ON TWO CLASSES OF INTERACTING STOCHASTIC PROCESSES ARISING IN CANCER MODELING

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ABSTRACT

The processes X and Y are said to interact, if the laws governing the changes of either of them at time t depend on the values of the other process at times up to t. For bivariate interacting Markov processes, their limiting behavior is analysed by means of approximation suggested by Fuhrmann, consisting of discretizing time, and assuming that in each resulting time interval the processes develop independently, according to the laws obtained by fixing the value of the other process at its level attained at the beginning of the interval.

In this way the conditions for a.s. extinction, escape to infinity with positive probability, etc., are obtained (by using martingale convergence theorem) for state-dependent branching processes studied by Roi, and for bivariate processes with one component piecewise deterministic .

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1. INTRODUCTION

The aim of this paper is to study certain properties of two classes of interacting stochastic processes inspired by some modeling of the development of cancer tumor in presence of an immune response.

As regards interacting processes in general, the situation is as follows. Consider, for simplicity, a bivariate stochastic process $\{X(t),Y(t),\ t \geq 0\}$. We say that the processes X and Y interact, if the laws governing the changes of the process $X(\cdot)$ at time t depend (among others) on the values assumed by the process $Y(\cdot)$ at times $\tau \leq t$, and conversely, the laws for changes of $Y(\cdot)$ at t depend on the values assumed by the process $X(\cdot)$ at times preceding t.

The real situations which are describable in terms of such interacting processes arise in a natural way, e.g. prey-predator interactions in biological sciences. The resulting processes are well-known for the difficulties involved in their analysis, even in the deterministic case of Volterra and Lotka type models.

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There are numerous results concerning the case where only one of the processes influences the other, but not conversely. In this category, one should mention the papers of Puri [9], [10], [11], as well as the currently fashionable studies of various processes in random environments (see e.g. Athreya and Ney [3], Athreya and Karlin [1], [2], Bartoszyński [5], Bartoszyński and Bühler [6], and Smith and Wilkinson [14]). However, there are very few results concerning "genuine" interaction, i.e. influence going in both directions.

In this paper we shall assume that $\{X(t),Y(t)\}$ is an interacting Markov process, and explore the following idea of approximating its two-way interaction. We choose a $T > 0$, and study the process $\{X^*(t),Y^*(t)\}$ defined, roughly speaking, as follows.

Given the values $X_k^* = X^*(kT+)$, $Y_k^* = Y^*(kT+)$, in the interval $(kT,(k+1)T]$ the process $X^*(t)$ develops according to the laws of $\{X(t),Y(t)\}$ with $Y(t)$ fixed at Y_k^*, and similarly, $Y^*(t)$ develops according to the laws obtained by keeping $X(t)$ fixed at X_k^*.

This idea was applied for studying some epidemic models, and also other Markov processes by Fuhrmann [7], where it is shown that (as the intuition would suggest) as T becomes small, one obtains an approximation to the original process under study.

In case of cancer modeling, we interpret $X(t)$ as the number of tumor cells at t, and $Y(t)$ as the number of antibodies at t. Generally speaking, the influence of X on Y represents the "boost" of antibody production by the presence and size of the tumor. On the other hand, the influence of Y on X is exhibited through the elimination of tumor cells by antibodies, by making the death rate of cancer cells dependent on Y. A reasonable deterministic version (pretending that X and Y are continuous) for this situation may for example be given by

$$X' = aX - bXY, \tag{1.1}$$

$$Y' = \alpha + \beta X - \gamma Y - \delta XY, \tag{1.2}$$

where the coefficients are some positive constants.

A possible stochastic version of this model would presuppose the following transition probabilities during $(t,t+h)$:

$$\begin{aligned} &P\{(X,Y) \to (X+1,Y)\} = aXh + o(h), \\ &P\{(X,Y) \to (X-1,Y-1)\} = bXYh + o(h), \\ &P\{(X,Y) \to (X,Y+1)\} = (\alpha+\beta X)h + o(h), \\ &P\{(X,Y) \to (X,Y-1)\} = \gamma Yh + o(h). \end{aligned} \tag{1.3}$$

For analysis of tumor growth by means of the approximation involved in discretizing time, it appears reasonable to treat the process $X(t)$, of tumor growth, to be a pure death (or birth and death) process in each of the intervals $(kT,(k+1)T]$, with the rate(s) depending on $Y(kT+)$. Also, at the moment $(k+1)T$ the cancer cells multiply according to a Galton-Watson branching process scheme, where each of the cells is replaced, independently, by a random number of its descendants. The number of descendants might have the probability generating function $p_0(T) + p_1(T)s + p_2(T)s^2$, where for small T, the term $p_1(T)$ dominates.

One of our aims will be to analyse the probability of a newly originated tumor to become extinct (or alternatively, to become "established", which may be interpreted as the event $[X(t) \to \infty]$), and therefore perhaps X should be treated as a discrete random variable. However, the number of antibodies may be reasonably assumed to be large enough to allow treating it as a continuous variable.

Thus, we shall analyse two classes of processes: one in which $Y(t)$ is discrete, and another one, in which $Y(t)$ is a continuous variable, the development of which is deterministic in $(kT,(k+1)T]$, and depends on the initial values of X and Y for this interval. For lack of better name, we shall call such processes semi-stochastic.

We shall begin in Section 2 with the analysis of a class of semi-stochastic processes. Special cases are considered in some detail in Sections 3 and 4. The main problem will be to study conditions under which the "stochastic component" $\{X_k\}$ satisfies the property

$$P(\lim X_k=0 \text{ or } \lim X_k=\infty) = 1,$$

and also conditions implying $P(\lim X_k=0) = 1$.

In Section 5 we present some results on interacting processes, where both components are stochastic. This analysis leads to state dependent branching processes of the type studied by Roi [12].

2. SEMI-STOCHASTIC PROCESSES

We start from the analysis of a bivariate stochastic process defined as follows.

