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The extent to which gene conversion can change allele frequencies in populations

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SUMMARY

The gene conversion parameters which affect allele frequencies in populations are defined, and their ranges and typical values are given for several genera of fungi, where meiotic octads and tetrads provide the best information on conversion. Both gene conversion and disparity in direction of conversion are common. Data from *Ascobolus immersus* show that conversion properties are largely stable with time, but can be changed environmentally and by genetic conversion control factors. Equations are given for the interactions of selection, mutation and gene conversion in determining equilibrium frequencies. Numerical examples, using typical values of conversion parameters from the fungal data, show that for alleles which are selectively neutral or have very low selection coefficients, conversion will often have very large effects on their equilibrium frequencies and may lead to fixation. Where selection coefficients are higher, conversion has major effects on the frequencies of deleterious recessive alleles, but lesser effects on deleterious dominant alleles: a critical comparison is that of s with $2y$. The available estimates for conversion parameters (at least in fungi) are of a magnitude to make gene conversion an important factor in evolution.

1. INTRODUCTION

The aim of this work was to study the effects of gene conversion on allele frequencies and its interactions with mutation and selection; to find typical values for the relevant conversion parameters, and thus to assess the importance of gene conversion as a factor in populations. Gene conversion is a process of chemical interaction between alleles, usually at meiosis, where one allele can 'convert' another to being of its own kind in a heterozygote. For example, at meiosis in an Aa individual, A may convert an a allele to A, affecting the expected $2A:2a$ ratio in the four products of meiosis. Conversion at meiosis can be detected from aberrant allele ratios in meiotic tetrads or octads (where a mitosis follows meiosis), and occurs far less often at mitosis: for general reviews, see Catcheside (1977) and Fogel *et al.* (1979). The mechanisms of gene conversion are quite distinct from other

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meiotic drive phenomena such as the spore killer factor in *Neurospora* (Turner & Perkins, 1979). Conversion, or conversion-like processes, has been found in all organisms suitably studied, including *Drosophila*, maize, fungi, bacteria and bacteriophage (see Catcheside, 1977).

Gutz & Leslie (1976) pointed out that conversion could affect allele frequencies and they gave some equations. Watt (1972) examined the effects of intragenic recombination as a source of genetic variability; Strobeck & Morgan (1978), Morgan & Strobeck (1979) and others examined other population aspects of intragenic recombination. Our main consideration is a two-allele situation in a large, random mating, diploid population with non-overlapping sexual generations, but most conclusions apply in other circumstances as well, though the equations needed may differ in detail. Experimental values are taken from fungi as their meiotic tetrads and octads provide the best quantitative data. All conversion classes are considered here, not just $3A:1a$ and $1A:3a$ ratios as in the Gutz & Leslie (1976) study: their net gene conversion constant, k, is equivalent to $4y$ in the present work if only 3:1 and 1:3 conversions occur. Some of these findings were reported in abstracts (Lamb, 1979, 1980).

2. MATERIALS AND METHODS

New data from Pasadena strains of the fungus *Ascobolus immersus* were obtained using methods previously described, e.g. by Lamb & Wickramaratne, 1973; Lamb & Helmi, 1978; Helmi, 1980. Crosses were made at 17·5 °C unless otherwise stated. The simulation program, for the interactions of conversion, mutation and selection, had this structure. Take a given initial allele frequency; calculate the three genotype frequencies (AA, Aa, aa) from random mating; carry out selection, then mutation, then gene conversion; use the resulting allele frequency in the gametes (or sexual spores) as the initial allele frequency in the next generation; repeat for many generations.

3. DEFINITIONS, BASIC THEORY AND FORMULAE

The most important conversion parameters are: c, the conversion frequency (as a fraction); b, the frequency of a particular allele (say A for A/a, or wild-type (+) for $+/m$ (mutant)) in the products of meiotic tetrads or octads with aberrant segregation ratios; d, the disparity in direction of conversion, that is, the difference in frequency between conversion in one direction (e.g. A to a) and in the other direction (a to A). $d = b - 0{\cdot}5$. Allele ratios are given as $A:a$ or $+:m$.

$$c = \frac{\text{number of tetrads or octads with aberrant segregation ratios}}{\text{total number of normal and aberrant ratio tetrads or octads}},$$

$$= \frac{4:0+3:1+1:3+0:4}{2:2+4:0+3:1+1:3+0:4} \quad \text{in tetrads,}$$

$$= \frac{8:0+7:1+6:2+5:3+3:5+2:6+1:7+0:8}{4:4+8:0+7:1+6:2+5:3+3:5+2:6+1:7+0:8} \quad \text{in octads.}$$

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Only aberrant ratios from gene conversion are included, not ones from non-disjunction, mutation, chromosome aberrations or other sources; aberrant 4:4 (i.e. with post-meiotic segregation) and correction 4:4 octads (where hybrid DNA correction gives a normal 4:4 ratio) count as normal 4:4 segregations for their allele ratio.

$$b = \frac{(4:0\times 4)+(3:1\times 3)+(1:3\times 1)+(0:4\times 0)}{4\times \text{total number of aberrant ratio tetrads}} \quad \text{in tetrads, and in octads}$$

$$b = \frac{(8:0\times 8)+(7:1\times 7)+(6:2\times 6)+(5:3\times 5)+(3:5\times 3)+(2:6\times 2)+(1:7\times 1)+(0:8\times 0)}{8\times \text{total number of aberrant ratio octads}}.$$

With more conversion to A than to a, $b > 0{\cdot}5$, d is positive; with more conversion to a than to A, $b < 0{\cdot}5$, d is negative. Conversion only affects allele ratios if occurring in a heterozygote, for which the normal allele frequency from meiosis is 0·5 for both alleles. Further analysis of meiotic products from tetrads for post-meiotic segregation could increase the accuracy of estimation of b from tetrads; e.g. a phenotypically $3A:1a$ tetrad may or may not show post-meiotic segregation at the next mitosis, corresponding to $5A:3a$ or $6A:2a$ octads respectively, with different allele ratios.

Let the force of gene conversion on allele frequencies be y, where $y = c(b-0{\cdot}5)$, that is, the product of conversion frequency and disparity. y is the amount by which the frequency of A (or +) is increased (or decreased if y is negative) from the normal value of 0·5 in the meiotic products of heterozygotes. c could in theory have any value from 0 to 1·0, but in practice values of over 0·4 are extremely rare. The 'wider ratio' conversion classes, 8:0, 7:1, 1:7 and 0:8 in octads, 4:0 and 0:4 in tetrads, are usually much rarer than 'narrower ratio' classes, 6:2, 5:3, 3:5, 2:6 or 3:1 and 1:3, and in the absence of corresponding-site interference, each wider ratio class occurs with a frequency related to that of particular narrower ratio classes: see Lamb & Wickramaratne (1973). Values of b are thus unlikely to be much in excess of 0·75 (nearly all aberrant ratios 6:2 or 3:1) or much below 0·25 (nearly all aberrant ratios 2:6 or 1:3). While y in theory has absolute maximum and minimum values of 0·5 and $-0{\cdot}5$, the most extreme values in practice are not likely to be much outside the range 0·1 to $-0{\cdot}1$.

