Theoretical and Applied Genetics 38, 223–225 (1968)

Simulation of Genetic Systems

XI. Normalizing Selection*

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Summary. The effects of intense normalizing selection have been studied, using computer simulation, for models of 3, 4, 5, 6, 8, 12 and 24 loci. The effectiveness of such selection in reducing heterozygosity decreases with increase of the number of loci to a limit that is only slightly greater than that consequent from random genetic dispersion, if the loci are freely recombining. Tight linkage markedly reduces the rate of loss of heterozygosity for small numbers of loci, but this effect of tight linkage decreases with increase of the number of loci.

WRIGHT (1935) considered the effects of selection favoring an intermediate optimum, concluding that this would result in either fixation of all loci, or of all but one, in a large number of possible combinations. The number of such possible combinations depends on the number of loci, the relative magnitudes of the gene effects, and the position of the norm. The optimum model is based on a multigenic system acting additively to determine the phenotype on what is termed the primary scale. Selection favoring an intermediate value on this primary scale specifies the following function relating fitness to additive value.

$$\text{Fitness} = [s_i - 0]^2$$

where s_i is the value on the primary scale, and 0 is the value of the optimum. This has been termed the quadratic optimum model, WRIGHT's deviations squared model, etc. FRASER, BURNELL and MILLER (1967) give a different version of this function, based on the norm being located at the mid-point of the primary scale, and on equal gene effects. Alleles are specified to have effects of 0 or 1 and the phenotypic value on the primary scale is then the number of alleles with effects of 1.

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

where n is the number of loci, A is the phenotypic value on the primary scale, and β specifies the intensity of selection. As β tends to zero, the normalizing selection tends to the extreme of double truncation selection for the mid-point of the primary scale. For $\beta = 2.0$, the function corresponds to a symmetric "deviations squared" model.

ROBERTSON (1956) considered the effect of selection based on deviations from the population mean (stabilizing selection), concluding that such selection will send gene frequencies to 0 or 1 with a metastable equilibrium at $q_i = 0.5$. He considered that such selection will not lead to the maintenance of genetic variation, but leads instead to its extinction by fixation.

FRASER (1960) used computer simulation to examine the effects of extreme double truncation selection on a 10 locus model. He concluded that normalizing selection will lead to fixation of an intermediate homozygote but at a rate determined by the rate of random genetic dispersion, i.e. at an extremely slow rate in all but very small populations. LEWONTIN (1965) using a deterministic computer analysis of the effects of double truncation selection on a 5 locus model with varying degrees of linkage, found that tight linkage (0.05, 0.01) caused a marked reduction of the rate of loss of heterozygosity, with a concomitant increase of gametic disequilibrium involving a marked development of relationally balanced repulsion disequilibrium developed in the runs made at tight linkage (see also FRASER 1967, FRASER and BURNELL 1967). An important feature of LEWONTIN's analysis of normalizing selection is that the decreased rate of loss of heterozygosity which results from tight linkage is sensitive to the intensity of double truncation selection. Decreased intensity of selection results in a decreased effect of tight linkage. The effect of variation of the intensity of selection can also be determined by maintaining the intensity of normalizing selection constant, varying the number of loci. This will vary the intensity of selection per locus. The present paper details and discusses results of this type.

A computer program, GSD-2, was used which allows simulation of finite populations for multigenic systems of $n \leqq 30$. Recombination is specified for adjacent loci, with all loci located equi-spaced along a single chromosome. Two alleles are specified per locus having effects of 0 or 1, giving a phenotypic range from 0 to 2 n. This program has previously been used for studies of the effects of normalizing selection on the evolution of inversion polymorphism (FRASER, BURNELL and MILLER 1967, FRASER and BURNELL 1967).

The present study involved runs of GSD-2 made for (1) n = 2, 3, 4, 5, 6, 8, 12, 24, (2) population size = 256 parents, (3) rate of recombination between adjacent loci = 0.5, 0.02. The latter value is within the range of "tight" linkage as determined by LEWONTIN (1965), FRASER (1967), and, therefore, our studies involve a comparison of multigenic ($r = 0.5$) and polygenic ($r = 0.02$) systems. (4) The intensity of selection was specified as $\beta = 0.1$, specifying an intense normalizing selection. A series

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* This research was supported by NIH Grant GM-11778.

