SOME STOCHASTIC GROWTH PROCESSES

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Abstract. The growth of non-saturating and saturating populations is modeled by a general kind of stochastic differential equation. The transition density functions of the solutions of these equations, obtained using the Stratonovich stochastic integral, are obtained in closed form. Moments, first passage time probability densities and probabilities of extinction can be found explicitly in a number of cases. Specifically considered are Malthusian growth, a general non-saturating process, a general saturating process which contains the Pearl-Verhulst model as a special case, and Gompertzian growth. This last-named process is examined with a view to the stochastic modeling of large populations of tumor cells.

1. INTRODUCTION

Recently there has been much interest in problems connected with the effects of random influences on the growth of populations. Goel et al. (1971) and Montroll (1972) have studied populations whose size \( N(t) \) at time \( t \) satisfies a stochastic differential equation of the form

\[
dN(t) = kN(t)G(N(t)/K)dt + N(t)dw(t),
\]

(1)

where \( G(\cdot) \) is a saturation function, \( K \) is the (constant) saturation level, \( k \) is a growth rate parameter and \( w(t) \) is a Wiener process with zero mean. The random term \( N(t)dw(t) \) might reflect fluctuations in the physical features of the environment or the effects of other species. In the latter case, \( n \) equations of type (1) can be used as a (degenerate) model of the Lotka-Volterra type where the number of species is \( n \).

There seems, however, to be a basic problem in the approach of the above-mentioned references in that when the random term is added to the deterministic equation, which represents a saturating (bounded) process, the resulting random process \( N(t) \) takes values in \((0, \infty)\). Hence the
"saturating" feature is, in the strict sense, lost.

In this paper we will consider populations whose sizes satisfy stochastic equations of the type

\[ dN(t) = h(N(t))dw(t), \]  

(2)

where the function \( h(N) \) may or may not be of the saturating form. Such equations imply that a growth rate parameter will be taken to be a Gaussian white noise, which may be looked upon as the formal derivative, \( dw(t)/dt \), of a Wiener process. Furthermore, we will not necessarily assume that \( w(t) \) has a zero mean.

It is known that, provided \( h(N) \) satisfies certain regularity conditions (Doob,1953), equation (2) has the solution

\[ N(t) = N(0) + \int_0^t h(N(t'))dw(t'), \]

(3)

which is a continuous Markov process. That is, \( N(t) \) is a diffusion process whose transition probability density function (p.d.f.), satisfies the Fokker-Planck equation

\[ \frac{\partial P}{\partial t} = -\frac{\partial}{\partial N}[M(N)p] + \frac{\nu}{2} \frac{\partial^2}{\partial N^2}[h(N)^2p], \]

(4)

where

\[ p(N,t|N_0)dN = P[N < N(t) < N+dN| N(0) = N_0], \]

(5)

\( \nu \) being the variance parameter of \( w(t) \).

Ito and Stratonovich Calculi.

The first infinitesimal moment, \( M(N) \), depends upon the way in which the stochastic integral in (3) is defined. Using obvious subscripts to denote whether the Ito or Stratonovich definition is being employed (Jasinski,1970), we have

\[ M_I(N) = mh(N), \]

(6)

\[ M_S(N) = mh(N) + \frac{\nu h(N)h'(N)}{2}, \]

(7)

where \( m \) is the mean value of \( dw(t)/dt \) and the prime denotes differentiation. The additional term in the Stratonovich first moment indic-
ates that $h(N(t))$ and $dw(t)/dt$ have the covariance,

$$\text{COV}_s[h(N(t)), dw(t)/dt] = (V/2)E[h(N(t))h'(N(t))], \tag{8}$$

where $E$ denotes mathematical expectation.

