Growth Models with Stochastic Differential Equations. An Example from Tumor Immunology*

GERD ROSENKRANZ
Sonderforschungsbereich 123, Universität Heidelberg, Im Neuenheimer Feld 293, 6900 Heidelberg, West Germany

Received 10 July 1984; revised 25 March 1985

ABSTRACT

The effects of demographic and environmental stochasticity on the qualitative behavior of a mathematical model from tumor immunology are studied. The model is defined in terms of a stochastic differential equation whose solution is a limiting diffusion process to a branching process with random environments.

INTRODUCTION

Differential equations are mathematical tools to describe and study the growth of populations. Since a deterministic approach neglects random influences on the growth process, stochastic differential equations can be regarded as more adequate models for the development of a population. In this paper a mathematical model from tumor immunology originally proposed by Garay and Lefever [5] is considered in order to elaborate the effects of random fluctuations.

In biological processes there are mainly two sources of variability: demographic stochasticity, which is due to randomness in the survival ability or fertility of individuals within a population, and environmental stochasticity, which results from random fluctuations in the environment affecting the population as a whole. Mathematical models including both kinds of stochasticity are branching processes with random environments as introduced by Smith and Wilkinson [11] and Athreya and Karlin [2].

Processes of this type, which are hardly tractable if the reproduction rate of a population depends on the actual population size, can be approximated by diffusion processes. This fact was first observed by Feller [3] for Galton-

* This work was supported by the Deutsche Forschungsgemeinschaft.

 0025-5564/85/$03.30

Watson processes and generalized by Keiding [8] for the case of controlled branching processes with random environments.

The limiting diffusion processes can be obtained as solutions of stochastic differential equations of the form

$$dX(t) = \mu(X(t))\,dt + \sigma(X(t))\,dW(t),$$

where W denotes a standard Wiener process. $X(t)$ then has the well-known properties

$$\lim_{h \to 0} \frac{1}{h} E_x\{X(t+h) - X(t)\} = \mu(x),$$

$$\lim_{h \to 0} \frac{1}{h} E_x\{[X(t+h) - X(t)]^2\} = \sigma^2(x).$$

[E_x denotes expectation given $X(t) = x$.] From these relations it can be seen that the mean increment of the stochastic process $X(t)$ during a small time interval, given that it has reached x, is the same as the increment of the solution of the ordinary differential equation

$$\frac{dX(t)}{dt} = \mu(X(t)).$$

The variability is completely described by a function σ^2; its special form arises from the approximated branching process under consideration.

In what follows, we briefly review the Garay-Lefever model and its properties. The main part of the paper gives a description of the qualitative behavior of a stochastic version of this model defined in terms of a stochastic differential equation as described above.

1. THE MODEL

The kinetic model of Garay and Lefever [5] assumes that the onset of a tumor involves the combination of three principal phenomena:

(1) the transformation of normal into neoplastic cells (with some constant rate A),

(2) the replication of transformed cells (with some rate λ),

(3) the immunological interaction of the host organism with transformed cells.

The first two steps are simple to model, whereas the immunological step cannot be accounted for in an explicit form. In a first approach it can be described as follows: The recognition of the transformed cells by free effector cells (for example T-lymphocytes or natural killer cells) is followed by the

lysis of the former and the dissociation of the complex into free effector cells and some dead or nonreplicating cells. The kinetic of this step is assumed to be Michaelian.

Within this framework, the growth in time of the target (tumor) population is given by the equation [9]

$$\frac{dX}{dt} = (N - X)\left(A + \frac{\lambda}{N}X\right) - \frac{kEX}{1 + kX/l}. \tag{1.1}$$

Here X denotes the number of transformed cells per unit volume, N the maximum number of target cells per unit volume, E the total number of free and bounded effector cells, and k and l are rate constants. In vivo, cytotoxic parameters as well as replication rates are influenced by environmental factors such as the supply of oxygen and nutrients, chemical agents, radiation, etc. As a result, parameters undergo random variations in the course of time.

