Controlling a Lethal Growth Process*

by

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1. Introduction

The particles, referred to in this paper, may be diseased cells in a tumor, bacteria causing an infection or parasites infesting a vegetal or animal organism. In each case the carrier of a tumor, infection, etc., will be referred to as the "organism" or the "host".

We will assume that the number of particles grows in time according to a linear growth process and that the mortality rate of the host increases with the number of particles present.

Furthermore it will be possible to remove a random number of the particles by treatments, such as radiotherapy, chemotherapy, etc., but this benign effect will be counterbalanced by undesirable ones due to the toxicity of the treatments. These countereffects will impose limitations on the dosage and frequency of treatments.

Finally we specify the objectives of treatment and here we will make only a few choices from among many. In scheduling treatments and dosages we may try to maximize the expected (or average) lifetime of organisms under treatment. Alternatively we could try to maximize the probability of survival in a given interval (o,T) of time. Other objectives could be proposed; each one will lead to a different mathematical model so, for the sake of exposition, we must limit ourselves a few of the more "reasonable" ones.

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2. The Mathematical Model

a. The growth model.

We assume that at time $t = o$, there are N particles present.

If at any instant t of time there are n particles present, we assume that the probability that one new particle is born in $(t, t+dt)$ is given by $\lambda n\, dt$ and that this event depends only on the number of particles at time t. This assumption states that the (unrestricted) growth process of the particles is a Yule-Furry process. [1, p. 139]

The Yule-Furry process corresponds roughly to an "exponential" growth model, since regardless of anything else the expected number of particles at time t is given by

$$N e^{\lambda t} \tag{1}$$

and its variance by

$$N e^{\lambda t} (e^{\lambda t} - 1) \tag{2}$$

b. Assumptions on treatments

We assume that a treatment of a given dosage destroys particles with probability p and leaves them unaffected with probability $q = 1 - p$, according to a Bernouilli scheme with the number of trials equal to the number of particles present at the time of treatment.

Specifically, if there are n particles present at the time of treatment, then the probability that k, $o \leq k \leq n$ survive is given by:

$$p_k = \binom{n}{k} p^{n-k} q^k, \qquad o \leq k \leq n . \tag{3}$$

The probability p will depend on the dosage and on the type of particles. We assume that the therapist can choose the value of p, but that a high value of p is likely to destroy not only the particles, but the host as well. If we denote by $\Psi(p)$ the probability that the host survives a treatment with parameter p, then in general $\Psi(p)$ will be a decreasing function of p on the interval $[0,1]$, such that $\Psi(0) = 1$. We will assume that $\Psi(p)$ is known.

c. Lethality assumptions

We postulate that if the host is alive at time t, the probability that he dies during $(t, t+dt)$ depends only on the number of particles at time t and on the number, dosages and times, of treatments already received. Specifically we assume that the probability that an organism, which has n particles in it and has received already ν treatments has a probability

$$(4) \qquad \left[\sigma + \mu n + \theta(p_1,\ldots,p_\nu,\ t_1,\ldots,t_\nu)\right]dt$$

of dying in $(t, t+dt)$.

The quantity σ may be interpreted as the death rate of an uninfected individual. We will assume that σ is constant for the class of individuals considered, but it is easy to extend our results to the case where σ is a function of time.

The term μn expresses that the deathrate due to the disease is assumed to be proportional to the number of particles (e.g. to the volume of the tumor or the number of bacteria present).

The last term corresponds to the "long range" aftereffects of the earlier treatments and is hard to assess. In our further calculations we will make the following simplifying assumption: Since in practice the treatments will be roughly of equal dosage and more or less equal timelength a apart, we will assume that the last term reduces to

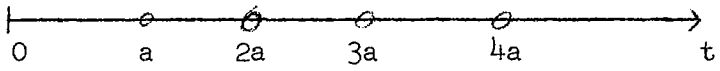
(5) $\nu\,\theta(p,a)dt$

where $\theta(p,a)$ is some function of the (average) dosage and of the time-length between treatments.

