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An Age and Position Dependent Model for the Growth of a Column of Cells

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Abstract

A probabilistic model is developed for the growth of cells in a one dimensional column. The integral equation used by demographers to describe age dependence in population modeling is extended to incorporate position dependence and accounts for cell division and growth in the column which depend on the position of the cells and their ages. The model provides a basic description of the growth characteristics associated with a plant root or a thin leaf.

Keywords: age and position dependence, cell division, one dimensional cell growth, root and leaf growth.

1. Introduction

A survey of recent publications related to mathematical models of cell division and cell growth indicates that most attention has been focused on these processes in relation to tumors that affect humans [1-8] with less attention to models related specifically to plant growth [9-11]. In general, the models target mechanisms operating within cells involving complex chemical and biological processes that have an impact on cell division, dispersion, and interaction. In relation to plant growth, Sharova [12], Yang et al. [13], and Maughan et al. [14] provide comprehensive insights into the nature of these complex chemical and biological process. However, the survey did not reveal any publications,

other than those referred to below, concerned with the problem addressed in this article, which is the development of an age specific position dependent probabilistic model of the growth of a one dimensional column of cells.

Consider the cells in a one dimensional column typified by a growing root or a thin leaf. If a point in this column is marked then on a small time scale and under high magnification the movement of this mark over time traces out a polygonal curve where the vertices would represent the instances when cell division has occurred in the column below the marked point. If this procedure is repeated many times then the mean of these polygonal curves could be represented by a trajectory which has continuous derivatives and an S-shape which reflects the eventual slowing down of the growth of the column.

If many equidistant points are marked in the initial column then the problem is to describe simultaneously in time the set of trajectories traced out by these points. An excellent survey of the biological factors associated with this problem was given as early as 1976 by Erikson [15]. There are two methods which may be used to find a solution to this problem: a deterministic logistic approach, which originated with Salamon et al. [16]; and the approach used by demographers in modeling the growth of human populations [17].

In the logistic approach a typical trajectory is fitted by a logistic or one of many other S-shaped functions. With this approach all of the age dependent properties of the cells are ignored and only some artificial average cell is considered. Furthermore, the cell division and cell growth processes are not modeled explicitly and there is no output concerning characteristics of the two subpopulations of viable cells, which are capable of division, and vegetative cells, which are not capable of division. Winley [18] has noted in the context of stochastic population modeling that although a logistic model is appealing its appeal is based more on its simplicity than its realism since it ignores important characteristics such as the age distribution of the individuals in the population.

The second approach is that used by demographers and incorporates the age specific characteristics of the cells in the column. An early but thorough exposition of the development and use of the model in the context of modeling human populations is given by Keyfitz [17]. The model takes the form of an integral equation which involves an age and time dependent density function for the random variable representing the generation time of a viable cell which is the time from the birth of a cell, as a result of cell division, to the instant when it divides (dies). Although this integral equation model includes age dependency it does not include position dependency and therefore it is

assumed that cells of the same age exhibit the same behavior regardless of where they are positioned in the column.

The purpose of this article is to describe a probabilistic model which takes into account the age and position characteristics of the viable and vegetative cells in the column. Consequently, it addresses the deficiencies of the logistic approach, which ignores the age characteristics of cells and explicit modeling of the cell division and growth processes, and the deficiency of the demographic approach, which ignores position dependent characteristics of cells in the column. In common with the logistic approach the model is formulated in a Lagrangian reference system where the position of a cell in the column at any time is referenced by the position of its ancestor in the column at time zero.

Definitions and notations are presented next with examples of the logistic approach. This is followed by the development of the age specific position dependent model which is structured into three dependent stages. The description of the first stage includes a discussion of the case where the density function for the generation time is dependent on only the age of the cell and its position. An example related to the growth of a plant root is given in order to illustrate the mathematical techniques used throughout the three stages and this is followed by concluding remarks.

2. Definitions and Notation

The column consists of a mixture of cells, some of which are viable (fissioning or dividing) cells and the remaining cells are vegetative (nonviable or quiescent) cells. Both types of cells are capable of growth (elongation), but only the viable cells can divide and when this occurs exactly 2 new cells are born. On average $\alpha(t, p)$ of these 2 new cells are viable and the other $2 - \alpha(t, p)$ are vegetative and $\alpha(t, p)$ is referred to as the vegetative parameter.

The total height of the column at time $t = 0$ is 1 unit and $y(t, p)$ is the height of a cell from the base of the column at time t . If the cell was in the column at time $t = 0$ then p refers to its initial height from the base and $0 \leq p \leq 1$. If the cell was formed as the result of cell division(s) in the interval of time $(0, t)$ then p refers to the height of its viable ancestor above the base at time $t = 0$. Thus cells can be characterized in terms of p which is either their or their ancestor's, initial position in the column. As a result of the elongation of cells in the column $y(t, p)$ is a non decreasing function of t and $y(0, p) = p$. If

$\frac{\partial y(t, p)}{\partial t} > 0$ then there is growth in the column below the cell at position p and if

$\frac{\partial y(t, p)}{\partial t} \big|_{p=1} = 0$ then all growth in the column has ceased. The stretch ratio $\sigma(t, p) =$

$\frac{\partial y(t, p)}{\partial p}$ and it is a measure of how much an element dp in the initial column has

stretched in time t . It is a non decreasing function of t such that $\sigma(0, p) = 1$ and $\sigma(t, p) \geq 1$ for $t > 0$. When $\sigma(t, p)$ becomes constant in time growth has ceased for the element dp .

