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The Interaction of Selection and Linkage III* Synergistic Effect of Blocks of Genes

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Summary. We have examined the effect of selection in populations when the genes controlling the selected character do not have uniform recombination relations. In particular we have examined the outcome of selection for an intermediate optimum phenotype controlled by two blocks of genes additive within blocks, but multiplicative between blocks. This is analogous to "main effect" genes and "modifiers". The question examined was what effect linkage structures of these groups had on the changes in gene frequency and rate of advance under selection.

The results of replicated Monte Carlo runs of large populations at three intensities of selection were:

1. A tightly linked block of genes maintains genes in intermediate gene frequencies, undergoes rapid selections of balanced gametic types and shows a very rapid rise in fitness followed by a long period of plateau at a fairly high fitness value.

2. A loosely linked block of genes goes to fixation of balanced numbers of loci at $q = 0.0$ and $q = 1.00$. This results in a slower rise in fitness but a higher plateau, nearly at a fitness of unity.

3. When one block of genes is tightly linked and the other loosely linked the effects of each type of block are exaggerated. The loosely linked genes go to fixation more rapidly, the tightly linked genes stay closer to intermediate values, fitness rises more quickly than for loosely linked genes but goes to a higher plateau than for tightly linked genes.

The previous publications of this series (LEWONTIN 1964a, b) as well as other works on the theory of linkage and selection (see BELLMANN and AHRENS, 1966, for a substantial bibliography) have concentrated on fairly simple genetical systems. In particular it has been convenient to investigate simple genomes consisting of n loci formed into 1 or several linkage groups but with the same amount of recombination between adjacent genes. Using such models it has been possible to map out the effect of changing the intensity of linkage on the rate of progress under selection, the kinds of gametic combinations built up in the population, the nature of equilibria if any, and so on. Because of the analytic difficulties of these complex processes most of the work has proceeded by the numerical analysis of various selection models with various parameter values. Such quasi-empirical studies can obviously be extended in any direction. More models of selection, more complex physiological interaction between loci, variations in mating structure, increasing numbers of loci, are all open for study. It seems to us, however, that an important lacuna in our knowledge exists with respect to the structure of the genetical system itself.

That is, one may imagine that the genes controlling some character are not homogeneously distributed through the genome with completely additive effects but rather that the genome is organized into blocks of genes, roughly additive among themselves, but interacting with other such blocks to produce the phenotype upon which selection acts. The introduction of such structure into our models results in a very large field of possible inquiry. The number of blocks, the degree of their interaction with each other, the linkage relations among them, are all variables. The problem must then be attacked piecemeal, but

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with some system in order to see any patterns emerging from what might be a chaos of results. The first of these results, based on a fairly simple model, is presented in this paper. More complex ones will follow.

The Model

We assume a phenotypic character controlled by 20 genes, divided into two physiological blocks of 10 genes each. Within each block the genes are additive in their effect both between alleles (no dominance) and between loci (no epistasis). The phenotypic effect of one block, however, multiplies with the phenotypic effect of the other block. Thus we may give an alternative interpretation to the two blocks of genes, considering one as the "main effect" block and the other as consisting of modifiers of the additive effect of the first block. The exact quantitative model is as follows:

Let A_i = phenotypic effect of the i^{th} "modifier" locus
Let B_j = phenotypic effect of the j^{th} "main effect" locus

$$\left.\begin{matrix} A_i \\ B_j \end{matrix}\right\} = \begin{cases} 0 \text{ if the locus is homozygous } 0/0 \\ 1 \text{ if the locus is heterozygous } 0/1 \\ 2 \text{ if the locus is homozygous } 1/1 \end{cases}$$

$$\text{Score} = \sum_{i=1}^{10} A_i \cdot \sum_{j=1}^{10} B_j . \qquad (1)$$

For this model the score has a range from 0, when all loci in both blocks are homozygous $0/0$, to 400 when all loci in both blocks are homozygous $1/1$.

