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Randomization Effect of The Site Mutation Rate on The Error Threshold in the Crow−Kimura Model*

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Abstract In order to complement the randomization of the Eigen model and the Crow-Kimura model, the site mutation rate in the Crow-Kimura model is treated as a Gaussian distributed random variable. The characteristics of the error threshold as well as the relationship between the extension of the error threshold and the fluctuation strength of the randomized mutation rate are investigated. It is shown that both the relative concentrations and the order parameter indicate the error threshold is no longer a phase transition point but a smooth crossover region in the presence of a sizable fluctuation of the site mutation rate. The quantitative analysis demonstrates that the relationship between the width of the crossover region and the fluctuation strength in the mutation randomized Crow-Kimura model is nonlinear. The obtained results are compared with those from the randomized Eigen model and it is found that for the two randomized models the relationship between the width and the fluctuation strength is linear for the randomized fitness and nonlinear (exponential) for the randomized site mutation rate. For the randomized Crow-Kimura model the width caused by the randomized fitness is comparable to that caused by the randomized site mutation rate. Nevertheless, for the randomized Eigen model the width is mainly caused by the randomized site mutation rate. A full picture about the randomization effects of the fitness and site mutation rate on the error threshold based of the Eigen model and the Crow-Kimura model is then outlined. The implications of the above results for anti-viral strategies, cancer therapy and breeding of animals and plants are discussed.

Key words mutation rate, Crow-Kimura model, quasispecies, error threshold, Gaussian distributed random variables
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In 1971 Manfred Eigen[1] proposed a model for the origin of genetic information in a prebiotic scenario which contains biological, physical, chemical, mathematical and information-theoretic aspects and is dubbed as the Eigen molecular quasispecies model (Eigen model). The Eigen model is nevertheless a far-reaching model and has turned out to be very useful for describing the evolution dynamics of a general species population with a mechanism of selection and mutation. In the Eigen model, since the species is subject to a mutation during the self-replicating process the mutation is coupled with the selection, which is the so-called coupled mutation selection scheme. Another successful molecular quasispecies model is the Crow-Kimura model where the mutation and selection are considered as two independent processes, more specifically, the molecular self-replication is accurate (even if there are some errors, they could be repaired completely), and the mutation is caused by environmental factors, such as radiations, mutagens, free radicals and thermal fluctuations. The Crow-

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Kimura model is therefore called as the parallel mutation selection scheme[2]. Both the two schemes of mutation and selection are relevant to biology and they are similar to each other in the case of low mutation rates[3-4] although which is the better and more practical scheme remains a question of debate. Both the Eigen model and the Crow-Kimura model have been extensively studied in the past four decades[5-15]. They shared so much in common, especially their steady state properties. For instance, both of them give the error threshold in many fitness landscapes and display the quasispecies for small mutation rates, which serve the most interesting and important features of the two models[2, 5]. The quasispecies means the distribution of some mutant sequences localized around the master sequence. The error threshold is a point above which there is no genetic information in the macromolecules and all of the sequences are randomly distributed in the sequence space. The characteristics of the quasispecies and error threshold have been confirmed by many experiments[16-18], which certainly illuminates the prediction power of the two models.

Species evolution in nature is however always influenced by many stochastic factors, for instance, random genetic mutations and environmental fluctuations. Essentially, it is a process of interaction between species populations and their environments. The important physical parameters appearing in species evolution models are therefore subject to various random factors and should be stochastic. Indeed, the randomized study on biological processes both in theory and experiment has become quite active[19-22]. The foot-and-mouth disease virus (FMDV) evolution experiments found that the relative fitness of the virus appears a fluctuating pattern around a constant average fitness[23-24]. The fitness and mutation rate are the two key physical parameters both in the Eigen model as a coupled mutation selection scheme and the Crow-Kimura model as a parallel mutation selection scheme. They measure the selection and mutation of species evolution and govern the dynamics and steady state properties of the two models.

