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An Integral Equation Model for a Binary Fission Process

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Abstract

A new probabilistic modeling approach is used to describe the transient and stable stages of growth of a population consisting of viable cells and vegetative cells. Viable cells are capable of division at the end of a random life-time (generation time) and when a cell divides it produces exactly two newborn cells. On average, at time t , $\alpha(t)$ of these two newborn cells are viable cells and $2 - \alpha(t)$ are vegetative cells, which do not divide at any time. The model is developed by modifying the integral equation used by demographers to study the growth of human populations. The solution of the model is studied using various biologically plausible assumptions concerned with the inputs $\alpha(t)$ and the probability distribution of the generation time and comparisons made with other modeling approaches indicate that the new model is easier to formulate and analyze, provides a more complete analysis, and enables the incorporation of assumptions concerning environmental and internal cell factors that influence the production rate of viable cells.

Keywords: age structured generation time distribution, integral (renewal) equation, transient and stable stages of growth, vegetative parameter, viable and vegetative cells.

1. Introduction

Consider a population of cells consisting of a mixture of two types: viable (fissioning or dividing) cells; and vegetative (non viable or quiescent) cells. Viable cells are capable of division at the end of a random generation time and when a viable cell divides (dies) it produces exactly two newborn cells. On average, at time t , $\alpha(t)$ of these two newborn cells are viable cells and $2 - \alpha(t)$ are vegetative cells, which are not capable of division.

The construction of mathematical models of the growth of such a population of cells has early beginnings. Thornley [1] gives expressions for the mean numbers and the age structures by assuming that the cell division process is initially stable with a constant generation time for the viable cells. Powell [2] also assumes a stable viable cell population and working with a variable generation time considers the age structure and growth rate of only the viable cells. He suggests, on the basis of extensive empirical evidence, that the generation time distribution is adequately represented by an Erlangian distribution. This assumption is supported by Kendall [3] who also deals with the particular case where $\alpha(t) = 2$ and subsequently developed a generalized Erlangian model for the generation time distribution [4]. Extensive measurements of the generation times of individual cells were first published by Kelly and Rahn [5] and subsequently Rahn [6] proposed the Yule distribution for the generation time and this has support from other empirical studies [7].

The problem has also been formulated as an age dependent Bellman-Harris process as a part of the study of branching processes which have their background in the physical and biological sciences with the major developments being due to Bellman and Harris [8,9]. This approach developed separately from the models favored by demographers, such as the integral model of Sharpe and Lotka [10] and the stochastic models of Kendall [14], and early detailed discussions of branching processes and their relationship to the other lines of development in population dynamics are given by Jagers [11] and Bharucha-Reid [12].

The model developed in this article is new and is based on a modification to the integral (renewal) equation of population dynamics favored by demographers and attributed to Sharpe and Lotka [10]. A complete age dependent analysis of the transient and stable stages of the growth of a population can be formulated in both discrete and continuous forms where discrete formulations typically use matrices and difference equations and continuous forms use integral equations and various types of differential equations. These various formulations have their advantages and disadvantages and the

integral equation formulation gives a superior approximation for the intrinsic rate of natural increase and provides a simple basis for perturbation analysis ([13]). In addition, the formulation of the integral equation model is simple, under reasonable assumptions the solution of the model is amenable to the use of Laplace transforms [14], and numerical solution techniques are well documented [15-20].

Following definitions and notation the formulation of the new integral equation model is described. A complete analysis of the transient and stable stages of growth is presented for the case where the vegetative parameter is constant, which is a common assumption for a reasonable well nourished population of cells. This is followed by the incorporation and comparison of biologically plausible assumptions about the generation time distribution. Next the model is analyzed for the case where the vegetative parameter is time dependent and two examples are used to illustrate how this assumption allows time dependent influences internal to the cells or in the external environment to be accounted for in the model. Throughout the relevant sections comparisons are made with other modeling approaches in order to illustrate the advantages of the integral equation model. These are summarized as part of the conclusion which also indicates how the model may be used if the generation time distribution is represented in natural forms such as a histogram or a concentrated form.

It is noted that there is an extensive body of literature in recent times concerned with understanding the complex processes of cell division in both plants and animals. The focus is on biochemical and genetic mechanisms that operate within and between cells and influence cell division. In particular, the mechanisms of asymmetric cell division have been studied extensively. Mathematical models have been developed to describe these complex micro-level processes and although a detailed consideration of these findings and models is beyond the scope of this article it is recognized that it may be possible in the future to extend the meso-level model of the growth of the cell populations presented in this article to reflect the increasing body of knowledge concerned with complex micro-level internal cell processes. For a selection of recent articles related to these processes the reader is referred to Antil et al. [21], Hove and Heidstra [22], Knoblich [23], Portugal et al. [24], Serakinci et al. [25], Sharma et al. [26], Steuer [27], Wu et al. [28], Zhang et al. [29], and Zheng et al. [30].

2. Definitions and Notation

The following notation and definitions are used for the population of viable cells:

$\alpha(t)$ is referred to as the vegetative parameter and $0 \leq \alpha(t) \leq 2$. If $\alpha(t) = 0$ then neither of the two newborn cells are viable and if $\alpha(t) = 2$ then they are both viable;

$M(t)$ is the expected number of cells in the population at time t , with $M(0) = K \geq 1$;

$B(t)dt$ is the expected total number of births due to $M(t)$ cells in the time t to $t + dt$;

$D(t)dt$ is the expected total number of the $M(t)$ cells that divide (die) in time t to $t + dt$,

$R(t)$ is the intrinsic rate of increase and $R(t) = \frac{1}{M(t)} \frac{dM}{dt}$;

$a(x, t)$ is the age density function of cells of age x such that $M(t)a(x, t)dx$ is the expected number of cells at time t in the age range x to $x + dx$. In particular, $a(0, t)$ is the crude

birth rate and $a(0, t) = \frac{B(t)}{M(t)}$;

$\beta(x, t)$ is the age specific fecundity and $\beta(x, t)dx$ is the fraction of newborn viable cells at time t due to the division of mothers (viable cells) of age x to $x + dx$;

$f(x)$ is the probability density function for the generation time X , which is a random variable representing the lifetime of a cell timed from the instant it was born, as a result of the division of its mother, until it divides and $f(x)dx$ is the probability that a newborn cell will divide between ages x and $x + dx$;

$l(x)$ is the survivor function and is the probability that a newborn cell will not have divided before age x , and is the probability that $X > x$;

$\mu(x)$ is age specific fission rate and $\mu(x)dx$ is the probability that $x < X \leq x + dx$ given that $X > x$.

It is noted that only one of $f(x)$, $l(x)$, and $\mu(x)$ is independent,

$$f(x) = l(x)\mu(x), \quad l(x) = \exp\left[-\int_0^x \mu(s)ds\right] \quad (1)$$

and,

$$\beta(x, t) = \alpha(t)\mu(x). \quad (2)$$

Similar definitions hold where subscripts V and T are used to describe the vegetative and total cell populations, respectively.

3. Formulation of the Integral Equation Model

Based on the definitions viable cells alive at time t must have been born between time $t - x$ and $t - (x + dx)$ and not divided before reaching age x . Consequently, $M(t)a(x, t)dx = B(t - x)l(x)dx$. The birth rate of viable cells at time t of age x to $x + dx$ is $B(t)a(x,$

$t)dx = B(t - x)\alpha(t)\mu(x)l(x)dx$ from (2), which from (1) is $B(t - x)\alpha(t)f(x)dx$. Similarly, $D(t)a(x, t)dx = B(t - x)l(x)\mu(x) = B(t - x)f(x)dx$. Summing over all ages gives,

$$\left. \begin{aligned} M(t) &= \int_0^\infty B(t - x)l(x)dx, \\ B(t) &= \alpha(t) \int_0^\infty B(t - x)f(x)dx, \\ D(t) &= \int_0^\infty B(t - x)f(x)dx. \end{aligned} \right\} \quad (3)$$

The integral equation for $B(t)$ used by demographers for modeling human population growth has the form $B(t) = \int_0^\infty B(t - x)l(x)\beta(x, t)dx$ [13]. Hence, (3) may be derived from the integral equation used by demographers by using the modifications represented by (1) and (2).

