The Accumulation of Deleterious Genes in a Population— Muller's Ratchet

JOHN HAIGH

Mathematics Division, Sussex University, Brighton, England

A quantitative study of the operation of Muller's Ratchet for the accumulation of deleterious genes in an asexually reproducing population is made. For a population of size N, in which deleterious mutations occur at rate λ/genome/ generation, and the relative fitness of an individual with k mutants is $(1 - s)^k$, the most important parameter is $n_0 = Ne^{-\theta}$, where $\theta = \lambda/s$. If n_0 is large ($\gg 25$), deleterious mutations will accumulate very slowly, and independently of each other; if n_0 is small (<1), the rate of accumulation of deleterious mutations will be greater than a natural population could plausibly bear; an estimate of the speed of the Ratchet for intermediate values of n_0 is made. It is pointed out that the frequency distribution for the numbers of individuals carrying k mutants will retain its shape, but will move bodily to the right at the same average speed as the Ratchet. When favourable mutations also occur, the frequency distributions can move right of left; an estimate of the probability that any particular step is right or left is made, and it is shown that, for a given *net* rate of arrisal of deleterious mutations, the greater the rate of beneficial mutation, the greater the chance that beneficial mutations will accumulate.

INTRODUCTION

In a population which reproduces asexually, and in which back mutation does not occur, all offspring of an individual will carry all deleterious mutants on the genome of a parent, together with any new deleterious mutations. Thus, the number of deleterious mutations in an individual is at least as many as his parent carried which, as Felsenstein (1974) pointed out, was an argument advanced by Muller (1964) as a possible reason for the evolution of recombination. This effect is known as Muller's Ratchet; once a line has k mutants, it will never have fewer than k, and the Ratchet winds on inexorably, to the detriment of the population. It is our intention to discuss this Ratchet effect, both qualitatively and quantitatively, and then to examine a modification in which favourable mutations are allowed to appear to offset the deleterious ones.

251

THE MODEL

Our model is the classical Wright–Fisher model of an asexually reproducing population of fixed size N. The relative fitness of an individual with k deleterious mutations is taken to be $(1 - s)^k$ ($s > 0$), and we assume that new deleterious mutations arise at a rate λ per genome per generation. It seems reasonable [and was done by Kimura and Maruyama (1966)] to assume that the actual number of new mutations has a Poisson distribution with mean λ. Thus, if $X_k(t)$ is the number of individuals in generation t who carry k mutants and $\mathbf{X}(t) = (X_0(t), X_1(t),...)$, then the distribution of $\mathbf{X}(t + 1)$ will be multinomial with parameters N and $\{p_k(t), k = 0, 1,...\}$, where

$$p_k(t) = \sum_{j=0}^{k} X_{k-j}(t)(1 - s)^{k-j} e^{-\lambda} \frac{\lambda^j}{j!} \Big/ T_1(t), \tag{1}$$

with

$$T_r(t) = \sum_{i=0}^{\infty} X_i(t)(1 - s)^{ir} \qquad (r = 1, 2,...). \tag{1a}$$

It is convenient to record

$$E(X_k(t + 1) \mid \mathbf{X}(t)) = N p_k(t), \tag{2a}$$

$$\mathrm{Var}(X_k(t + 1) \mid \mathbf{X}(t)) = N p_k(t)(1 - p_k(t)), \tag{2b}$$

$$\mathrm{Cov}(X_k(t + 1), X_j(t + 1) \mid \mathbf{X}(t)) = -N p_k(t)\, p_j(t). \tag{2c}$$

A particular distribution $\mathbf{n} = (n_0, n_1,...)$ will be *stationary* if

$$E(\mathbf{X}(t + 1) \mid \mathbf{X}(t) = \mathbf{n}) = \mathbf{n};$$

from (1) and (2a), such a distribution satisfies

$$n_k = N \sum_{j=0}^{k} n_{k-j}(1 - s)^{k-j} \frac{\lambda^j e^{-\lambda}}{j!} \Big/ T, \tag{3}$$

where $T = \sum_{i=0}^{\infty} n_i(1 - s)^i$.

From (3), with $k = 0$, we see that $n_0 = N n_0 e^{-\lambda}/T$; hence, if $n_0 \neq 0$, $T = N e^{-\lambda}$ and so

$$n_k = \sum_{j=0}^{k} n_{k-j}(1 - s)^{k-j} \lambda^j/j!, \tag{4}$$

for $k = 0, 1, 2,...$, whose sole solution is

$$n_k = n_0 \theta^k/k!, \qquad \theta = \lambda/s. \tag{5}$$

Since $N = \sum_{k=0}^{\infty} n_k$, the only stationary distribution with $n_0 > 0$ is

$$n_k = Ne^{-\theta}\theta^k/k! \qquad (k = 0, 1,...). \tag{6}$$

It is easy to see that the only other solutions to (3) are the family with $n_0 = n_1 = \cdots = n_{J-1} = 0$, $n_{J+k} = Ne^{-\theta}\theta^k/k!$ for some $J \geqslant 1$. These differ from (6) only in that every individual has at least J mutations, so the fitness of the classes, *relative to the most fit class*, remain the same.

