

Looking for the optimal rate of recombination for evolutionary dynamics

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We consider many-site mutation-recombination models of evolution with selection. We are looking for situations where the recombination increases the mean fitness of the population, and there is an optimal recombination rate. We found two fitness landscapes supporting such nonmonotonic behavior of the mean fitness versus the recombination rate. The first case is related to the evolution near the error threshold on a neutral-network-like fitness landscape, for moderate genome lengths and large population. The more realistic case is the second one, in which we consider the evolutionary dynamics of a finite population on a rugged fitness landscape (the smooth fitness landscape plus some random contributions to the fitness). We also give the solution to the horizontal gene transfer model in the case of asymmetric mutations. To obtain nonmonotonic behavior for both mutation and recombination, we need a specially designed (ideal) fitness landscape.

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I. INTRODUCTION

Recombination is one of the key factors in evolution and is assumed to be one of the possible advantages of sex [1]. While the asexual evolution models by Crow-Kimura [2,3] and Eigen [4] can be mapped to systems of linear differential equations (using some nonlinear algebraic transformations [5]), the models of recombination are described only via strongly nonlinear differential equations, and they are much more complicated than the Crow-Kimura and Eigen models. A growing body of literature recognizes the importance of recombination [6–9]. Recombination can be modeled using discrete time models and few loci [6,10], as well as by looking continuous time models with symmetric or random fitness landscapes, on the basis of Crow-Kimura or Eigen models [11–16]. The latter class of models assumes a simpler mathematical formulation, while qualitatively both classes of models give similar results. This study is motivated by [17], where recombination is considered as an evolvable trait. This evolutionary mechanism leads to different system properties in evolutionary dynamics. First, it increases mean fitness, providing an advantage in the case of negative epistasis; i.e., the Malthusian fitness function $r = f(m)$, is convex near $m = 1$, where $m = 1 - 2l/L$, l is the total number of mutations from the wild sequence, and L is the genome length [10]. While in [10] this result was derived for the discrete time few allele diploid model, the phenomenon is rather general and occurs in all the considered infinite population evolution models with recombination. Second, the finite size of the population can benefit due to recombination [18]. For a single peak fitness landscape, the recombination decreases the mean fitness, as has been found numerically in [19] for the version of the

Eigen model and analytically in [14] for the Crow-Kimura model. Moreover, the strong common effect of recombination and neutrality was first found numerically in [15] for the Crow-Kimura model and analytically in [16] for the Eigen model. Then a question arises (see [6], which attempts to model the phenomenon using an infinite allele Wright-Fisher model with recombination): Is there a limitation to the recombination rate, and when does it give an advantage?

The answer to this question is the goal of our work here. In the current paper, we are looking at situations with nonoptimal behavior of the mean fitness as a function of the recombination rate. Here we will work with the Crow-Kimura model of infinite population, and also with the finite population model (birth and death model for the offspring), as the simplest finite population model with recombination and long genome length. For the relation between different evolution models (Crow-Kimura, discrete time Eigen model, Wright-Fisher model) we recommend to readers the work [20]. We will consider both horizontal gene transfer (HGT) [12], where two replicators exchange by a gene, and recombination, where two replicators exchange by a whole piece of genome, between two randomly chosen loci.

To describe the evolutionary dynamics, several popular fitness landscapes are used: single peak fitness, symmetric fitness landscape, fitness landscape with neutrality, and random fitness landscape. We will consider recombination on most of these landscapes.

We give the definition of our model (Crow-Kimura model with recombination) in the Appendix. In Sec. II, we investigate the evolution model with neutrality (the substantial part of mutations from the peak sequence are neutral). In Sec. III, we derive the analytical results for the recombination with different forward and backward mutation rates, which is typical in evolution. In Sec. IV, we investigate the effect of recombination on a rugged fitness landscape.

