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A NONDIFFERENTIABLE SEMIGROUP GENERATED BY A MODEL OF CELL POPULATION DYNAMICS

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In this paper we are concerned with regularity of operator semigroup generated by population models defined by functional-integral equations. Contrary to the semigroups defined by functional-differential equations, our semigroups do not necessarily become increasingly more regular with time. We furnish an example of a special case of a cell population model which generates a nondifferentiable semigroup.

1. Introduction

In this paper we are concerned with regularity of operator semigroup generated by population models defined by functional-integral equations. Contrary to the semigroups defined by functional-differential equations, our semigroups do not necessarily become increasingly more regular with time. We furnish an example of a special case of a cell population model which generates a nondifferentiable semigroup.

The model we employ for this demonstration was originally analyzed by (Arino *et al.*, 1991). In that paper, we established basic properties and asymptotic behaviour of the semigroup of solutions. For the convenience of the Reader, we repeat the hypotheses, model derivations and basic existence results in Section 2. Then we proceed with construction of the nondifferentiable case.

We have constructed and analyzed mathematically several related models of cell population dynamics, covering a range of possible variants of cell cycle regulation. They can be found in the papers (Arino and Kimmel, 1987; 1989; 1991; 1993; Arino *et al.*, 1991; Kimmel and Arino, 1991; Kimmel and Axelrod, 1991; Kimmel *et al.*, 1984).

A classical reference concerning semigroups of operators is the book by Hille and Phillips (1957). A more modern treatment, emphasizing nonnegative semigroups can be found in the book edited by Nagel (Nagel, 1986).

2. The Model and its Basic Properties

We consider a quasi-probabilistic model of the cell cycle in which the main determinant of cell generation time is x, the amount of a cell constituent present in the daughter cell immediately after division; x may denote either total cell mass or the amount of a

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selected substance, for example RNA (as in Kimmel *et al.*, 1984), of supposed critical importance for cell growth. We follow cells with various amounts of this constituent.

There are two sources of variability in the basic model. The first is unequal division of cells in mitosis; daughter cells of unequal size have different x. The second is an independent additional variability in the duration of cell cycle, caused mainly by the stochastic character of processes in the G_1 phase; generally, for two unrelated daughter cells with identical x, the duration of cell cycle may be different. This latter variability is superimposed on a deterministic law of cell growth.

We proceed as in (Kimmel *et al.*, 1984) and in (Arino *et al.*, 1991). The most important notion of the model is the distribution of cell mass flux at the beginning of the G_1–phase (the onset of the cell cycle). It is denoted by $n(t,x)$ and treated as an unnormed distribution density of the pair (t,x) (see the remark below).

The interpretation is that $n(t,x)\,dtdx$ is equal to the number of cells with mass between x and $x+dx$ which entered G_1 in the time interval from t to $t+dt$. The following assumptions define the model:

1. Suppose that a mitotic cell just before division has mass y. The density of probability of the daughter cell's mass x, conditional on y, is denoted by $f(x,y)$. It is necessary that $f(x,y)=0$, whenever $x>y$, and that $f(y-x,y)=f(x,y)$.
2. The fate of the daughter cell produced during division, which re-enters the cycle with birthmass x, is described in probabilistic terms:
   a) The time τ it spends in the cycle is a random variable with conditional distribution density $\gamma(\tau,x)$, given x.
   b) The mass y of this cell when it reenters division is a function $\phi(\tau,x)$ of the time it spends in the cycle and of its birthmass x.

These hypotheses are depicted in Figure 1.

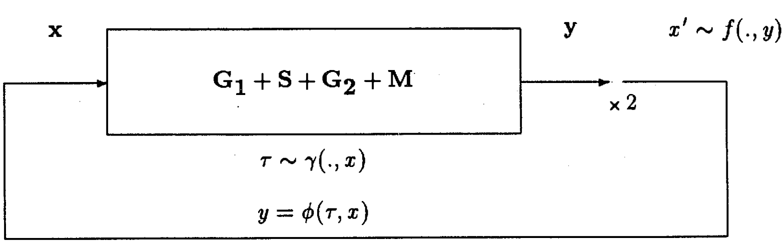

Fig. 1. Schematic diagram of the basic model.

