

Branching Process Models for Mutant Genes in Nonstationary Populations

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A deleterious gene achieves a population balance between the opposing forces of selection and mutation. In this paper we explore the nature of this stochastic balance when the surrounding normal population is not at equilibrium. Assuming that new mutations occur according to a Poisson process and thereafter evolve by the rules of a continuous time branching process, we derive explicit formulas and recurrence relations determining the probability distribution of the current number of mutant individuals. In fact, we compute expectations for a variety of interesting random variables for genetic models involving autosomal dominant and X-linked diseases. We can also handle haplotype information on linked markers. This feature will be especially helpful in understanding the linkage disequilibrium strategy of positional cloning in population isolates. In the presence of exponential growth of the normal population, our formulas reduce to the evaluation of certain Laplace transforms. © 1997 Academic Press

1. INTRODUCTION

Population genetics has been both a source of inspiration and a fruitful application area for the theory of branching processes (Fisher, 1930, 1958; Haldane, 1927). In the current paper we model the stochastic balance achieved between selection and mutation for a deleterious gene. There is a considerable body of previous theory on branching processes with immigration dealing with precisely this problem for stationary populations (Gladstien and Lange, 1978; Haldane, 1939; Lange, 1982; Lange *et al.*, 1981; Lange and Gladstien, 1980; Skellam, 1949). However, human populations experience systematic patterns of growth and decline incompatible with stationarity. At first glance, revising existing branching process theory to handle nonstationarity appears to be a hopelessly complicated task. Such pessimism is misplaced though. Little is lost and much is gained by making the realistic assumption that new mutations occur according to a Poisson process (Bartlett, 1960;

Kaplan *et al.*, 1995; Karlin and Taylor, 1981). This simplifying assumption more than compensates for the complications of nonstationarity in the surrounding population.

Part of the impetus for our current investigations derives from the positional cloning strategy for disease genes. It has dawned on a number of geneticists recently that population isolates offer unique opportunities to map disease genes using the method of linkage disequilibrium (Bodmer, 1986; Hästbacka *et al.*, 1992; Kaplan *et al.*, 1995; Pritchard *et al.*, 1991; Sirugo *et al.*, 1992; Uhrhammer *et al.*, 1995). Once a disease locus is roughly mapped to a given chromosome region, that region can be saturated with genetic markers. With enough markers in a small region, each new mutation carries a unique marker haplotype signature. If the number of different mutations represented in a population isolate is small, then recombination events disrupting these haplotype signatures can be easily visualized by saturation typing of currently affected people. Because the preserved segment of each disrupted haplotype signature necessarily contains the disease locus, it is trivial to construct the smallest region of overlap for the locus. In effect, the marker haplotypes of contemporary affecteds preserve a fossil record of recombination events that may have happened

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generations ago. This ability of linkage disequilibrium mapping to take advantage of ancient as well as contemporary recombination events explains its increased power relative to ordinary linkage analysis based on family studies.

With this motivation in mind, we briefly survey in the next section the genetic models prompting our theoretical development of single and multitype branching processes with Poisson streams of mutants. This descriptive section is followed by sections summarizing various mathematical facts about Poisson processes and applying these facts to the calculation of the moments and the probability distributions of the number of current mutant individuals. We particularly stress the interplay between exponential growth of the surrounding population and Laplace transforms of the underlying branching process. In this context we construct some specific numerical examples for both single and multitype processes. Our concluding discussion comments critically on the assumptions and limitations of the model and suggests some further problems for consideration.

2. GENETIC MODELS

In the current study we consider branching process models for autosomal dominant and X-linked diseases. Because gene carriers for such diseases seldom interact, branching process models are ideal. In contrast, autosomal recessive diseases are poor candidates for branching process models since selection occurs only when two carriers mate. Every new mutation at an autosomal dominant or X-linked disease locus creates a clan of carrier individuals that persists for a random number of generations. If the mutation is deleterious, then the associated branching process is subcritical, and the clan eventually goes extinct. The number and sizes of the currently existing clans determine the distribution of the current number of carriers. Given a low mutation rate, we expect that carriers form a very small fraction of the overall population.

It is critically important to characterize the stochastic process governing new mutations. Suppose the mutation rate at the disease locus is η . At an autosomal locus, each new birth involves transmission of two copies of existing genes at the disease locus. Thus, each birth in the population to normal parents has an independent chance 2η of being a new mutation. If the population of normal people is reasonably large, then standard arguments from elementary probability theory suggest that these independent Bernoulli trials trigger a Poisson process (Ross, 1983). The varying intensity of this process is proportional to

the varying intensity of births to normal people. Growth of the normal population is determined by the excess of births over deaths.

For instance, if we crudely model growth of the normal population by a continuous time-branching process, then in a population of size s with death rate γ per person, there are on average $s\gamma dt$ deaths in a small time interval of length dt . If each death is compensated by b births on average, then there are on average $2\eta bs\gamma dt$ new mutations during the given period. Simultaneously, the normal population grows by the amount $(b-1)s\gamma dt$. In other words, the large normal population experiences deterministic exponential growth at rate $\lambda = (b-1)\gamma$. If the normal population has size s_0 at time 0, then the intensity measure for the Poisson process of new mutations is exponential with density $2\eta bs_0\gamma e^{\lambda t}$ at time t .

By definition mutant individuals have lower reproductive capacity than normal individuals. If we model the clan emanating from a new mutation by a continuous time branching process, then we imagine each mutant person living for an exponential length of time with mean $1/\alpha$, where α is the death rate. At the end of his (or her) life, a mutant produces n offspring with probability q_n . These coefficients are compactly summarized by the total-progeny generating function $Q(s) = \sum_{n=0}^{\infty} q_n s^n$. To avoid theoretical subtleties, we assume that $Q(s)$ has all moments finite. For an autosomal dominant, only half of the children of a mutant are themselves mutant on average. If the mutant has N total children, then his total number of mutant children can be represented as the random sum $S_N = \sum_{n=1}^N W_n$, where W_n is an indicator random variable taking the value 1 when his n th child is mutant. It is well known that the generating function $P(s)$ of S_N is formed by taking the functional composition of $Q(s)$ with $1/2 + s/2$, the generating function of each W_n (Feller, 1968).

EXAMPLE 2.1. Geometric branching process. The geometric generating function $Q(s) = p/(1-qs)$ permits an unlimited number of progeny. Here $0 < p < 1$ and $q = 1 - p$. Because the group of fractional linear transformations is closed under functional composition, the mutant progeny generating function

$$\begin{aligned} P(s) &= Q\left(\frac{1}{2} + \frac{s}{2}\right) \\ &= p \left/ \left[1 - q \left(\frac{1}{2} + \frac{s}{2}\right) \right] \right. \\ &= \frac{p^*}{1 - q^*s} \end{aligned}$$

is geometric with $p^* = 2p/(2-q)$ and $q^* = q/(2-q)$.

EXAMPLE 2.2. *Birth–death process.* For another example, consider a birth–death process with birth rate β and death rate δ . At a birth, a mutant dies and splits into two children, each of which is independently assigned the status of normal or mutant with probability $\frac{1}{2}$. At a death, a mutant dies and leaves behind no children. This simple model generates a continuous time branching process with overall death rate $\alpha = \delta + \beta$, total-progeny generating function $Q(s) = \delta/(\delta + \beta) + (\beta/(\delta + \beta))s^2$, and mutant-progeny generating function

$$P(s) = Q\left(\frac{1}{2} + \frac{s}{2}\right) = \frac{\delta + \beta/4}{\delta + \beta} + \frac{\beta/2}{\delta + \beta}s + \frac{\beta/4}{\delta + \beta}s^2.$$

If we ignore those births that exactly replace the mutant parent with one mutant and one nonmutant child, then the resulting stochastic process is an ordinary birth–death process with birth rate $\beta^* = \beta/4$, death rate $\delta^* = \delta + \beta/4$, and overall death rate $\alpha^* = \delta + \frac{1}{2}\beta$.

With an X -linked gene, we are forced to consider a two-type branching process (Gladstien and Lange, 1978; Lange, 1982; Lange and Gladstien, 1980). Now affected males and carrier females must be separately tracked. If we make the simplifying assumptions that males and females are equally common and experience equally frequent mutation, then the intensity measure for new mutations to affected males is $\frac{1}{4}$ that of the autosomal dominant case. Indeed, there are only half as many males as total people, and males possess one rather than two X chromosomes. The intensity measure for new mutations to carrier females is $\frac{1}{2}$ that of the autosomal dominant case. As we note more generally in the next section, the Poisson stream of new mutant males is independent of the Poisson stream of new mutant females.

We also must worry about different death rates and different mutant-progeny generating functions for affected males (type 1 particles) and carrier females (type 2 particles). The potentially different generation times for affected males and carrier females can be accommodated by taking unequal death rates α_1 and α_2 . Of course, within the confines of the continuous branching process models, all lifetimes are exponentially distributed. This Markovian assumption is certainly no less realistic than the alternative of fixed lifetimes assumed in discrete-time branching processes.

