NATURAL SELECTION FOR SELECTIVELY DELETERIOUS TRAITS

Marion Cook
En Vignette, Echenevex, 01170 Gex, France

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ABSTRACT. A short-term advantage in terms of population dynamics arising from the presence of a rare gene deleterious to the individual, and hence detrimental to his family, is modelled. The advantage depends on the reduction in variance through time in mean fitness of a population. This can result in a higher long-term growth rate in a fluctuating environment compared to that for a population free of the deleterious gene. Although recurrent mutation is necessary to maintain such a gene in the population, this advantage persists if mutation rates are sufficiently low. The effect can be relatively strong where females are *XX* and males *XY* when a rare lethal gene is borne on the *X* chromosome.

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In a recent article on mutation, mean fitness and genetic load, Crow[1] reiterates the point that the great majority of mutations, except those very close to neutrality, are deleterious in the great majority of environments they will encounter. This raises the question, how does a natural population tolerate a high mutation rate?

In human populations the ubiquity of deleterious genes with lethal effect has been demonstrated by studies of the offspring of cousin marriages[2,3,4]. Techniques of detecting and partitioning the genetic load caused by inbreeding showed[2] that outwardly normal individuals carry a genetic load equivalent to that of approximately one to eight lethal genes which, if homozygous, would result in traits leading to early death.

The reason for the high frequency of these deleterious genes is not yet fully agreed on, although there is little question that they all arise originally through mutation[5]. Dobzhansky[6,7] was of the opinion that such genes may offer considerable advantage to their heterozygous carriers by producing some sort of hybrid vigour. According to this theory, a gene can be maintained in the population even though it gives rise to segregation load. Conversely, Muller[8,9] believed such genes produced no advantage of any kind, and that their frequency is now high because the usual effect of natural selection has been artificially reduced in modern society. Muller's theory predicts an increase in the mutational load of deleterious genes in accord with their mutation rate, unless they are selected against.

Is this genetic load just the price that has to be paid for the ability to respond to change or is there perhaps a reason for

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the recurrent mutation at certain genetic loci? It is thought by some (see ref. 10) that there may be no such thing as random or undirected mutation, mutations only being generated if and when needed. The argument below will be confined to mutation load.

Assume a newly mutated recessive gene, *d*, appears in a diploid carrier, *Dd*, that must mate in a wild-type population. This population if fairly constant in size has a longterm geometric mean fitness, *LGMF*, of one, each mating between two individuals producing on average two surviving offspring to compensate for the eventual loss of the parents. Of course some matings are less and some are more fruitful, and there is a range in family size from zero to many. A family with many offspring has a higher probability of preserving the newly mutated gene than a family with few offspring[5]. The chance, *c*, of losing the mutant gene *d* in the filial generation in a mating between the mutant carrier, *Dd*, and a wild-type, *DD*, depends on fitness, *f*, in terms of surviving offspring:

$$c = \frac{1}{2^f} \qquad (1)$$

If no offspring are produced or survive the mutant gene *d* will be lost, if there is one surviving offspring the probability of *d* being lost is 1/2, if two the probability is 1/4, and so on.

The same probability of losing the mutant gene applies when it is the dominant allele, *D*, and the wild-type is *dd*.

If the newly mutated gene were deleterious, the equation (1) dependent on family size would apply to the chance of offspring not inheriting the gene in a mating between a carrier, *Dd*, and a wild-type, assuming in the dominant case the gene was sub-lethal.

Fisher[11] has shown that after *n* generations the probability of a single neutral gene surviving, in the Wright-Fisher model, is only about $2/n$ where *n* is large.

The probability of a deleterious gene surviving would be even lower, since affected individuals are less likely to breed. The turnover rate of the deleterious gene at the *D* locus in the population under recurrent mutation would be rapid and the gene rare.

Consider now a large diploid population diallelic at each of two loci, the *D* locus with the rare deleterious gene requiring recurrent mutation for its maintenance in the population, and the *A* locus coding for general viability, not requiring recurrent mutation under fluctuating selection in a two-state environment, since the polymorphism is protected. Individuals from families that are the fittest in terms of surviving offspring will tend to possess the currently fitter allele at the *A* locus. Since the turnover rate of the rare deleterious gene at the *D* locus would be fast, carriers being mostly from large families would likewise tend to possess the currently fitter allele at the *A* locus.

At the *A* locus, each allele will tend to increase in frequency in the environment favouring it. This can cause fluctuations in population size. It has been found[12,13] that reduction in variance through time in mean fitness can lead to a higher *LGMF* of a population. If a proportion of individuals bearing the currently fitter allele at the *A* locus did not breed, the polymorphism could be buffered. A role for the rare deleterious gene at the *D* locus might lie here, since affected individuals might not survive to breed and would tend to possess the currently fitter *A* locus allele.

A diallelic locus such as the *A* locus affecting general viability has been modelled[14,15] (and see Models below). It was shown that where the fitness of a male in terms of offspring depended on the reproductive success of his mate there was additive variance in fitness in a two-state environment under fluctuating selection, the resulting polymorphism being protected. Indications were that the population fluctuated less in size when males from small families were more successful in attaining mates, and that this lower variance through time in mean fitness usually raised the *LGMF* [14]. With birds males from small clutches tend to be bigger in size[16] and more competitive than males from large clutches. Male competition is demonstrated in many ground lekking species, smaller males being pushed to the edge of the lek where they are prone to predation. A similar buffering effect could be provided in the absence of male competition by the *D* locus for the rare deleterious gene if affected individuals tended to be from large families, since few survive to breed.

The effect of a rare deleterious gene on population fitness when carried on the *X* chromosome and on an autosomal chromosome was modelled using computer simulations written in Turbo Pascal.

The Models

In the models males are assumed to contribute only genes to the next generation. Mating is random, and there is no kin selection, sib competition or male competition.

The population is assumed to be large. Generations are non-overlapping and discrete.

