

Solution of the Crow-Kimura model with changing population size and Allee effectDavid B. Saakian,^{1,2,3,*} Kang Hao Cheong,^{4,†} and Jin Ming Koh⁴¹*Theoretical Physics Research Group, Advanced Institute of Materials Science, Ton Duc Thang University, Ho Chi Minh City, Vietnam*²*Faculty of Applied Sciences, Ton Duc Thang University, Ho Chi Minh City, Vietnam*³*A. I. Alikhanyan National Science Laboratory (Yerevan Physics Institute) Foundation, 2 Alikhanian Brothers Street, Yerevan 375036, Armenia*⁴*Engineering Cluster, Singapore Institute of Technology, 10 Dover Drive, Singapore 138683, Singapore*

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The Crow-Kimura model is commonly used in the modeling of genetic evolution in the presence of mutations and associated selection pressures. We consider a modified version of the Crow-Kimura model, in which population sizes are not fixed and Allee saturation effects are present. We demonstrate the evolutionary dynamics in this system through an analytical approach, examining both symmetric and single-peak fitness landscape cases. Especially interesting are the dynamics of the populations near extinction. A special version of the model with saturation and degradation on the single-peak fitness landscape is investigated as a candidate of the Allee effect in evolution, revealing reduction tendencies of excessively large populations, and extinction tendencies for small populations. The analytical solutions for these dynamics are presented with accuracy $\mathcal{O}(1/N)$, where N is the number of nucleotides in the genome.

DOI: [10.1103/PhysRevE.98.012405](https://doi.org/10.1103/PhysRevE.98.012405)**I. INTRODUCTION**

The modeling of evolutionary mechanisms is of great interest to biophysicists and ecologists, for it enables the quantitative analysis of dynamic real-world wildlife populations [1–3]. In microbiology and medicine, evolutionary models enable predictions on the mutation of disease strains [4,5] and the growth of cancer tumors [6,7]. Statistical biophysics developments, such as spin-coherent Schwinger quasispecies formulations [8,9], have yielded generalizations for arbitrary replication and degradation functions; evolution models with space-independent fitness have also been established, with analytical solutions found within the Hamilton-Jacobi formalism [10]. Statistical physics has also been successfully applied to problems on multiagent systems, human cooperation [11], and vaccination dynamics [12].

In evolution, the application of statistical physics is especially successful for three reasons: there are many degrees of freedom (genome length in viruses is ~ 1000), there is a close analogy between energy and fitness, and the equations in quasispecies theory are weakly nonlinear (mappable to systems of linear equations via nonlinear algebraic transformations.) The quasispecies evolution model with fixed population size [13–15] describes the deterministic evolution of replicators with many genes, with selection and simple point mutations for any allele. There are, however, situations in which the change of population size plays a principal role, for instance, in cases of coevolution [16] and extinction [17–20]. In these cases, it is crucial to examine the time-dependent evolutionary dynamics, which is oftentimes mathematically nontrivial. The nonlinearities in population dynamics modeling may give rise to counterintuitive phenomena such as the

possibility of proliferation amidst disadvantageous conditions, by switching between losing behavioral strategies [21–25], and the survival advantage offered by genetic and phenotypic diversity [26–28] despite them being resource-costly to maintain.

In the present paper, we examine the Crow-Kimura population model, commonly used to describe genetic population dynamics in the presence of mutation and selection pressure [14,29–32]—see [33] for introductory theoretical information. The evolution of proteins and nucleic acids near the molecular level has also been described with suitable modifications [9]. With constant population sizes, exact dynamics of the original Crow-Kimura population model have already been derived in previous studies, for the case of single-peak [34] and symmetric fitness landscapes [35]. Here we solve the dynamics of a generalized version of the Crow-Kimura model with saturation, without holding constant population size.