Assuming a random replication rate and a mean variance of the offspring distribution which guarantees that the number of target cells predicted by the stochastic model remains less than N, we have the stochastic equation

$$dX = \left\{(N - X)\left(A + \frac{\lambda X}{N}\right) - \frac{kEX}{1 + kX/l}\right\} dt + \sqrt{u^2\left(\frac{X}{N}\right)^2 (N - X)^2 + v^2 \frac{X(N - X)}{N}}\, dW. \tag{1.2}$$

(For details see Appendix I.) The constants u^2 and v^2 are a measure of the strength of environmental and demographic stochasticity, respectively.

Since solutions of (1.1) and (1.2) cannot be obtained in closed form, we study their qualitative behavior, i.e. the behavior of $X(t)$ for large t. For this purpose we transform $X(t)$ and discuss the properties of

$$Y(t) := \frac{k}{l} X\left(\frac{t}{\lambda}\right).$$

$Y(t)$ is the solution of the stochastic differential equation

$$dY(t) = \left\{(1 - \theta Y)(\alpha + Y) - \frac{\beta Y}{1 + Y}\right\} dt + \sqrt{\omega^2 Y^2 (1 - \theta Y)^2 + \tau^2 Y(1 - \theta Y)}\, dB, \tag{1.3}$$

where $\alpha = kAN/l\lambda$, $\beta = kE/\lambda$, $\theta = l/kN$, $\omega^2 = u^2/\lambda$, $\tau^2 = v^2 k/l\lambda$, and B is a standard Wiener process. Now the parameter α gives the relative rate of

neoplastic cell production, β gives the relative rate of neoplastic cell destruction, and θ results from the upper limit for the tumor population, while ω^2 and τ^2 measure the relative strength of external and internal fluctuations. The transformed deterministic equation is obtained from (1.3) by setting $\tau^2 = \omega^2 = 0$.

In the scquel we always assume $\omega^2 > 0$ and $\tau^2 > 0$ when we analyze the stochastic model. The case $\tau^2 = 0$ and $\omega^2 > 0$ has been treated by Lefever and Horsthemke [9], who formally replaced the growth rate in the deterministic equation (1.1) by white noise in order to get a stochastic model. The equation considered in the present paper can therefore be regarded as a generalization to incorporate demographic stochasticity.

2. PROPERTIES OF THE DETERMINISTIC MODEL

The qualitative behavior of the model

$$\frac{dY}{dt} = (1-\theta Y)(\alpha + Y) - \frac{\beta Y}{1+Y} =: \mu(Y) \tag{2.1}$$

can be summarized as follows: For fixed α, there exists a $\theta_c < 1/(1+\alpha)$ such that

(a) for $\theta \geqslant \theta_c$ (2.1) has exactly one stationary solution which is asymptotically stable;

(b) for $0 < \theta < \theta_c$ there is at least one $\beta > 0$ such that (2.1) has three stationary solutions $y_1 < y_2 < y_3$, of which y_1 and y_3 are locally asymptotically stable and y_2 is unstable.

Case (b) can be reformulated more precisely: If $0 \leqslant Y(0) < y_2$, then $Y(t) \to y_1$ for $t \to \infty$, if $y_2 < Y(0) \leqslant 1/\theta$, then $Y(t) \to y_3$.

Proof. Solving $\mu(y) = 0$ for β yields

$$\beta = \frac{(1+y)(\alpha+y)(1-\theta y)}{y}. \tag{2.2}$$

If the mapping $y \to \beta(y)$ is one-to-one, (2.1) has exactly one stationary solution for every β. Now

$$\beta'(y) = 1 - \frac{\alpha}{y^2} - \theta(1+\alpha+2y),$$

which is negative for y near 0 and near $1/\theta$. Note that $\beta'(y) > 0$ is equivalent to

$$[1-\theta(1+\alpha)]\,y^2 - 2\theta y^3 > \alpha. \tag{2.3}$$

The left-hand side of (2.3) is a monotonely decreasing function of θ for $y \geqslant 0$ and equal to y^2 if $\theta = 0$. Hence there is a θ_c such that (2.3) has no nonnegative solution for $\theta > \theta_c$. Of course, $\theta_c < 1/(1+\alpha)$. Now let $y_0 > 0$ be a stationary solution of (2.1). From the relation

$$y_0(1+y_0)\mu'(y_0) = y_0\beta'(y_0)$$

we see that y_0 is asymptotically stable if $\beta'(y_0) < 0$. Hence if $\theta \geqslant \theta_c$, then $\beta'(y) < 0$ for every $0 < y \leqslant 1/\theta$, which implies (a): if not, there exists some y with $\beta'(y) > 0$, which proves (b).

