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# Asymptotic Behavior in a Cell Proliferation Model with Unequal Division and Random Transition using Translation Semigroups

**Youssef El Alaoui[1] and Larbi Alaoui[2*]**

[1]Faculty of Science, University Mohamed V, Agdal, Rabat, Morocco; is.youssefelalaoui@gmail.com
[2]International University of Rabat, Sala Al-Jadida, Rabat – 11100, Morocco; larbi.alaoui.ma@gmail.com

## Abstract

**Objectives:** We provide a theoretical framework for the mathematical analysis of a cell cycle model described by a delay integral equation to get properties on the asymptotic behavior of the solutions. **Methods:** We relate the model to the class of translation semigroups of operators that are associated with a core operator $\phi$ and are solutions of equations of the type $m(t) = \phi(m_t)$. Then by using the theory developed for such class of semigroups we establish results on the existence, uniqueness, positivity, compactness and spectral properties of the solution semigroup in order to conclude the asynchronous exponential growth (AEG) property for the model. **Findings:** The framework yields an innovative analysis method for the model where only conditions on the parameters of its associated core operator are considered. It allows better control of the parameters for getting the AEG property and the derivation in an automatic way of characterizations of associated generator, spectral properties and AEG property only in terms of the core operator $\phi$. Indeed the Malthusian parameter $\lambda_0$ is characterized as the only solution of the equation $r(\widetilde{\phi}_\lambda) = 1$ where $\widetilde{\phi}_\lambda := \phi(e^{\lambda\cdot} \otimes \cdot)$, coincides with the spectral bound of the generator of the solution semigroup and is a dominant eigenvalue of this generator. **Application/ Improvements:** The provided framework will pave the way for the study of other aspects such as oscillations, bifurcation and chaos to get better insights of the dynamics of the model solutions.

**Keywords:** Asymptotic Behavior, Cell Proliferation, Translation Semigroups

## 1. Introduction

In this paper we consider a cell cycle model that is based on branching processes for its modeling and that uses a delay integral equation to describe the process of cellular proliferation[1–3]. The model reads as follows

$$n(t,y) = 2\int_0^{\tilde{\theta}}\int_0^A h(y,\xi(\tau,\sigma)\ \gamma(\tau,\sigma)n(t-\tau,\sigma)\,d\sigma\,d\tau, \quad (1)$$
$$t \geq 0, y \in (0,A)$$

where n(t, y) denotes the size density of birth rate with respect to time t and size y. In (1) it is assumed that the mass of any cell does not exceed the value A and that the time a cell can spend in the division cycle does not exceed the value $\tilde{\theta}$. Equation (1) describes the evolution of the density n(t, y) with respect to time and size. In this case $\int_{t_1}^{t_2}\int_{x_1}^{x_2} n(t,x)\,dx\,dt$ is the number of cells with sizes in $(x_1, x_2)$ born in the time interval $(t_1, t_2)$. In (1) the quantity

**Author for correspondence*

$\xi(\tau,\sigma)$ denotes the size at age $\tau$ of a cell that was born with size $\sigma$ and h(x,y) denotes the conditional density of probability for the distribution of the size at birth of daughter cells if the mother cell has mass y. So $\int_{x_1}^{x_2} h(x,y)dx$ is the probability for a daughter cell to have size in the interval $[x_1,x_2]$ knowing the mother cell had size y. As it is mentioned the derivation of the model is based on branching processes. Such processes have been widely used to describe dynamics of biological populations[4]. Equation (1) is however to be considered as a delay Volterra equation where the density n (·, ·) is expressed in terms of the history. Results on the existence of solutions of (1) and their asymptotic behavior have been given in[2] only in a direct way. In this paper we aim to provide a mathematical analysis of the model (1) within a well founded theoretical framework for it.

The framework we are proposing is based on the use of tools from the theory developed in[7-11] for the class of translation semigroups that are associated with core operators $\phi$ in the sense that they are solutions of equations of the type

$$m(t) = \phi\,(m_t) \tag{2}$$

which are considered on Banach spaces of the form $L^p((-r, 0), F)$ where $0 < r \leq \infty$, F is a Banach space and $m_t(s) := m(t + s)$. In this paper we take p = 1 since we are dealing with cells densities.