We will include in our analysis a simple model of the Allee effect [36,37] in evolution, which is of great relevance in cancer biology and ecology [17,38]. With the Allee effect, the population growth declines for both too small and too large a population size, the former attributable to a positive correlation between individual fitness and population density, and the latter due to resource scarcity. Modeling of declining growth at large population sizes can easily be carried out through the logistic growth model; a more subtle problem is to find a simplistic counterpart for small population sizes.

A modified Crow-Kimura model with saturation and degradation effects is first formulated. A special case of the model with a single-peak fitness function is then considered, with certain key properties identified as analogous to the Allee effect. Lastly, a finite-population version of the model is constructed. Throughout the paper, an analytical approach to the relevant evolution time dynamics is adopted, yielding solutions and asymptotic forms that may be of general significance to biophysics and ecology.

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II. SATURATION MODEL

We consider a virus evolution model with degradation and saturation effects as an illustration. Starting from the Crow-Kimura model [33], we introduce a modified saturation term similar to that used in [39]. The rate of change of the l -th Hamming class population size $P_l(t)$ may be written as

$$\begin{aligned} \frac{dP_l(t)}{dt} &= P_l(r_l - 1 - D) + P_{l-1} \left(\frac{N-l+1}{N} \right) \\ &\quad + P_{l+1} \left(\frac{l+1}{N} \right) - \kappa P_l(t) \hat{P}, \\ \hat{P} &= \sum_l P_l, \end{aligned} \quad (1)$$

where r_l is the fitness. We adopt the time scale of mutations in this model, therefore the mutation rate is set to unity. D describes the overall degradation of the population, and $1/\kappa$ is the carrying capacity. We carry out the summation for \hat{P} over the range $0 \leq l \leq N$, and we drop the P_{l-1} and P_{l+1} terms for $l=0$ and N cases, respectively. Notably, we have the same fractions $P_l / \sum_j P_j$ in the steady state for any \hat{P} , while the dynamics of the total population changes. In contrast, in the ordinary Crow-Kimura model, $\hat{P} = \sum_i r_i P_i$ is taken, and the population size is assumed to be constant.

We consider the saturation term $\hat{P} = \sum_i P_i$ as studied in [39] for its analytical simplicity. It is worth noting that \hat{P} can, in general, be replaced by a different function, and a slightly modified formula from the present one will then arise. If different saturation effects for differing genotypes are considered, it becomes necessary to introduce a saturation landscape, in addition to the fitness landscape currently considered. The analysis of these two coupled landscapes motivates future work and is beyond the scope of the present paper.

A. Smooth fitness landscape

Let r_l be the associated fitness of a genotype with l mutations. We also define a fitness function $f(x)$ with $x \in [-1, 1]$:

$$r_l = f(x), \quad x = 1 - 2l/N. \quad (2)$$

Summing over the equations, we can easily obtain the following:

$$\frac{d\hat{P}(t)}{dt} = g(t)\hat{P} - \kappa\hat{P}(t)\hat{P}(t), \quad (3)$$

where $g(t)$ is defined as

$$\begin{aligned} g(t) &\equiv \left[\sum_l P_l(r_l - 1 - D) + P_{l-1} \left(\frac{N-l+1}{N} \right) \right. \\ &\quad \left. + P_{l+1} \left(\frac{l+1}{N} \right) \right] / \hat{P}. \end{aligned} \quad (4)$$

Thus if at time t the population distribution has a peak at the point $l \equiv [1 - x(t)]/2$, then the following form for $g(t)$ will hold:

$$g(t) = f(x) - D. \quad (5)$$

The solution to Eq. (3) may first be found. Letting $y = 1/\hat{P}$, we may observe that

$$\frac{dy}{dt} = -g(t)y + \kappa. \quad (6)$$

Then we have a solution

$$\begin{aligned} \hat{P} &= \left[e^{-G(t)} \left\{ \hat{P}_0^{-1} + \kappa \int_0^t e^{G(a)} da \right\} \right]^{-1}, \\ G(t) &= \int_0^t d\tau g(\tau), \end{aligned} \quad (7)$$

