Biological evolution model with conditional mutation rates

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Abstract

We consider an evolution model, in which the mutation rates depend on the structure of population: the mutation rates from lower populated sequences to higher populated sequences are reduced. We have applied the Hamilton-Jacobi equation method to solve the model and calculate the mean fitness. We have found that the modulated mutation rates, directed to increase the mean fitness.

Keywords: Crow-Kimura model, modulated mutation rates, complex system

1. Introduction

Ideas and methods of statistical physics have been applied to study various interesting interdisciplinary research problems, such as literary authorship disputes [1, 2, 3], financial fluctuations [4, 5, 6, 7, 8, 9], and biological evolution [10, 11, 12, 13, 14]. In this paper, we will address an interesting problem in molecular models of biological evolution.

In recent decades, there was much progress in the study of asexual biological evolution models [10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26] with fixed fitness landscape and constant mutation rates. In such models, a genome with L genes is represented by a chain of L spins (alleles) and every spin takes the values ± 1, similar to the Ising model [27]. There are 2^L different

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types of sequences $S_i \equiv (\sigma_1^{(i)}, \sigma_2^{(i)}, \ldots, \sigma_L^{(i)})$, $0 \leq i \leq 2^L - 1$ with corresponding probabilities p_i and the fitness r_i. The Hamming distance between S_i and S_j is given by

$$d_{ij} \equiv (L - \sum_{k=1}^{L} s_i^{(k)} s_j^{(k)})/2.$$

Without the loss of generality, we can choose the sequence with the largest r_i value as a reference sequence and denote it as S_0 with all spin components being +1. During a short period of time dt, any allele can change the type (from +1 to -1 or from -1 to +1) with the probability μdt.

There are two famous molecular models of biological evolution. One is the Eigen model [10, 14, 20, 22] with coupled mutation-selection scheme, in which mutation and reproduction appear in the same term in the equations for p_i; another is the Crow-Kimura model [11, 17, 21] with parallel mutation-selection scheme, in which the equations for p_i appear in different terms. The Crow-Kimura model has been mapped into the quantum statistical model of the Ising model in the transverse magnetic field [17]; in such a mapping, the genome length L is corresponding to to the lattice size of the lattice spin model [27]. A lattice model may have a phase transition when the lattice size approaches to infinite. To get different phases for evolutionary dynamics, we need rather large genome length [21] and population size.

The calculated quantities in biological evolution models include the mean fitness [17, 19, 22], the steady state distribution [23, 24, 28], and population dynamics [25, 29]. These solutions supported the idea that there is something more than a "climbing of fitness hills" [30] (the population moves in the genome space to the genome with the maximal fitness) and there are essentially collective (emergent) phenomena in evolution, including the error threshold [10] (the phase transition from the phase where the majority of population is around the high peak to the phase with uniform distribution of population) and selection via the flatness phenomenon [13] (the group of sequences with the equal fitness, the flat peak, can attract more population than single sequence with a higher fitness). The refereed phenomena have a collective behavior, while "hill climbing" can be organized simply, without any collective interaction. The collective phenomenon is a result of the statistical physics aspects of evolution models, as has been realized by Tarazona [15].

The mentioned phenomena was found in the evolution with the fixed fitness landscape and looks like a cooperation between replicators with different genomes. The fixed fitness landscape had been modified to take into account some more realistic situation. Bratus, *et al.* [31] considered explicit space and global regulation of the Eigen model to study the diffusive stability of the model. A spatial quasispecies model was studied in [32]. The experimental results reported in [33] support the idea that there are more involved collective effects in evolution, when viruses of different types (quasispecies) interact with each other during the evolution processes, getting some advantage for the whole population. During the experiments two virus populations have been isolated, the wild-type, and the second virus population with the suppressed mutation rate

due to a special point mutation. As a result, the second virus population has approximately the same fitness landscape as the first one, while carries 6 times less mutations. After putting the virus population in the new environment, the first, more heterogenous population, was much more effective at infecting new cells than the second one. It has been suggested that there are some cooperative interactions between viruses with different genomes. It is a highly involved phenomenon. While the mutation process is mainly random, its strength is somehow modulated according to the current structure of population. The phenomenon observed in [34] has been identified either as a second level selection (the high fitness does not mean that such a sequence will attract the majority of population), or as a selection via evolvability, when the evolving population tends to have an evolution advantage in changing environments. It is impossible to describe such a phenomena using a simple evolution scheme with a constant mutation rate and fitness landscape. There are good experimental confirmations that the mutation rate has been well modulated for different parts of genome [35]. The cooperative phenomenon in case of cancer cells clonal evolution is even stronger than in case of viruses [36].

