ON A FUNCTIONAL EQUATION MODEL OF TRANSIENT CELL-GROWTH

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Abstract

A cell-growth model with applications to modelling the size distribution of diatoms is examined. The analytic solution to the model without dispersion is found and is shown to display periodic exponential growth rather than asynchronous (or balanced) exponential growth. It is shown that a bounding envelope (hull) of the solution to the model without dispersion takes the same shape as the limiting steady size-distribution (SSD) to the dispersive case as dispersion tends to zero. The effect of variable growth rate on the shape of the hull is also discussed.

1 Introduction

In this paper we study further a stochastic model for cell growth in plankton based on a modified Fokker-Planck equation which was examined in (Basse et al., 2004c) (a reference which we henceforth denote by I). We show that the steady size-distribution (SSD) obtained in I is in fact entirely due to the smoothing nature of the dispersion operator and that removal of this term in the model produces a solution which is, in most cases, discontinuous. All is not lost however, as we further prove in this paper that the hull (a bounding envelope, to be defined later) of the discontinuous solutions is, under certain conditions, the SSD solution obtained in I as the dispersion tends to zero and furthermore is a global attractor (in a sense).

Many cell types exhibit logarithmic phase of cell growth (exponential growth). Previous work has shown that models based on that described in I can also exhibit that behaviour and, specifically, show SSD type behaviour. The solutions obtained in this previous work make the assumption of exponential growth rate to proceed. Here we obtain a full transient solution to our model and show how the SSD of the exponential growth phase appears out of our solution.

The cells are assumed to be undergoing growth, division and mortality at known rates.

Let $n(x,t)$ denote the number density functions of cells of size x at time t; hence, for $0 \le a < b$ the quantity $\int_a^b n(x,t)\,dx$ is the number of cells between size a and size b at time t. In I the cell growth process was modelled by a modified Fokker-Planck equation of the form

$$\begin{aligned}\frac{\partial}{\partial t}n(x,t) + \frac{\partial}{\partial x}\left(g(x,t)n(x,t)\right) + \mu(x,t)n(x,t), &= \alpha^2 B(\alpha x,t)n(\alpha x,t) - B(x,t)n(x,t) \\ &\quad + \frac{\partial^2}{\partial x^2}\left(D(x,t)n(x,t)\right), \qquad (1.1)\end{aligned}$$

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where D (m^2/s) is the dispersion coefficient, g (m/s) is the rate of growth and μ $(1/s)$ is the rate of death. The function B $(1/s)$ is the rate at which cells divide into α equally sized daughter cells. Here $\alpha > 1$ is regarded as a constant, and the functions D, g, μ and B are all non-negative. A value of $\alpha = 2$ is most appropriate for cell division in many problems, *i.e.* when a cell on division produces two daughter cells. However other possibilities exist, *i.e.* if n corresponds to a grouping of cells *e.g.* say $n = 10$ and two extra cells are produced through cell division (so that $n = 12$) then $\alpha = 1.2$ is appropriate. D, the dispersion coefficient, allows for varying rates of DNA content growth and intercell heterogeneity of DNA content. We show in Appendix B that D arises naturally when the cell growth process is modelled by a random walk.

The partial differential equation (1.1) is supplemented by the boundary conditions

$$\lim_{x\to\infty} n(x,t) = 0; \tag{1.2}$$

$$\frac{\partial}{\partial x}(D(0,t)n(0,t)) - g(0,t)n(0,t) = 0. \tag{1.3}$$

The condition (1.2) is a decay condition on n as $x \to \infty$ for any fixed time. Equation (1.3) is a "no flux" condition on the boundary $x = 0$ and represents the fact that cells may never have negative size, and thus no cells enter or leave the region $x < 0$.

Of particular interest are solutions to the initial-value boundary-value problem (1.1) - (1.3) that correspond to SSD's; where the shape of the size-distribution remains constant while growing or decaying exponentially.

In I separable solutions of the form $n(x,t) = T(t)y(x)$ were assumed, ($y(x)$ in this case would then be an SSD). This separation was shown to lead to the solution

$$T(t) = T_0 e^{\Lambda t}, \tag{1.4}$$

where T_0 is a constant. It was also shown that when the condition that $y(x)$ is a probability density function is imposed,

$$\Lambda = \int_0^\infty ((\alpha-1)B(x) - \mu(x))\, y(x)\, dx, \tag{1.5}$$

with the sign of Λ determining whether the number density function decays or grows exponentially in time. Sufficient conditions were obtained for the existence of continuous SSD's. Existence of SSD's, however, does not tell us anything regarding their asymptotic stability. In the present paper we show an SSD to be, in a sense, a global attractor. Further information and references to work in the literature on this model may be found in I.

An example of a model which is known to tend asymptotically to a steady size-distribution (or, more correctly, steady 'age'-distribution) can be found in (Chiorino et al., 2001).

The model we study here can be considered as a limiting case of the Fokker-Planck model (1.1) and can be written as

$$\frac{\partial n}{\partial t}(x,t) + \frac{\partial g(x)n(x,t)}{\partial x} + \mu(x)n(x,t) = \alpha^2 B(\alpha x,t)n(\alpha x,t) - B(x,t)n(x,t), \quad t,x > 0. \tag{1.6}$$

This equation is found from (1.1) by setting $D \equiv 0$ and, as in I, setting $g(x)$ and $\mu(x)$ to be growth and death rates depending purely on x; The functional equation (1.6) has hyperbolic characteristics associated with its principal symbol, and it is supplemented by the side conditions

$$n(0,t) = 0, \qquad t > 0 \tag{1.7}$$

$$n(x,0) = n_0(x), \qquad x \geq 0, \tag{1.8}$$

to ensure the problem is well-posed. Another condition we impose, for the sake of realism, is $n \geq 0$.

Following I we model the cell growth of diatoms, although we observe most animal cells display similar behaviour. Cell growth in diatoms is characterized by cell division only at a critical size l (we call this behaviour single size division). Evidence for this is developed in (Round et al., 1990), where size is characterized by DNA content. Cells double in size as well as doubling their chromosomes and segregate a full complement of components to each daughter cell. The DNA content passed on to each daughter cell in this case is prescribed fairly precisely as $l/2$, where, as we have stated, the value of l represents the unique threshold value of the DNA content at which division occurs. This behaviour is in contrast with more complex organisms where cell division occurs over a specified size interval. Mathematically, we can model single size division by a function of the form $B(x) = b\delta(x-l)$, where b is a constant and δ denotes the Dirac delta distribution. In this case the equation (1.6) becomes

$$\frac{\partial n}{\partial t}(x,t) + \frac{\partial g(x)n(x,t)}{\partial x} + \mu(x)n(x,t) \quad = \quad \alpha bn(l^-,t)\delta(x-l/\alpha) - bn(l^-,t)\delta(x-l), \qquad (1.9)$$

where $x = l^-$ is to denote the limit as $x \longrightarrow l$ from below. We note that the continuity of $n(x,t)$ cannot be guaranteed at $x = l$, therefore it does not follow that $\delta(x-l)n(x,t) = \delta(x-l)n(l,t)$. We henceforth specify $\delta(x-l)n(x,t)$ as denoting $\delta(x-l)n(l^-,t)$—observing in this case that cells above size l do not take part in the division process—and this has been used in the statement of the right-hand-side of (1.9). We observe that it is also possible to use the limit from the right. This yields similar results but we feel it is not as physically relevant as continuity from the left, and thus do not go into detail regarding this case.

Steady size-distribution behaviour is characterised by the distribution of cell sizes remaining a constant shape while growing or shrinking (usually exponentially). When the growth rate is exponential the behaviour is also known as asynchronous or balanced exponential growth (AEG or BEG). Biological interest in this dates from Malthus(Malthus, 1798, 1970). SSD behaviour can also be expressed in terms of strongly continuous semigroups. A definition pertinent to the current work is given below and is based on the work of (Rossa, 1995).

Definition: Let $T(t)$ be a strongly continuous semigroup of bounded operators with infinitesimal generator A on a Banach space B. It is said that

1. $(T(t))_{t\geq 0}$ exhibits AEG with intrinsic growth rate λ_0 if there exists a non-zero finite rank projection P on B such that
$$\lim_{t\longrightarrow\infty} \|e^{-\lambda_0 t}T(t) - P\| = 0.$$

2. $(T(t))_{t\geq 0}$ exhibits Periodic Exponential Growth (PEG) with intrinsic growth rate λ_0 if there exists a non-zero finite rank projection P onto a subspace F of B and a periodic semigroup $(R_\tau(t))_{t\geq 0}$ a rotation semigroup on F with period $\tau > 0$ such that
$$\lim_{t\longrightarrow\infty} \|e^{-\lambda_0 t}T(t) - R_\tau(t)P\| = 0.$$

The above definition relates to a semigroup operator $T(t)$ that maps the initial data, given by (1.8), into the solution $n(x,t)$ at time t. The second part of the definition will later be seen to apply to the solution to (1.9).

In Section 2 we restrict analysis to the case where the two coefficients g and μ are constant. In Section 2.3 we show it is possible to express $n(x,t)$ as the solution to a retarded functional equation. In Sections 2.4 and 2.5 we show that the solutions to (1.9) grow or decay exponentially with time, exhibiting periodic exponential growth as defined above. In Section 3 we show that (under certain conditions) the hull of the solution when $D = 0$ is equal to the limiting SSD (from I) as $D \longrightarrow 0$ with the requirement of continuity from the left. Finally, in Section 4 we find a general expression for the hull of $n(x,t)$ with variable growth rate $g = g(x)$. We often assume that $\alpha = 2$ in parts of the remainder of this paper when the mathematics for general $\alpha > 1$ is more complicated.

2 Solution of the Differential Functional Equation

When g and μ are constants, Equation (1.9) may be written

$$n_t + gn_x + \mu n = F(x,t), \tag{2.1}$$

with the right-hand-side defined as

$$F(x,t) = \alpha bn(l^-,t)\delta(x-l/\alpha) - bn(l^-,t)\delta(x-l) - \mu n(x,t). \tag{2.2}$$

Observe that $F(x,t) \equiv 0$ when $x \neq l/\alpha$ or $x \neq l$, and we can straightforwardly find the solution of the resultant homogeneous equation for x in any of the three regions $R_1 = (0, l/\alpha)$, $R_2 = (l/\alpha, l)$, $R_3 = (l, \infty)$, as

$$n_i(x,t) = F_i(x-gt)e^{-\mu t}, \qquad i \in \{1,2,3\}, \tag{2.3}$$

where n_i denotes the solution of n within the region R_i. This solution follows from the variable substitutions performed in (2.5) and the fact that the δ distributions are zero in each region.

Now consider the region R_1; in this region, from (1.8) we have

$$F_1(x) = n_0(x)H(x),$$

where H denotes the Heavside function, so that

$$n_1(x,t) = \begin{cases} n_0(x-gt)e^{-\mu t} & 0 < t < \frac{x}{g}, \\ 0 & t > \frac{x}{g}. \end{cases} \tag{2.4}$$

In the following we assume that $n_0 \in H^0$, where H^0 denotes the Sobolev space of order zero (*i.e.* $H^0 = L^2$) and that n_0 has finite isolated discontinuities,. To proceed further we must consider the jump conditions across the boundaries of the regions R_i, $i \in \{1,2,3\}$. To do this we first find a functional equation for n.

