Solution of classical evolutionary models in the limit when the diffusion approximation breaks down

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(Received 16 August 2016; published 26 October 2016)

The discrete time mathematical models of evolution (the discrete time Eigen model, the Moran model, and the Wright-Fisher model) have many applications in complex biological systems. The discrete time Eigen model rather realistically describes the serial passage experiments in biology. Nevertheless, the dynamics of the discrete time Eigen model is solved in this paper. The 90% of results in population genetics are connected with the diffusion approximation of the Wright-Fisher and Moran models. We considered the discrete time Eigen model of asexual virus evolution and the Wright-Fisher model from population genetics. We look at the logarithm of probabilities and apply the Hamilton-Jacobi equation for the models. We define exact dynamics for the population distribution for the discrete time Eigen model. For the Wright-Fisher model, we express the exact steady state solution and fixation probability via the solution of some nonlocal equation then give the series expansion of the solution via degrees of selection and mutation rates. The diffusion theories result in the zeroth order approximation in our approach. The numeric confirms that our method works in the case of strong selection, whereas the diffusion method fails there. Although the diffusion method is exact for the mean first arrival time, it provides incorrect approximation for the dynamics of the tail of distribution.

DOI: 10.1103/PhysRevE.94.042422

I. INTRODUCTION

To describe evolution of biological organisms, one may use either discrete time models (e.g., the discrete time Wright-Fisher (WF) model [1–3], the Moran model [4], or the Eigen model [5,6]) or continuous time models (e.g., the continuous time Eigen model [6–8], the Crow-Kimura model [9–12], and the Moran model [4]). The former is proper for the evolution with nonoverlapping generations, and the latter is proper for the evolution with overlapping generations. Both situations are possible in biology. Bacteria typically have overlapping generations, whereas for the viruses both situations are possible. Persistent infections might be closer to overlapping generations, whereas viruses causing cell lysis and needing to alternatively copy positive and negative strands would be closer to have nonoverlapping generations [13]. In this paper we solve some problems of discrete time models, which are more involved than the continuous time models.

The Wright-Fisher model [1,2] and the diffusion approximation [3,14] play a central role in population genetics. The discrete time evolution models are defined as systems of iteration equations in discrete time versions, and we try to map them into continuous time differential equations to get an analytical solution in the large population limit. Kimura considered evolution in the neutral fitness landscapes as a diffusion process and popularized the diffusion equation method [14]. The diffusion equation method was widely applied in chemistry and stochastic models as well as an approximation of the master equation [15]. An alternative method for investigating the chain of ordinary differential equations is the Hamilton-Jacobi equation (HJE) method for the investigation of the chemical master equation [16–20] and for the evolution models [21–23]. The HJE method is very successful for the molecular evolution models [6,9] where mutation creates transitions between different states, whereas in the Wright-Fisher and Moran models of population genetics we have random sampling due to the finiteness of the population. In the case of continuous time evolution models [6,9], the HJE gives a complete solution for the models: both the exact steady state [21,22] and the exact dynamics [23,24] for the smooth fitness landscapes. However, the diffusion method gives completely incorrect results for the Eigen model with nonzero fitness (selection) [23].

The limit of the application of the diffusion method is an open problem for the population genetics models. The method has been widely criticized in the literature for the uncontrolled application in population genetics models [25]. It has been assumed that in population genetics models the diffusion method works for weak selection [26]. We will consider thoroughly the problem limits of the application of the diffusion method in the case of strong selection, which is the case at least for viruses [27] and bacteria [28,29].

This paper is organized as follows. In Sec. II, we solve the discrete time Eigen model [5] by the HJE; the model is widely applied to study virus evolution and to analyze the experimental data for the serial transmission of viruses in a chemical reactor. In Sec. III, we apply the HJE to study the discrete time Wright-Fisher model [1–3]. In Sec. IV, we discuss our approach and results, and in the Appendix we solve the Moran model using the HJE method. Our method gives an exact expression for the fixation probability for the latter case.

