Theoretical and Applied Genetics 38, 243–248 (1968)

Effect of Initial Linkage Disequilibrium and Epistasis on Fixation Probability in a Small Population, with two Segregating Loci *

TOMOKO OHTA **

National Institute of Genetics, Mishima

Summary. The probability of ultimate fixation was studied for 2 loci small populations by the method of Monte Carlo simulation and also partly by analytical treatment. The analytical solutions for fixation probability known at present and the difficulty of their application to more complex situations were discussed. Monte Carlo experiments were carried out for large values of $N_e s_1$, $N_e s_2$ and $N_e \varepsilon$, for which the analytical solutions have not been obtained.

One of the main purposes was to investigate the effect of initial linkage disequilibrium (D) on fixation probability. When s_1, s_2 and ε are 0, the effect of disequilibrium is given by $\{1 - 2N_e c/(2N_e c + 1)\}D$ with KIMURA's model and $\{1 - 2N_e c/(2N_e c - c + 1)\}D$ with the model of KARLIN and MCGREGOR. When $|N_e s_1|$ and $|N_e s_2|$ were small and $\varepsilon = 0$, the effect of disequilibrium was shown to be almost the same as in the selectively neutral case (formulas 8). When those parameters are not small, the effect of disequilibrium is larger because of the rapid approach to fixation.

Another purpose of this study was to investigate the effect of epistasis on fixation probability. KIMURA obtained the solution for joint fixation of A and B when the selective advantage is given to genotype AB as the joint effect of A and B. The present study has verified his formula and showed that linkage does not affect $u(AB)$ under initial linkage equilibrium. Also some cases of additive × additive epistasis were studied.

Recently, numerous papers have been published about the effect of epistasis and linkage on the evolution of multi-loci systems. The deterministic treatment of the problem is concerned mainly with the evolution of the gametic frequencies in 2 loci systems when there exist linkage and epistasis of various kinds (KIMURA ,1956, LEWONTIN and KOJIMA, 1960, BODMER and PARSONS, 1962, PARSONS, 1963, LEWONTIN, 1964a, b, NEI, 1964a, b, FELSENSTEIN, 1965, JAIN and ALLARD, 1966, KIMURA, 1965, WRIGHT, 1965, 1967, SINGH and LEWONTIN, 1966). In the deterministic models, the evolutionary path and rate may depend on epistasis and linkage but the final equilibrium point is predetermined. However, in a finite population, the final state depends on the amount of random drift. Thus, for many problems of artificial selection in which a small number of individuals are selected in each generation, a stochastic treatment is required.

An elegant theory on the limit of artificial selection has been established by ROBERTSON (1960) based on the theory of gene fixation in a single locus developed by KIMURA (1957, 1962, 1964), who used the method of the Kolmogorov backward equation. However, KIMURA's results and method are not readily applicable to multi-loci systems, when there is linkage and/or epistasis.

The probability of fixation in a simple 2 loci model with 2 alleles in each locus and with no selective difference among genotypes, has been studied by KIMURA (1963) and KARLIN and MCGREGOR (1968). They clarified the effect of linkage and initial linkage disequilibrium on the final state. Their methods, also, do not appear to be applicable to more complex situations where selective differences exist.

The effect of linkage and epistasis on the limit to artificial selection in complex situations were investigated by the method of Monte Carlo simulation (FRASER, 1957, MARTIN and COCKERHAM, 1960, LATTER, 1965, 1966, HILL and ROBERTSON, 1966). Among those authors, HILL and ROBERTSON (1966) analysed the effect of linkage in a 2 loci model, assuming additive gene effects and no linkage disequilibrium in the initial generation. They reported that linkage reduces the probability of fixation when gene effects are large, and they interpreted their results as due to the reduction of the effective population number.

The purpose of the present study was to investigate the effect of initial linkage disequilibrium on the probability of fixation in small populations. Such an investigation should be important in clarifying the outcome of artificial selection when it is carried out for a hybrid population produced by crossing 2 different strains. The present author has also investigated the effect of epistasis when a selective advantage arises for a particular combination of alleles in two different loci. Such epistatic interaction might be found not infrequently in nature through interaction of enzymes.

1. Genetic Model and the Method

Let us assume 2 loci each with 2 alleles; A and a in the one and B and b in the other locus. A and B represent the advantageous alleles both in epistatic and additive models. The recombination value between the 2 loci will be denoted by c. The selective values of 10 genotypes are given in Table 1. In the table, s_1 and s_2 stand for the additive effects of A and B, and, ε is the epistatic effect of AB combination. No dominance was assumed.