In the framework of the Eigen model, the fitness and mutation rate were treated as Gaussian distributed random variables[25-27]. The change of the error threshold due to the randomization was systematically and exhaustively examined and the interesting feature for a randomized quasispecies to pass through the error threshold was found and well understood. It was found that the error threshold appears as a crossover region instead of a phase transition point in the randomized Eigen model, and the width of the crossover region defined[26-27] increases linearly with the fluctuation strength of the randomized fitness and nonlinearly with the fluctuation strength of the randomized mutation rate. The width induced by the randomized mutation rate is much greater than that caused by the randomized fitness. The width is sizable for large fluctuations, especially in the case of the randomized mutation rate, which suggests that the upper limit of the crossover region should be reached in order to completely drive viruses to go extinct. In the existing work[25], the fitness was described as a Gaussian distributed random variable in the framework of the Crow-Kimura model and the modification of the error threshold due to the randomization was investigated. With a parallel mutation selection scheme, the randomization of the mutation rate has been not yet reported. The mutation in the parallel scheme may be caused by many environmental factors, such as radiations, mutagens, free radicals and thermal fluctuations as mentioned before. Some of them are usually uncontrollable and unpredictable. As a result, the mutation rate should be a random variable.

In this work, in order to complement the randomization of the Eigen model and the Crow-Kimura model, the mutation rate in the Crow-Kimura model is treated as a Gaussian distributed random variable. The focus of the present work is placed on the characteristics of the error threshold as well as the relationship between the extension of the error threshold and the fluctuation strength of the randomized mutation rate. The obtained results are compared with those from the randomized Eigen model to see the similarity and difference between the two randomized models having different mutation and selection schemes. In section 1, we introduce the conventional Crow-Kimura model and the randomized Crow-Kimura model as well. In section 2, based on the mutation randomized Crow-Kimura model, the ensemble averaged relative concentrations are computed and a quantitative analysis for the extension of the error threshold is performed. Meanwhile, to further examine the change of the error threshold an order parameter is calculated for different

values of the fluctuation strength of the randomized mutation rate. In addition, the obtained results are compared with those coming from the Crow-Kimura model with the randomized fitness and from the randomized Eigen model. Finally, concluding remarks are made in section 3.

1 Models

The Crow-Kimura quasispecies model was proposed to study the *Drosphilla*'s evolution before the Eigen quasispecies model, which was given some consideration in Chapter 6 in the textbook by Crow and Kimura (1970)[2]. Just like the Eigen model, the Crow-Kimura model was traditionally formulated in the language of chemical kinetics and can describe the basic processes of mutation and selection for molecules with self-replicating and information decoding functions, for instance, DNA and RNA. In the Crow-Kimura model, different individuals are represented by macromolecular sequences with length N. If one only considers the purine and pyrimidine each site of a sequence is a binary variable, and the i-th sequence can be denoted by $S_i = (s_1^i, s_2^i, ..., s_N^i)$, where $s_n = -1$ or 1 represents the purine or the pyrimidine. The total number of all possible sequences is 2^N. In the population, the sequence without mutation is called the wild sequence or reference sequence and the other sequences are the mutant sequences. The evolution dynamics of the sequences is given by

$$\dot{x}_i = \left(r_i - \sum_{j=1}^{2^N} r_j x_j\right) x_i + \sum_{j=1}^{2^N} m_{ij} x_j \qquad (1)$$

Here, x_i and r_i are the relative concentration and fitness of the i-th sequence, respectively. The latter reflects the replication rate of the sequence. A simple single peak fitness landscape is adopted in the present paper, in which $r_1 = A_0, r_i = A_i = A_1 (1 < i \leqslant 2^N)$ and for all the mutant sequences they have the same fitness. The factor $\sum_{j=1}^{2^N} r_j x_j$ is the mean fitness of the population (or the dilution flux) which keeps the total concentration constant. m_{ij} represents the mutation rate from S_j to S_i per unit period of time. We adopt the specification for the mutation rate given by Baake *et al.*[8].

$$m_{ij} = \begin{cases} \mu, & h(i,j) = 1 \\ 0, & h(i,j) > 1 \\ -N\mu, & h(i,j) = 0 \end{cases} \qquad (2)$$

where μ is the mutation rate for each site, $h(i,j)$ represents the Hamming distance between sequences S_i and S_j, $h(i,j) = (N - \sum_{k=1}^{N} s_k^i s_k^j)/2$, which is the number of the different sites between the two sequences. The above coupled set of equations governs the evolution of the master sequence and mutant sequences, with which one may discuss the dynamics and steady state properties of the population. The coupled set of equations contains 2^N equations, which precludes any direct calculation even for moderate values of N. Nevertheless, we may classify all possible sequences according to the Hamming distance from the master sequence. The sequences with the same Hamming distance form a class and one has therefore $N + 1$ classes. The classification simplifies the problem greatly. In addition, the transformation defined by the Eq. (3)[8] is used in the present paper which turns the coupled set of equations into a set of linear equations. The set of linear equations can be written in the matrix form and its coefficient matrix determines the evolution dynamics of the classes (the population). The relative concentration for each class in its steady state is uniquely determined by the right eigenvector of the largest eigenvalue of the coefficient matrix[5, 28]. The steady state is the state when time goes to infinite, which is an asymptotic state thereof. In the present paper, we only focus on the steady state properties of the relative concentrations of the classes.

