

A Diffusion Model for Restricted Gompertzian Growth

Stochastic models of population growth have often been obtained by the randomization of a growth rate or other parameter in a deterministic differential equation describing the temporal evolution of the population size. This approach has been used by many authors in the study of Malthusian growth in randomly varying environments (Lewontin & Cohen, 1969; Goel, Maitra & Montroll, 1971; Capocelli & Ricciardi, 1973a).

In the modeling of real populations it is often necessary to include some form of density dependence in the growth rate, which usually manifests itself in a saturating process. A simple example is provided by the Pearl-Verhulst logistic process. Various approaches to the stochastic treatment of this process have recently appeared. Some of these have regarded the growth rate parameter as a random process (Levins, 1969; Goel et al., 1971; Tuckwell, 1973) whereas others have concerned themselves with the effects of fluctuations in the carrying capacity (Levins, 1969; May, 1973).

Whereas the logistic process is usually used to model populations of organisms, growing cell populations have been

found in many instances to evolve according to the Gompertz equation

$$\frac{dN}{dt} = rN(A - \log N), \quad (1)$$

where  $N(t)$  is the population size at time  $t$ . The solution of this equation with initial condition  $N(0) = N_0$  is

$$N(t) = \exp[A - (A - \log N_0)e^{-rt}], \quad (2)$$

so that as  $t$  increases indefinitely the population size asymptotically approaches the saturation level  $e^A$ . The growth law (2) has been found to describe the gross features of the development of populations of cells in many tumors and embryos (Laird, 1965; Laird, 1969).

A stochastic version of the Gompertzian growth process has been considered by Goel et al. (1971) and by Capocelli & Ricciardi (1973b) in which a term  $F(t)N(t)$  was added to the right hand side of equation (1),  $F(t)$  being a white noise (i.e., a delta-correlated, Gaussian stationary process). The resulting stochastic process  $N(t)$  can be shown to be a transformed unrestricted Ornstein-Uhlenbeck process and thus its transition probability density function obtained in closed form. This method, however, destroys an essential feature of the Gompertz growth process because the random process  $N(t)$  generated has a semi-infinite range and no longer represents a saturating population. It will now be demonstrated that the Gompertz

equation (1) can be treated as a stochastic differential equation in such a way that the saturating feature of the process is preserved.

Let the growth rate parameter  $r$  in (1) be a white noise,  $r(t)$ , with mean value function  $m$  and variance parameter  $V$ . Then  $N(t)$ , the stochastic process so generated, has the range  $(0, e^A)$ , the upper limit now being the same as that of (2). When the Stratonovich stochastic calculus is employed in the integration of the resulting stochastic differential equation (Jaswinski, 1970), the transition probability density function of  $N(t)$  may still be found in closed form. In fact, the transformed process,

$$Y(t) = -\log(A - N), \quad (3)$$

derived from (1) by the method of Lax (1966), is a Wiener process (Brownian motion) on  $(-\infty, \infty)$  so that one has for the transition probability density function of  $N(t)$  for an initial value  $N_0$ ,

$$p(N, t | N_0) = \frac{N^{-1} (A - \log N)^{-1}}{(2\pi Vt)^{1/2}} \exp \left[ -\frac{\left\{ \log \left( \frac{A - \log N_0}{A - \log N} \right) - mt \right\}^2}{2Vt} \right] \quad (4)$$

Since the process  $N(t)$  generated by this procedure is Markov,  $p(N, t | N_0)$  provides a complete description of the process. The mathematical expectation and variance of the number of cells at time  $t$ , given a certain initial population size, can be computed from (4), though exact analytic expressions for these quantities

appear to be difficult to obtain. We note that the first passage time probability density function can also be obtained because the transformation (3) is a strictly monotonic function. Hence the known results for the unrestricted Wiener process (Cox & Miller, 1965) can be utilized. For further mathematical details see the forthcoming paper of Smith & Tuckwell (1973).

The application of the techniques of stochastic differential equations outlined above for the case of a white noise growth rate parameter in (1) may provide a starting point for a new method of attack on the stochastic treatment of the temporal development of various tumours (as well as other organisms or tissues where the Gompertz growth law has been found to apply). Treating  $r(t)$  as a white noise with the above statistical properties is of course an approximation at the macroscopic level to the complex dynamics of tumor growth. It is evident too that the expression (4) will lead to calculated moments of  $N(t)$  which will not exhibit the somewhat erratic behaviour of the corresponding experimental quantities (Simpson-Herren & Lloyd, 1970). However, insofar as yielding a direct method of computing the moments of the distributions of tumor sizes, the diffusion model approach seems to have advantages over models which attempt to incorporate details of cellular kinetic parameters (Roti Roti & Okada, 1973) or those based on computer simulation (Shackney, 1973; Valleron & Frindel, 1973). It remains, of course, a challenging problem to relate the stochastic macroscopic behaviour to the various transition probabilities at the cellular level.

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