3. Periodic Treatments of constant dosage

Our discussion will be concerned with the case where treatments are administered periodically and are all of the same dosage.

We now assume that treatments are given at times a, 2a,... and that all treatments has the same probability p of destroying particles then present.



a. Growth and survival between treatments

Suppose that at time $t = ak +$ (immediately after the (k-th) treatment) there are n_k particles present and that the organism is still alive. $(k = o,1,...)$

We first calculate the conditional probability that at time t, $ak < t < a(k+1)$ the organism is still alive and that there are n cells, then present.

We denote this conditional probability by $P^{(k)}(n,t)$. The probabilities $P^{(k)}(n,t)$ satisfy the following system of difference-differential equations:

$$(6) \qquad \frac{d}{dt} P^{(k)}(n,t) = -\left[\sigma + (\lambda+\mu)n + k\theta\right] P^{(k)}(n,t) + \lambda(n-1)P^{(k)}(n-1,t), \quad n \geq n_k .$$

with:

$$(7) \qquad P^{(k)}(n,t) = 0, \qquad n < n_k$$

$$P^{(k)}(n_k, ak+) = 1 .$$

We solve the systems of equations (6) and (7) using generating functions, defining:

$$(8) \qquad G^{(k)}(z,t) = \sum_{n=0}^{\infty} P^{(k)}(n,t) z^n, \qquad 0 \leq z \leq 1 .$$

We obtain from (6):

$$(9) \qquad \frac{\partial}{\partial t} G^{(k)}(z,t) = \left[\lambda z^2 - (\lambda+\mu)z\right] \frac{\partial}{\partial z} G^{(k)}(z,t) - (\sigma+k\theta)G^{(k)}(z,t) ,$$

with:

$$(10) \qquad G^{(k)}(z, ak+) = z^{n_k} .$$

Equation (9) with initial conditions (10) can be solved by classical methods. Its characteristic equations are:

$$(11) \qquad \frac{dt}{1} = \frac{dz}{(\lambda+\mu)z - \lambda z^2} = \frac{dG^{(k)}}{-(\sigma+k\theta)G^{(k)}} ,$$

which upon integration yields:

$$(12)\qquad \log G^{(k)} + (\sigma+k\theta)y = C_1$$

$$t + (\lambda+\mu)^{-1} \log z^{-1}\left[z - \frac{\lambda+\mu}{\lambda}\right] = C_2$$

so that the most general solution of (9) is given by:

$$(13)\qquad \log G^{(k)}(z,t) + (\sigma+k\theta)t = \Phi\left[t + (\lambda+\mu)^{-1} \log z^{-1}\,(z - \frac{\lambda+\mu}{\lambda})\right]$$

where $\Phi(\cdot)$ is an arbitrary differentiable function.

Setting $t = ak+$, we obtain from (10) and (13) that:

$$(14)\qquad n_k \log z + (\sigma+k\theta)ak = \Phi\Big[ak + (\lambda+\mu)^{-1} \log z^{-1}\,(z - \frac{\lambda+\mu}{\lambda})\Big]\,,$$

which yields:

$$(15)\qquad \Phi(u) = n_k \log (\frac{\lambda+\mu}{\lambda})\left[1 - e^{(\lambda+\mu)\,(u-ak)}\right]^{-1} + ak\,(\sigma + k\theta)$$

and finally:

$$(16)\qquad G^{(k)}(z,t) =$$

$$e^{-(t-ak)\,(\sigma+k\theta + \lambda nk + \mu nk)}$$

$$z^{n_k}\left\{1 - \frac{\lambda z}{\lambda+\mu}\left[1 - e^{-(\lambda+\mu)\,(t-ak)}\right]\right\}^{-n_k}\,.$$

We emphasize that $G^{(k)}(z,t)$ is a conditional generating function, given the event that the organism is alive at time $ak+$ and that there are n_k particles present.

b. Destruction of particles at treatments

Given that there are n_k particles at time $ak+$ and that the host is alive, what is the probability that there are n_{k+1} particles at time $a(k+1)+$ and that the host is alive?

