degradation. We should calculate

$$Z = \text{Tr} e^{-\beta H},$$

$$-H = e^{-\gamma(1-\sum_{n=1}^N \sigma_n^x/N)} f_0(\frac{1}{N} \sum_{n=1}^N \sigma_n^x) \equiv A, \tag{S.15}$$

at the limit $N \rightarrow \infty$.

We see that our Hamiltonian is mean-field-like, which is why the partition function could be calculated. We expand the exponent and derive a sum

$$Z = \text{Tr} e^{-\beta H} = \sum_{L=0}^\infty \frac{\beta L}{L!} \text{Tr} AAA \ldots A. \tag{S.16}$$

The total number of $A$ in the product after $\text{Tr}$ is $L$. We introduce sums $\sum_L |S_l \rangle < S_l \rangle \equiv \hat{I}$ between $AA$, where $\hat{I}$ is the identity operator. As in ref. 4, we can use Suzuki-Trotter method to study above expansion. Based on $\exp[\gamma \sigma^x/N] = \cosh[\gamma/N] + \sigma^x \sinh[\gamma/N]$, we have up to $O(\gamma/N)$

$$< s_i | \exp[\frac{\gamma}{N} \sigma^x] | s_j > = [\frac{\gamma}{N}]^{1-s_i s_j}. \tag{S.17}$$

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Then it is easy to calculate
\[
<s_1^l \ldots s_N^l > [e^{-\gamma(1-\sum_{n=1}^{N} \sigma_n^z/N)} f_0(\frac{1}{N} \sum_{n=1}^{N} \sigma_n^z)] s_1^{l+1} \ldots s_N^{l+1} >
\]
\[= e^{-\gamma(1-\sum_{n=1}^{N} \sigma_n^z)^2/2} f_0(\frac{\sum_{n=1}^{N} s_n^{l+1}}{N}).
\] (S.18)

We used that \(\sigma_z|s >= s|s \). Now we have
\[
Z = \sum_{L=0}^{\infty} \frac{\beta L}{L!} \sum_{s_n=\pm 1} \sum_{l=1}^{L} \left[ e^{-\gamma(1-\sum_{n=1}^{N} \sigma_n^z/N)} f_0(\frac{\sum_{n=1}^{N} s_n^{l+1}}{N}) \right]^{(N-\sum_{n=1}^{N} s_n^{l+1})/2} f_0(\frac{\sum_{n=1}^{N} s_n^{l}}{N}).
\] (S.19)

Let us introduce at any expansion term \(L \) identities
\[
1 = \int_{-\infty}^{\infty} \frac{N \beta}{L} dM_i \delta(\frac{\beta N M_i}{L} - \frac{\beta \sum_{n=1}^{N} s_n^{l}}{L}).
\]

We use the integral representation for the delta functions,
\[
1 = \int_{-\infty}^{\infty} dM_i \int_{-i \infty}^{i \infty} dh_i \frac{N \beta}{2 \pi i L} \exp[-\frac{N \beta}{L} M_i h_i + \sum_{n=1}^{N} h_i s_n^l \beta].
\] (S.20)

Then \(Z \) is transformed into
\[
Z = \sum_{L=0}^{\infty} \frac{e^{-L \gamma} \beta^L}{L!} \sum_{s_n=\pm 1} \prod_{l=1}^{L} \int_{-\infty}^{\infty} dM_i \int_{-i \infty}^{i \infty} dh_i \frac{f_0(M_i) N \beta}{2 \pi i L} \exp[-\frac{N \beta}{L} M_i h_i + \sum_{n=1}^{N} h_i s_n^l \beta].
\] (S.21)

or
\[
Z = \sum_{L=0}^{\infty} \frac{\beta^L e^{-L \gamma}}{L!} \prod_{l=1}^{L} \int_{-\infty}^{\infty} dM_i \int_{-i \infty}^{i \infty} dh_i \frac{f_0(M_i) N \beta}{2 \pi i L} \exp\left(-\frac{N \beta}{L} \sum_{l=1}^{L} M_i h_i + N \ln z[B, \{ \frac{h_i}{L} \}, L] \right),
\] (S.22)

