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Unimodality of steady size distributions of growing cell populations

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To the memory of Tosio Kato, in admiration of his work and recalling a very happy collaboration

Abstract. We consider an equation for the evolution of growing and dividing cells, and show, using a result of Kato and McLeod, that the probability density function for the stationary size distribution is necessarily unimodal.

1. Introduction

In [1, 2] Hall and Wake consider the evolution of a population of growing and dividing cells. If we let $n(x, t)dx$ be the number at time t of cells of sizes between x and $x+dx$, then $n(x, t)$ satisfies the following hyperbolic functional partial differential equation:

$$n(x, t)_t = -(g(x)n(x, t))_x - b(x)n(x, t) + \alpha^2 b(\alpha x)n(\alpha x, t), \;\; x \in \mathbb{R}_+. \tag{1.1}$$

In this equation a mother cell of size x divides into $\alpha > 1$ (usually $\alpha = 2$) daughter cells of the same size x; $g(x)$ is the growth rate, and $b(x)$ is the division rate, of a cell of size x.

Note that there is no mortality of cells, so the reasonable boundary conditions for (1.1) are

$$g(0)n(0, t) = 0 \text{ and } \lim_{x\to\infty} g(x)n(x, t) = 0 \;\; \forall t > 0. \tag{1.2}$$

Denote the right-hand side of (1.1) by $A(n)$. Below we shall assume that $b(x) \geq 0$, $g(x) \geq 0$ for all $x \in \mathbb{R}_+$ and that $b(x)/g(x) \in L^1(\mathbb{R}_+)$. Defining

$$h(x) = \exp\left(-\int_0^x \frac{b(s)}{g(s)}ds\right),$$

using the machinery developed in [4] and a result of [1], we have the following proposition:

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PROPOSITION 1.1. 1. (1.1)–(1.2) *generates a semiflow on the space*

$$X = \left\{ u \in C(\mathbb{R}_+) \mid \sup_{x \in \mathbb{R}_+} \frac{g(x)}{h(x)} |u(x)| < \infty \right\}.$$

2. *The semiflow preserves the cone of non-negative functions in X.*
3. *There is a unique eigenvalue $\lambda > 0$ for which the operator A has a non-negative eigenfunction $y(x)$; furthermore $y(x)$ is positive for all $x \in (0, \infty)$.*

The key observation is that the change of variable $n = hu/g$ transforms (1.1) into a problem in which a generator of a strongly continuous semigroup is perturbed by a bounded operator. [4] treat the case of $\alpha = 2$ and of cells of non-zero minimal size and finite maximal size, but the arguments go through with minor changes. Positivity of $y(x)$ for non-zero x follows from the arguments of [1] for the case of constant $b(x)$ and $g(x)$. Note that if we let $N(t)$ be the total cell population, $N(t) = \int_0^\infty n(x, t)\, dx$, we have that λ is the growth rate of $N(t)$, that is, $N(t) = N(0)e^{\lambda t}$, so that (1.1) is only applicable to exponentially growing populations.

It is the eigenfunction $y(x)$ that we are interested in. It has the interpretation of the probability density function describing the stationary size distribution (SSD). Hence we supplement the equation it has to satisfy,

$$(g(x)y(x))' + \lambda y = -b(x)y(x) + \alpha^2 b(\alpha x)y(\alpha x), \tag{1.3}$$

with the conditions

$$y(x) \geq 0 \text{ for all } x \in [0, \infty) \tag{1.4}$$

and the normalization condition (since $y(x)$ is a probability distribution)

$$\int_0^\infty y(x)\, dx = 1. \tag{1.5}$$

Obviously, to be able to determine $y(x)$ we need to know λ. There are two cases where the value for λ can be worked out explicitly; these are the cases $b(x) = \beta$ and of $g(x) = \gamma x$ with $b(x)$ growing superlinearly at infinity. In the first case by integrating (1.3) we have

$$\lambda = (\alpha - 1)\beta.$$

In the second case we have that $\int_0^\infty g(x)y(x)dx$ is finite, and multiplying (1.3) by x and integrating we have

$$\lambda = \frac{\int_0^\infty g(x)y(x)dx}{\int_0^\infty xy(x)dx}, \tag{1.6}$$

so that in this case $\lambda = \gamma$.

The simplest interesting case of (1.3) arises if we assume that $g(x) = 1$ and $b(x) = \beta$, a positive constant. Then (1.3) becomes

$$y'(x) = -\alpha\beta y(x) + \alpha^2\beta y(\alpha x), \tag{1.7}$$

subject to (1.4) and (1.5). Note that by integrating (1.7) between zero and infinity and using (1.5), we immediately have that $y(0) = 0$. Equations of the form (1.7) have been described fairly completely in [3]; that paper is extensively used in [1], which also concentrates on (1.7).