3. PROPERTIES OF THE STOCHASTIC MODEL

In this section, we summarize the results concerning the qualitative behavior of the stochastic model (1.3). The proofs of the results are contained in Appendices II and III.

At first, we study the case $0 < \tau^2 < 2\alpha$. Under this assumption, the boundaries 0 and $1/\theta$ are inaccessible, i.e. cannot be reached in finite time, which implies $P\{0 < Y(t) < 1/\theta\} = 1$ for all t. The function $Y(t)$ has a stationary distribution $F(y)$ which can be given explicitly, and $\lim_{t\to\infty} P\{Y(t) \leqslant y\} = F(y)$. Let $f := F'$. For any choice of the parameters we obtain $f(0) = 0$. The value of $f(1/\theta)$ depends on τ^2 and θ in the following way: if $\beta > \beta_c := \tau^2(1+\theta)/2$, then $f(1/\theta) = 0$; if $\beta < \beta_c$, then $f(1/\theta)$ is infinite.

For ω^2 sufficiently large, the number of local maxima of f in $(0, 1/\theta)$ depends on the value of β as follows: There exist β_1 and β_2 with $\beta_c \leqslant \beta_1 < \beta_2$ such that as long as $\beta > \beta_c$,

(a) if $\beta > \beta_2$, f has one local maximum in $(0, 1/2\theta)$;

(b) if $\beta_1 < \beta < \beta_2$, f has one local maximum in $(0, 1/2\theta)$ and in $(1/2\theta, 1/\theta)$;

(c) if $\beta < \beta_1$, f has one local maximum in $(1/2\theta, 1/\theta)$.

If $\tau^2 \geqslant 2\alpha$, $1/\theta$ remains inaccessible, but the process becomes extinct with probability one. Moreover, the time to extinction is finite with positive probability. But since zero is a regular boundary in the sense of Feller [4] and $\mu(0) = \alpha > 0$, $Y(t)$ suffers delayed reflection at 0. (See [6, §24].) This means that after the process has reached zero, it stays there for a finite time before growing again. The limiting behavior of this process can be described by

$$\lim_{T\to\infty} \frac{1}{T}\int_0^T P\{Y(t) \leqslant y\}\, dt = G(y),$$

where G is some distribution function which can be given explicitly (see Appendix III). In contrast with the above mentioned case, G has a jump

discontinuity at zero which is equal to

$$G(0+) = \lim_{T\to\infty} \frac{1}{T}\int_0^T P\{Y(t) = 0\}\, dt.$$

For $y > 0$, G is differentiable. Setting $g := G'$ we find $g(0+) = \infty$ and $g(1/\theta) = 0$, if $\beta > \beta_c$ and infinite if $\beta < \beta_c$. Furthermore, there exists a $\beta_0 > \beta_c$ such that

(a) if $\beta < \beta_c$ or $\beta > \beta_0$, g has no local maximum in $(0, 1/\theta)$;
(b) if $\beta_c < \beta < \beta_0$, g has one local maximum in $(0, 1/\theta)$

if τ^2 is sufficiently large.

4. DISCUSSION

We briefly discuss the interesting results of the preceding analysis from the mathematical point of view as well as their implications for the tumor model.

First, we have seen that variation of the noise parameters ω^2 and τ^2, which are measures of the strength of external and demographic variability, results in drastic changes in the qualitative behavior of the model. Such abrupt changes are called phase transitions by some authors [1,7]. In addition to the results of these inquiries it can be seen from the model treated that transition phenomena can also be caused by the increase or decrease of internal fluctuation.

