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The Detection of Particular Genotypes in Finite Populations I. Natural Selection Effects*

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1. INTRODUCTION

A problem of wide interest considered first by Robertson (1978) concerns the task of estimating the distribution of the time of the first appearance of a recessive visible gene (e.g., a lethal homozygote) in a finite population starting with a single heterozygote. This inquiry is relevant in artificial selection practices as it pertains to early detection of carriers of deleterious genes. From the perspective of evolutionary dynamics, this problem concerns the elapsed time to observation of new mutant types, equal or unequal crossover events, insertion or deletion sequences, etc. It may also lend insight into the objectives of medical genetic screening that attempts to identify carriers of defective genes or chromosomal anomalies.

The model investigated is as follows. Consider a finite population of N diploid individuals, comprising the two genotypes AA and Aa in numbers $N-i$ and i, respectively. Two mechanisms for producing the next generation were considered by Robertson (1978), reflecting the consequences of random mating and finite sampling effects.

I. The population composition corresponds to $2N-i$ A-gametes and i a-gametes. The next generation of j a-gametes (and $2N-j$ of A) is produced by Binomial (Wright–Fisher) sampling, the diploid individuals then being formed by pairing the gametes at random. Robertson considered the case of a visible homozygous genotype aa, and so the process of diploid formation terminates with the appearance of the first such homozygote.

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II. The same model can be derived under the assumption of random mating, the process continuing as long as no *aa*-homozygote is sampled in the next generation.

Robertson estimated the number of generations until the first visible homozygote appears, using simulation techniques and matrix numerical methods. He perceived the order of magnitude of $N^{1/3}$ generations for the expected time to detection. This particular model was analyzed by use of diffusion approximations in Karlin and Tavaré (1980). The object of this paper is to examine a number of variations on the basic problem. We indicate briefly several extensions and further issues:

(a) What happens in the presence of differential viability selection forces? (b) The recessive homozygote may entail unobserved natural abortions, prolonging the expected time to detection. What are the consequences of these events in the model? (c) It is possible that mating types involving heterozygote carriers entail reduced fertility compared to wild type matings. What is the effect of variable fertility rates on the behavior of the model?

(d) It is possible that the homozygous genotype *aa* cannot always be detected with certainty. So how do different detection contingencies influence the time to detection? We may be interested in a screening program that partially succeeds in detecting heterozygous carriers, *Aa*. How does the type of the incomplete detection scheme influence the outcome of the process? Generally, how do different screening methods alter the probability of detection of a lethal genotype?

(e) An analysis of nonrandom mating patterns, including the cases of selfing lines, matings confined to a particular type, and other regular breeding schemes may be of economic–genetic interest, especially in artificial selection practices.

For the models I and II we would like to ascertain:

(i) The probability that the process will end in detection of the mutant type as opposed to fixation of the wild type. (ii) The expected time until either loss of the *a* allele, or *aa*-detection. (iii) Functionals of the process, including the aggregate number of heterozygous carriers ever occurring in the population until detection of the first recessive homozygote, and the mean, variance and higher moments of the detection and/or fixation times. (iv) Apart from cumulative heterozygosity, another measure of genetic cost to the population is the number of carriers that occur in the population at the time of detection. The properties of the distribution of this variable are of interest.

In our analysis we employ diffusion approximation to variations of the finite model set forth in I and II above. The novelty in the analysis is that the

underlying discrete process has not only an absorbing state, but also a killing rate which depends on the population configuration. This killing rate derives from terminating the process either by detection of the genotype *aa* or, perhaps, detection of a heterozygous carrier.

Such diffusion processes with killing already occur in the literature. One example involves the determination of the probability that a recombinant type appears before fixation (Karlin *et al.*, 1966); another involves the formation of high order mutants (Karlin, 1973).

The statement of the problem involves first passage times to either an absorbing state (corresponding to loss of the *a*-allele) or to a point not described in the state space of the process (corresponding to detection of particular gametes or genotypes). Thus, in the present detection model the outcome indicating the first appearance of a recessive homozygote terminates the breeding line in which it occurs and the corresponding difusion is now governed by infinitesimal drift and variance effects as usual, but also an infinitesimal killing rate which is also a function of the state variable.

It is true that the order of time to detection in a variety of these models is of relatively low dependence on population size; in fact of the order $N^{1/3}$ generations. This result can be interpreted in the following way. In a large population with the absence of selection and mutation effects, there is only a competition between fixation and the chance of detection if the initial number of heterozygotes is of order $N^{1/3}$. In this case detection (given that it occurs) takes of order $N^{1/3}$ generations. For an initial number of heterozygotes of order much smaller than $N^{1/3}$, then the only effective outcome is loss of the *a*-allele, and, therefore, no detection. If, on the other hand, the initial number is of order much larger than $N^{1/3}$, then detection of the *aa*-homozygote is effectively the only possibility. Further, conditional on detection occurring, the time to detection is also of order $N^{1/3}$ generations. The time scale $N^{1/3}$ stands in sharp contrast to the classical result on the expected time to the establishment of a new mutant gene conditioned on its fixation which is about $4N$ generations.

In seeking an incisive analysis of these models there are two processes of prime relevance. (i) The realizations in the approximating diffusion process $\{Y(t), t \geqslant 0\}$ ($Y(t)$ = number of heterozygote carriers at time t) end in one of two mutually exclusive outcomes: either that of random elimination of the heterozygote carriers through repeated sampling, leading to loss of allele *a* or detection of a visible recessive homozygote the *aa*-genotype. (ii) The second diffusion process arises by restricting consideration to the realizations of the process ending in killing (i.e., detection). The time scale translated from this diffusion to the discrete case is again $N^{1/3}$ generations.

Both diffusions are remarkably tractable and relate to a classical differential equation analyzed abundantly in studies on radio waves and light spectra. The basic solutions are known as Airy functions of the first and

second kind. They can be represented in terms of appropriate Bessel functions and have been extensively tabulated.

In Karlin and Tavaré (1980) we ascertained analytically for the model without selection the probability of loss as against detection of a homozygote recessive as a function of the initial heterozygote numbers and the cumulative number of heterozygotes over the population lifetime, i.e., until loss of allele a or its detection. We also calculated for the conditioned process (conditioning on the detection outcome) the same functionals and also the distribution of the maximum heterozygote numbers attained prior to detection. In particular, for an initial state corresponding to a *single* heterozygote, we determined the expected time until detection conditioned on detection to be $2.09N^{1/3}$ generations. The aggregate average numbers of heterozygotes over the life of this conditioned process is about $1.78N^{2/3}$. Analytic formulas for a variety of other functionals were also given.

Our main objective in this work is to analyze the effects on detection of selection differentials between AA-homozygotes and Aa-heterozygotes. If we suppose that selection acts on the heterozygotes, the selection difference being s (which may be positive or negative), then the diffusion method elaborated in Section 3 below shows that the scalings again have to be of order $N^{1/3}$, as long as the selection coefficient is of order $N^{-1/3}$ or less. The "usual" scaling of the selection coefficient in the framework of the Wright–Fisher model is N^{-1}; this result shows that we can have quite strong selection intensities before we significantly alter the probability of detection.

For models in which we allow mutation from the A-allele to the a-allele, the mutation rate is taken to be of order N^{-1}, and the correct order of magnitude for the time scale is again $N^{1/3}$; see Karlin and Tavaré (1981a). These facts show that the order of magnitude $N^{1/3}$ is quite a robust result for a wide spectrum of genetic models concerned with detecting particular genotypes in finite populations.

