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Selection for recombination in a polygenic model – the mechanism

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Summary

A polygenic model has been simulated in order to reveal the process whereby selection in an infinite population can lead to an increase in the frequency of alleles causing higher rates of recombination (*CH* alleles). Directional selection generates repulsion linkage disequilibrium $(+ - + -)$, which is less strong in *CH* gametes (gametes carrying *CH* alleles). In consequence, *CH* gametes contribute greater phenotypic variability, and therefore respond more to directional selection: that is, they accumulate more selectively favoured alleles. *CH* alleles then increase in frequency by hitch-hiking. In contrast, normalizing selection, or frequent changes in the direction of selection, favour alleles for a low recombination rate.

1. Introduction

In an earlier paper (Maynard Smith, 1980) it was shown that a gene increasing recombination rate can increase in frequency in an infinite population under normalizing selection with a shifting optimum. This was demonstrated by simulating a 6-locus model, with a seventh locus determining recombination. However, that paper did not provide any insight into the underlying mechanism, and therefore could say little about the range of parameter values for which recombination would increase. This paper attempts to remedy that defect. Further analysis of essentially the same model gives a qualitative insight into the mechanism. The argument turns out to be an extension of that given by Felsenstein (1965), who was concerned with the slightly different question of how linkage will affect the rate of response to directional selection. It is concluded that continued directional selection will almost always lead to an increase in recombination. No general prediction can be made about the effect of selection for a fluctuating optimum, since it depends not only on the intensity of selection but also on the number of generations for which selection in a given direction is continued.

2. The model

In an infinite random-mating diploid population, the phenotype is determined by genes at six linked loci, with two alleles per locus. The alleles have unit additive effects, so that the phenotype can vary from 0 to 12. Fitness depends on phenotype according to a Gaussian, additive or multiplicative scheme. In the Gaussian scheme,

$$W = \exp(-(X-OPT)^2/2S^2),$$

where W = fitness, X = phenotype, OPT = optimal phenotype, and S measures the intensity of selection (a large value of S specifying weak selection).

Recombination is determined by a pair of alleles, *CH* and *CL*, at a seventh locus terminally situated on the same chromosome. These alleles determine the value of a parameter, r, which is high in *CH*/*CH* homozygotes and low in *CH*/*CL* and *CL*/*CL*. Thus low recombination has been assumed to be dominant: simulations with high recombination dominant gave qualitatively similar results. The probability of a single crossover per chromosome is r, and of no crossover 1-r. Thus the recombination rate between neighbouring loci is $r/6$. Double and higher-order recombinants are ignored to save computer time. Double recombinants were allowed for in Maynard Smith (1980): their effect is slightly to increase the rate of spread of alleles for high recombination under directional selection. Unless otherwise stated, simulations were started in linkage equilibrium, with allele frequencies of 0·5 at the recombination locus, and of 0·07, 0·08, 0·09, 0·11, 0·12 and 0·13 of the high allele at the phenotypic loci, giving a mean phenotype of 1·2.

3. Notation

$p(CH)$ = frequency of the *CH* allele,
M, V = mean and variance of population,

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V_{LE} = variance the population would have if all alleles, at their actual frequencies, were in linkage equilibrium,

CH gamete, *CL* gamete = gametes carrying the *CH* and *CL* alleles respectively,

$M(CH)$, $V(CH)$ = mean and variance of a population constituted by the random assortment of *CH* gametes,

$M(CL)$, $V(CL)$ = mean and variance of a population constituted by the random assortment of *CL* gametes,

$V_{LE}(CH)$ = variance of a population in linkage equilibrium, for the allele frequencies appropriate to *CH* gametes,

$V_{LE}(CL)$ has an equivalent meaning for *CL* gametes.

4. Directional selection causes an increase in recombination

Fig. 1A shows the increase in $p(CH)$ for a typical simulation of directional selection with a fixed optimum. This contrasts with the decrease in $p(CH)$ under normalizing selection. For example, in an identical simulation – except that $OPT = 6$, and initial frequency of all genes = 0·5 (so that the mean and optimum phenotypes were the same) – $p(CH)$ fell from 0·5 to 0·386 in 50 generations.

