A Quantal Response Process Associated with Integrals of certain Growth Processes.*,**

by

Prem S. Puri

Department of Statistics

Division of Mathematical Sciences

Mimeograph Series No. 205

September 1969

* This investigation was supported in part by research grant GM-10525 from the National Institute of Health, Public Health Service, at University of California at Berkeley.

** To appear in the proceedings of the symposium on "Mathematical Aspects of Life Sciences" held at Queen's University in June 1969.

A Quantal Response Process Associated with Integrals of certain Growth Processes.*,**

PREM S. PURI

Purdue University, West Lafayette, Indiana

1. Introduction.

This paper is a continuation to the results presented in an earlier paper of the author [4] and may be read in the sequel, although we shall attempt to make it as self contained as possible. The models considered in [4] involved the infecting particles which were assumed to be undergoing growth processes such as a birth and death process. Such is the case when these particles are self-reproducing in nature, such as bacteria, viruses, etc. The methods presented in this paper are not only applicable to such situations but also to those where the infecting material is not necessarily self-reproducing in nature, such as certain carcinogenic agents and toxic materials. As in [4], we shall be concerned with a growth process X(t) related to the infecting material, where, to begin with, the state space of the process is not necessarily the set of nonnegative integers; ~~but is assumed to be the nonnegative half of the real line~~. Also, we shall be concerned with experimental studies of quantal response to infection, where we shall have three factors in mind; the infecting material, the host and a well defined response, which the infecting material elicit from the host during the course of the experiment. At time t = o, a certain dose of the infecting material is injected into each of the n experimental hosts, which are then followed for their response. Let n(t) denote the number of hosts not responding by time t. The plot against t of n(t)/n is commonly known as the time dependent response curve. In [4], a class of stochastic models for response

---

* This investigation was supported in part by research grant GM-10525 from the National Institute of Health, Public Health Service, at University of California at Berkeley.

** To appear in the proceedings of the symposium on "Mathematical Aspects of Life Sciences" held at Queen's University in June 1969.

curves was introduced and studied in some detail. There, the reader may also find a brief survey of some of the earlier mathematical models related to such curves. Most of these models are based on a common hypothesis, namely the existence of a fixed threshold, so that as soon as the process X(t) touches this threshold the host responds. In [4], this hypothesis was abondoned in favor to a more appropriate hypothesis suggested by LeCam, namely that the state of the underlying growth process at any moment determines not the presence or the absence of response, but only the probability of response of the host. In contrast to this, the models based on a fixed threshold hypothesis, would be (in the present sense) deterministic in character.

One of the reasons that have lead some researchers to believe in the threshold hypothesis is the fact that in certain experimental studies, the observed number of infecting particles at death of the host showed no trend with the change in the injected dose (see Meynell and Meynell [3]). In [4], it was shown how such an observation can be explained easily even under the new model without relying on the threshold hypothesis (see also sec. 4.4). While under the threshold hypothesis, the state of the growth process of the infecting particles at the moment of response of the host is fixed by assumption, this same state is now a random variable under the new models. Thus, the study of the distributions of the response time and of the state of the process at the moment of response becomes quite relevant. The latter random variable has also been found to be of independent importance in certain experimental studies concerning bacteriophage reproduction (see Puri [6]). In this paper, a method, alternative to the one used in [4], for obtaining the distribution of these two random variables is presented. The method is then illustrated through applications to the situations involving different types of the underlying growth processes of the infecting particles. In each case, the distribution of the two random variables is obtained & studied. These results are presented here with the hope that some of these could easily serve as potential mathematical models applicable to variety of live situations arising specially in biological sciences.

2. A brief account of an earlier model.

For the sake of convenience, we name the response as death of the host. Let T denote the length of life of the host starting from t = o, the moment when the dose was injected. Then Pr $(T > t)$ treated as a function of time t is the theoretical counterpart of the response curve or alternatively the survival curve. Let X(t) denote the state of the growth process of the infecting material at time t, with X(0) equal to the initial dose injected. We now introduce another process Z(t) defined as

$$(1) \qquad Z(t) = \begin{cases} 1 & \text{if the host is alive at } t \\ 0 & \text{otherwise.} \end{cases}$$

Because of its very nature, we choose to call the process Z(t), the Quantal response process for the host.

