"On the Existence and Positivity of a Mass Structured Cell Population Model"

Beniich, N. ; Abouzaid, B. ; Dochain, Denis

ABSTRACT

In this paper, we address the problem of the existence, the uniqueness and the positivity of a class of integro-partial differential equation describing the growth of a mass structured cell population coupled with a ordinary integro-differential equation accounting for substrate consumption. We use the semi-group theory and the fixed point theorem to achieve this objective.
On the Existence and Positivity of a Mass Structured Cell Population Model

Nadia Beniich
INMA, Département de Mathématique
Faculté des Sciences, BP 20, El Jadida, Morocco

Bouchra Abouzaid
Labsipe, Ecole Nationale des Sciences Appliquees
El Jadida, Morocco

Denis Dochain
ICTEAM, Université Catholique de Louvain
4-6 avenue Georges Lemaitre, B-1348 Louvain-La-Neuve, Belgium

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Abstract

In this paper, we address the problem of the existence, the uniqueness and the positivity of a class of integro-partial differential equation describing the growth of a mass structured cell population coupled with an ordinary integro-differential equation accounting for substrate consumption. We use the semi-group theory and the fixed point theorem to achieve this objective.

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1 Introduction

In recent years, there has been a great deal of research on modeling, control and analysis of cell population balance models. Such models describe the dynamic of cell growth and take into account the biological facts that the cell properties (e.g. mass or age) are distributed among the cell of the population. These models consist of a nonlinear partial integro-differential equation with non linear boundary condition coupled with an ordinary integro-differential equation [4, 5, 6]. In addition to the complex structure of such models, another difficulty is due to the intrinsic physiological functions, namely the growth rate function, the cell division probability density function, and the partitioning probability density function, whose selection may appear to be a complex task in many instances. For these reasons, the existing results on the analysis of such systems, including the analysis of the solution, the study of the existence, multiplicity and stability of equilibrium profile or on the control have only been obtained numerically. Mantzaris et al. [4]-[9] have presented several finite difference, spectral and finite element algorithms for solving cell population balance models. Several controllers have been proposed for this class of systems to control the different moments by using a nonlinear linearizing controller [4]. The analysis study of the existence of multiple equilibrium profiles and the stability analysis has been the object of several research. However, this analysis was performed always for the nonlinear ordinary differential equations of the first moment of cell population number and substrate concentration but not for the original mathematical model consisting of the partial and ordinary integro-differential equations.

Our primary objective in this paper is to present results about the existence, uniqueness and positivity of the solution of the original mathematical model, this analysis is primordial to the control design for cell population models. For these considerations, we discuss the existence and uniqueness of nonnegative state trajectories of such a model by using the semi-group theory and the fixed point theorem.

The paper is organized as follows: In the second section we present the basic dynamical model, and use a new formulation of the problem within the framework of the non-linear systems such as \( \dot{x}(t) = A(x)x \), where \( A(x) \) is a linear unbounded operator in a Banach space for a fixed \( x \). The sufficient conditions of existence, uniqueness and positivity of this class of systems is given in section 3. Section 4 contains our main results.

2 Mathematical model

Let us consider a cell population growing in a continuous stirred tank reactor. The cells are distinguishable from each other in terms of their mass or any
other property of the cell, which obeys the conservation law. Let \( N(m, t) \) be the number of cells which have a mass between \( m \) and \( m + dm \) at time \( t \). The cells are considered to grow with a rate \( r(m, S) \) that depends on their mass and on the concentration of the limiting substrate \( S \). We also assume that the value of the mass is standardized and that \( m \in [0, 1] \). The cell division and the birth processes of the cell population are described by the division rate \( \Gamma(m, S) \) defined as follows (see [4]):

\[
\Gamma(m, S) = \frac{f(m)}{1 - \int_0^m f(m')dm'} r(m, S) = \gamma(m) r(m, S)
\]