2.1 Algebraic functional equation

In this section we derive a functional equation for $n(x,t)$. To this end we first make the following substitutions in (1.9):

$$\begin{aligned} \xi &= x - gt, \qquad \tau = t, \\ U(\xi,\tau) &= U(x-gt,t) = n(x,t), \end{aligned} \tag{2.5}$$

to yield the differential equation

$$U_\tau + \mu U = \overline{F}(\xi,\tau) = F(\xi + g\tau,\tau).$$

By use of an integrating factor the following expression is derived for U:

$$\begin{aligned} U(\xi,\tau) &= \frac{\alpha b}{g} H\left(\tau - \left[\frac{l}{g\alpha} - \frac{\xi}{g}\right]\right) n\left(l^-, \frac{l}{g\alpha} - \frac{\xi}{g}\right) e^{\mu\left[\frac{l}{g\alpha} - \frac{\xi}{g} - \tau\right]} \\ &\quad - \frac{b}{g} H\left(\tau - \left[\frac{l}{g} - \frac{\xi}{g}\right]\right) n\left(l^-, \frac{l}{g} - \frac{\xi}{g}\right) e^{\mu\left[\frac{l}{g} - \frac{\xi}{g} - \tau\right]} + C(\xi)e^{-\mu\tau}, \end{aligned} \tag{2.6}$$

where C is an arbitrary function of ξ yet to be determined. The substitution $n(x,t) = U(x - gt, t)$ is now used to give

$$\begin{aligned} n(x,t) &= \frac{\alpha b}{g} H(x - l/\alpha) n\left(l^-, \frac{l}{g\alpha} - \frac{x}{g} + t\right) e^{\mu\left[\frac{l}{g\alpha} - \frac{x}{g}\right]} - \frac{b}{g} H(x - l) n\left(l^-, \frac{l}{g} - \frac{x}{g} + t\right) e^{\mu\left[\frac{l}{g} - \frac{x}{g}\right]} \\ &\quad + C(x - gt)e^{-\mu t}. \end{aligned} \tag{2.7}$$

On setting t to zero, we find

$$\begin{aligned} C(x) &= n_0(x) H(x) - \frac{\alpha b}{g} H(x - l/\alpha) n\left(l^-, \frac{l}{g\alpha} - \frac{x}{g}\right) e^{\mu\left[\frac{l}{g\alpha} - \frac{x}{g}\right]} \\ &\quad + \frac{b}{g} H(x - l) n\left(l^-, \frac{l}{g} - \frac{x}{g}\right) e^{\mu\left[\frac{l}{g} - \frac{x}{g}\right]}, \end{aligned} \tag{2.8}$$

and on substituting the expression for $C(x)$ back into (2.7),

$$\begin{aligned} n(x,t) &= n_0(x - gt) H(x - gt) e^{-\mu t} + \frac{\alpha b}{g} n\left(l^-, \frac{l}{g\alpha} - \frac{x}{g} + t\right) e^{\mu\left[\frac{l}{g\alpha} - \frac{x}{g}\right]} \mathscr{H}_1(x,t) \\ &\quad - \frac{b}{g} n\left(l^-, \frac{l}{g} - \frac{x}{g} + t\right) e^{\mu\left[\frac{l}{g} - \frac{x}{g}\right]} \mathscr{H}_2(x,t). \end{aligned} \tag{2.9}$$

Here the functions $\mathscr{H}_1(x,t)$ and $\mathscr{H}_2(x,t)$ are defined as

$$\mathscr{H}_1(x,t) = H\left(x - \frac{l}{\alpha}\right) - H\left(x - \frac{l}{\alpha} - gt\right) = \begin{cases} 1 & \frac{l}{\alpha} < x < \frac{l}{\alpha} + gt, \\ 0 & \text{otherwise,} \end{cases},$$

$$\mathscr{H}_2(x,t) = H(x - l) - H(x - l - gt) = \begin{cases} 1 & l < x < l + gt, \\ 0 & \text{otherwise.} \end{cases}$$

We note that these two functions only take on the values 1 or 0 and the regions in which these functions take on these respective values is shown in Figure 2.1.

We observe equation (2.9) is a functional equation whose solution yields n. To solve this equation it is necessary to consider the jump conditions at $x = l/\alpha$ and $x = l$; a task which we now turn to.

2.2 Jump discontinuities in $n(x,t)$

In this section the jumps in $n(x,t)$ at $x = l/\alpha$ and $x = l$ are determined, and are used to find an expression for $F_3(l - gt)$ and a retarded functional equation for F_2.

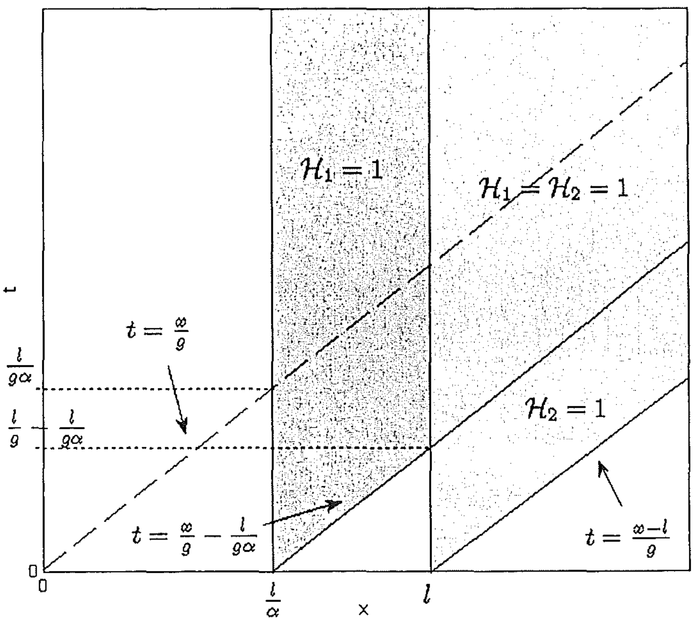

Figure 2.1: Regions of support for $\mathscr{H}_1$ and $\mathscr{H}_2$. $\mathscr{H}_1$ is non-zero for $\frac{l}{\alpha} < x < \frac{l}{\alpha} + gt$; $\mathscr{H}_2$ is non-zero for $l < x < l + gt$. The solution $n(x,t)$ is zero for $0 < x < \min\{gt, l/\alpha\}$.

For any $t > 0$, we have

$$\lim_{x \to \frac{l}{\alpha}^-} n(x,t) = n_0\left(\frac{l}{\alpha}^- - gt\right) H\left(\frac{l}{\alpha}^- - gt\right) e^{-\mu t}$$

$$\lim_{x \to \frac{l}{\alpha}^+} n(x,t) = n_0\left(\frac{l}{\alpha}^+ - gt\right) H\left(\frac{l}{\alpha}^+ - gt\right) e^{-\mu t} + \frac{\alpha b}{g} n(l^-,t).$$

Thus,

$$n\left(\frac{l}{\alpha}^+, t\right) - n\left(\frac{l}{\alpha}^-, t\right) = \frac{\alpha b}{g} n(l^-,t), \qquad \text{a.e. } t > 0. \tag{2.10}$$

Figure 2.1 shows that when $0 < t < \frac{l}{g} - \frac{l}{g\alpha}$, then $\mathscr{H}_1(l^+,t) = \mathscr{H}_1(l^-,t) = 0$. We therefore get

$$n(l^+,t) - n(l^-,t) = -\frac{b}{g} n(l^-,t), \qquad \text{a.e. } 0 < t < \frac{l}{g} - \frac{l}{g\alpha}. \tag{2.11}$$

Figure 2.1 also shows that when $t > \frac{l}{g} - \frac{l}{g\alpha}$, $\mathscr{H}_1(l^+,t) = \mathscr{H}_1(l^-,t) = 1$; so in this case we get

$$n(l^+,t) - n(l^-,t) = -\frac{b}{g} n(l^-,t) + \frac{\alpha b}{g}\left[n\left(l^-, \frac{l}{g\alpha} - \frac{l}{g} + t^-\right) - n\left(l^-, \frac{l}{g\alpha} - \frac{l}{g} + t^+\right)\right] e^{\mu\left[\frac{l}{g\alpha} - \frac{l}{g}\right]}, \tag{2.12}$$

where we note the possible discontinuity in the function n in time by utilising the symbols t^-, t^+ to denote t from below and above. We are now in a position to find an equation for the jump condition across the boundary of the regions R_2 and R_3. From Equations (2.11) and (2.12), we see that

$$F_3(l-gt)-F_2(l-gt) = \begin{cases} -\frac{b}{g}F_2(l-gt), & 0<t<\frac{l}{g}-\frac{l}{g\alpha}, \\ -\frac{b}{g}F_2(l-gt)+\frac{\alpha b}{g}e^{\mu\left[\frac{l}{g\alpha}-\frac{l}{g}\right]}\left[F_2\left(2l-\frac{l}{\alpha}+gt^+\right)\right. & \\ \qquad\qquad \left.-F_2\left(2l-\frac{l}{\alpha}+gt^-\right)\right], & \frac{l}{g}-\frac{l}{g\alpha}<t. \end{cases} \tag{2.13}$$

Thus, $F_3(l-gt)$ may be expressed solely in terms of F_2, with $F_3(x)=n_0(x)$ when $x>l$. All that remains now is to solve for F_2.

From equation (2.10), we find that the jump condition across the boundary of the regions R_1 and R_2 gives

$$F_2\left(\frac{l}{\alpha}-gt\right)-\lambda F_2(l-gt) \;=\; n_0\left(\frac{l}{\alpha}-gt\right)H\left(\frac{l}{\alpha}-gt\right), \qquad \text{a.e. } t>0, \tag{2.14}$$

where

$$\lambda=\frac{\alpha b}{g},$$

and we have used $F_1=n_0(x)\,H(x)$. It is convenient for the sequel to redefine the independent variable, and to facilitate this we let $z=\frac{l}{\alpha}-gt$, and $u=l-\frac{l}{\alpha}>0$; it then follows that

$$F_2(z)=n_0(z)\,H(z)+\lambda F_2(z+u), \qquad z\le\frac{l}{\alpha}, \tag{2.15}$$

and for $\frac{l}{\alpha}<z<l$ we clearly have $F_2(z)=n_0(z)$, as follows from (2.9) and (2.3). It should be observed that (2.15) constitutes a retarded functional equation for F_2 when moving in the direction of the left-hand axis of z.[1]

We will now proceed to find a solution to $F_2(z)$ for the special case when $\alpha=2$; which is of particular interest for diatoms and other animal cells.