In the mutation randomized Crow-Kimura model, we regard the site mutation rate as a Gaussian distributed variable. Its probability density distribution is given by

$$p(u) = \frac{1}{\sqrt{2\pi\omega^2}} \exp\left(\frac{-(u - \bar{u})^2}{2\omega^2}\right) \qquad (3)$$

Here, u is a variable, $\bar{u}$ and ω^2 denote the averaged value and variance of the random variable. In order to compare with the deterministic Crow-Kimura model, $\bar{u}$ is identical to the mutation rate μ used in the deterministic Crow-Kimura model. The fluctuation strength of the random variable is defined as $d = \omega/\bar{u}$, representing the relative width of the Gaussian distributed random variable. As a result of the randomization of the site mutation rate, the relative concentration of each class becomes a random variable and is characterized by its ensemble averaged value and the deviation from the mean value. We are

only interested in the steady state properties of the randomized concentration.

2　Results and discussions

2.1　Characteristics of the error threshold in the mutation randomized Crow−Kimura model

In the numerical simulations, we set the sequence length N=20, the fitness of the wild class A_0 = 10 and the fitness of all the mutant classes $A_i = A_1 = 1$, so a single peak fitness is used here. For the deterministic Crow-Kimura model, the relative concentration of each class at its steady state versus the site mutation rate (μ) is calculated (Figure 1) in which number 0 represents the wild class, and numbers 1, 2, 3… denote the mutant classes 1, 2, 3… . When the site mutation rate(μ) is small, the quasispecies distribution appears, namely, the mutant classes gather around the wild class which peaks there. As μ increases, the relative concentration of the wild class decreases, and the relative concentrations of the mutant classes increase. If μ goes beyond the error threshold, all classes have the same negligible concentration. The error threshold is located at μ_0=0.49, which is a sharp point similar to a phase transition in physics.

For the mutation randomized Crow-Kimura model, the site mutant rate is replaced by a Gaussian distributed random variable. We take ten thousand (or more) random samples and perform the ensemble average. The ensemble averaged relative concentrations of the classes at their steady states *versus* the site mutation rate μ are computed (Figure 2) where the fluctuation strength d=0.05. One can see that when the fluctuation strength is small (d=0.05), the change of the error threshold is slight. As a whole, the averaged relative concentrations in this case are basically consistent with those obtained from the deterministic Crow-Kimura model. Nevertheless, with the increment of the fluctuation strength, the change of the error threshold becomes more and more obvious. The error threshold extends downwardly as well as upwardly. The downward extension suppresses the dominance of the wild class in the population and therefore destroys the quasispecies structure. The upward extension pushes the real error threshold to a larger value. This situation is illustrated (Figure 3) in which d=0.25, the error threshold has completely turned into a smooth crossover region. Although the error threshold is modified significantly for a sizable fluctuation strength, the relative concentrations in the region outside the crossover region are almost consistent with those given by the deterministic Crow-Kimura model, which implies that they are relatively stable against the site mutation rate fluctuation.

The error threshold can be changed by the fluctuation of the site mutation rate and could be even sizable when the fluctuation strength is large. This can be seen from an alternative angle. Let us consider an order parameter $m = 1 - 2\langle h\rangle/N$, where $\langle h\rangle$ is the

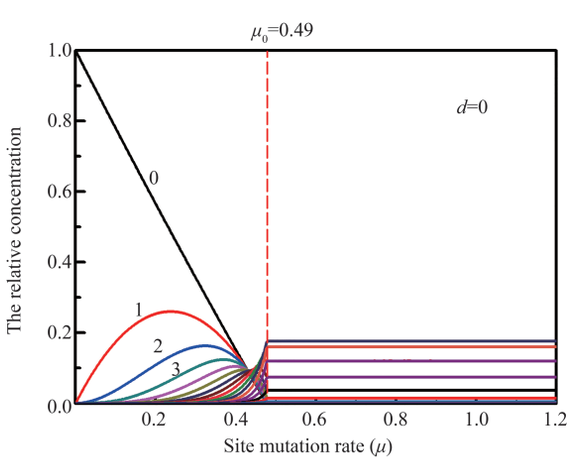

Fig. 1　Relative concentrations of the classes in their steady states based on the deterministic Crow−Kimura model *versus* the site mutation rate (μ)

The error threshold is located at μ_0=0.49. Number 0 in the figure represents the master class, and numbers 1, 2, 3… denote different mutant classes.

