PHYSICAL REVIEW E **99**, 022407 (2019)

Allele fixation probability in a Moran model with fluctuating fitness landscapes

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(Received 26 June 2018; revised manuscript received 1 November 2018; published 11 February 2019)

Evolution on changing fitness landscapes (seascapes) is an important problem in evolutionary biology. We consider the Moran model of finite population evolution with selection in a randomly changing, dynamic environment. In the model, each individual has one of the two alleles, wild type or mutant. We calculate the fixation probability by making a proper ansatz for the logarithm of fixation probabilities. This method has been used previously to solve the analogous problem for the Wright-Fisher model. The fixation probability is related to the solution of a third-order algebraic equation (for the logarithm of fixation probability). We consider the strong interference of landscape fluctuations, sampling, and selection when the fixation process cannot be described by the mean fitness. Such an effect appears if the mutant allele has a higher fitness in one landscape and a lower fitness in another, compared with the wild type, and the product of effective population size and fitness is large. We provide a generalization of the Kimura formula for the fixation probability that applies to these cases. When the mutant allele has a fitness (dis-)advantage in both landscapes, the fixation probability is described by the mean fitness.

DOI: 10.1103/PhysRevE.99.022407

I. INTRODUCTION

A century has passed since Fisher published his seminal paper [1] on population genetics. The theoretical framework developed by Fisher, Haldane, and Wright and, in particular, Wright's concept of the fitness landscape remain the foundation of numerous theoretical and experimental studies on genetic drift and allele fixation [2]. However, most of this research addresses evolution in a stable environment: The fitness of an individual is associated only with a combination of alleles in different loci.

Evolution in fluctuating environments is one of the central problems of modern evolution theory [3–12]. Classical population genetics approaches are based on different formalizations of selection and mutation processes. In most cases, external influences are not addressed, and the set of parameters depends only on the internal state and does not change in time. However, experimental studies provide evidence that seasonal variations [3] or nutrients fluctuations [4,5] can continuously affect the fitness landscape. The theoretical aspects of this problem have attracted considerable interest [7–11,13–15]. Of special note is the existence of mesoscopic (fitness) flux [10] that has been assumed to be related to adaptation. One of the crucial evolutionary characteristics to calculate is the allele fixation probability. Kimura's classic results on fixation probability [16] in the Wright-Fisher [17–19] and Moran models [20,21] comprise one of the cornerstones of population genetics. Previous research [11] has already addressed fixation probabilities in dynamic environments; here, however, we re-examine the problem, in an attempt to obtain more general and accurate expressions.

Under the standard stochastic approach, the population has a constant finite size N, and its evolution is characterized by a fixed selective value s. The fitness of an individual depends on the allele type in one specific locus: The wild-type allele a corresponds to the constant fitness value 1, and the mutant allele A to the Wrightian fitness e^{-s}. In a population evolving under the Wright-Fisher model, the generations do not overlap. In this case, a new generation is formed by uniform sampling with replacement. Under the Moran model, evolution model implies overlapping generations with a random birth-death process at discrete time intervals. Both models incorporate genetic drift but involve different iteration processes. In the Moran model, the count of each allele changes by one per generation, whereas the Wright-Fisher model allows substantial increases in allele frequency. For static fitness landscapes, there is no qualitative difference between the Moran and Wright-Fisher models, apart from the simple rescaling of the selective parameter s in the allele fixation probability. However, the Moran model allows explicit expressions for many evolutionary traits, e.g., in this case, Kimura's result for the fixation probability in static fitness landscape is exact, whereas, in the Wright-Fisher model, it is characterized by the relative accuracy $O(1/N) + O(s^2N)$ [22].

In Ref. [11], the evolutionary process was considered for the case of strong selection ($N|s| \gg 1$) and large differences between selection coefficients ($|s_2 - s_1|N \gg 1$) on different landscapes. To deduce the fixation probability, the diffusion equation (first approximation) was used, with subsequent truncation of the random fluctuations of the periods with the

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given fitness by two first moments (second approximation), following the earlier studies [13–15]. This approach, actually, is the annealing approximation to the quenched disorder problem in statistical physics.

