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A TRANSPORT EQUATION MODELLING CELL GROWTH

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ABSTRACT

The well-posedness of Rotenberg's time-dependent transport equation describing cell population dynamics is established under natural assumptions on the maturation "interaction" and reproduction law. Necessary conditions and sufficient conditions for the existence of a steady-state solution are given. Some results on the long term behavior of solutions are derived.

1. INTRODUCTION

The dynamics of a population of biological cells, such as populations of bacteria and certain eukaryotic cells, can be described by a linear transport equation for the number density of the cells, where the maturation velocity $\mu \in [0,1]$, the maturation rate $v = \frac{d\mu}{dt}$ and time $t \geq 0$ are the independent variables. We have $\mu = 1$ just before mitosis and $\mu = 0$ just after mitosis. Under suitable assumptions we have the initial-boundary value problem

$$\frac{\partial f}{\partial t} + v\frac{\partial f}{\partial \mu} + R(\mu, v) f(\mu, v, t) = (Jf)(\mu, v, t), \tag{1}$$

$$f(0, v, t) = \frac{m}{v}\int_0^\infty k(v, v')\, v' f(1, v', t)\, dv', \tag{2}$$

$$f(\mu, v, 0) = f_0(\mu, v), \tag{3}$$

where $k \geq 0$,

$$\int_0^\infty k(v, v')\, dv \equiv 1, \tag{4}$$

$0 \leq m \leq 1$, and

$$(Jg)(\mu, v) = \int_0^\infty r(\mu; v, v')\, g(\mu, v')\, dv' \tag{5}$$

with $r \geq 0$ and

$$\int_0^\infty r(\mu; v, v')\, dv' = R(\mu; v'). \tag{6}$$

Here the reproduction law (3), initially introduced by Lebowitz and Rubinow [1], describes the change of the number density of the cells at mitosis, the condition (4) and $m \in [0,1]$ standing for the requirement that the number of cells does not grow exponentially in time. The model itself as well as its Fokker-Planck approximation were introduced by Rotenberg [2], who obtained numerical results on the asymptotic behavior of the solution of the Fokker-Planck model. A concise derivation of the "exact" model and a synopsis of the relevant literature have been presented by Pilz [3].

A natural space to solve Eqs. (1)-(3) in is the Banach space

$$X = L_1([0,1] \times \mathbb{R}^+; d\mu\, dv)$$

with the "restrictions" to $\{\mu = 0\}$ and $\{\mu = 1\}$ belonging to the Banach space

$$Y = L_1(\mathbb{R}^+; v\, dv),$$

where the derivative $v \frac{\partial f}{\partial \mu}$ is taken in the distributional sense. Then, for $f \geq 0$ in X, $\|f\|_X$ stands for the total number of cells with distribution function $f(\mu, v)$, while $\|g\|_Y$, for $g \geq 0$ in Y, stands for the total flux of cells with distribution function $g(v)$ which have just undergone or are about to undergo mitosis. Clearly, J is a positive operator with

$$\|Jg\|_X = \|Rg\|_X \quad \text{if } g \geq 0 \text{ and } Rg \in X, \tag{7}$$

while K, defined as

$$(Kg)(v) = \frac{m}{v} \int_0^\infty k(v, v')\, v'\, g(v')\, dv' \tag{8}$$

is a positive operator on Y satisfying

$$\|Kg\|_Y = m\, \|g\|_Y \quad \text{if } g \geq 0 \text{ in } Y. \tag{9}$$

For K we will consider an arbitrary positive operator on Y satisfying (9), so that (8) with $k(v, v')$ satisfying (4) and $m \in [0,1]$ is merely a formal representation of K. In this way we account for reproduction laws such as the "perfect memory" law $k(v, v') = \delta(v - v')$ where $\delta(\cdot)$ is Dirac's delta function.

In this article we will apply well-known methods from linear transport theory [4, 5, 6] to establish the well-posedness of the time-dependent problem, to study the existence of stationary solutions and the large time behavior of time dependent solutions. Semigroup theory (e.g. [7]) will be one of the major tools. A comprehensive theory of linear time dependent kinetic equations, which was developed by Beals and Protopopescu [6] (also [4], Ch. 11-12), only applies to the present problem if $R(\mu, v)$ is bounded and does not yield much information on the long term behavior of solutions. For this reason we will rely instead on methods applied before to electron drift in a weakly ionized gas under the influence of a constant electric field, especially the work in this direction by Frosali et al. [8] (also [9, 10, 11]). We will give necessary conditions and sufficient conditions for the existence of a stationary solution and for the convergence of the time dependent solution to the steady-state profile.

Throughout this paper, $D(T)$, $\operatorname{Ran} T$, $\operatorname{Ker} T$, $\sigma(T)$, $\rho(T)$, $\sigma_p(T)$, $\sigma_r(T)$ and $\sigma_c(T)$ will stand for the domain, range, kernel, spectrum, resolvent set, point spectrum, residual spectrum and continuous spectrum of a linear operator T, while $\overline{T}$ will denote its minimal closed extension. For definitions of these notions we refer to textbooks on functional analysis (e.g. [7, 12]).