where
\[
B = \ln(\frac{N}{\gamma}),
\] (S.23)

and
\[
z[B, \{ \frac{h_i}{L} \}, L] = \sum_{s_n=\pm 1} \exp\left(\frac{B}{2} \sum_{l=1}^{L} [(s_{l+1} s_l - 1) + \frac{h_l s_l \beta}{L}] \right),
\] (S.24)
has been calculated in ref. 4 as formula 41. One has at $L \to \infty$

$$z = Tr \exp[\int_0^1 dx (\beta h(x) \sigma^z + Le^{-B} \sigma^z)],$$

(S.25)

where the exponent is time ordered (4), and $h(l/L) \equiv h_l$. We consider a saddle point equation. Assume that the saddle point value of $h(x)$ is translation invariant, $h(x) = h, M_l = M$. Then we can miss the time ordering and derive

$$z = Tr \exp[h \beta \sigma^z + Le^{-B} \sigma^z] = 2 \cosh[\sqrt{\bar{h}^2 \beta^2 + L^2 e^{-2B}}] = 2 \cosh[\sqrt{h^2 \beta^2 + \frac{L \gamma^2}{N^2}}].$$

(S.26)

Now we have

$$Z = \sum_{L=0}^{\infty} \frac{1}{L!} \int_{-\infty}^{\infty} dh \int_{-\infty}^{\infty} dM [\beta e^{-\gamma} f_0(M)]^L e^{-NMh\beta + N \ln 2 \cosh(\sqrt{\beta^2 \frac{L \gamma^2}{N^2}})}.$$  

(S.27)

Our expression is correct for the $L \to \infty$ and $\bar{h} \to \infty$, as we missed multiple integrations and pre-exponent terms. At this limit the last expression transforms into

$$Z = \sum_{L=0}^{\infty} \frac{1}{L!} \int_{-\infty}^{\infty} dh \int_{-\infty}^{\infty} dM [\beta e^{-\gamma} f_0(M)]^L e^{-NMh\beta + N \sqrt{\beta^2 h^2 + \frac{L \gamma^2}{N^2}}}.$$  

(S.28)

Let us consider another expression

$$Z_0 = \int_{-\infty}^{\infty} dh dx \int_{-\infty}^{\infty} dM dme^{-NMh\beta - N\beta mx + N\beta \sqrt{h^2 + x^2} + \beta f_0(M)e^{-\gamma(1-m)}}.$$  

(S.29)

Expanding the last term in the exponent, and performing $dx, dm$ integration, we derive

$$Z_0 = \sum_{L=0}^{\infty} \frac{1}{L!} \int_{-\infty}^{\infty} dh \int_{-\infty}^{\infty} dM [\beta e^{-\gamma} f_0(M)]^L e^{-NMh\beta + N \sqrt{\beta^2 h^2 + \frac{L \gamma^2}{N^2}}}.$$  

(S.30)

We see that series for $Z$ and $Z_0$ (only few principal terms in the series S.28 and S.30 are important) coincide for $L \to \infty$, therefore $Z = Z_0$, and we derive our formula for the mean fitness from Eq. S.29

$$\frac{\ln Z}{\beta} = \max\{[e^{-\gamma(1-m)} f_0(M)] - NMh - Nmx + N \sqrt{h^2 + x^2}\}.$$  

(S.31)

At the limit $\beta \to \infty$ and re-scaling $x \to x/N, h \to h/N, M \to k$, we derive

$$\frac{\ln Z}{\beta} = e^{-\gamma(1-m)} f_0(k) - h m - x k + \sqrt{h^2 + x^2}.$$  

(S.32)

The saddle point condition gives

$$k = \frac{x}{\sqrt{x^2 + h^2}}, \quad m = \frac{h}{\sqrt{x^2 + h^2}}.$$  

(S.33)
and thus

\[ k^2 + m^2 = 1, \sqrt{x^2 + h^2} - mh - kx = 0, \quad (S.34) \]

which implies

\[ \frac{\ln Z}{\beta} = [e^{-\gamma(1-\sqrt{-k^2})}f_0(k)]. \quad (S.35) \]