The two diallelic loci show complete dominance, there being no overdominance or partial dominance. The *A* locus determining general viability has a protected polymorphism under fluctuating selection in a two-state environment, while the *D* locus requires recurrent mutation to maintain the rare deleterious gene.

At the general viability locus the dominant genotype *A-* confers a fitness (b_d in the equations below) up to the time of mating on both males and females of b in environment one and b^{-1} in environment two, while the recessive genotype *aa* confers a fitness (b_r) of b^{-1} in environment one and b in environment two.

After mating the viability locus continues to affect reproductive success through its action on the female, *A-* conferring a fitness (f_d in the equations below) of f in environment one and f^{-1} in environment two, *aa* a fitness (f_r) of f^{-1} in environment one and f in environment two. Action of the viability locus on the male has no effect on his reproductive success after the time of mating.

To simplify the argument and highlight the maternal effect it is assumed that genes at the viability, *A*, locus have no effect on the young before independence or before mating, i.e. $b = 1$. For each population trajectory, the value of f giving a $LGMF = 1$ is first computed using the simulation below without mutation at the *D* locus, i.e. in the absence of the deleterious gene. Initial allele frequencies at the *A* locus are not important since the polymorphism is protected[14].

At the deleterious gene locus, mutation of the wild type gene to its deleterious allele is assumed to take place continuously. The reverse mutation is ignored since it usually occurs at a lower rate and because the frequency of the deleterious allele is so low. To simplify the equations presented below it is assumed that mutation only occurs in the wild genotype, either *DD* or *dd*, not in a carrier, *Dd*, and since the chance of two mutations occurring together is so small this possibility is ignored. These assumptions are reasonable at the low mutation rates used and do not affect the outcome. A constant mutation rate, u, is used throughout each computer run of a population trajectory.

The chance of the mutant gene not being passed on by a male or female carrier *Dd* to offspring is determined as in equations:

$$c_d = 1 / 2^{f_d} \qquad (2a)$$

$$c_r = 1 / 2^{f_r} \qquad (2b)$$

c_d being the chance the mutant gene at the *D* locus will be lost if an *A-* female is the mother, and c_r the chance if an *aa* female is the mother. Where maternal fitness is f^{-1} it is assumed that only one young survives in the occasional successful case, the probability of losing the mutant gene thus being 0.5.

Population trajectories are computed over cycles of n generations until allele frequencies settle into a repeating sequence, usually in fewer than 200 generations. The conditions cycle through $0.5n$ generations in environment one, in which a female genotype sees a fitness of f at the general viability, *A*, locus if the environment is favourable, or f^{-1} if unfavourable, and $0.5n$ generations in environment two, in which the female genotype experiences the alternate environment. The number of generations in each environment is considered identical to facilitate comparisons, but this is not a requisite. Selection, s, against the deleterious gene at the *D* locus is the same in both environments.

Deleterious Gene Locus on an Autosomal Chromosome

The effect of the *D* locus with the deleterious gene recessive or dominant, when linked to the *A* locus, is investigated. Males equal females in frequency throughout population trajectories.

Deleterious gene recessive

The frequency of $AD = G_0$, $Ad = G_1$, $aD = G_2$ and $ad = G_3$; and G_{00} represents the frequency of the diploid *ADAD*, G_{01} of *ADAd*, etc. Genotype frequencies are in Hardy-Weinberg ratios at the start of each generation, the sum, S, across frequencies being unity.

Genotypes surviving to breed are:

$$\begin{aligned}
G'_{00} &= b_d G_{00} & G'_{12} &= b_d G_{12} \\
G'_{01} &= b_d G_{01} & G'_{13} &= (1-s) b_d G_{13} \\
G'_{02} &= b_d G_{02} & G'_{22} &= b_r G_{22} \\
G'_{03} &= b_d G_{03} & G'_{23} &= b_r G_{23} \\
G'_{11} &= (1-s) b_d G_{11} & G'_{33} &= (1-s) b_r G_{33}
\end{aligned} \qquad (3)$$

in Fig. 1, $b = 1$, and selection against the genotype *dd* is total, $s = 1$, the recessive gene *d* being lethal in both environments.

These frequencies now are not Hardy-Weinberg ratios, $S' < 1$:

$$S' = G'_{00} + G'_{01} + G'_{02} + G'_{03} + G'_{11} + G'_{12} + G'_{13} + G'_{22} + G'_{23} + G'_{33} \qquad (4)$$

Female gamete frequencies are:

$$\begin{aligned}
G_{0fd} &= [(1-u(1-c_d))(2G'_{00}+G'_{02}) + (1+c_d)(G'_{01}+(1-r)G'_{03}+rG'_{12})] / 2 \\
G_{1fd} &= [(1-c_d)(G'_{01}+(1-r)G'_{12}+rG'_{03}+u(2G'_{00}+G'_{02})) + 2G'_{11} + G'_{13}] / 2 \\
G_{2fd} &= [(1-u(1-c_d))G'_{02} + (1+c_d)((1-r)G'_{12}+rG'_{03})] / 2 \\
G_{3fd} &= [(1-c_d)((1-r)G'_{03}+rG'_{12}+uG'_{02}) + G'_{13}] / 2 \\
G_{2fr} &= [(1-u(1-c_r))2G'_{22} + (1+c_r)G'_{23}] / 2 \\
G_{3fr} &= [(1-c_r)(G'_{23}+u2G'_{22}) + 2G'_{33}] / 2
\end{aligned} \qquad (5)$$

the subscripts *fd* and *fr* label gametes from *A-* and *aa* females respectively. Recombination, *r*, (0 indicating no crossing-over to 0.5) and mutation, *u*, are included. The chance of the mutant gene *d* surviving is $1 - c$, the *c* values used depending on the environment. These frequencies are not Hardy-Weinberg ratios.