(1)

where \( f(m) \) is the division probability density function which is assumed to depend only on the cell mass, and is taken to be a left hand side truncated Gaussian distribution with the mean of \( \mu_f \) and standard deviation of \( \sigma_f \). The probability \( p \) that a mother cell of mass will give birth to a daughter cell of mass \( m \) is assumed to be independent of substrate concentration. This function should further satisfy the following normalization conditions:

\[
\int_0^m p(m, m')dm = 1,
\]

and should also be such that biomass is conserved at cell division, i.e.:

\[
p(m, m') = p(m' - m, m').
\]

We finally assume that the probability function is a symmetrical beta distribution with a parameter of \( q \) defined by the following equation:

\[
p(m, m') = \frac{1}{B(q, q)} \left( \frac{m}{m'} \right)^{q-1} \left( 1 - \frac{m}{m'} \right)^{q-1}
\]

(2)

We assume also that no cell death occurs and that cells grow in a batch bioreactor.

Under these assumptions, the cell population dynamics are described by the following integro-differential equations, see e.g. [4]:

\[
\frac{\partial N(m, t)}{\partial t} + \frac{\partial}{\partial m} \left[ r(m, S)N(m, t) \right] + \Gamma(m, S)N(m, t) = 2 \int_m^{+\infty} \Gamma(m', S)p(m, m')N(m', t)dm'
\]

(3)

subject to the initial condition :

\[
N(m, 0) = N_0.
\]

(4)

System (3)-(4) is completed by the following boundary conditions:

\[
N(0, t) = 0.
\]

(5)
The cell population equation (3) consists of four terms: the accumulation term, the growth term, the division term and the birth term.

The behavior of the cell population depends on the substrate concentration, the source of nutrient for its growth. The mass balance equation for the substrate expresses in particular, that the substrate consumption is proportional to the total biomass production

\[ \int_0^{+\infty} r(m, S(t))N(m, t)dm \]

with a yield coefficient \( Y \) which is the ratio of the biomass production rate over the rate of substrate consumption, assumed to be constant. The substrate concentration mass balance will be read as follows:

\[ \frac{dS(t)}{dt} = \frac{1}{Y} \int_0^{+\infty} r(m, S(t))N(m, t)dm, \]  

subject to the initial condition:

\[ S(0) = S_0, \]  

In this work, we are interested in the existence of the solution for this class of models in the case where:

\[ r(m, S) = \frac{\mu_{max}S}{K_s + S}m = r(S)m. \]  

We consider the Banach space \( H = L^1(0, \infty) \oplus \mathbb{R} \), where \( L^1(0, \infty) \) is endowed with usual norm:

\[ \|y\|_1 = \int_0^{\infty} |y(m)|dm, \text{ for all } y \in L^1(0, \infty). \]

Let \( x(t) = \begin{pmatrix} x_1(t) \\ x_2(t) \end{pmatrix} \) where \( x_1(t) \in L^1(0, \infty) \) and \( x_2(t) \in \mathbb{R} \) such that:

\[ x_1(t)(.) = N(., t) \text{ and } x_2(t) = S(t). \]

Then the evolution of \( x(t) \) is described by the following system:

\[ \dot{x}_1(t) = -r(x_2(t))m \frac{\partial x_1(t)}{\partial m} - r(x_2(t))x_1(t) + mr(x_2(t))\gamma(m)x_1(t) \]  
\[ -2r(x_2(t)) \int_m^{+\infty} m'\gamma(m')p(m, m')x_1(t)(m')dm' \]

\[ \dot{x}_2(t) = \frac{r(x_2(t))}{Y} \int_m^{+\infty} m'x_1(t)(m')dm' \]  

