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The effects of normalizing and disruptive selection on genes for recombination

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SUMMARY

Deterministic simulations have been carried out of populations under normalizing and disruptive selection for a trait determined by genes with additive effects at six loci. In some simulations a pair of alleles at a seventh locus determined the rate of recombination between the seven loci. Normalizing selection with a single optimum, fixed or fluctuating, invariably led to genetic homozygosity. If the optimum fluctuates widely, the approach to homozygosity may be accompanied by a large decline in the mean fitness of the population. Disruptive selection was simulated by having two 'niches' with separate optima and separate density-dependent regulation, but with the adult population mating randomly. If the optima are widely separated, this leads to stable polymorphism. Selection produced linkage disequilibrium, normalizing selection causing repulsion and disruptive selection coupling between + and − alleles. This linkage disequilibrium accelerates the phenotypic response to selection, but delays changes in gene frequency. Selection always favoured alleles for low recombination at the expense of alleles for high recombination.

1. INTRODUCTION

The aim of this investigation was to discover whether normalizing or disruptive selection can favour modifying genes which increase recombination. The question seems a natural one for the following reason. Normalizing selection is probably the commonest type of selection in the wild. Also, it inevitably causes epistatic effects on fitness, even when genes affect the selected trait additively. Thus, it pays to have a + allele at one locus if there are − alleles at others, and vice versa. Given epistatic effects on fitness, there will be linkage disequilibrium and selection on modifiers of recombination.

A related question concerns the selective advantage of sexual reproduction. Treisman (1976) argued that a sexual population could follow, by genetic evolution, an environment in which the optimal phenotype fluctuated, whereas a set of sexual clones might contain no single clone able to survive both the high and low extremes. Thus all clones would go extinct, and only the sexual population would survive. Clearly, this argument fails if it can be shown that a sexual population subjected to a fluctuating optimum becomes genetically homozygous.

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The first part of this paper confirms that a sexual population under selection for a fluctuating optimum does indeed become homozygous. After carrying out these simulations, I became aware that Lande (1977) had in fact predicted this result from an analytical model. The topic is therefore treated briefly. However, attention is drawn to a paradoxical feature of normalizing selection. If the optimum fluctuates widely, the mean fitness of a population, averaged over a full cycle, may fall dramatically as it approaches homozygosity under selection.

To investigate changes in the frequency of genes modifying recombination, the most relevant situations are those in which genetic heterozygosity is maintained, because selection will then be long-continued. Three types of model have been proposed:

(i) *Balance between selection in different niches.* Levene (1953) showed that if different alleles are favoured in different niches, polymorphism can be maintained, even if mating is random. It is a feature of Levene's model that a constant proportion C_i of the population is raised in the ith niche, as would be the case if the density-dependent regulation of the population occurred in separate niches. If, in contrast, one supposes that a constant proportion C_i of fertilized eggs are distributed to the ith niche, no polymorphism is possible (Dempster, 1955). Bulmer (1971*a*) showed that a Levene-type model can maintain genetic heterozygosity for a polygenic trait.

(ii) *Balance between selection and mutation.* Lande (1975) has shown that a quantitatively plausible account can be given of genetic polymorphism for a polygenic trait with a fixed optimum, without assuming an unreasonably high rate of mutation.

(iii) Franklin & Lewontin (1970) simulated a model in which each locus, in addition to its additive effects on the selected trait, had heterotic effects on fitness.

Only the first, Levene-type, model is investigated here.

2. MODELS AND METHODS OF STIMULATION

Analyses of normalizing selection are of two kinds, according to whether they do or do not take into account linkage disequilibrium. Robertson (1956), ignoring linkage disequilibrium, showed that, if genetic variance is additive, normalizing selection with a fixed optimum leads to genetic homozygosity. Bulmer (1971*b*) introduced linkage disequilibrium into the model. For a population with an infinite number of loci, he showed that normalizing selection does not alter gene frequencies, but does nevertheless alter the genetic variance by generating linkage disequilibrium. In his notation

$$V_G = V_g + C_{\mathrm{HW}} + C_L.$$

V_G = total genetic variance,

V_g = 'genic' variance, i.e. the variance which would exist if the population were in Hardy–Weinberg and linkage equilibrium. For N additive loci, with each substitution having unit effect on the phenotype,

$$V_g = \sum_{i=1}^{n} 2p_i q_i.$$

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C_{HW} = contribution to the variance due to departure from Hardy–Weinberg. This component turns out to be small, and will be ignored.

