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# GENE INTERACTION AND THE RELATIONSHIP BETWEEN MUTATION AND GENETIC DEATH[1]

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Deleterious alleles, with the exceptions of completely dominant and completely recessive lethals, are variable in expression with regard to fitness, since they contribute to the genetic extinction of some carriers and not of others. In most cases the variability of expression of a deleterious allele probably has both genetic and non-genetic components; that is, gene interaction is not uncommon in genomes eliminated by selection. When two or more deleterious alleles interact to affect the fitness of a carrier more severely than the product of their individual effects, the population dynamics of mutational equilibria and genetic death rates are profoundly affected.

Depending upon the pervasiveness of gene interactions in components of fitness, the theoretical expectation of the total effects of induced mutation may be greatly reduced over formerly accepted expectations. The reduction in the predicted genetic death rate is very close to the reciprocal of

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the mean number of deleterious alleles contributing to each genetic death.

HALDANE (1937) indicated that the rate of genetic elimination of genomes [MULLER'S (1950) "genetic death" rate] at equilibrium was very close to (a) the sum of the mutation rates to complete recessives, plus (b) twice the sum of the mutation rates to complete or partial dominants, regardless of the severity of the effects of individual mutations. Subsequent thinking concerning the effects of induced mutation has been profoundly influenced by this proposed relationship. In particular, MULLER (e. g., 1950) has repeatedly emphasized that every mutation with any dominant harmful effect, however slight, is expected to cause an average of one "genetic death" upon its elimination from the population.

HALDANE based his calculations on the "average fitness" of each mutant allele, treating this value as an independent probability function. He did not consider genetic interactions, but stated that "one gene is destroyed for each individual eliminated by natural selection." Actually, of course, the entire genome is destroyed. If the mean number of deleterious alleles carried by individuals eliminated by selection differs by more than one from the mean of the population, the relationship between mutation and genetic death proposed by HALDANE does not hold.

MULLER (1950) seems to have been aware of this reservation, but rejected the likelihood of important amounts of genetic interaction when he wrote, "The number of mutant genes in different individuals form approximately a Poisson series. Those individuals who undergo genetic elimination,

constituting some 20 per cent or more of populations living in a state of genetic equilibrium, do not on the average have much more than one gene in excess of the survivors." There is no clear evidence to support this statement, however.

## THE GENETIC DEATH RATE

Since one genetic death may result in the removal from the population of more than one deleterious mutant allele, a mathematical statement of the relationship between mutation and genetic death must account for the entire diploid genome (the special case of sex-linked genes will not be considered in this presentation).

Let $Q$ be the total number of deleterious mutant alleles per individual genome in the adult population; for $2N$ loci with a gene frequency $q_i$ at each, $Q = 2N\bar{q} = 2\sum_{i=1}^{i=N} q_i$; the sum $Q + \Delta Q$ is the total number of deleterious alleles per genome in the class of genomes eliminated by natural selection--

$Q + \Delta Q = 2\sum_{i=1}^{i=N} (q_i + \Delta q_i)$, where $\Delta q_i$ is the excess in deleterious gene frequency at the $i$th locus in the class of all genomes eliminated by selection; $D$ is the rate of the selective elimination of genomes (genetic death rate); and $2N\langle\mu(1-q)\rangle$ is the total number of mutations per diploid genome per generation--

$2N\langle\mu(1-q)\rangle = 2\sum_{i=1}^{i=N} \mu_i(1-q_i)$. At genetic equilibrium the number of

deleterious alleles lost by natural selection is equal to the number produced by mutation:

$$Q = \frac{Q - D(Q + \Delta Q) + 2N \left\langle \mu(1-q) \right\rangle}{1 - D}.$$

The genetic death rate is

$$D = \frac{2N \left\langle \mu(1-q) \right\rangle}{\Delta Q}.$$

For dominant alleles that are completely independent in their effects on fitness, "those individuals who undergo genetic elimination ··· do not on the average have much more than one gene in excess of the survivors," that is, $\Delta Q \approx 1$.

If epistasis in components of fitness is common enough that $\Delta Q$ is significantly greater than one, the total death rate for a given mutation rate is correspondingly reduced. Mutant alleles with very small effects on fitness may be lost primarily as synergists of major mutations or as contributors to polygenic, quasi-continuous systems. In such circumstances this class of mutants would account for a smaller proportion of the genetic death rate than has been supposed.