Table 1 defines growth parameters of interest and indicates the relationships among them. It is noted that only one of these is independent of the others and all of these may be calculated as outputs from the model.

Table 1: Relationships among growth parameters

Growth Parameters	Notations and Relationships
Distance	$y(t, p)$
Growth rate (velocity)	$v(t, p) = \frac{\partial y}{\partial t} = y(0, p) + \int_0^t v(z, p) dz$
Relative growth rate	$\rho(t, p) = \frac{1}{y} \frac{\partial y}{\partial t} = \frac{v}{y}, \quad y(t, p)$ $= y(0, p) \exp\left(\int_0^t \rho(z, p) dz\right)$
Stretch ratio	$\sigma(t, p) = \frac{\partial y}{\partial p}, \quad y(t, p) = \int_0^p \sigma(t, z) dz$
Divergence	$\delta(t, p) = \frac{\partial \sigma}{\partial t} = \frac{\partial v}{\partial p} = \frac{\partial^2 y}{\partial p \partial t}, \quad y(t, p) =$ $\int_0^t \int_0^p \delta(u, z) dz du$
Relative elemental growth rate (RELEL)	$g = \frac{\delta}{\sigma} = \frac{1}{\sigma} \frac{\partial \sigma}{\partial t} = \frac{\partial \ln \sigma}{\partial t}, \quad y(t, p) =$ $\int_0^p \exp\left(\int_0^t g(z, u) dz\right) du$

The following definitions and notation apply to viable cells in position p at time t and similar definitions hold where subscripts V and T are used to describe the vegetative and total cell populations, respectively:

$M(t, p)dp$ is the mean number of cells in the element dp at time t ;

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

$a(x, t, p)$ is the age density function of cells of age x at time t ;

$g(x, t, p)$ is the growth function of cells of age x at time t . If the cell was in the initial column and it has not divided by time t then $g(x, t, p)$ is the average length of that cell at time t . Otherwise, it is the average length of a cell whose age at time t is x and its ancestor occupied position p in the initial column;

$f(x, t - x, p)$ is the probability density function of the generation time, X , for cells of age x ;

$\mu(x, t - x, p)$ is the age specific fission rate of cells of age x ;

$l(x, t - x, p)$ is the survivor function which is the probability that a viable cell born at time $t - x$ has not divided by age x .

If $f(x, t - x, p)$ is the density function of the random variable X which represents the generation time for a cell timed from the instant it was born from the division of its mother until it divides (or dies) then $f(x, t - x, p)dx$ is the probability that a cell born at time $t - x$ in position p will divide between ages x and $x + dx$. Then $l(x, t - x, p)$ is the probability that $X > x$ and $\mu(x, t - x, p)dx$ is the probability that $x < X \leq x + dx$ given that $X > x$. It is noted that only one of these variables characterizing cell division is independent since,

$$f(x, t-x, p) = \mu(x, t-x, p) l(x, t-x, p) \text{ and } l(x, t-x, p) = 1 - \int_0^x f(u, t-x, p) du, \quad (1)$$

and the dependence on time is expressed in terms of $t - x$ the time at which the cell was formed by the division of its mother cell.

Before presenting the development of the probabilistic age and position dependent model the deterministic logistic approach is illustrated with two examples.

Examples of the Logistic Approach: Suppose that $y(t, p)$ is approximated by the

deterministic S-shaped function, $\frac{Kp^2}{1 + (Kp - 1)\exp(-rt)}$ where $r > 0$, $y(0, p) = p$, and $Kp > 1$.

As t increases $y(t, p)$ increases from its initial value of p to an asymptotic value of Kp^2 .

$$\text{The stretch ratio } \sigma(t, p) = \frac{\partial y(t, p)}{\partial p} = \frac{Kp[2 + (Kp - 2)\exp(-rt)]}{[1 + (Kp - 1)\exp(-rt)]^2} =$$

$\frac{y(t,p)}{p} \left\{ 1 + \frac{[1 - \exp(-rt)]y(t,p)}{Kp^2} \right\}$ and as t increases $\sigma(t, p)$ increases from an initial value

of 1 to an asymptotic value of $2Kp$. This corresponds roughly to growth in the root of a plant

However, if $y(t, p) = \frac{Kp(1-p)}{1 + [K(1-p) - 1]\exp(-rt)}$ where $r > 0$, $y(0, p) = p$, and $K(1 -$

$p) > 1$ then $y(t, p)$ increases with t from p to the asymptotic value $Kp(1 - p)$. The stretch

ratio $\sigma(t, p) = \frac{y(t, p)}{p(1-p)} [1 - 2p + y(t, p)\exp(-rt)]$ and it increases from $\sigma(0, p) = 1$ to an

asymptotic value of $K(1 - 2p)$. Since $\sigma(t, p) \geq 1$ it follows that for the model to be reasonable $0 \leq p \leq (1 - 1/K)/2$ and so the length of the initial column must not exceed $(1 - 1/K)/2$ with $K > 1$. The expression for the stretch ratio indicates that this model is applicable to the type of growth expected in a thin leaf where the displacement of any point p is $p(K - 1 - pK)$ and in particular the tip of the leaf is displaced by $(K - 1)^2/4K$.