The derivation of the model equation is carried out in several successive steps. Let us first suppose that cells spend in the cycle exactly τ time units and have birthmass equal to ξ. Then the distribution density of the flux at the beginning of the next G_1 phase is equal to

$$2f[x,\phi(\tau,\xi)] \tag{1}$$

But τ is distributed with density $\gamma(.,\xi)$ conditional on ξ and ξ is distributed with density $n(s,\xi)$ at time s. Therefore the distribution density of the pair (t,ξ) is equal to

$$\gamma(\tau,\xi)n(s,\xi) \tag{2}$$

Consequently, the joint density $\tilde{n}(s+\tau,x;\tau,\xi)$ (contribution to the flux density through next G_1 of cells of size ξ at their birth which spend time τ in the cycle and which were born at time s with size x) is equal to the product of (1) and (2). After a change of variables $(s,x;\tau,\xi)$ into $(t,x;\tau,\xi)$ where $t=s+\tau$ (the Jacobian is equal to 1), we obtain

$$\tilde{n}(t,x;\tau,\xi)=2f[x,\phi(\tau,\xi)]\gamma(\tau,\xi)n(t-\tau,\xi) \tag{3}$$

Continuity of the flow requires that $n(t,x)=\int\int\tilde{n}(t,x;\tau,\xi)\,\mathrm{d}\tau\mathrm{d}\xi$. Integrating (3) provides the equation of the model

$$n(t,x)=2\int_0^\infty\int_0^\infty f[x,\phi(\tau,\xi)]\gamma(\tau,\xi)n(t-\tau,\xi)\,\mathrm{d}\xi\mathrm{d}\tau \tag{4}$$

Remark 1. The derivation outlined above includes intuitive manipulations on informal unnormed densities. These manipulations can be formalized if $n(.)$ and $\tilde{n}(.)$ are treated as densities of the expectations of counting measures of a branching process describing our model (like in (Arino and Kimmel, 1993)).

The expression for the total number $N(t)$ of cells present at time t is derived in the following way. The density of cell flux through G_1 including cells born with size x at time s which spend time τ in the cycle, is equal to $n(s,x)\gamma(\tau,x)$. The population at time t includes cells born between $t-\tau$ and t:

$$\begin{aligned} N(t) &= \int_0^\infty\int_0^\infty\int_{t-\tau}^t n(s,x)\gamma(\tau,x)\,\mathrm{d}s\mathrm{d}\tau\mathrm{d}x \\ &= \int_0^\infty\int_0^t n(s,x)\bar{\Gamma}(t-s,x)\,\mathrm{d}s\mathrm{d}x \end{aligned} \tag{5}$$

where $\bar{\Gamma}$ is the tail of the distribution of cell cycle length, i.e. $\bar{\Gamma}(u,x)=\int_u^\infty\gamma(\tau,x)\,\mathrm{d}\tau$.

We proceed to specifying the basic hypotheses on functions f, γ and ϕ, which formalize the requirements of cell cycle dynamics.

Hypothesis 1. $f\in L^1_{loc}(\mathbb{R}^2_+)$; $f\geq 0$; $\int f(y,x)\,\mathrm{d}y=1$; $f(x-y,x)=f(y,x)$; *$f(y,x)$ is nonnegative and there exists $d_1\in(0,1/2)$ such that $f(y,x)$ is positive if and only if $y\in(d_1x,d_2x)$, where $d_2=1-d_1$.*

Hypothesis 2. $\gamma\in L^1_{loc}(\mathbb{R}^2_+)$; $\int\gamma(\tau,x)\,\mathrm{d}\tau=1$; *$\gamma(\tau,x)$ is nonnegative and there exist two continuous decreasing functions τ_1 and τ_2 such that* $\lim_{\xi\to\infty}\tau_1(\xi)>0$; *$\tau_1<\tau_2$, and $\gamma(\tau,\xi)$ is positive if and only if $\tau\in(\tau_1(\xi),\tau_2(\xi))$.*