2. THE TIME-DEPENDENT PROBLEM

To define $v \frac{\partial g}{\partial \mu}$, $g(0, v)$ and $g(1, v)$ for an arbitrary function $g \in Y$, we introduce the test function space Φ of all bounded complex Borel functions φ on $(0,1) \times \mathbb{R}^+$ of compact support which are continuously differentiable along the integral curves of the vector field $v \frac{\partial}{\partial \mu}$ with bounded directional derivative, as well as the set $\Phi_0 = \{\varphi \in \Phi : \varphi(0, v) = \varphi(1, v) = 0\}$. Then we may define $v \frac{\partial g}{\partial \mu}$ for every $g \in X$ by

$$\int_0^\infty\int_0^1 v\frac{\partial g}{\partial\mu}\varphi\,d\mu\,dv = -\int_0^\infty\int_0^1 v\frac{\partial\varphi}{\partial\mu}g\,d\mu\,dv, \quad \varphi\in\Phi_0,$$

and the restrictions $g(0,\cdot)$ and $g(1,\cdot)$, not necessarily belonging to Y, by[1]

$$\int_0^\infty\int_0^1 v\Big(\frac{\partial g}{\partial\mu}\varphi+\frac{\partial\varphi}{\partial\mu}g\Big)d\mu\,dv = \int_0^\infty v\,\{g(1,v)\varphi(1,v)-g(0,v)\varphi(0,v)\}\,dv, \quad \varphi\in\Phi. \tag{10}$$

We then define the linear operator T_K by $(T_K g)(\mu,v) = -v\frac{\partial g}{\partial\mu} - Rg$ where $D(T_K)$ consists of those $g\in X$ such that $v\frac{\partial g}{\partial\mu}+Rg\in X$, $g(0,\cdot)\in Y$, $g(1,\cdot)\in Y$ and $g(0,\cdot)=Kg(1,\cdot)$.

Throughout this article we assume that $\int_0^1 R(\hat\mu,v)\,d\hat\mu$ is finite for almost every $v\in\mathbb{R}^+$.

Let us consider the auxiliary problem

$$\frac{\partial f}{\partial t} + v\frac{\partial f}{\partial\mu} + R(\mu,v)f(\mu,v,t) = F(\mu,v,t) \tag{11}$$

with initial-boundary conditions (2) and (3). We have

PROPOSITION 1. For every initial condition $f_0\in X$ there is a unique solution $f:\mathbb{R}^+\to X$ of Eq. (11) with initial-boundary conditions (2) and (3) satisfying

$$\|f(t)\|_X \le \|f_0\|_X, \quad t\ge 0. \tag{12}$$

This solution can be represented as $f(t)=S_0(t)f_0$, where $\{S_0(t)\}_{t\ge 0}$ is a bounded strongly continuous, positive semigroup on X generated by T_K if $0\le m<1$ and by $\overline{T_K}$ if $m=1$.

Proof: Consider the auxiliary problem

$$v\frac{\partial g}{\partial\mu} + \{\lambda+R(\mu,v)\}g(\mu,v) = F(\mu,v) \tag{13}$$

and

$$g(0,v) = \frac{m}{v}\int_0^\infty k(v,v')\,v'\,g(1,v')\,dv', \tag{14}$$

[1]In general, $g(0,\cdot)$ and $g(1,\cdot)$ belong to $L_{1,loc}(\mathbb{R}^+;v\,dv)$, the space of all functions g for which $v\,g(v)$ is integrable on all bounded Borel sets of $\mathbb{R}^+$; cf. [4,6].

where $\lambda>0$. We easily find

$$(L_\lambda F)(\mu,v) \overset{\text{def.}}{=} g(\mu,v) = exp\Big(-\frac{\lambda\mu}{v}-\frac{1}{v}\int_0^\mu R(\hat\mu,v)\,d\hat\mu\Big)g(0,v) \; +$$

$$+\frac{1}{v}\int_0^\mu exp\Big(-\frac{\lambda(\mu-\mu')}{v}-\frac{1}{v}\int_{\mu'}^\mu R(\hat\mu,v)\,d\hat\mu\Big)F(\mu',v)\,d\mu', \tag{15}$$

where

$$g(0,v) - \frac{m}{v}\int_0^\infty k(v,v')\,v'\,exp\Big(-\frac{\lambda}{v'}-\frac{1}{v'}\int_0^1 R(\hat\mu,v')\,d\hat\mu\Big)g(0,v')\,dv' =$$

$$= \frac{m}{v}\int_0^\infty k(v,v')\int_0^1 exp\Big(-\frac{\lambda(1-\mu')}{v'}-\frac{1}{v'}\int_{\mu'}^1 R(\hat\mu,v')\,d\hat\mu\Big)F(\mu',v')\,d\mu'\,dv'. \tag{16}$$

By integration we find that Eq. (16) can be viewed as a vector equation in Y where the integral operator has norm $\le m$. Moreover, since the exponential factor in the integrand is strictly less than 1 for $\lambda>0$, this equation has at most one solution in Y, even if $m=1$. For $0\le m<1$ we find a unique solution for every $F\in X$, which is nonnegative if $F\ge 0$.

