Weak mixed phase in the mutator model

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We consider the mutator model with unidirected transitions from the wild type to the mutator type, with different fitness functions for the wild types and mutator types. We calculate both the fraction of mutator types in the population and the surpluses, i.e., the mean number of mutations in the regular part of genomes for the wild type and mutator type, which have never been derived exactly. We identify the phase structure. Beside the mixed (ordinary evolution phase with finite fraction of wild types at large genome length) and the mutator phase (the absolute majority is mutators), we find another new phase as well—it has the mean fitness of the mixed phase but an exponentially small (in genome length) fraction of wild types. We identify the phase transition point and discuss its implications.

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I. INTRODUCTION

Statistical physics has been successfully applied to evolution theory, especially to the quasispecies model suggested for primordial life [1] and the description of virus evolution [2–4]. The reasons behind its success are the similarities between fitness and energy, the large number of degrees in the considered problem (the number of nucleotides in genome), and the quasilinearity of the evolution equations (the nonlinear system of differential equations can be mapped to the linear system of differential equations using a nonlinear algebraic transformation [5]). Many models have been solved exactly [6,7]. Lately, the quasispecies model has also found applications to fields such as cancer research [8] and learning theory [9]; it has become a key model of modern interdisciplinary research, attracting increasing attention from researchers.

An important aspect of modern evolution is related with the phenomenon of the mutator, first suggested in oncobiology [10–15]. The mutator concept has serious applications to bacteria as well [16–25]. While in the ordinary quasispecies model all the replicators replicate with constant mutation rate and fitness, in the mutator model there is a special gene that increases the mutation rate. We define the types without the mutation in the special genes as wild type and the types with mutation in that gene as mutator types. We can analyze the change of fitness landscape as well. This is related to the genome instability phenomenon in cancer, which has been considered as one of hallmarks of cancer [26]. The existence of mutators provides some advantage to the evolving population.

There has been some theoretical work to understand the mutator phenomenon related to the standard quasispecies model [17–29], and also some simplifications of the evolution process with constant mutation rates regardless of Hamming classes [30,31]. For us, what is especially important is the finding of the phase transition in the mutator model from the mixed phases to the mutator phase [18]. In Ref. [27], we gave a comprehensive investigation of the mutator model for the case of bilaterial mutator type–wild type transitions, focusing mainly on the case of symmetric transitions. In Ref. [29], we investigated the dependence of the mean fitness on the genome length in the case of bilateral asymmetric wild type–mutator type transitions. An intriguing phenomenon has been found: In the case of nonzero epistasis, the large system of ordinary differential equations can be mapped into a single nonlinear partial differential equation, though after some critical length this property is not valid. In Ref. [28], we solved exactly the mutator model for the linear fitness function with finite genome length, but we got rather cumbersome expressions. The statistical physics and mathematics for the asymmetric transition mutator model are the richest ones in infinite population size evolution models, especially for the limiting case: unidirected transitions from the wild type to the mutator type. Some results have been derived for the case when the fitness landscape is the same in both the mutator phase and the mixed phase [18,27], but the general case of the model with different fitness landscapes for wild type and mutator type was unsolved. The goal of this work is the solution of this general case, the identification of the phase structure and the calculation of the main characteristics: mean fitness and surpluses (mean number of mutations) in wild types and mutator types.

Let us now consider the mutator model. The genome is described as a chain of $N+1$ letters (genes) taking values ± 1, comprising a special gene and N ordinary genes. For the normal allele of a special gene, we have wild types. There are 2^N wild types, and the fraction of ith type in the population is given by p_i. For the alternative allele, we have 2^N mutator types, and their fractions are given by q_i.

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The probability distribution over the sequence space evolves according to the following system of equations:

$$\begin{aligned}\frac{dp_i(t)}{dt} &= p_i(t)\big(r_i^1 - \mu_1 - a_1 - R\big) \\ &\quad + \frac{\mu_1}{N}\sum_{j:d(i,j)=1} p_j(t) + a_2 q_i, \\ \frac{dq_i(t)}{dt} &= q_i(t)\big(r_i^2 - \mu_2 - a_2 - R\big) \\ &\quad + \frac{\mu_2}{N}\sum_{j:d(i,j)=1} q_j(t) + a_1 p_i, \\ R &= \sum_i \big(p_i(t) r_i^1 + q_i(t) r_i^2\big), \end{aligned} \tag{1}$$