The mode of selection in our model is a simple intermediate optimum with fitness, W, falling off linearly as the phenotypic score deviates from the optimum. That is

$$\left.\begin{matrix} S = 1 - |\text{score} - \text{optimum}| \cdot K & W > 0 \\ W = 0 & \text{otherwise} \end{matrix}\right\} \quad (2)$$

where K is chosen to determine the intensity of selection. For example, if we set the optimum equal to 100, then a genotype with 10 0 alleles and 10 1 alleles at the modifier loci and the same gene dosage at the main effect loci will have a sum of

$$\text{score} = \Sigma A_i \Sigma B_j = (10)\ (10) = 100$$

Therefore it will be exactly at the optimum and the fitness, $W = 1$. On the other hand if there were 10 0 alleles and 10 1 alleles at the "modifier" loci, but 8 0 and 12 1 alleles at the "main effect" loci the score would be

$$\text{score} = \Sigma A_i \cdot \Sigma B_j = (10)\ (12) = 120$$

and

$$W = 1 - 20\ \text{K}$$

If $K = .01$, $W = .8$, while if $K = .1$, $W = 0$ (since it is in fact less than zero).

In all the results in this paper we have chosen a symmetrical optimum model with the optimum at 100. Thus there will be no average selection for either 0 or 1 alleles. As we will see, the actual location of the optimum is not critical provided it falls within the range of phenotypes produceable under our model. Three intensities of selection have been used called *Strong* (S), *Medium* (M) and *Weak* (W) corresponding to K values of 0.1, 0.03 and 0.01. In the case of S selection only one class of genotypes survives that with a phenotype of exactly the optimum. In M and W selection, fitness falls off more gradually from the optimum according to equation 2.

Five linkage relations were examined for each intensity of selection. *Tight* linkage (T) symbolizes 1% recombination between adjacent genes along the chromosome in a block. *Loose* linkage (L) symbolizes 50% recombination between adjacent genes in the block. Since there are two blocks of genes, there are five possible linkage relations: LL, LT, TL, TT and $T - T$, where LT, for example means that the genes of the first block are loosely linked and the genes of the second block tightly linked. The special case $T - T$ stands for tight linkage in both blocks with the two blocks tightly linked to each other.

The Method

The large number of genes involved in this system requires a numerical, rather than a literal solution. Even a numerical solution, however, becomes extremely cumbersome if exact solutions are attempted. With 20 genes, each with 2 alleles, there are $2^{20} = 1{,}048{,}576$ possible gametic types. To calculate the change in frequency of each of these in each generation as a result of selection and recombination would require either the handling of 2^{20} simultaneous equations or the construction of a vector of 2^{20} elements by the method of "genetic operators" introduced by LEWONTIN (1964a). This is clearly out of the question even for modern high-speed computers so that an alternative must be found. The alternative is to use the method of Monte Carlo simulation, first introduced into genetic problems by FRASER (1957). Usually this method is initiated in order to investigate the effect of small population size on an evolutionary process. In the present case, however, the finite population is meant to approximate an infinite one, and the sampling error effect introduced by the finite population is a distraction. Thus we have used rather large populations (500 males and 500 females) and replicated each one twice to be certain that any differences observed can really be accounted for by changes in parameter values rather than by random differences between runs. The complete details of Monte Carlo simulation are given by FRASER (1957) and by BELLMANN and AHRENS (1966) and will not be repeated here since our methods are essentially the same as theirs. We use the method of BOFINGER and BOFINGER (1958) for creating random numbers. In effect we load the computer with numerical representation of diploid individuals' genotypes and operate on those numerical representations as if they were individuals undergoing selection, mating and gamete production. By beginning with a known initial population composition we can trace the genetical evolution of the population in time and see the influence of various parameters.

Results

It would be impossible to present the generation by generation results of all replicates in complete detail. In particular the questions we are interested in are (1) How does the pattern of recombination effect the changes n genotypic composition of the two blocks of genes over time?

(2) How does the pattern of recombination effect the rate of advance of the population under selection?