If $F\ge 0$ in X, a simple integration yields [cf. Eq. (18)]

$$\lambda\|L_\lambda F\|_X + \|R\,L_\lambda F\|_X = \int_0^\infty\int_0^1\{\lambda+R(\mu,v)\}\,g(\mu,v)\,d\mu\,dv =$$

$$= \int_0^\infty\Big(1-exp\Big(-\frac{\lambda}{v'}-\frac{1}{v'}\int_0^1 R(\hat\mu,v')\,d\hat\mu\Big)\Big)v'\,g(0,v')\,dv' \; +$$

$$+\int_0^\infty\int_0^1\Big(1-exp\Big(-\frac{\lambda(1-\mu')}{v'}-\frac{1}{v'}\int_{\mu'}^1 R(\hat\mu,v')\,d\hat\mu\Big)\Big)F(\mu',v')\,d\mu'\,dv'.$$

On the other hand, integrating Eq. (16) we get

$$\int_0^\infty\Big(1-m\,exp\Big(-\frac{\lambda}{v'}-\frac{1}{v'}\int_0^1 R(\hat\mu,v')\,d\hat\mu\Big)\Big)v'\,g(0,v')\,dv' =$$

$$= m\int_0^\infty\int_0^1 exp\Big(-\frac{\lambda(1-\mu')}{v'}-\frac{1}{v'}\int_{\mu'}^1 R(\hat\mu,v')\,d\hat\mu\Big)\Big)F(\mu',v')\,d\mu'\,dv'.$$

These two equations together yield

$$\lambda \|L_\lambda F\|_X + \|R L_\lambda F\|_X = (1 - \tfrac{1}{m}) \|g(0)\|_Y + \|F\|_X, \quad F \geq 0 \text{ in } X. \tag{17}$$

Hence, for $0 \leq m < 1$ we have a unique solution $g = L_\lambda F$. It satisfies

$$\lambda \|L_\lambda F\|_X + \|R L_\lambda F\|_X \leq \|F\|_X, \quad F \in X. \tag{18}$$

By the Hille-Yosida theorem [7], for $0 \leq m < 1$ we have a unique solution of Eq. (11) with initial-boundary conditions (2) and (3) for every $f_0 \in X$, which is nonnegative if $f_0 \geq 0$ and can be represented as

$$f(t) = S_0(t) f_0, \quad t \geq 0,$$

where $\{S_0(t)\}_{t\geq 0}$ is a strongly continuous contraction semigroup on X.

If $m = 1$ we introduce a factor $m \in (0,1)$ on the right-hand side of Eq. (3) and solve Eq. (11) with the corresponding initial-boundary conditions of the type (2)-(3), which yields

$$f_m(t) = S_{0,m}(t) f_0, \quad t \geq 0 \text{ and } 0 \leq m < 1.$$

For nonnegative f_0 this solution is monotonically increasing in m while $\|f_m\|_X \leq \|f_0\|_X$ uniformly in t and m. Hence we may define f(t) as the strong limit of $f_m(t)$ in X as $m \uparrow 1$. Also, using the uniform estimate $\|L_{\lambda,m} F\|_X \leq \frac{1}{\lambda} \|F\|_X$ for $\lambda > 0$, we define L_λ as the strong limit of $L_{\lambda,m}$ in X as $m \uparrow 1$. Then, taking the limit in the identity relating $S_{0,m}(t)$ and $L_{\lambda,m}$, we find

$$L_\lambda g = \int_0^\infty e^{-\lambda t} S_0(t) g \, dt, \quad \lambda > 0.$$

Hence, L_λ is the resolvent of the generator of the strongly continuous semigroup $\{S_0(t)\}_{t\geq 0}$. We may now repeat the calculation leading to (17) and find

$$\lambda \|L_\lambda F\|_X + \|R L_\lambda F\|_X = \|F\|_X, \quad F \geq 0 \text{ in } X. \tag{19}$$

In general, $g(0,\cdot)$ and $g(1,\cdot)$, with $g = L_\lambda F$, do not belong to Y.[2]

It is now straightforward to check that, for $0 \leq m < 1$, the function $g = L_\lambda F$ belongs to $D(T_K)$ and that $T_K g = \lambda g - F$. Hence, in this case T_K is the closed operator generating the semigroup $\{S_0(t)\}_{t\geq 0}$. For $m = 1$ we have a sequence $g_m \in D(T_{mK})$ such that $g_m \to g$ and $T_{mK} g_m \to (\lambda g - F)$ in the strong topology of X. Consequently, $g \in D(\overline{T_K})$ and $\overline{T_K}$ generates $\{S_0(t)\}_{t\geq 0}$. □

To study Eqs. (1)-(3) we introduce the auxiliary Banach space X_R as the set of all Lebesgue measurable complex functions on $[0,1] \times \mathbb{R}^+$ such that $Rf \in X$, equipped with the norm

$$\|f\|_\bullet = \|Rf\|_X,$$

provided $R(\mu, v)$ does not vanish on a set of positive measure. Otherwise, we thus get a space $\tilde{X}_R$ which yields X_R on division by the linear space of functions f such that $\|Rf\|_X = 0$, so that $\|f\|_\bullet = \iint_\Sigma R(\mu,v) f(\mu,v) \, d\mu \, dv$ with Σ the support of R. Then J is a contraction from X_R to X satisfying $\|Jf\|_X = \|f\|_\bullet$ for all $f \in X_R$.

Let us represent the solution of the auxiliary equation

$$v \frac{\partial g}{\partial \mu} + \{\lambda + R(\mu,v)\} g(\mu,v) = (J g)(\mu,v) + F(\mu,v) \tag{20}$$

with boundary condition (2) as

$$T_\lambda F = g = L_\lambda (J g + F), \tag{21}$$

where $h = J g$ satisfies

$$(1 - J L_\lambda) h = J L_\lambda F. \tag{22}$$

We will solve Eq. (22) in X and define $g = L_\lambda h \in X \cap X_R$.