In order to review some of the methods used in [4], we take this occassion to give a brief account of one of the models (model B) studied there. It was assumed there that the infecting particles are self-reproducing entities such as bacteria or viruses, and that X(t) is a linear time homogeneous birth and death process with birth and death rates λ and μ respectively. X(t) then denotes here the number of live particles at time t, with X(0)=m, the number of live particles injected at t = 0. The basic assumption that relates the processes Z(t) and X(t) is given by

$$(2) \quad \Pr\Big(Z(t+\tau) = 0 \mid Z(t) = 1, X(t) = x \Big) = f(x)\,\tau + o(\tau) .$$

The function f(x), in general called the risk function, is defined on the state space of the process X(t), is nonnegative and satisfies certain regularity conditions. Let

$$(3) \quad P_{x,1}(t) = \Pr\Big(Z(t) = 1, X(t) = x \mid X(0) = m, Z(0) = 1 \Big)$$

with

$$(4) \quad G_{X,1}(s;t) = \sum_{x=0}^{\infty} s^x P_{x,1}(t) = E\,(s^{X(t)} Z(t) \mid X(0) = m, Z(0) = 1) ,$$

defined for $|s| \leq 1$. Thus

$$(5) \quad \Pr(T > t) = \Pr\Big(Z(t) = 1\Big) = E\,Z(t) = G_{X,1}(1;t).$$

Following the standard argument, it was shown in [4] that the generating function (g.f.) G satisfies the partial differential equation

$$(6)\quad G_t = [\lambda s^2 - (\lambda + \mu)\, s + \mu]\, G_s - \sum_{x=0}^{\infty} s^x f(x)\, P_{x,1}(t)\ ,$$

with G_t and G_s denoting the partial derivatives of G with respect to t and s respectively. Here (6) is to be solved subject to the boundary condition

$$(7)\qquad G_{x,1}(s;0) = s^m .$$

Once (6) is solved for G, this yields using (5) the desired distribution of the response time T. However, as it stands, (6) is too general to lend itself to an easy solution, since f(x) is left unspecified. Following [4], we consider the simple case where $f(x) = \beta x$, with β being a positive constant. With this, (6) simplifies to yield

$$(8)\quad G_t = [\,\lambda s^2 - (\lambda+\mu+\beta)s + \mu]\ G_s .$$

The solution of (8) subject to (7) is easily obtained as

$$(9)\quad G_{X,1}(s;t \mid m) = \left[\frac{r_1\,(s-r_2) - r_2\,(s-r_1)\exp\{\,\lambda\,(r_1-r_2)\,t\,\}}{(s-r_2) - (s-r_1)\exp\{\,\lambda\,(r_1-r_2)\,t\,\}}\right]^m$$

where r_1 and r_2 are, with positive and negative signs, respectively

$$(10)\quad r_1,\ r_2 = \frac{1}{2\lambda}\left[(\lambda+\mu+\beta) \pm \{\,(\lambda+\mu+\beta)^2 - 4\mu\lambda\}^{\frac{1}{2}}\right] .$$

Since $(1-r_1)\,(1-r_2) = -\,\beta/\lambda < 0$, it is easy to see that

$$(11)\qquad 0 < r_2 < 1 < r_1 .$$

From (9), it easily follows that

$$(12)\quad \Pr\,(\,T = \infty\,) = \lim_{t\to\infty}\ \Pr\,(\,T > t) = \lim_{t\to\infty}\ G_{X,1}(\,1;t|m\,) = r_2^m\ ,$$

so that T is not a proper random variable.

Another problem that was solved in [4], was to obtain the distribution of the number X_T of particles at the moment T of death of the host, irrespect of what T is. The method that was adopted there is the following.

Let $t_1 > t$. Then it is easy to see that

$$(13) \quad \Pr\left(X(t) = k,\ T = t_1 \right) = - \frac{\partial}{\partial t_1} \Pr\left(X(t) = k,\ Z(t_1) = 1 \right),$$

from which it follows that

$$(14) \quad \Pr\left(X_T = k \mid T < \infty \right) = \frac{-1}{\Pr(T < \infty)} \int_0^\infty \left. \frac{\partial \Pr(X(t)=k,\ Z(t_1)=1}{\partial t_1} \right|_{t_1 = t} dt .$$

Now if

$$(15) \quad G_{X,1}(u;t,t_1) = \sum_{k=o}^{\infty} u^k \Pr\left(X(t) = k,\ Z(t_1) = 1 \right),$$

and

$$(16) \quad H(u \mid T < \infty) = \sum_{k=o}^{\infty} u^k \Pr(X_T = k \mid T < \infty),$$

each defined for $|u| \leq 1$, then (14) yields

$$(17) \quad H(u \mid T < \infty) = - \frac{1}{\Pr(T < \infty)} \int_0^\infty \frac{\partial}{\partial t} \left. g_{X,1}(u;\ t,\ t_1) \right|_{t_1 = t} dt .$$

The expression for $g_{X,1}(u;\ t,\ t_1)$ can be obtained from $G_{X,1}(u;\ t)$ with a little effort. Using this, (16) gives the desired distribution of X_T. The final expression for (16) in the present case turns out to be

$$(18) \quad H(u \mid T < \infty) = \frac{(1-r_1)\ (1-r_2)\ u\ (u^m - r_2^m)}{(u-r_1)\ (u-r_2)\ (1 - r_2^m)} .$$

In the next section, we shall give an alternative approach to finding the distributions of both T and X_T. This approach appears simple and is more revealing. A flavour of this approach, the reader may already find in [4] (section 4), although there it was not pressed too far.