where $d(i, j)$ is the Hamming distance between two sequences i and j (the number of point mutants that transforms the type i to type j), and μ_1 and r_i^1 are the mutation rate and fitness for the wild types respectively. For the wild type, the mutation rate is nonzero (equals μ_1/N) only between the sequences which are related via change of a single allele. We denote by μ_2 and r_i^2 the mutation rate and fitness of the mutator type respectively. a_1 and a_2 are the transition rates between wild types and mutator types. Consider the symmetric fitness landscapes for both wild types and mutator type. We define as the lth Hamming class the collection of all $N_l \equiv \frac{N!}{l!(N-l)}$ sequences with the same Hamming distance 1 from the reference sequence. We define P_l and Q_l as a sum of all p_i and q_i from the lth Hamming class, so $P_l = N_l p_i$, $Q_l = N_l q_i$, where p_i and q_i are the probabilities of single sequences from the lth Hamming class. We bet the following equations for P_l and Q_l, for $0 \leqslant l \leqslant N$:

$$\begin{aligned}\frac{dP_l(t)}{dt} &= P_l(t)[f_1(x_l) - \mu_1 - a_1 - R] \\ &\quad + \mu_1\left(\frac{N-l+1}{N}P_{l-1} + \frac{l+1}{N}P_{l+1}\right) + a_2 Q_l, \\ \frac{dQ_l(t)}{dt} &= Q_l(t)[f_2(x_l) - \mu_2 - a_2 - R] \\ &\quad + \mu_2\left(\frac{N-l+1}{N}Q_{l-1} + \frac{l+1}{N}Q_{l+1}\right) + a_1 P_l, \\ R &= \sum_l (P_l(t) f_1(x_l) + Q_l(t) f_2(x_l)), \end{aligned} \tag{2}$$

where $x_l = 1 - 2l/N$, and $f_1(x) = f(x)$, $f_2(x) = g(x)$ are the fitness functions.

Previously, we solved the case when both transition rates are nonzero [27]. The unidirected transition case $a_2 = 0$, $a_1 \equiv \alpha > 0$ is a singular case. In Sec. II, we solve the Crow-Kimura version of the mutator model with unidirected transitions and calculated the fraction of mutator type. In Sec. III, we solve the eigen model version of the mutator model. In the Appendix, we calculate the finite genome size corrections of the Crow-Kimura model version of the mutator model.

II. THE CALCULATION OF BULK VALUES OF FRACTIONS

We consider the unidirected transition version of Eq. (2):

$$\begin{aligned}\frac{dP_l(t)}{dt} &= P_l(t)(f_1(x_l) - \mu_1 - \alpha - R) \\ &\quad + \mu_1\left(\frac{N-l+1}{N}P_{l-1} + \frac{l+1}{N}P_{l+1}\right), \\ \frac{dQ_l(t)}{dt} &= Q_l(t)(f_2(x_l) - \mu_2 - a_2 - R) \\ &\quad + \mu_2\left(\frac{N-l+1}{N}Q_{l-1} + \frac{l+1}{N}Q_{l+1}\right), \\ R &= \sum_l (P_l(t) f_1(x_l) + Q_l(t) f_2(x_l)). \end{aligned} \tag{3}$$

Now, taking $\mu_1 = 1$, we consider the steady-state solution of the system by Eq. (3) for the wild types:

$$\begin{aligned} RP_l &= P_l(t)(f(x_l) - 1 - \alpha) \\ &\quad + \left(\frac{N-l+1}{N}P_{l-1} + \frac{l+1}{N}P_{l+1}\right). \end{aligned} \tag{4}$$

For nonzero P_l, we get that R is the maximum eigenvalue of the matrix on the right-hand side of equation. There is a well-developed theory for such a problem. We first calculate the mean fitness in the limited of infinitely large L and denote it as R_0. The derivation is given in Refs. [4,32], then will look $1/L$ corrections. We will look also the surpluses

$$\begin{aligned} s &= \sum_l (P_l + Q_l)(1 - 2l/N), \\ S_1 &= \frac{\sum_l P_l(1 - 2l/N)}{\sum_l P_l}, \\ S_2 &= \frac{\sum_l Q_l(1 - 2l/N)}{\sum_l Q_l}. \end{aligned} \tag{5}$$

We look the asymptotic expansions via degrees of $1/L$,

$$\begin{aligned} R &= R_0 + R_1/L, \\ S_1 &= s_0 + \frac{s_1}{L}, \\ S_2 &= s_0 + \frac{s_2}{L}, \quad S = s_0 + O(1/L), \end{aligned} \tag{6}$$

where s_0 is the bulk value of surplus. Then it is easy to derive the equations for the bulk terms in Eq. (7).