Let

$$\varphi: \ \eta \times R^+ \to R^+, \tag{2.1}$$

be an arbitrary deterministic function, where $\eta = \{0,1,2,\ldots\}$ and $R^+ = [0,\infty)$.

Let $\{(X_k,Y_k),k=0,1,2,\ldots\}$ be a Markov process on some probability space, taking values in $\eta \times R^+$, and defined as follows.

(a) Given (X_k,Y_k), the value of Y_{k+1} equals

$$Y_{k+1} = \varphi\,(X_k,Y_k), \text{ a.s.}; \tag{2.2}$$

(b) Given (X_k,Y_k), the random variable X_{k+1} has the probability generating function (pgf)

$$E(u^{X_{k+1}}|X_k,Y_k) = g(u;X_k,Y_k), \quad |u| \leq 1, \tag{2.3}$$

with

$$g(0;0,Y_k) = 1, \quad \text{a.s.}; \tag{2.4}$$

(c) X_0 and Y_0 are constants, a.s.

Let

$$\psi(x,y) = \begin{cases} \log[g'(1;x,y)/x], & \text{if} \quad x > 0 \\ 0, & \text{if} \quad x = 0, \end{cases} \tag{2.5}$$

where g' denotes (here and in the sequel) the derivative of g with respect to the first argument.

Let $\theta = \{n_k, k=0,1,\ldots\}$ be a sequence of positive integers with $n_k \to \infty$. For any y_0, let

$$\pi^{(0)}(\theta,y_0) = y_0 \tag{2.6}$$

and for k=0,1,2,...

$$\pi^{(k+1)}(\theta,y_0) = \varphi\,(n_k,\pi^{(k)}(\theta,y_0)). \tag{2.7}$$

Define next for k=0,1,2,...

$$r^{(k+1)}(\theta,y_0) = \psi(n_k,\pi^{(k)}(\theta,y_0)). \tag{2.8}$$

We impose on ψ the following condition.

HYPOTHESIS 1. *For any θ and y_0, the sequence $\{r^{(k)}(\theta,y_0)\}$ converges to a limit $r^* > 0$, independent of θ and y_0.*

The intuitive meaning of Hypothesis 1 is as follows. As $X_k \to \infty$, the process $\{Y_k\}$ behaves in a manner determined by $\{X_k\}$, and Hypothesis 1 states that in this case the average number of "offspring" per parent (in the population whose size is represented by X_k) tends to $\exp(r^*)$.

We have the following

<u>THEOREM 1</u>. <u>Let</u>

$$E(X_{k+1}|X_k,Y_k) < \infty, \quad \text{a.s.} \tag{2.9}$$

<u>Then the sequence</u>

$$W_k = \frac{X_k}{\exp[\sum_{j=1}^{k} \psi(X_{j-1},Y_{j-1})]}, \quad k=1,2,\ldots \tag{2.10}$$

<u>converges a.s. to a random variable</u> W.

<u>Proof</u>. Observe that W_k is a martingale with respect to the usual σ-fields generated by $(X_0,Y_0,\ldots,X_k,Y_k)$. Indeed,

$$\begin{aligned} E(W_{k+1}|X_k,Y_k,\ldots,X_0,Y_0) &= \exp[-\sum_{j=1}^{k+1} \psi(X_{j-1},Y_{j-1})]E(X_{k+1}|X_k,Y_k) \\ &= \exp[-\sum_{j=1}^{k+1} \psi(X_{j-1},Y_{j-1})]g'(1;X_k,Y_k) \\ &= \exp[-\sum_{j=1}^{k+1} \psi(X_{j-1},Y_{j-1})]X_k\exp[\psi(X_k,Y_k)]=W_k. \end{aligned} \tag{2.11}$$

Since W_k is a nonnegative martingale, it converges a.s. to a limit, say W. By Fatou lemma

$$E(W) \leq \liminf_{k\to\infty} E(W_k) = E(W_1) < \infty \tag{2.12}$$

so that $W < \infty$, a.s. □

<u>THEOREM 2</u>. <u>On the set where</u>

$$\lim_k \sum_{j=1}^{k} \psi(X_{j-1},Y_{j-1}) = -\infty \tag{2.13}$$

<u>we have</u> $X_k \to 0$ <u>a.s.</u>

For the proof, observe that condition (2.13) implies that the denominator in (2.10) converges to 0. Thus, for W_n to converge, we must have $X_k \to 0$. □

We have also

THEOREM 3. *If for every* $j > 0$ *there exists* n_j *such that*

$$\liminf_{k\to\infty} P(X_{k+n_j}=0 | X_k=j) > 0, \tag{2.14}$$

then

$$P(\lim X_k=0 \text{ or } \lim X_k=\infty) = 1. \tag{2.15}$$

Proof. We present the proof which, under somewhat more restrictive conditions, is given in Bartoszyński [4].

Let $j > 0$ be fixed, and let for $M > N$

$$B_N^M = \{X_k=j \text{ for some } k \text{ with } N \le k \le M\} . \tag{2.16}$$

Then

$$B_N = \bigcup_M B_N^M \tag{2.17}$$

is the event "at least one visit to j after time N". The assertion (2.15) will follow if we show that for every $j > 0$ we have $P(\bigcap_N B_N) = 0$, or equivalently, $\lim P(B_N) = 0$. The latter condition will in turn follow if we show that $P(B_N^M)$ can be made arbitrarily small for all $M > N$ by choosing sufficiently large N.

Now, we may write

$$B_N^M = \{X_M=j\} \cup \bigcup_{k=N}^{M-1} \{X_k=j, X_{k+1}\neq j, \ldots, X_M\neq j\} , \tag{2.18}$$

so that

$$P(B_M^N) = P(X_M=j) + \sum_{k=N}^{M-1} P(X_k=j, X_{k+1}\neq j, \ldots, X_M\neq j) \tag{2.19}$$

$$= P(X_M=j) + \sum_{k=N}^{M-1} P((B_{k+1}^M)^c | X_k=j) P(X_k=j).$$

For the case when $\sum_k P(X_k=j) < \infty$, we obtain

(2.20) $$P(B_N^M) \le \sum_{k=N}^{M} P(X_k=j) \le \sum_{k=N}^{\infty} P(X_k=j)$$

which tends to 0 as $N \to \infty$.