We close this section with the remark that besides the above model with $f(x) = \beta x$, another model was also considered in some details in [4], where the risk function f depended not only on $X(t)$ but also on its integral $Y(t) = \int_0^t X(\tau)\, dt$. The integral $Y(t)$ represents the total time lived by all the live bacteria during the time interval $(0,t)$ and as such is contemplated as a measure of the amount of toxins produced by the live bacteria during $(0,t)$, assuming of course, that the rate of toxin excretion is constant per bacterium per unit time. We shall demonstrate through the approach presented in the next section, that integrals such as $Y(t)$ arise very naturally while studying the problem of response time distribution, without even making the risk function f depend on such integrals. In effect, it turns out that the study of the distribution of T is equivalent to studying the distribution of a certain related integral.

3. An alternative approach via the distribution of an integral of the growth process:

We shall introduce the approach in maximum possible generality. Let $\underset{\sim}{X}'(t) = \left(X_1(t),\ldots, X_k(t)\right)$ be some vector valued growth process, with its state space $\mathcal{X}$ being a subset of the k-dimensional euclidean space. Let $Z(t)$ be the quantal response process as defined before, with

(19) $\Pr\left(Z(t+\tau) = 0 \mid Z(t) = 1, \underset{\sim}{X} = \underset{\sim}{x}\right) = f(\underset{\sim}{x},t)\,\tau + o(\tau)$

where it is assumed that the risk function $f(\underset{\sim}{x},t)$ is defined for every point $(\underset{\sim}{x},t)$ of the product set $\mathcal{X} \times [0,\infty)$, is measurable and is nonnegative. Furthermore, it is required that the risk function f be such that the integral $\int_0^t f\left(\underset{\sim}{X}(\tau,\omega), \tau\right) d\tau$ exists and is finite for every finite $t > 0$ and for almost every realisation ω of the process $\underset{\sim}{X}(t)$. Here $\underset{\sim}{X}(\tau,\omega)$ denotes the state of process $\underset{\sim}{X}(t)$ at time τ for a given sample path ω of the process. For a given ω, it can be easily shown using (19) and a standard argument that

(20) $$E(Z(t) \mid \omega) = \exp\left\{ - \int_0^t f(\underset{\sim}{X}(\tau,\omega), \tau)\, d\tau \right\}$$

Taking its expectation over all the realisations of the process $\left\{\underset{\sim}{X}(t)\right\}$, one immediately obtains

(21) $$P(T > t) = E\left(Z(t)\right) = E\left[\exp\left\{ - \int_0^t f\left(\underset{\sim}{X}(\tau), \tau\right) d\tau \right\} \right].$$

Thus the distribution of T can equivalently be obtained through a suitable transform such as Laplace transform or a characteristic function (c.f) of the distribution of the integral $\int_0^t f\left(\underset{\sim}{X}(\tau), \tau\right) d\tau$. By using the same argument, it is easy to establish that in the case of our model of section 2, the g.f. $G_{X,1}(s;t)$ of (4) is nothing but a transform of the joint distribution of X(t) and the integral $\int_0^t f\left(X(\tau)\right) d\tau$.

More exactly

$$(22)\quad G_{X,1}(s;t) = E\left(s^{X(t)}\, Z(t)\right) = E\left\{ s^{X(t)} \exp\left[- \int_0^t f\left(X(\tau)\right) d\tau\right]\right\} .$$

The word transform for the integral $\int_0^t f\left(X(\tau)\right) d\tau$ is used here rather loosely without loss of any generality for this can always be achieved by a slight modification of replacing the function f by v.f , where v plays the role of the dummy variable that appears in a Laplace transform. Thus while obtaining the distribution of T through the g.f G of (4), one obtains, as a bye-product, the joint distribution of X(t) and the integral $\int_0^t f\left(X(\tau)\right) d\tau$, without any extra cost.