II. THE SOLUTION OF THE DISCRETE TIME EIGEN MODEL

The discrete time Eigen model [5] describes the serial transfer of a virus population in a chemical reactor. We

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consider the following discrete time iteration process:

$$p_i(n+1) = \frac{\sum_j Q_{ij} r_j p_j(n)}{\sum_j r_j p_j(n)}, \tag{1}$$

where $p_i(n)$'s are the frequencies of different types at time step n, r_i is the fitness of the ith type, and Q_{ij}'s are the transition probabilities due to mutations. The index i labels different types of genomes. For simplicity we assume two types of nucleotides in the genome, thus the genome is a chain of L alleles, taking values ± 1, similar to the Ising model [30]. There are 2^L types, labeled by index $0 \leqslant i \leqslant 2^{L-1}$. We have for the mutation matrix $Q_{ij} = q^{L-d(i,j)}(1-q)^{d(i,j)}$, q is the probability of errorless reproduction of one nucleotide. $d(i,j)$ is the total number of mutations to get genome j from the genome i. We define the zeroth sequence with only $+1$ alleles. We assume a symmetric fitness: the fitness is a function of total number of mutations calculated from zeroth sequence. The fitness function is defined as $f(x) \equiv r_i$, $x = 1 - 2d(0,i)/L$.

The dominator describes the dilution of population in a chemical reactor.

We assume the following ansatz for the nth moment of time:

$$N_i p_i(n) = \exp[LU(x,t)], \quad x = 1 - 2\frac{d(0,i)}{L}, \quad t = \frac{n}{L}, \tag{2}$$

where $N_i \equiv \frac{L!}{i!(L-i)!}$ is the number of sequences in the ith Hamming class, the collection of sequences having the same i number of mutations from the zeroth sequence. We will map our large system of (iteration) equations into a single nonlinear partial differential equation for continuous variables. Then in the limit of large L and $1-q \ll 1$, we have

$p_i(n+1)/p_i(n) = \exp[LU(x,t+1/L) - LU(x,t)] = \exp[U'_t(x,t)]$, $\sum_j r_j p_j = f[s(t)]$. The numerator of Eq. (1) has been already calculated before in detail [21]. Eventually, taking the logarithm of both sides of Eq. (1), we derive

$$\frac{\partial U(x,t)}{\partial t} = \ln f(x) + \gamma\left(\frac{1+x}{2}e^{2U'} + \frac{1-x}{2}e^{-2U'} - 1\right) - \ln f[s(t)], \tag{3}$$

where we denoted $\gamma = L(1-q)$ and $U' = \frac{\partial U}{\partial x}(x,t)$. At time t we have a surplus $s(t) = \sum_{i=0}^{L} N_i p_i(n)(1-2i/L)$ and mean fitness $f[s(t)]$.

Equation (3) is the HJE for the Crow-Kimura model [21] with the effective fitness $g(x) = \ln(r_i)$, $x = 1 - 2i/L$ and effective time measured in L. In Ref. [23] we derived the exact dynamics for such a Hamiltonian. Therefore, we have an exact dynamics for the discrete time Eigen model as well. According to Ref. [23], there are two different phases for the dynamics of the maximum, depending on the initial distribution. In Fig. 1 we compare our analytical results for the dynamics of themaximum of distribution with the numerical solution of Eq. (1). Moreover, the shock waves are possible for the smooth fitness functions as for the Crow-Kimura model [31]. Although there have been attempts to apply the diffusion approximation for the quasispecies models with nonzero selection [32,33], this is a rather poor approximation, giving the wrong results

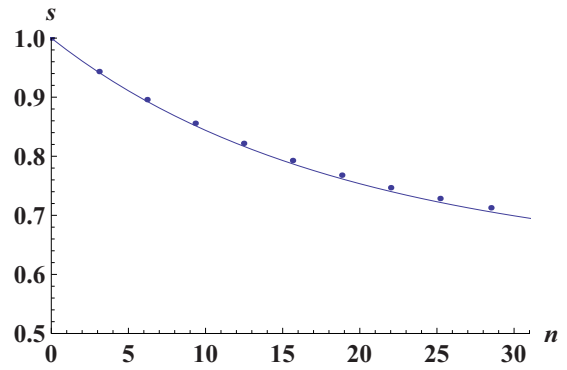

FIG. 1. A comparison of the dynamics for the discrete time Eigen model with $L = 100$, $r_i = \exp(-2i)$, $q = 1 - 1/L$, $s = \sum_i (1 - 2i/L)p_i(n)$ at the start of $p_0(0) = 1$, and other p's are equal to 0. The smooth line corresponds to the numerical solution of Eq. (1), and the solid circles are the analytical results by Eq. (8) from Ref. [23] for $x_0 = 1$.

even after several generations, see Figs. 4 and 5 in Ref. [23]. Diffusion approximation gives growing of the mean fitness with time, whereas our method, supported by numerics, gives nonmonotonic behavior for the mean fitness.