It is to be noticed that the aforementioned theory related to translation semigroups has shown to be very useful for the study of models from population dynamics that are formulated in form of integral equations or partial differential equation and for the study of delay differential equations[5–11].

The use of translation semigroups for the study of the model (1) has not been done before and the framework we are proposing based on translation semigroups allows us to derive various properties for the solutions of the considered model from those of the associated core operator. The way we proceed in this sense consists of showing that under reasonable assumptions on the parameters of the model the core operator $\phi$ associated with (1) exhibits important properties that allow us to easily show that the solutions of (1) define a strongly continuous translation semigroup of bounded linear operators which has the asynchronous exponential growth property (AEG). Results on this solution semigroup yielding its AEG property are indeed derived by simply using properties of $\phi$. To be more precise we may say that properties on $\phi$ characterize those of the solution semigroup of (1) and this fact makes it possible to only use minimal assumptions to get the AEG property.

We recall that the AEG property for a semigroup $(T(t))_{t\geq 0}$ means that there exist $\lambda_0 > 0$ and a projection P of rank one and a constant $\delta > 0$ such that $\| e^{-\lambda_0 t}\, T(t) - P \| \leq M\, e^{-\delta t}$, for t> 0. The coefficient $\lambda_0$ is the so-called Malthusian parameter. There therefore exists a vector v such that $e^{-\lambda_0 t}$ T (t) x behaves as c(x)v for t > 0 large enough and for every element x of the state space, where c(x) is a constant depending on x, and v is independent of x. For the case of the model (1) this means that the cell population asymptotically stabilizes around a fixed distribution not depending on the initial condition. The main result of our analysis is given in Theorem 3.5 which shows the AEG property for the model (1) by only using sufficient conditions on the associated core operator. Contrary to the work in[2] through the characterization of properties of the solution semigroup in terms of those of the core operator we have a better control on such conditions. In particular only eventual norm continuity of the solution semigroup is needed instead of its eventual compactness. Furthermore the proposed framework allows us to get that the Malthusian parameter is the spectral bound of the generator of the solution semigroup and to get a characterization of it in terms of $\phi$. This is made possible because of the automatic derivation of properties of the solution semigroup such as spectral ones, positivity and uniform continuity from those of the associated core operator.

Notice that the techniques used in this paper could be also adapted for models from population dynamics that are based on partial differential equations. We intend to do so in a separate paper in particular for the cell models considered in[12,13] and also for the epidemic models from[14–16].

The remainder of the paper is organized as follows. In Section 2 we give some tools from the theory developed for translation semigroups that we are using for the analysis of (1). Section 3 is devoted to the establishment of various properties leading to the AEG property for the model (1). Section 4 concludes this paper.

## 2. Translation Semigroups of Operators

As mentioned above, for the study of the model (1) we are mainly interested in setting it under a theoretical framework that is related to the class of translation semigroups

$(T_\phi(t))_{t\geq 0}$ which are solutions of evolution equations of the type (2).

We are considering this class of semigroups on the Banach space of states

$E = L^1((-r, 0), F)$

where $0 < r < \infty$ and F is a Banach space endowed with a norm $\|\cdot\|_F$.

The norm on E is given by

$$\|f\| = \int_{-r}^{0} \|f(s)\|_F ds$$

A family of bounded linear operators $(T(t))_{t\geq 0}$ on E is called a semigroup on E if it satisfies $T(0) = I$, (where I denotes the identity operator on E) and $T(t + s) = T(t)T(s)$ (Semigroup property) for $t,s \geq 0$. It is called a strongly continuous semigroup (or a $C_0$-semigroup) on the space E if it furthermore satisfies $\lim_{t\to 0+}\|T(t)x-x\|=0$, for all $x \in X$. The generator of a semigroup $(T(t))_{t\geq 0}$ on X is the operator A on E such that $Ax := \lim_{t\to 0+}(1/t)(T(t)x-x)$, for every x in its domain $D(A) := \{x \in X, \lim_{t\to 0+}(1/t)(T(t)x-x)$ exists in E$\}$.