Let us derive Eq. \textbf{S.29} directly from Eq. \textbf{S.28}. We transform Eq. \textbf{S.28}, introducing intermediate integration via variables \( dx, dm \)

\[
Z = \sum_{L=0}^{\infty} \frac{1}{L!} \int_{-\infty}^{\infty} dh dx \int_{-\infty}^{\infty} dM dm [\beta e^{-\gamma} f_0(M)]^L e^{-NMh\beta-m(N\beta x-\gamma L)+N\beta \sqrt{h^2+x^2}}. \quad (S.36)
\]

Now we have a sum like \( \sum_L a^L/L! \), where

\[ a = \beta e^{-\gamma} f_0(M) e^{m\gamma}. \quad (S.37) \]

It is an expansion of the \( \exp[a] \), therefore we recover that \( Z = Z_0 \). What is the accuracy of our derivation? We ignored in Eq. \textbf{S.36} the pre-exponent terms, it is rigorous for \( \beta \to \infty \).

Let us consider the case of nonzero degradation. Now we have two terms in Hamiltonian,

\[ H = H_1 + H_2, \]

\[ H_1 = -e^{-\gamma(1-\sum_{n=1}^{N} \sigma_n^z/N)} f_0 \left( \frac{1}{N} \sum_{n=1}^{N} \sigma_n^z, \right), \]

\[ H_2 = d_0 \left( \frac{1}{N} \sum_{n=1}^{N} \sigma_n^z, \right), \quad (S.38) \]

and instead of Eq. \textbf{S.16}, we have

\[
Z = \sum_{L} \frac{(-\beta)^L}{L!} \text{Tr} \sum_{L_1+L_2=L} H_{\alpha_1} \cdots H_{\alpha_L}, \quad (S.39)
\]

where \( \alpha_i = 1, 2 \), the sum is over all distribution of \( H_1, H_2 \) over \( L \) situations. For the large values of \( L \), we again consider the symmetric \( h_l \) ansatz, and instead of Eq. \textbf{S.27} obtain

\[
Z = \sum_{L_1, L_2=0}^{\infty} \frac{\beta^{L_1}(-\beta)^{L_2}}{L_1!L_2!} \int_{-\infty}^{\infty} dh \int_{-\infty}^{\infty} dM [e^{-\gamma} f_0(M)]^{L_1} d_0(M)^{L_2} \times e^{-NMh\beta-N \ln 2 \cosh(\sqrt{\beta^2h^2+m^2L_1^2})}. \quad (S.40)
\]

We see that the situation is similar to Eq. \textbf{S.27}, only under the integration we have an additional multiplier

\[
\sum_{L_2=0}^{\infty} \frac{(-\beta)^{L_2}}{L_2!} d_0(M)^{L_2} = \exp[-\beta d_0(M)]. \quad (S.41)
\]
Therefore, instead of Eq. S.29 we derive

$$Z_0 = \int_{-\infty}^{\infty} dh dx \int_{-\infty}^{\infty} dM dme^{-NMh\beta - N\beta mx + N\beta \sqrt{r^2 + x^2} + \beta f_0(M)e^{-\gamma(1-m)} - \beta d_0(M)},$$  \hspace{1cm} (S.42)

and instead of Eq. S.35, we have

$$\ln \frac{Z}{\beta} = [e^{-\gamma(1-\sqrt{r^2})}f_0(k) - d_0(k)],$$  \hspace{1cm} (S.43)

which is Eq. 5 in the main text.

II. Derivation of Eq. 17 in the Main Text by Series Expansion

Let us repeat the calculation of previous section for the case, when there are two groups of spins, $s_1, \ldots, s_{\nu N}$ and $s_{\nu N+1}, \ldots, s_N$, with corresponding magnetization $k_1, k_2$ for the given $i$-th configuration, and the fitness is defined as

$$r_i = f_0(k_1, k_2).$$ \hspace{1cm} (S.44)

We should calculate

$$Z = Tr e^{-\beta H},$$
$$H = -e^{-\gamma(1-\sum_{n=1}^{N} \sigma_n^z/N)}f_0(\frac{1}{\nu N} \sum_{n=1}^{\nu N} \sigma_n^z, \frac{1}{(1-\nu)N} \sum_{n=\nu N+1}^{N} \sigma_n^z),$$ \hspace{1cm} (S.45)

at the limit $N \to \infty$.

