SIMULATION OF GENETIC SYSTEMS
XII. MODELS OF INVERSION POLYMORPHISM[1]

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Received April 10, 1967

FRASER, BURNELL and MILLER (1966) and FRASER and BURNELL (1967) have used computer simulation to examine the factors affecting the establishment of inversion polymorphism in the following model: A genetic system of n loci, with two alleles per locus, acting additively on a primary scale of phenotype (see WRIGHT 1935; FRASER 1960; LEWONTIN 1965); normalizing selection acting on the primary phenotype specifies the fitness. Two models of selection have been introduced, symmetric double truncation (see FRASER 1960; LEWONTIN 1965), and a generalization of WRIGHT's "squared deviations from an optimum" model.

$$\text{Fitness} = 1 - \left| 1 - \frac{A}{n} \right|^{\beta}$$

where A is the phenotype on the primary scale if alleles have effects of 0 and 1. The value of β specifies the intensity of normalizing selection; for $\beta = 2.0$, the model becomes WRIGHT's squared deviations model. Figure 1 shows the relationship of fitness to the primary scale for a range of values of β.

The term, "potency" is useful in discussion of this model. The potency is the allelic sum, which has the range 0–$2n$ for zygotes, and 0–n for gametes. The model we have used includes variation of the degree of recombination (r) between adjacent loci, from 0.5 (independence) to zero, with the restriction that for $r < 0.5$, then n loci were equally spaced along a single chromosome. Consequently, the recombinational length of a chromosome is $(n - 1)r$.

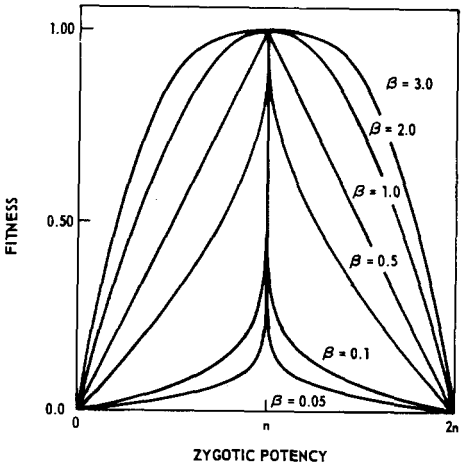

FIGURE 1.—The relationship of fitness to zygotic potency for a range of values of β, showing how the intensity of normalizing selection decreases with increase of β.

[1] Supported in part by Public Health Service grant GM 11778.

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The initial populations were of N parents, in which equal allelic frequencies were specified ($q_i = 0.5$), at gametic equilibrium, or at some degree of potency disequilibrium. (The latter is defined by FRASER and BURNELL 1967, and discussed by FRASER 1967).

The effects of normalizing selection were first considered by WRIGHT (1935). ROBERTSON (1956) extended his analysis, concluding that this mode of selection would lead to homozygosis for an intermediate potency. FRASER (1960) using computer simulation concluded that although normalizing selection would lead to eventual fixation, the loss of heterozygosity would be extremely slow in large populations, particularly if n was not small. LEWONTIN (1964, 1965) in a deterministic computer analysis of a 5-locus model showed that for $r < 0.5$ the rate of loss was considerably reduced, particularly for $r < 0.10$ (see also FRASER 1967). Ross ALLAN (personal communication) has shown that increasing the number of loci results in a marked decrease of the rate of loss of heterozygosity, with a concomitant decrease of the effect of linkage. In runs of a computer model for $n = 30$, he found that the rate of loss of heterozygosity was only slightly greater than that found for no selection. No difference of the rate of loss of heterozygosity was detected between runs made at $r = 0.5$ and $r = 0.02$.

In this model, for N infinite and $r \neq 0$, then normalizing selection will have markedly different effects dependent on the variation of gene frequencies (σ_{q_i}). If $\sigma_{q_i} = 0$, then normalizing selection will result in all gene frequencies changing equally until q_i takes a value such that the distribution of potencies is centered on the norm, e.g. for symmetric normalizing selection the gene frequencies will change until $q_i = 0.5$. The situation of $\sigma_{q_i} = 0$ is an algebraic fiction that will not occur in nature and that cannot be maintained indefinitely in computer analyses owing to round-off errors, and consequently, we will refer to this situation as a metastable equilibrium. If N is finite then random genetic dispersion will increase σ_{q_i} and selection will then act such that heterozygosity is lost with loci becoming fixed for either the 0 or 1 type allele such that the potency approximates to the norm. Even though the situation of $\sigma_{q_i} = 0$ is an artificial state it is useful as a starting point for our analyses.

The introduction of inversions into such populations involved replacing a specified number of chromosomes with a defined chromosome identified such that recombination was completely suppressed in individuals heteromorphic for the "inversion" chromosome. Only one type of inversion was introduced into any particular population. Our previous studies (FRASER, BURNELL and MILLER 1966; FRASER and BURNELL 1967) have shown that the probability of establishing a stable inversion polymorphism is markedly dependent on the initial frequency of the inversion, particularly where N is small, or where the potency of the inversion *markedly* deviates from the balanced state, i.e. where the potency of the inversion deviates from $n/2$. If the potency of the inversion equals $n/2$, then the population becomes fixed for the inversion. Decrease of the rate of recombination (r) and increase of N and β, all decrease the probability of establishing inversion polymorphism. Increasing the number of loci increases the probability of establishing inversion polymorphism to a degree that there is a real probability of es-

tablishing stable polymorphism for inversions at frequencies of $1/(2N)$, i.e. mutational frequencies. Gametic disequilibrium has been shown to have a marked effect with relatively small amounts of repulsion disequilibrium resulting in a marked decrease of the probability of establishing stable polymorphism.

The effect of normalizing selection on this model of inversion polymorphism can be represented in the following form.

Let the array of frequencies of normal chromosomes be

$$\{g_i\} \quad \text{for } i = 0, \ldots, n$$

where g_i is the frequency of chromosomes having a potency of i. Let q_I be the frequency of an inversion chromosome whose potency is I such that

$$q_I + \Sigma g_i = 1.0.$$

The zygotic frequencies will then be

$$q^2_I : 2q_I \{g_i\} : \{g_i g_j\} \quad \text{for } i = 0, \ldots, n \quad j = 0, \ldots, n.$$

The fitness of a particular zygote is given by

$$\text{Fitness} = 1 - \left| 1 - \frac{P}{n} \right|^{\beta}$$

where P is the zygote's potency.