Different mutant-progeny generating functions are appropriate because males and females transmit their X chromosomes differently. Furthermore, selection against an X -linked recessive acts only on affected males; it acts on both sexes for an X -linked dominant. Let $Q_1(s)$ be the total-progeny generating function for affected males. All

of the daughters and none of the sons of an affected male will carry the mutant gene. This implies that the mutant-progeny generating function for the two types of mutant offspring of an affected male is $P_1(s_1, s_2) = Q_1(\frac{1}{2} + s_2/2)$. If $Q_2(s)$ is the total-progeny generating function for carrier females, then similar reasoning shows that $P_2(s_1, s_2) = Q_2(\frac{1}{2} + s_1/4 + s_2/4)$ is the mutant-progeny generating function for the two types of mutant offspring of a carrier female. In deriving these two expressions for $P_1(s_1, s_2)$ and $P_2(s_1, s_2)$, we use the multivariate version of the functional composition rule mentioned earlier for autosomal dominants.

Finally, let us return to the autosomal dominant case and consider the effect of a linked marker locus. If there are k alleles at the marker locus with population proportions r_1, \dots, r_k , then any chromosome carrying a mutant gene at the disease locus can be labeled by the cosegregating marker allele at the marker locus. In particular, new mutations can be subdivided by allele type at the marker locus. Just as with labeling by sex, this gives rise to k independent Poisson mutation processes with intensities scaled by the factors r_1, \dots, r_k , respectively.

In this setting, the same death rate α and the same total-progeny generating function $Q(s)$ are assigned to all affected types. However, we must exercise care in deriving the mutant-progeny generating function $P_i(s_1, \dots, s_k)$ of a type i parent because the parent's second homologous chromosome comes into play. Once we condition on the marker type of his or her homologous chromosome, then we must decide for each of his children whether the disease allele is passed at the disease locus, and if so, whether recombination occurs between the disease and marker loci. If the recombination fraction between the two loci is θ , then these considerations imply that

$$P_i(s_1, \dots, s_k) = r_i Q\left(\frac{1}{2} + \frac{s_i}{2}\right) + \sum_{j \neq i} r_j Q\left(\frac{1}{2} + \frac{1}{2}[(1 - \theta)s_i + \theta s_j]\right). \quad (1)$$

This is not the same as the erroneous formula

$$P_i(s_1, \dots, s_k) = Q\left(\frac{1}{2} + \frac{1}{2}\left[(1 - \theta + \theta r_i)s_i + \theta \sum_{j \neq i} r_j s_j\right]\right),$$

which would apply if a new homologous chromosome were chosen for the parent at the birth of each child. If θ is small, then these two expressions are nearly equal. Even for θ large, they give identical means

$\frac{1}{2}(1 - \theta + \theta r_i) Q'(1)$ and $\frac{1}{2}\theta r_j Q'(1)$ for the number of type i and type $j \neq i$ mutant offspring, respectively.

3. BACKGROUND MATERIAL ON POISSON PROCESSES

At this juncture it is prudent to summarize some key facts about abstract Poisson processes (Kingman, 1983). Recall that a Poisson process defines a random set of points on some measurable space Ω equipped with a σ -finite measure μ . If the random set is denoted by Π and A is a measurable subset of Ω , then the counting variable

$$N_A = \# \{ \Pi \cap A \}$$

is either always finite or always countably infinite. If $\mu(A) < \infty$, then N_A is finite and follows a Poisson distribution with mean $\mu(A)$. If $\mu(A) = \infty$, then N_A is infinite. To complete the definition of a Poisson process, we assume that μ possesses no atoms and that any finite collection $\{A_1, \dots, A_k\}$ of disjoint measurable sets of Ω generates a collection $\{N_{A_1}, \dots, N_{A_k}\}$ of independent counting variables.

We will repeatedly use a general version of Campbell's theorem (Kingman, 1983). This result deals with random sums of the sort

$$S = \sum_{X \in \Pi} f(X), \quad (2)$$

where the real-valued function $f: \Omega \rightarrow \mathbb{R}$ is measurable and X is a generic point of Π . Campbell's theorem says that the random sum (2) defining S converges absolutely with probability 1 if and only if

$$\int_{\Omega} \min\{|f(x)|, 1\} d\mu(x) < \infty. \quad (3)$$

If this condition holds, then

$$E(e^{\theta S}) = \exp \left\{ \int_{\Omega} [e^{\theta f(x)} - 1] d\mu(x) \right\} \quad (4)$$

is valid for any complex number θ for which the integral on the right converges. If θ is imaginary, then we have a representation of the characteristic function of S . Taking logarithms provides the cumulant generating function. In particular,

$$E(S) = \int_{\Omega} f(x) d\mu(x)$$

$$\text{Var}(S) = \int_{\Omega} f(x)^2 d\mu(x),$$

whenever the indicated integrals converge. If $f(x)$ is non-negative and integer valued, then formula (4) metamorphoses into the generating function identity

$$E(u^S) = \exp \left\{ \int_{\Omega} [u^{f(x)} - 1] d\mu(x) \right\}$$

for $u \in [0, 1]$.

More generally if f_1, \dots, f_n are n such functions satisfying condition (3), then the random sums $S_i = \sum_{X \in \Pi} f_i(X)$ converge absolutely and have joint characteristic function

$$E(e^{\sum_i \theta_i S_i}) = \exp \left\{ \int_{\Omega} [e^{\sum_i \theta_i f_i(x)} - 1] d\mu(x) \right\}$$

for all θ_i imaginary. If in addition the f_i satisfy the conditions $\int_{\Omega} f_i(x)^2 d\mu(x) < \infty$, then the covariances between the sums reduce to

$$\text{Cov}(S_i, S_j) = \int_{\Omega} f_i(x) f_j(x) d\mu(x).$$

Finally, if all f_i are nonnegative and integer valued, then we have the joint generating function

$$E \left(\prod_i u_i^{S_i} \right) = \exp \left\{ \int_{\Omega} \left[\prod_i u_i^{f_i(x)} - 1 \right] d\mu(x) \right\}.$$

Another feature of Poisson processes that we will exploit is called marking (Kingman, 1993). The most primitive version of marking is known as coloring. Suppose we independently choose a color for each random point. Then it is well known that the random points of a fixed color form a Poisson process (Kingman, 1993). Furthermore, the Poisson processes generated for different colors are independent. Subdividing new mutants by sex or linked marker alleles are specific examples of coloring. In marking, we generalize this construction by supposing that there is a second measurable space Γ of marks for each point $x \in \Omega$. In contrast to coloring, marking can ascribe subtle quantitative differences to different random points. For each random point $X = x \in \Pi$, a mark $y \in \Gamma$ is independently chosen by sampling from a distribution $p(x, \cdot)$ on Γ . If the distributions $p(x, \cdot)$ are compatible in the sense that

$x \rightarrow p(x, B)$ is measurable for each measurable $B \subset \Gamma$, then we get a Poisson process on the product space $\Omega \times \Gamma$ with intensity measure

$$\nu(C) = \iint_{(x, y) \in C} p(x, dy) \, d\mu(x).$$

This result, known as the marking theorem (Kingman, 1993), will allow us to compute via Campbell's theorem certain branching process moments and probabilities with surprising ease.

4. APPLICATIONS TO SINGLE-TYPE PROCESSES

We are now in a position to apply the Poisson process theory just sketched to the single-type branching process generated by mutations at an autosomal dominant locus. If our primary interest is the current number of mutant people, then the relevant state space for the Poisson process of new mutations is the interval $\Omega = (-\infty, 0]$. Let μ be the associated intensity measure that captures the deterministic growth of the surrounding normal population. When the normal population is growing at rate λ , the intensity measure μ has an exponential density $ce^{\lambda t}$, where the constant c was explicitly calculated for a continuous time branching process. We mark a new mutant at time $t \in \Omega$ by the number $y \in \Gamma = \mathbb{Z}_+ = \{0, 1, 2, \dots\}$ of mutant people in its clan at the present time 0. The discrete density $p(t, y)$ of y is explicitly known for a few special cases such as birth–death processes (Harris, 1989). However, it is worth stressing that most of the theoretical formulas that follow do not require detailed premises about how a clan evolves but only the assumption that different clans evolve independently.

The marking theorem implies that we get an induced Poisson process on the product space $(-\infty, 0] \times \mathbb{Z}_+$ with intensity measure $\nu(t, y) = p(t, y) \mu(t)$. There are several functions $f: (-\infty, 0] \times \mathbb{Z}_+ \rightarrow \mathfrak{R}$ that define via Eq. (2) genetically interesting sums S on this induced process. In most cases Campbell's theorem permits straightforward derivation of the moments of S .

EXAMPLE 4.1. Current number of mutant people. If $f(t, y) = y$, then S represents the current number of mutant people. Assuming that a clan has evolved for a length of time t , let

$$\phi(t, s) = \sum_{y=0}^{\infty} p(t, y) s^y \tag{5}$$

be the generating function of the current number of mutant people in the clan. Also let $m_k(t) = \sum_{y=0}^{\infty} y^k p(t, y)$ be the k th moment of $\phi(t, s)$. Campbell's theorem implies that S converges absolutely whenever,

$$\int_{-\infty}^0 m_1(-t) \, d\mu(t) < \infty.$$

This sufficient condition is also necessary when $\int_{-\infty}^0 d\mu(t) < \infty$. It is noteworthy that S can even converge for supercritical clans, provided the rate of growth of the surrounding normal population exceeds that of $m_1(t)$.