Let us discuss for a bit the relation of the discrete time Eigen model with the standard continuous time Eigen model, described via the distributions $\bar{p}_i(t)$,

$$\dot{\bar{p}}_i(t) = \sum_j Q_{ij} r_j \bar{p}_j(t) - \bar{p}_i(t) \sum_j r_j \bar{p}_j(t). \tag{4}$$

For the same r_i, Q_{ij} two models have an identical steady state $p_i = \bar{p}_i$. Nevertheless, their dynamics are different as are different dynamics of the Crow-Kimura model and Eigen models with the same fitness $f(x)$ [23]. Moreover, although the Crow-Kimura model with the smooth function $f(x)$ has the same steady distribution as the continuous time Eigen model with the fitness function $e^{f(x)}$, they have different dynamics. There is a case with a striking difference: The Crow-Kimura model with the linear fitness function $f(x) = kx$ has a smooth dynamics, whereas the Eigen model with the exponential fitness function e^{kx} can have shock waves [34].

III. THE WRIGHT-FISHER MODEL

The Wright-Fisher model describes the dynamics of population with two alleles a and b with some mutation probabilities, selection coefficients, and constant population size L. $p_i(n)$ is the fraction of population with the i,a alleles at time n, $0 \leqslant i \leqslant L$. We consider the iteration of p_i via the formula [4],

$$p_j(n+1) = \sum_i p_i(n) P_{ij},$$
$$P_{ij} = \binom{L}{j} (\eta_i)^j (1-\eta_i)^{L-j}. \tag{5}$$

Here P_{ij} is the $i \to j$ transition probability, and η_i's are the parameters of the model, defined through mutation and

selection coefficients,

$$\eta_i = \frac{i(1+s)(1-u)+v(L-i)}{i(1+s)+(N-i)},$$
$$\eta(x) = \frac{x(1+s)(1-u)+v(1-x)}{1+sx}. \tag{6}$$

Here $(1+s)$ is the ratio of the first and second allele fitnesses, u is the mutation probability from a to b, and v is the inverse mutation probability.

Actually, η_i resembles the discrete time Eigen model for the specific choice of mutation matrix Q_{ij}: In the denominator we have just the sum by the frequencies multiplied by their Wrightian fitnesses, whereas the numerator is the same as in (1).

We are interested in the steady state distribution (when there are back and forward mutations), in the dynamics of the maximum, in the fixation probability in the case of nonzero selection, and mean first arrival time.

The diffusion approach assumes that at the limit $L \to \infty$ the array of p_i can be replaced via a smooth function $p(x)$,

$$p_i = Cp(x), \quad x = i/L, \tag{7}$$

where C is some coefficient and x becomes a continuous variable at the limit of large L. Then after one iteration we can write, expanding in Eq. (5) the $p_j - p_i$ in degrees of $1/L$,

$$p(x,n+1) = p'(x,n)A(x) + p''(x,n)B(x),$$
$$A(x) = \sum_j P_{ij}\frac{i-j}{L}, \tag{8}$$
$$B(x) = \sum_j P_{ij}\frac{(i-j)^2}{2L^2}.$$

This is a typical case of diffusion approximation where one ignores the terms with a higher order derivative $\sim p^{(n)}$.

Instead of diffusion approach Eqs. (7) and (8), in this paper we will use an alternative ansatz,

$$p_i(n) = \exp[LU(x,n)], \tag{9}$$

and clarify when the diffusion method gives correct results.

Let us use an ansatz (9) and an approximate expression,

$$\frac{L!}{i!(L-i)!} = \exp[-Lx\ \ln\ x - L(1-x)\ln(1-x)].$$

We replaced the sum via index i in Eq. (5) via an integration by continuous variable $y \equiv i/L$ then used a substitution $y - x = x$ and used the saddle point method. Eventually we obtained the following iteration rule:

$$U(x,n+1) = \Psi(x,h) + U(x+h,n)|_{\max(h)},$$
$$\Psi(x,h) = \{-x\ln x - (1-x)\ln(1-x) + x\ln\eta(x+h),$$
$$+(1-x)\ln[1-\eta(x+h)]\}. \tag{10}$$

We cannot derive a simple differential equation for the dynamics of the maximum at any period in time.

A. The steady state distribution of the Wright-Fisher model

When there is only a mutation (neutral case without selection), Eq. (6) reduces to

$$\eta_i = x(1-u) + (1-x)v. \tag{11}$$

In this case it is of special interest to find the steady state of the iteration law by Eq. (5),

$$p_j = \sum_i p_i P_{ij}. \tag{12}$$

We consider the steady state solution and identify $U(x,n) \to U(x)$ for a large n after infinite relaxation. We expand the solution of $U(x)$ in Eq. (10) via degrees of u,v, $U(x) = \sum_{l=1} U_l(x)$. Thus we have for the steady state distribution p_i,

$$p_i(n) = \exp\left[L\sum_{l=1} U_l(x)\right], \tag{13}$$

and $U_l(x) \sim u^l$, which is equivalent to the expansion via degrees of $y - x$.