The simulation was performed following the scheme of HILL and ROBERTSON (1966), namely, selection and recombination were carried out deterministically and sampling was performed by generating pseudo-random numbers. The only difference of the present procedure from that of HILL and ROBERTSON was

* Contribution No. 669 from the National Institute of Genetics, Mishima, Shizuoka-ken, Japan.

** Supported by a post-doctoral fellowship from the Japan Soc. for the Promotion of Science.

Table 1. *Fitnesses of 10 genotypes in selective values*

Genotype	Fitness
AB/AB	$1 + s_1 + s_2 + \varepsilon$
AB/Ab	$1 + s_1 + s_2/2 + \varepsilon/2$
AB/aB	$1 + s_1/2 + s_2 + \varepsilon/2$
AB/ab, Ab/aB	$1 + s_1/2 + s_2/2 + \varepsilon/2$
Ab/Ab	$1 + s_1$
aB/aB	$1 + s_2$
Ab/ab	$1 + s_1/2$
aB/ab	$1 + s_2/2$
ab/ab	1

that selection, recombination and sampling were all done at the zygotic level instead of the gametic level.

The simulation was carried out by a high speed computer, IBM 7090. Let us assign to the 4 genotypes, AB, Ab, aB and ab the numbers, 1, 2, 3 and 4. In the experiment, initial frequencies of $1 \sim 4$ gamete types were read into the computer together with other parameters. In each generation, selection, recombination and mating were carried out in this order using the following formulas. Let g_i be the frequency of the ith gamete and let z_{ij} be the frequency of the zygote formed by the union of the ith with the jth gamete.

Selection: $$z'_{ij} = z_{ij} + \Delta z_{ij},$$
$$\Delta z_{ij} = \frac{z_{ij}(w_{ij} - \bar{w})}{\bar{w}}$$

Recombination:
$$g_1 = z'_{11} + (z'_{12} + z'_{21})/2 + (1 - r)\, z'_{14}/2 + r\, z'_{23}/2$$
$$g_2 = z'_{12}/2 + z'_{22} + r\, z'_{14}/2 + (1 - r)\, z'_{23}/2 + z'_{24}/2$$
$$g_3 = z'_{13}/2 + r\, z'_{14}/2 + (1 - r)\, z'_{23}/2 + z'_{33} + z'_{34}/2$$
$$g_4 = (1 - r)\, z'_{14}/2 + r\, z'_{23}/2 + (z'_{24} + z'_{34})/2 + z'_{44}$$

mating: $$z_{ij} = g_i \times g_j \quad (i = j)$$
$$= 2\, g_i \times g_j \quad (i \neq j)$$

In the above expressions w_{ij} is the fitness measured in selective values of individuals with genotype ij and $\bar{w}$ is the average selective value of the population. Then, the sampling of N zygotes was done by generating N uniform pseudo-random numbers X $(0 < X < 1)$ using the subroutine RAND 3 in FORTRAN IV. Each experiment was continued until fixation or through 6N generations. In most experiments, one genotype became fixed in the population by this generation. The final average frequencies were taken as the limit. 100 replications (experiments) were done for each case. The value of N could be altered, but in the present study, it was either 10 or 20.

2. Basic Theory of 2 Loci Model

The Effect of Epistasis on Fixation Probability

Let us consider a haploid population of effective size N_e and assume that fitnesses and frequencies of genotypes are as in Table 2. We will denote by p and q the frequencies of A and B. If u is the probability of fixation, then the Kolmogorov backward equation at steady state is,

$$p(1-p)\frac{\partial^2 u}{\partial p^2} + q(1-q)\frac{\partial^2 u}{\partial q^2} + 2N_e p(1-p) \times (s_1 + \varepsilon q)\frac{\partial u}{\partial p} + 2N_e q(1-q)(s_2 + \varepsilon p)\frac{\partial u}{\partial q} = 0. \quad (1)$$

Table 2. *Fitnesses and frequencies of 4 genotypes*

Genotype	Fitness	Frequency
AB	$1 + s_1 + s_2 + \varepsilon$	pq
Ab	$1 + s_1$	$p(1-q)$
aB	$1 + s_2$	$q(1-p)$
ab	1	$(1-p)(1-q)$

For the special case of $s_1 = s_2 = 0$, KIMURA (personal communication) obtained, from the above equation, the following formula for $u(AB)$, i.e., the probability of joint fixation of A and B

$$u(A\ B) = \frac{1 - e^{-2N_e \varepsilon p q}}{1 - e^{-2N_e \varepsilon}}. \quad (2)$$

It is interesting to note that the above formula coincides with the formula for the probability of fixation in the case of a single locus in which a single allele denoted by AB has selective advantage ε and initial frequency pq. With initial linkage disequilibrium, however, the above formula does not hold, since random combination of alleles can not be assumed in this case.