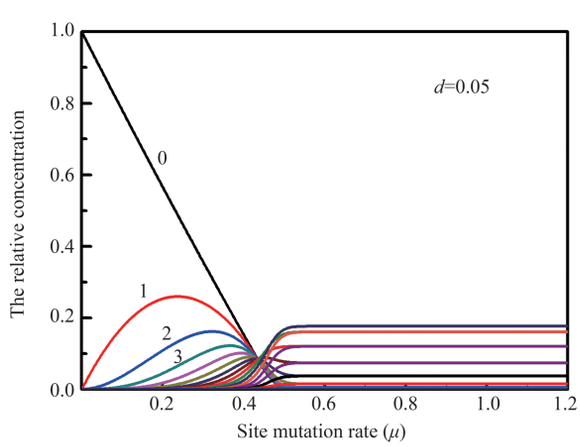

Fig. 2　The ensemble averaged relative concentrations of the classes in their steady states *versus* the site mutation rate (μ) with d=0.05 and the number of random samples n=10 000

Number 0 represents the master class, and numbers 1, 2, 3… denote different mutant classes.

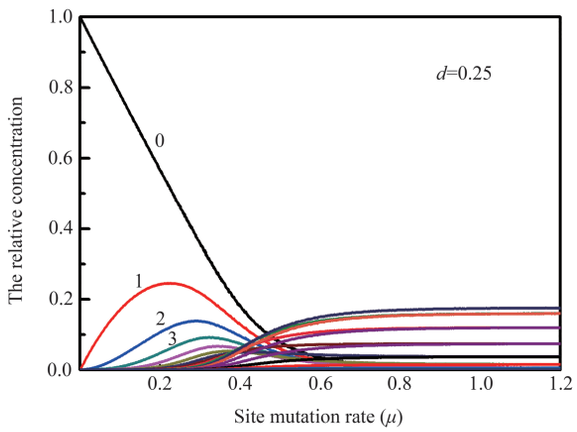

Fig. 3　Same as Figure 2 but *d*=0.25

averaged Hamming distance of the population from the wild class weighted by the relative concentrations of the classes in their steady states[29]. Since the averaged Hamming distance carries the information of the relative concentrations the above order parameter may indicate the change due to the randomization of the site mutation rate. For m=1, the population is composed entirely of the wild class. When m=0, all classes of the population are distributed randomly in the sequence space. In the case of m=− 1, the population consists completely of the complementary class to the wild class. The order parameter m as a function of the site mutation rate μ is presented (Figure 4) for the cases of d=0, 0.05 and 0.25. It can be seen that the order parameter in the deterministic Crow-Kimura model declines dramatically at the error threshold, which demonstrates that quantity m really acts as an order parameter to indicate the phase transition. When d is small, the deviation of the order parameter from that obtained from the deterministic Crow-Kimura model is small even around the error threshold, as shown in the case of d=0.05 (Figure 4). The deviation becomes more and more significant, especially around the error threshold as d gets larger and larger, and the phase transition at the error threshold is replaced by a smooth crossover around the error threshold. We show the above situation in the case of d=0.25 where the smooth curve of the order parameter passes through the error threshold and extends to a region far away from the error threshold. Therefore, both the relative concentrations and the order parameter indicate the error threshold is no longer a phase transition point but a smooth crossover region in the presence of a sizable fluctuation of the site mutation rate.

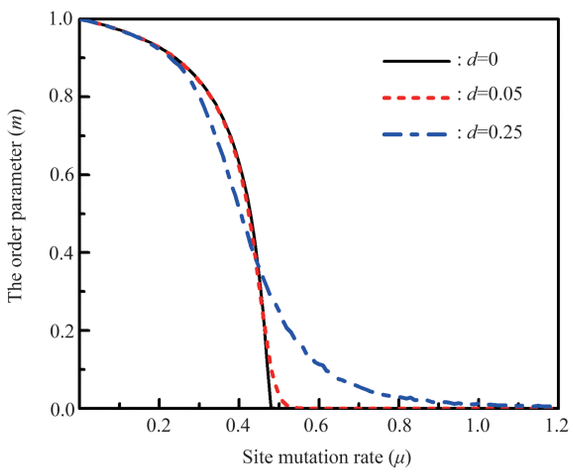

Fig. 4　The order parameter in the population steady state *versus* the site mutation rate μ for different values of the fluctuation strength (d) and the number of random samples n=10 000

The solid line is for d=0（for the deterministic Crow-Kimura model）. The dashed line is for d=0.05, and the dashed-dotted line is for d=0.25.