We will also examine models allowing differential fertility rates acting on the three feasible mating types $AA \times AA$, $AA \times Aa$ and $Aa \times Aa$. We can also treat the possibility that a fraction of unobserved aborted aa-homozygotes occur. In these models the time scale needs, in some cases, to be modified to N^{δ}, $\delta > 1/3$. Normalizations of the order $N^{1/2}$ and more generally N^{δ} already occur in certain finite population studies allowing very strong selection effects (Robertson and Narain, 1971; Guess and Levikson, 1978) and in situations of variable mutation rates (Karlin and McGregor, 1964).

We will now describe briefly the layout of the paper. In Section 2 we formulate precisely the basic discrete model of the phenomenon. In Section 3 the diffusion approximations are resolved, incorporating differential viability effects. A hierarchy of functionals are determined including the detection probability, moments of detection and fixation time, the expected cumulative

heterozygosity. Section 4 is devoted to an analysis of the model admitting variable fertility rates over the mating types. Discussion and interpretation of our results are interspersed throughout the paper with several key points highlighted in the concluding section.

In the following paper we consider a model where in addition to the fact that *aa*-individuals are visible as they appear, there is also an opportunity to screen for heterozygote carriers. This can be interpreted as a model involving partial penetrance of heterozygotes. We also assess the effect on detection of examining more individuals than are used as parents in the subsequent generation. This is often practiced in implementing artificial selection programs. In a similar vein, screening a number of relatives is done in seeking heterozygote carriers of certain rare genetic disorders. This will reduce the time until such defective genes are detected. A number of further variants including alternative homozygote detection schemes are considered.

2. The Models

(i) *Discrete Models*

We assume that the homozygote is visible, and therefore detectable as soon as it appears. Consider a monecious population of N diploid individuals, and a single locus at which there are two possible alleles, denoted by A and a. We are interested in the time to formation of the first homozygote, *aa*. It is convenient to let X_n be the number of heterozygotes at time n. If $X_n = i$, and we have not yet seen any recessive homozygotes, the number of A-alleles at time n is $2N - i$, and the number of a-alleles is i. To form the next generation, we suppose that selection acts on the AA, Aa genotypes, giving relative survival rates of $1: 1 + s$, respectively. Here, s may be negative (heterozygote disadvantage) or positive (heterozygote advantage). After selection, the probability of being an AA is

$$p_i = \Pr\{AA \text{ after selection} \mid X_n = i\} = \frac{N - i}{N + is}, \tag{1}$$

while

$$q_i = \Pr\{Aa \text{ after selection} \mid X_n = i\} = \frac{i(1 + s)}{N + is}. \tag{2}$$

A and a alleles are then formed in the ratio $x_i: 1 - x_i$, where

$$x_i = p_i + \frac{q_i}{2}. \tag{3}$$

We now have a conceptually infinite pool of gametes A, a in proportions $x_i: 1-x_i$. To form the gametes used to produce the next generation, we take a sample size $2N$. For definiteness we will consider the classical Wright–Fisher sampling scheme, so that the probability of producing j a-alleles (and $2N-j$ A-alleles), given i a-alleles at time n, is

$$\tilde{P}_{ij} = \binom{2N}{j} (1-x_i)^j x_i^{2N-j}, \qquad 0 \leqslant i, j \leqslant N. \tag{4}$$

We now need to pair up the genes to form the diploid individuals at time $n+1$. Clearly, the process continues if we form no aa genotypes, whereas if we form an "aa," then the process stops by detection. It is clear that we need to compute the probability C_j of producing no aa-pairs, given $2N-j$ A's, j a's, and using random pairing. It is elementary to verify that

$$\begin{aligned} C_j &= \frac{2^j N!(2N-j)!}{(2N)!(N-j)!}, \qquad j = 0, 1, \ldots, N \\ &= 0, \qquad\qquad\qquad\quad j = N+1, \ldots, 2N. \end{aligned} \tag{5}$$

Cf. Robertson (1978). It follows that if $X_n = i$, then $X_{n+1} = j$ with probability $P_{ij} = \tilde{P}_{ij} C_j$. Using (4) and (5) we have

$$P_{ij} = \binom{N}{j} [2x_i(1-x_i)]^j [x_i^2]^{N-j}, \qquad j = 0, 1, \ldots, N. \tag{6}$$

In the terminology of Markov chains, a transition matrix such as that given in (6) is called sub-Markovian, because the transition matrix no longer has all the row-sums equal to unity. In our model, this follows because the process can be terminated by the appearance of an aa-homozygote.

In the discrete state space case, we can add on an extra state, H, to transform the process into a standard Markov chain. The transition probabilities into the state H are given by

$$P_{iH} = 1 - \sum_{j=0}^{N} P_{ij} = 1 - (1 - (1-x_i)^2)^N, \qquad 0 \leqslant i \leqslant N, \tag{7}$$

while

$$P_{HH} = 1, \qquad P_{Hi} = 0, \qquad 0 \leqslant i \leqslant N. \tag{8}$$

Of course, state 0 is absorbing, since once the population comprises only A alleles, we can never observe an aa-homozygote.

In the case of the model involving no selection ($s = 0$) the transition matrix reduces to

$$P_{ij} = \binom{N}{j}\left(\frac{i}{N}\left(1-\frac{i}{2N}\right)\right)^j\left(1-\frac{i}{2N}\right)^{2N-2j}, \qquad i,j = 0, 1,..., N$$
$$P_{iH} = 1 - \left(1-\frac{i^2}{4N^2}\right)^N, \tag{9}$$

as given by Robertson (1978). See also Karlin and Tavaré (1980).

(ii) *An Alternative Derivation of the Model via Random Mating*

There is another instructive way to derive the form of the transition matrices in (6) and (9), which is the more natural for generalization. We work with the diploids all the time, and assume random mating in our population of size N. Let $\mathbf{i} = (i_1, i_2, i_3)$ be a vector denoting the number of AA, Aa, aa genotypes at time n. Of course, $i_1 + i_2 + i_3 = N$, and since we are assuming that no recessive homozygote has yet appeared, $\mathbf{i}$ is of the form $\mathbf{i} = (N - i, i, 0)$. Selection alters the relative odds of being AA or Aa in the ratio p_i: q_i, where p_i is given by (1). In order for the process to continue to time $n + 1$, and for $X_{n+1} = j$, we must transform the vector $\mathbf{i} = (N - i, i, 0)$ into the vector $\mathbf{j} = (N - j, j, 0)$. The probability of this event, computed by considering the outcomes of the three possible mating types at time n under Wright–Fisher sampling of N zygote offspring yields

$$P_{ij} = \binom{N}{j}(2x_i(1-x_i))^j(x_i^2)^{N-j}. \tag{10}$$

The transition matrix in (10) is precisely that derived in (6) by the pairing method. Eqs. (10) and (6) merely reaffirm the equivalence of random mating and random union of gametes in this finite population context. We remark that it would be easy to derive corresponding models using sampling schemes other than the classical Wright–Fisher model, but we will not do so here.

The problems of interest include the following. What is the probability of never observing a recessive homozygote? This is just the probability of reaching state 0—the a-allele is lost from the population—before reaching state H. In principle, this can be solved by finding the solution $(u_0, u_1,..., u_N)$ to the system of equations

$$u_i = \sum_{j=1}^{N} P_{ij}u_j + P_{i0}u_0, \qquad i = 1, 2,..., N, \tag{11}$$

under the initial condition $u_0 = 1$. This system can be solved numerically for small values of N, but it seems difficult to get explicit results for the u_l. Secondly, what is the mean time taken to observe a recessive homozygote conditional on this event occurring? Similarly, what is the mean time until the process stops, either by reaching the absorbing state 0 or the detection state H? Again, for small values of N it is possible to use standard theory and numerical methods to get some insights to these problems (cf. Robertson, 1978).