2.3 Solution of the functional equation for $\alpha=2$

We now solve the functional equation (2.15) for F_2 by recursion when $\alpha=2$. Observe that the mathematics is simplified since when $\alpha=2$, $u=l/\alpha=l/2$. It is possible to write down the solution for general α but the algebraic complexities make it cumbersome except for a specific α. We provide some considerations for more general α in the Appendix A.1. Thus, for this case (2.15) is

$$F_2(z)=\begin{cases} n_0(z), & \frac{l}{2}<z<l, \\ n_0(z)+\lambda F_2\left(z+\frac{l}{2}\right), & z<\frac{l}{2}. \end{cases} \tag{2.16}$$

From this we may conclude that

$$\begin{aligned} F_2(z) &= n_0(z)+\lambda n_0\left(z+\frac{l}{2}\right), \qquad 0<z<\frac{l}{2} \\ &= \lambda n_0\left(z+\frac{l}{2}\right)+\lambda^2 n_0(z+l), \quad -\frac{l}{2}<z<0 \end{aligned}$$

[1] When the take $\delta(x-l)n(x,t)=\delta(x-l)n(l^+,t)$, we obtain a functional equation for F_3 of the same form as we obtain here, but with $\lambda=\alpha b/(b+g)$.

and it follows by backward recursion

$$F_2(z) = \lambda^m n_0\left(z+\frac{ml}{2}\right)+\lambda^{m+1}n_0\left(z+\frac{(m+1)l}{2}\right), \quad -\frac{ml}{2}<z<-\frac{(m-1)l}{2}, \tag{2.17}$$

where $0 \leq m \in \mathbb{Z}$. Note that $F_2(z)$ is continuous at $z = -ml/2$ only if

$$\lambda^m n_0(0^+)+\lambda^{m+1}n_0\left(\frac{l^+}{2}\right) = \lambda^{m+1}n_0\left(\frac{l^-}{2}\right)+\lambda^{m+2}n_0(l^-)$$
$$\iff \quad n_0(0) = \lambda^2 n_0(l^-) - \lambda\,[n_0]_{l/2^-}^{l/2^+}.$$

Thus in most cases F_2, and therefore the solution $n(x,t)$, will be discontinuous.

We now derive an explicit solution for $n(x,t)$ from the previous results. We have already found explicit solutions to $F_1(z)$, and $F_2(z)$, leaving the region $l < x$, which is governed by $F_3(z)$, to be addressed. It should first be noted that if n_0 is piece-wise continuous then, by the expressions above, $F_2(z)$ will also be piece-wise continuous. Thus, from (2.13) we see that, almost everywhere[2],

$$F_3(l-gt) = \left(1-\frac{b}{g}\right)F_2(l-gt), \quad t>0. \tag{2.18}$$

In effect, b/g is the proportion of cells dividing upon reaching size l. When $b<g$ this ratio can be interpreted as the probability of any given cell dividing when it reaches size l. Moreover, we are forced to require $b<g$ for the solution to have any physical relevance, since it is impossible for there to be a negative number of cells at any size.

Equation (2.18) states the behaviour of $F_3(z)$ for $z<l$, where z is defined as the argument of F_3. For $z>l$ we merely need to note that $F_3(x) = n_3(x,0)$ when $x>l$ (the domain of definition of $n_3(x,t)$ provides the restriction $x>l$). Thus, $F_3(z) = n_0(z)$ when $z>l$.

We now have all the information we need to write the full analytical solution for $n(x,t)$ (in terms of the solution in the three regions) as:

$$n_1(x,t) = n_0(x-gt)e^{-\mu t}H(x-gt), \quad t>0. \tag{2.19}$$

$$n_2(x,t) = \begin{cases} n_0(x-gt)e^{-\mu t}, & \frac{l}{2}<x-gt<l, \\ e^{-\mu t}\left[\lambda^m n_0\left(x-gt+\frac{ml}{2}\right)+\lambda^{m+1}n_0\left(x-gt+\frac{(m+1)l}{2}\right)\right], & \frac{-ml}{2}<x-gt<\frac{-(m-1)l}{2}, \\ & 0\leq m\in\mathbb{Z}, \end{cases} \tag{2.20}$$

$$n_3(x,t) = \begin{cases} n_0(x-gt)e^{-\mu t}, & l<x-gt, \\ \left(1-\frac{b}{g}\right)n_2(x,t), & x-gt<l, \end{cases} \tag{2.21}$$

where in (2.21), the domain of definition of n_2 in x has been extended to $l<x$.

We end this section with a small lemma:

Lemma 2.1. *There exists a unique solution to* (2.1) *with* $n_0 \in H^0(\mathbb{R})$ *which is in* $H^0(\mathbb{R})$.

Proof. Existence by the above construction, and uniqueness by standard contradiction. □

[2] We say 'almost everywhere' because the discontinuities in F_2 can only be of measure zero.

2.4 Periodic nature of $n(x,t)$ in time

We again consider firstly the special case with $\alpha = 2$. We now derive a formula for $n_2(l,t)$ which will make apparent the periodic nature of the solution in the region $t > x/g$. On replacing z with $l - gt$, and m by $m-1$ in (2.17), we see that

$$F_2(l-gt) = \begin{cases} n_0(l-gt), & 0 < t < \frac{l}{2g}, \\ \dots & \\ \lambda^{m-1} n_0\left(l - gt + \frac{(m-1)l}{2}\right) + \lambda^m n_0\left(l - gt + \frac{ml}{2}\right), & \frac{ml}{2g} < t < \frac{(m+1)l}{2g}, \\ & m \in \mathbb{Z}_+, \text{ on a general interval.} \end{cases} \tag{2.22}$$

Having found $F_2(l-gt)$, we can easily obtain an expression for $n(l^-,t)$, which can be substituted back into equation (2.9) to obtain a solution for $n(x,t)$ when $t > \frac{x}{g} - \frac{l}{2g}$.

Now define the function

$$h(t) = n_0(ml - gt)e^{(-\mu+J)\left(t - \frac{ml}{g}\right)}, \quad \frac{ml}{g} < t < \frac{(m+1)l}{g}, \tag{2.23}$$

for any $0 \le m \in \mathbb{Z}$, with

$$J = -\frac{2g}{l}\ln(\lambda) + \mu, \tag{2.24}$$

and where $\lambda = \alpha b/g$. Examination of h shows that it is merely the extension of $n_0(l-gt)e^{(-\mu+J)t}$ on $0 < t < l/g$ as an l/g-periodic function for all t. We now claim that for $t > l/2g$ we have

$$\begin{aligned} n_2(l,t) &= e^{-Jt}[h(t) + h(t - l/2g)] \\ &= F_2(l-gt)e^{-\mu t}. \end{aligned} \tag{2.25}$$

We can see this is the case when we expand the right-hand-sideof (2.25) using (2.23) to yield

$$\begin{aligned} e^{-Jt}[h(t) + h(t - l/2g)] &= e^{-\mu\left(t - \frac{ml}{g}\right)} e^{-J\frac{ml}{g}} n_0(ml - gt) + e^{-\mu\left(t - \frac{(m-1)l}{g} - \frac{l}{2g}\right)} e^{-J\left(\frac{(m-1)l}{g} + \frac{l}{2g}\right)} n_0((m-1)l - gt + l/2), \\ &= e^{-\mu t}[\lambda^{2m} n_0(ml - gt) + \lambda^{2m-1} n_0(ml - gt - l/2)], \quad \frac{2ml}{2g} < t < \frac{(2m+1)l}{2g}. \end{aligned} \tag{2.26}$$

And, similarly

$$e^{-Jt}[h(t) + h(t - l/2g)] = e^{-\mu t}[\lambda^{2m} n_0(ml - gt) + \lambda^{2m+1} n_0(ml - gt + l/2)], \qquad \frac{(2m+1)l}{2g} < t < \frac{(2m+2)l}{2g}. \tag{2.27}$$

Now, analysing the expression above in intervals of length $l/2g$ shows

$$e^{-Jt}[h(t) + h(t - l/2g)] = e^{-\mu t} \begin{cases} n_0(l-gt) + \lambda n_0(l - gt + l/2), & \frac{l}{2g} < t < \frac{l}{g}, \\ \lambda^2 n_0(2l - gt) + \lambda n_0(l - gt + l/2), & \frac{l}{g} < t < \frac{3l}{2g} \\ \dots . & \end{cases}$$

Thus, equation (2.25) has been shown to be correct in that it behaves in the manner specified by (2.22). We have now shown that $n(l^-,t)$ is periodic in t (when $t > l/2g$) with period $l/2g$ and has an exponential growth or decay determined by the J in (2.24). Thus, from (2.9), we see that $n(x,t)$ is periodic in t for any fixed x when $t > x/g$.

In Appendix A.1 we discuss the solution behaviour for any $\alpha > 1$, and it is shown that $n(l^-,t)$ is a temporally periodic function when $t > \frac{l}{g\alpha}$, with a period $\frac{l(\alpha-1)}{g\alpha}$; this is consistent with the period found here. A clear example of periodic behaviour at a fixed x is given in Figure 2.4, where the solution is also observed to be growing exponentially in time.

2.5 Periodic Exponential Growth

Here we relate the behaviour of the solution to the definition for PEG given in Section 1. Consider the solution $n(x,t)$ restricted to $0 < x < l$. The Banach space B that we are working on is the space of all tempered distributions with support on $[0,l)$ considered as a subspace of the Sobolev space H^{-1}. All restrictions of initial conditions to $[0,l)$ are in this space. We restrict our discussion below to the case where $\alpha = 2$; a case for which we have found the exact solution.

We look for a strongly continuous semigroup $T(t)$ mapping any initial distribution $n_0(x)$ to the function $n(x,t)$. This semigroup is fully specified by (2.19) and (2.20). It is clear that for any $f \in B$ we have

$$\lim_{t\to 0^+} T(t)f = f. \tag{2.28}$$

Thus $T(t)$ is a strongly continuous semigroup on B. The generator A of T is found by examining

$$\lim_{t\to 0^+} \frac{T(t)f - f}{t}.$$

From (2.1), we find that the action of the generator A on all piecewise continuous functions on $[0,l)$ is

$$Af(x) = -gf_x(x) - \mu f(x) + \alpha b\delta(x - l/\alpha)f(l^-). \tag{2.29}$$

The rotation and projection operators come from the fact that for every $x < l$, the solution is of the form $e^{-Jt}p(t)$ for $t \geq l/g$, with p being the periodic function $[h(t) - h(t - l/2g)]$ having period $l/2g$. Let $\tau = l/2g$. From (3.7) we see that when $t > l/g$ we have

$$n(x,t) = T(t)n_0(x) = H\left(x - \frac{l}{2}\right)\frac{2b}{g}Be^{-Jt}p\left(\frac{l}{2g} - \frac{x}{g} + t\right)e^{\mu\left[\frac{l}{2g} - \frac{x}{g}\right]}, \qquad 0 < x < l/2. \tag{2.30}$$

Let $t_0 = \frac{3l}{2g}$ be the least integer multiple of τ greater than l/g. Then define the projection operator P as

$$Pf(x) = \begin{cases} 0, & 0 < x < \frac{l}{2}, \\ e^{Jt_0}T(t_0)f(x), & \frac{l}{2} < x < l, \end{cases} \tag{2.31}$$

So that we have

$$Pf(x) = H\left(x - \frac{l}{2}\right)\frac{2b}{g}Bp\left(\frac{l}{2g} - \frac{x}{g} + t_0\right)e^{\mu\left[\frac{l}{2g} - \frac{x}{g}\right]}. \tag{2.32}$$

We now choose $R_\tau(t)$ such that $R_\tau(t)Pf(x) = e^{Jt}T(t)f(x)$ for $0 < x < l$ and $t > t_0$. To achieve this we first let

$$\xi = \xi(x) = \left[x - gt \mod \frac{l}{2}\right] + \frac{l}{2},$$

where the modulo operator is always condsidered to be positive. Following this, define

$$R_\tau(t)f(x) = \begin{cases} f(x), & 0 < x < \frac{l}{2}, \\ f(\xi)e^{\mu\left(\frac{\xi - x}{g}\right)}, & \frac{l}{2} < x < l, \end{cases} \tag{2.33}$$

where the modulo operator is always considered to be positive. If we now set $\lambda_0 = -J$, the definition of PEG given in Section 1 will have been satisfied.

