

On the Distribution of the State of a Process at
the Moment of a Quantal Response

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Mimeograph Series #280

•April 1972

*Part of these results were presented at a Symposium on "Mathematical Aspects of Life Sciences" held in summer 1969 at Queen's University, Canada. This investigation was supported in part by Research Grant GM-10525 from the National Institute of Health, Public Health Service, at University of California, Berkeley.

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1. INTRODUCTION AND THE METHOD. For time dependent response curves, two types of models have been considered in literature; those that depend on a threshold hypothesis (See Gani [1], Gart [2], Wiggins [13], Williams [14]) and the others which do not (See Puri [6], [8]). While the number of the organisms at the moment of response in the first type is fixed, nonrandom and is equal to the threshold, this same number in the second type of models is a random quantity (See [6]). Thus the distribution of the number of organisms X_T at the response moment T becomes relevant for these later type of models. Again, in a model connected with Phage-reproduction, where the response was the burst of the bacterium, the author was concerned (See [8]) with the joint distribution of the numbers X_{1T} and X_{2T} of the vegetative and mature phages released at the burst. Both in [6] and [8], the methods adopted for obtaining such distributions were unfortunately too lengthy. More recently, other authors (See for example Srinivasan and Rangan [12]) have also adopted the same lengthy methods for this purpose in similar situations. We shall present below a much simpler approach for obtaining such distributions. This approach was inspired by the methods used by the author elsewhere (See [9], [10], [11]). Later we shall demonstrate the effectiveness of the method through two applications.

Let $X(t)$ with state space \mathcal{X} , be some possibly vector-valued continuous time stochastic process, defined on a suitable underlying probability space $(\Omega, \mathcal{A}, \mathcal{P})$. Let $f(x, t)$ be a nonnegative real valued (measurable) function defined

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for every point (x, t) of the product set $\mathcal{X} \times [0, \infty)$. Let this function be such that the integral $\int_0^t f(\underline{X}(\tau, \omega), \tau) d\tau$ exists and is finite for every $t > 0$ and for almost every realization ω of the process $\underline{X}(t)$. Here $\underline{X}(\tau, \omega)$ denotes the state of the process $\underline{X}(t)$ at time τ for a given sample path ω of the process. We now introduce the quantal response process $Y(t)$ as $Y(t)=1$, if the response has not occurred until time t and is equal to zero otherwise, where

$$(1) \quad P(Y(t+\tau)=0 | Y(t)=1, \underline{X}(t)=\underline{x}) = f(\underline{x}, t)\tau + o(\tau),$$

and $Z(0)=1$. It is assumed that the quantal response process $Y(t)$ does not influence the process $\underline{X}(t)$ in any way, rather as is evident from (1), is influenced itself by the process $\underline{X}(t)$. Also the state 'zero' is an absorption state for the process $Y(t)$. Thus for a given realization ω of the process $\underline{X}(t)$, it can be easily shown using (1) and a standard argument that

$$(2) \quad P(Y(t)=1 | \omega) = E(Y(t) | \omega) = P(T > t | \omega) = \exp\{-\int_0^t f(\underline{X}(\tau, \omega), \tau) d\tau\},$$

where T denotes the response time. From (2) it easily follows that

$$(3) \quad E(Y(t) \exp\{i \underline{u}' \underline{X}(t)\}) = E(\exp\{i \underline{u}' \underline{X}(t) - \int_0^t f(\underline{X}(\tau), \tau) d\tau\}),$$

where \underline{u} is the vector of real dummy variables. Without regards to where T falls, our main objective here is to find the distribution of the vector \underline{X}_T , denoting the state of the process $\underline{X}(t)$ at the moment T of response. Again, in general, the response time T may not be an honest random variable, so that we shall be interested in the conditional distribution of \underline{X}_T given that T is finite. As before, for a given realization ω of the process $\underline{X}(t)$, it can be easily shown that