(3) What interaction, if any, is there between the pattern of recombination and the intensity of selection in determining the rate of change of the population?

We will show by graphical, semi-diagrammatic, plots the outcome of various parameter sets. In each case only one replicate is shown but the differences between replicates are small as compared with the differences between parameter sets. For the graphs of change in percent of the population acceptable, the replicates are so close that no differences can be shown at the level of resolution of our graphs.

The general pattern of response to the particular form of selection we have used is shown in Figure 1, for three different intensities of selection. Only one block of genes is shown and recombination is 50% between all gene pairs. The ten loci are started at slightly different gene frequencies with the frequency of the *1* allele less than .50 in all cases. Because of the symmetry of the model, the first thing that happens is a symmetrizing of all the gene frequencies around .50. This occurs within 15 generations in the medium and strong selection runs but requires about 30 gene-

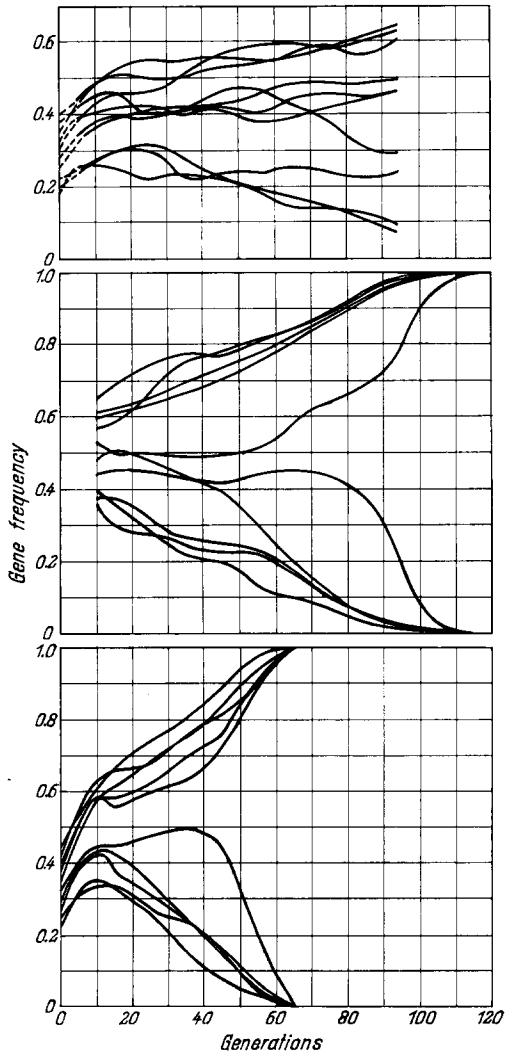

Fig. 1. Result of intermediate optimum selection on gene frequencies of a 10 locus system with free recombination. Ordinate shows gene frequency, abscissa shows generations. Three parts show the result of three intensities of selection.

