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A CLASS OF DIFFUSION PROCESSES WITH KILLING ARISING IN POPULATION GENETICS*

SAMUEL KARLIN† AND SIMON TAVARÉ‡

Abstract. An interesting class of diffusion stochastic processes is studied. These processes arise from discrete models of gene formation and detection in finite populations. The diffusion processes are governed not only by the usual infinitesimal drift and diffusion terms, but also by a state dependent killing rate, which corresponds to formation of certain types of individuals. For one case, the spectral decomposition of the transition function is available, which allows a complete study of the process. Its behavior is compared with other variants of the detection problem.

Key words. Markov chains, diffusion processes, population genetics, killing times

Introduction. In this paper we analyze a class of Markov diffusion processes with killing that arise from the following problem in population genetics. Consider a population of N individuals. We classify each individual as one of the three genotypes AA, Aa, aa, and suppose that individuals of genotype aa are visible as being "defective" in some way. This may correspond, for example, to the a-allele being lethal (showing a lethal disease) when in homozygous form (i.e., when occurring in double doses), or to the aa-genotype being visibly different to the other genotypes.

Given that the population currently comprises no aa-individuals, how long does it take to produce the first one under some given mating scheme? The study of this question was initiated by the geneticist Robertson (1978), using discrete Markov chain methods and simulations. The analysis of such first-formation times is considered to be an important problem in evolutionary theory since the results also apply to the time to appearance of a new allele in homozygous form, this allele arising as the result of mutation or recombination. Interest in the problem also derives from application of the results to artificial selection schemes and medical genetic screening.

In this paper, we take account of the possibility that the heterozygous individuals Aa may be phenotypically identical to the visible genotype aa. This may be interpreted in a different way by supposing that some genetic screening system sometimes results in the detection of heterozygous individuals as well as detection of aa-individuals. The method we use to analyze first-detection times begins with a discrete-time, discrete-state Markov chain describing the evolution of heterozygote numbers through time. These Markov chains are defective in the sense that the process will end either by loss of the a-allele from the population (formation of a homozygous aa-individual is then impossible) or the process may end in detection (either an Aa or an aa-individual is found); the Markov chain is then sub-Markovian (see § 1). In common with many investigations in population genetics theory, analysis is simpler via the use of diffusion process approximations (cf. Ewens (1979)). In the case at hand, we are led to a class of diffusion processes on the interval $(0, \infty)$ which are *killed* whenever a detection event occurs. In this class of models, a full description of the detection process can be obtained via spectral decomposition of the transition density (see § 3) of the process. A variety of other functionals of these processes are also derived. For a wide range of qualitative results assessing the effects of partial penetrance, family structure, and superimposed natural selection forces, see Karlin and Tavaré (1981a, b).

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† Mathematics Department, Stanford University, Stanford, California 94035.

‡ Mathematics Department, Stanford University, Stanford, California 94305, and Statistics Department, Colorado State University, Fort Collins, Colorado 80523.

1. The models. Let X_n denote the number of heterozygotes in the population of fixed size N at times $n=0,1,2,\cdots$. Suppose that at time n, the population comprises $N-i$ AA-genotypes and i Aa-heterozygotes; we assume that detection has not yet taken place so that there are no aa-genotypes in the population. To produce the individuals of the next generation, we use a standard diploid Wright–Fisher model (cf. Ewens (1979, Chap. 5)), which determines that the population at time $(n+1)$ will comprise $N-j-k$ AA, j Aa and k aa-types with probability

$$\frac{N!}{j!k!(N-j-k)!}\left(1-\frac{i}{2N}\right)^{2(N-j-k)}\left(\frac{i}{N}\left(1-\frac{i}{2N}\right)\right)^{j}\left(\frac{i}{2N}\right)^{2k}. \tag{1}$$

Let α be the probability that a heterozygote carrier is detected (equivalently, α is the probability that a heterozygote appears the same as the genotype aa, which is detected immediately). Assuming that detection operates independently for each heterozygote, the probability that $X_{n+1}=j$ and that detection has not yet occurred is given from (1) by

$$P_{ij}=\binom{N}{j}\left(1-\frac{i}{2N}\right)^{2(N-j)}\left[\frac{i}{N}\left(1-\frac{i}{2N}\right)(1-\alpha)\right]^{j}, \tag{2}$$

$i,j=0,1,\cdots,N$. This follows because we require $k=0$, and if j heterozygotes are formed, none is detected with probability $(1-\alpha)^j$. The matrix determined by (2) is substochastic, since the row sums are not unity. To remedy this we can add on a fictitious state H, which accounts for all population configurations in which detection occurred. Then

$$P_{iH}=1-\sum_{j=0}^{N}P_{ij}=1-\left[1-\frac{i^2}{4N^2}-\alpha\frac{i}{N}\left(1-\frac{i}{2N}\right)\right]^{N}, \qquad i=0,1,\cdots,N, \tag{3}$$

while $P_{Hi}=0$, $P_{HH}=1$. Properties of the evolution of this Markov chain can be found by matrix numerical methods, although explicit results seem hard to find. Instead, we will resort to the method of diffusion approximation. The aim is to find the infinitesimal parameters of the associated diffusion process $\{Y(t),\ t\geqq 0\}$ which mirror the behavior of $\{X_n,\ n\geqq 0\}$. In the present case the diffusion process is determined by the infinitesimal mean $\mu(x)$ and variance $\sigma^2(x)$ in conjunction with a killing rate $k(x)$ which derives from the process terminating whenever a detection event occurs.