Although this approach with double approximations is useful in principle, it lacks accuracy control. In particular, the diffusion equation has some limitations: It is correct for $Ns^2 \ll 1$ [22] but it is complicated to calculate the $O(1/N)$ corrections. To calculate the probability of allele fixation for the given initial landscape, $O(1/N)$ corrections to the bulk solution are required, which is impossible to achieve with the diffusion equation approach. To overcome this obstacle, it is possible to use a method related to the Hamilton-Jacobi equations [23], considering an equation for the logarithm of the fixation probability and $O(1/N)$ corrections to the bulk solution.

In this paper, we consider a generalization of the biallelic Moran model for a fluctuating environment, starting with two different fitness landscapes with a transition between them. The model has three regimes: the slow transitions, where we can simply average Kimura's formula for the fixation probability via the value of the selection coefficient; the fast transitions when we can use an effective fitness; and the intermediate case with strong interference of evolutionary dynamics and transitions between landscapes. For the latter process, the perturbative methods could fail, and we will apply the rigorous methods that have proven their efficacy for similar evolution models. For the solution of the quenched disorder problem of evolutionary dynamics in the stochastic landscape, we use an exact method as opposed to the annealing approximation [11,13–15]. We applied such a method recently to solve exactly the problem of hidden Markov models [24].

II. THE RESULTS

A. The model

The state of the finite population is represented by the distribution of wild-type a and mutant A alleles. If we define the probability of having i copies of the first allele in the population at the time moment n as $p_i(n)$ and the transition probabilities between states as P_{ij}, then the evolutionary dynamics is described by the following iteration rule:

$$p_i(n+1) = \sum_j P_{ij} p_j(n). \tag{1}$$

Consider the initial condition, where the population contains i copies of A. We seek the probability of this allele fixation, denoted by y_i. For the values y_i, we have the following equation with a transposed transition matrix:

$$y_i = \sum_j P_{ji} y_j, \tag{2}$$

with the following boundary conditions:

$$y_0 = 0, \quad y_N = 1. \tag{3}$$

Equation (2) has explicit meaning: The fixation of A with the initial state i will occur eventually if the system first gets to the jth state with probability P_{ji} and then reaches fixation.

The Moran model can be represented as the following Markov chain: p_i are the probabilities of different states in Eq. (1), and P_{ij} are the transition probabilities [20]:

$$P_{i+1,i} = \frac{i(N-i)}{N^2} = \mu_i, \quad P_{i-1,i} = \frac{i(N-i)r}{N^2} = \lambda_i, \tag{4}$$

and $P_{ii} = 1 - P_{i-1,i} - P_{i+1,i}$. Here N is the population size, $r = e^{-s}$ is the fitness, and s is the selection coefficient. For this case, the fixation probability can be obtained via the following exact solution [20]:

$$y_i = \frac{1 - e^{-si}}{1 - e^{-sN}}. \tag{5}$$

In the present study, we seek to deduce the fixation probability for the general case of the Moran model with the accuracy $O(1/N)$, using the mathematical tools that have been elaborated on for the gene autoregulation model [25].

As described above, we analyze the behavior of a finite-size population evolving under the Moran model. In this system, the individuals are haploid, and one biallelic locus is considered. We aim to generalize the original Moran model for a fluctuating environment. To formalize the fluctuations that affect the selection values of the evolving system, new transition parameters for the environmental state are introduced. Two options for the probabilistic description of environmental changes can be considered, with the underlying process being either Markovian or non-Markovian. Here we examine the first case, where the current state of the system determines the probability of its state at the next time interval. If we apply the Markovian rule to define the transition between two environmental states with rates d_1 and d_2, respectively, then the probability of k successive choices of the first environment is $\sim \exp(-kd_1)$ and, for the second environment, $\sim \exp(-kd_2)$.