where \hat{P}_0 is the initial population size \hat{P} at time $t=0$. We now consider the analytical form of $g(t)$. An ansatz for P_l may be assumed, with the following form:

$$P_l = \exp[Nu(x)], \quad x = 1 - 2l/N. \quad (8)$$

Expanding $u(x \mp 2/N)$ in the exponent of $P_{l\pm 1} = \exp[Nu(x \mp 2/N)]$, and holding the main degrees in N , we obtain $P_{l\pm 1} = \exp[Nu(x) \mp 2u'(x) + 2u''(x)/N + \dots] \approx P_l \exp[\mp 2u'] + \mathcal{O}(1/N)$. Thus a relative accuracy $\mathcal{O}(1/N)$ is obtained:

$$\frac{du}{d\tau} = f(m) - D + \frac{1+m}{2} e^{2u'} + \frac{1-m}{2} e^{-2u'} - \kappa \hat{P}(N\tau). \quad (9)$$

We observe that the N -dependence term is linear in our equation, and is also independent of x . This explains why the dynamics of the relative distribution of P_l is the same as in the canonical Crow-Kimura model [35], inclusive of the dynamics of the distribution maxima.

We take a solution for the latter equation:

$$u = u_1(\tau) + u_0(\tau, m), \quad u_1 = -k \int_0^\tau d\tau \hat{P}(N\tau). \quad (10)$$

Let us now define $g(t)$, such that it is independent of $u_1(x)$. We assume that the population is originally located at some $x = x_0$. According to [35], it is appropriate to distinguish the regions $x_0 < x_c$ and $x > x_c$, where x_c is the solution of the equation

$$f'(x_c) = \frac{x_c}{\sqrt{1-x_c^2}}. \quad (11)$$

When $x_c < x_0 < 1$, we have the following system of equations to define $g(t)$:

$$\begin{aligned} g(t) &= f[x(t/N)] - D, \quad t = T(x), \\ T(x) &= -\frac{1}{2} \int_{x_0}^x \frac{d\xi}{\sqrt{[f(x) + 1 - f(\xi)]^2 - 1 + \xi^2}}, \end{aligned} \quad (12)$$

where $x(t)$ gives the dynamics of the maximum of the distribution at any given time.

In Eq. (12), we take into account the difference in time scales while calculating the growth of populations and the surplus dynamics. For small values of x_0 , we first use the solution as presented in Eq. (12). In these cases, the integrals should be summed up over the intervals (x_0, x_1) and (x, x_1) . This gives

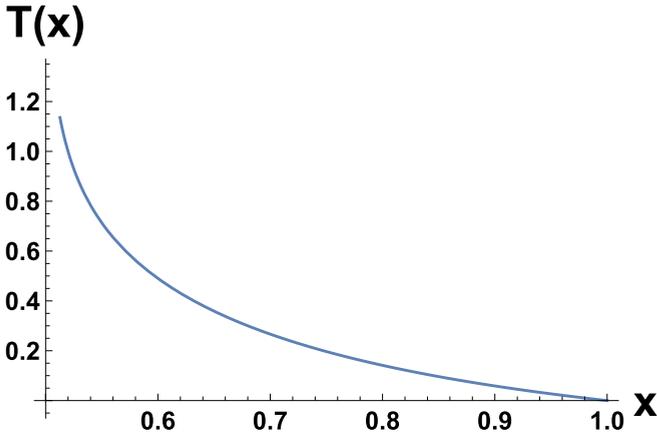


FIG. 1. Plot of $T(x)$ as computed from Eq. (12), with $x_0 = 1$ and $N = 1000$. The tendency for the population to diverge from x_0 as time progresses can be observed, reflecting the effects of mutation on the gene pool. The inverse function $X(t)$ can also be derived. Numerical calculations coincide with the presented analytics by Eq. (12) with accuracy of 0.2%.