The infinitesimal parameters of $\{Y(t),\ t\geqq 0\}$ are identified from those of $\{X_n,\ n\geqq 0\}$ in the following way:

Define the processes $Y_N(t)$ by

$$Y_N(t)=\frac{X[(2N)^{\gamma}t]}{(2N)^{\gamma}}, \qquad t\geqq 0, \quad N\geqq 1, \tag{4}$$

where $\gamma>0$, and suppose that, for some $\delta>0$, $(2N)^{\delta}\alpha\to A>0$ as $N\to\infty$. We look for the relationship between γ and δ that makes $Y_N(t)$ converge to a diffusion process $Y(t)$ as $N\to\infty$.

To this end write $\Delta_N t=(2N)^{-\gamma}$. Straightforward computations based on (2) and (3) show that if $\delta=2\gamma$, $0<\gamma<\frac{1}{3}$ and $(2N)^{-\gamma}i\to x$ as $N\to\infty$ then

$$\begin{gathered}(\Delta_N t)^{-1}\left(1-\sum_{j=0}^{N}P_{ij}\right)\to Ax, \qquad \left[\sum_{j=0}^{N}(j-i)P_{ij}\right]\to 0,\\ (\Delta_N(t))\left(\sum_{j=0}^{N}(j-i)^2P_{ij}\right)\to x, \qquad (\Delta_N(t))^3\sum_{j=0}^{N}(j-i)^4P_{ij}=O(\Delta_N t)\end{gathered} \tag{5}$$

and $N \to \infty$, uniformly for x in compact intervals of $(0, \infty)$. If F is a function with at least two bounded continuous derivatives, then a Taylor expansion together with (5) shows that

$$(6) \qquad (\Delta_N t)^{-1}\left[\sum_{j=0}^{N} P_{ij}F(j\Delta_N t)-F(i\Delta_N t)\right] \to \frac{x}{2}F''(x)-AxF(x) \quad \text{as } N \to \infty.$$

This examination of the infinitesimal generators of $Y_N(\cdot)$ suggests that as $N \to \infty$, $Y_N(t) \to Y(t)$, where $Y(\cdot)$ is a diffusion process on $[0, \infty)$ with infinitesimal parameters $\sigma^2(x) = x$, $\mu(x) = 0$, $k(x) = Ax$, in the case $0 < \gamma < \frac{1}{3}$, $\delta = 2\gamma$.

There are two other diffusion approximations available for this process, depending on the relative magnitude of γ and δ. In *both* cases, $\sigma^2(x) = x$, $\mu(x) = 0$, but the killing rate $k(x)$ changes:

$$\gamma = \tfrac{1}{3}, \qquad \delta = \tfrac{2}{3}: \quad k(x) = \frac{x^2}{2} + Ax,$$

$$\gamma = \tfrac{1}{3}, \qquad \delta > \tfrac{2}{3}: \quad k(x) = \frac{x^2}{2}.$$

These are derived analogously to (5) and (6).

The parameters are summarized in Table 1.

TABLE 1

Diffusion approximation to detection process. Time scale in units of $(2N)^\gamma$ *generations.* $A = \lim_{N\to\infty}(2N)^\delta\alpha$. $Y(\cdot)$ *is a diffusion on interval* $[0, \infty)$ *with infinitesimal parameters:*

	mean, $\mu(x)$	variance, $\sigma^2(x)$	killing, $k(x)$
(a) Airy model			
$\gamma = \frac{1}{3}, \delta > \frac{2}{3}$	0	x	$x^2/2$
(b) Weak detection model			
$\gamma = \frac{1}{3}, \delta = \frac{2}{3}$	0	x	$x^2/2 + Ax$
(c) Strong detection model			
$0 < \gamma < \frac{1}{3}, \delta = 2\gamma$	0	x	Ax

The preceding calculations suggest that the discrete process determined by (2) and (3) can be approximated by a diffusion process in three functionally different ways, depending on the magnitude of the detection probability α of heterozygotes. We are immediately led to a qualitative description of these processes. In case (a), the detection probability is so small as to be effectively irrelevant and the process ends by detection of a homozygote. We call this the Airy model (cf. Robertson (1978), Karlin and Tavaré (1981a). In case (b) the process can end by detection of either a homozygote or heterozygote. We call this case the weak detection model. Finally, in case (c), the strong detection model, the detection probability α is so large that the process effectively ends in detection of a heterozygote.