The distribution of the state $\underset{\sim}{X}_T$ of the process $\underset{\sim}{X}(t)$ at the moment T of death of the host, can be obtained by using a similar argument. Since T, in general, may not be a proper random variable, let us redefine X_T conveniently as

$$(23)\qquad \underset{\sim}{X}_T = \begin{cases} \underset{\sim}{X}(t) & \text{if the host dies at } t \\ \underset{\sim}{X}(\infty) & \text{if it never dies.} \end{cases}$$

Then for a given realisation ω of the process $\left\{ \underset{\sim}{X}(t) \right\}$,

it can be easily shown that

$$(24)\quad E\left(\exp\left[i\,\underset{\sim}{u}'\,\underset{\sim}{X}_T\right] \mid \omega\right) = \int_0^\infty e^{i\,\underset{\sim}{u}'\,\underset{\sim}{X}(t,\omega)}\, e^{-\int_0^t f\left(\underset{\sim}{X}(\tau,\omega),\tau\right)d\tau}\, f\left(\underset{\sim}{X}(t,\omega),t\right) dt$$

$$+\; e^{i\,u'\,\underset{\sim}{X}(\infty,\omega)}\, e^{-\int_0^\infty f\left(\underset{\sim}{X}(\tau,\omega),\tau\right)d\tau} \quad .$$

Here $\underset{\sim}{u}' = (u_1,\ldots,u_k)$ is the dummy vector valued variable, needed to define the c.f. Taking expectation of (24) over all the realisations of the process $\left\{\underset{\sim}{X}(t)\right\}$ and interchanging the expectation and the integral sign on the right side of (24) by virtue of Fubini's theorem, we obtain

$$(25)\quad E\left(e^{i\,\underset{\sim}{u}'\underset{\sim}{X}_T}\right) = \int_0^\infty E\left\{\exp\left[iu'\underset{\sim}{X}(t) - \int_0^t f(\underset{\sim}{X}(\tau),\tau)\,d\tau\right].f(\underset{\sim}{X}(t),t)\right\} dt$$

$$+\; E\left\{ e^{i\,\underset{\sim}{u}'\,\underset{\sim}{X}(\infty)}\, e^{-\int_0^\infty f\left(\underset{\sim}{X}(\tau),\,\tau\right)d\tau} \right\} \quad .$$

From this we immediately have

$$(26)\quad E\left(e^{i\,\underset{\sim}{u}'\,\underset{\sim}{X}_T} \mid T<\infty\right) = \frac{1}{\Pr(T<\infty)} \int_0^\infty E\left\{\exp\left[iu'\underset{\sim}{X}(t) - \int_0^t f(\underset{\sim}{X}(\tau),\tau)\,d\tau\right].f(\underset{\sim}{X}(t),t)\right\}dt$$

In the next section, we shall illustrate the usefulness of the formulas (21) and (26) by applying these to situations with varying growth processes. In general, $\underset{\sim}{X}(t)$ may be a vector valued process. For instance, in [6], the author encountered a situation where in $\underset{\sim}{X}(t) = \left(X_1(t), X_2(t)\right)$, $X_1(t)$ represented a simple birth and death process, while $X_2(t)$ represented the total number of deaths occurring during $(0,t)$ for the process $X_1(t)$. In the examples of next section, however, we shall restrict ourselves to the case where the growth process is not vector valued, so that $\underset{\sim}{X}(t)$ is replaced by $X(t)$. Furthermore, unless otherwise stated, it will be assumed that $f(x,t) = \beta x$, for convenience. More sophisticated integrals will naturally arise if one bends upon taking more complicated forms of the risk function f. The distribution problems of such integrals have been studied by Bartlett [1] and elsewhere by the author([5],[7],[8]).

4. Applications.

In this section we shall restrict ourselves to the case with $f(x,t) = \beta x$, so that the formulas (21) and (26) simplify to yield

$$E\,Z(t) = \varphi(0,t)\,, \tag{27}$$

and

$$E\left(e^{iuX_T} \mid T < \infty\right) = \frac{-i\beta}{P(T<\infty)} \int_0^\infty \frac{\partial \varphi(u,t)}{\partial u}\,dt\,, \tag{28}$$

where

$$\varphi(u,t) = E\left(e^{iuX(t)}\, e^{-\beta\int_0^t X(\tau)d\tau}\right). \tag{29}$$

In particular, if the state space of the process X(t) is the set of nonnegative integers, it is preferable to use g.f's instead of c.f's, so that

$$E\,Z(t) = G(1;t) = E\left(e^{-\beta\int_0^t X(\tau)d\tau}\right)\,, \tag{30}$$

and

$$E\left(s^{X_T} \mid T < \infty\right) = \frac{\beta s}{P(T<\infty)} \int_0^\infty G_s(s;t)\,dt\,, \tag{31}$$

where

$$G(s;t) = E\left(s^{X(t)}\, e^{-\beta\int_0^t X(\tau)\,d\tau}\right). \tag{32}$$

As expected, it is evident from (31) that $\Pr(X_T = 0 \mid T < \infty) = 0$.