Indeed, consider

[2] If $\sigma = \operatorname{ess\,inf}_{v>0} \frac{1}{v} \int_0^1 R(\hat{\mu}, v) \, d\hat{\mu} > 0$, then $g(0,\cdot) \in Y$, even if $m = 1$; cf. Eq. (16).

$$\hat{g}_n = \sum_{k=0}^{n} (J\,L_\lambda)^k F \tag{23}$$

for $F \geq 0$. Then

$$\|F\|_X + \|J\,L_\lambda\,\hat{g}_n\|_X = \|\hat{g}_{n+1}\|_X$$

if $F \geq 0$. Thus, in combination with $0 \leq \hat{g}_n \leq \hat{g}_{n+1}$ and Eq. (18), we get for $F \geq 0$ in X

$$\|F\|_X = \|(J\,L_\lambda)^{n+1}F\|_X + \|\hat{g}_n\|_X - \|R\,L_\lambda\,\hat{g}_n\|_X =$$

$$= \|(J\,L_\lambda)^{n+1}F\|_X + \lambda\,\|L_\lambda\,\hat{g}_n\|_X + (1-m)\,\|[L_\lambda \hat{g}_n]\,(\mu=1)\|_Y \geq \lambda\,\|L_\lambda\,\hat{g}_n\|_X. \tag{24}$$

Hence the infinite series

$$T_\lambda\,F = g = \sum_{k=0}^{\infty} L_\lambda\,(J\,L_\lambda)^k F$$

converges in the strong X-topology and satisfies Eq. (21) as well as the inequality

$$\|T_\lambda\,F\|_X + \beta_\lambda(F) \leq \frac{1}{\lambda}\|F\|_X, \quad F \geq 0 \text{ in X}, \tag{25}$$

where

$$\beta_\lambda(F) = \lim_{n\to\infty} \|(J\,L_\lambda)^{n+1}F\|_X.$$

Note that the equality sign holds true if $m = 1$.

As an application of the Hille-Yosida theorem, we have obtained

THEOREM 2. Equations (1)-(3) have a unique solution $f: \mathbb{R}^+ \to X$ for every $f_0 \in X$ which is non-negative if $f_0 \geq 0$ and can be represented as

$$f(t) = S(t)\,f_0, \quad t \geq 0,$$

where $\{S(t)\}_{t\geq 0}$ is a strongly continuous contraction semigroup on X.

It is not so easy to find the generator G_K of the semigroup $\{S(t)\}_{t\geq 0}$. However, if the solution g to Eq. (21) [a unique solution, since $1 \notin \sigma_p(J\,L_\lambda)$, which is immediate from Eqs. (7) and (18)] belongs to $X \cap X_R$ for every $F \in X$, then the equations

$$T_\lambda = L_\lambda + L_\lambda\,J\,T_\lambda, \tag{26}$$

which is valid if $T_\lambda[X] \subseteq X \cap X_R$, and

$$L_\lambda = T_\lambda - T_\lambda\,J\,L_\lambda, \tag{27}$$

which is valid whether $T_\lambda[X] \subseteq X \cap X_R$ or not, imply that $T_\lambda[X] = L_\lambda[X]$, which is equivalent to $\{S_0(t)\}_{t\geq 0}$ and $\{S(t)\}_{t\geq 0}$ having generators defined on the same domain. This situation occurs if

$$\operatorname*{ess\,inf}_{\mu\in[0,1],v\geq 0} R(\mu,v) > 0, \tag{28}$$

since in this case $X \subseteq X_R$. This situation also occurs if

$$\operatorname*{ess\,sup}_{\mu\in[0,1],v\geq 0} R(\mu,v) < +\infty, \tag{29}$$

since in this case J is bounded on X.

Put

$$C(t)\,F = \int_0^t [S(\tau)\,F]\,(\mu=1)\,d\tau,$$

which is well-defined if $0 \leq m < 1$.

THEOREM 3. Suppose $0 \leq m < 1$. Then the following statements are equivalent:

(i) $\|S(t)\,F\|_X + (1-m)\,\|C(t)\,F\|_Y = \|F\|_X, \quad F \geq 0$ in X,

(ii) $\lambda \|T_\lambda F\|_X + (1-m)\|[T_\lambda F](\mu=1)\|_Y = \|F\|_X, \quad F \geq 0$ in X,
(iii) The generator of $\{S(t)\}_{t\geq 0}$ is $\overline{T_K + J}$ where $D(T_K + J) = D(T_K) = L_\lambda[X]$,
(iv) $1 \notin \sigma_r(J L_\lambda)$ for some (and hence all) $\lambda > 0$,
(v) $\beta_\lambda \equiv 0$ for some (and hence all) $\lambda > 0$.

Proof: From (17) and (24) [for $n \to \infty$] we easily derive

$$\beta_\lambda(F) + \lambda \|T_\lambda F\|_X + (1-m)\|[T_\lambda F](\mu=1)\|_Y = \|F\|_X, \quad F \geq 0 \text{ in X}.$$

Since $T_\lambda F = \int_0^\infty e^{-\lambda t} S(t) F\, dt$, we may convert this equality to

$$\beta_\lambda(F) + \lambda \int_0^\infty e^{-\lambda t} \|S(t) F\|_X dt + (1-m)\lambda \int_0^\infty e^{-\lambda t} \|C(t) F\|_Y dt = \|F\|_X, \quad F \geq 0 \text{ in X}.$$

Hence, (i), (ii) and (v) are equivalent statements.