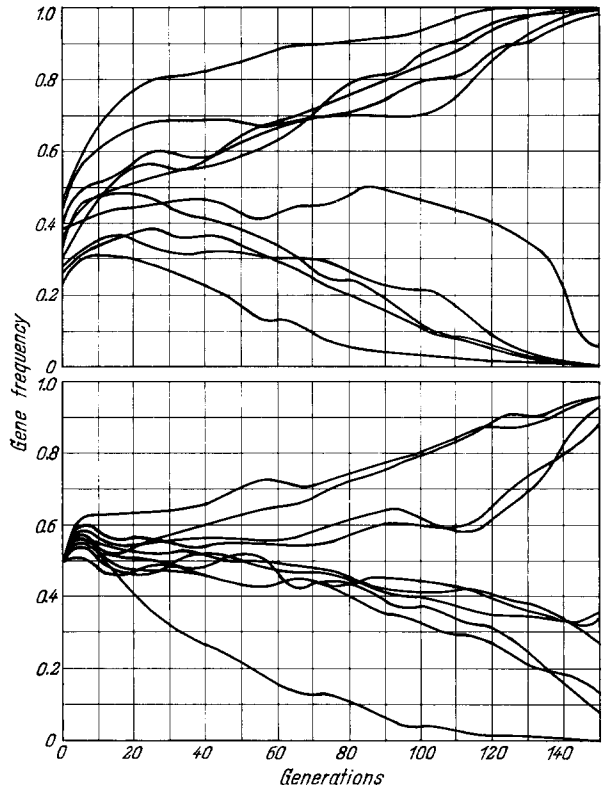

Fig. 2. Changes in gene frequency under selection for 10 loci each in two blocks of genes each of which is freely recombining. Ordinate: gene frequency; abscissa: generations.

rations in the case of weak selection. Thereafter, half of the loci go toward fixation at 100% of the *1* allele and half go to fixation of 0% of the *1* allele. Although it is not shown in the graphs explicitly, the mean gene frequency of the *1* allele over all ten loci remains almost exactly .5 for the entire course of selection after the initial rise.

These results are exactly parallel to those found by LEWONTIN (1964b) in an exact treatment of 5-locus intermediate optimum models. Figure 1 A, B and C of the present paper are essentially the same in all features to Figure 5 A, 4 A and 3 A respectively of that earlier publication. Thus, the introduction of the stochastic element and the slight change in the form of the optimizing selection has no effect on the nature of the results.

We now turn to the first question posed: What effect does the recombination pattern have on changes in gene frequency? The answer is given in Figures 2, 3 and 4. In all three figures we show only the results for intermediate selection, the same features appearing at the other selection intensities. In each case one block of genes is shown with initial gene frequencies at the 10 loci of .225, .250, .275, . . ., .425, .450, while the other block is shown with all loci starting at an initial gene frequency of .50.

In Figure 2 the gene frequencies for both blocks of genes are shown to have a similar behavior when both blocks have loose linkage ($r = .50$). Half of the loci in each block go to fixation at $q = 1.0$ and the other half if $q = 0.0$, the mean gene frequency in each block being held almost exactly at .50. The gene frequencies in the first block of loci fix more rapidly because of the initial spread in gene frequencies.

In Figure 3 the results are shown when the two blocks of genes are tightly linked ($r = .01$) *within*

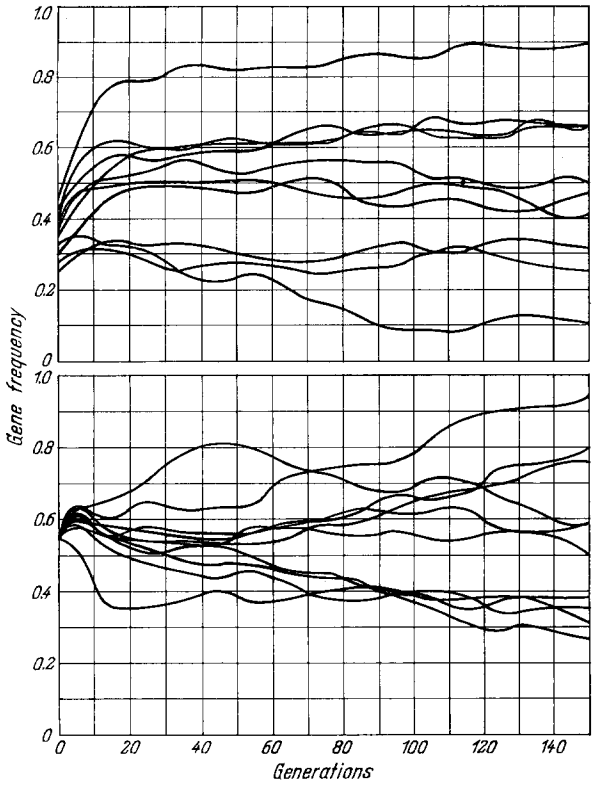

Fig. 3. Same as figure 2 when both blocks of genes are tightly linked but not linked to each other.

