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The effect of biased conversion on the mutation load

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Summary

The mutation load is sensitive to changes in the segregation ratio caused, for example, by biased conversion. If the distortion, measured by the force of conversion, is greater than the loss of fitness in the mutation heterozygotes, then the mutation load will be far away from its normal value. Examples are given where a small positive bias together with realistic fitness parameters increase the mutation load by more than two orders of magnitude.

In practical terms this implies that great restrictions should be placed on the use of substances and treatments that may induce mutations associated with a positive conversion bias.

1. Introduction

Every new deleterious mutation that is induced in a population will be lost in a future generation, given that the population size is large enough to prevent chance fixations. The mutation load of a locus is the proportion of genes that is lost per generation due to the deleterious effect of mutation (Haldane, 1937; Muller, 1950). It belongs to elementary population genetics to show that the mutation load equals the mutation rate times a constant which normally lies between one and two. For dominant mutations the coefficient is close to two, while it approaches one when the mutations are strictly recessive and there is no inbreeding in the population (see, e.g. Crow & Kimura, 1970, p. 300).

These load calculations are based on a premise that is rarely explicitly discussed, namely that there is Mendelian segregation at the locus. This assumption may not be strictly true. Detailed studies in fungi have shown that the process of gene conversion acts on heterozygous loci in meiosis, changing homologous alleles into each other at a low but appreciable frequency. The process is often associated with a bias, making conversions from one allele to the other more common than the reverse process. The importance of biased conversion from a population genetical point of view is that the segregation ratio at heterozygous loci becomes slightly distorted. The magnitude of the distortion has been called the force of conversion and is denoted by y (Lamb & Helmi, 1982).

The force of conversion has been shown to depend on the species investigated, the genetic background of the cross, the locus tested, the environmental condition, and – most importantly – the molecular difference between the two homologous alleles. The bias is stronger if the alleles differ by a frame shift mutation than by a base pair substitution. The conversion bias is also normally directed against base pair deletions while base pair additions are favoured, according to studies in *Sordaria* and *Ascobolus*. Bias appears in general to be weaker in yeast, but has recently been shown to be considerable in connection with insertion mutations (Nag *et al.* 1989). All meiotic organisms are presumed to produce conversions, but the details of the process is unknown outside the fungi. The available information about gene conversion is reviewed by Lamb (1984, 1986).

Thus, in certain organisms and possibly all, some deleterious mutations are counteracted by the conversion process while others are favoured due to their molecular relationship to the normal type. The conversion force is numerically small, which makes it difficult to study, but may well be orders of magnitude greater than the mutation rate. A number of authors have investigated the effect homologous gene conversion has on allele frequencies (see e.g. Gutz & Leslie, 1976; Lamb & Helmi, 1982; Nagylaki, 1983*a*, *b*; Walsh, 1983; Lamb, 1985; Bengtsson, 1985), but its potentially dramatic effect on the mutation load has, as far as I know, yet gone unnoticed. The genetic load due to the balance between segregation distortion and selection has been studied before (see pp. 311–312 in Crow & Kimura, 1970), but since these studies have normally ignored the effect of mutation, their results are only of partial relevance here.

I will therefore present some numerical results on the mutation load under biased conversion, plus describe approximations of its magnitude for certain parameter combinations. Different types of deleterious

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mutations will be considered separately to make the effect of biased conversion as clear as possible, but backmutations will be allowed from the damaged to the normal allelic state. All conversion events in the model are, of course, homologous; for a study of the mutation load of a multigene family where conversions occur between loci, see the recent article by Ohta (1989).

2. Model

We assume a locus at which deleterious mutations occur with frequency u. Mutant alleles revert to the normal type with frequency v. Mutant homozygotes have fitness $1-s$, while heterozygotes for mutated alleles have fitness $1-hs$. The fitness of normal homozygotes is 1. The gametic segregation in heterozygotes is distorted, so that the ratio between gametes with the normal and mutated alleles is $0{\cdot}5+y$ to $0{\cdot}5-y$. The degree of inbreeding in the population is f. The order of the assumed events is: birth–selection–segregation distortion during gamete production–mutation–union of gametes.

