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GENERALIZED BARTOSZYŃSKI'S VIRUS MODEL†

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ABSTRACT

A new stochastic process is introduced for describing a mechanism of viruses. The process generalizes the Bartoszyński's process (Bartoszyński, 1975a, 1975b, 1976) by allowing the stochastic perturbation between consecutive jumps to take into account the persistent infection (the infection without breaking infected cells). It is shown that the new process can be obtained by a weak limit of a sequence of Markov branching processes. Along with the construction of the new process, we study how the stochastic perturbation influences the risk of a symptom in an infected host. For this purpose, the quantal response model and the threshold model are investigated and compared through their induced survival functions.

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1. INTRODUCTION

Bartoszyński (1975a, 1975b, 1976) presented the following model describing the growth of rabies virus in a human host after infection by a rabid animal. Let $X(t)$ be the amount of virus at time t with $X(0) = z$.

(i) $X(t)$ increases by jumps at times $T_1, T_2, \ldots$ by amounts $Y_1, Y_2, \ldots$ which are *iid* with d.f. H.

(ii) Let $N(t)$ be the number of jumps until the time t. Then

$$X(t) = \begin{cases} ze^{-ct}, & \text{if } N(t) = 0, \\ ze^{-ct} + \sum_{j=1}^{N(t)} Y_j e^{-c(t-T_j)}, & \text{if } N(t) > 0. \end{cases}$$

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(iii) $\Pr(\text{jump in}(t, t+h) \mid X(t)) = ahX(t) + o(h)$.

The biological background of the process is as follows. Once viruses enter a susceptible host, they enter a cell and produce within it a certain number of copies of itself, eventually causing the cell to break and spill its contents. At the same time, the presence of the virus in the organism causes the production of antibodies, which in turn destroy the viruses. In the model, $X(0) = z$ is the initial amount of the virus in the organism and the exponential decrease between jumps corresponds the destruction of the viruses by the antibodies. Each jump corresponds to the cell breaking due to the copies of viruses inside it and the size of jump represents the number of copies of viruses coming from the broken cell. That the intensity of jump is proportional to the amount of the virus can be interpreted as "the more the viruses, the more cells invaded, and consequently broken."

Although Bartoszyński introduced the above model specifically for rabies virus, its formulations appear general enough for the description of any virus within any organism (Trajstman and Tweedie, 1982). However, in the B-process (Bartoszyński's process), viruses are able to give birth to their offsprings only by destroying infected cells. The inevitable destruction of the host cell is not the only outcome of viral infection. Many viruses enter into a host-parasite relationship that allows them to be carried and released for long periods without lysis (Ross, 1986). In this paper, a new process called a *generalized B-process* is introduced to take into account the slow releasing of offsprings (called the persistent infection) by adding a stochastic perturbation to the deterministic decrease between two consecutive jumps in the B-process, which results from the combination of the gradual death of viruses by antibodies and the slow birth of viruses by the persistent infection. The relation between the stochastic perturbation and the persistent infection can be best described by showing that the generalized B-process can be obtained by a weak limit of a sequence of certain Markov branching processes which model the persistent infection in a natural way. See Section 3 for details.

Along with the process itself, we study a mechanism of how viruses cause a symptom to an infected host. A symptom might be the death of the host for rabies virus, some physical responses such asthma-like symptom for influenza virus, or the proliferation of infected cells resulting in tumors. Generally, there are two mechanisms widely used in practice: the threshold model and the quantal response model. The threshold model assumes the existence of a threshold

and a symptom occurs as soon as the amount of the virus becomes greater than the threshold. The quantal response model assumes that the occurrence of the symptom is stochastically related to the amount of the virus. The idea of the quantal response model was originally introduced by LeCam replacing the threshold model and subsequently by Puri (1967) and Puri and Senturia (1972). While the threshold model is easy to understand and implement, there are several reasons that the quantal response model can replace the threshold model. First, the hypothesis of existence of a fixed threshold may not be strictly correct. Second, it is not clear what value one ought to choose for the threshold in a given situation, and third, the threshold hypothesis makes the algebra unnecessarily intractable due to the involvement of the first passage time problem. Kim (1998) compared the two mechanisms in the B-process by looking at the induced distributions of the survival time: the time elapsing between the first infection and the occurrence of a symptom on the host. In the present paper, we do the same comparison of the two mechanisms with the generalized B-process. Our main interests are on the influence of the stochastic perturbation on the risk of the symptom. One surprising result found in this paper is that the stochastic perturbation affect the risks of symptoms of the two model (the quantal response model and the threshold model) qualitatively differently. While the stochastic perturbation increases the risk in the quantal response model, the risk is reduced in the threshold model.