$$(4) \quad E(I_T \cdot \exp\{i \underline{u}' \underline{X}_T\} | \omega) \\ = \int_0^\infty \exp\{i \underline{u}' \underline{X}(t, \omega) - \int_0^t f(\underline{X}(\tau, \omega), \tau) d\tau\} f(\underline{X}(t, \omega), t) dt,$$

where I_T denotes the indicator of the set $[T < \infty]$. Taking expectation of (4) over all the realizations of the process and interchanging the expectation and the integral sign on the right side of (4) by virtue of Fubini's theorem, we obtain

$$(5) \quad E(I_T \cdot \exp\{i \underline{u}' \underline{X}_T\}) = \int_0^\infty E[f(\underline{X}(t), t) \exp\{i \underline{u}' \underline{X}(t) - \int_0^t f(\underline{X}(\tau), \tau) d\tau\}] dt.$$

From this we immediately have the desired result

$$(6) \quad E(\exp\{i \underline{u}' \underline{X}_T\} | T < \infty) \\ = [P(T < \infty)]^{-1} \int_0^\infty E[f(\underline{X}(t), t) \exp\{i \underline{u}' \underline{X}(t) - \int_0^t f(\underline{X}(\tau), \tau) d\tau\}] dt,$$

where

$$(7) \quad P(T < \infty) = 1 - E[\exp\{-\int_0^\infty f(\underline{X}(\tau), \tau) d\tau\}].$$

The joint distribution of T and \underline{X}_T can be easily given in an analogous manner, by the transform

$$(8) \quad E[I_T \exp\{i \underline{u}' \underline{X}_T - \sigma T\}] \\ = \int_0^\infty \exp(-\sigma t) E[f(\underline{X}(t), t) \exp\{i \underline{u}' \underline{X}(t) - \int_0^t f(\underline{X}(\tau), \tau) d\tau\}] dt,$$

where $\text{Re}(\sigma) \geq 0$.

We shall be concerned below with the situations where we assume that $f(\underline{x}, t) = \underline{\theta}'(t) \cdot \underline{x}$, where $\underline{\theta}(t)$ is a vector of nonnegative functions. Also, in

our examples, the process $X(t)$ will be nonnegative integer valued, in which case (6) could be more conveniently written in terms of probability generating function (p.g.f.) as

$$\begin{aligned}
 (9) \quad & E\left(\prod_{i=1}^k s_i^{X_i(T)} \mid T < \infty\right) \\
 & = [P(T < \infty)]^{-1} \int_0^{\infty} E[\theta'(t) X(t) \left(\prod_{i=1}^k s_i^{X_i(t)}\right) \exp\{-\int_0^t \sum_{i=1}^k \theta_i(\tau) X_i(\tau) d\tau\}] dt \\
 & = [P(T < \infty)]^{-1} \sum_{i=1}^k s_i \int_0^{\infty} \theta_i(t) \frac{\partial G(s;t)}{\partial s_i} dt,
 \end{aligned}$$

where

$$(10) \quad G(s;t) = E\left[\prod_{i=1}^k \{s_i^{X_i(t)} \exp(-\int_0^t \theta_i(\tau) X_i(\tau) d\tau)\}\right],$$

and $|s_i| \leq 1, i = 1, 2, \dots, k$.

2. APPLICATIONS.

2.1. THE CASE OF TIME HOMOGENEOUS MARKOV BRANCHING PROCESSES.

In [6], the author considered a model where $X(t)$ was assumed to be a linear time homogeneous birth and death process. The method adopted there for computing the distribution of X_T was algebraically involved. Instead, the method introduced here is so convenient that even if $X(t)$ were a more general growth process such as a time homogeneous Markov branching process, it presents no additional difficulties in computing the transform (9) for $k=1$. This we shall now demonstrate. Let $X(t)$, representing the number of organisms at time t , be a time homogeneous Markov branching process as defined in Harris [3]. Let a positive constant b be the associated risk of death of an organism and let $h(s)$ be the p.g.f. of the probabilities $p_k, k=0, 2, 3, \dots$, with $\sum_{i=0}^{\infty} p_k = 1$, where p_k is the