In order to analyze these models, we will resort to the method of diffusion approximation with the added contingency of killing, corresponding to the detection event. This will enable us to determine the effects of selection on the model, and to ascertain the appropriate time-scale and state space scale under which a recessive homozygote will be seen "instantly," "never," or when the process can be modeled in a way that allows both possibilities.

3. The Diffusion Approximation

(i) *The Selection Model*

In order to illustrate the methods, we now analyze in some detail the selection model defined by Eqs. (6) and (7). If we suppose that $s > 0$, one might expect that large s would facilitate observation of the recessive homozygote, whereas negative s would lead to a higher chance of loss of the a-allele.

In this section we will suppose that $(2N)^\gamma s = S$, and try to find γ so that we have a limiting diffusion process to approximate the X_n process. In this manner we can assess the order of magnitude of s for which the diffusion approximation reflects both the fixation of allele A *and* the possibility of killing of allele a. To do this we look at state space scalings of the form $Y_n = X_n \cdot (2N)^{-\alpha}$, for some $\alpha > 0$, and compute the "infinitesimal" parameters of the Y_n process. To this end, let $\Delta Y = Y_{n+1} - Y_n = (2N)^{-\alpha}(X_{n+1} - X_n)$. Using Eqs. (6) and (7) we find that if $x = i(2N)^{-\alpha}$,

$$\mathbb{E}[\Delta Y \mid Y_n = x] = \frac{1}{(2N)^\gamma}\left(xS - \frac{x^3 S}{2(2N)^{1-2\alpha}} - \frac{2x^2}{(2N)^{1-\gamma-\alpha}} + \cdots\right), \quad (12)$$

$$\mathbb{E}[(\Delta Y)^2 \mid Y_n = x] = \frac{1}{(2N)^\alpha}\left(x - \frac{2x^2}{(2N)^{1-\alpha}} - \frac{2x^3}{(2N)^{1-2\alpha}} + \cdots\right), \quad (13)$$

$$\Pr\{Y \text{ killed} \mid Y_n = x\} = \frac{1}{(2N)^\alpha}\left(\frac{x^2}{2(2N)^{1-3\alpha}} + \frac{2Sx}{(2N)^{\gamma+1-3\alpha}} + \cdots\right). \quad (14)$$

From (12)–(14), we see that necessarily $\alpha = \gamma$, and $1 - 3\alpha = 0$, which is the unique scaling required to produce a diffusion approximation with killing that incorporates the selection parameter S. If we let

$$Y_N(t) = \frac{X[(2N)^{1/3}t]}{(2N)^{1/3}},$$

then $Y_N(t)$ converges as $N \to \infty$ to a diffusion $Y(t)$ with state space $[0, \infty)$, and with infinitesimal parameters specified by

$$\begin{aligned} \mu(x) &= \lim_{N\to\infty} (2N)^{1/3} E[\Delta Y \mid Y_N(t) = x] = Sx, \\ \sigma^2(x) &= \lim_{N\to\infty} (2N)^{1/3} E[(\Delta Y)^2 \mid Y_N(t) = x] = x, \\ k(x) &= \lim_{N\to\infty} (2N)^{1/3} \Pr\{Y \text{ killed} \mid Y_N(t) = x\} = \frac{x^2}{2}. \end{aligned} \tag{15}$$

The time and state units of the approximating diffusion are translated in terms of the original process as follows. A time unit for the Y process corresponds to $(2N)^{1/3}$ generations of the X process and a state value y for Y refers to $y(2N)^{1/3}$ heterozygotes for X.

The killing function $k(x)$ possesses the interpretation that $k(x)h + o(h)$ is the probability of the Y process being killed (i.e., an aa-homozogote being formed) during the time interval $(t, t + h)$, given the process had value x at time t.

It is useful to discuss the behavior of the process which is obtained by ignoring the killing term $k(x)$. The resultant process has infinitesimal drift $\mu(x) = Sx$, and infinitesimal variance $\sigma^2(x) = x$; this arises in other contexts as the diffusion approximation to certain dynamic population growth processes; see Karlin and Taylor (1981, Chap. 15). It is possible to give a representation of the behavior of the Y process solely in terms of this process. In particular, the boundary behavior of this diffusion is germane. Using standard methods, we ascertain that the boundary point $\{0\}$ is an exit (or absorbing) state, while the boundary at ∞ is natural. Hence, if the process is never killed, then it must be absorbed at $\{0\}$ and so Y mirrors the behavior of our original discrete model.

It is worth making a few comments about the order of magnitude of the selection parameters $s = s_N$ as the population size N increases. If, for example, $s_N = S/N$, corresponding to "weak" selection pressure, then the infinitesimal mean is effectively zero and selection has no influence. If $s_N = S(2N)^{-\gamma}$ with $0 < \gamma < 1/3$, then the parameter in (12) grows, corresponding to "instantaneous" detection. If, for example, $\gamma > 1/3$ then effectively selection is zero. The sensitive order of magnitude for s_N is

$s_N = S(2N)^{-1/3}$, which allows for quite strong selection pressure. We can conclude that if $X_0 = i \approx xN^{1/3}$, then both detection of the recessive homozygote and fixation are possible, and the time to detection is of the order of $N^{1/3}$ generations.

(ii) *Methods of Analysis*

Diffusion processes with killing can be analyzed by a method similar to the case with no killing. Let us define $u(x, t) = \Pr\{Y \text{ process has not been killed by time } t \mid Y(0) = x\}$. Then $u(x, t)$ satisfies the differential equation

$$\frac{\partial u}{\partial t} = \frac{1}{2}\sigma^2(x)\frac{\partial^2 u}{\partial x^2} + \mu(x)\frac{\partial u}{\partial x} - k(x)u. \tag{16}$$

Clearly, $u(x, t)$ is a positive decreasing function of t. Hence, as $t \to \infty$, $u(x, t)$ converges to a limiting value $u(x, \infty) = u(x)$, and $\partial u/\partial t \to 0$. The function $u(x)$ is the probability that the process is never killed for an initial state x. Since 0 is an exit boundary, we conclude that $u(x)$ is the probability of fixation at 0, i.e., the probability that we never observe an *aa*-homozygote. From (16), $u(x)$ satisfies the differential equation

$$\frac{1}{2}\sigma^2(x)\frac{d^2u}{dx^2} + \mu(x)\frac{du}{dx} - k(x)u = 0, \tag{17}$$

with boundary condition $u(0) = 1$, $u(\infty) = 0$ and $u(x)$ decreasing in x.

If we let T be the lifetime of the process (the minimum of the time to loss and the time to detection of allele a), then we are often interested in computing the expected value

$$w(x) = \mathbb{E}\left(\int_0^T f(Y(u))\,du \mid Y(0) = x\right) \tag{18}$$

for suitable functions f. For example, if we set $f(x) \equiv 1$, then $w(x) = \mathbb{E}[T \mid Y(0) = x]$, the expected lifetime. Standard theory (e.g., Karlin and Taylor (1981, Chap. 15, Sect. 4)) shows that $w(x)$ of (18) satisfies the differential equation

$$\tfrac{1}{2}\sigma^2(x)\,w''(x) + \mu(x)\,w'(x) - k(x)\,w(x) = -f(x) \tag{19}$$

subject to appropriate boundary conditions. The solution may be written in the form

$$w(x) = \int_0^\infty G(x, y)\,f(y)\,dy, \tag{20}$$

where $G(x, y)$ is the Green's function of the process. $G(x, y)$ may be interpreted informally as the mean time the process spends at y, given that it started at x, before the process stops (i.e., up to loss or detection). In what follows, we give the function $G(x, y)$ and use (20) to determine $w(x)$.