Hypothesis 3. $\phi\in C_{loc}(\mathbb{R}^2_+)$; $\phi\geq 0$; *$\phi(.,\xi)$ and $\phi(\tau,.)$ is increasing.*

Hypothesis 4. *ϕ is increasing; $\phi_i(\xi) > \xi$, if $\xi < a_i$; $\phi_i(a_i) = a_i$; $\phi_i(\xi) < \xi$, if $\xi > a_i$; $i = 1, 2$, where $\phi_i(\xi) = d_i\phi[\tau_i(\xi), \xi]$ and $0 < a_1 < a_2 < \infty$ are constants.*

The assumptions on f express the fact that $f(., y)$ is the density of the conditional distribution of the mass of daughter cell provided the mass of the mother cell is y. The support property reflects the fact that the mass partition to daughter cells may not exceed a maximum degree of inequality.

The assumptions on γ express the fact that $\gamma(., x)$ is the density of the conditional distribution of the cell cycle duration given the birthmass of the cell x. The support property takes into account the following requirements, (a) cell cycle time varies only in certain limits, (b) it should be in inverse relationship to the birthmass and (c) a minimum cell cycle time is required even for cells with large birthmass.

The assumptions on ϕ express the fact that the mass at division of the cell is larger for cells with higher birthmass and cells which stay longer in the cycle.

Hypothesis 4 assures that if the initial conditions have support confined to an interval, then the solution stays in that interval. This is important from the point of view of the biological feasibility of the model. More precisely, we have the following lemma (Lemma 2 in (Arino *et al.*, 1991)).

Lemma 1. *Let us choose $I = [A_1, A_2]$ such that $0 < A_1 \le a_1 < a_2 \le A_2 < \infty$. Then, if*

$$\text{supp} n_0(s, .) \subset I = [A_1, A_2], \ s \in [-\theta_2, 0]$$

then

$$\text{supp} n(t, .) \subset [\phi_1(A_1), \phi_2(A_2)] \subset I, \ t > 0$$

Therefore, supp$n(t, .)$ *is asymptotically contained in* $[a_1, a_2]$.

To formally construct a solution to equation (4) after time t_0, it is necessary to know it on the set $\{(t, y) : t_0 - \tau_1(y) > t > t_0 - \tau_2(y), y > 0\}$. Along the solution n, the restriction of n to $\Delta_t = \{(s, y) : s \in (t - \tau_2(y), t - \tau_1(y)), y > 0\}$ comprises the data necessary and sufficient to continue the solution. We will adopt the standard notation (Hale, 1977):

$$n_t(s, y) = n(t + s, y); \qquad t > 0, (s, y) \in \Delta$$

$$\Delta = \{(s, y) : y > 0, \ s \in (-\tau_2(y), 0)\} \tag{6}$$

The fact that $n(t, .)$ has a bounded support contained in $I = [A_1, A_2]$ implies that the system (4) has maximum and minimum delays

$$\theta_1 = \tau_1(A_2)$$

and

$$\theta_2 = \tau_2(A_1)$$

Therefore, the initial data can be restricted to Δ and the solution constructed in steps of length θ_1.

In view of Lemma 1, we may also use a slightly different domain $\Delta' = (-\theta_2, 0) \times I$, instead of Δ.

Lemma 2. *Suppose that Hypotheses 1, 2, 3, and 4 are satisfied. If $n_0 > 0$ belongs to $X = L^1(\Delta')$, then there exists a function $n : \Omega \to \mathbb{R}$, where $\Omega = \Delta' \cup (\mathbb{R}_+ \times I)$, $n \geq 0$, $n \in L^1_{loc}(\Omega)$; and $\lim_{t\to\infty} n_t = n_0$ in X. The solution is unique in the sense of an equivalence class in $L^1_{loc}(\Omega)$.*

The following is a version of Lemma 4 of (Arino *et al.*, 1991) with slightly relaxed hypotheses.

Lemma 3. *Under hypotheses of Lemma 2 supplemented by $f \in L^\infty_{loc}(\mathbb{R}^2_+)$ and $\gamma \in L^1_{loc}(\mathbb{R}^2_+)$, the family of mappings $\{G(t), t \geq 0\}$,*

$$G(t) : X \to X, \; G(t)n_0 = n_t \tag{7}$$

is a strongly continuous semigroup of positive bounded linear operators on X. $G(t)$ is compact from X into X for any $t > 2\theta_2$.

