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Functional Differential Equations Arising in Cell-growth

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Abstract Non-local differential equations are notoriously difficult to solve. Cell-growth models for population growth of a cohort structured by size, simultaneously growing and dividing, give rise to a class of non-local eigenvalue problems, whose "principal" eigenvalue is the time-constant for growth/decay. These and other novel non-local problems are described and solved in special cases in this paper.

Keywords Non-local differential equations; non-local eigenvalue problems; delay equation; pantograph equation; zero-flux condition; cohort of cells; Green's function

1 Introduction

Nonlocal calculus is relatively undeveloped. Thus occurs when cause and effect are separated in space, size, age, or time and give rise to functional differential equations. These problems frequently require unusual boundary and/or initial conditions to ensure they are well-posed - which would be expected for problems which come from modelling situations. Some well-known are

Example 1.1

$y'(t) = y(t-T)$ for all $t \in R$, $T > 0$, which unlike the corresponding local equation when $T = 0$ has a countably infinite number of linearly independent solutions

$$B = \left\{ e^{\lambda_i t} : i = 1, \ldots n, \ldots \right\}$$

where the λ_i 's satisfy the transcendental equation

$$\lambda = e^{-\lambda T},$$

and so there is only one real solution in B.

This delay equation, which is well-known of course, needs to have an initial condition $y(t) = y_0(t)$, $-T<t \leq 0$, to make it well-posed. Even more bizarre behaviour emerges if $T<0$, when the "future dictates the past".

Example 1.2

$y'(t) = y(\alpha t)$, for all $t \in R^+$, $\alpha > 0$ also has an interesting solution set which is markedly different if $\alpha \gtrless 1$. This is a special case of the "pantograph equation". See [1] and [2]. If $y\left(0\right) = y_0$ is given, it is well-posed if $\alpha < 1$. For $\alpha > 1$, it has quite different behaviour.

2 The Cell-growth Model

It was well-known to biologists prior to the 1980's that cell-populations, structured by size (x which is synonymous here to DNA content) which evolve by simultaneously growing, dividing and dying, grow asymptotically towards a steady-size distribution (SSD) which has constant shape with increasing or decreasing size depending on the parameters. In a series of papers, for example [3] this was obtained mathematically by using a generalised Fokker-Planck equation.

$$n_t = (Dn)_{xx} - (gn)_x - \mu n + \alpha^2 B(\alpha x)\, n(\alpha x, t) - B(x)\, n(x,t)\,, \tag{1}$$

for the evolving, with time t, of number density of cells $n(x,t)$, where D is the dispersion coefficient, g is the per-capita growth rate, μ is the per-capita death rate and $B(x)$ is the frequency of division of cells of size αx into α cells of size x, with $\alpha > 1$. Although it does not require α to be an integer from a mathematical point of view, usually $\alpha = 2$.

The equation (1) is usually accompanied by the zero-flux condition

$$[D(x)\, n(x,t)]_{x=0} - g(0)\, n(0,t) = 0, \qquad t > 0, \tag{2}$$

and decay at infinity

$$n(x,t)\,, n_x(x,t) \to 0, \qquad \text{as} \qquad x \to \infty. \tag{3}$$

The proof that there are SSD-like solutions is established beyond all doubt by observing that there are solutions of the form

$$n(x,t) = e^{-\lambda t} y(x)\,, \qquad x, t > 0$$

where $\lambda, y(x)$ satisfy

$$(Dy)''(x) - (gy)'(x) - \mu y + \alpha^2 B(\alpha x) - B(x)\, y(x) + \lambda y = 0, x > 0,' = \frac{d}{dx} \tag{4}$$

with

$$\left.\begin{array}{l} y(x) \geq 0, (Dy)'(0) - (gy)(0) = 0, \\ y(\infty) = y'(\infty) = 0 \end{array}\right\} \tag{5}$$

where $y(\infty)$ denotes

$$\lim_{x\to\infty} y(x)\,.$$

The first equation in (5) is that of a zero-flux condition.

Without loss of generality we can take $y(x)$ to be a probability density function, and so

$$\int_0^\infty y(x)\, \mathrm{d}x = 1. \tag{6}$$

The problem in equations (4), (5), (6) are what we shall call a non-local, singular Sturm-Liouville eigenvalue problem. The question of the existence of SSD-like solutions becomes that of : "Is there an eigenvalue λ, and eigenfunction y of this problem?" Further, is it unique within a multiplicative constant (equation (6) eliminates the multiplicity anyway).

3 Results

3.1 Special cases

$B(x) = b$ (a constant), with splitting at any size x. There is only one eigenvalue. Note that there will be other eigenfunctions but not with a mono-signed eigenfunction, which must satisfy

$$\int_0^\infty y(x)\,\mathrm{d}x = 0. \tag{7}$$

The eigenvalue is $\lambda = \mu - b(\alpha - 1)$ with solution for $y(x)$ a Dirichlet series of the general form

$$y(x) = \sum_{n=0}^{\infty} b_n e^{-kx^n}, \tag{8}$$

where k, b_n are constants.

This function is just one peak and does not exhibit the two peaks formed in practice with data sets. This means that

$$\mu \gtrless b(\alpha - 1) \qquad \text{ensures a } \begin{matrix}\text{dying}\\ \text{growing}\end{matrix} \text{ cohort of cells.}$$

It is interesting that this is independent of the growth rate g and dispersion rate D. Which outcome you want depends if the cells are ones you want (muscle cells etc.) or ones you do not (tumour cells).

3.2 General

$B(x)$ Without the requirement of having a mono-signed eigenfunction it is possible to prove there is a countable number of eigenvalues by restricting the domain to $x \in (0, L)$ with L arbitrarily large. To get two bumps in the one mono-signed eigenvalue we require something like $B(x) = b\delta(x - \ell)$, where $\delta(x - \ell)$ is the Dirac-delta function and ℓ is the cell-splitting size.

We expect this result to apply as $L \to \infty$ and conjecture this is so. See [4].

3.3 More General Non-local Eigenvalue Problems

The above can be extended to problems like

$$\left.\begin{aligned} &-y''(x) + ay'(x) + by(x) = \lambda y(g(x)), 0 < x < \infty \\ &y(0) = 0, \qquad y(\infty) = 0, \end{aligned}\right\} \tag{9}$$

and $g(x)$ is a continuous function mapping $[0, \infty)$ to itself. Letting $z = 1 - e^{-x}$,$Y(z) = y(x)$, we can then transform the problem (9) into a problem on a finite domain $[0, 1]$, use the Green's function for the compact domain to obtain a compact operator and so the problem can be re-stated as a functional integral equation using the Green's function of the operator on the left-hand side of equation (9). This again shows that there is a countable number of eigenvalues, and each eigenvalue has finite multiplicity.

3.4 Stability

In most of the above cases we are able to prove that the monosigned SSD behaviour is globally attracting. That is, $n(x,t) \sim Ce^{-\lambda t} y(x)$ for large time irrespective of the sign of λ, and the difference decays faster as t increases.

4 Discussion

Recently we came across the non-local heat equation - not based on a physically real problem which appears well-posed, but is actually not finite for arbitrarily small time:

$$\left.\begin{array}{lll} U_{xx}(1-x,t) = U_t(n,t), & 0 < x < 1, & t > 0 \\ U(0,t) = U(1,t) = 0, & & \\ U(x,0) \text{ given.} & & \end{array}\right\} \tag{10}$$

Then $U(x,t)$ is unbounded as t increases. This shows like all the above problems, that there are astounding unexpected results coming from this and that the earlier non-local problems which appear deceptively simple.

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