Campbell's theorem gives the generating function and n th cumulant of S as

$$\begin{aligned} \sum_{k=0}^{\infty} \Pr(S = k) s^k &= \exp \left\{ \int_{-\infty}^0 [\phi(-t, s) - 1] \, d\mu(t) \right\} \\ \kappa_n(S) &= \int_{-\infty}^0 m_n(-t) \, d\mu(t). \end{aligned}$$

In particular, if $d\mu(t) = ce^{\lambda t} dt$, then these can be expressed in terms of the Laplace transforms

$$\hat{\phi}(\lambda, s) = \int_0^{\infty} e^{-\lambda t} \phi(t, s) \, dt \tag{6}$$

$$\hat{m}_n(\lambda) = \int_0^{\infty} e^{-\lambda t} m_n(t) \, dt \tag{7}$$

as $\exp[c\hat{\phi}(\lambda, s) - c/\lambda]$ and $c\hat{m}_n(\lambda)$.

EXAMPLE 4.2. Number of extant clans. If $f(t, y) = 1_{\{y>0\}}$, then S is the number of extant clans. The sum S counts the random number of points on the subset $\{(t, y) \in (-\infty, 0] \times \mathbb{Z}_+ : y > 0\}$ of the induced Poisson process. It follows that S has Poisson distribution with mean $\int_{-\infty}^0 [1 - \phi(-t, 0)] \, d\mu(t)$. If $d\mu(t) = ce^{\lambda t} dt$, then the mean becomes $c/\lambda - c\hat{\phi}(\lambda, 0)$. Note that $\Pr(S = 0)$ is just the probability that the mutant gene is currently extinct.

EXAMPLE 4.3. Distribution of the largest clan. If $f(t, y) = 1_{\{y>k\}}$, then S is the number of clans with more than k current members. Again S follows a Poisson distribution whose mean

$$E(S) = \int_{-\infty}^0 \sum_{y>k} p(-t, y) \, d\mu(t)$$

reduces to the sum of Laplace transforms

$$c \sum_{y>k} \hat{p}(\lambda, y) = c \sum_{y>k} \int_0^{\infty} e^{-\lambda t} p(t, y) \, dt \tag{8}$$

under exponential growth. To extract the distribution of the largest clan $W = \max\{Y\}$ over all random points (T, Y) of the induced Poisson process simply note that

$$\Pr(W \leq k) = \Pr(S = 0) = e^{-E(S)}.$$

EXAMPLE 4.4. Number of extinct clans. If $f(t, y) = 1_{\{y=0\}}$, then S is the number of extinct clans stretching back into the infinite past. Now S counts the random number of points on the subset $\{(t, y) \in (-\infty, 0] \times \mathbb{Z}_+ : y = 0\}$. Clearly, S has a Poisson distribution with mean $\int_{-\infty}^0 \phi(-t, 0) d\mu(t)$, which reduces to $c\hat{\phi}(\lambda, 0)$ in the case of exponential growth.

EXAMPLE 4.5. Number of clans of limited size. Generalizing the last example slightly, we can take $f(t, y) = 1_{\{y \leq k\}}$. In this situation S is the number of clans with current size bounded above by k . Once again S follows a Poisson distribution. Its mean

$$E(S) = \int_{-\infty}^0 \sum_{y \leq k} p(-t, y) d\mu(t)$$

becomes $E(S) = c \sum_{y \leq k} \hat{p}(\lambda, y)$ under exponential growth.

5. LAPLACE TRANSFORMS FOR SINGLE-TYPE PROCESSES

Putting the theory of the last section into practice depends on our ability to evaluate the required Laplace transforms (6), (7), and (8). For continuous time branching processes, we can make considerable headway. Recall that α is the lifetime intensity of a mutant person and that $P(s)$ is the generating function for his mutant progeny. Our point of departure is the partial differential equation

$$\frac{\partial}{\partial t} \phi(t, s) = \frac{\partial}{\partial s} \phi(t, s) u(s) \quad (9)$$

derived in standard references such as (Harris, 1989; Karlin and Taylor, 1975), where $u(s) = \alpha[P(s) - s]$. If we take Laplace transforms of (9), then integration by parts reduces the transform of the left-hand side to

$$\begin{aligned} \int_0^\infty e^{-\lambda t} \frac{\partial}{\partial t} \phi(t, s) dt &= e^{-\lambda t} \phi(t, s) \Big|_0^\infty + \lambda \int_0^\infty e^{-\lambda t} \phi(t, s) dt \\ &= -s + \lambda \int_0^\infty e^{-\lambda t} \phi(t, s) dt. \end{aligned}$$

If $\hat{m}_1(\lambda) = \int_0^\infty e^{-\lambda t} (\partial/\partial s) \phi(t, 1) dt < \infty$, then it is valid to simplify the transform of the right-hand side of (9) by interchanging partial differentiation and integration. In summary, if we adopt the abbreviation $g(s) = \hat{\phi}(\lambda, s)$, then transforming (9) yields the ordinary differential equation

$$-s + \lambda g(s) = g'(s) u(s), \quad (10)$$

which can be supplemented by the initial condition $g(1) = 1/\lambda$, owing to the identity $\phi(t, 1) = 1$ for all $t > 0$.

For a subcritical branching process, it is possible to write the solution of (10) as

$$g(s) = g(0) e^{\lambda h(s)} + \frac{s}{\lambda} - \frac{e^{\lambda h(s)}}{\lambda} \int_0^s e^{-\lambda h(r)} dr, \quad (11)$$

where

$$\begin{aligned} h(s) &= \int_0^s \frac{1}{u(r)} dr \\ &= \int_0^s \left[\frac{1}{u(r)} - \frac{1}{u'(1)(r-1)} \right] dr + \frac{\ln(1-s)}{u'(1)}. \end{aligned} \quad (12)$$

Straightforward differentiation proves that $g(s)$ defined by Eqs. (11) and (12) satisfies the ordinary differential equation (10). The constant $g(0)$ is determined by the requirement that $\lim_{s \rightarrow 1} g(s) = 1/\lambda$. This can only occur if the first and third terms of Eq. (11) cancel in the limit. Therefore,

$$g(0) = \frac{1}{\lambda} \int_0^1 e^{-\lambda h(r)} dr.$$

Note that the integral (12) defining $h(s)$ converges, provided $u(s)$ avoids the value 0 on $[0, 1)$. The point $s = 1$ is a singularity for $h(s)$, but the second representation of $h(s)$ in (12) and the fact that $u'(1) < 0$ for a subcritical process show that the integral defining $g(0)$ is well behaved for $\lambda \geq 0$.

The function $g(s)$ has a power series expansion $\sum_{n=0}^\infty g_n s^n$ whose coefficients are the Laplace transforms $g_n = \hat{p}(\lambda, n)$. Although it is usually impossible to evaluate the g_n explicitly, one can easily compute them recursively, based on Eq. (10). If $u(s) = \sum_{n=0}^\infty u_n s^n$, then equating coefficients of s^n in (10) yields

$$-1_{\{n=1\}} + \lambda g_n = \sum_{k=1}^{n+1} k g_k u_{n-k+1},$$

which in turn produces the recurrence relation

$$g_{n+1} = \frac{1}{(n+1)u_0} \left(-1_{\{n=1\}} + \lambda g_n - \sum_{k=1}^n k g_k u_{n-k+1} \right). \quad (13)$$

Given $g_0 = g(0)$ and enough patience, one now can compute an arbitrary number of the coefficients g_n .

Once we are in possession of the coefficients g_n of $g(s) = \hat{\phi}(\lambda, s)$, we can compute the coefficients of

$$V(s) = \sum_{n=0}^{\infty} v_n s^n = e^{cg(s) - c/\lambda}, \quad (14)$$

which we identified in Example 4.1 as the generating function of the current number of mutant people under a regime of exponential growth at rate λ . Differentiating (14) gives $V'(s) = cg'(s)V(s)$ and ultimately the recurrence relation

$$v_n = \frac{c}{n} \sum_{k=0}^{n-1} (n-k) g_{n-k} v_k \quad (15)$$

after equating coefficients of s^{n-1} (Pourhamadi, 1984). The initial condition $v_0 = e^{cg_0 - c/\lambda}$ primes the recurrence pump.