2.6 Computational results

A computer program was written in MATLAB code to evaluate $n(x,t)$ for any initial conditions. Snapshots in time of $n(x,t)$ are shown in Figures 2.2 and 2.3. The parameter values $g = 0.3$ and $l = 3$ mean that the periodic function $h(t) - h(t - l/2g)$ has a period of five time-units. This periodic behaviour can be seen in the plots at multiples of five time-units. The snapshots at times that are 2.5 modulo 5 show a discontinuity in the solutions which travels to the right as time increases. When this discontinuity hits l it returns back to $l/2$ and in this way is kept in the solution indefinitely. A proportion $(1 - b/g)$ of the solution in R_2 leaks through l and propagates out to infinity.

Figure 2.4, showing the solution in time at $x = 2$, illustrates the periodic nature of the solution with exponential growth superimposed.

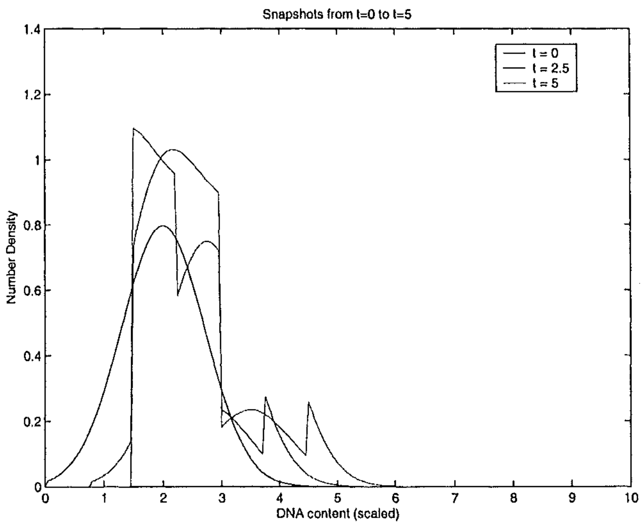

Figure 2.2: Snapshots showing the first five time-units behaviour of $n(x,t)$ with initial conditions given by a Gaussian with mean 2 and standard deviation 0.5 truncated at $x = 0$. The parameter values for the model are $\alpha = 2$, $b = 0.2$, $g = 0.3$, $l = 3$ and $\mu = 0.025$.

From the results up to this point it is seen that the solution to the transient cell growth problem has the following characteristics:

1. The solution exhibits an exponential growth or decay rate as determined by the value of J

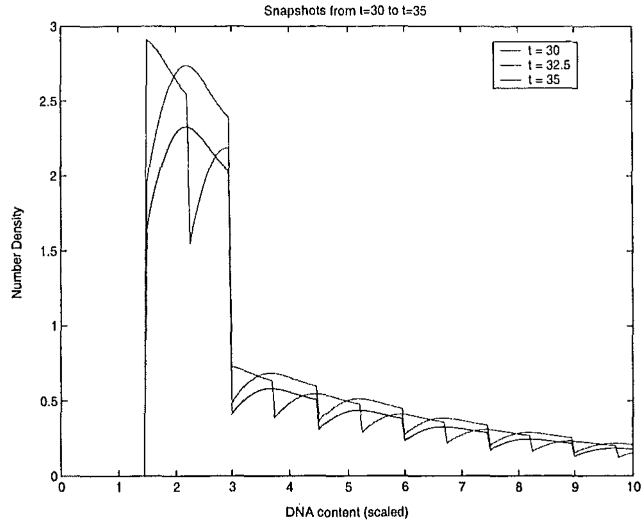

Figure 2.3: Snapshots showing the behaviour of $n(x,t)$ using the same parameters as in Figure 2.2 for time-units 30 to 35. By now the periodic behaviour in the section $1.5 < x < 3$ is obvious.

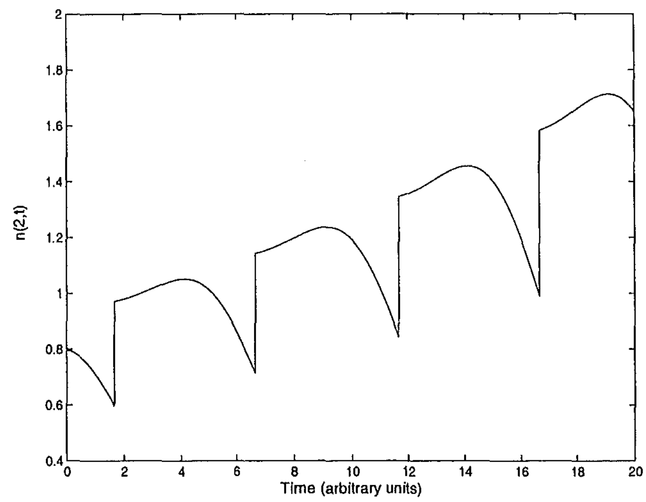

Figure 2.4: The behaviour of $n(x,t)$ from Figure 2.3 at $x = 2$, illustrating the periodic nature of the solution superimposed with exponential growth.

2. The solution is periodic at each x with a temporal period

$$\frac{l(\alpha-1)}{g\alpha}.$$

3. The solution depends continuously upon the initial value condition, n_0.

4. The solution does not exhibit any steady size-distribution behaviour.

This last point could lead one to believe that the model we have been studying, which has a hyperbolic principal symbol, is not appropriate for the phenomena (SSD behaviour) we are interested in. However, as we will show in the next section a certain envelope of the solution which we have examined in this section has SSD type behaviour. Moreover, this envelope is identical in analytical detail to the separated solution obtained from the parabolic model (1.1) in I when $D \longrightarrow 0$.

3 The relationship between the SSD solutions as $D \longrightarrow 0$ and the solution when $D = 0$

In this section it is shown that the hull of the solution to $n(x,t)$ in the region $0 < x < gt$ is equivalent to an SSD solution to (2.1). The form of the SSD in this case is equivalent to the limit as $D \longrightarrow 0$ of the SSD when $D \neq 0$, as described in I. This is arrived at by separation of variables, and imposing the condition that y is a probability density function, giving the growth rate $\Lambda = (\alpha - 1)by(l) - \mu$.

3.1 Preliminary statements

We begin by defining a bounding envelope of the solutions found in the previous section, namely

$$N(x) = \sup_{t \geq x/g} An(x,t)e^{Jt}, \qquad x \geq 0, \tag{3.1}$$

for any constant $A \neq 0$, and where J is the decay rate of the solution, as defined for $\alpha = 2$ in (2.24) or for general α by (A.10). From the solution found in Section 2.3 it is apparent N is a bounded function of x only. We define the *hull* of the solution to (2.1) to be the probability-density distribution

$$H(x) = \frac{N(x)}{\int_0^\infty N(y)\,dy}, \qquad x \geq 0, \tag{3.2}$$

which produces an appropriate normalization to the hull when the integral in the denominator is finite.

For any $\alpha > 1$ it is shown in the Appendix A.1 that $n(l^-,t)$ behaves like a periodic function multiplied by an exponential growth/decay term for $t > \frac{l}{g\alpha}$. Thus, we may say

$$n(l^-,t) = Be^{-Jt}p(t), \qquad t > \frac{l}{g\alpha}, \tag{3.3}$$

for appropriate constant B. Moreover, we know that p is $\left(\frac{l}{g} - \frac{l}{g\alpha}\right)$-periodic.

Now, in the region $0 < x < gt$ (see Figure 2.1) we have $\frac{l}{g\alpha} - \frac{x}{g} + t > \frac{l}{g\alpha}$; or $t - \frac{x}{g} > 0$. So that

$$n\left(l^-, \frac{l}{g\alpha} - \frac{x}{g} + t\right) = Be^{-Jt}p\left(\frac{l}{g\alpha} - \frac{x}{g} + t\right). \tag{3.4}$$

Therefore,

$$n\left(l^-, \frac{l}{g\alpha} - \frac{x}{g} + t\right) = Be^{-Jt}p\left(\frac{l}{g\alpha} - \frac{x}{g} + t\right), \qquad 0 < x < gt. \tag{3.5}$$

Moreover,

$$n\left(l^-,\frac{l}{g}-\frac{x}{g}+t\right)=Be^{-Jt}p\left(\frac{l}{g}-\frac{x}{g}+t\right),\qquad 0<x<gt. \tag{3.6}$$

We may thus substitute the right-hand sides of the above equations into (2.9) to give

$$n(x,t)=\frac{\alpha b}{g}Be^{-Jt}p\left(\frac{l}{g\alpha}-\frac{x}{g}+t\right)e^{\mu\left[\frac{l}{g\alpha}-\frac{x}{g}\right]}\mathscr{H}_1(x,t)-\frac{b}{g}Be^{-Jt}p\left(\frac{l}{g}-\frac{x}{g}+t\right)e^{\mu\left[\frac{l}{g}-\frac{x}{g}\right]}\mathscr{H}_2(x,t), \tag{3.7}$$

when $0<x<gt$.

3.2 Calculation of the shape of the hull

In this section we calculate the shape of the hull of the transient solution.[3] To expedite this we find $N(x)$ (which we also refer to as the hull) with the intent of scaling afterwards to finally obtain $H(x)$. Note that when $0<x<gt$, $\mathscr{H}_1(x,t)=1$ for all $x>l/\alpha$ and 0 otherwise; likewise $\mathscr{H}_2(x,t)=1$ for all $x>l$ and 0 otherwise. Again we consider the three regions R_1, R_2 and R_3.

When $x\in R_1$ and $x<gt$, equation (2.9) shows that $n(x,t)=0$. Therefore, the hull in the region R_1 is

$$N(x)=0. \tag{3.8}$$

When $x\in R_2$ and $x<gt$, we have

$$\begin{aligned} n(x,t) &= \frac{\alpha b}{g}n\left(l^-,\frac{l}{g\alpha}-\frac{x}{g}+t\right)e^{\mu\left[\frac{l}{g\alpha}-\frac{x}{g}\right]} \\ &= B\frac{\alpha b}{g}e^{(J-\mu)\left[\frac{x}{g}-\frac{l}{g\alpha}\right]}e^{-Jt}p\left(\frac{l}{g\alpha}-\frac{x}{g}+t\right). \end{aligned} \tag{3.9}$$

Thus,

$$N(x)=\sup_{t>\frac{x}{g}}\frac{n(x,t)e^{Jt}}{B}=\frac{\alpha b}{g}e^{(J-\mu)\left[\frac{x}{g}-\frac{l}{g\alpha}\right]}\left\{\sup_{t>\frac{x}{g}+\frac{l}{g\alpha}}p(t)\right\}. \tag{3.10}$$

The bracketed term in the above equation shall now be denoted by $N(l)$ since, given J as in (A.10), we see that

$$N(l^-)=\sup_{t>\frac{l}{g}}\frac{n(l^-,t)e^{Jt}}{B}=\sup_{t>\frac{l}{g}}p(t)=\sup_{t>\frac{x}{g}+\frac{l}{g\alpha}}p(t), \tag{3.11}$$

for any $x>0$. This makes the hull continuous from the left (although we could just have easily let the hull be undefined at $x=l$).