B. The equation of the fixation probability for the Markov model

To calculate the fixation probability for the fluctuating fitness case, we first analyze Eq. (2), which is represented by a linear system of equations. The system (2) has a trivial solution $y_i = 1$; moreover, it has been shown [22] that $y_i = e^{-si}$ is another solution. Thus, Eq. (2) is a degenerate system of linear equations. Under the constraint Eq. (3), the linear combination of these two solutions leads to the well-known Kimura's formula Eq. (5). From our perspective, this is the key idea that can be applied to the problem in the dynamic environment. In this case, having four solutions and four constraints, we will construct a linear combination of the solutions that satisfies the boundary conditions.

Let us consider a dynamic environment with a finite number of states and denote two distinct states. The state of the whole system is defined now via a couple of parameters, the environmental state α and the copy number of the A allele in the population. The number of allele A copies changes from one generation to another with the probability P_{ij}^{α} for the αth environment. At the time moment n, if we have the environment α and the probability $p_j^{\alpha}(n)$ of having j alleles of the first type, then the behavior of the system is described by the following equation:

$$p_i^\beta(n+1) = \sum_{j,\beta} P_{ij}^\alpha p_j^\alpha(n)\pi_{\beta,\alpha}, \tag{6}$$

where $\alpha, \beta \in \{1, 2\}$, $\pi_{\beta,\alpha}$ are the transition probabilities of the environment types. For the case with two landscapes, we have a forward transition probability d_1 (from the first state to the second), and a backward transition probability d_2, hence: $\pi_{2,1} = d_1, \pi_{1,1} = 1 - d_1, \pi_{1,2} = d_2, \pi_{2,2} = 1 - d_2$.

Using a similar notation as in the Moran model setting, we denote as y_i^α the fixation probability of the first allele A with the initial condition of having i copies of this allele in the αth environment. We have the following equation for the fixation probabilities, putting the transposed transition matrix in the right-hand side:

$$y_i^\beta = \sum_{j,\alpha} P_{ji}^\alpha y_j^\alpha \pi_{\alpha,\beta}, \tag{7}$$

where the boundary conditions have the following form:

$$y_0^\beta = 0, \quad y_N^\beta = 1. \tag{8}$$

Thus, if the number of different environments is m, then we have $2m$ boundary conditions.

First, we seek smooth solutions of the system (7). The trivial solution is $y_i^\beta = 1$. To find nontrivial solutions, we assume that the expression $\ln[y_i^\beta]/N$ is smooth. As shown below, three nontrivial solutions, smooth inside the interval [0,1], exist. Two of these have singularities at the border and are omitted. Thus, we should consider a linear combination of the trivial and nonsingular nontrivial solutions as a solution to the Eqs. (7) and (8).

C. The exponential ansatz for fixation probability

At the limit of large N, we introduce a continuous variable $x = i/N$. Then consider the following ansatz:

$$y_i^\alpha = v_\alpha(x)e^{Nu(x)}, \tag{9}$$

assuming $1/N$ expansion for the logarithm of fixation probability. Putting this ansatz into Eq. (7), we obtain a differential equation for the function $u(x)$ and, solving the latter equation, we can calculate $u(x)$. An ansatz (9) has been introduced first in Ref. [26] for the solution of the master equation, two related chains of equations and later has been successfully applied in a series of studies [22,25]. We will find several solutions of Eq. (7) and identify their linear combination which satisfies the conditions of Eq. (8).

Substituting the expression (9) into Eq. (7) and omitting the small terms, we obtain:

$$\sum_\beta \pi_{\alpha,\beta} v_\beta[(e^p - 1)e^{-s_\beta} + (e^{-p} - 1)] - v_\alpha$$

$$\equiv \sum_\beta v_\beta A_{\alpha\beta} = 0, \tag{10}$$

where we denoted $p \equiv u'(x)$. Thus, we have a linear system of two equations ($\alpha = 1, 2$) and $A_{\alpha\beta}$ are the functions of the variable e^p.

