

THE SURVIVAL OF A MUTANT GENE UNDER SELECTION. II

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R. A. Fisher (1930) has obtained approximate expressions for the probability of survival of a new mutant in a finite population of haploid individuals in which the generations are non-overlapping. Suppose that we have M haploid individuals which are either of genotype a or A , and suppose that a has a small selective advantage over A so that the relative numbers of offspring have expectations proportional to $1 + s$ and 1 respectively, where s is small and positive. If each generation is produced by binomial sampling with probabilities proportional to the numbers of a and A individuals in the previous generation multiplied by their respective selective values, and if initially there is only one individual of type a , the probability of the population ultimately becoming entirely of this type is approximately

$$\frac{2s}{1 - e^{-2sM}}$$

so long as s^2M is small. This also holds when s is small and negative.

Fisher obtains this result by a heuristic argument which involves approximating to the process by using a diffusion equation and fitting the solution of the latter at the boundaries by a complicated argument. In the present paper we obtain a more general and more exact result which may be stated as follows. If the initial number of mutants is k_0 the probability of the population ultimately being entirely of mutant type can be written

$$P_M = \frac{1 - e^{-2\theta k_0}}{1 - e^{-2\theta M}}$$

where θ is a number satisfying the inequalities

$$s(1 + s)^{-1} \leq \theta \leq s,$$

where s , the selection coefficient, is arbitrary but positive.

Suppose that in any generation there are k a -individuals and $M - k$

A-individuals. Then the probability of any individual in the next generation being *a* is

$$p_k = \frac{(1 + s)k}{M + sk},$$

and the probability of it being *A* is $q_k = 1 - p_k$. The process is thus a Markov chain in which the transition probability from state *k* to state *j* is

$$\binom{M}{j} p_k^j q_k^{M-j}.$$

There are two absorbing states at $k = 0$ and $k = M$ whose ultimate probabilities we denote by P_0 and P_M . There are no other absorbing states and these two are accessible from all other states. It follows from the elementary theory of Markov chains that the system must end in one of these states so that $P_0 + P_M = 1$. Let k_t and k_{t+1} be the values of *k* in generations *t* and *t* + 1 and suppose that there exists a constant θ depending on *s* but not on k_t , such that, for all values of k_t and all *t*,

$$(1) \quad E(e^{-2\theta k_{t+1}}) = e^{-2\theta k_t}$$

where *E* denotes the conditional expectation with k_t fixed. Then if k_0 is the initial number of *a*-individuals we have, by repeated application of (1)

$$e^{-2\theta k_0} = P_0 + P_M e^{-2\theta M},$$

so that

$$(2) \quad P_M = \frac{1 - e^{-2\theta k_0}}{1 - e^{-2\theta M}}.$$

In fact, however, there is no constant θ such that (1) is satisfied for all k_t , but if we put $\theta = s$ we get

$$\begin{aligned} E(e^{-2s k_{t+1}}) &= (q_k + p_k e^{-2s})^M \\ &= \left\{ \frac{M - k_t + (1 + s)k_t e^{-2s}}{M + s k_t} \right\}^M \end{aligned}$$

and for *s* small this is very nearly equal to $\exp -2s k_t$. Thus we may guess that (2) will give a good approximation to P_M when $\theta = s$. For $k_0 = 1$ this is, to the first order, Fisher's result.

One way of proving this would be to show that the error in (1) with $\theta = s$, is so small that its cumulative effect is still small when so many generations have elapsed that it is overwhelmingly probable that $k = 0$ or *M*. However, it is very difficult to estimate the number of generations required for this to be so. We therefore approach the problem in another way

by considering another Markov chain whose transition probabilities approximate to those of the genetic problem.

Suppose in fact that we have a Markov chain with $M + 1$ states $k = 0, 1, \dots, M$ and transition probabilities from state k to state j defined by

$$\binom{M}{j} \pi_k^j (1 - \pi_k)^{M-j},$$

where

$$(3) \quad \pi_k = \frac{1 - e^{-2\theta k M^{-1}}}{1 - e^{-2\theta}},$$

and θ is a positive constant. Then, writing k for k_t ,

$$\begin{aligned} E\{\exp -2\theta k_{t+1}\} &= \{1 - \pi_k + \pi_k \exp -2\theta\}^M \\ &= \left\{ \frac{e^{-2\theta k M^{-1}} - e^{-2\theta} + e^{-2\theta} - e^{-2\theta(1+kM^{-1})}}{1 - e^{-2\theta}} \right\}^M \\ &= \exp -2\theta k_t, \end{aligned}$$

for all values of k_t .

Thus for this chain the probability of ultimate absorption in the state $k = M$ is given exactly by

$$(4) \quad P'_M = \frac{1 - \exp -2\theta k_0}{1 - \exp -2\theta M}.$$

We now show that if $\pi_j \geq p_j$ for all $j = 0, \dots, M$ in the previous model, $P'_M \geq P_M$ for all k_0 . Write $P_M(k, t)$ for the probability of absorption in the state $j = M$ in t or less generations using the probabilities $\{p_j\}$ and starting from the state k . Let $P'_M(k, t)$ be the similar probability using the probabilities $\{\pi_k\}$.