To facilitate the subsequent analysis, we introduce a differential equation of particular use in the present context. The Airy equation is given by

$$u''(x) - xu(x) = 0. \tag{21}$$

This equation arises in the study of radio waves and light spectra (Airy, 1838), and has been extensively analyzed. The two standard solutions of (21) are the so-called Airy functions of the first and second kind, $A(x)$ and $B(x)$, respectively. These are represented by

$$A(x) = \frac{x^{1/2}}{3}\left(I_{-1/3}\left(\frac{2x^{3/2}}{3}\right) - I_{1/3}\left(\frac{2x^{3/2}}{3}\right)\right) \tag{22}$$

and

$$B(x) = \frac{x^{1/2}}{3^{1/2}}\left(I_{-1/3}\left(\frac{2x^{3/2}}{3}\right) + I_{1/3}\left(\frac{2x^{3/2}}{3}\right)\right), \tag{23}$$

where $I_v(\cdot)$ is the Bessel function of imaginary argument of order v. These functions have been tabulated (e.g., Miller, 1946). $A(x)$ is monotone decreasing for x positive, $B(x)$ monotone increasing, and their asymptotic behavior as $x \to \infty$ is as follows:

$$\begin{aligned} A(x) &= \frac{1}{2\pi^{1/2}} x^{-1/4} \exp\left\{-\frac{2}{3}x^{3/2}\right\}(1 + O(x^{-3/2})), \\ B(x) &= \frac{1}{\pi^{1/2}} x^{-1/4} \exp\left\{\frac{2}{3}x^{3/2}\right\}(1 + O(x^{-3/2})). \end{aligned} \tag{24}$$

See, for example, Abramowitz and Stegun (1970).

With these preliminaries at hand, we return to the analysis of the selection model.

(iii) *The Probability of Detection*

Using Eq. (17), we can compute the probability $u(x)$ of never detecting the homozygous genotype, *aa*. Substituting from (15) into (17) shows that $u(x)$ satisfies the differential equation

$$\frac{d^2u}{dx^2} + 2S\frac{du}{dx} - xu = 0, \tag{25}$$

with $u(0) = 1$ and $u(\infty) = 0$. To solve this equation we make the preliminary transformation $u(x) = e^{-Sx}\eta(x)$, which results in the equation

$$\frac{d^2\eta(x)}{dx^2} - (x + S^2)\,\eta(x) = 0. \tag{26}$$

A decreasing positive solution is

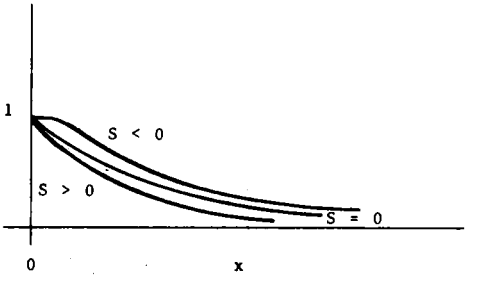
$$\eta(x) = A(x + S^2), \tag{27}$$

and hence (imposing the normalization $u(0) = 1$)

$$u(x) = \frac{e^{-Sx}A(x + S^2)}{A(S^2)}. \tag{28}$$

We can contrast the qualitative effect of positive and negative selection coefficients on the probability of loss or detection of the a-allele as expressed in formula (28). Direct analysis reveals that $u(x, S)$ of (28) is monotone decreasing in S. Moreover, for $S > 0$, $u(x, S)$ is convex decreasing while for $S < 0$, $u(x, S)$ is first concave, then convex with a single inflection point as depicted schematically next.

Shape of $u(x, S)$ = probability of loss of allele a.



This qualitative behavior is also shown in the discrete model. See Fig. 1.

For moderate values of S, the tabulated values of the Airy function can be used to evaluate the expression in (28). As an example, we chose $s = \pm 0.1$ in the discrete model, and examined the approximation to the detection probability $v(x) = 1 - u(x)$. For populations starting with one heterozygote, we take $x = (2N)^{-1/3}$ and $S = s(2N)^{1/3}$ in (28). The results, together with matrix results for the discrete case, are given in Table I.

(iv) *Moments of Detection and Fixation Times*

Expected values of functionals of the process can be computed using (20) once the appropriate Green's function $G(x, y)$ has been identified. We can establish that

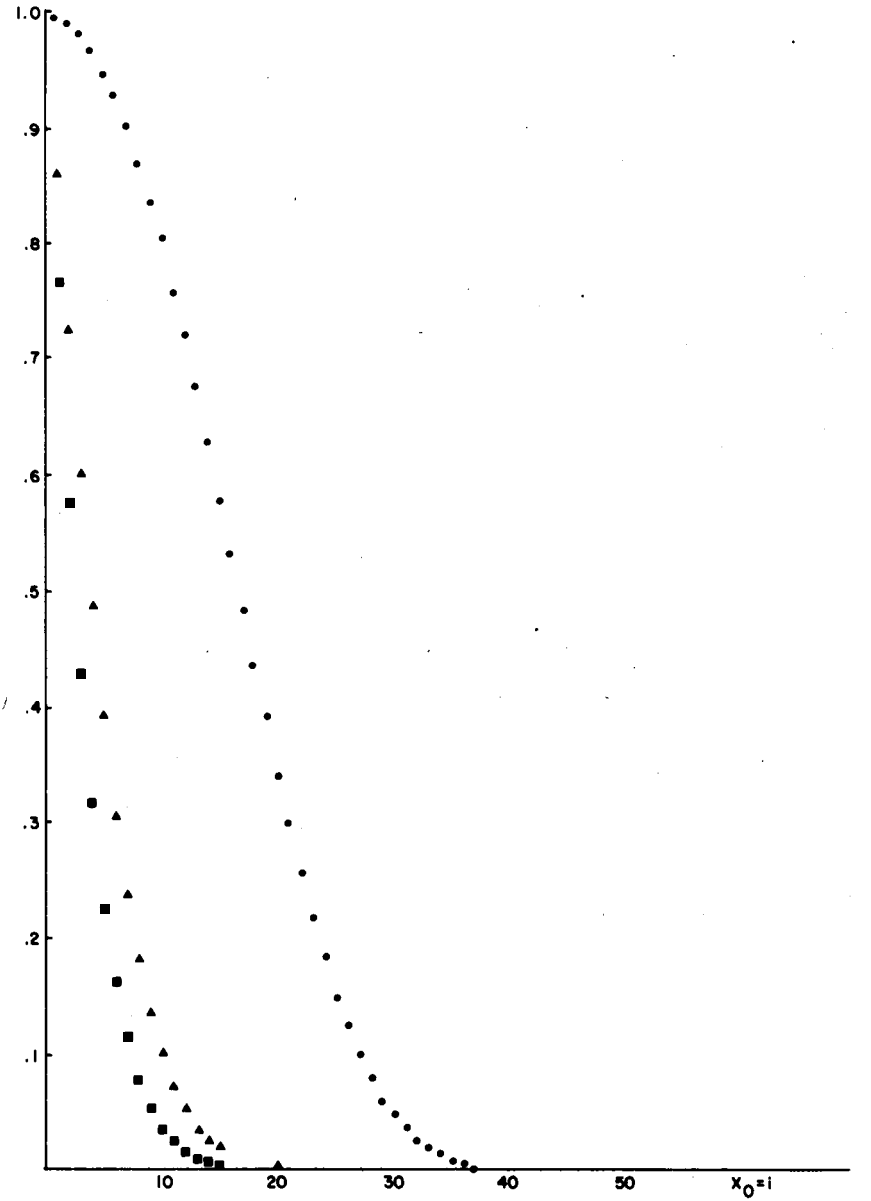


FIG. 1. Probability of loss of a-allele occurring before detection in populations of size 50. Matrix results.