Let G be the generator of $\{S(t)\}_{t\geq 0}$. Then $D(G) = T_\lambda[X]$. Now note that

$$\lim_{n\to\infty} \|T_\lambda F - L_\lambda \hat{g}_n\|_X = 0$$

where $\{L_\lambda \hat{g}_n\}_{n=1}^\infty \subseteq X \cap X_R$, and

$$\beta_\lambda(F) = \lim_{n\to\infty} \|(JL_\lambda)^{n+1} F\|_X = \lim_{n\to\infty} \|F - (\lambda - G) L_\lambda \hat{g}_n\|_X = 0.$$

Thus if (iii) is true, then $\beta_\lambda(F) = 0$ and (v) will be true. On the other hand, if (iii) is false, then there exist $F \in X$ and $\epsilon > 0$ such that

$$\|T_\lambda F - g\|_X + \|F - (\lambda - [T_K + J]) g\|_X \geq \epsilon, \quad g \in L_\lambda[X].$$

Applying this for $g = L_\lambda \hat{g}_n$ we find

$$\left\| \sum_{k=n+1}^\infty L_\lambda (J L_\lambda)^k F \right\|_X + \|(JL_\lambda)^{n+1} F\|_X \geq \epsilon, \quad n = 0, 1, 2, \cdots.$$

Noting that the first term vanishes as $n \to \infty$, we obtain $\beta_\lambda(F) \geq \epsilon$. Thus (iii) and (v) are equivalent statements.

Now note that $\beta_\lambda(F)$ can be extended to a bounded linear functional on X. Consequently, $\beta_\lambda(F) = \int_0^\infty \int_0^1 \varphi_\lambda(\mu, v) F(\mu, v)\, d\mu\, dv$ for some $\varphi_\lambda \in L_\infty([0,1] \times \mathbb{R}^+; d\mu\, dv)$. Because $\beta_\lambda(J L_\lambda F) = \beta_\lambda(F)$, $(J L_\lambda)^* \varphi_\lambda = \varphi_\lambda$. Thus (v) is equivalent to $1 \notin \sigma_p((J L_\lambda)^*)$, which in turn is equivalent to (iv), due to the fact that $1 \notin \sigma_p(J L_\lambda)$. □

COROLLARY 4. Suppose $m = 1$. Then the following statements are equivalent:
(i) $\|S(t) F\|_X = \|F\|_X, \quad F \geq 0$ in X,
(ii) $\lambda \|T_\lambda F\|_X = \|F\|_X, \quad F \geq 0$ in X,
(iii) The generator of $\{S(t)\}_{t\geq 0}$ is $\overline{T_K + J}$ where $D(T_K + J) = D(T_K) = L_\lambda[X]$,
(iv) $1 \notin \sigma_r(J L_\lambda)$ for some (and hence all) $\lambda > 0$,
(v) $\beta_\lambda \equiv 0$ for some (and hence all) $\lambda > 0$.

Proof: As the proof of Theorem 3. □

We remark that either (28) or (29) is a sufficient condition for the conclusions of Theorem 3 and Corollary 4 to hold true.

3. THE STATIONARY PROBLEM

Before we proceed, we note that L_λ can be defined also for $\lambda = 0$, provided one considers this operator, L_0, as a positive operator mapping X into functions g for which $Rg \in X$. Then

$$\|J L_0 g\|_X = \|R L_0 g\|_X \leq \|g\|_X.$$

This means in particular that $J L_0$ is a positive contraction on X. As a result,

$$\left\| \int_0^\infty J S_0(t) g\, dt \right\|_X = \|J L_0 g\|_X \leq \|g\|_X, \quad g \geq 0 \text{ in X}.$$

By a stationary solution of Eqs. (1)-(3) we mean a function $\varphi \in X \cap X_R$ such that[3]

$$S(t)\varphi \equiv \varphi, \quad t \geq 0. \tag{30}$$

[3] The requirement $\varphi \in X_R$ is made for technical reasons. There does not seem to be an intrinsic reason to impose such a requirement.

From Eq. (30) we find for $\lambda > 0$

$$T_\lambda \varphi = \int_0^\infty e^{-\lambda t} S(t)\varphi\, dt = \frac{1}{\lambda}\varphi,$$

so that $\|R\varphi\|_X \le \|\varphi\|_X$ and Eq. (21) with $F = \varphi$ and $g = T_\lambda\varphi$ reduces to

$$(1 - L_\lambda J)\varphi = \lambda L_\lambda \varphi,$$

where $\varphi \in X_R$ is applied to be able to define $J\varphi$. Using $\|J L_\lambda \varphi\|_X = \|R L_\lambda \varphi\|_X \le \|\varphi\|_X$ as well as the property $\|\lambda L_\lambda \varphi\|_X \to 0$ as $\lambda \downarrow 0$ we get

$$(1 - L_0 J)\varphi = 0. \tag{31}$$

Conversely, suppose $\varphi \in X$, $R\varphi \in X$ and $L_0 J\varphi = \varphi$. Applying the resolvent identity we obtain

$$(1 - L_\lambda J)\varphi = (L_0 - L_\lambda) J\varphi = \lambda L_\lambda L_0 J\varphi = \lambda L_\lambda \varphi.$$

Thus $g = \frac{1}{\lambda}\varphi$ is a solution of Eq. (21) with $F = \varphi$ and hence its unique solution. Therefore $T_\lambda \varphi = \frac{1}{\lambda}\varphi$, which implies $S(t)\varphi \equiv \varphi$. Thus any such φ is a stationary solution.