[3] The shape of the hull is the same when $\delta(x-l)n(x,t)=\delta(x-l)n(l^+,t)$ is chosen rather than $\delta(x-l)n(x,t)=\delta(x-l)n(l^-,t)$. This is because the shape of the hull is derived from (2.9) with the sole alteration of limits from below (l^-) being replaced by limits from above (l^+).

Finally, when $x \in R_3$ and $x < gt$ we have

$$\begin{aligned} n(x,t) &= \frac{\alpha b}{g} n\left(l^-, \frac{l}{g\alpha} - \frac{x}{g} + t\right) e^{\mu\left[\frac{l}{g\alpha} - \frac{x}{g}\right]} \\ &\quad -\frac{b}{g} n\left(l^-, \frac{l}{g} - \frac{x}{g} + t\right) e^{\mu\left[\frac{l}{g\alpha} - \frac{x}{g}\right]} \\ &= B\frac{\alpha b}{g} e^{(J-\mu)\left[\frac{x}{g} - \frac{l}{g\alpha}\right]} e^{-Jt} p\left(\frac{l}{g\alpha} - \frac{x}{g} + t\right) \\ &\quad -B\frac{b}{g} e^{(J-\mu)\left[\frac{x}{g} - \frac{l}{g}\right]} e^{-Jt} p\left(\frac{l}{g} - \frac{x}{g} + t\right). \end{aligned} \tag{3.12}$$

We observe that since p is $\left(\frac{l}{g} - \frac{l}{g\alpha}\right)$-periodic,

$$p\left(\frac{l}{g\alpha} - \frac{x}{g} + t\right) = p\left(\frac{l}{g\alpha} - \frac{x}{g} + t + \frac{l}{g} - \frac{l}{g\alpha}\right) \tag{3.13}$$

$$= p\left(\frac{l}{g} - \frac{x}{g} + t\right), \tag{3.14}$$

so that when $l < x$,

$$\begin{aligned} N(x) &= \sup_{t > \frac{x}{g}} \frac{n(x,t)e^{Jt}}{B} \\ &= \frac{b}{g} e^{(J-\mu)\left[\frac{x}{g} - \frac{l}{g}\right]} \left(\alpha e^{(J-\mu)\left[\frac{l}{g} - \frac{l}{g\alpha}\right]} - 1\right) N(l). \end{aligned} \tag{3.15}$$

We defer the normalization of H until we discuss the solutions of I.

3.3 Equivalence of the hull to the limiting SSD solutions as $D = 0$

In I the SSD solutions in the limiting case are derived by separation of variables when $D \neq 0$ and then taking the limit as $D \to 0$. It was shown that by separation of variables and imposing the condition that $y(x)$ was a probability density function, a specific growth or decay rate could be obtained of $\Lambda = (\alpha - 1)by(l) - \mu$, where $y(l)$ is the value of the SSD at $x = l$. The limiting SSD's are then expressed using a constant $L_1 = (\alpha - 1)by(l)$, where for notational convenience we have redefined the L used in I to L_1. These limiting SSD's are equivalent to the separated solution found by letting $D = 0$ at the outset (with a suitable change to the terms involving δ such as we made in (1.9)). It should be noted that L_1 is the growth/decay rate Λ plus μ. Thus, if in this case we define

$$L = -J + \mu = \frac{g\alpha}{l(\alpha - 1)} \ln\left(\frac{\alpha b}{g}\right) \tag{3.16}$$

and recognize that $H(l)$ in this case is the analogue of $y(l)$ in I, we get

$$H(x) = \begin{cases} 0, & 0 < x < \frac{l}{\alpha}, \\ \frac{\alpha b H(l)}{g} e^{-\frac{L}{g}\left(x - \frac{l}{\alpha}\right)}, & \frac{l}{\alpha} < x < l \\ \frac{bH(l)}{g} e^{-\frac{L}{g}x}\left(\alpha e^{\frac{Ll}{g\alpha}} - e^{\frac{Ll}{g}}\right), & l < x. \end{cases} \tag{3.17}$$

The above expressions are of exactly the same form as the limiting SSD solutions as $D \to 0$ with the understanding that $H(l)$ corresponds to $y(l)$. The only difference between them being the constants L and L_1. In both cases, however, L (or L_1) is the growth rate plus μ.

The requirement that $L = L_1$ gives a restriction on $y(l)$ as follows:

$$(\alpha - 1)by(l) = \frac{\alpha g}{l(\alpha - 1)} \ln\left(\frac{\alpha b}{g}\right)$$

or

$$y(l) = \frac{\alpha g}{bl(\alpha - 1)^2} \ln\left(\frac{\alpha b}{g}\right). \tag{3.18}$$

This implies that the limiting SSD from I is continuous from the left. Moreover, the hull when $D = 0$ is exactly equal to the limiting SSD as $D \to 0$ when $L = L_1$, $H(l) = y(l)$. Thus, the hull is the equivalent of the limiting SSD as $D \to 0$ with the requirement of continuity from the left.[4] This SSD is a probability density function, so that we have appropriately normalised the hull by setting $H(l) = y(l)$. Note that such a limiting SSD only exists for $g < \alpha b$ (*i.e.* $\ln(\alpha b/g) > 0$). Moreover, from Section 4.4 we see that the hull in the region $x < l$ is equal to $(1 - b/g)\phi(x)$, where $\phi(x)$ is the hull in the region $l/\alpha < x < l$ with its domain of definition extended to $l < x$. The non-negativity of the hull therefore requires that $b \leq g$. Hence we require that $b \leq g < \alpha b$ for the hull to match a limiting SSD from I. We now make the following observations:

1. $H(x)$ is independent of the initial condition n_0
2. $H(x)$ is a global attractor in the sense that for any finite interval $0 \leq x \leq a$,

   $$\sup_{t<\tau<t+\frac{l}{g}-\frac{l}{g\alpha}} An(x,\tau)e^{J\tau} \to H(x),$$

   as $t \to \infty$, for some constant A. We henceforth refer to the above expression (with or without the scaling constant) as the *transient hull* of $n(x,t)$.
3. If $g \geq \alpha b$ then $L \leq 0$ and $N \notin L^1$. This makes it impossible to match any limiting SSD's from I since in I they are probability density functions.

Figures (3.1) and (3.2) show examples of hulls for different sets of parameters. Figure (3.2) illustrates what the (unscaled) hull looks like when $g > \alpha b$; observe that it cannot be made into probability density function by scaling and hence cannot match any limiting SSD from I.

[4] When $\delta(x-l)n(x,t) = \delta(x-l)n(l^+,t)$ is chosen, we obtain the condition $y(l) = \frac{\alpha g}{b(\alpha-1)^2} \ln\left(\frac{\alpha b}{b+g}\right)$. This is the condition for the limiting SSD to be continuous from the right. Similar comments for the right-continuous case apply as in the left-continuous case. Moreover, if we do not consider by convention that $n(x,t)$ is continuous from the left in x, the result regarding the equivalence of the hull and the limiting SSD continuous from the left holds for *almost every* $x > 0$ rather than for all x.

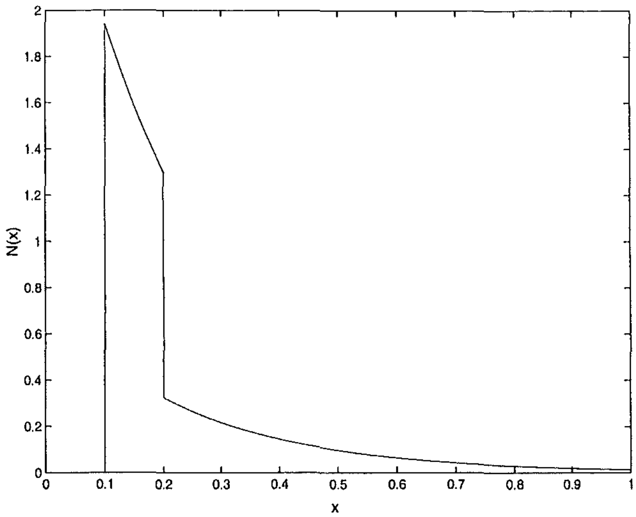

Figure 3.1: A plot of the hull when $\alpha = 2$, $l = 0.2$, $b = 3$, $g = 4$ and $N(l) = 1.3$.

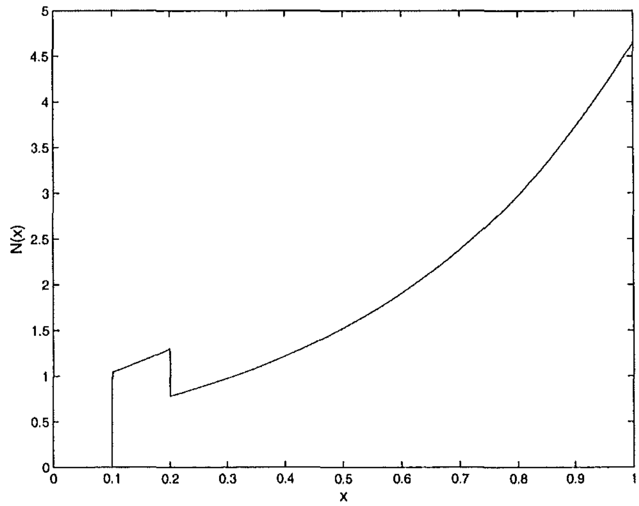

Figure 3.2: An unscaled hull when $\alpha b < g$. Parameters are $\alpha = 2$, $b = 2$, $g = 5$, $l = 0.2$, $N(l) = 1.3$. In this case there is no limiting SSD from I continuous from the left corresponding to the hull. Obviously in this case there is no appropriate normalisation to make the hull a probability density function.

4 Variable growth rate and the shape of the hull

If we now specify a positive function $g(x) \in H^1$ for the growth-rate of cells of size x instead of a constant g as we have used up to this point, we obtain the equation

$$n_t + g(x)n_x + g'(x)n + \mu n = \alpha b\delta(x - l/\alpha)n(l^-,t) - b\delta(x-l)n(l^-,t). \qquad (4.1)$$

The use of a variable g function can allow the one compartment model to represent (to an extent) different stages of cell-growth, in which different growth rates might be experienced. In (Basse et al., 2004a,b), the phases G_1 and G_2 of human cell growth, occurring immediately after (G_1) or before cell division (G_2), effectively act as (stochastic) time delays. This may be approximated loosely by a growth function which is constant except on two finite intervals around l/α and l where the growth rate is reduced.

