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On Evolution in a Population with an Infinite Number of Types*

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1. Introduction

Since Fisher [6], a great deal of work has been done on the effects of mutation and selection on the genetic behavior of populations. Even the simplest case, that of a population determined by a single locus with a single pair of alleles, has yielded important results. Further research made on more complicated cases, involving two loci and maybe more than two alleles in each, revealed new characteristics. However, a deeper understanding of long-term evolutionary processes appears to require study of polygenic models involving many types for which the classical methods turn to be technically cumbersome and hardly useful. To this end the development of an infinite-locus, infinite-type model is technically the most feasible, and is further justified by the immense number of possible types theoretically offered by the chromosomal system. For certain situations such a course has already been taken by Kimura and Crow [11], Karlin [7, 10] and others.

The purpose of this paper is to formulate a model for an evolving population having an infinite number of types, to facilitate study of the classical problem of the long-term effects of mutation and selection on the genetic composition of a population. We shall begin with the simplest case, that of an asexual population, and then extend most of the results to a certain sexual and diploid model. We shall also observe some interesting, long-term quantitative effects of sex and diploidity over a many-type population.

2. The Model and Its Basic Properties

Consider a population with an infinite number of possible types. For convenience we shall identify the various types as points of a natural vectorial

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domain Ω reflecting certain measurable intrinsic features. We shall concentrate on changes in frequency distribution of the types in the population. More precisely, let A be any set in Ω, and let $\mu_t(A)$ denote the proportion of the population with types corresponding to A at generation t. Between generations t and $t+1$, selection and mutation pressures affect the population in the following manner:

(1) Consider selection first. Each individual of type x produces viable offspring of the same type x in quantity proportional to $\gamma(x, t)$; i.e., the ratio between the average number of viable offspring produced at time t by an x-type individual and that produced by a y-type individual is represented by

$$\frac{\gamma(x, t)}{\gamma(y, t)}.$$

Thus, after selection, the frequency of A-type individuals in the population will be proportional to $\int_A \gamma(x, t)\, \mu_t(dx)$, which is contributed to by all parents of types in A, and which, after normalization, may be written as

$$\mu_{t+1}(A) = \frac{\int_A \gamma(x, t)\, \mu_t(dx)}{\int_\Omega \gamma(x, t)\, \mu_t(dx)}. \tag{2.1}$$

(2) After selection, mutation can alter the type of the offspring, in accordance with a given intrinsic probability law. Formally writing, let $p_t(B; x)$ be the probability that an offspring of an x-type parent of generation t is altered in form so that of a type belonging to set B in Ω.

Under selection followed by mutation, a parent of type x produces viable offspring of types belonging in A in quantity proportional, on the average, to

$$\gamma(x, t)\, p_t(A, x).$$

The total number of A-type offspring is thus proportional to

$$\int_\Omega \gamma(x, t)\, p_t(A, x)\, \mu_t(dx)$$

which, after normalization and conversion to frequencies, becomes

$$\mu_{t+1}(A) = \frac{\int_\Omega \gamma(x, t)\, p_t(A, x)\, \mu_t(dx)}{\int_\Omega \gamma(x, t)\, \mu_t(dx)}. \tag{2.2}$$

In this paper we shall restrict our investigation to the one-dimensional case wherein the various types are characterized by a single measurable feature. For definiteness, Ω is identified with the real line. Within this restriction we shall concentrate on a most relevant "*fitness model*," in which the biological feature

(nonsexual) bacterias, about 10^{-6} among fungi, and 10^{-5} or more among mammals [13].

Comparisons of asexual and diploid systems which take into account refinements in the mutation law reveal new qualitative phenomena that may be crucial to an understanding of the evolution of diploidity. Since the long-term asymptotic rate of evolution depends solely on the mutation law, and not on the system, modifications to this law, even when only partially compensating the slow response of diploid systems to immediate change, *must be overcompensating in the long run* (see Figs. 3 and 4).

Roughly speaking, we may conclude that an asexual system is advantageous when rapid response to irregular environmental change is in order, though long-term evolutionary change is meager. This may be the case, for example, with some protozoa. The more stable diploid system, by contrast, in maintaining a higher mutation rate, gains the advantage whenever the "efficiency" of a long-term adaptation is crucial for the survival of the species, which is the case with all advanced forms of life.

Apart from "irregular" costs of evolution, which have been shown to be reduced by diploidity, we have tried also to examine the "regular" costs resulting from a slow, long-term adaptation. Since our concern is with the viability of a total population throughout the evolutionary process, rather than with rate of mortality per gene substitution, we have measured the relative "net" effect of the "regular" adaptation by comparing population size after t generations with and without mutations. In this case, we have seen (3.9) that even when most of the mutations are deleterious, and whatever the "relative cost" of evolution in the short term, mutations eventually prove profitable for sufficiently long periods of stationary adaptation, whether in asexual or diploid sexual systems (Sec. 4).

A very special but biologically interesting case of the model concerns mutation–selection balance. In this case, though the limit fitness distribution of the population depends heavily on the distribution of the mutations, the *limit average fitness of the population as a whole depends only on the rate μ of deleterious mutations per gamete per generation.* The degree of deleteriousness and its distribution among the nonneutral mutations does not affect their ultimate cumulative effect.

More precisely, we have seen that in an asexual population this cumulative effect tends exactly to a multiplicative factor $1 - \mu$, whereas in a random-mating diploid population the limit effect is simply $(1 - \mu)^2$, which is the frequency of nonmutants among all diploid offspring. For both systems we may conclude that the asymptotic effect of cumulative deleterious mutations is very slight—equal, indeed, to the effect of immediate death of all mutant offspring in a maximum-fit population.

stability under irregular short-term change that *enables* diploid systems to maintain a higher rate of mutation. This may lead in turn, as we shall see, to a higher asymptotic long-term rate of evolution, affording the population a better mechanism for coping with a long-term trend of environmental change.

Experimental data so far collected on the mutation rate in different populations seems to confirm this theoretical implication of the model. For example, a range of 10^{-7}–10^{-8} mutations per locus per generation was found among most

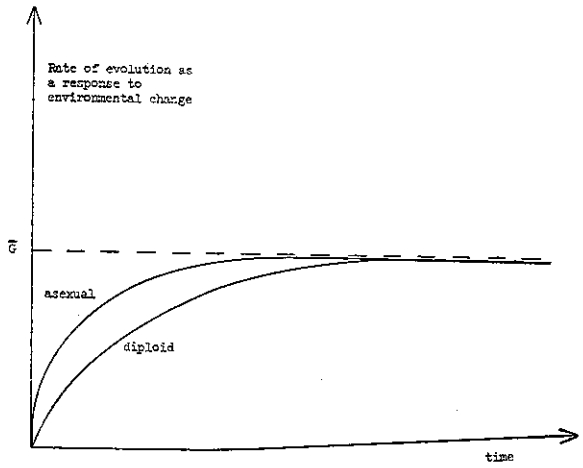

FIG. 3. Responses of a (sexual) population and an asexual population to environmental change, with both systems evolving under the same law of mutation.

The asexual system is quicker to respond (and may thus respond well even to temporal change). The long-term response to long-term change is asymptotically equal in both systems, depending only on the operant law of mutation.

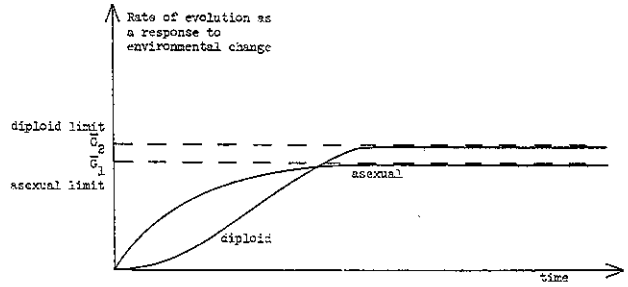

FIG. 4. Diploid and asexual responses to the same environmental change, where the diploid population's delay in immediate response is "compensated" by a higher rate of mutation.