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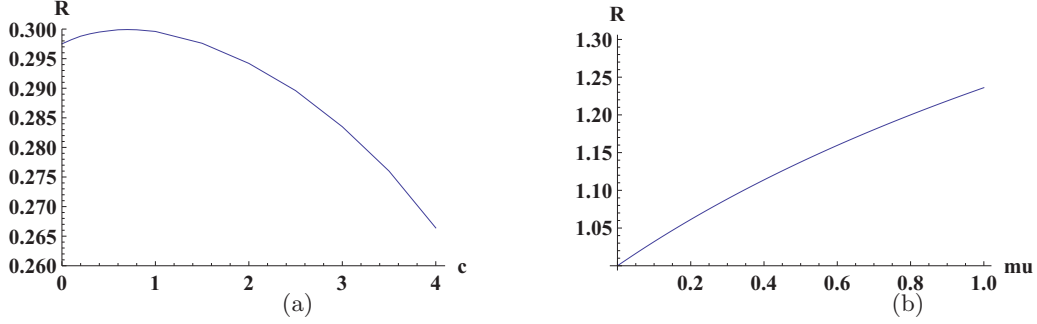


FIG. 1. The infinite population models of evolution. (a) The evolution model with $L = 100$, $\mu = 1.2$, $\mu = 1$, and $\nu = 0.8$ neutrality. The mean fitness is plotted versus the recombination rate c . (b) The evolution model with asymmetric mutations, without the recombination and fitness function $f(m) = 2m + 2$. The mean fitness R is plotted versus μ , the ratio of the backward and forward (from the wild sequence) mutation rates. We see that even when $\mu \rightarrow 0$ the mean fitness is positive, instead of becoming negative. For a finite population, the mean fitness should go to -2 at $\mu = 0$.

II. THE EFFECT OF RECOMBINATION IN THE CASE OF PARTIALLY NEUTRAL FITNESS LANDSCAPE AND FINITE GENOME LENGTH

A. The horizontal gene transfer model and main known results

We consider the Crow-Kimura model version of HGT. One has the following system for P_l , total probabilities of sequences in the l th Hamming class (the group of all the sequences with l total number of mutations) for the model with two types of alleles in any loci [12,14]:

$$\begin{aligned} \frac{dP_l}{dt} = & P_l r_l + \frac{\mu}{L} [(L-l+1)P_{l-1} + (l+1)P_{l+1}] \\ & - P_l \left(\mu + \sum_k r_k P_k \right) \\ & - c P_l + c \left[\left(1 - \frac{\bar{l}}{L}\right) \left(1 - \frac{l}{L}\right) + \frac{\bar{l} l}{L L} \right] P_l \\ & + c \left[\left(1 - \frac{\bar{l}}{L}\right) \frac{l+1}{L} P_{l+1} + \frac{\bar{l}}{L} \left(1 - \frac{l-1}{L}\right) P_{l-1} \right], \end{aligned} \quad (1)$$

where $\bar{l} = \sum_{l=0}^L l P_l$. The first two lines of Eq. (1) are from the Crow-Kimura model, and r_k is the Malthusian fitness of the k th Hamming class. The coefficients l and $(L-l)$ arise due to combinatorics; see [21]. We chose the mutation rate 1. The term $-P_l \sum_k r_k P_k$ supports a constant population size. The further lines in Eq. (1) describe the recombination process. During the period of time dt , we replace any allele in the genome of the given sequence with the probability cdt by the allele at the same position of other sequences (choosing randomly the second sequence from the population; see [12]). Therefore, there is a term $-cP_l$ in the third line of Eq. (1). The remaining terms in the third line correspond to the replacement of an allele with an allele of the same type. The last term corresponds to the replacement of an allele with an allele of another type.

For the mean fitness in the case of single peak fitness ($r_0 = S$ and $r_l = 0$, $l \geq 1$), we obtained in [14]

$$R = (S - \mu) + \frac{\mu}{LS} \left(\mu - \frac{c\mu^2}{S - \mu} \right). \quad (2)$$

Near the error threshold, $\mu \rightarrow S$, the influence of recombination on mean fitness becomes stronger. The single peak fitness landscape is not a realistic one; however, it is useful for analysis, because the evolution model in this case is similar to the one on the random fitness landscape [22,23].

Consider the evolution model with the following fitness landscape: the peak sequence and its νL neighbors have high Malthusian fitness values S , while other sequences have zero Malthusian fitness values. To describe such a case, we need more advanced techniques (recombination on two-dimensional fitness landscape [14]). The recombination can significantly increase the mean fitness in the case of strong neutrality around some wild type (most one-point mutations are neutral) [16]. The estimate of the increase is

$$\Delta R = \mu \frac{\sqrt{\nu(1 + \frac{cl}{\mu})}}{\sqrt{L}}, \quad (3)$$

where ν is the fraction of the neutral mutations from the wild genotype, and l is the length of a piece of the genome, exchanged during the recombination.

Combining both formulas (1) and (2), we obtain for the HGT that there are positive terms $O(\sqrt{\nu}/\sqrt{L})$ and negative terms $O(1/L)$. Therefore, there is chance for nonmonotonic behavior. In the next subsection we investigate the phenomenon quantitatively.