● – selection coefficient $s = -.5$
▲ – selection coefficient $s = .0$
■ – selection coefficient $s = .1$

TABLE I

Detection Probability for $s = \pm 0.1$, Starting from 1 Heterozygote[a]

		$s = 0.1$		$s = -0.1$	
N	S	DA	Exact	DA	Exact
5	0.1710	0.395	0.340	0.261	0.223
10	0.2154	0.340	0.299	0.194	0.162
20	0.2714	0.297	0.264	0.141	0.116
50	0.3684	0.253	0.232	0.088	0.071
100	0.4642	0.229	0.215	0.059	0.047
500	0.7937	0.197	0.186 ± 0.011*	0.019	0.015 ± 0.003*

* Simulation result.

[a] DA is diffusion approximation, N is population size. Exact results refer to the matrix solution of (11).

$$G(x, y) = 2\pi e^{-Sx} C(y; S^2) \frac{e^{Sy} A(x + S^2)}{y}, \qquad y \leqslant x$$
$$= 2\pi e^{Sy} C(x; S^2) \frac{e^{-Sx} A(y + S^2)}{y}, \qquad y \geqslant x, \tag{29}$$

where $C(y; \theta) = B(y + \theta) - (B(\theta)/A(\theta)) A(y + \theta)$. Hence if T is the time to detection or loss then its mean value is

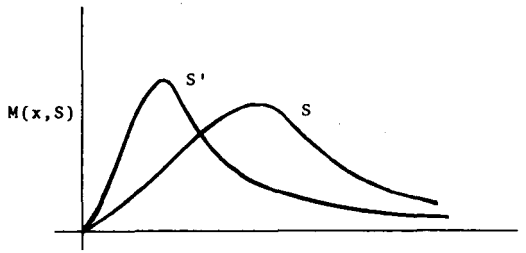
$$M(x, S) = E[T \mid Y(0) = x] = \int_0^\infty G(x, y)\, dy, \tag{30}$$

where G is given by (29). For small values of x, analysis of this result shows that the mean lifetime is of order $\ln N$ generations in the discrete model starting from $X_0 = 1$.

In Table II we give the mean and variance of the lifetime of the discrete process (i.e., time until loss or detection) for a variety of population sizes. The exact results were computed using standard matrix methods for absorbing Markov chains (cf. Kemeny and Snell, 1976).

It is of interest to exhibit the relative dependence of $M(x, S)$ on the selection parameter. The curves $M(x, S)$ and $M(x, S')$ for $S' > S$ intersect once as drawn below.

The picture agrees with our intuition since an increased selection coefficient for Aa diminishes the chances of loss of allele a but enhances the



chance of detection, especially with greater heterozygote numbers. These conclusions are backed up by the discrete results in Fig. 2.

(v) *Cumulative Number of Heterozygotes Sustained until Detection or Loss of Allele a*

We consider next the expected total number $H(x)$ of heterozygotes that appear before detection or fixation, starting with $Y(0) = x$. We use (20) and (29) with $f(x) = x$. This leads to

$$H(x) = 2\pi e^{-Sx} A(x + S^2) \int_0^x C(y; S^2)\, e^{Sy}\, dy + 2\pi C(x; S^2)\, e^{-Sx} \int_x^\infty e^{Sy} A(y + S^2)\, dy. \tag{31}$$

To interpret (31) in units of the original process, the cumulative heterozygosity becomes $(2N)^{2/3} H(x)$.

TABLE II

Mean and Variance of Lifetime of Discrete Process Starting from One Heterozygote[a]

	$s = +0.1$		$s = -0.1$	
N	Mean	Variance	Mean	Variance
5	2.71	4.62	2.50	4.09
10	3.09	6.94	2.75	5.84
20	3.53	10.38	2.99	8.15
50	4.15	17.40	3.29	12.04
100	4.67	25.24	3.49	15.49
500*	6.08 ± 0.17	36.30	3.76 ± 0.13	22.98

* Simulation result.

[a] N is the population size, s the selection parameter.

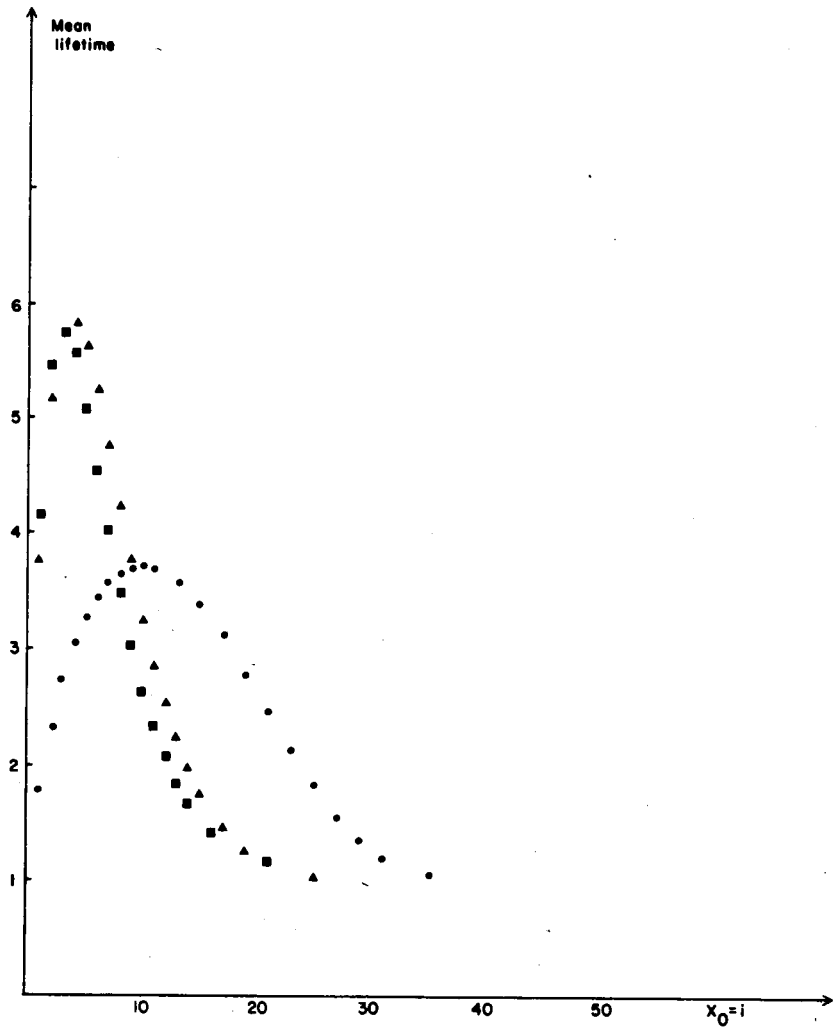


FIG. 2. Mean lifetime (time to detection *or* loss) in populations of size 50. Matrix results.