us

$$t = \frac{1}{2} \left(\int_{x_0}^{x_1} \frac{d\xi}{\sqrt{[f(x) + 1 - f(\xi)]^2 + \xi^2 - 1}} + \int_x^{x_1} \frac{d\xi}{\sqrt{[f(x) + 1 - f(\xi)]^2 + \xi^2 - 1}} \right), \quad (13)$$

where x_1 is defined by the equation

$$[f(x) + 1 - f(x_1)]^2 + x_1^2 - 1 = 0. \quad (14)$$

We have thus presented the analytical solution of the evolutionary dynamics in our Crow-Kimura population model with saturation. Figure 1 shows the plot of $T(x)$ as computed from Eq. (12), illustrating the tendency for the population to move away from x_0 as time progresses, due to the effect of mutations. Notably, our analytical solution for the maxima of distribution dynamics is accurate to order $\mathcal{O}(1/N)$, stemming from the ansatz used in Eq. (9).

A comparison between our analytical results, as given by Eqs. (7) and (12), and numerical solutions of base equations Eqs. (1) and (2) is also presented in Fig. 2. Clearly, they are in good agreement.

As there are two phases in the dynamics of the maximum point, it can be expected that there exist two phases for the extinction dynamics as well, in models with saturation and degradation effects.

Considering a static system, we may identify $\kappa \hat{P}$ with the eigenvalue of the system (mean fitness R). Using the well known result for the mean fitness

$$R = \max [f(x) - D + \sqrt{1 - x^2} - 1, 0], \quad (15)$$

we may find for the steady state population \hat{P}

$$\hat{P} = \max [f(x) - D + \sqrt{1 - x^2} - 1, 0] / \kappa. \quad (16)$$

Figure 3 illustrates the accuracy of our analytical results, with negligible deviation between analytical and numerical calculations.

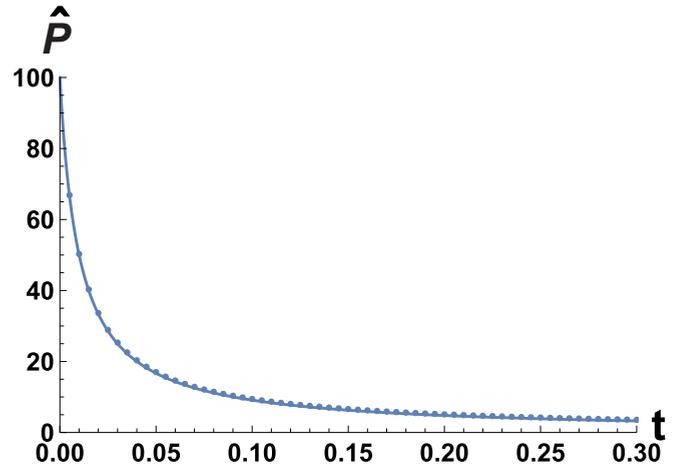


FIG. 2. Comparison of our analytical solution (solid line), as given by Eqs. (7) and (12), and numerical solutions (dots) of base equations Eqs. (1) and (2). A fitness function $f(x) = x^2$ was used, with parameters $D = 0.3$, $N = 1000$, $x_0 = 1$, and $\kappa = 1$.

B. Single-peak fitness landscape

Consider the choice

$$r_0 = J + a, \quad J + a - 1 > D, \quad (17)$$

with $r_l = a, l > 0$. We obtain the following system of equations from Eq. (1):

$$\begin{aligned} \frac{dP_0(t)}{dt} &= P_0(J + a - 1 - D) + P_1 \frac{1}{N} - \kappa P_0(t) \hat{P}, \\ \frac{dP_l(t)}{dt} &= P_l(a - 1 - D) + P_{l-1} \frac{(N - l + 1)}{N} \\ &\quad + P_{l+1} \frac{(l + 1)}{N} - \kappa P_l(t) \hat{P}, l \geq 1, \\ \hat{P} &= \sum_l P_l. \end{aligned} \quad (18)$$