3. Development of the Age and Position Dependent Model

The model is developed in three stages. The first stage is concerned only with a point process made up of viable and vegetative cells which are considered to be points. The inputs to this stage are the generation time density function $f(x, t - x, p)$ and the vegetative parameter $\alpha(t, p)$. Among the various outputs from the first stage the following are required as inputs for one or both of the next two stages: the average cell densities $M(t, p)$ and $M_v(t, p)$ in the element dp ; the age probability density functions $a(x, t, p)$ and $a_v(x, t, p)$; and $\mu(x, t - x, p)$. The second stage uses the inputs $a(x, t, p)$ and $\mu(x, t - x, p)$ from the first stage and determines plausible biological growth functions for $g(x, t, p)$ and $g_v(x, t, p)$. These, together with $M(t, p)$, $M_v(t, p)$, $a(x, t, p)$, and $a_v(x, t, p)$, become inputs for the third stage which involves the growth (elongation) of the cells. The main output from this stage is the stretch ratio $\sigma(t, p)$ from which other growth parameters of interest displayed in Table 1 may be determined.

Figure 1 shows the flow of the inputs and outputs in relation to each of the three stages of the model development. The detailed development of stages 1, 2, and 3 is presented in the following subsections.

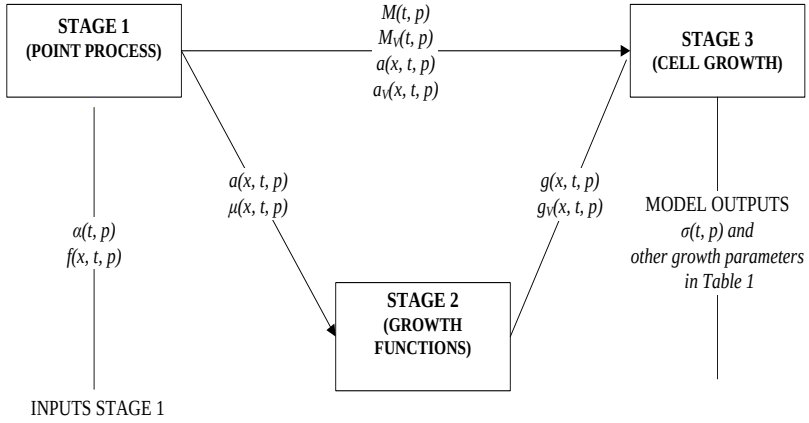


Figure 1: The flow of inputs and outputs among the three stages of model development

3.1 Stage 1 (The Point Process)

The expected number of points representing viable cells at time t in the element of the column p to $p + dp$ is considered and 2 new points are recorded whenever a cell divides. From the definitions it follows that the expected number of cells of age x to $x + dx$ within the element dp is $M(t, p)a(x, t, p)dx dp = B(t - x, p)l(x, t - x, p)dx dp$. Knowing the initial mean density of the cells and the initial age density, at time t this becomes,

$$M(t, p)a(x, t, p) = \begin{cases} B(t - x, p)l(x, t - x, p), & 0 \leq x < t, \\ M(0, p)a(x - t, 0, p)l(x, t - x, p) / l(x - t, t - x, p), & x \geq t. \end{cases} \quad (2)$$

Integrating in (2) with respect to x gives,

$$M(t, p) = M_0(t, p) + \int_0^t B(t - x, p)l(x, t - x, p)dx, \quad (3)$$

$$\text{where, } M_0(t, p) = M(0, p) \int_t^\infty a(x - t, 0, p) \frac{l(x, t - x, p)}{l(x - t, t - x, p)} dx,$$

$$= M(0, p) \int_0^\infty a(x, 0, p) \frac{l(x + t, -x, p)}{l(x, -x, p)} dx,$$

$$= \int_t^\infty B(t - x, p)l(x, t - x, p)dx. \quad (4)$$

Thus $M_0(t, p)$ represents the expected number of survivors from the initial viable cells and the integral term in (3) represents the expected number of cells that have been born as a result of cell divisions since time $t = 0$. Similarly, if $D(t, p)dp$ represents the rate of cell division within the element dp at time t then $D(t, p) = D_0(t, p) +$

$$\int_0^t B(t-x, p) f(x, t-x, p) dx, \text{ where, } D_0(t, p) = M(0, p) \int_0^\infty a(x, 0, p) \frac{f(x+t, -x, p)}{l(x, -x, p)} dx.$$