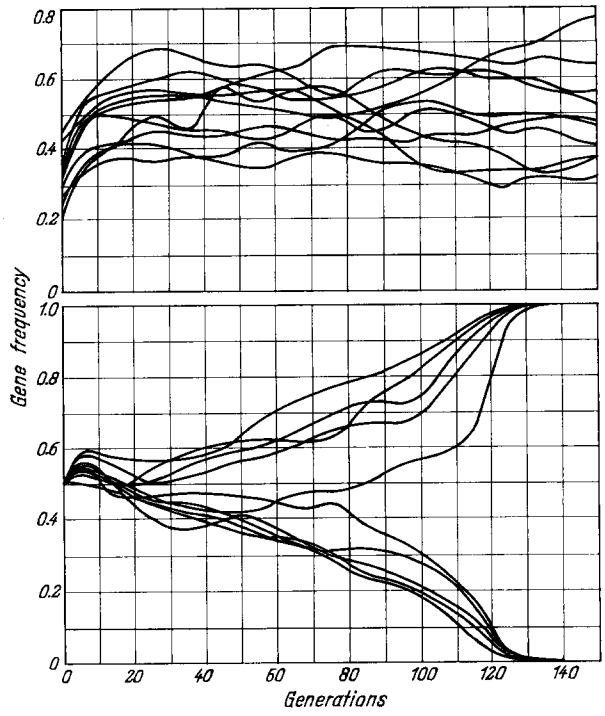

Fig. 4. Same as figure 2 when one block of genes is tightly linked and the other closely linked.

each block, but there is no linkage between blocks. After some initial divergence of gene frequencies, there is a much slower spread of the gene frequencies so that after 150 generations there is still no fixation of any locus at $q = 0.0$ or $q = 1.0$. This is in sharp contrast with the loosely linked case shown in Figure 2. This delay in fixation of genes by selection, as a result of tight linkage, was described by LEWONTIN (1946b) for an exact treatment of a 5-locus optimum model and the present results simply confirm that effect in more complex systems. Surprising results are shown in Figure 4 where the "main effect" loci are tightly linked ($r = .01$) while the "modifier" loci are loosely linked. Here a synergistic effect is observed. When a comparison is made with figures 2 and 3 it can be seen that the loosely linked loci go to fixation even faster than in figure 2 while the tightly linked loci keep their intermediate gene frequencies even more markedly than in figure 3. That is the loosely linked block and the tightly linked block each shows a more exaggerated effect than when both blocks have the same degree of linkage. Thus, the presence of a tightly linked block of genes diverts the effect of natural selection to a loosely linked block, causing gene frequency changes to be more rapid while, in turn, very little gene frequency change occurs for the tightly linked block. We can conclude then that the effect of natural selection in changing gene frequencies can be extremely different in different blocks of genes in the same genome because of differences in linkage relations in the genome. Moreover this variation in effect is enhanced by a synergistic effect of loosely and tightly linked blocks on each other.

The effect of the various linkage relations on the rate of change of fitness in the population is shown in figures 5—9. The fitness of the population is the proportion of the population saved and this in turn is inversely related to the genetic variance of the population. The modul of selection is such that the highest probability of survival is for a genotype with equal number of *0* and *1* alleles over its 20 loci. If the population consists of large numbers of heterozygotes, there will be segregation and generation of extreme homozygotes so that the population has a low fitness. However, when the population reaches the stage of fixation of genes with half the loci in each block fixed at the *0* allele and half at the *1* allele, there will be no further segregation and the fitness of the population will be unity.