We can rewrite the equation (9)-(10) in the abstract form:

\[ \dot{x}(t) = A(x(t))x(t) \]  
\[ x(0) = \begin{pmatrix} N_0 \\ S_0 \end{pmatrix}. \]
Let \( D \) be defined as:
\[
D = \{ x \in L^1(0, \infty) : x \text{ absolutely continuous, } \frac{d}{dm}x \in L^1(0, \infty) \text{ and } x(0) = 0 \} \oplus \mathbb{R},
\]
(12)
The nonlinear (unbounded) operator \( A(x) \) is defined on its domain \( D \) by:
\[
A(x)x = \begin{pmatrix} A_1(x) + A_2(x) & 0 \\ A_3(x) & 0 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}
\]
(13)
where:
\[
A_1(x)x_1 = -r(x_2)m\frac{\partial x_1}{\partial m} - r(x_2)(1 + m\gamma(m))x_1
\]
(14)
\[
A_2(x)x_1 = 2r(x_2)\int_{m}^{\infty} m'\gamma(m')p(m, m')x_1(t)(m')dm'
\]
(15)
\[
A_3(x)x_1 = \frac{r(x_2)}{Y} \int_{m}^{\infty} m'x_1(m')
\]
(16)

**Remark 2.1** By this formulation and semi-group theory we are looking for the existence, uniqueness and the positivity of the solution, Contrary to the previous work where this model was solved only numerically see [7, 8, 9].

### 3 Basic concepts and results

Let \( X \) be a Banach space endowed with the norm denoted by \( \| \cdot \| \), \( u_0 \in X \) and let \( B_{u_0} := \{ u \in X, \| u - u_0 \| \leq r \} \) the closed ball centred at \( u_0 \) with radius \( r \). This section is concerned with the existence and uniqueness of global solution of the following class of non linear infinite dimensional systems:
\[
\begin{cases}
\dot{u}(t) = A(u(t))u(t) \\
u(0) = u_0
\end{cases},
\]
(17)
for all fixed \( u \in B_{u_0} \), \( A(u) \) is an unbounded linear operator defined on the subspace \( D \subset X \). Assume that \( D \) is endowed with a norm denoted by \( \| \cdot \|_{D} \).

Recall that if \( A \) is a bounded linear operator from \( D \) to \( X \), then:
\[
\| A \|_{D \rightarrow X} = \sup_{x \in X} \frac{\| Ax \|}{\| x \|_{D}}
\]

We suppose that for all \( u \in B_{u_0} \) and \( T > 0 \), the operators \( A(u) \) satisfies the following assumptions:

\( (H_1) - \) \( A(u) \) is a generator of \( C_0 \)-semigroup \( T_u(t) \) \( t \geq 0 \) on \( X \).
There exist two constants $M \geq 1$ and $w$ such that for any finite sequence $u_1, u_2, \ldots, u_k$, with $k \in \mathbb{N}$, we have:

$$\prod_{i=1}^{k} T_{u_i}(t) \leq Me^{kw} \text{ for all } t \in [0, T]$$

The operator $A(u)$ is a bounded linear operator from $D$ to $X$, i.e. there exists $M_u$ such that for all $v \in D$ $\|A(u)v\|_X \leq M_u\|v\|_D$.

There is a positive constant $L$ such that:

$$\|A(u) - A(v)\|_{D \rightarrow X} \leq L\|u - v\|_X$$

holds for every $u, v \in B_{u_0}$

The following result, which is an equivalent version of Theorem 4.3, pp.202 of [12], gives sufficient conditions for the existence and the uniqueness of the solution of system (17) on the interval $[0, T]$.

**Theorem 3.1** Assume that for all $u \in B_{u_0}$, the family of operators $A(u)$ satisfies the assumptions $(H_1)$, $(H_2)$, $(H_3)$, $(H_4)$ and $u_0 \in D$ then the system (17) has a unique solution $u \in B_{u_0}$ on the interval $[0, T]$.

**Proof**

We define firstly the set $S$, for $0 < T' \leq T$, by:

$$S = \{u | u \in C([0, T']) \text{ and } \|u - u_0\| \leq r\}.$$  \hspace{1cm} (18)

Assumptions $(H_1)$, $(H_2)$ and $(H_3)$ ensure that for all $v \in S$, the system:

$$\begin{cases}
\dot{u}(t) &= A(v(t))u(t) \\
 u(0) &= u_0,
\end{cases}$$  \hspace{1cm} (19)

has a unique solution $U_v(t)u_0$ such that $\|U_v(t)\| \leq Me^{wt}$ (see Theorem 4.2, pp.140 of [12]).

