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A CELL GROWTH MODEL REVISITED

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Dedicated to the memory of Anatolii Dmitrievich Myshkis

Abstract. In this paper a stochastic model for the simultaneous growth and division of a cell-population cohort structured by size is formulated. This probabilistic approach gives straightforward proof of the existence of the steady-size distribution and a simple derivation of the functional-differential equation for it. The latter one is the celebrated pantograph equation (of advanced type). This firmly establishes the existence of the steady-size distribution and gives a form for it in terms of a sequence of probability distribution functions. Also it shows that the pantograph equation is a key equation for other situations where there is a distinct stochastic framework.

Key Words. Steady-size distribution; Asymptotic behavior; Poisson process; Pantograph equation

AMS(MOS) subject classification. 35B40, 35B41, 35 L45, 92C17

1. Introduction. In this paper we revisit a cell growth model developed by [7]. This model was originally developed to model plant cells [8], however, it has found applications in tumour growth in humans [2]. A feature of this model is that a well-known functional differential equation, the pantograph equation (see [5], [13] for background), arises from a separation of variables solution to a Fokker-Planck equation. Specifically, let $n(x,t)$ denote the number density functions of cells of size x at time t i.e.,for $0 \le a < b$ the quantity $\int_a^b n(x,t)\,dx$ is the number of cells of size between a and b at time t, x is "a variable size" of the cells in the cohort, often taken as "DNA content." The cell growth process is modelled by a modified Fokker-Planck

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equation, setting the dispersion term to zero for simplicity, of the form

$$\begin{aligned}\frac{\partial}{\partial t}n(x,t) &= -\frac{\partial}{\partial x}\left(gn(x,t)\right) + \alpha^2 Bn(\alpha x,t) \\ &\quad - (B+\mu)\, n(x,t), \end{aligned} \tag{1}$$

where g is the rate of growth, μ is the rate of death, and B is the rate at which cells divide into α equally sized daughter cells. Here, $\alpha > 1$ is the "multiplicity of division", that is cells of size x divide to give α cells of size x/α. The first term on the right hand side of (1) is the growth term; the second is the addition to the cohort at size x from division of bigger size αx with frequency B; and the last is the loss term from this cohort due to division to cells of size x/α (also with frequency B), and the death of cells with a per capita death rate of μ. For the original model that we study here g, μ and B are positive constants. It is conceded that the assumption that B, in particular, is constant is not in fact biologically realistic, see sections I.4 and III.4.2 in [12]. However, we made this assumption so as to explore the deeper connections with the classical pantograph equation. The partial differential equation (1) is supplemented by the boundary conditions

$$\lim_{x\to\infty} n(x,t) = 0; \tag{2}$$

$$\lim_{x\to\infty} \frac{\partial}{\partial x}n(x,t) = 0; \tag{3}$$

$$n(0,t) = 0. \tag{4}$$

In fact we need only the boundary condition (4): as (2) and (3) follow as consequences when $n(x,t=0) = n_0(x)$ satisfy these conditions. The steady size distributions (SSDs) for the number density function correspond to solutions of the form $n(x,t) = N(t)y(x)$ (i.e., separable solutions). Solutions of this form yield

$$\begin{aligned}\frac{N'(t)}{N(t)} &= -\frac{gy'(x)}{y(x)} + \alpha^2\frac{By(\alpha x)}{y(x)} - (B+\mu) \\ &= \Lambda, \end{aligned}$$

where Λ is a constant of separation and $'$ denotes differentiation with respect to the indicated argument. The above relation yields

$$N(t) = N_0 e^{\Lambda t}, \tag{5}$$

where N_0 is a constant, and the equation

$$-gy'(x) + \alpha^2 By(\alpha x) - (B+\mu)\, y(x) = \Lambda y(x). \tag{6}$$

Under suitable scaling (e.g. by choosing $N_0 = \int_0^\infty n_0(x)dx$) a solution $y \in L^1[0,\infty)$ to equation (6) corresponds to a probability density function in the model. The boundary conditions (2)- (4) imply that