Suppose now that

(2.21) $$\sum_k P(X_k=j) = \infty .$$

From (2.19), after letting $M \to \infty$ in the summands, it follows that

(2.22) $$1 \ge P(B_N^M) \ge P(X_M=j) + \sum_{k=N}^{M-1} P(B_{k+1}^c | X_k=j)P(X_k=j).$$

Consequently, as $M \to \infty$, we have

(2.23) $$\sum_{k=N}^{\infty} P(B_{k+1}^c | X_k=j)P(X_k=j) < \infty .$$

In view of (2.21) and (2.23) we must therefore have

(2.24) $$\liminf_{k\to\infty} P(B_{k+1}^c | X_k=j) = 0,$$

which contradicts the assumption (2.14). □

Define now

(2.25) $$Z_k = \frac{1}{k} \sum_{j=1}^{k} \psi(X_{j-1}, Y_{j-1}).$$

We then have

<u>THEOREM 4</u>. <u>Assume that condition</u> (2.14) <u>holds.</u> <u>Then under Hypothesis 1</u>, $X_k \to \infty$ <u>iff</u> $Z_k \to r^*$, <u>a.s., in which case on the set</u> $[W > 0]$ <u>we have</u> $X_k \sim We^{kr^*}$, <u>a.s.</u> <u>Furthermore,</u> $X_k \to 0$ <u>iff</u> $Z_k \to 0$, <u>a.s.</u>

<u>Proof</u>. By (2.14), we have $P(X_k \to 0 \text{ or } X_k \to \infty) = 1$. If $X_k \to \infty$, then by Hypothesis 1, we have $\psi(X_k,Y_k) \to r^* > 0$, a.s. for any initial Y_0. It follows that $Z_k \to r^*$, a.s.

On the other hand, if $X_k \to 0$, then $X_n = 0$, and hence $\psi(X_n,Y_n) = 0$, $\forall n \geq N$ for some N. It follows that $\exp(kZ_k)$ is finite, hence $Z_k \to 0$. □

Remark 1. A condition which implies (2.14) is

(2.26) $$\inf_y P(X_k \to 0 | X_0=j, Y_0=y) > 0,$$

or equivalently (since 0 is an absorbing state for the process X_k)

(2.27) $$\inf_y P(X_{n_j}=0 | X_0=j, Y_0=y) > 0$$

for some $n_j > 0$. This follows from the fact that

(2.28) $$\begin{aligned} P(X_{k+n_j}=0|X_k=j) &= \int P(X_{k+n_j}=0|X_k=j,Y_k=y)dP(Y_k \leq y|X_k=j) \\ &= \int P(X_{n_j}=0|X_0=j,Y_0=y)dP(Y_k \leq y|X_k=j) \\ &\geq \inf_y P(X_{n_j}=0|X_0=j,Y_0=y). \end{aligned}$$

Here the second equality follows from the Markovian character of the process $\{(X_k,Y_k)\}$.

Remark 2. We now comment briefly on the limiting behavior of the process $\{Y_k\}$. In the case when $X_k \to 0$, the limiting behavior of $\{Y_k\}$ depends on the function $\varphi(0,\cdot): R^+ \to R^+$. On the other hand, if $X_k \to \infty$, the behavior of $\{Y_k\}$ is determined by the properties of the sequence $\{\pi^{(k)}(\theta,y_0)\}$ defined by (2.6) and (2.7).

In particular, let conditions (C_1) and (C_2) given below hold.

(C_1) As $k \to \infty$, the sequence $\{\pi^{(k)}(\theta,y_0)\}$ has a limit π^* independent of θ and y_0.

(C_2) As $k \to \infty$, the sequence $\{q^{(k)}(y_0)\}$ defined by

(2.29) $$q^{(0)}(y_0) = y_0,\ q^{(k+1)}(y_0) = \varphi\,(0,q^{(k)}(y_0)), \quad k=0,1,\ldots$$

has a limit q^* independent of y_0.

Then, under (2.15), if $\pi^* \neq q^*$, we have $X_k \to \infty$ iff $Y_k \to \pi^*$, a.s., and $X_k \to 0$ iff $Y_k \to q^*$, a.s.

3. A STATE DEPENDENT BRANCHING SCHEME FOR $\{X_k\}$

We shall now consider a special case of the process from the preceding section. The process $\{Y_k\}$ will be defined as before, through a function φ: $\eta \times R^+ \to R^+$, so that $Y_{k+1} = \varphi\,(X_k,Y_k)$, while for given (X_k,Y_k), the pgf. of X_{k+1} will be of the form

(3.1) $$E(u^{X_{k+1}}|X_k,Y_k) = [g(u;Y_k)]^{X_k}, \quad |u| \leq 1$$

where for each $y \geq 0$

(3.2) $$g(u;y) = \sum_n p_n(y)u^n$$

is a pgf.

We start from the subcritical case.