The survival frequencies of the various zygotic classes will then be given by

$q^2_I(1 - \left\| 1 - \frac{2I}{n} \right\|^{\beta})$	Inversion homozygotes
$2q_I \{g_i(1 - \left\| 1 - \frac{I+i}{n} \right\|^{\beta})\}$	Inversion heterozygotes for $i = 0, \ldots, n$
$\{g_i g_j(1 - \left\| 1 - \frac{i+j}{n} \right\|^{\beta})\}$	Normal homozygotes for $i = 0, \ldots, n$; $j = 0, \ldots, n$.

A stable inversion polymorphism can occur, under symmetric normalizing selection, at $q_I = 0.5$. The inversion chromosomes will be balanced against an array of normal chromosomes which will reduce in the case of no recombination to $\{g_i\}$ for $i = n - I$.

This reduction will not proceed to this limit if $r \neq 0$. In this case the array of normal chromosomes will have a mean potency of $n - I$, with variation around this mean determined by the amount of recombination. For simplicity we will consider the situation for $r = 0$, and $I = (n/2) - 1$. Then, at balanced equilibrium the array of frequencies of normal chromosomes reduces to $g_{(n/2+1)}$.

The population fitness at this point of balanced equilibrium will then be

$$\bar{w} = 2q_I g_{(n/2)+1} + q^2_I(1 - \left| 1 - \frac{2I}{n} \right|^{\beta}) + g^2_{(n/2)+1}(1 - \left| 1 - \frac{n+2}{n} \right|^{\beta})$$

$$= 1 - q^2_I \left| 1 - \frac{n-2}{n} \right|^{\beta} - g^2_{(n/2)+1} \left| 1 - \frac{n+2}{n} \right|^{\beta}$$

The model is symmetric allowing the expression to be reduced to

$$\bar{w} = 1 - 2q^2_I \left| \frac{2}{n} \right|^{\beta}.$$

The segregation load at balanced equilibrium for the inversion is then

$$\tfrac{1}{2}(2/n)^{\beta}.$$

A similar argument can be made for the genetic structure of the population in the absence of the inversion.

$$\bar{w} = g_0 g_0 \left(1 - \left| 1 - \frac{0}{n} \right|^{\beta}\right) \ldots\ldots g_{n/2} g_{n/2} \left(1 - \left| 1 - \frac{n}{n} \right|^{\beta}\right)$$

If $r = 0$, then the population will be modified by normalizing selection to the array of frequencies of normal chromosomes being reduced to

$$g_{n/2} = 1.0; \bar{w} = 1.0.$$

If $r \neq 0$, then $\bar{w}$ will be less than 1 by an amount dependent on recombination and segregation extending the array of frequencies. Suppose the population is at the metastable equilibrium of $q_i = 0.5$, and that the array of frequencies of normal chromosomes is then $\{g_i'\}$, the population fitness will then be

$$\begin{aligned}\bar{w} &= \Sigma g'_i\, g'_{n-i} + \sum_{i \neq n-j} g'_i\, g'_j \left(1 - \left| 1 - \frac{i+j}{n} \right|^{\beta}\right) \\ &= 1 - \sum_{i \neq n-j} g'_i\, g'_j \left| 1 - \frac{i+j}{n} \right|^{\beta}.\end{aligned}$$

The recombination load at the metastable equilibrium is then given by

$$\sum_{i \neq n-j} g'_i\, g'_j \left| 1 - \frac{i+j}{n} \right|^{\beta}$$

The end points of selection in this model are

(a) $q_I = 1.0$ $\qquad \bar{w} = 1 - \left| 1 - \frac{2I}{n} \right|^{\beta}$

(b) $q_I = 0.5; \{g_i\} = g_{n-I}$ $\qquad \bar{w} = 1 - \tfrac{1}{2} \left(\frac{2I}{n}\right)^{\beta}$

(c) $q_I = 0.0; q_i = 0.0$ or 1.0 $\qquad \bar{w} = 1$

(d) $q_I = 0.0; q_i = 0.5$ $\qquad \bar{w} = 1 - \Sigma g_i g_j \left| 1 - \frac{i+j}{n} \right|^{\beta}$

LEWONTIN (1965) and FRASER (1967) have discussed some of the complexities of (d) above, showing that

$$\sum_{i \neq n-j} g_i g_j \left| 1 - \frac{i+j}{n} \right|^{\beta} = f[D_{ij}],$$

where $[D_{ij}]$ is the matrix of coefficients of gametic disequilibrium.

The development of a stable inversion polymorphism will be dependent in a rather complicated way on the values of β, r, and the potency of the inversions. It should be possible, but difficult, to expand this sketchy treatment to allow a full appreciation of the model, but in the absence of such an expansion it has been possible to establish some of the limits to the validity of this model of inversion polymorphism using computer simulation.

WRIGHT (personal communication) has raised the objection that the intensities of selection studied in this model ($\beta < 0.2$) would be improbable in nature. Another objection is that the restriction of population size to the range of 64–1024 parents introduced another artificiality. We have attempted to examine the validity of these objections in two ways. In one we have made use of a computer program (GSD-4) based on the recurrence expression introduced by LEWONTIN (1964), modified to the β form of selection, and to allow inclusion of inversions.

The GSD-4 program, as are all programs of this type, is subject to round-off errors, and it is limited to $n < 8$. It does, however, allow us to examine this model of normalizing selection in the absence of the random genetic dispersion consequent from finite population size. The other way we have examined these objections is to use the GSD-2 computer simulation program to examine the effect of a wide range of values of β.