KIMURA (personal communication) also showed that, when $|N_e s_1|$, $|N_e s_2|$ and $|N_e \varepsilon|$ are small, the approximate solution of (1) is

$$u(A\ B) = pq\{1 + N_e s_1(1-p) + N_e s_2(1-q) + N_e \varepsilon(1 - pq) + \cdots\}. \quad (3)$$

However, the general solution of (1) is not known at present and some results of Monte Carlo simulation will be presented in the next section.

Effect of initial linkage disequilibrium on fixation probability

When there are no selective differences among genotypes, the fixation process of a 2 loci system can be analysed by the exact treatment (KIMURA, 1963, KARLIN and MCGREGOR, 1968). KIMURA (1963) has shown, under random mating and constant population size, that

$$L = \frac{C(A_i B_j)_t}{2N_e} + c\, S(A_i B_j)_t \quad (4)$$

is a time invariant quantity $(t \geqq 1)$, where $C(A_i B_j)_t$ is the probability that a chromosome chosen at random carries alleles A_i and B_j at generation t and $S(A_i B_j)$ is the probability that a chromosome chosen at random carries A_i and another chromosome also chosen at random carries B_j at generation t. From the above relation (4), $C(A_i B_j)_\infty$, that is the probability of fixation of $A_i B_j$, can be derived.

$$C(A_i B_j)_\infty = S(A_i B_j)_\infty = \frac{C(A_i B_j)_1 + 2N_e c\, S(A_i B_j)_1}{2N_e c + 1}. \quad (5)$$

In the special case of a pair of alleles in each locus ($i = 1, 2$ and $j = 1, 2$), we have for example,

$$C(A_1 B_1)_\infty = \frac{C(A_1 B_1)_1 + 2N_e c\, S(A_1 B_1)_1}{2N_e c + 1} = C(A_1 B_1)_1 + \frac{2N_e c}{2N_e c + 1}\{S(A_1 B_1)_1 - C(A_1 B_1)_1\}. \quad (5')$$

KARLIN and MCGREGOR (1968) obtained the analytical solution of fixation probability by transformation of the transition probability matrix.

The probabilities are,

$$\left.\begin{aligned} u(AB) &= g_1 - 2N_e c D/(2N_e c - c + 1) \\ u(Ab) &= g_2 + 2N_e c D/(2N_e c - c + 1) \\ u(aB) &= g_3 + 2N_e c D/(2N_e c - c + 1) \\ u(ab) &= g_4 - 2N_e c D/(2N_e c - c + 1) \end{aligned}\right\} \quad (6)$$

where, g_1, g_2, g_3 and g_4 are the initial frequencies of $A\,B$, $A\,b$, $a\,B$ and $a\,b$, and D is the initial linkage disequilibrium which is equal to $g_1 g_4 - g_2 g_3$. $C(A\,B)_\infty$ of KIMURA is equal to $g_1 - 2N_e c D/(2N_e c + 1)$ by these notations and is slightly different from KARLIN and MCGREGOR's result. Dr. Takeo MARUYAMA has pointed out to the present author that the difference is due to the models used. Namely, KIMURA's model concerns the recurrence relation of the probabilities from zygotes to zygotes, whereas KARLIN and MCGREGOR's model analysed the probability transition from gametes to gametes. Thus, it may be understood that KIMURA's model fits to diploid organisms and KARLIN and MCGREGOR's, to haploid cases. Usually, N_e is large enough to give practically the same probability for both models.