To describe the implications of the mathematical results in tumor immunology, we mention first that the range of variations of the parameters α, β, θ is

$$10^{-19} < \alpha < 10^{-16}, \qquad 10^{-2} < \beta < 10, \qquad 10^{-1} < \theta < 5.$$

(A detailed discussion can be found in [5] and [9].) As for the deterministic model, we find $\theta_c \simeq 1$, since α is very small. We know from Section 2 that for cell systems with $\theta \geqslant 1$ there exists only one stationary solution. This solution is situated near zero only if $\beta \simeq 1$, as follows from (2.2). Therefore rejection of the tumor is only possible if the effector/target cell ratio or the cytotoxic activity of the effector cells is sufficiently high. The latter is for example the case for T-lymphocytes. In cell systems with $\theta < 1$ one often finds $\beta < 1$, which implies that the smallest stationary solution has values much larger than zero. Thus the deterministic treatment predicts that immune surveillance mechanisms are insufficient to ensure rejection in those cases.

If $0 < \tau^2 < 2\alpha$ in the stochastic model, two maxima of the stationary distribution are possible, i.e., two values of the number of tumor cells occur with high probability even if the deterministic model predicts only a large

number of transformed cells. However, the probability of very few tumor cells is zero. If $\tau^2 > 2\alpha$, this probability is always positive, which implies that rejection is possible. Nevertheless, there can still be a maximum of the probability distribution at positive values of the tumor-cell number. Finally, if β is smaller than some critical value, large numbers of tumor cells are probable.

On the whole, one can state that the presence of noise favors rejection. This result is in agreement with the conclusions of Lefever and Horsthemke [9], who treated deterministic growth in random environment.

APPENDIX I. DIFFUSION LIMIT OF BRANCHING PROCESSES

We formally derive diffusion limits for discrete-time density-dependent branching processes with random environments, following Keiding [8] and Tier and Hanson [12]. Although we shall as usual use the "discrete generation" terminology, the results may have a more natural interpretation for time-equidistant sampling of populations with overlapping generations.

Let Z_m be a nonnegative integer-valued random variable equal to the number of individuals in generation m. The number of offspring born to the ith individual in each generation is denoted by B_i. The population size of generation $m+1$ is then given by

$$Z_{m+1} = \sum_{i=1}^{Z_m} B_i .$$

Environmental fluctuations are taken into account by introducing a random variable Ξ_m into the offspring distribution. We assume that the $\{\Xi_m\}$ are independently identically distributed. The offspring distribution is then given by

$$p_j(z,\xi) = P\{B_i = j \mid Z_m = z,\ \Xi_m = \xi\}.$$

The variables $\{B_i, \Xi_m\}$ are assumed to be independent.

To obtain a diffusion limit we consider sequences of branching processes $\{Z_m^{(n)}\}$ with $Z_0^{(n)} = n$, environments $\{\Xi_m^{(n)}\}$, and offspring distributions $p_j^{(n)}(z,\xi)$. Now we ask for conditions under which the processes $X_n(t) := (1/n)Z_{[nt]}^{(n)}$ ($[nt]$ denotes the integer part of nt) converge weakly to a diffusion process $X(t)$.

Define random variables

$$\mu_k^{(n)} := \sum j^k p_j^{(n)}\left(Z_{[nt]}^{(n)}, \Xi_{[nt]}^{(n)}\right),$$

$$\zeta_k^{(n)} := \sum \left(j - \mu_1^{(n)}\right)^k p_j^{(n)}\left(Z_{[nt]}^{(n)}, \Xi_{[nt]}^{(n)}\right).$$