Male gamete proportions are:

$$\begin{aligned}
G_{0md} &= [(1-u(1-c_d))(2G'_{00}+G'_{02}) + (1+c_d)(G'_{01}+(1-r)G'_{03}+rG'_{12})] / 2S' \\
G_{1md} &= [(1-c_d)(G'_{01}+(1-r)G'_{12}+rG'_{03}+u(2G'_{00}+G'_{02})) + 2G'_{11} + G'_{13}] / 2S' \\
G_{2md} &= [(1-u(1-c_d))(G'_{02}+2G'_{22}) + (1+c_d)((1-r)G'_{12}+rG'_{03}+G'_{23})] / 2S' \\
G_{3md} &= [(1-c_d)((1-r)G'_{03}+rG'_{12}+G'_{23}+u(G'_{02}+2G'_{22})) + G'_{13} + 2G'_{33}] / 2S'
\end{aligned} \qquad (6)$$

the subscript *m* labels male gametes. The chance of male mutant carriers *Dd* passing on the gene *d* depends on the female they mate with, e.g. G_{1md} contains the chance of male gamete *Ad* being passed on if mating is with an *A-* female, G_{1mr} if mating is with an *aa* female; G_{0mr}, G_{1mr}, etc. being calculated as in (6) by replacing c_d with c_r. In the union of gametes equation (7) below the male gamete frequency G_{1md} is used if fusion is with a G_{fd} type female gamete and G_{1mr} if fusion is with a G_{fr} type gamete. Although some males have not survived to breed, female reproductive success is not affected, and Hardy-Weinberg ratios are used.

Next comes the random union of gametes, the surviving zygotes depending on maternal fitness after mating:

$$
\begin{aligned}
G''_{00} &= f_d(G_{0fd} \times G_{0md}) \\
G''_{01} &= f_d(G_{0fd} \times G_{1md}) + f_d(G_{1fd} \times G_{0md}) \\
G''_{02} &= f_d(G_{0fd} \times G_{2md}) + f_d(G_{2fd} \times G_{0md}) + f_r(G_{2fr} \times G_{0mr}) \\
G''_{03} &= f_d(G_{0fd} \times G_{3md}) + f_d(G_{3fd} \times G_{0md}) + f_r(G_{3fr} \times G_{0mr}) \\
G''_{11} &= f_d(G_{1fd} \times G_{1md}) \\
G''_{12} &= f_d(G_{1fd} \times G_{2md}) + f_d(G_{2fd} \times G_{1md}) + f_r(G_{2fr} \times G_{1mr}) \\
G''_{13} &= f_d(G_{1fd} \times G_{3md}) + f_d(G_{3fd} \times G_{1md}) + f_r(G_{3fr} \times G_{1mr}) \\
G''_{22} &= f_d(G_{2fd} \times G_{2md}) + f_r(G_{2fr} \times G_{2mr}) \\
G''_{23} &= f_d(G_{2fd} \times G_{3md}) + f_d(G_{3fd} \times G_{2md}) + f_r(G_{2fr} \times G_{3mr}) + f_r(G_{3fr} \times G_{2mr}) \\
G''_{33} &= f_d(G_{3fd} \times G_{3md}) + f_r(G_{3fr} \times G_{3mr})
\end{aligned}
\qquad (7)
$$

f_d and f_r being the fitness of *A-* and *aa* females respectively after mating, *f* values used depend on the environment.

The size of the new generation, S", is calculated:

$$S'' = G''_{00} + G''_{01} + G''_{02} + G''_{03} + G''_{11} + G''_{12} + G''_{13} + G''_{22} + G''_{23} + G''_{33} \qquad (8)$$

Before starting selection on the new generation at equation (3), genotype frequencies are restored to Hardy-Weinberg ratios:

$$
\begin{aligned}
G_{00} &= G''_{00} / S'' & G_{12} &= G''_{12} / S'' \\
G_{01} &= G''_{01} / S'' & G_{13} &= G''_{13} / S'' \\
G_{02} &= G''_{02} / S'' & G_{22} &= G''_{22} / S'' \\
G_{03} &= G''_{03} / S'' & G_{23} &= G''_{23} / S'' \\
G_{11} &= G''_{11} / S'' & G_{33} &= G''_{33} / S''
\end{aligned}
\qquad (9)
$$

This recursion is repeated for $0.5n$ generations in each environment using appropriate *c* and *f* values. At the end of the first generation $S" = S_1$, at the end of the second, $S" = S_2$, etc.

At the end of the *n* generation cycle the *LGMF* is assessed:

$$LGMF = \sqrt[n]{S_1 \cdot S_2 \cdot S_3 \ldots S_n} \qquad (10)$$

The presence of the lethal gene under cycling conditions can raise the *LGMF* of the population by lowering the variance through time in mean fitness if there is linkage with the viability locus. In Fig. 1 the rate of mutation of *D* to *d* is 1×10^{-5}. The optimal rate of recombination when environments alternate is 0.2, and the optimal mutation rate around 1×10^{-6}, lower rates are also favourable but higher rates lower the *LGMF*. With longer environmental periods tighter linkage is favourable, and the optimal rate of mutation can be higher, up to 1×10^{-4} with cycles over 10 generations in length.