It can be shown that the terms that are dropped in Eq. (10), while, deriving from Eq. (7), are small under the constraint $Ns \gg 1$. The bulk terms in Eq. (10) are of order $\sim ps$, where $p \sim s$, whereas the correction terms are $\sim p'/N \sim s/N$. Hence, Eq. (10) is valid within the $1/(Ns)$ accuracy.

Consider Eq. (10) as a system of linear equations for $v_1(x)$, $v_2(x)$ at any point x. Zero determinant condition takes the form:

$$A_{11}A_{22} - A_{12}A_{21} = 0, \tag{11}$$

where the expressions for $A_{\alpha\beta}, \alpha, \beta \in \{1, 2\}$, are defined in the Appendix. Equation (11) is a fourth-order equation with respect to e^p. As $p = 0$ is a solution, we can reduce (11) to the third-order equation. Assuming smoothness of $v_\alpha(x)$, $u(x)$ as functions of x, we obtain a unique solution for u'. Two other solutions have singularities near the borders 0 and 1. Knowing the expression for $u(x)$, we can also calculate the corresponding ratio $w = v_2/v_1$:

$$w(x) = -\frac{A_{11}}{A_{12}}. \tag{12}$$

D. The main formulas for fixation probability

Using Eqs. (11) and (12), and a relation $w(1) = 1$ from the Appendix, we obtain the following solution:

$$y_i^1 = [1 - v(x)e^{Nu(x)}]c, \quad y_i^2 = [1 - v(x)w(x)e^{Nu(x)}]c,$$

$$c = \frac{1}{1 - v(1)e^{Nu(1)}}, \tag{13}$$

where $u(x) = \int p(x)dx$ and $v(x)$ is calculated in the Appendix.

Examining the average fixation probability $y_i = \frac{d_1 y_i^2 + d_2 y_i^1}{d_1 + d_2}$, assuming $v' \ll Nu'(x)$, which is correct at least for $Ns \gg 1$, we can consider the following approximation:

$$y_i = \frac{1 - e^{Nu(x)}}{1 - e^{Nu(1)}}. \tag{14}$$

Equations (13) and (14) are the *central results* of this work.

E. The case of the scaling for the s_1, s_2, d_1, d_2

For the case of scaling by

$$d_1 \sim 1/N^2, \quad d_2 \sim 1/N^2, \quad s_1 \sim 1/N, \quad s_2 \sim 1/N, \tag{15}$$

we get look simpler formulas, the following equation for p instead of Eq. (11):

$$-(d_1 s_2 + d_2 s_1) + [-d_1 - d_2 + s_1 s_2 x(1 - x)]p$$

$$+ (s_1 + s_2)p^2 x(1 - x) + p^3 x(1 - x) = 0. \tag{16}$$

Analyzing Eq. (16), we obtain two different regimes of solutions:

$$\frac{|d_1 s_2 + d_2 s_1|}{d_1 + d_2} N \gg 1 \tag{17}$$

and

$$\frac{d_1 s_2 + d_2 s_1}{d_1 + d_2} N \ll 1. \tag{18}$$

We consider the case of Eq. (17).

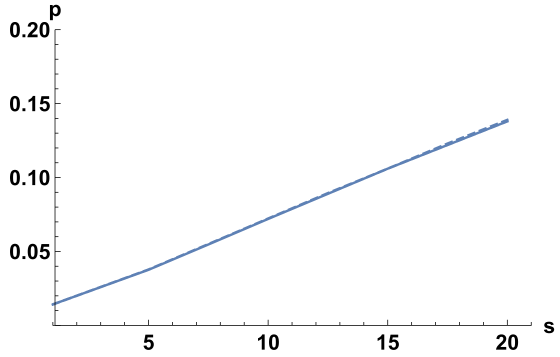

FIG. 1. The fixation probability p for a mutant with initial conditions defined in the first landscape versus the selection parameter s. The parameter values are $N = 100$, $s_1 = s/(2N)$, $s_2 = s/N$, $d_1 = d_2 = s^2/N^2$. The solid line corresponds to the numerical simulation, and the dotted line to the analytical solution. The analytical and numerical results coincide with the accuracy better than 1% with the result obtained as the average fixation probability over two landscapes or with the fixation probability for average fitness.