This paper is organized as follows. In Section 2, the generalized B-process is defined. In Section 3, it is shown that the generalized B-process can be obtained as a weak limit of a sequence of Markov branching processes. In Section 4, the two mechanisms of symptom - the quantal response model and the threshold model are studied with the generalized B-process. All proofs are in Appendix A at the end of the paper.

2. THE MODEL

Before presenting a formal definition of the generalized B-process, we give some informal discussion about how to construct the process. By the definition of the B-process $X(t)$, we have

$$X(t) = X(0)e^{-ct}$$

provided no jump until time t, which is equivalent to that between the lysis of infected cells, the process $X(t)$ satisfies a differential equation

$$dX(t) = -cX(t)dt. \tag{2.1}$$

To give stochastic perturbation, we can use a stochastic differential equation instead of (2.1). That is, (2.1) is replaced by

$$dX(t) = -cX(t) + \sigma(X(t))dW(t), \tag{2.2}$$

where W is a Wiener process. Suitable choice of $\sigma^2(x)$ would be $\sigma^2(x) = \sigma^2 x$ for some nonnegative constant σ^2 since it will make the process have a branching property. To sum up all the arguments, we can construct the generalized B-process as follows.

(i) $X(t)$ has jumps at the times $T_1, T_2 \ldots$ with amount $Y_1, Y_2, \ldots$.

(ii) For $t \in [T_n, T_{n+1})$, $X(t)$ satisfies a stochastic differential equation

$$dX(t) = -cX(t) + \sigma^2 X(t)dW(t). \tag{2.3}$$

(iii) $\Pr(\text{jump in}(t, t+h) \mid X(t)) = ahX(t) + o(h)$.

The above construction, even if it gives a clear view of how the process behaves, needs clarification of many mathematical details. First of all, the stochastic differential equation (2.3) should be defined in a consistent way since it is defined on the intervals between jumps which are random. Also the description of jump mechanism (iii) need more explanation since $X(t)$ is stochastic rather than deterministic. Furthermore, even after the above points are clarified, it is not immediately clear that such a process exists.

To avoid all the difficulties, we turn our attention to a (infinitesimal) generator of Markov process. It is well known that the solution of the stochastic differential equation (2.3) has a generator A on $C_0^2(R^+)$- twice continuously differentiable function with compact support- of the form

$$Af(x) = -cx\frac{\partial f(x)}{\partial x} + \frac{1}{2}\sigma^2 x\frac{\partial^2 f(x)}{\partial x^2}. \tag{2.4}$$

On the other hand, if $c = 0$ and $\sigma^2 = 0$ (*i.e.* no death of the virus), then the generator becomes

$$Af(x) = ax\int_0^\infty [f(x+y) - f(x)]dH(y) \tag{2.5}$$

for a bounded function f. Combining (2.4) and (2.5), now we define the generalized B-process as follows.

DEFINITION 2.1. *The generalized B-process is a nonnegative valued Markov process with the origin as an absorbing state such that the generator is*

$$Af(x) = -cx\frac{\partial f(x)}{\partial x} + \frac{1}{2}\sigma^2 x\frac{\partial^2 f(x)}{\partial x^2} + ax\int_0^\infty (f(x+y) - f(x))dH(y) \qquad (2.6)$$

and the domain of A contains $C_0^2(R^+)$.

THEOREM 2.1. *The generalized B-process is well defined on* $[0,\infty)$. *That is there exists a unique nonexplosive process whose generator is (2.6) provided* $\int_0^\infty xdH(x) < \infty$.

3. THE APPROXIMATION

To see how the process includes the idea of the persistent infection, consider a Markov branching process such that the branching rate is λ and the family size distribution is given by

$$p_0 I(Z=0) + p_2 I(Z=2) + (1-p_0-p_2)h(Z),$$

where Z is a number of offsprings and h is a certain probability mass function concentrated on the nonnegative integers greater than 2. Here p_0 is the probability of a virus being killed by antibodies and p_2 is the probability of a virus being born by the persistent infection and $h(z)$ is a probability mass function of the number of offsprings from the lysis infection. If $p_2 = 0$, then the process corresponds to the B-process. Actually Bühler and Keller (1985) showed that the B-process is obtained by a limit of such Markov branching processes. The main result of this section is to show that in case when $p_2 > 0$, the limit of such Markov processes is the generalized B-process.