A series of runs were made using the GSD-4 program for $n = 6$, $q_i = 0.5$, $D_{ij} = 0$, with an inversion of potency of 2, introduced at an initial frequency of q_I. A series of values of β and r were examined. The introduction of the inversion into the population disturbs the metastable equilibrium, if the inversion is introduced at any frequency other than a critical frequency (C). If $1.0 > q_I > C$ then the genetic structure of the population changes to a decreased frequency of the inversion, followed by an increase to the stable frequency of 0.5. The array of normal chromosomes, $\{g_i\}$, reduces to $\{g_{n-I}\}$. If $q_I < C$, the frequency of inversion decreases to its eventual loss from the population. These changes are illustrated in Figure 2, for runs made with $\beta = 0.2$, $r = 0.0156$, (2^{-6}). Recombination rates will be given on a scale of powers of 2, since this gives a better scale for demon-

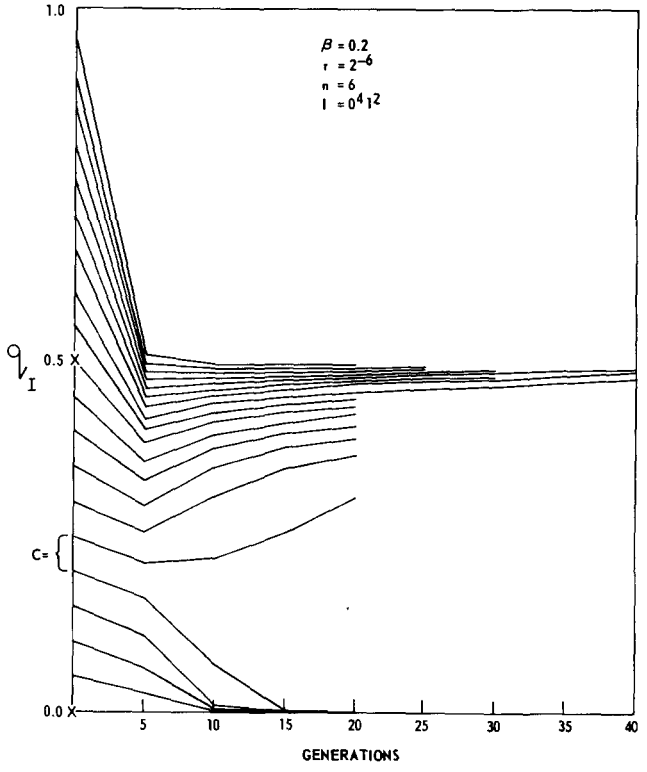


FIGURE 2.—Data obtained from runs of the GSD-4 deterministic computer program for a 6-locus model, over a range of values of the initial frequency of the inversion, showing the mode of evaluation of C for a particular set of parameters.

strating the effects of reduced rates of recombination than the more usual scale of percentage recombination.

The evaluation of C for particular values of β and r was accomplished by running the GSD-4 program for a range of values of q_l, determining whether the change of q_l between the 29th and 30th generations of selection was positive or negative. (This period was selected because it exceeds the interval of initial decrease of q_l). The results (Figure 3) show that increase of β changes the relationship of C to r through a family of curves. For β small (0.005, 0.01), at which the intensity of selection approximates closely to the extreme intensity of symmetric double truncation, the value of C increases with decrease of r to a limit. These estimates of C can be compared to the values found by FRASER, BURNELL and MILLER (1967) for double truncation selection in a 6-locus model, with $r = 0.25$ for $N = 1024$. They found a marked frequency dependence of the establishment of stable polymorphism, having a well defined inflexion at $q_l \simeq 0.12$, for β small and $r = 0.25$. The equivalent value of C for $r = 0.25$, $\beta = 0.05$–0.01 from Figure 3 is .136–.142. The comparison of N finite (1024) to N infinite does not indicate any marked change of C.

Increase of β from 0.01 to 0.1 results in the relationship of C to r showing a maximum at $r = 2^{-4}$ (Figure 3). This can be interpreted as the lack of recombination of the inversion conferring a maximum advantage when the recombination load of the genetic system is at a maximum, i.e. for $r = 2^{-1}$. Such advantage de-

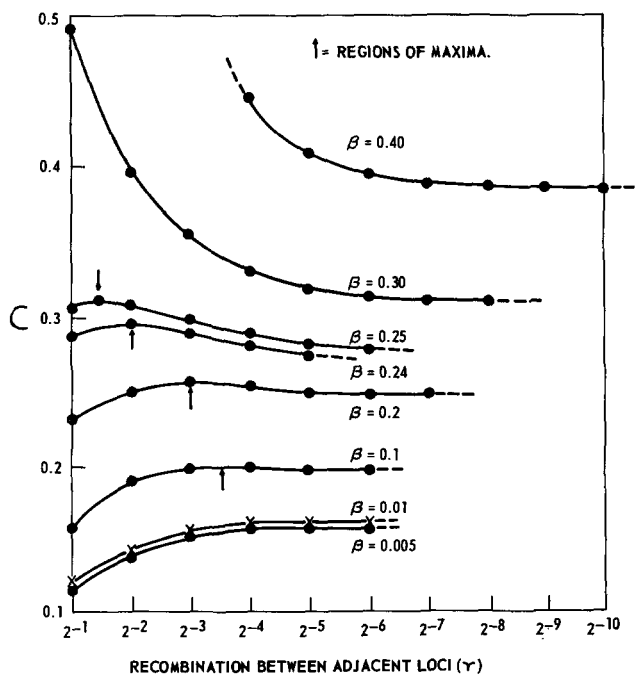


FIGURE 3.—The relationship of C to rate of recombination for a range of values of β (intensity of normalizing selection). The data are for a 6-locus model, with an $0^{4}1^{2}$ type inversion.

creases, and C consequently increases as the recombination load decreases reaching a minimum when the rate of recombination is such that the normalizing selection can produce a maximum of gametic disequilibrium. Further reduction of recombination effectively transforms the genetic system into a multiple allelic system. Here, the inversion has no significant advantage from its lack of recombination, and the value of C is determined almost solely by the potency of the inversion.

The same increase of C to a maximum can be seen for greater values of $\beta = 0.2$, 0.24, 0.25, but the maximum occurs for larger values of r as β increases (Figure 3). An explanation in terms of the maximum gametic disequilibrium occurring at a particular rate of recombination needs to be modified in terms of the value of r at which the maximum gametic disequilibrium develops increasing with increase of β. The hypothesis would be that maximum gametic disequilibrium occurs at a higher rate of recombination as the intensity of selection is reduced. This hypothesis will be examined further below.

The data obtained for $\beta = 0.20$ allow a further comparison between the deterministic and simulation studies (Figure 3). FRASER, BURNELL and MILLER (1967) examined the establishment of inversion polymorphism for $q_I = 0.25$, $n = 6$, $N = 1024$, $r = 0.25$, for a range of values of β. They found that the probability of establishing stable polymorphism decreases markedly for $\beta > 0.18$. Interpolation of $C = 0.25$ for $r = 0.25$ in Figure 3 gives a value of $\beta \simeq 0.2$. Once again there is a reasonable agreement between the results obtained from finite and infinite sized populations.