C_L = contribution to the variance due to departure from linkage equilibrium. For a population in Hardy–Weinberg equilibrium, $C_L = V_G - V_g$.

Bulmer (1971*b*) showed that, with an infinite number of freely associating loci, normalizing selection does not alter V_g but produces negative values of C_L by generating repulsion linkage disequilibrium ($+ - + -$ gametes). Bulmer (1974) showed that the same is true if loci are linked, the absolute values of C_L now being greater. These results have been confirmed by Monte Carlo simulation (Bulmer, 1976). With a finite number of loci, V_g does change, but it is still true that the initial rapid response to selection is caused by a change in C_L. Of course, changes in V_G caused by changes in gene frequency remain if selection is relaxed, whereas C_L rapidly decays to zero.

Lande (1975) developed a model incorporating selection and mutation, and allowing for linkage disequilibrium. The model assumes additive genetic variance for the selected trait, within and between loci, and no gene-environment interaction. In an extension of this model, Lande (1977) showed that the expressed genetic variance which is maintained by selection is independent both of the system of mating and of the linkage map of the loci. Further, for the Gaussian and quadratic deviation fitness functions, the genetic variance converges to its equilibrium value independent of the population mean. It follows that the expressions he obtains for the genetic variance are, in these cases, valid even if the optimum phenotype is fluctuating in time. In particular, if there is no mutation, a population exposed to a fluctuating optimum will become genetically homozygous, regardless of the linkage relations or breeding system. (The reason why this conclusion does *not* hold for a Levene model with two or more niches is that, in this case, fitnesses are frequency-dependent.)

I was unaware of this prediction of Lande's when I undertook the simulations described in the next section, which can therefore be taken as a confirmation of his theoretical prediction.

The models simulated in this paper have the following features:

(i) The population is infinite, diploid and random-mating. Simulations are deterministic.

(ii) A phenotypic trait is determined by alleles at 6 loci. At each locus, genotypes 00, 01 and 11 contribute 0, 1 and 2 to the phenotype. Effects between loci are additive. Hence the phenotype can range from 0 to 12. All simulations were started with the six gene frequencies at 0·2, 0·3, 0·4, 0·6, 0·7 and 0·8, and in Hardy–Weinberg and linkage equilibrium.

(iii) In some simulations the six loci assorted independently. In others, the six loci are arranged linearly along a chromosome, and recombination between them is determined by a pair of alleles at a seventh locus on the same chromosome.

(iv) There is no environmental variance.

(v) Selection follows the Gaussian fitness function. If the optimum phenotype

is θ, the fitness of an individual of phenotype z is $\exp\{-(z-\theta)^2/2w^2\}$, where w, the 'environmental tolerance', is inversely related to the rate at which fitness falls off either side of the optimum.

Programmes were run on an ICL 1904S, and written in ALGOL 68, a language which facilitates the storage of chromosomes as binary numbers, and the calculation of phenotypes, cross-over products, etc., by performing logical operations on these numbers one element at a time.

3. NORMALIZING SELECTION WITH A SINGLE OPTIMUM

The six-locus model has been run for a fixed optimum, and for a single optimum oscillating regularly with various periods and amplitudes. A typical result is shown in Fig. 1. The main features of this run are:

(i) The population tends to genetic homozygosity.

(ii) The initial rapid fall in the population variance is largely due to changes in C_L, the linkage disequilibrium component, due to coupling $(+-+-)$ associations.

(iii) The geometric mean fitness over a full environmental cycle, W_c, was calculated. Selection reduced W_c from 0·081 to 0·018 in 40 generations.

Table 1 lists the parameter values for which simulations have been run, where w = 'environmental tolerance', defined above, T = period of environmental fluctuation, in generations, $2A$ = range of environmental fluctuation (A = amplitude), the form of the fluctuation being 'saw-tooth'.

In all cases the population tended towards genetic homozygosity, and there was an initial sharp fall in variance due to coupling disequilibrium. Whether the mean fitness W_c rose or fell depended on A/w. For large environmental fluctuations, W_c fell; for small fluctuations, W_c rose.