Now, we define a Markov branching process $Z_n(t)$ with $Z(0) = nz$ such that the branching rate is λ_n and the family size distribution is given by $p_0^n = d_n/\lambda_n$, $p_2^n = \lambda_n^{-1}\{b_n + r_n(H(1/n) - H(0))\}$ and $p_k^n = r_n/\lambda_n(H(k/n) - H((k-1)/n))$ for $k \geq 2$ where $d_n = \sigma^2/2 + (c+a)/2n$, $b_n = \sigma^2 - (c+a)/2n$, $r_n = a/n^2$ and $\lambda_n = p_n + q_n + r_n$. Let $X_n(t) = Z_n(nt)/n$.

THEOREM 3.1. *The sequence of processes* $\{X_n(t)\}$ *converges to the generalized B-process in the sense of convergence of the finite dimensional distribution. If* $\mathrm{E}(Z) < \infty$, *then the convergence also holds in* $D[0,\infty)$ *with the Skorohod topology.*

4. Mechanisms of Symptom

To define the quantal response model, we introduce a new stochastic process $Z(t)$ such that

$$Z(t) = \begin{cases} 1, & \text{if the symptom occurred before time } t, \\ 0, & \text{otherwise.} \end{cases}$$

The quantal response model can be described by

$$\Pr\{Z(t+h) = 1 | Z(t) = 0,\ X(t) = 0\} = \lambda h X(t) + o(h).$$

Let $S(t : z)$ be a survival function of an infected host with z being initial amount of viruses. Then it is easy to see that

$$S(t : z) = \mathrm{E}\left\{\exp\left(-\lambda \int_0^t X(s)ds\right)\right\}.$$

Since the process is a branching process, we get

$$S(t : z) = \exp(-z\Psi(t)) \tag{4.1}$$

for some nonnegative nondecreasing function Ψ. The next theorem gives a differential equation for $\Psi(t)$.

THEOREM 4.1. *$\Psi(t)$ is a solution of a differential equation*

$$\frac{d\Psi(t)}{dt} + c\Psi(t) + \frac{\sigma^2\Psi(t)^2}{2} - (a+\lambda) + a\phi(\Psi(t)) = 0 \tag{4.2}$$

with an initial condition $\Psi(0) = 0$ where

$$\phi(s) = \int_0^\infty e^{-sy} dH(y).$$

From Theorem 4.1, we see that $\Psi(t)$ satisfies

$$t = \int_0^{\Psi(t)} \frac{du}{a + \lambda - cu - \sigma^2 u^2/2 - a\phi(u)}. \tag{4.3}$$

Let $L(u) = a+\lambda-cu-\sigma^2u^2/2-a\phi(u)$. Then since $L(0) = \lambda > 0$ and $dL(u)/du < 0$, there exists a unique positive root w of $L(u) = 0$, and hence $\Psi(t) \to w$ as $t \to \infty$ and so $S(\infty : z) = \exp(-wz)$, which shows that the survival function

does not vanish eventually. Biologically, an infected host has positive chance of not developing any symptom at all.

In (4.3), we can see that as σ^2 increases, the denominator of the integrand decreases and so for fixed t, $\Psi(t)$ decreases. This observation means that the stochastic perturbation reduces the risk of the symptom in the quantal response model. Now, we wonder whether this surprising result can be applied to any other mechanisms. To see this, let us consider the threshold model, in which the symptom occurs as soon as the amount of the virus becomes larger than a given threshold. Even though no analytical result is available, the simulation result in Figure 4.1 shows that the risk of the symptom increases as σ^2 increases. So the conclusion is that an underlying mechanism of the symptom plays a crucial role for characterizing the qualitative nature of the risk of symptoms as well as quantitative properties. This contradicts the usual belief that a mechanism of symptoms only affects the survival function quantitatively. As mentioned in Introduction, the threshold model is popularly used for its conceptual simplicity and our results shows that this kind of conveniences may result in wrong conclusion. To sum up, choosing a mechanism should be done with great care.