Increase of β from 0.25 to 0.30 changes the form of the relationship of C to r such that no intermediate maximum occurs; C decreases from a maximum at 2^{-1}, towards a limit reached in the range $2^{-8} \leqslant r \leqslant 2^{-6}$ (Figure 3). It is probable that a maximum does occur but for a value of $r > 2^{-1}$, which has no genetic meaning.

The hypothesis that maximum gametic disequilibrium is reached at a value of r that increases with increase of β has been examined by making a series of runs of the GSD-4 program for $q_I = 0$, for several values of β, over a range of values of r. The matrix of coefficients of gametic disequilibrium (corrected for gene frequency as devised by LEWONTIN (1965) was computed at the 20th generation of selection. FRASER (1967), LEWONTIN (1965) have discussed several features of the D'_{ij} matrix. The complete data are given in Table 1. The gene frequencies are also given to show that the effect of round-off errors is restricted to the 6th decimal place, i.e. the metastable equilibrium is not affected to any significant degree. A feature of the D'_{ij} matrix in the present model is its symmetry, e.g. $D'_{12} = D'_{56}$ and it can be reduced to nine terms: D'_{12}, D'_{23}, D'_{34}, D'_{13}, D'_{24}, D'_{14}, D'_{25}, D'_{15}, D'_{16}. These are plotted in Figure 4.

The data of Figure 4 show that the relationship of D'_{ij} to r forms a family of curves. The values of D'_{12}, D'_{34} become increasingly negative with decrease of r, reaching a maximum at about $r = 2^{-4}$, and then decreasing to a limit value of approximately -0.2. The values of D'_{23} similarly increase to a maximum but at about $r = 2^{-6}$. The values *of* D'_{13}, D'_{24} increase to the limit of approximately 0.2 without passing through an intermediate maximum. The values of D'_{14}, D'_{25}, D'_{15},

TABLE 1

Values of q_i *and* D'_{ij} *at the 20th generation of selection as specified in the text*

		Recombination between adjacent loci					
	r	2^{-1} (0.05)	2^{-2} (0.25)	2^{-3} (0.125)	2^{-4} (0.062)	2^{-5} (0.031)	2^{-6} (0.015)
$\beta = 0.20$							
q_i	1	.500000	.500000	.500000	.500001	.500001	.500001
	2	.500000	.500000	.500000	.500001	.500001	.500001
	3	.500000	.500000	.500000	.500001	.500002	.500001
	4	.500000	.500000	.500000	.500001	.500001	.500001
	5	.500000	.500000	.500000	.500000	.500000	.499999
	6	.500000	.499997	.499996	.499995	.499995	.499996
D'_{ij}	1.2	—.0699	—.1460	—.3046	—.3767	—.3184	—.2645
	2.3	—.0699	—.1241	—.1769	—.1957	—.2028	—.2031
	3.4	—.0699	—.1255	—.2209	—.2521	—.2232	—.2083
	1.3	—.0699	—.0811	—.1084	—.1539	—.1855	—.1963
	2.4	—.0699	—.0732	—.0882	—.1248	—.1591	—.1789
	1.4	—.0699	—.0680	—.0825	—.1165	—.1517	—.1746
	2.5	—.0699	—.0613	—.0552	—.0745	—.1203	—.1563
	1.5	—.0699	—.0626	—.0567	—.0731	—.1168	—.1533
	1.6	—.0699	—.0671	—.0649	—.0795	—.1175	—.1519

$\beta = 0.24$	r	2^{-1} (0.05)	2^{-2} (0.25)	2^{-3} (0.125)	2^{-4} (.062)	2^{-5} (.031)	2^{-6} (.015)	2^{-7} (.0078)	2^{-8} (.0039)
q_i	1	.500001	.500000	.500001	.500001	.500001	.500001	.500001	.500001
	2	.500001	.500000	.500001	.500001	.500001	.500001	.500001	.500001
	3	.500001	.500001	.500000	.500001	.500002	.500001	.500001	.500001
	4	.500000	.500001	.500001	.500001	.500001	.500001	.500000	.500000
	5	.499998	.500000	.500000	.500000	.500000	.499999	.499999	.499999
	6	.499997	.499997	.499996	.499995	.499996	.499997	.499997	.499998
D'_{ij}	1.2	—.0168	—.1377	—.2787	—.3629	—.3143	—.2631	—.2327	—.2165
	2.3	—.0168	—.1188	—.1737	—.1959	—.2027	—.2030	—.2019	—.2011
	3.4	—.0168	—.1194	—.2045	—.2444	—.2214	—.2077	—.2028	—.2011
	1.3	—.0168	—.0778	—.1057	—.1515	—.1841	—.1956	—.1989	—.1997
	2.4	—.0168	—.0707	—.0865	—.1231	—.1581	—.1784	—.1891	—.1945
	1.4	—.0168	—.0652	—.0794	—.1138	—.1501	—.1738	—.1867	—.1933
	2.5	—.0168	—.0594	—.0562	—.0747	—.1198	—.1559	—.1771	—.1883
	1.5	—.0168	—.0603	—.0571	—.0731	—.1159	—.1526	—.1751	—.1872
	1.6	—.0168	—.0641	—.0643	—.0794	—.1166	—.1511	—.1736	—.1863

$\beta = 0.30$	r	2^{-1} (0.05)	2^{-2} (0.25)	2^{-3} (0.125)	2^{-4} (.062)	2^{-5} (.031)	2^{-6} (.015)	2^{-7} (.0078)	2^{-8} (.0039)
q_i	1	.500000	.500000	.500001	.500001	.500001	.500001	.500001	.500001
	2	.500000	.500000	.500001	.500001	.500001	.500001	.500001	.500001
	3	.500000	.500000	.500001	.500001	.500001	.500001	.500001	.500001
	4	.500000	.500000	.500001	.500001	.500001	.500001	.500000	.500000
	5	.500000	.500000	.500000	.500000	.500000	.499999	.499999	.499999
	6	.499997	.499998	.499996	.499995	.499995	.499996	.499997	.499998