2.2　The characteristics and comparison of the crossover regions appearing in the randomized Crow− Kimura and Eigen models

The position of the error threshold in the deterministic Crow-Kimura model is easily determined, since the distribution of the classes has a dramatic change at the error threshold. However, in the randomized Crow-Kimura model, the change is smooth and the phase transition point is replaced by the smooth crossover region. Precisely determining the error threshold position is then impossible and unnecessary. Instead, we use the width of the crossover region to describe the quantitative change of the error threshold due to the randomization, which was firstly introduced by Li *et al.*[26-27]. The width is defined as follows. Its starting point is the phase transition point (the error threshold) in the deterministic Crow-Kimura model, and its endpoint is the location where the relative difference of the relative concentration of two complementary classes is less than 0.01. The relative difference is given by

$$c = \frac{x_i - x_j}{(x_i + x_j)/2} \qquad (4)$$

with $i + j = N$. For different complementary classes, their relative concentrations behave in a similar manner in the crossover region. With the above definition, the width of the crossover region w can be evaluated. When the fluctuation strength d is taken to be 0.05, 0.10, 0.15, 0.20, 0.25 and 0.30 the corresponding values of the width w are 0.04, 0.115, 0.215, 0.310, 0.440 and 0.598, respectively. It is shown that as the fluctuation strength increases the width gets wider and wider. It can be found that the relationship between the width and the fluctuation strength of the site mutation rate is nonlinear (exponential) by fitting the above values (Figure 5) in which the width of the crossover region *versus* the fluctuation strength in the cases of the random fitness and random site mutation rate is presented. Feng *et al.* [25] demonstrated in that there is a crossover region around the error threshold as the fitness of the master and mutant classes are replaced by Gaussian distributed random variables in the Crow-Kimura model. In order to fully examine the characteristics of the error threshold in the randomized Crow-Kimura model (Figure 5), our mutation randomization results are compared with those given by Feng *et al.* By fitting the width values, we found that the relationship between the width and the fluctuation strength is linear in the randomized fitness case.

For the randomized Crow-Kimura model, in the case of the randomized site mutation rate, when the fluctuation strength d is taken to be 0.15 and 0.25, the width of the crossover region w_μ is 44% and 90% of the value of the error threshold, respectively. In the case of the randomized fitness, when the fluctuation strength d is equal to 0.15 and 0.25 the corresponding width w_f is 32% and 54% of the error threshold. Therefore, the width caused by the randomized fitness is comparable to that caused by the randomized site mutation rate. Nevertheless, for the randomized Eigen model, when d equals 0.15 and 0.25 the width w_μ is 47% and 104% in the case of the randomized site mutation rate. In the case of the randomized fitness, when d is taken to be 0.15 and 0.25 the width w_f is only 9% and 16%[26]. So, the width caused by the randomized fitness is much less than that caused by the randomized site mutation rate, namely, the extension of the error threshold is mainly caused by the randomized site mutation rate for the same fluctuation strength. The above results are shown in Table 1. The relationship between the width and the fluctuation strength in the randomized Eigen model is linear for the randomized fitness and nonlinear (actually exponential) for the randomized site mutation rate, which is the same as that in the randomized Crow-Kimura model. Meanwhile, the fitness fluctuation in the randomized Crow-Kimura model causes much more extension of the error threshold than that in the randomized Eigen model and the site mutation rate fluctuation in the randomized Eigen model induces more extension of the error threshold than that in the randomized Crow-Kimura model. Therefore, the two randomized models are the same qualitatively but quite different quantitatively in the sense of the relationship between the extension and the fluctuation strength.

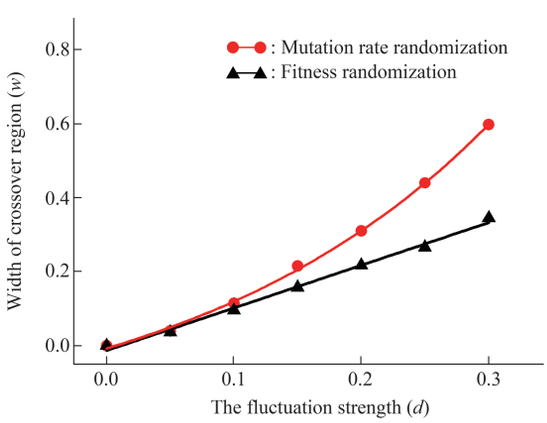

Fig. 5 The width of the crossover region varies with the fluctuation strength in the two different randomizations of the Crow−Kimura model.