From (3) it is seen that $\frac{dM}{dt} = B(t) - D(t) = [\alpha(t) - 1]D(t) = \frac{\alpha(t) - 1}{\alpha(t)} B(t)$ and if

there are K viable cells initially then,

$$M(t) = K + \int_0^t \frac{\alpha(u) - 1}{\alpha(u)} B(u)du. \quad (4)$$

Also, the intrinsic rate of increase of the population of viable cells is,

$$R(t) = \frac{[\alpha(t) - 1]B(t)}{\alpha(t)M(t)} = \frac{[\alpha(t) - 1]a(0, t)}{\alpha(t)} \quad (5)$$

The set of equations (3) requires a full history of the remote past. To overcome this difficulty it is assumed that the number of viable cells K and the age density $a(x, 0)$ at some time origin are known. Then the birth rate at time t due to viable cells alive at the

origin is given by $\alpha(t)K \int_0^\infty a(x, 0) \frac{f(x+t)}{l(x)} dx$ and the birth rate due to viable cells born since

the origin is $\alpha(t) \int_0^t B(t - x)f(x)dx$ and so from (3),

$$\left. \begin{aligned} B(t) &= \alpha(t)K\Psi_1(t) + \alpha(t) \int_0^t B(t - x)f(x)dx, \\ \text{where, } \Psi_1(t) &= \int_0^\infty a(x, 0) \frac{f(x+t)}{l(x)}, \end{aligned} \right\} \quad (6)$$

and similarly,

$$M(t) = K\Psi_2(t) + \left\{ \begin{array}{l} \int_0^t B(t-x)l(x)dx, \\ \text{where, } \Psi_2(t) = \int_0^\infty a(x,0) \frac{l(x+t)}{l(x)}. \end{array} \right\} \quad (7)$$

Considering the number of viable cells alive at time t of age x to $x + dx$ gives,

$$M(t)a(x,t) = \begin{cases} Ka(x-t,0) \frac{l(x)}{l(x-t)}, & x \geq t, \\ B(t-x)l(x), & 0 \leq x < t. \end{cases} \quad (8)$$

By taking the Laplace transform of $M(t)$ in (4) and in (7) it is easy to show that both expressions for $M(t)$ are the same. For the purposes of calculation (4) is simpler than (7). However, (7) is instructive in the sense that it separates the population at time t into survivors from the initial population ($K\Psi_2(t)$) and those produced since the time origin

$$\left(\int_0^t B(t-x)l(x)dx \right).$$

Using the subscripts V and T for the vegetative and total cell populations, respectively, the following equations can be derived by arguments similar to those used in describing the population of viable cells.

$$\left. \begin{array}{l} B_V(t) = \frac{2 - a(t)}{\alpha(t)} B(t), \\ M_V(t) = M_V(0) + \int_0^t B_V(u)du, \\ R_V(t) = a_V(0,t), \\ M_V(t)a_V(x,t) = \begin{cases} M_V(0)a_V(x-t,0), & x \geq t, \\ B_V(t-x), & 0 \leq x < t, \end{cases} \end{array} \right\} \quad (9)$$

and,

$$\left. \begin{aligned}
 B_T(t) &= B(t) + B_V(t) = \frac{2B(t)}{\alpha(t)}, \\
 M_T(t) &= K + M_V(0) + \int_0^t \frac{B(u)}{\alpha(u)} du, \\
 R_T(t) &= \frac{a_T(0,t)}{2}, \\
 M_T(t)a_T(x,t) &= \begin{cases} Ka(x-t,0) \frac{l(x)}{l(x-t)} + M_V(0)a_V(x-t,0), & x \geq t, \\ B(t-x)l(x) + B_V(t-x), & 0 \leq x < t. \end{cases}
 \end{aligned} \right\} \quad (10)$$

Equations (3)-(10) provide separately a full description of the populations of viable and vegetative cells as well as the total population of all cells. Furthermore, the model enables analysis of the transient stage of growth, when viable cells which were present in the initial population are still present, and analysis of the stable stage of growth when all the viable cells in the initial population have divided. The following describes the required inputs and the main outputs for the integral equation model:

Inputs: **(a)** $\alpha(t)$ the vegetative parameter; **(b)** K , $M_V(0)$, $a(x, 0)$, and $a_V(x, 0)$ the initial numbers and age densities of viable and vegetative cells, respectively; and **(c)** only one of $f(x)$ (the density function for the generation time), $l(x)$ (the survivor function), or $\mu(x)$ (the age specific rate of cell division).

Outputs: **(a)** the total birth rates $B(t)$, $B_V(t)$, and $B_T(t)$, the mean number of cells $M(t)$, $M_V(t)$, and $M_T(t)$, and the age density functions $a(x, t)$, $a_V(x, t)$, and $a_T(x, t)$ for the populations of viable cells, vegetative cells, and the total population of all cells, respectively, during the transient and stable stages of growth; and **(b)** other growth parameters of interest (e.g. crude birth rates and doubling times).

4. A Constant Vegetative Parameter α

To illustrate the use of the integral equation model to analyze both the transient and stable stages of growth consider the case where the vegetative parameter $\alpha(t)$ is the constant α with $0 < \alpha \leq 2$. The case where $\alpha = 0$ is not analyzed here since under this condition no viable cells are produced as the result of the division of any of the viable cells present in the initial population and as soon as all of those viable cells have divided the total population consists entirely of vegetative cells. The analysis of this simple situation is left for the interested reader. If the cells are at least reasonably well nourished then $1 < \alpha \leq 2$ [2].

4.1 The Transient Stage of Growth

If $G^*(s) = \int_0^\infty \exp(-st)G(t)dt$ is the Laplace transform of $G(t)$ then taking Laplace transforms in (6) $B^*(s) = \alpha K \Psi_1^*(s) + \alpha B^*(s) f^*(s)$, which gives $B^*(s) = \frac{\alpha K \Psi_1^*(s)}{1 - \alpha f^*(s)}$ and

inversion of $B^*(s)$ gives $B(t) = \sum_{j=0}^{\infty} A_j \exp(r_j t)$ where $s = r_0$ is the largest real root of $1 - \alpha f^*(s) = 0$. Complex roots occur in conjugate pairs with real parts less than r_0 and

$$A_j = \frac{K \Psi_1^*(r_j)}{\int_0^\infty x f(x) \exp(-r_j x) dx} \text{ for } j = 0, 1, 2, \dots.$$

Using the solution for $B(t)$ and equations (7)-(10) enables a complete analysis of the process during the transient stage of growth when there are still viable cells in the population which were present in the initial population.