3. The Nondifferentiable Semigroup

We consider equation (4), under the following additional assumption:

Hypothesis 5.

$$\gamma(\tau, \xi) = \gamma(\tau)$$

that is, we assume that γ does not depend on the size variable.

Hypothesis 5 leads to a special case of our model being identical to the *transition probability* model, considered e.g. by Webb (1987).

If this is so, and n is a solution of equation (4), then the function h, defined by

$$h(t) = \int_{A_1}^{A_2} n(t, x)\,\mathrm{d}x \tag{8}$$

verifies the equation

$$h(t) = 2\int_{\theta_1}^{\theta_2} \gamma(\tau) h(t - \tau)\,\mathrm{d}\tau \tag{9}$$

Equation (9) determines a strongly continuous semigroup $U(t)$ of bounded linear operators on the space $Z = L^1(-\theta_2, 0)$. In fact, formula (8) provides a map $P : X \to Z$, which obviously satisfies the following property :

$$PG(t)n_0 = U(t)Pn_0, \qquad \text{for every} \quad t \geq 0$$

The above identity shows that $U(t)$ verifies the following relation $U(t+s)P = U(t) \circ U(s)P$ (that is, U is a C–semigroup in the sense of Miyadera (1992)). On the other hand, P is surjective. A right inverse R of P is, for example, the map $h \to (A_2 - A_1)^{-1}h$. So, we conclude that $U(t)$ verifies the semigroup relation. We also deduce the following formula

$$U(t) = PG(t)R \tag{10}$$

which shows that U is strongly continuous.

It also shows that each trajectory $\{U(t)h\}$ can be determined in terms of a function u from $(-\theta_2, \infty)$ into $\mathbb{R}$ as the set of the phase-shift translations u_t.

Formula (10) shows also that if $G(t)$ is differentiable, norm continuous or compact, or verifies any of these properties eventually, then the same is true for $U(t)$. And, if any of these properties fails to be true for $U(t)$, it also fails for $G(t)$. We will use this observation to build an example of equation (4) which generates a nondifferentiable semigroup.

Before proceeding further, we notice that there is a relation between the generators of G and U. In fact, we have, using for example the representation of the resolvent operator in terms of the Laplace transform, and denoting A_G and A_U, the generators of G and U: $D(A_U) = P(D(A_G))$, and $A_U = PA_GR$.

We have $A_G n = (\mathrm{d}/\mathrm{d}t)(n(\tau, x))$ on the domain $D(A_G)$ which is the set of n in X, such that $(\mathrm{d}/\mathrm{d}t)(n(\tau, .))$ is in X and $n(0,.) = Ln$ (where L is the operator defined by the right hand side of equation (13) in (Arino *et al.*, 1991). Therefore the domain of A_U is the set of functions h on $(-\theta_2, 0)$ absolutely continuous with respect to the Lebesgue measure on the interval (these functions have continuous extensions on the closed interval), such that moreover $h(0) = \int_{\theta_1}^{\theta_2} \gamma(\tau)h(-\tau)\,\mathrm{d}\tau$. For each $h \in D(A_U)$, we have $A_U h = h'$.

This implies in particular that each trajectory starting from an element h of $D(A)$ can be represented as the set of the translates u_t of a function u defined on $(-\theta_2, \infty)$, which is locally absolutely continuous on its domain. So, a necessary condition for a semigroup determined by equation (9) to be eventually differentiable is that its solutions are locally absolutely continuous on an interval (T, ∞). In particular, they should be continuous.

For the counterexample we will construct next, the contradiction will come from the fact that the solution is unbounded on each interval of length larger than θ_2. Obviously, U does not depend on the function f in equation (4). Based on Lemma 3 the semigroup G is eventually compact so that U itself is eventually compact.

