AN APPROXIMATE STOCHASTIC MODEL FOR PHAGE REPRODUCTION IN A BACTERIUM

J. GANI

(received 27 July 1961, revised 18 October 1961)

1. Introduction

The stochastic birth-death process considered in this paper provides an approximate model for phage reproduction in a bacterium. In a recent paper, Hershey [1] has discussed reproduction and recombination in phage crosses, and a deterministic model for the reproductive process has been the subject of a previous note by the author [2]. A very readable account of the process is given by Sanders [3] in his recent article, *"The life of viruses"*.

Consider a medium initially containing $N < \infty$ bacteria, which we may for simplicity assume to reproduce as a birth process with constant parameter. Into this medium is inserted one phage particle (or several), which immediately penetrates (infects) a bacterium, and proceeds to reproduce within it as a birth-death process with constant parameters $\lambda > \mu$. After a phage has invaded a bacterium, changes occur on the surface of the bacterium to prevent its penetration by further phages. Usually a single phage invades a bacterium, but towards the end of the infective process when the number of phages and bacteria are of the same order, there is a larger probability that a bacterium is infected by two or more phages simultaneously; in our model, this probability is taken to be negligible. The death of a phage corresponds in fact to its reaching maturity, after which it no longer reproduces. When a fixed number r (two to three hundred) of these mature phages have been produced, the bacterium, which is itself incapable of fission after infection by a phage, breaks open as it dies, releasing the phage offspring. Immature phages cannot attack bacteria, but the r mature phages immediately penetrate a further r uninfected bacteria; the phages reproduce faster than the bacteria, and this sequence of processes usually continues until the bacteria are all dead.

Let us now discuss the phage reproduction occurring in a single bacterium. We should like to find the distribution of time T_r up to the occurrence of the r-th death in an ordinary birth-death process: this is not in fact known. Assuming for the moment that the process continues indefinitely, without stopping when r mature phages are produced, it is possible to write the differential equations for the probabilities.

$$P_{ij}(t) = Pr\{i \text{ survivals and } j \text{ deaths in time } t\}$$

in the form

$$(1.1)\quad P'_{ij}(t) = (i-1)\lambda P_{i-1,j}(t) - i(\lambda+\mu)P_{ij}(t) + (i+1)\mu P_{i+1,j-1}(t)$$

for all values of $i, j = 0, 1, 2, \cdots$, with $P_{ij}(t)$ identically zero for $i = j = 0$, and i or $j < 0$.

If we further define the joint probability generating function (p.g.f.) $\phi(u, v, t)$ as

$$(1.2)\qquad \phi(u, v, t) = \sum_{i,j=0}^{\infty} P_{ij}(t)u^i v^j \quad (|u|, |v| \leqq 1),$$

the equations (1.1) lead to the partial differential equation

$$(1.3)\qquad \frac{\partial\phi}{\partial t} = \{\lambda u^2 - (\lambda+\mu)u + \mu v\}\frac{\partial\phi}{\partial u},$$

which, when $v = 1$, reduces to the well-known equation for the generating function of probabilities of survivals. The equation (1.3) can be solved: solutions have in fact been obtained for somewhat different but equivalent forms of it by Kendall [4] and Bartlett [5]. However, expansion of the p.g.f. is unwieldy, and it seems difficult to obtain the $P_{ij}(t)$ explicitly from it. A different approach using the Laplace transforms with respect to time

$$(1.4)\qquad q_{ij}(s) = \int_0^\infty e^{-st}P_{ij}(t)dt \quad (R(s) > 0)$$

leads to the relations

$$(1.5)\quad \{(\lambda+\mu)+s\}q_{10}(s) = 1 \quad \text{for} \quad i = 1, j = 0,$$

$$\{i(\lambda+\mu)+s\}q_{ij}(s) = (i-1)\lambda q_{i-1,j}(s) + (i+1)\mu q_{i+1,j-1}(s) \text{ for all other } i, j,$$

with $q_{ij}(s)$ identically zero for $i = j = 0$, and i or $j < 0$. These are again not readily solved.

2. An approximation to the birth-death process

It is natural at this point to approximate to the standard birth-death process by one for which it is possible to obtain the probabilities $P_{ij}(t)$ explicitly. Such a process is that where births occur in a non-homogeneous Poisson process, the probability of a birth in the interval $(t, t+\delta t)$ being

$$(2.1)\qquad \lambda e^{\alpha t}\delta t + o(\delta t)$$

https://doi.org/10.1017/S1446788700027476 Published online by Cambridge University Press

where $\alpha = \lambda - \mu > 0$ and $e^{\alpha t}$ is the mean number of survivals at time t in the standard birth-death process. The death process remains unchanged. We should now strictly refer to probabilities $P_{ij}(0, t)$ and the p.g.f., $\phi(u, v; 0, t)$, since the process is no longer homogeneous in time; for simplicity, however, we retain the notations $P_{ij}(t)$, $\phi(u, v, t)$ which are quite clear in this case.