4.2 The Stable Stage of Growth

For large values of t when the growth is stable and all of the viable cells in the initial population have divided $B(t) = A_0 \exp(r_0 t)$ and α is greater than, equal to, less than unity implies that r_0 is positive, zero, negative, respectively. Consequently,

$$M(t) = \begin{cases} \frac{(\alpha - 1)A_0 \exp(r_0 t)}{\alpha r_0}, & \alpha \neq 1, \text{ and } M(t) a(x, t) = \begin{cases} A_0 \exp[r_0(t - x)] I(x) & 0 \leq x < t, \\ 0, & x \geq t. \end{cases} \\ K, & \alpha = 1, \end{cases}$$

For the population of vegetative cells:

$$B_V(t) = \frac{2 - \alpha}{\alpha} A_0 \exp(r_0 t), \quad M_V(t) = \begin{cases} \frac{\alpha - 2}{\alpha - 1} K + M_V(0) + \frac{2 - \alpha}{\alpha r_0} A_0 \exp(r_0 t), & \alpha \neq 1, \\ A_0 t + M_V(0), & \alpha = 1, \end{cases}$$

$$\text{and } M_V(t) a(x, t) = \begin{cases} \frac{2 - \alpha}{\alpha} A_0 \exp[r_0(t - x)], & 0 \leq x < t, \\ M_V(0) a_V(x - t, 0), & x \geq t. \end{cases}$$

For the total population:

$$B_T(t) = \frac{2A_0}{\alpha} \exp(r_0 t)$$

$$M_T(t) = \begin{cases} \frac{\alpha-2}{\alpha-1} K + M_V(0) + \frac{A_0}{\alpha r_0} \exp(r_0 t), & \alpha \neq 1, \\ A_0 t + K + M_V(0), & \alpha = 1, \end{cases} \quad \text{and}$$

$$M_T(t) a_T(x, t) = \begin{cases} A_0 \exp[r_0(t-x)] \left[l(x) + \frac{2-\alpha}{\alpha} \right], & 0 \leq x < t, \\ M_V(0) a_V(x-t, 0), & x \geq t. \end{cases}$$

The crude birth rates are:

$$\text{for the viable cells } R(t) = a(0, t) = \begin{cases} \frac{\alpha}{\alpha-1} r_0, & \alpha \neq 1, \\ \frac{A_0}{K}, & \alpha = 1, \end{cases};$$

$$\text{for} \quad \text{the} \quad \text{vegetative} \quad \text{cells}$$

$$R_V(t) = a_V(0, t) = \begin{cases} \frac{2-\alpha}{\alpha} A_0 \exp(r_0 t), & \alpha \neq 1, \\ M_V(0) + \frac{\alpha-2}{\alpha-1} K + \frac{2-\alpha}{\alpha r_0} A_0 \exp(r_0 t), & \alpha = 1, \end{cases};$$

and for the total population of all of the cells

$$R_T(t) = \frac{a_T(0, t)}{2} = \begin{cases} \frac{1}{\alpha} A_0 \exp(r_0 t), & \alpha \neq 1, \\ M_V(0) + \frac{\alpha-2}{1-\alpha} K + \frac{1}{\alpha r_0} A_0 \exp(r_0 t) \\ \frac{A_0}{M_T(t)}, & \alpha = 1. \end{cases}$$

From these results the following observations can be made:

The viable cell population is stationary at K when $\alpha = 1$. Otherwise, as t increases it decreases to a limiting value of zero when $0 < \alpha < 1$ and it increases without bound for $1 < \alpha \leq 2$. If $1 < \alpha \leq 2$ then the youngest viable cells are present in the greatest proportion. As t increases the number of young viable cells increases for $1 < \alpha \leq 2$, decreases for 0

$\alpha < 1$, and is constant for $\alpha = 1$. The viable cell population has a stable age distribution (i.e. independent of t) for $1 < \alpha \leq 2$. The average age of dividing cells in the stable population is $\alpha \int_0^\infty x f(x) \exp(-r_0 x) dx$ where $\alpha f(x) \exp(-r_0 x)$ is referred to as the density function for Powell's [2] carrier distribution.

The vegetative cell population is constant at $M_V(0)$ for $\alpha = 2$. Otherwise, as t increases it

increases to a limiting value of $\frac{2-\alpha}{1-\alpha} K + M_V(0)$ for $0 < \alpha < 1$ and it increases without bound for $1 < \alpha < 2$. If $\alpha = 1$ then vegetative cells are being produced at a constant rate A_0 for large values of t . As t increases the number of young vegetative cells increases for $1 < \alpha < 2$, decreases to a limit of zero for $0 < \alpha < 1$, and remains constant for $\alpha = 1$.

Although $a(x, t)$ is independent of t for large values of t this is not generally true for $a_V(x, t)$

and as $t \rightarrow \infty$, $a_V(x, t) \rightarrow \begin{cases} r_0 \exp(-r_0 x), & 1 < \alpha < 2, \\ 0, & 0 < \alpha < 1. \end{cases}$ It is interesting to note that if

$M_V(0) = \frac{2-\alpha}{\alpha-1} K$, which is only possible if $1 < \alpha \leq 2$, then the age distribution for the

vegetative cells produced since the origin is stable at $\begin{cases} r_0 \exp(-r_0 x), & 1 < \alpha < 2, \\ 0, & 0 < \alpha < 1. \end{cases}$ Under

these conditions the age distribution for the total population of all the cells produced

since the origin is stable at $\alpha r_0 \left[l(x) + \frac{2-\alpha}{\alpha} \right]$ for $1 < \alpha \leq 2$.

The total cell population increases to a limiting value of $\frac{2-\alpha}{1-\alpha} K + M_V(0)$ for $0 < \alpha < 1$

and increases without bound otherwise. As t increases the number of young cells in the total population increases for $0 < \alpha \leq 2$, decreases to a limit of zero for $0 < \alpha < 1$, and is constant for $\alpha = 1$.

5. The Generation Time Distribution

Before considering plausible choices for the generation time distribution of viable cells the following simplifying assumptions are made: $a(t) = \alpha$, as discussed above; and the initial population consists entirely of K newborn viable cells with $K \geq 1$. This means that: $M_V(0) = 0$; $a(x, 0) = \delta(x)$, which is the Dirac delta function; and $a_V(x, t) = 0$ for all x and t when $\alpha = 2$. Hence, from (4), (6) and (7),

$$B(t) = \alpha K f(t) + \alpha \int_0^t B(t-x) f(x) dx, \quad (11)$$

$$M(t) = K l(t) + \int_0^t B(t-x) l(x) dx = K + \frac{\alpha-1}{\alpha} \int_0^t B(u) du. \quad (12)$$

Using these assumptions various plausible choices for the generation time distribution are considered.

5.1 Constant Generation Time (τ)

Under this assumption each viable cell has a fixed lifetime of τ which means that the generation time density function $f(x) = \delta(\tau - x)$ and, from (1), $l(x)$ is the Heaviside

$$\text{function } H(\tau - x) = \begin{cases} 1, & x \leq \tau, \\ 0, & x > \tau. \end{cases}$$

For the transient stage of growth using Laplace transforms in (11) gives $B(t)$, which when substituted in (12) and (8) gives $M(t)$ and $M(t)a(x, t)$, and (9) describes the vegetative cell population. For the stable stage of growth the equations derived previously may be applied with $A_0 = K/\tau$ and $r_0 = \ln(\alpha)/\tau$.

The main results of the analysis for the viable and vegetative cell populations are displayed in Table 1. These results include those derived by Thornley [1] who only considered the case where $\alpha = 2$ (i.e. no vegetative cells are produced) and they provide a more complete description of the process, particularly during the transient stage of growth. Thornley [1] notes that at time t , in the stable population, there are twice as many newborn viable cells as there are viable cells that are about to divide. In the stable population from the equation for $M(t)a(x, t)$ in Table 1 it is seen that the corresponding ratio is α for the more general process considered here where vegetative and viable cells are present. Also, it is noted from the equation for $M(t)$ that the doubling time for the

stable population of viable cells is given by $\frac{\tau \ln 2}{\ln(\alpha)}$ when $\alpha \neq 1$.

