Tumour Cell Biology and Some New Non-local Calculus

Graeme Wake, Ali A. Zaidi and Bruce van-Brunt

Abstract Living cell populations which are simultaneously growing and dividing are usually structured by size, which can be, for example, mass, volume, or DNA content. The evolution of the number density $n(x, t)$ of cells by size x, in an unperturbed situation, is observed experimentally to exhibit the attribute of that of an asymptotic "Steady-Size-Distribution" (SSD). That is, $n(x, t) \sim$ scaled (by time t) multiple of a constant shape $y(x)$ as $t \to \infty$, and $y(x)$ is then the SSD distribution, with constant shape for large time. A model describing this is given, enabling parameters to be evaluated. The model involves a linear non-local partial differential equation. Similar to the well-known pantograph equation, the solution gives rise to an unusual first order singular eigenvalue problem. Some results and conjectures are given on the spectrum of this problem. The principal eigenfunction gives the steady-size distribution and serves to provide verification of the observation about the asymptotic growth of the size-distribution.

Keywords Cell-division · Eigenvalue problems · Survival thresholds

1 Introduction and Model

Non-local equations occur quite frequently in applications, yet are rarely included in the curriculum of university courses. This is a pity in view of the richness these problems present in their solutions. The most familiar example of this is the differential **time**-delay equation

G. Wake (✉) · A. A. Zaidi
Institute of Natural and Mathematical Sciences, Massey University, Auckland, New Zealand
e-mail: G.C.Wake@massey.ac.nz

A. A. Zaidi
e-mail: A.A.Zaidi@massey.ac.nz

B. van-Brunt
Institute of Fundamental Sciences, Massey University, Palmerston North, New Zealand
e-mail: B.vanBrunt@massey.ac.nz

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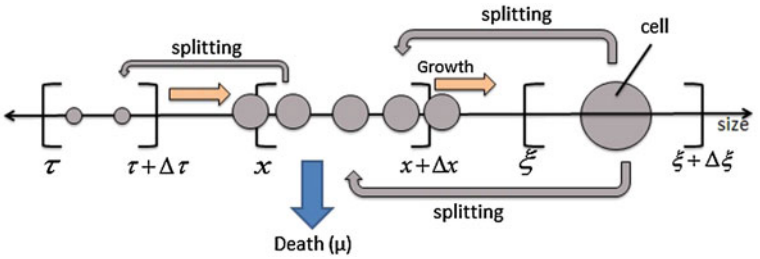

Fig. 1 Cell growth and division for the cohort

$$\begin{aligned} u'(t) &= u(t-T), \qquad t \geq 0 \\ u(t) &= u_0(t), \qquad -T \leq t < 0. \end{aligned}$$

The solution to this is well-known (see Bellman and Cooke [1]) and we note that the solution of the differential equation has a countable infinity of linearly independent solutions, whereas when $T = 0$ there is only one. Extensions to multidimensional systems with delays are given in Wake and Byrne [2].

We proceed now to introduce our model. Firstly, we consider the symmetrical case, where cells of size $\xi = \alpha x$ ($\alpha > 1$) are splitting to give α cells of size x, with frequency b and simultaneously growing at a rate g units per time. Here α can be, in principle, any number greater than one, but is most usually two (binary division). It need not be an integer, amoeba cells show this, say 10 cells can aggregate and simultaneously divide to give 11 cells thereby giving $\alpha = 1.1$. The key requirement is that volume is preserved at the point of division: a cell of size αx is producing α cells of size x. This is shown schematically in Fig 1.

With a per-capita death rate μ, the equation describing this process, see Hall and Wake [3], is

$$\underbrace{\frac{\partial n}{\partial t} + \frac{\partial (gn)}{\partial x}}_{\text{growth}} = \underbrace{b\alpha^2 n(\alpha x, t)}_{\substack{\text{division of} \\ \text{larger cells}}} - \underbrace{bn(x,t)}_{\substack{\text{division into} \\ \text{smaller cells}}} - \underbrace{\mu n(x,t)}_{\text{cell-death}} \tag{1}$$

in the first quadrant ($x, t > 0$) of the plane. This is complemented by the boundary conditions

$$n(0,t) = 0, \quad n(x,t) \to 0 \quad \text{as} \quad x \to \infty, \tag{2}$$

and initial condition

$$n(x,0) = n_0(x). \tag{3}$$

Cells dividing asymmetrically are essential for generating diverse cell types during development. The capacity for symmetric stem-cell self-renewal may confer developmental plasticity, increased growth and **enhance regenerative** capacity; however,