THEOREM 5. *Assume that the function* φ *satisfies the condition* (C_1), *and let* $g'(1;y)$ *be continuous at the point* π^*. *If*

(3.3) $$g'(1;\pi^*) < 1,$$

then $X_k \to 0$, *a.s.*

Proof. We have now $\psi(x,y) = \log g'(1;y)$ for $x > 0$, and hence the martingale (2.10) becomes

(3.4) $$W_n = \frac{X_n}{\exp\{\sum_{j=1}^{n} \log g'(1;Y_{j-1})\}} .$$

Suppose that $X_n \to \infty$. Then $Y_n \to \pi^*$, and consequently,

(3.5) $$\frac{1}{k}\sum_{j=1}^{k} \log g'(1;Y_{j-1}) \to \log g'(1;\pi^*) < 0.$$

Applying Theorem 2, this yields $X_n \to 0$, which gives a contradiction. □

Let $\mathcal{S}^{(N)}$ be the class of all sequences $\theta = \{n_0, n_1, \ldots\}$ of integers such that $n_0 \neq 0$, $n_k \to \infty$, and

(3.6) $$n_{k+1} \geq 2n_k, \; k=0,1,\ldots,N-1, \; n_r \geq n_N \text{ for all } r \geq N.$$

Let $\pi^{(k)}(\theta,y_0)$ be defined by (2.6) and (2.7), and satisfy condition (C_1), so that $\pi^{(k)}(\theta,y_0) \to \pi^*$, independent of θ and y_0. We now impose

ASSUMPTION 1. For any $\varepsilon > 0$ and $K > 0$, there exists an N such that for all $Y_0 \leq K$ and all $\theta \in \mathcal{S}^{(N)}$ we have

(3.7) $$\pi^{(k)}(\theta,Y_0) \leq \pi^* + \varepsilon$$

for all $k \geq N$.

ASSUMPTION 2. For every $y \geq 0$ we have $p_0(y) + p_1(y) < 1$.

ASSUMPTION 3. For $n = 0,1,\ldots$ the sum

(3.8) $$q_n(y) = \sum_{k=n}^{\infty} p_k(y)$$

is a nonincreasing function of y.

Remark 3. Before proceeding further, let us observe that monotonicity in (3.8) is preserved if we take sums of the form

(3.9) $$\sum_{k=n}^{\infty} p_k^{(m)}(y), \quad m=1,2,\ldots$$

where $p_k^{(m)}(y)$ is the coefficient of u^k in $[g(u;y)]^m$. This assertion simply amounts to stating that a convolution of elements of a stochastically decreasing family is again stochastically decreasing.

Observe also that if $g(0;0) > 0$, then (2.15) holds. Indeed, from Assumption 1 we get

$$p_0(y) = 1 - \sum_{k=1}^{\infty} p_k(y) \geq 1 - \sum_{k=1}^{\infty} p_k(0) = g(0;0) > 0, \tag{3.10}$$

so that condition (2.27) holds.

We shall now state the following lemma due to Von Bahr and Esseen [15], which will be needed later.

LEMMA. Let $\eta_1,\ldots,\eta_n$ be a finite sequence of random variables. Denote $S_i = \eta_1 + \ldots + \eta_i$, and assume that $E(\eta_i|S_{i-1}) = 0$, $E|\eta_i|^{1+\lambda} < \infty$, $i=1,\ldots,n$ for some λ with $0 < \lambda \leq 1$. Then there exists a constant $c(\lambda)$ such that

$$E|S_n|^{1+\lambda} \leq c(\lambda) \sum_{i=1}^{n} E|\eta_i|^{1+\lambda} . \tag{3.11}$$

In fact, as shown by Rubin [13], we have

$$c(\lambda) = \sup_x \left[\frac{|1+x|^{1+\lambda}-1-(1+\lambda)x}{|x|^{1+\lambda}} \right], \tag{3.12}$$

with $1 \leq c(\lambda) \leq 2$, for $0 \leq \lambda \leq 1$.

We shall now prove

THEOREM 6. Let Condition (C_1) and Assumptions 1, 2 and 3 hold. Moreover, assume that for some λ with $0 < \lambda \leq 1$ and $\nu > 0$, the random variables with pgf $g(u;y)$ have finite moment of the order $1 + \lambda$ for all $y \in [\pi^*,\pi^*+\nu]$. In addition, let $g'(1;y)$ be continuous at $y = \pi^*$. Then the condition

$$g'(1;\pi^*) > 1 \tag{3.13}$$

implies $P(X_k \to \infty) > 0$, provided $X_0 \neq 0$.

Proof. Assuming that (3.13) holds, choose $\varepsilon_0 > 0$ such that $\varepsilon_0 < \nu$ and $\mu = g'(1;\pi^*+\varepsilon_0) > 1$. We shall show first that there exists a beginning of a sample path $(X_0,Y_0),(X_1,Y_1),\ldots,(X_N,Y_N)$, having positive probability, such that $X_{k+1} \geq 2X_k$, $k=0,1,\ldots,N-1$ and $Y_N \leq \pi^* + \varepsilon_0$.

Indeed, let N be determined from Assumption 1 for $\varepsilon = \varepsilon_0$ and $K = Y_0$. By Assumption 2, there exists $n_1 = n_1(Y_0) \geq 2$ such that with probability at least $[p_{n_1}(Y_0)]^{X_0} > 0$, we have $X_1 = n_1X_0$. Put $Y_1 = \varphi(X_0,Y_0)$ and choose $n_2 = n_2(Y_1) \geq 2$ such that with probability at least $[p_{n_2}(Y_1)]^{X_1} > 0$ we have $X_2 = n_2X_1$. Proceeding in this way for N - 1 steps we infer that with probability at least

$$(3.14) \qquad [p_{n_1}(Y_0)]^{X_0}[p_{n_2}(Y_1)]^{X_1} \cdots [p_{n_{N-1}}(Y_{N-2})]^{X_{N-1}} > 0$$

we have $X_{k+1} \geq 2X_k$ for $k=0,1,\ldots,N-1$, and hence $Y_N \leq \pi^* + \varepsilon_0$.