$$\lim_{x\to\infty} y(x) = 0, \tag{7}$$

$$\lim_{x\to\infty} y'(x) = 0, \tag{8}$$

$$y(0) = 0, \tag{9}$$

and requirement that y be a probability density function leads to the conditions $y(x) \geq 0$ for all $x \in [0,\infty)$ and

$$\int_0^\infty y(x)\,dx = 1. \tag{10}$$

Integrating equation (6) from 0 to ∞ gives

$$\Lambda = (\alpha - 1)B - \mu,$$

and equation (6) reduces to

$$gy'(x) + \alpha By(x) - \alpha^2 By(\alpha x) = 0. \tag{11}$$

Equation (11) is a special case of the pantograph equation, which has been studied extensively. A detailed analysis can be found in [11]. The pantograph equation has found applications ranging from a partition problem in number theory to the collection of current in an electric train. The reader is directed to [10] for an overview of the literature and further analysis of the equation.

There are two other problems where the pantograph equation plays a central rôle that have a distinct statistical flavour, *viz.* the absorption of light in the Milky Way, [1] and a ruin problem in risk theory, [6]. Although these problems seem distant from the cell growth model, there is nonetheless a concrete link: all these models are based on the same type of pseudo Poisson process; consequently, they have the same limit distribution. The link is more transparent using an approach of [4] that is based on a probabilistic technique (see [3]). In the next section we detail this approach and recover some known results about the cell growth model in a fundamentally different framework. Specifically, we give a straightforward proof of the existence of an SSD, the derivation of the pantograph equation for this distribution (invariant measure) and a solution in the form of a sequence of probability distribution functions.

2. Limit Distribution for Cell Growth. Consider a spatially homogeneous population of cells and suppose that the size x of a cell grows linearly as a function of time. Suppose further that at random moments defined by a Poisson process a cell of size x splits into α new cells of size x/α. Again we concede that in reality, for the most part, cells only divide in two and the resulting daughter cells are not exactly the same size. Asymmetrical division of cells is currently under investigation. Here, $\alpha \geq 1$. Specifically, we suppose that the jumps $x \to x/\alpha$ occur in random moments

$$0 = t_0 < t_1 < \cdots < t_n < \cdots ,$$

where the sequence $\{\tau_n\}$ defined by

$$\tau_n = t_{n+1} - t_n,$$

for $n = 1, 2, \ldots$ consists of independently and exponentially distributed random variables, i.e., for $t > 0$,

$$P\{\tau_n > t\} = e^{-t}.$$

For simplicity, we assume that the between jumps the cell size x has a unit rate of growth so that after Δt time a cell of size x grows to size $x + \Delta t$. This assumption corresponds to choosing B and g such that $\alpha B/g = 1$ in the Fokker-Planck equation. The results detailed below follow *mutatis mutandis* for a more general choice of constants.

LEMMA 1. *There exists a limit distribution (invariant measure) for the size of a cell. This distribution is independent of the initial cell size x_0.*

Proof. Consider a cell of initial size x_0 that splits (jumps) at random moments $t_1, t_2, \ldots, t_n, \ldots$. Let t_{n^-} denote the moment immediately before the nth splitting. The size of a cell at t_{1^-} is

$$x(t_{1^-}) = x_0 + \tau_1.$$

The cell then splits into α equal parts at t_1 so that at t_{2^-} the size is

$$x(t_{2^-}) = \frac{1}{\alpha}(x_0 + \tau_1) + \tau_2.$$

Similarly, at t_{3^-}

$$\begin{aligned} x(t_{3^-}) &= \frac{1}{\alpha}\left(\frac{1}{\alpha}(x_0 + \tau_1) + \tau_2\right) + \tau_3 \\ &= \frac{x_0}{\alpha^2} + \tau_3 + \frac{\tau_2}{\alpha} + \frac{\tau_1}{\alpha^2}, \end{aligned}$$

and in general

$$x(t_{n^-}) = \frac{x_0}{\alpha^{n-1}} + \tau_n + \frac{\tau_{n-1}}{\alpha} + \cdots + \frac{\tau_1}{\alpha^{n-1}}. \tag{12}$$