In the current work we construct a simple generalization of the traditional quasispecies model with the mutation rate modulated by the sequence distribution in the population. The mutation rate between the adjacent Hamming classes (groups of sequences with the same number of mutations from the reference sequence) depends on the ratio of the number of viruses on these chasses, therefore we have somehow modulated asymmetry of mutation rates. The asymmetry of mutation rates is well confirmed experimentally [37]. In our model the population itself modulates the mutation rates, while in [33] it is done artificially. What is common in both cases, the existence of different mutations rates, the heterogeneity of population, brings to the evolutionary advantage. The advantage of our model is that it is still exactly solvable. The dependence of the fitness on the population distribution is well known phenomenon in evolutionary game models [38, 39]. Another well known case of the changing of the mutation rate by the virus population is a mutator phenomenon, well confirmed by experiments [40]. Our model assumes the modulation of mutation rate by population distribution, and it is much more involved to solve the current model than the mutator model [29, 41].

Here we consider the parallel mutation selection scheme of the Crow-Kimura model [11, 17, 21], the selection and mutations are two parallel processes, contrary to the Eigen model where the selection is coupled with the mutation [14].

We consider the case of symmetric fitness landscape when the fitness is a function of number of mutations from the reference sequence. For such a model with symmetric original distribution of viruses, it is possible to get a short set of $L+1$ equations [12, 16, 18] for the probabilities. The probabilities of the sequences at the same Hamming distance from the reference sequence (number of mutations from the reference sequence to the given sequence) are the same, there are $N_l = \frac{L!}{l!(L-l)!}$ sequences in the l-th Hamming class (the collection of all the sequences with the l mutations from the reference sequence).

In the Crow-Kimura model [11, 17, 21], we consider the following system of equations for the probabilities P_l of the whole Hamming class:

$$\frac{dP_l}{dt} = r_l P_l + \frac{\mu}{L}(P_{l-1}(L-l+1) + (l+1)P_{l+1} - LP_l) - P_l \sum_{n=0}^{L} r_n P_n, \quad (1.1)$$

Here r_l is the fitness of the sequence from the l-th Hamming class. The last term in Eq.(1.1) ensures that the balance condition $\sum_n P_n = 1$ is maintained in time evolution.

2. The model with conditional mutation rates for the Hamming class probabilities

2.1. The statics of the model for the smooth fitness landscape

Let us modify the mutation rates in the model by Eq.(1.1): the mutation rates from one class to the adjacent are attenuated, if the original class has a smaller probability than the class after mutation:

$$\begin{aligned}\frac{dP_l}{dt} &= r_l P_l + \frac{\mu}{L}(P_{l-1}(L-l+1)J(P_{l-1}-P_l) + (l+1)P_{l+1}J(P_{l+1}-P_l) \\ &- P_l((L-l)J(P_l-P_{l+1}) + lJ(P_l-P_{l-1}))) - P_l\sum_{n=0}^{L} r_n P_n. \quad (2.1)\end{aligned}$$

where $J(y) = 1,\ y > 0$ and $J(y) = c,\ y < 0$. We take $0 \le c \le 1$. For the steady state solution $\hat{P}_l$ we have a system of equations

$$\begin{aligned}&r_l\hat{P}_l + \frac{\mu}{L}(\hat{P}_{l-1}(L-l+1)J(\hat{P}_{l-1}-\hat{P}_l) + (l+1)\hat{P}_{l+1}J(\hat{P}_{l+1}-\hat{P}_l) \\ &-\hat{P}_l((L-l)J(\hat{P}_l-\hat{P}_{l+1}) + lJ(\hat{P}_l-\hat{P}_{l-1}))) = R\hat{P}_l, \\ &R = \sum_{n=0}^{L} r_n\hat{P}_n, \quad (2.2)\end{aligned}$$

where R is the mean fitness. We see that R is the eigenvalue of the matrix on the left hand side of the latter equation. The non-diagonal elements of the matrix are all positive numbers, therefore we can apply the Perron-Frobenius theorem, stating that the maximal eigenvalue R_0 of such matrix is unique. Thus the solution of the linear system

$$\begin{aligned}\frac{dP_l}{dt} &= r_l P_l + \frac{\mu}{L}(P_{l-1}(L-l+1)J(P_{l-1}-P_l) + (l+1)P_{l+1}J(P_{l+1}-P_l) \\ &- P_l((L-l)J(P_l-P_{l+1}) + lJ(P_l-P_{l-1}))) \quad (2.3)\end{aligned}$$

after large period of time is

$$P_l = \hat{P}_l \exp[R_0 t]. \quad (2.4)$$

We replace r_l with the function $f(x)$:

$$r_l = f(1-2l/L) \equiv f(x), \quad x \equiv 1-2l/L, \tag{2.5}$$

where we choose the function under the constraint

$$\begin{aligned} &f(x) \geq 0, \quad x > 0, \\ &f(0) = 0. \end{aligned} \tag{2.6}$$