D'_{ij}	1.2	—.0626	—.1274	—.2472	—.3410	—.3077	—.2608	—.2317	—.2161
	2.3	—.0626	—.1119	—.1675	—.1955	—.2024	—.2027	—.2018	—.2010
	3.4	—.0626	—.1117	—.1850	—.2325	—.2183	—.2067	—.2024	—.2010
	1.3	—.0626	—.0734	—.1010	—.1474	—.1817	—.1945	—.1983	—.1995
	2.4	—.0626	—.0672	—.0838	—.1203	—.1564	—.1776	—.1887	—.1943
	1.4	—.0626	—.0616	—.0749	—.1095	—.1474	—.1724	—.1860	—.1930
	2.5	—.0626	—.0567	—.0566	—.0750	—.1189	—.1552	—.1767	—.1881
	1.5	—.0626	—.0571	—.0567	—.0728	—.1145	—.1515	—.1744	—.1869
	1.6	—.0626	—.0603	—.0623	—.0787	—.1152	—.1500	—.1728	—.1858

D'_{16} become decreasingly negative with decrease of r towards a minimum at $2^{-3} \leqslant r \leqslant 2^{-2}$, become increasingly negative with further decrease of r, towards the limit value. FRASER (1967) has shown, following LEWONTIN (1965), that the changes of D'_{ij} with decrease of r, can be considered in terms of three types of systems of many loci. These are (a) "multiple allelic" which holds for r sufficiently small to reduce the system to the equivalent of a set of multiple alleles. The maximum negative value of $[D'_{ij}]$ will be reached when the frequency distribution of gametic potencies is reduced to the central class: [000111], setting a limit value of 0.2 to $[D'_{ij}]$; (b) "polygenic" following MATHER's (1939, 1941) use of the term, describing a system of many loci whose characteristics are markedly affected by linkage. Normalizing selection of such a system will generate *linkage* disequilibrium, acting against the recombination load; (c) "multigenic" which term is introduced as descriptive of a system in which linkage has little if any role in determining the gametic disequilibrium. The data of Figure 4 can be interpreted as the system of six loci being multigenic for $2^{-3} < r < 2^{-1}$, polygenic for $2^{-5} < r < 2^{-4}$ and multiple allelic for $r < 2^{-5}$. We suggest that in the absence of information about linkage it would be better to use the term "multigenic" rather than "polygenic" with its connotations of a linkage component.

The data of Figure 4 demonstrate that there is no marked shift of the value of r at which maximum gametic disequilibrium is generated. This disproves the suggestion made above that the maximum of C occurring at larger values of r with increase of β is due to a similar relation of the maximum of $[D_{ij}]$ to r and C.

The results obtained from the above analysis of the 6-locus model in infinite populations are in fairly close agreement with the results obtained by FRASER, BURNELL and MILLER (1967) obtained by computer simulation of the same model in finite populations. The same general conclusions from their studies are valid for the present results; this model of inversion polymorphism cannot be accepted as an adequate explanation except for populations exhibiting a high degree of random genetic dispersion with a high degree of maintenance of genetic variability, favoring a strong genetic drift.

FRASER and BURNELL (1967) have extended the above model of inversion polymorphism to 30 loci finding that it is a valid explanation for inversion polymorphism in such systems. Their results were obtained with the GSD-2 simulation program with $N = 256$. It is not practical to use a deterministic approach for models involving so many loci, but the agreement between the finite and deterministic approaches for the six-locus model can be taken as strong support for

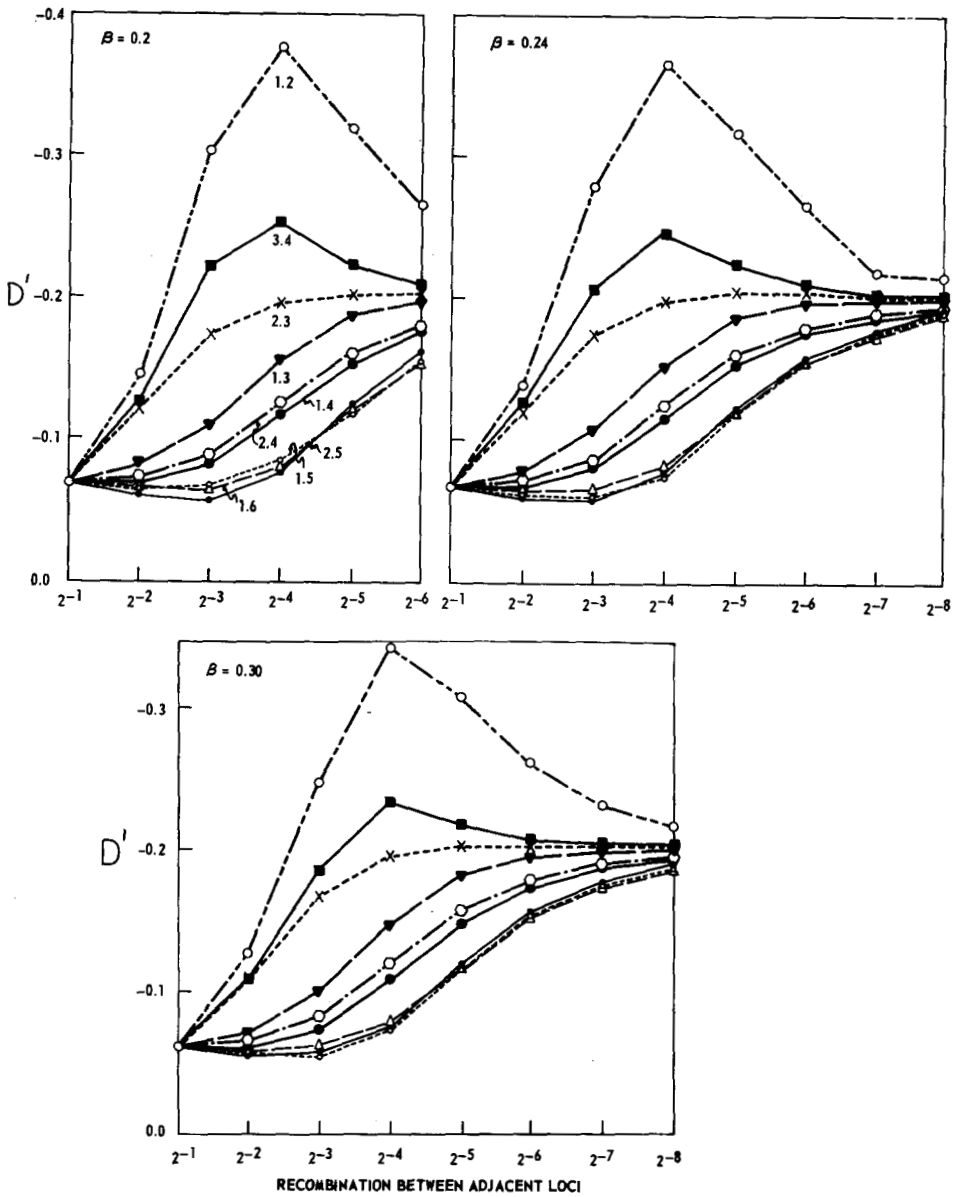


FIGURE 4.—The values of D_{ij} for a 6-locus model at the metastable equilibrium of $q_i = 0.5$, are shown for three intensities of normalizing selection, at the 20th generation of selection.