● – selection coefficient $s = -.5$
▲ – selection coefficient $s = .0$
■ – selection coefficient $s = .1$
$X_0 = i$ – initial number of heterozygotes

The factor $N^{2/3}$ is argued as follows:
Let T be the time to detection *or* fixation. We want to approximate

$$E\left(\sum_{n=1}^{T} X_n \mid X_0 = i\right) = (2N)^{1/3}\mathbb{E}\left[\sum_{n=1}^{T} \frac{X_n}{(2N)^{1/3}} \,\middle|\, X_0 = i\right]$$

$$= (2N)^{2/3}\mathbb{E}\left[\sum_{n=1}^{T} \frac{X_n}{(2N)^{1/3}} \cdot \frac{1}{(2N)^{1/3}} \,\middle|\, X_0 = i\right]$$

$$\sim (2N)^{2/3}\mathbb{E}\left[\sum_{n=1}^{[(2N)^{1/3}\tilde{T}]} Y_N(n) \frac{1}{(2N)^{1/3}} \,\middle|\, Y_N(0) = \frac{i}{(2N)^{1/3}} = x\right],$$

where $\tilde{T}$ is the time in diffusion units

$$\sim (2N)^{2/3}\mathbb{E}\left[\int_0^{\tilde{T}} Y(u)\,du \mid Y(0) = x\right]$$

$$= (2N)^{2/3} H(x).$$

4. The Diffusion Approximation Conditioned on Detection

The functionals of primary interest in the present context involve only those sample paths which result in detection. We denote by $Y_D(t)$ the process conditioned on detection occurring. This process is again a diffusion (cf. Karlin and Taylor, 1981, Chap. 15) with infinitesimal coefficients

$$\begin{aligned} \mu_D(x) &= \mu(x) + \frac{v'(x)}{v(x)}\sigma^2(x), \\ \sigma_D^2(x) &= \sigma^2(x), \\ k_D(x) &= \frac{k(x)}{v(x)}, \end{aligned} \tag{32}$$

where $v(x) = 1 - u(x)$ is defined by (28).

The Green's function of the process conditioned on detection is given by

$$G_D(x,y) = G(x,y)\frac{v(y)}{v(x)} \tag{33}$$

With the aid of (33) paralleling subsections (iii)–(v) of Section 3 we can efficatiously compute various functionals of the $\{Y_D(t)\}$ process.

(i) *Mean Time to Detection, $M_D(x)$, Conditioned that Detection Occurs*

We find that

$$M_D(x) = \int_0^\infty G_D(x, y)\, dy.$$

(The subscript D keeps in view the conditioning event of eventual detection.) For small values of x, $M_D(x)$ is approximately constant ($M_D(x) \to C$ as $x \to 0$), from which we deduce the following: in populations of size N with one initial heterozygote, the mean time to detection is of order $C(2N)^{1/3}$ generations. The constant C for $S = 0$ is approximately 1.66. With general selection the constant is

$$C = M_D(0+) = 2\{SA(S^2) - A'(S^2)\}^{-1} \int_0^\infty \frac{e^{Sy} A(y + S^2)\, v(y)}{y}\, dy.$$

It is expected and indeed it is correct that the mean time to detection $M_D(x, S)$ is monotone decreasing as a function of S for fixed x. The behavior of the discrete process is exhibited in Fig. 3 and Table III.

The variance of the time until detection conditioned on detection is of order $N^{2/3}$, and the mth moment of the distribution of this detection time is of order $N^{m/3}$.

(ii) *Aggregate Numbers of Heterozygotes Conditioned on Detection*

This is derived analogously to (v) of Section 3. The result is

$$H_D(x) = \int_0^\infty G_D(x, y)\, y\, dy. \tag{34}$$

Its evaluation for x small is the constant value C^*, where

$$C^* = H_D(0+) = 2\{SA(S^2) - A'(S^2)\}^{-1} \int_0^\infty e^{Sy} A(y + S^2)\, v(y)\, dy.$$

Therefore, in terms of the discrete process, the cumulative number of heterozygotes until detection conditioned on detection, starting from 1 (or a few) heterozygotes, is $C^*(2N)^{2/3}$. The intuitive reason for the order $(2N)^{2/3}$ derives from the fact that the cumulative heterozygosity is initial number x multiplied by the lifetime of each, which are measured in $(2N)^{1/3}$ units per generation (cf. subsection (v) of Section 3). When $S = 0$, $C^* = 1.12$.

It follows that the average number of heterozygotes produced before detection, starting from a single initial carrier is approximately $C^* \cdot (2N)^{2/3}$, which is a higher order of magnitude than the corresponding result for the

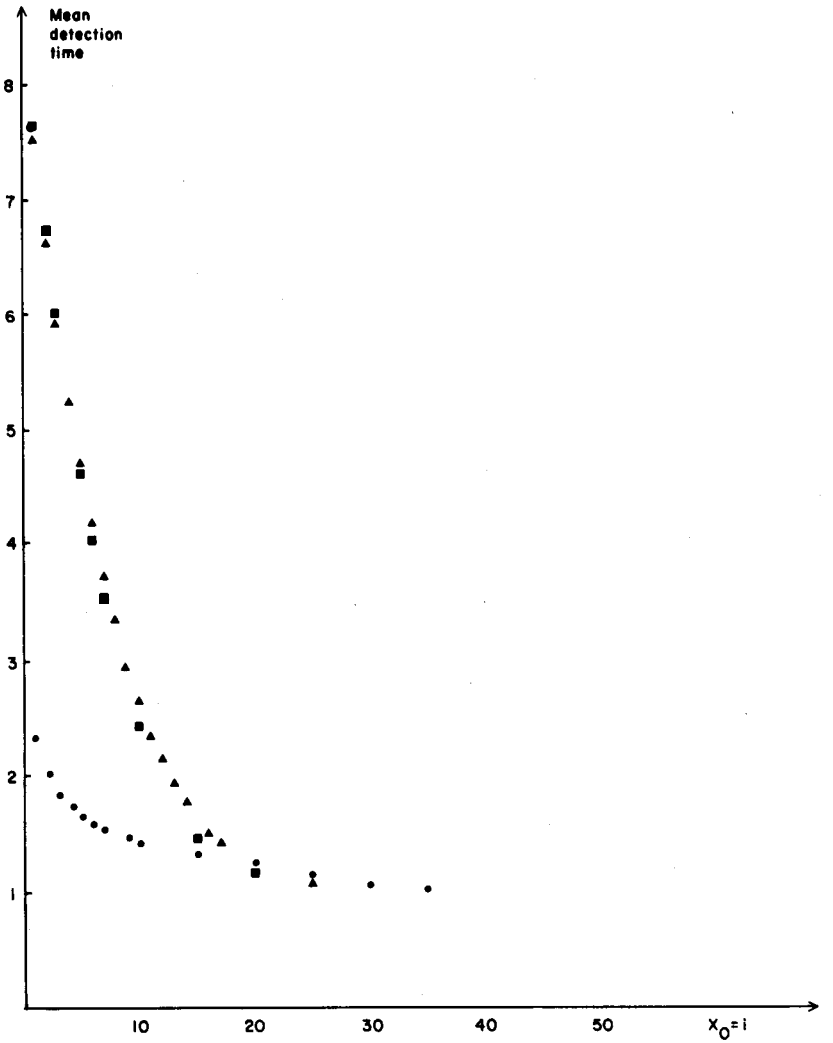


FIG. 3. Mean conditional detection time in populations of size $N = 50$. Matrix results.

● – selection coefficient $s = -.5$
▲ – selection coefficient $s = .0$
■ – selection coefficient $s = .1$
$X_0 = i$ – initial number of heterozygotes

TABLE III

Mean and Variance of (Conditional) Detection Time in Discrete Populations of Size N Starting with One Heterozygote[a]

	$s = 0.1$		$s = -0.1$	
N	Mean	Variance	Mean	Variance
5	3.49	5.34	3.37	5.06
10	4.43	8.31	4.17	7.85
20	5.62	12.87	5.12	12.07
50	7.67	22.53	6.63	20.74
100	9.64	33.61	7.93	30.29
500*	16.14 ± 0.59	83.93	11.21 ± 2.22	93.89

* Simulation result.

[a] s is the selection parameter.

process allowing for both loss and detection of allele a. The result is then of order $C(2N)^{1/3}$ for an initial population size of one heterozygote carrier which is derived from (31) with $x = (2N)^{-1/3}$. The intuitive reason behind this is that in order to be detected, the process must build up a larger number of heterozygotes; for the process where fixation is allowed, most of the outcomes result in rapid fixation, and hence the production of fewer heterozygotes.