The asymptotic long-term rate of evolution, being dependent on the law of mutation, is higher in the diploid system. Its relative "stability" under temporal change enables it to maintain a higher rate of mutation.

in question *is defined to be a particular measure of the intrinsic average rate of reproduction.* It is important to observe, however, that the same model may be applicable also to other specific biological features, provided they are *correlated* with the net rate of reproduction.

An intrinsic reproduction rate that varies from parent to offspring may reflect *various* genetic modifications. We assume, however, that the *ratio* between offspring and parent reproduction rates follows the same probabilistic law for all parental types; i.e., mutation has statistically the same *relative* effect on the reproduction rates of all types.

Equivalently, if we define, for convenience, the property measured by x to be a logarithmic function of the rate or reproduction, then the *difference* between a parent and its offspring has the same distribution $G(u)$ over the whole population. We call $G(u)$ the "distribution of the mutation." Stated formally, the probability of having an offspring belonging to a given class B is given by

$$p_t(B, u) = \int_B dG(x - u). \tag{2.3}$$

With respect to the particular measure of the x-property the reproduction rate of an x-type parent is given by

$$\gamma(x, t) = \lambda^x, \qquad (\lambda > 1). \tag{2.4}$$

The property of x, as here defined, will be called the *fitness property of the type.* A one-dimensional process with (2.3) and (2.4) will be called *a stationary-conditioned process.* Later we shall take up certain nonstationary processes where the mutation distributions $G_t(x)$ are allowed to vary with time.

The proportion among types for the one-dimensional case is conveniently measured by the frequency distribution $F_t(x)$ of the x-parameter over the population, i.e., the proportion of types $\leqslant x$ in generation t. Using (2.3) and (2.4), (2.2) becomes

$$F_{t+1}(x) = \frac{\int_{-\infty}^{\infty} \lambda^u G(x - u)\, dF_t(u)}{\int_{-\infty}^{\infty} \lambda^u\, dF_t(u)}. \tag{2.5}$$

We shall address ourselves principally to the following questions:

(1) What is the long-term development of the fitness distribution $F_t(x)$ in the population?

(2) More specifically, how do *average fitness* $E_t x \overset{\text{def}}{=} \int_{-\infty}^{\infty} x\, dF_t(x)$ and *fitness variance* $V_t(x) \overset{\text{def}}{=} \int_{-\infty}^{\infty} [x - E_t(x)]^2\, dF_t(x)$ change in time?

(3) What is the long-term effect of the mutation and selection forces on the average growth of the population?

(4) What is the asymptotic behavior of the centered distribution $F_t(x - E_t x)$ of types about their average fitness? More precisely, when the average fitness is constantly increasing (as we shall see), what proportion of the types fall within a certain fixed number of units about the average? Does this proportion tend to zero and does the population spread out? Or else, under what conditions does the sequence $\{F_t(x - E_t x)\}$ converge?

(5) In the case of convergence (which occurs quite generally), what determined the limit stable configuration of types about the average, and what are its basic properties basic properties? Especially, how is it influenced by the nature of the mutation distribution?

We shall examine in particular the special case of mutation–selection balance; i.e., the case wherein the average type remains in a fixed region, and we shall be concerned also with the limit configuration of types about the *initial* average, and hence with the long-term effect of mutation–selection balance on the efficiency of the population as a whole.

An explicit formula for the generating function of the fitness distribution $F_t(x)$ will be calculated in Section 3, and from this formula we shall deduce a variety of qualitative and quantitative conclusions for $F_t(x)$. The long-term effects of mutations on populations growth rate will also be determined, with implications for the "cost of evolution."

A good deal of the investigation is devoted to changes in average fitness $E_t x$ of the population. The one-generation change $E_{t+1}x - E_t x$ will be called the *rate of evolution* in generation t. Under plausible biological assumptions, it will be shown that this rate tends to a (finite) asymptotic limit if and only if the mutation change is bounded from above; i.e., if the relative advantage of an offspring over its parent is bounded. It will be shown further, where this is the case, that the asymptotic rate of evolution after many generations is equal to the maximal improvement due to mutation within a single generation, independent either of the parameter λ, ($\lambda > 1$) or of the initial distribution of fitnesses of the population.

We shall also see that under these conditions the population does not spread out; rather its variance $V_t(x)$ tends to a finite limit, and the centered distributions $F_t(x - E_t x)$, measuring relative fitnesses (as compared with the average), converge to a finite-variance limit distribution, which is independent of the initial distribution and can be expressed explicitly in terms of the mutation distribution (see Fig. 1).

An interesting relationship between the limit and mutation distributions is given by the *bounded load evolution theorem*, which furnishes us with the limit genetic load of the population as a simple function of probability of maximal-fit mutation. This same theorem will also provide us with a simple criteria for the genetic load to be bounded throughout the process.

of the population allowed us to deduce more general relations between various biological properties (such as genetic load) and basic properties of the mutation distribution.

We have also seen that the rate of evolution tends to a limit that depends simply on the maximal mutation change. Moreover, this limit rate of evolution was calculated (with a weaker average meaning) for cases where incidents of mutation occur periodically or randomly in time.

One interesting finding is that although the rate of evolution tends to the same limit in all asexual, haploid, random-mating diploid, or mixed random-mating and selfing systems; this rate is consistently higher, in any given generation, in the asexual population. It is lowest, on the other hand, in the random-mating diploid population, and it increases monotonically with the rate of selfing. In view of the prevalence of the diploid system in natural populations, and the effort so often made in nature to retard selfing rate, this striking result may contribute, from another point of view, to the suggestion of [4] that the chief evolutionary advantage of a sexual (and, here, diploid) system is not to ensure the population a faster rate of adaptation (as is often believed) but rather, quite the opposite, *to curb too-rapid genetic responses* to irregular and temporal environmental changes. The diploid property of preserving "nonadapted" genotypes longer clearly minimizes the "cost of evolution" imposed by such rapid responses. With long-term environmental changes and evolutionary adaptation, on the other hand, we saw that the slight advantage of the asexual system is in fact marginal, since the rate of evolution tends to the same limit in both systems. Here again, the prevalence of the diploid system may constitute indirect evidence for the importance of irregularity in environmental change throughout the course of evolution. The presumed higher survivability of the diploid system under irregular change may also be reflected in its markedly higher maintenance of variability. Analytically, this may be indicated by the ratio of maximal fitness to average fitness in the population, which in a diploid system tends precisely to the square of its limit in the haploid system.

It must be emphasized, however, that until now all quantitative and qualitative comparisons between sexual (diploid) and asexual (haploid) systems have been made under the simplistic postulate that *the law of mutation operates equally in both systems*. Considering the scale of differences between diploid and asexual species, this cannot be taken as more than a first approach to the subject. Further study must take into consideration the possibility of a significant difference in law of mutation between the two systems and must be based on careful analysis of experimental data. Furthermore, on the strength of the above theoretical results, *we can anticipate that differences in reproductive systems will demand modifications in the mutation law*. In the first place, it is conceivable that the relative delay in the diploid response to environmental change is at least partially compensated by a higher rate of mutation. It is, moreover, just this higher

Using the same methods, we may also prove that the variance of a bounded load process $\{F_t^q(x)\}$ (i.e., as before, a process with a strictly positive probability for the maximal mutation) tends to a finite limit for all $0 \leqslant q \leqslant 1$.

RESULTS. In any stationary diploid process of evolution (with the above restriction on the mutation distribution):

(1) The larger the selfing rate, the higher the average rate of evolution up to time t ($t = 1, 2, 3,...$); i.e., the average increase in mean fitness. This finding is more general than the others yielded by our model, since it holds, as we have seen, for *any* definition of fitness as an increasing function of the reproduction rate. In any case, the average rate of evolution will be less than that in an asexual system.

(2) This effect of the selfing rate (as well as that of the heterozygotic effect) is marginal, in the sense that the rate does not affect the limit average rate of evolution.