From formula (16) we have:

$$(17)\quad G^{(k)}(z,ak+a-) = \sum_{n=0}^{\infty} z^n P^{(k)}(n,ak+a-) = e^{-a(\sigma + k\theta + \lambda n_k + \mu n_k)} \cdot z^{n_k} \left[1 - \frac{\lambda z}{\lambda+\mu}\left[1 - e^{-(\lambda+\mu)a}\right]\right],$$

but:

$$(18)\quad P^{(k+1)}(n_{k+1},\ ak+a+) = \Psi(p) \sum_{n=n_{k+1}}^{\infty} \binom{n}{n_{k+1}} p^{n-n_{k+1}} q^{n_k}$$

so that

$$(19)\quad \tilde{G}^{(k+1)}(z,\ ak+a+) = \sum_{n_{k+1}=0}^{\infty} P^{(k+1)}(n_{k+1},\ ak+a+)\, z^{n_{k+1}} = \Psi(p)\, G^{(k)}(p + qz,\ ak+a-) \quad .$$

The function $\tilde{G}^{(k+1)}(z,\ ak+a+)$ is the conditional generating function of the probabilities, that the organism is alive after the $(k+1)$ st treatment and that there are n_{k+1} particles, given that it is alive after the k-th treatment and that there were then n_k particles.

Formulae (16), (17) and (19) will enable us to calculate the probability that the host is alive and that there are n particles at <u>any</u> point in time.

c. <u>The general transition probabilities</u>.

Let $P(n,t)$ be the probability that at time t, the host is alive at time t and carries n particles, given that there were N particles at time $t = o$. The $P(n,t)$ are continuous functions of t except at the points ak, $k \geq 1$, where they have jumps.

We define the generating function.

$$(20) \qquad H(z,t) = \sum_{n=o}^{\infty} P(n,t)z^n ,$$

for all t, except $t = ak$, $k = 1,2,\ldots,$ where the function will be left and right continuous only.

We have:

$$(21) \qquad H(z,o) = z^N ,$$

and for $ak < t < a(k+1)$:

$$(22)\qquad H(z,t) = \sum_{n_k=o}^{\infty} P(n_k, ak+)\, G^{(k)}(z,t) =$$

$$\sum_{n_k=o}^{\infty} P(n_k, ak+)\, e^{-(t-ak)(\sigma + k\theta + \lambda n_k + \mu n_k)}$$

$$= e^{-(t-ak)(\sigma+k\theta)}\, z^{n_k} \left\{ 1 - \frac{\lambda z}{\lambda+\mu}\left[1 - e^{-(\lambda+\mu)(t-ak)}\right] \right\}^{-n_k},$$

$$H\left\{ \frac{e^{-(t-ak)(\lambda+\mu)}\, z}{1 - \frac{\lambda z}{\lambda+\mu}\left[1 - e^{-(\lambda+\mu)(t-ak)}\right]},\ ak+ \right\}$$

Formula (22) shows that it suffices to know $H(z,ak+)$ for $k \geq o$, to express $H(z,t)$ at all other points t. Also:

$$(23)\qquad H(z,ak+a-) =$$

$$e^{-a(\sigma+k\theta)}\, H\left\{ \frac{z\, e^{-a(\lambda+\mu)}}{1 - \frac{\lambda z}{\lambda+\mu}\left[1 - e^{-a(\lambda+\mu)}\right]} \right\},$$

by setting $t = ak+a-$ in (22).

Finally we have by (19) that:

$$(24)\qquad H(z,ak+a+) = \Psi(p)\, H(p + qz,\ ak+a-).$$

The generating functions $H(z,ak+)$ can be calculated recursively from:

$$(25)\qquad H(z,o+) = z^N,$$

$$H(z,ak+a+) = \Psi(p)\, e^{-a(\sigma+k\theta)}$$

$$H\left\{ \frac{(p+qz)\, e^{-a(\lambda+\mu)}}{1 - \frac{\lambda(p+qz)}{\lambda+\mu}\left[1 - e^{-a(\lambda+\mu)}\right]}\ ,\ ak+ \right\}$$

If we know the functions $H(z,ak+)$, then using (22) we obtain $H(z,t)$ for all other values of t.