When there is a selective difference among genotypes, those methods are not applicable at present. In order to treat the problem of fixation with selection involved, we must use the method of Komogorov backward equation. The equation at the steady state and under additive gene effect is as follows:

$$\begin{aligned} &\tfrac{1}{4} g_1 (1-g_1)\, u''_{11} + \tfrac{1}{4} g_2 (1-g_2)\, u''_{22} + \tfrac{1}{4} g_3 (1-g_3)\, u''_{33} \\ &- \tfrac{1}{2} g_1 g_2\, u''_{12} - \tfrac{1}{2} g_1 g_3\, u''_{13} - \tfrac{1}{2} g_2 g_3\, u''_{23} \\ &+ \tfrac{1}{2} N_e s_1 \{g_1 (1-g_1-g_2)\, u'_1 + g_2 (1-g_1-g_2)\, u'_2 - \\ &\qquad - g_3 (g_1+g_2)\, u'_3\} \\ &+ \tfrac{1}{2} N_e s_2 \{g_1 (1-g_1-g_2)\, u'_1 - g_2 (g_1+g_3)\, u'_2 + \\ &\qquad + g_3 (1-g_1-g_3)\, u'_3\} \\ &- N_e c D \{u'_1 - u'_2 - u'_3\} = 0 \end{aligned} \quad (7)$$

where u''_{ij} is the second derivative of u with respect to g_i and g_j and u'_i is the first derivative of u with respect to g_i. The above equation is analogous to equation (6) of HILL and ROBERTSON (1966), who presented the forward equation for the same problem.

When $|N_e s_1|$ and $|N_e s_2|$ are small, the present author obtained the following set of approximate solutions

$$\left.\begin{aligned} u(A\,B) &\doteqdot g_1 - d + N_e s_1 (1-g_1-g_2)(g_1-d) \\ &\quad + N_e s_2 (1-g_1-g_3)(g_1-d) \\ u(A\,b) &\doteqdot g_2 + d + N_e s_1 (1-g_1-g_2)(g_2+d) \\ &\quad + N_e s_2 \left\{\frac{d}{2N_e c} - (1-g_1-g_3)(g_1-d)\right\} \\ u(a\,B) &\doteqdot g_3 + d \\ &\quad + N_e s_1 \left\{\frac{d}{2N_e c} - (1-g_1-g_2)(g_1-d)\right\} \\ &\quad + N_e s_2 (1-g_1-g_3)(g_3+d) \\ u(a\,b) &= 1 - u(A\,B) - u(A\,b) - u(a\,B)\,, \end{aligned}\right\} \quad (8)$$

where $d = 2N_e c D/(2N_e c + 1)$.

Using the above solutions, $u(A)$ may be obtained by $u(A\,B) + u(A\,b)$, and the result agrees with the one obtained by HILL and ROBERTSON (1966). They obtained their result by summing up the expected change of frequency of A from $t = 0$ to $t = \infty$.

When $s_1 = s_2 = 0$, formulas (8) reduce to,

$$\left.\begin{aligned} u(A\,B) &= g_1 - d \\ u(A\,b) &= g_2 + d \\ u(a\,B) &= g_3 + d \\ u(a\,b) &= g_4 - d\,. \end{aligned}\right\} \quad (9)$$

It is interesting to note that the result agrees with that obtained by KIMURA (1963) as shown in (5). From (8) and (9), we see that the effect of initial linkage disequilibrium on $u(A\,B)$ is almost the same irrespective of presence or absence of selective differences as long as $|N_e s_i| \ll 1$. For a large $|N_e s_i|$, equation (7) can not be solved at present. So, in order to obtain information for such a case, Monte Carlo study was performed, as is reported in the next section.

3. Result and Discussion

Epistasis and Fixation Probability under free Recombination and Initial Linkage Equilibrium

To verify KIMURA's formula (2), Monte Carlo experiments were performed for a 2 loci model with epistasis but without any additive gene effect, namely, with the fitnesses of 10 genotypes as in Table 1 in which $s_1 = s_2 = 0$ is assumed. The model used is slightly different from the haploid model described in section 2, since here the population is diploid. In the haploid model, $A\,b$ or $a\,B$ type does not have any selective advantage but in the diploid model, they may have selective advantage $\varepsilon/2$ when they are combined together, forming $A\,b/a\,B$ zygote.

In Figure 1, values of $u(A\,B)$ obtained by Monte Carlo experiments and also by Formula (2) are plotted, together with experimental values of $u(A)$. In the figure, p (initial frequency of A) is fixed ($p = 0.1$ and 0.5) and the value of $u(A\,B)$ is shown as a function of q (initial frequency of B). The agreement between the Monte Carlo results (solid