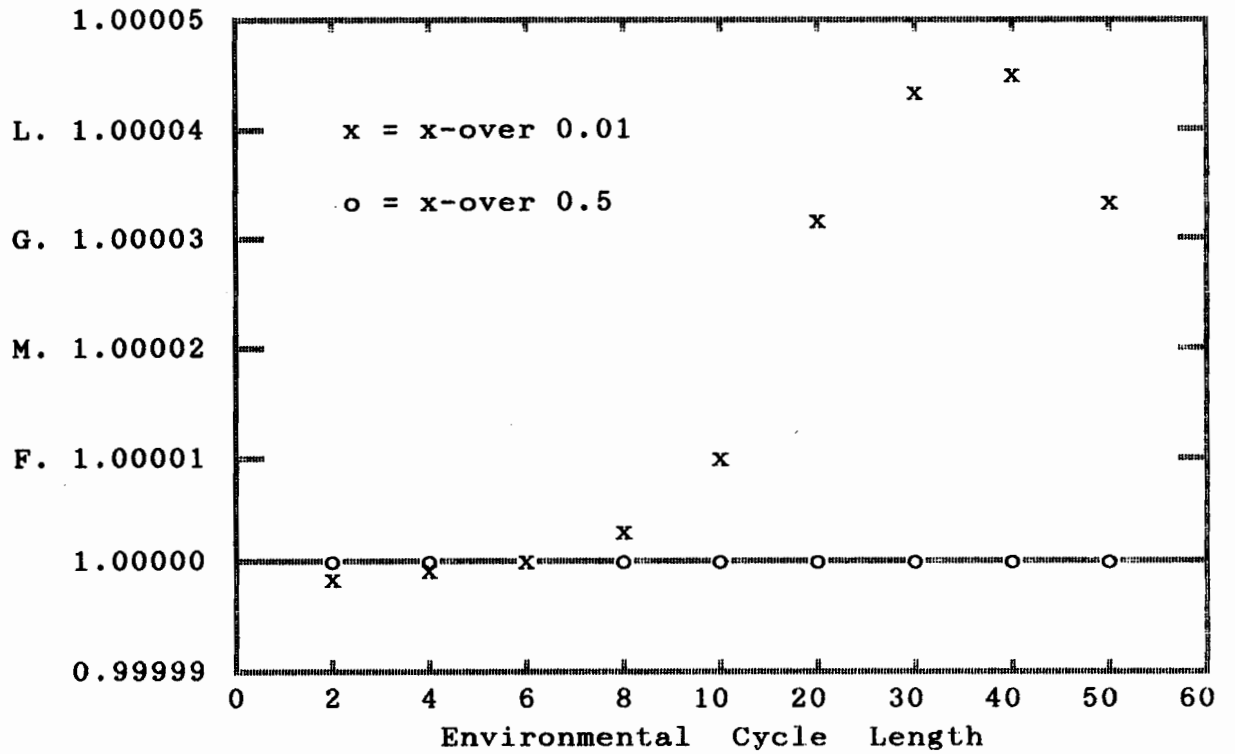

FIG. 1. The *LGMF* of the population when the deleterious locus is on an autosomal chromosome and the gene is recessive and lethal, s = 1. Environmental cycle length is in generations. Mutation is constant, $u = 1 \times 10^{-5}$. In the absence of the lethal gene the *LGMF* = 1. Free recombination slightly lowers the *LGMF* below 1.

Although the rise in *LGMF* appears small in Fig. 1, around 2×10^{-6}, it is relatively large when compared to the frequency of the lethal recessive *dd* in the population, around 1×10^{-7}. A mutation rate of 1×10^{-4} allows a *LGMF* > 1.0001 for cycles longer than 10 generations.

Under stochastic conditions only tight linkage with low mutation rates produces higher mean *LGMF* results than those for a lethal free population. To study stochastic effects a population with mutation for the deleterious gene *d* and a population without mutation for the deleterious gene *d* are run in parallel, without

interbreeding, and their respective *LGMF*s computed.

Higher *LGMF* values can be obtained if the deleterious gene *d* is assumed to be sub-lethal. As with mutation rates, this value cannot be too high or the deleterious gene will become common, and the chance factor not apply.

Deleterious gene dominant

Starting with Hardy-Weinberg ratios, S = 1 across genotype frequencies, genotypes surviving to breed are:

$$
\begin{aligned}
G'_{00} &= (1-s)\,b_d G_{00} & \qquad G'_{12} &= (1-s)\,b_d G_{12} \\
G'_{01} &= (1-s)\,b_d G_{01} & \qquad G'_{13} &= b_d G_{13} \\
G'_{02} &= (1-s)\,b_d G_{02} & \qquad G'_{22} &= (1-s)\,b_r G_{22} \\
G'_{03} &= (1-s)\,b_d G_{03} & \qquad G'_{23} &= (1-s)\,b_r G_{23} \\
G'_{11} &= b_d G_{11} & \qquad G'_{33} &= b_r G_{33}
\end{aligned}
\qquad (11)
$$