The calculation is similar to the previous section, only we should introduce at any slice two fields $M_i^1, M_i^2$, and have

$$Z = \sum_{L=0}^{\infty} \frac{e^{-L\gamma \beta L}}{L!} \sum_{s_n^z = \pm 1} \prod_{l=1}^{L} \int_{-\infty}^{\infty} dM_i^1 \int_{-\infty}^{\infty} dh_i^1 \int_{-\infty}^{\infty} dM_i^2 \int_{-\infty}^{\infty} dh_i^2 \frac{f_0(M_i^1, M_i^2)}{4\pi^2} \times N\nu \beta N(1-\nu) \beta L \exp\left\{-\frac{N\nu \beta}{L} \sum_{l=1}^{L} M_i^1 h_i^1 - \frac{N(1-\nu) \beta}{L} \sum_{l=1}^{L} M_i^2 h_i^2 \right\} \times$$
$$\sum_{l=1}^{L} \frac{\nu N}{\gamma} \sum_{l=1}^{\nu N} \left( \frac{N}{2} s_n^l s_n^{l+1} - 1 \right) \sum_{l=1}^{\nu N} \frac{h_i^1 s_n^l \beta}{L} \sum_{l=1}^{\nu N} \left( \frac{N}{2} \frac{s_n^{l+1} s_n^l - 1}{2} \right) + \frac{h_i^2 s_n^l \beta}{L} \right\}. \hspace{1cm} (S.46)$$

Assume that the saddle point values of magnetization are translation invariant, $h_i^1 = h_1^1, h_i^2 = h_2^1, M_i^1 = M_1, M_i^2 = M_2$, we derive

$$Z = \sum_{L=0}^{\infty} \frac{1}{L!} \int_{-\infty}^{\infty} dh_1 dh_2 \int_{-\infty}^{\infty} dM_1 dM_2 \left[ e^{-\gamma f_0(M_1, M_2)} \right]^L \times$$
$$e^{-N(\nu M_1 h_1 + (1-\nu)M_2 h_2)\beta + N\nu \ln 2 \cosh(\sqrt{\beta^2 h_1^2 + \frac{\gamma^2 \beta^2}{N^2}}) + N(1-\nu) \ln 2 \cosh(\sqrt{\beta^2 h_2^2 + \frac{\gamma^2 \beta^2}{N^2})}. (S.47)$$
At the limit $\beta \to \infty$, we have
\[
Z = \sum_{L=0}^{\infty} \frac{1}{L!} \int_{-\infty}^{\infty} dh \int_{-\infty}^{\infty} dM [\beta e^{-\gamma f_0(M_1, M_2)}]^L \times e^{-N(M_1 h_1 + M_2 h_2 (1-\nu)) + N \nu \sqrt{\beta^2 h_1^2 + \frac{\nu\lambda^2}{N^2} + N(1-\nu) \sqrt{\beta^2 h_2^2 + \frac{\nu\lambda^2}{N^2}}}}. \tag{S.48}
\]