Equation (12) shows that there exists a limit distribution for cell size x as $n \to \infty$ and that this distribution is independent of the initial cell size x_0. Indeed, the limit distribution function coincides with a probability distribution function of the random variable

$$Z = \eta_0 + \frac{\eta_1}{\alpha} + \frac{\eta_2}{\alpha^2} + \cdots + \frac{\eta_n}{\alpha^n} + \cdots , \tag{13}$$

where the η_k are independently, exponentially distributed random variables. ∎

Let

$$F(x) = F_{\tau_n}(x) = 1 - P\{\tau_n > x\} = \begin{cases} 1 - e^{-x}, & x > 0 \\ 0, & x \leq 0, \end{cases} \tag{14}$$

$$p(x) = p_{\tau_n}(x) = F'(x) = \begin{cases} e^{-x}, & x > 0 \\ 0, & x < 0. \end{cases} \tag{15}$$

Denote the probability distribution function (pdf) for (13) by $z(x)$ and let $y(x) = z'(x)$. The function y thus corresponds to the probability density function for (13). The next theorem shows that the probability density function defined by (13) satisfies the pantograph equation (11) with $\alpha B/g = 1$ and $y(0) = 0$.

THEOREM 1. *The probability distribution function for (13) satisfies*

$$\begin{aligned} z'(x) + z(x) &= z(\alpha x) \\ z(0) &= 0; \end{aligned} \tag{16}$$

the probability density function for (13) satisfies

$$\begin{aligned} y'(x) + y(x) &= \alpha y(\alpha x) \\ y(0) &= 0. \end{aligned} \tag{17}$$

Proof. The proof follows a method developed by [4], which is based on the self-similarity of Z. In particular, equation (13) can be recast

$$Z = \eta_0 + \frac{1}{\alpha}\left(\eta_1 + \frac{\eta_2}{\alpha} + \frac{\eta_3}{\alpha^2} + \cdots\right) = \eta_0 + \frac{1}{\alpha} Z_1, \tag{18}$$

where Z_1 has the same distribution as Z.

Given random independent variables w_1 and w_2 with pdfs $G_1(x)$ and $G_2(x)$ respectively, the pdf of their sum $w_1 + w_2$ is given by the Stieltjes convolution (see [9])

$$(G_1 \# G_2)(x) = \int_{-\infty}^{\infty} G_1(x-t)\, dG_2(t).$$

In addition, for any $\beta > 0$ the pdf of βG_1 is $G_1(x/\beta)$. The pdf for Z_1/α is therefore $z(\alpha x)$ and the pdf for η_0 is $F(x)$. Equation (18) thus implies

$$z(x) = z(\alpha x) \# F(x). \tag{19}$$

The Stieltjes convolution (19) can be expressed as a Laplace convolution. Since $z(x) = 0$ for $x \leq 0$ and $dF(x) = p(x)\, dx$,

$$z(\alpha x) \# F(x) = \int_0^x z(\alpha(x-t)) e^{-t}\, dt;$$

consequently,

$$z(x) = z(\alpha x) * p(x), \tag{20}$$

where $*$ denotes the Laplace convolution. Now,

$$z'(x) = z(0)e^{-x} + \alpha \int_0^x z'(\alpha(x-t)) e^{-t}\, dt,$$

and noting that $z(0) = 0$ integration by parts yields

$$\begin{aligned} z'(x) &= \alpha \left\{ -\frac{e^{-t}}{\alpha} z(\alpha(x-t)) \Big|_0^x - \frac{1}{\alpha} \int_0^x z(\alpha(x-t)) e^{-t}\, dt \right\} \\ &= z(\alpha x) - z(x). \end{aligned}$$

We thus see that z satisfies (16). Equation (17) follows immediately from (16) by differentiation noting that $z'(0) = 0$. ∎

3. A Solution Method. [11] showed that problems such as (16) and (17) do not have unique solutions. Indeed, there are an infinite number of solutions to these problems. The requirement that solutions to (16) are also probability distribution functions, however, resolves this uniqueness problem. In essence, there is only one solution to (16) such that

$$\lim_{x \to \infty} z(x) = 1. \tag{21}$$

A similar comment applies to problem (17) if condition (10) is imposed. These uniqueness results can be found in [6] and [7].