F. The fast transitions

For Eq. (17), our analytical methods give the fixation probability with the accuracy $O(1/N)$, see Figs. 1 and 2. Keeping only the first two terms in Eq. (16), we obtain the condition for the fast transition between environments,

$$\frac{s_1 s_2}{4d} \ll 1. \tag{19}$$

The inequality (19) is always valid when either $s_1 = 0$ or $s_2 = 0$. Expanding Eq. (10) in degrees of p and keeping the first degree of p and s_1, s_2, we obtain Eq. (5) with the substitution $s \to \bar{s}$:

$$\bar{s} = \frac{s_1 d_1 + s_2 d_2}{d_1 + d_2}. \tag{20}$$

The coefficients $\frac{d_2}{d_1+d_2}$ and $\frac{d_1}{d_1+d_2}$ are the probabilities of staying in environments α and β. Therefore, Eq. (16) gives the $e^{-\bar{s}i}$ solution with the average selective value $\bar{s}$. The linear combination of this solution and the trivial solution gives Kimura's formula with effective $\bar{s}$.

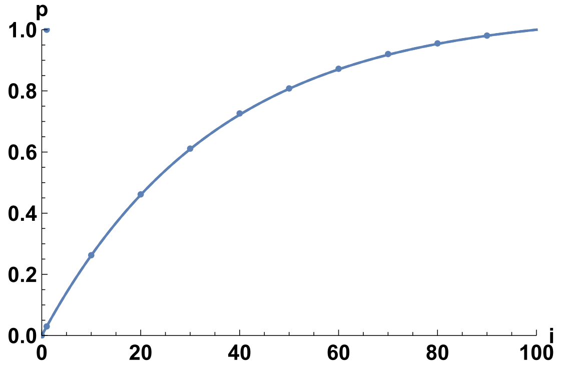

FIG. 2. The fixation probability versus the initial number i of mutants with evolution starting in the first environment. The parameter values are $N = 100$, $s_1 = 0.02$, $s_2 = 0.04$, $p_1 = 1 - 0.001$, $p_2 = p_1$. The solid line corresponds to the numerical result and the dotted line to the analytical result. The analytical solution coincides with the numerical result with a 0.2% accuracy.

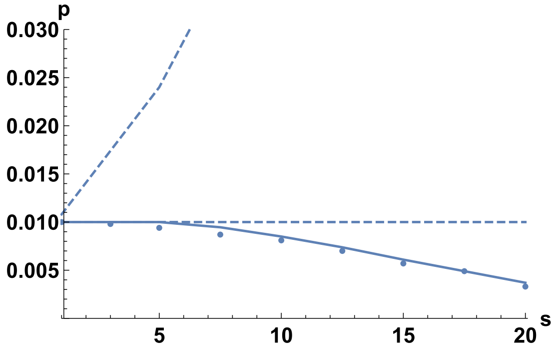

FIG. 3. The fixation probability p for the initial conditions in the first landscape case versus the selection parameter s. The parameter values are $N = 100$, $s_1 = -s/N$, $s_2 = s/N$, $d_1 = d_2 = s^2/N^2$. The solid line corresponds to the results of the numerical simulation. The upper dashed line corresponds to the averaged fixation probability over the two landscapes [slow transition approximation, Eq. (5) is averaged via the landscape probabilities], and the dots to the analytical solution. The lower dashed line is the fixation probability with averaged fitness for the fast transition rate approximation [given by Eq. (5) with a selection coefficient by Eq. (20)]. The analytical result has a relative accuracy better than 10% at $s = 20$, while the fast transition approximation gives an error ∼200%.

