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Biased conversion as the primary function of recombination

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Summary

Recombination is hard to understand in darwinian terms when the process is identified with the production of crossover chromosomes. As an alternative explanation I propose instead that biased conversion is the primary function of meiotic recombination. In particular I show that a conversion process directed against the most common type of genetic damage can substantially reduce the mutational load, even if the conversion force is weak and if the conversion process occasionally creates new mutations.

1. Introduction

Recombination in higher organisms is a complex molecular process by which genetic information is exchanged between homologous chromosomes in meiosis. Recombination occurs as crossing-over and as conversion, i.e. a non-reciprocal copying of a stretch of the genetic information in one chromosome into the other chromosome. Non-homologous conversions may be important in creating new genetic variation, but such events are rare and will not be further considered here. The conversion process is said to be biased if for a pair of alleles the second allele is converted into the first more often than the first is converted into the second. With such a bias the conversion process acts as a repair mechanism if the second allele is a mutant while the first is of wild type.

In population genetics it is generally assumed that meiotic recombination has evolved as a mechanism for the production of crossovers. This explanation is, however, associated with a problem in that it is, in the first approximation, disadvantageous for an individual to produce crossover chromosomes (Fisher, 1930 and Feldman, Christiansen & Brooks, 1980; see also e.g. Williams, 1975, Maynard Smith, 1978 and Bell, 1982, for discussions and suggested solutions to the problem). As an alternative explanation I would instead like to propose that biased conversion is the primary function of recombination and that crossing-over has nothing to do with the *raison d'être* of the process. This theory of recombination must answer two immediate objections.

The first is that a molecular process for conversion cannot 'know' which of two different alleles is the correct one and which is the one to repair. For example, if conversion primarily acts against deleted base-pairs, then the process will also incorrectly copy additional base-pairs into normal chromosomes when given the relevant genetic variation. Such complementary effects of the conversion process have been found in *Ascobolus immersus* and *Sordaria brevicollis*. In these organisms there is a strong bias against certain mutations in crosses with the wild type, while the bias goes against the *wild type* in crosses with mutations of the opposite molecular kind (Rossignol, 1969; Leblon, 1972; Yu-Sun, Wickramaratne & Whitehouse, 1977; Rossignol, Paquette & Nicolas, 1978). Thus, when the conversion process is biased against a certain type of mutation, it will act both as a repair and as a mutation inducing mechanism. This effect must be taken into account when the evolutionary role of biased conversion is to be considered.

Secondly, conversion is a process which only rarely acts on allelic differences. Lamb (1984) has collected the available data on the conversion force (a measure of the segregation distortion induced by biased conversion) and only few of the observations fall above 10^{-2} in absolute size. It is therefore not at all intuitively clear how biased conversion can be of any great evolutionary importance when its measurable effect is so small.

My argument for the role of biased conversion in the evolution of recombination is based on the analysis of a population genetical model in which these two objections can be quantified. It is then seen that the conversion process can be important in reducing the mutational load for an organism, even when its effect on any particular locus is small or even occasionally deleterious. The argument is given in as brief and simple a form as possible, assuming in the model an

organism that is haploid and random mating. Similar results can, however, be obtained with more complicated models.

2. Model

Consider a small chromosomal segment in a haploid organism and let the normal allelic type be called A_1. This allele mutates with frequencies μ and ν to the deleterious types A_2 and A_3. The selection values against these alleles are s and t, which we assume to be much greater than the mutation rates. Mating is at random in the population and conversion between the alleles may occur in meiosis.

The idea behind having three types of alleles in the model is to let A_2 and A_3 be mutations of opposite molecular kinds to the standard allele A_1, for example base-pair deletions and additions. This implies that if the gametic output from A_1A_2 heterozygotes due to a bias in conversion is $(\frac{1}{2}+y)\,A_1:(\frac{1}{2}-y)\,A_2$, then the gametic output from A_1A_3 heterozygotes must be $(\frac{1}{2}-y)\,A_1:(\frac{1}{2}+y)A_3$. The parameter y which acts as a measure of the strength of the biased conversion is called the conversion force (Lamb & Helmi, 1982).

To simplify the argument we will throughout the article assume that the bias in the conversion process acts against the A_2 alleles and favours the A_3 alleles, i.e. that $y \geqq 0$. Both kinds of alleles are disfavoured by selection and will be rare in the population. The A_2A_3 heterozygotes will therefore be formed only *very* rarely and their conversion properties can in the present context be ignored.