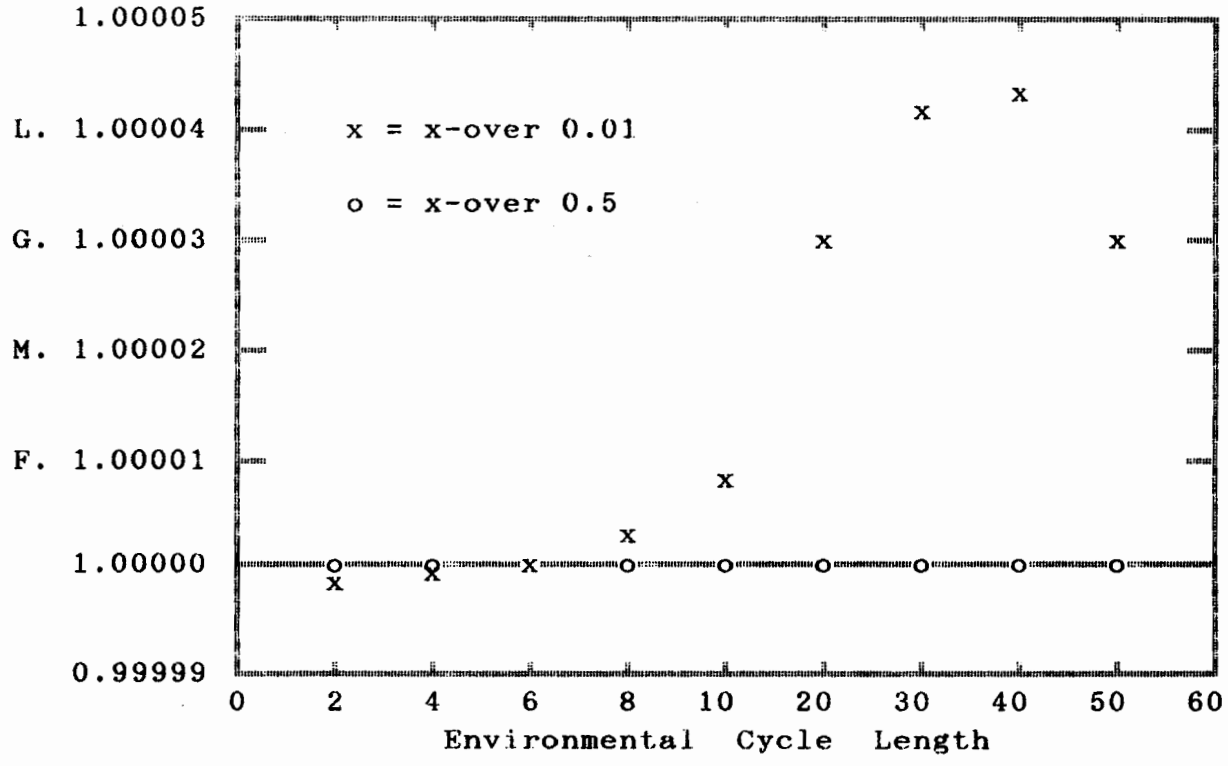

FIG. 2. The *LGMF* of the population when the deleterious gene is dominant and sub-lethal, s = 0.001. Mutation is constant, $u = 1 \times 10^{-5}$. In the absence of the deleterious gene the *LGMF* = 1. Free recombination slightly lowers the *LGMF* below 1.

Selection against the rare dominant genotype *D-* has to be low for the *LGMF* to be raised, and s = 0.001 is used in Fig. 2, the gene being sub-lethal in both environments.

Female gamete frequencies are:

$$
\begin{aligned}
G_{0fd} &= [2G'_{00} + (1-c_d)(G'_{01}+(1-r)G'_{03}+rG'_{12}+u(2G'_{11}+G'_{13})) + G'_{02}] / 2 \\
G_{1fd} &= [(1+c_d)(G'_{01}+rG'_{03}+(1-r)G'_{12}) + (1-u(1-c_d))(2G'_{11}+G'_{13})] / 2 \\
G_{2fd} &= [G'_{02} + (1-c_d)(rG'_{03}+(1-r)G'_{12}+uG'_{13})] / 2 \\
G_{3fd} &= [(1+c_d)((1-r)G'_{03}+rG'_{12}) + (1-u(1-c_d))G'_{13}] / 2 \\
G_{2fr} &= [2G'_{22} + (1-c_r)(G'_{23}+u2G'_{33})] / 2 \\
G_{3fr} &= [(1+c_r)G'_{23} + (1-u(1-c_r))2G'_{33}] / 2 \qquad (12)
\end{aligned}
$$

these frequencies are not Hardy-Weinberg ratios, S'< 1 (4).

Male gamete proportions are:

$$
\begin{aligned}
G_{0md} &= [2G'_{00} + (1-c_d)(G'_{01}+(1-r)G'_{03}+rG'_{12}+u(2G'_{11}+G'_{13})) + G'_{02}] / 2S' \\
G_{1md} &= [(1+c_d)(G'_{01}+rG'_{03}+(1-r)G'_{12}) + (1-u(1-c_d))(2G'_{11}+G'_{13})] / 2S' \\
G_{2md} &= [G'_{02} + (1-c_d)(rG'_{03}+(1-r)G'_{12}+u(G'_{13}+2G'_{33})+G'_{23}) + 2G'_{22}] / 2S' \\
G_{3md} &= [(1+c_d)((1-r)G'_{03}+rG'_{12}+G'_{23}) + (1-u(1-c_d))(G'_{13}+2G'_{33})] / 2S' \qquad (13)
\end{aligned}
$$

Hardy-Weinberg ratios are used, S' being obtained from (4). G_{0mr}, G_{1mr}, etc. are obtained by replacing c_d with c_r in (13).

Offspring are calculated from (7), and S" from (8).

The *LGMF* is assessed at the end of the cycle using (10).

Results (Fig. 2) are very similar to the recessive case. Linkage of the viability locus and the deleterious gene locus is again necessary to obtain a rise in the *LGMF*. The optimal rate of mutation of *d* to *D* can be high if selection, s, is low.

Lower rates of selection, $s < 0.001$, also allow the *LGMF* to be raised, but higher rates do not always do so.

On an autosomal chromosome a deleterious gene, *D* or *d*, at a locus linked to a viability locus, may thus raise the *LGMF* of a population, even though detrimental at the level of the family.

Deleterious Gene Locus on the X Chromosome

The rare deleterious gene at the *D* locus is assumed to be recessive and carried on the *X* chromosome only. First the *A* locus is considered to be carried on an autosomal chromosome, then on the *X* chromosome only. Although males equal females in frequency before selection, they do not do so after selection. It is assumed that this has no effect on female reproductive success, males being polygynous and all females mating.

Viability locus on an autosomal chromosome

Starting with Hardy-Weinberg ratios, S = 1, female genotypes *XX* surviving to breed are calculated from equation (3). Selection against the recessive genotype *dd* is total, s = 1 for Fig. 3, the gene being lethal in environment one and two.

Male genotypes XY surviving to breed are assessed, $G_{/0} = A$ and $G_{/2} = a$, the frequency of $AD/A = G_{0/0}$, $AD/a = G_{0/2}$, $Ad/A = G_{1/0}$, $G_{1/2} = Ad/a$, etc.:

$$\begin{aligned} G'_{0/0} &= b_d G_{0/0} & G'_{2/0} &= b_d G_{2/0} \\ G'_{0/2} &= b_d G_{0/2} & G'_{2/2} &= b_r G_{2/2} \\ G'_{1/0} &= (1-s) b_d G_{1/0} & G'_{3/0} &= (1-s) b_d G_{3/0} \\ G'_{1/2} &= (1-s) b_d G_{1/2} & G'_{3/2} &= (1-s) b_r G_{3/2} \end{aligned} \quad (14)$$

Selection is total, $s = 1$. Selection, being against the male genotype d, is relatively more intense than in the female.