At the instant that a viable cell divides exactly 2 new cells are born and on average only $\alpha(t, p)$ of these new cells are viable. Consequently,

$$B(t, p) = G(t, p) + \alpha(t, p) \int_0^t B(t-x, p) f(x, t-x, p) dx, \quad (5)$$

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

It is seen from (3) to (6) that $B(t, p)$, $M(t, p)$ and $D(t, p)$ have a similar structure and if $B(t, p)$ is known for $t < 0$ then,

$$\left. \begin{aligned} B(t, p) &= \alpha(t, p) \int_0^\infty B(t-x, p) f(x, t-x, p) dx, \\ M(t, p) &= \int_0^\infty B(t-x, p) l(x, t-x, p) dx, \\ \text{and } D(t, p) &= \int_0^\infty B(t-x, p) f(x, t-x, p) dx. \end{aligned} \right\} \quad (7)$$

From (7) it is seen that,

$$B(t, p) = \alpha(t, p) D(t, p), \quad (8)$$

and $\frac{\partial M(t, p)}{\partial t} = B(t, p) - D(t, p)$, which means that $\frac{\partial M(t, p)}{\partial t} = \frac{1}{\gamma(t, p)} B(t, p)$, where

$\gamma(t, p) = \frac{\alpha(t, p)}{\alpha(t, p) - 1}$ for $\alpha(t, p) \neq 1$. Consequently,

$$M(t, p) = M(0, p) + \int_0^t \frac{B(u, p)}{\gamma(u, p)} du. \quad (9)$$

It can be shown that (9) and (3) are equivalent but (9) is simpler and will be used subsequently.

The following equations for the vegetative (V) and total cell populations (T) are derived by arguments similar to those used to describe the viable cell population:

$$B_V(t, p) = [2 - \alpha(t, p)]D(t, p) = \left[\frac{2 - \alpha(t, p)}{\alpha(t, p)} \right] B(t, p), \quad (10)$$

$$M_V(t, p) = M_V(0, p) + \int_0^t B_V(u, p) du, \text{ and}$$

$$M_V(t, p)a_V(x, t, p) = \begin{cases} M_V(0, p) a_V(x - t, 0, p), & x \geq t, \\ B_V(t - x, p), & 0 \leq x < t. \end{cases} \quad (11)$$

Then,

$$B_T(t, p) = \frac{2B(t, p)}{\alpha(t, p)}, \quad (12)$$

$$M_T(t, p) = M_T(0, p) + \int_0^t \frac{B(u, p)}{\alpha(u, p)} du, \text{ and}$$

$$M_T(t, p)a_T(x, t, p) = \begin{cases} M(0, p)a(x - t, 0, p) \frac{l(x, t - x, p)}{l(x - t, t - x, p)} + M_V(0, p)a_V(x - t, 0, p), & x \geq t, \\ B(t - x, p) l(x, t - x, p) + B_V(t - x, p), & 0 \leq x < t. \end{cases} \quad (13)$$

Now the point process of the first stage has been formulated. $B(t, p)$ is calculated from (5) and $D(t, p)$ is obtained as a by-product from (8). Then $M(t, p)$ is calculated from (9) and finally $a(x, t, p)$ is obtained from (2). Equations (10) to (13) complete the analysis of the point process.

The Case of a Time Independent Fission Density: Before proceeding to stage 2 of the model formulation it noted that in the particular case where the generation time probability density function $f(x, t - x, p)$ and the vegetative parameter $\alpha(t, p)$ are independent of t then based on the theory of the age specific model presented by Keyfitz [17] the determination of $B(t, p)$ is amenable to the use of Laplace transforms as follows.

Equations (5) and (6) become, $B(t, p) = G(t, p) + \alpha(p) \int_0^t B(t - x, p) f(x, p) dx$, where

$$G(t, p) = \alpha(p)M(0, p) \int_0^\infty a(x, 0, p) \frac{f(x, p)}{l(x, p)} dx. \text{ Taking Laplace transforms and using the}$$

convolution theorem gives $B^*(s, p) = \frac{G^*(s, p)}{1 - \alpha(p)f^*(s, p)}$ where $F^*(s, p)$

$= \int_0^\infty \exp(-su)F(u, p)du$ is the Laplace transform of $F(u, p)$. Inversion of $B^*(s, p)$ gives $B(t,$

$p) = \sum_{j=0}^\infty A_{j,p} \exp(r_{j,p}t)$ where $r_{0,p}$ is the largest real root and $r_{j,p}$ ($j = 1, 2, 3, \dots$) is a

complex root for s of $1 - \alpha(p)f^*(s, p) = 0$. The real part of any of the complex roots is less

than $r_{0,p}$ and the $A_{j,p}$ are given by $\frac{G^*(r_{j,p}, p)}{\alpha(p) \int_0^\infty x \exp(-r_{j,p}x) f(x, p) dx}$, for $j = 0, 1, 2, \dots$.

Consequently, for large values of t (i.e. in the stable or asymptotic population) $B(t, p) = A_{0,p} \exp(r_{0,p}t)$ ([19]).