Assume that for some continuous functions a, b, c, one has

$$E_z\mu_1^{(n)} = 1 + \frac{a(z/n)}{n} + o\left(\frac{1}{n}\right),$$

$$E_z\left(\mu_1^{(n)} - 1\right)^2 = \frac{b^2(z/n)}{n} + o\left(\frac{1}{n}\right),$$

$$E_z\xi_2^{(n)} = c^2(z/n) + o(1)$$

(E_z denotes expectation given $Z_{[nt]}^{(n)} = z$). Then under some further assumptions on the moments of the offspring distribution of order $2+\delta$, $\delta > 0$, and on the growth of a, b, c (for the details see [10]), the processes $X_n(t)$ converge weakly to a diffusion process which is the solution of the stochastic differential equation

$$dX = Xa(X)\,dt + \sqrt{X^2b^2(X) + Xc^2(X)}\,dW.$$

For the tumor model under consideration we assume $\mu_1^{(n)} = 1 + h_n(Z_{[nt]}^{(n)}, \Xi_{[nt]}^{(n)})$, where

$$h_n(z,\xi) := (N_n - z)\left(A_n z^{-1} + \frac{\xi}{N_n}\right) - \frac{k_n E_n}{n + k_n l_n^{-1} z}$$

with $A_n = A/n$, $k_n = k/n$, $l_n = l/n$, $N_n = Nn$, $E_n = En$, is the growth rate per cell given z and ξ. Now if $E\{\Xi_{[nt]}^{(n)}\} = \lambda/n$, $E\{\Xi_{[nt]}^{(n)}\}^2 = u^2/n$, and $E\{\Xi_{[nt]}^{(n)}\}^{2+\delta} = o(1/n)$, we obtain

$$E_z\mu_1^{(n)} = 1 + \frac{1}{n}\left(N - \frac{z}{n}\right)\left(\frac{A}{z/n} + \frac{\lambda}{N}\right) - \frac{kE}{1 + kl^{-1}z},$$

$$E_z\left(\mu_1^{(n)} - 1\right)^2 = \frac{u^2}{N^2}\left(N - \frac{z}{n}\right)^2 + o\left(\frac{1}{n}\right).$$

It remains to specify $E_z\xi_2^{(n)}$, the mean variance of the number of offspring. Since the number of cells per unit volume must not exceed N, both variance terms have to vanish at N. This is already the case for the term expressing environmental stochasticity. Therefore we may assume the simplest form for the other term and choose $c^2(x) = v^2(N - x)/N$. We mention that the qualitative behavior of $X(t)$ which we study in this paper essentially depends on the strength of environmental and demographic stochasticity, whereas the concrete form of c only plays a minor role.

APPENDIX II. BOUNDARY CLASSIFICATION OF THE SOLUTION OF EQUATION (1.3)

To classify the boundaries 0 and $1/\theta$ according to [4] we have to evaluate ($0 < a < b < 1/\theta$)

$$\Phi_{a,b} := \int_a^b \phi(x)\,dx$$

with

$$\phi(x) := \exp\left\{ -2\int^x \frac{\mu(y)}{\sigma^2(y)}\, dy \right\}$$

for $a \to 0$ and $b \to 1/\theta$, and

$$\mu(x) = (1-\theta x)(\alpha + x) - \frac{\beta x}{1+x}$$

$$\sigma^2(x) = \omega^2 x^2 (1-\theta x)^2 + \tau^2 x(1-\theta x)$$

(see [6]). We find that

$$\begin{aligned} I(x) &:= \int^x \frac{dy}{\sigma^2(y)} \\ &= \frac{1}{\theta^2\omega^2} \int^x \frac{dy}{y(y-1/\theta)(y-y_1)(y-y_2)} \\ &= \frac{1}{\theta^2\omega^2} \left\{ A \ln x + B \ln \left| x - \frac{1}{\theta} \right| + C \ln |x - y_1| + D \ln |x - y_2| + E \right\}, \end{aligned}$$

where A, B, C, D, E are constants and $y_{1,2} = (1/2\theta)(1 \pm \sqrt{1 + 4\theta\tau^2/\omega^2})$ are not elements of the interval $[0, 1/\theta]$. Evaluation of the constants yields $A = \theta^2\omega^2/\tau^2$; hence

$$\phi_1(x) := e^{-2\alpha I(x)} \sim x^{-2\alpha A/\theta^2\omega^2} = x^{-2\alpha/\tau^2}$$