Straightforward population genetical analysis shows that the frequency of the mutant alleles will under these assumptions evolve to the value given by the smallest positive root in q, $\hat{q}$, of the third degree equation

$$uW+q(1-q)(1-f)(1-hs)(1-2y)(1-u-v) + (qf+q^2(1-f))(1-s)(1-u-v)-qW=0, \quad (1a)$$

where

$$W=1-2q(1-q)(1-f)hs-(qf+q^2(1-f))s.$$

The load due to mutation, L, at this stable equilibrium is

$$L=2\hat{q}(1-\hat{q})(1-f)hs+(\hat{q}f+\hat{q}^2(1-f))s. \quad (1b)$$

The values in the tables have been calculated from these expressions using a numerical solution of (1 *a*). All results are given with three or more significant digits.

3. Results

The mutation loads associated with different parameter combinations are listed in Tables 1–3. To give a systematic description of the results, it is convenient to regard the approximations that can be made of expression (1) above. If we assume that the equilibrium frequency of the mutated allele is of order $u^{\frac{1}{2}}$ or smaller and then disregard all terms of size $u^{\frac{3}{2}}$, the following simplified form of (1 *a*) is obtained:

$$q^2((1-f)(1-s)+2(1-f)hs+fs-(1-f)(1-hs)\times(1-2y)) + q((1-f)(1-hs)(1-2y)+f(1-s)-1)+u=0. \quad (2)$$

Further simplifications can be made of this expression, depending on the relationship between the parameters. Four cases will be considered.

1. When h or f is considerable, the equilibrium frequency of the mutated allele will be very small. The first term in expression (2) can then be disregarded and the equilibrium frequency be written as

$$\hat{q}=u/(s((1-f)h+f)+2y(1-f)(1-hs)). \quad (3a)$$

With this approximation the load becomes

$$L=us(2(1-f)h+f)/(s((1-f)h+f)+2y(1-f)(1-hs)). \quad (3b)$$

For completely dominant mutations in a random mating population the load is

$$L=2us/(s+2y(1-s)). \quad (3c)$$

This approximation fits the entries in Table 1 very well. The result implies that the mutation load of dominant mutations is unaffected by a perturbation of the segregation ratio, as long as the perturbation is small compared to the selection value.

2. For recessive mutations in very large random mating populations (h and f very close to 0) and for segregation distortion small compared to the mutation rate, the following standard approximation holds

$$\hat{q}=(u/s)^{\frac{1}{2}}. \quad (4a)$$

For such recessive mutations the load is

$$L=u. \quad (4b)$$

3. The situation that remains to be considered is when h and f are small and y not insignificant. This situation will be split into two cases depending on whether the bias goes in favour of the normal allele ($y>0$) or the mutated allele ($y<0$). If the bias favours the normal allele, then the equilibrium frequency will be close to

$$\hat{q}=u/2y, \quad (5a)$$

and the mutation load can be approximated by

$$L=su^2/4y^2. \quad (5b)$$

This approximation holds reasonably well in Table 2 when the segregation distortion is greater than 0·0001. When $s=0{\cdot}01$ it holds also for $y=0{\cdot}0001$. The approximation tells us that when the conversion process favours the normal allele and the square of the segregation distortion is much greater than the mutation rate, then the mutation load will be considerably smaller than expected.

4. When h and f are small and the segregation distortion favours the mutant alleles ($y<0$), the mutation rate u can be ignored in expression (2). Then the equilibrium frequency becomes

$$\hat{q}=-2y/(s-2y) \quad (6a)$$

and the load

$$L=4sy^2/(s-2y)^2. \quad (6b)$$

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Table 1. *The effect of biased conversion on the mutation load. The table gives the load divided by the mutation rate for dominant mutations with different selection values. The following assumptions hold throughout the table: $u = 10^{-6}$, $v = 0$, $h = 1$, $f = 0$. With no bias ($y = 0$) the value is 2·00*

y	$s = 1{\cdot}00$	$s = 0{\cdot}10$	$s = 0{\cdot}01$
0·01	2·00	1·69	0·671
0·001	2·00	1·96	1·67
0·0001	2·00	2·00	1·96
−0·0001	2·00	2·00	2·04
−0·001	2·00	2·04	2·49
−0·01	2·00	2·44	−a

[a] No load estimate has been calculated since the mutant frequency is very high for this parameter combination