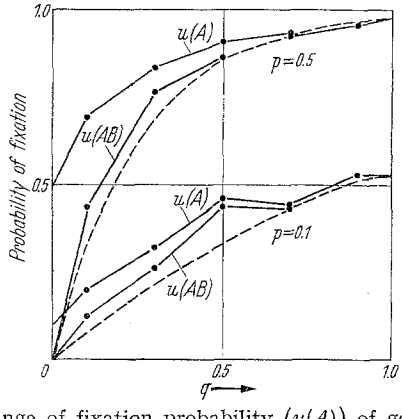

Fig. 1. Change of fixation probability ($u(A)$) of gene A and of gene combination AB ($u(AB)$) with the change of the initial frequency (q) of gene B for the epistatic model. Solid circles represent the results of Monte Carlo experiment. $u(A)$ at $q = 0$ and 1 were computed by single locus formula. The broken lines show the theoretical results expected from KIMURA's formula (2). Parameters are, $p = 0.1$ and 0.5, $N_e \varepsilon = 4$ and $c = 0.5$

circles) and the theoretical prediction (brooken lines) is satisfactory.[1] The theoretical results (see formula 2) coincide with a single locus case in which initial frequency is pq. It may be considered just as a coincidence that the two loci case with epistasis and free recombination agrees with the single locus case. Cases with different degrees of linkage should represent the situation somewhere between those 2 cases. Thus, it is expected that linkage does not affect the fixation probability of $A\,B$ under the condition of initial linkage equilibrium. This condition is important and the effect of linkage will become pronounced when initially $D \neq 0$.

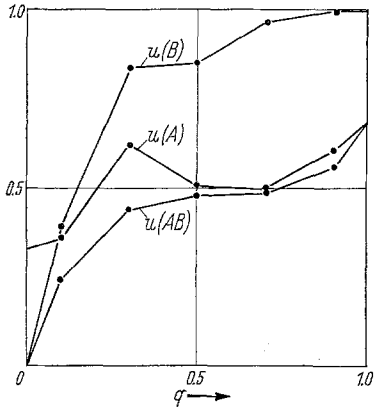

Fig. 2. Values of fixation probabilities $u(A)$, $u(B)$ and $u(A\,B)$ are plotted as functions of q (abscissa) when additive × additive epistasis is present. $u(A)$ at $q = 0$ and 1 were computed by single locus formula and solid circles show the results of Monte Carlo experiments. Parameters are, $p = 0.1$, $N_e\,\varepsilon = 4$, $N_e\,s_1 = N_e\,s_2 = 2$ and $c = 0.5$ where s_1, s_2 and ε are selection coefficients, c is the recombination value and N_e is the effective population number

For the general case of additive × additive epistasis, the analytical solution has not yet been obtained except for the case where $N_e\,s_1$, $N_e\,s_2$ and $N_e\,\varepsilon$ are small. Let us fix p and change q so that u is considered as a function of q (abscissa). From formula(3), the curve is convex when $N_e\,s_1$, $N_e\,s_2$ and $N_e\,\varepsilon$ are small and positive. Figure 2 shows the result of Monte Carlo experiments when those parameters are large. The point at $q = 0$ and 1 are obtained by applying the single locus theory. The lines have certain fluctuations, but, they suggest that for positive s_1, s_2 and ε, the curves for $u(A\,B)$, $u(A)$ and $u(B)$ are of the convex type. Under the presence of the initial linkage disequilibrium, these curves may be entirely changed. Investigation of the epistatic cases where s_1 and s_2 are negative and ε is positive may also be interesting, since they might be fairly common in nature, but such cases were not investigated by the present author.

Effect of Initial Linkage Disequilibrium under the Presence of Additive Gene Effects or Epistasis

The effect of initial linkage disequilibrium may not be very important in natural populations unless the linkage is extremely tight, and epistasis is relatively strong. The importance arises in the analysis of artificial selection when it starts from a hybrid population between 2 different strains. In such a hybrid population, gene frequencies are 1/2 and linkage disequilibrium is at the maximum at the loci where different alleles were previously fixed in the 2 strains. ROBERTS (1967) reported that in his selection experiment on body weight of the mouse higher selection limits were obtained when the hybrid population was maintained several generations by random mating before selection. In his case, the linkage disequilibrium seems to have been partly reduced before selection.

Let us consider a 2 loci case with additive gene effects. The tighter is the linkage, the larger is the effect of the initial linkage disequilibrium. In the special case of $s_1 = s_2 = 0$, we have analytical solutions and we know that the fixation probabilities depend on $N_e\,c$ in KIMURA's model and also in diffusion model (see formulas 5 and 9). However, they depend on both $N_e\,c$ and c in KARLIN and MCGREGOR's model, though the actual results do not differ much unless N_e is extremely small. From formulas (9), we note that when the coefficient of D, i.e., $2\,N_e\,c/(2\,N_e\,c + 1)$ is equal to unity, there will be no effects of disequilibrium on the final fixation probabilities, since $u(A\,B) = g_1 + g_2\,g_3 - g_1\,g_4 = (g_1 + g_2)\,(g_1 + g_3) = u(A) \cdot u(B)$. It means that as $N_e\,c$ approaches infinity, the effect of the initial disequilibrium disappears.