By the continuity of $U_{u_0}$, there exist a $t_1 > 0$ such that

$$\|U_{u_0}(t) - u_0\| \leq \frac{r}{2} \text{ for all } 0 \leq t \leq t_1.$$  

For $T' > 0$, we define the function $F$ in $S$ by:

$$F : S \rightarrow S$$

$$v \rightarrow F(v)(t) = U_v(t)u_0$$
and we show that the function $F$ has a fixed point in $S$ by showing that $F$ is a contraction function.

\[
\|F(u_1)(t) - F(u_2)(t)\| = \|U_{u_1}(t)u_0 - U_{u_2}(t)u_0\|
\]
\[
= \| \int_0^t \frac{d}{ds} U_{u_1}(t-s) U_{u_2}(s)u_0 \| 
\]
\[
= \| \int_0^t U_{u_1}(t-s)(A(u_1) - A(u_2)) U_{u_2}(s)u_0 \| ds 
\]
\[
\leq M \|u_0\| \int_0^t e^{w(t-s)} \|(A(u_1) - A(u_2))\|_{D \to X} ds,
\]

where $\| \cdot \|_\infty$ is the supremum norm defined in $C[0, T']$.

If $w \leq 0$, then

\[
\|F(u_1)(t) - F(u_2)(t)\| \leq MLT' \|u_0\| \|(u_1 - u_2)\|_\infty
\]

and if $w > 0$, then

\[
\|F(u_1)(t) - F(u_2)(t)\| \leq MLe^{wT'}/w \|u_0\| \|(u_1 - u_2)\|_\infty.
\]

In the both cases, there exist $t_2$ such that:

\[
\|F(u_1)(t) - F(u_2)(t)\| \leq \frac{1}{2} \|(u_1 - u_2)\|_\infty, \text{ for all } t \in [0, t_2]
\]

then for $T' = \min\{t_1, t_2\}$,

\[
\|F(u_1)(t) - u_0\| \leq \|U_{u_1}(t)u_0 - U_{u_0}(t)u_0\| + \|U_{u_0}(t)u_0 - u_0\|
\]
\[
\leq \frac{1}{2} \|(u_1 - u_0)\|_\infty + \frac{r}{2}
\]
\[
\leq r
\]

If $u_1$ and $u_2 \in S$ we have:

\[
\|F(u_1) - F(u_2)\|_\infty \leq \frac{1}{2} \|(u_1 - u_2)\|_\infty \tag{20}
\]

So that $F$ is a contraction. From the contraction mapping theorem it follows that $F$ has a unique fixed point $u \in S$ which is the desired solution on $[0, T']$ of (17).

**Remark 3.2** In the same way we can show the existence of the solution on $[T', T_1]$ for $T_1 > T'$, we conclude then the existence of the solution for all $t \geq 0$. 
The presence of integral term in the cell population model complicates the determination of the resolvent operators. In theorem 3.1, we replace the assumption on the resolvent operators in Theorem 4.3 of [12], p.202 by \((H_2)\) given in terms of the semi-groups.

If for all \(u \in B_{u_0}\), \(A(u)\) is a generator of a contraction \(C_0\)-semigroup, then assumption \((H_2)\) is satisfied.

Assume that \(X\) is a real Banach lattice endowed with a partial order which is denoted here by \(\leq\). The associated positive cone is given by \(X^+ = \{x \in X : 0 \leq x\}\) is supposed to be a closed set of \(X\) (see [11]) and for all \(x, y \in X, x \leq y\) if and only if \(y - x \in X^+\).

Recall that a linear operator \(\Lambda\) on \(X\) is said to be a positive if and only if for all \(0 \leq x, 0 \leq \Lambda x\) and a \(C_0\) semigroup \(\Lambda(t)\) is said to be a positive if \(\Lambda(t)\) is a positive operator for all \(t \geq 0\).

