Fixation probability of a mutant influenced by random fluctuation of selection intensity*

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SUMMARY

The probability of fixation of a mutant gene in a finite population was investigated by taking into account the effect of random fluctuation of selection intensity. It was shown that not only the product of the effective population number and average selection coefficient ($N_e\bar{s}$) is important, but also the ratio of the mean and the variance of selection coefficient ($\bar{s}/V_s$) has an important influence on fixation probability. In particular, when this ratio is small, a mutant gene, even if selected against, becomes fixed in the population like a selectively neutral mutant. In general, when random fluctuation of selection intensity is not negligible it may be convenient to use 'effective selection coefficient'. The bearing of the present findings on the neutral mutation-random drift theory of evolution and variation at the molecular level was discussed.

The probability of fixation of a mutant gene in a finite population was obtained by Kimura (1957) based on diffusion models. His formula gives the fixation probability in terms of the initial frequency, the selection coefficients of the mutant and the effective population number. The formula has since been used in various problems in population genetics including the theory of limit in artificial selection as developed by Robertson (1960). In natural populations, however, the selection coefficients of mutant genes are likely to fluctuate from generation to generation due to random fluctuation in environmental conditions and also by the fact that surrounding genetic background of a mutant changes by recombination. For example, a mutant gene may associate in one generation with lethals and in another with an advantageous gene. If such random fluctuation in selection intensity is large relative to its average value, it is expected that the selective force of an individual mutant may not work efficiently and that many mutant genes, even if selected for or against will show behaviour similar to neutral mutants. Kimura (1962) also obtained a quite general formula for the probability of fixation of a mutant gene and investigated some special cases of random fluctuation of selection intensity.

In the present paper, I shall examine the effect of such fluctuation on mutant fixation using Kimura's general formula but considering more realistic situations.

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Such an investigation should be of special interest from the standpoint of molecular evolution, since many gene substitutions are now considered to be the results of random fixation of selectively neutral or nearly neutral mutations (Kimura, 1968, 1969; King & Jukes, 1969). It is likely that mutants having selective values at the neighbourhood of neutrality are important in the evolution and variation at the molecular level (Kimura & Ohta, 1971; Ohta & Kimura, 1971a). I shall also discuss the concept of 'nearly neutral mutations' by taking into account random fluctuation of selection intensity.

Let us consider a diploid population having the 'variance' effective size N_e. It has been shown by Kimura (1962) that if $M_{\delta x}$ and $V_{\delta x}$ are respectively the mean and the variance of the change per generation of the frequency (x) of the mutant allele, then the probability of fixation of the mutant is

$$u(p) = \frac{\int_0^p G(x)\,dx}{\int_0^1 G(x)\,dx},$$ (1)

where

$$G(x) = \exp\left\{-2\int \frac{M_{\delta x}}{V_{\delta x}}dx\right\}$$ (2)

and p is the initial frequency of the mutant allele.

In a special case of genic selection as considered by Kimura (1962), if the selective advantage s of the mutant fluctuates randomly from generation to generation with the fixed mean $\bar{s}$ and variance V_s, we have

$$\begin{aligned} M_{\delta x} &= \bar{s}x(1-x), \\ V_{\delta x} &= V_s x^2(1-x)^2 + x(1-x)/(2N_e). \end{aligned}$$ (3)

Then formula (2) reduces to

$$G(x) = \left(\frac{\lambda_1 - x}{x - \lambda_2}\right)^{k/\sqrt{(1+4r)}},$$ (4)

where

$$k = 2\bar{s}/V_s$$

and

$$\begin{aligned} \lambda_1 &= \tfrac{1}{2}(1 + \sqrt{(1+4r)}), \\ \lambda_2 &= \tfrac{1}{2}(1 - \sqrt{(1+4r)}), \end{aligned}$$

with

$$r = 1/(2N_e V_s).$$

From the inspection of formula (4) one can see that as k (the ratio of mean and variance of the selection coefficient) gets small, $G(x)$ approaches unity and hence $u(p)$ approaches p, i.e. the value expected in the selectively neutral case. In order to study this relationship in more detail, numerical integrations were performed with the help of a computer using Simpson's method of quadrature.