for small positive values of x. Since we can write $\phi = \phi_1\phi_2$ where ϕ_2 is bounded near 0, we see that $\Phi_{0,b}$ is finite if $2\alpha < \tau^2$ and infinite otherwise. Therefore zero is attractive if $2\alpha < \tau^2$ and repelling (and inaccessible) otherwise. In addition, it can be shown that zero is regular in the first case, i.e., the process can reach zero and restart again. To prove regularity it suffices to show that

$$\Psi_{a,b} := \int_a^b \psi(x)\, dx$$

remains finite for $a \to 0$, where

$$\psi(x) := \frac{1}{\sigma^2(x)\phi(x)}.$$

Since

$$\psi(x) = \frac{1}{\omega^2 x^2 (1-\theta x)^2 + \tau^2 x(1-\theta x)} H(x)\, x^{2\alpha/\tau^2} \sim x^{(2\alpha/\tau^2)-1}$$

for x near zero (H is some function bounded in a neighborhood of zero), the assertion is proved.

As for the upper boundary $1/\theta$, there are constants K, K' such that

$$\Phi_{a,1/\theta} \geqslant K\int_a^{1/\theta} \exp\left\{ 2\int^{1/\theta} \frac{\beta\, dy}{(1+y)(1-\theta y)\left(\omega^2 y(1-\theta y)+\tau^2\right)} \right\}$$

$$\geqslant K\int_a^{1/\theta} \exp\left\{ K'\int^{1/\theta} \frac{\beta}{1-\theta y}\, dy \right\} = \infty .$$

Thus $1/\theta$ is repelling and inaccessible.

APPENDIX III. PROPERTIES OF THE STATIONARY DISTRIBUTION

For the existence of a stationary distribution of the solution of (1.3) it is necessary that $\Psi_{0,1/\theta} < \infty$. In view of Appendix II, we only need to prove $\Psi_{a,1/\theta} < \infty$ for some $a > 0$. Now

$$J(x) := \int^x \frac{dy}{(1+y)(1-\theta y)\left(\omega^2 y(1-\theta y)+\tau^2\right)}$$

$$= K(x) + \frac{A'}{\theta^2\omega^2} \ln\left| x - \frac{1}{\theta} \right| + B'$$

with constants A', B' and a bounded function $K(x)$. Evaluation of the constants yields $A' = -4\theta^2\omega^2/\tau^2(1+\theta)$. Hence

$$\psi(x) = \frac{M(x)}{1-\theta x} e^{-2\beta J(x)}$$

$$= \theta M(x)\, e^{K(x)} \left| x - \frac{1}{\theta} \right|^{[2\beta/\tau^2(1+\theta)]-1}$$

with some function $M(x)$ which is bounded near $1/\theta$. Thus the assertion is proved. Summarizing the preceding results, we obtain

$$\psi(0) = \begin{cases} 0 & \text{if } 0 < \tau^2 < 2\alpha, \\ \infty & \text{if } \tau^2 > 2\alpha, \end{cases}$$

$$\psi(1/\theta) = \begin{cases} 0 & \text{if } \beta > \tau^2(1+\theta)/2, \\ \infty & \text{if } \beta < \tau^2(1+\theta)/2. \end{cases}$$

The distribution functions F and G mentioned in Section 3 can be given in

terms of ψ as follows:

$$F(y) = \begin{cases} 0 & \text{if} \quad y \leqslant 0, \\ \dfrac{\Psi_{0,y}}{\Psi_{0,1/\theta}} & \text{if} \quad y > 0, \end{cases}$$

$$G(y) = \begin{cases} 0 & \text{if} \quad y \leqslant 0, \\ \dfrac{1+2\alpha\Psi_{0,y}}{1+2\alpha\Psi_{0,1/\theta}} & \text{if} \quad y > 0. \end{cases}$$

Since there are constants C, C' such that $\psi = Cf = C'g$, it suffices to study the properties of ψ. In particular, we are interested in local maxima of ψ in $(0, 1/\theta)$.