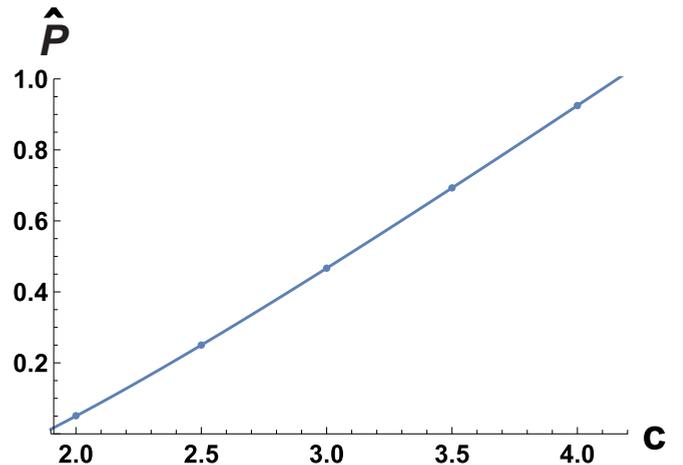


FIG. 3. Plot of steady state population size \hat{P} against fitness parameter c . A fitness function $f(x) = cx^2/2$ was used, with parameters $D = 0.2$, $N = 1000$, $x_0 = 1$, and $\kappa = 1$. The solid line represents our analytical result; dots represent numerical calculations.

Let us assume that either $P_l \sim P_{l-1}$ (steady state regime) or, depending upon initial conditions, $P_l \ll P_{l-1}$ (a large majority of the population is initially in the $l = 0$ state). Then we can ignore the contribution of P_{l+1} terms with accuracy $\mathcal{O}(1/N)$:

$$\begin{aligned} \frac{dP_0(t)}{dt} &= P_0(J + a - 1 - D) - \kappa P_0 \hat{P}, \\ \frac{dP_l(t)}{dt} &= P_l(a - 1 - D) + P_{l-1} - \kappa P_l \hat{P}, N \gg l \geq 1. \end{aligned} \quad (19)$$

By considering the system of equations, we obtain

$$\begin{aligned} \frac{dP_0}{dt} &= P_0(J + a - 1 - D) - \kappa P_0 \hat{P}, \\ \frac{d\hat{P}}{dt} &= JP_0 - (D - a)\hat{P} - \kappa \hat{P}^2. \end{aligned} \quad (20)$$

Let us use an ansatz of

$$P_0 = x \hat{P}. \quad (21)$$

Then we obtain

$$\begin{aligned} \frac{dx}{dt} &= x(J - 1) - Jx^2, \\ \frac{d\hat{P}}{dt} &= [Jx - (D - a)]\hat{P} - \kappa \hat{P}^2. \end{aligned} \quad (22)$$

Denoting $y = 1/P$, we may derive

$$\begin{aligned} x &= \frac{ce^{(J-1)t}}{ce^{(J-1)t} - 1} \frac{J-1}{J}, \\ -\frac{dy}{dt} &= [Jx - (D - a)]y - \kappa. \end{aligned} \quad (23)$$

The case $a = 0$ has a rather simple solution. We have for the population dynamics of a given initial population size $\hat{P}(0)$ the following:

$$\begin{aligned} \hat{P}(t) &= \frac{D\hat{P}(0)(J - D - 1)(Je^{(J-1)t} - 1)}{JD\kappa\hat{P}(0)e^{(J-1)t} - (J-1)e^{Dt}\alpha + \kappa\hat{P}(0)(J-D-1)}, \\ \alpha &= [D(-J + D + 1) + (D + 1)\kappa\hat{P}(0)]. \end{aligned} \quad (24)$$

In Fig. 4, we compare our analytical results for $\hat{P}(t)$ as given by Eq. (24) against numerical computations. The single-peak fitness model used in this subsection is idealized, and can be considered mathematically equivalent to the random fitness model [40] with an accuracy $\mathcal{O}(1/N)$, thereby serving as a good approximation for viruses [41].