In a population polymorphic for A (frequency p) and a (frequency q, $p+q=1$), aa individuals give all a meiotic products, AA give all A, while Aa give A with frequency $cb+0{\cdot}5(1-c)$, which is $0{\cdot}5+y$, and a with frequency $c(1-b)+0{\cdot}5(1-c)$, which is $0{\cdot}5-y$. One can therefore produce equations for p from populations with any degree of non-random mating and/or differential fertility of the three genotypes. For typical Hardy–Weinberg conditions, with random mating and no differential fertility,

$$p_{n+1} = p_n^2 + 2p_n(1-p_n)\ (0{\cdot}5+y), \tag{1}$$

where $n+1$ is the generation after n. The change in p in one generation,

$$\Delta p = 2pqy = 2p(1-p)\ y. \tag{2}$$

Conversion will act fastest on allele frequencies when the proportion of heterozygotes is maximum, which is when $p = q = 0{\cdot}5$ for a random mating population. To follow

changes in p over many generations is simple with a computer by using equation (1) repetitively, but a general equation can be obtained by the method of Gutz & Leslie (1976), giving:

$$p_n = \frac{(p_0/q_0) \cdot e^{2yn}}{1 + (p_0/q_0) \cdot e^{2yn}}, \tag{3}$$

where n is the number of generations, p_0 and q_0 are the initial frequencies of A and a, and p_n is the frequency of A in the nth generation. The condition for obtaining equation (3), that Δp is small compared to p, means that (3) is most accurate when Δp is near zero and/or when p approaches 1·0 or 0.

In organisms where tetrad or octad analysis is impossible, it is difficult to estimate c and b separately, but the combined effects of conversion frequency and disparity will still affect allele frequencies in the meiotic products (e.g. sperm, ova, pollen, ovules; sexually-produced spores in fungi) of heterozygotes, even when only one product of a tetrad survives, as in oogenesis.

4. FUNGAL DATA ON c, b, d AND y

Figs. 1 and 2 show values of c and b calculated here for a range of mutations in a number of fungi. Data sets were chosen to include as many loci in as many species as possible, but excluding those concentrating on loci with known high conversion frequencies. The values of c in Fig. 1 vary from 0 to 0·29 for particular alleles, with most in the range 0·002 to 0·10. The mutations involved include spontaneous ones and ones induced by standard agents UV, EMS, NMG and ICR–170, with spontaneous and induced mutations having similar ranges and distributions for c and b. Limited data from *Neurospora crassa* and *Bombardia lunata* show c values in the region of 0·01 (see Catcheside, 1977); in *Venturia inequalis* (Boone & Keitt, 1956), N-46 had $c = 0{\cdot}146$, $b = 0{\cdot}35$. Further *Ascobolus* data, e.g. Girard & Rossignol (1974), include a number of c values over 0·3, that is, over 30 % of all octads having gene conversion at a single site. Conversion can thus be extremely common, and zero values of c are rare, especially in large samples.

Fig. 2 shows a very wide spread of b values, going to the most extreme values that might reasonably occur, around 0·25 and 0·75. Because of different sample sizes for different mutants in the same disparity category, no significance values are given in Fig. 2. When we analysed the original data (references in Fig. 2), the great majority of b values outside the range 0·45–0·55 showed disparities significant at the $P = 5$, 1 or 0·1 % levels, except for the yeast data. Yeast was thought to show little disparity (Fogel, Hurst & Mortimer, 1971), but there are now clear cases of disparity: for the 30 sites studied by Fogel *et al.* 1979, disparity was significant for 12 at $P = 5$ %. In our own *Ascobolus* data, even some disparities within the range $b = 0{\cdot}45$–$0{\cdot}55$ were significant, e.g. NG$w5 \times +$, K, where $b = 0{\cdot}46$, with disparity significant at $P = 2$ % ($\chi_1^2 = 5{\cdot}94$). Taking the data as a whole, disparity in favour of wild-type ($b > 0{\cdot}5$) is about as frequent as disparity in favour of mutant ($b < 0{\cdot}5$), with individual distributions for b values very roughly symmetrical about $b = 0{\cdot}5$, as might be expected from molecular considerations of conversion (for discussion

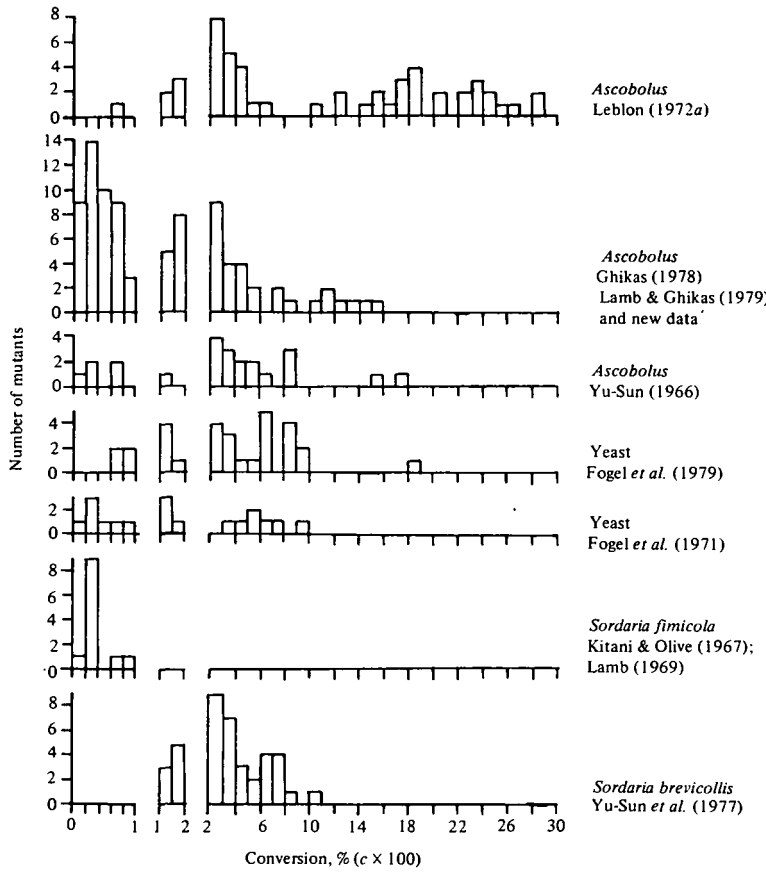

Fig. 1. Frequency distribution for conversion frequencies from a range of fungi.