Fig. 1 illustrates the probability of fixation as a function of the absolute value of k ($= |2\bar{s}/V_s|$) for various values of $4N_e\bar{s}$. The value of initial frequency (p) was set arbitrarily at 0·01. However, as long as p is small, the shape of the curve does not change with the change of p and all one needs to do is to modify the scale of
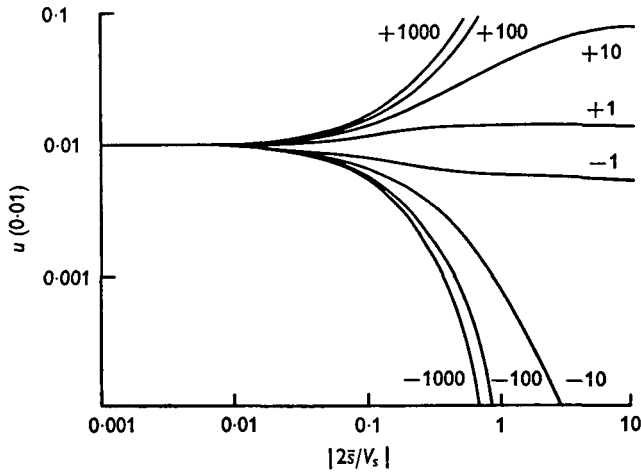
Fig. 1. Fixation probability of a mutant with initial frequency 0·01 as a function of the absolute value of k, $|2\bar{s}/V_s|$ for various levels of $4N_e\bar{s}$. The number beside each curve represents the value of $4N_e\bar{s}$.
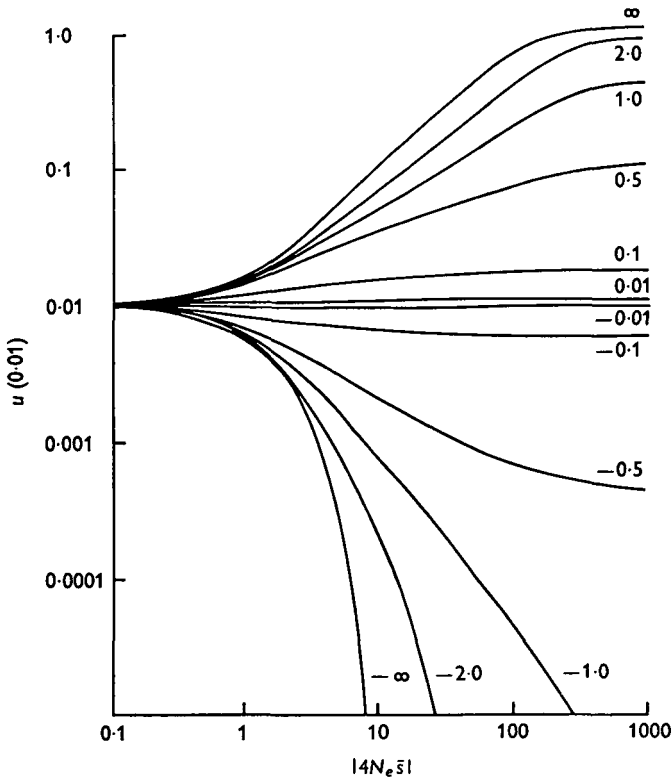

Fig. 2. Fixation probability of a mutant with initial frequency 0·01 as a function of $4N_e\bar{s}$ for various levels of $2\bar{s}/V_s$. The figure beside each curve is the value of $2\bar{s}/V_s$. The curves corresponding to $2\bar{s}/V_s = \pm\infty$ represent cases with no random fluctuation of selection intensity.

fixation probability correspondingly. We can see a strong influence of random fluctuation on the fixation probability when the ratio, $|2\bar{s}/V_s|$ is small. The cases with negative $\bar{s}$ and k (curves beyond neutrality) are particularly interesting because such mutants will have some chance of eventual fixation due to random fluctuation in s even if they are selected against on the average.

Fig. 2 shows the relationship between fixation probability and $4N_e\bar{s}$ for various levels of k. We again notice a large effect of random fluctuation in s on $u(p)$. These curves in the figure may be convenient to measure the 'effectiveness' of selection in the presence of random fluctuation as I shall discuss later. In the above model, we have assumed that V_s is constant. It should be noticed here that V_s is between generation variance. This assumption is pertinent when random fluctuation is caused by random fluctuation in the environmental conditions. However, when random fluctuation in selective value is mainly due to random fluctuation in the genetic background (caused by random sampling and combination of background genes) it is more realistic to assume that V_s is inversely proportional to the number of individuals carrying that mutant allele, namely

$$V_s = \frac{\sigma_w^2}{2Nx},\tag{5}$$

where σ_w^2 is the variance of fitness among individuals and N is the number of breeding individuals in the population which we equate with N_e. If we substitute formula (5) for V_s in formula (3) and calculate $u(p)$ from formulae (1) and (2), we obtain a result which shows that such random fluctuation has relatively little effect on $u(p)$. Namely, as compared with the case of $\sigma_w^2 = 0$, it has an effect roughly equivalent to reducing the effective population number from N_e to $N_e/(1 + \sigma_w^2)$.