Let us transform to another form, using the identity
\[
1 = N \beta \int dx \delta(N \beta x - \gamma L) \sim \int dm dx e^{-N \beta m x + m \gamma L}.
\]
Then we can replace $\gamma L$ terms by $N \beta x$, and Eq. S.48 transforms into
\[
Z_0 = \int_{-\infty}^{\infty} dh_1 dh_2 dx \int_{-\infty}^{\infty} dM_1 dM_2 dm \sum_{L} \frac{[\beta f_0(M_1, M_2)e^{-\gamma(1-m)}]^L}{L!} \times e^{-N \beta (M_1 h_1 + (1-\nu)M_2 h_2) - N \beta m x + N \beta \nu \sqrt{h_1^2 + x^2} + N \beta (1-\nu) \sqrt{h_2^2 + x^2} + \beta f_0(M_1, M_2)e^{-\gamma(1-m)}}. \tag{S.49}
\]
As we missed the pre-exponent terms, our expression is correct with $1/\beta$ accuracy. The sum over $L$ gives an exponent, and we derive
\[
Z = \int_{-\infty}^{\infty} dh_1 dh_2 dx \int_{-\infty}^{\infty} dM_1 dM_2 dx \times e^{-N \beta (M_1 h_1 + (1-\nu)M_2 h_2) - N \beta m x + N \beta \nu \sqrt{h_1^2 + x^2} + N \beta (1-\nu) \sqrt{h_2^2 + x^2} + \beta f_0(M_1, M_2)e^{-\gamma(1-m)}}. \tag{S.50}
\]
After mapping $h_1 \to x_1/N$, $h_2 \to x_2/N$, $M_1 \to k_1$, $M_2 \to k_2$, $x \to h/N$, we derive Eq. 17 of the main text
\[
\frac{\ln Z}{\beta} = \nu \sqrt{x_1^2 + h^2 + (1-\nu) \sqrt{x_2^2 + h^2}} - k_1 x_1 \nu - (1-\nu) k_2 x_2 - mh + f_0(k_1, k_2)e^{-\gamma(1-m)}. \tag{S.51}
\]

### III. Mean Fitness for Four-Value Case

To specify four value spins, as in ref. 5, we consider two configurations $s_1^n, s_2^n, 1 \leq n \leq N$, where $s_1^n = \pm 1$, $s_2^n = \pm 1$. We assume that two configurations have an overlap $m_3$
\[
\sum_{n=1}^{N} s_1^n s_2^n = N m_3, \tag{S.52}
\]
as well as magnetization $m_1, m_2$
\[
\sum_{n=1}^{N} s_1^n = N m_1, \sum_{n=1}^{N} s_2^n = N m_2. \tag{S.53}
\]
Now the fitness of configuration and the degradation rate are functions of the $m_1, m_2, m_3$

\[ r_i = f_0(m_1, m_2, m_3), \]
\[ D_i = d_0(m_1, m_2, m_3). \]  \hfill (S.54)

We define the factors $x_{\alpha_1, \alpha_2}$ describing the fraction of spins in configurations $s_{1n}^1, s_{2n}^2$, having
\[ \pm 1 \] signs

\[
x_{++} = \frac{L_1 - L_2 + N - L_3}{2N} = \frac{m_1 - m_2 - m_3 + 1}{4},
\]
\[
x_{++} = \frac{L_1 + L_2 - N + L_3}{2N} = \frac{m_1 + m_2 + m_3 + 1}{4},
\]
\[
x_{--} = \frac{-L_1 - L_2 + N - L_3}{2N} = \frac{m_1 - m_2 + m_3 + 1}{4},
\]
\[
x_{--} = \frac{-L_1 + L_2 + N - L_3}{2N} = \frac{m_1 + m_2 - m_3 + 1}{4}, \hfill (S.55)
\]

where $L_1 = N(2m_1 + 1)/2, L_2 = N(2m_2 + 1), L_3 = N(2m_3 + 1)/2$ are the numbers of corresponding up spins. The number of such configurations is

\[
N(L_1, L_2, L_3) = \frac{N!}{(N x_{++}!(N x_{--}!(N x_{+-})!)(N x_{-+})!)}. \hfill (S.56)
\]

There are one-spin flip mutations from the configurations $L_1, L_2 \pm 1, L_3 \pm 1; L_1 \pm 1, L_2, L_3 \pm 1; L_1 \pm 1, L_2 \pm 1, L_3$ to the configuration $L_1, L_2, L_3$. We should consider separately the up and down flips of the spins $s_{1n}^1, s_{2n}^2$, as well as for both spins simultaneously.