In the following subsections, we present the results for the various well known growth processes where in each case the state space is the set of nonnegative integers. For each case, we first derive the transform

$$(33) \qquad \varphi(s,u;t) = E\left(s^{X(t)} e^{-u\int_0^t X(\tau)d\tau}\right).$$

Then using this, (30) and (31) we obtain the distributions of T and X_T.

<u>4.1 Poisson Process.</u> Let X(t) be a standard Poisson process with constant input parameter ν, with X(0) = 0. By using an argument similar to Puri [5], it can be easily shown that here the transform φ of (33) satisfies the integral equation

$$(34) \quad \varphi(s,u;t) = e^{-\nu t} + \nu s \int_0^t e^{-\nu\tau} e^{-(t-\tau)u} \varphi(s,u;t-\tau)\, d\tau .$$

This can be easily transformed into the differential equation

$$(35) \qquad \varphi_t = \nu \left(s e^{-ut} - 1\right) \varphi ,$$

which yields, subject to $\varphi(s,u;0) = 1$, the desired solution as

$$(36) \qquad \varphi(s,u;t) = \exp\left[-\nu t + \frac{\nu s}{u}\left(1 - e^{-ut}\right)\right]$$

Thus from (30) we have

$$(37) \quad P(T>t) = E\,Z(t) = \varphi(1,\beta;t) = \exp\left[-\nu t + \frac{\nu}{\beta}\left(1 - e^{-\beta t}\right)\right]$$

Clearly T is a proper random variable here. Again the equation (31) yields

$$(38) \quad E\left(s^{X_T}\right) = \beta s \int_0^\infty \frac{\partial\varphi(s,\beta;t)}{\partial s}\, dt$$

$$= \nu s \int_0^\infty \left(1-e^{-\beta t}\right) \exp\left[-\nu t + \frac{\nu}{\beta} s\left(1-e^{-\beta t}\right)\right] dt.$$

From this, it follows that for $k \geq 1$,

$$(39)\quad \Pr(X_T = k) = \frac{\nu\,(\nu/\beta)^{k-1}}{\Gamma(k)} \int_0^\infty e^{-\nu t}\,(1 - e^{-\beta t})^k\, dt$$

$$= \frac{\nu\,(\nu/\beta)^{k-1}}{\Gamma(k)} \sum_{r=o}^{k} \binom{k}{r} (\nu + r\beta)^{-1} .$$

For the case, where ν is time dependent, one can easily show that

$$(40)\quad \varphi\,(s,u;t) = \exp\left[-\int_0^t (1 - s\,e^{-u(t-\tau)})\;\nu\,(\tau)\,d\tau\right]$$

From this the analogues of (37) and (38) can be obtained in a straight forward manner.

Finally the above model can find its use, for instance, for the case, where the host (patient) faces events such as heart attacks or accidents according to a Poisson process and the problem is to study the distribution of the length of life of the host.

4.2 A Death Process with Immigration. Let $X(t)$ be a simple linear death process with immigration, with μ denoting as the constant nonnegative death rate, $\nu(t)$ the time dependent nonnegative rate of immigration. It is assumed that the function $\nu(t)$ is integrable over (o,t) for every $t \geq o$. Let $X(o) = m$. The case with $\nu(t) = 0$, corresponds to the simple death process without immigration, and is therefore a special case with $\lambda = 0$ of the simple birth and death process dealt with in section 2.

Thus with $\nu = 0$, $m = 1$, we can easily obtain that

$$(41)\quad E\left(s^{X(t)}\, e^{-u\int_0^t X(\tau)d\tau} \,\middle|\, \nu = 0,\, m = 1\right) = \varphi\,(s,u;t \mid \nu = 0,\, m = 1)$$

$$= \frac{\mu}{\mu + u} + \left(s - \frac{\mu}{\mu + u}\right) e^{-(\mu + u)t} .$$

On the other hand, for the case with $m = 0$ but $\nu(t) \geq 0$, an argument similar to the one used in ([7], [9]), leads to

$$(42)\quad E\left(s^{X(t)}\, e^{-u\int_0^t X(\tau)d\tau} \mid m = 0\right) = \exp\left\{ - \int_0^t \left[1 - \varphi(s,u;t-\tau \mid \nu = 0,\, m = 1)\right] \cdot \nu(\tau)\, d\tau \right\}$$

Now combining (41) and (42) while using the property of independent growth of the particles and the linearity property of the integral $\int_0^t X(\tau)d\tau$, we immediately obtain for the general case ,

$$(43)\quad \varphi\,(s,u;t) = \left[\varphi\,(s,u;t \mid \nu = 0,\, m = 1)\right]^m \cdot \exp\left\{ - \int_0^t \left[1 - \varphi\,(s,u;\, t-\tau \mid \nu = 0,\, m = 1)\right] \nu(\tau)\, d\tau \right\} ,$$

where φ on the right side is as given by (41).