2. Methods of analysis and notation. The behavior of the detection process $Y(t)$, $t \geqq 0$, must include a specification of the nature of the boundary at 0. For all the models described in Table 1, 0 is an exit boundary; that is, if $Y(t) = 0$, then $Y(t+s) = 0$ for all $s > 0$. This corresponds to the absorbing nature of the state 0 in

the discrete process specified in (2) and (3). Since $k(0)=0$, the behavior of such a process splits naturally into two groups of sample paths, those ending in detection (before loss of the a-allele), and those ending in loss of allele a (before detection).

We will use the notation $P_x\{A\}$ for $P\{A|Y(0)=x\}$, $E_x[Z]$ for $E[Z|Y(0)=x]$. In what follows, T_L denotes the time to loss, while T_D denotes the time to detection. Both T_L and T_D are, in general, defective random variables. If we let

$$\zeta = T_D \wedge T_L = \min(T_D, T_L)$$

be the lifetime of the process with infinitesimal parameters $\sigma^2(x), \mu(x), k(x)$, then many interesting functionals of the form $w(x)=E_x[\int_0^\zeta f(Y(u))\,du]$ are computed as solutions to differential equations of the form

$$\mathscr{L}w(x) \equiv \frac{\sigma^2(x)}{2}w''(x)+\mu(x)w'(x)-k(x)w(x)=-f(x), \tag{7}$$

for bounded continuous functions f over $[0,\infty]$ and boundary conditions on w (cf. Karlin and Taylor (1981, Chap. 15)).

Solutions of (7) are given in the usual way by

$$w(x)=\int_0^\infty G(x,y)f(y)\,dy, \tag{8}$$

where $G(x,y)$ is the relevant Green's function of the problem.

Since the sample paths split naturally into two groups, it is then of some interest to ascertain properties of the process conditioned on either detection occurring first or on loss occurring first. *We use a subscript D* to denote the condition that detection occurs before loss. For example, the conditioned Green's function is denoted by $G_D(x,y)$. A subscript L denotes quantities conditioned on loss occurring first.

Ideally, one would like to describe the complete time-dependent behavior of the detection process. That is, we would like to identify the transition density function $p(t,x,y)$ of $Y(t)$, such that for any $J\subseteq(0,\infty)$,

$$P_x\{Y(t)\subseteq J\}=\int_J p(t,x,y)\,dy.$$

In the present problem, taking $J=(0,\infty)$ results in $\int_0^\infty p(t,x,y)\,dy = P_x\{\zeta>t\}$, and so the distribution of the lifetime can be readily evaluated. The spectral representation of the transition density can be found for the strong detection model (see § 3), although it seems harder to ascertain explicit formulas in the other cases. As a consequence, we will compare the behavior of time-independent properties of the different detection processes, deriving a number of differential equations for probabilistic functionals of the detection processes. We begin, however, with the strong detection model.

3. Time-dependent behavior of strong detection model. Let $p(t,x,y)$ be the transition density of a diffusion process $Y(t)$ with infinitesimal parameters $\sigma^2(x), \mu(x), k(x)$ given in Table 1. For bounded continuous functions $f(y)$ define the function $g(x,t)$ by

$$g(x,t)=\int_0^\infty p(t,x,y)f(y)\,dy, \qquad x>0, \quad t>0.$$

Then $g(x,t)$ satisfies the differential equation

$$\frac{\partial g}{\partial t}=\mathscr{L}g=\frac{\sigma^2(x)}{2}\frac{\partial^2 g}{\partial x^2}+\mu(x)\frac{\partial g}{\partial x}-k(x)g(x), \tag{9}$$

with $g(x, 0) = f(x)$, $x > 0$, and with a boundary condition depending on the nature of the boundary point $\{0\}$. In this case the spectral representation involves only a discrete spectrum. Formal separation of variables in the usual way in (9) produces the spectral expansion

$$g(x, t) = \sum_{n=0}^{\infty} e^{-\lambda_n t} a_n \Phi_n(x), \qquad x, t > 0, \tag{10}$$

where the eigenfunctions $\Phi_n(x)$ satisfy $\mathscr{L}\Phi_n = -\lambda_n \Phi_n$, $\Phi_n(0) = 0$, since 0 is an exit boundary in the present case. The $\{\Phi_n\}$ are orthogonal with respect to the weight function

$$m(x) = \left[\sigma^2(x) \exp\left\{-2 \int^x (\mu(y)/\sigma^2(y))\, dy\right\}\right]^{-1} = \frac{1}{x}, \qquad \int_0^\infty \Phi_n(x)\Phi_m(x) \frac{dx}{x} = \delta_{mn} \pi_n^{-1},$$

and, from completeness of the system $\{\Phi_m(x)\}$ in $L^2((0, \infty)\, dx/x)$, we have $a_n = \pi_n \int_0^\infty f(y)\Phi_n(y) m(y)\, dy$. The transition function p is then given by

$$p(t, x, y) = m(y) \sum_{n=0}^{\infty} e^{-\lambda_n t} \Phi_n(x)\Phi_n(y)\pi_n, \qquad t, x, y > 0. \tag{11}$$