Let us expand $\Psi(x,h) + U(x+h)$ in degrees of h. We have a system of two equations for two variables $U(x)$ and $h(x)$,

$$\Psi(x,h) + U(x+h) = U(x),$$
$$\Psi'_h(x,h) + U'(x+h) = 0. \tag{14}$$

Holding only the quadratic terms $\sim u^2$, we get

$$\Psi_2(x,h) = \frac{\{[k(-1+x)+x]u - h_1\}^2}{2(-1+x)x}, \tag{15}$$

where we denoted $k = v/u$, $\Psi(x,h) = \Psi_2(x,h) + O(u^3)$. Putting the latter expression into Eq. (13) and approximating $U(x+h) = U(x) + U'(x)h$, we obtain

$$h_1(x) = u[-x + k(1-x)],$$
$$U'_1(x) = 2u\frac{-x+k(1-x)}{x(1-x)}. \tag{16}$$

Integrating Eq. (16) from the maximum point $x_0 = k/(k+1)$ we get the diffusion theory result from [4]

$$U_1(x) = 2(u+v)\ln\ 2(u+v) - 2u\ \ln\ 2u - 2v\ \ln\ 2v$$
$$+2v\ \ln\ x + 2u\ \ln(1-x),$$
$$p = e^{LU_1(x)}. \tag{17}$$

Having the first order solutions $h_1(x), U_1(x)$, we can calculate the next corrections putting in Eq. (13) $U(x) = U_1(x) + U_2(x)$, $h(x) = h_1(x) + h_2(x)$. Let us denote $\Psi_3(x,h)$ as the third order terms $\sim u^3$ in the expansion of $\Psi(x,h)$ as well as $\Psi'_2(x,h) = d\Psi_2(x,h)/dh$, $h'_1 = dh(x)/dx$. We obtain a system of equations for $U_2(x), h_2(x)$,

$$\Psi_3(x,h) + \Psi'_2(x,h)h_2(x) + U'_1(x)h_2(x) + U'_2(x)h_1(x)$$
$$+U''_1(x)h_1(x)/2 = 0,$$
$$\Psi'_3(x,h) + U'_2(x,h) + \Psi'_2(x,h)h_2(x)$$
$$+U''_1(x)h_1(x) = 0. \tag{18}$$

Solving the system (18) we find U_2', then integrating from the point x_0, we derive

$$U_2(x)/u^2 = -\frac{1}{3}(1+k)[5+5k+7k\ \ln(k)] + \frac{1}{3}(1+k) \times \left(-\frac{5}{-1+y+ky} + \frac{5k^2}{k+y+ky} + 7\ \ln(1-y-ky) + 7k\ \ln(k+xy+ky) \right), \quad (19)$$

where we denote $k = v/u$.

B. The limits of diffusion approximation

The diffusion theory result Eq. (17) is valid when we can ignore the second term in the exponent for p in Eq. (13), thus $\exp(LU_2) \ll 1$. Equation (19) gives $U_2(x) \sim (x-x_0)^2$ behavior, where x_0 is the maximum of distribution. In the expression,

$$p = \exp[LU_1(x) + LU_2], \quad (20)$$

U_2 has both $\sim u^2(x-x_0)^2$ and $\sim v^2(x-x_0)^2$ terms. Therefore, we get the following constraint for the validity of the diffusion theory:

$$L(x-x_0)^2(u^2+v^2) \ll 1, \quad (21)$$

whereas our approach is correct under the much softer constraint,

$$(u^2+v^2) \ll 1. \quad (22)$$

In Fig. 2 we compare the numerical solution for (5) and (6) (solid dots) with the diffusion theory result (17) (dashed line) and our result (smooth line) Eqs. (13) and (19) for the steady state distribution. The accuracy of our method is much higher.