4. Solution of the recurrence (25)

We define the functions $M_k(z)$, $k \geq o$ by:

$$(26)\qquad M_o^N(z) = z^N$$

$$M_k^N(z) = \Psi^{-k}(p) e^{ak\sigma + \frac{1}{2}a\theta k(k-1)}\ H(z,ak+)$$

for $k \geq o$, then (25) reduces to

$$(27)\qquad M_o(z) = z$$

$$M_{k+1}(z) = M_k\left[\frac{(p+qz)e^{-a(\lambda+\mu)}}{1 - \frac{\lambda}{\lambda+\mu}(p+qz)\left[1 - e^{-a(\lambda+\mu)}\right]}\right],$$

If we define:

$$(28)\qquad \alpha = p(\lambda+\mu)\, e^{-a(\lambda+\mu)}\ ,$$

$$\beta = q(\lambda+\mu)\, e^{-a(\lambda+\mu)}\ ,$$

$$\gamma = \lambda + \mu - \lambda p(1 - e^{-a(\lambda+\mu)})\ ,$$

$$\delta = \lambda q(1 - e^{-a(\lambda+\mu)})\ ,$$

then we have:

$$(29) \qquad M_{k+1}(z) = M_k\left[\frac{\alpha + \beta z}{\gamma + \delta z}\right], \qquad k \geq o \ .$$

We observe that $M_o(z) = z$ and that the successive $M_k(z)$ are obtained by successively substituting a linear fractional form for z. This implies that the functions $M_k(z)$ remain linear fractional functions for all k, so that we may set:

$$(30) \qquad M_k(z) = \frac{A_k + B_k z}{C_k + D_k z} \ ,$$

where A_k, B_k, C_k and D_k do not depend on z.

Moreover:

$$(31) \qquad \begin{pmatrix} A_o & B_o \\ C_o & D_o \end{pmatrix} = \begin{pmatrix} o & 1 \\ 1 & o \end{pmatrix}$$

and

$$\begin{pmatrix} A_{k+1} & B_{k+1} \\ C_{k+1} & D_{k+1} \end{pmatrix} = \begin{pmatrix} A_k & B_k \\ C_k & D_k \end{pmatrix} \begin{pmatrix} \gamma & \delta \\ \alpha & \beta \end{pmatrix}, \qquad k \geq o$$

whence:

$$(32) \qquad \begin{pmatrix} A_k & B_k \\ C_k & D_k \end{pmatrix} = \begin{pmatrix} o & 1 \\ 1 & o \end{pmatrix} \begin{pmatrix} \gamma & \delta \\ \alpha & \beta \end{pmatrix}^k , \qquad k \geq o \ .$$

The k-th power of the 2×2 - matrix on the right may be expressed conveniently if we know the eigenvalues of the matrix.

The eigenvalues of the matrix

$$\begin{pmatrix} \gamma & \delta \\ \alpha & \beta \end{pmatrix}$$

are given by:

$$(33) \qquad \rho_{1,2} = \frac{1}{2}\left[(\mu + \lambda q) + (\lambda + \mu q)\, e^{-a(\lambda+\mu)}\right]$$

$$\pm \frac{1}{2}\left\{(\mu + \lambda q)^2 + 2\left[\lambda\mu p^2 - q(\lambda+\mu)^2\right] e^{-a(\lambda+\mu)} + (\lambda + \mu q)^2\, e^{-2(\lambda+\mu)a}\right\}^{\frac{1}{2}} ,$$

and it is easy to check that they are always positive and distinct, provided $0 < p < 1$.