As indicated in Example 4.1, the k th cumulant of the current number of mutant people equals $c\hat{m}_k(\lambda)$ under exponential growth at rate λ . To find $\hat{m}_k(\lambda)$ in terms of the derivatives of $g(s)$ at $s = 1$, let

$$y^{\underline{k}} = y(y-1)\cdots(y-k+1)$$

denote a falling factorial power. Corresponding to the k th moment $m_k(t)$, we have the k th factorial moment $m_k(t) = \sum_{y=0}^{\infty} y^{\underline{k}} p(t, y)$, which coincides with $(\partial^k/\partial s^k)\phi(t, 1)$ and has Laplace transform $g^{(k)}(1)$. It is a well-known combinatorial fact that $y^{\underline{k}} = \sum_{j=1}^k \left\{ \begin{smallmatrix} k \\ j \end{smallmatrix} \right\} y^j$, where the constants $\left\{ \begin{smallmatrix} k \\ j \end{smallmatrix} \right\}$ are Stirling numbers of the second kind (Blom *et al.*, 1994). This relation persists after forming moments and then taking their Laplace transforms. Hence

$$m_k(t) = \sum_{j=1}^k \left\{ \begin{smallmatrix} k \\ j \end{smallmatrix} \right\} m_j(t) \quad (16)$$

$$\hat{m}_k(\lambda) = \sum_{j=1}^k \left\{ \begin{smallmatrix} k \\ j \end{smallmatrix} \right\} g^{(j)}(1). \quad (17)$$

For instance,

$$\begin{aligned} \hat{m}_1(\lambda) &= g^{(1)}(1) \\ \hat{m}_2(\lambda) &= g^{(2)}(1) + g^{(1)}(1) \\ \hat{m}_3(\lambda) &= g^{(3)}(1) + 3g^{(2)}(1) + g^{(1)}(1) \\ \hat{m}_4(\lambda) &= g^{(4)}(1) + 6g^{(3)}(1) + 7g^{(2)}(1) + g^{(1)}(1). \end{aligned} \quad (18)$$

Thus, the problem of computing the cumulants of the current number of mutant people reduces to the problem of computing the derivatives $g^{(k)}(1)$. Consider again Eq. (10) characterizing $g(s)$. According to Liebnitz's rule, evaluating the k th derivative of (10) at $s = 1$ produces

$$-1_{\{k=1\}} + \lambda g^{(k)}(1) = \sum_{j=0}^k \binom{k}{j} g^{(j+1)}(1) u^{(k-j)}(1).$$

By virtue of the fact $u(1) = 0$, this equation gives the initial value

$$g^{(1)}(1) = \frac{1}{\lambda - u^{(1)}(1)} \quad (19)$$

and the recurrence

$$g^{(k)}(1) = \frac{1}{\lambda - ku^{(1)}(1)} \sum_{j=0}^{k-2} \binom{k}{j} g^{(j+1)}(1) u^{(k-j)}(1) \quad (20)$$

for $k > 1$. Combining Eq. (17), the initial value (19), and the recurrence (20) yields, for example,

$$\begin{aligned} \hat{m}_1(\lambda) &= \frac{1}{\lambda - u^{(1)}(1)} \\ \hat{m}_2(\lambda) &= \frac{\lambda - 2u^{(1)}(1) + u^{(2)}(1)}{[\lambda - 2u^{(1)}(1)][\lambda - u^{(1)}(1)]}. \end{aligned}$$

EXAMPLE 5.1. Geometric branching processes revisited. For the geometric branching process discussed in Example 2.1,

$$u(s) = \alpha \left[\frac{p^*}{1 - q^*s} - s \right] = \frac{\alpha(p^* - q^*s)(1-s)}{1 - q^*s}.$$

When $p^* > q^*$, this choice yields

$$\begin{aligned} h(s) &= \int_0^s \frac{1}{u(r)} dr \\ &= \frac{c_1}{\alpha} \int_0^s \frac{1}{p^* - q^* r} dr + \frac{c_2}{\alpha} \int_0^s \frac{1}{1-r} dr \\ &= -\frac{c_1}{\alpha q^*} \ln \frac{p^* - q^* s}{p^*} - \frac{c_2}{\alpha} \ln(1-s) \end{aligned}$$

for constants $c_1 = -(q^*)^2/(p^* - q^*)$ and $c_2 = p^*/(p^* - q^*)$. It follows that

$$\begin{aligned} g_0 &= \frac{1}{\lambda} \int_0^1 e^{-\lambda h(s)} ds \\ &= \frac{1}{\lambda} \int_0^1 \left(1 - \frac{q^* s}{p^*}\right)^{c_1 \lambda / (\alpha q^*)} (1-s)^{c_2 \lambda / \alpha} ds \\ &= \frac{1}{\lambda} \sum_{k=0}^{\infty} \frac{(c_1 \lambda / [\alpha q^*])^k}{k!} \left(-\frac{q^*}{p^*}\right)^k \int_0^1 s^k (1-s)^{(c_2 \lambda / \alpha)} ds \\ &= \frac{1}{\lambda} \sum_{k=0}^{\infty} \frac{(c_1 \lambda / [\alpha q^*])^k}{((c_2 \lambda / \alpha) + k + 1)^{k+1}} \left(-\frac{q^*}{p^*}\right)^k. \end{aligned} \quad (21)$$

The coefficients $u_n = \alpha [p^*(q^*)^n - 1_{\{n=1\}}]$ determine the remaining g_n through the recurrence (13). Finally, the derivatives

$$u^{(n)}(1) = \alpha \left[n! \left(\frac{q^*}{p^*}\right)^n - 1_{\{n=1\}} \right] \quad (22)$$

recursively determine the derivatives $g^{(n)}(1)$ and ultimately the $\hat{m}_n(\lambda)$. ■

EXAMPLE 5.2. Birth–death processes revisited. For the birth–death process discussed in Example 2.2, we find in the subcritical case $\delta^* > \beta^*$ that

$$\begin{aligned} u(s) &= \delta^* - (\delta^* + \beta^*)s + \beta^* s^2 \\ &= (s-1)(\beta^* s - \delta^*) \end{aligned}$$

$$\begin{aligned} h(s) &= \int_0^s \frac{1}{u(r)} dr \\ &= \frac{1}{\delta^* - \beta^*} \ln \left[\frac{\delta^* - \beta^* s}{\delta^*(1-s)} \right]. \end{aligned}$$

To compute g_0 from its defining integral, we make the change of variables $r = (1-s)/(1 - (\beta^*/\delta^*)s)$; this gives

$$\begin{aligned} g_0 &= \frac{1}{\lambda} \int_0^1 e^{-\lambda h(s)} ds \\ &= \frac{1}{\lambda} \int_0^1 \left(\frac{1-s}{1 - (\beta^*/\delta^*)s} \right)^{\lambda/(\delta^* - \beta^*)} ds \\ &= \frac{1 - \beta^*/\delta^*}{\lambda} \int_0^1 r^{\lambda/(\delta^* - \beta^*)} \left(1 - \frac{\beta^*}{\delta^*} r\right)^{-2} dr \\ &= \frac{1 - \beta^*/\delta^*}{\lambda} \int_0^1 r^{\lambda/(\delta^* - \beta^*)} \sum_{n=0}^{\infty} (n+1) \left(\frac{\beta^*}{\delta^*} r\right)^n dr \\ &= \frac{1 - \beta^*/\delta^*}{\lambda} \sum_{n=0}^{\infty} \frac{n+1}{n+1 + \lambda/(\delta^* - \beta^*)} \left(\frac{\beta^*}{\delta^*}\right)^n. \end{aligned} \quad (23)$$

The recurrence (13) for the remaining coefficients g_n becomes

$$\begin{aligned} g_{n+1} &= \frac{1}{(n+1)\delta^*} \{ -1_{\{n=1\}} \\ &\quad + [\lambda + n(\delta^* + \beta^*)] g_n - (n-1)\beta^* g_{n-1} \}, \end{aligned}$$

and the recurrence (20) has the explicit solution

$$g^{(k)}(1) = \frac{(2\beta^*)^{k-1}}{\lambda + k(\delta^* - \beta^*)} \prod_{j=2}^k \frac{\binom{j}{2}}{\lambda + (j-1)(\delta^* - \beta^*)}. \quad (24)$$

EXAMPLE 5.3. Polynomial branching processes. If the progeny-generating function $Q(s)$ is a polynomial of degree $n > 1$, then so are the mutant-progeny generating function $P(s) = Q(\frac{1}{2} + s/2)$ and the function $u(s) = \alpha[P(s) - s]$. For cubic polynomials, the leading coefficient u_3 of $u(s)$ is positive, and $u(s)$ has a negative root r_- and an additional positive root $r_+ > 1$ whenever $u'(1) < 0$. If $P(s) = p_0 + p_1 s + p_2 s^2 + p_3 s^3$, then $u(s) = \alpha(s-1)[p_3 s^2 + (p_3 + p_2)s - p_0]$, and these two extra roots are

$$r_{\pm} = \left[-\left(1 + \frac{p_2}{p_3}\right) \pm \sqrt{\left(1 + \frac{p_2}{p_3}\right)^2 + 4\frac{p_0}{p_3}} \right] / 2.$$

The partial fraction decomposition (Feller, 1968)

$$\frac{1}{u(s)} = \frac{1}{u'(1)(s-1)} + \frac{1}{u'(r_+)(s-r_+)} + \frac{1}{u'(r_-)(s-r_-)}$$

leads to the representations

$$h(s) = \frac{\ln(1-s)}{u'(1)} + \frac{\ln(1-s/r_+)}{u'(r_+)} + \frac{\ln(1-s/r_-)}{u'(r_-)}$$

$$g_0 = \frac{1}{\lambda} \int_0^1 (1-s)^{-\lambda/u'(1)}$$

$$\times \left(1 - \frac{s}{r_+}\right)^{-\lambda/u'(r_+)} \left(1 - \frac{s}{r_-}\right)^{-\lambda/u'(r_-)} ds.$$

For higher order polynomials, one cannot rule out complex roots. If these occur, then they occur as complex conjugate pairs. Hence, if all roots of $u(s)$ are distinct,

$$g_0 = \frac{1}{\lambda} \int_0^1 \prod_v \left(1 - \frac{s}{v}\right)^{-\lambda/u'(v)} \prod_w \left| \left(1 - \frac{s}{w}\right)^{-\lambda/u'(w)} \right|^2 ds, \quad (25)$$

where v ranges over all real roots (1 included) and w over all complex roots in the upper half plane. Although the integral (25) appears analytically intractable, it should yield readily to standard quadrature methods. In harder examples, even $h(s)$ must be evaluated numerically.