For the convenience of the reader, we will change the notations, from this point on. We modify equation (9), as follows. First, we can assume that $\theta_2 = 1$, then, we denote θ_1 by a, so that we have : $0 \leq a < 1$. Finally, we denote k the function 2γ and z the solutions. The state space is $Z = L^1(-1, 0)$. The equation reads now

$$z(t) = \int_a^1 k(\tau)z(t-\tau)\,\mathrm{d}\tau \tag{11}$$

We keep the notation $U(t)$ for the semigroup associated with equation (11). From the above considerations, we know that $U(t)$ is eventually compact. Regarding differentiability, we have the following result.

Theorem 1. *Let k be a function defined on $(0,1)$, such that $k \geq 0$ and k belongs to $L^1(0,1)$. Denote $U(t)$ the semigroup associated to equation (11). Then,*

i) *Either, for some $p > 1$, k is in $L^p(0,1)$. Then, $U(t)$ sends eventually $L^1(0,1)$ into $C([0,1])$. If in addition one of the iterates k_j of k (defined by formula (14)) has a bounded variation on $[0, j+1]$, then the semigroup $U(t)$ is eventually differentiable;*

ii) *Or, k does not belong to any $L^p(0,1)$, for any $p > 1$. If in addition k is nondecreasing on $(0,1)$, then $U(t)$ is not eventually differentiable.*

Remark 2. Each function with bounded variation generates a Radon measure on its domain. We use the notation $\mathrm{d}f(t)$ to denote the measure of the "infinitesimal" interval $[t, t + \mathrm{d}t]$, so that the measure of any Borel subset A of the domain of f is denoted $\int_A \mathrm{d}f(t)$.

Before proving the theorem, a few preparatory ingredients have to be introduced, notably, a result on the convolution of L^p functions that we state and (for the sake of completeness) prove next.

Lemma 4. *Let f and g be two functions defined on $(0,1)$. Assume that $f \in L^{p_1}(0,1)$, and $g \in L^{p_2}(0,1)$. Let h denote the convolution product of f and g on $(0,1)$, that is,*

$$h(x) = \int_0^x f(x-y)g(y)\,\mathrm{d}y \tag{12}$$

Then, $h \in L^p(0,1)$, where $1/p = \max(1/p_1 + 1/p_2 - 1, 0)$.

Proof. Note that if we assume that $1/p_1 + 1/p_2 = 1$, then one can immediately deduce from the Hölder inequality that h is in $L^\infty(0,1)$, and $\|h\|_\infty \leq \|f\|_{p_1}\|g\|_{p_2}$. If $1/p_1 + 1/p_2 < 1$, then one can replace p_1 by a smaller value p_1', so that $1/p_1' + 1/p_2 = 1$. Since $L^{p_1}(0,1) \subset L^{p_1'}(0,1)$, we conclude once again that $h \in L^\infty(0,1)$, and the same inequality as above holds. Suppose finally that $1/p_1 + 1/p_2 > 1$. Define q_i, $i = 1,2$, by $1/p_i + 1/q_i = 1$. We have $1/q \overset{def}{=} 1 - 1/p = 1/q_1 + 1/q_2$, and for each $k \in L^q$,

$$\left| \int_0^1 k(x)h(x)\,\mathrm{d}x \right| \leq \int_0^1 \int_0^1 |k(u+v)||f(u)||g(v)|\,\mathrm{d}u\mathrm{d}v$$

Introducing the number $a = q_2/(q_1 + q_2)$, and writing $|k|$ as $|k|^\alpha |k|^{1-\alpha}$, and using the Hölder inequality separately for the products $|k|^\alpha(u+v)|f(u)|$ and $|k|^{1-\alpha}(u+v)|g(v)|$, respectively, we obtain finally the inequality

$$\left| \int_0^1 k(x)h(x)\,\mathrm{d}x \right| \leq \|k\|_q \|f\|_{p_1} \|g\|_{p_2}$$

from which the conclusion of the Lemma follows easily. ■

Remark 3. 1) The formula given in Lemma 4 can easily be extended to the convolution of an arbitrary number of functions, say, n functions $\in L^{p_i}(0,1)$, $i = 1, \ldots, n$. The product is in L^p, where $p = \max(1/p_1 + \ldots + 1/p_n - (n-1), 0)$.