Equation (4.1) can be reduced to a form similar to (2.1) by a series of transformations which shall now be shown. Let

$$x' = \int_0^x \frac{1}{g(s)}\, ds; \qquad u(x',t) = n(x,t). \tag{4.2}$$

Then

$$g(x)n_x = g(x)u_{x'}\frac{\partial x'}{\partial x} = u_{x'}. \tag{4.3}$$

Now let $h(x') = g'(x)$. We then have

$$u_t + u_{x'} + h(x')u + \mu u = \alpha b\delta(x - l/\alpha)n(l^-,t) - b\delta(x-l)n(l^-,t). \tag{4.4}$$

We now make note of the fact that

$$\begin{aligned} \int \delta(x-l)n(l^-,t)\, dx' &= \int \frac{\delta(x-l)}{g(x)} n(l^-,t)\, dx \\ &= H(x-l)\frac{n(l^-,t)}{g(l)} \\ &= H(x'-x'(l))\frac{u(x'(l)^-,t)}{g(l)}, \end{aligned}$$

and also of the fact that a similar result holds when we replace l/α by l. Therefore if we integrate both sides of (4.4) with respect to x' and subsequently differentiate by x', we obtain

$$u_t + u_{x'} + h(x')u + \mu u = \frac{\alpha b}{g(l/\alpha)}\delta(x'-x'(l/\alpha))u(x'(l)^-,t) - \frac{b}{g(l)}\delta(x'-x'(l))u(x'(l)^-,t). \tag{4.5}$$

Finally, let

$$w(x',t) = u(x',t)\exp\left[\int_0^{x'} h(s)\, ds\right]. \tag{4.6}$$

Then

$$u_t = w_t \exp\left[-\int_0^{x'} h(s)\, ds\right]; \qquad u_{x'} = (w_{x'} - h(x')w)\exp\left[-\int_0^{x'} h(s)\, ds\right]. \tag{4.7}$$

Thus, when we express (4.1) using the independent variable x' and dependent variable w, we obtain

$$\begin{aligned} (w_t + w_{x'} + \mu w)\exp\left[-\int_0^{x'} h(s)\, ds\right] &= \frac{\alpha b}{g(l/\alpha)}\delta(x'-x'(l/\alpha))w(x'(l)^-,t)\exp\left[-\int_0^{x'(l)} h(s)\, ds\right] \\ &\quad - \frac{b}{g(l)}\delta(x'-x'(l))w(x'(l)^-,t)\exp\left[-\int_0^{x'(l)} h(s)\, ds\right], \end{aligned}$$

implying

$$\begin{aligned} w_t + w_{x'} + \mu w &= \frac{\alpha b}{g(l/\alpha)}\delta(x'-x'(l/\alpha))w(x'(l)^-,t)\exp\left[-\int_{x'(l/\alpha)}^{x'(l)} h(s)\, ds\right] \\ &\quad - \frac{b}{g(l)}\delta(x'-x'(l))w(x'(l)^-,t). \end{aligned} \tag{4.8}$$

Notice that the differential equation above is similar to (2.1) with $g = 1$. The differences being that the constants multiplying the delta functions have been changed.

4.1 The hull of w

In this section we find the hull of w, which we shall then use to find the hull of n for a general positive growth function $g(x)$. The hull in this case is taken in the region $x' < t$. First, notice that

$$\begin{aligned}\frac{\alpha b}{g(l/\alpha)}\exp\left[-\int_{x'(l/\alpha)}^{x'(l)} h(s)\,ds\right] &= \frac{\alpha b}{g(l/\alpha)}\exp\left(-\int_{l/\alpha}^{l}\frac{g'(\xi)}{g(\xi)}\,d\xi\right)\\ &= \frac{\alpha b}{g(l/\alpha)}\frac{g(l/\alpha)}{g(l)} = \frac{\alpha b}{g(l)}. \end{aligned} \tag{4.9}$$

This simplifies (4.8), so that it is now virtually the same as the constant growth case (2.1) when $g = 1$.

Similar steps to those used in the case where g is constant may now be taken to find the solution of w. As mentioned above, w satisfies (2.1) for $g = 1$ with the modifications of the right hand side being divided by $g(l)$ and both l, l/α being replaced by $x'(l), x'(l/\alpha)$ respectively. Note that $x'(l/\alpha) < x'(l)$; therefore we can treat $x'(l)$ and $x'(l/\alpha)$ much like l and l/α in the case with constant g to give the result that $w(x'(l),t)$ is a $[x'(l) - x'(l/\alpha)]$-periodic function multiplied by an exponential function for $t > x'(l/\alpha)$. Specifically

$$w(x'(l),t) = Be^{-Jt}p(t), \qquad t > x'(l/\alpha), \tag{4.10}$$

where $p(t)$ is the afore-mentioned periodic function, B is a constant and

$$J = -[x'(l) - x'(l/\alpha)]^{-1}\ln\left(\frac{\alpha b}{g(l)}\right) + \mu. \tag{4.11}$$

This leads to a hull of the same shape as in the constant growth case with $\frac{\alpha b}{g}$ replaced by $\frac{\alpha b}{g(l)}$ and $\frac{b}{g}$ replaced by b. The hull must then be multiplied by

$$\exp\left[-\int_0^{x'} h(s)\,ds\right]$$

to find the hull U of u. Following this, the hull N of n is

$$N(x) = U\left(\int_0^x \frac{1}{g(s)}\,ds\right). \tag{4.12}$$

From the above observations, we find the hull W of w to be

$$W(x') = 0, \qquad 0 < x' < x'\left(\frac{l}{\alpha}\right), \tag{4.13}$$

$$W(x') = \frac{\alpha b}{g(l)}W(x'(l))e^{-L(x'-x'(\frac{l}{\alpha}))}, \qquad x'\left(\frac{l}{\alpha}\right) < x' < x'(l) \tag{4.14}$$

$$\begin{aligned} W(x') &= \frac{b}{g(l)}W(x'(l))e^{-L(x'-x'(l))}\left(\alpha e^{-L(x'(l)-x'(\frac{l}{\alpha}))} - 1\right)\\ &= \frac{b}{g(l)}W(x'(l))e^{-Lx'}\left(\alpha e^{Lx'(\frac{l}{\alpha})} - e^{Lx'(l)}\right), \qquad x'(l) < x'. \end{aligned} \tag{4.15}$$

where $L = -J + \mu$ as in the constant growth case.

Remark: The hull W is an attractor of the transient hull,

$$\sup_{t\leq\tau\leq t+x'(l)-x'(l/\alpha)} w(x',\tau)e^{J\tau}$$

in the same way as in the constant growth case (*i.e.* uniformly on finite intervals $[0,a]$, $0<a<\infty$). Correspondingly we have

$$N(x)=\sup_{t>x'} w(x',t)\exp\left[\int_0^{x'} h(s)\,ds+Jt\right]$$

is an attractor of the transient hull of n, given by

$$\sup_{t-x'(l)+x'(l/\alpha)\leq\tau\leq t} w(x',\tau)\exp\left[\int_0^{x'} h(s)\,ds+J\tau\right].$$

In the above statements all hulls have been left unscaled.

4.2 A consideration to simplify the calculation of the hull of n

We claim that the hull $N(x)$ of $n(x,t)$, for variable growth-rate $g(x)$, satisfies the differential equation:

$$(g(x)N(x))'+LN(x)=\alpha b\delta(x-l/\alpha)N(l^-)-b\delta(x-l)N(l^-). \tag{4.16}$$

Putting the above equation through the transforms described in Equations (4.2) and (4.6); having $N(x)$ transform to $U(x')$ via the transformation in (4.2), then to $W(x')$ via the transformation in (4.6), we find that (4.16) is satisfied if and only if

$$W'+LW=\frac{\alpha b}{g(l)}\delta(x'-x'(l/\alpha))W(x'(l)^-)-\frac{b}{g(l)}\delta(x'-x'(l))W(x'(l)^-). \tag{4.17}$$

It is easy to check that $W(x')$ satisfies Equation (4.17). Thus, after applying reverse transformations to W and U, we see that the hull $N(x)$ satisfies (4.16).

Note that (4.16) is the same as that for the separated solution (SSD) $y(x)$ in I with $D=0$. (Again, the value of L is different when we approach the problem via separation of variables.) Note that here we cannot say that the hull matches a limiting SSD as $D\to 0$, since the separated problem when $D\neq 0$ seems intractable, so a proof is yet to be found.

4.3 The general shape of $N(x)$

The solution to $N(x)$ is obtained by using the fact that

$$g(x)N'(x)+(L+g'(x))N(x)=0, \qquad x\notin\{l,l/\alpha\}, \tag{4.18}$$

and jump conditions on N at $x=l/\alpha$ and $x=l$, found by integrating both sides of (4.16) over an interval containing l (resp. l/α) and letting both limits of the integral tend to l (resp. l/α). The jump conditions are as follows:

$$[N]_{l/\alpha^-}^{l/\alpha^+}=\frac{\alpha b}{g(l/\alpha)}N(l^-); \qquad [N]_{l^-}^{l^+}=-\frac{b}{g(l)}N(l^-). \tag{4.19}$$

From this we find a three-part solution:

$$N_i(x) = C_i \exp\left(-\int_0^x \frac{L}{g(s)}\,ds\right)[g(x)]^{-1}, \qquad i \in \{1,2,3\}, \tag{4.20}$$

where the domain of N_i is R_i for $i \in \{1,2,3\}$ and R_i is as we have defined in Section 2. Note that for notational convenience we set $N(l) = N(l^-) = N_2(l)$.

The condition that $N_2(l) = N(l)$ fixes the value of C_2, giving

$$N_2(x) = N(l)\exp\left(\int_x^l \frac{L}{g(s)}\,ds\right)\frac{g(l)}{g(x)}. \tag{4.21}$$

The jump condition at $x = l$ fixes C_3 and leads to the result that $N_3(x) = (1 - b/g(l))N_2(x)$, where the domain of definition of $N_2(x)$ has been extended to $l < x$.

Finally, the jump condition at $x = \frac{l}{\alpha}$ implies

$$N_1(l/\alpha) = N_2(l/\alpha) - \frac{\alpha b}{g(l/\alpha)}N_2(l), \tag{4.22}$$

so that

$$\begin{aligned} C_1 &= \left[N_2(l/\alpha) - \frac{\alpha b}{g(l/\alpha)}N_2(l)\right]\exp\left(\int_0^{l/\alpha}\frac{L}{g(s)}\,ds\right)g(l/\alpha) \\ &= N_2(l)\left[\exp\left(\int_0^l \frac{L}{g(s)}\,ds\right)g(l) - \alpha b \exp\left(\int_0^{l/\alpha}\frac{L}{g(s)}\,ds\right)\right]. \end{aligned} \tag{4.23}$$

Therefore,

$$N_1(x) = \frac{N_2(l)}{g(x)}\exp\left(\int_x^{l/\alpha}\frac{L}{g(s)}\,ds\right)\left[\exp\left(\int_{l/\alpha}^l \frac{L}{g(s)}\,ds\right)g(l) - \alpha b\right]. \tag{4.24}$$

The choice of L, however, forces $N_1(x)$ to be identically zero, since $L = [x'(l) - x'(l/\alpha)]^{-1}\ln\left(\frac{\alpha b}{g(l)}\right)$, and so, in (4.24),

$$\exp\left(\int_{l/\alpha}^l \frac{L}{g(s)}\,ds\right)g(l) - \alpha b = \exp(L[x'(l) - x'(l/\alpha)])g(l) - \alpha b = \frac{\alpha b}{g(l)}g(l) - \alpha b = 0. \tag{4.25}$$

We may thus summarise the solution of the hull $N(x)$ as follows:

$$N(x) = \begin{cases} 0, & 0 < x < l/\alpha, \\ N(l)\exp\left(\int_x^l \frac{L}{g(s)}\,ds\right)\frac{g(l)}{g(x)}, & l/\alpha < x < l, \\ \left(1 - \frac{b}{g(l)}\right)N(l)\exp\left(\int_x^l \frac{L}{g(s)}\,ds\right)\frac{g(l)}{g(x)}, & l < x, \end{cases} \tag{4.26}$$

with N continuous from the left at l.