Looking at the pictures of [1, 2] one observes that all the SSD functions $y(x)$ are unimodal. The object of the present note is to give a proof of this fact. We first prove the result for the (biologically unrealistic) case of constant $g(x)$ and $b(x)$ and then show how this entails unimodality for reasonable choices of $g(x)$ and $b(x)$, such as, for example, $g(x) = \gamma x$ and $b(x) = \beta x^r$ (here $\gamma,\ \beta$, are positive constants, $r > 1$). Since unimodality of the SSD is a necessary consequence of this type of model, deviation from it in experimental situations must indicate that a more sophisticated model for the dynamics of the cell population is required. We also note that the solution $N(0)\exp(\lambda t)y(x)$ in the case of $g(x) = \gamma x$ does not have good attractivity properties; see [4].

2. Main Result

Below we denote by $y(x)$ the SSD solution of (1.7). First of all, we prove the following elementary results:

LEMMA 2.1. *If $y(x)$ has a minimum, it must have an infinite number of such minima.*

Proof. Assume on the contrary that there is a finite number of minima. Note that if x_0 is the last point of minimum for $y(x)$,

$$y(\alpha x_0) = \frac{1}{\alpha} y(x_0),$$

so that at $\alpha x_0 > x_0$ we have that $y(\alpha x_0) < y(x_0)$. If $y(x)$ has a minimum at x_0, $y^{(2m)}(x_0) > 0$ for some positive integer m. Below we give the argument for $m = 1$; the degenerate case follows along similar lines. If $m = 1$, it suffices to differentiate the equation (1.7) at $x = x_0$ once (in the general case it has to be done $2m - 1$ times). Thus we have

$$y''(x_0) = \alpha^3\beta y(\alpha x_0).$$

Hence $y'(\alpha x_0) > 0$, which implies that there is a minimum at some $x_* > x_0$, leading to a contradiction. □

LEMMA 2.2. *If $y(x)$ has an infinite number of minima, these cannot accumulate at a finite point.*

Proof. Let x_0 be the last accumulation point. Then by the above argument there must exist a minimum between x_0 and αx_0. □

Now, using Lemmas 2.1 and 2.2 we can prove

THEOREM 2.3. *$y(x)$ is unimodal.*

Proof. Kato and McLeod [3] (see Theorems 3 and 9 there) discuss the equation

$$y'(x) = Ay(\theta x) + By(x), \tag{2.8}$$

which is the same as (1.7) under the identification $\theta = \alpha$, $B = -\alpha\beta$, $A = \alpha^2\beta$. Hence the parameter κ of Theorem 3 in [3], given by $\kappa = \mathrm{Re}\, k_0$, where k_0 is any solution of

$$k = \frac{\log(-B/A)}{\log\theta},$$

becomes

$$\kappa = \mathrm{Re}\left(\frac{\log(\alpha\beta/(\alpha^2\beta))}{\log\alpha}\right) = -1.$$

Hence by Theorem 9 of [3], any solution of (1.7) which is $o(x^\kappa) = o(x^{-1})$ as $x \to \infty$ is necessarily a multiple of

$$y_0 = e^{-\alpha\beta x}\left[1 + \sum_{n=1}^{\infty}(-1)^n \frac{(\alpha^2\beta)^n \exp\{\alpha\beta(1-\alpha^n)x\}}{(-\alpha\beta)^n(1-\alpha)(1-\alpha^2)\cdots(1-\alpha^n)}\right]. \tag{2.9}$$

It is clear that $y_0 = O(\exp(-\alpha\beta x))$ for large x, and hence from (1.7) it is obvious that y_0 is ultimately monotone decreasing, and so therefore is any solution of (1.7) that is $o(x^{-1})$. Since we have by Lemmas 2.1, 2.2 that any non-unimodal solution has necessarily an infinite number of minima going off to infinity, we see that any solution of (1.7) that is $o(x^{-1})$ is necessarily unimodal. However, since $y(x)$ is an SSD (in fact the main result of [1] is the computation of C such that $Cy_0(x)$ is the SSD), by the normalization condition it has to be $o(x^{-1})$.

As discussed in [2], it is not biologically realistic to assume that the growth rate $g(x)$ and the division rate $b(x)$ of a cell of size x are independent of x. [2] discuss the case of $g(x) = \gamma x$ and $b(x) = \beta x^r$, where γ, β, r are all positive constants. [2] show that in this case the SSD can be written in the form

$$y(x) = C\frac{1}{x^2}Y_0(x^r),$$

where Y_0 is a solution of the same form as y_0 of (2.9), i.e. $Y_0(x)$ satisfies equation (2.8) for some choice of θ, $A > 0$ and $B < 0$. Hence all the arguments of Theorem 2.3 hold, and the SSD is unimodal. □

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