Each of the figures 5—9 shows the increase of fitness with time for various intensities of selection and various linkage relations. In figure 5 is shown the changes in fitness corresponding the gene frequency changes of figure 1. Only a single block of genes is considered in order to get a point of comparison for the studies of two blocks. The solid lines

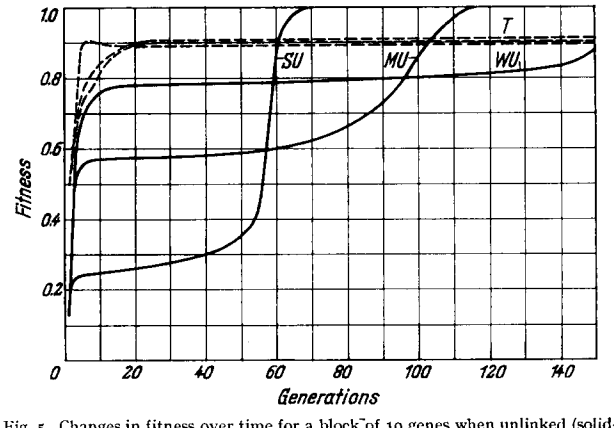

Fig. 5. Changes in fitness over time for a block of 10 genes when unlinked (solid-lines) or tightly linked (dashed lines). Three intensities of selection, strong (S), medium (M) and weak (W) are shown. Ordinate: fitness, abscissa: generations.

in figure 5 show the changes in fitness under three intensities of selection for unlinked genes ($r = .50$). In the initial generations the fitness is inversely proportional to the intensity of selection as is expected since intense selection means that a small proportion of individuals falls in the accepted class. However, the speed of response to selection is directly proportional to selection intensity. Thus fitness rises sooner, more sharply, and to higher values in the strongly selected than in the weakly selected cases. This again is hardly surprising. What is interesting is the essential identity of the results for all the levels of selection intensity when tight linkage ($r = .01$) is considered. Except for a small difference in speed of response in the initial generations, all runs with tight linkage rise to high fitness and remain at about .90 with only a very slow increase. The very rapid rise of fitness, followed by the virtual plateau is a result of the selection of balanced *gametic* types in the tightly linked cases. Gene frequencies remain at intermediate values, but repulsion linkages build up so that no extreme homozygotes are segregating. The loosely linked cases increase in fitness more slowly by the fixation of alleles but eventually surpass the fitness of the tightly linked cases since no segregation at all goes on after genes are fixed. These alternative modes of increasing fitness: accumulation of repulsion linkages in tightly linked genes and fixation of alternative alleles for loosely linked genes was previously observed by LEWONTIN (1964b) for smaller numbers of loci and for another mode of optimizing reaction. A new phenomenon in the present results is the virtual identity of the fitness levels for all tightly linked cases, because of the very rapid accumulation of repulsion linkages.

Figure 6 shows the same phenomenon when two blocks of genes are considered. Here two unlinked (UU) are contrasted with two linked blocks (TT). Again the tightly linked blocks cause a much more rapid rise in fitness because of selection of repulsion gametes and again there is little difference in the level of fitness reached in the tightly linked cases, irrespective of the intensity of selection. In figure 6 the cause of this equality can be seen in detail. The initial fitness of the strongly selected case is a little lower than for medium selection which is much lower than for strong selection. The speed of advance under selection is in the reverse order however so that after about 20 generations all three cases reach about the same fitness. Thereafter the more strongly selected case actually has a slightly higher fitness than for medium selection which is, in turn, slightly higher than weak selection.

A different form of this comparison is made in figures 7, 8 and 9 where the three selection intensities are separately displayed. All three selection intensities show that tight linkage causes a more rapid rise in fitness than loose linkage. Moreover there is only a slight increase in the speed of advance when the two linked complexes are linked to each other (TT as compared with $T-T$). A most interesting phenomenon appears when one block of genes is unlinked and one tightly linked. This is best seen in the case of strong selection (figure 9) but the first stages are also seen for medium selection (figure 8). In the early generations of the evolution of the populations