From this it can be seen that a necessary and sufficient condition for positivity of the hull is that $b \le g(l)$. This is the analogue of the condition $b \le g$ for positivity of the hull for constant growth rate. Moreover, for the unscaled hull to have a finite integral the condition we require is $g(l) < \alpha b$. Thus, the conditions needed for the hull to be a probability density function are $b \le g(l) < \alpha b$.

4.4 Verification that the variable g hull reduces to the constant g hull when g is constant

We now show that the above expression matches (3.17) when g is constant. Let N denote the hull from (4.26) and H denote the hull from (3.17), with $H(l) = N(l)$. Consider (4.26) when g is constant. It is easy to check that L in this case is the same as in (3.17), namely

$$L = \frac{g\alpha}{l(\alpha-1)} \ln\left(\frac{\alpha b}{g}\right).$$

The hull $N(x)$, in the region $l/\alpha < x \leq l$, is now,

$$\begin{aligned} N(l)\exp\left[\frac{L}{g}(l-x)\right] &= N(l)\frac{\alpha b}{g}\exp\left\{\frac{L}{g}\left[l - x - \frac{g}{L}\ln\left(\frac{\alpha b}{g}\right)\right]\right\} \\ &= N(l)\frac{\alpha b}{g}\exp\left[-\frac{L}{g}\left(x - \frac{l}{\alpha}\right)\right], \end{aligned} \tag{4.27}$$

which is the same expression as in (3.17). Now consider (3.17) when $l < x$. Let $\phi(x) = H(x)$ for $l/\alpha < x \leq l$, and extend the domain of definition of ϕ to $l < x$. Note that in the region $l < x$ we have

$$H(x) = \phi(x) - \frac{b}{g}H(l)\exp\left[-\frac{L}{g}(x-l)\right]. \tag{4.28}$$

But from what we saw in (4.27) we can now see that

$$H(l)\exp\left[-\frac{L}{g}(x-l)\right] = \phi(x). \tag{4.29}$$

Thus, Equations (3.17) and (4.26) agree for $l/\alpha < x$. Moreover ,both equations agree when $0 < x < l/\alpha$, where they both specify the hull as being zero. Thus, they specify the same hull when g is constant.

Incidentally, in the calculation of the hull for variable g the supremum of the periodic function $p(t)$ is taken over $x' < t$, which becomes $x/g < t$, as expected, when g is constant.

4.5 Example of a specific growth function

We now give an example growth function $g(x)$ to illustrate the effect that the varying growth rate has on the shape of the hull. We have constructed $g(x)$ so that it is approximately constant except in two regions around l/α and l respectively. The specific function we use here is

$$g(x) = 3 - 2G\left(x, \frac{l}{\alpha}\right) - G(x,l), \tag{4.30}$$

where

$$G(x,y) = \exp\left(\frac{-(x-y)^2}{2(0.2)^2}\right). \tag{4.31}$$

A plot of this growth function is shown in Figure 4.1. The regions of slower growth in the above growth function are designed to simulate time-lag before and after cell division, as in the G_1 and G_2 phases of human cell growth mentioned above.

The hull corresponding to the growth function $g(x)$ is shown in Figure 4.2. One would expect the cells to collect in the regions of slower growth, and thus affect the shape of the hull in a similar way.

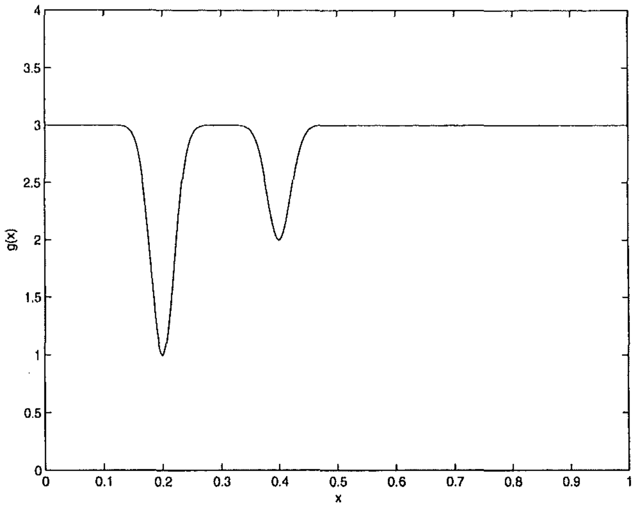

Figure 4.1: An example growth function $g(x)$. It consists of a constant minus two gaussian-like functions with peaks at $\frac{l}{\alpha}$ and l. In this case $l = 0.4$ and $\alpha = 2$. The regions of slower growth in the above growth function are designed to simulate time-lag before and after cell division. This is characteristic of human cell-growth, where the cells go through G_1-phase immediately after cell division and G_2-phase immediately prior.

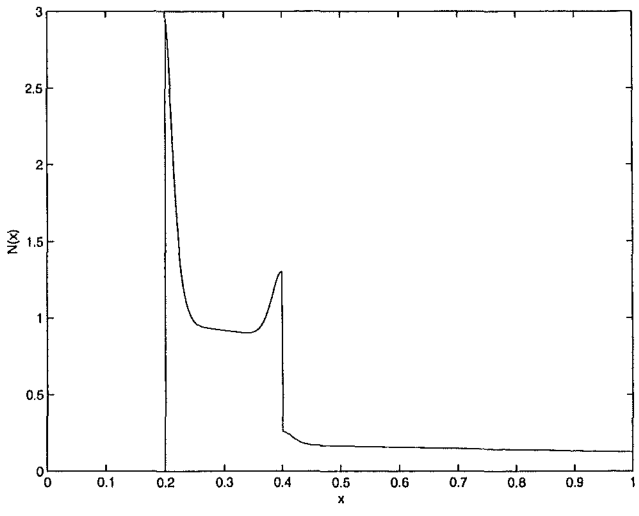

Figure 4.2: The hull corresponding to the growth function in Figure 4.1, with $\alpha = 2$, $b = 1.6$, $l = 0.4$ and $N(l) = 1.3$. The cells tend to collect in the regions of slower growth.

5 Conclusions

The transient hull of the solution to (2.1) with $g(x) \in H^1$ displays SSD behaviour when the growth and division parameters satisfy the inequality

$$b \leq g(l) < \alpha b.$$

It was found that $g(l) < \alpha b$ in order for the (unscaled) hull to be in L^1; this is essential in order for the H to be a probability density function as is also required in I for $y(x)$. The transient hull distributions track along the SSD path

$$n(x,t) \sim H(x)e^{\Lambda t}, \tag{5.1}$$
$$\Lambda = -J \tag{5.2}$$

for large time t where the sign of the exponent J is determined by the equation (A.10)). Therefore the cell cohort has survival or extinction outcomes if

$$\ln\left(\frac{\alpha b}{g(l)}\right)\left[\int_{l/\alpha}^{l}\frac{1}{g(s)}\,ds\right]^{-1}\begin{cases} > \mu & \text{survival } (J<0), \\ < \mu & \text{extinction } (J>0). \end{cases}$$

This applies to both of the constant-growth and variable-growth cases. In the constant-growth case these conditions become:

$$\ln\left(\frac{\alpha b}{g}\right)\frac{\alpha g}{l(\alpha-1)}\begin{cases} > \mu & \text{survival } (J<0), \\ < \mu & \text{extinction } (J>0). \end{cases}$$

When g is constant, the hull of the solution for models with hyperbolic symbol provides a solution of the limiting case of SSD's of models with dispersion as the dispersion tends to zero. This has implications for cell growth models of this kind.

A variable growth-rate changes the shape of the hull, and if it can be shown that the hull in this case is the limit as $D \to 0$ of SSD's dependent on D, then potentially the general expression for the variable growth-rate hull could be used in the inverse problem of determining the growth rate at each size of a population of cells.

Recent investigations of cell cohorts other than the plankton cells also satisfy the assumptions of this model; in particular the assumption of division at a fixed size with fixed division rate ($B(x) = b\delta(x-l)$). Basse et al. (2004b) have investigated a multi-compartment cell population model for human tumour cell lines with compartments for each phase of the cell-cycle. When this four compartment model is collapsed into a lumped compartment model such as we have here, we obtain division at fixed size. This justifies to some extent the assumption, made in this paper, of single size division expressed using δ.

6 Acknowledgements

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References

Basse, B., Baguley, B. C., Marshall, E. S., Joseph, W. R., van Brunt, B., Wake, G. C., Wall, D. J. N., 2004a. Modelling cell death in human tumour cell lines exposed to the anticancer drug paclitaxel. J. Math. Biol. , 329–357.

Basse, B., Wake, G. C., Wall, D. J. N., 2004b. Modelling cell population growth with applications to cancer therapy in human tumour cell lines. Prog Biophys Mol, Biol. 85, 353–368.

Basse, B., Wake, G. C., Wall, D. J. N., van Brunt, B., 2004c. On a cell-growth model for plankton. IMA: J. Mathematics Applied in Medicine and Biology 21 (1), 49–61.

Chiorino, G., Metz, J., Tomasoni, D., Ubezio, P., 2001. Desynchronization rate in cell populations: Mathematical modeling and experimental data. J. Theor. Biol. 208, 185–199.

Malthus, T. R., 1798, 1970. A essay on the principle of population (and: A summary view of the principles of population). penguin, Harmondsworth, Middlesex.

Okubo, A., 1980. Diffusion and Ecological Problems: Mathematical Models. Springer-Verlag, Berlin.

Rossa, B., 1995. Asynchronous exponential growth in a size structured cell population with quiescent compartment. Vol. 2: Carcinogenesis and Cell & Tumor Growth. Wuerz Publishing Ltd, Winnipeg, Canada, Ch. 14, pp. 183–200.

Round, F. E., Crawford, R. M., Mann, D. G., 1990. The Diatoms. Cambridge University Press, Cambridge.

A Appendix

A.1 Periodic behaviour of $n_2(l,t)$ as $t \longrightarrow \infty$ for $1 < \alpha$

In this section it is shown that $n_2(l,t)$ is an $\frac{l(\alpha-1)}{g\alpha}$-periodic function for $t > \frac{l}{g\alpha}$ when $1 < \alpha$.