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of runs were also made with no selection. (5) The initial populations were specified as at $q_i = 0.5$, D_{ij}, i.e., at equal allelic frequencies in gametic equilibrium. Two measures of genetic structure were output at the specified generations of selection: the proportion of heterozygous loci (*het*) and the mean recombination index (*rec*). These measures were computed over the population of unselected progeny. The latter measure has been described previously (Fraser, 1967). It ranges from 0.0, all chromosomes having a 000. . . 0 or 111 . . . 1 configuration, to 1.0, all chromosomes having a 010 . . . 1 or 101 . . . 0 configuration. These measures have values of 0.5 in the initial populations. Eight replicate runs were made for each set of values.

The values of *het* and *rec*, averaged over replicates, are shown in figures 1 and 2 for no selection. Any decrease of heterozygosity in the absence of selection is due solely to the random genetic dispersion consequent from the finite population size. Each locus is an independent entity with free recombination and the value for $n = 24$ is, therefore, an average over 144 loci since 6 replicate runs were made. A considerable reliance can be placed on the value of 0.456 for *het* found at the 48th generation in these runs, with progressively less reliance for the values found for smaller numbers of loci. There is an indication that a slightly greater loss of heterozygosity occurs in the runs made at tight linkage with small numbers of loci. The data shown in figure 2 indicate that no significant changes of *rec* occurred.

The values of *het* and *rec* are shown for $\beta = 0.1$ in figures 3 and 4. Consider first the runs made at free recombination. There is a marked loss of heterozygosity that is greater for n even, than for n odd. The rate of decrease of heterozygosity markedly decreases with increase of the number of loci tending to a limit, which is only slightly more than the value found in the control runs. With selection for $n = 24$ and $r = 0.5$, the value of *het* at the 48th generation was 0.437, compared to the analogous value of 0.456 found in the control runs. The difference between runs made with odd and even numbers of loci is in agreement with Wright's (1935) conclusion. The decreased rate of loss of heterozygosity with increase of the number of loci is in agreement with Robertson (1956), Fraser (1960).

The data in figure 3, for tight linkage contrasts markedly with that for free recombination. The loss of heterozygosity is at a minimum for $n = 3$, increases to a maximum for $n = 8$, and then decreases towards a limit for $n = 24$. With selection for $n = 24$ and $r = 0.02$ the value of *het* at the 48th generation was 0.436, which compares very closely to that of 0.437 found for free recombination. These results are in agreement with Lewontin (1965) for n small, in that tight linkage markedly reduces the rate of heterozygosity, but this agreement decreases as n increases, with tight linkage having no effect for $n = 24$. There is a slight increase of the rate of loss of heterozygosity in models of $n = 24$, for selection (0.436 at the 48th generation) contrasted with no selection (0.456 at the 48th generation).

The data of *rec* given in figure 4 show very little difference between free recombination and tight linkage for $n = 3$, 4, and 5. This contrasts with the

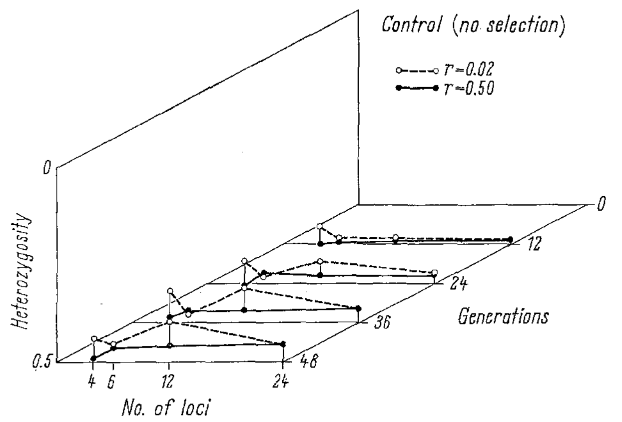


Fig. 1. Average heterozygosity is shown plotted against generations of selection, and number of loci, for free recombination ($r = 0.50$) and tight linkage ($r = 0.02$) in runs made with no selection