$$(34) \qquad \begin{pmatrix} \gamma & \delta \\ \alpha & \beta \end{pmatrix} = \begin{pmatrix} \delta & \delta \\ \rho_1-\gamma & \rho_2-\gamma \end{pmatrix} \begin{pmatrix} \rho_1 & 0 \\ 0 & \rho_2 \end{pmatrix} \begin{pmatrix} \rho_2-\gamma & -\delta \\ \gamma-\rho_1 & +\delta \end{pmatrix} \frac{1}{\delta(\rho_2-\rho_1)} .$$

We obtain successively:

$$(35) \qquad \begin{pmatrix} A_k & B_k \\ C_k & D_k \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix} \begin{pmatrix} \delta & \delta \\ \rho_1-\gamma & \rho_2-\gamma \end{pmatrix} \begin{pmatrix} \rho_1^k & 0 \\ 0 & \rho_2^k \end{pmatrix} \begin{pmatrix} \rho_2-\gamma & -\delta \\ \gamma-\rho_2 & +\delta \end{pmatrix} \frac{1}{\delta(\rho_2-\rho_1)}$$

and finally after simplification:

(36) $$A_k = \alpha \cdot \frac{\rho_1^k - \rho_2^k}{\rho_1 - \rho_2} ,$$

$$B_k = \frac{\rho_1^{k+1} - \rho_2^{k+1}}{\rho_1 - \rho_2} - \gamma \cdot \frac{\rho_1^k - \rho_2^k}{\rho_1 - \rho_2} ,$$

$$C_k = \gamma \frac{\rho_1^k - \rho_2^k}{\rho_1 - \rho_2} - \rho_1\rho_2 \frac{\rho_1^{k-1} - \rho_2^{k-1}}{\rho_1 - \rho_2} ,$$

$$D_k = \delta \cdot \frac{\rho_1^k - \rho_2^k}{\rho_1 - \rho_2} .$$

Substitution in (26) gives an explicit expression for the functions $H(z,ak+)$ in terms of the original parameters of the problem.

For further use, we evaluate $M_k(1)$, given by

(37) $$M_k(1) =$$

$$\frac{\rho_1^{k+1} - \rho_2^{k+1} + (\rho_1^k - \rho_2^k)\left[p\,\mu\, e^{-a(\lambda+\mu)} - (\mu + \lambda q)\right]}{\left[\mu + \lambda\, e^{-a(\lambda+\mu)}\right](\rho_1^k - \rho_2^k) - q(\gamma+\mu)^2\, e^{-a(\gamma+\mu)}\,(\rho_1^{k-1} - \rho_2^{k-1})}$$

or in a more convenient form:

(38) $$M_k(1) =$$

$$\frac{\rho_1^{k+1} - \rho_2^{k+1} + (\alpha-\gamma)(\rho_1^k - \rho_2^k)}{\rho_1^{k+1} - \rho_2^{k+1} + (\delta-\beta)(\rho_1^k - \rho_2^k)} , \qquad k \geq o .$$

The following lemma is of importance:

Lemma

For any given values of $\lambda > o$, $\mu > o$, $a > o$, $p > o$ the sequence $M_k(1)$ is monotone decreasing in k and $o < M_k(1) < 1$.

Proof:

Using (38) and setting $T_k = (\rho_1^k - \rho_2^k)\,(\rho_1^{k+1} - \rho_2^{k+1})^{-1}$ for brevity, we obtain the following inequalities successive by:

$$(39) \qquad \gamma - \alpha = \lambda q + \mu\left[1 - p\, e^{-a(\lambda+\mu)}\right] > o \ ,$$

$$(40) \qquad \beta - \delta = q\left[\lambda + \mu\, e^{-a(\lambda+\mu)}\right] > o \ ,$$

$$(41) \qquad (\gamma - \alpha)-(\beta - \delta) = \mu\left[1 - e^{-a(\lambda+\mu)}\right] > o,$$

$$(42) \qquad T_k - T_{k+1} = -(\rho_1\rho_2)^k(\rho_1-\rho_2)^2\left[\rho_1^{k+1} - \rho_2^{k+1}\right]^{-1}\left[\rho_1^{k+2} - \rho_2^{k+2}\right]^{-1} < o \ .$$

The first three inequalities shows that $M_k(1) < 1$. To show that $M_k(1) > o$ and decreasing, we denote by ρ_1 the largest of the two eigenvalues and note that

$$(43) \qquad M_{k+1}(1) - M_k(1) = \frac{(T_k - T_{k+1})\,(\gamma-\alpha-\beta+\delta)}{\left[1 - (\beta-\delta)\,T_k\right]\left[1 - (\beta-\delta)\,T_{k+1}\right]} \ .$$

The numerator is (43) is negative. It suffices to show that the denominator is positive.