Male genotype frequencies total:

$$S'_m = G'_{0/0} + G'_{0/2} + G'_{1/0} + G'_{1/2} + G'_{2/0} + G'_{2/2} + G'_{3/0} + G'_{3/2} \quad (15)$$

Female gamete frequencies are calculated from (5). These frequencies are not Hardy-Weinberg ratios, since dd females have not survived to breed. Segregation is involved here, not recombination, and the value used for r is 0.5.

Male gamete proportions are:

$$\begin{aligned} G_{0md} &= [(1-u(1-c_d))(G'_{0/0}+(1-r)G'_{0/2}+rG'_{2/0})] / 2S'_m \\ G_{1md} &= [G'_{1/0} + u(1-c_d)(G'_{0/0}+(1-r)G'_{0/2}+rG'_{2/0}) + (1-r)G'_{1/2} + rG'_{3/0}] / 2S'_m \\ G_{2md} &= [(1-u(1-c_d))((1-r)G'_{2/0}+G'_{2/2}+rG'_{0/2})] / 2S'_m \\ G_{3md} &= [(1-r)G'_{3/0} + u(1-c_d)((1-r)G'_{2/0}+rG'_{0/2}+G'_{2/2}) + G'_{3/2} + rG'_{1/2}] / 2S'_m \end{aligned} \quad (16a)$$

$$\begin{aligned} G_{/0m} &= [G'_{0/0} + (1-r)G'_{2/0} + rG'_{0/2} + G'_{1/0} + (1-r)G'_{3/0} + rG'_{1/2}] / 2S'_m \\ G_{/2m} &= [(1-r)G'_{0/2} + G'_{2/2} + rG'_{2/0} + (1-r)G'_{1/2} + rG'_{3/0} + G'_{3/2}] / 2S'_m \end{aligned} \quad (16b)$$

G_{0mr} etc. are calculated by replacing c_d with c_r in (16a). Male X (16a) and Y (16b) gametes are in Hardy-Weinberg ratios, $r = 0.5$.

Female offspring are calculated from (7).

Male offspring are:

$$\begin{aligned} G''_{0/0} &= f_d(G_{0fd} \times G_{/0m}) \\ G''_{0/2} &= f_d(G_{0fd} \times G_{/2m}) \\ G''_{1/0} &= f_d(G_{1fd} \times G_{/0m}) \\ G''_{1/2} &= f_d(G_{1fd} \times G_{/2m}) \\ G''_{2/0} &= f_d(G_{2fd} \times G_{/0m}) + f_r(G_{2fr} \times G_{/0m}) \\ G''_{2/2} &= f_d(G_{2fd} \times G_{/2m}) + f_r(G_{2fr} \times G_{/2m}) \\ G''_{3/0} &= f_d(G_{3fd} \times G_{/0m}) + f_r(G_{3fr} \times G_{/0m}) \\ G''_{3/2} &= f_d(G_{3fd} \times G_{/2m}) + f_r(G_{3fr} \times G_{/2m}) \end{aligned} \quad (17)$$

S" is calculated from female (8) or male offspring totals, which are identical. The *LGMF* is assessed at the cycle end (10).

The presence of the rare deleterious gene d raises the *LGMF* of a population by lowering the variance through time in mean

fitness if cycles are longer than two generations (Fig. 3). Under stochastic conditions higher mean *LGMF* values are obtained than for a lethal free population. Higher *LGMF* values can be obtained if the deleterious gene is assumed to be sub-lethal.