Table 2. *The effect of biased conversion on the mutation load. The table gives the load divided by the mutation rate for recessive mutations with different selection values. The following assumptions hold throughout the table; $u = 10^{-6}$, $v = 0$, $h = 0$, $f = 0$. With no bias ($y = 0$) the value is 1·000*

y	$s = 1{\cdot}00$	$s = 0{\cdot}10$	$s = 0{\cdot}01$
0·01	$2{\cdot}49 \times 10^{-3}$	$0{\cdot}250 \times 10^{-3}$	$25{\cdot}0 \times 10^{-6}$
0·001	0·172	$23{\cdot}8 \times 10^{-3}$	$2{\cdot}49 \times 10^{-3}$
0·0001	0·819	0·537	0·172
−0·0001	1·22	1·86	5·83
−0·001	5·83	42·0	402
−0·01	402	$4{\cdot}00 \times 10^{3}$	−[a]

[a] No load estimate has been calculated since the mutant frequency is very high for this parameter combination

With this approximation the load estimate becomes independent of the mutation rate. Instead it is determined by the ratio between the segregation distortion favouring the mutant allele and the selection value against mutant homozygotes. When the load is divided by the mutation rate, a value is obtained that may be orders of magnitude greater than when no segregation distortion occurs. This situation is relevant for all cases in Table 2 where the segregation distortion is numerically greater than −0·0001. It holds also for this value when $s = 0{\cdot}01$.

The last two cases show that biased conversion can have a drastic effect on the mutation load at a locus. The important question is then in which parameter range this drastic effect commences. Is it only for unrealistically small values of h and f that the load moves drastically away from its normal range around twice the mutation rate?

To answer this question, the load has been calculated while the parameters are changed one by one away from the following parameter combination: The basic mutation rate is assumed to be 10^{-6} and the back mutation rate is ten times smaller. The mutants are slightly deleterious, with a selection value of 0·05 against the homozygotes and a weak amount of dominance ($h = 0{\cdot}10$). The population has a small amount of inbreeding ($f = 0{\cdot}01$). The conversion force is weak and favours either the normal ($y = 0{\cdot}005$) or the mutant allele ($y = -0{\cdot}005$).

Table 3. *The load divided by the mutation rate for variations on the parameter combination: $u = 10^{-6}$, $v = 10^{-7}$, $s = 0{\cdot}05$, $h = 0{\cdot}10$, $y = \pm 0{\cdot}005$, $f = 0{\cdot}01$*

Parameter change	Load divided by mutation rate when $y = 0{\cdot}005$	Load divided by mutation rate when $y = -0{\cdot}005$
None	0·680	1649
$u = 10^{-7}$	0·679	16451
$u = 10^{-5}$	0·680	169
$v = 10^{-8}$	0·680	1649
$v = 10^{-6}$	0·680	1648
$h = 0{\cdot}05$	0·424	1916
$h = 0{\cdot}15$	0·865	956
$h = 0{\cdot}25$	1·115	8·13
$f = 0{\cdot}001$	0·670	1834
$f = 0{\cdot}05$	0·718	831
$f = 0{\cdot}1$	0·758	23·3

These parameter combinations have been chosen to describe the mutations which are presumed to have the largest effect on the mutation load, namely weakly deleterious mutations with some heterozygous effect (see, e.g. Crow & Simmons, 1983). The inbreeding factor is included to ascertain that the underlying assumption about an infinite population size does not have an unrealistic effect on the results. The force of conversion has been taken from the estimates made in fungi (reviewed by Lamb, 1984).

When the conversion bias favours the normal allele (left column in Table 3) the effect on the load is clear but not drastic; it is reduced to about a third of the value it would take if there were no segregation distortion (1·907). The load is very accurately approximated by expression (3*b*). None of the changes in the investigated parameters affect the result dramatically.

The situation is wildly different when the conversion process favours the mutated alleles (right column in Table 3). The load is now more than 800 times greater than what it would be if there were no segregation distortion at the locus! The approximation given by (6*b*) works reasonably well, but underestimates constantly the effect of the bias (its estimate of the load divided by the mutation rate is 1389). Small changes in the parameters can have dramatic effects, as seen from the Table. For this parameter combination the load is only weakly affected by the mutation rate as shown by approximation (6*b*). It is therefore not surprising that great fluctuations occur when the load is divided by mutation rates differing by orders of magnitude. More interesting is the importance of the exact degree of dominance and level of

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inbreeding. For example, a change in the degree of dominance from 25 to 15% gives a more than 100-fold increase of the load.