4. SELECTION ON MODIFIERS OF RECOMBINATION

It is supposed that the adult members of the population mate randomly, and that the zygotes produced are distributed randomly to two 'niches', with separate optimal phenotypes θ_1 and θ_2. Relative fitnesses within a niche are proportional to $\exp(-(z-\theta_i)^2/2w^2]$, $i = 1, 2$. However, fractions C_1 and C_2 of the next adult population are produced from the two niches. In some simulations, $C_1 = C_2 = \frac{1}{2}$; in others, the relative sizes of the two niches fluctuate regularly.

As before, the phenotype is determined by six additive loci, each with two alleles. The loci were linearly arranged. Two alleles, C^+ and C^-, at a seventh locus, on the same chromosome and terminal in position, determined recombination, as follows:

(i) in C^+/C^+, all loci segregate independently. What experimental evidence there is shows that alleles for high recombination tend to be recessive (Schaap, 1978).

(ii) In C^+/C^- and C^-/C^- the probabilities of 0, 1 and 2 crossovers in the region were taken as $(1-r)^2$, $2r(1-r)$ and r^2, the six types of single crossover being equally likely, and the 15 types of double crossovers being equally likely. r was taken as 0·05. This approximates to a total length of chromosomes of 10 units,

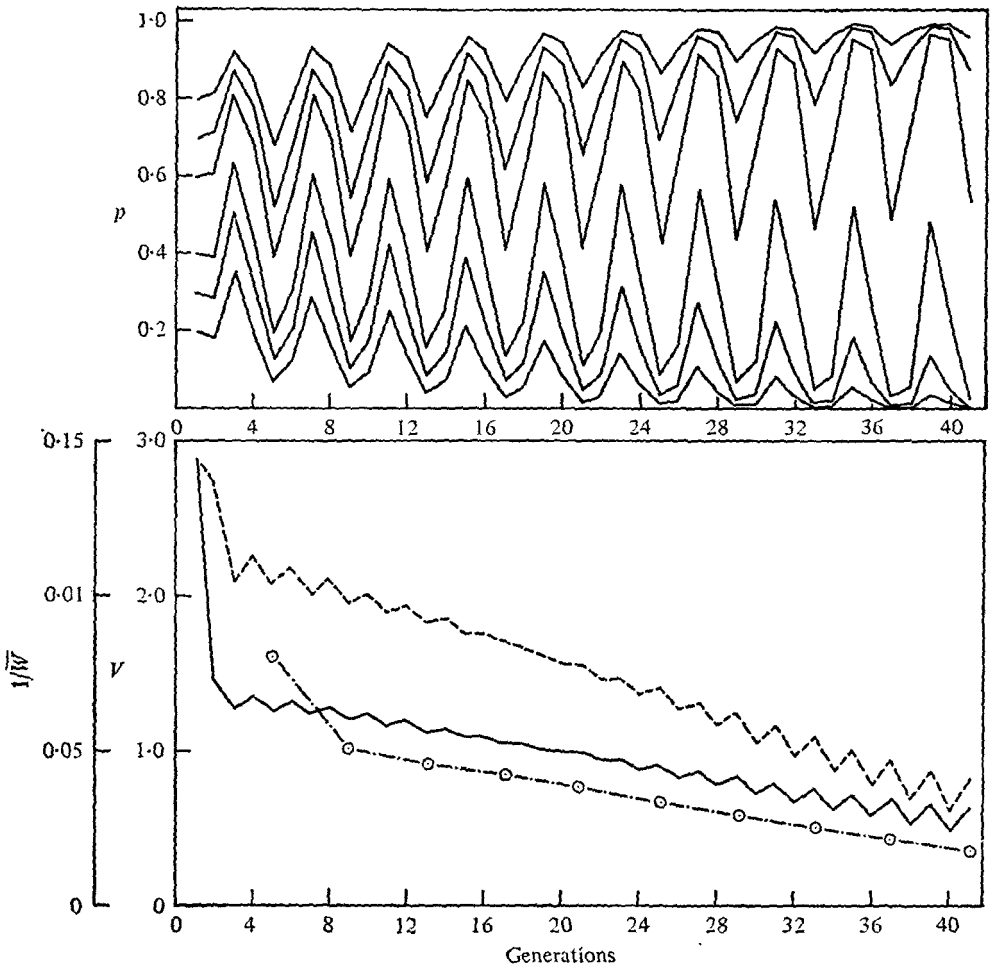

Fig. 1. Normalizing selection with a fluctuating optimum: range of fluctuation $2A = 6$; period $T = 4$; environmental tolerance $w = 0{\cdot}707$. p, Gene frequency; $\bar{W}$, geometric mean fitness over a cycle; V, phenotypic variance. In the lower graph: full line, genetic variance, V_G; broken line, genic variance, V_g; chain dotted line, mean fitness, $\bar{W}$.

Table 1. *Parameter values used in simulations of normalizing selection, and associated changes in mean fitness, W_c*

Range of environmental fluctuation ($2A$)	Environmental tolerance (w)	Period of fluctuation (generations) (T)	Change in mean fitness (W_c)
0	0·5–1·414	—	Up
2	1·414	4	Up
4	1	4	Down
6	0·707	4	Down
8	0·707	4,8	Down
8	1·414	2,4,8	Down

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Table 2. *Selection in two niches with fixed optima*

Optimal phenotypes in 2 niches	Selective tolerance (w)	Relative niche sizes	Period in generations (T)	Maintenance of genetic variance	Frequency of allele C+ for high recombination in generation				Nature of linkage disequilibrium
					1	8	16	20	
5, 7	1·22	Equal	–	No	0·5	0·478	0·410	0·374	Repulsion
4, 8	1	Equal	–	Yes (just)	0·5	0·498	–	–	Coupling
3, 9	1	Equal	–	Yes	0·5	0·481	0·420	0·391	Coupling
4,8	1	0·8 : 0·2 and 0·2 : 0·8	4	Yes (just)	0·5	0·5	0·495	–	Coupling
2, 10	0·707		2	Yes	0·5	0·438	0·319	0·281	Coupling