Without loss of generality, we may now assume that the process starts from values $X_0^* \geq K_0 = 2^N X_0$ and $Y_0^* \leq \pi^* + \varepsilon_0$. To complete the proof, we shall show that there exists a sequence $\{K_n\}$ such that $K_0 \leq K_1 \leq \cdots \to \infty$ and

$$(3.15) \qquad P(X_n \geq K_n \text{ for all } n \mid X_0^*, Y_0^*) > 0.$$

We may write, for any $K_0, K_1, \ldots, K_m$:

$$(3.16) \qquad P_m = P(X_j \geq K_j, j=1,\ldots,m \mid X_0^*,Y_0^*)$$

$$= \sum_{r_{m-1}\geq K_{m-1}} \cdots \sum_{r_1 \geq K_1} P(X_1=r_1 \mid X_0^*,Y_0^*)$$

$$\cdot\ P(X_2=r_2 \mid X_1=r_1, Y_1=\varphi(X_0^*,Y_0^*)) \cdots$$

$$\cdot\ P(X_{m-1}=r_{m-1} \mid X_{m-2}=r_{m-2}, Y_{m-2}=\varphi(X_{m-3},Y_{m-3}))$$

$$\cdot\ P(X_m \geq K_m \mid X_{m-1}=r_{m-1}, Y_{m-1}=\varphi(X_{m-2},Y_{m-2})).$$

In view of Assumption 1 and (3.9) the last term may be bounded below by

$$P(X_m \geq K_m | X_{m-1}=r_{m-1}, Y_m=\pi^*+\varepsilon_0). \tag{3.17}$$

Denoting by $\xi_1, \xi_2, \ldots$ the independent random variables with pgf $g(u;\pi^*+\varepsilon_0)$, we may further bound the probability in (3.17) as follows:

$$\begin{aligned} P(X_m \geq K_m | X_{m-1}=r_{m-1}, Y_{m-1}=\pi^*+\varepsilon_0) &= P(\xi_1+\ldots+\xi_{K_{m-1}}+\xi_{K_{m-1}+1}+\ldots+\xi_{r_{m-1}} \geq K_m) \\ &\geq P(\xi_1+\ldots+\xi_{K_{m-1}} \geq K_m) \\ &= P(X_m \geq K_m | X_{m-1}=K_{m-1}, Y_{m-1}=\pi^*+\varepsilon_0). \end{aligned} \tag{3.18}$$

Proceeding by induction, we obtain for the probability P_m the bound

$$\begin{aligned} P_m &\geq \prod_{j=1}^{m} P(X_j \geq K_m | X_{j-1}=K_{j-1}, Y_{j-1}=\pi^*+\varepsilon_0) \\ &= \prod_{j=1}^{m} \{1-P(X_j < K_j | X_{j-1}=K_{j-1}, Y_{j-1}=\pi^*+\varepsilon_0)\} . \end{aligned} \tag{3.19}$$

It now reamins to show that one can choose the constants K_n such that $\lim_{m\to\infty} P_m > 0$, or equivalently,

$$\sum_{n=1}^{\infty} P(\xi_1+\ldots+\xi_{K_{n-1}} < K_n) < \infty . \tag{3.20}$$

Assume that

$$\lim(K_n/K_{n-1}) = 1. \tag{3.21}$$

Since $\mu = E\xi_i > 1$, we have $\mu - K_n/K_{n-1} \geq d > 0$ for all $n \geq n_0$. Consequently, we have for $n \geq n_0$, using Markov inequality

$$\begin{aligned} P(\xi_1+\ldots+\xi_{K_{n-1}} < K_n) &= P\left[\frac{\sum_{i=1}^{K_{n-1}}(\xi_i-\mu)}{K_{n-1}} < \frac{K_n}{K_{n-1}} - \mu\right] \\ &\leq P\left[\left|\frac{\sum_{i=1}^{K_{n-1}}(\xi_i-\mu)}{K_{n-1}}\right| \geq d\right] \leq \frac{E\left|\sum_{i=1}^{K_{n-1}}(\xi_i-\mu)\right|^{1+\lambda}}{d^{1+\lambda}K_{n-1}^{1+\lambda}} . \end{aligned} \tag{3.22}$$

By the lemma, the last term may be bounded by

$$(3.23)\qquad \frac{c(\lambda)K_{n-1}E|\xi-\mu|^{1+\lambda}}{d^{1+\lambda}K_{n-1}^{1+\lambda}} = \frac{c(\lambda)E|\xi-\mu|^{1+\lambda}}{d^{1+\lambda}} \frac{1}{K_{n-1}^{\lambda}} .$$

It now suffices to put $K_n = [n^{(1+\delta)/\lambda}]$ for some $\delta > 0$. The condition (3.21) holds, and the series (3.20) converges. □

A partial solution for the critical case is given by the following theorem, which may be easily established.

<u>THEOREM 7</u>. <u>Assume that condition</u> (C_1) <u>and Assumption 3 hold. Suppose in addition that</u> Y_0 <u>is such that</u> $\sup_k Y_k \leq \pi^*$ <u>regardless of the behavior of</u> $\{X_k\}$. <u>Then the condition</u>

$$(3.24)\qquad g'(1;\pi^*) = 1$$

<u>implies</u> $P(X_k \to 0) = 1$.

Let now q_0 be the smallest root of the equation $x = g(x;\pi^*)$. We have then

<u>THEOREM 8</u>. <u>Under Assumption 3, if</u> Y_0 <u>is such that</u> $\sup_k Y_k \leq \pi^*$ <u>regardless of the behavior of</u> $\{X_k\}$, <u>then</u>

$$(3.25)\qquad P(X_k \to 0) \leq (q_0)^{X_0}.$$

<u>Proof</u>. We may write

$$(3.26)\qquad \frac{1-g(u;y)}{1-u} = \sum_n q_n(y)u^n$$

where $q_n(y)$ is given by (3.8). It follows from Assumption 3 that $g(u;y)$ is nondecreasing in y for every u. Consequently, the probability of extinction of a process $\{X_k\}$ starting from a single element may be bounded above by q_0, which yields (3.25). □

4. A SPECIAL CASE

Motivated by the idea of modeling cancer growth in the presence of antibodies, we may further specialize the model, by making the following assumptions.