6. APPLICATIONS TO MULTITYPE PROCESSES

In a multitype process, marking of new mutants is more complicated and involves specifying both the type of a mutant and the current number of mutant people of each type in the clan descending from the mutant. We will use the notation $(j, \mathbf{y}) = (j, y_1, \dots, y_k)$ to indicate a new mutant of type j with y_i current descendants of type i . Each mark (j, \mathbf{y}) is an element of the Cartesian product

$$\Gamma = \mathbb{Z}_k \times \overbrace{\mathbb{Z}_+ \times \dots \times \mathbb{Z}_+}^{k \text{ times}},$$

where $\mathbb{Z}_k = \{1, \dots, k\}$. A new mutant at time t has probability $r_j p_j(-t, \mathbf{y})$ of possessing mark (j, \mathbf{y}) . Here r_j is the probability that the new mutant is assigned type j , and $p_j(-t, \mathbf{y})$ is the conditional probability that such a mutant eventually generates the current clan counts \mathbf{y} .

The marking theorem says that the Poisson process of new mutations on $\Omega = (-\infty, 0]$ induces a Poisson process on the product space $\Omega \times \Gamma$ with intensity measure

$$v(t, j, \mathbf{y}) = r_j p_j(-t, \mathbf{y}) \mu(t).$$

Again there are many functions $f: \omega \times \Gamma \rightarrow \mathfrak{R}$ defining genetically interesting sums S through Eq. (2). To facilitate our exposition in the following examples, we will continue to indicate vectors in bold and employ the product of powers notation $\mathbf{s}^{\mathbf{y}} = \prod_{j=1}^k s_j^{y_j}$.

EXAMPLE 6.1. *Number of mutant people of type j .* If $f_j(t, i, \mathbf{y}) = y_j$, then S_j represents the current number of mutant people of type j . Assuming a type i clan has evolved for a length of time t , let

$$\phi_i(t, \mathbf{s}) = \sum_{\mathbf{y}} p_i(t, \mathbf{y}) \mathbf{s}^{\mathbf{y}}$$

be the joint generating function of its current vector of mutant types. Also let $m_{i\mathbf{n}}(t) = \sum_{\mathbf{y}} \mathbf{y}^{\mathbf{n}} p_i(t, \mathbf{y})$ be a moment of order $\mathbf{n} = (n_1, \dots, n_k)$ of $p_i(t, \mathbf{y})$. Campbell's theorem gives the joint generating function and \mathbf{n} th cumulant of $\mathbf{S} = (S_1, \dots, S_k)$ as

$$\sum_{\mathbf{y}} \Pr(\mathbf{S} = \mathbf{y}) \mathbf{s}^{\mathbf{y}}$$

$$= \exp \left\{ \sum_{i=1}^k r_i \int_{-\infty}^0 [\phi_i(-t, \mathbf{s}) - 1] d\mu(t) \right\}$$

$$\kappa_{\mathbf{n}}(\mathbf{S}) = \sum_{i=1}^k r_i \int_{-\infty}^0 m_{i\mathbf{n}}(-t) d\mu(t).$$

In particular,

$$E(S_j) = \sum_{i=1}^k r_i \int_{-\infty}^0 m_{i\mathbf{e}_j}(-t) d\mu(t)$$

$$\text{Var}(S_j) = \sum_{i=1}^k r_i \int_{-\infty}^0 m_{i2\mathbf{e}_j}(-t) d\mu(t)$$

$$\text{Cov}(S_j, S_\ell) = \sum_{i=1}^k r_i \int_{-\infty}^0 m_{i\mathbf{e}_j + \mathbf{e}_\ell}(-t) d\mu(t),$$

where the vectors \mathbf{e}_j and \mathbf{e}_ℓ have all entries 0 except for a 1 in position j and ℓ , respectively. If $\hat{m}_{i\mathbf{n}}(\lambda) = \int_0^\infty e^{-\lambda t} m_{i\mathbf{n}}(t) dt$, then under exponential growth these cumulants become

$$E(S_j) = c \sum_{i=1}^k r_i \hat{m}_{i\mathbf{e}_j}(\lambda)$$

$$\text{Var}(S_j) = c \sum_{i=1}^k r_i \hat{m}_{i2\mathbf{e}_j}(\lambda) \quad (26)$$

$$\text{Cov}(S_j, S_\ell) = c \sum_{i=1}^k r_i \hat{m}_{i\mathbf{e}_j + \mathbf{e}_\ell}(\lambda).$$

EXAMPLE 6.2. *New mutations after time t_0 .* If $f_j(t, i, \mathbf{y}) = 1_{\{t \geq t_0\}} y_j$, then the sum S_j counts the number of type j people originating from new mutations after time $t_0 < 0$. The expectation

$$E(S_j) = \sum_{i=1}^k \int_{t_0}^0 r_i m_{ie_j}(-t) d\mu(t)$$

can be simplified by defining the row vectors and matrix

$$\mathbf{S} = (S_1, \dots, S_k), \quad \mathbf{r} = (r_1, \dots, r_k), \quad M(t) = (m_{ie_j}[t]).$$

Under exponential growth we then have

$$E(\mathbf{S}) = c \int_0^{-t_0} \mathbf{r} M(t) e^{-\lambda t} dt. \quad (27)$$

This integral will explicitly calculated in the next section.

EXAMPLE 6.3. *Number of recombinant mutants.* In the model of a mutant gene and linked marker, let $f_j(t, i, \mathbf{y}) = 1_{\{i \neq j\}} y_j$. Then $\sum_{j=1}^k S_j$ counts the number of mutant people whose mutant chromosomes show recombination between the disease and marker loci relative to the original mutant chromosome of their clan. This sum has mean and variance

$$E\left(\sum_{j=1}^k S_j\right) = \sum_{j=1}^k \sum_{i \neq j} r_i \int_{-\infty}^0 m_{ie_j}(-t) d\mu(t)$$

$$\text{Var}\left(\sum_{j=1}^k S_j\right) = \sum_{j=1}^k \sum_{\ell=1}^k \sum_{i \notin \{j, \ell\}} r_i \int_{-\infty}^0 m_{ie_{j+\ell}}(-t) d\mu(t).$$

Under exponential growth these simplify to

$$E\left(\sum_{j=1}^k S_j\right) = c \sum_{j=1}^k \sum_{i \neq j} r_i \hat{m}_{ie_j}(\lambda)$$

$$\text{Var}\left(\sum_{j=1}^k S_j\right) = c \sum_{j=1}^k \sum_{\ell=1}^k \sum_{i \notin \{j, \ell\}} r_i \hat{m}_{ie_{j+\ell}}(\lambda). \quad (28)$$

EXAMPLE 6.4. *Number of extant clans.* If $f(t, j, \mathbf{y}) = 1_{\{\mathbf{y} \neq \mathbf{0}\}}$, then S counts the number of extant clans. In view of the marking theorem, S has a Poisson distribution with mean

$$E(S) = \int_{-\infty}^0 \left[1 - \sum_{j=1}^k r_j \phi_j(-t, \mathbf{0}) \right] d\mu(t).$$

If $d\mu(t) = ce^{\lambda t} dt$, then the mean reduces to the value $c/\lambda - c \sum_{j=1}^k r_j \hat{\phi}_j(\lambda, \mathbf{0})$. Again $\Pr(S=0)$ is just probability that the mutant gene is currently extinct.

EXAMPLE 6.5. *Number of extinct clans.* If $f(t, j, \mathbf{y}) = 1_{\{\mathbf{y}=\mathbf{0}\}}$, then S counts the number of extinct clans. Now S has a Poisson distribution with mean $\int_{-\infty}^0 \sum_{j=1}^k r_j \phi_j(-t, \mathbf{0}) d\mu(t)$, which becomes $c \sum_{j=1}^k r_j \hat{\phi}_j(\lambda, \mathbf{0})$ in the case of exponential growth.

7. LAPLACE TRANSFORMS FOR MULTITYPE PROCESSES

From our commentary on the above examples, it is clear that making further progress depends on our ability to compute the Laplace transforms of the generating functions $\phi_i(t, \mathbf{s})$ and the moments $m_{i\mathbf{n}}(t)$. Although the generating functions are fairly intractable, we will start with them in investigating the lower order moments. The multivariate analog of the partial differential Eq. (9) is now the system of partial differential equations

$$\frac{\partial}{\partial t} \phi_i(t, \mathbf{s}) = \sum_{j=1}^k \frac{\partial}{\partial s_j} \phi_i(t, \mathbf{s}) u_j(\mathbf{s}), \quad (29)$$

where $u_j(\mathbf{s}) = \alpha_j [P_j(\mathbf{s}) - s_j]$ incorporates a unique death rate α_j and a unique mutant-progeny generating function $P_j(\mathbf{s})$ for a type j mutant (Athreya and Ney, 1972; Karlin and Taylor, 1975). Taking Laplace transforms of (29) produces the system of ordinary differential equations

$$-s_i + \lambda \hat{\phi}_i(\lambda, \mathbf{s}) = \sum_{j=1}^k \frac{\partial}{\partial s_j} \hat{\phi}_i(\lambda, \mathbf{s}) u_j(\mathbf{s}), \quad (30)$$

which we can differentiate with respect to the entries of \mathbf{s} and evaluate at the point $\mathbf{s} = \mathbf{1}$. This procedure will yield algebraic equations for the Laplace transforms of the moments.