the generality of results obtained by the simulation of finite populations where $n > 6$. Although, our results have shown the validity of this model if n is large, WRIGHT's objection that the intensities of normalizing selection which were used are improbable in nature, needs to be considered. Runs have, therefore, been made with the GSD-2 simulation program to examine a wide range of intensities

of normalizing selection. The runs were made for $N = 256$, $n = 30$, $r = 0.025$, $D'_{ij} = 0$ with $q_i = 0.5$, for an inversion with a potency of 14, introduced at an initial frequency of 0.25. The runs were continued to the 100th generation of selection. Initially, 16 replicates were run for each value of β. Further sets of 16 replicates were then made to extend the data for a wider range of values of β. The results from the first set of replicates are shown in Figure 5 as q_I plotted against generation of selection.

The results of Figure 5 show an increasing variability of q_I with increase of β, with a strong indication that this increase reaches a maximum at about $\beta = 2.0$. Runs were made to check this feature of the data, both for the values of β in Figure 5, and for other values of β. The results are shown in Figure 6 as frequency histograms of inversion frequency at the 100th generation of selection.

The results shown in Figure 6 are presented in full to illustrate the type of variability of q_I found in this model. A simplified representation is given in Figure 7 in which the standard deviation of q_I over replicates is shown for genera-

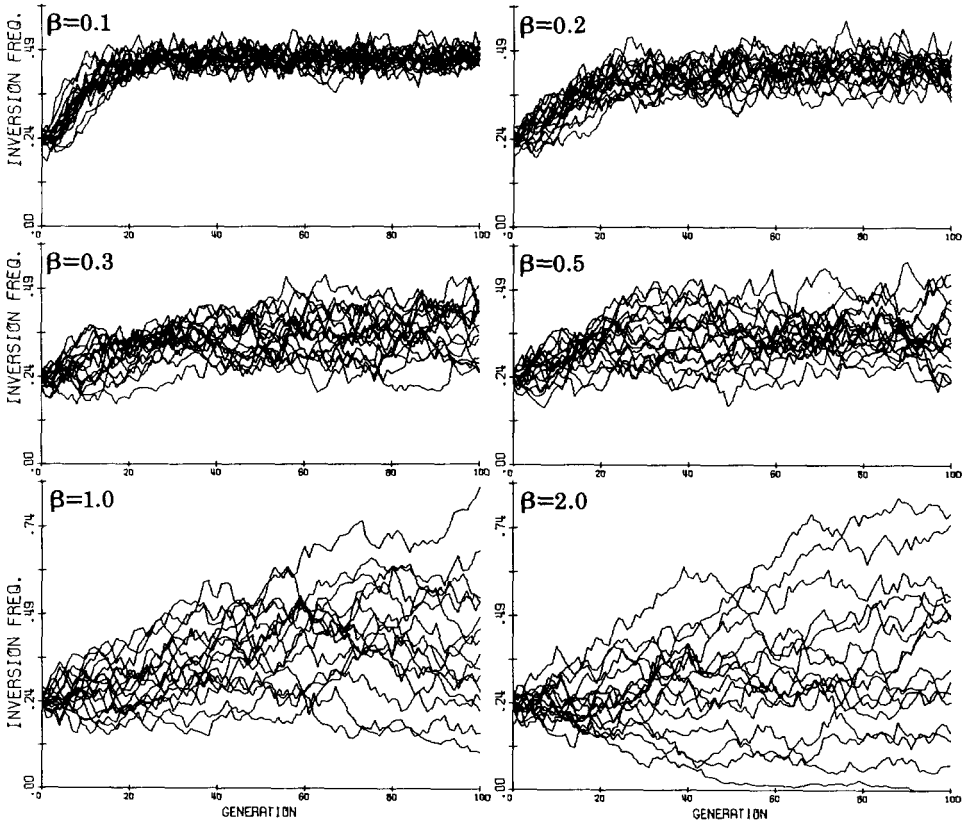
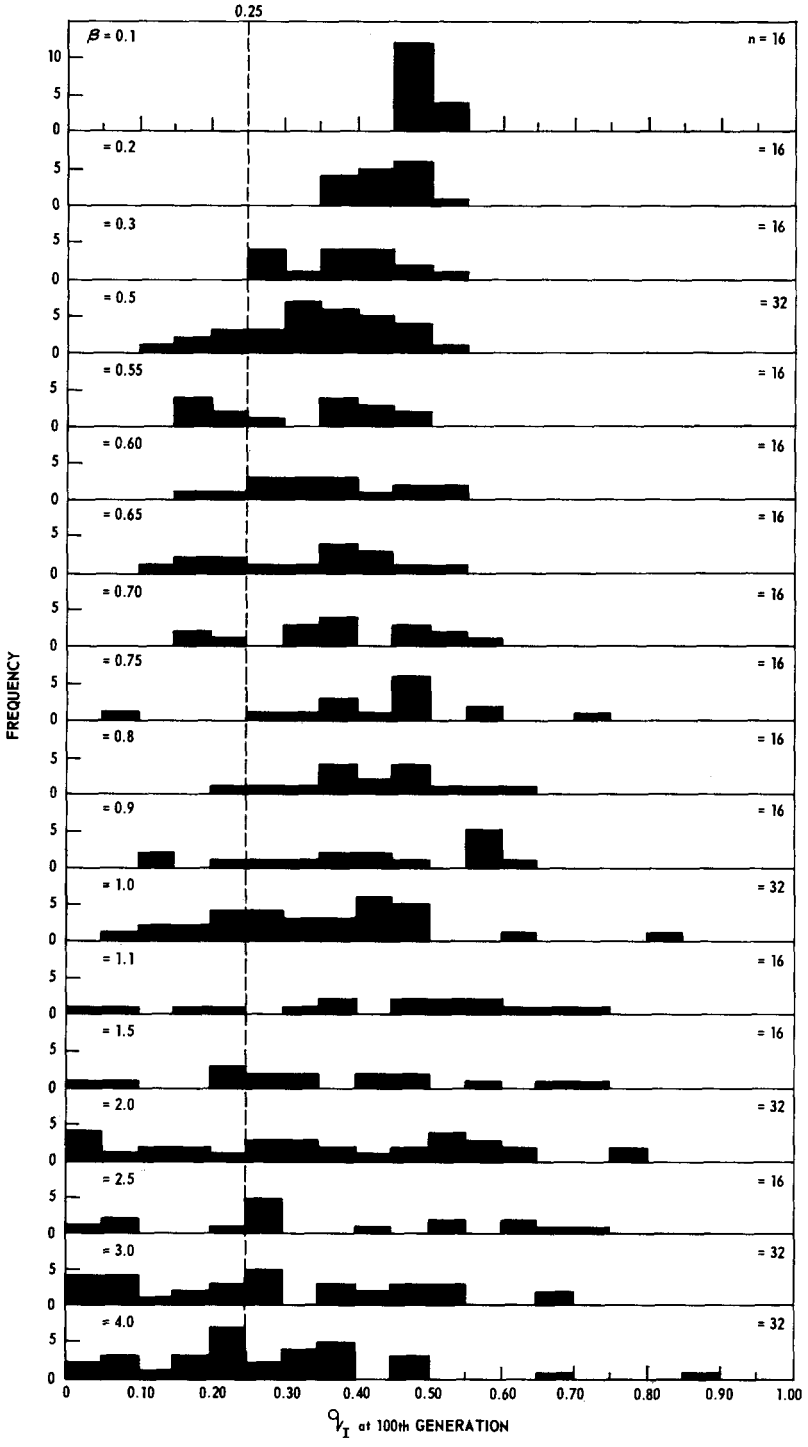