Table1. Summary of results for a fixed generation time τ

Stage	Type of Cell
Transient	<p>Viable Cells</p> <p>For $n\tau \leq t < (n+1)\tau$ where $n = 0, 1, 2, \dots$: $B(t) = K \sum_{j=1}^{\infty} \alpha^j \delta(j\tau - t)$; $M(t) = \alpha^n K$;</p> $M(t)a(x, t) = \begin{cases} KH(\tau - x) \sum_{j=1}^{\infty} \alpha^j \delta(j\tau + x - t), & 0 \leq x < t, \\ 0, & x \geq t. \end{cases}$ <p>Vegetative Cells</p> <p>For $n\tau \leq t < (n+1)\tau$ where $n = 0, 1, 2, \dots$: $B_V(t) = \frac{2-\alpha}{\alpha} K \sum_{j=1}^{\infty} \alpha^j \delta(j\tau - t)$;</p> $M_V(t) = \begin{cases} \frac{2-\alpha}{\alpha} K(1 - \alpha^n), & \alpha \neq 1, \\ nK, & \alpha = 1; \end{cases}$ $M_V(t)a(x, t) = \begin{cases} \frac{2-\alpha}{\alpha} K \sum_{j=1}^{\infty} \alpha^j \delta(j\tau + x - t), & 0 \leq x < t, \\ 0, & x \geq t. \end{cases}$
Stable	<p>Viable Cells</p> $B(t) = \frac{K}{\tau} \alpha^{\frac{t}{\tau}}; M(t) = \begin{cases} \frac{\alpha-1}{\ln(\alpha)} K \alpha^{\frac{t-\tau}{\tau}}, & \alpha \neq 1, \\ K, & \alpha = 1; \end{cases}$ $M(t)a(x, t) = \begin{cases} \frac{K}{\tau} H(t-x) \alpha^{\frac{t-x}{\tau}}, & 0 \leq x < t, \\ 0, & x \geq t. \end{cases}$ <p>Vegetative Cells</p> $B_V(t) = \frac{2-\alpha}{\tau} K \alpha^{\frac{t-\tau}{\tau}}; M_V(t) = \begin{cases} \frac{(\alpha-2)}{(\alpha-1)} \frac{K}{\ln(\alpha)} [\ln(\alpha) + (1-\alpha) \alpha^{\frac{t-\tau}{\tau}}], & \alpha \neq 1, \\ \frac{Kt}{\tau} + M_V(0), & \alpha = 1. \end{cases}$

5.2 Variable Generation Times Involving the Completion of a Fixed Number of Events

An alternative model of the generation time for viable cells assumes that cell division occurs at the completion of a fixed number of n events which take place in each

cell in a specific order at different rates $\beta_1, \beta_2, \beta_3, \dots, \beta_n$, respectively. This model is referred to as the Generalized Erlangian Model and was proposed by Kendall [4].

If $P_k(x)$ is the probability that exactly k events have been completed by age x then

$$\frac{dP_0(x)}{dx} = -\beta_1 P_0(x); \frac{dP_k(x)}{dx} = \beta_1 P_{k-1}(x) - P_{k+1}(x), \text{ for } j = 1, 2, 3, \dots, n - 1, \text{ and}$$

$$\frac{dP_n(x)}{dx} = \beta_n P_{n-1}(x). \text{ Taking Laplace transforms gives } sP_n^*(s) = \prod_{j=1}^n \frac{\beta_j}{s + \beta_j} \text{ which}$$

when inverted gives the generation time density function,

$$f(x) = \left(\prod_{j=1}^n \beta_j \right) \sum_{j=1}^n A_j \exp(-\beta_j x), \quad (13)$$

where A_j is the limit of $\frac{s + \beta_j}{\prod_{i=1}^n (s + \beta_i)}$ as $s \rightarrow -\beta_j$ for $j = 1, 2, 3, \dots, n$, and the expected

value of the generation time is $(\prod_{j=1}^n \beta_j) \sum_{j=1}^n \frac{A_j}{\beta_j}$.

If it is assumed in the Generalized Erlangian Model (13) that $\beta_j = \beta$, for $j = 1, 2, 3, \dots, n$ then the density function for the generation time is,

$$f(x) = \frac{\beta^n x^{n-1} \exp(-\beta x)}{(n-1)!}, \quad (14)$$

which is an Erlangian or Pearson type III density function with mean generation time n/β . This is referred to as the Erlangian Model and was proposed by Kendall [3].

If it assumed in (13) that $\beta_j = j\beta$ for $j = 1, 2, 3, \dots, n$ then,

$$f(x) = [1 - \exp(-\beta x)]^{n-1} n\beta \exp(-\beta x), \quad (15)$$

which is the density function for Yule's distribution and the mean generation time is $\frac{n}{\beta} \sum_{j=0}^{n-1} \frac{(-1)^j}{(j+1)^2} n^{-1} C_j$. This is referred to as Rahn's Model [6].

If $n = 1$ in equations (13)-(15) then cell division occurs at the completion of a single event and the generation time has a simple exponential distribution,

$$f(x) = \beta \exp(-\beta x), \quad (16)$$

with mean value $1/\beta$. This is referred to as the simple exponential or Malthusian Model.

Comparing the mean values of the generation times using equations (14)-(16) it is seen that,

$$n/\beta \text{ (Erlangian Model)} \geq \frac{n}{\beta} \sum_{j=0}^{n-1} \frac{(-1)^j}{(j+1)^2} {}_{n-1}C_j \text{ (Rahn's Model)} \geq 1/\beta \text{ (Malthusian Model),}$$

with equalities when $n = 1$.

It is noted that Rahn [6] obtained the Yule distribution by assuming that cell division occurs at the completion of n independent events which are not necessarily completed in sequence but each has a duration with an exponential density $\beta \exp(-\beta x)$. This assumption is quite different from the assumption that leads to the Yule distribution as described above in (15) and emphasizes the general principle that a generation time density function must not be selected only on the basis that it exhibits a reasonable fit to experimental data. There must also be sound physiological evidence to support the selection.

The Malthusian, the Erlangian, the Generalized Erlangian, and Rahn's formulations for the generation time are now used in the integral equation model for the population of cells.

The Malthusian Model

The use of the Malthusian Model (16) in the integral equation formulation is analyzed using the assumptions which lead to (11) and (12) where, from (1), $I(x) = \exp(-\beta x)$. For the transient stage of growth substituting (16) in (11) and taking Laplace transforms gives $B(t)$ and then $M(t)$ and $M(t)a(x, t)$ are obtained from (12) and (8), respectively. Corresponding expressions for the population of vegetative cells are obtained from (9). For the stable stage of growth the equations derived in section 4.2 are applied with $A_0 = \alpha\beta K$ and $r_0 = \beta(\alpha - 1)$.

Hence, for the transient stage of growth:

$$B(t) = \alpha\beta K \exp[\beta(\alpha - 1)t]; M(t) = K \exp[\beta(\alpha - 1)t];$$

$$M(t)a(x, t) = \begin{cases} \alpha K \exp[\beta(\alpha t - \alpha x - t)], & 0 \leq x < t, \\ 0, & x \geq t, \end{cases}$$

$$B_V(t) = (2 - \alpha)\beta K \exp[\beta(\alpha - 1)t]; M_V(t) = \frac{2 - \alpha}{\alpha - 1} K \{ \exp[\beta(\alpha - 1)t] - 1 \};$$

$$\text{and } M_V(t)a_V(x, t) = \begin{cases} (2 - \alpha)\beta K \exp[\beta(\alpha - 1)(t - x)], & 0 \leq x < t, \\ 0, & x \geq t. \end{cases}$$

For the stable stage of growth the corresponding expressions are the same as for the transient stage. From the expression for $M(t)$ it is seen that the doubling time for the

population of viable cells is $\frac{\ln 2}{\beta(\alpha - 1)}$.