(iii) *The Number of Heterozygotes in the Population at the Time of Detection.*

Given that the process ends in detection, the position P_D at which detection occurs is a bona-fide random variable. Using a result derived in Karlin and Tavaré (1981a), the density function $w_D(x; y)$ of the position of detection given an initial value $Y_D(0) = x$ is given by

$$w_D(x; y) = G_D(x, y)\, k_D(y), \qquad y \geqslant 0. \tag{35}$$

Using (29), (32), (33), it follows that

$$\begin{aligned} w_D(x; y) &= \frac{A(S^2)\, \pi e^{-Sx} A(x + S^2)\, y e^{Sy} C(y; S^2)}{[A(S^2) - e^{-Sx} A(x + S^2)]}, \qquad y \leqslant x \\ &= \frac{A(S^2)\, \pi e^{-Sx} C(x; S^2)\, y e^{Sy} A(y + S^2)}{[A(S^2) - e^{-Sx} A(x + S^2)]}, \qquad y \geqslant x. \end{aligned} \tag{36}$$

For a small initial number of heterozygotes, interest focuses on the form of the density as $x \to 0$. From (36), the resultant density is given by

$$w_D(0 + ; y) = \{SA(S^2) - A'(S^2)\}^{-1}\, y e^{Sy} A(y + S^2), \qquad y \geqslant 0. \tag{37}$$

TABLE IV

Mode y_0 of Detection Position Density (37)	
S	y_0
0.1	0.945
0.0	0.885
–0.1	0.825
–0.5	0.709

The densities specified in (37) are unimodal; the mode is at the solution y_0 of the equation $-A(y+S^2)/A'(y+S^2) = y(1+Sy)^{-1}$. Some values of the mode are given in Table IV.

For example, the most likely number of heterozygotes in the population at the time of detection starting from a single heterozygote will be about $(2N)^{1/3}y_0$ individuals.

5. Distribution of Detection Times with Differential Fertility Rates

In this section we analyze the effect of differential fertility schedules among the different mating types. If, for example, the *aa*-genotype is lethal, then it is conceivable that the mating type $Aa \times Aa$ is less productive than the others.

Since no *aa*-genotypes have yet appeared we only need to specify the fertilities of the mating types:

$$AA \times AA \quad f_1; AA \times Aa \quad f_2; Aa \times Aa \quad f_3.$$

X_n will again denote the number of heterozygotes in the population at time n. The transition probability matrix of the chain is then given by

$$P_{ij} = \binom{N}{j} p_i^{N-j} q_i^j, \qquad 0 \leqslant i, j \leqslant N,$$

$$P_{iH} = 1 - (1-r_i)^N, \qquad 0 \leqslant i \leqslant N,$$

where

$$p_i = C\left\{\left(1-\frac{i}{N}\right)^2 f_1 + \frac{i}{N}\left(1-\frac{i}{N}\right) f_2 + \frac{i^2}{4N^2} f_3\right\},$$

$$q_i = C\left\{\frac{i}{N}\left(1-\frac{i}{N}\right) f_2 + \frac{i^2}{2N^2} f_3\right\},$$

$$r_i = \frac{Ci^2}{4N^2} f_3,$$

and C is the normalizing constant

$$C = \left\{ \left(1 - \frac{i}{N}\right)^2 f_1 + \frac{2i}{N}\left(1 - \frac{i}{N}\right) f_2 + \frac{i^2 f_3}{N^2} \right\}^{-1}.$$

We will examine two cases of this model in some detail.

(i) $f_1 = f_2 = 1, f_3 = f$

We look for scalings of the form

$$X_n = i = x(2N)^{\alpha}, \qquad f = F(2N)^{-\gamma}.$$

In the spirit of the previous sections, we find the sizes of α and γ in such a way that the resulting diffusion process reflects the possibilities of both fixation and detection. The results are summarized in Table V. Case (a) in Table V shows that it is possible to have constant (that is, independent of N) fertility f among heterozygote $\times$ heterozygote matings. In this case, the correct time scale is again in units of $(2N)^{1/3}$ generations, as in the models discussed earlier. There is another interesting way of describing this model. If we suppose that in the gene pool of AA, Aa, aa individuals, a fraction $1 - f$ of the aa-genotype die before sampling (corresponding, perhaps, to spontaneous abortion), then we obtain a model formally equivalent to (i).

Note that in this model, there is no unique approximating diffusion, although, as shown in Table V, the functional form of the approximating process is constant over a range of α-values. The case described in (c) is the 'boundary' case.

TABLE V

Diffusion Approximation to Fertility Model (i)[a]

	$\mu(x)$	$\sigma^2(x)$	$k(x)$
(a) $\alpha = \frac{1}{3}, \gamma = 0$	0	x	$\frac{Fx^2}{2}$
(b) $\frac{1}{3} < \alpha < \frac{1}{2}, \gamma = 3\alpha - 1$	0	x	$\frac{Fx^2}{2}$
(c) $\alpha = \gamma = \frac{1}{2}$	$-2x^2$	x	$\frac{Fx^2}{2}$

[a] α is the state space index, γ the fertility index. The time scaling is always in units of $(2N)^{\alpha}$.

We will indicate briefly some of the results for cases (a) and (b). The probability of detection is given by

$$v(x) = 1 - \frac{A(F^{1/3}x)}{A(0)}, \quad , \tag{38}$$

which can be evaluated simply through use of the tables in Miller (1946). The Green's function of the process is given by

$$G(x, y) = 2\pi(B(\eta y) - 3^{1/2}A(\eta y))\frac{A(\eta x)}{\eta y}, \qquad y \leqslant x$$

$$= 2\pi(B(\eta x) - 3^{1/2}A(\eta x))\frac{A(\eta y)}{\eta y}, \qquad y \geqslant x,$$

where $\eta = F^{1/3}$. When $\gamma = 0$, so that (a) obtains, we use this result to show that the mean time to detection, conditional on this happening, is again of order $(2N)^{1/3}$ generations in the original model starting with one heterozygote. In this case, (38) shows that the detection probability is smaller than the case when $F = f = 1$.

For populations starting with one heterozygote, we have the approximate result for the detection probability

$$v \approx 0.7290\left(\frac{f}{2N}\right)^{1/3} - 0.1667\left(\frac{f}{2N}\right), \tag{39}$$

leading to the values in Table VI.

(ii) $f_1 = 1, f_2 = 1 - d, f_3 = f$

We now suppose that $X_n = i = x(2N)^{\alpha}, f = F(2N)^{-\gamma}$, and $d = D(2N)^{-\delta}$. In this case, the balance between the indices α, δ, γ is given in Table VII.

Some qualitative conclusions can be drawn immediately from Table VII. First, we can see that the parameter d has to go to zero as the population size increases at a rate at least that of the state space scale. If not, the process (effectively) does not produce enough heterozygotes in order to be able to detect tha *aa*-genotype. However, as model (i) case (a) shows, the fertility in the $Aa \times Aa$ matings can be constant, when $\alpha = \delta = 1/3$, $\gamma = 0$. In this case, the time scale is again in units of $(2N)^{1/3}$ generations, and so will be the (conditional) mean time to detection.

As a sample of the results we obtained for this model, we compute the detection (or fixation) probability in the case given in Table VII(ai). The fixation probability $u(x)$ satisfies the equation

$$\frac{x}{2}u''(x) - Dxu'(x) - \frac{Fx^2}{2}u(x) = 0,$$

TABLE VI

Probability of Detection in Population of Size N with $Aa \times Aa$ Fertility Rate f[a]

f	$N = 50$	$N = 100$
0.01	0.034	0.027
0.1	0.073	0.058
0.2	0.092	0.073
0.4	0.115	0.092
0.6	0.132	0.105
0.8	0.145	0.115
0.9	0.150	0.120
0.99	0.155	0.124

[a] Results computed from (39). They agree with values computed from tables of the Airy function. Population starts with 1 heterozygote.