It is evident from (1), (1a), and (2a) that the theoretical distribution of $E(\mathbf{X}(t+1))$ when $\mathbf{X}(t)$ is not close to this stationary distribution $\mathbf{n}$ is complicated. Computer simulations (for details of how these were carried out see below) of populations in which $\mathbf{X}(0)$ was wildly different from $\mathbf{n}$—for example, $X_0(0) = N$, $X_k(0) = 0$ for $k \geqslant 1$, or $X_0(0) = X_{20}(0) = N/2$, $X_k(0) = 0$ for $k \neq 0, 20$—were most encouraging, in that the actual distribution $\mathbf{X}(t)$ moved rapidly towards $\mathbf{n}$ or one of its translates. Thus, it seems reasonable that we should consider the behaviour of $\mathbf{X}(t+1)$ when $\mathbf{X}(t)$ is close to $\mathbf{n}$. If n_0 is small, a small perturbation may reduce the class with no mutants to zero, in which case the Ratchet effect ensures that the distribution prior to perturbation cannot be regained. However, aside from this point, suppose the class sizes differ from $\{n_k\}$ by *small* amounts $\{\delta_k\}$ so that the kth class has size $n_k + \delta_k$, where $\sum\delta_k = 0$. Then, in the next generation, it is easy to see that the mean change in the size of the kth class is

$$\delta_k((1 - s)^k - 1) + \lambda\delta_{k-1}(1 - s)^{k-1} + \frac{\lambda^2}{2}\delta_{k-2}(1 - s)^{k-2} + \cdots \tag{7}$$

The sign of the first term is different from that of δ_k, and, since $\sum_i \delta_i = 0$, the mean of any $\delta_i(i \neq k)$ conditional on the value of δ_k also has a sign different from that of δ_k; hence (7) shows that the overall tendency is for disturbances from $\{n_k\}$ in one generation to be, on average, compensated in the next.

THE RATCHET EFFECT

Consider a population which starts in the equilibrium defined by Eq. (6). Since each class has an integral number of members, we shall take $X_k(0)$ to be the nearest integer to n_k, and let us assume first that $n_0 = Ne^{-\theta} \geqslant 0.5$, so that $X_0(0) \geqslant 1$. From (1a) and (2a),

$$E(T_1(t + 1) \mid \mathbf{X}(t)) = \sum_{k=0}^{\infty} Np_k(t)(1 - s)^k,$$

which, using (1) simplifies to

$$E(T_1(t + 1) \mid \mathbf{X}(t)) = Ne^{-\lambda s}T_2(t)/T_1(t).$$

Similarly, we find

$$\text{Var}(T_1(t + 1) \mid \mathbf{X}(t)) = Ne^{-2\lambda s} \left\{ e^{\lambda s^2} \frac{T_3(t)}{T_1(t)} - \frac{T_2^2(t)}{T_1^2(t)} \right\}.$$

Upon expanding T_3/T_1, T_2/T_1 as power series in s, we obtain

$$\text{Var}(T_1(t + 1) \mid \mathbf{X}(t)) = Ne^{-2\lambda s}\{s^2(\lambda + \sigma^2(t)) + O(s^3)\},$$

where $\sigma^2(t)$ is the variance associated with a random variable which takes the value k with probability $X_k(t)/N$, for $k = 0, 1,\dots$. However, since $E(X_k(t)) = n_k = Ne^{-\theta}\theta^k/k!$, we see that $\sigma^2(t) \simeq \theta$. Thus,

$$\text{Var}(T_1(t + 1) \mid \mathbf{X}(t)) \simeq Ne^{-2\lambda s}\{\lambda s(1 + s) + O(s^3)\},$$

and, in a similar but simpler calculation,

$$E(T_1(t + 1) \mid \mathbf{X}(t)) \simeq Ne^{-\lambda}.$$

These last two expressions show that, when N is large and s is small, the mean of $T_1(t + 1)$ far exceeds its standard deviation [e.g., $\lambda = 1$, $N = 10^4$, $s = 0.1$, the mean is about 3700 and the variance is about 30^2; generally, the coefficient of variation is $O(s/N)^{1/2}$], so $T_1(t)$ changes slowly, and thus remains close to $Ne^{-\lambda}$ for a long time. $T_1(t)$ has an easy interpretation, since $T_1(t)/N$ is the mean fitness of the population in generation t.

So long as $X_0(t) > 0$, $X_0(t + 1)$ has a binomial distribution with parameters N and $p_0(t) = X_0(t) e^{-\lambda}/T_1(t)$; hence, with N large and $T_1(t)$ relatively constant, the distribution of $X_0(t + 1)$ is well approximated by a Poisson distribution with mean $X_0(t)$. Thus, the process for the Ratchet's elimination of C_0, the class with no deleterious mutations, is very close to the process for the extinction of a Poisson branching process, of initial size $n_0 = Ne^{-\theta}$, with each member averaging one descendent. Such a branching process has an infinite mean time to extinction; the same is not true for the process to eliminate C_0 (since C_0 can never contain more than N members, and, indeed, if C_0 greatly exceeds n_0 in size at any time, the number of descendents it contributes to C_0 will average at less than unity), but since we shall be concerned mainly with populations in which $n_0 \ll N$, it is clear that the variance of the time to eliminate C_0 will be very large, and the true finite mean time to lose C_0 will be atypical.