We remark that the stationary solutions are exactly those vectors $\varphi \in X \cap X_R$ such that $L_0 J\varphi = \varphi$. This is equivalent to finding those vectors ψ such that $\psi \in X$, $L_0\psi \in X$ and $J L_0 \psi = \psi$. The connection between φ and ψ is then given by $\psi = J\varphi$ and $\varphi = L_0\psi$.

We easily derive the following.

THEOREM 5. Equations (1)-(3) do not have nontrivial stationary solutions, unless $m = 1$.

Proof: Suppose φ is a stationary solution. Then $S(t)|\varphi| \ge S(t)\varphi \ge 0$ and

$$\|\varphi\|_X = \||\varphi|\|_X \ge \|S(t)|\varphi|\|_X \ge \|S(t)\varphi\|_X = \|\varphi\|_X,$$

so that $|\varphi|$ is a stationary solution also. Thus we may choose $\varphi \ge 0$, so that $\psi = J\varphi \ge 0$ in X.

From the proof of Theorem 3, we have for any stationary solution $\varphi \ge 0$

$$\beta_\lambda(\varphi) + \|\varphi\|_X + \frac{1-m}{\lambda}\|\varphi(\mu{=}1)\|_Y = \|\varphi\|_X,$$

where we used $\lambda T_\lambda \varphi \equiv \varphi$. Hence, for $0 \le m < 1$ we have $\varphi(\mu{=}1) = 0$ and hence $\varphi(\mu{=}0) = 0$ and $\varphi = 0$. □

To find cases where a stationary solution exists, we consider cell growth problems where

$$r(\mu; v, v') = r(v, v'), \quad R(\mu, v) = R(v). \tag{32}$$

Then requiring $\varphi(\mu, v)$ to be μ-independent leads to the pair of equations

$$R(v)\varphi(v) = \int_0^\infty r(v, v')\varphi(v')\, dv', \tag{33}$$

$$v\varphi(v) = \int_0^\infty k(v, v') v' \varphi(v')\, dv', \tag{34}$$

where $\{\varphi, R\varphi\} \subseteq L_1(\mathbb{R}^+)$.

In the following two examples we assume that $r(v, v') = S(v)R(v')$ for $v, v' \in E$ and vanishes if one of v and v′ does not belong to E. Here E is a closed set in $\mathbb{R}^+$, S and R are nonnegative, $\|S\|_1 = 1$, R is bounded and $R(v) \ne 0$ for almost every $v \in E$. Further, we assume that $\int_E \{S(v)/R(v)\}\, dv$ is finite. Then a stationary solution which does not depend on μ must be proportional to $S(v)/R(v)$ on E and vanish outside E. If $k(v, v') = \delta(v - v')$ or $k(v, v') = \{vS(v)/R(v)\}/\int_E \{\hat{v}S(\hat{v})/R(\hat{v})\}\, d\hat{v}$, Eq. (34) holds true trivially and we have the above stationary solution.

To consider the stationary problem in general, we must solve Eq. (16) in Y and pass to the limit $m \uparrow 1$, we must find the resolvent kernel $A(v, v')$ of the integral equation

$$h(v) - \int_0^\infty k(v, v')\, \exp\Big(-\frac{1}{v'}\int_0^1 R(\hat{\mu}, v')\, d\hat{\mu}\Big) h(v')\, dv' = f(v) \tag{35}$$

in $L_1(\mathbb{R}^+)$. For $k(v, v') = \delta(v - v')$ we find

$$\Lambda(v,v') = \left(1 - exp\left(-\frac{1}{v'}\int_0^1 R(\hat\mu, v')\,d\hat\mu\right)\right)^{-1} \delta(v-v'),$$

which leads to a bounded operator on $L_1(\mathbb{R}^+)$ if and only if $\operatorname{ess\,inf}_{v>0} \frac{1}{v}\int_0^1 R(\hat\mu, v)\,d\hat\mu > 0$. On the other hand, for $k(v,v') = \kappa(v)$ with $\|\kappa\|_1 = 1$ we find

$$\Lambda(v,v') = \delta(v-v') + \frac{\kappa(v)\, exp\left(-\int_0^1 R(\hat\mu, v')\,d\hat\mu/v'\right)}{1 - \int_0^\infty \kappa(\hat v)\, exp\left(-\int_0^1 R(\hat\mu,\hat v)\,d\hat\mu/\hat v\right) d\hat v},$$

which leads to a bounded operator on $L_1(\mathbb{R}^+)$ if and only if $R(\mu, v)$ does not vanish identically.

THEOREM 6. Take $m = 1$. Suppose the following four conditions are fulfilled:

1. $r(\mu; v, v') \le m_0(\mu)\, r_0(v,v')$ where $m_0, r_0 \ge 0$ and $m_0 \in L_1(0,1)$.
2. The integral operator $\tilde J_0$ with kernel $r_0(v,v')/v'$ is weakly compact on $L_1(\mathbb{R}^+)$.
3. The integral operator $\tilde J_1$ with kernel $r_0(v,v')/v\,v'$ is bounded on $L_1(\mathbb{R}^+)$.
4. The integral operator $\tilde M_0$ with kernel $\int_0^\infty \Lambda(v,\hat v)\,k(\hat v, v')\,d\hat v$ is bounded on $L_1(\mathbb{R}^+)$.