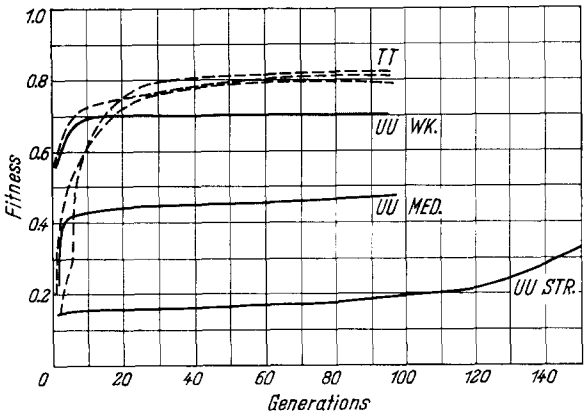

Fig. 6. Changes in fitness when two blocks of genes are both unlinked (UU) or both tightly linked(TT) for three levels of selection. Ordinate: fitness, abscissa: generations.

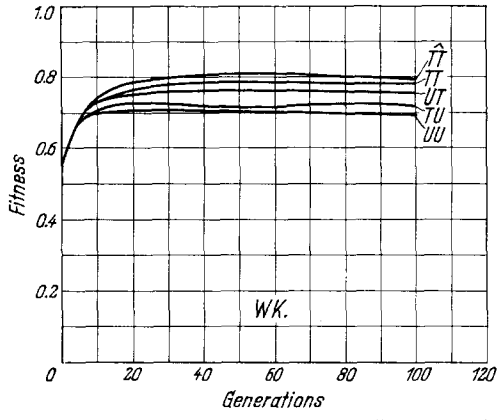

Fig. 7. Changes in fitness under weak selection for five different combinations of linkage relations between two blocks of genes. Ordinate: fitness, abscissa: generations.

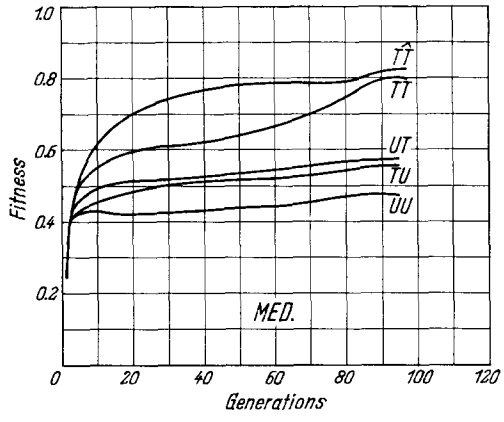

Fig. 8. Same as figure 7 for medium selection.

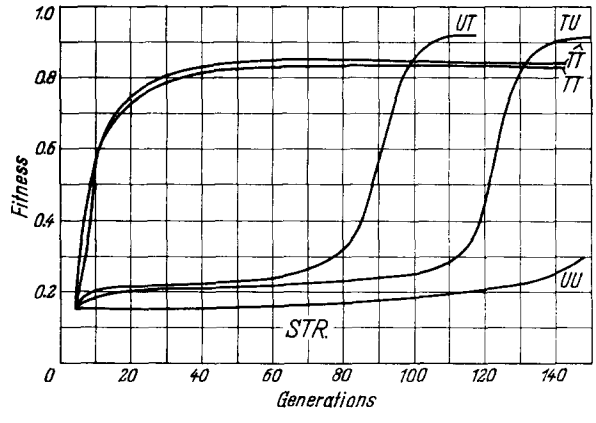

Fig. 9. Same as figure 7 fo rstrong selection.

the mixed linked and unlinked cases behave like the unlinked one. Then, there is a sudden increase in fitness surpassing the level of the linked cases. The events can best be understood by noting the difference between the curve labelled *UT* and that labelled *TU*. In the first case the unlinked block of genes began with a distribution of initial gene frequencies between .225 and .450 while the linked block started with all gene frequencies at .50. Since free recombination leads to a faster spread of gene frequencies than tight linkage, the linkage relations in the *UT* case operate to reinforce the differences already present in distribution of gene frequencies. In the *TU* case however, the tight linkage retards further spread of gene frequencies in the frequencies in the "main effect" block while the loose linkage of "modifier" genes causes those gene frequencies to spread out from their initial values of .50. As a result the *UT* case shows an earlier rise in fitness than the *TU* case. Finally, it should be noted that both *UT* and *TU* cases have a higher plateau level of fitness (.95) than the *TT* or *T* — *T* cases (.85) because of fixation of genes during the early part of the selection.