While C_0 is in the process of extinction, the sizes of the other classes C_1, C_2,..., are also governed by the multinomial process (1), in which, of course, the probabilities $\{p_k(t)\}$ are changing each generation. Hence the size of C_i, in the generation in which C_0 is lost, has a complicated distribution, but whose mean will be close to the original value n_i. To simplify the notation, suppose C_0 is eliminated in generation t_0 and, for $t \geqslant 0$, $k \geqslant 0$, write $Y_k(t) = X_{k+1}(t + t_0)$.

Then we can establish the following result, whose proof can be found in the Appendix.

THEOREM 1. $E(Y_k(t) \mid \mathbf{Y}(0) = (n_1, n_2, \ldots)/(1 - e^{-\theta})) \simeq m_k(t)$, where

$$m_k(t) = n_{k+1}(1 - (1 - \gamma(t))^{k+1})/(1 - e^{-\theta\gamma(t)}) \qquad (8)$$

and $\gamma(t) = (1 - s)^t$.

Note. The $\{n_i\}$ here are the quantities defined by Eq. (6); we have argued that, at the time C_0 is eliminated, the mean sizes of C_i will be close to n_i for any given i, and this is the justification for our use of Theorem 1 to examine the pattern of behaviour of $\{X_k(t)\}$ subsequent to generation t_0.

COROLLARY. Let τ be the integer closest to $-\log \theta/\log(1 - s)$. Then

(a) $E(Y_k(\tau) \mid \mathbf{Y}(0) = (1/(1 - e^{-\theta}))(n_1, n_2, \ldots)) \simeq 1.6n_k$ for k small,

(b) $E(U_1(\tau)) \simeq Ne^{-\lambda}/(1 - 0.4s)$, where $U_1(u) = \sum_{k=0}^{\infty} Y_k(u)(1 - s)^k$.

Proof. See Appendix.

Assuming that, at the time C_0 is eliminated, the given value of $\mathbf{Y}(0)$ is a reasonable description of the other class sizes, we see that the new fittest class, C_1, reduces in size from about n_1 to about $1.6n_0$ in approximately $-\log \theta/\log(1 - s)$ generations. Furthermore, after this drop, the mean size of C_1 in the next generation is $NY_0(\tau) e^{-\lambda}/U_1(\tau) \simeq Y_0(\tau)(1 - 0.4s)$, so each member in the fittest class is giving rise to about $1 - 0.4s$ offspring into that class. It is clear, if s is small, the elimination of this new fittest class will owe more to the operation of random drift than to deterministic forces. Thus, we can express the total time to lose the second class as $D_2 + X_2$, where D_2 is a fixed quantity, about $s^{-1} \log \theta$, and X_2 is a random variable, having a distribution rather akin to the time to extinction of a Poisson branching process, of initial size $1.6n_0$, and where each member has (at least initially) an average of $1 - 0.4s$ offspring.

But note that, while the fittest class has been falling from size n_1 to n_0, and then drifting to absorption at zero, $Y_1(u)$ has been falling from n_2 to its new equilibrium value n_1, etc., and so, when we lose the second class, it is plausible to suggest that the composition of the class sizes is similar to the distribution assumed for $\mathbf{Y}(0)$ in the theorem above. Thus, we argue that the process for the loss of classes, after the first, is a repetition of the way in which we have described the loss of the second class. The time Z_i to lose the ith class is a sum, $Z_i = D_i + X_i$, where $D_i \simeq s^{-1} \log \theta$ and X_i has the distribution described above for X_2.

The important points to note are the way in which this time depends on the three parameters, N, s, and λ, which define the process. Writing $\theta = \lambda/s$, the most important single quantity is $n_0 = Ne^{-\theta}$. If n_0 is large (say, $n_0 \geqslant 25$),

each class is lost more or less independently of the history of the process. This is because, after a class is lost, there is a shift to the next equilibrium in a time which will tend to be small compared with the long (random) time to lose a class of at least 25 members purely by random drift. On the other hand, if n_0 is very small, the loss of classes is quite rapid, since the potential fittest classes are entirely absent from the population; suppose K is the smallest integer such that $n_K = Ne^{-\theta}\theta^K/K!$ exceeds 0.5. Then, since $n_{K-1} < 0.5 < n_K$ and $n_K = n_{K-1}\theta/K$, we see that $0.5 < n_K < 0.5\theta/K$, and the mean number in the fittest class in the next generation is $Nn_K(1-s)^K e^{-\lambda}/T \simeq n_K(1-s)^K$. Thus, the time to lose the fittest class here is akin to the time to absorption of a Poisson branching process of initial size $n_K(1 \leqslant n_K < 0.5\theta/K)$, with each individual having on the average $(1-s)^K$ offspring; even for moderately small values of K, this time will be very small.