We shall take up later the possible biological meanings and implications of the unexpected findings (1) and (2).

5. SUMMARY AND DISCUSSION

The objective of this study has been to analyze, qualitatively and quantitatively, the behavior of an infinite-type population undergoing changes in "fitness" (or any equivalent adaptational property) as a result of mutation-selection pressures.

Though much of the work deals with the more easily treated asexual model, most of the results are qualitatively generalized to a haploid model as well as to a random-mating diploid model (Theorem 4.1). Some of the results have also proved valid for the more complex case of combined random and positive-assortative mating.

For all these systems, we have seen first that, assuming the initial fitness is bounded, a boundedness on possible genetic improvement in a single generation is mathematically equivalent to a bounded rate of evolution. Under these natural assumptions, we have seen that if the process is stationary (i.e., if environmental conditions are constant) throughout a considerable time, then the "relative fitness distribution" of the population tends to a limit that depends only on the specific mutation law.

On the other hand, where a population achieves a stable distribution of relative fitnesses, the feature of the mutation distribution maintaining this population composition is uniquely defined and not difficult to calculate.

An explicit identity relates the mutation law and the limit stable composition

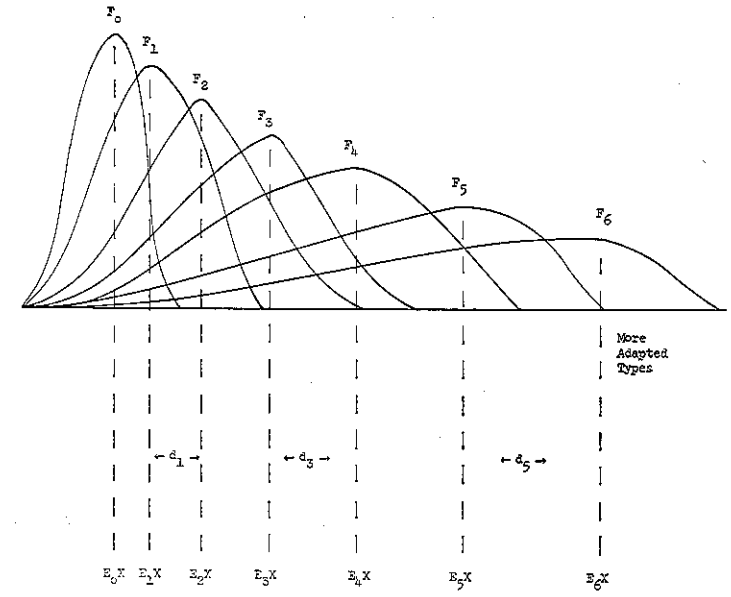

FIG. 1. Changes in type distribution in a population affected by mutation and selection pressures.

The distance d_t between the average type $E_t x$ of generation t and the average type $E_{t+1}x$ of the next generation, measuring the average change in the population in one generation, is the "rate of evolution" at time t. This rate of change tends to a fixed number that depends on the law of mutation alone. In addition, the distribution $F_t(x)$ of types in generation t tends to a stable "shape," shifting monotonically to the right as the total population becomes more adapted. Any stable shape is characteristic of a different law of mutation, which is essentially deducible from that shape.

Of special concern will be the case of *mutation selection balance*; i.e., the case in which *maximal adaptation* has already been achieved, so that the effect of any new mutation is either neutral or deleterious. It will be shown that under this condition the limit average rate of reproduction in the population (the classic fitness is its strict sense) is dependent only on the frequency of deleterious mutations, and not on the distribution of their deleterious effect. More precisely, the limit average rate of reproduction for the population is equal to that of the most fit individual in the population, when all its deleterious offspring are eliminated. Some theoretical results of this finding will also be taken up.

Almost all the above results will be extended in Section 4 to a certain sexual-diploid model. Quantitative differences between diploid and haploid populations will be carefully examined, with possible implications for the evolutionary advantage of diploidity and sex. Most of the mathematical proofs are omitted here, but will be given in a separate paper [2].

3. Asexual Processes

In order to study the fitness distributions $F_t(x)$ it is convenient to work with the associated generating functions

$$\varphi_t(s) = \int_{-\infty}^{\infty} s^x \, dF_t(x) \tag{3.1}$$

and

$$\psi(s) = \int_{-\infty}^{\infty} s^x \, dG(x).$$

The average reproduction rate in the population (in the sense how much does it "multiply" itself in one generation) is clearly proportional to

$$E_t\lambda^x = \int_{-\infty}^{\infty} \lambda^x \, dF_t(x) = \varphi_t(\lambda),$$

and we assume that $\varphi_t(\lambda) < \infty$. It is not difficult to establish that this condition holds for all t if and only if both the generating function $\varphi_0(s)$ of the initial population and the mutation generating function $\psi(s)$ are defined for all $1 \leqslant s < \infty$. From a biological point of view this assumption asserts in effect that individuals which differ too much in fitness either from the average of the population or from their parents are rare.

In terms of generating functions, (2.5) becomes

$$\begin{aligned}
\varphi_{t+\lambda}(s) &= \frac{1}{E_t\lambda^x} \int_{-\infty}^{\infty} s^x \, d\left\{\int_{-\infty}^{\infty} \lambda^u G(x-u) \, dF_t(u)\right\}, \\
&= \frac{1}{\varphi_t(\lambda)} \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} s^{x+u}\lambda^u \, dG(x) \, dF_t(u), \\
&= \frac{1}{\varphi_t(\lambda)} \int_{-\infty}^{\infty} \lambda^u s^u \, dF_t(u) \int_{-\infty}^{\infty} s^x \, dG(x), \\
&= \frac{\varphi_t(\lambda s)\,\psi(s)}{\varphi_t(\lambda)},
\end{aligned} \tag{3.3}$$

and, by iteration,

$$\varphi_t(s) = \frac{\varphi_0(\lambda^t s)}{\varphi_0(\lambda^t)} \prod_{k=0}^{t-1} \frac{\psi(\lambda^k s)}{\psi(\lambda^k)}. \tag{3.4}$$

For convenience, this relation may be written in symbolic form as

$$X_t = Z_t + \sum_{k=0}^{t-1} Y_k, \tag{3.5}$$

viability of the population in mutation–selection balance) is due to conservation of nonadapted genotypes. This result supports the suggestion (see the discussion and also [4]) that the main function of sexual systems is to protect the population against irregular environmental changes by maintaining a high genetic variability, even at the expense of a somewhat lower fitness in the near term.

Mixed assortation and random mating. The preceding analysis compared the extreme cases of random mating $\{F_t^{(0)}(x)\}$ and complete selfing $\{F_t^{(1)}(s)\}$ (or, equivalently, the asexual case $\{F_t(x)\}$). To study the general effect of the diploidity parameter q (and hence the selfing rate, which by (4.10) is readily given as a monotonic function of q), we state without a proof the following theorem.

Theorem 4.4. *With a given, empirically weak restriction on the mutation distribution (specifically, being an order-2 Polyá type*[1]*), for any increasing function $r(x)$ of the homozygotic fitness x, and at any given time $t = 1, 2, 3, \ldots$ the average value*

$$E\{r(x_t^q)\} = \int_{-\infty}^{\infty} r(x) \, dF_t^q(x)$$

of $r(x)$ in the population is larger when q is larger (and hence when the selfing rate p is larger).

As a special case of the theorem (choose $r(x) = x$), EX_t^q increases with q for all t. And by choosing $r(x) = \lambda^x$, we see that the average classical fitness $E\lambda^{x_t^q} = \varphi_t^q(\lambda)$ also increases with q.

More generally, for any definition of "fitness" as an increasing function of the viability (and thus of x_t^q), the "average fitness" in the population at any given time is increasing with q.

Corollary. *For all $0 \leqslant q \leqslant 1$,*

$$\frac{EX_t^q}{t} \xrightarrow{t\to\infty} \bar{G}, \tag{4.20}$$

i.e., the limit average rate of evolution is the same for all selfing rates and heterozygotic effects.