We now specialize to the case in which $\sigma^2(x) = x$, $\mu(x) = 0$ and $k(x) = Ax$. It remains to determine the system $\{\lambda_m, \Phi_n(x)\}$. To this end, let

$$\theta = +\sqrt{2A},$$

and define

$$\Phi_n(x) = x\, e^{-\theta x} L_n^{(1)}(2\theta x), \qquad x \geqq 0, \quad n \geqq 0,$$

where $L_n^{(1)}(z)$ is the Laguerre polynomial (Erdélyi, et al. (1953, p. 188, (7))

$$L_n^{(1)}(z) = \sum_{m=0}^{n} (-1)^m \binom{n+1}{n-m} \frac{z^m}{m!}.$$

We have

$$\begin{aligned} \mathscr{L}\Phi_n(x) &= x\theta\, e^{-\theta x}[2\theta x L_n^{(1)''}(2\theta x) + (2 - 2\theta x) L_n^{(1)'}(2\theta x) - L_n^{(1)}(2\theta x)] \\ &= -\theta(n+1) x\, e^{-\theta x} L_n^{(1)}(2\theta x) = -\theta(n+1)\Phi_n(x). \end{aligned}$$

For the second equality, see, e.g., Abramowitz and Stegun ((AS)) (1970, p. 781, 22.6.15). Completeness of the system $\{\Phi_m(x)\}$ in $L^2((0, \infty), dx/x)$, follows from completeness of $L_n^{(1)}(x)$ in $L^2((0, \infty), x\, e^{-x}\, dx)$ by transformation; see Szegö (1975, p. 110). Using AS (p. 775, 22.2.12), $\pi_n^{-1} = (n+1)/4\theta^2$, and the spectral expansion of the transition density follows from (11) as

$$p(t, x, y) = 4\theta^2 x\, e^{-\theta(x+y)} \sum_{n=0}^{\infty} e^{-\theta(n+1)t} \frac{L_n^{(1)}(2\theta x) L_n^{(1)}(2\theta y)}{n+1}, \qquad t, x, y > 0. \tag{12}$$

Thus, $p(t, x, y) = 4\theta^2 x\, e^{-\theta(x+y+t)} + O(e^{-2\theta t})$ as $t \to \infty$.

It is useful at this stage to compute the Laplace transform

$$\hat{p}(\gamma, t; x) = \int_0^\infty e^{-\gamma y} p(t, x, y)\, dy, \qquad \gamma > 0.$$

This relies on the readily verified identity

$$\int_0^\infty e^{-py} L_n^{(1)}(y)\, dy = 1 - \left(1 - \frac{1}{p}\right)^{n+1}, \qquad p > 0, \quad n \geqq 0 \tag{13a}$$

and the result that

$$\sum_{n=0}^{\infty} \frac{z^{n+1} L_n^{(1)}(x)}{n+1} = \frac{1-\exp(xz/(z-1))}{x}, \tag{13b}$$

valid for $x>0$, $|z|<1$; cf. Erdélyi et al. (1953, p. 215 (27)). Using (13a, b), we arrive at

$$\begin{aligned} \hat{p}(\gamma, t; x) &= 4\theta^2 x\, e^{-\theta x} \sum_{n=0}^{\infty} \frac{\exp[-\theta(n+1)t] L_n^{(1)}(2\theta x)}{n+1} \int_0^{\infty} e^{-(\gamma+\theta)y} L_n^{(1)}(2\theta y)\, dy \\ &= 2\theta x\, e^{-\theta x} \sum_{n=0}^{\infty} \frac{\exp[-\theta(n+1)t] L_n^{(1)}(2\theta x)}{n+1} \left(1-\left(\frac{\gamma-\theta}{\gamma+\theta}\right)^{n+1}\right) \\ &= \exp\left\{-\theta x \frac{\gamma+\theta b(t)}{\gamma b(t)+\theta}\right\} - \exp\left\{-\frac{\theta x}{b(t)}\right\}, \end{aligned} \tag{14}$$

where $b(t) = (1-e^{-\theta t})/(1+e^{-\theta t})$.