We have the following spin-flip processes, connecting configuration $(L_1, L_2, L_3)$ with the neighbors:

- $s_1$ up flip to $L_1 + 1, L_2, L_3 + 1$, with the number of the neighbors $N x_{+-}(L_1, L_2, L_3)$;
- $s_1$ up flip to $L_1 + 1, L_2, L_3 - 1$, with the number of the neighbors $N x_{--}(L_1, L_2, L_3)$;
- $s_1$ down flip to $L_1 - 1, L_2, L_3 + 1$, with the number of the neighbors $N x_{+-}(L_1, L_2, L_3)$;
- $s_1$ down flip to $L_1 - 1, L_2, L_3 - 1$, with the number of the neighbors $N x_{++}(L_1, L_2, L_3)$;
- $s_2$ up flip to $L_1, L_2 + 1, L_3 + 1$, with the number of the neighbors $N x_{--}(L_1, L_2, L_3)$;
- $s_2$ up flip to $L_1, L_2 + 1, L_3 - 1$, with the number of the neighbors $N x_{--}(L_1, L_2, L_3)$;
- $s_2$ down flip to $L_1, L_2 - 1, L_3 + 1$, with the number of the neighbors $N x_{+-}(L_1, L_2, L_3)$;
- $s_2$ down flip to $L_1, L_2 - 1, L_3 - 1$, with the number of the neighbors $N x_{+-}(L_1, L_2, L_3)$;
• $s_2$ down flip to $L_1, L_2 - 1, L_3 - 1$, with the number of the neighbors $N_{x_+ +}(L_1, L_2, L_3)$;
• $s_1$ and $s_2$ up flips to $L_1 + 1, L_2 + 1, L_3$, with the number of the neighbors $N_{x_- -}(L_1, L_2, L_3)$;
• $s_1$ and $s_2$ down flips to $L_1 - 1, L_2 - 1, L_3$, with the number of the neighbors $N_{x_+ +}(L_1, L_2, L_3)$;
• $s_1$ up, $s_2$ down flips to $L_1 + 1, L_2 - 1, L_3$, with the number of the neighbors $N_{x_- +}(L_1, L_2, L_3)$;
• $s_1$ down to $s_2$ up flips to $L_1 - 1, L_2 + 1, L_3$, with the number of the neighbors $N_{x_+ -}(L_1, L_2, L_3)$.

The configuration $(L_1, L_2, L_3)$ could be reached from the neighbors by any of 12 mentioned mutation acts with a reverse mutation.

Let us calculate the mean fitness as in Section I.A. We denote $\tilde{L} \equiv (L_1, L_2, L_3)$ and define

$$A_{\tilde{L}, \tilde{L}'} \equiv \sum_j A_{ij} \sqrt{\frac{N(L_1, L_2, L_3)}{N(L_1', L_2', L_3')}},$$  \hspace{1cm} (S.57)

where configuration $i$ has parameters $(L_1, L_2, L_3)$ and the sum is over the configuration $j$ having parameters $(L_1', L_2', L_3')$. Following Eqs. S.4 and S.7, we should consider

$$\sum_{\tilde{L}'} A_{\tilde{L}, \tilde{L}'};$$  \hspace{1cm} (S.58)

and calculate the maximum over $\tilde{L}$. In Eq. S.58 we should consider the contribution of configurations having spin flips with the number of different types $l_i, 1 \leq i \leq 12$, and the total number of mutations $n = \sum_{i=1}^{12} l_i$. The sum S.58 could be considered as a random walk in the three-dimensional space $(L_1, L_2, L_3)$ between configurations $\tilde{L}', \tilde{L}$. Originally the system starts at some point $L' \equiv (L_{1,n}, L_{2,n}, L_{3,n})$ with a number of configurations $N(L_{1,n}, L_{2,n}, L_{3,n})$. To calculate S.58, we should take the product of $x_{\pm, \pm}$ along the path of one point mutations, connecting the configuration $L_{1,n}, L_{2,n}, L_{3,n}$ with the $(L_1, L_2, L_3)$, times $N^n \sqrt{N(L_1, L_2, L_3)/N(L_{1,n}, L_{2,n}, L_{3,n})}$, as has been done in the previous section. We use the identity