We define the ansatz

$$P_l = \exp\left(LU(x_l)\right), x_l = 1 - 2l/L, \tag{7}$$

with $O(1/L)$ accuracy:

$$\begin{aligned} \frac{l}{L} &= \frac{1-x}{2}, \\ P_{l\pm1} &= P_l \exp[- \pm 2U']. \end{aligned} \tag{8}$$

The Hamilton-Jacobi equation, rescaling the time L times:

$$\frac{\partial U}{\partial t} = f_1(x) - 1 - \alpha + \frac{1-x}{2}e^{-2U'} + \frac{1+x}{2}e^{2U'}. \tag{9}$$

We are interested in the static solution,

$$U(x) = Rt + U_0(x), \tag{10}$$

where R is the mean fitness. Putting the ansatz into Eq. (9), we obtain

$$R = f_1(x) - 1 - \alpha + \frac{1-x}{2}e^{-2p} + \frac{1+x}{2}e^{2p}, \tag{11}$$

where we denoted $p = U'$. To have a real value solution, we impose a condition:

$$R \geqslant \min\left[f_1(x) - 1 - \alpha + \frac{1-x}{2}e^{-2p} + \frac{1+x}{2}e^{2p}\right]_p$$
$$\equiv [f_1(x) - 1 - \alpha + \sqrt{1-x^2}]. \tag{12}$$

Replacing the inequality sign in Eq. (12), we obtain [6]

$$f'(x_0) - \frac{x_0}{\sqrt{1-x_0^2}} = 0,$$
$$R_0 = f(x_0) + \sqrt{1-x_0^2} - 1 - \alpha. \tag{13}$$

According to our ansatz, Eq. (7), there is a narrow peak (width $\sim 1/\sqrt{N}$ in the x space). In the definition of $s = \frac{\sum_l P_l x_l}{\sum_l P_l}$, we can just take the value of x_l at the maximum point $x = s_0$ of $U(x)$ function, obtaining $s = s_0 + O(1/L)$. At the maximum point $x = s_0$, we have $U'(s_0) = 0$, so Eq. (11) gives an accuracy $O(1/L)$

$$R_0 = f(s_0) - \alpha. \tag{14}$$

From the solution of the Crow-Kimura model [32], we have after rather lengthy derivations

$$R_1 = \frac{1}{\sqrt{1-x_0^2}}\left[1 - \sqrt{1 - \left(1-x_0^2\right)^{3/2} f''(x_0)}\right],$$
$$s_1 = \left(R_1 - s\frac{f''(s_0)}{f'(s_0)}\right)\frac{1}{f'(s_0)}. \tag{15}$$

Consider the following representation for P_l near the maximum point,

$$P_l = \frac{\sqrt{A}}{\sqrt{2L}}\exp\left[-\frac{A(l-l_0)^2}{2L} + \frac{k_1(l-l_0)}{L}\right], \tag{16}$$

where [32]

$$A = \frac{f'(s_0)}{2s_0} \tag{17}$$

and (see Ref. [32])

$$k_1 = \frac{1}{2s_0}\left(R_1 - s_0\frac{f''(s_0)}{f'(s_0)}\right). \tag{18}$$

Our goal is to calculate

$$P = \sum_l P_l \tag{19}$$

and s_2, which has not been solved in previous works.

Let us first define P in the bulk approximation. The sum via l in the steady state gives