Again since $P(T > t) = \varphi\,(1,\beta;t)$, it is evident from (41) and (42) that T is a proper random variable if and only if $\int_0^\infty \nu(\tau)\, d\tau = \infty$. In the event when $A = \int_0^\infty \nu(\tau)\, d\tau < \infty$, we have from (43),

$$(44)\quad Pr(T = \infty) = \left(\frac{\mu}{\mu + \beta}\right)^m \exp\left\{ - \frac{\beta}{\mu + \beta}\, A \right\} = \varphi\,(s,\beta;\infty) ,$$

where $\varphi\,(s,\beta;\infty) = \lim_{t \to \infty} \varphi\,(s,\beta;t)$.

with regards to the distribution of X_T, using (31) we have

$$(45)\quad E\left(s^{X_T} \mid T < \infty\right) = \frac{\beta s}{P(T < \infty)} \int_0^\infty \frac{\partial\, \varphi\,(s,\, \beta;\, t)}{\partial\, s}\, dt .$$

Unfortunately using the expression (43) for φ, (45) cannot be put in any reasonable closed form. On the other hand, note that $G_{X,1}\,(s;t)$ of (4) is same as $\varphi\,(s,\beta;t)$ as per equation (22). As such, occassionally a considerable simplification is achieved for the derivation of the expression (45) by using the forward Kolmogorov differential equation given by

(46) $G_t = (s-1)\,\nu(t)\,G + \left[\mu - (\beta+\mu)s\right] G_s$,

which is subject to the initial condition $G(s,\beta;0) = s^m$.

This yields

(47) $$G_s = \frac{1}{\mu - (\beta+\mu)\,s}\left[G_t - (s-1)\,\nu\,(t)\,G\right].$$

The right side of (47) is defined for $s \neq \frac{\mu}{\beta + \mu}$. It is sufficient, however, to obtain (45) for $s \neq \frac{\mu}{\beta + \mu}$, for when $s = \frac{\mu}{\beta + \mu}$, (45) can be easily obtained by a continuity argument. Thus for $s \neq \frac{\mu}{\beta + \mu}$, using (47) in (45), we have

(48) $$E\,(s^{X_T} \mid T<\infty) = \frac{\beta s}{\Pr(T<\infty)} \int_0^\infty \frac{1}{\mu - (\beta+\mu)\,s}\left\{G_\tau\,(s,\beta;\tau) - (s-1)\nu(\tau)\,.\,G(s,\beta;\tau)\right\} d\tau$$

$$= \frac{\beta s}{\Pr(T<\infty)}\left\{\frac{1}{\mu-(\beta+\mu)s}\right\}\left\{G(s,\beta,\infty)-s^m - (s-1)\,.\int_0^\infty \nu(\tau)G(s,\beta;\tau)\,d\tau\right\}$$

Using (44), this finally simplifies to

(49) $$E(s^{X_T} \mid T<\infty) = \frac{\beta s\left\{\left(\frac{\mu}{\mu+\beta}\right)^m e^{-\frac{\beta}{\mu+\beta}A} - s^m - (s-1)\int_0^\infty \nu(\tau)\;G(s,\beta;d\tau)d\tau\right\}}{\left\{\mu - (\beta+\mu)s\right\}\left\{1 - \left(\frac{\mu}{\mu+\beta}\right)^m e^{-\frac{\beta}{\mu+\beta}A}\right\}} ,$$

where $G(s,\beta;\tau)$ is same as $\varphi\,(s,\beta;\tau)$ given by (43). We observe that for the case with $\nu(\tau) = 0$, (49) simplifies to

(50) $$E\left(s^{X_T} \mid T<\infty\right) = \frac{\left(\frac{\beta}{\mu+\beta}\right)}{1-\left(\frac{\mu}{\mu+\beta}\right)^m} \cdot \frac{s^m - \left(\frac{\mu}{\mu+\beta}\right)^m}{\left(s-\frac{\mu}{\mu+\beta}\right)},$$

which yields a truncated geometric distribution for X_T given by the probabilities

(51) $$\Pr\left(X_T = k \mid T<\infty\right) = \frac{\frac{\beta}{\mu+\beta}}{1-\left(\frac{\mu}{\mu+\beta}\right)^m} \left(\frac{\mu}{\mu+\beta}\right)^{m-k}; \quad k=1,2,\ldots,m.$$

4.3 A simple Death Process with the risk function $f(x) = \beta(m-x)$.

Let $X(t)$ be a simple linear death process with constant death rate μ & with $X(0) = m$. This being a special case of Section 4.2 with $\nu(\tau) = 0$, we have from (41)