By (41) we have:

$$(44) \qquad 1 - (\beta-\delta)T_k > 1 - (\gamma-\alpha)T_k > 1 - (\gamma-\alpha)\lim_{k\to\infty} T_k = 1 - (\gamma-\alpha)\,\rho_1^{-1} \ .$$

But $o < \gamma-\alpha < \rho_1$ so that $1 - (\gamma-\alpha)\rho_1^{-1} > o$. To prove this, we note that the quadratic function

$$(45) \qquad \rho^2 - (\beta+\gamma)\rho + \beta\gamma - \alpha\delta$$

evaluated at $\gamma-\alpha$ is equal to $\alpha(\alpha-\gamma+\beta-\delta)$ which is negative, so that

$$(46) \qquad o < \rho_2 < \gamma-\alpha < \rho_1 \quad .$$

This completes the proof of the lemma.

5. Maximizing the probability of survival in $[o,T]$.

Suppose we are given a number $T > o$ and are asked to find a and p so as to maximize the probability that the host is still alive at time T.

If no treatment at all is given, the probability that the host is alive at time T is given by:

$$(47) \qquad H(1,T) = e^{-\sigma T} - NT(\lambda+\mu)\left[1 - \frac{\lambda}{\lambda+\mu}\left(1 - e^{-(\lambda+\mu)T}\right]^{-N}\right.$$

using formula (22).

If k treatments are given in $(o,t]$, then we have necessarily

$$(48) \qquad \frac{T}{k+1} < a \leq \frac{T}{k} \quad , \qquad k \geq 1 \quad .$$

The probability that the host is then alive at time T, which we will denote by $H_k(T)$, is then given by:

$$(49) \qquad H_k(T) = e^{-(T-ak)(\sigma+k\theta)}\, H\left\{\frac{e^{-(T-ak)(\lambda+\mu)}}{1 - \frac{\lambda}{\lambda+\mu}\left[1 - e^{-(\lambda+\mu)(T-ak)}\right]} \quad , \; ak+\right\}$$

by formula (22).

Using (26), $H_k(T)$ can be written successively as:

$$(50) \qquad H_k(T) = \Psi^k(p)\, e^{-T(\sigma+k\theta) + \frac{1}{2}a\theta k(k+1)}$$

$$M_k^N \left\{ \frac{e^{-(\lambda+\mu)(T-ak)}}{1 - \frac{\lambda}{\lambda+\mu}\left[1 - e^{-(\lambda+\mu)(T-ak)}\right]} \right\}$$

$$= \left\{ \frac{A_k\left[\mu+\lambda\, e^{-(\lambda+\mu)(T-ak)}\right] + B_k(\lambda+\mu)\, e^{-(\lambda+\mu)(T-ak)}}{C_k\left[\mu+\lambda\, e^{-(\lambda+\mu)(T-ak)}\right] + D_k(\lambda+\mu)\, e^{-(\lambda+\mu)(T-ak)}} \right\}^N$$