3. Results

Given these assumptions, the population will establish itself at a mutation-selection equilibrium at which the frequencies of the deleterious alleles approximatively are

$$\left.\begin{aligned}\hat{p}_2(y) &= (1-2y)\,\mu/\{s+2y\,(1-s)\},\\ \hat{p}_3(y) &= (1+2y)\,\nu/\{t-2y\,(1-t)\}\end{aligned}\right\} \quad (1)$$

and the mean fitness in the population is

$$\hat{W}(y) = 1-s\hat{p}_2(y)-t\hat{p}_3(y) = 1-L(y), \quad (2)$$

where $L(y)$ is the mutational load at the locus. If there is no conversion or if the conversion process has no bias, then these values become

$$\hat{p}_2(0) = \mu/s,$$
$$\hat{p}_3(0) = \nu/t,$$
$$\hat{W}(0) = 1-(\mu+\nu).$$

The purpose of our analysis is to consider how the conversion process is influenced by the selection at the A locus, and to see how the process will change in evolution due to this selection. The most satisfying analysis would be based on a study of the initial increase of alleles at a linked modifier locus influencing the properties of the conversion process at the A locus. Here, however, a simpler analysis will be presented, which is based on the assumption that the conversion process will change in evolution in such a way that the mean fitness in the population always increases. (For a discussion of this principle in modifier evolution, see Karlin & McGregor, 1974).

Our first result concerns the origin of biased conversion, i.e. the evolution of the process from a situation where it does not exist. Biased conversion will evolve in our model, given the assumptions described above, if

$$\lim_{y\to 0} d\hat{W}(y)/dy > 0, \quad (3)$$

which can be shown to be equivalent to

$$\hat{p}_2(0) > \hat{p}_3(0). \quad (4)$$

Biased conversion is, thus, selectively favoured in the population if it acts against the initially most common of the deleterious alleles. This result may sound trivial, but it has some surprising interpretations. If, for example, the two types of mutation are induced with the same frequency ($\mu = \nu$) but the A_3 alleles are more deleterious than the A_2 alleles ($t > s$), then conversion directed agains the *better* of the two types of alleles, A_2, will evolve, since these mutations will initially be the most common ones in the population.

Secondly, the conversion force, y, will not continue to increase during evolution, but will reach some intermediary value, where the mutation-inducing and the repair effects of the conversion process are balanced. At this value, $\tilde{y}$, the following expression holds

$$\mu s/\{s+2\tilde{y}(1-s)\}^2 = \nu t/\{t-2\tilde{y}(1-t)\}^2. \quad (5)$$

As with all other y values in our model, $\tilde{y}$ is necessarily smaller than $t/2(1-t)$.

There is, thus, an upper bound to what value the conversion force will evolve towards, and the smallness of the conversion force normally found cannot, *a priori*, be taken as evidence against the process having evolved through adaptive evolution.

But the most important question remains: Is biased conversion associated with such a strong selective advantage that it may explain both the origin and the continued existence of recombination? To approach this question we look at the change in the mutational load at the A locus that is produced by the conversions. It is easy to show that the relative decrease of the mutational load at the locus, $\{L(0)-L(y)\}/L(0)$, produced by a conversion force y is equal to

$$2\mu y/(\mu+\nu)\,\{s+2y(1-s)\} - 2\nu y/(\mu+\nu)\,\{t-2y(1-t)\}. \quad (6)$$

The potential magnitude of this decrease can be illustrated by an example: If $\mu = 10^{-5}$, $\nu = 10^{-7}$ and $s = t = 0{\cdot}05$, then a conversion force of $8{\cdot}0 \times 10^{-3}$ will reduce the mutational load at the locus by 24%.

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Such a reduction of the mutational load at a single locus could in most situations be completely ignored. However, the situation becomes very different if the conversion process acts in the same way at many loci in the genome, and if all of these are damaged by mutations similar to those at the A locus. The reduction in the mutational load should then be considered over all loci. It is notoriously difficult to judge the *total* load for the whole genome from the load at single loci, but if we assume that the total load is a linear function of the load at a typical locus, then the *proportional decrease* in the load will be the same for the locus and the genome as a whole. The substantial decrease in the mutational load at the A locus found in the example above could, thus, be valid for the genome as a whole, if the A locus is typical for the other loci in its mutation and conversion properties.