A necessary and sufficient condition for the positivity of a \(C_0\) semigroup \((\Lambda(t))_{t \geq 0}\) is given in the following proposition:

**Proposition 3.3 ([3])** Let \(\Lambda(t)\) be a \(C_0\) semigroup on a real Banach lattice \(X\), generated by \(A\), such that \(\Lambda(t) \leq Me^{\omega t}\) for all \(t \geq 0\); for some \(M \geq 1\) and \(\omega \in \mathbb{R}\), then: \(\Lambda(t)\) is positive if and only if the resolvent operator \(R(\lambda; A) := (\lambda I - A)^{-1}\) is a positive linear operator for all \(\lambda > \omega\).

By this proposition we obtain the following results on the positivity of the solution of (17) and the proof of Theorem 4.2, pp.140 of [12]:

**Theorem 3.4** If \(X\) is a real Banach lattice space, the operators \(A(u), u \in B_{u_0}\) satisfies the assumptions \((H_1), (H_2), (H_3)\) and \((H_4)\) and if for all \(u \in B_{u_0} \cap X^+, T_u\) is a positive \(C_0\) semi group on \(X\), then the system (11) has a unique positive solution for all positive initial condition.

4 Application to the cell population model

This section is concerned with the existence, the uniqueness and the positivity of the global solution of (3)-(6).

Let us define the linear operator:

\[
A_x(m) = -km \frac{\partial x}{\partial m}(m) - kx(m) - km\gamma(m)x(m)
\]

defined in its domain:

\[
\Delta = \{x \in L^1(0, \infty), \text{ absolutely continuous } m \frac{dx}{dm} \in L^1(0, \infty), \ x(0) = 0\}.
\]
where \( k \) is a nonzero constant.

In order to apply the result given in Theorem 3.4, we need the following lemmas.

**Lemma 4.1** The operator \( A \) defined on \( \Delta \) is generator of a \( C_0 \) semi-group in \( L^1(0, +\infty) \).

**Proof**

To show that the operator \( A \) generate a \( C_0 \) semi-group in \( L^1(0, +\infty) \), we apply the Hille-Yosida theorem [1].

- \( A \) is a closed and densely defined.

- We shall now show that \( \lambda I - A \) is invertible for all \( \lambda > k \).

  For all \( g \in L^1(0, +\infty) \), we solve the following differential equation in \( \Delta \):

  \[(\lambda I - A)x = g\]

  The solution of this equation has the following form:

  \[x(m) = \frac{1}{k} \int_0^m \frac{1}{s} g(s) \exp\left(\frac{-1}{k} \int_s^m \lambda + k + k\tau \gamma(\tau) \frac{d\tau}{\tau}\right) ds\]

  \[= \frac{1}{k} \int_0^m \frac{1}{s} g(s) \frac{s^{\frac{1}{k}}}{m} \exp\left(- \int_s^m \frac{1 + \tau \gamma(\tau)}{\tau} d\tau\right) ds\]

  We must show that \( x \in \Delta \):

  \[\int_0^\infty |x(m)| dm \leq \frac{1}{|k|} \int_0^\infty \int_0^m \frac{1}{s} |g(s)| \left(\frac{s}{m}\right)^{\frac{1}{k}} ds dm \leq \frac{1}{|k|} \left(\int_s^\infty \left(\frac{1}{m}\right)^{\frac{1}{k}} dm\right) s^{\frac{1}{k} - 1} |g(s)| ds\]

  \[\leq \frac{1}{|k|} \int_0^\infty |g(s)| ds = \frac{1}{\lambda - k} \|g\|_1\]

  We conclude then that \( x \in L^1(0, +\infty) \), \( m \frac{\partial x}{\partial m} \in L^1(0, +\infty) \) and \( x(0) = 0 \).