Then the stationary problem has a solution $\varphi \in X \cap X_R$ such that $\{\varphi(0,\cdot), \varphi(1,\cdot)\} \subseteq Y$.

Proof. From Eqs. (15)-(16) and the definition of $\Lambda(v,v')$ it is clear that

$$(J\,L_0F)(\mu,v) = \int_0^\infty \int_0^1 \{\Sigma_1(\mu,v;\mu',v') + \Sigma_2(\mu,v;\mu',v')\}\, F(\mu',v')\,d\mu'\,dv',$$

where

$$\Sigma_1(\mu,v;\mu',v') = \int_0^\infty \int_0^\infty \frac{r(\mu; v, v")}{v"}\, exp\left(-\frac{1}{v"}\int_0^\mu R(\hat\mu, v")\,d\hat\mu\right) \cdot$$

$$\cdot\, \Lambda(v",\hat v)\; k(\hat v, v')\; exp\left(-\frac{1}{v'}\int_{\mu'}^1 R(\hat\mu, v')\,d\hat\mu\right) dv"\,d\hat v$$

and

$$\Sigma_2(\mu,v;\mu',v') = \frac{r(\mu; v, v')}{v'}\, H(\mu-\mu')\; exp\left(-\frac{1}{v'}\int_{\mu'}^\mu R(\hat\mu, v')\,d\hat\mu\right),$$

where $H(\cdot)$ is the unit step function. Then Σ_1 and Σ_2 satisfy

$$0 \le \Sigma_1(\mu,v;\mu',v') \le \left(\int_0^\infty \int_0^\infty \frac{r_0(v,v")}{v"}\,\Lambda(v",\hat v)\; k(\hat v, v')\,dv"\,d\hat v\right) m_0(\mu)$$

$$0 \le \Sigma_2(\mu,v;\mu',v') \le \frac{r_0(v,v')}{v'}\, m_0(\mu)\, H(\mu-\mu').$$

Now note that[4]

$$X = L_1(\mathbb{R}^+) \otimes_\pi L_1(0,1),$$

while $J\,L_0$ is dominated by

$$(\tilde J_0 \tilde M_0) \otimes (<\cdot,1>m_0) + \tilde J_0 \otimes \left(m_0(\mu)\int_0^\mu (\cdot)(\mu')\,d\mu'\right). \qquad (36)$$

As a result of assumptions 2 and 4, $\tilde J_0 \tilde M_0$ and $\tilde J_0$ are weakly compact on $L_1(\mathbb{R}^+)$. Further, the "μ-factors" in (36) are compact operators on $L_1(0,1)$. Hence, the operator in (36) is weakly compact on X. Since $J\,L_0$ is a positive operator on an L_1-space dominated by a weakly compact operator, it is weakly compact itself [15] and hence its square is compact. On the other hand, $\|(J\,L_0)^n F\|_1 = \|F\|_1$ for all $F \ge 0$ in X and $n \in \mathbb{N}$. Thus $1 \in \sigma_p(J\,L_0)$ and hence there exists $\psi \ge 0$ in X such that $J\,L_0\,\psi = \psi$.

Next, notice that

$$(L_0\,F)(\mu,v) = \tfrac{1}{v}\, exp\left(-\tfrac{1}{v}\int_0^\mu R(\hat\mu, v)\,d\hat\mu\right) h(v) + \tfrac{1}{v}\int_0^\mu exp\left(-\tfrac{1}{v}\int_{\mu'}^\mu R(\hat\mu,v)\,d\hat\mu\right) F(\mu',v)\,d\mu',$$

where $h(v) = g(0,v)$ [cf. (15)]. Thus the kernel of the integral operator $L_0J\,L_0$ is dominated by

$$\left(\int_0^\infty \int_0^\infty \frac{r_0(v,v")}{v\,v"}\,\Lambda(v",\hat v)\; k(\hat v, v')\,dv"\,d\hat v\right) m_0(\mu) + \frac{r_0(v,v')}{v\,v'}\, m_0(\mu)\, H(\mu-\mu'),$$

which makes $L_0J\,L_0$ into a bounded operator on X, as a consequence of assumptions 3 and 4. But then $L_0\psi = L_0J\,L_0\psi \in X$ and hence $\varphi = L_0\psi$ is a stationary solution. □

Conditions in order that an integral operator on an L_1-space is either weakly compact or bounded may be found in [12].

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[4] The norm of X may be viewed as the completion of the cross norm [12]

$$\|f\|_\pi = inf\{\textstyle\sum_{i=1}^n \|g_i\|_1\|h_i\|_1 : f(\mu,v) = \sum_{i=1}^n g_i(\mu)\,h_i(v),\ n \in \mathbb{N}\}.$$

4. LONG TERM BEHAVIOR OF THE DISTRIBUTION FUNCTION

Suppose φ is a nonnegative stationary solution. Then[5]

$$E_\varphi = \overline{\{h \in X: |h| \leq c\varphi \text{ for some } c \geq 0\}}$$

is a closed invariant ideal of $\{S(t)\}_{t\geq 0}$, and hence $\{T_\lambda\}_{t\geq 0}$, in X. It coincides with the subspace of all $h \in X$ supported on the support E of φ.