of mechanisms, see Catcheside, 1977, and Fogel *et al.* 1979). There are differences between sets of data for *c* and *b*, such as the range of *b* values differing markedly between the data of Ghikas (1978) and Yu-Sun (1966) for the Pasadena strains of *Ascobolus immersus*, but those sets contain different proportions of spontaneous and induced mutations, and different proportions of mutations induced with different mutagens (e.g. UV and EMS, which induce base substitutions and frame-shifts; ICR, which mainly induces frame-shifts, and NMG, which mainly induces base substitutions – references in Yu-Sun, Wickramaratne & Whitehouse, 1977). The work of Leblon (1972*a*, *b*) and ourselves (see Helmi, 1980) using reversion to identify the molecular nature of mutants and comparing this with their conversion properties, shows that frame-shifts and base substitutions can both have highly significant disparities in conversion direction. In *Ascobolus*, Leblon (1972*a*) found that most ICR-induced mutations (probably frame-shifts) had much more conversion to mutant than to wild-type, while NMG-induced mutations (probably base

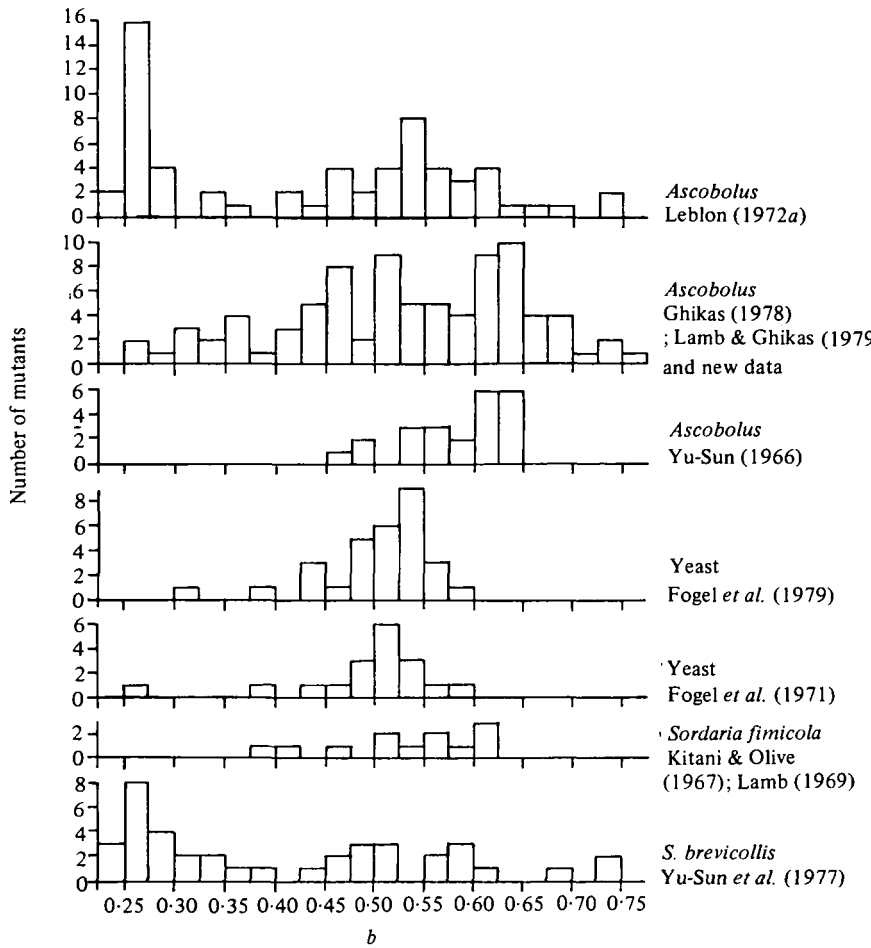

Fig. 2. Frequency distribution, from a range of fungi, for b, the frequency of a particular allele (wild-type or A here) in the products of meiotic tetrads or octads with aberrant segregation ratios. $b > 0{\cdot}5$ shows conversion disparity in favour of wild-type or A; $b < 0{\cdot}5$ shows disparity in favour of mutant or a.

substitutions) tended to have the opposite disparity, but very variable tendencies for each type of mutant were found in *Ascobolus* by Lamb & Ghikas, 1979. The *Ascobolus* data and the Yu-Sun *et al.* (1977) *Sordaria* data on the relation between a mutation's inducing agent, molecular nature and its conversion properties are discussed by Lamb & Ghikas, 1979.

The various c and b values were used to calculate y, the force acting on allele frequencies. The distributions, the means of the absolute values and the standard deviations of those means for y are shown in Table 1. The mean absolute values of y ranged from $1{\cdot}7 \times 10^{-4}$ in *Sordaria fimicola* to $1{\cdot}8 \times 10^{-2}$ in one of the *Ascobolus*

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Table 1. *Distribution of values of the conversion force, y, for various mutations in sets of fungal data**

Positive values of y							Negative values of y								
10^{-2} to 10^{-1}	10^{-3} to 10^{-2}	10^{-4} to 10^{-3}	10^{-5} to 10^{-4}	10^{-6} to 10^{-5}	0 to 10^{-6}	0	0 to 10^{-6}	10^{-6} to 10^{-5}	10^{-5} to 10^{-4}	10^{-4} to 10^{-3}	10^{-3} to 10^{-2}	10^{-2} to 10^{-1}	Total number of values	$\lvert\bar{y}\rvert$	σ of $\lvert\bar{y}\rvert$
Ascobolus immersus, European strains. Leblon, 1972															
6	13	9	0	0	0	0	0	0	0	3	8	23	62	$1{\cdot}76\times10^{-2}$	$2{\cdot}04\times10^{-2}$
Ascobolus immersus, Pasadena strains. Ghikas, 1978; Lamb & Ghikas, 1979; and new data															
6	21	19	6	0	0	3	0	0	1	17	13	0	86	$2{\cdot}90\times10^{-3}$	$4{\cdot}88\times10^{-3}$
Ascobolus immersus, Pasadena strains. Yu-Sun, 1966															
0	15	5	0	0	0	0	0	0	1	0	2	0	23	$3{\cdot}36\times10^{-3}$	$2{\cdot}99\times10^{-3}$
Saccharomyces cerevisiae, Fogel *et al.* 1979															
0	10	8	0	1	0	0	0	0	0	5	6	0	30	$1{\cdot}30\times10^{-3}$	$1{\cdot}25\times10^{-3}$
Saccharomyces cerevisiae, Fogel *et al.* 1971															
0	3	4	0	0	0	4	0	0	0	4	2	0	17	$9{\cdot}36\times10^{-4}$	$1{\cdot}77\times10^{-3}$
Sordaria fimicola, Kitani & Olive 1967; Lamb, 1969															
0	0	8	1	0	0	0	0	0	1	2	0	0	12	$1{\cdot}71\times10^{-4}$	$7{\cdot}35\times10^{-5}$
Sordaria brevicollis, Yu-Sun *et al.* 1977															
0	9	3	0	0	0	0	0	0	1	2	17	7	39	$6{\cdot}25\times10^{-3}$	$6{\cdot}16\times10^{-3}$

* $\lvert\bar{y}\rvert$ is the mean of the absolute values of y, and σ is its standard deviation. $y = c(b-0{\cdot}5)$.