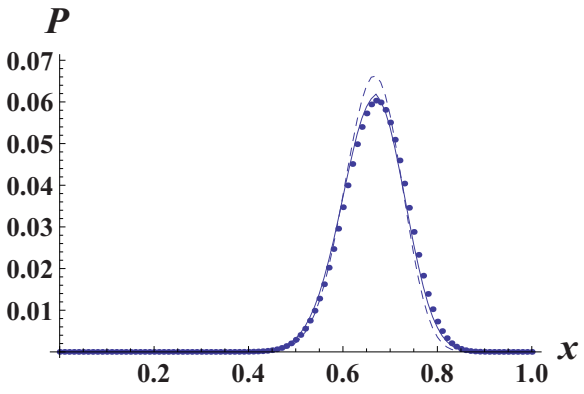

FIG. 2. A comparison of the steady state distribution of the Wright-Fisher model by Eq. (5) $L = 100$, $u = 0.1$, $v = 0.2$, $s = 0$. The smooth line is our result by Eqs. (13), (17), and (19), and the dashed line is calculated by the diffusion theory of Eq. (17). The solid circles are the results of the numerical solution of Eq. (5) after many iterations.

C. The dynamics in the Wright-Fisher model with mutations

Let us consider the short time evolution in the Wright-Fisher model when the population was initially focused at x_0. Replacing Ψ by Ψ_2 and taking $U(x+h) = U(x) + U'(x)h$, we get after the integration via h,

$$U(x,n+1) = U(x,n) + a(x)U'(x,n) + \frac{b(x)U'(x,n)^2}{2}, \quad (23)$$

where $a(x) = [v(-1+x) + ux]$, $b(x) = \frac{1}{x(1-x)}$. It is the HJE $du/dt + H(x,u') = 0$ with the Hamiltonian,

$$-H(x,p) = a(x)U'(x,n) + \frac{b(x)U'(x,n)^2}{2}. \quad (24)$$

For the maximum of the distribution we get an equation using the methods of characteristic [26],

$$dx/dt = H_p'(x,0) = -a(x). \quad (25)$$

The same equation has been derived by the diffusion method for the mean of distribution. A similar derivation gives the variance of distribution [35], identical to the result by the diffusion method [4].

We can use the methods of the HJE for the quadratics Hamiltonian [(A15)–(A17)] to calculate the whole distribution.

Our approach and the diffusion method give identical results near the maximum. Equation (23) deviates from our rigorous result in Eq. (10) for $L|x-x_0| \gg 1$ as we dropped the higher order terms in the expansion of $\Psi(x,h)$ in Eq. (10) to get Eq. (23). Thus, the diffusion approximation gives an incorrect result for the dynamics of $\ln\ p_i(n)$ for i, far from the peak of distribution even for zero mutation rates.

D. The fixation probability in the diffusion approach

Consider the Wright-Fisher model without mutations but with the selection described via the parameter s. There are two absorbing states for the Markov model $i = 0$ and $i = L$, and we are interested in the probability $\pi_i \equiv \pi(x)$, $x = i/L$ that the system with starting state i will proceed to state $i = 0$. This is the fixation probability of the allele a. By definition,

$$\pi(0) = 0, \quad \pi(1) = 1. \quad (26)$$

Consider the Wright-Fisher model in Eq. (5) with η_i given as

$$\eta_i = \frac{i(1+s)}{i(1+s)+(L-i)}, \quad \eta(x) = \frac{x(1+s)}{1+sx}. \quad (27)$$

In Ref. [4] Eq. (2.141), the following exact relation has been derived for π_i:

$$\pi_j = \sum_i \pi_i P_{ji}. \quad (28)$$

Equation (28) just describes that the probability of going to fixation from state i equals the sum of probabilities of going to states j multiplied to the fixation probability in the jth state. We have a transposed matrix compared with Eq. (5) [4]. Equation (12) gives the steady state distribution of the WF model, whereas the meanings of π_i and p_i are different in these two cases.

Using the approximation of Eq. (8) for the choice in Eq. (27), the following equation has been derived [36] for $\pi(x)$:

$$\pi'(x)sx(1-x)+\pi''(x)x(1-x)/(2L), \tag{29}$$

taking into account the border conditions (26), it has been derived [36]

$$\pi(x)=\frac{1-\exp(-2Lxs)}{1-\exp(-2Ls)}. \tag{30}$$

We are interested in the case,

$$Ls\gg 1,\quad s\ll 1. \tag{31}$$

Equation (30) gives [4]

$$p(x)\approx\exp(-2Lsx). \tag{32}$$

E. The fixation probability in the HJE approach

Let us calculate $\pi(x)$ using an alternative method. We assume the following ansatz:

$$\begin{aligned}\pi_i &= A[1-p_i],\\ p_i &\equiv p(x)=\exp[LU(x)].\end{aligned} \tag{33}$$

To ensure the second constraint from Eq. (26), we get

$$A=\frac{1}{1-\exp[LU(1)]}. \tag{34}$$

For the p_i's we have the same Eq. (28) as for π_i.