It has been pointed out that the Stratonovich calculus is the better one to adopt if the solution of a stochastic equation represents a "physical" random process (Gray & Caughey, 1965), and this argument has found mathematical support in a theorem of Wong & Zakai (1965). This would imply that when modeling the stochastic behaviour of populations with equations such as (1) or (2), one should employ the Stratonovich definition of the stochastic integral, though some authors have expressed some skepticism concerning the fact that there is a "choice" of calculi (see, e.g., Mortensen, 1969).

A distinct advantage in using the Stratonovich calculus is that regular calculus rules are preserved. This means that one can often find explicit (closed-form) solutions of the Fokker-Planck equation by simply transforming the original stochastic differential equation to that of a Wiener process (Lax, 1966; Tuckwell, 1974). Similarly, in some cases, the first passage time p.d.f. may also be written down in closed form (see section 3).

2. NON-SATURATING GROWTH PROCESSES

During certain stages of growth, many populations of cells or organisms evolve according to deterministic equations of the general form

$$\frac{dN}{dt} = rN^b, \quad 0 < b < 1, \tag{9}$$

where $r$ is the growth rate parameter which contains the net effect of the processes of birth, death, immigration and emigration. When $r$ is regarded as a random process, $r(t)$, its fluctuations represent the influences of the stochastic behaviour of environmental variables such as nutrient or food supply, climatic conditions, etc. To obtain some insight into how these fluctuations affect the growth of a population
we may regard \( r(t) \) as a Gaussian white noise, with the properties

\[
E[r(t)] = m, \tag{10}
\]

\[
\text{COV}[r(t_1), r(t_2)] = V \delta(t_1 - t_2). \tag{11}
\]

Under these assumptions equation (9) is of the form of (2) and the transition p.d.f. of \( N(t) \) thus provides a complete description of the process.

If we put \( b = 1 \) in (9) we obtain the usual Malthusian model which has been treated from a mathematical viewpoint by Gray & Caughey (1965) and in studies of population growth by Goel et al. (1971) and by Capocelli & Ricciardi (1973). We will emphasize and discuss the difference in the results obtained when the Ito and Stratonovich versions of the first infinitesimal moment are employed in equation (4).

The case \( 0 < b < 1 \), which represents a general non-saturating process, has not been treated before. Deterministic solutions take the form

\[
N(t) = [(1 - b)rt + N_0^{1-b}]^{1/(1-b)} \tag{12}
\]

and biological motivation is obtained from experimental results on certain tumor systems (Mendelschon & Dethlefsen,1968; Lala,1971). It turns out that the random process \( N(t) \) for this range of values of \( b \) has features which clearly distinguish it from the Malthusian case.

2.1 Malthusian Growth (\( b = 1 \)).

The transformed process,

\[
Y(N) = \int \left[ h(N') \right]^{-1} dN', \tag{13}
\]

which satisfies the equation of the Wiener process, in this case takes values in \((-\infty, \infty)\). The transition p.d.f. can be found immediately in closed form for both Ito and Stratonovich approaches, which means that a direct comparison of the results is possible. The following expressions are readily obtained.
Ito Calculus.

\[ p_I(N,t|N_0) = \frac{N^{-1}}{\sqrt{2\pi vt}} \exp \left( -\frac{\log(N/N_0) - (m - V/2)t}{2vt} \right), \quad (14) \]

\[ E_I(N(t)|N_0) = N_0 \exp(mt), \quad (15) \]

\[ \text{VAR}_I(N(t)|N_0) = N_0^2 \exp(2mt) [\exp(Vt) - 1], \quad (16) \]

\[ p_I(m,V) = \begin{cases} 
0 & \text{if } m > V/2, \\
1/2 & \text{if } m = V/2, \\
1 & \text{if } m < V/2. 
\end{cases} \quad (17) \]

Here \( \text{VAR} \) denotes variance and \( P \) is the probability of ultimate extinction, which is in this case defined to be

\[ \lim_{t \to \infty} \Pr\{N(t) \leq \Delta \mid N(0) = N_0\}, \quad 0 < \Delta < \infty. \quad (18) \]

This definition must be employed here because the boundaries of the diffusion process (\( N = 0 \) and \( N = \infty \)) are natural (see Feller, 1952, for method of classification) which means that they can never be reached in a finite time. With \( N = 0 \) an accessible boundary, a different definition is employed (see section 2.2).