## QUASI-CONTINUOUS COMPONENTS OF FITNESS

Quasi-continuous systems, which may be of major importance in the genetic variability of fitness, involve the interaction of many genes. The term quasi-continuous variation was introduced by GRÜNEBERG (1952) to describe polygenic developmental systems in which the normal phenotype is invariant over a broad range of genetic variation, and

sharply discontinuous beyond a genetic threshold. Such a system was first described by WRIGHT (1934); quasi-continuous systems with thresholds at either extreme of a range of genetic variability are said to be canalized (WADDINGTON 1953, 1957; RENDEL 1959). Developmental studies indicate that such systems may be quite common. Since normal development is an important component of fitness, it seems reasonable to ask whether a significant proportion of the genetic variability in fitness might be based in quasi-continuous systems, both morphological and physiological, and to explore the implications of such systems with regard to death rates and mutational equilibria.

Following WRIGHT (1934), one may conveniently consider quasi-continuous traits in terms of a normally distributed parameter that has genetic and nongenetic components of variance. Normal alleles are seen as each contributing additively to the parameter; deleterious alleles contribute either nothing or less than their normal counterparts. Genomes for which the value of the parameter falls below a minimum threshold are eliminated by selection. For quasi-continuous systems with $2N$ loci, where the parameter is measured in units of average effect of gene substitutions, the mean is $Q + 2N \left\langle \mu(1-q) \right\rangle$ units below $2N$.
The threshold is $z$ standard deviations below the mean.

Environmental effects, chance, and all other nongenetic sources of variability contribute to the variance of the parameter's distribution. The nongenetic, or chance, component is $\sigma_c^2$. The genetic component of variance can be subdivided into (a) genetic distribution, $\sigma_d^2$, which is the variance in the number of deleterious alleles per genome;

and (b) genetic effect, $\sigma_e^2$, which is the variance in the degree of effect of different gene substitutions. The total variance of the component is $\sigma_{cde}^2$, and the genetic component is $\sigma_{de}^2$ (Fig. 1).

The genetic death rate is $A_{(z)}$, the area of the unit normal distribution to the left of $2\sigma$ below the mean. The average number of deleterious alleles, in excess of the population mean, carried by genomes below the threshold ($\Delta Q$) is the contribution of $\sigma_d^2$ to subthreshold values:

$$\Delta Q = \frac{QY_{(z)}\sigma_d^2}{A_{(z)}\sigma_{cde}^2} ,$$

where $Y_{(z)}$ is the vertical coordinate on the unit normal distribution at $z$ standard deviations below the mean. The mean number of deleterious alleles lost by selection each generation, and hence the total mutation rate for the system at equilibrium, is

$$2N\langle\mu(1-q)\rangle = D\Delta Q = A_{(z)}\Delta Q = QY_{(z)}\left(\frac{\sigma_d^2}{\sigma_{cde}^2}\right).$$

The average negative effect of each of the alleles lost by selection, and hence that of new mutations at equilibrium, is $\frac{\sigma_{cde}^2}{\sigma_{cd}^2}$ relative to the average negative effect of deleterious alleles in the population. This relationship is consistent with the expectation that mutant alleles with smaller effects attain equilibrium gene frequencies that are higher, relative to their

mutation rates, than those attained by mutant alleles with more severe effects.

## EQUILIBRIUM GENE FREQUENCY

At individual loci, the equilibrium adult gene frequency, $q_i$, is a function of its mutation rate, $\mu_i$; the genetic death rate, D; and the difference, $\Delta q_i$, between $q_i$ and the gene frequency of the allele in genomes eliminated by selection (D and $\Delta q_i$ can refer to the total genetic death rate and gene frequency differential, or to the genetic death rate and gene frequency differential of an independent component of fitness).

$$q_i = \frac{q_i - D(q_i + \Delta q_i) + \mu_i(1-q_i)}{1 - D} = 1 - \frac{D\Delta q_i}{\mu_i} .$$

The mutation rate is $\mu_i = \frac{D\Delta q_i}{1-q_i}$ .

## SYNERGISM IN QUASI-CONTINUOUS SYSTEMS

If a deleterious allele in a quasi-continuous system were isolated and identified, its carriers would be found to have a fitness of less than one. The mean of the continuous parameter in the population of known carriers would be shifted toward the threshold, which is tantamount to shifting the threshold toward the mean. If the number of loci in the system were reasonably large, the variance would not be greatly affected. If the threshold were z standard deviations from the mean value of the parameter in the total population, the threshold would be only (z - e1) standard deviations from

the mean value of the parameter in the population of known carriers (where $e1$ is the effect of the known deleterious allele in standard deviations). The genetic death rates due to the system are equal to the area of the tail of the unit normal distribution below $z$ and $(z - e1)$ standard deviations, $A_{(z)}$ in the total population and $A_{(z-e1)}$ among known carriers. The fitness value derived by empirical observation would be