B. Our results for recombination on partially neutral landscape with the $O(1/L)$ terms

The solution for the mean fitness with accuracy $O(1/L)$ is given in the Appendix for the case of complete neutrality, $\nu = 1$. For $\nu < 1$, the expressions are too cumbersome, which is why we are just doing the numerics.

We have found a situation where the increase of mean fitness due to recombination is a nonmonotonic function of recombination rate. For the competition of negative [Eq. (2)] and positive terms [Eq. (3)], it is important that the system be near the error threshold, where the $O(1/\sqrt{L})$ term is suppressed, and we can observe an optimal mutation rate; see Fig. 1(a). The effect disappears if the system is far from the error threshold or the genome length is too large.

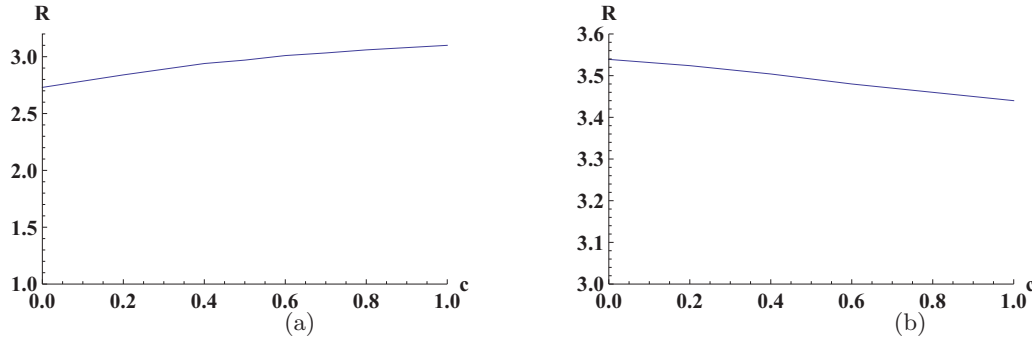


FIG. 2. The finite population evolution with asymmetric mutations. (a) The evolution model with recombination at $L = 50$, $k = 2$, $f(m) = km + 2$, $\mu = 0.5$ for the finite population size N . The recombination increases the mean fitness, as the mutations are directed far from the wild sequence. (b) The evolution model with recombination at $L = 50$, $k = -2$, $f(m) = km$, $\mu = 0.5$ for the finite population size N . The recombination acts against the mean fitness, as the mutations are directed to the wild sequence.

III. MEAN FITNESS OF RECOMBINATION AT DIFFERENT BACKWARD AND FORWARD MUTATION RATES

We consider the evolutionary dynamics when forward and back mutation rates are different. Nonsymmetric mutation rates are typical for evolutionary biology [24]. Here we give the solution of recombination models for such a case, calculating the mean fitness, searching again for nonmonotonic behavior of mean fitness.

A. The general fitness case

Consider the following model. The genome has a length L and two alleles at every locus, the mutation rate from the wild sequence is 1, the back mutation rate is μ , and the recombination rate is c .

In the Appendix, we derive the following equation for the mean fitness:

$$R = \max \left[f(m) + \sqrt{1 - m^2} \sqrt{\left(1 + c \frac{1 - s}{2}\right) \left(\mu + c \frac{1 + s}{2}\right)} - \frac{c}{2} (1 - ms) - \frac{1 + m}{2} - \mu \frac{1 - m}{2} \right] \Big|_{-1 \leq m \leq 1},$$

$$R = f(s). \quad (4)$$

In order to define the mean fitness, we should solve the system of equations for m and s , where the Hamming class with k mutations has a fitness r_k .

The point here is that, for asymmetric mutations, our formula is counterintuitive; see Fig. 1(b). While the finite population with directed mutations should get a fitness $R = -2$, the mean fitness $R = 1$ for the infinite population case. While, at infinite population, the recombination does not change the mean fitness, in the case of finite population it should move the mean fitness to the infinite population result; see Fig. 2(a). In Fig. 2(b), we see the opposite tendency: the recombination acts against the mutations, decreasing the mean fitness.

B. The mean fitness of the recombination model with the additive fitness landscape and random distribution of the fitness values

Consider the model where the fitness is additive for every locus [6]. Then, using Eq. (4) for the choice $f(m) = \gamma x$ for the fitness function, we obtain the following expression for the mean fitness:

$$R = \sqrt{(\gamma + (\mu - 1)/2)^2 + \mu} - \frac{1 + \mu}{2}. \quad (5)$$

The mean fitness is independent of recombination, as in the case of symmetric mutations.