The function φ, governing the development of the process $\{Y_k\}$ (antibodies) will be assumed to be the solution of the differential equation (1.2), for initial values $X_k = X(kT+)$, $Y_k = Y(kT+)$, evaluated at time T, so that

$$Y_{k+1} = \varphi(X_k, Y_k) = Y_k e^{-(\gamma+\delta X_k)T} + \frac{\alpha+\beta X_k}{\gamma+\delta X_k}(1-e^{-(\gamma+\delta X_k)T}) . \tag{4.1}$$

As regards to the process $\{X_k\}$, we assume that it develops as follows: given (X_k, Y_k), representing the value at kT+, in the interval $(kT,(k+1)T]$ the process $\{X(t)\}$ is a pure death process, with death intensity $a + bY_k$. At time $(k+1)T$, the existing elements of this process multiply according to a Galton-Watson branching scheme, with pgf of the number of offspring $h(u)$. Thus,

$$E(u^{X_{k+1}} | X_k, Y_k) = [h(u)e^{-(a+bY_k)T} + 1 - e^{-(a+bY_k)T}]^{X_k} . \tag{4.2}$$

We denote

$$\rho = h'(1). \tag{4.3}$$

We have the following

THEOREM 9. *If either $a > 0$ or $h(0) > 0$, then condition (2.15) holds.*

Proof. Observe that

$$P(X_{k+1}=0 | X_k, Y_k) = [h(0)e^{-(a+bY_k)T} + 1 - e^{-(a+bY_k)T}]^{X_k} \tag{4.4}$$

$$= [1-(1-h(0))e^{-(a+bY_k)T}]^{X_k} \geq [1-(1-h(0))e^{-aT}]^{X_k} > 0,$$

so that condition (2.27) is met. □

As a corollary to theorems 5 and 6 we obtain

COROLLARY 10. *If*

(4.5) $$\log \rho < aT + b\,\frac{\beta}{\delta}\,T,$$

then $X_k \to 0$, *a.s. On the other hand, if* $h(u)$ *is not linear, the random variable* η *with pgf* $h(u)$ *satisfies* $E|\eta|^{1+\lambda} < \infty$ *for some* $\lambda > 0$, *and*

(4.6) $$\log \rho > aT + b\,\frac{\beta}{\delta}\,T,$$

then $P(\lim X_k = \infty) > 0$, *whenever* $X_0 \neq 0$.

Proof. For the subcritical case (4.5) observe that the function φ given by (4.1) is continuous, and $Y_k \to \beta/\delta$ as $X_k \to \infty$.

For the supercritical case, observe that

(4.7) $$\sup_{k \geq n} Y_k \leq \max[Y_n, \frac{\alpha}{\gamma}, \frac{\beta}{\delta}],$$

which follows from the facts that

(4.8) $$\min(\alpha/\gamma, \beta/\delta) \leq \frac{\alpha+\beta x}{\gamma+\delta x} \leq \max(\alpha/\gamma, \beta/\delta)$$

for all $x=0,1,\ldots$, and that $\varphi(x,y)$ is a convex combination of y and $(\alpha+\beta x)/(\gamma+\delta x)$. Consequently, Assumption 1 is satisfied.

Assumption 2 holds trivially, while for Assumption 3 we may proceed as follows. The quantity $q_n(y)$ in (3.8) is the coefficient of u^{n+1} in the expansion of $(1-g(u;y))/(1-u)$, which may be written as

(4.9) $$\frac{1-[h(u)e^{-(a+by)T}+1-e^{-(a+by)T}]}{1-u}$$

$$= \frac{1-h(u)}{1-u}\,e^{-(a+by)T} = \sum_n q_n e^{-(a+by)T},$$

where $q_n = p_n + p_{n+1} + \ldots$, so that $q_n e^{-(a+by)T}$ is a decreasing function of y. The proof follows now from Theorem 6. □

As a corollary to Theorem 9 we obtain also the following.

COROLLARY 11. If $\log \rho = aT + b \frac{\beta}{\delta} T$, and in addition $\alpha/\gamma \leq \beta/\delta$, $Y_0 \leq \beta/\delta$, then $P(X_k \to 0) = 1$.

The above results are of some potential significance as regards to the knowledge of tumor growth. Assume namely that the immune response $\{Y(t)\}$ is governed by the differential equation $Y' = \alpha + \beta X - \gamma Y - \delta XY$ where $X = X(t)$ is the tumor size. If T is chosen reasonably small, our process (X_k, Y_k) may be regarded as an approximation to $(X(t), Y(t))$, provided that that pgf. h(u) is properly chosen. Suppose that

$$h(u) = (1-p(T))u + p(T)u^2, \tag{4.10}$$

so that at each time kT, on the average, the fraction p(T) of tumor cells undergo mitosis. We have then

$$\rho = 1 + p(T). \tag{4.11}$$

The condition of subcriticality, i.e. when the tumor becomes a.s. extinct, is

$$\frac{\log(1+p(T))}{T} < a + b \frac{\beta}{\delta}. \tag{4.12}$$

Assume that $a \approx 0$. This amounts to neglecting the possibility of death of a tumor cell for reasons other than elimination by antibodies. Then the relation (4.12) may be approximately written as $b > d/H$ where $d \approx p(T)/T$ is the average number of tumor cells undergoing mitosis per unit time, and $H = \beta/\delta$ is the asymptotic level of immune response (i.e. level which would be approached in the presence of large tumors). Here b, the crucial parameter, is the rate of elimination of tumor cells by antibodies.

On the other hand, a may be regarded as an effect of some therapy aimed at destroying the tumor cells. Then the subcriticality condition becomes $a > d - bH$.

It is worth observing that the conditions under which the tumor process is sub or supercritical do not involve the parameters α and γ, which characterize respectively the rates of antibody formation and destruction in absence of the tumor. However, they determine the likely initial number of antibodies, equal α/γ, and in this way influence the probability of the tumor becoming extinct in the supercritical case.