$$\sqrt{\frac{N(L_1, L_2, L_3)}{N(L_{1,n}, L_{2,n}, L_{3,n})}} \equiv \prod_{l=1}^{n} \sqrt{\frac{N(L_{1,l-1}, L_{2,l-1}, L_{3,l-1})}{N(L_{1,l}, L_{2,l}, L_{3,l})}},$$  \hspace{1cm} (S.59)
where \( N(L_{1,0}, L_{2,0}, L_{3,0}) \equiv N(L_1, L_2, L_3) \). We should consider the sum over all possibilities. The weight of any such \( n \)-th order term in the sum \( S.57 \) is the product of corresponding factors \( x_{\pm \pm} \) times \( \sqrt{\frac{N(L_{1,l-1}, L_{2,l-1}, L_{3,l-1})}{N(L_{1,l}, L_{2,l}, L_{3,l})}} \) along the path (connecting the point \((L_{1,n}, L_{2,n}, L_{3,n})\) with \((L_1, L_2, L_3)\)). Therefore, for any path we have a weight

\[
N^n \prod_{l=1}^{n} x_{\alpha_l, \beta_l} \sqrt{\frac{N(L_{1,l}, L_{2,l}, L_{3,l})}{N(L_{1,l-1}, L_{2,l-1}, L_{3,l-1})}},
\]

where \( \alpha_l, \beta_l \) specify the two spin alignment at the step \( l \).

At the limit \( n/N \to 0 \), we have

\[
\begin{align*}
x_{-.}(L_1, L_2, L_3) & = \sqrt{\frac{N(L_1, L_2, L_3)}{N(L_1 + 1, L_2, L_3 + 1)}} = \frac{\sqrt{(1 + m_2)^2 - (m_1 + m_3)^2}}{4}, \\
x_{+-}(L_1, L_2, L_3) & = \sqrt{\frac{N(L_1, L_2, L_3)}{N(L_1 - 1, L_2, L_3 + 1)}} = \frac{\sqrt{(1 + m_2)^2 - (m_1 + m_3)^2}}{4}, \\
x_{--}(L_1, L_2, L_3) & = \sqrt{\frac{N(L_1, L_2, L_3)}{N(L_1 - 1, L_2, L_3 - 1)}} = \frac{\sqrt{(1 - m_2)^2 - (m_1 - m_3)^2}}{4}, \\
x_{++}(L_1, L_2, L_3) & = \sqrt{\frac{N(L_1, L_2, L_3)}{N(L_1 - 1, L_2, L_3 - 1)}} = \frac{\sqrt{(1 - m_2)^2 - (m_1 - m_3)^2}}{4}, \\
x_{+-}(L_1, L_2, L_3) & = \sqrt{\frac{N(L_1, L_2, L_3)}{N(L_1, L_2 + 1, L_3 + 1)}} = \frac{\sqrt{(1 + m_2)^2 - (m_2 + m_3)^2}}{4}, \\
x_{--}(L_1, L_2, L_3) & = \sqrt{\frac{N(L_1, L_2, L_3)}{N(L_1, L_2 + 1, L_3 - 1)}} = \frac{\sqrt{(1 - m_2)^2 - (m_2 - m_3)^2}}{4}, \\
x_{-+}(L_1, L_2, L_3) & = \sqrt{\frac{N(L_1, L_2, L_3)}{N(L_1, L_2 - 1, L_3 + 1)}} = \frac{\sqrt{(1 - m_2)^2 - (m_2 - m_3)^2}}{4}, \\
x_{++}(L_1, L_2, L_3) & = \sqrt{\frac{N(L_1, L_2, L_3)}{N(L_1, L_2 - 1, L_3 - 1)}} = \frac{\sqrt{(1 + m_2)^2 - (m_2 + m_3)^2}}{4}, \\
x_{--}(L_1, L_2, L_3) & = \sqrt{\frac{N(L_1, L_2, L_3)}{N(L_1 + 1, L_2 + 1, L_3)}} = \frac{\sqrt{(1 + m_3)^2 - (m_1 + m_2)^2}}{4}, \\
x_{++}(L_1, L_2, L_3) & = \sqrt{\frac{N(L_1, L_2, L_3)}{N(L_1 - 1, L_2 - 1, L_3)}} = \frac{\sqrt{(1 + m_3)^2 - (m_1 + m_2)^2}}{4}, \\
x_{+-}(L_1, L_2, L_3) & = \sqrt{\frac{N(L_1, L_2, L_3)}{N(L_1 - 1, L_2 + 1, L_3)}} = \frac{\sqrt{(1 - m_3)^2 - (m_1 - m_2)^2}}{4}, \\
x_{-+}(L_1, L_2, L_3) & = \sqrt{\frac{N(L_1, L_2, L_3)}{N(L_1 - 1, L_2 + 1, L_3)}} = \frac{\sqrt{(1 - m_3)^2 - (m_1 - m_2)^2}}{4},
\end{align*}
\]
Let us denote the number of considered mutation schemes as $l_1, l_2, l_3, l_4, l_5, l_6, l_7, l_8, l_9,
l_{10}, l_{11}$, and $l_{12}$. We see that we can group together members with equal probabilities, and,
therefore, we consider only 6 types of spin flips with $n_1 = l_1 + l_4, n_2 = l_2 + l_3, n_3 = l_5 + l_8,$
$n_4 = l_6 + l_7, n_5 = l_9 + l_{10}, n_6 = l_{11} + l_{12}$ and $n_1 + n_2 + n_3 + n_4 + n_5 + n_6 = n$. Taking into
account the other combinatorial factors, we get for S.60