$$RQ = \sum_l Q_l g(x_l) + \alpha P. \tag{20}$$

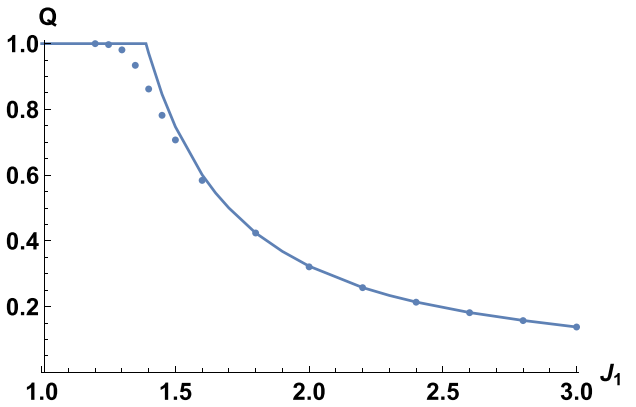

FIG. 1. $Q \equiv q$ vs the parameter J_1 for the mutator model with $J_1 = 1$, $J_2 = 2$, $N = 1000$, $f_1(x) = J_1 x$, $f_2(x) = J_2 x$, $\alpha = 1$. The smooth nonhorizontal line is given by our analytical formulas Eq. (26) (below the critical point we take a solution $Q = 1$), and the solid dots are the numerical results by Eq. (4). There is a phase transition point near $J_1 \approx 1.39$.

This is an exact equation. Consider the following representation for Q_l:

$$Q_l = \frac{\sqrt{A}}{\sqrt{2L}}\exp\left[-\frac{A(l-l_0)^2}{2L} + \frac{k_2(l-l_0)}{L}\right]. \tag{21}$$

Consider the $1/L$ expansion of $\sum_l Q_l g(x_l)$:

$$\sum_l Q_l g(x_l) \approx Q[g(s_0) + R_2/L],$$
$$R_2 = [g'(s_0)k_2 + g''(s_0)]. \tag{22}$$

The second equation in Eq. (22) has been derived directly from Eq. (21).

A. The bulk term for the mutator fraction

We have a peak of the distribution near the point $x_l = s_0$. Then $R = < f(x) > p + q < f_2(x) >$ together with Eq. (20) gives a system of equations to define s_0, q:

$$Rq = qg(s_0) + \alpha p,$$
$$R = pf(s_0) + qg(s_0), \tag{23}$$

where $p = 1 - q$ or

$$[(1-q)f(s_0) + qg(s_0)]q = qg(s_0) + \alpha(1-q). \tag{24}$$

Thus, we obtain

$$q^2(g(s_0) - f(s_0)) + [f(s_0) - g(s_0) + \alpha)]q - \alpha = 0. \tag{25}$$

A trivial solution is $q = 1$. An alternative solution is

$$q = \frac{\alpha}{f(x_0) - g(x_0)}. \tag{26}$$

Equation (26) is our main result. Figure 1 illustrates the accuracy of our theoretical result.

For the linear fitness function $f(x) = cx$, we have

$$s_0 = \frac{\sqrt{c^2+1} - 1}{c}, \tag{27}$$

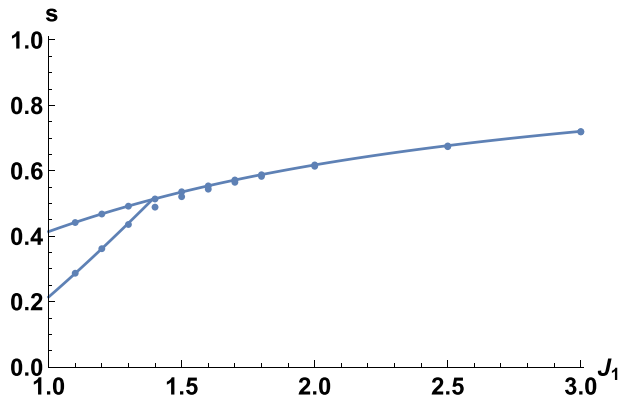

FIG. 2. The surpluses s_1, s_2 vs J_1 for the mutator model with $N = 1000$, $f_1(x) = J_1 x$, $f_2(x) = J_2 x$, $J_1 = 1, J_2 = 2$, $\alpha = 1$. The smooth line is given by our analytical formulas, and the solid dots are the numerical results by Eq. (4). We start from any initial configuration and then solve the system of equations using Runge-Kutta methods. The upper line corresponds to s_1, and the low line to s_2. There is a phase transition point near $J_1 \approx 1.39$.

and for the quadratic case $f(x) = cx^2/2$,

$$s_0 = 1 - \frac{1}{c}. \tag{28}$$

For the case when the mutator has the same fitness function as the wild type but different mutation rates, we get the solution

$$q = 1. \tag{29}$$

The latter result is correct for infinite genome length. For finite but large genome length, we have $P \ll Q$. The asymptotic expression has been derived in Ref. [27].