To solve the model we assume the following ansatz [23, 24]

$$P_l = \exp[Lu(x,t)]. \tag{2.7}$$

Then we obtain the following Hamilton-Jacobi equation (HJE):

$$\begin{aligned} \frac{\partial u(x,t)}{\partial t} &+ H(x,u') = 0, \\ -H &= f(x) + \mu[\frac{1+x}{2}e^{2u'}J(u') + \frac{1-x}{2}e^{-2u'}J(-u') - \frac{1+x}{2}J(u') \\ &- \frac{1-x}{2}J(-u') - f(s(t))], \end{aligned} \tag{2.8}$$

where $u' = \partial u(x,t)/\partial x$, $s(t)$ is the maximum point for the $u(x,t)$. To solve Eq.(2.8) we drop the last term, then recover the solution of Eq.(2.8) considering the transformation $u \to u - \int f(s(t))dt$.

Thus we look at the equation

$$\begin{aligned} \frac{\partial u(x,t)}{\partial t} &+ H(x,u') = 0, \\ -H &= f(x) + \mu[\frac{1+x}{2}e^{2u'}J(u') + \frac{1-x}{2}e^{-2u'}J(-u') \\ &- \frac{1+x}{2}J(u') - \frac{1-x}{2}J(-u')]. \end{aligned} \tag{2.9}$$

We have two branches of the Hamiltonian: for $u' > 0$,

$$-H_+ = f(x) + \mu[\frac{1+x}{2}e^{2u'} + \frac{1-x}{2}e^{-2u'}c - \frac{1+x}{2} - \frac{1-x}{2}c], \tag{2.10}$$

and for $u' < 0$

$$-H_- = f(x) + \mu[\frac{1+x}{2}e^{2u'}c + \frac{1-x}{2}e^{-2u'} - \frac{1+x}{2}c - \frac{1-x}{2}]. \tag{2.11}$$

The asymptotic solution of Eq.(2.9) can be used to calculate the mean fitness $R = \sum_l P_l r_l$ at the steady state. Let us assume that there is a solution for the HJE

$$u(x,t) = R_0 t + u_0(x). \tag{2.12}$$

Such an assumption is certainly correct in the case of our model with a single maximal eigenvalue of the corresponding system of linear equations (2.3).

Then the mean fitness in the steady state is

$$R = R_0 \tag{2.13}$$

To define the R_0, we follow idea of [23]. At any point x, we define the potentials $U_{\pm}(x)$ as

$$U_{\pm}(x) = \min_p[-H_{\pm}(x,p)]. \tag{2.14}$$

Let us put the ansatz by Eq.(2.12) in the HJE by Eq.(2.9). We have a real number solution, when

$$R_0 = \max_{-1\leq x\leq 1} U(x) \equiv U(x_m). \tag{2.15}$$

If we assume that the maximum of distribution is at some point s,

$$\begin{aligned} U(x) = U_+, x > s, \\ U(x) = U_-(x), x < s \end{aligned} \tag{2.16}$$

The s is defined by the equation [18]

$$R_0 = f(s) \tag{2.17}$$

Assuming that the maximum of $U(x)$ is at some $x > s$, we derive:

$$U(x) = f(x) + [\sqrt{c(1-x^2)} - \frac{1-x}{2} - c\frac{1+x}{2}]\mu. \tag{2.18}$$

Equations (2.13), (2.15) and (2.18) can be used to obtain analytic result for R.

To test the accuracy of our analytic equations for R, we used the Euler algorithm [42] to solve Eq. (2.1) directly for the fitness function $r = f(x) = kx^2/2$ and $L = 500$. The numerical results for c=0.75, 0.5, and 0.25 are shown as black dots in Fig. 1, which are consistent very well with the smooth curves calculated from our analytic equations for R. The dashed line corresponds to the case $c = 1$ of the Crow-Kimura model. Figure 1 shows that for a give k, R increases when c decreases from 1, i.e. modulated mutation rates in our model can enhance the mean fitness. To make this point even more clear, we plot the mean fitness R as a function of c for mutation rate $\mu = 1$, the fitness function $f(x) = kx^2/2$ with k =1, 2, and 3 in Fig. 2, which also shows that R increases as c decreases from 1.