The Erlangian Model

The use of the Erlangian Model (14) in the integral equation formulation is analyzed using the assumptions which lead to (11) and (12). Substituting (14) in (11) and taking Laplace transforms gives,

$$B^*(s) = \alpha K \beta^n \sum_{j=1}^{\infty} \frac{\alpha^{j-1} \beta^{(j-1)n}}{(s + \beta)^{jn}}, \text{ which on inversion gives,}$$

$$B(t) = K \exp(-\beta t) \sum_{j=1}^{\infty} \frac{\alpha^j \beta^{jn} t^{jn-1}}{(jn-1)!},$$

and from (12),

$$M(t) = K \left\{ 1 + (\alpha - 1) \sum_{j=1}^{\infty} \alpha^{j-1} \left[1 - [1 + \beta t + \frac{(\beta t)^2}{2!} + \frac{(\beta t)^3}{3!} + \dots + \frac{(\beta t)^{jn-1}}{(jn-1)!}] \exp(-\beta t) \right] \right\}.$$

From (8),

$$M(t)a(x, t) = \begin{cases} K \exp[\beta(x-t)] l(x) \sum_{j=1}^{\infty} \frac{\alpha^j \beta^{nj}}{(jn-1)!} (t-x)^{jn-1}, & 0 \leq x < t, \\ 0, & x \geq t, \end{cases}$$

$$\text{where, from (2.1), } l(x) = [1 + \beta x + \frac{(\beta x)^2}{2!} + \frac{(\beta x)^3}{3!} + \dots + \frac{(\beta x)^{n-1}}{(n-1)!}] \exp(-\beta x).$$

For the vegetative cells, from (9),

(17)

$$\left. \begin{aligned}
 B_V(t) &= \frac{K(2-\alpha)}{\alpha} \exp(-\beta t) \sum_{j=1}^{\infty} \frac{\alpha^j \beta^{jn} t^{jn-1}}{(jn-1)!}, \\
 M_V(t) &= \frac{K(2-\alpha)}{\alpha} \sum_{j=1}^{\infty} \alpha^j \left[1 - [1 + \beta t + \frac{(\beta t)^2}{2!} + \frac{(\beta t)^3}{3!} + \dots + \frac{(\beta t)^{jn-1}}{(jn-1)!}] \exp(-\beta t) \right], \\
 M_V(t)a_V(x, t) &= \begin{cases} \frac{K(2-\alpha)}{\alpha} \exp[\beta t(x-t)] \sum_{j=1}^{\infty} \frac{\alpha^j \beta^{nj}}{(jn-1)!} (t-x)^{jn-1}, & 0 \leq x < t, \\ 0, & x \geq t. \end{cases}
 \end{aligned} \right\} \quad (18)$$

Equations (17) and (18) provide an analysis of the transient stage of growth.

The analysis of the stable stage of growth for the viable cells gives,

$$\left. \begin{aligned}
 B(t) &= \frac{\beta K \alpha^{\frac{1}{n}}}{n} \exp[\beta(\alpha^{\frac{1}{n}} - 1)t], \\
 M(t) &= \frac{\alpha^{\frac{1}{n}} (\alpha - 1) K \exp[\beta(\alpha^{\frac{1}{n}} - 1)t]}{\alpha n (\alpha^{\frac{1}{n}} - 1)}, \\
 M(t)a(x, t) &= \begin{cases} \frac{\beta K \alpha^{\frac{1}{n}}}{n} \exp[\beta(t-x)(\alpha^{\frac{1}{n}} - 1)] l(x), & 0 \leq x < t, \\ 0, & x \geq t. \end{cases}
 \end{aligned} \right\} \quad (19)$$

For the stable population of vegetative cells the results are most easily expressed in terms of the results in (19),

$$\left. \begin{aligned}
 B_V(t) &= \frac{(2-\alpha)}{\alpha} B(t), \\
 M_V(t) &= \frac{2-\alpha}{\alpha-1} [M(t) - K], \\
 M_V(t)a_V(x, t) &= \begin{cases} \frac{2-\alpha}{\alpha l(x)} M(t)a(x, t), & 0 \leq x < t, \\ 0, & x \geq t. \end{cases}
 \end{aligned} \right\} \quad (20)$$

For the stable stage of growth it noted that the average age of a cell that is about to divide is $\frac{n}{\frac{1}{\beta\alpha^n}}$ and the expected lifetime of a newborn viable cell is n/β . Also, from

$$(19) \text{ the doubling time for the stable population of viable cells is } \frac{\ln 2}{\frac{1}{\beta(\alpha^n - 1)}}.$$

Kendall's [3] analysis using the Erlangian Model uses a different approach and is restricted to the case where $\alpha = 2$ (i.e. no vegetative cells are produced) and $K = 1$. His analysis considers the population of viable cells at time t and defines $P(N_n, N_{n-1}, \dots, N_1; t)$ as the probability that there are N_i cells undergoing the i -th of the n sequential events where $i = 1, 2, 3, \dots, n$. The probability generating function $\Phi(z_n, z_{n-1}, \dots, z_1; t)$ for the distribution of cells undergoing the events 1, 2, 3, ..., n is shown to be $Z(\beta t) \exp(-\beta t)$

where $Z(u)$ satisfies $\frac{d^n Z(u)}{du^n} = Z^2(u) \exp(-u)$ with the boundary conditions for $0 \leq i \leq n-1$ satisfying $\frac{d^i Z(u)}{du^i} \Big|_{u=0} = z_{i+1}$. Kendall notes that this differential equation for $Z(u)$

$$n-1 \text{ satisfying } \frac{d^i Z(u)}{du^i} \Big|_{u=0} = z_{i+1}.$$

is intractable for values of $n \geq 2$. However, it is shown that if v_i is the expected value of

N_i then $\frac{dv_1}{d\theta} = 2v_n - v_1$ and $\frac{dv_i}{d\theta} = v_{i-1} - v_i$, for $1 < i \leq n$, where $\theta = \beta t$. This system is

solved to give $v_i = \left(\frac{2}{n}\right)^{\frac{1-i}{n}} \sum_{j=0}^{n-1} w^{j(1-i)} \exp[\beta t(2^{\frac{1}{n}} w^j - 1)]$ where $w = \exp\left(\frac{2i\pi}{n}\right)$ is the

n^{th} complex root of unity and so $M(t) = \sum_{i=1}^n v_i = \exp(-\beta t) \sum_{m=0}^{\infty} \left\{ 2^m \left[\sum_{j=0}^{n-1} \frac{(\beta t)^{mn+j}}{(mn+j)!} \right] \right\}$.

The result for $M(t)$ in (17) reduces to that obtained by Kendall when $K = 1$ and $\alpha = 2$. It is noted that the integral equation formulation which led to (17) is easier than Kendall's approach and certainly gives more general results because it accounts for the possibility of vegetative cells and allows for an initial population size $K \geq 1$. Furthermore, the analysis of the stable stage of growth using (19) and (20) for the integral equation model carries the generalization of Kendall's results further.