For intermediate values of n_0, a process which starts in equilibrium has a different pattern for the loss of the first class from the loss of subsequent classes. After the first class has been lost, subsequent classes are lost according to the sequence Z_2, Z_3,... described above, and, apart from the value of $n_0 = Ne^{-\theta}$, secondary quantities are $\log \theta$ and s; the time to lose a class is an

TABLE I[a]

$N \times 10^{-3}$	s	λ	θ	$Ne^{-\theta}$	μ	σ	$\hat{W}$
2	0.2	1.4	7	1.83	12.2	8.12	10.6
	0.1	0.7			20.6	13.9	19.2
	0.05	0.35			28.4	15.2	36.3
5	0.2	1.4		4.56	16.8	13.4	20.9
	0.1	0.7			33.0	23.1	29.5
	0.05	0.35			48.2	43.3	46.6
10	0.2	1.4		9.12	37.1	38.5	38.1
	0.1	0.7			48.3	39.1	46.7
	0.05	0.35			57.4	30.9	63.8
15	0.2	1.4		13.7	54.9	49.9	55.3
	0.1	0.7			48.6	35.1	63.9
	0.05	0.35			102.8	105.0	81.1
50	0.2	1	10	2.27	17.6	11.7	14.8
					16.6	11.0	14.8
	0.1	1			27.9	21.0	23.4
					29.0	17.8	23.4
	0.05	0.5			28.6	14.3	40.6
					39.3	23.1	40.6

TABLE I—*Continued*

$N \times 10^{-3}$	s	λ	θ	$Ne^{-\theta}$	μ	σ	$\hat{W}$
100	0.2	2	10	4.54	29.4	21.1	23.4
					23.6	12.6	23.4
	0.1	1			28.7	25.3	32.0
	0.05	0.5			56.7	43.0	49.1
200	0.2	2		9.08	42.1	30.0	40.5
	0.1	1			51.4	35.7	49.1
					45.1	25.6	49.1
	0.05	0.5			63.2	31.7	66.3
500	0.2	2.6	13	1.13	13.4	7.4	12.4
					12.0	6.2	12.4
	0.1	1.3			18.9	12.0	21.0
					18.8	9.3	21.0
	0.05	0.65		2.26	37.4	24.9	38.1
					37.1	23.8	38.1
1000	0.2	2.6		2.26	15.3	8.6	16.7
	0.1	1.3			28.5	18.9	25.3
	0.05	0.65			39.2	22.8	42.4
2000	0.2	2.6		4.52	20.6	12.6	25.2
	0.1	1.3			42.7	28.1	33.8
	0.05	0.65			55.1	37.7	50.9
5000	0.2	2.6		11.3	47.3	37.2	50.8
	0.1	1.3			56.0	35.8	59.4
					76.8	43.3	76.5

^a For ease of reading, parameters are omitted when they are the same as in the line above. For the given values of N, s and λ, θ, and $n_0 = N \exp(-\theta)$ are shown. The populations were simulated until 26 classes were lost; μ and σ are the mean and standard deviation of the time to lose the 25 classes 2, 3,..., 26, and $\hat{W}$ is the estimate of the mean time to lose a class from (9).

increasing function of n_0, log θ and s^{-1}. These remarks lead one, in an attempt to quantify this relationship, to estimate W, the mean number of generations to lose a class (after the loss of the first class) via simulation as follows.

Select a range of values of N, s, λ such that $1 \leqslant n_0 \leqslant 15$, set up the process in equilibrium, and simulate its multinomial behaviour until 25 classes have been lost (after the first) (Table I). Record the successive times to lose these classes, and fit a line of the form

$$W = a_0 + a_1 Ne^{-\theta} + a_2 \log \theta + a_3 s^{-1}$$

by multiple regression. These simulations can also be used (Table II) to check

TABLE II

Actual Numbers of Generations to Lose Classes 2, 3,... 11 in Turn for
Some of the Simulations Used in Table I

$Ne^{-\theta}$	$N \times 10^{-3}$	s	λ	Classes									
				2	3	4	5	6	7	8	9	10	11
1.83	2	0.2	1.4	23	18	15	8	4	20	13	9	7	41
4.56	5	0.1	0.7	30	21	30	21	16	53	106	35	67	16
13.7	15	0.05	0.35	116	55	521	78	20	42	43	107	25	143
2.27	50	0.2	2	15	30	15	15	16	8	7	13	12	22
4.54	100	0.1	1	29	111	75	7	31	7	19	12	22	23
9.08	200	0.05	0.5	26	67	23	39	85	32	85	60	92	33
1.13	500	0.2	2.6	13	18	21	12	5	7	15	6	3	28
2.26	1000	0.1	1.3	16	30	17	13	15	38	7	88	23	35
4.52	2000	0.05	0.65	58	37	50	20	57	67	85	15	50	184

TABLE III[a]

$Ne^{-\theta}$	$N \times 10^{-3}$	s	λ	A	B	C	D	E
1.83	2	0.2	1.4	2	10	8	1	16
4.56	5	0.1	0.7	12	35	21	8	6
13.7	15	0.05	0.35	21	54	85	35	20
2.27	50	0.2	2.0	29	7	2	1	10
4.54	100	0.1	1.0	8	2	34	2	57
9.08	200	0.05	0.5	15	71	19	7	37
1.13	500	0.2	2.6	7	37	10	1	1
2.26	1000	0.1	1.3	14	9	24	5	1
4.52	1000	0.05	0.65	6	4	6	13	16

[a] For the same values of N, s, λ as in Table II, columns A,..., E show the actual number of generations to lose the first class in five independent simulations.

the plausibility of the idea that the times to lose successive generations, after the first, have the same distribution, and also (Table III) to verify the idea that the times to lose the first class may well have a different distribution from the times to lose subsequent ones.