G. The case of strong interference of evolutionary dynamics and transitions

Consider now the case (17) with

$$s_1 s_2 < 0, \quad |s_1 + s_2| \ll |s_1|. \tag{21}$$

We consider the symmetric transition case with

$$d_1 = d_2 = d. \tag{22}$$

Following Eqs. (20) and (21) we ignore the p^0 and p^2 terms in Eq. (16) and derive a simple expression,

$$p = \sqrt{\frac{2d}{x(1-x)}}. \tag{23}$$

Our analytics is well supported by numerics. The critical value of $N|s_2 - s_1|$, when the effective fitness approach fails, grows with the order $\sqrt{N}$, see Figs. 3 and 4. The effective fitness-based estimate (horizontal dashed lines in Figs. 3 and 4) fails, whereas our analytical result (solid dots) is rather close to the numerical result (smooth line).

III. CONCLUSION

In the current study, we investigated the evolutionary process on a fluctuating fitness landscape which arguably is a more realistic representation of the evolutionary processes than a static landscape. Evolutionary dynamics on fluctuating landscapes is a fundamental problem in evolutionary biology. We considered the case of random transitions between two landscapes. For many evolutionary processes, it is of principal interest to calculate the fixation probability. We developed a method to calculate the fixation probability for the transitions

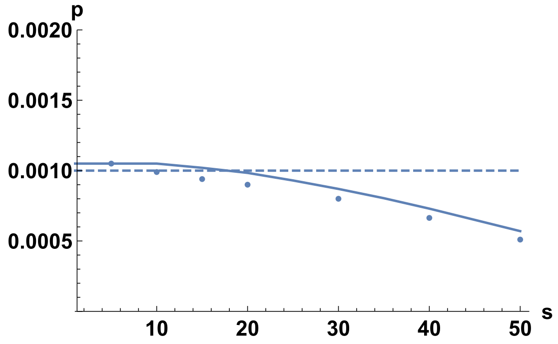

FIG. 4. The fixation probability p versus the parameter s for a mutant with evolution starting in the first landscape. The parameter values are $N = 1000, s_1 = -s/N, s_2 = s/N, d_1 = d_2 = s^2/N^2$. The solid line corresponds to the numerical result, and the dots correspond to the analytical solution. The dashed line corresponds to the averaged fixation probability over the two landscapes.

between any finite number of landscapes when these transitions are described by a Markov model, deriving an ordinary differential equations with several branches and choosing the proper solution without singularities. The diffusion equation approach [11] does not allow the calculation of the fixation probability with a high accuracy. Therefore, we applied an alternative approach [22] that provides for a consistent solution for large Ns as well as $O(1/N)$ correction terms. Such accuracy is essential to calculate the fixation probability for a given initial environment. Here the fixation probability was derived by solving a third-order algebraic equation. Our analytical results were confirmed by numerical calculations: Both stochastic simulations and algebraic derivations were obtained for the rapid transition between environments. To our knowledge, the proposed method is the first that works for intermediate values of parameters, with a substantial interference of landscape fluctuations and evolutionary factors, such as sampling fluctuations and selection. The diffusion method that was used in Ref. [11] is correct only under the constraint $Ns^2 \ll 1$. However, Desai and colleagues [11] have considered not only small but also large values $s^2N = 10^4$, which certainly are out of the validity interval $Ns^2 \ll 1$ of the diffusion approximation, as they also applied a series of further approximations. The "effective diffusion process," invented first in Ref. [13] and widely applied in Ref. [11], requires accuracy control. This is a version of annealed approximation to the quenched disorder problem in statistical physics. The approximation appears to be applicable to the cases considered by Kimura [13], but for the intermediate region (fluctuation of landscapes have the same periods the fixation process), the application of the method is questionable. Nevertheless, Desai and colleagues observed large deviations of the fixation probability from the value given by the averaged fitness (see Figs. 3 and 4) for large values of $N|s_1 - s_2|$ and different signs of s_1, s_2. Our formula (13) applies with a good accuracy but it is possible to derive more accurate expressions using the higher-order corrections in the $1/N$ expansion. Equation (14) gives the precise fixation probability for all cases including both mutants that are beneficial in both environments and those that are deleterious in one environment but beneficial in the other one. Thus, we obtained a single formula for all combinations of parameter values, as opposed to six different formulas in Ref. [11] that were derived from the diffusion equation via further approximations. Qualitatively, the dependence of x in Eq. (13) is defined by the "potential" $u(x)$ via the term $\sim\exp[Nu(x)]$, and the effective potential $u(x)$ in Eq. (13) is defined similarly to the potentials in the previously developed models of other processes with transitions between different environments, such as mutator models [22] and gene autoregulation models [25].