The problem may also be formulated as a Bellman-Harris process but for this approach it is necessary to specify q_i for $i = 0, 1, 2$, which is the probability that when a viable cell divides i viable cells are produced [8]. To relate this to the vegetative parameter α used in the integral equation formulation it is reasonable to use $q_0 = 0$, $q_1 =$

$2 - \alpha$, and $q_2 = \alpha - 1$ so that $\sum_{i=0}^2 iq_i = \alpha$ where it is assumed that $1 < \alpha \leq 2$ and so the

cells are reasonably well nourished. If $N(t)$ is the number of viable cells in the population at time t , $P_j(t)$ is the probability that there are j viable cells in the population at time t , and

$F(z, t) = \sum_{j=0}^{\infty} P_j(t)z^j, |z| \leq 1$ is the associated probability generating function then

$$F(z, t) = \int_0^t h(F(z, t-x))f(x)dx + zl(t) \text{ with } h(u) = (2 - \alpha)u + (\alpha - 1)u^2 \text{ ([12])}.$$

Using the Erlangian Model (14) for $f(x)$ gives,

$$\begin{aligned} F(z, t) \exp(\beta t) &= [1 + \beta t + \frac{(\beta t)^2}{2!} + \dots + \frac{(\beta t)^{n-1}}{(n-1)!}]z + \frac{(2 - \alpha)\beta^n}{(n-1)!} \int_0^t F(z, x) \exp(\beta x) (t-x)^{n-1} dx \\ &\quad + \frac{(\alpha - 1)\beta^n}{(n-1)!} \int_0^t F^2(z, x) \exp(\beta x) (t-x)^{n-1} dx. \end{aligned}$$

Differentiating n times gives,

$$\frac{\partial^n}{\partial t^n} [F(z, t) \exp(\beta t)] = \beta^n \exp(\beta t) F(z, t) [(\alpha - 1)F(z, t) + 2 - \alpha]. \quad (21)$$

Bharucha-Reid [12] shows that if

$M_2(t) = 2(\alpha - 1) \int_0^t M^2(x) f(x) dx + \alpha \int_0^t M_2(x) f(x) dx$ then the variance of $N(t)$ is given

by $M_2(t) + M(t)[1 + M(t)]$ and $M_2(t)$ satisfies the differential equation,

$$\frac{\partial^n}{\partial t^n} [M_2(t) \exp(\beta t)] = \beta^n [2(\alpha - 1)M^2(t) + \alpha M_2(t)] \exp(\beta t), \quad (22)$$

where $M_2(0) = 0$.

In the particular case where $n = 1$ (Malthusian Model) (21) becomes,

$\frac{\partial F}{\partial t} = (\alpha - 1)\beta F(F - 1)$ with the initial condition $F(z, 0) = z$, which corresponds to $K = 1$.

$$F(z, t) = \begin{cases} z, & \alpha = 1, \\ \frac{z \exp[-(\alpha - 1)\beta t]}{1 - [\exp[-(\alpha - 1)\beta t]z]}, & 1 < \alpha \leq 2, \text{ and for } t > 0 \end{cases}$$

$$P_j(t) = \begin{cases} \exp[-(\alpha - 1)t] \left[1 - \exp[-(\alpha - 1)t]\right]^{j-1}, & j \geq 1, \text{ when } 1 < \alpha \leq 2, \text{ and} \\ 0, & j = 0, \end{cases}$$

$$P_j(t) = \begin{cases} 1, & j = 1, \\ 0, & j \neq 1, \end{cases} \text{ when } \alpha = 1. \text{ Hence, } M(t) = \sum_{j=0}^{\infty} j P_j(t) = \frac{\partial F}{\partial z} \Big|_{z=1} = \exp[\beta(\alpha - 1)t].$$

Equation (22) becomes $\frac{\partial M_2(t)}{\partial t} + \beta(1 - \alpha)M_2(t) = 2\beta(\alpha - 1)\exp[2\beta(\alpha - 1)t]$ which

gives,

$$M_2(t) = \begin{cases} 2\exp[\beta(\alpha - 1)t] \left[\exp[\beta(\alpha - 1)t] - 1\right], & 1 < \alpha \leq 2, \\ 0, & \alpha = 1. \end{cases} \text{ Hence, the variance for } N(t)$$

is

$$\begin{cases} \exp[\beta(\alpha - 1)t] \left[\exp[\beta(\alpha - 1)t] - 1\right], & 1 < \alpha \leq 2, \\ 0, & \alpha = 1, \end{cases} \text{ and the coefficient of variation is}$$

$$\sqrt{1 - \exp[-\beta(\alpha - 1)t]} \text{ for } 1 < \alpha \leq 2, \text{ and it approaches 1 for large values of } t.$$

It is seen that by formulating the problem as a Bellman-Harris process with appropriate values for q_i it is possible to determine the distribution for the size of the viable cell population and obtain the variance of this population size for the Malthusian Model ($n = 1$). However, the n^{th} order differential equations (21) and (22) for $F(z, t)$ and $M_2(t)$, respectively, indicate the extra difficulties in obtaining results for $n \geq 2$ by analytic methods compared to the analysis using the integral equation model. Also, in practice it seems reasonable to assume that an estimate of the vegetative parameter α would be easier to obtain than the values of q_i and, from an estimate of α , the integral equation model provides extensive information without requiring any knowledge of the values for q_i .

The Generalized Erlangian Model and Rahn's Model

As might be expected it is difficult to obtain analytic results using the Generalized Erlangian Model (13) for the generation time density and the same is true for the use of Rahn's Model (15). For example, using Rahn's Model (15) and the Generalized Erlangian Model (13), in (11), and taking Laplace transforms gives,

$$B^*(s) = \frac{\alpha K n! \beta^n}{\prod_{j=1}^n (s + j\beta) - n! \alpha \beta^n} \text{ and } B^*(s) = \frac{\alpha K \left(\prod_{j=1}^n \beta_j \right) \sum_{j=1}^n \frac{A_j}{(s + \beta_j)}}{1 - \alpha \left(\prod_{j=1}^n \beta_j \right) \sum_{j=1}^n \frac{A_j}{(s + \beta_j)}}, \text{ respectively.}$$

In both cases the inversion is in general a difficult procedure with the results being dependent on the value of α . However, for each of these models in the case where $n = 1$ (Malthusian Model), and the case where $n = 2$ and $1 < \alpha \leq 2$, which corresponds to a situation where the cells are reasonable well nourished, it is possible to obtain closed form expressions for $B(t)$ and $M(t)$ for the transient and stable stages of growth. These results are displayed in Table 2 which also includes for comparative purposes the corresponding results for the Erlangian Model (14) obtained from the relevant parts of (17).

Other characteristics of the populations of viable and vegetative cells as well as the total population may be obtained from the results in Table 2 using the descriptions derived from the integral equation model presented previously. For example, from Table 2 it is seen that for the stable population of viable cells where $n = 2$ and $1 < \alpha \leq 2$ a comparison of the doubling times for the different models of the generation time density may be made and,

$$T_E = \frac{\ln 2}{\beta(\sqrt{\alpha} - 1)} \text{ (Erlangian Model)} > T_R = \frac{2 \ln 2}{\beta(\sqrt{1 + 8\alpha} - 3)} \text{ (Rahn's Model)} >$$

$$T_M = \frac{\ln 2}{\beta(\alpha - 1)} \text{ (Malthusian Model). Also, the doubling time for the Generalized}$$

Erlangian Model is given by $T_{GE} = \frac{2 \ln 2}{\sqrt{(\beta_1 - \beta_2)^2 + 4\alpha\beta_1\beta_2} - (\beta_1 + \beta_2)}$ and it is seen

that,

$$\begin{cases}
 T_{GE} \leq T_M, & \Phi(\beta_1, \beta_2) \geq 1, \\
 T_M < T_{GE} \leq T_R, & 1 > \Phi(\beta_1, \beta_2) \geq \frac{\sqrt{17} - 3}{2}, \\
 T_R < T_{GE} \leq T_E, & \frac{\sqrt{17} - 3}{2} > \Phi(\beta_1, \beta_2) \geq \sqrt{2} - 1, \\
 T_E < T_{GE}, & \sqrt{2} - 1 > \Phi(\beta_1, \beta_2) > 0,
 \end{cases}
 \quad \text{where,}$$

$$\Phi(\beta_1, \beta_2) = \frac{\sqrt{(\beta_1 + \beta_2)^2 + 4\beta_1\beta_2} - (\beta_1 + \beta_2)}{2\beta}.$$

Table 2. $B(t)$ and $M(t)$ for the Generalized Erlangian, Rahn's, and the Erlangian