C. Distinctive phases in the model

We distinguish selective, nonselective, and extinction phases. In the selective phase, the following holds:

$$\hat{P} = J + a - 1 - D > 0, \quad \frac{P_0}{\hat{P}} = \frac{J-1}{J}. \quad (25)$$

On the other hand, in the nonselective phase,

$$\hat{P} = a - D, \quad \frac{P_0}{\hat{P}} = 0, \quad (26)$$

and, in the extinction phase,

$$\hat{P} = 0. \quad (27)$$

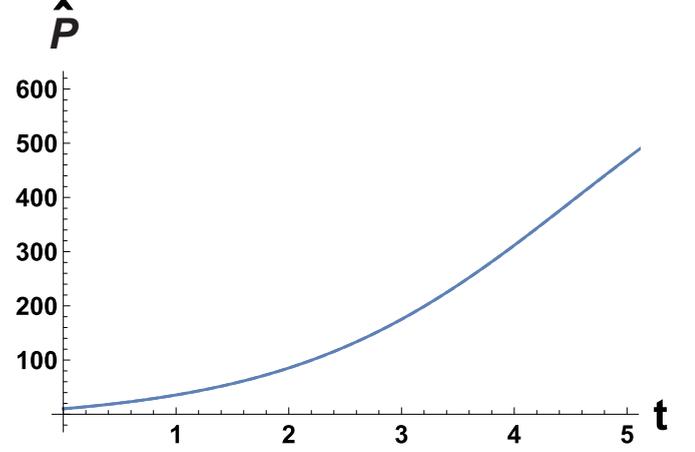


FIG. 4. The analytical population dynamics, as given by Eq. (24). The analytical and numerical solutions coincide with accuracy $\mathcal{O}(1/N)$. A single-peak fitness function $r_0 = 2$ was used, with parameters $D = 0.2$, $N = 1000$, $x_0 = 1$, $\hat{P}(0) = 10$, $\kappa = 0.001$, and $a = 0$.

A key research focus in cancer biology is the potential extinction of cancer cells due to strong mutations, wherein the tumor system approaches the nonselective phase. A proposal was suggested in [17] for the cancer cell population to be forced into extinction by exploiting the Allee effect. In order to appropriately model the extinction of such evolving systems at small populations, it is necessary to take into account the saturation functions, which may be nonlinear.

III. SINGLE-PEAK FITNESS MODEL WITH STRONGLY NONLINEAR SATURATION AND ALLEE EFFECT

While considering the saturation effect, we can examine instead of the saturation-related term $-\hat{P}$ in the equation an alternative term

$$\alpha \hat{P} - \kappa^2 \hat{P}^2 \quad (28)$$

where κ plays the role of carrying capacity, consistent with the formalism adopted previously, and α describes the extent of cooperation of replicators:

$$\begin{aligned} \frac{dP_l(t)}{dt} &= P_l(r_l - 1 - D) + P_{l-1} \frac{(N-l+1)}{N} \\ &\quad + P_{l+1} \frac{(l+1)}{N} + (\alpha \hat{P} - \kappa^2 \hat{P}^2) P_l(t), \\ \hat{P} &= \sum_l P_l. \end{aligned} \quad (29)$$

Consider the case of a single-peak fitness function. We have for the selective phase

$$\hat{P} = \frac{-\sqrt{\alpha^2 + 4\kappa^2(-D + J - 1)} + \alpha}{2\kappa^2}, \quad (30)$$

and for the nonselective phase

$$\hat{P} = \frac{-\sqrt{\alpha^2 + 4\kappa^2(-D - 1)} + \alpha}{2\kappa^2}. \quad (31)$$