The exponential growth bound of the semigroup $(T(t))_{t\geq 0}$ with generator A is denoted by $\omega(A)$ or also by $\omega(T(t))$ and is given by $\omega(A) := \lim_{t\to 0+}(1/t)\log\|T(t)\|$.

On the Banach space E the following result characterizes the solution semigroup of equation (2) as a translation semigroup.

**Theorem 2.1**[7]

Let $\phi: E \to F$ be Lipschitz continuous with Lipschitz constant $|\phi|$. Then the operator A such that

$A_\phi f = f', f \in D(A_\phi) := \{f \in W^{1,1}((-r,0), F), f(0) = \phi f\}$

is the generator of a $C_0$-semigroup $(T_\phi(t))_{t\geq 0}$ on E that satisfies

$$T_\phi(t)f(s) = \begin{cases} f(t+s) & \text{if } t+s<0 \quad \text{(Translation property)} \\ \phi(T_\phi(t+s)f) & \text{if } t+s\geq 0 \end{cases}$$

and we have

$$\|T_\phi(t)f - T_\phi(t)g\| \leq M e^{|\phi|t} \|f-g\|, \qquad f,g \in E$$

Furthermore the problem

$$\begin{cases} \text{Find } m \in L^1_{loc}((-r,\infty),F) \cap C(]0,\infty),F) \\ \text{such that } \begin{cases} m(t)=\phi(m_t),\ t\geq 0 \\ m_0 = f \end{cases} \end{cases}$$

has a unique solution which is given by

$$m(t) = \begin{cases} f(t) & \text{a.e. } t \in (-r,0) \\ \phi(T_\phi(t)f) & t \geq 0 \end{cases}$$

If $f \in D(A_\phi)$ then we have $m(t) = [T_\phi(t)f](0)$ for all $t\geq 0$. In the case where F is a Banach lattice and the operator $\phi$ is positive we get that $(T_\phi(t))_{t\geq 0}$ is also positive.

The class of translation semigroups associated with equations of type (2) was introduced in[17] and related properties were thoroughly investigated in the works[7-11]. In these works a nice theory related to various properties on this class of semigroups was established. Among these properties are those related to their positivity, irreducibility, compactness, asynchronous exponential growth, differentiability, existence of equilibriums and their stability. Next we give some of these results that yield to the property of asynchronous exponential growth of such semigroups and that are relevant for the analysis of the cell cycle model we are considering in this paper.

We start first of all by introducing corresponding notations.

We consider the families of operators $(\tilde{\phi}_\lambda)_{\lambda\in C}$ given by

$$\tilde{\phi}_\lambda x = \phi(e^{\lambda\cdot} \otimes x), \quad \text{for } x \in F$$

where

$$(e^{\lambda\cdot} \otimes x)(s) := e^{\lambda s}x, \quad \text{for } s \in R$$

We also need the following operators also extracted from $\phi$[7]

$\phi_0 := \phi : E_0 := E \to F;$

$\phi_1 : E_1 := L_1((-r,0),E_0) \to E_0,\ (\phi_1 f)(s) = \phi(f(s));$

$\phi_n : E_n := L^1((-nr,0),E) \to E_{n-1},\ (\phi_n f)(s) = \phi_1(f(s+\cdot)),\ n \geq 2;$

i.e., $(\phi_n f)(s)(\tau) = \phi[f(s + \tau)]$, for $s \in (-(n-1)r, 0)$, $\tau \in (-r, 0)$ and $n \geq 2$.

For each $n \geq 1$ the norm on the Banach space $E_n := L^1((-nr, 0),E)$ is given by

$$\|f\|_n = \int_{-nr}^{0} \|f(s)\|_E ds$$

**Lemma 2.2**[9]

Let $\phi \in L(E,F)$ and assume there exists $n \geq 1$ such that the following condition is satisfied

$(H_{\phi,n})$ There exists $n \geq 1$ such that $\{(\varphi_1 \circ \varphi_2 \circ \ldots \circ \varphi_n)f, f \in U_n^c\}$ is equicontinuous in $C([-r,0],F)$, [$U_n^c$ is the unit ball of $C([-r,0],E)$]

Then the semigroup $(T_\phi(t))_{t\geq 0}$ is eventually norm continuous.