A brief qualitative explanation of this result is as follows:

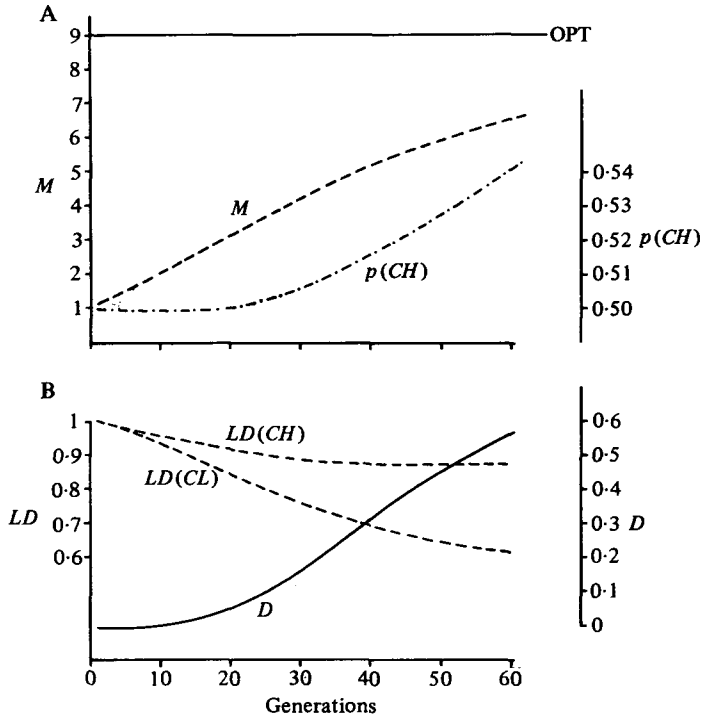

Fig. 1. Directional selection. Gaussian fitness function, with $OPT = 9$ and $S = 10$. $r = 0{\cdot}5$ in CH/CH and 0·01 in CH/CL and CL/CL. A, changes in mean, M, and $p(CH)$. B, changes in linkage disequilibrium, LD, and difference, D, between the mean phenotypes of CH/CH and CL/CL zygotes: $LD(CH) = V(CH)/V_{LE}(CH)$, $LD(CL) = V(CL)/V_{LE}(CL)$, and $D = M(CH) - M(CL)$.

(i) directional selection generates repulsion linkage disequilibrium, which is greater in *CL* than in *CH* gametes;

(ii) as a result, $V(CH) > V(CL)$: therefore $M(CH)$ increases more rapidly then $M(CL)$ under directional selection;

(iii) therefore, the average fitness of individuals carrying *CH* gametes is higher, and so $p(CH)$ increases.

These points will be discussed in turn.

(i) *Directional selection causes repulsion linkage disequilibrium*

A convenient measure of linkage disequilibrium in a polygenic model is V/V_{LE}. If coupling linkages, $+++$ and $---$, are in excess, then $V > V_{LE}$, and if repulsion linkages are in excess, $V < V_{LE}$. Fig. 1B shows that repulsion disequilibrium develops in both *CH* and *CL* gametes, but more rapidly in the latter because recombination destroys disequilibrium in *CH* gametes.

It is puzzling at first sight that directional selection should generate repulsion, because the most-favoured gametes are $++++$ (or $----$). The result is not new, however. Fraser (1957) found the result in a computer simulation. Felsenstein (1965) showed that, in a discrete generation model, if gametes are initially in linkage equilibrium, and if fitnesses are multiplicative, then linkage equilibrium is maintained under selection. But if fitness increases less rapidly with phenotype than in the multiplicative scheme, as for example with additive or Gaussian fitness schemes, then selection generates repulsion linkages, as illustrated in Table 1. It is not a universal truth that directional selection generates repulsion linkages: if fitness increases more rapidly with phenotype than in the multiplicative case, then coupling disequilibrium results. But for plausible selection schemes the result is repulsion.

An alternaive approach is *via* Bulmer's (1980) infinite-locus model, which has the advantage that neither allele frequencies nor V_{LE} change under selection.

Let V, V' = variance of (unselected) parent and offspring generations,

V_{MP} = variance of (selected) mid-parent, and

V_{WF} = within-family variance.

Then, for additive inheritance, Bulmer argues as follows:

$V' = V_{MP} + V_{WF}$, $V_{WF} = V/2$,

and, for Gaussian directional selection, $V_{MP} < V/2$.

Hence $V' < V$. Since V_{LE} does not change, the reduction of variance under selection must be ascribed to repulsion disequilibrium.

(ii) *Favoured alleles accumulate more rapidly on CH gametes*

Felsenstein (1965) went on to show that, because of

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Table 1. *Changes in linkage disequilibrium under selection*

Gamete type	$++$	$+-$	$-+$	$--$
Frequency before selection	p_1p_2	p_1q_2	q_1p_2	q_1q_2
Frequency after selection				
addtitive	$p_1p_2(1+s)$	p_1q_2	q_1p_2	$q_1q_2(1-s)$
multiplicative	$p_1p_2s^2$	p_1q_2s	q_1p_2s	q_1q_2

For the additive case, $\mathrm{LD} = p_1p_2q_1q_2(1-s^2) - p_1p_2q_1q_2$
$= -s^2p_1p_2q_1q_2.$
For the multiplicative case, $\mathrm{LD} = p_1p_2q_1q_2s^2 - p_1p_2q_1q_2s^2 = 0.$