THEOREM 8. Suppose the following three conditions are fulfilled:

1. The generator of $\{S(t)\}_{t\geq 0}$ does not have purely imaginary eigenvalues.
2. $\{S(t)\}_{t\geq 0}$ does not have a nontrivial closed invariant ideal.[6]
3. There exists a nontrivial nonnegative stationary solution φ.

Then

$$\lim_{t\to\infty} \|S(t)g - \langle g,\gamma\rangle\|_1 = 0, \quad g \in X,$$

for a suitable $\gamma \in L_\infty(\mathbb{R}^+ \times [0,1]; dv\, d\mu)$.

Proof. The result is almost immediate from Corollary 2.7 of Part C-IV of [14]. The only thing to be established is that X_2 (in the notation of [14]) coincides with X. But this can be proven in exactly the same way as in the proof of the corresponding result of [8]. □

REMARKS. 1. Sufficient conditions for the absence of purely imaginary eigenvalues for the generator of $\{S(t)\}_{t\geq 0}$ are given in the appendix.

2. The conditions of Theorem 8 imply the uniqueness of the stationary solution, up to a multiplicative constant.

3. $\langle g,\gamma\rangle = 0$ if and only if g belongs to the closed linear span of $\mathrm{Ran}(1-S(t))$, $t > 0$; cf. [14].

If $\{S(t)\}_{t\geq 0}$ has a nontrivial closed invariant ideal $\mathfrak{J}$ in X, then $\mathfrak{J}$ is precisely the set of all $h \in X$ with support in some closed set E. Since $S(t) \geq S_0(t) \geq 0$, $\mathfrak{J}$ will be a closed invariant ideal

[5] Here we take the closure in the strong topology of X.

[6] Said otherwise, $\{S(t)\}_{t\geq 0}$ is irreducible. See [16] for the terminology.

for the semigroup $\{S_0(t)\}_{t\geq 0}$ and hence for $\{L_\lambda\}_{\lambda>0}$. But then L_0 maps $\mathfrak{J}$ into the closure of $\mathfrak{J} \cap X_R$ in X_R. As in the proof of Theorem 6, we may write $(L_0F)(\mu,v)$ as the sum of two integral operators with kernels $\tilde{\Sigma}_1$ and $\tilde{\Sigma}_2$ where

$$\tilde{\Sigma}_1(\mu,v;\mu',v') = \int_0^\infty \tfrac{1}{\hat{v}}\, exp\Big(-\tfrac{1}{\hat{v}}\int_0^\mu R(\hat{\mu},v)\,d\hat{\mu}\Big)\cdot$$

$$\cdot\, \Lambda(v,\hat{v})\; k(\hat{v},v')\; exp\Big(-\tfrac{1}{v'}\int_{\mu'}^1 R(\hat{\mu},v')\,d\hat{\mu}\Big)\, dv"\, d\hat{v}$$

and

$$\tilde{\Sigma}_2(\mu,v;\mu',v') = \tfrac{1}{\hat{v}}\, H(\mu-\mu')\; exp\Big(-\tfrac{1}{\hat{v}}\int_{\mu'}^\mu R(\hat{\mu},v)\,d\hat{\mu}\Big)\,\delta(v-v').$$

From the specific choice of $\tilde{\Sigma}_2$ it is clear that $E = E_0 \times [0,1]$ for some closed set $E_0 \subseteq \mathbb{R}^+$. Hence, if the integral operator $\tilde{M}_0$ on $L_1(\mathbb{R}^+)$ with kernel $\int_0^\infty \Lambda(v,\hat{v})k(\hat{v},v')\,d\hat{v}$ is irreducible (for instance, if its kernel is almost everywhere nonzero), then so is $\{S(t)\}_{t\geq 0}$.

APPENDIX

Let us rewrite Eqs. (26) and (27) as the Duhamel formulas

$$S(t) = S_0(t) + \int_0^t S_0(\tau)\, J\, S(t-\tau)\, d\tau, \quad t \geq 0, \tag{A.1}$$

valid if the generators of $\{S_0(t)\}_{t\geq 0}$ and $\{S(t)\}_{t\geq 0}$ have the same domain, and

$$S(t) = S_0(t) + \int_0^t S(t-\tau)\, J\, S_0(\tau)\, d\tau, \quad t \geq 0, \tag{A.2}$$

valid in general.

We have

PROPOSITION 7. Suppose either (28) or (29) holds true. Then the generator of the semigroup $\{S(t)\}_{t\geq 0}$ does not have purely imaginary eigenvalues.

Proof: Suppose $i\lambda$, $\lambda \in \mathbb{R}$, is an eigenvalue of the generator and f is a corresponding eigenfunction. Then $S(t)f = e^{i\lambda t}f$ and hence $S(t)|f| \equiv |f|$. Using (A.1) we find

$$|f| = S(t)\,|f| = S_0(t)\,|f| + \int_0^t S_0(t-\tau)\,J\,S(\tau)\,|f|\,d\tau = S_0(t)\,|f| + \int_0^t S_0(\tau)\,J\,|f|\,d\tau$$

as well as

$$f = e^{-i\lambda t}S(t)f = e^{-i\lambda t}S_0(t)f + \int_0^t e^{-i\lambda\tau}S_0(\tau)\,J\,f\,d\tau.$$

Comparing the norms we find $\|S_0(t)\,|f|\|_X = \|S_0(t)\,f\|_X$ for all $t \geq 0$ and hence $f \geq 0$ and $\lambda = 0$. □

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