Using the Stirling formula and Eq. (31) for $p(x)$, we obtain from Eq. (28),

$$\begin{aligned}U(x) &= \max[\Psi(x,h)+U(x+h)]|_h,\\ \Psi(x,h) &= (x+h)\ln\eta(x)+(1-x-h)\ln[1-\eta(x)]\\ &\quad -(x+h)\ln(x+h)-(1-x-h)\ln(1-x-h),\end{aligned} \tag{35}$$

or

$$\begin{aligned}U(x)&=\Psi(x,h)+U(x+h),\\ \Psi'(x,h)&+U'(x+h)=0.\end{aligned} \tag{36}$$

Now our small parameter is s. We repeat the method from the previous section,

$$U(x)=U_1(x)+U_2(x)+\cdots, \tag{37}$$

where $U_1\sim s$, $U_2\sim s^2$. The second order term in the expansion of Ψ is

$$\Psi(x,h)=-\frac{[x(1-x)s-h]^2}{2x(1-x)}. \tag{38}$$

Using the expression (38), we get from Eq. (35) the system of equations for $h_1(x),U_1(x)$,

$$\begin{aligned}-\frac{[x(1-x)s-h_1(x)]^2}{2x(1-x)}+U_1'(x)h_1(x)=0,\\ \frac{[x(1-x)s-h_1]}{x(1-x)}+U_1'(x)=0.\end{aligned} \tag{39}$$

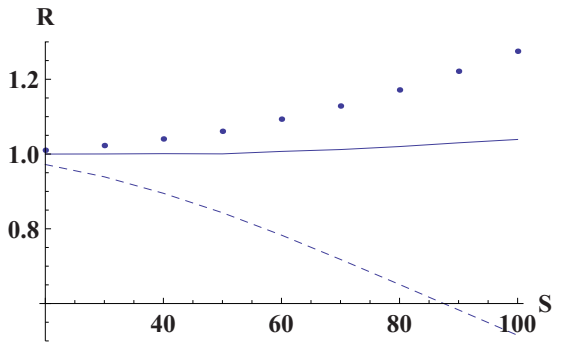

FIG. 3. The ratio of the analytical results and the numerics $R\equiv(1-\pi_i^{\text{theor}})/(1-\pi_i^{\text{num}})$, π_i is the fixation probability in the WF model by Eqs. (26) and (27) with $L=1000$. π_i^{num} is the numerical result, and π_i^{theor} is the analytical result. We consider the case of $i=100$. The selection is defined as $s=S/L$. The dashed line corresponds to the result given by the diffusion theory result Eq. (30), the solid dots are calculated by Eq. (44) of Ref. [26], and the smooth line is our analytical result of Eq. (41). Although at small selection S, all three analytical methods give accurate results ($R\approx 1$), and for the higher values of S our method is much more accurate than the diffusion method.

Thus we obtain

$$\begin{aligned}U_1'(x)&=-2s,\\ h_1&=-x(1-x)s.\end{aligned} \tag{40}$$

To calculate higher order terms, we replace in Eq. (36) $h(x)=h_1(x)+h_2(x)$, $U(x)=U_1(x)+U_2(x)$. Looking again at Eq. (18) we get with $O(s^2)$ accuracy,

$$\begin{aligned}p(x)&=\exp\left[-2sLx\left(1-s\frac{(1+x/2)}{3}\right)\right],\\ \pi(x)&=\frac{1-\exp\left[-2sLx\left(1-s\frac{(1+x/2)}{3}\right)\right]}{1-\exp\left[-2sL\left(1-s\frac{(1+1/2)}{3}\right)\right]}.\end{aligned} \tag{41}$$

We see that the diffusion theory result is correct for

$$Ls^2x\ll 1. \tag{42}$$

In Ref. [26] it has been assumed that the diffusion theory result is correct under the condition,

$$Ls^2\ll 1. \tag{43}$$

The last condition is broken at least for the case of bacteria [28]. In Fig. 3 we compare our analytical result in Eq. (43) with the results of the diffusion method as well as with the expression for the fixation probability suggested in Ref. [26],

$$\pi(x)=\frac{1-\exp[-2Lx\ \ln(1+s)]}{1-\exp[-2L\ \ln(1+s)]}. \tag{44}$$

F. The diffusion equation for the mean first arrival time

For the mean arrival time one has the following exact equation [4]:

$$\bar{t}_i=\sum_{j=0}^{L}p_{ij}\bar{t}_j+1.$$

To solve this equation, we again use the diffusion approximation, assuming that $\frac{d^{n+1}T}{dx^{n+1}} \ll L\, d^n x \frac{d^n T}{d^{n+1}x}$, and the following formula has been derived in Ref. [4]:

$$\bar{t}(x) = -2L\frac{(1-x)\ln(1-x)}{x}.$$

The solution is a smooth function, contrary to the case in the previous section. Therefore, there is no constraint like Eq. (21) now, and the diffusion theory yields the exact result at the limit $L \to \infty$ [37,38].