Stratonovich Calculus.

The quantities \( p_S, E_S, \text{VAR}_S, \) and \( p_S \) are obtained from the corresponding expressions (14) - (17) by simply replacing \( m \) by \( m + V/2 \). Furthermore, whereas

\[ \text{COV}_I[N(t),r(t)] = 0, \quad (19) \]

we have, from (8),

\[ \text{COV}_S[N(t),r(t)] = (N_0V/2) \exp((m + V/2)t). \quad (20) \]

In considering the asymptotic behaviour of the above quantities as \( t \to \infty \), we must distinguish seven cases. For the Ito approach:

(i) \(-V < m < -V/2\) : \( E(N) \to 0; \ \text{VAR}(N) \to 0; \ P = 1.\)

(ii) \( m = -V/2\) : \( E(N) \to 0; \ \text{VAR}(N) \to N_0^2; \ P = 1.\)
(iii) \(-V/2 < m < 0\) : \(E(N) + \sigma; \text{VAR}(N) + \infty; P = 1\).

(iv) \(m = 0\) : \(E(N) = N_0; \text{VAR}(N) + \infty; P = 1\).

(v) \(0 < m < V/2\) : \(E(N) + \infty; \text{VAR}(N) + \infty; P = 1\).

(vi) \(m = V/2\) : \(E(N) + \infty; \text{VAR}(N) + \infty; P = 1/2\).

(vii) \(V/2 < m < \infty\) : \(E(N) + \infty; \text{VAR}(N) + \infty; P = 0\).

The results for the Stratonovich approach are again obtained by replacing \(m\) by \(m + V/2\) in the inequalities (i) - (vii).

Lewontin & Cohen (1969) have already pointed out that it seems "paradoxical" for the expected population size to become infinite as \(t + \infty\), while the extinction probability is unity. This, and other "paradoxes", occur in both calculi. For example, when we examine the expected overall growth rate, we find

\[ E_t [dN(t)/dt] = E_t[r(t)]E_t[N(t)], \quad (21) \]

and \(E_t[N(t)] > 0\) for all \(t\). Thus the expected rate of change of the population size has the sign of \(m\). Hence it is possible, if \(0 < m < V/2\), for the expected value of \(dN/dt\) to be always positive even though the probability of extinction is one. Paradoxes such as these do not lead to any intuitive support for a choice of calculi, but it is pointed out that the Stratonovich calculus does yield the somewhat appealing result that extinction is certain only if the average value of the growth rate parameter, \(r(t)\), is negative.

2.2 General Non-Saturating Process (0 < b < 1).

In this case the transformation

\[ Y(N) = \int_{N'}^{N} N'^{-b}dN' = N^{-b}/(1-b), \quad (22) \]

leads to a process \(Y(t)\) which is a Wiener process in \([0, \infty)\). The boundary at the origin is regular (Feller, 1952) so that boundary conditions may be imposed upon the solutions of \((4)\). Clearly \(N = 0\) is absorbing, so that

\[ p(0,t|N_0) = 0 \quad (23) \]

is the appropriate constraint. Employing the Stratonovich calculus
(as we shall throughout the rest of this paper), the Fokker-Planck equation becomes

\[
\frac{\partial P}{\partial t} = \frac{\partial}{\partial N} \left[ N^b \left( m + \frac{bVN^{b-1}}{2} \right) p \right] + \frac{V}{2} \frac{\partial^2}{\partial N^2} \left[ N^{2b} p \right].
\]

(24)

The solution of this equation (Green's function) satisfying (23) is

\[
p(N,t|N_0) = \frac{N^{-b}}{\sqrt{2\pi Vt}} \left( \exp \left[ \frac{-[Y(N) - Y(N_0) - mt]^2}{2Vt} \right] - \exp \left[ \frac{-2mN_0^{1-b}}{V(1-b)} \right] \exp \left[ \frac{-[Y(N) + Y(N_0) - mt]^2}{2Vt} \right] \right),
\]

(25)

where \( Y(N) \) is defined in equation (22).