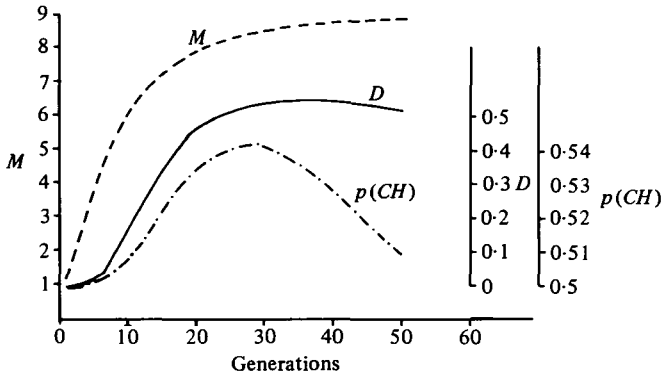

Fig. 2. Directional selection. Parameters and notation as in Figure 1, except that $S = 4$.

repulsion disequilibrium, linkage slows down the response to selection. What is true when comparing populations is also true when comparing gametes within a population. Fig. 1 B shows that $M(CH)$ increases more rapidly than $M(CL)$. This is a direct result of the fact that $V(CH) > V(CL)$. It is worth noting that the difference in mean follows, in time, the difference in variance.

(iii) *CH alleles increase in frequency*

The inrease in frequency of CH alleles occurs because they are linked to favoured phenotypic alleles. It does not require a Gaussian fitness scheme. With an additive scheme (that is, fitness of phenotype i is $W(i) = a + bi$), $p(CH)$ again increases. But, as theory predicts, with a multiplicative scheme $W(i) = (1+s)^i$, $p(CH)$ remains constant, and $V(CH) = V(CL) = V$.

With a fixed optimum, $p(CH)$ does not increase indefinitely. Fig. 2 shows a simulation identical to Fig. 1, except that selection is more intense. The initial increase in $p(CH)$ is, as expected, more rapid. However, after 27 generations $p(CH)$ starts to decline. This is because the population mean is close to the optimum, so that the normalizing component of selection is now more important than the directional. Knowing $M(CH)$, $V(CH)$, $M(CL)$ and $V(CL)$, and assuming normality, it is possible to estimate the mean fitness of populations composed of CH and CL chromosomes, from the formula

$$\overline{W} = \frac{S}{(V+S^2)^{\frac{1}{2}}} \exp\left[-\frac{(M-OPT)^2}{2(V+S^2)}\right].$$

In all simulations, the fitnesses calculated in this way accurately predict the direction of change of $p(CH)$.

The conclusion that $p(CH)$ increases under directional selection is not sensitive to the values of r in CH and CL genotypes (provided, of course, that allele CH does increase r). For example, if the simulation of Fig. 1 is repeated, but with r in CH/CL and CL/CL genotypes equal to 0·1, instead of 0·01, then $p(CH)$ increases to 0·509 in 60 generations, instead of to 0·541. Thus the rate of change is reduced, but the direction is unaltered.

5. Selection with a fluctuating optimum

Fig. 3 shows two simulations with a fluctuating optimum. In both, $p(CH)$ fluctuates, but in Fig. 3 B the general tendency, after an initial rise, is downwards, whereas in Fig. 3 A it is upwards. The oscillatory nature of the response is easy to understand. During 'up' selection, + alleles accumulate on CH gametes, and $p(CH)$ increases: when the direction of selection changes, CL gametes, with fewer + alleles, are favoured, and $p(CH)$ falls. Whether the general tendency is up or down depends in a rather sensitive way on the length of time for which selection in a given direction continues, relative to the intensity of selection and the frequencies of recombination. It is therefore hard to make generalizations. But high recombination is favoured if selection in a given direction continues for a long time, and if periods of selection in different directions are separated by periods of relaxed selection during which the composition of CH and CL gametes becomes more similar. Low recombination is favoured if there are frequent reversals in the direction of selection, or if there are prolonged periods of normalizing selection, when the mean and the optimum coincide.