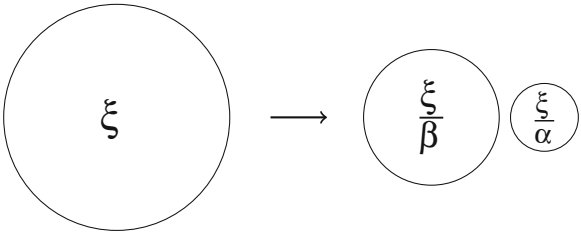

Fig. 2 Schematic representation for binary asymmetrical cell division with $\alpha > \beta > 1$

it may also confer an inherent risk of cancer. When the machinery that regulates asymmetric divisions is disrupted, however, these cells begin dividing symmetrically and form tumours. This needs underpinning rigour to understand the dynamics of cancer-cell growth and regulation of cell-growth. The context is developed in the paper by Basse et al. [4].

A new model is therefore needed of cell-growth with asymmetrical division [two or more daughter cells of different sizes (usually DNA content)] from a single "division-event". This model must capture the key features from earlier models with symmetrical cell-division, where the cell-size distribution tends asymptotically to one of constant shape where the cohort is not disturbed; this being a well-known observation. That is, $n(x,t) \sim T(t)y(x)$ as $t \to \infty$. The function $y(x)$ is also still called a steady-size-distribution (SSD). We consider for simplicity binary asymmetrical cell-division. This is the case where a cell of size ξ divides into two daughter cells of different sizes $\frac{\xi}{\beta}$ and $\frac{\xi}{\alpha}$, shown in Fig 2.

The asymmetry requires the introduction of a transfer rate $W(x,\xi)$ which is the number of cells of size x produced by a cell of size ξ, from its division. This amends Eq. (1) to

$$\frac{\partial n}{\partial t} + \underbrace{\frac{\partial (gn)}{\partial x}}_{\text{growth}} = \underbrace{\int_x^\infty bW(x,\xi)n(\xi,t)d\xi}_{\text{division of larger cells}} - \underbrace{\left(\int_0^x W(\tau,\xi)\frac{\tau}{x}d\tau\right) bn(x,t)}_{\text{loss of cells by division}} - \underbrace{\mu n(x,t)}_{\text{cell-death}}.$$

The second term recognises that there are $W(\tau,x)$ smaller cells produced by the division of a cell of size $x(>\tau)$. Further mass conservation for division requires

$$\int_0^x W(\tau,\xi)\tau d\tau = x, \tag{4}$$

and so we get a new non-local equation

$$\frac{\partial n}{\partial t} + \frac{\partial (gn)}{\partial x} = \int_x^\infty bW(x,\xi)n(\xi,t)d\xi - bn(x,t) - \mu n(x,t). \tag{5}$$

The problem (2), (3), (4) is expected to be well-posed for suitable W.
The two cases above require the following W:

1. Symmetrical division
$$W(x,\xi) = \alpha\delta\left(\frac{\xi}{\alpha} - x\right),$$
where δ is the Dirac-delta function;
2. Binary asymmetrical division
$$W(x,\xi) = \delta\left(\frac{\xi}{\alpha} - x\right) + \delta\left(\frac{\xi}{\beta} - x\right),$$
and mass conservation requires $\frac{1}{\alpha} + \frac{1}{\beta} = 1$ from (4).

Cases (2) and (1) coincide when $\alpha = \beta = 2$.
Using the W in case (2) in Eq. (4) gives a new equation

$$\frac{\partial n}{\partial t} + \frac{\partial (gn)}{\partial x} = b\alpha n(\alpha x, t) + b\beta n(\beta x, t) - (b+\mu)n(x,t). \tag{6}$$

2 Preliminary Results

We illustrate the ideas with the simplifying assumptions that b, g, and μ are constant. We use the more general Eq. (6).

SSD behaviour suggests that there are separable solutions of the form $n(x,t) = T(t)y(x)$ which in Eq. (6) gives $\frac{T'(t)}{T(t)} = \text{constant}(= -\lambda)$ and so

$$n(x,t) \sim e^{-\lambda t} y(x), \tag{7}$$

for some λ, which then gives the interesting non-local ode

$$\begin{aligned} g y'(x) &= b\alpha y(\alpha x) + b\beta y(\beta x) - (b+\mu-\lambda)y(x), \\ &\text{with } y(0) = y(\infty) = 0. \end{aligned} \tag{8}$$

If $y(x)$ is a probability density function this requires (by integration)

$$\lambda = \mu - b, \tag{9}$$

which determines the growth ($b > \mu$) or decay ($b < \mu$) of the solution in Eq. (7) with constant shape of $y(x)$.