Proof. Since $EX_t^0 \leqslant EX_t^q \leqslant EX_t^1$ and

$$\lim_{t\to\infty} \frac{EX_t^0}{t} = \lim_{t\to\infty} \frac{EX_t^1}{t} = \bar{G},$$

the proof is immediate.

[1] For a definition of an order-2 Polyá function, see [8]. It should be mentioned, however, that the normal, Poisson, binomial, rectangular, γ and β distributions, as well as nearly all widely used distributions, are of Polyá density of order 2.

From this and (4.16) we get

$$E_F\gamma(u, v) = \theta\lambda^{\bar{F}_0}(1 - \mu)^2.$$

and the rest immediately follows.

COROLLARY. *Let ν be the genotypic mutation rate (i.e., the rate per genotype per generation). Then*

$$E_F\gamma(u, v) = (1 - \nu)\, W_{(\sup)} \tag{4.18}$$

Proof. Since $1 - \nu = (1 - \mu)^2$, the proof is immediate, from (4.17).

RESULT. The limit average viability in random-mating diploid mutation–selection balance is smaller by a factor $1 - \mu$ than that in haploid mutation–selection balance, provided the gametic mutation rate is the same in both cases. If the *genotypic* mutation rate is kept the same, then the two limit rates of reproduction are equal.

PROPOSITION 4.3. *The limit genetic load of a bounded load random-mating diploid population is given by*

$$L_\infty = \frac{1}{[p(Y = \bar{G})]^2} - 1. \tag{4.19}$$

Thus the limit ratio of maximal fitness over average fitness for such a population is equal to the square of this limit ratio in an asexual population, provided the gametic mutation rates are the same.

Proof. Since the genetic load is not affected by shifts in distribution, consider a mutation–selection balance process with mutation distribution $G(x + \bar{G})$. From the definition of L_∞ and Proposition 4.2 we have

$$\begin{aligned} L_\infty &= \frac{\sup\{\gamma(u, v) |\ u, v \leqslant \bar{F}\} - E_F\gamma(u, v)}{E_F\gamma(u, v)} \\ &= \frac{\theta\lambda^{\bar{F}_0}}{\theta\lambda^{\bar{F}_0}[p(Y - \bar{G} = 0)]^2} - 1 \\ &= \frac{1}{[p(Y = \bar{G})]^2} - 1. \end{aligned}$$

The second part of the proposition is immediately implied. Q.E.D.

Remark. We think it is of biological interest to point out that the higher genetic load maintained in a diploid population (as well as the slightly lower limit

where X_t is a random variable distributed as $F_t(x)$ [and thus characterized by the generating function $Es^{x_t} = \varphi_t(s)$] and Z_t and Y_k are random variables defined by their generating functions

$$Es^{Z_t} = \frac{\varphi_0(\lambda^t s)}{\varphi_0(\lambda^t)}; \qquad Es^{Y_k} = \frac{\psi(\lambda^k s)}{\psi(\lambda^k)}. \tag{3.6}$$

Intuitively, we see that X_t (the fitness random variable of generation t) describes the varied fitness of "random" individual taken from the population of generation t. And with (3.5) it becomes convenient to study the evolutionary process $\{F_t(s)\}$ through the law of the "fitness random variables" $\{X_t\}$.

To better understand the right side of (3.5), consider the simplest *pure selection* process of evolution; i.e., a process without mutations. Since in such a process $\psi(s) \equiv 1$, we have, from (3.4),

$$\varphi_t(s) = \frac{\varphi_0(\lambda^t s)}{\varphi(\lambda^t)} = Es^{Z_t}$$

or, equivalently, $X_t = Z_t$. In other words, Z_t describes a fitness process corresponding to pure selection with the initial distribution $F_0(x)$. In exactly the same way, Y_k describes the k-th-generation fitness random variable of a pure selection process, starting with the mutation distribution $G(x)$ as an initial fitness distribution.

It is not difficult to show that pure selection pushes the average type of the population toward the maximal-fit type. Let $\bar{F}_0$ be the maximal-fit type of the initial population and let $\bar{G}$ be the maximal possible mutation (i.e., the maximum of X_0 and Y_0). More generally, for any distribution $H(x)$, let

$$\bar{H} = \mathrm{Inf}\{x \mid H(x) = 1\}$$

denote the upper bound of a variable distributed as $H(x)$.

One may show, and it is intuitively clear, that $EZ_t \xrightarrow{t\to\infty} \bar{F}_0$ and $EY_k \xrightarrow{t\to\infty} \bar{G}$ Combining this fact and (3.5) we arrive at the following theorem

THEOREM 3.1. *Assume the initial fitness in the population is bounded* (i.e., $\bar{F}_0 < \infty$). *Then the rate of evolution tends to the value of the maximal possible mutation*

$$EX_{t+1} - EX_t \xrightarrow{t\to\infty} \bar{G}. \tag{3.7}$$

Manifestly, this is also true for the average rate

$$\frac{EX_t}{t} \to \bar{G}. \tag{3.8}$$

Proof. From (3.5) we obtain

$$EX_{t+1} - EX_t = EZ_{t+1} - EZ_t + EY_t .$$

We know already that

$$EZ_t \xrightarrow{t\to\infty} \bar{F}_0 ; \qquad EY_t \xrightarrow{t\to\infty} \bar{G}.$$

Thus

$$\lim_{t\to\infty}(EX_{t+1} - EX_t) = \bar{F}_0 - \bar{F}_0 + \bar{G} = \bar{G}.$$

The convergence of EX_t/t is implied by the convergence of the sequence $\{EX_{t+1} - EX_t\}$ (and obviously to the same limit). Q.E.D.

For biological applications we may assume that both initial fitness and maximal mutation are bounded; i.e., $\bar{F}_0 < \infty$ and $\bar{G} < \infty$. In this case, obviously, the maximal fitness in generation t, given by $\bar{F}_t = \bar{F}_0 + t\bar{G} < \infty$, will also be finite.

DEFINITION. A process of evolution with $F_0 < \infty$, $\bar{G} < \infty$ is said to be *regular*.

Theorem 3.1 asserts that in any regular process the limit rate of evolution (which is equal to the value of the maximal mutation) is independent of the initial distribution of types in the population or of the Malthusian growth rate λ.

Effect of mutations on population average growth rate. We have seen that the average growth rate of the population in generation t is proportional to $E\lambda^{X_t} = \varphi_t(\lambda)$. From (3.4) and (3.6) we have

$$\begin{aligned} E\lambda^{X_t} &= \frac{\varphi_0(\lambda^{t+1})}{\varphi_0(\lambda^t)} \prod_{k=0}^{t-1} \frac{\psi(\lambda^{k+1})}{\psi(\lambda^k)} , \\ &= E\lambda^{Z_t}\psi(\lambda^t). \end{aligned} \tag{3.9}$$

The first component, expressing the t-th-generation average growth rate under pure selection, tends to the value $\lambda^{\bar{F}_0}$, which is the maximal growth rate in the initial population. Thus we see that, for any initial population and environmental conditions, the t-th-generation expected growth rate of the population in the general case is proportional to $\psi(\lambda^t)$. The population relative growth rate in the first t generation is proportional to $\prod_{k=0}^{t-1}\psi(\lambda^k)$. This product thus expresses the cumulative mutational effect on the population of generation t.

Exploiting basic properties of generating functions, it is not difficult to show that if the probability of an advantageous mutation is positive (i.e., if $G(0) < 1$), then for t sufficiently *large*, $\prod_{k=0}^{t-1}\psi(\lambda^k) > 1$, and the long-term cumulative effect

extended to mother–fertility with the plausible mathematical assumption that it is also bounded.)

(3) Mutation–selection balance, in which the average gameter remains in a certain bounded region, is maintained if and only if all mutations are neutral or deleterious, but a proportion at least $1 - \mu > 0$ of the gametes suffer no mutation (or a neutral one).