Table 2. *Data from Pasadena strains of* Ascobolus immersus *on the stability of gene conversion parameters for two locus I mutations,* w*78 and* w*10**

Cross	Genetic control factor in +	Genetic control factor in *w*	Year of cross	Total asci	*c* †	*b* †
(*a*) Repeated crosses, same strains, similar time, *w*78						
53 + × EC11*w*78, 7 −	P	P	1976	3085	0·120 ± 0·006	0·599 ± 0·018
				3483	0·116 ± 0·006	0·609 ± 0·011
				2766	0·098 ± 0·006	0·613 ± 0·011
313 + × EC11*w*78, 7 −	P	P	1976	3014	0·119 ± 0·006	0·581 ± 0·012
				2831	0·145 ± 0·007	0·601 ± 0·017
				1544	0·148 ± 0·009	0·583 ± 0·023
U + × *w*78 −	P	K	1966	9433	0·019 ± 0·002	0·593 ± 0·026
				8901	0·018 ± 0·002	0·610 ± 0·027
(*b*) Repeated crosses, similar strains, different times, *w*78						
P5 − × 577*w*78 +	P	P	1966	8232	0·130 ± 0·004	0·647 ± 0·010
			1971	1480	0·093 ± 0·008	0·543 ± 0·030
			1971	2832	0·101 ± 0·006	0·555 ± 0·021
(*c*) Repeated crosses, similar strains, different times and/or different temperatures, w*10*						
P5 − × 415*w*10 +	P	P	1966	8661	0·132 ± 0·004	0·674 ± 0·010
			1971	2188	0·120 ± 0·007	0·605 ± 0·021
			1971	5637	0·101 ± 0·004	0·611 ± 0·014
			1972	2055	0·117 ± 0·007	0·635 ± 0·022
			1972	9661	0·174 ± 0·004	0·609 ± 0·008
			1972	18529	0·122 ± 0·003	0·650 ± 0·007
			1973	9827	0·129 ± 0·004	0·585 ± 0·010
			1973	15213	0·146 ± 0·003	0·601 ± 0·007
P5 − × 415*w*10 + at 10°	P	P	1967	29738	0·062 ± 0·002	0·593 ± 0·008
			1971	3512	0·050 ± 0·004	0·585 ± 0·026
			1972	6119	0·059 ± 0·003	0·596 ± 0·018
			1972	5503	0·052 ± 0·003	0·622 ± 0·020
P5 − × *w*10 +	P	K	1966	12067	0·030 ± 0·002	0·571 ± 0·018
			1971	6339	0·043 ± 0·003	0·435 ± 0·021
			1972	11695	0·032 ± 0·002	0·458 ± 0·018
P5 − × *w*10 + at 10°	P	K	1967	14463	0·022 ± 0·001	0·413 ± 0·020
			1971	3530	0·015 ± 0·002	0·349 ± 0·046

* Data of present authors and of Dr M. R. T. Wickramaratne; 1966 and 1967 results obtained in Professor S. Emerson's lab. at California Institute of Technology. Crosses were made at 17·5 °C unless otherwise stated.

† For definitions, see text; values are given ± S.E.

sets. Values of y in the range 1×10^{-5} to 3×10^{-2} and -1×10^{-4} to -7×10^{-2} were commonest, so gene conversion will usually have an appreciable effect on allele frequencies from meiosis in heterozygotes.

In our *Ascobolus* data, b values and the direction of disparity were properties of individual mutations, not of loci as a whole. For example, in P × P crosses at 17·5 °C, b values (with S.E.) for different alleles of locus I were: *w*10, 0·601 ± 0·007;

*w*78, 0·584 ± 0·005; *w*3C1, 0·391 ± 0·008; NG*w*5, 0·398 ± 0·022; *w*NG1, 0·446 ± 0·030; *w*Su$^+$, 0·668 ± 0·013. In the same crosses, *c* ranged from 0·080 ± 0·004 to 0·146 ± 0·003. Similar effects were found elsewhere e.g. in the *Sordaria brevicollis* data of Yu-Sun *et al.* 1977. For *grey*-3, *grey*-4 and *grey*-5, they found 3-fold differences in *c* for different alleles of the same locus, and *b* values ranged from extreme disparity in favour of wild-type to extreme disparity in favour of mutant, for alleles of the same locus.

For evolutionary aspects, it is important to know how stable the conversion parameter values are, but there seems to be no published work on this. We examined *Ascobolus immersus* data, accumulated over 14 years in our laboratory, for consistency of conversion properties for two locus I white ascospore mutations in $+ \times w$ crosses. Strains are vegetatively subcultured about twice a year but become sterile with time, so few pairs of strains remain crossable for more than a few years. Gene conversion at locus I is affected by at least three major conversion control sites, with the P/K/91 site closely linked to locus I (Lamb & Helmi, 1978). From Table 2(*a*) it can be seen that repeated crosses of the same strains at similar times gave fairly similar values for *c* and *b*, though with slightly more variation than expected by chance alone. The data for repeated crosses of similar strains (similar rather than identical, because of subculturing) made at different times are shown in Table 2(*b*) and (*c*). Variation for *c* and *b* both within years and between years was slightly more than expected by chance, perhaps due to imperfect environmental control. There were no consistent changes in *c* or *b* with time. At 17·5 °C, *w*10 and *w*78 consistently showed high *c* values and considerable disparity in favour of wild-type in all P × P crosses. The introduction of the K control factor into one parent in the 17·5° crosses greatly reduced *c* compared with P × P crosses, though by different amounts for *w*10 and *w*78; *b* values were unaffected for *w*78, but were reduced for *w*10, with a change in the direction of disparity in the later two results. Comparing the 10° and 17·5° results, low temperature approximately halved *c* in both P × P and P × K crosses, with little change in *b* for P × P crosses and a slight lowering of *b* in P × K crosses. These results show that *c* and *b* can be affected by genetic and environmental factors: see also Wickramaratne & Lamb, 1978, and Lamb & Helmi, 1978.

In conclusion, *c* and *b* were generally stable with time in given environmental conditions for given genotypes, but genetic factors could have large or small effects on these parameters, as could temperature. In populations, different individuals might therefore have different values of *c*, *b* and *y*.