probability that an organism is replaced on death by k new organisms. We assume that $h'(1) < \infty$. Let $f(x) = \theta x$ be the risk function for the response of the host and $X(0) = m$, where θ is a positive constant. Let

$$(11) \quad \phi(s, \theta; t) = E[s^{X(t)} \exp\{-\theta \int_0^t X(\tau) d\tau\} | m=1] .$$

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

$$(12) \quad G(s, t) = [\phi(s, \theta; t)]^m .$$

It can be shown that ϕ satisfies the forward Kolmogorov differential equation

$$(13) \quad \phi_t = [b h(s) - (\theta + b)s] \phi_s ,$$

which is subject to the initial condition $\phi(s, \theta; 0) = s$. Here ϕ_t and ϕ_s are the partial derivatives of ϕ with respect to t and s respectively. Again, it was shown in [7] that

$$(14) \quad \lim_{t \rightarrow \infty} \phi(s, \theta; t) = q ,$$

where q is the unique root, lying between zero and one, of the equation

$$(15) \quad h(u) = \left(1 + \frac{\theta}{b}\right) u .$$

Here $q < 1$ if either $\theta > 0$ or $\theta=0$ and $h'(1) > 1$, and $q=1$ if $\theta=0$ and $h'(1) \leq 1$.

Let $\theta > 0$, so that

$$(16) \quad \lim_{t \rightarrow \infty} G(s; t) = q^m ,$$

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

$$(17) \quad P(T=\infty) = \lim_{t \rightarrow \infty} G(1;t) = q^m,$$

and hence T is not a proper random variable. Again, for $s \neq q$, we have from (13)

$$(18) \quad \phi_s = [b h(s) - (\theta + b)s]^{-1} \cdot \phi_t.$$

From (12) and (18), it follows that

$$(19) \quad G_s = \frac{m[\phi(s, \theta; t)]^{m-1} \phi_t}{b h(s) - (\theta + b)s}; \text{ for } s \neq q.$$

Thus we have from (9) with $k=1$, and for $s \neq q$,

$$(20) \quad \begin{aligned} E(s^{X_T} | T < \infty) &= \frac{\theta s}{1-q^m} \int_0^\infty \frac{m[\phi(s, \theta; t)]^{m-1}}{b h(s) - (\theta + b)s} \cdot \phi_t dt \\ &= \frac{\theta s}{(1-q^m)[b h(s) - (\theta + b)s]} \int_0^\infty G_t(s; t) dt \\ &= \frac{\theta s (q^m - s^m)}{(1-q^m)[b h(s) - (\theta + b)s]}, \end{aligned}$$

where at the end we have used (16) and the fact that $G(s; 0) = s^m$. Since, being a p.g.f. (20) is continuous in s , its expression for $s=q$ can easily be found by its continuity. Thus (20) gives the desired p.g.f. of X_T . Also in the above analysis we have demonstrated how the Kolmogorov forward differential equation for ϕ helps in the present approach in getting the expression for the p.g.f. of X_T , without even obtaining first the explicit expression for ϕ .