FIGURE 5.—Inversion frequency plotted against generation of normalizing selection for the $0^{16}1^{14}$ inversion. Sixteen replicate runs are shown for each intensity of normalizing selection. The diagram was computer-controlled.


0.25
β = 0.1
n = 16
= 0.2
= 16
= 0.3
= 16
= 0.5
= 32
= 0.55
= 16
= 0.60
= 16
= 0.65
= 16
= 0.70
= 16
= 0.75
= 16
= 0.8
= 16
= 0.9
= 16
= 1.0
= 32
= 1.1
= 16
= 1.5
= 16
= 2.0
= 32
= 2.5
= 16
= 3.0
= 32
= 4.0
= 32
FREQUENCY
0 5 10
0 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
q_I at 100th GENERATION

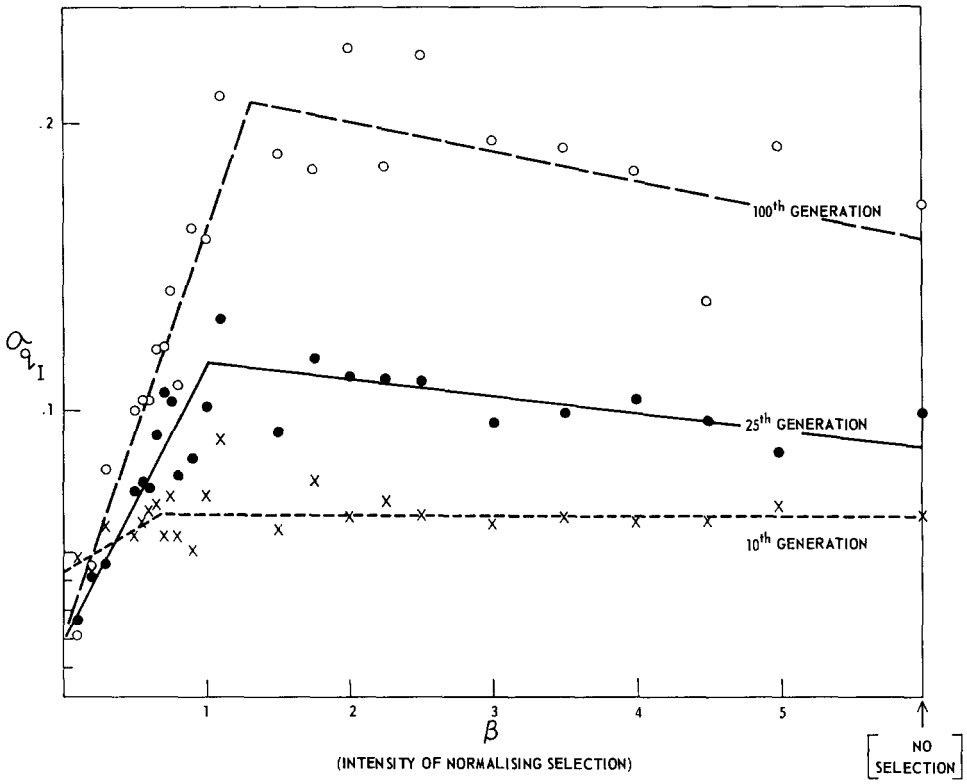


FIGURE 7.—The standard deviation over replicate runs of q_I from the data of Figure 5, for the 10th, 25th and 100th generations of selection, showing that σq_I tends to a maximum in the range of $\beta \simeq 1.0$.

tions 10, 25 and 100. It would appear that the variability of q_I increases, with increase of β, to a maximum at about $\beta = 1.0$. This is most evident at generation 100. The results shown in Figures 6 and 7 confirm the occurrence of a maximal variability in the runs made with β in the range 1.0. An interpretation of this phenomenon can be based on genetic drift (WRIGHT 1948). With β small the intensity of selection is high and the change of q_I is essentially deterministic—if $q_I > C$ then Δq_I is positive and if $q_I < C$ then Δq_I is negative. In this model, for small values of β, q_I is greatly in excess of C, with the result that q_I increases rapidly towards the limit of $q_I = 0.5$. For larger values of β, the situation is still essentially deterministic but Δq_I is smaller. Further increase of β results in a greater reduction of the deterministic component, and also results in an increase of C; the situation is one of genetic drift in which the deterministic component

FIGURE 6.—Frequency histograms of inversion frequency at the 100th generation of selection of a 30-locus model in which the $0^{16}1^{14}$ inversion was introduced at an initial frequency of 0.25. Intensities of normalizing selection are given to the left. Numbers of replicate runs are given to the right.