The result of this lemma on the eventual norm continuity of the semigroup $(T_\phi(t))_{t\geq 0}$ will be used to show that the spectral bound of the generator $A_\phi$ is equal to its growth bound and is a simple pole of $A_\phi$ (see Lemma 2.4 below).

**Definition 2.3**[7]

The operator $\phi$ is called of compact type if for each $\lambda \in \mathbb{R}$ there exists $n \geq 1$ such that $\widetilde{\phi}_\lambda^n$ is compact (This is the case in particular if $\phi$ is compact).

**Lemma 2.4**[7,5]

Let F be a Banach lattice and $\phi \in L(E,F)$ be positive and of compact type. Assume that $\widetilde{\phi}_\lambda$ is irreducible for some $\lambda \in \mathbb{R}$. Then we have

**i)** $\Sigma(A_\phi) = \{\lambda \in C$ such that $1 \in \sigma(\widetilde{\phi}_\lambda)\}$; $\sigma(A_\phi)$ is a pure point spectrum and it holds

Dim $(\mathrm{Kernel}(\lambda I_E - A_\phi)) = \dim(\mathrm{Kernel}(I_F - \widetilde{\phi}_\lambda))$;

**ii)** $R(\widetilde{\phi}_\lambda) > 0$ and $\lambda \to r(\widetilde{\phi}_\lambda)$ is continuous, decreasing,

$r(\widetilde{\phi}_\lambda) \to 0$ as $\lambda \to \infty$, and $r(\widetilde{\phi}_\lambda) \to \infty$ as $\lambda \to -\infty$;

**iii)** If furthermore the condition $(H_{\phi,n})$ of Lemma 2.2 is satisfied then there exists a unique solution $\lambda_0$ of the equation $r(\widetilde{\phi}_\lambda) = 1$; $\lambda_0$ satisfies $\lambda_0 = s(A_\phi) = \omega(A_\phi)$; $\lambda_0$ is a simple pole and a dominant spectral eigenvalue of $A_\phi$.

We recall that a nonnegative operator (resp. semigroup $(T(t))_{t\geq 0}$) on an ordered Banach space X with dual space denoted by $X^*$ is called irreducible on X if for each positive element x of X and for each positive element $x^*$ of the dual space $X^*$ of X there exists $n \in N$ (resp. $t \geq 0$) such that $< T^n x; x^* >> 0$ (resp. $<T(t)x, x^*>> 0$). [Here an element x is called positive if it is nonnegative (i.e., $x \geq 0$) and satisfies $x \neq 0$. An operator T is called positive if it is nonnegative (i.e., $T \geq 0$ and Tx is positive for every positive element x).

Based on the previous results the following theorem gives sufficient conditions on the operator $\phi$ yielding to the AEG property of the translation semigroup $(T_\phi(t))_{t\geq 0}$.

**Theorem 2.5**[5,7]

Assume that $\phi \in L(E, F)$ is positive and of compact type and that the condition $(H_{\phi,n})$ of Lemma 2.2 is satisfied. Let $\xi$ be the projection onto the eigen space of $A_\phi$ that is associated with the unique solution $\lambda_0 = s(A_\phi) = \omega(A_\phi)$ of the equation $r(\widetilde{\phi}_\lambda) = 1$. Then $\xi$ is positive and we have

$$\| e^{-\lambda_0 t} T_\phi(t) - \xi \| \leq M e^{-\delta t}$$

for some constants $\delta > 0$, $M \geq 1$ and for all $t \geq 0$.

More precisely there exist $x_{\lambda_0}$ and $x^*_{\lambda_0}$ two positive eigenvectors respectively of $\widetilde{\phi}_{\lambda_0}$ and $\widetilde{\phi}^*_{\lambda_0}$ associated with the eigenvalue $1 = r(\widetilde{\phi}_{\lambda_0}) = r(\widetilde{\phi}^*_{\lambda_0})$ such that $< x_{\lambda_0}, x^*_{\lambda_0} >= 1$ and the projection $\xi$ is given by

$$\xi f = C(f)(e^{\lambda_0 \cdot} \otimes x_{\lambda_0})$$

where

$$C(f) = \frac{< x^*_{\lambda_0}, \phi(\theta \mapsto \int_0^\theta e^{\lambda_0(\theta - s)} f(s) ds) >}{< x^*_{\lambda_0}, \phi(\theta \mapsto \theta e^{\lambda_0 \theta} \otimes x_{\lambda_0}) >}, \qquad f \in E.$$