Let $h''(1) < \infty$. Then from (20) we immediately have

$$(21) \quad E(X_T | T < \infty) = \frac{m}{1-q^m} + \frac{h'(1) - 1}{(\theta/b)},$$

$$(22) \quad \text{Var}(X_T | T < \infty) = \frac{(1-h'(1))^2}{(\theta/b)^2} + \frac{b}{\theta} [h''(1) + 1 - h'(1)] - \frac{m^2 q^m}{1-q^m}.$$

In certain experimental situations (See Meynell and Meynell [4]) the observed number of organisms at death (response) is of the order of 10^9 . Furthermore, it is observed that this number stays about the same on the average without regards to the initial dose m of organisms injected into the host at $t=0$. From this fact and (21), it follows that in such situations we must have $h'(1) > 1$ and that θ is considerably small but positive. This suggests that one could approximate the distribution of X_T for small θ , valid for such practical situations. Thus using (20) we obtain

$$(23) \quad \lim_{\theta \rightarrow 0} E[\exp\{iu\theta X_T\} | T < \infty, X(0)=m] = [1 - iu\theta(b(h'(1)-1))]^{-1}.$$

From this, it follows that for small θ ,

$$(24) \quad X_T \approx \frac{h'(1)-1}{2} \frac{b}{\theta} X_2^2.$$

The approximation (24) 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 [4]. This fact was observed once before in [6], where the underlying growth process was a 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 and Meynell [4] can be explained by the above theory without relying on the hypothesis of existence of a fixed threshold.

2.2. A PROBLEM CONNECTED WITH A MODEL OF PHAGE-REPRODUCTION.

In [8], the author studied a stochastic model for phage-reproduction in a bacterium. One of the problems that arose there was to find the joint distribution of the numbers of vegetative and mature phages released at the time

of lysis (bacterial burst). We consider only the following simplified version of the model for the sake of illustration here. Let us assume that the length of the eclipse period (See [1] and [8] for details) is negligible. (Alternatively we could consider the process conditional to the point of eclipse as our origin on the time scale). Let $X_1(t)$ and $X_2(t)$ denote the numbers of vegetative and mature phages at time t , respectively, with $X_1(0)=1$ and $X_2(0)=0$ as the initial conditions of the process. Let $X_1(t)$ be a linear nonhomogeneous birth and death process with $\lambda(t)$ and $\mu(t)$ as the time dependent birth and death rates. Since death corresponds to the conversion of a vegetative phage to a mature one, $X_2(t)$ represents the number of deaths that have occurred during $(0,t]$. As in [8], we assume that

$$(25) \quad P(Y(t+\Delta t)=0 | X_1(t)=x_1, X_2(t)=x_2, Y(t)=1) \\ = [b(t)x_1 + c(t)x_2] \Delta t + o(\Delta t),$$

where $b(t)$ and $c(t)$ are two given nonnegative functions, and where $Y(t)=1$ if lysis has occurred until time t , and is zero otherwise. Let

$$(26) \quad G(s_1, s_2; t) = E(s_1^{X_1(t)} s_2^{X_2(t)} \cdot Y(t)), \quad |s_i| \leq 1, \quad i=1,2.$$

It can be easily shown that the p.g.f. (26) satisfies the partial differential equation

$$(27) \quad G_t = [s_1^2 \lambda(t) - s_1(\lambda(t) + \mu(t) + b(t)) + s_2 \mu(t)] G_{s_1} - s_2 c(t) G_{s_2},$$

subject to the initial condition $G(s_1, s_2; 0) = s_1$, where G_t , G_{s_1} and G_{s_2} denote the corresponding partial derivatives of G . In [8], it was assumed that for all $t > 0$,

$$(28) \quad \frac{\mu(t)}{\lambda(t)} = \rho, \quad \frac{b(t)}{\lambda(t)} = \delta, \quad \frac{c(t)}{\lambda(t)} = \theta,$$

where ρ , δ and θ are nonnegative constants. While the assumption that the ratio $\mu(t)/\lambda(t)$ be a constant was based on certain experimental evidence (See Gani [1] and Ohlson [5]), the other ratios of (28) were assumed constant, only to enable us solve equation (27) more easily. Subject to (28) the equation (27) becomes

$$(29) \quad [\lambda(t)]^{-1} G_t - [s_1^2 - s_1(1+\rho+\delta) + \rho s_2] G_{s_1} + \theta s_2 G_{s_2} = 0.$$