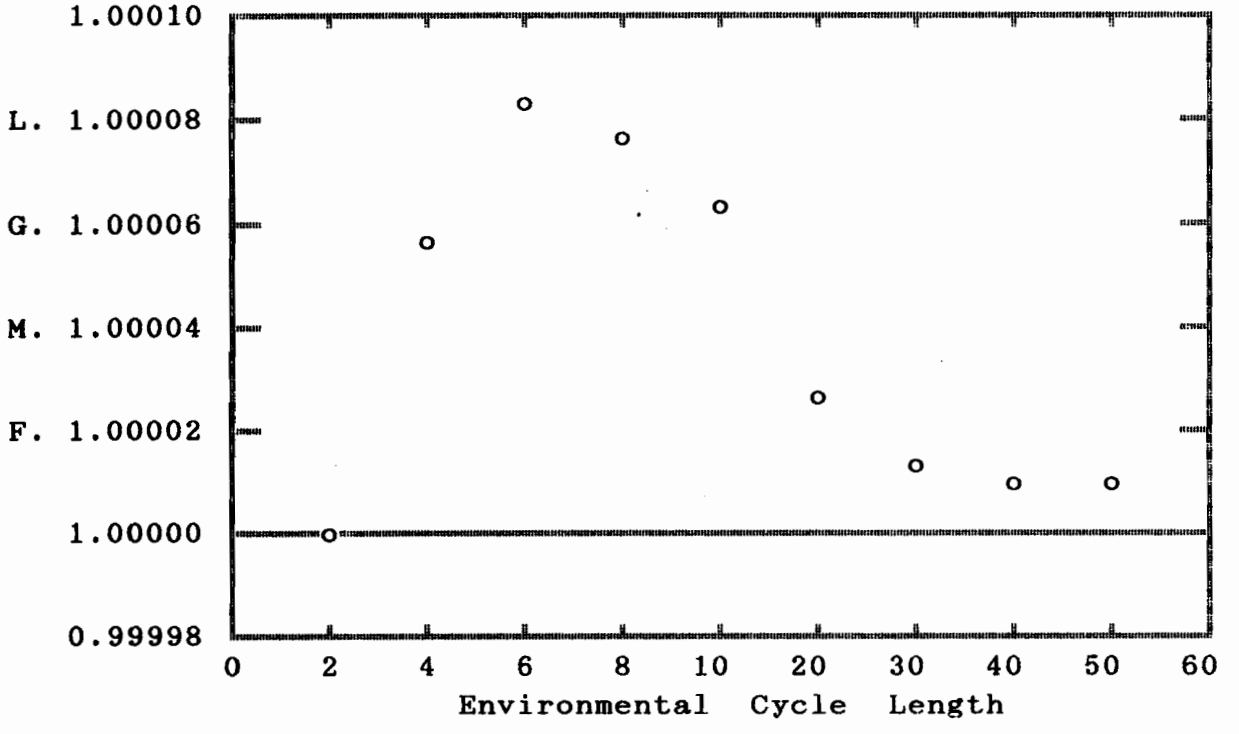

FIG. 3. The *LGMF* of the population when the viability locus is on an autosomal chromosome and the deleterious locus is on the *X* chromosome, the gene is recessive and lethal, s = 1. Segregation, not recombination, is involved. The rate of mutation is constant, $u = 1 \times 10^{-4}$. In the absence of the lethal gene the *LGMF* = 1.

Viability locus on the *X* chromosome

Starting with Hardy-Weinberg ratios, S = 1, female genotypes *XX* surviving to breed are calculated from equation (3); selection against the recessive genotype *dd* is total, s = 1 for Fig. 4, the gene being lethal in both environment one and two.

Male genotypes *XY* surviving to breed are calculated, the frequency of *AD/Y* = $G_{0/Y}$, *Ad/Y* = $G_{1/Y}$, *aD/Y* = $G_{2/Y}$ and *ad/Y* = $G_{3/Y}$, Y being the Y chromosome:

$$\begin{aligned} G'_{0/Y} &= b_d G_{0/Y} \\ G'_{1/Y} &= (1-s)\, b_d G_{1/Y} \\ G'_{2/Y} &= b_r G_{2/Y} \\ G'_{3/Y} &= (1-s)\, b_r G_{3/Y} \end{aligned} \qquad (18)$$

Selection is total, s = 1. Selection is relatively more intense than in the female, being against the male genotype *d*.

Male genotype frequencies total:

$$S'_m = G'_{0/Y} + G'_{1/Y} + G'_{2/Y} + G'_{3/Y} \qquad (19)$$

Female gamete frequencies are calculated from (5). These frequencies are not Hardy-Weinberg ratios, S'< 1, since *dd* females have not survived to reproduce.

Male gamete proportions are:

$$G_{0md} = [(1-u(1-c_d))G'_{0/Y}\ ] \ / \ 2S'_m$$
$$G_{1md} = [G'_{1/Y} + u(1-c_d)G'_{0/Y}] \ / \ 2S'_m$$
$$G_{2md} = [(1-u(1-c_d))G'_{2/Y}\ ] \ / \ 2S'_m$$
$$G_{3md} = [G'_{3/Y} + u(1-c_d)G'_{2/Y}] \ / \ 2S'_m \qquad (20a)$$

$$G_Y = [G'_{0/Y} + G'_{1/Y} + G'_{2/Y} + G'_{3/Y}] \ / \ 2S'_m \qquad (20b)$$

G_{0mr} etc. are calculated by replacing c_d with c_r in (20a). Male X (20a) and Y (20b) gamete proportions are Hardy-Weinberg ratios.