$$1 - s_1 = \frac{1 - A_{(z-e1)}}{1 - A_{(z)}} .$$

A second allele from the same quasi-continuous system would have a fitness of

$$1 - s_2 = \frac{1 - A_{(z-e2)}}{1-A_{(z)}} .$$

The two alleles together, on the hypothesis of independent action, would be expected to exhibit a fitness equal to the product of their individual fitnesses: $(1 - s_1)(1 - s_2)$. However, although their direct contributions to the continuous parameter are additive and independent, they act synergistically with respect to fitness (FRASER 1965) to produce a genetic death rate of $A_{(z-e1-e2)}$ and a combined fitness value of $\frac{1 - A_{(z-e1-e2)}}{1 - A_{(z)}}$. See Fig. 2.

Canalization. If there is an upper as well as a lower threshold, so that selective losses occur for high as well as

low values of the continuous parameter, the system is said to be canalized. In most systems mutations would probably occur predominantly in one direction, from active to inactive (although more symmetrical systems are conceivable). However, selective losses of inactive alleles at the lower threshold might regularly exceed new mutations, the equilibrium being maintained by corresponding selective losses of active alleles at the higher threshold. The result would be a stabilized polymorphism of inactive genes with frequencies higher than could be accounted for by mutation rates and empirical fitness coefficients alone. The relationship between the genetic death rate and the total mutation rate, $D = \frac{2N\langle\mu(1-q)\rangle}{\Delta Q}$, would continue to hold; the contribution to $\Delta Q$ from deaths above the higher threshold would, however, be negative. Similarly, the gene frequency would continue to be $q_i = 1 - \frac{D\Delta q_i}{\mu_i}$ at equilibrium.

## PLEIOTROPY

Pleiotropy, the participation of a single gene in diverse developmental systems, is observed often enough to be taken as a general condition of development. The direct activity of the gene may not be multiple, although the possibility is not ruled out. Pleiotropic genes may be acting in the same way in different systems, or participate in genetic systems which interact with several other systems. An allele may be favorable in one system and unfavorable in another. In any case pleiotropy in components of fitness may greatly complicate the fate of genes in populations. Full

understanding of the dynamics of genes in populations must await full understanding of the dynamics of genes in development, an understanding which has hardly begun.

There is an additional important factor in the relationship between mutation and genetic death, not directly concerning gene interaction. In natural populations genetic variability in maternal ability is probably about as great as variability in other aspects of fitness. Genetic conditions affecting maternal ability cause twice as many "genetic deaths" per mutation as do genetic conditions affecting viability. In a stable population with a balanced sex ratio, the average number of mature offspring per mature female is two. A single dominant causing sterility or the death of infant offspring is responsible for two genetic deaths upon its selective removal from the population. One can consider these deaths to be the two offspring which failed to develop. Alternatively, one can consider one of the genetic deaths to be that of the affected female, functionally dead in an evolutionary sense. In that case, the other genetic death is that of male which would otherwise have been the father. This functional death is obvious in permanently or seasonally monagamous populations, but in any population the mean productivity of the males is similarly reduced.

In monagamous populations the same effect exists in the case of mutations affecting male productivity. Similar effects may exist in varying degrees for sex limited viability factor.

## SUMMARY

The total rate of genetic deaths per generation, D, is related to the total number of new deleterious mutations per genome, $2N\langle\mu(1-q)\rangle$, as follows:

$$D = \frac{2N\langle\mu(1-q)\rangle}{\Delta Q},$$

where $\Delta Q$ is the number of deleterious alleles, in excess of the adult population mean, that are present in diploid genomes eliminated by selection.

The number of deaths resulting from a given mutation rate is less than heretofore supposed by approximately the degree to which $\Delta Q$ exceeds 1, which is a measure of the degree to which synergistic action of deleterious alleles occurs. There is some evidence that $\Delta Q$ may in fact be significantly greater than 1, and this is certainly the case if quasi-continuous variabiability is a significant component of the variability of fitness of populations.

Mutational equilibria are also affected by gene interaction. At equilibrium

$$q_i = 1 - \frac{D\Delta q_i}{\mu_i},$$

where $q$ is the adult gene frequency of a deleterious allele at the ith locus, $(q_i + \Delta q_i)$ is the gene frequency of the allele in genomes eliminated by natural selection, D is the total

rate of selective elimination of genomes, and $\mu_i$ is the mutation rate.

Although genes within quasi-continuous (threshold) systems may contribute additively to a developmental parameter, their effects on fitness are strongly synergistic. Selective losses from such systems may regularly involve the interaction of several deleterious alleles.

The above equations hold for canalized systems, although contributions to $\Delta Q$ and $\Delta q_i$ from genetic eliminations at the two extremes of the canalized distribution differ in sign.