5. INTERACTING PROCESSES

In this section we shall assume that $\{(X_k,Y_k),k=0,1,\ldots\}$ forms a Markov chain with X_k,Y_k taking nonnegative integer values, and such that

(i) X_0,Y_0 are constants, a.s.;

(ii) given $X_k,Y_k (k=0,1,\ldots)$, the random variables (X_{k+1},Y_{k+1}) have joint pgf.

$$E(u^{X_{k+1}}v^{Y_{k+1}}|X_k,Y_k) = [g_1(u;X_k,Y_k)]^{X_k}[g_2(v;X_k,Y_k)]^{Y_k}, \tag{5.1}$$

where for all integers x,y,

$$g_1(u;0,y) \equiv 1,\ g_2(v;x,0) \equiv 1 \tag{5.2}$$

and

$$g_i(s;x,y) = \sum_{n=0}^{\infty} s^n p_n^{(i)}(x,y), \quad i=1,2 \tag{5.3}$$

are pgf's.

We denote

$$\mu_i(x,y) = g_i'(1;x,y), \quad i=1,2. \tag{5.4}$$

Assume that for all x,y,

(5.5) $$g_i(s;x,y) \not\equiv s, \quad i=1,2.$$

Then (see Harris [8]), all states except (0,0) are transient, and we have

(5.6) $$P(X_k \to 0 \text{ or } \infty \text{ and } Y_k \to 0 \text{ or } \infty) = 1.$$

In this section we shall study the joint limit behavior of the process $\{X_k,Y_k\}$, and also the conditions, expressed in terms of moments, which imply that one of the processes has a positive probability of escaping to ∞, given that the other process behaves in a certain way. The results complement, in a sense, those of Roi [12], who studied conditions implying a.s. absorption to the origin for multivariate state dependent braching processes.

For reasons of symmetry, it is enough to concentrate on one of the processes only, say $\{X_k\}$.

It will be convenient to start from a theorem concerning a univariate state dependent branching process $\{Z_k\}$, with

(5.7) $$E\{u^{Z_{k+1}}|Z_k\} = [g(u;Z_k)]^{Z_k}; \quad k=0,1,2,\ldots,$$

where for every integer $z \geq 0$ the pgf $g(u;z)$ is assumed to satisfy $g(u;z) \not\equiv u$ and $g(u;0) \equiv 1$.

We denote

(5.8) $$\mu(z) = g'(1;z).$$

Let $\xi(r),\xi_1(r),\ldots$ be a sequence of I.I.D. nonnegative integer valued random variables with common pgf $g(u;r)$.

We now have

<u>THEOREM 11</u>. <u>Assume there exists a sequence</u> $\{K_n, n=0,1,\ldots\}$, <u>with</u> $0 < K_0 < K_1 < K_2 < \ldots$, <u>such that for</u> $j=1,2,\ldots$

(5.9) $$r\mu(r) > K_j,$$

for all $r \geq K_{j-1}$, and that for some sequence $\Lambda = \{\lambda_r\}$, with $0 < \lambda_r \leq 1$, $r = K_0, K_0 + 1, \ldots,$

(5.10) $$\sum_{j=1}^{\infty} D(j,\Lambda) < \infty ,$$

where

(5.11) $$D(j,\Lambda) = \sup_{r \geq K_{j-1}} \left[c(\lambda_r) \frac{rE|\xi(r)-\mu(r)|^{1+\lambda_r}}{(r\mu(r)-K_j)^{1+\lambda_r}} \right]$$

with $c(\lambda)$ being the constant appearing in the lemma from Section 3. Then

(5.12) $$P\{Z_k \to \infty | Z_0=K_0\} > 0.$$

Proof. Let $\{K_n\}$ be a sequence satisfying the assumptions of the theorem. For m=1,2,..., let

(5.13) $$P_m = P\{Z_j \geq K_j, j=1,\ldots,m | Z_0=K_0\} .$$

We may then write

(5.14) $$P_m = \prod_{j=1}^{m} P\{Z_j \geq K_j | Z_{j-1} \geq K_{j-1}, \ldots, Z_1 \geq K_1, Z_0=K_0\}$$

$$= \prod_{j=1}^{m} [1-P\{Z_j < K_j | Z_{j-1} \geq K_{j-1}, \ldots, Z_1 \geq K_1, Z_0=K_0\} .$$

To prove the assertion (5.12) it suffices to show that $\lim_{m\to\infty} P_m > 0$, which is equivalent to

(5.15) $$\sum_{j=1}^{\infty} P\{Z_j < K_j | Z_{j-1} \geq K_{j-1}, \ldots, Z_1 \geq K_1, Z_0=K_0\} < \infty$$

Using Markov property, we may estimate the terms of the series in (5.15) as follows

(5.16) $$P\{Z_j < K_j | Z_{j-1} \geq K_{j-1}, \ldots, Z_1 \geq K_1, Z_0 = K_0\}$$

$$= \frac{P\{Z_j < K_j, Z_{j-1} \geq K_{j-1}, \ldots, Z_1 \geq K_1 | Z_0 = K_0\}}{P\{Z_{j-1} \geq K_{j-1}, \ldots, Z_1 \geq K_1 | Z_0 = K_0\}}$$

$$= \frac{1}{P_{j-1}} \sum_{r \geq K_{j-1}} P\{Z_j < K_j | Z_{j-1} = r\}$$

$$\cdot P\{Z_{j-1} = r | Z_{j-2} \geq K_{j-2}, \ldots, Z_1 \geq K_1, Z_0 = K_0\}$$

$$= \frac{1}{P_{j-1}} \sum_{r \geq K_{j-1}} P\{\xi_1(r) + \ldots + \xi_r(r) < K_j\}$$

$$\cdot P\{Z_{j-2} = r | Z_{j-2} \geq K_{j-2}, \ldots, Z_1 \geq K_1, Z_0 = K_0\}$$

Using the fact that $r\mu(r) > K_j$ by (5.9), Markov inequality, and the lemma from Section 3, the first term of the product in the last sum may be bounded from above as follows:

(5.14) $$P\{\xi_1(t) + \ldots + \xi_r(r) < K_j\}$$

$$= P\{\sum_{i=1}^{r} (\xi_i(r) - \mu(r)) < K_j - r\mu(r)\}$$

$$\leq P\{|\sum_{i=1}^{r} (\xi_i(r) - \mu(r))|^{1+\lambda_r} > [r\mu(r) - K_j]^{1+\lambda_r}\}$$

$$\leq \frac{E|\sum_{i=1}^{r} (\xi_i(r) - \mu(r))|^{1+\lambda_r}}{[r\mu(r) - K_j]^{1+\lambda_r}}$$

$$\leq c(\lambda_r) \frac{rE|\xi(r) - \mu(r)|^{1+\lambda_r}}{[r\mu(r) - K_j]^{1+\lambda_r}}$$

$$\leq D(j, \Lambda),$$

where $D(j,\Lambda)$ is defined by (5.11).