Since zero population level is represented by an accessible barrier, in this case we can define the probability of extinction at \( t \) as

\[
P(t|N_0) = 1 - \int_0^\infty p(N,t|N_0) dN
\]

\[
= \phi \left( \frac{(b-1)^{-1} N_0^{1-b} - mt}{\sqrt{Vt}} \right) + \exp \left[ \frac{-2mN_0^{1-b}}{V(1-b)} \right] X \left[ 1 - \phi \left( \frac{(b-1)^{-1} N_0^{1-b} - mt}{\sqrt{Vt}} \right) \right],
\]

(26)

where \( \phi(\cdot) \) is the normal distribution function. This definition is the same as that employed by Feller (1951). Taking the limit as \( t \to \infty \), we find that the probabilities of ultimate extinction are

\[
P(\infty|N_0) = \begin{cases} 
1, & \text{if } m \leq 0, \\
(1/2)\exp[-2mN_0^{1-b}/((1-b)V)], & \text{if } m > 0.
\end{cases}
\]

(27)

From this result we see again that the use of the Stratonovich calculus leads to the prediction that \( m = 0 \) is the critical value associated with certain extinction. Furthermore, if survival is possible (\( m > 0 \)), then the probability of ultimate extinction is enhanced by increasing the variance parameter of the "intrinsic" growth rate. It might therefore be concluded that, the more uncertain the environment, the less is
the chance of survival for given values of \( N_0 \), \( b \) and \( m \).

3. SATURATING GROWTH PROCESSES

While some stages of growth may be governed by equations such as (9), growth in the latter stages is usually restricted by such factors as physical boundaries, competition, predation, limitations in food or nutrient supply etc. The growth rate then becomes "density-dependent" and diminishes as the carrying capacity (saturation level) is approached.

3.1 General Saturating Processes.

Montroll (1972) has introduced (c.f. equation (1)) the family of saturation functions

\[
G_\alpha(x) = \frac{1 - x^\alpha}{\alpha}.
\]  

(28)

The case \( \alpha = 1 \) yields the well known Pearl-Verhulst logistic process, whereas \( \alpha = 0 \) corresponds to the Gompertzian growth process (see section 3.2).

Several stochastic treatments of the logistic process have appeared, some treating the intrinsic growth rate as a random process (Levins, 1969; Tuckwell, 1974), others regarding the carrying capacity as a fluctuating parameter (Levins, 1969; May, 1973) or adding a noise term as in equation (1) (Goel et al., 1971).

An alternative form of saturation function is defined if we write

\[
\frac{dN}{dt} = rN\left[1 - \frac{N}{K}\right]^\nu, \quad \nu > 0.
\]  

(29)

If \( \nu = 1 \) we recover the standard logistic process, whereas \( \nu = 0 \) gives rise to the non-saturating Malthusian law. Suppose we let \( r \) in (29) be a Gaussian white noise, as in section 2; then the resulting stochastic equation is of the same form as (2). For positive integer values of \( \nu \) the transformed process

\[
Y(N) = \log\left[N/(K - N)\right] + \sum_{j=1}^{n-1} \left(\begin{array}{c} n-1 \\ j \end{array}\right) j^{-1} \left(\frac{N}{K-N}\right)^j, n=1,2,.. \]  

(30)
is a Wiener process in $(-\infty, \infty)$, and since (30) is a strictly monotonic function the transition p.d.f. of $N(t)$ can be obtained in closed form. Hence the conditional moments of $N(t)$ can be found by numerical integration. It can be seen that the probability of ultimate extinction, defined as in (18) because the boundaries $N=0$ and $N=K$ are natural, is unity whenever $m < 0$. As with all the processes so far considered, $N(t)$ does not have a stationary distribution as $t \to \infty$.