Stage	Model of the Generation Time Density Function
Transient	<p>Malthusian Model [$n = 1$ in equations (13)-(15)]: $B(t) = \alpha\beta K \exp[\beta(\alpha - 1)t], M(t) = K \exp[\beta(\alpha - 1)t]$</p> <p>Generalized Erlangian Model [$n = 2, 1 < \alpha \leq 2$, in (13)]:</p> $ B(t) = \frac{\alpha K \beta_1 \beta_2}{\sqrt{(\beta_1 - \beta_2)^2 + 4\alpha\beta_1\beta_2}} \left[\exp \left[\frac{\sqrt{(\beta_1 - \beta_2)^2 + 4\alpha\beta_1\beta_2} - (\beta_1 + \beta_2)}{2} t \right] \right. \\ \left. - \exp \left[\frac{-\sqrt{(\beta_1 - \beta_2)^2 + 4\alpha\beta_1\beta_2} - (\beta_1 + \beta_2)}{2} t \right] \right], M(t) = \frac{2(\alpha - 1)B(t)}{\alpha} $ <p>Rahn's Model [$n = 2, 1 < \alpha \leq 2$, in (15)]:</p> $ B(t) = \frac{2\alpha\beta K}{\sqrt{1 + 8\alpha}} \{ \exp \left[\frac{\beta}{2} (\sqrt{1 + 8\alpha} - 3) t \right] - \exp \left[\frac{-\beta}{2} (\sqrt{1 + 8\alpha} + 3) t \right] \}, \\ M(t) = \frac{4(\alpha - 1)K}{\sqrt{1 + 8\alpha}} \left\{ \frac{\exp \left[\frac{\beta}{2} (\sqrt{1 + 8\alpha} - 3) t \right]}{\sqrt{1 + 8\alpha} - 3} + \frac{\exp \left[\frac{-\beta}{2} (\sqrt{1 + 8\alpha} + 3) t \right]}{\sqrt{1 + 8\alpha} + 3} \right\} $ <p>Erlangian Model [$n = 2$ in (14)]:</p> $ B(t) = \frac{\beta K \sqrt{\alpha}}{2} \left[\exp(\beta t \sqrt{\alpha}) - \exp(-\beta t \sqrt{\alpha}) \right] \exp(-\beta t), \\ M(t) = \frac{K}{2\sqrt{\alpha}} \left[(\sqrt{\alpha} + 1) \exp[\beta(\sqrt{\alpha} - 1)t] + (\sqrt{\alpha} - 1) \exp[-\beta(\sqrt{\alpha} + 1)t] \right] $

Stable	<p>Malthusian Model [$n = 1$ in equations (13)-(15)]: $B(t)$ and $M(t)$ are exactly as for the transient stage of growth</p> <p>Generalized Erlangian Model [$n = 2, 1 < \alpha \leq 2$, in (13)]:</p> $B(t) = \frac{\alpha K \beta_1 \beta_2}{\sqrt{(\beta_1 - \beta_2)^2 + 4\alpha\beta_1\beta_2}} \exp \left[\left[\frac{\sqrt{(\beta_1 - \beta_2)^2 + 4\alpha\beta_1\beta_2} - (\beta_1 + \beta_2)}{2} \right] t \right],$ $M(t) = \frac{2(\alpha - 1)B(t)}{\alpha}$ <p>Rahn's Model [$n = 2, 1 < \alpha \leq 2$, in (15)]:</p> $B(t) = \frac{2\alpha\beta K}{\sqrt{1 + 8\alpha}} \exp \left[\frac{\beta}{2} \left(\sqrt{1 + 8\alpha} - 3 \right) t \right], M(t) = \frac{4(\alpha - 1)K \exp \left[\frac{\beta}{2} \left(\sqrt{1 + 8\alpha} - 3 \right) t \right]}{\sqrt{1 + 8\alpha} (\sqrt{1 + 8\alpha} - 3)}$ <p>Erlangian Model [$n = 2$ in (14)]:</p> $B(t) = \frac{\beta K \sqrt{\alpha}}{2} \exp \left[\beta (\sqrt{\alpha} - 1) t \right], M(t) = \frac{K (\sqrt{\alpha} + 1) \exp \left[\beta (\sqrt{\alpha} - 1) t \right]}{2\sqrt{\alpha}}$
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6. A Time Dependent Vegetative Parameter $\alpha(t)$

So far the discussion has been mainly concerned with the situation where the vegetative parameter $\alpha(t)$ is constant. It is more realistic to assume that it is time dependent which may reflect variations in the level of nourishment available, or other environmental factors, and factors operating within the cell itself which may cause the production rate of viable cells to vary with time.

As before, it is assumed that the initial population consists entirely of K newborn viable cells and so (13) becomes,

$$B(t) = \alpha(t) K f(t) + \alpha(t) \int_0^t B(t-x) f(x) dx, \quad (23)$$

and $f(x)$ is assumed to be the Erlangian density function (14). Unfortunately, in general the solution of (23) is no longer amenable to the use of the Laplace transforms as was the case when $\alpha(t)$ was constant. Instead, the substitution $B(t) = \alpha(t)v(t)\exp(-\beta t)$ is used in (23) to give,

$$v(t) = \frac{\beta^n K t^{n-1}}{(n-1)!} + \frac{\beta^n}{(n-1)!} \int_0^t \alpha(x)v(x)(t-x)^{n-1} dx. \quad (24)$$

Differentiating (24) n times with respect to t gives,

$$\frac{d^n v(t)}{dt^n} - \beta^n \alpha(t)v(t) = 0, \quad (25)$$

and assuming that $a(t)$ is analytic for $t \geq 0$, a series solution may be obtained for $v(t)$ in (25) as,

$$\left. \begin{aligned} v(t) &= K\beta^n t^{n-1} + \sum_{i=n}^{\infty} b_i t^i \text{ where} \\ b_i &= 0, 0 \leq i \leq n-2, \\ b_{n-1} &= K\beta^n, \\ b_{n+i} &= \frac{\beta^n i!}{(n+i)!} \sum_{j=0}^i \alpha_j, i = 0, 1, 2, \dots, \end{aligned} \right\} \quad (26)$$

and the α_j are the coefficients in the series expansion of,

$$\alpha(t) = \sum_{j=0}^{\infty} \alpha_j t^j. \quad (27)$$

Hence, the series solution for $B(t)$ is given by $B(t) = a(t)v(t)\exp(-\beta t)$ where $v(t)$ and $a(t)$ have the series expansions in (26) and (27), respectively. Substituting the series expansions for $B(t)$ and $a(t)$ in (4) gives the series expansion for $M(t)$ as,

$$\left. \begin{aligned} M(t) &= K + \sum_{i=0}^{\infty} \frac{c_i t^{i+1}}{(i+1)!} \text{ where} \\ c_i &= \sum_{j=0}^i \left\{ \alpha_j \left[\sum_{k=0}^{i-j} \frac{b_k (-\beta)^{i-j-k}}{(i-j-k)!} \right] \right\} - \sum_{k=0}^i \frac{b_k (-\beta)^{i-k}}{(i-k)!}, i \geq 0, \end{aligned} \right\} \quad (28)$$

where the b_i , α_i are given by (26) and (27), respectively.

In the particular case where $n=1$ (Malthusian Model) the expressions for $B(t)$ and $M(t)$ are simpler and,

$$\left. \begin{aligned} B(t) &= \beta K \alpha(t) \exp \left[\beta \int_0^t (\alpha(u) - 1) du \right], \\ M(t) &= \frac{B(t)}{\beta \alpha(t)} = K \exp \left[\beta \int_0^t (\alpha(u) - 1) du \right]. \end{aligned} \right\} \quad (29)$$

Consequently, closed form expressions for $B(t)$ and $M(t)$ can usually be obtained for the case $n=1$ for both the transient and stable stages of growth whereas for $n \geq 2$ series expansions are obtained using equations (26)-(28).