In this case we know also that the average gamete tends to have a fixed homozygotic fitness, and the (noncentered) homozygotic-fitness distribution tends to a stable limit distribution. We know also that

$$\frac{\Phi(\lambda^{1/2})}{\lambda^{\bar{F}/2}} = 1 - \mu \tag{4.16}$$

when $\Phi(s) = \int s^x\, dF(x)$ is the limit generating function.

Remark. It must be emphasized that Theorem 4.1 deals only with properties of homozygotic fitness. Nonetheless, whenever the above mating system is given, the composition of the genotypic population is uniquely determined and may be calculated from the distribution of the gametes. Moreover, we may deduce, as in immediate result of Theorem 4.1, that the centered distribution of "genotypic fitnesses" in the population also converges, and that the limit rate of evolution, measured by change in the fitness of the average *genotype* in the population, tends to the value of the maximal mutation $\bar{G}$ as well. Yet since the genotypic fitnesses are not linearly dependent on the homozygotic fitnesses, results concerned with genetic load or average rate of reproduction cannot be immediately derived from Theorem 4.1.

PROPOSITION 4.2. *Let μ be the mutation rate per gamete per generation. Then in random-mating diploid mutation–selection balance, the limit average viability of the population is given by*

$$E_F\gamma(u, v) = \theta\lambda^{\bar{F}_0}(1-\mu)^2 = (1-\mu)^2 \sup_{u,v\leqslant\bar{F}_0} \lambda^{\sigma}(u, v) = (1-\mu)^2\, W_{(\sup)} , \tag{4.17}$$

where W stands, as before, for the "classic fitness" in the sense of growth rate and $W_{(\sup)}$ is the supremal fitness in the initial population.

Proof. In a random mating process,

$$\begin{aligned} E_F\gamma(u, v) &= \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} \gamma(u, v)\, dF(u)\, dF(v), \\ &= \theta \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} \lambda^{(u+v)/2}\, dF(u)\, dF(v), \\ &= \theta[\Phi(\lambda^{1/2})]^2. \end{aligned}$$

so that

$$\varphi_t^{(0)}(s) = \frac{\varphi_0(\lambda^{t/2}s)}{\varphi_0(\lambda^{1/2})} \prod_{k=0}^{t-1} \frac{\psi(\lambda^{k/2}s)}{\psi(\lambda^{k/2})}. \tag{4.13}$$

For complete selfing, on the other hand ($p = 1$; thus $q = 1$, for all $\theta > 0$), we get

$$\varphi_{t+1}^{(1)}(s) = \frac{\psi(s)\,\varphi_t^{(1)}(\lambda s)}{\varphi_t^{(1)}(\lambda)} \tag{4.14}$$

so that

$$\varphi_{t+1}^{(1)}(s) = \frac{\varphi_0(\lambda^t s)}{\varphi_0(\lambda^t)} \prod_{k=0}^{t-1} \frac{\psi(\lambda^k s)}{\psi(\lambda^k)}. \tag{4.15}$$

In (4.14) and (4.15) we easily recognize identities (3.3) and (3.4) of Section 3. The immediate application of this finding (by no means unexpected) is that from a long-term evolutional point of view a completely selfing diploid system is equivalent to an asexual one.

More interesting, no doubt, is the fact that (4.12) and (4.13), which determine the random-mating process of evolution, are obtained from (3.3) and (3.4), respectively, by a simple decrease of the Malthusian parameter λ to $\lambda^{1/2}$. We take up now the quantitative and qualitative implications of this phenomenon for the random-mating process of evolution.

Random-Mating Diploid Population

Theorem 4.1. *The homozygotic-fitness distributions $F_t^{(0)}(x)$ in randommating diploid evolution are equal to the fitness distributions $F_t(x)$ in an asexual process having the same mutation distribution and a Malthusian parameter $\lambda^{1/2}$.*

The proof is immediate from (4.12) and (3.4). For any random-mating diploid process we have, as special cases:

(1) The limit rate of evolution is identical to that in the related asexual process

$$EX_{t+1} - EX_t \xrightarrow{t\to\infty} \bar{G},$$

though the rate of approach to this limit differs in the two processes.

(2) The centered distribution $F_t(X - EX_t)$ of the gametes about the "average" gamete tends to a limit stable distribution $F(X)$ with a finite variance. (Here we draw upon the fact that the "homozygotic fitness," as defined, is always bounded and the process is thus "regular." The result may well be

of mutations on the population is always profitable. On the other hand, when the *average* mutation is deleterious, we may show that for t sufficiently *small*, $\prod_{k=0}^{t-1} \psi(\lambda^k) < 1$, and the short-term effect of mutations is deleterious.

In general, we may conclude that short-term "cost of evolution" due to a higher mortality among mutants is eventually compensated by an average improvement in the fitness in the population (see Fig. 2). (Note that the term "cost of evolution" here is intended merely as a measure of relative loss in the population due to the genetic changes it overgoes; it thus differs from Haldane's traditional connotation.)

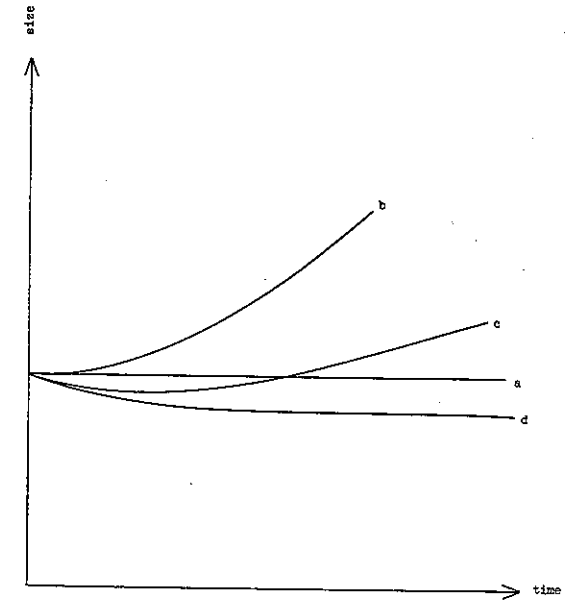

Fig. 2. Long-term effect of mutation on the "relative size" of a population.
The constant-value curve a describes the standard population size not subject to mutation. Curves b–d illustrate changes in relative sizes (with respect to the standard, a) in populations subjected to mutation. The convexity of all curves is a general mathematic truth. Curve b describes the theoretical case where the average mutation is initially advantageous. Curve d describes the case where *all* mutations are deleterious. Curve c indicates the case where the *average* mutation is deleterious but *some* mutations are advantageous; this very likely reflects the general case in nature.

Variance and convergence. Our purpose here will be to investigate the centered distribution of types about their average (i.e., the distribution of relative fitness in the population) and its asymptotic law as $t \to \infty$. The following theorem, which is crucially important to our model, can be proved from relations (3.4) and (3.5).

THEOREM 3.2. *The centered fitness distribution $F_t(X - EX_t)$ in a regular process of evolution (i.e., one with bounded initial fitness and bounded mutation) tends to a stable limit distribution $F(x)$ with a finite variance as $t \to \infty$. This limit distribution is dependent on the mutation distribution alone, and not on the initial fitness distribution.*

In other words, in the course of evolution, the proportion of types with "relative fitness" (i.e., with $X_t - EX_t$) in any given region tends to a fixed positive value. This value, like all asymptotic features of the process, is determined by the mutation law.

Theorems 3.1 and 3.2 assert that when mutation and selection pressures are time-homogeneous for a protracted period, the frequency distribution of relative fitnesses in the population tends to stability, where average improvement of the population as a whole is reflected by a steady shift of the absolute-fitness distribution to the right. This picture may be applicable for the case of long-term adaptation to a steadily changing environment.