5. THE EFFECTS OF GENE CONVERSION, MUTATION AND SELECTION ON ALLELE FREQUENCIES

The first situation considered is a large population with Hardy–Weinberg equilibrium conditions, including no selection, no fertility differences, no appreciable mutation or migration, and with random mating. Any non-zero value of *y* should then lead to fixation to the allele favoured by disparity in conversion direction.

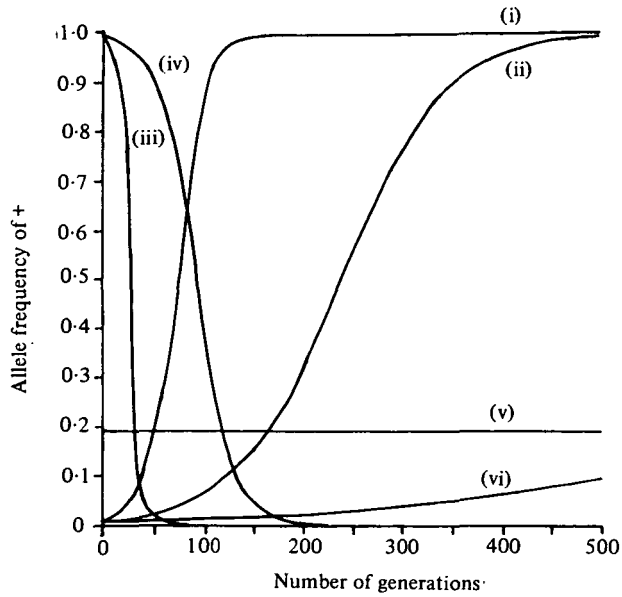

Fig. 3. Changes in allele frequencies with number of generations, from gene conversion in the absence of mutation and selection, calculated by using equation (1) repetitively. Random mating is assumed. (i) and (ii), *Ascobolus immersus*, new data, (i), +, *P*, $S \times w-78$, *P*, *S*, $c = 0{\cdot}27528$, $b = 0{\cdot}62389$, $y = 0{\cdot}0341$; (ii), +, *P*, non$S \times w-78$, *P*, non*S*, $c = 0{\cdot}11538$, $b = 0{\cdot}58408$, $y = 0{\cdot}0097$; (iii), *Ascobolus immersus*, Girard & Rossignol (1974), b_2, allele 130, $c = 0{\cdot}39296$, $b = 0{\cdot}23059$, $y = -0{\cdot}1059$; (iv), *Sordaria brevicollis*, Yu-Sun *et al.* (1977), YS50, $c = 0{\cdot}1030$, $b = 0{\cdot}2480$, $y = -0{\cdot}0260$; (v), yeast Fogel *et al.* (1971), *ura*1−1, $c = 0{\cdot}0359$, $b = 0{\cdot}5000$, $y = 0{\cdot}0000$; (vi), yeast, Fogel *et al.* (1971), *arg*4−1, $c = 0{\cdot}0594$, $b = 0{\cdot}5395$, $y = 0{\cdot}0024$.

Table 3. *Number of generations for gene conversion to change allele frequencies from* 0·05 *to* 0·95, *in the absence of mutation and selection, calculated by using equation* (1) *repetitively**

b	*c*								
	0	0·005	0·01	0·05	0·10	0·15	0·20	0·30	0·40
0·500	†	†	†	†	†	†	†	†	†
0·525	†	23556	11778	2356	1178	786	589	393	295
0·550	†	11778	5889	1178	589	393	295	197	148
0·575	†	7852	3926	786	393	262	197	131	99
0·600	†	5889	2945	589	295	197	148	99	74
0·625	†	4712	2356	472	236	158	118	79	59
0·650	†	3926	1963	393	197	131	99	66	50
0·675	†	3366	1683	337	169	113	85	57	43
0·700	†	2945	1473	295	148	99	74	50	37
0·725	†	2618	1309	262	131	88	66	44	33
0·750	†	2356	1178	236	118	79	59	40	30

* *b* values between 0·500 and 0·250 form the other half of a Table symmetric about the $b = 0{\cdot}500$ values, but changing allele frequencies from 0·95 to 0·05. Random mating is assumed.

† No change in allele frequencies as $y = 0$ if $c = 0$ and/or $b = 0{\cdot}5$.

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Except for genetic drift, which should be slight in a large population, changes in allele frequency with the number of generations should follow equation (1), or with less accuracy, equation (3). Fig. 3 shows the calculated changes in gene frequency using equation (1) for several fungal mutants, with experimentally determined values of c and b but with initial allele frequencies chosen for illustration. Polymorphism should only be retained if y is zero, which occurs if c and/or d are zero, as for case (v) in Fig. 3 where $b = 0{\cdot}5$.

To show the speeds with which conversion can alter allele frequencies, the numbers of generations required for gene conversion alone to change allele frequencies from 0·05 to 0·95 (a range including 'fast' and 'slow' regions of change) are shown in Table 3 for a range of c and b values. For values of c and b commonly found in fungi, such large changes take from less than 100 to a few thousand generations only. It is clear that for selectively neutral genes, in the absence of appreciable mutation, gene conversion is a powerful force in evolution, leading to fixation of the allele favoured by disparity in conversion direction. If mating is non-random, the effect of conversion is increased or decreased, depending whether the non-randomness increases or decreases, respectively, the proportion of heterozygotes.

The second situation considered is one with mutation and conversion, but no selection: any non-zero value of y will alter the equilibrium allele frequencies (indicated by the 'bar' symbol). Take the classic situation of mutations from A to a with frequency μ, and from a to A with frequency ν, which with no conversion gives at equilibrium:

$$\bar{p} = \frac{\nu}{\mu+\nu} \quad \text{and} \quad \bar{q} = \frac{\mu}{\mu+\nu}.$$

With random mating, the gain of A per generation from conversion is $2pqy$ and from mutation is νq, with loss from mutation of μp, so at equilibrium, when $\Delta p = 0$, one gets

$$\bar{p} = \frac{2y-\nu-\mu \pm \sqrt{[(v+\mu-2y)^2+8\nu y]}}{4y}, \tag{4}$$

which is equivalent to but more general than equation (8b) of Gutz & Leslie (1976).

With y having typical absolute values of 10^{-2} to 10^{-4} and mutation frequencies being in the range 10^{-5} to 10^{-8}, $\bar{p}$ and $\bar{q}$ will usually depend far more on conversion parameters than on mutation values: Watt (1972) pointed out the high frequency of non-reciprocal recombination in relation to mutation. Table 4 shows examples of the effects of y, μ and ν on $\bar{p}$, using equation (4). High positive and high negative values of y have profound effects on p over all normal ranges of μ and ν, and even very low values of y have appreciable effects, especially if μ and ν are not high. The simplifications when $\mu = 0$ or $\nu = 0$ were covered by Gutz & Leslie (1976).