For instance, abbreviating $\hat{\phi}_i(\lambda, \mathbf{s})$ as $g_i(\mathbf{s})$ and differentiating (30) with respect to s_ℓ gives

$$-1_{\{i=\ell\}} + \lambda \frac{\partial}{\partial s_\ell} g_i(\mathbf{s})$$

$$= \sum_{j=1}^k \left[\frac{\partial}{\partial s_j} g_i(\mathbf{s}) \frac{\partial}{\partial s_\ell} u_j(\mathbf{s}) + \frac{\partial^2}{\partial s_\ell \partial s_j} g_i(\mathbf{s}) u_j(\mathbf{s}) \right].$$

Because all $u_j(\mathbf{1})=0$, this last system of equations reduces at $\mathbf{s}=\mathbf{1}$ to

$$-1_{\{i=\ell\}} + \lambda \frac{\partial}{\partial s_\ell} g_i(\mathbf{1}) = \sum_{j=1}^k \frac{\partial}{\partial s_j} g_i(\mathbf{1}) \frac{\partial}{\partial s_\ell} u_j(\mathbf{1}). \quad (31)$$

Further simplification can be achieved by introducing the vector-valued functions

$$\mathbf{g}(\mathbf{s}) = \begin{pmatrix} g_1(\mathbf{s}) \\ \vdots \\ g_k(\mathbf{s}) \end{pmatrix}, \quad \mathbf{u}(\mathbf{s}) = \begin{pmatrix} u_1(\mathbf{s}) \\ \vdots \\ u_k(\mathbf{s}) \end{pmatrix}, \quad \mathbf{P}(\mathbf{s}) = \begin{pmatrix} P_1(\mathbf{s}) \\ \vdots \\ P_k(\mathbf{s}) \end{pmatrix}$$

and their differentials

$$d\mathbf{g}(\mathbf{s}) = \begin{pmatrix} \frac{\partial}{\partial s_1} g_1(\mathbf{s}) & \cdots & \frac{\partial}{\partial s_k} g_1(\mathbf{s}) \\ \vdots & & \vdots \\ \frac{\partial}{\partial s_1} g_k(\mathbf{s}) & \cdots & \frac{\partial}{\partial s_k} g_k(\mathbf{s}) \end{pmatrix}$$

and so forth. Note that $d\mathbf{g}(\mathbf{1})$ conveniently collects the Laplace transforms $\hat{m}_{ie_j}(\lambda) = (\partial/\partial s_j) g_i(\mathbf{1})$ into a $k \times k$ matrix. In addition to these matrices, let I_k be the $k \times k$ identity matrix.

We are now in a position to rewrite the system of Eqs. (31) in matrix notation as

$$-I_k + \lambda d\mathbf{g}(\mathbf{1}) = d\mathbf{g}(\mathbf{1}) d\mathbf{u}(\mathbf{1})$$

and solve it in the form

$$d\mathbf{g}(\mathbf{1}) = [\lambda I_k - d\mathbf{u}(\mathbf{1})]^{-1}. \quad (32)$$

Inverting this Laplace transform gives the usual matrix exponential representation $e^{t d\mathbf{u}(\mathbf{1})}$ of the first moment matrix $M(t) = (m_{ie_j}[t])$ (Athreya and Ney, 1972). If all death rates $\alpha_i = \alpha$, then the solution (32) can be reexpressed as

$$d\mathbf{g}(\mathbf{1}) = [(\lambda + \alpha) I_k - \alpha d\mathbf{P}(\mathbf{1})]^{-1}. \quad (33)$$

Equation (32) suggests that the spectral radius of $d\mathbf{P}(\mathbf{1})$ should be less than $1 + \lambda/\alpha$. This is indeed a sufficient condition for the existence of $d\mathbf{g}(\mathbf{1})$ (Yosida, 1980).

With the explicit value $M(t) = e^{t d\mathbf{u}(\mathbf{1})}$ in hand, we can now compute the promised integral (27); Indeed,

$$\begin{aligned} E(\mathbf{S}) &= c \int_0^{-t_0} \mathbf{r} e^{t d\mathbf{u}(\mathbf{1})} e^{-\lambda t} dt \\ &= c \int_0^{-t_0} \mathbf{r} e^{t[\mathbf{du}(\mathbf{1}) - \lambda I_k]} dt \\ &= c \mathbf{r} e^{t[\mathbf{du}(\mathbf{1}) - \lambda I_k]} [\mathbf{du}(\mathbf{1}) - \lambda I_k]^{-1} \Big|_0^{-t_0} \\ &= c \mathbf{r} \{ I_k - e^{t_0[\lambda I_k - \mathbf{du}(\mathbf{1})]} \} [\lambda I_k - \mathbf{du}(\mathbf{1})]^{-1}. \end{aligned} \quad (34)$$

To find the Laplace transforms of the second moments of the underlying continuous time branching process, first observe that

$$\hat{m}_{ie_j + e_\ell}(\lambda) = \begin{cases} \frac{\partial^2}{\partial s_j \partial s_\ell} g_i(\mathbf{1}), & j \neq \ell \\ \frac{\partial^2}{\partial s_j^2} g_i(\mathbf{1}) + \frac{\partial}{\partial s_j} g_i(\mathbf{1}), & j = \ell \end{cases}.$$

Hence, it suffices to compute the second differential

$$d^2 \mathbf{g}_i(\mathbf{s}) = \begin{pmatrix} \frac{\partial^2}{\partial s_1^2} g_i(\mathbf{s}) & \cdots & \frac{\partial^2}{\partial s_1 \partial s_k} g_i(\mathbf{s}) \\ \vdots & & \vdots \\ \frac{\partial^2}{\partial s_k \partial s_1} g_i(\mathbf{s}) & \cdots & \frac{\partial^2}{\partial s_k^2} g_i(\mathbf{s}) \end{pmatrix}$$

at $\mathbf{s}=\mathbf{1}$. We attack this problem by taking second derivatives in Eq. (30). In view of the fact $u_j(\mathbf{1})=0$, we find that

$$\begin{aligned} \lambda \frac{\partial^2}{\partial s_\ell \partial s_n} g_i(\mathbf{1}) &= \sum_{j=1}^k \left[\frac{\partial}{\partial s_j} g_i(\mathbf{1}) \frac{\partial^2}{\partial s_\ell \partial s_n} u_j(\mathbf{1}) \right. \\ &\quad + \frac{\partial^2}{\partial s_\ell \partial s_j} g_i(\mathbf{1}) \frac{\partial}{\partial s_n} u_j(\mathbf{1}) \\ &\quad \left. + \frac{\partial^2}{\partial s_n \partial s_j} g_i(\mathbf{1}) \frac{\partial}{\partial s_\ell} u_j(\mathbf{1}) \right]. \end{aligned}$$

In terms of second differentials, this equation can be rephrased as

$$\begin{aligned} \lambda d^2 g_i(\mathbf{1}) &= \sum_{j=1}^k \frac{\partial}{\partial s_j} g_i(\mathbf{1}) d^2 u_j(\mathbf{1}) + d^2 g_i(\mathbf{1}) d\mathbf{u}(\mathbf{1}) \\ &\quad + [d^2 g_i(\mathbf{1}) d\mathbf{u}(\mathbf{1})]^t, \end{aligned} \quad (35)$$

where the superscript t denotes matrix transpose.

To solve Eq. (35), we will need the Kronecker product

$$A \otimes B = \begin{pmatrix} a_{11}B & \cdots & a_{1k}B \\ \vdots & & \vdots \\ a_{k1}B & \cdots & a_{kk}B \end{pmatrix}$$

of two $k \times k$ matrices A and B and the vec operator that takes the columns of $A = (\mathbf{a}_1 \cdots \mathbf{a}_k)$ and stacks them one atop another in the form

$$\text{vec}(A) = \begin{pmatrix} \mathbf{a}_1 \\ \vdots \\ \mathbf{a}_k \end{pmatrix}.$$

If we apply the easily demonstrated identities (Magnus and Neudecker, 1988),

$$\text{vec}(AB) = (B^t \otimes I_k) \text{vec}(A) = (I_k \otimes A) \text{vec}(B),$$

and the symmetry of $d^2g_i(\mathbf{1})$, then Eq. (35) can be rewritten as

$$\begin{aligned} \lambda \text{vec}[d^2g_i(\mathbf{1})] &= \sum_{j=1}^k \frac{\partial}{\partial s_j} g_i(\mathbf{1}) \text{vec}[d^2u_j(\mathbf{1})] \\ &\quad + [d\mathbf{u}(\mathbf{1})^t \otimes I_k] \text{vec}[d^2g_i(\mathbf{1})] \\ &\quad + [I_k \otimes d\mathbf{u}(\mathbf{1})^t] \text{vec}[d^2g_i(\mathbf{1})] \end{aligned}$$

and solved as

$$\begin{aligned} \text{vec}[d^2g_i(\mathbf{1})] &= \{\lambda I_{k^2} - [d\mathbf{u}(\mathbf{1})^t \otimes I_k] - [I_k \otimes d\mathbf{u}(\mathbf{1})^t]\}^{-1} \\ &\quad \times \sum_{j=1}^k \frac{\partial}{\partial s_j} g_i(\mathbf{1}) \text{vec}[d^2u_j(\mathbf{1})]. \end{aligned} \quad (36)$$

If all death rates $\alpha_i = \alpha$, then this reduces to

$$\begin{aligned} \text{vec}[d^2g_i(\mathbf{1})] &= \{(\lambda + 2\alpha) I_{k^2} - \alpha[d\mathbf{P}(\mathbf{1})^t \otimes I_k] \\ &\quad - \alpha[I_k \otimes d\mathbf{P}(\mathbf{1})^t]\}^{-1} \\ &\quad \times \sum_{j=1}^k \frac{\partial}{\partial s_j} g_i(\mathbf{1}) \text{vec}[d^2u_j(\mathbf{1})]. \end{aligned} \quad (37)$$

By analogy to the case of first moments, this revised solution suggests that the spectral radius of $d\mathbf{P}(\mathbf{1})$ should be less than $1 + \lambda/2\alpha$. Again this is a sufficient condition for the existence of each $d^2g_i(\mathbf{1})$ (Yosida, 1980).