(52) $$\varphi(s,u;t) = \left[\left(\frac{\mu}{\mu+u}\right) + \left(s-\frac{\mu}{\mu+u}\right) e^{-(\mu+u)t}\right]^m.$$

Let the risk function for the death of the host be $f(x) = \beta(m-x)$. This particular risk function was found useful in building up a suitable stochastic model applicable to the survival of platelets in the human blood. The work pertaining to this, done in collaboration with Mr. C. Guillier, will be reported elsewhere. With this risk function, we have the expression for G of (22) as given by

(53) $$G_{X,1}(s;t) = e^{-\beta mt} E\left(s^{X(t)} e^{\beta\int_0^t X(\tau)d\tau}\right) = e^{-\beta mt}\varphi(s,-\beta;t).$$

Using (52) in (53), we obtain

(54) $$G_{X,1}(s;t) = \left[\left(\frac{\mu}{\mu+\beta}\right) e^{-\beta t} + \left(s-\frac{\mu}{\mu+\beta}\right) e^{-\mu t}\right]^m; \text{ for } \mu \neq \beta.$$

The case with $\mu = \beta$ is obtained by taking the limit of (54) as μ tends to β. Finally (54) yields

(55) $$P(T>t) = G(1,\beta;t) = \left[\left(\frac{\mu}{\mu-\beta}\right) e^{-\beta t} - \left(\frac{\beta}{\mu-\beta}\right) e^{-\mu t}\right]^m.$$

Clearly T is a proper random variable. Again, substituting (54) in (31), in a rather straightforward manner,

$$(56)\quad E(s^{X_T}) = \beta m \sum_{r=0}^{m} \binom{m}{r} \left(\frac{\mu}{\mu-\beta}\right)^{m-r} \left(s - \frac{\mu}{\mu-\beta}\right)^{r} \frac{1}{\mu+\beta(m-r)}$$

$$- \beta s m \sum_{r=0}^{m-1} \binom{m-1}{r} \left(\frac{\mu}{\mu-\beta}\right)^{m-1-r} \left(s - \frac{\mu}{\mu-\beta}\right)^{r} \frac{1}{\mu(r+1)+\beta(m-1-r)}$$

4.4 Time Homogeneous Markov Branching Processes.

Let $X(t)$, representing the number of particles alive at time t, be a time homogeneous Markov branching process as defined in Harris [2]. Let a positive constant b be the associated risk of death of a particle and let $h(s)$ be the g.f. of the probabilities p_k, $k = 0,2,3,\ldots$, with $\sum_{k=0}^{\infty} p_k = 1$, where p_k is the probability that a particle is replaced on death by k new particles. We assume that $h'(1) < \infty$. Let as before $f(x) = \beta x$ be the risk function for the death of the host and $X(0) = m$. Let

$$(57)\quad \Phi(s,\beta;t) = E\left(s^{X(t)} e^{-\beta \int_0^t X(\tau)d\tau} \mid m = 1\right).$$

Then, because of independent growth of the particles and the linearity property of the integral $\int_0^t X(\tau)d\tau$,

$$(58)\qquad G(s,\beta;t) = \left[\Phi(s,\beta;t)\right]^{m}.$$

It can be shown that Φ satisfies the forward Kolmogorov equation

(59) $\Phi_t = \left[b\, h\,(s) - (\beta + b)\, s \right] \Phi_s$;

which is subject to the initial condition $\Phi\,(s,\beta;0) = s$. Here Φ_t and Φ_s are the partial derivatives of Φ with respect to t and s respectively. It was shown in [8] that

(60) $$\lim_{t\to\infty} \Phi\,(s,\, \beta;\, t) = q\ ,$$

where q is the root lying between 0 and one of the equation

(61) $$h\,(u) = (1 + \frac{\beta}{b})\, u\ .$$

Here $q < 1$ if $\beta > 0$ or $\beta = 0$ and $h'\,(1) > 1$, and equal to one if $\beta = 0$ and $h'\,(1) \leq 1$. Let $\beta > 0$, so that

(62) $$\lim_{t\to\infty} G\,(s,\, \beta;\, t) = q^m$$

for all $|\, s\, | \leq 1$. Thus

(63) $$Pr\,(T = \infty) = \lim_{t\to\infty} G\,(1,\, \beta;\, t) = q^m$$

and hence T is not a proper random variable.