IV. DISCUSSION

In this paper we applied the exponential ansatz and the related HJE equation to solve discrete time models of evolution theory and investigated the limits of validity for the diffusion approximation. The investigated models are the working mathematical tools in virology and population genetics. We gave the exact solution for the dynamics of the discrete time Eigen model (a rather reasonable description for the virus serial transfer experiments) and advanced the solution of the Wright-Fisher model for the case of strong selection. Our analytical results are well confirmed by the numerics, see Figs. 1– 3. Figures 2 and 3 illustrate the higher accuracy of our analytical results compared with the diffusion theory results. Our key result Eq. (41) is more accurate than the analytical expression from Ref. [26], the current champion in accuracy. Although the Wright-Fisher model has been under active consideration for seven decades, some important issues remained still unsolved: the solution of the steady state, the fixation probability in the case of strong selection and mutations, and the limits of application for the diffusion theory. The diffusion equation works well for the first arrival time calculation where it yields exact results [4,37]. Our exponential ansatz allows us to solve the steady state expressions for the probability distribution or fixation probability with any given accuracy via a series expansion in the selection or mutation coefficients (the bulk term in this series is the result by diffusion approximation). Moreover, we can calculate also $O(1/L)$ correction terms, taking correction terms in the Stirling formula and following the standard methods of the HJE [39]. The diffusion method gives the correct dynamics for the maximum and variance of distribution but does not describe the dynamics of the tail of distribution. The diffusion approximation works well near the maximum of (steady state) distribution and when the initial state is close to the absorbing state in the case of fixation probability, even if there is a strong selection and the constraint of Eq. (43) is broken.

We can apply the truncated Hamiltonian version of the WF model to solve approximately the dynamics when the fitness changes with time. Such mathematical problems arose for the chemotherapy optimization in the case of cancer [40].

ACKNOWLEDGMENTS

D.B.S. thanks I. Kuntz, S. Manrubia, and R. Sanjuan for useful discussions. This work was supported by Taiwan Grants No. MOST 104-2811-M-001-102, No. MOST 104-2112-M-001 -002, MOST 105-2811-M-001 -078, and MOST 105-2112-M-001 -004.

APPENDIX: THE MORAN MODEL

1. The derivation of the HJE

We consider the following Markov model where p_i's are the probabilities of different states and P_{ij}'s are the transition probabilities [4]:

$$\begin{aligned} p_j &= \sum_i p_i P_{ij}, \\ P_{i,i+1} &= \frac{i(L-i)}{L^2} = \mu_i, \\ P_{i,i-1} &= \frac{i(L-i)r}{L^2} = \lambda_i, \\ P_{ii} &= 1 - P_{i,i-1} - P_{i,i+1}. \end{aligned} \tag{A1}$$

Here L is the population size $r = e^{-s}$, and s is the selection coefficient. We assume now that at any nth moment in time,

$$\begin{aligned} p_i(n) &= \exp[Lu(x,t)], \\ x &= \frac{i}{L}, \quad t\frac{n}{L}, \end{aligned} \tag{A2}$$

In the limit of large L we have

$$\begin{aligned} \frac{\partial u}{\partial t} &= \ln[\lambda(x)e^p + \mu(x)e^{-p} + 1 - \mu(x) - \lambda(x)], \\ \mu(x) &\equiv \mu_i = x(1-x), \\ \lambda(x) &\equiv \lambda_i = x(1-x)e^{-s}. \end{aligned} \tag{A3}$$

While deriving Eq. (A3), we ignored the terms u''/L, assuming

$$u''/L \ll u'. \tag{A4}$$

Equation (A3) is a Hamilton-Jacobi equation and can be solved using the methods of characteristics [23,41,42].