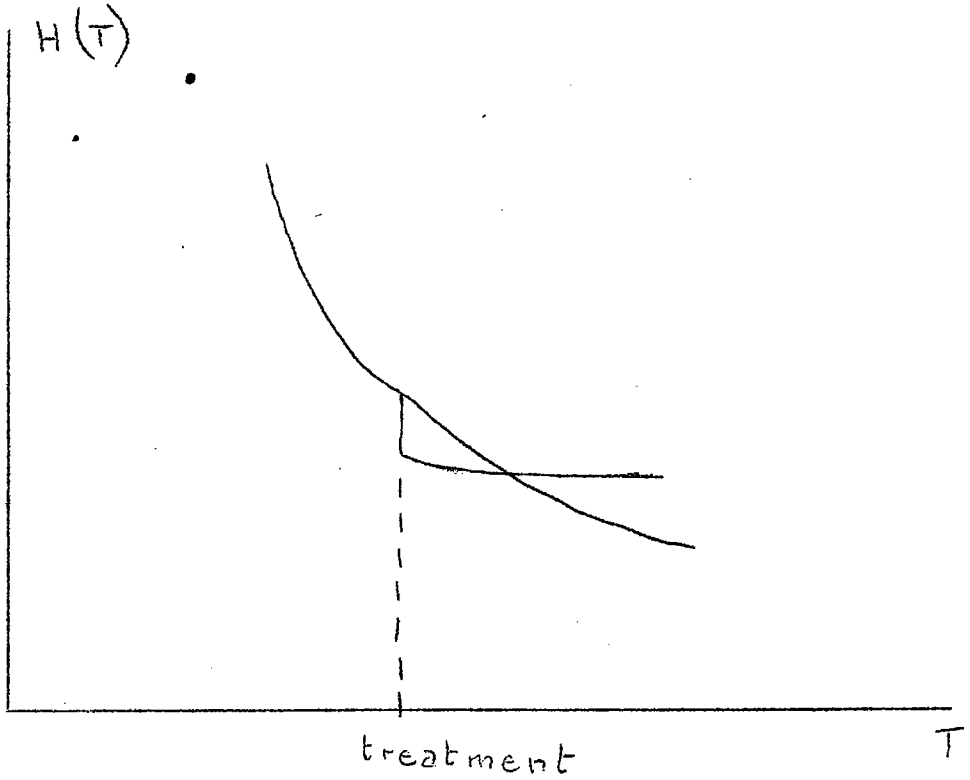
$$\cdot\, \Psi^k(p)\, e^{-T(\sigma+k\theta) + \frac{1}{2}a\theta k(k+1)} \quad .$$

The values of a and p for which the probability $H_k(T)$ is maximum can of course be found by numerical methods only.

The following discussion suggests a good initial guess for the values of a and p. The values found may then be improved upon by evaluating the function $H_k(T)$ at a number of values close to the initial guess.

A good initial guess is provided by requiring that T is an instant at which treatment is given, since the probabilities $H_k(T)$ are easier to calculate when $T = ka$ for some k and a.

On intuitive grounds the solutions so obtained will not be optimal. To see this we note that at an instant of treatment the function $H_k(t)$ has a downward jump, but that after the treatment the total mortality rate is smaller or equivalently the slope of the curve is less negative. This is illustrated on the graph below.



This corresponds to the well-known therapeutic phenomenon of treatment shock. It takes some time for the organism to reap the benefit of a treatment.

Let us now discuss the initial guess in some more detail.

If $T = ak$, then formula (50) reduces to:

$$(51) \qquad H_k(ak) = \Psi^k(p)^{-1} e^{-\sigma T} e^{-\frac{1}{2}a\theta k(k-1)} M_k^N(1)$$

$$= \Psi^k(p)^{-1} e^{-\sigma T - \frac{1}{2}\theta T(k-1)} M_k^N(1) \quad .$$

For a fixed value of a, we know that $M_k(1)$ decreases as k increases, whereas for a fixed value of k, $H_k(ak)$ decreases with a.

Here we consider the function in (51) only for those points where $T = ak$.

In general as k ranges over integer values and p ranges over $(o,1)$, the function $H_k(ak)$ will have a unique maximum at $k_o(p)$ for each p.

This shows that for a given p, the maximum of $H(1,T)$ is attained for a close to $\frac{T}{k_o(p)}$ and a search procedure using values of a near this initial guess should enable us to find the extreme value more accurately.