\[
\frac{[\sqrt{(1 + m_3)^2 - (m_1 + m_2)^2}]^{n_1} [\sqrt{(1 - m_2)^2 - (m_1 - m_3)^2}]^{n_2}}{n_1! n_2!} \times \\
\frac{[\sqrt{(1 + m_1)^2 - (m_2 + m_3)^2}]^{n_3} [\sqrt{(1 - m_1)^2 - (m_2 - m_3)^2}]^{n_4}}{n_3! n_4!} \times \\
\frac{[\sqrt{(1 + m_2)^2 - (m_1 + m_2)^2}]^{n_5} [\sqrt{(1 - m_3)^2 - (m_1 - m_2)^2}]^{n_6}}{n_5! n_6!} N^n .
\]

(S.61)

In the Jukes-Cantor mutation scheme (6) one has

\[
Q_{ij} = e^{-\gamma} \left( \frac{\gamma}{3N} \right)^n ,
\]

(S.62)

where $e^{-\gamma}$ is, as before, the fidelity of replication (no error probability) for the whole genome,
and $n$ is the Hamming distance between configurations $S_i$ and $S_j$ (7). Multiplying S.61 via
$Q_{ij}$ and taking the sum over $n_1, n_2, n_3, n_4, n_5, n_6$, we derive the expression for the mean
fitness ($\ln Z/\beta$) for the four-value spin case

\[
\frac{\ln Z}{\beta} = f_0(m_1, m_2, m_3) e^{-\gamma [1 - K_1 - K_2 - K_3]} - d_0(m_1, m_2, m_3),
\]

(S.63)

where

\[
K_1 = \frac{[\sqrt{(1 + m_3)^2 - (m_1 + m_2)^2} + \sqrt{(1 - m_3)^2 - (m_1 - m_2)^2}]}{6}, \\
K_2 = \frac{[\sqrt{(1 + m_2)^2 - (m_3 + m_1)^2} + \sqrt{(1 - m_2)^2 - (m_3 - m_1)^2}]}{6}, \\
K_3 = \frac{[\sqrt{(1 + m_1)^2 - (m_3 + m_2)^2} + \sqrt{(1 - m_1)^2 - (m_3 - m_2)^2}]}{6},
\]

(S.64)

and one should consider the maximum of Eq. S.63 over $m_1, m_2, m_3$. When $m_3 = 1$, the
last formula becomes similar to the Eq. 5 in the main text, $m_1 = m_2 \to k, \gamma/3 \to \gamma$ (only
the fidelity factor is different). Comparing mean fitness expression for two value spin case
(Eq. S.10), with the four value one (Eq. S.63), we see that all the qualitative conclusions
of the main text (modified error threshold formula in case of degradation; the special role
of the fitness landscape, where fitness decreases as a square root of Hamming distance; the modified selective value for the case of neutrality) are correct for the four-values spin model of biological evolution.