The way in which successive generations were obtained in the simulation was as follows. Given the class sizes $\{X_k(t)\}$, the mean class sizes for generation $(t + 1)$ were calculated from (2a); for a mean class size not exceeding 36, a Poisson random variable of that mean was generated, and if the mean class size exceeded 36, the usual approximating normal distribution was used. To keep the total population size constant at N, individuals were added to, or deleted from, the existing classes in the proportions required to achieve the aim. This procedure is very similar to that used by Bodmer and Cavalli-Sforza (1972), who reported that their programme had been adapted for the exact multinomial distribution by Guess, and found to give "undistinguishable" results from their own.

Forty-one sets of data, covering 33 different combinations of N, s and λ, were generated in this manner, with the results shown in Table I. The multiple regression line was calculated as

$$W = -18.9 + 3.78 \, Ne^{-\theta} + 7.2 \log \theta + 1.71s^{-1}, \tag{9}$$

with the coefficients of $Ne^{-\theta}$ and s^{-1} very highly significant. It is obviously unjustifiable to quote coefficients to such accuracy, so we suggest the use of

$$\hat{W} = 4Ne^{-\theta} + 7 \log \theta + 2s^{-1} - 20 \tag{9a}$$

to obtain an estimate of the speed of the Ratchet. The values of $\hat{W}$, calculated from (9), are also shown in Table I. As another check on (9), five populations with completely different parameters were simulated as above; the results are shown in Table IV. The usual warnings about the misleading results obtainable from using a regression to extrapolate well beyond the ranges used to derive the equation certainly apply here.

TABLE IV[a]

$N \times 10^{-3}$	s	λ	θ	$Ne^{-\theta}$	μ	σ	$\hat{W}$
20	0.12	1.02	8.5	4.07	20.8	11.5	26.2
50	0.12	1.02	8.5	10.2	46.9	26.9	49.4
50	0.06	0.51	8.5	10.2	61.3	30.5	63.7
20	0.06	0.51	8.5	4.07	42.7	27.4	40.5
10	0.03	0.255	8.5	2.03	41.6	26.0	61.4

[a] As for Table I (see text).

Note that the values of σ in Tables I and IV are not to be used as estimates of the standard deviation of W, because the times to lose successive generations (from which the observed value of W is calculated) are not independent. Rather,

they should be used (along with Table II) to get an *idea* of the variability of the speed at which the Ratchet operates. The regression estimate of the standard error of W is about 6.1, and it is evident that the use of W with this standard error to obtain a confidence interval for μ is justified for N, s, λ in the appropriate ranges.

Our description so far has concentrated on the fate of the fittest class; other items of interest are the vector $\mathbf{X}(t)$ itself, and the number $Z(t)$ of deleterious mutations in a randomly selected member of generation t. The above analysis suggests that the population moves towards the next equilibrium upon the loss of a class, so that $\mathbf{X}(t)$ will retain its shape, but moves one step to the right; consequently, $Z(t)$ tends to increase by one at the same rate as the Ratchet operates, and the simulations confirm this (see Fig. 1). Eshel (1971, 1972) and Guess (1974a, b) have obtained results which lend support.
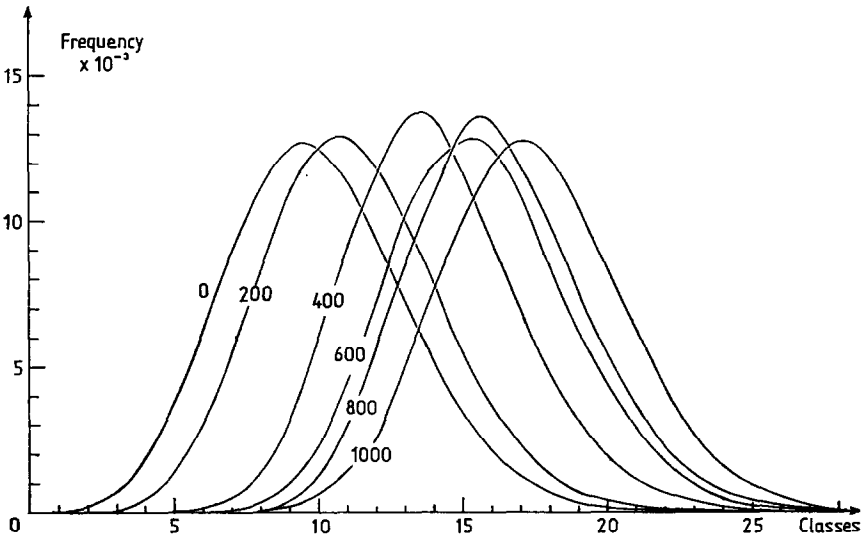
FIG. 1. For one simulation with $N = 10^5$, $\theta = 10$, $s = 0.02$, the distribution is shown at intervals of 200 generations. The values of $M_1(t)$ are 10.00, 11.24, 14.01, 15.63, 16.20, and 17.45.

Eshel considered an infinite population in which an individual of type x has relative fitness λ^x for some $\lambda > 1$, and that an x-individual mutates to $x + u$, in the next generation, according to some probability distribution $G(u)$. He looked at $F_t(x)$, the proportion of the population at time t with type $\leqslant x$, and the associated quantities

  (i) $E_t(x) = \int x \, dF_t(x)$, the mean fitness at time t;

  (ii) $V_t(x) = \int (x - E_t(x))^2 \, dF_t(x)$, the fitness variance;

  (iii) $F_t(x - E_t(x))$, the centred distribution.