The forward differential equations for these probabilities are now

$$(2.2) \quad P'_{ij}(t) = \lambda e^{\alpha t} P_{i-1,j}(t) - (\lambda e^{\alpha t} + i\mu) P_{ij}(t) + (i+1)\mu P_{i+1,j-1}(t)$$

for all values of $i, j = 0, 1, 2, \cdots$, with $P_{ij}(t)$ identically zero for $i = j = 0$ and i or $j < 0$. The joint p.g.f., $\phi(u, v, t)$, satisfies the equation

$$(2.3) \qquad \frac{\partial \phi}{\partial t} + \mu(u - v) \frac{\partial \phi}{\partial u} = \lambda e^{\alpha t}(u - 1)\phi,$$

which we proceed to solve. If we perform the transformation $T = (u - v)e^{-\mu t}$ leaving u, v unchanged, and write

$$F(u, v, T) = \phi(u, v, t)$$

we obtain from (2.3) that

$$(2.4) \qquad \frac{\partial F}{\partial u} = \frac{\lambda}{\mu}(u-1)(u-v)^{(\alpha/\mu)-1} T^{-\alpha/\mu} F(u, v, T).$$

The solution to this equation is of the form

$$(2.5) \quad \begin{aligned} F(u, v, T) &= \left\{\exp \frac{\lambda}{\mu} T^{-\alpha/\mu} \int_{u_0}^{u} (x-1)(x-v)^{(\alpha/\mu)-1} dx \right\} f(v, T) \\ &= \left\{\exp T^{-\alpha/\mu} \left[(u-v)^{\lambda/\mu} + \frac{\lambda}{\alpha}(v-1)(u-v)^{\alpha/\mu} - A \right]\right\} f(v, T) \end{aligned}$$

where A is a function of v which later vanishes. Rewriting this as $\phi(u, v, t)$, we find that

$$(2.6) \quad \phi(u, v, t) = \left\{\exp e^{\alpha t} \left[(u-v) + \frac{\lambda}{\alpha}(v-1) - A(u-v)^{-\alpha/\mu} \right]\right\} f(v, (u-v)e^{-\mu t})$$

The initial condition $P_{10}(0) = 1$ results in

$$(2.7) \quad \phi(u, v, 0) = u = \left\{\exp \left[(u-v) + \frac{\lambda}{\alpha}(v-1) - A(u-v)^{-\alpha/\mu} \right]\right\} f(v, u-v)$$

whence it follows that

$$(2.8) \qquad f(v, T) = (T + v) \exp -\left\{ T + \frac{\lambda}{\alpha}(v-1) - A T^{-\alpha/\mu} \right\}.$$

Thus $\phi(u, v, t)$ can finally be written as

$$\phi(u,v,t) = \{v + (u-v)e^{-\mu t}\} \exp\Big\{e^{\alpha t}\Big[(u-v) + \frac{\lambda}{\alpha}(v-1) - A(u-v)^{-\alpha/\mu}\Big]$$

$$- \Big[(u-v)e^{-\mu t} + \frac{\lambda}{\alpha}(v-1) - A(u-v)^{-\alpha/\mu}e^{\alpha t}\Big]\Big\}$$

$$= \{ue^{-\mu t} + v(1-e^{-\mu t})\} \exp\Big\{-\frac{\lambda}{\alpha}(e^{\alpha t}-1)$$

$$(2.9) \qquad + u(e^{\alpha t} - e^{-\mu t}) + v\Big[\frac{\lambda}{\alpha}(e^{\alpha t}-1) - (e^{\alpha t} - e^{-\mu t})\Big]\Big\}$$

$$= \{ue^{-\mu t} + v(1-e^{-\mu t})\} \exp\{-\rho(t) + uA(t) + v[\rho(t) - A(t)]\}$$

$$= e^{-\rho(t)}\Big\{\sum_{i=0}^{\infty}\sum_{j=0}^{\infty} u^i v^{j+1}(1-e^{-\mu t}) \frac{A^i}{i!} \frac{(\rho - A)^j}{j!}$$

$$+ \sum_{i=0}^{\infty}\sum_{j=0}^{\infty} u^{i+1} v^j e^{-\mu t} \frac{A^i}{i!} \frac{(\rho - A)^j}{j!}\Big\}$$

where for $t > 0$, $\rho(t) = (\lambda/\alpha)(e^{\alpha t} - 1) > 0$, $A(t) = e^{\alpha t} - e^{-\mu t} = (1 + \alpha\rho/\lambda)^{-\mu/\alpha}\{(1+\alpha\rho/\lambda)^{\lambda/\alpha} - 1\} > 0$, and it is easily shown that $\rho(t) - A(t) > 0$.