3, 9	0·707		2	Yes	0·5	0·476	0·440	0·421	Coupling
3, 9	0·707		4	Yes	0·5	0·498	0·488	0·480	Coupling
3, 9	0·707		8	Yes	0·5	0·511	0·475	0·402	Coupling

with six equal regions separating the seven loci. Appreciable computer time was saved by ignoring triple and higher order recombinants.

For one set of parameter values (optimal phenotypes 3 and 9, $w = 1$, equal niche sizes), additional runs were made with $r = 0{\cdot}1$ and $r = 0{\cdot}2$, with qualitatively similar results.

The results are summarized in Table 2. The main features are:

(i) Genetic variance was maintained, and coupling linkages generated, in all cases except the first; this case was an exception because the difference between the two optima was small compared to w, so that selection was in effect normalizing.

(ii) In all cases, the allelle for low recombination increased in frequency.

(iii) The results were not altered qualitatively when the relative sizes of the to niches fluctuated, although in these cases the decline in frequency of the allelle C^+ was less regular.

Since normalizing selection favours repulsion linkages and disruptive selection favours coupling linkages, it seemed possible that there might be selection for higher recombination if the two regimes were alternated (c.f. Charlesworth, 1976). Simulations were run in which the population was exposed alternately, for n generations, to normalizing selection with $\theta = 6$ and $w = 0{\cdot}707$, and to disruptive selection, with two equal niches with optima 3 and 9, and $w = 0{\cdot}707$. Two runs were carried out, with $n = 2$ and 4 – i.e. a total period of 4 and 8 generations. Although the frequency of C^+ fluctuated, the overall tendency in both runs was for a decline in the frequency of C^+. This result was unexpected. It may be that there are parameter values for which alternating disruptive and normalizing selection would favour higher recombination, but they would not be easy to find, and the system is too artificial to justify an extensive search.

4. CONCLUSIONS

Normalizing and disruptive selection are likely to be important forces tending to reduce recombination in natural populations. The direction of the effect is so consistent that one suspects that some general theorem might be proved analytically. Normalizing selection with a fluctuating optimum leads to genetic homozygosity, even when this involves a decline in mean fitness. It therefore seems unlikely that sexual populations succeed in competition with asexual clones because of their greater ability to track a fluctuating environment.

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