The proof of this theorem uses the fact that we can write $E = \mathrm{Kernel}(A_\phi - \lambda_0 I) \oplus \mathrm{Range}(A_\phi - \lambda_0 I)$ and that the growth bound of the restriction of the semigroup $(T_\phi(t))_{t\geq 0}$ to Range $(A_\phi - \lambda_0 I)$ is less than $\lambda_0$ since $\lambda_0$ is a dominant eigen value of $A_\phi$. Notice that instead of using the eventual compactness of the semigroup, its eventual norm continuity was sufficient to get the AEG property. Also the irreducibility of the semigroup was not needed.

## 3. Analysis of the Cell Cycle Model

We recall that the basic phases of the cell cycle are the G1 phase, S or synthesis phase, G2 phase and M or mitosis phase. At the M phase a cell divides into two identical cells. In equation (1) the quantity n(t,x)dtdx is equal to the number of cells with an RNA content between x and x+dx which divided in the time interval from t to t+dt. As mentioned above the model (1) was derived based on a branching process approach to describe the evolution of the density n(t,x) at the end of mitosis. It is to be considered as a refinement of an earlier cell cycle model described in[18,19] by an equation of the form

$$n(t,x) = 2\int_0^A g(x,u) n(t - \theta(x), u) du \qquad (3)$$

Contrary to (3), in (1) it is assumed that the time $\tau$ a daughter cell entering the cell cycle with birth mass x spends in the cycle is a random variable with conditional distribution density $\gamma(\tau,x)$ and its mass y when it reenters division is a function $\xi(\tau,x)$ of the time it spends in the cycle and of its birth mass x[2]. In (3) the time this cell spends in the cycle, and its mass when it reenters division are both functions of x only.

The use of translation semigroups for the mathematical analysis of the model (3) was already done in[5] and [9]In the following we are mainly interested in the mathematical analysis of the model (1) using the results on translation semigroups given in section 1.

Let us first introduce the assumptions on the model parameters that were made in[2] with the associated formulated biological interpretations.

The assumption considered on the function h is the following one

$$(H_h)\quad \left[\begin{array}{l} h\in L^1_{loc}(R^2_+), h\geq 0, \int_0^\infty h(y,x)dy=1, h(x-y,x)=h(y,x) \\ \text{support}[h(\bullet,x)]=[d_1x,d_2x],\ d_1\in\ (0,\frac{1}{2}], d_2=1-d_1 \end{array}\right]$$

This assumption expresses the fact that h(·, x) is the density of the conditional distribution of the mass of a daughter cell provided that the mass of the mother cell is x and that the mass partition to daughter cells may not exceed a maximum degree of inequality[1,2]

On the function $\gamma$ the following condition is assumed

$$(H_\gamma)\quad \left[\begin{array}{l} \gamma\in L^1_{loc}(R^2_+), \gamma\geq 0, \int_0^\infty \gamma(\tau,x)d\tau=1, \text{support}[\gamma(\cdot,\sigma)]=[\tau_1(\sigma),\tau_2(\sigma)] \\ \tau_i\in C(R_+), \tau_i>0, \tau_i \text{ is decreasing, } \tau_1<\tau_2 \text{ and } \lim_{\tau\to\infty}\tau_1(\tau)>0 \end{array}\right]$$

$(H_\gamma)$ expresses the fact that $\gamma(\cdot,y)$ is the density of the conditional distribution of the cell cycle duration given the birth mass of the cell y, that the cell cycle time varies only in certain limits and that a minimum cell cycle time is required even for cells with large birth mass[1,2]

Finally on the function $\xi$ the following condition is assumed

$$(H_\xi)\quad \left[\ \xi\in C_{loc}(R^2_+)\ \xi\geq 0, \text{and the functions } \xi(\cdot,\sigma) \text{ and } \xi(\tau,\cdot) \text{ are increasing}\ \right]$$