When $|N_e\,s_1|$ and $|N_e\,s_2|$ are small, the effects of D are as in the formulas (8). Those formulas show that the effect on $u(A\,B)$ is the same and the effect on $u(A)$ or $u(B)$ is slightly different when compared with the case of no selective differences. For large $N_e\,s_1$ and $N_e\,s_2$, we must rely on Monte Carlo study.

Figure 3 illustrates the result of Monte Carlo study when $N_e\,s_1 = 4$ and $N_e\,s_2 = 4$. Initial frequencies of A and B were taken as 0.1. Three levels of initial D were assumed. They are $D = +M \equiv +$ Maximum $(g_1 = 0.1,\ g_2 = g_3 = 0,\ g_4 = 0.9)$, $D = 0$ $(g_1 = 0.01,\ g_2 = g_3 = 0.09,\ g_4 = 0.81)$ and $D = -M \equiv -$ Maximum $(g_1 = 0,\ g_2 = g_3 = 0.1,\ g_4 = 0.8)$. For each level of D, 4 different values of $2\,N_e\,c$ were set. When $D = 0$, the result is suggestive of the effect of linkage as discussed by HILL and ROBERTSON (1966). Namely, the fixation probability is reduced by linkage. When $D = +M$ or $-M$, the effects of D decrease as $N_e\,c$ becomes larger and finally should disappear at $N_e\,c = \infty$.

Now, let us look at the difference of $u(A\,B)$ between the cases of $D = +M$ and $D = -M$. In the special case of $N_e\,s_1 = N_e\,s_2 = 0$, we know that the difference has the coefficient $1 - 2\,N_e\,c/(2\,N_e\,c + 1)$. From Figure 3, it is observed that the coefficient is larger than the above value. It means that the effect of D is larger when $|N_e\,s_1|$ and $|N_e\,s_2|$ are large. It is understood as the result of rapid approach to fixation when those parameters are large. Thus, it is considered in general that the effect of D is not less than the neutral case and its magnitude depends on the values of $|N_e\,s_i|$.

An example where $p = q = 0.5$ was studied by Monte Carlo experiments. It simulates the process of selection starting with a hybrid population made

[1] The Monte Carlo figures seem to be slightly higher than the predicted values because of the difference in the model. AB genotype is slightly more advantageous in the present diploid model than in the haploid model. Double heterozygotes Ab/aB or AB/ab ought to have the fitness value $1 + \varepsilon/4$ instead of $1 + \varepsilon/2$, in order to give the same advantage to AB as in the haploid model.

Table 3. *Comparison of fixation probabilities at* $D = 0$ *and* $D = -\frac{1}{4}$ *when* $p = q = \frac{1}{2}$ and $N_e s_1 = N_e s_2 = 2$

D \ $2N_e c$	$u(AB)$			$u(A)$		
	0	2	10	0	2	10
0	0.58	0.67	0.69	0.80	0.85	0.83
$-\frac{1}{4}$	0.00*	0.50	0.63	0.50*	0.71	0.82

* Values were obtained by the single locus formula.

from 2 different strains. If different alleles with additive effect were fixed at 2 or more loci in the parental strains, the hybrid population has a maximum linkage disequilibrium. If 2 such loci are linked, the effect of disequilibrium on selection limit may be large. In Table 3, the comparison of cases with $D = 0$ and $D = -M$ are made. In this case the pattern by which the difference decreases as $N_e c$ gets larger is not much different from the neutral case. Notice here that values assigned to $N_e s_1$ and $N_e s_2$ are 1/2 of those of the example of Figure 3. As ROBERTS (1967) showed in his experiment, to delay selection of a hybrid population by keeping it as a large random mating population should be recommended especially for the case $2N_e c < 5$ in order to obtain a higher selection limit.

Next, the effects of linkage disequilibrium were investigated using the model with epistasis, but no additive gene effects, employing 3 levels of $D(+M, 0, -M)$ as before. As shown in Figure 4, the essential feature of the effect of D is the same as in the additive model. The points at $N_e c = \infty$ were obtained by KIMURA's formula (2), based on random combination of alleles between the two loci.