From the above study it is evident that random fluctuation of selection coefficient due to random fluctuation in environmental conditions has a significant effect on fixation probability. An important parameter involved is the ratio of the mean and the variance of selection intensity, i.e. k. When $|k|$ is small the mutant will be fixed just as if it were neutral even if the value of $|N_e\bar{s}|$ is large. Especially when $|k| \leqslant 0.01$, the mutant is effectively neutral regardless of the value of $N_e\bar{s}$. Actually, however, the value of $\bar{s}$ must be quite small in order to have such a small $|k|$, since V_s must in general be much smaller than unity. Thus, random fluctuation of selection coefficient only makes genes effectively neutral if $\bar{s}$ is already small, say less than 10^{-3}.

However, random fluctuation will reduce the effect of selection considerably, even when it does not make selected genes practically neutral in behaviour. The cases with the absolute value of k around $0.5 \sim 1$ may be important in real biological populations. It may be convenient, in this context, to introduce the concept of 'effective selection coefficient' denoted by s_e. For example, if $k = 0.5$ and $4N_e\bar{s} = 1000$, the effective selection coefficient becomes approximately $4N_e s_e \approx 10$, if $k = -0.5$ and $4N_e\bar{s} = -100$, $4N_e s_e \approx -4$ as may be seen from Fig. 2.

This concept should have an important bearing on the evolution and variation at the molecular level. As pointed out by Ohta & Kimura (1971 *a, b*) there is no distinct borderline between neutral and deleterious mutations and the mutation frequency as a function of selection intensity must be continuous. They suggested that in considering the evolution of genetic systems by random genetic drift, we must take into account all mutations at the neighbourhood of selective neutrality which have finite chance of survival. Thus, the evolutionary rate in terms of mutant substitution may be expressed by the integral of the product of mutation rate and the fixation probability of the corresponding mutants. They called this integral, the effective neutral mutation rate.

From the present analysis, it is evident that we must take into account the random fluctuation of selection intensity before we can thoroughly understand the behaviour of nearly neutral mutations. In other words, we must replace the selection coefficient by the effective selection coefficient.

Besides its effect on the fixation probability, random fluctuation in selection intensity must have significant influence on the amount of genetic variations within a population. Recently Crow (1971) pointed out that when $2N_e V_s$ is large, the average number of generations until fixation of a mutant gene is significantly shortened and the genetic variabilities are thereby reduced.

In the present report, only the fixation probability for the case of genic selection has been analysed. It should be worthwhile to extend such investigation to cover a more general situation with arbitrary degree of dominance. In particular, the effect of random fluctuation of selection intensity on the stability of polymorphism due to overdominance will have to be investigated. It is likely that the retardation factor of Robertson (1962) is also influenced considerably by the ratio of the mean and variance of selection coefficient when it is small.

REFERENCES

CROW, J. F. (1971). Darwinian and non-Darwinian evolution. *Proceedings of the 6th Berkeley Symposium on Mathematical Statistics and Probability* (in the Press).

KIMURA, M. (1957). Some problems of stochastic processes in genetics. *Annals of Mathematical Statistics* **28**, 882–901.

KIMURA, M. (1962). On the probability of fixation of mutant genes in a population. *Genetics* **47**, 713–719.

KIMURA, M. (1968). Evolutionary rate at the molecular level. *Nature* **217**, 624–626.

KIMURA, M. (1969). The rate of molecular evolution considered from the standpoint of population genetics. *Proceedings of the National Academy of Sciences of the U.S.A.* **63**, 1181–1188.

KIMURA, M. & OHTA, T. (1971). Protein polymorphism as a phase of molecular evolution. *Nature* **229**, 467–469.

KING, J. L. & JUKES, T. H. (1969). Non-Darwinian evolution: Random fixation of selectively neutral mutations. *Science* **164**, 788–798.

OHTA, T. & KIMURA, M. (1971*a*). On the constancy of the evolutionary rate of cistrons. *Journal of Molecular Evolution* (in the Press).

OHTA, T. & KIMURA, M. (1971*b*). Genetic load due to mutations with very small effects. *Japanese Journal of Genetics* (in the Press).

ROBERTSON, A. (1960). A theory of limits in artificial selection. *Proceedings of the Royal Society* B **153**, 234–249.

ROBERTSON, A. (1962). Selection for heterozygotes in small populations. *Genetics* **47**, 1291–1300.