As a further development, it will be interesting to examine other situations in which the effective fitness notion fails as well as to attempt to obtain a solution for the non-Markovian random transitions between environments. Another potentially promising direction involves examination of periodic changes of the fitness, which might be an analytically solvable problem, and obtaining estimates for the realistic case of combined periodic trends and random transitions between landscapes.

APPENDIX: THE DETAILS OF DERIVATIONS

1. The general solution with $O(1/N)$ accuracy

We deduce the following expressions from Eq. (7):

$$\begin{aligned}
A_{11} &= [(e^{-p}-1)e^{-s_1}+e^{p}-1]x(1-x)p_1+(p_1-1),\\
A_{12} &= (1-p_1)x(1-x)[(e^{-p}-1)e^{-s_2}+e^{p}-1]+1-p_1,\\
A_{21} &= (1-p_2)x(1-x)[(e^{-p}-1)e^{-s_1}+e^{p}-1]+1-p_2,\\
A_{22} &= [(e^{-p}-1)e^{-s_2}+e^{p}-1]p_2x(1-x)+p_2-1, \qquad \text{(A1)}
\end{aligned}$$

where $p_1 = 1 - d_1, p_2 = 1 - d_2$. Let us consider the $O(1/N)$ correction terms to Eq. (11). Starting from Eq. (7), we denote $v_1 = v$ and $v_2 = wv$. From Eq. (A1) we get $w(1) = 1$.

To calculate the function $v(x)$, we need to introduce the correction terms in the exponent, using an ansatz instead of Eq. (10):

$$p_l^1 = ve^{Nu+r_1/N}, \quad p_l^2 = vwe^{Nu+r_2/N}. \qquad \text{(A2)}$$

Putting such an expression with correction terms into Eq. (11), we can define $r = r_2 - r_1$ and v. To derive r_1, r_2, we need to consider the second-order correction terms. As we are interested just in $v(x)$, we keep only the first correction terms to Eq. (11), derived after a careful analysis of Eq. (7).

We examine the terms:

$$\begin{aligned}
p_{l\pm1}^1 &= v(x\pm1/N)e^{Nu(x\pm1/N)}\\
&\approx v(x\pm1/N)e^{Nu(x)\pm u'(x)+u''(x)/(2N)+r_1},\\
p_{l\pm1}^2 &= v(x\pm1/N)w(x\pm1/N)e^{Nu(x\pm1/N)}\\
&\approx w(x\pm1/N)v(x\pm1/N)e^{Nu(x)\pm u'(x)+u''(x)/(2N)+r_2}.
\end{aligned} \qquad \text{(A3)}$$

We will separate the terms proportional to u'' as a matrix B, the terms proportional to w' as a D, and terms proportional to v' as a matrix C. Thus, we should seek in the expressions of matrix A the terms proportional to e^p and e^{-p}, skipping other terms. We get:

$$A_{12}wr + (B_{11} + wB_{12})\frac{u''}{2} + w'D_1 + (C_{11} + wC_{12})\frac{v'}{v} = 0,$$
$$A_{22}wr + (B_{21} + wB_{22})\frac{u''}{2} + w'D_2 + (C_{21} + wC_{22})\frac{v'}{v} = 0, \tag{A4}$$