Also, $\alpha(p)f^*(r_{0,p}, p) = \alpha(p) \int_0^\infty \exp(-r_{0,p}x) f(x, p) dx = 1$ and $f_Z(x, p) = \alpha(p) \exp(-r_{0,p}$

$x)f(x, p)$ may be regarded as the density function for a random variable Z with mean

$\bar{Z} = \alpha(p) \int_0^\infty x \exp(-r_{0,p}x) f(x, p) dx$ where Z is the age at which a cell division occurs in

the stable population.

Various biologically plausible functions may be used for $f(x, p)$ based on different assumptions about the process of cell development that occurs during the period from its birth until it divides.

If a cell divides at the completion of n sequential events $E_1, E_2, E_3, \dots, E_n$ where the events occur at rates $\beta_1, \beta_2, \beta_3, \dots, \beta_n$, respectively, then the probability that exactly k events have been completed by age x is $P_k(x)$ where,

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

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

inverted gives the density function for the generation time as $(\prod_{j=1}^n \beta_j) \sum_{j=1}^n A_j \exp(-\beta_j x)$,

where $A_j = \lim_{s \rightarrow -\beta_j} \left[\frac{s + \beta_j}{\prod_{i=1}^n (s + \beta_i)} \right]$, for $j = 1, 2, 3, \dots, n$, and the expected value of the

generation time is $(\prod_{j=1}^n \beta_j) \sum_{j=1}^n \frac{A_j}{\beta_j^2}$.

If it is assumed for cells in position p that $\beta_j = p$ for $j = 1, 2, 3, \dots, n$, then the density function for the generation time is $f(x, p) = \frac{p^n x^{n-1} \exp(-px)}{(n-1)!}$, which is an Erlangian density function with mean generation time n/p . If it assumed that $\beta_j = jp$ for $j = 1, 2, 3, \dots, n$ then $f(x, p) = [1 - \exp(-px)]^{n-1} np \exp(-px)$, which is the density function for Yule's distribution and the mean generation time is $\frac{n}{p} \sum_{j=0}^{n-1} \frac{(-1)^j}{(j+1)^2} {}^{n-1}C_j$. In both these

cases if $n = 1$, which means that cell division occurs at the completion of a single event, then the generation time has an exponential distribution with probability density function $f(x, p) = p \exp(-px)$ with mean value $1/p$. Under each of these three assumptions the expected value of the generation time decreases as we move from the base of the column to the tip of the column and so these assumptions are consistent with the growth of a plant root for some period of time.

It is noted that the Yule distribution is also obtained if it is assumed that cell division occurs at the completion of n independent events which are not necessarily completed in sequence but each has a duration with the exponential density function $p \exp(-px)$. This assumption is quite different from the assumption that leads to the Yule distribution above and emphasizes the general principle that a 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.

3.2 Stage 2 (Determining Growth Functions)

The purpose in this second stage is to describe biologically plausible growth functions $g(x, t, p)$ and $g_M(x, t, p)$ which reconcile the expected growth of an average cell with the mean length of its mother at the time the mother divided to produce it.

At time $t - x$ there are on average $M(t - x, p)a(s, t - x, p)dpds$ viable cells in the element dp of age s to $s + ds$. Then $\mu(s, t - x - s, p)ds$ is the fraction of these cells that will divide in the next time interval ds and each of these cells has expected length $g(s, t -$

$x, p)$. Hence, at time $t - x$ the expected total number of cells that will divide in the next time interval ds , to produce two new cells, is

$$\left[\int_0^{\infty} M(t-x, p) a(s, t-x, p) \mu(s, t-x-s, p) ds \right] dp ds \text{ and the average total length of these}$$

cells is,

$$\left[\int_0^{\infty} M(t-x, p) a(s, t-x, p) \mu(s, t-x-s, p) g(s, t-x, p) ds \right] dp ds . \text{ So at time } t-x \text{ the mean}$$

length of a viable cell that will divide in the next time interval ds

$$\text{is } \frac{\int_0^{\infty} M(t-x, p) a(s, t-x, p) \mu(s, t-x-s, p) g(s, t-x, p) ds}{\int_0^{\infty} M(t-x, p) a(s, t-x, p) \mu(s, t-x-s, p) ds} .$$

Any cell in the element dp at time t of age x to $x + dx$ must be the offspring of one of the dividing cells considered above. When a cell divides it produces exactly two new cells and it is reasonable to suppose that each of the newborn cells will have a length exactly half that of the cell which divided to produce it. If it is also assumed that the increase in the length of a cell since its birth is a linear function of its age then it is reasonable to have,

$$g(x, t, p) = g_v(x, t, p) = Cx + \frac{\int_0^{\infty} a(s, t-x, p) \mu(s, t-x-s, p) g(s, t-x, p) ds}{2 \int_0^{\infty} a(s, t-x, p) \mu(s, t-x-s, p) ds} , \quad (14)$$

where C (constant) > 0 . This expresses the plausible idea that in the element dp at time t the expected length of a cell (viable or vegetative) in the age range x to $x + dx$ is half the expected length of the viable cell which divided to produce it plus its growth since birth, which is assumed to be linear with respect to its age.