2. The dynamics

Consider the characteristics equation, the Hamilton equation for the coordinate x and momentum p. As the Hamiltonian is time independent, $q \equiv \frac{\partial u}{\partial t}$ is constant along the characteristics. We have from the HJE,

$$\begin{aligned} q &= \ln[\lambda(x)e^p + \mu(x)e^{-p} + 1 - \lambda(x) - \mu(x)], \\ e^p &= \frac{A - \sqrt{A^2 - 4\lambda\mu}}{2\lambda}, \\ A &= e^q - 1 + \lambda + \mu. \end{aligned} \tag{A5}$$

We have the Hamiltonian equation,

$$\frac{dx}{dt} = \frac{\lambda(x)e^p - \mu(x)e^{-p}}{\lambda(x)e^p + \mu(x)e^{-p} + 1 - \lambda(x) - \mu(x)}. \tag{A6}$$

Expressing e^p from (A5) via x and q and integrating dt/dx from Eq. (A6), we obtain

$$\frac{dx}{dt} = \pm\frac{\sqrt{[e^q - 1 + \lambda(x) + \mu(x)]^2 - 4\lambda(x)\mu(x)}}{e^q}. \tag{A7}$$

We can define time along the characteristics,

$$T(q,x) = \int_{x_0}^{x} dx \frac{e^q}{\sqrt{[e^q - 1 + \lambda(x) + \mu(x)]^2 - 4\lambda(x)\mu(x)}}. \tag{A8}$$

For the dynamics of the maximum $y(t) = x$, we set $q = 0$ and obtain the known result [4] $\frac{dy}{dt} = \lambda(x) - \mu(x)$.

Let us calculate now the population distribution at any moment in time. For the given x,t we first find q, which gives $T(q,x) = t$.

If the population originally is focused at point x_0, then we have the following expression for the distribution at the moment in time t:

$$u(x,t) = \int_0^x dy\, p(y) + qt, \tag{A9}$$

where

$$p(x) = \ln\left[\frac{A + \sqrt{A^2 - 4\lambda\mu}}{2\lambda}\right], \quad A = e^q - 1 + \lambda + \mu. \tag{A10}$$

The variance of the distribution is $\sum_i p_i(\frac{i}{N})^2 - (\sum_i p_i \frac{i}{N})^2 = \frac{1}{-Nu''_{xx}}$, which is calculated using the formula $b(x)^2 \int_{x_0}^x dy\{c(y)/[b(y)]^3\}$ from Ref. [35] with

$$b(x) = \lambda(x) - \mu(x), \quad c(x) = \lambda(x) + \mu(x). \tag{A11}$$

3. The fixation probability for the Moran model

We can derive the fixation probability using Eq. (28). For the Moran model this probability can be calculated exactly [4],

$$\pi(x) = \frac{1 - \exp(-Lxs)}{1 - \exp(-Ls)}. \tag{A12}$$

Let us derive this result in our approach. We again look at the limit $L \gg 1$ and again investigate Eq. (28) using the ansatz (31). We derive

$$(e^{u'} - 1)\lambda(x) + (e^{-u'} - 1)\mu(x) = 0. \tag{A13}$$

The solution is simply

$$e^{u'} = e^{-s}. \tag{A14}$$

TABLE I. The comparison of the distribution function $u(x)$ calculated exactly by (A9) $u_0(x)$ and approximately (A17) and $u_1(x)$ for the Moran model with $s = 0.1$ after $T = 2N$ generations. The original distribution was focused at $x = 0.2$.

x	0.3	0.4	0.5	0.6	0.7	0.8
$u_0(x)$	0.03084	0.20011	0.32604	0.48256	0.6784	0.9332
$u_1(x)$	0.03078	0.19987	0.32715	0.48734	0.6908	0.9575

Thus $u = -sx$, and the condition (A4) is valid. We have $p(x) = c\,\exp[-Lsx]$, and the condition Eq. (25) gives the exact result (A11).

4. The dynamics for the quadratic truncation of the Hamiltonian

Let us truncate the Hamiltonian from Eq. (5) in degrees of p,

$$q = \{[\lambda(x) + \mu(x)] - (\lambda - \mu)^2\}\frac{p^2}{2} + [\lambda(x) - \mu(x)]p \equiv \frac{Ap^2}{2} + Bp. \tag{A15}$$

Then

$$t = \int_{x_0}^x \frac{dy}{\sqrt{2qA + B^2}}, \tag{A16}$$

and

$$u(x,t) = \int_0^x dy\, p(y) + qt \qquad p(x) = \sqrt{2qA + B^2}/A - \frac{B}{A}. \tag{A17}$$

In Table I we compare the exact solution for $u(x)$ with the solution derived via quadratic truncation.

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