- We have:

  \[R(\lambda, A)g(m) = \frac{1}{k} \int_0^m \frac{1}{s} g(s) \left(\frac{s}{m}\right)^{\frac{1}{k}} \exp\left(- \int_s^m \frac{1 + \tau \gamma(\tau)}{\tau} d\tau\right) ds\]
Then:
\[ \| R(\lambda, A) \| \leq \frac{1}{\lambda - k} \text{ for all } \lambda > k \]

and for all \( n \in \mathbb{N} \), we have:
\[ \| R(\lambda, A)^n \| \leq \frac{1}{(\lambda - k)^n} \]

Then \( A \) is infinitesimal generator of \( C_0 \) semi-group \( (T(t))_{t \geq 0} \) such that \( \| T(t) \| \leq e^{kt} \) for all \( t \geq 0 \).

To discuss the positivity of the \( C_0 \) semi-group, we define respectively two partial orders in \( L^1(0, \infty) \) and \( H \):
for all \( f \) and \( g \) in \( L^1(0, \infty) \), \( f \leq g \) if and only if \( f(z) \leq g(z) \) for all \( z \in [0, +\infty) \),
and for all \( (f, a) \) and \( (g, b) \) in \( H \), \( (f, a) < (g, b) \) if and only if \( f(z) \leq g(z) \) for all \( z \in [0, +\infty) \) and \( a \leq b \).

For the first order we have the following Lemma:

Lemma 4.2 If \( k > 0 \), the \( C_0 \) semi group \( T(t) \) generated by \( A \) is positive.

Proof
From Proposition 3.3, the positivity of \( T(t) \) is equivalent to that of the resolvent operator \( R(\lambda, A) \).
For all positive \( g \) in \( L^1(0, +\infty) \), we have:
\[ R(\lambda, A)g(m) = \frac{1}{k} \int_0^m \frac{1}{s} g(s) \left( \frac{s}{m} \right)^\lambda \exp \left( - \int_s^m \frac{1 + \tau \gamma(\tau)}{\tau} d\tau \right) ds \geq 0 \]

This complete the proof of the lemma.

For \( \alpha_1 > 0 \), let us define
\[ B = \{ (x_1, x_2) \in H, x_1 \in H_1; x_2 \in \mathbb{R} \text{ such that } \| x_1 - N_0 \|_1 \leq \alpha_1, \| x_2 - S_0 \|_1 \leq \alpha_1 \}. \]

Our focus in the sequel is to prove that the family of the operators \( A(x) \), \( x \in B \cap H^+ \) satisfies the assumptions \((H_1)-(H_4)\). To do so, we have:

1) \( A(x) \) is generator of a positive \( C_0 \) semigroup \( (T_x(t))_{t \geq 0} \).

2) For all \( x \in B \), \( A(x) \) satisfies \((H_2)\).
3) For all \( x \in B \), \( A(x) \) is a bounded operator from \( D = \Delta \times \mathbb{R} \) to \( H \) with \( D \) is endowed with the following norm:

\[
\| x_1 \|_{\Delta} = \| x_1 \|_1 + \| m\gamma(m)x_1 \|_1 + \| \frac{m\partial x_1}{\partial m} \|_1
\]

and

\[
\|(x_1, x_2)\|_D = \| x_1 \|_{\Delta} + |x_2|
\]

and for all \( (a_1, a_2) \) and \( (b_1, b_2) \) in \( B \):

\[
\| A(a_1, a_2) - A(b_1, b_2) \|_D \to H \leq L(\| a_1 - b_1 \|_1 + |a_2 - b_2|) \quad (23)
\]

Recall that the operator \( A(x) \) defined as: for all \( x \in B \), the operator \( A_1(x) \) has the same structure as the operator \( A \) giving in (21), where \( k = r(x_2) \).

\[
A(x) = \begin{pmatrix}
A_1(x) + A_2(x) & 0 \\
A_3(x) & 0
\end{pmatrix}
\]

\[
= \begin{pmatrix}
A_1(x) & 0 \\
0 & 0
\end{pmatrix} + \begin{pmatrix}
A_2(x) & 0 \\
A_3(x) & 0
\end{pmatrix}
\]