The p.g.f. for the probabilities of survivals, is given by

$$(2.10) \qquad \phi(u, 1, t) = \{ue^{-\mu t} + (1-e^{-\mu t})\}e^{-A(t)(1-u)},$$

while that for the probabilities of deaths is

$$(2.11) \qquad \phi(1, v, t) = \{v(1-e^{-\mu t}) + e^{-\mu t}\}e^{-\{\rho(t)-A(t)\}(1-v)}.$$

3. Explicit probabilities of births, survivals and deaths

For the birth-death process continuing indefinitely, without stopping when r mature phages have been produced, it follows from (2.9) directly that the probabilities $P_{ij}(t)$ are

$$P_{0j}(t) = e^{-\rho(t)}(1-e^{-\mu t}) \frac{\{\rho(t) - A(t)\}^{j-1}}{(j-1)!} \qquad (j \geqq 1)$$

$$(3.1) \quad P_{i0}(t) = e^{-\rho(t)-\mu t} \frac{\{A(t)\}^{i-1}}{(i-1)!} \qquad (i \geqq 1)$$

$$P_{ij}(t) = e^{-\rho(t)}\Big\{(1-e^{-\mu t})\frac{A^i}{i!}\frac{(\rho - A)^{j-1}}{(j-1)!} + e^{-\mu t}\frac{A^{i-1}}{(i-1)!}\frac{(\rho-A)^j}{j!}\Big\} (i,j \geqq 1)$$

Clearly the probability $B_k(t)$ of k births in time t is of the Poisson form

$$(3.2)\qquad \begin{aligned} B_k(t) &= \exp\{-\int_0^t \lambda e^{\alpha\tau}d\tau\}\{\int_0^t \lambda e^{\alpha\tau}d\tau\}^k/k! \\ &= e^{-\rho(t)}\{\rho(t)\}^k/k! \qquad (k \geqq 0), \end{aligned}$$

the mean number of births in time t being $\rho(t)$. From (2.10), the probabilities $S_m(t)$ of m survivals after time t are

$$(3.3)\qquad \begin{aligned} S_0(t) &= (1-e^{-\mu t})e^{-\Lambda(t)} \\ S_m(t) &= e^{-\Lambda(t)}\left\{e^{-\mu t}\frac{\Lambda^{m-1}}{(m-1)!} + (1-e^{-\mu t})\frac{\Lambda^m}{m!}\right\} (m \geqq 1) \end{aligned}$$

It should be noted that the mean number of survivals after time t for this process is

$$(3.4)\qquad \frac{\partial}{\partial u}\phi(1, 1, t) = e^{\alpha t},$$

exactly as for the standard birth-death process, while its variance $e^{\alpha t}(1-e^{-(\lambda+\mu)t})$ is less than the variance $(\lambda+\mu)(\lambda-\mu)^{-1}e^{\alpha t}(e^{\alpha t}-1)$ of the standard process. Similarly from (2.11) the probabilities $D_r(t)$ of r deaths in time t are

$$(3.5)\qquad \begin{aligned} D_0(t) &= e^{-\mu t-\rho(t)+\Lambda(t)} \\ D_r(t) &= e^{-\{\rho(t)-\Lambda(t)\}}\left\{e^{-\mu t}\frac{(\rho-\Lambda)^r}{r!} + (1-e^{-\mu t})\frac{(\rho-\Lambda)^{r-1}}{(r-1)!}\right\} \ (r \geqq 1), \end{aligned}$$

and the mean number of deaths in time t is

$$(3.6)\qquad \frac{\partial}{\partial v}\phi(1, 1, t) = 1 - e^{\alpha t} + \rho(t) = \frac{\mu}{\alpha}(e^{\alpha t}-1).$$

Suppose the process now stops at the r-th death, the probability distribution of this death (or maturing of the r-th phage), which is improper since there is a non-zero probability that the process ends before, is given by

$$(3.7)\qquad \begin{aligned} g(t)dt &= \sum_{i=1}^{\infty} P_{i,r-1}(t)i\mu dt \\ &= \left\{\text{Term in } v^{r-1} \text{ of } \frac{\partial}{\partial u}\phi(1, v, t)\right\}\mu dt \\ &\doteq \{\text{Term in } v^{r-1} \text{ of } [e^{-\mu t}(1+\Lambda) + \Lambda v(1-e^{-\mu t})]e^{-(\rho-\Lambda)(1-v)}\}\mu dt \\ &= e^{-(\rho-\Lambda)}\left\{e^{-\mu t}(1+\Lambda)\frac{(\rho-\Lambda)^{r-1}}{(r-1)!} + \Lambda(1-e^{-\mu t})\frac{(\rho-\Lambda)^{r-2}}{(r-2)!}\right\}\mu dt \end{aligned}$$

We have thus constructed a birth-death process approximating to the original one, but for which each of the probabilities of births, deaths and survivals is explicitly known.

If the number of bacteria N is taken to be infinite, an equation for the distribution of the number infected up to time t (or the number of mature phages released up to t) can be obtained from Bellman and Harris' [6] theory of branching processes. If $Q_n(t)$ is the probability of n infected bacteria, and $\psi(s, t) = \sum_{n=1}^{\infty} Q_n(t)s^n$ the p.g.f. of this distribution, this satisfies the integral equation

$$\psi\{s, t) = s(1 - G(t)) + \int_0^t \{\psi(s, t-\tau)\}^r g(\tau)d\tau \tag{3.8}$$

where $g(t)dt$ is the improper probability distribution (3.7) and $G(t)$ the function $G(t) = \int_0^t g(\tau)d\tau$. There seems to be no simple way of solving this equation.

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Australian National University
Canberra, A.C.T., Australia.