2.2. Single peak fitness case

As another test of analytic equations in Section (2.1), we consider the single peak fitness of the Crow-Kimura model [11, 17, 21]. In this case we can take

$$\begin{aligned} f(1) = A, \\ f(x) = 0,\ x < 1. \end{aligned} \tag{2.19}$$

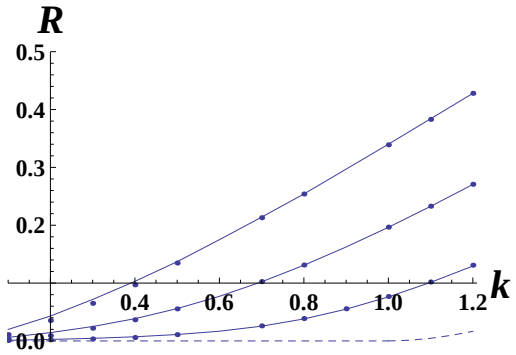

Figure 1: The mean fitness versus the parameter k for the model with $L = 500$, $f(x) = kx^2/2$ for $c = 0.25$, $c = 0.5$, $c = 0.75$, $\mu = 1$ (from up to down). The smooth lines are our analytical results obtained from Eqs. (2.13), (2.15) and (2.18) and the dots are corresponding to the numerical results by solving Eq. (2.1) with the Euler algorithm [42]. The dashed line corresponds to the case $c = 1$ of the Crow-Kimura model.

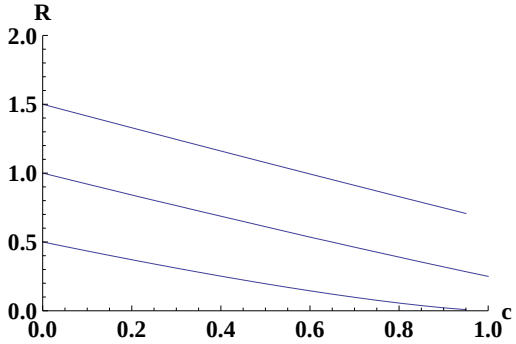

Figure 2: The mean fitness versus the parameter c for the model with $f(x) = kx^2/2$ for $k = 1, k = 2, k = 3, \mu = 1$ (from up to down). Equations (2.13), (2.15) and (2.18) were used to obtain analytic result for R

The maximum of the distribution is at l=0 (x=1), then it decreases monotonically. Thus, we should take the branch $U_+(x)$ of the potential.

Our analytic equations in Section (2.1) give

$$R = A - \mu, \tag{2.20}$$

which coincides with the result of the Crow-Kimura model [11, 17, 21].

3. Conclusion

It has been assumed that mutations are not completely random, their frequencies are somehow controlled during the evolutionary dynamics. The phenomenon is important both for the viruses evolution and clonal evolution of cancer cells. It is important to construct such a model. The construction of evolution models with the changing fitness landscape and mutation rate is the mainstream of current evolutionary research [43]. Our goal was to construct a simple generalization of the evolution model with controlled mutation rates. We considered the evolution model with the simplest version of cooperation: the mutation from one Hamming class to another class with higher population attenuated, thus enhancing the heterogeneity of population. Such cooperation strongly changes the evolution picture, creating the nonlinearity. Figure 2 illustrates how the mean fitness R changes with the parameter c. We solved the model in the simplest case, when the mutation rule is defined via the nearest neighbors, using a simple Hamilton-Jacobi equation approach, and the numerics supported our analytical result for the mean fitness, derived with a $O(1/L)$ relative accuracy. The clonal evolution of cancer not only is strongly nonlinear, but includes also some logic, swarm intellect. What we have done is to introduce simple modification of the clonal evolution model: when the population of one Hamming class is smaller than the population of the neighboring class, then decreases the mutation rate. Our model involves strongly non-linear (non-analytical) change of the model equations, versus simple analytical change of the dynamics rules due to population structure in evolution games. In this article we just considered the conditional mutation rate, but the same mathematical tools can be applied for the conditional fitness function as well.

Usually it is assumed that the heterogeneity of the population gives an evolutionary advantage in case of changing environments [38]. According to our results, the modulated mutation rate, directed to increase the population heterogeneity, can strongly increase the mean fitness of population as well. Our result is valid for the general case of the symmetric fitness landscape. We assume that similar situation (increased heterogeneity, highly complicated dynamics) exists in case of evolution models with conditional selection, as well as in evolutionary games.

The master equation in our case describes the dynamics of the fractions of population, as 1-dimensional chain of equations. The similar models have been considered in Parrondo games with capital dependent rules [44]. It is possible to write the master equation again as a chain of equations for the probabilities

having different capitals [45], and ,actually, there is a "period of potential", a parameter M in the Parrondo models. In the situation, when the mutation rule is defined by several M Hamming classes, we have a similar mathematical problem as in the case of Parrondo games with the parameter M.

One can also consider to introduce the conditional mutation rate in the mutator model for cancer [46]. It is interesting to find the dynamics of our model, while it is a much harder problem than the solution of the dynamics of the Crow-Kimura model [25]. A similar threshold like terms in the dynamics of the linear simple model bring the dynamics to the rather complex situation, similar to that in the Kolmogorov-Fisher equation [47].

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