**Remark 4.3** For each \( x = (x_1, x_2) \) in \( B \cap H^+ \) we have,

- \( A_2(X) \) and \( A_3(X) \) are linear bounded operators on \( H \).
- The family of the operators \( A(x) \) depend only on \( x_2 \in \mathbb{R} \).
- The function \( r(\cdot) \), the non-linear term in the operators \( A(X) \), is an upper bounded and Lipshitz function i.e, there exist two positive constants \( c_1 \) and \( c_2 \) such that for all \( (a,b) \in \mathbb{R}^2 \) we have

\[
|r(a)| \leq c_1 \\
|r(a) - r(b)| \leq c_2 |a - b| \quad (24) \quad (25)
\]

- \( \begin{pmatrix}
A_2(x) & 0 \\
A_3(x) & 0
\end{pmatrix} \) is a bounded operator in \( H \).

So, it is easy to show that if \( A_1(x) \) satisfies the properties \( (H_1)-(H_4) \) then it is the same for the operator \( A(x) \).

**Lemma 4.4** The family of the operators \( A_1(x) \) are generators of a \( C_0 \) semi-group \( (T_x(t))_{t \geq 0} \) for all \( x \in B \) and there exist \( w \) such that \( \| T_x(t) \| \leq e^{w|t|} \) for all \( T \in \mathbb{R} \) and all \( t \in [0,T] \).

If \( x \in B \cap H^+ \), \( (T_x(t))_{t \geq 0} \) is positive.
Proof
From Lemma 4.1, we deduce that the operator \( A_1(x) \) defined on \( \Delta \) by:
\[
A_1(x) = -r(x_2)m \frac{\partial x_1}{\partial m} - r(x_2)x_1 - r(x_2)m\gamma(m)x_1
\]
is generator of \( C_0 \) semi-group on \( L^1(0, \infty) \) for all \( x \in B \).
We have also for all \( x \in B \) for all \( \lambda > c_1 = \omega \):
\[
\| R(\lambda, A_1(x)) \| \leq \frac{1}{(\lambda - \omega)}
\]
Then for all \( x \in B \), \( (T_x(t))_{t \geq 0} \leq e^{wt} \) for all \( t \in [0, T] \) and for all \( T \in \mathbb{R}^+ \).
In other words, taking into account the Lemma 3.3, if \( x \in B \cap H^+ \), the \( C_0 \)-semigroup \( (T_x(t))_{t \geq 0} \) is positive.

\[ \square \]

Lemma 4.5 For all \( x \in B \), the operator \( A_1(x) \) is a bounded operator from \( D \) to \( H \) and for all \( (a_1, a_2) \) and \( (b_1, b_2) \) in \( B \cap H^+ \) there exist a positive constant \( L \) such that:
\[
\| A_1(a_1, a_2) - A_1((b_1, b_2)) \|_{D \rightarrow H} \leq L(\|a_1 - b_1\|_1 + |a_2 - b_2|)
\]
Proof
For \( (a_1, a_2) \) and \( (b_1, b_2) \) in \( B \cap H^+ \) we have:
\[
\|A_1(a_1, a_2)b\|_1 = \|r(a_2)m \frac{\partial b}{\partial m} + (r(a_2) + r(a_2)m\gamma(m))b\|_1
\]
\[
\leq c_1(\|m \frac{\partial b}{\partial m}\|_1 + \|b\|_1 + \|m\gamma(m)\|b\|_1)
\]
\[
\leq c_1\|b\|_\Delta
\]
and
\[
\|A_1(a_1, a_2)b - A_1(b_1, b_2)b\|
\]
\[
= \|(r(a_2) - r(b_2))(m \frac{\partial b}{\partial m} - 1 + m\gamma(m))b\|_1
\]
\[
\leq |(r(a_2) - r(b_2))||b||_\Delta
\]
\[
\leq c_2|a_2 - b_2||b||_\Delta
\]
This complete the proof of the lemma. \( \square \)

Theorem 4.6 For all positive initial conditions \( 0 < S_0 \) and \( N(0, m) \geq 0 \), the system (3)-(6) admits a unique solution \( (N(t), S(t)) \) in \( H \).