Problems such as (16) and (17) can be solved using Dirichlet series or, what leads to the same thing, Laplace transforms (cf. [6], [10] and [11]). Solutions to these problems can thus be expressed in the form

$$\begin{aligned} z(x) &= \sum_{n=1}^{\infty} a_n e^{-\alpha^n x}, \\ y(x) &= \sum_{n=1}^{\infty} -\alpha^n a_n e^{-\alpha^n x}. \end{aligned}$$

The probabilistic interpretation detailed in Section 2, however, brings to the fore a different solution method. This method entails a sequence generated by convolutions. We focus exclusively on the probability distribution function.

Let $\{z_n\}$ be the sequence defined by

$$\begin{aligned} z_0(x) &= 1 - e^{-x} \\ z_{n+1}(x) &= z_n(\alpha x) \# F(x), \end{aligned} \tag{22}$$

where $n \geq 0$ and $x \geq 0$. We show that this sequence converges to a probability distribution function z that is a solution to problem (16). One advantage of this method is that the approximations to the solution preserve the statistical structure of the problem. Each term of the sequence is a pdf, and it is clear from the definition of the sequence that z_n corresponds to the pdf for the random variable at the n^{th} splitting.

Lemma 2. *The sequence $\{z_n\}$ converges uniformly on intervals of the form $I = [0, a]$, where $a > 0$.*

Proof. We note first that

$$\begin{aligned} z_{n+1}(x) &= z_n(\alpha x) \# F(x) \\ &= \int_0^x z_n(\alpha(x - \xi)) e^{-\xi} \, d\xi. \end{aligned} \tag{23}$$

Since z_0 is continuous on $[0, \infty)$ it is clear that z_n is also continuous on this interval for all $n \geq 1$. For any continuous function $f : [0, \infty) \to \mathbb{R}$ and $b > 0$ let

$$\|f\|_b = \sup_{\xi \in [0,b]} |f(\xi)|.$$

It is sufficient to show that the series

$$\sum_{n=0}^{\infty} (z_{n+1}(x) - z_n(x)) \tag{24}$$

is uniformly convergent on I. For $x \in I$,

$$\begin{aligned} |z_{n+1}(x) - z_n(x)| &\leq \int_0^x |z_n(\alpha(x-\xi)) - z_{n-1}(\alpha(x-\xi))|\, e^{-\xi}\, d\xi \\ &\leq \|z_n - z_{n-1}\|_{\alpha x}\Lambda, \end{aligned}$$

where

$$\Lambda = 1 - e^{-a}.$$

The above calculation can be repeated to show that

$$|z_{n+1}(x) - z_n(x)| \leq \|z_1 - z_0\|_{\alpha^n a}\Lambda^n. \tag{25}$$

We have

$$z_1(x) = z_0(x) - \frac{e^{-x} - e^{-\alpha x}}{\alpha - 1}, \tag{26}$$

so that for all $x \in [0, \infty)$

$$|z_1(x) - z_0(x)| \leq \frac{1}{\alpha - 1}. \tag{27}$$

Inequalities (25) and (27) thus give

$$\|z_{n+1} - z_n\|_{\alpha^n a} \leq \frac{1}{\alpha - 1}\Lambda^n. \tag{28}$$

Since $0 < \Lambda < 1$, the Weierstrass M test can be used to show that the series converges uniformly on I. ∎

LEMMA 3. *Each term of the sequence $\{z_n\}$ is a pdf that is differentiable on $[0, \infty)$. The limit of the sequence is also a pdf.*

Proof. The sequence $\{z_n\}$ is defined by a convolution with a pdf $F(x)$. Since $z_0(x)$ is a pdf, $z_0(\alpha x)$ is also a pdf. Now, $z_1(x) = z_0(\alpha x) \# F(x)$. Since z_1 is defined by the convolution of two pdfs, z_1 must also be a pdf (cf. [14, p. 37]). The argument can be repeated to show that z_n must be a pdf for all