Consequently, the terms (5.16) are bounded from above by

$$(5.18)\quad D(j,\Lambda)\cdot\frac{1}{P_{j-1}}\sum_{r\geq K_{j-1}} P\{Z_{j-1}=r\,|\,Z_{j-2}\geq K_{j-2},\ldots,Z_1\geq K_1,Z_0=K_0\} = D(j,\Lambda)$$

and the assertion follows from the condition (5.10). □

Let us now return to the bivariate process $\{X_k,Y_k\}$, as defined at the beginning of this section. We start from formulating several conditions implying various assertions about the limiting behavior of the joint process $\{X_k,Y_k\}$, and also its components separately.

In the conditions below, $\{x_n\}$ and $\{y_n\}$ are sequences of nonnegative integers.

(A_1) Let $x_n\to\infty$, $y_n\to\infty$. Then

$$(5.19)\qquad \limsup_{N\to\infty}\prod_{j=1}^{N}[\mu_1(x_j,y_j)\mu_2(x_j,y_j)] < \infty .$$

(A_2) Let $x_n\to\infty$, $y_n\to 0$ or ∞. Then

$$(5.20)\qquad \limsup_{N\to\infty}\prod_{j=1}^{N}\mu_1(x_n,y_n) < \infty .$$

(A_3) Let $y_n\to\infty$. Then

$$(5.21)\qquad \limsup_{N\to\infty}\prod_{j=1}^{N}\mu_2(0,y_n) < \infty .$$

We have then

THEOREM 12. Assume (5.5). Then (A_1) implies $P\{X_n\to\infty \text{ and } Y_n\to\infty\} = 0$, while ($A_2$) implies $P\{X_n\to\infty\} = 0$. Finally, (A_2) and (A_3) imply $P\{X_n\to 0 \text{ and } Y_n\to 0\} = 1$.

Proof. Differentiating (5.1) with respect u and v we easily find that each of the sequences

(5.22) $$U_n = \frac{X_n}{\prod_{j=0}^{n-1} \mu_1(X_j,Y_j)} ,$$

(5.23) $$V_n = \frac{Y_n}{\prod_{j=1}^{n-1} \mu_2(X_j,Y_j)} ,$$

(5.24) $$W_n = \frac{X_n Y_n}{\prod_{j=1}^{n-1} [\mu_1(X_j,Y_j)\mu_2(X_j,Y_j)]}$$

$(n=1,2,\ldots)$ is a martingale. As in the proof of Theorem 1, we can show that each of the above martingales converges, a.s. to an a.s. finite limit.

Thus, on the set $[X_n \to \infty, Y_n \to \infty]$, the denominator in (5.24) must tend to ∞, which contradicts (A_1), and thus proves the first assertion.

The proof of the second assertion is analogous. To prove the last assertion observe that if (A_2) holds, then $X_n \to 0$, a.s. and we can define $M = \inf\{n: X_n=0\}$, with $M < \infty$, a.s.

We have then, for $n \geq M$

(5.25) $$V_n = \frac{Y_n}{\prod_{j=1}^{n=1} \mu_2(X_j,Y_j) \prod_{j=M}^{n} \mu_2(0,Y_j)}$$

and (A_3) implies that the denominator in V_n remains bounded on the set $[Y_n \to \infty]$; consequently $P\{Y_n \to \infty\} = 0$. □

Denoting by $\xi(r,\ell)$ and $\eta(r,\ell)$ the random variables with pgf's respectively $g_1(u;r,\ell)$ and $g_2(u;r,\ell)$ we have also the following bivariate analogue of Theorem 11.

<u>THEOREM 13</u>. <u>Assume that there exist strictly increasing sequences</u> $\{K_n\}$ <u>and</u> $\{L_n\}$ <u>of positive integers such that for</u> $j=1,2,\ldots$

(5.26) $$r\mu_1(r,\ell) > K_j,\ \ell\mu_2(r,\ell) > L_j$$

for all $r \geq K_{j-1}$, $\ell \geq L_{j-1}$. Moreover, assume that there exist sequences $\Lambda = \{\lambda_r\}$ and $\Lambda' = \{\lambda'_r\}$ with $0 < \lambda_r \leq 1$, $0 < \lambda'_r \leq 1$, such that

(5.27) $$\sum_{j=1}^{\infty} D^*(j,\Lambda,\Lambda') < \infty$$

where

(5.28) $$D^*(j,\Lambda,\Lambda') = \sup_{\substack{r \geq K_{j-1} \\ \ell \geq L_{j-1}}} \left\{ c(\lambda_r) \frac{rE|\xi(r,\ell)-\mu_1(r,\ell)|^{1+\lambda_r}}{[r\mu_1(r,\ell)-K_j]^{1+\lambda_r}} + c(\lambda'_\ell) \frac{\ell E|\eta(r,\ell)-\mu_2(r,\ell)|^{1+\lambda'_\ell}}{[\ell\mu_2(r,\ell)-L_j]^{1+\lambda'_\ell}} \right\}$$

Then $P\{X_k \to \infty, Y_k \to \infty | X_0=K_0, Y_0=L_0\} > 0$.

We omit the proof, as it follows closely the lines of the proof of Theorem 11.

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