B. The phase structure of the model

Consider again the general case, with different fitnesses. At small α, we have a small q. Increasing α, we met a situation q became 1 at some α. As $q \leqslant 1$, it is a phase transition point. We verify that there is a phase transition point, and for different fitness functions the second equation in the system by Eq. (23) gives for the critical point

$$g(s_0) = R. \tag{30}$$

After the critical point, we have again the mean fitness expression by Eq. (13). In the case of $f(x) = g(x)$, there was an exponentially small (in N) fraction of wild types [27]. We assume a similar situation for the case $f(x) \neq g(x)$ as well. We define such a phase as a weak mixed phase. Now we have different expressions for the surpluses of wild type and mutator type (see Fig. 2). Figure 3 illustrates the phase structure of the model. The mutator phase has the following expression for the mean fitness [27]:

$$g'(x_0) - \frac{x_0}{\sqrt{1 - x_0^2}} = 0,$$

$$R_0 = g(x_0) + \sqrt{1 - x_0^2} - 1. \tag{31}$$

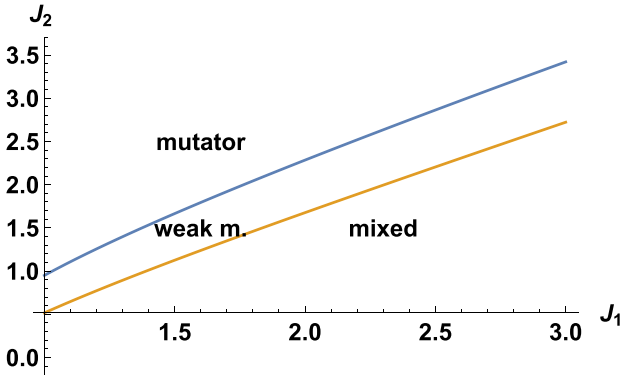

FIG. 3. The phase space of the mutator model with $f_1(x) = J_1 x$, $f_2(x) = J_2 x$, $J_2 = 2$, $\alpha = 2$. There are three phases: mutator phase (mutator), mixed phase (mixed), and weak mixed phase (weak m).

When the R_0 by Eq. (30) is larger than R_0 by Eq. (5), we have the mutator phase; otherwise, we are in the mixed phase or the weak mixed phase.

III. EIGEN MODEL VERSION FOR MUTATOR MODEL FOR DIFFERENT FITNESS IN WILD TYPE AND MUTATOR TYPE

The Eigen model version for the mutator model has been considered in Refs. [18,27]. We now formulate the model and provide analytical solutions.

Let us consider now the following system of equations for $p_i, q_i, 0 \leqslant i < 2^N - 1$:

$$\frac{dp_i(t)}{dt} = \sum_j p_j r_j e^{-h} Q_{ji} - p_i \sum_j (r_j p_j + \hat{r}_j q_j),$$

$$\frac{dq_i(t)}{dt} = \sum_j q_j \hat{Q}_{ji} + \sum_j p_j \hat{r}_j (1 - e^{-h}) Q_{ji}$$

$$- q_i \sum_j (r_j p_j + \hat{r}_j q_j). \tag{32}$$

Here r_i and $\hat{r}_i$ are the fitness functions for the wild type and mutator type. Q_{ij} and $\hat{Q}_{ij}$ are the corresponding mutation transition probabilities, with $Q_{ij} = q^{L-d(j,i)}(1-q)^{d(j,i)}$, where q is the probability of errorless replication per nucleotide for the p_i sequences. $1 - e^{-h} \approx h$ is the transition probability from the wild type to the mutant type.

We denote $Q_{ii} = q^L \equiv Q \equiv e^{-\gamma}$, where $\gamma = -N \ln(q) \approx N(1-q)$ is the parameter of mutation in the Eigen model. $\hat{Q}_{ij} = \hat{q}^{N-d(j,i)}(1-\hat{q})^{d(j,i)}$, where $\hat{q}$ is the probability of errorless replication per nucleotide for the q_i sequences. $d(i, j)$ is the Hamming distance between two sequences i and j: It is defined as the number of point mutations to get the sequence i from the sequence j.