3.2 Compertzian Growth and Tumor Biology

The Pearl-Verhulst logistic process characterizes, to a close approximation, the growth of many populations of organisms (bacterial, animal, human etc.) but many systems of cells in complex organisms are apparently much more accurately described by the Compertz equation,

$$\frac{dN}{dt} = rN \log(K/N), \quad 0 < N(0) < K,$$

(31)

Figure 1. Mean size data (x) and best fit Compertz curve for DMBA tumors (after Simpson-Herren & Lloyd, 1970). The upper line is a logistic curve (see text).

where $K$ is the saturation level. Solutions of this equation,

$$N(t) = K \exp[\log(N_0/K)e^{-rt}],$$

(32)
(or equivalent forms) were found to fit well the experimental growth data for many embryos, organs and tumors (Laird, 1964, 1965, 1969). Subsequently, in comprehensive studies, the Gompertz curve has been used to fit the mean size data of a variety of solid and ascites tumors (Simpson-Herren & Lloyd, 1970 and references therein). Figure 1 shows a typical Gompertzian growth curve. The data is for mammary adenocarcinomas induced by intra-gastric doses of DMBA (7,12-dimethylbenz(a) anthracene) in female Sprague-Dawley rats. Measurements were made (on growing tumors only) in two directions with calipers and the volumes calculated from an approximate formula for a prolate spheroid. For comparison, in the same figure, the (standard) logistic curve has been drawn with the same values of $N_0$, $K$, and $r$.

Measurements of the sizes of large numbers of tumors of the same age and type, in animals of the same species, show considerable variability. Figure 2 shows a plot of standard error versus time for (growing) DMBA tumors.

![Figure 2. Standard error versus time for the sizes of DMBA tumors (data courtesy of Simpson-Herren, 1973).](image)
Contributions to the variability are expected to come from differences in physiology, anatomy and host defense mechanisms from animal to animal. Furthermore, for cells within a given tumor, labeled mitosis techniques have shown that the cell cycle time has a distribution of values, and this, together with the growth fraction and rate of cell loss (see Lala, 1971, for a review of tumor cell population kinetics) affects the overall growth rate. These quantities will vary from animal to animal and depend upon such things as degree of vascularization and the spatial distribution of proliferating and non-proliferating cells (Burton, 1966; Greenspan, 1972) which in turn affect the oxygen and nutrient supply.

Further evidence of a stochastic element in tumor growth is manifested in the "surviving fraction" data, which represents the fraction, \( F(t) \), of host animals still alive at time \( t \). An example of the variation in time of this quantity is shown in Figure 3. The nature of the data indicates that there is an approximate critical lethal size, reached at various times by tumors in different hosts, or that there are

![Figure 3. Surviving fraction data for DMBA tumors (from Simpson-Herren & Lloyd, 1970)](image)

variations in the lethal size from animal to animal, or both of these factors may contribute to the variations in the time of death. If the
first factor is predominant, then the surviving fraction at time \( t \) can be estimated from the probability density, \( f(N^*, t | N_o) \), of the time of first passage of \( N(t) \), to the critical size \( N^* \), given an initial size \( N_o \), through the relation

\[
P(t) = 1 - \int_0^t f(N^*, t' | N_o) dt', \quad 0 < N_o < N^* < K,
\]

where the random process \( N(t) \) represents the number of tumor cells.

Of those studies which incorporate a stochastic approach to tumor growth, some have focused upon carcinogenesis, while many others have considered the relationship between cellular kinetic parameters and growth rate and the response of these quantities to chemotherapy. Recent reviews of such studies may be found in Aroesty et al. (1973), Iosifescu & Tautu (1973) and Smith (1972). Little attention, however, has been given to probabilistic descriptions of the overall growth of large populations of tumor cells.