Remark. Subject to the postulates of the model, one may readily demonstrate that in accordance with Fisher's fundamental law [6], the mean growth in the rate of reproduction, λ^x (i.e., the classical linear fitness) due to selection is nearly proportional to its variance. More precisely,

$$E\lambda^{x_{t+1}} - E\lambda^{x_t} = \operatorname{var}(\lambda^{x_t}) + [\psi'(1) - 1]\frac{E(\lambda^{2x_t})}{E\lambda^{x_t}}, \tag{3.11}$$

where the second term is relatively small measuring the immediate effect of last-generation mutation on the population. Unfortunately, Fischer's theorem is invalid for our "logarithmic" fitness model, and convergence of the mean growth rate thus does not imply convergence of the variance.

Let us now take any regular process $\{F_t(x)\}$; i.e., a process with bounded mutation and bounded fitness in the initial population, with $F(x)$ and $G(x)$ as the limit and mutation distributions, respectively. We denote their generating functions by $\Phi(s)$ and $\psi(s)$, respectively. In order to study the relations between the two distributions, we consider a new stable process $\{F_t^*(x)\}$ starting with the "stable" limit distribution $F(x)$ (i.e., $F_0^*(x) = F(x)$) and governed by the same mutation law (intuitively speaking, we seek to observe the process from a phase in which the limit distribution of relative fitness has already been reached). Let $\varphi_t^*(s)$ be the generating function of $F_t^*(x)$. Having defined $\varphi_0^*(s) = \Phi(s)$, we obtain, as a special case of (3.3),

$$\varphi_1^*(s) = \frac{\varphi_0^*(\lambda s)\,\psi(s)}{\varphi_0^*(\lambda)} = \frac{\Phi(\lambda s)\,\psi(s)}{\Phi(\lambda)}. \tag{3.12}$$

On the other hand, with $F(x)$ defined as a limit distribution of a process and G as

From this and (4.6) we have

$$\int_{-\infty}^{\infty} \gamma(x, y)\, dF_t^{\theta,p}(u \mid x) = p\lambda^x + (1 - p)\,\theta \int_{-\infty}^{\infty} \lambda^{(u+u)/2}\, dF_t^{\theta,p}(u)$$
$$= p\lambda^x + (1 - p)\,\theta\lambda^{x/2}\varphi_t^{\theta,p}(\lambda^{1/2}),$$

where $\varphi_t^{\theta,p}(s) \overset{\text{def}}{=} \int_{-\infty}^{\infty} s^x\, dF^{\theta,p}(x)$ is the generating function of $F_t^{\theta,p}(x)$. Substituting this result in (4.3) and (4.4) it is not difficult to show that

$$F_{t+1}^{\theta,p}(x) \propto p\int_{-\infty}^{\infty} \lambda^u G(x - u)\, dF_t^{\theta,p}(u) + \theta(1 - p)\,\varphi_t^{\theta,p}(\lambda^{1/2}) \int_{-\infty}^{\infty} \lambda^{u/2} G(x - u)\, dF_t^{\theta,p}(u) \tag{4.8}$$

and

$$\varphi_{t+1}^{\theta,p}(s) \propto \psi(s)\{p\varphi_t^{\theta,p}(\lambda s) + (1 - p)\,\theta\varphi_t^{\theta,p}(\lambda^{1/2})\,\varphi_t^{\theta,p}(\lambda^{1/2}s)\}.$$

Since $\varphi_{t+1}^{\theta,p}(1) = 1$, this may be written, after normalization, as

$$\varphi_t^{\theta,p}(s) = \psi(s)\frac{p\varphi_t^{\theta,p}(\lambda s) + (1 - p)\,\theta\varphi_t^{\theta,p}(\lambda^{1/2})\,\varphi_t^{\theta,p}(\lambda^{1/2}s)}{p\varphi_t^{\theta,p}(\lambda) + (1 - p)\,\theta[\varphi_t^{\theta,p}(\lambda^{1/2})]^2}. \tag{4.9}$$

We designate

$$q = \frac{p}{p + (1 - p)\,\theta}, \qquad 0 \leqslant q \leqslant 1. \tag{4.10}$$

It can be established readily that for any pair of parameters $\theta > 0$, $0 \leqslant p \leqslant 1$, the sequence $\{\varphi_t^{\theta,p}(s)\}_{t=0}^{\infty}$ may be determined *by the single parameter* q, so that

$$\varphi_t^{\theta,p}(s) = \varphi_t^q(s), \qquad t = 0, 1, 2, \ldots$$

and

$$\varphi_0^q(s) = \varphi_0^{\theta,p}(s) = \varphi(s)$$

by definition. Using q, which we shall call the "diploidity parameter," we have, for (4.4),

$$\varphi_{t+1}^q(s) = \frac{q\varphi_t^q(\lambda s) + (1 - q)\,\varphi_t^q(\lambda^{1/2}s)\,\varphi_t^q(\lambda^{1/2})}{q\varphi_t^q(\lambda) + (1 - q)[\varphi_t^q(\lambda^{1/2})]^2}. \tag{4.11}$$

As special cases of the diploid process $\{F_t^q(x)\}_{t=0}^{\infty}$, let us consider first the two extremes, random mating and complete selfing. In the first case, we have $p = 0$ (no selfing) and thus $q = 0$. For a complete random mating, (4.11) becomes

$$\varphi_{t+1}^{(0)}(s) = \frac{\psi(s)\,\varphi_t^{(0)}(\lambda^{1/2}s)}{\varphi_t^{(0)}(\lambda^{1/2})} \tag{4.12}$$

After mutation, in exactly the same fashion of Section 2, we eventually have

$$F_{t+1}(x) = \int_{-\infty}^{\infty} G(x-u)\, dF_t^{**}(u). \tag{4.4}$$

As in the asexual case, the analysis of the diploid population will concentrate on the "fitness property" of its various genotypes. To start with, let the gametic character x be defined by the "fitness" of the homozygote (x, x). More precisely, x, namely, the "homozygotic fitness" is defined such that the viability $\gamma(x, x)$ of the homozygote (x, x) is proportional at time t ($t = 0, 1, 2,...$) to λ^x

$$\gamma(x, x) = \lambda^{x-C_t}, \tag{4.5}$$

where, as before, $\lambda > 1$, and C_t is a constant that depends on the environmental conditions obtaining at time t and determines the proportion coefficient. The homozygotic fitness is bounded (above) at time by definition ($\gamma(x, x) \leqslant 1$; thus $x \leqslant C_t$).

For further investigation of the model, we employ the following two postulates:

(1) The viability of the heterozygotic type (x_1, x_2) differs from the geometric mean of the homozygotic viabilities $\gamma(x_1, x_1) \propto \lambda^{x_1}$ and $\gamma(x_2, x_2 \propto \lambda^{x_2}$ by a fixed multiplicative factor > 0, the "heterozygotic (multiplicative) effect"

$$\gamma(x_1, x_2) \propto \theta\lambda^{(x_1+x_2)/2}. \tag{4.6}$$

(Equivalently, we may speak of heterozygotic fitness in the same logarithmic sense used for homozygotic fitness; the postulate asserts that this heterozygotic fitness differs by a fixed constant C from the *arithmetic* mean $(x_1 + x_2)/2$ of the homozygotic fitnesses $\theta = \lambda^C$.)

(2) In any generation, a fixed frequency $0 \leqslant p \leqslant 1$ of each gamete remains in a complete homozygotic state as a result of selfing or positive assortation, whereas the remainder of the gametic population performs a random union of gametes. The quantity p will be called the "selfing rate." Assuming the frequency of each gamete in the population to be very small, we may neglect the probability of complete homozygocity due to random union of gametes.