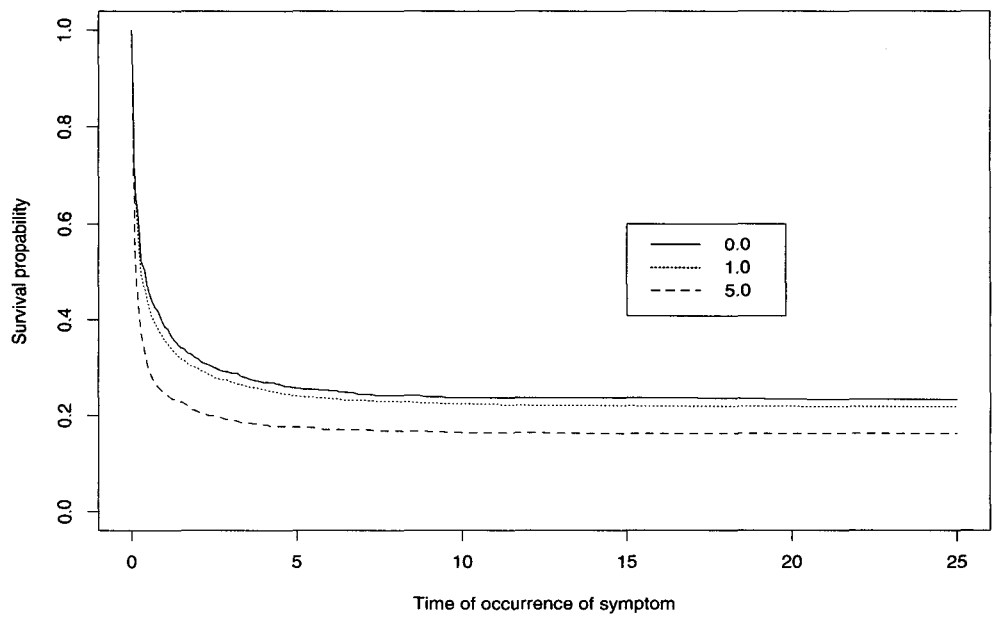

FIGURE 4.1 *Survival functions of the threshold model of the B-process with diffusion with various* σ^2.

APPENDIX

In this appendix, we present the proofs of the theorems in the paper.

First, we present a theorem, which plays a key role for the remains. The proof is in Lamperti (1967).

THEOREM A.1. *(Random time change)*

(i) Let $X(t)$ be a branching process. Define a random variable T and a stochastic process J by $T = \sup\{t : X(t) > 0\}$ and $J(t) = \int_0^t X(u)du$. Let $I(t)$ be the inverse process of $J(t)$ for $t < T$. Then the process $Y(t)$ defined by $Y(t) = X(I(t))$ for $t < T$ and $Y(t) = 0$ otherwise is a Lévy process with nonnegative jumps.

(ii) Conversely, let $Y(t)$ be a Lévy process with nonnegative jumps which has been stopped when (if) it reached 0 ($Y(0) > 0$). Assume that $\int_0^\infty 1/Y(u)du = \infty$ with probability 1. Define a process $I(t)$ by $I(t) = \int_0^t 1/Y(u)du$ and let $J(t)$ be an inverse process of $I(t)$. Then a process $X(t)$ defined by $X(t) = Y(J(t))$ is a branching process.

Proof of Theorem 2.1

Let $W(t)$ be a Wiener process with variance $\sigma^2 t$ and let $N(t)$ be a Poisson process with intensity a. Now we define a Lévy process $Y(t)$ by

$$Y(t) = -ct + W(t) + \sum_{i=1}^{N(t)} Y_i + z,$$

where Y_i's are *iid* random variables with a distribution function H. Then it is easy to see that the generator B of the process Y is

$$Bf(x) = -c\frac{\partial f(x)}{\partial x} + \frac{1}{2}\sigma^2\frac{\partial^2 f(x)}{\partial x^2} + a\int_0^\infty f(x+y) - f(x)dH(y).$$

Let $X(t)$ be a branching process obtained by the random time change of the Lévy process $Y(t)$. Then by Theorem 10.12 in Dynkin (1965), the generator of the process $X(t)$ is (2.6). When $\mathrm{E}(Y_i) < \infty$, then the law of large number implies that

$$\lim_{t\to\infty} \sum_{i=1}^{N(t)} \frac{Y_i}{N(t)} \to \mathrm{E}(Y_1)$$

with probability one. So the process $Y(t)$ is nonexplosive and so is $X(t)$.