If the matrix $d\mathbf{u}(\mathbf{1})$ can be diagonalized, then the solutions (32), (34), and (36) can be simplified. Thus, if

$d\mathbf{u}(\mathbf{1}) = TDT^{-1}$ for some diagonal matrix D and invertible matrix T , then Eqs. (32) and (34) involve

$$\begin{aligned} [\lambda I_k - d\mathbf{u}(\mathbf{1})]^{-1} &= T[\lambda I_k - D]^{-1} T^{-1} \\ e^{t_0[\lambda I_k - d\mathbf{u}(\mathbf{1})]} &= T e^{t_0(\lambda I_k - D)} T^{-1}. \end{aligned}$$

We also have

$$\begin{aligned} T^t \otimes T^t \{ \lambda I_{k^2} - [d\mathbf{u}(\mathbf{1})^t \otimes I_k] - [I_k \otimes d\mathbf{u}(\mathbf{1})^t] \} \\ \times (T^t)^{-1} (T^t)^{-1} \\ = \lambda I_k \otimes I_k - D \otimes I_k - I_k \otimes D. \end{aligned}$$

It follows that the matrix inverse appearing in Eq. (36) can be written as

$$\begin{aligned} \{ \lambda I_{k^2} - [d\mathbf{u}(\mathbf{1})^t \otimes I_k] - [I_k \otimes d\mathbf{u}(\mathbf{1})^t] \}^{-1} \\ = (T^t)^{-1} \otimes (T^t)^{-1} \{ \lambda I_k \otimes I_k - D \otimes I_k - I_k \otimes D \}^{-1} \\ \times T^t \otimes T^t. \end{aligned} \quad (38)$$

Note that the matrix $\lambda I_k \otimes I_k - D \otimes I_k - I_k \otimes D$ is diagonal and therefore trivially invertible.

EXAMPLE 7.1. *Autosomal dominant with linked marker.* Consider the model of an autosomal dominant with a linked marker discussed at the end of Section 2. If we let

$$R = \begin{pmatrix} r_1 & \cdots & r_k \\ \vdots & \ddots & \vdots \\ r_1 & \cdots & r_k \end{pmatrix},$$

then

$$d\mathbf{P}(\mathbf{1}) = \frac{Q'(\mathbf{1})}{2} [(1 - \theta)I_k + \theta R]. \quad (39)$$

The matrix R has $k - 1$ eigenvectors $\mathbf{e}_i - (r_i/r_k) \mathbf{e}_k$, $i = 1, \dots, k - 1$, corresponding to the eigenvalue 0 and a single eigenvector $\mathbf{1}$ corresponding to the eigenvalue 1. If we concatenate these eigenvectors into a square matrix

$$T = \begin{pmatrix} 1 & 0 & \cdots & 0 & 1 \\ 0 & 1 & \cdots & 0 & 1 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 1 & 1 \\ -\frac{r_1}{r_k} & -\frac{r_2}{r_k} & \cdots & -\frac{r_{k-1}}{r_k} & 1 \end{pmatrix},$$

then

$$\begin{aligned} R &= T \mathbf{e}_k \mathbf{e}_k^t T^{-1} \\ &= T \begin{pmatrix} 0 & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & 1 \end{pmatrix} T^{-1} \end{aligned} \quad (40)$$

with

$$T^{-1} = \begin{pmatrix} 1-r_1 & -r_2 & \cdots & -r_{k-1} & -r_k \\ -r_1 & 1-r_2 & \cdots & -r_{k-1} & -r_k \\ \vdots & \vdots & \cdots & \vdots & \vdots \\ -r_1 & -r_2 & \cdots & 1-r_{k-1} & -r_k \\ r_1 & r_2 & \cdots & r_{k-1} & r_k \end{pmatrix}.$$

The diagonalization (40) extends to the diagonalization

$$\begin{aligned} d\mathbf{u}(\mathbf{1}) &= \alpha [d\mathbf{P}(\mathbf{1}) - I_k] \\ &= \alpha \left\{ \frac{\mathcal{Q}'(1)}{2} [(1-\theta) I_k + \theta R] - I_k \right\} \\ &= \alpha T \left\{ \frac{\mathcal{Q}'(1)}{2} [(1-\theta) I_k + \theta \mathbf{e}_k \mathbf{e}_k^t] - I_k \right\} T^{-1}. \end{aligned}$$

8. NUMERICAL EXAMPLES

To illustrate numerically the theory developed above, let us consider the Finnish population as described by Hästbacka *et al.* (1992). The current population of Finland is about 5 million people, and its history extends about 2000 years. If we postulate an initial population of 1000 people, then under exponential growth we have $10^3 e^{2000\lambda} = 5 \times 10^6$, yielding a growth rate of $\lambda = 0.004259$ per year. Adopting 25 years as the average reproductive age implies a death rate of $\gamma = \frac{1}{25}$ in the simple branching process model discussed in Section 2 for the normal population. Because every death is compensated by b births, $\lambda = (b-1)\gamma$, and $b = 1.1065$. Assuming an equal sex ratio, we infer that normal people have on average $2b = 2.2129$ children. Finally, if we follow an autosomal dominant disease with a mutation rate of $\eta = 10^{-6}$ per birth per chromosome, then new mutations occur at time t with exponential intensity $ce^{\lambda t} = 2\eta b 5 \times 10^6 \gamma e^{\lambda t} = 0.4426e^{0.004259t}$.

Let us now set the fitness of mutant individuals at 0.75, and compare the birth–death and geometric branching process models. In both models mutant individuals

average $2bf = 1.6597$ children. Since only half of these children are mutant, both branching processes are subcritical. For the sake of simplicity, we assume the same death rate $\frac{1}{25}$ for mutant and normal people in each model. Under a birth–death model, we then have

$$\begin{aligned} \delta + \beta &= \frac{1}{25} \\ \frac{2\beta}{\delta + \beta} &= 1.6597. \end{aligned}$$

Solving for β and δ gives $\beta^* = \beta/4 = 0.0083$ and $\delta^* = \delta + \beta/4 = 0.0151$ in the notation of Example 2.2. It is natural to equate the mean number of children q/p under the geometric model to the mean number of children $2\beta/(\delta + \beta)$ under the birth–death model. This yields $p^* = 2p/(2-q) = 0.5465$ in the notation of Example 2.1.

Some of the most important features of the birth–death and geometric models for the Finnish population are set forth in Figs. 1 and 2 and Table 1. Before interpreting the information conveyed by these sources, let us pause to summarize our methods of calculation. A key quantity is the generating function $\phi(t, s)$ displayed in Eq. (5) for the number of people in a mutant clan that has evolved for a length of time t . The Laplace transform of this generating function we have denoted variously as

$$g(s) = \sum_{n=0}^{\infty} g_n s^n = \hat{\phi}(\lambda, s) = \sum_{n=0}^{\infty} \hat{p}(\lambda, n) s^n.$$

Equation (14) defines the generating function $V(s)$ of the number of current mutants. The coefficients of

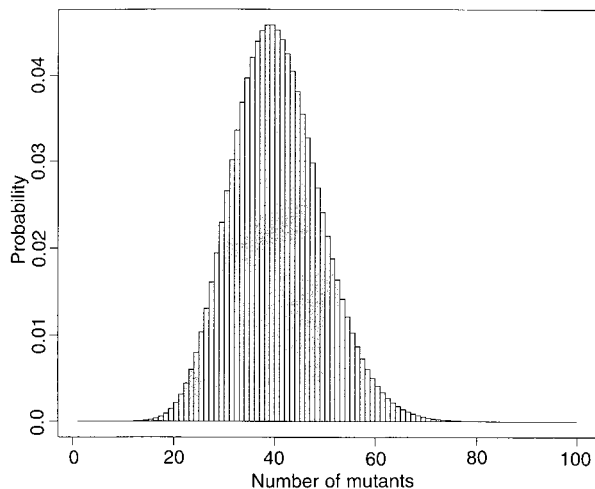


FIG. 1. Distribution of current mutants for a birth–death model.