Now $\psi'(y) = 0$ is equivalent to

$$\mu(y) - \tfrac{1}{2}(\sigma^2)'(y) = 0. \qquad (*)$$

Solving this equation for β yields the following relation between the parameter β and a local extremum of the stationary density:

$$\beta(y) = \frac{1+y}{y}\left\{(\alpha+y)(1-\theta y) - \omega^2 y(1-\theta y)(1-2\theta y) - \frac{\tau^2(1-2\theta y)}{2}\right\}.$$

Let y_0 be a positive solution of $(*)$. Then ψ has a maximum at y_0 if $\beta'(y_0) < 0$. This can be seen from

$$\operatorname{sgn}\psi''(y_0) = \operatorname{sgn}\left\{\mu'(y_0) - \tfrac{1}{2}(\sigma^2)''(y_0)\right\}$$

and

$$y_0(1+y_0)\left\{\mu'(y_0) - \tfrac{1}{2}(\sigma^2)''(y_0)\right\} = y_0^2\beta'(y_0).$$

Next we note that $\beta(1/2\theta) = (1+2\theta)(\alpha+1/2\theta)/2$ is independent of ω^2 and τ^2. From

$$\beta'(1/2\theta) = 2\theta^2(\tau^2 - 2\alpha) + \theta(\tau^2 - \alpha - 1) + \omega^2\left(\theta + \tfrac{1}{2}\right)$$

we find that $\beta'(1/2\theta) > 0$ for sufficiently large values of ω^2 or τ^2.

If $0 < \tau^2 < 2\alpha$ and ω^2 is large enough that $\beta'(1/2\theta) > 0$ and $\beta'(1/\theta) = \theta^2(\tau^2 - 2\alpha)/2 + \theta(\tau^2 - \alpha - 1) - \omega^2(1+\theta) - 1 < 0$, we see that there exist numbers β_1 and β_2 with the properties stated in Section 3, since $\beta'(y) \to -\infty$ for $y \to 0$.

Furthermore, $\beta(y)$ is concave for $\tau^2 > \tau_c^2 \geqslant 2\alpha$, because $\beta''(y) \leqslant 0$ is equivalent to

$$\tau^2 \geqslant 2\alpha - 2\theta y^3\{1 + \omega^2[2\theta(1+3y) - 3]\}.$$

Thus the assertions of Section 3 are completely proved.

REFERENCES

1 L. Arnold, W. Horsthemke, and R. Lefever, White and coloured noise and transition phenomena in nonlinear systems, *Z. Phys. B* 29:367–373 (1978).
2 K. B. Athreya and S. Karlin, On branching processes with random environments I, II, *Ann. Math. Statist.* 42:1499–1520, 1843–1858.
3 W. Feller, Diffusion processes in genetics, in *Proceedings of the 2nd Berkeley Symposium on Mathematical Statistics and Probability*, 1951, pp. 227–246.
4 W. Feller, The parabolic differential equations and the associated semigroups of transformations, *Ann. Math.* 55:468–519 (1952).
5 R. P. Garay and R. Lefever, A kinetic approach to the immunology of cancer. Stationary state properties of effector–target cell reactions, *J. Theoret. Biol.* 73:417–438 (1978).
6 I. I. Gichman and A. V. Skorokhod, *Stochastic Differential Equations*, Springer, Heidelberg, 1972.
7 W. Horsthemke and M. Malek-Mansour, The influence of external noise on nonequilibrium phase transitions, *Z. Phys. B* 28:135–139 (1976).
8 N. Keiding, Population growth and branching processes in random environments, in *Proceedings of the 9th International Biometric Conference*, Boston, 1976, pp. 149–165.
9 R. Lefever and W. Horsthemke, Bistability in fluctuating environments. Implications in tumor immunology, *Bull. Math. Biol.* 41:469–490 (1979).
10 G. Rosenkranz, Diffusion approximation of controlled branching processes with random environments, *Stochastic Analysis Appl.*, submitted for publication.
11 W. L. Smith and W. E. Wilkinson, On branching processes in random environments, *Ann. Math. Statist.* 40:814–827 (1969).
12 Ch. Tier and F. B. Hanson, Persistence in density dependent stochastic populations, *Math. Biosci.* 53:89–117 (1981).