The third situation considered includes selection as well as mutation and gene conversion. Crow (personal communication to Gutz & Leslie, 1976) pointed out that the algebra for gene conversion is similar to that for equal meiotic drive in both sexes; equations for interaction between meiotic drive and selection are given by

Table 4. *Effects of* y, μ *and* ν *values on equilibrium values,* $\bar{p}$, *calculated from equation* (4), *with just conversion and mutation*

y	$\mu = \nu = 10^{-5}$ both high $\bar{p}$	$\mu = \nu = 10^{-8}$ both low $\bar{p}$	$\mu \neq \nu$, $\mu = 10^{-5}$, $\nu = 10^{-7}$ $\bar{p}$
0·05	0·99990	0·9999999	0·999900
0·005	0·99900	0·9999990	0·999000
0·00005	0·90990	0·9999000	0·900111
0·0000005	0·51249	0·9901000	0·010976
0*	0·50000	0·5000000	0·009901
−0·0000005	0·48751	0·0099000	0·009016
−0·00005	0·09010	0·0001000	0·000909
−0·005	0·00100	0·0000010	0·000010
−0·05	0·00010	0·0000001	0·000001

* Values with $y = 0$ can not be calculated from equation (4), so the standard relation $\bar{p} = \nu/(\mu+\nu)$ was used.

Table 5. *Effects of* y *on equilibrium values,* $\bar{q}$, *for a deleterious recessive allele, calculated:* (*i*), *from equation* (5) *and* (*ii*), *from equation* (6), *with conversion, mutation and selection**

y	(i)(*a*) $\bar{q}$	(ii)(*a*) $\bar{q}$	(i)(*b*) $\bar{q}$	(ii)(*b*) $\bar{q}$
0·05	0·00010	0·00010	0·00010	0·00010
0·005	0·00099	0·00099	0·00100	0·00100
0·00005	0·00951	0·00951	0·06177	0·06180
0·0000005	0·01000	0·01000	0·09940	0·09950
0	0·01000	0·01000	0·10000	0·10000
−0·0000005	0·01000	0·01001	0·10044	0·10050
−0·00005	0·01051	0·01051	0·16171	0·16180
−0·005	0·10092	0·10099	0·99999	†
−0·05	0·91616	†	1·00000	†

* Both equations assume random mating. $\mu = 10^{-5}$ throughout. (*a*) s for $aa = 0{\cdot}1$; (b) $s = 0{\cdot}001$. $\nu = 10^{-7}$ in (i) for equation (5) but (ii), equation (6), assumes that $\nu q = 0$.

† No valid values produced: $\bar{q} > 1{\cdot}0$ because assumptions of rareness of a become invalid at high negative values of y.

Hiraizumi, Sandler & Crow, 1960, and Wright, 1969, but we wish to consider situations directly in terms of conversion parameters, especially y.

For a deleterious recessive, a, let the selection coefficient for aa be s, with $0 < s < 1$. In one generation, Δq is $\mu p - \nu q$ by mutation, $-2pqy$ by conversion and $[-sq^2(1-q)]/[1-sq^2]$ by selection. At equilibrium, when $\Delta q = 0$, it can be shown that

$$\bar{q}^4(2sy) - \bar{q}^3(2sy + \nu s + \mu s + s) - \bar{q}^2(2y - s - \mu s) + \bar{q}(\mu + \nu + 2y) - \mu = 0. \qquad (5)$$

Table 5(i), (*a*) and (*b*) shows the effects of different y values on $\bar{q}$ from equation (5), using particular μ, ν and s values, with large effects of y in the middle-to-upper parts of the positive and negative range found in fungi. A simplification, as used

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to obtain the classical relation $\bar{q} = \sqrt{(\mu/s)}$ when conversion is not considered, is to assume that when a is rare, $\nu q = 0$ and that selection approximates to $-sq^2(1-q)$. With conversion included, this gives:

$$\bar{q} = \frac{-2y \pm \sqrt{(4y^2 + 4s\mu)}}{2s}. \tag{6}$$

Table 5(ii)(*a*) and (*b*), based on equation (6), shows how drastically $\bar{q}$ can vary as y increasingly diverges from zero. Using the classic relation $\bar{q} = \sqrt{(\mu/s)}$ to determine μ or s is therefore subject to grave error unless y values are very small.

For a deleterious allele, A, with complete dominance, let the selection coefficient for AA and Aa be s, with $0 < s < 1$. In one generation, Δp is $\nu q - \mu p$ from mutation, $2pqy$ from conversion and $[-sp(1-p)^2]/[1-sp(2-p)]$ by selection. At equilibrium,

$$\begin{aligned}\bar{p}^4(2sy) + \bar{p}^3(s + s\nu + s\mu - 6sy) + \bar{p}^2(2y + 4sy - 2s - 3s\nu - 2s\mu) \\ + \bar{p}(s + \nu + \mu + 2s\nu - 2y) - \nu = 0.\end{aligned} \tag{7}$$

A simplification if A is rare is to assume that $\mu p = 0$ and that selection approximates to $-sp(1-p)^2$, which gives:

$$\bar{p} = \frac{s - 2y \pm \sqrt{[(2y-s)^2 - 4s\nu]}}{2s}. \tag{8}$$

When $y \geqslant 0$, equation (8) can give two values of $\bar{p}$ in the valid range between 0 and 1; e.g. for $y = 0{\cdot}005$, $s = 0{\cdot}1$, $\nu = 10^{-7}$, $\bar{p}$ values of 0·899999 and 0·0000011 are produced but the upper value should be discarded as equation (8) is only valid when p is very small. No valid values of $\bar{p}$ are obtained from (8) when $4s\nu > (2y-s)^2$, nor when $2y \geqslant s$: equation (7) is satisfactory in such cases.

Table 6(i), based on equation (7), shows how equilibria for a deleterious dominant vary with y for two values of s, 0·1 in (*a*), 0·001 in (*b*). Comparing Tables 5(*a*) and 6(i)(*a*), with the same s, μ and ν, it is clear that gene conversion has less effect on a deleterious dominant than on a deleterious recessive. Comparing Table 6(i)(*a*) and (*b*), y has greater effects on $\bar{p}$ when selection is less, so for only slightly deleterious dominant genes, conversion can still have very large effects on allele frequencies. The results in Tables 4, 5 and 6 were checked using the simulation program, which usually gave equilibrium values very close to those calculated. The very large differences between high and low positive values of y for a deleterious dominant (e.g. in Table 6(i)(*b*), the difference between the top two and the next two values of y) calculated from equation (7) were confirmed by simulation. Equation (7) occasionally gave more than one valid root, as shown for $y = 0{\cdot}005$ in Table 6(i)(*a*), where three valid roots occurred: see footnote† to Table 6. Simulation confirmed the upper and lower equilibrium points, which are stable, but the middle value represented an unstable equilibrium. With $s = 0{\cdot}1$, $\mu = 10^{-5}$, $\nu = 10^{-7}$ and $y = 0{\cdot}005$, initial p values from 0·0000001 to 0·9110019 gave $\bar{p}$ of 0·0000011, and initial p values from 0·9110020 to 0·999999 gave $\bar{p}$ of 0·998999, close to the calculated values from equation (7).