From (14), we can evaluate the distribution of the lifetime $\zeta = T_L \wedge T_D$ of the rocess. For $x>0$, $\hat{p}(0+, t; x) = \int_0^{\infty} p(t, x, y)\, dy = P_x\{\zeta > t\}$, whence

$$P_x\{\zeta > t\} = \exp\{-\theta x b(t)\} - \exp\left\{-\frac{\theta x}{b(t)}\right\}, \qquad x>0. \tag{15}$$

The Green's function (8) can be computed in the standard way or via

$$\begin{aligned} G(x, y) &= \int_0^{\infty} p(t, x, y)\, dt = 4\theta x\, e^{-\theta(x+y)} \sum_{n=0}^{\infty} \frac{L_n^{(1)}(2\theta x) L_n^{(1)}(2\theta y)}{(n+1)^2} \\ &= \begin{cases} (\theta y)^{-1} e^{-\theta x}(e^{\theta y} - e^{-\theta y}), & y<x, \\ (\theta y)^{-1}(e^{\theta x} - e^{-\theta x})\, e^{-\theta y}, & y \geqq x, \end{cases} \end{aligned} \tag{16}$$

the final equality resulting from an identity of Erdélyi, et al. (1953, p. 215 (21)).

Notice from (15) that $P_x\{\zeta > t\} \to 0$ as $t \to \infty$ for $x>0$, showing that the process must terminate. Indeed, if we set $u(x) = P_x\{T_L < T_D\}$, then $u(\cdot)$ solves $\mathscr{L}u = 0$ with $u(0) = 1$ and $u(x)$ decreasing positive. The required solution is

$$u(x) = e^{-\theta x}, \qquad x \geqq 0. \tag{17}$$

It follows that the probability that detection occurs first is

$$v(x) = 1 - u(x) = 1 - e^{-\theta x}, \qquad x \geqq 0.$$

Finally, the mean time to termination $M(x) = E_x[\zeta]$ is given by

$$M(x) = \int_0^{\infty} G(x, y)\, dy = \int_0^{\infty} P_x\{\zeta > t\}\, dt.$$

4. The process conditioned on detection. From a biological standpoint, the most interesting sample paths of the process involve those which result in detection. In this section, we analyze the behavior of the associated diffusion processes conditioned on killing (detection) occurring before the exit boundary is hit. The conditioned process is Markovian and setting $v(x) = P_x\{T_D < T_L\}$, a simple probabilistic argument shows that the conditional transition density p_D is given by

$$p_D(t, x, y) = \frac{p(t, x, y) v(y)}{v(x)}, \tag{18}$$

and this satisfies a backward diffusion equation of the form

$$\frac{\partial p_D}{\partial t}=\frac{\sigma_D^2(x)}{2}\frac{\partial^2 p_D}{\partial x^2}+\mu_D(x)\frac{\partial p_D}{\partial x}-k_D(x)p_D. \tag{19}$$

To identify the infinitesimal parameters $\sigma_D^2(x)$, $\mu_D(x)$, $k_D(x)$, we use (18) in conjunction with the diffusion equation satisfied by $p(t, x, y)$ to show that

$$\frac{\partial p_D}{\partial t}=\frac{\sigma^2(x)}{2}\frac{\partial^2 p_D}{\partial x^2}+\left\{\mu(x)+\sigma^2(x)\frac{v'(x)}{v(x)}\right\}\frac{\partial p_D}{\partial x}+\frac{\mathscr{L}v(x)}{v(x)}p_D.$$

But $\mathscr{L}v(x)=\mathscr{L}(1-u(x))=-\mathscr{L}u(x)-k(x)=-k(x)$, and so the infinitesimal parameters of the process conditioned on detection are identified as:

$$\sigma_D^2(x)=\sigma^2(x),\quad \mu_D(x)=\mu(x)+\sigma^2(x)\frac{v'(x)}{v(x)},\quad k_D(x)=\frac{k(x)}{v(x)}. \tag{20}$$

Returning to the case of strong detection, we can give an explicit form for $p_D(t, x, y)$ using (12), (18) and the result that $v(x)=1-e^{-\theta x}$. It then follows from (14) that the conditional Laplace transform $\hat{p}_D(\gamma, t; x)=\int_0^\infty e^{-\gamma y}p_D(t, x, y)\,dy$ is given by

$$\hat{p}_D(\gamma, t; x)=\left[\exp\left\{-\theta x\left[\frac{\gamma+\theta b(t)}{\gamma b(t)+\theta}\right]\right\}-\exp\left\{-\theta x\left[\frac{\gamma+\theta+\theta b(t)}{\theta+(\gamma+\theta)b(t)}\right]\right\}\right](1-e^{-\theta x})^{-1}. \tag{21}$$