General Implications of the Results

Fitness in our model is determined by an optimal selection scheme and this means that there is strong gene interaction on the fitness scale even though the genes in each block are additive in determining phenotype. When such strong interactions exist in the fitness scale, the effects of linkage relations on the progress under selection are very considerable. This has already been shown by LEWONTIN (1964) and our present results are in agreement with those earlier findings. The present results show in addition that differentiation of the genomes into loosely linked and tightly linked blocks of genes lead to synergistic effects of the linkage. In blocks of loosely linked genes fitness is increased by a fixation of *o* and *1* alleles in equal frequencies so that eventually there is no segregation of unbalanced homozygotes. This is a relatively slow process as in comparison with fitness changes in tightly linked blocks. These latter blocks increase in fitness by selecting among balanced gametes but do not reach the highest possible fitness because of some continued segregation. Thus, when fitness in loosely linked blocks finally does rise, in later generations, it surpasses the fitness level of tightly linked groups of genes. This is illustrated in figure 5. When there is a mixture of loosely linked and tightly linked blocks both types of fitness increase are realized with an exaggeration of both effects. Thus fitness rises sooner than it would if all the genes were loosely linked, but it rises higher than it would if all the genes were tightly linked. This is best shown in Figure 9. This is in contrast to the situation in heterotic equilibrium models discussed by LEWONTIN (1964a). In case of heterosis, as FISHER pointed out in 1930, there is an advantage to tight linkage of all genes concerned in a balanced polymorphism. In the present case, however, where speed of advance under selection and long-time plateaus of fitness are concerned, a mixture of loosely linked and tightly linked blocks is an adaptively superior system in that it leads both to fairly rapid progress under selection and high levels of plateau fitness. This fitness plateau, although lasting many hundreds of generations is of course not permanent. Eventually all the genes become fixed and fitness is unity.

Zusammenfassung

Es wurde der Selektionseffekt in Populationen untersucht, wenn Gene, die das selektierte Merkmal kontrollieren, keine einheitlichen Rekombinationsbeziehungen haben. Insbesondere haben wir das Selektionsergebnis für einen intermediären optimalen Phänotyp, der durch zwei Genblöcke bestimmt wird, untersucht, wobei Additivität innerhalb der Blöcke, aber Multiplikativität zwischen den Blöcken gilt. Dies entspricht „Haupteffekt"-Genen und „modifizierenden" Genen. Die zu klärende Frage lautete: Welchen Einfluß übt die Koppelungsstruktur dieser Gengruppen auf die Änderung der Genhäufigkeit und auf die Fortschrittsgeschwindigkeit während der Selektion aus.

Die Ergebnisse wiederholter Monte-Carlo-Simulationen großer Populationen bei drei Selektionsintensitäten waren:

1. Ein eng gekoppelter Genblock hält die Gene bei mittleren Genhäufigkeiten, unterzieht sich schnellen Selektionen balancierter Gametentypen und zeigt einen sehr schnellen Anstieg der Anpassung, dem ein langer Abschnitt bei ziemlich hohem gleichbleibendem Anpassungswert folgt.

2. Ein locker gekoppelter Genblock neigt zur Fixierung einer balancierten Anzahl von Loci bei $q = 0.0$ und $q = 1.00$. Dies geschieht bei einem langsameren Anstieg der Anpassung, aber zu einem höheren Plateau, etwa in der Nähe von eins.

3. Ist ein Genblock eng, der andere locker gekoppelt, so wird der Effekt jedes Blocktypes verstärkt. Die locker gekoppelten Gene kommen schneller zur Fixierung, die eng gekoppelten Gene bleiben dichter bei Zwischenwerten, die Anpassung steigt rascher als für locker gekoppelte Gene an und erreicht ein höheres Plateau als für eng gekoppelte Gene.

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