It is noted that (14) requires a complete knowledge of the remote past. To overcome this difficulty it is assumed that at time $t = 0$ the entire population of cells in the column of length 1 unit consists of $K \geq 1$ newborn viable cells each of length $1/K$. Then at time t any survivors from this initial population will be of age $x = t$ and of length $Cx + 1/K$. The remainder of the population at time t will consist of viable and vegetative cells which are the result of divisions that have taken place since time $t = 0$. These cells are of age 0

$\leq x < t$ and must have been the offspring of viable cells which were in the age range 0 to $t - x$ at the instant they divided. Consequently (14) becomes the division conservation relationship,

$$g(x, t, p) = \begin{cases} Cx + 1/K, & x = t \geq 0 \\ Cx + \frac{\int_0^{t-x} a(s, t-x, p) \mu(s, t-x-s, p) g(s, t-x, p) ds}{2 \int_0^{t-x} a(s, t-x, p) \mu(s, t-x-s, p) ds}, & 0 \leq x < t, \\ 0, & \text{otherwise,} \end{cases} \quad (15)$$

$$\text{and for the vegetative cells, } g_V(x, t, p) = \begin{cases} g(x, t, p), & 0 \leq x < t, \\ 0, & \text{otherwise.} \end{cases} \quad (16)$$

It is noted from (15) and (16) that $g(x, t, p)$ and $g_V(x, t, p)$ can be determined using $a(x, t, p)$ and $\mu(x, t-x, p)$ which are outputs from the first stage of the model where $\mu(x, t-x, p)$ is found from $f(x, t-x, p)$ in the first stage using (1). The biologically plausible growth functions $g(x, t, p)$ and $g_V(x, t, p)$ are then used as inputs to the third stage of the model.

3.3 Stage 3 (Growing the Column of Cells)

The growth functions $g(x, t, p)$ and $g_V(x, t, p)$ are now used to grow (elongate) the viable and vegetative cells, respectively. The average total length of those cells of age x to $x + dx$ in the element dp is

$[M(t, p)a(x, t, p)g(x, t, p) + M_V(t, p)a_V(x, t, p)g_V(x, t, p)]dx dp$ and hence

$$\int_0^\infty [M(t, p)a(x, t, p)g(x, t, p) + M_V(t, p)a_V(x, t, p)g_V(x, t, p)]dx dp \text{ is the contribution from}$$

cells of all ages and must be equal to the stretched element $dy(t, p)$. Consequently, the stretch ratio is given by,

$$\sigma(t, p) = \frac{\partial y(t, p)}{\partial p} = M(t, p)h(t, p) + M_V(t, p)h_V(t, p), \quad (17)$$

$$\text{where, } h(t, p) = \int_0^\infty a(x, t, p)g(x, t, p)dx \text{ and } h_V(t, p) = \int_0^\infty a_V(x, t, p)g_V(x, t, p)dx \quad (18)$$

are the mean lengths of the viable and vegetative cells, respectively.

After growth there are on average $M_T(t, p) dp$ cells spread over dy and so the density of cells in the stretched column is $\sigma(t, p)/M_T(t, p) = h_T(t, p)$. Since $\sigma(0, p) = 1$ it follows that, $M(0, p)h(0, p) + M_V(0, p)h_V(0, p) = 1$ and growing the whole column at time t ,

$$y(t, p) = \int_0^p \sigma(t, z) dz = \int_0^p [M(t, z)h(t, z) + M_V(t, z)h_V(t, z)] dz, \quad (19)$$

which satisfies the initial condition $y(0, p) = p$. In particular, the expected length of the whole column at time t is $y(t, 1) = \int_0^1 \sigma(t, z) dz$ and the average displacement of the point p is $y(t, p) - p$.

It is noted from (17) and (18) that the calculation of $\sigma(t, p)$ requires the inputs: $M(t, p)$, $M_V(t, p)$, $a(x, t, p)$, and $a_V(x, t, p)$, which are outputs from the first stage; and $g(x, t, p)$, and $g_V(x, t, p)$, which are outputs from the second stage. If the growth is the same for viable and vegetative cells (i.e. $g(x, t, p) = g_V(x, t, p)$) then (17) becomes $\sigma(t, p) = M_T(t, p)h_T(t, p)$ where $h_T(t, p) = \int_0^\infty a_T(x, t, p)g(x, t, p)dx$. In this case, from (18) $h_T(0, p)$ is the

initial mean length of the cells and $h_T(t, p)$ is the mean length of the cells in the stretched element and (19) becomes $y(t, p) = \int_0^p M_T(t, z)h_T(t, z)dz$.

4. An Example

Suppose that the probability that a newly formed viable cell at position p will divide between ages x and $x + dx$ is independent of time t . Thus the probability density function for the generation time of this viable cell is $f(x, p)$. Assuming that $f(x, p) = p \exp(-px)$, then from (1), $l(x, p) = \exp(-px)$, and $\mu(x, p) = p$. The mean time between divisions is $1/p$ which means that the division of cells at the base of the column has almost ceased but the rate of division increases until it is greatest at the tip of the column. This corresponds approximately with some period of the growth of a plant root.