Consider now the case when the fitness of genotype is a sum of contributions from loci, so the total fitness of genotype equals $\frac{1}{L} \sum_l P \gamma_l s_l$, where s_l is the type of allele ± 1 , and γ_l has a distribution $\rho(\gamma_l)$. Then we obtain for the mean fitness the following expression:

$$R = \int d\gamma \rho(\gamma) \left[\sqrt{[\gamma + (\mu - 1)/2]^2 + \mu} - \frac{1 + \mu}{2} \right]. \quad (6)$$

The mean fitness of the finite population model on the smooth fitness landscape reveals a monotonic behavior for the steady state case; see Figs. 2(a) and 2(b) (for a finite period of time it reveals some nonmonotonic behavior in the case of a linear fitness function). So the asymmetry of mutation rate is not enough to create a nonmonotonic behavior.

C. The mean fitness in the recombination model on the rugged fitness landscape

It is important to make a proper choice of the finite population algorithm in the case of recombination. For our simulations, we used a birth and death model with mutation and recombination, combining the ideas of both the Moran model and the Gillespie algorithm, but with the dilution process put strictly at the end of the iteration loop. We calculate the mean fitness of population R , then at one iteration loop there is a birth of new offspring with probability $R/(R + \mu + c)$, mutation with probability $\mu/(R + \mu + c)$, and recombination with probability $c/(R + \mu + c)$. If there is a birth event, it is distributed among the sequences proportional to their fitnesses. At the last stage, we randomly kill one of the chosen replicators.

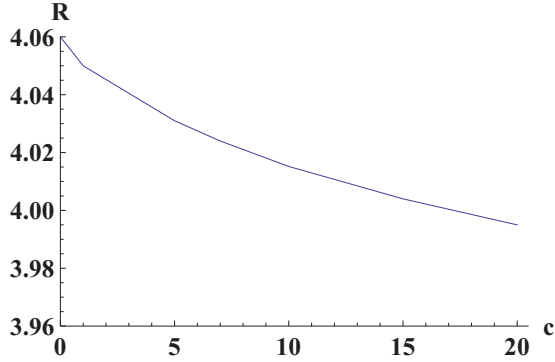


FIG. 3. The mean fitness R versus the recombination rate c , for the evolution model with recombination at $L = 50$ and population size $N = 1000$. We have five blocks with the length 10 for each. The total fitness of the genome is the sum of the fitnesses of the blocks, and the fitness of the block is a random number with normal distribution, with a variance $0.4^2/2$.

As the evolution model on the random fitness landscapes resembles the properties of the model on the single peak fitness landscape [22,23], we assume that the recombination reduces the mean fitness in such a model. Our numerics supports such a hypothesis; see Fig. 3. On the other hand, the finite size corrections of recombination models on the smooth fitness landscape should not be negative [25]. That is why we have decided to look at the mixture of random fitness landscape with smooth landscape.

Combining these two landscapes (a version of rugged fitness landscape), we obtain nonmonotonic behavior (see Fig. 4) when the strengths of both contributions to the fitness have the same order, so our intuition again is confirmed. The rugged fitness landscape has been assumed to be relevant to the life sciences, [26–28]; it is puzzling that it gives a possibility for the optimal choice of the recombination rate.

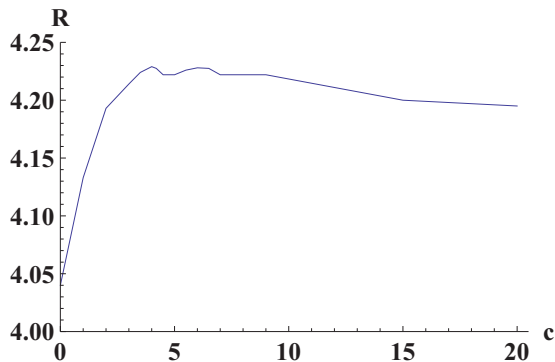


FIG. 4. The mean fitness R versus the recombination rate c , for the evolution model with recombination $L = 50$. The fitness is a sum of $f(m) = 2(m + 1)$ and five random numbers chosen for each of five blocks with the genome length 10. Each random number should be extracted from a normal distribution, with a variance $0.4^2/2$, for the finite population size $N = 1000$.