We prove by induction that $P'_M(k, t) \geq P_M(k, t)$ for all t and all k from which it will follow that $P'_M \geq P_M$. Suppose that $P'_M(k, t) \geq P_M(k, t)$ for all k and a particular value of t and assume for the moment that $P_M(k, t)$ is a non-decreasing function of k . Then

$$\begin{aligned} P'_M(k, t + 1) &= \sum_{j=0}^M \binom{M}{j} \pi_k^j (1 - \pi_k)^{M-j} P'_M(j, t) \\ &\geq \sum_{j=0}^M \binom{M}{j} \pi_k^j (1 - \pi_k)^{M-j} P_M(j, t). \end{aligned}$$

The last expression will be greater than

$$P_M(k, t + 1) = \sum_{j=0}^M \binom{M}{j} p_k^j (1 - p_k)^{M-j} P_M(j, t)$$

for $\pi_k \geq p_k$ if the expression

$$T = \sum_{j=0}^M \binom{M}{j} x^j (1-x)^{M-j} P_M(j, t)$$

is a non-decreasing function of x when $P_M(j, t)$ is a non-decreasing function of j . But

$$\begin{aligned} \frac{dT}{dx} &= \sum_{j=0}^M \binom{M}{j} \{jx^{j-1}(1-x)^{M-j} - (M-j)x^j(1-x)^{M-j-1}\} P_M(j, t) \\ &= \sum_{j=1}^M M \binom{M-1}{j-1} x^{j-1} (1-x)^{M-j} P_M(j, t) \\ &\quad - \sum_{j=0}^{M-1} M \binom{M-1}{j} x^j (1-x)^{M-j-1} P_M(j, t) \\ &= \sum_{j=0}^{M-1} M \binom{M-1}{j} x^j (1-x)^{M-j-1} \{P_M(j+1, t) - P_M(j, t)\} \geq 0. \end{aligned}$$

To complete the proof we have to show that $P_M(j, t)$ is non-decreasing in j . This is clearly true for $t = 1$ and we suppose it true for $t - 1$. Then

$$\begin{aligned} P_M(j+1, t) &= \sum_{k=1}^M p_{j+1}^k (1-p_{j+1})^{M-k} P_M(k, t-1) \\ &\geq \sum_{k=1}^M p_j^k (1-p_j)^{M-k} P_M(k, t-1) = P_M(j, t) \end{aligned}$$

by a similar argument to that given above. The result is therefore true for all t . In a similar way, or by symmetry, it follows that if $\pi_k \leq p_k$ for all k , then $P'_M \leq P_M$.

We next consider what values of θ will make $\pi_k \leq p_k$ or $\pi_k \geq p_k$ for all k . If $p_k \geq \pi_k$ we must have, writing $x = kM^{-1}$,

$$\frac{(1+s)x}{1+sx} \geq \frac{1-e^{-2\theta x}}{1-e^{-2\theta}}$$

for x in the range $0 \leq x \leq 1$. This is equivalent to asserting that

$$f(x) = x - 1 - xe^{-2\theta} - sxe^{-2\theta} + e^{-2\theta x} + sxe^{-2\theta x} \geq 0$$

in this range. Clearly $f(0) = f(1) = 0$. Furthermore

$$f''(x) = 4\theta e^{-2\theta x} \{\theta - s + s\theta x\}$$

Then $f(x) \geq 0$ in $(0, 1)$ if $f''(x) \leq 0$ in this range and $f(x) \leq 0$ if $f''(x) \geq 0$. Suppose s and θ are positive. Then $f''(x) \geq 0$ if $\theta > s$ and $f''(x) \leq 0$ if $\theta \leq s(1+s)^{-1}$. Applying this to the previous results we see that the probability of ultimate survival of the mutant a is given by the formula

$$(5) \quad P_M = \frac{1 - e^{-2\theta k_0}}{1 - e^{-2\theta M}}$$

where θ is a number satisfying the inequalities

$$s(1 + s)^{-1} \leq \theta \leq s.$$

This result is exact and holds for all k_0 and any positive s . The probability of success for a selectively disadvantageous mutant can be found by regarding A as the mutant and $1 - P_M$ as its chance of success. When s tends to zero, P_M tends to $k_0 M^{-1}$ as is otherwise obvious.

It is also interesting to consider the case where M tends to infinity and s is positive. Then $P_M = 1 - e^{-2\theta k_0}$ so that the probability of extinction is $P_0 = e^{-2\theta k_0}$. However, it is known that for an infinite population the probability of extinction is ζ^{k_0} where ζ is the non-negative non-unit root of the equation $z = P(z)$, and $P(z)$ is the generating function of the number of offspring. In the present case $P(z) = \exp(1 + s)(z - 1)$. We can in fact verify that this root can be written as $\zeta = \exp -2\theta$ where $s(1 + s)^{-1} \leq \theta \leq s$.