where we denoted

$$\begin{aligned} B_{11} &= x(1-x)p_1(e^{-p-s_1} + e^p),\\ B_{12} &= x(1-x)(1-p_1)(e^{-p-s_2} + e^p),\\ B_{21} &= x(1-x)(1-p_2)(e^{-p-s_1} + e^p),\\ B_{22} &= x(1-x)p_2(e^{-p-s_2} + e^p), \end{aligned} \tag{A5}$$

$$\begin{aligned} C_{11} &= x(1-x)p_1(-e^{-p-s_1} + e^p),\\ C_{12} &= x(1-x)(1-p_1)(-e^{-p-s_2} + e^p),\\ C_{21} &= x(1-x)(1-p_2)(-e^{-p-s_1} + e^p),\\ C_{22} &= x(1-x)p_2(-e^{-p-s_2} + e^p), \end{aligned} \tag{A6}$$

and

$$\begin{aligned} D_1 &= x(1-x)(1-p_1)(-e^{-p-s_1} + e^p),\\ D_2 &= x(1-x)p_2(-e^{-p-s_2} + e^p). \end{aligned} \tag{A7}$$

We calculate u'' from the expression for $u'(x)$. Then we define v'/v:

$$-\frac{v'}{v} = \frac{(D_1A_{22} - D_2A_{12})w'}{A_{22}(C_{11} + wC_{12}) - A_{12}(C_{21} + wC_{22})} + \frac{[(B_{11} + wB_{12})A_{22} - (B_{21} + wB_{22})A_{12}]}{A_{22}(C_{11} + wC_{12}) - A_{12}(C_{21} + wC_{22})}\frac{u''}{2}, \tag{A8}$$

and for $r(x)$

$$\begin{aligned} -r &= \frac{(D_1C_2 - D_2C_1)w'}{(A_{12}C_2 - A_{22}C_1)w}\\ &\quad + \frac{(B_{11} + wB_{12})C_2 - (B_{21} + wB_{22})C_1}{(A_{12}C_2 - A_{22}C_1)w}\frac{u''}{2},\\ C_1 &= B_{11} + wB_{12}, \quad C_2 = B_{21} + wB_{22}. \end{aligned} \tag{A9}$$

2. The case of scaling by Eq. (15)

Equations (A1), (A5), (A6), and (A7) give:

$$\begin{aligned} A_{11} &= -d_1 + x(1-x)(p^2 + ps_1),\\ A_{12} &= d_1, \quad A_{21} = d_2,\\ A_{22} &= -d_2 + x(1-x)(p^2 + ps_2), \end{aligned} \tag{A10}$$

$$B_{11} = 2x(1-x), \quad B_{12} = 0, \quad B_{21} = 0, \quad B_{22} = 2x(1-x). \tag{A11}$$

$$\begin{aligned} C_{11} &= x(1-x)(2p + s_1), \quad C_{12} = 0, \quad C_{21} = 0,\\ C_{22} &= x(1-x)(2p + s_2). \end{aligned} \tag{A12}$$

$$D_1 = 0, \quad D_2 = x(1-x)(2p + s_2), \tag{A13}$$

$$w(x) = 1 - x(1-x)(p^2 + ps_1)/d_1. \tag{A14}$$

Then

$$\begin{aligned} \frac{v'}{v} &= -\frac{A_{22} - A_{12}}{(2p + s_1)A_{22} - (2p + s_2)A_{12}w}u''\\ &\quad + \frac{(2p + s_2)A_{12}}{(2p + s_1)A_{22} - (2p + s_2)A_{12}w}w'. \end{aligned} \tag{A15}$$

We get the following equation instead of Eq. (11):

$$\begin{aligned} &-d_1S_2 - d_2S_1 + [-d_1 - d_2 + S_1S_2x(1-x)]p\\ &\quad + (S_1 + S_2)p^2x(1-x) + p^3x(1-x) = 0. \end{aligned} \tag{A16}$$

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