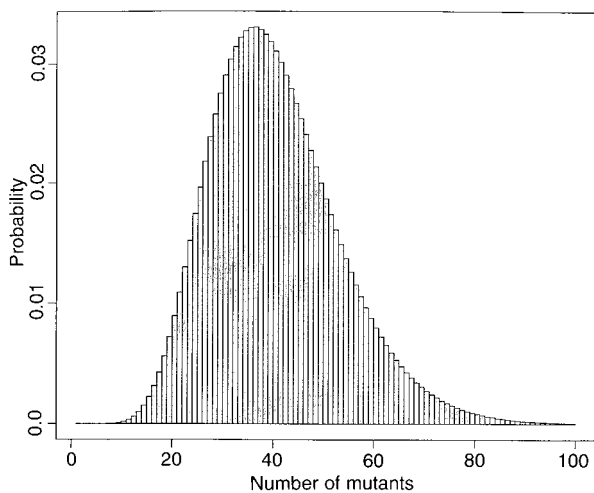


FIG. 2. Distribution of current mutants for a geometric model.

$V(s)$, which Figs. 1 and 2 plot, are determined by the recurrence (15) from the coefficients g_n . The g_n are determined by the recurrence (13) from g_0 and the coefficients of $u(s) = \sum_{n=0}^{\infty} u_n s^n = \alpha[P(s) - s]$, where $P(s)$ is the generating function of the number of mutant progeny of a mutant. Finally, g_0 is given by the infinite series (21) for a geometric process and by the infinite series (23) for a birth–death process.

The j th cumulant κ_j of the number of current mutants can be expressed as the Laplace transform $c\hat{m}_j(\lambda) = c \sum_{n=0}^{\infty} n^j \hat{p}(\lambda, n)$. The transform $\hat{m}_j(\lambda)$ can in turn be expressed in terms of the first j derivatives of $g(s)$ via Eq. (17), particular cases of which are highlighted in Eq. (18). Explicit formulas for the derivatives $g^{(j)}(1)$ appear in Eq. (24) for a birth–death process. For a geometric process one can substitute in Eqs. (19) and (20) the derivatives of $u(s)$ defined by Eq. (22).

Formulas for the mean number of extant and extinct clans are given in Table 1 in accord with the discussions in Examples 4.2 and 4.4. Finally, from Example 4.3, it is

TABLE 1

Moments for Univariate Branching Processes

Description	Symbolic form	Birth–death	Geometric
Mutant mean	κ_1	40.00	40.00
Mutant variance	κ_2	77.20	163.31
Mutant Skewness	$\kappa_3/(\sqrt{\kappa_2})^3$	0.3341	0.6987
Mutant kurtosis	$\kappa_4/\kappa_2^2 - 3$	0.1658	0.7846
Mean extant clans	$c/\lambda - cg_0$	28.55	22.02
Mean extinct clans	cg_0	75.38	81.91
Largest clan mean	$E(W)$	4.16	7.94

clear that the mean size $E(W)$ of the largest clan can be evaluated numerically by truncating the series

$$\begin{aligned} E(W) &= \sum_{k=0}^{\infty} \Pr(W > k) \\ &= \sum_{k=0}^{\infty} [1 - \Pr(W \leq k)] \\ &= \sum_{k=0}^{\infty} (1 - e^{-c \sum_{n < k} g_n}). \end{aligned}$$

Turning now to the figures and table, it is obvious that the mean number of current mutants only partially captures the information available. Not only does the geometric model show larger variance, skewness, and kurtosis than the birth–death model for the number of current mutants, but it also entails on average fewer extant mutant clans and a bigger largest clan. The greater variance of the geometric progeny distribution evidently causes more variation in clan size and a smaller clan survival rate. In compensation for a smaller survival rate, the geometric model favors the formation of a few large clans. Last of all, a glance at Figs. 1 and 2 suggests that assuming an approximately normal distribution for the number of current mutants would be a poor idea, particularly for the geometric model.

Multitype branching processes can be generated from the above single-type processes by following the cosegregation of a linked marker gene. Consider a marker locus having a recombination fraction $\theta = 0.01$ with the disease locus and having two alleles labelled 1 and 2 with population frequencies $r_1 = 0.75$ and $r_2 = 0.25$. If $Q(s)$ denotes the total progeny-generating function of a mutant, then the two-type branching process emanating from a new mutation is governed by the vector-generating function $\mathbf{P}(\mathbf{s}) = [P_1(s_1, s_2), P_2(s_1, s_2)]^t$ defined by Eq. (1). The differential $d\mathbf{P}(\mathbf{1})$ given in Eq. (39) plays a key role in computing the moments of the count vector $\mathbf{S} = (S_1, S_2)^t$ for the current numbers of the two mutant types. The mean $Q'(1)$ appearing in this formula equals $2\beta/(\delta + \beta)$ for a birth–death process and q/p for a geometric process.

Equation (26) provides the lower order moments of \mathbf{S} in terms of the Laplace transforms $\hat{m}_{in}(\lambda)$ of the moments $m_{in}(t) = \sum_{\mathbf{y}} \mathbf{y}^n p_i(t, \mathbf{y})$ of the numbers of mutants of various types emanating from a new mutation of type i . The matrix $(\hat{m}_{ie_j}[\lambda])$ is calculated in Eq. (33). In Eq. (37) the matrix

$$d^2 g_i(\mathbf{1}) = (\hat{m}_{ie_j + e_i}[\lambda]) - \text{diag}(\hat{m}_{ie_j}[\lambda])$$

is calculated, where $\text{diag}(\mathbf{w})$ denotes the diagonal matrix constructed from a vector \mathbf{w} . Alternatively, one can call on Eq. (38) after diagonalizing $d\mathbf{u}(\mathbf{1})$.

These formulas yield the same means $E(\mathbf{S}) = (30, 10)'$ under both models. Not surprisingly, the variances and covariances differ considerably. For the geometric model

$$\text{Var}(\mathbf{S}) = \begin{pmatrix} 121.21 & 1.27 \\ 1.27 & 39.56 \end{pmatrix},$$

and for the birth–death model,

$$\text{Var}(\mathbf{s}) = \begin{pmatrix} 57.50 & 0.38 \\ 0.38 & 18.90 \end{pmatrix}.$$

These results reinforce the fact that the geometric model shows greater variation. The small covariances $\text{Cov}(S_1, S_2)$ suggest that most clans die out before there is much recombination between the disease and marker loci. This contention is born out by the small expected number of recombinant mutants—0.4369 under both models—calculated from formula (28).

9. DISCUSSION

The enormous classic literature on branching processes summarized in books such as (Asmussen and Hering, 1983; Athreya and Ney, 1972; Harris, 1989; Jagers, 1975; Karlin and Taylor, 1975) barely touches on the non-stationary genetic models discussed here. Mathematicians who have considered branching processes with immigration have focused almost exclusively on the stationary case (Heathcote, 1975; Quine, 1970). Although the Russian school of probabilists constitutes a notable exception to this rule (Rahimov, 1995), its research deals with asymptotic theory and neglects the fruitful interaction between Poisson processes and branching processes. This interaction permits detailed calculation of moments and probabilities through the application of Campbell's theorem. More relevant to our interests is the work of Bartlett (1960) on nonstationary Poisson immigration in birth and death processes. His embryonic theory is taken up by Karlin and Taylor (1981), who derive formulas for the generating function and mean of the number of current mutant particles in a single-type branching process. Their formulas incorporate immigration only over a finite period of time in the same spirit as our Example 6.2.

Branching process theory can be erected in either discrete or continuous time. We have opted for continuous

time processes because they fit well with a Poisson stream of new mutations. In either discrete or continuous time, branching processes present notoriously difficult analytical problems. There are very few concrete models that permit exact calculation of probabilities. For multitype processes the problems are exacerbated. Needless to say, we have encountered many of these analytical barriers. A partial remedy for the absence of closed-form answers is the development of asymptotic approximations and appropriate numerical tools. For single-type processes, we have provided recurrence relations for computing moments and probabilities. These tools carry over to moment calculations in the multitype setting but not to the computation of relevant probabilities.

It is a pleasant fact that none of our applications of Campbell's theorem relies on the detailed evolutionary behavior of the mutant clans. All that is required is that clans evolve independently. Thus, complicated models such as age dependent branching processes fall within the scope of our theory. It is true, however, that carrying the genetic models to their logical numerical conclusions requires more structure. Only within the Markovian context of continuous time branching processes are numerical calculations straightforward. For the same reason, we have stressed exponential growth of the surrounding normal population. This assumption leads to the interesting and productive connections to Laplace transforms noted throughout this paper. In models with more erratic growth patterns among normal people, we should in theory be concerned about the same fluctuations in growth being echoed among the carriers of a mutant gene. Surely if plague and famine strike normal people, then they will strike mutant people as well.

At a gross level we should ignore these nagging exceptions to perfect models. What the current models do is provide insight, not an exact mimicry of nature. This insight may well prove useful in guiding the positional cloning strategy mentioned in the introduction. This is an active area of research in medical genetics (Hästbacka *et al.*, 1992; Kaplan *et al.*, 1995). Even fairly simple models such as the Luria and Delbrück's model for analyzing bacterial cultures have been applied successfully (Hästbacka *et al.*, 1992). Branching processes should shed new light on how to exploit population isolates best in mapping disease genes. In this regard it obviously would be beneficial to generalize our model for a disease locus linked to a single marker to a disease locus linked to multiple markers. We anticipate undertaking this task in the near future. In the meantime we hope the current paper will stimulate other scientists to explore this fascinating research frontier.

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