2) If, in particular, all p_i are equal, $p_i = \bar{p}$, for $i = 1, \ldots, n$, we have $p = \max(n/\bar{p} - (n-1), 0)$, which shows that the product of more than $\bar{p}/(\bar{p}-1)$ functions in $L^{\bar{p}}$ is in L^∞, and the product of more than $\bar{p}/(\bar{p}-1)+1$ is in $C([0,1])$ (the class of continuous functions on $[0,1]$).

In order to state the next Lemma, we have to introduce a few notations. Let z be a solution of equation (11). Let us assume, for the time being, that $a = 0$. For $t \geq 1$, we can express the solution in terms of the values of z on the interval $[t-2, t]$. This is done by expanding z inside the integral of (11) in terms of the integral. The new expression reads

$$z(t) = \int_0^2 k_2(\tau) z(t-\tau)\,\mathrm{d}\tau \tag{13}$$

where k_2 is defined by

$$k_2(\tau) = \begin{cases} \displaystyle\int_0^\tau k(s)k(\tau - s)\,\mathrm{d}s & \text{if } 0 < \tau < 1 \\ \displaystyle\int_{\tau-1}^1 k(s)k(\tau - s)\,\mathrm{d}s & \text{if } 1 < \tau < 2 \end{cases}$$

For $t \geq j$, $j \geq 2$, $z(t)$ can be expressed in terms of its values on $[t-j-1, t]$ and in terms of an integral operator with kernel k_{j+1} determined inductively by the formulae

$$k_{j+1}(\tau) = \begin{cases} \displaystyle\int_0^\tau k(s)k_j(\tau - s)\,\mathrm{d}s & \text{if } 0 < \tau < 1 \\ \displaystyle\int_0^1 k(s)k_j(\tau - s)\,\mathrm{d}s & \text{if } 1 < \tau < j \\ \displaystyle\int_{\tau-j}^1 k(s)k_j(\tau - s)\,\mathrm{d}s & \text{if } j < \tau < j+1 \end{cases} \tag{14}$$

For $t \geq j$, the integral equation for z takes the form

$$z(t) = \int_0^{j+1} k_{j+1}(\tau) z(t-\tau)\,\mathrm{d}\tau \tag{15}$$

Each of the three integrals on the right hand side of (14) can be interpreted as a convolution product of the same type as the one given in formula (12). By induction, one can then easily deduce from Remark 3 following Lemma 4, that for j large enough the functions k_j are continuous.

Proof of Theorem 1. Consider the case i) first. The first conclusion (continuity of the solution for t large enough) is an immediate consequence of the above preliminaries. Using formula (15) with j large enough for k_{j+1} to be bounded we have

$$|z(t) - z(s)| \leq C \int_0^j |z(t-\tau) - z(s-\tau)|\,\mathrm{d}\tau, \quad t, s \geq j$$

The result follows by continuity of the translation in L^1. The proof of differentiability requires a little more care. First of all, it is not difficult to show, using formula (14), that if k_j has bounded variation on $[0, j+1]$, for some j, then for each $l \geq j$, k_l has bounded variation on $[0, l+1]$. Let us fix a value j such that k_j is continuous and has bounded variation on $[0, j+1]$. Let z be any solution of equation (11). Let $Z(t)$ denote the function defined by $Z(t) = \int_0^t z(s)\,\mathrm{d}s$. We can rewrite equation (15) in the form

$$z(t) = -\int_0^{j+1} \mathrm{d}k_{j+1}(\tau) Z(t-\tau), \quad \tau > j$$

The above formula shows that the solution z has bounded variation on each bounded interval of the half-line $[j, \infty)$. Now, for any $t \geq s \geq 2j+2$, we deduce from the same formula (and using the fact that z is continuous for $t \geq j$) that

$$|z(t) - z(s)| \leq \left(\int_0^{j+1} |\mathrm{d}k_{j+1}(\tau)|\right)\left(\max_{j \leq \tau \leq t} |z(\tau)|\right)(t-s)$$

This inequality means that z is locally Lipschitz continuous on $[2j+2, \infty)$.