The distribution of the time to detection T_D, given $T_D<T_L$, is then determined by

$$P_x\{T_D\leqq t|T_D<T_L\}=1-\hat{p}_D(0+, t; x)=\frac{1-e^{-\theta x b(t)}}{1-e^{-\theta x}},\qquad t>0,\quad x>0, \tag{22}$$

where, as earlier, $b(t)=\{1-e^{-\theta t}\}/\{1+e^{-\theta t}\}$. The conditional density function of T_D is given by

$$f_D(t; x)=\frac{\theta x b'(t)\,e^{-\theta x b(t)}}{1-e^{-\theta x}},\qquad t>0,\quad x>0. \tag{23}$$

One case of particular interest is that in which the initial number of heterozygotes is very small. Taking $x\downarrow 0$ in (23) shows that

$$f_D(t; 0+)=\frac{2\theta\, e^{-\theta t}}{(1+e^{-\theta t})^2},\qquad t\geqq 0,$$

the mean time to detection then being $2\ln 2/\theta$. In terms of the original discrete process, this corresponds to about $\sqrt{2}\ln 2/\sqrt{\alpha}$ generations.

5. The process conditioned on loss. The other set of sample paths are those resulting in loss. Denoting the conditioning event that $T_L<T_D$ by L, an argument paraphrasing that leading to (20) identifies the infinitesimal parameters of this conditioned process as

$$\sigma_L^2(x)=\sigma^2(x),\quad \mu_L(x)=\frac{\sigma^2(x)u'(x)}{u(x)}+\mu(x),\quad k_L(x)=0, \tag{24}$$

where $u(x)=P_x\{T_L<T_D\}$, and recall $u(x)=e^{-\theta x}$. In the context of the strong detection model, these parameters reduce to $\sigma_L^2(x)=x$, $\mu_L(x)=-\theta x$. The resulting conditioned process is then identified as a diffusion branching process, where the transition density

has the form (cf. Karlin and McGregor (1960, p. 173 (13))

$$p_L(t,x,y)=4\theta^2 y\, e^{-2y\theta}\sum_{n=0}^{\infty} e^{-\theta(n+1)t}\frac{L_n^{(1)}(2\theta x)L_n^{(1)}(2\theta y)}{n+1}, \qquad t,x,y>0, \tag{25}$$

and the corresponding Laplace transform is given by

$$\hat{p}_L(\gamma,t;x)=\exp\left\{\frac{-2\theta x\gamma\, e^{-\theta t}}{2\theta+\gamma(1-e^{-\theta t})}\right\}-\exp\left\{\frac{-2\theta x}{e^{\theta t}-1}\right\}. \tag{26}$$

Given that $T_L<T_D$, the mean and variance of $Y(t)$ are given by $x\,e^{-\theta t}$ and $(x/\theta)\,e^{-\theta t}(1-e^{-\theta t})$, respectively, while the distribution of the loss time T_L is given by

$$P_x\{T_L\leqq t\,|\,T_L<T_D\}=\exp\left\{\frac{-2\theta x}{e^{\theta t}-1}\right\}, \qquad t>0. \tag{27}$$

This process is classical; see Feller (1951, p. 235) and Cox and Miller (1965, p. 235).

6. Asymptotic conditional distributions. The long-term transient behavior of these processes can also be described by their asymptotic conditional distributions. For $A\subseteq(0,\infty)$, we define

$$\begin{aligned} b(A)&=\lim_{t\to\infty}P\{Y(t)\in A\,|\,\zeta>t\},\\ c(A)&=\lim_{s\to\infty}\lim_{t\to\infty}P\{Y(s)\in A,\, s<t\,|\,\zeta>t\}. \end{aligned} \tag{28}$$

These distributions describe the behavior of the processes after a long time has elapsed, given that termination has not yet occurred (Seneta (1966)). The densities are given explicitly as

$$\begin{aligned} b(dy)&=\Phi_0(y)m(y)\,dy\Big/\left(\int_0^\infty \Phi_0(u)m(u)\,du\right),\\ c(dy)&=m(y)\pi_0[\Phi_0(y)]^2\,dy, \end{aligned} \tag{29}$$

which follows from the representation (11). For the strong detection process, and their conditioned counterparts, we find that

$$b(dy)=\theta\, e^{-\theta y}\,dy,\quad b_L(dy)=2\theta\, e^{-2\theta y}\,dy,\quad b_D(dy)=2\theta(e^{-\theta y}-e^{-2\theta y})\,dy. \tag{30}$$

The means and variances of these distributions are $m=\theta^{-1}$, $m_L=(2\theta)^{-1}$, $m_D=3(2\theta)^{-1}$ and $v=\theta^{-2}$, $v_L=(2\theta)^{-2}$, $v_D=5(2\theta)^{-2}$, respectively. This confirms the intuitive observation that if the process ends in loss it should be "nearer 0" than the process conditioned on detection. However, the distribution $c(\cdot)$ is invariant to conditioning and is given by

$$c(dy)=4\theta^2 y\, e^{-2\theta y}\,dy.$$

This is a gamma distribution with parameters $(2, 2\theta)$.