We choose fitness functions

$$r_j = f(x), \hat{r}_j = g(x), \tag{33}$$

where $x = d(j, 0)$. In the mixed phase, we have the fitness of the pure eigenmodel with the fitness function $f(x)e^{-h}$, so we can use the result of Ref. [33] for the mean fitness R and

surplus

$$R = \max\left[f(x)e^{-h+\gamma(\sqrt{1-x^2}-1)}\right]|_x, R = f(s). \quad (34)$$

Taking the sum via index i in the steady-state version of Eq. (33), we have

$$Q(f(s)e^{-h} - R) + (1 - e^{-h})P = 0. \quad (35)$$

Substituting for the expression for R, we get

$$Q(f(s)e^{-h} - [Qg(s) + (1 - Q)f(s)]) + (1 - e^{-h})(1 - Q) = 0. \quad (36)$$

Equation (36) defines the fraction of mutators in the population. Again we have three phases: mixed, mutator, and weak mixed. For the mutator phase, we have the following expression for the mean fitness:

$$R = \max\left[g(x)e^{-h+\gamma(\sqrt{1-x^2}-1)}\right], \quad (37)$$

where the maximum is via x. The system is selecting the mutator phase, when the mean fitness by Eq. (37) is higher than the one by Eq. (36), the transition between the mixed and weak mixed phases is at the point where

$$R = g(s). \quad (38)$$

Again, the case $f(x) = g(x)$ is a degenerate situation, giving for the large-L case $Q = 1$.

IV. CONCLUSION

The quasispecies model describes adequately both the origin of life and virus evolution. The related mutator phenomenon is an important concept of modern evolution theory and has in recent years attracted serious attention from many experts in statistical physics. The model has highly intriguing phase structure and nontrivial mathematics. In the case of symmetric transition rates between wild type and mutator type, we have rather simple and well-confirmed analytical results. More involved is the situation in the case of asymmetric transitions. In this article, we investigated the mutator model for the case of unidirected transitions from the wild type to the mutator type when the fitness functions are different. We handled some simple version of asymmetric transitions from wild type to mutator type. We solved the model, identifying both the phase structure and the order parameters. Besides the mutator phase (the evolutionary properties are completely defined by the mutator type, so we can simply drop the wild types in equations), there is a phase with mean fitness defined by the wild-type fitness landscape, but with a fraction of the wild population that decreases exponentially with the genome length.

We calculated the fraction of mutator types in the model, as well as the surpluses for the wild and mutator types. We defined the fraction of mutator types for the eigenmodel version of the mutator model as well. In the Appendix, we calculated the finite genome size corrections in the Crow-Kimura version of the model. All our results are derived for the infinite population case. As the unidirected transition version of mutator has such interesting statistical physics, we hope that the same should be with the finite population version of the model.

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APPENDIX: THE FINITE-SIZE CORRECTIONS

Now we should calculate q_1 and k_2, so we need two equations. Assuming $Q = q + q_1, P = p - q_1$, we get from the definition of the mean fitness by the last line of Eq. (2) and from Eq. (7):

$$\left(q + \frac{q_1}{L}\right)\left(f + \frac{R_1}{L}\right) + \left(g + \frac{R_2}{L}\right)\left(p - \frac{q_1}{L}\right) = R + \frac{R_1}{L};$$

see Eq. (16) for the definition of R_2. Looking the $1/L$ order terms gives

$$fq_1 + qR_1 + pR_2 - q_1 g - R_1 = 0. \quad (A1)$$

Then, looking the sum via l in the second equation in Eq. (3) at the steady state and Eq. (16), we get

$$(R + R_1/L - g - R_2/L)(q + q_1/L) - \alpha p + \alpha q_1/L = 0.$$

Looking at the $1/L$ order terms, we get

$$Rq_1 + q(R_1 - R_2) + \alpha q_1. \quad (A2)$$

Thus, we get a system of equations for q_1, R_2:

$$(f - g)q_1 + pR_2 = R_1(1 - q),$$
$$(R + \alpha)q_1 - qR_2 = -qR_1. \quad (A3)$$

Having the expression for R_2, we can calculate k_2 and then s_2:

$$k_2 = \frac{A}{g'}\left(R_2 - \frac{g''}{2A}\right). \quad (A4)$$

Then, from the second equation in Eq. (8), we get

$$s_2 = \frac{1}{g'}\left(R_2 - \frac{g''}{2A}\right) = \frac{1}{g'}\left(R_2 - \frac{s_0 g''}{2f'}\right). \quad (A5)$$

We have a system of equations to derive the expressions for s_2, R_2. For the linear fitness case $f(x) = cx$, our system of equations is degenerate, so perhaps we should look for some quadratic weak term to dismiss, calculating s_2, q_1 at that limit.

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