3.3 Randomized Gompertzian Growth.

In previous stochastic models related to Gompertzian growth (Goel et al., 1971; Montroll, 1972; Capocelli & Ricciardi, 1974), not directly concerned with tumor development, a noise term has been added to equation (31) as in equation (1). The resulting random process, \( N(t) \), is a transformed Ornstein-Uhlenbeck process and, as mentioned in section 1, the range of \( N(t) \) is semi-infinite.

As we have pointed out (Smith & Tuckwell, 1973) the upper limit, \( K \), of the deterministic Gompertz solutions, can be retained in a stochastic model if we take \( r \) in (31) to be a Gaussian white noise. Then the stochastic equation for \( N(t) \) is of the same form as (2) with \( h(N) = N \log(K/N) \). The change of variables

\[
Y(N) = \int [N' \log(K/N')]^{-1} dN' = -\log[\log(K/N)],
\]

results in a process \( Y(t) \) which is a Wiener process in \((-\infty, \infty)\). Thus the transition p.d.f. of \( N(t) \) is given by
\[ p(N,t|N_0) = \frac{[N \log(K/N)]^{-1}}{\sqrt{2\pi Vt}} \exp \left[ -\frac{(Y(N) - Y(N_0) - mt)^2}{2Vt} \right] \] (35)

where \( Y(N) \) is now defined as in (34). The boundaries \( N = 0 \) and \( N = K \) are again natural and no (proper) stationary distribution exists as \( t \to \infty \).

Analytic expressions for the mean and variance of \( N(t) \) appear difficult to obtain, but these quantities may be found numerically using (35). Nevertheless, it is possible to find the mean and variance of \( \log N(t) \) analytically:

\[ E[\log N(t)|N(0) = N_0] = \log K - \log(K/N_0)\exp[\frac{V}{2} - mt] \], (36)

\[ \text{VAR}[\log N(t)|N(0) = N_0] = [\log(K/N_0)]^2 \exp[\frac{V}{2} - mt]. \] (37)

The similarity between these expressions and those for the corresponding quantities in randomized Malthusian growth, is explained by noting that \( Z(t) = \log N(t) \) satisfies the simple equation

\[ \frac{dz}{dt} = r(t)\log K - Z. \] (38)

The transition p.d.f. of \( Z(t) \) can thus be obtained when either the Stratonovich or Ito calculus is used. However, the Fokker-Planck equation for the transition p.d.f. of \( N(t) \) (obtained above for the Stratonovich approach) with the Ito version of the first infinitesimal moment, does not appear to admit a ready analytic solution.

The first passage time p.d.f., for a final value \( N^* \) and initial value \( N_0 \), of the restricted random Gompertzian growth process we have considered, can be obtained in closed form from that of the Wiener process (Cox & Miller, 1965) because the function defined in (34) is strictly monotonic. Thus we have

\[ f(N^*, t|N_0) = \frac{[Y(N^*) - Y(N_0)]}{\sqrt{2\pi Vt^3}} \exp \left[ -\frac{(Y(N^*) - Y(N_0) - mt)^2}{2Vt} \right] \], (39)
where it has been assumed that \( m \) is positive and \( Y(N) \) is again as in equation (34).

It is considered that treating equation (31) as a stochastic differential equation, with the growth rate parameter \( r \) a random process, provides a useful method of representing the effects of random influences on the growth of large populations of tumor cells. As a first approximation, one could take \( r \) to be a white noise as in the above treatment, and this approach is being investigated. Numerical calculations of the moments of \( N(t) \) and a comparison with experimental data will be published in the near future, together with a discussion of the problems of parameter estimation and the incorporation of the "microscopic" transition probabilities into a single randomized growth rate.

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REFERENCES