It is assumed that the vegetative parameter $a(t, p) = \alpha$ (constant) $\neq 1$ and that at time $t = 0$ the entire population of cells in the column consists of $K \geq 1$ newborn viable cells each of length $1/K$. This means that: $M(0, p) = K$; $M_V(0, p) = 0$; $a(x, 0, p) = \delta(x)$ (where $\delta(\cdot)$ is the Dirac delta function); and initially the height of the column is 1 unit. The main purpose of the example is to illustrate the mathematical technique and consequently the derivation of results for the case where $\alpha = 1$, which is much simpler mathematically, is left for the interested reader.

From (5) and (6), $B(t, p) = \alpha K t \exp(-pt) + \alpha \int_0^t B(t-x, p) p \exp(-px) dx$. Taking

Laplace transforms gives, $B^*(s, p) = \frac{K \alpha p}{p(1-\alpha) + s}$ where $B^*(s, p)$ is the transform of $B(t, p)$.

After inversion of $B^*(s, p)$,

$B(t, p) = \alpha p K \exp[p(\alpha - 1)t]$ and then from (9) and (2),

$M(t, p) = K \exp[p(\alpha - 1)t]$ and,

$$a(x, t, p) = \begin{cases} \alpha p \exp(-\alpha p x), & 0 \leq x < t, \\ \delta(x - t) \exp(-\alpha p t), & x \geq t. \end{cases} \quad (20)$$

From (10) and (11), $B_{\sqrt{}}(t, p) = (2 - \alpha) p K \exp[p(\alpha - 1)t]$,

$$M_{\sqrt{}}(t, p) = \frac{(2 - \alpha)}{(\alpha - 1)} K \{ \exp[p(\alpha - 1)t] - 1 \} \text{ and,}$$

$$a_{\sqrt{}}(x, t, p) = \begin{cases} \frac{(\alpha - 1) p \exp[p(\alpha - 1)(t - x)]}{\exp[p(\alpha - 1)t] - 1}, & 0 \leq x < t, \\ 0, & x \geq t. \end{cases} \quad (21)$$

Substituting (20) into (15) with $\mu(x, p) = p$ gives,

$g(x, t, p) =$

$$\begin{cases} Cx + \frac{1}{K}, & x = t \geq 0, \\ Cx + \frac{1}{2} \left[C(t - x) + \frac{1}{K} \right] \exp[-\alpha p(t - x)] + \frac{\alpha p}{2} \int_0^{t-x} g(u, t - x, p) \exp(-\alpha p u) du, & 0 \leq x < t, \\ 0, & \text{otherwise.} \end{cases} \quad (22)$$

Substituting (20) and (22) into (18) gives,

$$h(t, p) = \left(Ct + \frac{1}{K} \right) \exp(-\alpha p t) + \alpha p \int_0^t g(u, t, p) \exp(-\alpha p u) du, \quad (23)$$

and from (22) and (23), $g(x, t, p) =$

$$\begin{cases} Cx + \frac{1}{2} h(t - x, p), & 0 \leq x < t, \\ Cx + \frac{1}{K}, & x = t \geq 0. \end{cases} \quad (24)$$

Substituting (24) into (23) gives,

$$h(t, p) = \left(\frac{1}{K} - \frac{C}{\alpha p} \right) \exp(-\alpha p t) + \frac{C}{\alpha p} + \frac{\alpha p}{2} \int_0^t h(t - u, p) \exp(-\alpha p u) du, \quad (25)$$

and taking Laplace transforms in (25) gives $h^*(s, p) = (\frac{1}{K} - \frac{2C}{ap}) \frac{2}{(\alpha p + 2s)} + \frac{2C}{\alpha ps}$

which on inversion gives,

$$h(t, p) = (\frac{1}{K} - \frac{2C}{ap}) \exp(\frac{-\alpha pt}{2}) + \frac{2C}{ap}, \quad (26)$$

and so from (24), $g(x, t, p) =$

$$\begin{cases} Cx + \frac{1}{2} \{ (\frac{1}{K} - \frac{2C}{ap}) \exp[\frac{-\alpha p(t-x)}{2}] + \frac{2C}{ap} \}, & 0 \leq x < t, \\ Cx + \frac{1}{K}, & x = t \geq 0, \\ 0, & \text{otherwise,} \end{cases} \quad (27)$$

and $g_v(x, t, p)$ is given by (16).

Substituting (27), (16), (20), and (21) into (18) gives,

$$h_v(t, p) = \left(\frac{\alpha-1}{\alpha-2} \right) \left(\frac{1}{K} - \frac{2C}{ap} \right) \left(\frac{\exp[\frac{P}{2}(\alpha-2)t] - 1}{\exp[p(\alpha-1)t] - 1} \right) - \frac{Ct}{\exp[p(\alpha-1)t] - 1} + \frac{C}{ap} + \frac{C}{p(\alpha-1)}. \quad (28)$$

Then substituting (20), (21), (26), and (28) in (17) gives,

$$\sigma(t, p) = \frac{KC \exp[p(\alpha-1)t]}{p(\alpha-1)^2} + 1 - \frac{KC}{p(\alpha-1)^2} - \frac{KC(2-\alpha)t}{(\alpha-1)}, \quad (29)$$

and from (19),

$$y(t, p) = p - \frac{KC(2-\alpha)tp}{(\alpha-1)} + \frac{KC}{(\alpha-1)^2} \sum_{n=1}^{\infty} \frac{[p(\alpha-1)t]^n}{nn!}. \quad (30)$$

Other growth parameters of interest may be calculated from Table 1.