Coming back to equation (11), and differentiating it on both sides, for $t > 2j+2$, we can see, still using the argument of continuity of the translation in L^1 that the right-hand side is continuous, therefore, $z'(t)$ is well defined and continuous on the interval $(2j+2, \infty)$. This completes the proof of part i).

We now turn to the proof of ii). Let k be a function for which the assumptions of ii) hold. Let k_1 denote the function defined by

$$k_1(t) = k(t+1), \ -1 \leq t < 0 \tag{16}$$

The assumptions on k imply that $k_1(t)$ tends to $+\infty$ and $|t|k_1(t)$ tends to 0, as t approaches 0.

Let z_0 be a positive initial function for equation (11). We will denote by z_l, for $l \geq 0$, the shift on $[-1, 0]$ of the solution on $((l-1), l)$. One can easily derive the following inequality

$$z_l(t) \geq [k_1(t)]^l \int_0^t \{(s-t)^{l-1}/[(l-1)!]\} z_0(s)\,\mathrm{d}s \tag{17}$$

Changing the variable s into $s/|t|$ inside the integral, we can estimate the right-hand side as follows

$$z_l(t) \geq [k_1(t)]^l |t|^l C_l \int_{-1/2}^0 z_0(|t|u)\,\mathrm{d}u \tag{18}$$

where $C_l > 0$, for all l. We will now select a function z_0 such that, for all $l > 0$, the right-hand side of formula (18) goes to $+\infty$, as $t \to 0$. We will assume that $z_0(t) \sim |t|^{-\alpha}$ (as $t \to 0$), for some a, $0 < a < 1$.

Before we show that we can actually make such a choice, let us draw its consequences on the proof of ii). If this can be done, it means that the solution z is unbounded on each interval of $(l-1,l)$, so, it never becomes continuous, neither can it can be differentiated. So, the proof of ii) will be complete.

Let us choose a function z_0 increasing to $+\infty$, near 0, such that $z \in L^1(-1,0)$. Suppose z_0 has been chosen as indicated (which, obviously, is feasible). And suppose that the solution associated with z_0 is continuous for all t large enough. This implies that for each l large enough, there exists $M < \infty$, so that $z_1(t) < M$, for all $t \in [-1,0]$. Using the estimate (18) and the equivalent expression for z_0 near 0, we obtain the following bound for the growth of k_1 near 0:

$$k_1(t) < 2(M^{1/l}/2^{\alpha/l})|t|^{\alpha/l-1}, \quad t \text{ near } 0$$

Clearly, $k_1 \in L^p(0,1)$, for some $p > 1$ (any p such that $1 < p < l/(l-\alpha)$), in contradiction with the assumption made in ii). ■

Example. There are many examples where either (i) or (ii) of Theorem 1 holds. For the case (i), we can consider any function k of bounded variation, which in particular implies that it is bounded. Amongst other examples, we can take $k(t) = 1/\sqrt{t}$. A straightforward computation shows that k_2 is bounded on $[0,2]$, of bounded variation, increasing on [0, 1], decreasing on [1, 2].

For the case (ii), a typical example is

$$k(t) = |\tau - 1|^{-1}([\ln|\tau - 1|]^2 + 1) - 1$$

4. Comments

The nondifferentiability of the semigroup affects the behaviour of the solution $h(t)$ (and consequently, the flux $n(t,x)$) which becomes unbounded. Interestingly, it is not the case with the total cell count $N(t)$. Indeed, in our special case, we have

$$N(t) = \int_0^t \bar{\Gamma}(t-\tau)h(\tau)\,d\tau, \quad t \geq 0$$

Since $\bar{\Gamma}$ is absolutely continuous and h is locally integrable, $N(t)$ is absolutely continuous and therefore also bounded on bounded intervals. Function $N(t)$ satisfies equation

$$N(t) = \int_0^t \gamma(t-\tau)N(\tau)\,d\tau, \quad t \geq 0 \tag{19}$$

since $N = \bar{\Gamma} * h \; = \bar{\Gamma} * \gamma * h \; = \gamma * \bar{\Gamma} * h \; = \gamma * N$.

We may conjecture that with initial data in the space of continuous functions, the semigroup generated by (19) is differentiable.

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