In order to illustrate the procedure two examples are considered using the Erlangian density function (14) for the generation time. In the first example $a(t)$ decreases exponentially over time which corresponds to a situation where factors

operating within the cell or its environment lead to a decrease in the production rate of viable cells over time. The second example illustrates a situation where the change in $\alpha(t)$ is represented by an S-shaped logistic function where $\alpha(t)$ increases over time to a limiting value. In both examples expressions for $B(t)$ are found for the transient stage of growth for the case $n \geq 2$ and for the case $n = 1$ (Malthusian Model) both $B(t)$ and $M(t)$ are found for the transient and stable stages of growth. The results are presented in Table 3.

Table 3. Solutions for choices of $\alpha(t)$

Vegetative Parameter $\alpha(t)$	Transient Solution for $B(t)$		Stable Solution for $B(t)$
	$n \geq 2$	$n = 1$ (Malthusian Model)	$n = 1$ (Malthusian Model)
Example 1 (Exponential Decrease) $\alpha(t) = c + L \exp(-\lambda t)$, $\lambda > 0, L > 0$, $0 < c < L + c \leq 2$.	$B(t) = \beta K \alpha(t) v(t);$ $v(t) = \beta^n K t^{n-1} + \sum_{i=n}^{\infty} b_i t^i;$ $b_i = 0, \text{ for } 0 \leq i \leq n-2,$ $b_{n-1} = \beta^n K,$ $b_{n+k} = \frac{\beta^n k!}{(n+k)!} \sum_{j=0}^k \alpha_j b_{k-j},$ $\text{for } k = 0, 1, 2, \dots;$ $\alpha_0 = c + L, \alpha_j = \frac{L(-\lambda)^j}{j!},$ $\text{for } j = 1, 2, 3, \dots$	$B(t) = \beta K \alpha(t) \times$ $\exp \left\{ \beta \left[\frac{L}{\lambda} + (c-1)t - \frac{L \exp(-\lambda t)}{\lambda} \right] \right\}$ $M(t) = K \times$ $\exp \left\{ \beta \left[\frac{L}{\lambda} + (c-1)t \right] \right\}$	$B(t) = c \beta K \times$ $\exp \left\{ \beta \left[\frac{L}{\lambda} + (c-1)t \right] \right\}$ $M(t) = K \times$ $\exp \left\{ \beta \left[\frac{L}{\lambda} + (c-1)t \right] \right\}$

Example 2. (Logistic) $\alpha(t) = \frac{Lc}{c + (L - c) \exp(-\lambda t)},$ $\lambda > 0,$ $1 < c < L \leq 2.$	$B(t) = \alpha(t)v(t) \exp(-\beta t);$ $v(t) = \sum_{i=0}^{\infty} b_i t^i$ $b_i = 0, \text{ for } 0 \leq i \leq n - 2,$ $b_{n-1} = \beta^n K, b_n = 0,$ $b_{n+k} = \frac{c\beta^n b_k k!}{(n+k)!} + \frac{(c-L)k!}{L(n+k)!} \times \sum_{j=1}^k \frac{(-\lambda)^j b_{n+k-j} (n+k-j)!}{j! (k-j)!},$ $\text{for } k = 1, 2, 3, \dots.$	$B(t) = \beta K \alpha(t) \exp[\beta(L-1)t] \times \left[\frac{c}{\alpha(t)} \right]^{\frac{\beta L}{\lambda}}$ $M(t) = K \exp[\beta(L-1)t] \times \left[\frac{c}{\alpha(t)} \right]^{\frac{\beta L}{\lambda}}$	$B(t) = \beta K L \left(\frac{c}{L} \right)^{\frac{\beta L}{\lambda}} \times \exp[\beta(L-1)t]$ $M(t) = K \left(\frac{c}{L} \right)^{\frac{\beta L}{\lambda}} \times \exp[\beta(L-1)t]$
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From Example 1 in Table 3 for the case $n = 1$ it is seen that in the stable population of viable cells $M(t)$ is dependent on the value of c . For $0 < c < 1$, $M(t) \rightarrow 0$ for large values of t , leaving only vegetative cells in the population. In this case the halving

time for the population of viable cells is $\frac{\ln 2}{\beta(1-c)}$. For $c = 1$, $M(t) = K \exp(\frac{\beta L}{\lambda} t)$ which

corresponds to a constant number of viable cells. For $1 < c < L + c \leq 2$ the number of viable cells increases without bound as t increases but approaches $K \exp(\frac{\beta L}{\lambda} t)$ as c

approaches 1 and the doubling time is $\frac{\ln 2}{\beta(c-1)}$.

From Example 2 in Table 3 it is seen that for $n = 1$ the number of viable cells increases without bound as t increases. The doubling time for the stable population of

viable cells is $\frac{\ln 2}{\beta(L-1)}$.

7. Conclusion

The integral (renewal) equation model used by demographers to describe the growth of human populations has been modified to develop a model which describes the growth of a population of viable and vegetative cells. The viable cells are capable of dividing to produce 2 new cells where on average $\alpha(t)$ of these newborn cells are viable and $2 - \alpha(t)$ are vegetative cells, which are not capable of division. The model has been

analyzed using various biologically plausible forms for the inputs $\alpha(t)$ and $f(x)$ which is the density function for the generation time of the viable cells. Throughout the presentation the use of the integral equation model is compared to other modeling approaches and the integral equation approach is shown to have advantages.

The formulation of the model is simple and is based on a modification of the integral (renewal) equation of population dynamics which has a long history of importance in the study of many biological and physical phenomena particularly where the age structure of the population varies with time [13,31]. The outputs from the model enable a complete analysis of the total population of all of the cells as well as the subpopulations of viable and vegetative cells during both the transient and stable stages of growth. In addition, a range of other growth parameters (e.g. doubling times and crude birth rates) may be determined which in turn may be used to compare the effects of different assumptions about inputs to the model. Other approaches do not include the possibility of the production of vegetative cells (e.g. Kendall [3] and Thornley [1]) and there is a preoccupation among other approaches with only the stable stage of growth with no analysis of the earlier transient stage when viable cells present in the initial population have not all divided (e.g. Powell [2] and Thornley [1]). This preoccupation may not be justified in terms of the variability of environmental and other factors which influence the growth process.

If the input parameter $\alpha(t)$ is constant, which is a common assumption in other approaches, the model may be solved easily using Laplace transforms and a rigorous presentation of the theory of this method of solution has been presented as early as 1941 by Feller [14]. Estimates of $\alpha(t)$ are easier to obtain than the input parameters needed in other approaches (e.g. a Bellman-Harris process). If $\alpha(t)$ is time dependent then under plausible assumptions about the generation time distribution series solutions may be obtained from the model. Also, well established numerical techniques are available for solving the model [17-20].

Finally, although the details are not presented in this article, in practice values of the density function for the generation time may be obtained from experimental data most naturally represented in either histogram or concentrated form. One approach is to fit theoretical forms (e.g. Erlangian curves) to this empirical data but this is not without difficulties as indicated in the introductory remarks for section 5.2 and, as noted by Feller [14], unless the curve fitting is done by the method of moments then the asymptotic values of $B(t)$ will depend on the method used. Consequently, it is often an advantage to use the empirical data in its natural form.

If the data is in histogram form then $\frac{B(t)}{\alpha(t)}$ in (23) may be represented by a system of

integro-difference equations and solutions for $B(t)$ can be obtained in each of the consecutive time intervals used in the histogram. If the data is in concentrated form then

$\frac{B(t)}{\alpha(t)}$ in (23) becomes a set of difference equations involving Dirac delta functions and

again solutions for $B(t)$ can be obtained in each of the consecutive time intervals.

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