It is noted from (26) and (28) that for large values of t the mean lengths of viable and vegetative cells are, respectively,

$$h(t, p) = \frac{2C}{ap} \text{ and } h_v(t, p) = \begin{cases} \frac{C(2\alpha-1)}{ap(\alpha-1)}, & \alpha > 1 \text{ and, from (29), the stretch ratio is,} \\ Ct, & \alpha < 1, \end{cases}$$

$$\sigma(t, p) = \begin{cases} \frac{KC \exp[p(\alpha-1)t]}{p(\alpha-1)^2}, & \alpha > 1, \\ \frac{KC(2-\alpha)}{(1-\alpha)}, & \alpha < 1. \end{cases}$$

Also, a viable cell which is about to divide has an average age of $\frac{1}{ap}$.

In particular, from (30), at time t the tip of the root is

$$1 + \frac{KC}{(\alpha - 1)^2} \left[\sum_{n=1}^{\infty} \frac{[(\alpha - 1)t]^n}{nn!} - (\alpha - 1)(2 - \alpha)t \right] \text{ units above the base and the root has grown}$$

$$\text{by } \frac{KC}{(\alpha - 1)^2} \left[\sum_{n=1}^{\infty} \frac{[(\alpha - 1)t]^n}{nn!} - (\alpha - 1)(2 - \alpha)t \right] \text{ units from its initial length of 1 unit.}$$

5. Conclusion

A probabilistic model has been described which takes into account age and position dependence in the growth of a column of cells. The model is developed in three stages. The first stage concerns a point process made up of viable and vegetative cells (V). The inputs to this stage are the probability density function for the generation time $f(x, t - x, p)$ and the vegetative parameter $\alpha(t, p)$. The outputs are: the age specific fission rate $\mu(x, t - x, p)$; the expected cell densities $M(t, p)$ and $M_V(t, p)$; and the age probability density functions $a(x, t, p)$ and $a_V(x, t, p)$. The second stage uses outputs from the first stage to develop biologically plausible growth functions $g(x, t, p)$ and $g_V(x, t, p)$ which are then used in the third stage together with outputs from the first stage to grow (elongate) the points. The output from the third stage is the stretch ratio $\sigma(t, p)$ which may be used to compute a variety of related growth parameters (see Table 1).

In the second stage of the model development the growth function $g(x, t, p)$ represents the expected total length of a cell whose ancestor at time zero occupied position p and whose age now at time t is x . As the cell was produced by the division of a viable cell at time $t - x$ it is reasonable to generalize the division conservation relationship in (15) to become, $g(x, t - x, p) = E(x, t - x, p) + P(t - x, p)$ where the dependence on time is expressed in terms of the time $t - x$ at which the cell was produced. This could be referred to as a maternal influence as it implies that the state of the mother cell at the instance of formation is dominant. P refers to the mother (parent) cell so the dependence on $t - x$ is quite definite and $2P(t - x, p)$ is the mean length of a mother cell which is just about to divide at time $t - x$. Also, it is noted from the example (see equation (24)) that the mean length of cells which are about to divide at time $t - x$ is $h(t - x, p)$ and this is also the mean length of all of the viable cells in the population at that time. This is a consequence of the survivor function $l(x, p)$ being an exponential and only in this case is the age specific rate of division of a cell independent of the age of the cell. For any other survivor function $g(x, t - x, p)$ would be a more complicated function. If it is decided that environmental factors (E) are more dominant then it would be

necessary to consider a function $E(x, t, p)$. In the second stage of model formulation $E(x, t - x, p)$ has been simplified into a linear dependence on x only which is neither position nor time dependent.

The model has been formulated in a Lagrangian reference system which requires that the various parameters be expressed in terms the initial position p of the ancestor of a cell. If the variable p in $f(x, t - x, p)$ and $\alpha(t, p)$ is replaced by the variable y which represents the height of the cell above the base of the column at time t then the consequent Eulerian reference system can still be structured by this model. Although analytic solutions would not be obtained easily from the formulation, it would be possible to obtain numerical solutions.

The model has application to situations where growth occurs in a one dimensional column and is affected by the age and position of the elements in the column. This is typical of the growth of a plant root or a thin leaf but may be relevant to other biological systems. Now that the model has been developed it is important that further biological realism be incorporated into the modeling assumptions. In addition, the model needs to be evaluated against experimental data and this process will require statistical techniques to fit curves for the inputs $f(x, t - x, p)$ and $\alpha(t, p)$ and to evaluate the outputs from the model against the empirical data. These statistical techniques are not discussed here as the primary purpose of this article is the present and illustrate the formulation of the new probabilistic model.

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