Table 6. *Effects of* y *on equilibrium values, with conversion, mutation and selection*: (i), $\bar{p}$ *for a deleterious and completely dominant allele, calculated from equation* (7); (ii), $\bar{q}$ *for a deleterious allele with no dominance, calculated from equation* (9)*

y	(i)(*a*) $\bar{p}$	(i)(*b*) $\bar{p}$	(ii)(*a*) $\bar{q}$	(ii)(*b*) $\bar{q}$
0·05	0·9999000	0·9999000	0·000050	0·000099
0·005	0·9989886			
	and	0·9989999	0·000091	0·000909
	0·0000011†			
0·00005	0·0000010	0·0001099	0·000100	0·009090
0·0000005	0·0000010	0·0001000	0·000100	0·009989
0	0·0000010	0·0001000	0·000100	0·010000
−0·0000005	0·0000010	0·0000989	0·000100	0·010009
−0·00005	0·0000010	0·0000901	0·000100	0·011110
−0·005	0·0000009	0·0000091	0·000111	0·999989
−0·05	0·0000005	0·0000010	0·022308	0·999999

* Both equations assume random mating; $\mu = 10^{-5}$, $\nu = 10^{-7}$. (i)(*a*), s for AA and $Aa = 0{\cdot}1$; (i)(*b*), s for AA and $Aa = 0{\cdot}001$; (ii)(*a*), s for $Aa = 0{\cdot}1$, s for $aa = 0{\cdot}2$; (ii)(*b*), s for $Aa = 0{\cdot}001$, s for $aa = 0{\cdot}002$.

† Equation (7) gave three real roots here, 0·9989886, 0·910931 and 0·0000011, with the middle value representing an unstable equilibrium. There are two stable equilibrium points for each y for a range of y values from about 0·0011 to 0·049.

For a deleterious gene, a, with no dominance, let selection coefficients be s for Aa and $2s$ for aa. In one generation, Δq is $\mu p - \nu q$ by mutation, $-2pqy$ by conversion and $[-sq(1-q)]/[1-2sq]$ by selection. At equilibrium,

$$\bar{q}^3(4sy) - \bar{q}^2(2s\mu + 2s\nu + s + 2y + 4sy) + \bar{q}(\mu + \nu + 2s\mu + s + 2y) - \mu = 0. \qquad (9)$$

A simplification if a is rare is to assume that $\nu q = 0$, when

$$\bar{q} = \frac{s + 2y + 2s\mu \pm \sqrt{[(s + 2y + 2s\mu)^2 - 16sy\mu]}.}{8sy} \qquad (10)$$

Table 6(ii), based on equation (9), shows how $\bar{q}$ for a deleterious allele with no dominance varies with y for two values of s, 0·1 in (*a*), 0·001 in (*b*). The effect of y on $\bar{q}$ is intermediate between the great impact on a deleterious recessive allele and the lesser impact on a deleterious dominant's allele frequency. The effects of conversion increase as s diminishes. The dramatic difference in $\bar{q}$ values at more strongly negative values of y (e.g. Table 6(ii)(*b*), $y = -0{\cdot}00005$ and $-0{\cdot}005$) was confirmed by simulation.

The equations so far are for selection at the diploid stage. In many fungi, such as *Ascobolus*, *Sordaria* and *Neurospora*, the diploid phase is extremely brief and selection probably occurs primarily in the haploid vegetative phase. For a haploid where allele a is deleterious, with selection coefficient s against a in the haploid phase only, one gets the equilibrium situation:

$$\bar{q}^3(sy) - \bar{q}^2(2y + s + \mu s + \nu s + 2sy) + \bar{q}(\mu + \nu + 2y + s + s\mu) - \mu = 0. \qquad (11)$$

Conversion then has major effects on allele frequencies when s is low, but lesser effects when selection coefficients are high. The situations in fungi with both diploid and haploid vegetative stages, and in haploids which can form heterokaryons, are more complicated.

The differences in $\bar{p}$ or $\bar{q}$ values from the accurate equations (5), (7) and (9), compared with the simplified equations (6), (8) and (10), respectively, are often small (e.g. compare Table 5(i) and (ii)) for the figures quoted, but the accurate versions give valid answers for a wider range of conditions. It is safer to use the accurate equations as they make fewer assumptions, and the differences between accurate and simplified equations can be much greater for different values, e.g. if ν is much larger in (5) or (9).

An anonymous referee suggested considering the interaction of conversion, selection and mutation in terms of 'effective fitness', where the changes in allele frequency from conversion in the heterozygote are treated as if they altered the fitness of the two homozygotes. Thus the present gene conversion equation (2) for Δp gives the same results as having 'effective fitness' of $1+2y$ for AA, 1 for Aa, $1-2y$ for aa; y may be positive or negative. In other words, the effect of gene conversion acting alone on gene frequency is the same as that of additive action on fitness, with A having selective advantage 2y. Although equations (5), (7) and (9) are the accurate, definitive ones, the 'effective fitness' approach gives much simpler equations for $\bar{p}$ or $\bar{q}$ in some circumstances, as follows. (i) When y and s are small, their selective advantages can be added together. (ii) s and the absolute value of y should be much larger than μ and ν: this is a serious limitation which means that the subsequent equations often do not work with low absolute values of y, where quite a few y values in Table 1 are not much higher, or are lower than, typical mutation frequencies. (iii) The equations can be derived from the 'effective fitness' relations or from equations (5) and (7) by taking the lowest order term (e.g. in (5), taking the $\bar{q}$ term but ignoring the $\bar{q}^4$, $\bar{q}^3$, and $\bar{q}^2$ terms) and within that term, ignoring small values (μ and ν in the $\bar{q}$ term in (5)): this gives a reasonable approximation if the relevant allele frequency (e.g. of q in (5)) is small.