This assumption expresses the fact that the mass at division of the cell is larger for cells with higher birth mass and cells that stay longer in the cycle[1,2]

In addition to the conditions $(H_h)$, $(H_\gamma)$ and $(H_\xi)$ and for the establishment of the AEG property for the model (1) the following assumptions were also used in[2]

$$(H'_h)\quad \left[\ h\in L^\infty_{loc}(R^2_+)\ \right]$$

$$(H'_\gamma)\quad \left[\ \gamma\in L^\infty_{loc}(R^2_+)\ \right]$$

$$(H^*)\quad \left[\begin{array}{l} \text{There exist constants } a_1 \text{ and } a_2 \text{ such that } 0<a_1<a_2<\infty \\ \text{and for } i=1,2 \text{ the function } \xi_i: \sigma\mapsto d_i\xi(\tau_i(\sigma),\sigma) \text{ is increasing} \\ \text{on } R_+,\ \xi_i(\sigma)>\sigma \text{ for } \sigma<a_i, \xi_i(a_i)=a_i, \xi_i(\sigma)<\sigma \text{ for } \sigma>a_i \end{array}\right]$$

It is to be noticed that the analysis of model (1) is done in[2] using the space of states $X:=L^1(\Delta:=\{(s,y) : s \in (-\tau_2(y), 0), y\in I := [A_1,A_2]\})$ and using the aforementioned assumptions to prove in a direct way that the solutions of the model build a semigroup on X that is eventually compact and is irreducible on the set $X_1$ of functions in X that vanish when the y component of the variable is outside the interval $[a_1,a_2]$.

Within the mathematical analysis framework we are proposing for the model (1) we will only consider the following less restrictive assumptions

$$(\mathscr{A}_h)\quad \left[\ h\in L^\infty((0,A)^2),\ h\geq 0\ \right]$$

$$(\mathscr{A}_\gamma)\quad \left[\ \gamma\in L^\infty((0,\tilde{\theta})\times(0,A)),\ \gamma\geq 0\ \right]$$

$$(\mathscr{A}_\xi)\quad \left[\begin{array}{l} \xi \text{ is a.e. continuous on } [0,\tilde{\theta}]\times[0,A] \\ \text{and is with values in } (0,A) \end{array}\right]$$

$$(\mathscr{A}^*_\xi)\quad \left[\begin{array}{l} \text{For } 0<a<b<A \text{ the support of the function} \\ (\sigma,\tau,x)\mapsto h(x,\xi(\tau,\sigma))\gamma(\tau,\sigma) \text{ on } [(0,A)-(a,b)]\times(0,\tilde{\theta})\times(a,b) \\ \text{is with Lebesgue measure } \neq 0 \end{array}\right]$$

**Remark 3.1**

If the assumptions $(H_h)$, $(H_\gamma)$, $(H_\xi)$ and $(H^*)$ hold then the assumption $(\mathscr{A}^*_\xi)$ also holds since in this case the set $\{(x,\tau,\sigma): \sigma\in(a,b), \tau\in(\tau_1(\sigma), \tau_2(\sigma)), x\in[(0,A) - (a,b)] \cap (d_1\xi(\tau,\sigma),d_2\xi(\tau,\sigma))\}$ is with measure $\neq 0$ for $0 < a < b < A$.

As a logical space of states we consider the Banach space

$E: =L^1((-\tilde{\theta}, 0), F)$ with $F: =L^1(0, A)$

As already mentioned $\tilde{\theta}$ is the maximal possible time spent by a cell during the division cycle and A is the maximal possible mass of a cell.

Equation (1) can be written in the form of (2) with $\phi: E \to F$ given by

$$\phi(f)(x)=2\int_0^{\tilde{\theta}}\int_0^A h(x,\xi(\tau,\sigma))\gamma(\tau,\sigma)f(-\tau,\sigma)\ d\sigma\ d\tau$$

With this in mind we are now ready to give properties of the solution semigroup of the model (1) yielding to its AEG property by an application of the results of section 2 considering properties of the associated core operator $\phi$.