It is of interest to extend this theory to more elaborate models. Suppose that the population consists of diploid individuals and that a distinction is made between the sexes so that we have N_1 males and N_2 females. In any generation let the number of aa , Aa , and AA individuals be k , $N_1 - k - l$, l and r , $N_2 - r - s$, s in the males and females respectively. Then, in the absence of selection, the probabilities of a male gamete being a or A will be proportional to $(N_1 + k - l)$ and $(N_1 - k + l)$ respectively. If we again suppose that a -gametes have a selective advantage s , the probabilities $\phi_M(a)$, $\phi_M(A)$ of male gametes of types a , A entering into the formation of an individual of the next generation will be given by

$$\phi_M(a) = \frac{\frac{1}{2}(1 + s)(N_1 + k - l)}{N_1 + \frac{1}{2}s(N_1 + k - l)},$$

$$\phi_M(A) = \frac{\frac{1}{2}(N_1 - k + l)}{N_1 + \frac{1}{2}s(N_1 + k - l)},$$

with similar expressions for $\phi_F(a)$, $\phi_F(A)$ obtained by replacing k and l by r and s . Thus this model assumes purely gametic selection and this will be equivalent to zygotic selection only when the heterozygote is exactly intermediate in selective value between the two homozygotes.

In the N_1 male individuals in the next generation the number of a -genes will be the sum of the numbers derived from male and female parents and these will be distributed independently. Thus if k_{t+1} , l_{t+1} are the numbers of aa and AA individuals in the next generation and ϕ is any constant we obtain

$$E\{\exp \phi(N_1 + k_{t+1} - l_{t+1})\} = \{p_M(A) + p_M(a)e^\phi\}^{N_1}\{p_F(A) + p_F(a)e^\phi\}^{N_1}$$

where E denotes an expectation conditional on the values at the t -th generation.

By the theory given above we can approximate to $p_M(a)$ and $p_M(A)$ by

$$\pi_M(a) = \frac{1 - \exp -\theta(N_1 + k_t - l_t)N_1^{-1}}{1 - \exp -2\theta},$$

$$\pi_M(A) = \frac{\exp -\theta(N_1 + k_t - l_t)N_1^{-1} - \exp -2\theta}{1 - \exp -2\theta}$$

where $s(1 + s)^{-1} \leq \theta \leq s$. Putting $\phi = -2\theta$ we then find that

$$\begin{aligned} & \{\pi_M(A) + \pi_M(a)e^{-2\theta}\}^{N_1} \\ &= \left\{ \frac{\exp -\theta(N_1 + k_t - l_t)N_1^{-1} - \exp [-2\theta - \theta(N_1 + k_t - l_t)N_1^{-1}]}{1 - \exp -2\theta} \right\}^{N_1} \\ &= \exp -\theta(N_1 + k_t - l_t). \end{aligned}$$

Similarly

$$\{\pi_F(A) + \pi_F(a)e^{-2\theta}\}^{N_1} = \exp -\theta(N_2 + r_t - s_t)N_1N_2^{-1}.$$

and we can similarly find $E\{\exp -2\theta(N_2 + r_{t+1} - s_{t+1})\}$. Thus, using the modified probabilities

$$\begin{aligned} & E \exp -2\theta\{N_1 + k_{t+1} - l_{t+1} + r_{t+1} - s_{t+1}\} \\ &= \exp -\theta\{(N_1 + k_t - l_t)(1 + N_2N_1^{-1}) + (N_2 + r_t - s_t)(1 + N_1N_2^{-1})\}. \end{aligned}$$

We cannot make any further progress unless we assume that $N_1 = N_2 = \frac{1}{2}N$, which results in

$$E \exp -2\theta\{k_{t+1} - l_{t+1} + r_{t+1} - s_{t+1}\} = \exp -2\theta\{k_t - l_t + r_t - s_t\}.$$

There are only two absorbing states in the Markov chain and these are $(k = N_1, r = N_2)$ and $(l = N_1, s = N_2)$. If the ultimate probabilities of these are P_M and $1 - P_M$ we find, by using the same kind of argument as before, that

$$(6) \quad P_M = \{1 - \exp -2\theta[N + k_0 - l_0 + r_0 - s_0]\}\{1 - \exp -4\theta N\}^{-1}.$$

It is then plausible that this gives the probability of survival in the diploid population if θ has some value satisfying $s(1 + s)^{-1} \leq \theta \leq s$. A proof that this is so, along the lines of the previous proof would be lengthy and will not be attempted here. Note, however, that so long as $N_1 = N_2$ (6) agrees with the result (5) if the diploid population is considered to consist of $2N$ haploid individuals. When $N_1 \neq N_2$ the probability of survival is not known.

These results have been established solely for genetic selection, or what

amounts in practice to the same thing, zygotic selection in the absence of dominance. It would be important to obtain similar results with dominance effects but this appears to be more difficult.

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References

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