7. Functionals of the Airy model. It appears to be difficult to evaluate the spectrum of the Airy model explicitly, although application of the Rayleigh–Ritz method to the eigenvalue problem $(x/2)\phi_n''(x)-(x^2/2)\phi_n(x)=-\lambda_n\phi_n(x)$, $\phi_n(0)=0$, $n=0,1,\cdots$ using a system of Laguerre functions as a basis yields estimates $\lambda_0=1.07$, $\lambda_1=2.740$, $\lambda_2=4.718$. We can conclude that time-dependent properties in the Airy model decrease at a rate proportional to $e^{-1.07t}$ as $t\to\infty$.

Before continuing to the next section, we record without details (cf. Karlin and Tavaré (1981a)) two results for the Airy model with infinitesimal parameters $\sigma^2(x)=x$, $\mu(x)=0$, $k(x)=x^2/2$. The probability $u(x)$ that loss occurs before detection is given by

$$u(x)=P_x\{T_L<T_D\}=\frac{A(x)}{A(0)}, \tag{31}$$

where $A(x)$ is the (first) Airy function represented explicitly by

$$A(x)=\frac{x^{1/2}}{3}\left[I_{-1/3}\left(\frac{2x^{3/2}}{3}\right)-I_{1/3}\left(\frac{2x^{3/2}}{3}\right)\right], \tag{32}$$

where I_v is the modified Bessel function,

$$I_v(x)=\left(\frac{x}{2}\right)^{\mu}\sum_{k=0}^{\infty}\frac{(x^2/4)^k}{k!\Gamma(\nu+k+1)}.$$

The appropriate Green's function of the process is given as

$$G(x,y)=\begin{cases}2\pi(B(x)-\sqrt{3}\,A(x))A(y)/y, & x\leqq y,\\ 2\pi(B(y)-\sqrt{3}\,A(y))A(x)/y, & x\geqq y,\end{cases} \tag{33}$$

$B(x)$ being the (second) Airy function:

$$B(x)=\frac{x^{1/2}}{\sqrt{3}}\left[I_{-1/3}\left(\frac{2x^{3/2}}{3}\right)+I_{1/3}\left(\frac{2x^{3/2}}{3}\right)\right].$$

8. The place at which detection occurs. The final question we consider in this paper involves a description of the place at which detection occurs. The distribution of the place P at which detection occurs can then be used to assess how many heterozygotes are carried in the population at the time of detection. Let $W(x,J)=P_x\{\text{process killed in } J\}$, $J\subseteq(0,\infty)$. It is easy to prove

$$W(x,J)=\int_J G(x,y)k(y)\,dy, \tag{34}$$

and it follows that $W(x,\cdot)$ has a density

$$w(x,y)=G(x,y)k(y), \qquad y>0. \tag{35}$$

We remark that P need not be a bona fide random variable. Indeed,

$$\int_0^{\infty} G(x,y)k(y)\,dy = W(x,(0,\infty))=P_x\{T_D<T_L\}=1-u(x)$$

for the processes with no conditioning. We will examine the density $w(x,y)$ for the strong detection model and the Airy model described in Table 1.

For the strong detection model, the density $w(x,y)$ is given from (16) and (35) by

$$w(x,y)=\begin{cases}\dfrac{\theta}{2}\,e^{-\theta x}(e^{\theta y}-e^{-\theta y}), & y\leqq x,\\[2ex] \dfrac{\theta}{2}\,e^{-\theta y}(e^{\theta x}-e^{-\theta x}), & y\geqq x.\end{cases} \tag{36}$$

It is readily verified that $\int_0^{\infty} w(x,y)\,dy=1-e^{-\theta x}=1-u(x)$, in agreement with (17). Using either (36) or (35) in conjunction with the conditioned parameters (20), the

detection position P, conditional on detection occurring, has density

$$w_D(x, y) = \begin{cases} \dfrac{\theta e^{-\theta x}(e^{\theta y} - e^{-\theta y})}{2(1-e^{-\theta x})}, & 0 < y \leqq x, \\ \dfrac{\theta e^{-\theta y}(e^{\theta x} - e^{-\theta x})}{2(1-e^{-\theta x})}, & y \geqq x \end{cases} \tag{37}$$

This density has Laplace transform $\hat{w}_D(x; \gamma) = \int_0^\infty e^{-\gamma y} w_D(x, y)\, dy$ given by $\hat{w}_D(x; \gamma) = \theta^2(e^{-\theta x} - e^{-\gamma x})/((\gamma^2 - \theta^2)v(x))$, and it follows that

$$E_x[P] = \frac{x}{v(x)}, \qquad \operatorname{var}_x[P] = \frac{2}{\theta^2} - \frac{x^2}{v(x)}\left[1 + \frac{1}{v(x)}\right],$$

where $v(x) = 1 - e^{-\theta x}$. In the particular case that $x = 0$, P has an exponential distribution with parameter θ.