The solution of (29) is given by (See Puri [8])

$$(30) \quad G(s_1, s_2; t) = \frac{1}{2}(1+\rho+\delta) + \frac{1}{2} \theta v \exp\{-\frac{1}{2} \theta t^*\} J_p'(\sqrt{v} \exp\{-\frac{1}{2} \theta t^*\}), \\ \cdot [J_p(\sqrt{v} \exp\{-\frac{1}{2} \theta t^*\})]^{-1} \\ + J_p^{-2}(\sqrt{v} \exp\{-\frac{1}{2} \theta t^*\}) \left[(s_1 - \frac{1}{2}(1+\rho+\delta)) J_p^2(v) - \frac{1}{2} \theta v J_p'(v) J_p(v) \right]^{-1} \\ - \int_0^{t^*} J_p^{-2}(\sqrt{v} \exp\{-\frac{1}{2} \theta u\}) du \Big]^{-1};$$

$J_p(w)$ is the Bessel function defined by

$$(31) \quad J_p(w) = \sum_{k=0}^{\infty} \frac{(-1)^k (w/2)^{2k+p}}{k! \Gamma(k+p+1)} ;$$

$J_p'(w)$ is the derivative of $J_p(w)$; $p = (1+\rho+\delta)/\theta$; $t^* = \int_0^t \lambda(u) du$, and $v = 2\sqrt{\rho s_2}/\theta$.

In [8], the joint distribution of the numbers X_{1T} and X_{2T} , respectively, of vegetative and mature phages released at burst, was obtained under the assumption that $c(t) \equiv 0$ or equivalently that $\theta = 0$. The general case with $\theta > 0$ was algebraically too involved to obtain the distribution while using the methods of [8]. The present method however appears to simplify the algebra considerably. We assume that $\int_0^{\infty} \lambda(u) du = \infty$, so that from (30) it follows that

$$(32) \quad P(T=\infty) = \lim_{t \rightarrow \infty} G(1,1;t) = 0.$$

Thus from (9) we have on using (28)

$$(33) \quad E(s_1^{X_{1T}} s_2^{X_{2T}}) = \delta s_1 \int_0^\infty \lambda(t) G_{s_1}(s_1, s_2; t) dt + \theta s_2 \int_0^\infty \lambda(t) G_{s_2}(s_1, s_2; t) dt.$$

Again on using (29) we equivalently can write

$$(34) \quad E(s_1^{X_{1T}} s_2^{X_{2T}}) = [s_1^2 - (1+\rho)s_1 + \rho s_2] \int_0^\infty \lambda(t) G_{s_1}(s_1, s_2; t) dt - \int_0^\infty G_t(s_1, s_2; t) dt.$$

On the other hand

$$(35) \quad \int_0^\infty G_t(s_1, s_2; t) dt = \lim_{t \rightarrow \infty} G(s_1, s_2; t) - G(s_1, s_2; 0) = -s_1,$$

and also using (30), straight forward calculations lead to

$$(36) \quad \int_0^\infty \lambda(t) G_{s_1}(s_1, s_2; t) dt = -J_p^2(v) \left\{ \left[s_1 - \frac{1+\rho+\delta}{2} \right] J_p^2(v) - \frac{1}{2} \theta v J_p'(v) J_p(v) \right\}^{-1}.$$

Substituting these in (34) immediately yields the desired result

$$(37) \quad E(s_1^{X_{1T}} s_2^{X_{2T}}) = s_1 + \frac{s_1^2 - (1+\rho)s_1 + \rho s_2}{\left[\frac{1+\rho+\delta}{2} - s_1 \right] + \frac{1}{2} \theta v [J_p'(v)/J_p(v)]}.$$

Finally, the lack of simplicity of (37) (as it involves Bessel functions) should help the reader appreciate the intensity of the prohibitive algebra that one would need to go through while using instead the methods of [6] and [8] to arrive at (37).

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