Of course Eq. (8) is an eigenvalue problem with a spectrum which satisfies the boundary value problem

$$gy'(x) = b\alpha y(\alpha x) + b\beta y(\beta x) - 2by(x), \quad y(0) = y(\infty) = 0. \tag{10}$$

This has a solution in the form of a double Dirichlet series, scaled so as to be a probability density function

$$y(x) = \sum_{m,n=0}^{\infty} c_{m,n} e^{-(\alpha^m + \beta^n)x}, \tag{11}$$

where $c_{m,n}$ satisfy a complicated recurrence relation, which enables the $c_{m,n}$ to be calculated recursively.

There are, of course, other eigenvalues $\{\lambda_n\}$ and eigenfunctions, which are necessary to fit the initial condition (3).

We expect

$$n(x,t) = \sum_{n=0}^{\infty} a_n y_n(x) e^{-\lambda_n t},$$

with λ_0 given by Eq. (9), and $y_0(x)$ given by Eq. (11).

The nature of these is as yet partially unknown. We would expect $\lambda_n > \lambda_0$, for $n > 0$ and that the set $\{y_n(x)\}$ is complete in some norm. The eigenfunctions are the non-trivial solutions of Eq. (8) when $\lambda = \lambda_n$ with the boundary conditions stated. Usually these are "normalised" in some way (see later).

Some higher eigenvalues and eigenfunctions come from use of the Mellin transform

$$M[y; s] = \int_0^{\infty} x^{s-1} y(x) dx.$$

We obtain the higher eigenvalues and eigenfunctions by using, when $\lambda = \lambda_n$, $y = y_n$, $n \geq 1$,

$$M[y_n; k] = \begin{cases} 0, & k = 1, \ldots, n \\ 1, & k = n+1. \end{cases}$$

Taking transforms of (8), when $k = n$, gives

$$\lambda_n = b + \mu - b\left(\frac{1}{\alpha^n} + \frac{1}{\beta^n}\right) \tag{12}$$

and $y_n(x)$ will be another Dirichlet series.

Clearly:
$n = 0$ in Eq. (12) gives the result in Eq. (9),
$n = 1$ gives $\lambda_1 = \mu$;

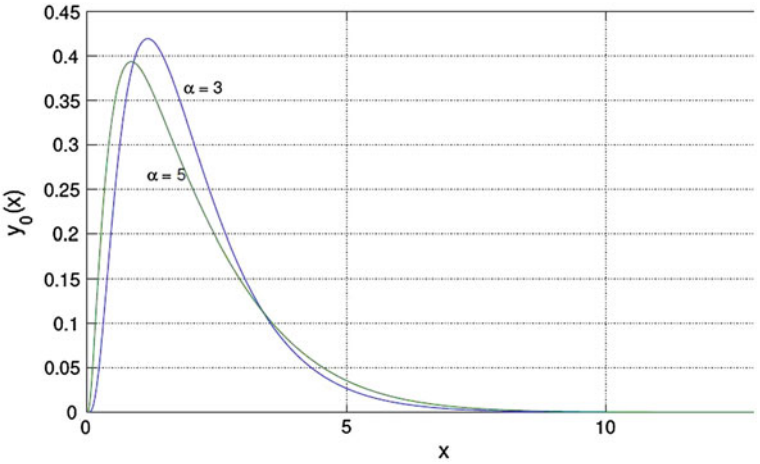

Fig. 3 SSD's for binary asymmetrical division $x \to (\frac{x}{\alpha}, \frac{x}{\beta}) : \frac{1}{\alpha} + \frac{1}{\beta} = 1$

and (λ_n) is monotonic increasing in n, with $(\lambda_n) \to (b + \mu)$ as $n \to \infty$.

We have "normalised" the eigenfunctions by requiring $M[y_n; n + 1] = 1$.

Of course, we have yet to establish whether or not these eigenfunctions are a complete set or even if there are other solutions, as λ_0 is the smallest eigenvalue, clearly $y_0(x)$ is the SSD.

However, the SSD's for various α, β can be computed from Eq. (10) and some are shown in Fig. 3.

3 Concluding Remarks

Cells dividing asymmetrically are essential for generating diverse cell types during development. The capacity for symmetric stem-cell self-renewal may confer developmental plasticity, increased growth and **enhance regenerative** capacity; however, it may also confer an inherent risk of cancer. When the machinery that regulates asymmetric divisions is disrupted, however, these cells begin dividing symmetrically and form tumours. This needs underpinning rigour to understand the dynamics of cancer-cell growth and regulation of cell-growth. This work is relevant to the underlying understanding of cell tumour growth. The application is stimulating new mathematics, for example the spectral theory of non-local singular eigenvalue problems.

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