We move on now to the Airy model. In this case, the detection rate described after (1) is so small relative to the population size N that the approximating diffusion has infinitesimal parameters $\sigma^2(x) = x$, $\mu(x) = 0$, $k(x) = x^2/2$. The density $w_D(x, y)$ of the detection position, given detection occurs first, is given from (31) and (32) by

$$w_D(x, y) = \begin{cases} \dfrac{A(0)\pi A(x) y[B(y) - \sqrt{3}\, A(y)]}{A(0) - A(x)}, & 0 < y \leqq x, \\ \dfrac{A(0)\pi[B(x) - \sqrt{3}\, A(x)] y A(y)}{A(0) - A(x)}, & y \geqq x. \end{cases} \tag{38}$$

Focusing attention again on the case $x = 0$ leads to the density

$$w_D(0, y) = 2\sqrt{3}\, \pi A(0) y A(y), \qquad y \geqq 0. \tag{39}$$

The density $w_D(0, y)$ is unimodal, as the following argument shows. At any point satisfying $[yA(y)]' = 0$, we must have $y^{-1} = -A'(y)/A(y) = g(y)$, say. But since $A''(\xi) = \xi A(\xi)$

$$g'(y) = \frac{-A''(y)}{A(y)} + \left(\frac{A'(y)}{A(y)}\right)^2 = -y + \left(\frac{A'(y)}{A(y)}\right)^2.$$

Starting from $A''(x) - xA(x) = 0$, multiplying by $A'(x)$ and integrating from y to infinity yields $[A'(y)]^2 = y[A(y)]^2 + \int_y^\infty [A(x)]^2\, dx \geqq y[A(y)]^2$. Hence, $g'(y) > 0$. Hence, the graphs of $1/y$ and $g(y)$ intersect exactly once and so the density is unimodal, as claimed. (Incidentally, the preceding argument also shows that $A(y)$ is log-concave on $(0, \infty)$.) Numerical solution of the equation $[yA(y)]' = 0$ gives the mode at $y_0 \approx .885$, showing that the most likely detection position starting from a very small number of heterozygotes in the discrete model is about $1.12N^{1/3}$ individuals. We see a distinct qualitative difference in the behavior of the two systems. The strong detection model ends in detection much faster than the Airy model, and this is reflected in the fact that the mode of the detection position in the strong case is at 0, whereas in the Airy case it is at .885.

Moments of the detection position starting from $x = 0$ can be readily evaluated using the result that for $n \geqq 3$, $g_n = \int_0^\infty y^n A(y)\, dy = (n-1)(n-2)g_{n-3}$, where $g_0 = \frac{1}{3}$, $g_1 = -A'(0)$ and $g_2 = A(0)$. For example, $E_0[P] = 2\sqrt{3}\, \pi A^2(0) \approx 1.372$, while $\operatorname{var}_0[P] \approx .693$. The expected position of detection corresponds to about $1.73N^{1/3}$ individuals in the discrete process, a much higher number than in the strong detection case.

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REFERENCES

M. ABRAMOWITZ AND I. STEGUN (1970), *Handbook of Mathematical Functions*, Dover, New York.

D. R. COX AND H. D. MILLER (1965), *The Theory of Stochastic Processes*, Methuen, London.

A. ERDÉLYI, W. MAGNUS, F. OBERHETTINGER AND F. G. TRICOMI (1953), *Higher Transcendental Functions*, Vol. II, McGraw-Hill, New York.

W. J. EWENS (1979), *Mathematical Population Genetics*, Springer-Verlag, Berlin.

W. FELLER (1951), *Diffusion processes in genetics*, Proc. Second Berkeley Symposium on Mathematical Statistics and Probability, pp. 227–246.

S. KARLIN AND J. L. MCGREGOR (1960), *Classical diffusion processes and total positivity*, J. Math. Anal. Appl., 1, pp. 163–183.

S. KARLIN AND S. TAVARÉ (1981a), *The detection of a recessive visible gene in finite populations*, Genetical Research, Cambridge, 37, pp. 33–46.

——— (1981b), *The detection of particular genotypes in finite populations*, II. *The effects of partial penetrance and family structure*, Theoret. Pop. Biol., 19, pp. 215–229.

S. KARLIN AND H. M. TAYLOR (1981), *An Introduction to Stochastic Processes*, Vol. II, Academic Press, New York.

A. ROBERTSON (1978), *The time to detection of recessive visible genes in small populations*, Genetical Research, Cambridge, 31, pp. 255–264.

E. SENETA (1966), *Quasi-stationary distributions and time-reversion in genetics*, J. Roy. Statist. Soc. B, 28, pp. 253–277.

G. SZEGÖ (1975), *Orthogonal Polynomials*, AMS Colloquium Publications, 23, American Mathematical Society, Providence, RI.