It should be remarked here that the degree of linkage has not much effect on $u(AB)$ when there is no initial linkage disequilibrium (line at $D = 0$). As pointed out before, the cases with various degrees of linkage represent the situation somewhere between the case of single locus and that of 2 independent loci.

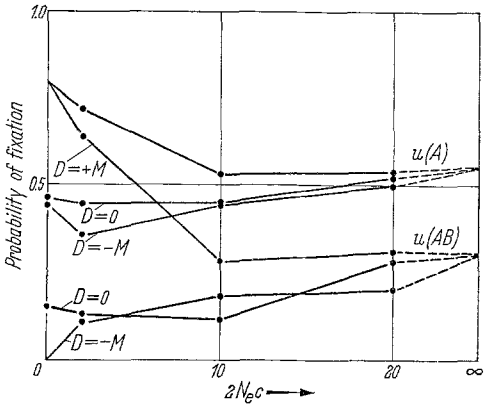

Fig. 3. Relationship between fixation probabilities and $2N_e c$ for additive model for 3 levels of initial linkage disequilibrium ($D = +$ Maximum, $D = 0$, $D = -$ Maximum). The values at $2N_e c = \infty$ were obtained theoretically assuming 2 independent loci and the values at $2N_e c = 0$ for $D = +M$ was obtained by single locus formula. Parameters are, $p = q = 0.1$ and $N_e s_1 = N_e s_2 = 4$

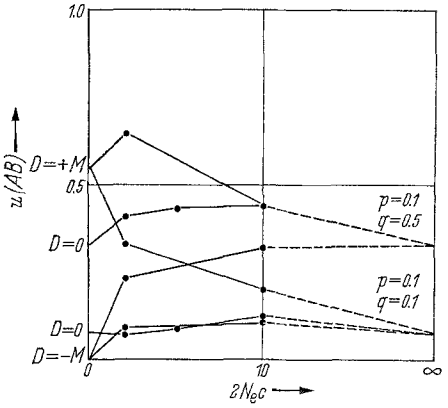

Fig. 4. Relationship between fixation probabilities and $2N_e c$ under epistatic gene effect for 3 levels of D. $u(AB)$ at $2N_e c = \infty$ was obtained by KIMURA's formula (2) and the values at $2N_e c = 0$ were obtained by single locus formula. Parameters are, $p = 0.1$, $q = 0.1$ and 0.5 and $N_e \varepsilon = 4$

Zusammenfassung

Es wurde die Wahrscheinlichkeit einer irreversiblen Fixierung für zwei Loci und kleine Populationen sowohl mit Hilfe von Monte-Carlo-Simulationsmethoden als auch an Hand analytischer Verfahren untersucht. Die analytischen Lösungen, die derzeit für die Fixierungswahrscheinlichkeit bekannt sind, und die Schwierigkeit ihrer Anwendung auf komplizierte Fälle werden diskutiert. Es werden für große Werte von $N_e s_1$, $N_e s_2$ und $N_e \varepsilon$, für die analytische Lösungen nicht erhalten werden konnten, Monte-Carlo-Versuche ausgeführt. Eines der Hauptanliegen war es, den Einfluß eines ursprünglichen Koppelungsungleichgewichtes (D) auf die Fixierungswahrscheinlichkeit zu untersuchen. Wenn s_1, s_2 und ε gleich 0 sind, ist die Wirkung des Ungleichgewichtes nach KIMURAS Modell durch $\{1 - 2N_e c/(2N_e c + 1)\}D$ und nach dem Modell von KARLIN und MCGREGOR durch $\{1 - 2N_e c/(2N_e c - c + 1)\}D$ gegeben. Unter der Bedingung, daß $|N_e s_1|$ und $|N_e s_2|$ klein sind und $\varepsilon = 0$ ist, kann gezeigt werden, daß die Wirkung des Ungleichgewichtes etwa der eines selektiv neutralen Falles (Formeln 8) entspricht. Sind die oben erwähnten Parameter nicht klein, so ist die Auswirkung des Ungleichgewichtes wegen der schnellen Annäherung an die Fixierung größer. Es wurde ferner die Wirkung der Epistasie auf die Fixierungswahrscheinlichkeit untersucht. KIMURA erhielt für die gemeinsame Fixierung von A und B eine Lösung, wenn der Genotyp AB infolge des Zusammenwirkens von A und B einen selektiven Vorteil besitzt. Die vorliegenden Untersuchungen bestätigen KIMURAS Formel und zeigen, daß Koppelung den Wert $u(AB)$ bei Vorliegen eines ursprünglichen Koppelungsgleichgewichtes nicht berührt. Darüber hinaus werden einige Fälle von Epistasie des Typs additiv mal additiv untersucht.