The operators $\widetilde{\phi}_\lambda$ associated with $\phi$ are as follows.

$$\widetilde{\phi}_\lambda f(x) = \phi(e^{\lambda \cdot} \otimes f) = \int_0^A k_\lambda(x,\sigma) f(\sigma) d\sigma, \quad f \in F,\ x \in (0,A)$$

Where

$$k_\lambda(x,\sigma) = 2\int_0^{\tilde{\theta}} e^{-\lambda\tau} h(x,\xi(\tau,\sigma))\gamma(\tau,\sigma) d\tau, \quad x,\sigma \in (0,A).$$

**Proposition 3.2**

Assume that $(\mathscr{A}_h)$, $(\mathscr{A}_\gamma)$ and $(\mathscr{A}_\xi)$ are satisfied. Then the operator $\phi$ is in L(E, F) and is of compact type.

***Proof***

First the operator $\phi$ defines a bounded linear operator from E into F since for $f \in E$ we have

$\|\phi f\|_F \leq 2A\|h\|_\infty \|\gamma\|_\infty \|f\|$. Now since the kernel $k_\lambda$ is bounded on $(0, A)^2$ we get that the operator $\widetilde{\phi}_\lambda$ is weakly compact. The weak compactness of $\widetilde{\phi}_\lambda$ and the fact that the Banach space F has the Dunford-Pettis property allow us to conclude that $\widetilde{\phi}_\lambda^2$ is compact on F. So, the operator $\phi$ is of compact type.

**Proposition 3.3**

Assume that $(\mathscr{A}_h)$, $(\mathscr{A}_\gamma)$, $(\mathscr{A}_\xi)$ and $(\mathscr{A}_\xi^*)$ are satisfied. Then for $\lambda \in \mathbb{R}$ the operator $\widetilde{\phi}_\lambda$ is positive and irreducible on F and r ( $\widetilde{\phi}_\lambda$ ) is positive and a simple pole of $\widetilde{\phi}_\lambda$ associated with an eigen function of F which is almost everywhere positive. Furthermore the results of Lemma 2.4 also hold for the core operator $\phi$ of the model.

***Proof***

For $\lambda \in \mathbb{R}$ the operator $\widetilde{\phi}_\lambda$ is given by the kernel $k_\lambda(x,\sigma)$ that by assumption$(\mathscr{A}_\xi^*)$ satisfies

$\int_S \int_{S'} k_\lambda(x,\sigma) dx d\sigma > 0$, for each subset S of [0, A] such that S and S':=[0;A]-S are both with Lebesgue measure >0. Therefore[20] $\widetilde{\phi}_\lambda$ is irreducible with spectral radius r( $\widetilde{\phi}_\lambda$ ) > 0 and r( $\widetilde{\phi}_\lambda$ ) is a simple pole of $\widetilde{\phi}_\lambda$ associated with a positive eigen function. The remaining of the proof is now a direct consequence of Lemma 2.4.

The following proposition assures that the solution semigroup of the model (1) is exactly the translation semigroup that is associated with the core operator $\phi$.

**Proposition 3.4**

Let $(\mathscr{A}_h)$, $(\mathscr{A}_\gamma)$ and $(\mathscr{A}_\xi)$ be satisfied. Then the operator $A_\phi$ on E such that $A_\phi f := f'$ with the domain $D(A_\phi) = \{f \in E$, f abs. continuous, $f' \in E$ and $f(0) = \phi f\}$ is the generator of the C0-semigroup of translation $(T_\phi(t))_{t\geq 0}$ on E that is associated with the core operator $\phi$. Furthermore $(T_\phi(t))_{t\geq 0}$ is eventually norm continuous and for $f \in E$ the solution of (1) such that $n_0 = f$ is given by

$n(t, \cdot) = (T_\phi(t)f), \quad t \geq 0.$

***Proof***

To show the eventual norm continuity of $(T_\phi(t))_{t\geq 0}$ we use Lemma 2.2 and show that the assumption $(H_{\phi,n})$ of this lemma is satisfied for n = 2. More precisely we show that $\{\phi_1 \circ \phi_2 f,\ f \in U_2^c\}$ is equicontinuous in C $([-\tilde{\theta}, 0], F)$ where $U_2^c$ is the unit ball of the space C $([-2\tilde{\theta},0],E)$.