Let $\{F_t^{\theta,p}(x)\}_{t=0}^{\infty}$ be the process determined by the parameters θ, p with $F_0^{\theta,p}(x) = F_0(x)$. Invoking assumption (2) with this process, let us consider all gametes associated at time t with a given gamete x. Of these, p will be of its own sort, whereas the rest will be distributed $F_t^{\theta,p}(x)$ in the manner of the whole population. For the conditioned distribution, then,

$$F_t^{\theta,p}(u \mid x) = \begin{cases} (1-p)F_t^{\theta,p}(u) + p & \text{if } u \leqslant x \\ (1-p)F_t^{\theta,p}(u) & \text{if } u > x. \end{cases} \tag{4.7}$$

the limit rate of evolution (Theorem 3.1), it follows that $F_1^*(x) = F(X - \bar{G})$ and, therefore

$$\varphi_1^*(s) = s^{\bar{G}}\Phi(s). \tag{3.13}$$

From (3.12) and (3.13), we have

$$s^{-\bar{G}}\psi(s) = \frac{\Phi(\lambda)\,\Phi(s)}{\Phi(\lambda s)} \overset{\text{def}}{=} R\Phi(s). \tag{3.14}$$

In other words, the intrinsic mutation law in a given population is uniquely determined and can be calculated from the limit fitness distribution, if known.

In many cases, one has reason to believe that observed fitness distribution is in fact close to its theoretical limit. Information on the distribution of mutations, generally inaccessible by direct investigation, is then furnished by the transformation R, which expresses the mutation generating function in terms of the limit generating function.

EXAMPLE. The nagative Poisson distribution of fitnesses

$$p(X = a - bn) = e^{-\alpha}\frac{\alpha^n}{n!}, \qquad (n = 0, 1, 2,...)$$

is a limit distribution of a regular process of evolution, governed by another negative Poisson distribution of the mutations.

Proof. Since the generating function of such a distribution is

$$\Phi(s) = s^a \exp\{\alpha(s^{-b} - 1)\}$$

the generating function of the mutation may be expressed as

$$R\Phi(s) = \frac{s^a\lambda^a}{(\lambda s)^a}\exp\{\alpha[(s^{-b} - 1) + (\lambda^{-b} - 1) - (\lambda^{-b}s^{-b} - 1)]\}$$

$$= \exp\left\{\frac{\alpha(\lambda^b - 1)}{\lambda^b}(s^{-b} - 1)\right\},$$

which is again a negative Poisson generating function.

Limit genetic load and mutation-selection balance. We use Ewen's definition for the genetic load

$$L = \frac{W_{\max} - E(W)}{E(W)}$$

where W represents the intrinsic rate of reproduction (classical fitness). From

the definition we see that $0 \leqslant L \leqslant \infty$, but especially we expect a finite genetic load in any given population. In our case, the genetic load of generation t is

$$L_t = \frac{\lambda^{\bar{F}_t} - \varphi_t(\lambda)}{\varphi_t(\lambda)} . \tag{3.16}$$

We note at once that the assumption of regularity (i.e., of bounded mutation and bounded initial fitness) is equivalent to the reasonable requirement that the genetic load remain finite each generation. Analytically, however, this is insufficient to afford the limit population a finite load since L_t may increase without bound with time.

For biological applications, of course, we are interested in processes in which genetic load not only remains finite each generation but is also kept uniformly bounded throughout the process, so that the limit genetic load

$$L_\infty = \frac{\lambda^{\bar{F}} - \Phi(\lambda)}{\Phi(\lambda)} \tag{3.17}$$

also remains finite; namely, *bounded-load processes of evolution.*

It is evident from (3.17) that the requirement of "bounded load" is equivalent to the boundedness of the limit relative fitness (i.e., $\bar{F} < \infty$). This is a stronger property than having a finite variance at the limit, as implied by regularity alone (Theorem 3.2). As we shall see immediately, this "bounded-load" feature depends only on the nature of the maximal mutation change possible in each stage of the process.

THEOREM 3.3 (*Bounded-Load Theorem*). *A regular process of evolution is of "bounded load" if the probability of its maximal mutation is strictly positive. This probability, p, may be expressed simply in terms of the limit distribution as*

$$p = \frac{\Phi(\lambda)}{\lambda^{\bar{F}}} . \tag{3.18}$$

Equivalently, the genetic load of the stable limit population may be expressed in terms of the maximal-mutation probability alone

$$L_\infty = \frac{1-p}{p} . \tag{3.19}$$

EXAMPLES. On the basis of this theorem (for its proof, the reader is referred to [2]), we may recognize the negative Poisson process (which, we recall, appeared to approach another negative Poisson limit distribution) as a "bounded-load" process. From the "bounded-load theorem" we know that this is also the case, for example, with a binomial process (i.e., with binomial distribution of

of the population. For example, if one is to assume a random union of gametes (i.e., $F_t(x \mid x_1) = F_t(x)$ for all x and x_1), then (4.1) becomes

$$p_t\{(x_1, x_2) \mid a_1 \leqslant x_1 < b_1 ; a_2 \leqslant x_2 \leqslant b_2\} = [F_t(b_1) - F_t(a_1)][F_t(b_2) - F_t(a_2)]$$

In general, from generation t to generation $t+1$, pairing, selection, and mutation govern the population in the following manner:

(1) Pairing (resulting from a given mating system) causes rearrangement of the gametes such that for any gamete x the conditioned distributions $F_t(x \mid x_1)$, describing the gametic arrangement in generation t, changes to $F_t^*(x \mid x_1)$. As with the haploid case (Remark 2, Sec. 3), it is assumed that gametic frequencies (and therefore the distribution $F_t(x)$) are not directly affected by the mating system.

(2) Assuming equal fertility for all types, a viability function $\gamma(x_1, x_2)$ determines the proportion of survivors among all offspring of type (x_1, x_2). (Remark: Viability fitness is stipulated for convenience; the model can be constructed with mother–fertility fitness without difficulty, yielding the same results.)

(3) Before new mating, mutation alters the gametes in accordance with the same law as in the asexual model, independent of the genotype to which the gametes belong. In other words, a distribution function $G(u)$ exists such that after mutation a proportion $G(u)$ of the gametes exceeds their original type by a difference of not more than u.

To study the effect of selection on the gametic population, we shall consider all newborn offspring between generations t and $t+1$ (before selection). Since $\gamma(x, u)$ of all offspring of (x, u) type survives, it is also the proportion of survivors among those *x-gametes* that happened to be associated with a u-gamete. The proportion of survivors among *all* x-gametes is thus

$$\int_{-\infty}^{\infty} \gamma(u, x)\, dF_t^*(u \mid x) \tag{4.2}$$

where $F_t^*(u \mid x)$ stands for the conditioned distribution of newborn offspring. The proportion $F_t^{**}(x)$ of gametes with a value $\leqslant x$ among those offspring after selection is given by the integration of (4.2) over all such gametic types

$$F_t^{**}(x) \propto \int_{-\infty}^{x} \int_{-\infty}^{\infty} \gamma(u, v)\, dF_t^*(u \mid v)\, dF_t(v)$$

and by normalization,

$$F_t^{**}(x) = \frac{\int_{-\infty}^{x} \int_{-\infty}^{\infty} \gamma(u, v)\, dF_t^*(u \mid v)\, dF_t(v)}{\int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \gamma(u, v)\, dF_t^*(u \mid v)\, dF_t(v)} \tag{4.3}$$

the rate of reproduction mutltiplicatively, recombination due to random mating does not affect the gametic frequencies, provided the disequilibrium coefficient is initially zero. It is not difficult to extend this result to any n-locus population, provided gene frequency at each locus is independent of the other loci (i.e., provided all possible disequilibrium coefficients are zero). With this as an initial assumption, all the results of Sections 1–3 are readily applied to a haploid population with random mating. The results can also be extended to a mixture of random mating and self-assortation. Under the same postulate, as we shall see in the next section, most results of the asexual model can be extended to a certain diploid model.

4. A Diploid Model

Assumptions and general properties. As we have done with the single-parameter asexual model, we consider now a population with an infinite number of types of gametes, which for convenience we identify with the points of the real line. The real number x associated with a given gamete is said to be its "characteristic value." Each genotype in the diploid population is thus identified with a pair (x_1, x_2) of real numbers, according to the values of its gametes. As was the case with the asexual model, our concern will be to study changes in the composition of the population resulting from pressures of mutation (acting independently on gametes), selection (acting on pairs of gametes), and pairing (rearranging of gametes). Throughout the analysis we shall characterize the population by two factors:

(1) The distribution of types among all the *gametes* of the population;
(2) the arrangement of gametes into pairs (*genotypes*).