$n \geq 1$. Each z_n is continuous on $[0, \infty)$. Equation (23) and the Fundamental Theorem of Calculus therefore imply that the z_n are differentiable and

$$z'_{n+1}(x) = \alpha \int_0^x z'_n(\alpha(x-\xi))e^{-\xi}\, d\xi. \tag{29}$$

Lemma 2 shows that there is a z such that $z_n(x) \to z(x)$ as $n \to \infty$ for $x \in [0, \infty)$. To show that z must be a pdf we study the characteristic functions associated with the z_n. The characteristic function of z_n is given by

$$\phi_n(t) = \int_0^\infty e^{it\xi} z'_n(\xi)\, d\xi.$$

Equation (22) implies that

$$\phi_{n+1}(t) = Q_n(t)\psi(t),$$

where Q_n is the characteristic function for $z_n(\alpha x)$ and

$$\psi = \frac{1}{1 - it}$$

is the characteristic function for F. Now,

$$\begin{aligned} Q_n(t) &= \int_0^\infty e^{it\xi} dz_n(\alpha\xi) \\ &= \int_0^\infty e^{it\xi/\alpha} z'_n(\xi)\, d\xi \\ &= \phi_n(t/\alpha); \end{aligned}$$

therefore,

$$\phi_{n+1} = \frac{1}{1 - it}\phi_n(t/\alpha),$$

and consequently

$$\phi_{n+1} = \prod_{k=0}^{n+1} \left(1 - \frac{it}{\alpha^k}\right)^{-1}.$$

The product

$$\prod_{k=0}^{\infty} \left(1 - \frac{it}{\alpha^k}\right)^{-1}$$

converges uniformly on all compact intervals of $\mathbb{R}$;hence,

$$\phi_n(t) \to \phi(t) = \prod_{k=0}^{\infty} \left(1 - \frac{it}{\alpha^k}\right)^{-1},$$

where ϕ is continuous on $\mathbb{R}$. We can now appeal to a standard result in probability theory (cf. [14, p. 42]) that guarantees the existence of a unique pdf z corresponding to ϕ; moreover, $z_n \to z$ as $n \to \infty$. ∎

THEOREM 2. *Let z denote the limit of the sequence defined by (22). Then z is the unique solution to equation (16).*

Proof. Integrating the right hand side of equation (29) by parts gives

$$z'_{n+1}(x) = z_n(\alpha x) - z_{n+1}(x). \tag{30}$$

Now,

$$\begin{aligned} |z'_{n+1}(x) - z'_n(x)| &= |z_n(\alpha x) - z_{n+1}(x) - (z_{n-1}(\alpha x) - z_n(x))| \\ &\leq |z_n(\alpha x) - z_{n+1}(x)| + |z_{n-1}(\alpha x) - z_n(x)|, \end{aligned}$$

and since $\{z_n\}$ is uniformly convergent on I, the above inequality shows that $\{z'_n\}$ is uniformly convergent on I. We thus have that z is differentiable on I and that $z'_n \to z'$ as $n \to \infty$. Equation (30) therefore implies that z is a solution to equation (16).

The uniqueness of solutions to equation (16) satisfying the given boundary conditions has been established in [6] and [7]. For completeness, however, we give a proof.

Suppose that there are two distinct solutions z and w to the boundary-value problem. Let $\delta = z - w$. Then

$$\delta'(x) = \delta(\alpha x) - \delta(x) \tag{31}$$

$$\delta(0) = 0 \tag{32}$$

$$\lim_{x\to\infty} \delta(x) = 0. \tag{33}$$

By hypothesis, the solutions are distinct and therefore $\delta(x) \neq 0$ for some $x > 0$. Without loss of generality we can assume that $\delta(x) > 0$ for some $x > 0$. Now, δ is differentiable, *a fortiori*, continuous for $x \geq 0$, and the boundary conditions (32) and (33) imply that there exists a global maximum M at some point $0 < x_m < \infty$. We thus have $M = \delta(x_m) > 0$ and $\delta'(x_m) = 0$. Equation (33) implies that $\delta(\alpha x_m) = \delta(x_m)$; therefore, the global maximum must also be achieved at αx_m. The arguments can be repeated to show that the global maximum is achieved at $\alpha^n x_m$ for all $n \geq 0$; consequently, $\delta(\alpha^n x_m) = M$. Since $M \neq 0$, we have the contradiction that $\lim_{x\to\infty} \delta(x) \neq 0$. We thus conclude that $\delta(x) = 0$ for all $x > 0$. ∎

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