It is possible that the maximum will be attained for may pairs (a,p). If this is the case, then we have a further degree of freedom in choosing a policy (a,p). Whether this is so will depend on the actual choice of the functions $\Psi(p)$ and $\theta(a,p)$.

6. Maximizing the Expected Lifetime.

If L denotes the lifetime of the host, then:

$$(52) \qquad E(L) = \int_o^\infty H(1,t)dt \quad .$$

This integral converges rapidly due to the exponential factors appearing in the integrand, but again, it would be to our advantage to have a good initial guess for the values of a and p which maximize it, rather than to tabulate E(L) for many a and p values.

We note that:

$$(53) \qquad E(L) = \sum_{k=o}^{\infty} \int_{ak}^{a(k+1)} H(1,t)dt$$

so that, by use of (22), we may approximate E(L) by numerical integration once we know the function $H(z, ak+)$ for $k = o,1,\ldots$.

To obtain a good initial guess for the optimal a and p in this case, we note the following. Suppose that the death of the host is recorded only at ak+a+ if it occurs during the interval (ak, ak+] and let L^* be the time until death is recorded, then with probability one we have:

$$(54) \qquad L \leq L^* < L + a$$

and hence $E(L) \leq E(L^*) < E(L) + a$. However we have:

$$(54) \qquad E(L^*) = \sum_{k=1}^{\infty} ak \left\{H(1,ak-a+) - H(1, ak+)\right\}$$

$$= a \sum_{k=o}^{\infty} H(1, ak+)$$

$$= a \sum_{k=o}^{\infty} \Psi^k(p)\, e^{-ak\sigma-\frac{1}{2}a\theta k(k-1)}\, M_k^N(1) \quad ,$$

and the numerical computation of this sum is easy, using (37) or (38).

It is also worthwhile to compare the expected lifetime with treatment to the expected lifetime without treatment.

The latter is given by:

$$(\lambda+\mu)^N \int_o^{\infty} e^{-\sigma t - N(\lambda+\mu)t} \left[\mu+\lambda\, e^{-(\lambda+\mu)t}\right]^{-N} dt$$

by use of (47).

7. Computational work

The computational procedure for finding optimal pairs (a,p) suggested in this paper, was programmed for the IBM 7094 at Purdue University, by Mrs. Louise Lui, to whome the author expresses his sincere thanks.

The values of $H_k(ak-)$ in formula (51) were computed for several examples. Five values beyond the maximum value $H_{k_o}(ak_o-)$ were computed to get an idea of the dependence on k. When the value of $\frac{T}{k_o}$ was small compared to T, it was chosen as the approximation.

If k_o was small, so that $\frac{T}{k_o}$ was large compared to T, the function $H_{k_o}(T)$ was calculated for several values of a in the interval $(\frac{T}{k_o+1}, \frac{T}{k_o})$ in order to find an improved value of the a (corresponding to a given p) for which the survival probability was maximum. This procedure was repeated for about twenty values of p, chosen in the interval $(o,1)$.

A major difficulty in exploring numerical examples was to find more or less "realistic" expressions for the function $\Psi(p)$ and suitable choices for the parameters λ, μ, σ, θ, and T.

Since the examples we worked were purely "ad hoc" and had no foundation in real experimental work, we prefer not to report any such numerical results. The computational procedure is quite fast. It took approximately 20 seconds to search the optimal pair (a,p) for any given set of parameter values.

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13. ABSTRACT

A host carries a lethal growth of size N at time t = o. The growth increases according to a Yule-Furry process and the mortality rate of the host due to the growth is assumed to be proportional to the number of particles in the growth.

Periodically the host is given treatment which removes particles from the growth according to a Bernoulli sampling scheme with probability p. The treatment itself has a certain lethality, which we assume to be an increasing function of p. Moreover the mortality rate of the host increases by a term which is proportional to the number of treatments already received and depends on their intensity (p).

The problem of choosing the spacing and intensity of the treatments, so as to maximize the probability of survival of the host is an interval of time, or the expected survival time, is discussed.

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