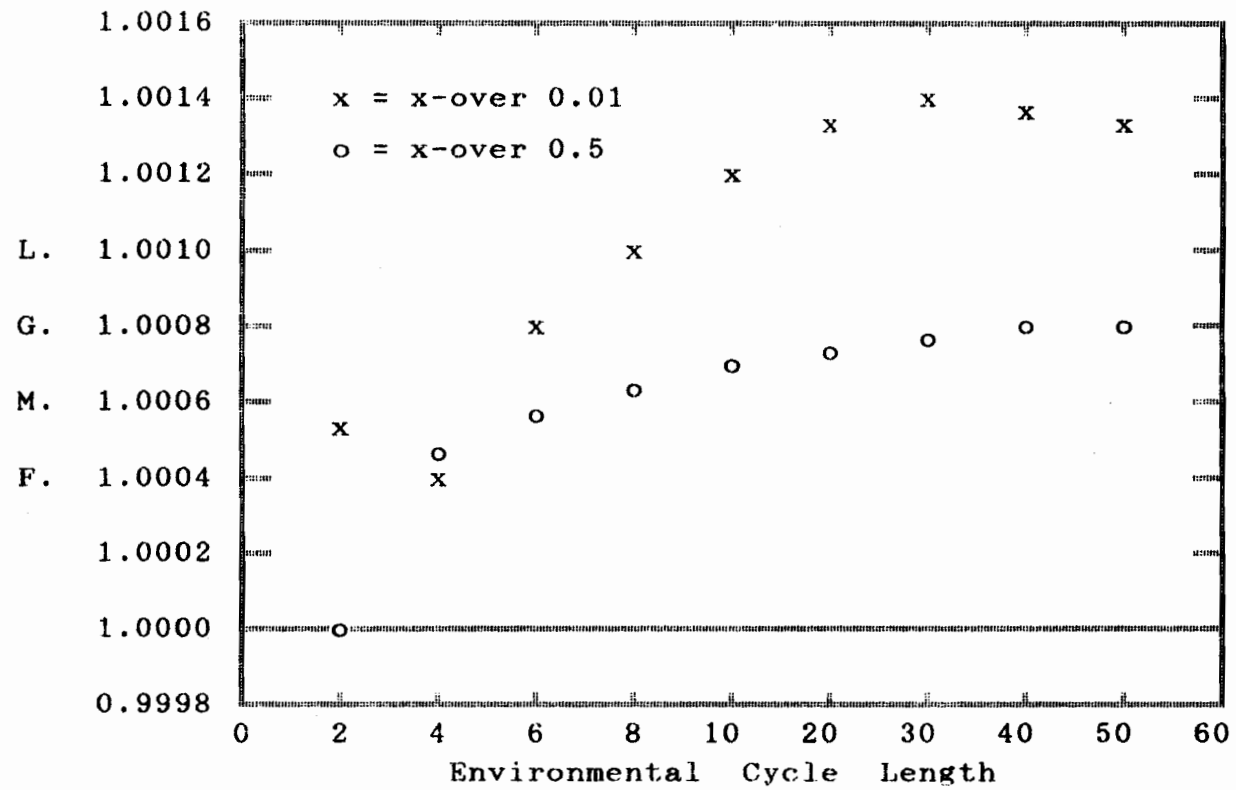

FIG. 4. The *LGMF* of the population when the viability locus and the deleterious locus are both on the X chromosome, the gene is recessive and lethal, s = 1. The rate of mutation is constant, $u = 1 \times 10^{-4}$. In the absence of the lethal gene the *LGMF* = 1.

Female offspring are calculated from (7).

Male offspring are:

$$G''_{0/0} = f_d(G_{0fd} \times G_Y)$$
$$G''_{1/0} = f_d(G_{1fd} \times G_Y)$$
$$G''_{2/0} = f_d(G_{2fd} \times G_Y) + f_r(G_{2fr} \times G_Y)$$
$$G''_{3/0} = f_d(G_{3fd} \times G_Y) + f_r(G_{3fr} \times G_Y) \qquad (21)$$

S" is calculated from female (8) or male offspring totals, which are identical. The *LGMF* is computed at the cycle end (10).

The advantage is relatively strong (Fig. 4) where the deleterious gene locus is linked to the viability locus. Linkage always raises the *LGMF* above 1, and free recombination also does if cycle length is longer than two generations. Under stochastic conditions the population with the lethal gene *d* does better on average than the lethal free population. Higher *LGMF* values can be obtained if the deleterious effect is sub-lethal.

Where the deleterious locus is carried on the *X* chromosome, two effects can act at the same time to raise the *LGMF* of the population; the deleterious gene can interact with all viability genes carried on autosomal chromosomes, and it can interact with any viability gene that might be carried on the *X* chromosome, the optimal rate of mutation being 1×10^{-4} in both cases.

Conclusion

The results indicate that a rare lethal or sub-lethal gene, even though always detrimental to the immediate family of an affected individual, can lower the variance through time in mean fitness of the population as a whole, leading to a higher LGMF. This buffering effect is particularly advantageous in terms of population dynamics when environmental cycles are long. The rare deleterious gene at the *D* locus tends to become associated with the currently fittest allele at the general viability, *A*, locus. Fitter families tend to be larger and are more likely to have the currently fittest *A* locus allele, but they also have a greater chance of passing on a rare mutant gene to their offspring. This damps down oscillations in gene frequencies, the *A* locus allele being lost along with the deleterious gene at the *D* locus.

Although the effect of a single deleterious gene locus appears slight, the effect of all such loci considered together might not be negligible, and could account for the persistence of such mutations. At present the total deleterious mutation rate remains unknown in any animal except *Drosophila*, and represents a major gap in the understanding of population genetics[1].

The possibility that deleterious genes may possess superior fitness in heterozygous conditions would not apply to the present findings. The advantage found depends on the probability of a rare deleterious gene being lost each generation. For this chance

factor to act over generations, continuous mutation is necessary. Of interest, the optimal mutation rates in the models are in accordance with those considered optimum for species survival[5].

Investigations of induced mutation led Wallace[17,18] and later Mukai[19,20] to propose that there is an optimum level of heterozygosity in a population. They found induced heterozygosity conferred a beneficial effect in highly homozygous populations, but a detrimental effect in populations with heterozygosity above a certain level (a level much lower than that found in most natural populations). Wallace considered overdominance of genes with mild effect to be responsible. Whether the present findings have any bearing on the Wallace-Mukai phenomenon, if real (for an overview see Crow[1]), remains to be determined. If they do, the models indicate that overdominance is not necessarily involved, and that lethal genes can play a similar role to deleterious genes with a mild effect.

The frequency of lethals in natural populations was noticed by Sturtevant (in ref. 21) to be lower than would be expected from known mutation rates with complete recessivity, suggesting partial dominance[1]. The mean persistence of lethals is estimated to be around 40 to 67 generations[1,22]. In the present models mutant genes are rapidly lost, in 40 to 80 generations depending on environmental cycle length, due to the chance factor involved in heterozygous carriers passing on the gene. Whether the mutant gene is recessive with a large effect or dominant with a mild effect makes little difference to the rate of loss. The models indicate that partial dominance is not necessarily involved, and this could account for the observation[1] that sub-lethals and lethals are lost from populations at similar rates.

With the Wallace-Mukai optimum heterozygosity theory in mind, it is a moot point as to whether the models would work so well in a multigenic heterozygous background (unless the detrimental effects found in such a background[17] were due to too high a level of induced mutation, in which case the chance factor could not act). Also, if the above findings were relevant to population dynamics, sub-lethal and lethal genes might be expected to be more common. There could be a more efficient buffering system.

One candidate for a more efficient system would be male homosexuality if genetically determined, since reproductivity would not be affected by the loss of females from the population, nor parental investment wasted by the loss of offspring from the family. Recent studies have suggested there might be a genetic component in human homosexuality. In particular Hamer *et al*[23] have identified a correlation between male sexual orientation and the inheritance of polymorphic markers on the X chromosome.

Preliminary investigations of the population dynamics of dominant and recessive autosomal genes and an X linked gene for male homosexuality give supportive results in each case. The

models presented above are relevant, but optimum mutation rates can be higher if females do not express the gene, and thus the *LGMF* greatly increased. Linkage is not always necessary in the autosomal case. The lower the proportion of homosexuals breeding, the greater the *LGMF* of the population. This is so even when homosexual males contribute in no direct way to the population's fitness. When they do contribute, especially if to the fitness of relatives, the *LGMF* is further greatly increased.

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