6. Discussion

Previous discussions of the evolution of recombination (e.g. Charlesworth, 1974; Bell & Maynard Smith, 1987) have tended to emphasize the point that genes for high recombination will spread if selection frequently favours a change in the sign of the linkage disequilibrium. This seems to be a not particularly

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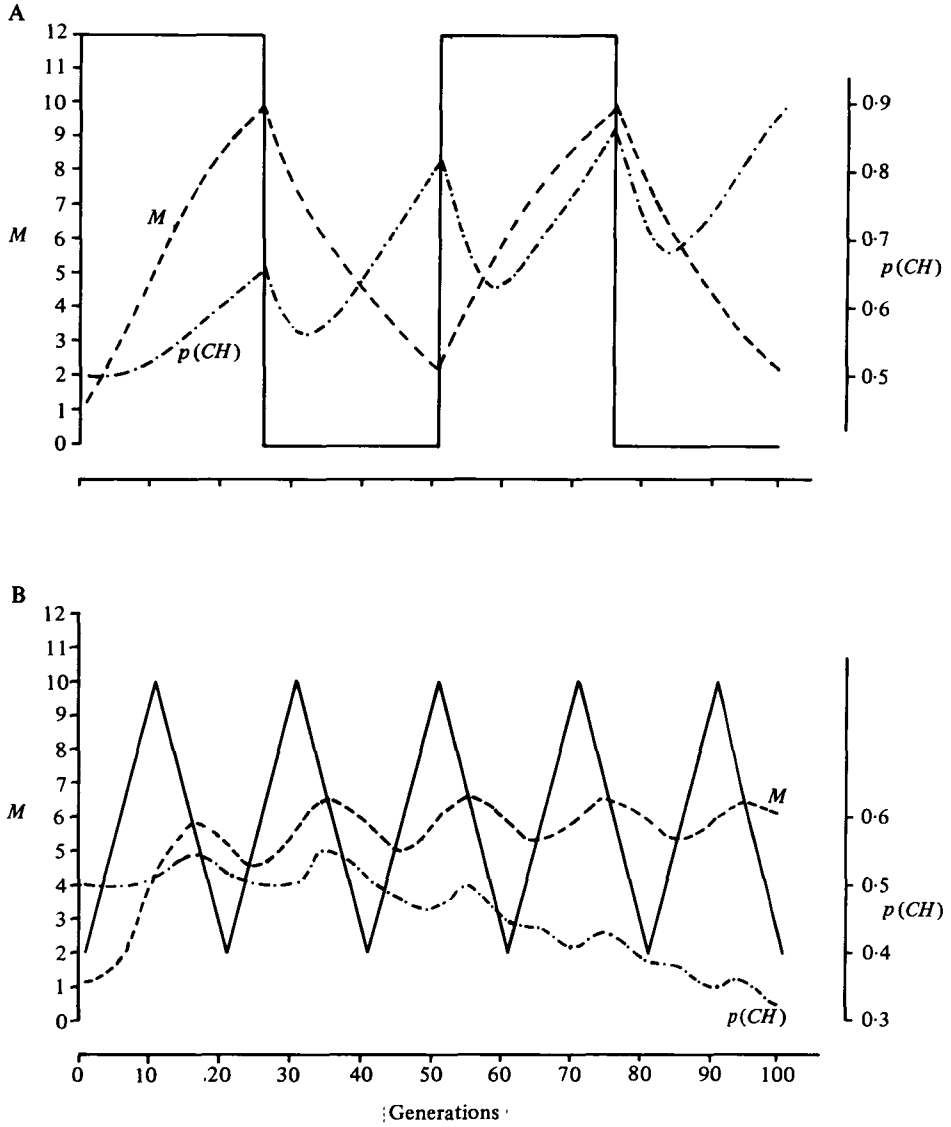

Fig. 3. Fluctuating optimum. Changes in optimum phenotype (full line), mean phenotype, M, and $p(CH)$. $r = 0{\cdot}5$ in CH/CH and 0·01 in CH/CL and CL/CL. A, fitness $W(i) = i/12$ when $OPT = 12$ and $i - i/12$ when $i = 0$. B, Gaussian fitness function with $S = 4$.

helpful way of looking at the effects of selection on polygenic traits. Instead, the essential point is that directional selection generates repulsion linkages (Fraser, 1957; Felsenstein, 1965), which is stronger in low- than in high-recombination chromosomes. The phenotypic variance of high-recombination chromosomes is therefore higher, and they respond more to selection, accumulating selectivity favoured alleles. So long as the direction of selection does not change, this leads to an increase in the frequency of high-recombination alleles. The effect, of course, depends on the recombination locus being linked to the fitness loci.

Hence recombination alleles will spread under long-continued directional selection. Directional selection on trait A for a number of generations, followed by selection on trait B, and then on trait C, and so on, would also lead to the spread of recombination alleles. This qualitative conclusion does not depend on the intensity of selection, or on a requirement that recombination in low-recombination genotypes be very low. In contrast, normalizing selection, or frequent reversals in the direction of selection, lead to the spread of alleles for low recombination.

Empirically, the strongest evidence that directional selection favours high recombination rates is the demonstration by Burt & Bell (1987) that 'excess chiasma number' (that is, chiasma number minus haploid chromosome number) in male mammals is highest in domesticated breeds.

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