Acknowledgement

The author expresses her deep gratitude to Dr. M. KIMURA for his kind advice and guidance throughout the course of this study. She also thanks Dr. T. MARUYAMA for stimulating discussions during the preparation of the manuscript.

Literature

1. BODMER, W. F., and P. A. PARSONS: Linkage and recombination in evolution. Advan. Genet. **11**, 1–100 (1962). — 2. FELSENSTEIN, J.: The effect of linkage on

directional selection. Genetics **52**, 349–363 (1965). — 3. FRASER, A.: Simulation of genetic systems by automatic digital computers. I. Introduction. Austral. J. Biol. Sci. **10**, 484–491 (1957). — 4. HILL, W. G., and A. ROBERTSON: The effect of linkage on limits to artificial selection. Genet. Res. Camb. **8**, 269–294 (1966). — 5. JAIN, S. K., and R. W. ALLARD: The effects of linkage, epistasis, and inbreeding on population changes under selection. Genetics **53**, 633–659 (1966). — 6. KARLIN, S., and J. MCGREGOR: Rates and probabilities of fixation for two locus random mating finite populations. Genetics **58**, 141–159 (1968). — 7. KIMURA, M.: A model of a genetic system which leads to closer linkage by natural selection. Evolution **10**, 278–287 (1956). — 8. KIMURA, M.: Some problems of stochastic processes in genetics. Ann. Math. Statist. **28**, 882–901 (1957). — 9. KIMURA, M.: On the probability of fixation of mutant genes in a population. Genetics **47**, 713–719 (1962). — 10. KIMURA, M.: A probability method for treating inbreeding systems especially with linked genes. Biometrics **19**, 1–17 (1963). — 11. KIMURA, M.: Diffusion models in population genetics. Monographs on applied probability and statistics. London: Methuen & Co. Ltd. 1964. — 12. KIMURA, M.: Attainment of quasi linkage equilibrium when gene frequencies are changing by natural selection. Genetics **52**, 875–890 (1965). — 13. KIMURA, M.: Personal communication (1967). — 14. LATTER, B. D. H.: The response to artificial selection due to autosomal genes of large effect. II. The effects of linkage on limits to selection in finite populations. Austral. J. Biol. Sci. **18**, 1009–1023 (1965). — 15. LATTER, B. D. H.: The response to artificial selection due to autosomal genes of large effect. III. The effects of linkage on the rate of advance and approach to fixation in finite populations. Austral. J. Biol. Sci. **19**, 131–146 (1966). — 16. LEWONTIN, R. C.: The interaction of selection and linkage. I. General considerations; heterotic models. Genetics **49**, 49–67 (1964a). — 17. LEWONTIN, R. C.: The interaction of selection and linkage. II. Optimum models. Genetics **50**, 757–782 (1964b). — 18. LEWONTIN, R. C., and K. KOJIMA: The evolutionary dynamics of complex polymorphisms. Evolution **14**, 458–472 (1960). — 19. MARTIN, F. G., and C. C. COCKERHAM: High speed selection studies. Biometrical Genetics. Oxford: Pergamon Press, 1960. — 20. NEI, M.: Effects of linkage and epistasis on the equilibrium frequencies of lethal genes. I. Linkage equilibrium. Japan. J. Genet. **39**, 1–6 (1964a). — 21. NEI, M.: Effects of linkage and epistasis on the equilibrium frequencies of lethal genes. II. Numerical solutions. Japan. J. Genet. **39**, 7–25 (1964b). — 22. PARSONS, P. A. P.: Polymorphism and the balanced polygenic combination. Evolution **17**, 564–574 (1963). — 23. ROBERTS, R. C.: The limits to artificial selection for body weight in the mouse. III. Selection from crosses between previously selected lines. Genetical Res. **9**, 73–85 (1967). — 24. ROBERTSON, A.: A theory of limits in artificial selection. Proc. Roy. Soc. B. **153**, 234–249 (1960). — 25. SINGH, M., and R. C. LEWONTIN: Stable equilibria under optimizing selection. Proc. Natl. Acad. Sci. U. S. **56**, 1345–1348 (1966). — 26. WRIGHT, S.: Factor interaction and linkage in evolution. Proc. Roy. Soc. London B **162**, 80–104 (1965). — 27. WRIGHT, S.: "Surfaces" of selective values. Proc. Natl. Acad. Sci. U. S. **58**, 165–172 (1967).