IV. CONCLUSION

We have investigated the role of recombination when there is an optimal choice of recombination rate. From the biological perspective, it is quite a reasonable feature of evolutionary dynamics. Nevertheless, it is quite a nontrivial problem to find models with such a property. The simplest case we have found is the case of evolution with finite genome length and partial neutrality. We considered also the finite population [29] version of HGT with simple symmetric landscapes. We again found only monotonic behavior of $R(c)$. While the recombination reduces the mean fitness for a pure random fitness landscape with finite population (see Fig. 3), we found a nonmonotonic behavior in the case of rugged fitness landscape; see Fig. 4. Thus, to have an optimal recombination rate (a reasonable restriction to the evolutionary dynamics), the living matter needs a specially designed fitness landscape: a rugged fitness landscape, which already has been assumed to be highly typical in evolution [26–28]. There are different versions of the rugged fitness landscape: the most popular is the NK fitness landscape where the Hamiltonian of N spins is described via k -spin interaction with randomly chosen couplings (quenched disorder) [26]. We used the simpler one, just adding to the symmetric fitness landscape a random noise. Such models can be solved in statistical physics [30,31]. In [27], the authors considered the evolutionary dynamics with an evolvable mutation rate and concluded that an optimization is impossible in the case of some phenomenological versions of a rugged fitness landscape. In view of our results, the optimal choice of both recombination and mutation rates assumes a special design of the fitness landscape (an “ideal” landscape). We have applied different algorithms and realized that birth-death models are the best choice for recombination tasks with finite population, selection, and mutations.

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APPENDIX: THE HORIZONTAL GENE TRANSFER MODEL

Our goal is to calculate the mean fitness with accuracy $O(1/L)$. Before, it was calculated with accuracy $O(1/\sqrt{L})$ in [16].

1. The neutral model

We consider the model with the fitness landscape $r_0 = r_1 = J$; other fitnesses are zero. We have

$$\begin{aligned} & P_l [J(P_0 + P_1) + 1 - r_l] \\ &= -c P_l \left[\left(1 - \frac{l}{L}\right) \frac{l}{L} + \left(1 - \frac{l}{L}\right) \frac{l}{L} \right] + \frac{L-l+1}{L} P_{l-1} \\ & \quad \times \left[1 + c \frac{l}{L} \right] + \frac{l+1}{L} P_{l+1} \left[1 + c \left(1 - \frac{l}{L}\right) \right]. \end{aligned} \quad (\text{A1})$$

If we ignore the recombination, then we get that

$$P_l = \frac{J-1}{J} + O\left(\frac{1}{\sqrt{L}}\right), \quad P_l = \frac{P_1}{J^{l-1}}, \quad l > 1. \quad (\text{A2})$$

Denote $q = \frac{1}{J}$. We get

$$cP_l = P_l q^{l-1} = (1-q)q^{l-1}, \quad \hat{l} = \sum_l P_l l = (1-q) \frac{d}{dq} \left(\sum_l q^l \right) = \frac{1}{1-q} = \frac{J}{J-1}. \quad (\text{A3})$$

The recombination brings us to the smaller correction of Eq. (A2).

Consider the following expansion for P_0, P_1 :

$$P_1 = \frac{J-1}{J} + \frac{p_1}{\sqrt{L}} + \frac{y}{L}, \quad P_0 = \frac{p_0}{\sqrt{L}} + \frac{x}{L}. \quad (\text{A4})$$

Let us first derive the terms p_0, p_1 . With an accuracy of $O(1/L)$, we have from Eq. (A1)

$$P_0(R-J+1) = \frac{P_1}{L}, \quad P_1(R-J+1) = P_0, \quad R = J(P_0 + P_1). \quad (\text{A5})$$

We first find

$$(R-J+1) = \Delta, \quad \Delta = \sqrt{\frac{1+c}{L}}, \quad P_0 = \frac{J-1}{J} \Delta = \frac{p_0}{\sqrt{L}}, \quad p_0 = \frac{J-1}{J} \sqrt{1+c}. \quad (\text{A6})$$

For P_1 , we deduce

$$P_1 = (J-1) \frac{1 + \Delta/(J-1)}{1 + \Delta} = \frac{J-1}{J} \left(1 + \Delta \frac{2-J}{J-1} \right) = \frac{J-1}{J} + \frac{p_1}{\sqrt{L}}, \quad p_1 = \frac{2-J}{J} \sqrt{1+c}. \quad (\text{A7})$$

Consider now the higher order correction terms.