## ACKNOWLEDGMENT

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## FIGURE CAPTIONS

Fig. 1. The hypothetical underlying normal parameter of a quasi-continuous genetic system. The curves depicted are (1) genetic distribution component, variance $= \sigma_d^2$; (2) total genetic component, variance $= \sigma_{de}^2$; and total parameter, variance $= \sigma_{cde}^2$. Genomes for which the value of the parameter falls below the threshold at $-2\sigma$ are eliminated by natural selection; the genetic death rate for the system is the ratio of the tail area to the total area.

Fig. 2. Synergism in a quasi-continuous system. Top: Distribution and death rate in an outbred population. Center: Distribution and death rate in the class of individuals carrying an identified deleterious allele, which displaces the mean e1 standard deviations. Bottom: Distribution and death rate in the class of individuals carrying two identified deleterious alleles, which displace the mean e1 and e2 standard deviations respectively. The fundamental action of the two deleterious alleles is additive with respect to the parameter, but the effect on the genetic death rate is synergistic.

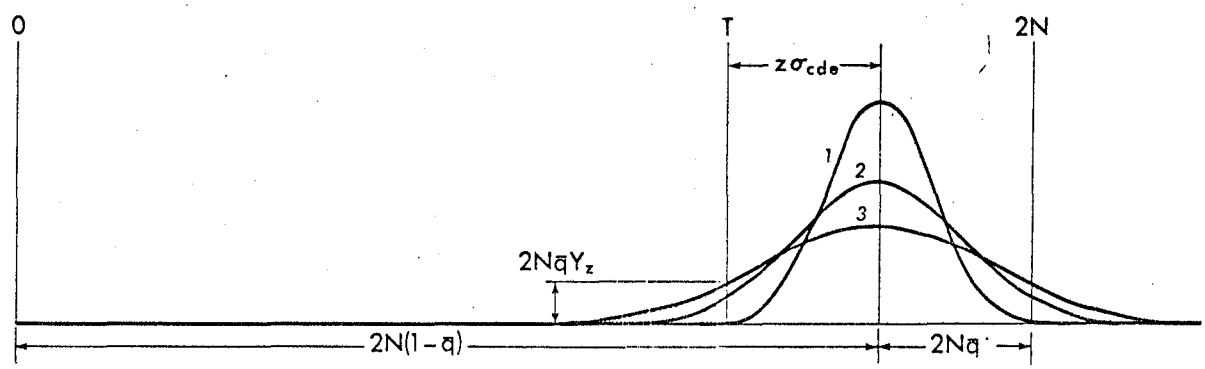


Fig. 1

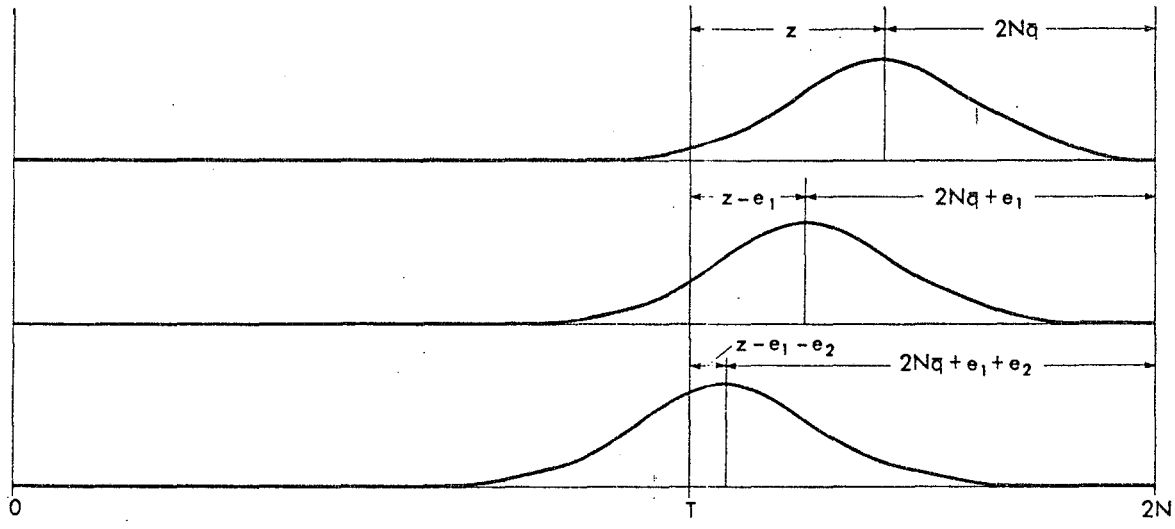


Fig. 2

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