He showed that (i) $E_{t+1}(x) - E_t(x)$, the rate of evolution, converges if and only if there is an upper bound to the amount of beneficial mutation; (ii) under these circumstances, $V_t(x)$ converges to a finite limit σ^2, and (iii) $x - E_t(x)$ converges in distribution.

Guess (1974a, b) considered a finite population of fixed size N, in which any mutation is to a completely new allele. He showed that, when fitness is multiplicative (as in our process), the sequence of relative fitnesses of the N individuals converges weakly to a nondegenerate stationary distribution which can, in principle, be computed explicitly. As Guess points out, the series involved converge too slowly for practical purposes.

The part of the next theorem, whose proof is in the Appendix, pertaining to $M_1(t)$, $M_2(t)$ is similar to that of Moran (1975).

THEOREM 2. *Write $M_r(t) = \sum_i i^r X_i(t)/N$ $(r = 1, 2,...)$. Then, if E denotes expectation of quantities in generation $t + 1$ conditional on $\mathbf{X}(t)$,*

$$E(M_1(t + 1)) = M_1(t) + [\lambda + H_1(s) - H_1(0)], \tag{10}$$

$$E(M_2(t + 1) - M_1^2(t + 1))$$
$$= (1 - N^{-1})[M_2(t) - M_1^2(t) + [\lambda + H_2(s) - H_2(0) - H_1^2(s) + H_1^2(0))]], \tag{11}$$

$$E(Z^2(t + 1)) - E(Z(t + 1))^2 = \lambda + H_2(s) - H_1^2(s), \tag{12}$$

where

$$H_r(s) = \sum_k k^r X_k(t)(1 - s)^k \Big/ \sum_k X_k(t)(1 - s)^k. \tag{13}$$

The rth central moment of the distribution $\mathbf{X}(t)$ can be written $M_r'(t)$; in this notation, expanding $H_1(s)$, $H_2(s)$ about $s = 0$, we see that

$$E(M_1(t + 1)) = M_1(t) + \lambda - sM_2'(t) + (s^2/2)(M_3'(t) - M_2'(t)) + O(s^3), \tag{14}$$

$$E(M_2'(t + 1))$$
$$= (1 - N^{-1})[M_2'(t) + \lambda - sM_3'(t) + (s^2/2)(M_4'(t) - M_3'(t) - 3M_2'(t)^2) + O(s^3)]. \tag{15}$$

For the distribution (6), the values of M_2', M_3' are θ and (15) indicates that M_2' will have a stationary value just less than θ; thus, from (14), $E(M_1(t + 1)) > M_1(t)$, which shows that $M_1(t)$, and hence $Z(t)$, tends to increase. The expansion of (14) to give an estimate of the rate of the Ratchet is a delicate matter, and it seems wise to use just (14), (15) to suggest the conditions under which the Ratchet will move more swiftly: from (15), if $M_3'(t)$ is rather more than θ, $M_2'(t + 1)$ will tend to be below θ, and so, from (14), $M_1(t + 2)$ will tend to exceed $M_1(t + 1)$; this suggests a picture of a positively skewed distribution

tending to increase the mean number of mutations two steps later, and so
dragging the Ratchet forward via a decrease in the variance. See Fig. 2, which
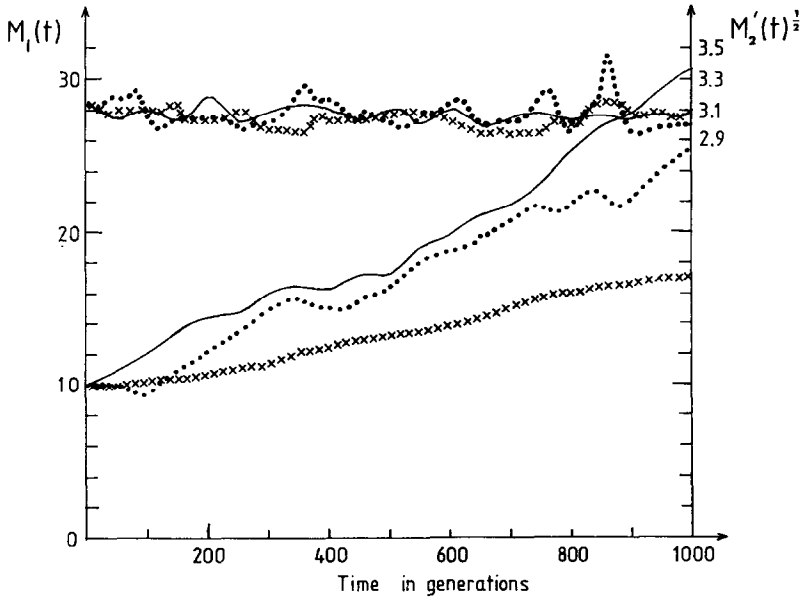confirms that $M_1(t)$ will tend to decrease when $M_2'(t)$ is large.

FIG. 2. Simulations of the progress of $M_1(t)$ (lower graphs, scale on left axis) and
$(M_2'(t))^{1/2}$ (upper graphs, scale on right axis) for 1000 generations. In each case, $N = 10^5$
and $\theta = 10$, with $s = 0.01$ (xxxx), $s = 0.03$ ($\cdots\cdots$), and $s = 0.05$ (———).