More precisely, let $F_t(x)$ be the proportion of gametes with a value $\leqslant x$ in the population of generation t. For any given gamete x_1, moreover, we shall be interested in the proportion $F_t(x \mid x_1)$ of gametes with a value $\leqslant x$ among all gamets paired with x_1. The proportions $F_t(x \mid x_1)$ will be called the conditioned distributions of generations t. Once these distributions are known, the proportion of genotypes (x_1, x_2) with $a_1 \leqslant x_1 \leqslant b_1$ and $a_2 \leqslant x_2 \leqslant b_2$ is given simply (for any $a_1 \leqslant b_1$; $a_2 \leqslant b_2$) by

$$p_t\{(x_1, x_2) \mid a_1 \leqslant x_1 \leqslant b_1 ; a_2 \leqslant x_2 \leqslant b_2\} = \int_{a_1}^{b_1} [F(b_2 \mid u) - F(a_2 \mid u)]\, dF(u). \tag{4.1}$$

Furthermore, for some mating systems, $F_t(x \mid x_1)$ can be expressed in terms of $F_t(x)$. In such cases, it may be sufficient to know only the gametic composition

mutations) but not with a "uniform process." More precisely, if we allow mutation fitness to distribute uniformly with a positive maximum, then the genetic load is bound to increase indefinitely (though the variance, as implied by Theorem 3.2, will tend to a *finite* limit).

An important application of the bounded-load theorem concerns the case of *mutation–selection balance*, i.e., in its most general meaning, the case in which mutation and selection pressures confine the average type of the problem *within some given bounded region.* Theorem 3.1 establishes as a necessary condition for mutation–selection balance the requirement that the maximum fitness of the offspring will be the fitness of their parents; for otherwise the rate of evolution (which, by definition, is the *change* in the average type) tends to a nonzero limit. It can be demonstrated, however, that a *necessary and sufficient* condition for maintaining a balance is that, in addition to this requirement, the process be of bounded load.

In other words, a necessary and sufficient condition for a stationary process to maintain mutation–selection balance is that all mutations be either deleterious or neutral but that at least some of the offspring (with positive probability) resemble their parents in fitness.

A natural, though not the sole, application of such a process is the evolutional *blind alley*, wherein a population has already achieved maximal adaptation to a fixed environment, although a steady flux of deleterious mutations maintains its variability. Here the probability p that no deleterious mutation will occur is of course positive (presumably near 1), and the process is of bounded load.

Theorems 3.2 and 3.3 imply that the various types in the population tend, under mutation–selection balance, to a limit stable distribution with a finite variance and a finite genetic load. This distribution is uniquely determined by the mutation law. The average type (postulated *a priori* only to be bounded) thus tends to a finite limit. More precisely, we have

$$EX_t \xrightarrow{t\to\infty} E_\infty , \qquad |E_\infty| < \infty \tag{3.20}$$

and

$$F_t(x) \xrightarrow{t\to\infty} F_\infty(x) = F(x + E_\infty). \tag{3.21}$$

Equivalently, in terms of generating functions,

$$\varphi_t(s) \xrightarrow{t\to\infty} \varphi_\infty(s) = s^{E_\infty}\Phi(s). \tag{3.22}$$

This assertion implies our next theorem.

Theorem 3.4. (*Mutation–Selection Balance Theorem*). *The average rate of reproduction $E\lambda^x$ of a population under mutation-selection balance tends to a limit*

that depends only on the probability $1 - p$ *of deleterious mutations, and not on the extent or distribution of their deleterious effects. More precisely,*

$$E\lambda^{x_t} \xrightarrow{t\to\infty} p\lambda^{F_0}, \tag{3.23}$$

where p *is the probability that an offspring will resemble its parent, and* λ^{F_0} *is the maximal rate of reproduction in the population (which clearly remains fixed with time).*

Proof. From (3.21) we know that $\bar{F}_\infty = \bar{F} + E_\infty$. We know also that $\bar{F}_t = F_\infty$ for all t (the maximal fitness of the population is unchanged). From (3.22) and the bounded-load theorem we obtain

$$p = \frac{\Phi(\lambda)}{\lambda^{\bar{F}}} = \frac{\lambda^{E_\infty}\Phi(\lambda)}{\lambda^{\bar{F}+E_\infty}} = \frac{\varphi_\infty(\lambda)}{\lambda^{F_0}}.$$

Thus

$$E\lambda^{x_t} = \varphi_t(\lambda) \to \varphi_\infty(\lambda) = p\lambda^{F_0}. \qquad \text{Q.E.D.}$$

Under some conditions, one may perceive environmental changes that do not affect maximal-fit types but may well affect other types. When we take into account artificial and semiartificial selection, we see that such conditions are fairly prevalent. From Theorem 3.4 we obtain directly the next corollary.

COROLLARY. *The limit rate of reproduction in the population as a whole is unaffected by those environmental changes that affect only deleterious mutants (though the distribution of fitnesses within the limit population is affected by such changes). Moreover, if totally lethal conditions for all deleterious mutations are artificially superimposed (i.e., if a portion* $1 - p$ *of the population is systematically eliminated each generation), the limit rate of reproduction* $p\lambda^{F_0}$ *is trivially obtained within one generation.*

Since the probability $1 - p$ of having any deleterious mutation is likely to be small, we may conclude that the average *fitness loss* imposed on an entire haploid population by accumulation of deleterious mutations cannot be large. As we shall see in Section 4, this also remains true, to a large extent, in a diploid population.

EXAMPLE (*Accumulation of independent and noninteracting deleterious mutations*). Assume that a large number of possible mutations occur independently, each with a very low probability. Assume, moreover, that each mutation decreases the fitness by a fixed value $\delta > 0$. Since the number of possible mutations is very large, we have as a good approximation a generalized negative Poisson distribution of the mutations

$$p(Y = -\delta n) = e^{-\alpha}\frac{\alpha^n}{n!} = p\,\frac{\alpha^n}{n!} \tag{3.24}$$

where $p \overset{\text{def}}{=} e^{-\alpha}$ is the probability of fitness resemblance to the parent. Equivalently, the mutation generating function is

$$\psi(s) = \exp\{-\alpha(1 - s^{-\delta})\} = p^{1-s^{-\delta}}. \tag{3.25}$$

We have seen that this mutation law corresponds to a limit distribution that is also a negative Poisson. Furthermore, it is easily shown that the generating function of this limit distribution is given by

$$\varphi_\infty(s) = p^{\frac{1-s^{-\delta}}{1-\lambda^{-\delta}}}\, s^{F_0} \tag{3.26}$$

with

$$p^{\frac{1}{1-\lambda^{-\delta}}}$$

as the stable proportion of maximal-fit types in the limit population. The average loss in reproduction rate thus tends to p

$$E\lambda^{x_t} \xrightarrow{t\to\infty} \varphi_\infty(\lambda) = p\lambda^{F_0} \tag{3.27}$$

which we know also from Theorem 3.4.

Remark 1. Some of the results of this section may be extended to the nonstationary case in which the mutation distribution $G_t(s)$ in generation t depends on time. As with the stationary case, the generating function of generation t

$$\varphi_t(s) = \int_{-\infty}^{\infty} s^x\, dF_t(x)$$

may be calculated directly from the initial distribution of types in the population and the (varied) mutation law within the first $t - 1$ generations. It may be shown that under various conditions the average rate of evolution EX_t/t tends to the average of the maximal mutations $(1/t)\sum_{t=0}^{\infty} \bar{G}_t$. Especially if $G_t(x) \xrightarrow{\text{measure}} G(x)$ and $\bar{G}_t \to \bar{G}$, then $EX_t/t \to \bar{G}$.

Remark 2. It has already been shown (Smith, [12]) that in a two-locus infinite haploid population with mutations occurring independently and affecting