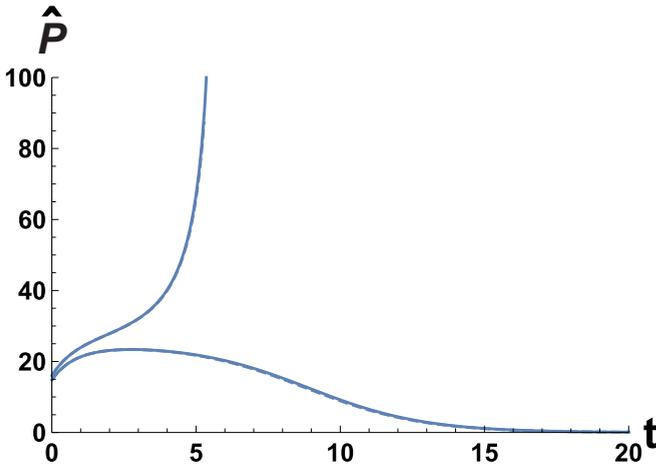


FIG. 5. The population dynamics, as given by Eqs. (29) (smooth line) and (32) (dashed lines). A single-peak fitness function was used, with parameters $r_0 = 2$, $D = 1.5$, $N = 1000$, $x_0 = 1$, $\kappa = 0.001$, and $\alpha = 0.02$. The lower line corresponds to $\hat{P}(0) = 14.8$; the upper line corresponds to $\hat{P}(0) = 16$. There is a phase transition near the point $\hat{P}(0) = 15$. The model has a declining tendency for population size at large $\hat{P} > 20\,000$, and extinction occurs for small initial population size $\hat{P}(0) < 15$, typical of the Allee effect.

Similar to previous analytical results, Eqs. (30) and (31) are accurate to $\mathcal{O}(1/N)$, due to the omission of terms of $1/N$ order in its derivation. At the extinction phase, we again have zero population. Using similar procedures carried out in the previous subsection, we obtain the following system of equations:

$$\begin{aligned} \frac{dx}{dt} &= x(J - 1) - Jx^2, \\ \frac{d\hat{P}}{dt} &= [(J + a)x(t) - (D - a)]\hat{P} + \alpha\hat{P}^2 - \kappa^2\hat{P}^3. \end{aligned} \quad (32)$$

We present in Fig. 5 a plot of \hat{P} as calculated from Eqs. (29) and (32), shown as solid lines and dashed lines, respectively. The model has a decreasing tendency for population size at large $\hat{P}(0) > 20\,000$, and eventual extinction occurs for small initial population size $\hat{P} < 15$, a behavior that is typical of the Allee effect. The analytical result given by Eq. (32) coincides

with the numerical result given by Eq. (29) with accuracy $\mathcal{O}(1/N)$.

IV. CONCLUSION

In the present paper, we have solved a modified version of the Crow-Kimura model with evolving population size and saturation effects, and have demonstrated the extinction dynamics through analytical approaches. This can be seen as a generalization of previous studies on the Crow-Kimura model, in which the population size is oftentimes taken to be time-independent [13–15]. In particular, we have incorporated Allee-like limiting effects for both small and large population sizes through a modified model, considering a genome with a large number of constituent genes. Our analytical results for the population dynamics including extinction cases are accurate to order $\mathcal{O}(1/N)$, and are indeed fully corroborated by our numerical results. Here we have examined the Allee effect using a quadratic population size-dependent saturation function; in general, however, our proposed method accommodates higher-order saturation functions as well.

It is necessary to be mindful, while analyzing the evolutionary dynamics in a many-genotype system with saturation effects, that there are two distinct time scales: a slow one describing changes in genotype distribution, and a fast one describing changes in population size. We assume that both mechanisms exist in the same model, for strong enough nonlinear saturation forces. At sufficiently large population sizes, population growth rate decreases due to saturation, whereas for excessively small population sizes the system goes to extinction. When the population size is very small, we need to consider the master equation [42].

Our key contribution in this paper is the generalization of the Crow-Kimura model, describing the growth and extinction dynamics when the fitness depends on many genes with epistasis. It is notable that the results presented in the current paper are not just limited to the modeling of genetic populations, but may be extended in analogous fashion to other disciplines where the Crow-Kimura model is applicable—for instance, to cancer tumor modeling, where evolution dynamics are strongly nonlinear with substantial saturation effects [43].

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