Again, for $s \neq q$, we have from (59)

(64) $$\Phi_s = \frac{\Phi_t}{b\, h\,(s) - (\beta + b)\, s}\ .$$

From (58) and (64) it follows that

(65) $$G_s = \frac{m \left[\Phi\,(s,\, \beta;\, t) \right]^{m-1} \cdot\ \Phi_t}{b\, h\,(s) - (\beta + b)\, s} \quad ;\ \text{for } s \neq q\ .$$

Thus we have from (31), for $s \neq q$,

$$(66) \quad E\left(s^{X_T} \mid T < \infty\right) = \frac{\beta s}{1 - q^m} \int_0^\infty \frac{m\left[\Phi(s, \beta; t)\right]^{m-1} \Phi_t}{b\,h(s) - (\beta + b)\,s}\, dt$$

$$= \frac{\beta s}{(1-q^m)\left[b\,h(s) - (\beta + b)\,s\right]} \cdot \int_0^\infty G_t(s, \beta; t)\, dt$$

$$= \frac{\beta s \;(q^m - s^m)}{(1-q^m)\left[b\,h(s) - (\beta + b)\,s\right]} ,$$

where in the end we have used (62) and the fact that $G(s, \beta; 0) = s^m$. Since, being a probability generating function (p.g.f.) (66) is continuous in s, its expression for $s = q$ can easily be found by its continuity. Thus (66) gives the desired p.g.f. of X_T. Also, in the above, we have demonstrated as to how the Kolmogorov forward differential equation for G helps in getting the expression for the p.g.f. of X_T, without even obtaining first the explicit expression for G.

Let $h''(1) < \infty$. Then from (66) we immediately have

$$(67) \quad EX_T = \frac{m}{1 - q^m} + \frac{h'(1) - 1}{(\beta/b)} ,$$

$$(68) \quad \text{Var}\, X_T = \frac{(1 - h'(1))^2}{(\beta/b)^2} + \frac{b}{\beta}\left[h''(1) + (1 - h'(1))\right] - \frac{m^2 q^m}{1-q^m} .$$

In certain experimental situations (see Meynell & Meynell [3])the observed number of particles at death is of the order of 10^9. Furthermore, it is observed that this number stays about the same <u>on the average</u> without regards to the initial dose m of particles injected into the host at $t = 0$. From this fact and (67), it follows that in such situations we must have $h'(1) > 1$ and that β is considerably small, but positive. This suggests that one could approximate the distribution of T for small β, valid for such practical situations. Thus using (66) we obtain

(69) $$\lim_{\beta \to 0} \; E\left(e^{iu\beta X_T} \mid T<\infty,\, X(0)=m\right) = \left[1-iwb(h'(1)-1)\right]^{-1} .$$

From this, it follows that for small β ,

(70) $$X_T \approx \frac{h'(1)-1}{2} \frac{b}{\beta} \chi_2^2 .$$

The approximation (70) is only in law. The fact that this approximation is independent of the initial dose m, is quite compatible with the observations made by Meynell and Meynell [3]. This fact was observed once before in [4], where the underlying growth process was a simple linear birth and death process. We now have shown that a similar result holds even for the more general case of branching processes. Once again this also shows that the observation made by Meynell & Meynell [3] can be explained by the above theory without relying on the hypothesis of existence of a fixed threshold.

In the closing we remark that formulas analogous to (21) and (26) have also been obtained and studied for the case where the (time) parameter set of the process is a discrete one, unlike the cases considered here where it is continuous. These results, however, will be reported elsewhere.

REFERENCES

[1] Bartlett, M.S. (1961), "Equations for stochastic path integrals", Proc. Camb. Phil. Soc., 57, 3, pp 568-73.

[2] Harris, T.E. (1963) The theory of branching processes, Springer-Verlag, Berlin

[3] Meynell, G.G. and Meynell, E.W. (1958) "The growth of microorganisms in vivo with particular reference to the relation between dose and latent period", J. Hyg. Camb., 56, pp 323-346.

[4] Puri, Prem S. (1966a), "A class of stochastic models of response to injection of virulent bacteria in the absence of defense mechanisu", Proceedings of fifth Berkeley Symposium on Mathematical Statistics and Probability, 4, pp. 511-535.

[5] Puri, Prem S. (1966b), "On the homogeneous birth-and-death process and its integral", Biometrika, 53, pp 61-71.

[6] Puri, Prem S. (1969), "Some new results in the mathematical theory of phage-reproduction", J. Appl. Prob. (in Press).

[7] Puri, Prem S. (1968), "Some further results on the birth-and-death process and its integral", Proc. Camb. Phil. Soc., 64, pp 141-154.

[8] Puri, Prem S. (1969), "Some limit theorems on branching processes and certain related processes", SANKHYĀ, Series A, 31, Pt 1, pp 57-74.

[9] Puri, Prem S. (1967). "Some limit theorems on branching processes related to development of biological populations", J. Math. Biosciences, 1, pp 77-94.