TABLE VII

Diffusion Approximations to Variable Fertility Model (ii)[a]

γ, α	$\mu(x)$	$\sigma^2(x)$	$k(x)$
(i) $\delta = \alpha$			
(a) $1 + \gamma - 3\alpha = 0$, $\frac{1}{3} \leqslant \alpha < \frac{1}{2}$	$-Dx$	x	$\frac{Fx^2}{2}$
(b) $\delta = \gamma = \alpha = \frac{1}{2}$	$-Dx - 2x^2$	x	$\frac{Fx^2}{2}$
(ii) $\delta > \alpha$ As in Table V.			

[a] In all cases, the time scale is of order $(2N)^{\alpha}$.

subject to $u(0) = 1$, $u(\infty) = 0$. The solution is given by

$$u(x) = e^{Dx} \frac{A(F^{1/3}x + F^{-2/3}D^2)}{A(F^{-2/3}D^2)}.$$

The corresponding Green's function are given by

$$G(x, y) = 2\pi e^{Dx}\left[B_1(y) - \frac{B_1(0)}{A_1(0)}A_1(y)\right]\frac{e^{-Dy}A_1(x)}{y}, \qquad y \leqslant x$$

$$= 2\pi e^{Dx}\left[B_1(x) - \frac{B_1(0)}{A_1(0)}A_1(x)\right]\frac{e^{-Dy}A_1(y)}{y}, \qquad y \geqslant x,$$

where $A_1(x) = A(F^{1/3}x + F^{-2/3}D^2)$, and $B_1(x) = B(F^{1/3}x + F^{-2/3}D^2)$.

The Green's functions derived in this section can be used as described earlier to quantify the role of the parameters F and D on the detection problem.

6. Discussion

This paper continues the study of the problem of ascertaining the distributional properties of the time to first appearance of a visible recessive homozygote in a finite population. This question was addressed first by Robertson (1978) using simulation and numerical methods. We provided in Karlin and Tavaré (1980) a natural analytical setting (a diffusion stochastic process with killing rate) by which to study the Robertson model and many variations. In this framework we calculated explicit formulas for a wide variety of functionals germane to the detection problem. In particular, apart from the probability and mean time to detection or loss of the recessive gene, we determined

(a) the aggregate heterozygosity ("genetic cost") sustained in the population until loss or detection of the recessive allele;

(b) the maximum level of heterozygote numbers ever reached before detection;

(c) the heterozygote numbers at the time of detection.

In this paper we further analyze the effects of superimposed viability selection differentials and also variable fertility rates with respect to the genotype and mating types, respectively.

The corresponding results of the detection model with superimposed viability selection can be summarized as follows. If we suppose that selection acts on the heterozygotes, the selection difference being s (which may be positive or negative), then the diffusion method shows that the time and state scalings again have to be of order $(2N)^{1/3}$, as long as the selection coefficient is of order $S(2N)^{-1/3}$. If $s = O(N^{-\gamma})$, $\gamma > 1/3$ the diffusion approximation has infinitesimal coefficients $\mu(x) = 0$, $\sigma^2(x) = x$, $k(x) = x^2/2$ identifying the process as the same as that in Karlin and Tavaré (1980). The "usual" scaling of the selection coefficient in the setup of the Wright–Fisher model is N^{-1};

this fact shows that we can have quite strong selection intensities before we significantly alter the probability of detection. It is interesting that for all values of the selection parameter S, the fixation probability is a monotone decreasing function and, as expected, this probability is monotone decreasing with respect to S. The effect of selection favoring the homozygote wild type ($S < 0$) produces an initial concave dependence on the heterozygote numbers.

We calculated for the process conditioned on detection a variety of functionals. We highlight several of the numerical evaluations for an initial state corresponding to a single heterozygote with no selection differentials, $S = 0$. Specifically the expected time until detection conditioned on eventual detection, is $2.09N^{1/3}$ generations. The average aggregate numbers of heterozygotes over the life of this process is $1.78N^{2/3}$. During this period the probability exceeds $1/2$ that the maximum number of heterozygotes achieved a level exceeding $2.02N^{1/3}$. The same calculations can be done for any initial population state and analytic formulas are available. Conditioned on detection, starting with a single heterozygote, the number of heterozygotes at the time of detection has a modal value $1.12N^{1/3}$ heterozygotes in the discrete model and a mean number of about $1.73N^{1/3}$ individuals. Explicit results are given for the case of general selection coefficient S. In Figs. 1–3, and Tables I–IV a variety of matrix results for the discrete process are given for comparison.

The consequences of the action of differential fertility rates f_1, f_2, f_3 expressed on the three feasible mating types $AA \times AA$, $AA \times Aa$ and $Aa \times Aa$ respectively, are more varied. Under fertility selection some modifications on the scalings are sometimes required. The associated diffusion models relate to classical differential equations involving combinations of Bessel functions. In these terms many biologically interesting functionals are explicitly available as elaborated in Sections 2–5.

We investigated two levels of fertility rates. The first case prescribes $f_1 = 1$, $f_2 = 1$, $f_3 = f$ where a fraction $1 - f$ of the progeny from $Aa \times Aa$ matings die unobserved. When f is very small ($f \sim F/(2N)^\gamma$), the time scale of the discrete model needs, in some cases, to be modified (increased) to $(2N)^\alpha$, $\frac{1}{2} > \alpha > \frac{1}{3}$ to allow for aa-detection, and then the heterozygote numbers are counted to order $(2N)^\alpha$, (see Section 5 for the details). If $\gamma = 0$, ($f = F$) so that a fraction $1 - f$ of $Aa \times Aa$ abort or die in each generation without observation, we ascertained that the chance for detection of the recessive allele is of the same order as with no selection and only the detection killing rate in the diffusion approximation model is reduced from 1 by a factor F, and to this degree the aa-homozygote detection contingencies are reduced.

In the same general model with parameters $f_1 = 1$, $f_2 = 1 - d$, $f_3 = f = F/(2N)^\gamma$ and $d = D/(2N)^\delta$ the effects on the detection problem paraphrase a

viability selection mechanism as in Section 2 with heterozygote disadvantage, viz., with $S = -D$. However, the interpretations for the discrete case can involve different time and state scalings.

Thus, for $f_1 = 1, f_2 = 1 - d = 1 - D/(2N)^{\delta}, f_3 = F/(2N)^{\gamma}$, the parameter d induces a viability selection against the heterozygote while f_3 merely reduce the detection (killing) rate.

Unlike the viability selection model, the usual time and state scaling $(2N)^{1/3}$ may be altered in the variable fertility model, requiring normalizations to the order $(2N)^{\delta}$, $\frac{1}{3} \leqslant \delta \leqslant \frac{1}{2}$. In certain finite population studies allowing very strong selection effects (Robertson and Narain, 1971) and in situations of variable mutation rates (Karlin and McGregor, 1964), normalizations of the order $N^{1/2}$ have occurred. For example, if the fitnesses of genotypes AA, Aa, aa in a finite size population of N are 1, $1 - hS$, and $1 - S$, respectively, where S is fixed, $h \sim 1/N^{1/2}$ and initial numbers of aa-homozygotes of the order $N^{1/2}$, then the expected time to elimination of the recessive type is of the order $N^{1/2}$. For the detection problem in all cases of viability selection the time to detection conditional on this occurring is of order $(2N)^{1/3}$ generations.

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