For $l/\alpha < x < l$, we know that $F_2(x) = n_0(x)H(x)$. This, combined with (2.15) gives us the necessary information to calculate the behaviour of $F_2(z)$ as z decreases. In the following working we will assume $n_0(z) = 0$ for $z \leq 0$. Thus, $n_0(z) = n_0(z)H(z)$. First let $\lambda = \frac{\alpha b}{g}$, then we have

$$F_2(z) = n_0(z)H(z) + \lambda n_0\left(z + l - \frac{l}{\alpha}\right), \quad \frac{l}{\alpha} - \left(l - \frac{l}{\alpha}\right) < z < \frac{l}{\alpha}. \tag{A.1}$$

It is easily shown by induction that

$$F_2(z) = n_0(z) + \lambda n_0\left(z + l - \frac{l}{\alpha}\right) + \ldots + \lambda^m n_0\left(z + m\left[l - \frac{l}{\alpha}\right]\right), \tag{A.2}$$

$$\frac{l}{\alpha} - m\left(l - \frac{l}{\alpha}\right) < z < \frac{l}{\alpha} - (m-1)\left(l - \frac{l}{\alpha}\right), \tag{A.3}$$

for all $0 < m \in \mathbb{Z}$. However, $n_0(z) = 0$ when $z < 0$ and it is desirable that terms equal to zero be removed from the expression for $F_2(z)$. To this end we proceed by noting that there exists some $0 \leq k \in \mathbb{Z}$ such that

$$\frac{l}{\alpha} - k\left(l - \frac{l}{\alpha}\right) \geq 0; \qquad \frac{l}{\alpha} - (k+1)\left(l - \frac{l}{\alpha}\right) < 0. \tag{A.4}$$

Thus, let $G(z) = F_2(z)$ in the region $\frac{l}{\alpha} - k\left(l - \frac{l}{\alpha}\right) < z < \frac{l}{\alpha} - (k-1)\left(l - \frac{l}{\alpha}\right)$. That is, let

$$G(z) = n_0(z) + \ldots + \lambda^k n_0\left(z + k\left[l - \frac{l}{\alpha}\right]\right), \qquad \frac{l}{\alpha} - k\left(l - \frac{l}{\alpha}\right) < z < \frac{l}{\alpha} - (k-1)\left(l - \frac{l}{\alpha}\right) \tag{A.5}$$

We then have[5]

$$F_2(z) = \begin{cases} G(z) & \frac{l}{\alpha} - k\left(l - \frac{l}{\alpha}\right) < z < \left(l - \frac{l}{\alpha}\right), \\ n_0(z) + \lambda G\left(z + l - \frac{l}{\alpha}\right) & 0 < z < \frac{l}{\alpha} - k\left(l - \frac{l}{\alpha}\right). \end{cases} \tag{A.6}$$

Again, it is easily shown by induction that

$$F_2(z) = \begin{cases} \lambda^j G\left(z + j\left[l - \frac{l}{\alpha}\right]\right) & \frac{l}{\alpha} - (k+j)\left(l - \frac{l}{\alpha}\right) < z < -(j-1)\left(l - \frac{l}{\alpha}\right), \\ \\ \lambda^j n_0\left(z + j\left[l - \frac{l}{\alpha}\right]\right) & \\ +\lambda^{j+1} G\left(z + (j+1)\left[l - \frac{l}{\alpha}\right]\right) & -j\left(l - \frac{l}{\alpha}\right) < z < \frac{l}{\alpha} - (k+j)\left(l - \frac{l}{\alpha}\right), \end{cases} \tag{A.7}$$

for all $0 \leq j \in \mathbb{Z}$. Replacing z with $l - gt$, we find

$$F_2(l - gt) = \begin{cases} \lambda^j G\left(l - gt + j\left[l - \frac{l}{\alpha}\right]\right) & j\frac{l}{g} - (j-1)\frac{l}{g\alpha} < t < (k+j+1)\left(\frac{l}{g} - \frac{l}{g\alpha}\right), \\ \\ \lambda^j n_0\left(l - gt + j\left[l - \frac{l}{\alpha}\right]\right) & \\ +\lambda^{j+1} G\left(l - gt + (j+1)\left[l - \frac{l}{\alpha}\right]\right) & (k+j+1)\left(\frac{l}{g} - \frac{l}{g\alpha}\right) < t < (j+1)\frac{l}{g} - j\frac{l}{g\alpha}, \end{cases} \tag{A.8}$$

for all $0 \leq j \in \mathbb{Z}$. Thus, $n(l^-, t)$ may be expressed, for $t > \frac{l}{g\alpha}$

$$n(l^-, t) = n_2(l, t) = e^{-\mu t} F_2(l - gt) = e^{-Jt} p(t), \tag{A.9}$$

where

$$J = -\frac{g\alpha}{l(\alpha - 1)} \ln(\lambda) + \mu, \tag{A.10}$$

and $p(t)$ is the $\left(\frac{l}{g} - \frac{l}{g\alpha}\right)$-periodic function defined for $t > \frac{l}{g\alpha}$ by

$$p(t) = e^{(J-\mu)\left(t - j\left[\frac{l}{g} - \frac{l}{g\alpha}\right]\right)} \begin{cases} G\left(l - gt + j\left[l - \frac{l}{\alpha}\right]\right), & j\frac{l}{g} - (j-1)\frac{l}{g\alpha} < t < (k+j+1)\left(\frac{l}{g} - \frac{l}{g\alpha}\right), \\ \\ n_0\left(l - gt + j\left[l - \frac{l}{\alpha}\right]\right) & \\ +\frac{\alpha b}{g} G\left(l - gt + (j+1)\left[l - \frac{l}{\alpha}\right]\right), & (k+j+1)\left(\frac{l}{g} - \frac{l}{g\alpha}\right) < t < (j+1)\frac{l}{g} - j\frac{l}{g\alpha}, \end{cases} \tag{A.11}$$

$0 \leq j \in \mathbb{Z}$. The desired result has thus been proved.

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[5] Since $\frac{l}{\alpha} - k\left(l - \frac{l}{\alpha}\right) > 0$, know that $\frac{l}{\alpha} - (k-1)\left(l - \frac{l}{\alpha}\right) > \left(l - \frac{l}{\alpha}\right)$. Hence the upper-bound of $z < \left(l - \frac{l}{\alpha}\right)$ in the following equation.

A.1.1 The case when $\alpha = 2$

Here it will be shown that the working above reduces to the answer obtained in the main body of the paper when $\alpha = 2$. First note that $\alpha = 2$ implies k, the greatest integer for which

$$\frac{l}{g\alpha} - k\frac{l(\alpha-1)}{g\alpha} \geq 0,$$

is 1. Thus, the domain of definition of $G(z)$ becomes $0 < z < l/2$, with

$$G(z) = n_0(z) + \lambda n_0(z + l/2), \qquad 0 < z < \frac{l}{2}, \tag{A.12}$$

where $\lambda = 2b/g$ in this case. Also, since $\alpha = 2$, one of the time intervals in the piece-wise definition of $p(t)$ disappears, and the resulting expression for $p(t)$ is

$$\begin{aligned} p(t) &= e^{(J-\mu)(t-j\frac{l}{2g})}\left\{n_0\left(l - gt + j\frac{l}{2g}\right)\right. \\ &\left.\qquad + \lambda n_0\left(l - gt + (j+1)\frac{l}{2g}\right)\right\}, \qquad (j+1)\frac{l}{2g} < t < (j+2)\frac{l}{2g}, \end{aligned} \tag{A.13}$$

where $0 \leq j \in \mathbb{Z}$.

It is now straight forward to check that the $F_2(l - gt) = e^{\mu t} n_2(l,t) = e^{(-J+\mu)t} p(t)$ satisfies Equation (2.22) for $t > \frac{l}{2g}$.

B Appendix

In this section we show a derivation of (1.1) with constant coefficients g, D and μ.

B.1 The discrete system

Consider a number of cells either growing or shrinking by Δx in each discrete time interval of Δt. Cells of size x divide at any given instant of time with a probability of $B(x)\Delta t$ into α daughter cells of size x/α.

Let the probability that a cell grows at any time-step be p and the probability that a cell shrinks be $q = 1 - p$. Further, let $n(x,t)$ be the number density function for cells of size x at time t. Then the discrete system may be expressed as,

$$\begin{aligned} \int_{x-\Delta x/2}^{x+\Delta x/2} n(\xi,t)\, d\xi &= p\int_{x-3\Delta x/2}^{x-\Delta x/2} n(\xi,t-\Delta t)(1 - B(\xi)\Delta t)\, d\xi + q\int_{x+\Delta x/2}^{x+3\Delta x/2} n(\xi,t-\Delta t)(1-B(\xi)\Delta t)\, d\xi \\ &\quad + \alpha\int_{\alpha x-\alpha\Delta x/2}^{\alpha x+\alpha\Delta x/2} B(\xi)(\Delta t) n(\xi,t-\Delta t)\, d\xi, \qquad x >> \Delta x. \end{aligned} \tag{B.1}$$

Assuming n has only isolated points of discontinuity, then as $\Delta x \to 0$ we may approximate this as

$$\begin{aligned} n(x,t) &= pn(x-\Delta x, t-\Delta t)(1 - B(x-\Delta x)\Delta t) + qn(x+\Delta x, t-\Delta t)(1 - B(x-\Delta x)\Delta t) \\ &\quad + \alpha^2 B(\alpha x)(\Delta t) n(\alpha x, t - \Delta t), \end{aligned} \tag{B.2}$$

for almost every $x >> \Delta x$.

B.2 The continuous limit

Consider now the expression for $n(x,t)$ when $x>0$. Assuming that Δx and Δt are small in relation to x and t, and further that the terms on the right hand side of the equation can be expanded in Taylor series around x and t, we find:

$$n(x-\Delta x, t-\Delta t) = n(x,t) - \Delta x\frac{\partial n}{\partial x} - \Delta t\frac{\partial n}{\partial t} + \frac{(\Delta x)^2}{2}\frac{\partial^2 n}{\partial x^2} + \ldots, \tag{B.3}$$

$$n(x+\Delta x, t-\Delta t) = n(x,t) + \Delta x\frac{\partial n}{\partial x} - \Delta t\frac{\partial n}{\partial t} + \frac{(\Delta x)^2}{2}\frac{\partial^2 n}{\partial x^2} + \ldots, \tag{B.4}$$

$$n(x, t-\Delta t) = n(x,t) - \Delta t\frac{\partial n}{\partial t} + \ldots. \tag{B.5}$$

Each partial derivative in the above expression is calculated at x and t. Substituting the above into the expression for $n(x,t)$, letting $\varepsilon = p-q$ and using the fact that $p+q=1$, we find

$$n_t = -[pB(x-\Delta x) + qB(x+\Delta x)]n(x,t) + \alpha^2 B(\alpha x)n(\alpha x,t) - \frac{(\Delta x)\varepsilon}{\Delta t}n_x + \frac{(\Delta x)^2}{2\Delta t}n_{xx} + \ldots, \tag{B.6}$$

with the remaining higher order terms all having $(\Delta t)^k(\Delta x)^j$, $k \geq 0$, $j \geq 1$ as a factor. Consider now the limiting process as the parameters $\Delta t, \Delta x$ and ε tend to zero. Supposing also that as $\Delta t \longrightarrow 0$, the parameters Δx and ε are $O(\sqrt{\Delta t})$. Then let,

$$g = \lim_{\Delta x, \Delta t, \varepsilon \to 0} \frac{(\Delta x)\varepsilon}{\Delta t}, \qquad D = \lim_{\Delta x, \Delta t \to 0} \frac{(\Delta x)^2}{2\Delta t}. \tag{B.7}$$

Note that the higher order terms vanish as $\Delta t, \Delta x, \varepsilon \longrightarrow 0$. Thus we obtain

$$n_t = -gn_x + Dn_{xx} - B(x)n(x,t) + \alpha^2 B(\alpha x)n(\alpha x,t), \qquad x > 0, \tag{B.8}$$

as the continuous limit of the discrete process described above. This is equivalent to (1.1) with no death and constant D and g. To add a death rate μ into the equation, it is required to multiply the right-hand side of (B.1) by $(1-\mu\Delta t)$ to describe a proportion $(\mu\Delta t)$ of cells dying at each time step.

A similar derivation to the one shown above, without the division function $B(x)$, can be found in (Okubo, 1980).