The uniqueness holds trivially since the generator B generates a unique Markov process. □

Proof of Theorem 3.1

Since $X_n(t)$ is a branching process, the Lévy process $Y_n(t)$ obtained by the random time change has a Laplace transform (Lamperti, 1967; Silverstein, 1968) as

$$\mathrm{E}\Big[\exp\left(-u(Y_n(t)-Y_n(0))\right)\Big] = \exp\Big[n^2\lambda_n t(p_0^n e^{u/n}+p_1^n e^{-u/n}+\sum_{k=2}^{\infty} p_k^n e^{-ku/n}-1)\Big].$$

Expanding $\exp(x) = 1 + x + x^2/2 + o(x)$, we have

$$\begin{aligned}\mathrm{E}\left[\exp\left(-u(Y_n(t)-Y_n(0))\right)\right] &= \exp\Big[tn\lambda_n(p_0^n-p_2^n)u+\frac{t\lambda_n(p_0^n+p_2^n)u^2}{2} \\ &\quad + tn^2\lambda_n\sum_{k=1}^{\infty} e^{-uk/n}\Big(H\big(\frac{k}{n}\big)-H\big(\frac{k-1}{n}\big)\Big)+o(1)\Big] \\ &\to \exp\Big[cut+\frac{t\sigma^2u^2}{2}+at\Big(\int_0^{\infty} e^{-uy}dH(y)-1\Big)\Big],\end{aligned}$$

where the last term is the Laplace transform of the Lévy process obtained by the random time change of the generalized B-process. By the continuity of the random time change (Helland, 1978), the proof is done. □

Proof of Theorem 4.1

Let $\mathcal{F}_t = \sigma(X(u), u \le t)$ and $Y_t = \exp(-\lambda\int_0^t X(u)du)$. Further, let

$$\mathrm{E}^z(Y_t) = \mathrm{E}(Y_t|X(0)=z).$$

Since $S(t:z) = \mathrm{E}^z(Y_t)$, we have

$$
\begin{aligned}
&\left(\frac{1}{h}\right)\left[\mathrm{E}^z(S(t:X(h))) - S(t:z)\right] \\
&= \left(\frac{1}{h}\right)\mathrm{E}^z\left[\mathrm{E}^{X(h)}(Y_t) - \mathrm{E}^z(Y_t)\right] \\
&= \left(\frac{1}{h}\right)\mathrm{E}^z\left[\mathrm{E}^z\left(\exp(-\lambda\int_0^t X(u+h)du)|\mathcal{F}_h\right) - \mathrm{E}^z\left(\exp(-\lambda\int_0^t X(u)du)|\mathcal{F}_h\right)\right] \\
&= \left(\frac{1}{h}\right)\mathrm{E}^z\left[Y_{t+h}\exp(\lambda\int_0^h X(u)du) - Y_t\right] \\
&= \left(\frac{1}{h}\right)\mathrm{E}^z(Y_{t+h} - Y_t) + \left(\frac{1}{h}\right)\mathrm{E}^z\left[Y_{t+h}\left(\exp(\lambda\int_0^h X(u)du) - 1\right)\right] \\
&\to \frac{\partial}{\partial t}S(t:z) + \lambda z S(t:z) \qquad \text{(A.1)}
\end{aligned}
$$

because

$$
\left(\frac{1}{h}\right)Y_{t+h}\left(\exp(\lambda\int_0^h X(u)du) - 1\right) \to Y_t\lambda z
$$

pointwise boundedly. However, the generator (2.6) of the process implies that

$$
\begin{aligned}
&\left(\frac{1}{h}\right)\mathrm{E}^z\left[S(t:X(h)) - S(t:z)\right] \\
&\to -cz\frac{\partial S(t:z)}{\partial z} + \frac{1}{2}\sigma^2 z\frac{\partial^2 S(t:z)}{\partial z^2} \\
&\quad + az\int_0^\infty S(t:z+y) - S(t:z)dH(y). \qquad \text{(A.2)}
\end{aligned}
$$

Combining (A.1) and (A.2), we have

$$
\begin{aligned}
&-cz\frac{\partial S(t:z)}{\partial z} + \frac{1}{2}\sigma^2 z\frac{\partial^2 S(t:z)}{\partial z^2} + az\int_0^\infty S(t:z+y) - S(t:z)dH(y) \\
&= \frac{\partial S(t:z)}{\partial t} + \lambda z S(t:z). \qquad \text{(A.3)}
\end{aligned}
$$

Substituting (4.1) into (A.3), we obtain (4.2). □

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