We derive the following system of two equations from (A2):

$$\begin{aligned} P_0[J(P_0 + P_1) + 1 - J] &= -cP_0 \frac{\bar{l}}{L} + \frac{P_1}{L} \left[1 + c \left(1 - \frac{\bar{l}}{L} \right) \right], \\ P_1[J(P_0 + P_1) + 1 - J] &= -cP_1 \left[\left(1 - \frac{\bar{l}}{L} \right) \frac{1}{L} + \left(1 - \frac{1}{L} \right) \frac{\bar{l}}{L} \right] \\ &\quad + P_0 \left(1 + c \frac{\bar{l}}{L} \right) + \frac{2P_2}{L} \left[1 + c \left(1 - \frac{\bar{l}}{L} \right) \right]. \end{aligned} \quad (\text{A8})$$

We consider the $O(1/L^{3/2})$ terms in the first equation and $O(1/L)$ term in the second one:

$$P_0[J(P_0 + P_1) + 1 - J] = -cP_0 \frac{\bar{l}}{L} + \frac{P_1}{L} (1+c), \quad P_1[J(P_0 + P_1) + 1 - J] = -cP_1 \left[\frac{1+\bar{l}}{L} \right] + P_0 + \frac{2P_2}{L} (1+c), \quad (\text{A9})$$

$$Jx(p_0 + p_1) + Jp_0(x+y) = -c\bar{l}p_0 + p_1(1+c), \quad (J-1)(x+y) + p_1J(p_0 + p_1) = -c \frac{J-1}{J} (1+\bar{l}) + x + 2 \frac{J-1}{J^2} (1+c). \quad (\text{A10})$$

Solving the system for x, y , we calculate the mean fitness as

$$R = (J-1) + J \left(\frac{p_0 + p_1}{\sqrt{L}} y + \frac{(x+y)}{L} \right). \quad (\text{A11})$$

Our numerics confirms well Eq. (A11). For $J = 3$, $c = 1$, and $L = 1000$ the numerics gave 2.04345, while our analytics give 2.04344.

2. The derivation of the mean fitness of HGT model with asymmetric mutations

We consider the Crow-Kiumra model version of HGT with asymmetric mutations: we have rate 1 for the forward mutation and rate μ for the backward mutations. One has the following system for P_l (total probabilities of sequences in the l th Hamming class):

$$\begin{aligned} \frac{dP_l}{dt} &= P_l r_l + [(L-l+1)P_{l-1} + (l+1)P_{l+1}\mu] - P_l L \left(1 + \frac{1}{L} \sum_k r_k P_k \right) \\ &\quad - [l + \mu(L-l)]P_l - cL \left[\left(1 - \frac{\bar{l}}{L} \right) \frac{l}{L} + \frac{\bar{l}}{L} \left(1 - \frac{l}{L} \right) \right] P_l \\ &\quad + cL \left[\left(1 - \frac{\bar{l}}{L} \right) \frac{l+1}{L} P_{l+1}\mu + \frac{\bar{l}}{L} \left(1 - \frac{l-1}{L} \right) P_{l-1} \right], \end{aligned} \quad (\text{A12})$$

From [31]

$$P_t = \exp[u(m,t)L] \quad (\text{A13})$$

and $m = 1 - 2l/L$, and we obtain the Hamilton-Jacobi equation

$$\begin{aligned} \frac{\partial u}{\partial t} = -H(m,p), \quad H = f(m) - \frac{1+m}{2} - \mu \frac{1-m}{2} + \frac{1+m}{2} \left(1 + c \frac{1-s}{2}\right) e^{2u'} \\ + \frac{1-m}{2} \left(1 + c \frac{1+s}{2}\right) e^{-2u'} \mu - \frac{c}{2}(1-ms). \end{aligned} \quad (\text{A14})$$

Looking for the minimum of the $H(m,p)$ via p , we obtain $U(m) = \min[H(m,p)]_p$:

$$U(x) = f(m) + \frac{1+m}{2} \left(1 + c \frac{1-s}{2}\right) e^{2u'} + \frac{1-m}{2} \left(1 + c \frac{1+s}{2}\right) e^{-2u'} \mu - \frac{c}{2}(1-ms) - \frac{1+m}{2} - \mu \frac{1-m}{2}. \quad (\text{A15})$$

Then we find the mean fitness R by searching for the maximum of $U(m)$,

$$R = \max[U(m)]_m, \quad (\text{A16})$$

according to [31], and obtain Eq. (3).

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