In the resulting equations (Table 7), the unstable equilibrium condition (deleterious dominant, positive y, $2y < s$, no mutation) arises because 'effective fitnesses' give the equivalent of heterozygote disadvantage, while the stable equilibrium for a deleterious recessive, negative y, $2y > s > 0$) comes from the equivalent of heterozygote advantage. The equation $\bar{q} = \mu/2y$ for a deleterious recessive, positive y, with mutation, illustrates the strengths and weaknesses of the equations in Table 7: if one compares the accurate $\bar{q}$ results in Table 5(i) (*a*) and (*b*), from equation (5), with ones calculated from $\bar{q} = \mu/2y$, those from higher values of y (0·05, 0·005) give a good fit, with $\bar{q}$ not depending much on s, but for lower values of y (0·00005, 0·0000005) the fit is very poor and $\bar{q}$ does depend on $s-$ in this lower region, y is no longer much greater than both μ and ν. Some equations in Table 7 are very sensitive to values of y, working well for some, poorly for others, but the equation $\bar{p} = \nu/(s-2y)$ for a deleterious dominant, negative y, with mutation, works well over a wider range of y values.

Table 7. *Equations for interaction of gene conversion, selection and mutation, using the 'effective fitness' approach**

	Deleterious recessive			Deleterious dominant		
Genotype	*AA*	*Aa*	*aa*	*AA*	*Aa*	*aa*
Selective fitness	1	1	$1-s$	$1-s$	$1-s$	1
'Effective fitness'	$1+2y$	1	$1-2y-s$	$1+2y$	1	$1-2y+s$
	Positive y					
				$2y > s$		
	NM,† A fixed			NM, A fixed		
	M,† $\bar{q} = \mu/2y$			M, $\bar{q} = \mu/2y$		
				$2y < s$		
				NM, unstable equilibrium at $\bar{q} = 2y/s$: either allele may be fixed		
				M, unstable equilibrium at $\bar{q} = 2y/s$		
				Two stable equilibria, $\bar{q} = \mu/2y$ $\bar{p} = \nu/(s-2y)$		
	Negative y					
	$2y+s < 0$					
	NM, a fixed			NM, a fixed		
	M, $\bar{p} = -\nu/(2y+s)$			M, $\bar{p} = \nu/(s-2y)$		
	$2y+s > 0$					
	NM and M. Stable equilibrium with $\bar{q} = -2y/s$					

* See last part of text, section 5, for limitations of this approach, which cannot be used unless s and the absolute value of y are much greater than μ and ν, which is not always the case.

† NM = with no mutation; M = with mutation.

One big advantage of the equations in Table 7, from the 'effective fitness' approach, is that they bring out clearly the importance of the relationship between s and $2y$ in determining the relationships between $\bar{q}$ or $\bar{p}$ and y, which is not so easily seen from the accurate equations (5), (7) and (9), nor from Tables 5 and 6. Thus from Table 7, for a deleterious recessive there are obviously two discontinuities in slope for $\bar{q}$ as y decreases, firstly when y changes sign, and secondly when $2y+s$ changes sign, with different equations (Table 7) for the three different conditions. In the case of no dominance, there is a sharp step in the curve of equilibrium frequency against y as $s+2y$ changes sign.

The equilibria discussed in this work are generally stable, except for one case noted above, and there is usually only one equilibrium value for a given set of parameters, but for deleterious dominants in the region $0 < 2y < s$, there can be two equilibrium points for a given set of μ, ν, y and s values, as shown by the two different equations in Table 7 for a deleterious dominant, y positive, $2y > s$. Checking these two equations against values from equation (7) in Table 6 (i) (*a*) and (*b*), the equation $\bar{q} = \mu/2y$ gives a good fit only when y and $\bar{p}$ are high, but

$\bar{p} = \nu/(s-2y)$ gives a good fit only when y and $\bar{p}$ are low. For $s = 0{\cdot}1$, which gave two stable equilibrium points for $\bar{p}$ when $y = 0{\cdot}005$ in Table 6(i)(*a*), the equations in Table 7 give two stable equilibrium points for $\bar{p}$ over the range $0 < 2y < 0{\cdot}1$, that is, for y is positive and less than 0·05, while trials with the accurate equation (7) give two stable equilibrium points for each y value for y values roughly from 0·0011 to 0·049.

The present equations are for large populations with random mating but can be easily modified for non-random mating. For small populations, genetic drift would be an important factor and could accelerate or retard gene frequency changes due to conversion. A mathematical treatment of interactions between drift, conversion, selection and mutation is beyond the scope of this paper.

6. DISCUSSION

For values of conversion parameters typical of the fungal data, gene conversion must be an important factor in determining allele frequencies, and will usually be much more important than mutation pressure. Where alleles are selectively neutral or nearly so, the equilibrium frequency (or fixation or elimination) of an allele will be largely determined by whether it is favoured or disfavoured by the disparity in conversion direction. Where selection coefficients are not low, conversion properties will still have a large influence on the frequency of recessive alleles, but have less influence on a dominant allele. The extreme equilibrium frequencies calculated in some circumstances for large populations could become fixation or elimination by genetic drift.

The fungal data here are the best available for c, b, d and y. Limited data are available on c from higher organisms, e.g. in the work of Chovnick and others with *Drosophila* (see Watt, 1972; Gutz & Leslie, 1976), but figures obtained from detecting recombinants in heteroallelic crosses can seriously underestimate the true conversion frequency because co-conversion at the two sites gives no recombination between them. To assess the importance of conversion, one also needs to determine b (or to determine y directly from allele frequencies in meiotic products) which is not possible if selective methods detect only certain categories of conversion, such as only conversion to wild-type. Even if higher organisms should for some reason have lower conversion frequencies and/or smaller disparities than in fungi, conversion would still be an important long term factor, promoting the replacement of one allele by another, without causing any reduction in surviving offspring number, unlike selection. Conversion could thus speed up the replacement of one allele by another even if the allele promoted had no selective advantage, or even a slight selective disadvantage. This replacement, unlike ones caused by genetic drift, could occur as easily in large populations as in small ones.

The present analysis could be extended to mitotic conversion, but that is much less frequent, and likely to be much less important, than meiotic conversion. It could also be extended to multiple alleles at a locus, some aspects of which were dealt with by Watt (1972). The genetic functions of meiotic and mitotic gene

conversion are largely unknown and may differ for these two processes. Some interesting speculations summarized by Baltimore (1981) include maintaining the relative homogeneity of species-specific, interspersed repetitive DNA and of tandem gene families. He suggests that gene conversion may have played an extensive rôle in the evolution of mammalian immunoglobulin genes.

The molecular factors controlling disparity values and meiotic conversion frequencies are not fully understood, but conversion properties of a heterozygous site depend on the site, on the genome region and on the action of genetic and environmental factors controlling conversion (see Catcheside, 1977; Lamb & Helmi, 1978, and Helmi, 1980). Through co-conversion, 'hitch-hiking' effects are possible, and recombination between a pair of alleles and a linked *cis*-acting conversion control factor (e.g. the P/K/91 system controlling conversion at locus I in *Ascobolus*, Lamb & Helmi, 1978) could affect *b*, possibly even reversing the direction of disparity.

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