The solid line with circle denotes the width in the random site mutation rate case. The line with triangle represents that in the random fitness case which is obtained by fitting the width values [25].

Table 1 The relative width values of the error threshold in the randomized Eigen model and randomized Crow−Kimura model.

Model	N	μ_0	(w_f/μ_0) / %		(w_μ/μ_0) / %	
		d=0	d=0.15	d=0.25	d=0.15	d=0.25
Eigen model	20	0.112	47	104	9	16
Crow-Kimura model	20	0.49	32	54	44	90

3 Concluding remarks

In the present paper, in order to complement the randomization of the Eigen model and the Crow-Kimura model the site mutation rate in the Crow-Kimura model has been treated as a Gaussian

distributed random variable. We paid attention to the characteristics of the error threshold as well as the relationship between the extension of the error threshold and the fluctuation strength of the randomized mutation rate. It has been shown that both the relative concentrations and the order parameter indicate the error threshold is no longer a phase transition point but a smooth crossover region in the presence of a sizable fluctuation of the site mutation rate. The error threshold extends not only downwardly but also upwardly. The downward extension suppresses the dominance of the wild class in the population and destroys the quasispecies structure thereof. The upward extension pushes the real error threshold to a larger value. The relationship between the width and the fluctuation strength in the mutation randomized Crow-Kimura model is nonlinear. The obtained results were compared with those from the randomized Eigen model and it is found that for the two randomized models the relationship between the width and the fluctuation strength is linear for the randomized fitness and nonlinear (exponential) for the randomized site mutation rate. Therefore, they are the same qualitatively in the sense of the relationship between the extension and the fluctuation strength. Nevertheless, they are quite different quantitatively. For the randomized Crow-Kimura model the width caused by the randomized fitness is comparable to that caused by the randomized site mutation rate. For the randomized Eigen model the extension of the error threshold is mainly caused by the randomized site mutation rate. Up to now we have had a full picture about the randomization effects of the fitness and site mutation rate on the error threshold based on the Eigen model and the Crow Kimura model.

The full picture might have the following implications for anti-viral strategies, cancer therapy and breeding of animals and plants. (1) The downward and upward extension of the error threshold suggests that one may use the fluctuation of the fitness and site mutation rate to destroy the quasispecies structure and roughly kill viruses. The extension itself implies a kind of residual life which appears in the crossover region[27]. Therefore, the upper limit of the crossover region should be reached to completely drive biological populations to go extinct[30]. (2) Radiation mutagens or chemical mutagens have been used to increase the mutation rate of viruses to eliminate them, which means one may also change and control the width of the crossover region externally, for instance, by electromagnetic field, radiations and thermal fluctuations for many purposes.

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Crow−Kimura模型中位点突变率对误差阈的随机效应*

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摘要　为了补充Eigen模型和Crow-Kimura模型的随机效应研究，Crow-Kimura模型中的位点突变率被处理成高斯分布随机变量，从而研究误差阈值的特征以及误差阈值的扩展与随机突变率涨落强度之间的关系. 准物种浓度和群体序参数分析表明，在位点突变率涨落较大时，误差阈值不再是相变点，而是平滑的转变区域. 定量分析表明，随机Crow-Kimura模型中转变区宽度与涨落强度之间的关系是非线性的. 将Crow-Kimura模型与Eigen模型的随机特征进行比较发现，在两个模型中适应值随机化使得转变区域的宽度和随机变量涨落强度之间的关系是线性的，而位点突变率随机化中两者的关系是非线性的（指数）. 对于随机化的Crow-Kimura模型，适应值随机化与位点突变率随机化引起的误差阈扩展效应相当. 对于随机Eigen模型，误差阈的扩展效应则主要是由位点突变率的随机化引起的. 之后，本文概述了Eigen模型和Crow Kimura模型中适应值和位点突变率随机化对误差阈值随机效应的影响，并讨论了上述结果对抗病毒策略、癌症治疗和动植物育种的重要意义.

关键词　突变率，Crow-Kimura模型，准物种，误差阈，高斯分布

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