THE EFFECT OF BENEFICIAL MUTATIONS

The simplest way to modify the model above to incorporate beneficial muta-
tions is to assume that such mutations arise on a genome at rate μ, independently
of the deleterious mutations arising at rate λ, with the actual numbers of muta-
tions having Poisson distributions. The relative fitness of an individual is $(1 - s)^k$,
where k is the excess of bad mutations over good ($-\infty < k < \infty$). The
Markov process in which the state in generation t is the vector $\mathbf{X}(t)$ has no
equilibrium distribution, but the relative numbers of net bad mutations on the
individuals will remain close together—see Ewens' explanation of this, as
reported by Kingman (1976).

It is interesting to compare this process with Muller's Ratchet. Suppose
$\lambda > \mu > 0$, and that λ, μ remain constant over time. (This implicitly assumes
an infinite number of loci.) Then the appropriate Ratchet is the one in which
the rate of deleterious mutations is $\lambda - \mu$, and we shall seek to find the pro-

bability that, in this new process, a new fitter class becomes established before the current fittest class is lost by drift.

Suppose we have just lost the fittest class by drift; the new fittest class has size x_t in t generations time, and probability that a fitter individual arises in the following generation is (assuming μ is small) μx_{t+1}. If t is not large, (8) shows us that x_{t+1} has an average value of approximately $n_1\gamma(t)/(1 - e^{-\theta\gamma(t)})$, and the absolute fitness of such an individual is $(1 - s)^{-1} Ne^{-\lambda}/U_1(t + 1)$ which, from (19), is approximately

$$(1 - \exp(-\theta\gamma(t + 1)))/(1 - \exp(-\theta\gamma(t + 2))) = 1 + \frac{x_{t+2} - (1 - s)x_{t+1}}{(1 - s)x_{t+1}}.$$

Since the probability that a mutant gene of fitness $1 + \epsilon$ becomes established is approximately 2ϵ, the probability that, in generation t, a fitter mutatnt arises which is destined to become established is approximately

$$2\mu(x_{t+2} - (1 - s)x_{t+1})/(1 - s).$$

Thus, the probability that we do *not* produce a new, fitter class during the lifetime of the present fittest class is estimated as

$$\exp\left[-\frac{2\mu}{1 - s} \sum (x_{t+2} - (1 - s)x_{t+1})\right], \tag{16}$$

the summation being over the values of t during which the current class remains the fittest.

If the mean size of this class during its (mean) lifetime of K generations is $\bar{x}$, (16) is approximately

$$\exp\left[-\frac{2\mu}{1 - s} (sK\bar{x} - sx_0 - x_1)\right] \simeq \exp\left[-\frac{2\mu}{1 - s} (sK\bar{x} - (1 - 2s)n_1)\right]. \tag{17}$$

We could use (9) to estimate K, but estimation of $\bar{x}$ is difficult. Perhaps the most useful deduction from (17) is that, since (17) decreases as μ increases, if $\lambda - \mu$ is given, the probability that a new fitter class arises before the current fittest class is lost (and hence the probability that it is beneficial, rather than deleterious, mutations that will tend to accumulate) is an increasing function of μ. Also, if K, $\bar{x}$ are large (which will tend to correspond to $Ne^{-\theta}$ large), beneficial mutations will tend to accumulate.

CONCLUSION

In naturally occurring populations, there will be beneficial as well as deleterious mutations; no population can support an indefinite rise in the number of

deleterious mutations it carries, so we suggest that natural populations will reach such a size N that $Ne^{-\theta}$ (here $\theta = (\lambda - \mu)/s$) has at least a moderate size, or, as an alternative, if $Ne^{-\theta}$ is small, μ cannot also be small.

As Maynard Smith (1978, Chap. 3) points out, back mutation is largely irrelevant to the operation of the Ratchet: if the Ratchet is operating, the fittest class will be small, (say, $\leqslant 50$) and the number of generations it remains the fittest class will seldom exceed 500; hence the total number of individuals in the optimal class, summed over the time it remains the optimal class has an upper estimate of 25,000; a back mutation rate of 10^{-8} means that the chance of an optimal member undergoing back mutation is less than 0.0025.

Appendix

Proof of Theorem 1.   By induction. Since $m_k(0) = n_{k+1}/(1 - e^{-\theta})$, the result is exact for $t = 0$.

Suppose inductively that the result holds for all k, and all $t \leqslant u$. Then

$$E(Y_k(u + 1) \mid \mathbf{Y}(u)) = N \sum_{j=0}^{k} Y_{k-j}(u)(1 - s)^{k-j} \frac{e^{-\lambda \lambda^j}}{j!} \Big/ U_1(u), \qquad (18)$$

where

$$U_1(u) = \sum_{k=0}^{\infty} Y_k(u)(1 - s)^k.$$

Hence

$$E(U_1(u)) \simeq \sum_{k=0}^{\infty} n_{k+1} \frac{(1 - (1 - \gamma(u))^{k+1})}{1 - e^{-\theta \gamma(u)}} (1 - s)^k,$$

using the inductive assumption. This simplifies, using (6), to

$$E(U_1(u)) \simeq \frac{Ne^{-\lambda}(1 - e^{-\theta \gamma(u+1)})}{(1 - s)(1 - e^{-\theta \gamma(u+1)})}. \qquad (19)$$

We have already shown that $T_1(t)$ has a small coefficient of variation, and the same will hold for the analogous quantity $U_1(u)$. Thus, we can approximate

$$E\left(\frac{Y_i(u)}{U_1(u)}\right) \quad \text{as} \quad \frac{E(Y_i(u))}{E(U_1(u))},$$

and, from (18) and the inductive assumption,

$$E(Y_k(u+1) \mid \mathbf{Y}(0)) = \frac{1}{1 - e^{-\theta}} (n_1, n_2, \ldots))$$

$$\simeq \frac{Ne^{-\lambda}(1-s)(1-e^{-\theta\gamma(u)})}{Ne^{-\lambda}(1-e^{-\theta\gamma(u+1)})} \sum_{j=0}^{k} m_{k-j}(1-s)^{k-j} \lambda^j/j!,$$

which, using (8), simplifies to the required quantity $m_k(u+1)$.