4. Discussion

It is generally assumed that meiotic recombination has its evolutionary origin in a system for DNA repair (see, e.g. Bodmer, 1970 and Maynard Smith, 1978). It has also been proposed that repair is still the primary function of recombination (see Bernstein, 1977; Bernstein, Byers & Michod, 1981; and the references given by them). The idea presented here is similar to the last view, but differs from the suggestion made by Bernstein and co-workers in that biased conversion both 'repairs' mutations and 'induces' mutations. What I have shown above is that a system for biased conversion can evolve through darwinian adaptive evolution if its balance between repairing and inducing mutations is such that the total mutational load for the organism thereby becomes reduced. I have also shown that the reduction in load produced by biased conversion can be substantial, even when the conversion force is small.

Another difference between the ideas presented by Bernstein and his colleagues and by me is that I believe that the recombination process has to do with the elimination of true mutations, while Bernstein *et al.* (1981) favour the view that recombinational repair only corrects DNA lesions having arisen within the germ line of individuals (on pp. 540–41 in their article they discuss the difference between lesions and mutations and state their belief that only natural selection can eliminate mutations).

Feldman *et al.* (1980) have shown that darwinian evolution will favour crossing-over between two loci at which deleterious mutations occur, if the fitness interaction between the different alleles is of a particular, non-multiplicative kind. As an explanation for the existence of recombination their suggestion differs markedly in its cytological details from the one presented here. The evolutionary frame-work is, however, very similar, since both ideas are based on locally weak selective forces which become strong when integrated over the genome as a whole. The advantage of recombination is, furthermore, in both cases found in a deterministic setting, where the adaptive value of recombination grows out of the ever present danger of genetic damages and does not depend on ecological factors such as the population size or a variability over time in the selective forces. It will be interesting to try to compare the strengths of the adaptive advantages that these two different systems can produce; my guess is that the effect studied by Feldman *et al.* (1980) will only be able to produce a very small reduction in the mutational load, unlike the effect studied above.

The argument presented by me does not depend on which types of mutation the conversion process disfavours. It seems, however, reasonable to believe that the largest part of the mutational load in most organisms is caused by base-pair deletions and that, therefore, the conversion process primarily acts against these mutations. Indirect evidence for this view comes from *Sordaria* and *Ascobolus*, where a large number of presumed base-pair substitution mutations and frame-shift mutations have been isolated and studied for their conversion properties relative to wild-type alleles. When the average conversion forces of the two types of mutations are compared (using 101 mutations from five loci), it is seen that the conversion force for (or against) the frame-shift mutations is always significantly larger than the force associated with the base-pair substitutions (see Table 2 in Lamb, 1984, which is based on data from Leblon, 1972, and Yu-Sun *et al.* 1977). The average force for or against the frame-shift mutations ranges over the five loci from $4{\cdot}7 \times 10^{-3}$ to $3{\cdot}8 \times 10^{-2}$. The value $8{\cdot}0 \times 10^{-3}$ used in the numerical example above, and which produced a reduction in the mutational load of 24%, has been chosen to represent a typical value on the basis of these results.

One should, however, be open to the possibility that the bias in conversion is directed against different types of mutations in different organisms, depending on which mutations produce the largest mutational load. It is also possible that there are many conversion systems acting in meiosis which are directed against different – though never opposite – kinds of DNA damages and which work with different strengths.

Biased conversion has here only been discussed in terms of its force, measured by y. This force depends in its turn on the frequency with which conversions occur at the studied locus and the bias that exists in the copying of the different alleles. One and the same conversion force may therefore be produced by different combinations of these processes. I do not think we can today say anything meaningful about why, for example, conversions are not even more rare but associated with a stronger bias. It is probable that the frequency of conversions is determined by a number of constraints, of which an important one

may be the relationship between conversions and crossovers.

If the meiotic recombination process is due to the adaptive effects of biased conversion, then crossing-over must find an explanation of its own. It may be that, *once* recombination had evolved, the relative disadvantage of producing crossovers was more than compensated by the positive effects these chromosomes had on the stability of the reduction division. A very simple fact which seems to favour the view that crossing-over is a derived function of conversion rather than the reverse, is that crossovers generally occur at the sites of conversion, while most conversions occur without being associated with crossing-over (for discussions of the relationship between conversion and crossing-over, see *e.g.* Whitehouse, 1982; von Wettstein, Rasmussen & Holm, 1984 and Fink & Petes, 1984).

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