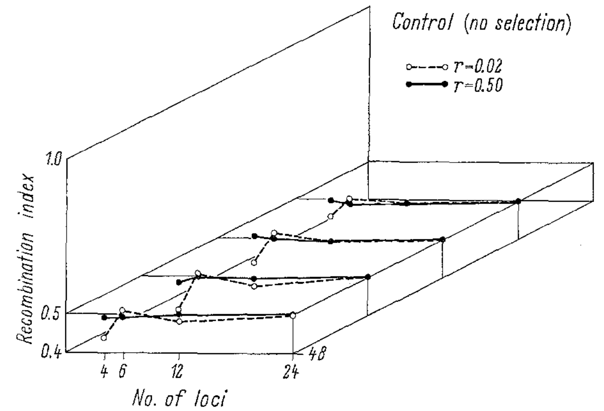
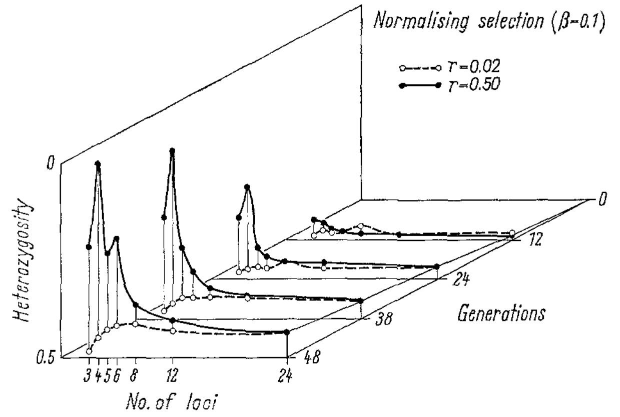
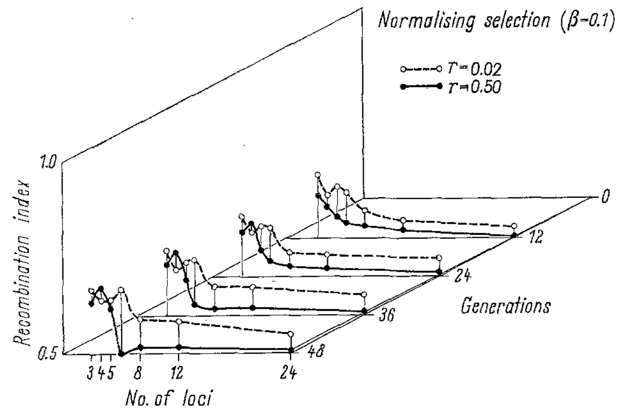


Fig. 2. As in figure 1 for the average recombination index





Figures 3 and 4. As in figures 1 and 2, but for a normalizing selection of $\beta = 0.1$

consistently greater recombination index found in the tight linkage runs for $n = 6, 8, 12, 24$. The low values for $n = 3, 4, 5$ are probably a sampling artifact due to the marked shift towards homozygosity that has occurred in these runs. It appears that normalizing selection can effect repulsion gametic disequilibrium for systems of tightly linked loci, even though the same selection is ineffective in reducing heterozygosity.

Conclusions

Normalizing selection has been shown to be ineffective in reducing the genetic variability of a system of freely recombining loci unless the number of loci is small. Small in this sense is of the order of 6—8 loci or less, whereas large is of the order of 12 or more loci. LEWONTIN (1965) showed that tight linkage markedly reduces the effect of selection on systems of a few loci, such that the rate of loss of heterozygosity is negligible. Our results show that this effect of tight linkage is not manifest in systems of many loci. The rate of loss of heterozygosity in such systems is not affected by linkage.

Although linkage has no effect in systems of many loci on the rate of loss of heterozygosity, it does have an effect on the development of gametic disequilibrium. It is evident that normalizing selection in a system of many tightly linked loci results in the development of relationally balanced chromosomes, even though the intensity of selection per locus is too small to affect the rate of loss of heterozygosity (see MATHER 1943).

Zusammenfassung

Es wird die Wirkung normalisierender Selektion für 3, 4, 5, 6, 8, 12 und 24 Loci unter Verwendung von Computer-Simulationen untersucht. Die Wirksamkeit derartiger Selektion hinsichtlich der Reduzierung der Heterozygotie nimmt mit zunehmender Zahl der Loci bis zu einem Grenzwert ab, der nur größer ist als der aus zufälliger genetischer Dispersion folgende, wenn die Loci frei miteinander rekombinieren. Enge Koppelung reduziert die Rate des Heterozygotenverlustes bei kleiner Zahl von Loci beträchtlich, jedoch nimmt dieser Effekt der engen Koppelung mit steigender Zahl der Loci ab.

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