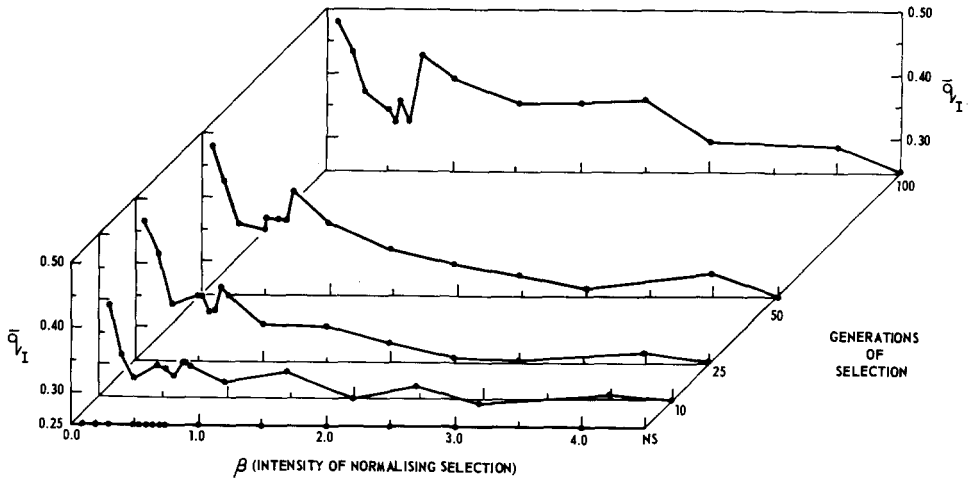


FIGURE 8.—Frequency of inversion, averaged over replicate runs, plotted against generation of selection, and intensity of normalizing selection.

and the random genetic component interact, increasing σq_I. Further increase of β reduces the deterministic component to negligible values and the situation increasingly approximates to that of no selection. The data are presented in a different form in Figure 8, in which the mean $\bar{q}_I$ over replicates is plotted against generation of selection for different values of β.

The results in Figure 8 show that $\bar{q}_I$ increases for all values of β. It would appear that this model of inversion polymorphism is valid for a wide range of values of β. An extremely interesting feature of the data is that the increase of q_I towards the limit of 0.5 decreases with increase of β, to a minimum at about $\beta = 0.6$, then increases with further increase of β to a secondary maximum at about $\beta = 0.75$, thereafter decreasing with increase of β. The maximum at $\beta = 0.75$ can be considered as due to genetic drift reaching a maximum at about this intensity of selection. A check of this hypothesis could be made by repeating the runs for a different size of population. These runs were made for $q_I = 0.25$ and it will be necessary to make other runs for $q_I \simeq 1/(2N)$ i.e. at mutational frequencies. Our data should be regarded as indicative rather than definitive.

DISCUSSION

There are aspects of the model which we have used that require further examination. A major feature is the postulate of an initial state of maximum genetic variability i.e. $q_i = 0.5$, $D_{ij} = 0$. WRIGHT (1935), ROBERTSON (1956), FRASER (1960), LEWONTIN (1965) and Ross ALLAN (personal communication) have shown that the effect of normalizing selection on such a genetic system is to cause eventual fixation for a balanced homozygote if n is even, or fixation of all but one locus if n is odd. The rate of decrease of genetic variability is reduced by decrease of r, and increase of n, but normalizing selection, as noted by ROBERTSON (1956)

will not increase the genetic variability. It is necessary to consider modes of selection and gene action that will result in the maintenance of genetic variability. There are three possible modes of selection that could be expected to maintain genetic variability. These are (1) disruptive selection with two or more norms, (2) cyclic or seasonal variation of the norm, and (3) random fluctuation of the norm. ALLAN (personal communication) has examined the effects of cyclic and fluctuating systems of selection, finding in finite populations ($N = 256$) that there is a loss of genetic variability. We have examined the effects of disruptive selection for two norms in the same size of population, finding that, eventually, the population centers on a single norm, i.e. if the two norms are considered as ecological niches then, eventually, the population becomes restricted to a single niche. It can, however, be argued that these results were obtained for single populations, and that the separation into a number of semi-isolated populations would considerably change the effectiveness of such modes of selection in maintaining genetic variability. The maintenance of inversion polymorphism over long periods in small, isolated laboratory cultures, and the general occurrence of genetic variability in such stocks is some argument for other factors than mode of selection being predominant in the maintenance of genetic variability. LERNER (1954) has argued that such a factor is the occurrence of overdominance; the intrinsic advantage of heterozygosity. This can be introduced into the "optimum" model.

$$\text{Fitness} = (1-x)\left(1 - \left|1 - \frac{A}{n}\right|^{\beta}\right) + x\frac{n'}{n}$$

where n' is the number of heterozygous loci, and x specifies the relative importance of normalizing selection and overdominance of fitness.

WRIGHT and DOBZHANSKY (1946) showed that inversion polymorphism could be maintained by frequency dependent mating. EHRMAN (1966), SPIESS, LANGER and SPIESS (1966) and KAUL and PARSONS (1965) have shown that such frequency dependent mating does occur in *Drosophila pseudoobscura* for the inversion genotypes, with the low frequency genotypes being favored. It is pertinent to question whether such a genetic control of mating behavior is a primary or a secondary feature of inversion polymorphism. Our results indicate that the periodic reduction of population size, as occurs in Drosophila, would result in the loss of inversion polymorphism, unless normalizing selection was extremely intense. Consequently, it is not unreasonable to suggest that frequency dependent mating could evolve as a means of stabilizing inversion polymorphism, ensuring its maintenance in small populations. The inclusion of terms for overdominance, and for the evolution of frequency dependent mating are clearly necessary for a full consideration of the optimum model, as it applies to inversion polymorphism.

SUMMARY

The establishment of inversion polymorphism is considered in reference to an optimum model of the relationship of gene action to fitness. Previous results, showing by computer simulation that this model is not sufficient for genetic systems of six loci, have been confirmed and extended by a computer analysis using

a deterministic approach. The frequency dependence of establishment of polymorphism has been examined for a range of intensities of selection and degrees of recombination. It is shown that some complexities of this frequency dependence are not consequent from differences in the establishment of gametic disequilibrium. The method of computer simulation has been extended to a 30-locus model, for a wide range of intensities of selection, indicating that this model is sufficient for inversions extending over many loci.

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