Proof of Corollary to Theorem 1.   (a) τ has been chosen to correspond to $\gamma(\tau) \simeq \theta^{-1}$. Hence,

$$m_k(\tau) = n_{k+1}(1 - (1 - \theta^{-1})^{k+1})/(1 - e^{-1})$$

$$\simeq \frac{k+1}{\theta} \cdot n_{k+1} \cdot \frac{1}{1 - e^{-1}} \qquad \text{for} \quad k \text{ small.}$$

Now $(k+1)n_{k+1}/\theta = n_k$, and $(1 - e^{-1})^{-1} \simeq 1.6$, which proves (a).

  (b) From (19), since $\gamma(\tau+1) = (1-s)\gamma(\tau) \simeq (1-s)/\theta$,

$$E(U_1(\tau)) \simeq \frac{Ne^{-\lambda}(1 - e^{-(1-s)})}{(1-s)(1-e^{-1})}$$

$$= Ne^{-\lambda}\Big/\Big(1 - \frac{e-2}{e-1} s + o(s)\Big)$$

$$\simeq Ne^{-\lambda}/(1 - 0.4s).$$

Proof of Theorem 2.

$$E(M_1(t+1)) = \sum_i i p_i(t); \qquad \text{using (1),}$$

$$= \sum_i (i - j + j) \sum_{j=0}^{i} X_{i-j}(t)(1-s)^{i-j}e^{-\lambda} \frac{\lambda^j}{j!} \Big/ T_1(t)$$

$$= H_1(s) + \lambda,$$

from which (10) follows, since $M_1(t) = H_1(0)$. Also,

$$E(M_1^2(t+1)) - E(M_1(t+1))^2$$

$$= \frac{1}{N^2} \sum_{i,j} ij\, E(X_i(t+1)\, X_j(t+1)) - \frac{1}{N^2}\Big(\sum_i i\, E(X_i(t+1))\Big)^2$$

$$= \frac{1}{N^2} \sum_{i,j} ij\, \text{Cov}(X_i(t+1), X_j(t+1)),$$

and, using (2b), (2c),

$$E(M_1{}^2(t+1)) - E(M_1(t+1))^2 = \frac{1}{N} \sum_i i^2 p_i(t) - \frac{1}{N} \sum_{i,j} ij p_i(t)\, p_j(t).$$

Thus,

$$E(M_2(t+1) - M_1{}^2(t+1))$$

$$= (1 - N^{-1}) \left[\sum_i i^2 p_i(t) - \left(\sum ip_i(t) \right)^2 \right]$$

$$= (1 - N^{-1})[H_2(s) + 2\lambda H_1(s) + \lambda^2 + \lambda - (\lambda + H_1(s))^2]$$

$$= (1 - N^{-1})[\lambda + H_2(s) - H_1{}^2(s)], \tag{19}$$

from which (11) is immediate.

Since
$$E(Z(t+1) \mid \mathbf{X}(t+1)) = M_1(t+1),$$

$$E(Z(t+1)) = \sum_i ip_i(t),$$

and thus, because

$$E(Z^2(t+1)) = \sum i^2 p_i(t),$$

(12) follows from (19).

REFERENCES

BODMER, W., AND CAVALLI-SFORZA, L. L. 1972. Variation in fitness and molecular evolution, *Proc. Sixth Berkeley Symp.* **5**, 255–275.

ESHEL, I. 1971. On evolution in a population with an infinite number of types, *Theor. Pop. Biol.* **2**, 209–236.

ESHEL, I. 1972. Evolution processes with continuity of types, *Advan. Appl. Prob.* **4**, 475–507.

FELSENSTEIN, J. 1974. The evolutionary advantage of recombination, *Genetics* **78**, 737–756.

GUESS, H. A. 1974a. Evolution in finite populations with infinitely many types, *Theor. Pop. Biol.* **5**, 417–430.

GUESS, H. A. 1974b. Limit theorems for some stochastic evolution models, *Ann. Prob.* **2**, 14–31.

KIMURA, M., AND MARUYAMA, T. 1966. The mutational load with epistatic gene interactions in fitness, *Genetics* **54**, 1337–1351.

KINGMAN, J. F. C. 1976. Coherent random walks arising in some genetical models, *Proc. R. Soc. London, Ser. A* **351**, 19–31.

MAYNARD SMITH, J. 1978. "The Evolution of Sex," Cambridge Univ. Press, London/New York.

MORAN, P. A. P. 1975. Wandering distributions and the electrophoretic profile, *Theor. Pop. Biol.* **8**, 318–330.

MULLER, H. J. 1964. The relation of recombination to mutational advance, *Mutat. Res.* **1**, 2–9.