4. Discussion

It is clear from these calculations that biased conversion of a magnitude known to exist in certain organisms can have a very drastic effect on the mutation load. The weaker and more recessive that the mutations are, the more affected is the mutation load.

The results are best understood if one considers the expected life time of a new deleterious mutation. If the fitness of mutant heterozygotes is $1-hs$, then a new mutation is expected to stay in the population for $(hs)^{-1}$ generations (or longer if hs is very small). The chance that, during any particular generation, it is involved in a conversion event contributing to the bias is y. Therefore, if $(hs)^{-1}$ times y is smaller than 1, then most mutations will be lost before they partake in any conversion event, and there will be no particular effect of the conversion process on the mutation load. If, on the other hand, the conversion force is greater than the average fitness loss of the heterozygotes, then the load is strongly affected by the conversion process, particularly if the bias favours the mutant type. Under this condition the conversion process acts as a mutation-inducing force or a repair mechanism, depending on whether the bias goes for or against the mutation.

Thus, if an organism has evolved a general bias against a certain type of common mutations it will suffer a smaller mutation load than if the segregation was strictly Mendelian. The argument assumes, however, that the molecularly opposite type of mutation is uncommon, since otherwise the increased load for the second kind of mutations would outweight the gain for the first type. In this journal I suggested some years ago that biased conversion has evolved to obtain such a reduction in the mutation load (Bengtsson, 1985). More careful genetical modelling, studying genetic variation at a locus modifying the conversion process, has later shown that the logic in the argument was correct in indicating in what direction conversion bias will develop. However, due to gametic correlations between the alleles at the modifier locus and the selected locus, the population will not evolve to a state where the mutation load for the selected locus is at its exact minimum (Bengtsson & Uyenoyama, in the press).

As often occurs in population genetics, the effect of biased conversion on the mutation load is determined by a product of two parameters – one small, one large, and both difficult to estimate. In the present case the product is between the force of conversion associated with deleterious mutations, y, and the inverse of the heterozygous effects of these mutations, $(hs)^{-1}$. It is known that most deleterious mutations have some effects on heterozygotes, but the magnitude of the effect has been the source of one of the greatest controversies in population genetics. It seems fair to conclude that most new deleterious mutations are associated with a loss of fitness in heterozygotes smaller than 0·10 and possibly 0·01; whether it is smaller than 0·001 is uncertain (see discussions in Crow & Simmons, 1983; Charlesworth & Charlesworth, 1987; Sved & Wilton, 1989).

The force of conversion, on the other hand, has hardly been studied at all. Indeed, the segregation ratio seems in general to have been given very little empirical attention. This is, of course, partly due to the practical difficulties involved in estimating a distortion from Mendelian segregation. To have a reasonable chance to show statistically that there is a deviation of magnitude y away from the expected 1 : 1 segregation, an order of y^{-2} gametes must be scored without any misclassifications. There is at present just no data available, but an average value of the conversion force between 0·01 and 0·001 for certain molecular classes of new mutations is a perfect possibility, also in such well studied genetical organisms as *Homo* and *Drosophila*.

We can, thus, conclude that it is today impossible to know if biased conversion plays a major role in determining the magnitude of the mutation load in organisms such as ourselves, but that the possibility must be considered and further investigated.

I would also like to point out a further conclusion from the present study. If the conversion process in meiotic organisms has evolved so that it carries a bias against certain common types of deleterious mutations, say base pair deletions, then great restrictions should be placed on the use of chemicals and treatments that may induce new mutations of opposite molecular kind, i.e. base-pair additions. All mutagen testing and control has so far been based on the simple dictum that every deleterious mutation will sooner or later get lost from the population and that the molecular nature of the mutation does not matter. The calculations presented here (see, e.g. Table 3) show that this may be totally misleading. Mutations associated with a weak positive bias may produce a very high mutation load, even though the 'payment' of the mutation load is deferred to later generations. From this practical point of view, it is urgent that much more information is collected about the conversion force associated with different types of mutations in various organisms.

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