Remark 4.7 The existence, uniqueness and positivity of the global solution, have been shown without any condition on the model parameters.
5 Conclusion

In this paper, we have studied the existence and uniqueness of the solution of the mass structured cell population balance model. By using the semi-group theory and a fixed point theorem, it has been proved the existence of the cell numbers $N(\cdot, t)$ in $L^1(0, +\infty)$ and the substrate $S(t)$ in $\mathbb{R}^+$ for all $t > 0$. It has also been proved that $N(\cdot, t)$ and $S(t)$ remain positive for all $t > 0$ and for all $m \in [0, +\infty]$ if the initial conditions are positive. The existence, multiplicity and stability of equilibrium points of this model is under investigation.

References

[1] R.F. Curtain, H.J. Zwart, An Introduction to Infinite-Dimensional Linear Systems Theory, Springer Verlag, New York, 1995. https://doi.org/10.1007/978-1-4612-4224-6

[2] J. M. Eakman, A. G. Fredrickson and H. M. Tsuchiya, Statistics and dynamics of microbial cell populations, Chemical Engineering Progress, 62 (1966), 37–49.

[3] M. Laabissi, M.E. Achhab, J.J. Winkin, D. Dochain, Trajectory analysis of nonisothermal tubular reactor nonlinear models, Systems & Control Letters, 42 (2001), no. 3, 169–184. https://doi.org/10.1016/s0167-6911(00)00088-8

[4] N.V. Mantzaris, P. Daoutidis, Cell population balance modeling and control in continuous bioreactors, Journal of Process Control, 14 (2004), 775–784. https://doi.org/10.1016/j.jprocont.2003.12.001

[5] N.V. Mantzaris, J.J. Lio, P. Daoutidis, F. Srienc, Numerical solution of a mass structured cell population balance model in an environment of changing substrate concentration, Journal of Biootechnology, 71 (1999), 157–174. https://doi.org/10.1016/s0168-1656(99)00020-6

[6] N.V. Mantzaris, F. Srienc, P. Daoutidis, Nonlinear productivity control using a multi-staged cell population balance model, Chemical Engineering Science, 57 (2002), 1–14. https://doi.org/10.1016/s0009-2509(01)00356-6

[7] N.V. Mantzaris, P. Daoutidis, F. Srienc, Numerical solution of multi-variable cell population balance models: I. Finite difference methods, Computers and Chemical Engineering, 25 (2001), 1411–1440. https://doi.org/10.1016/s0098-1354(01)00709-8
[8] N.V. Mantzaris, P. Daoutidis, F. Srienc, Numerical solution of multi-variable cell population balance models. II. Spectral methods, *Computers and Chemical Engineering*, 25 (2001), 1441–1462. https://doi.org/10.1016/s0098-1354(01)00710-4

[9] N.V. Mantzaris, P. Daoutidis, F. Srienc, Numerical solution of multi-variable cell population balance models. III. Finite element methods, *Computers and Chemical Engineering*, 25 (2001), 1463–1481. https://doi.org/10.1016/s0098-1354(01)00711-6

[10] R.H. Martin, *Nonlinear Operators and Differential Equations in Banach Spaces*, John Wiley & Sons, New York, 1976.

[11] R. Nagel, *One-Parameter Semigroups of Positive Operators*, Lecture Notes in Mathematics, Vol. 1184, Springer, New York, 1986. https://doi.org/10.1007/bfb0074922

[12] A. Pazy, *Semigroups of Linear Operators and Applications to Partial Differential Equations*, Springer-Verlag, New York, 1983. https://doi.org/10.1007/978-1-4612-5561-1

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