Let $f \in U_2^c$, $x \in (0, A)$ and $\alpha,\alpha' \in [-\tilde{\theta},0]$. We have

$$\begin{aligned}
\phi_1 \circ \phi_2 f(\alpha,x) &= 2\int_0^A \int_0^{\tilde{\theta}} h(x,\xi(\tau,\sigma)\ \gamma(\tau,\sigma)\phi_2 f(\alpha\!\!( -\tau,\sigma) d\tau\, d\sigma \\
&= \int_0^A \int_0^{\tilde{\theta}} \Gamma(x,\tau,\sigma)\varphi_1[f(\alpha+\cdot)](-\tau)(\sigma) d\tau\, d\sigma \\
&= \int_0^A \int_0^{\tilde{\theta}} \Gamma(x,\tau,\sigma)\varphi[f(\alpha-\tau)](\sigma) d\tau\, d\sigma \\
&= \int_0^A \int_{\alpha-\tilde{\theta}}^{\alpha} \Gamma(x,\alpha-\tau',\sigma)\varphi[f(\tau')](\sigma) d\tau'\ d\sigma \quad (\tau' := \alpha\text{-}\tau)
\end{aligned}$$

where $\Gamma(x,\tau,\sigma) := 2h(x,\xi(\tau,\sigma))\gamma(\tau,\sigma)$.

This fact yields in an easy way that $\{\phi_1\ \phi_2 f,\ f \in U_2^c\}$ is equicontinuous in C $([-\tilde{\theta}, 0]), F)$.

With all the properties established so far we get the following result on the AEG property of the cell cycle model (1).

**Theorem 3.5**

Assume that $(\mathscr{A}_h)$, $(\mathscr{A}_\gamma)$, $(\mathscr{A}_\xi)$ and $(\mathscr{A}_\xi^*)$ are satisfied. Let $\lambda_0$ be the unique solution of the equation r( $\widetilde{\phi}_\lambda$ ) = 1 and let $\mu \in L^1(0,A)$ (resp. $\mu^* \in L^\infty(0,A)$) be a nonnegative function that is non identically 0 such that $\mu$ is an eigen function of $\widetilde{\phi}_{\lambda_0}$ (resp. of $\widetilde{\phi}_\lambda^*$ ) associated with the eigen value 1 and $<\mu,\mu^*>= 1$. Then for any $f \in E$ such that $f \geq 0$ and the support of f is nonempty, there exists a unique solution $n(\cdot,\cdot)$ of (1) such that $n_0 = f$ on $(-\tilde{\theta},0)$ and there exists a constant C(f) > 0 which only depends on f such that

$$n(t, x) = C(f) \exp(\lambda_0 t)\mu(x) + o[\exp(\lambda_0 t)], \quad t \geq 0 \tag{4}$$

***Proof***
It is a direct consequence of Propositions 3.2-3.4 and of Theorem 2.5.

**Remark 3.6**
The function $\mu$ in Theorem 3.5 is solution of the following equation

$$\mu(x)=2\int_0^A\int_0^{\tilde{\theta}} e^{-\lambda_0\tau}h(x,\xi(\tau,\sigma)\ \gamma(\tau,\sigma)\mu(\sigma)d\tau d\sigma,\quad x\in(0,A) \quad (5)$$

Also the function $\mu^*$ in Theorem 3.5 is solution of the following equation

$$\mu^*(y)=2\int_0^A\int_0^{\tilde{\theta}} e^{-\lambda_0\tau}h(x,\xi(\tau,y))\gamma(\tau,y)\mu^*(x)d\tau dx,\quad y\in(0,A) \quad (6)$$

Any other solution of (5) (resp. of (6)) is a multiple of $\mu$ (resp. of $\mu^*$).

The constant C(f) in (4) is given by

$$C(f)=\frac{<\mu^*,\phi(\theta\mapsto\int_0^\theta e^{\lambda_0(\theta-s)}f(s)ds)>}{<\mu^*,\phi(\theta\mapsto\theta e^{\lambda_0\theta}\otimes\mu)>}$$

$$=\frac{\int_0^A\int_0^{\tilde{\theta}}\int_0^A\int_0^{-\tau}\mu^*(x)e^{\lambda_0(-\tau-s)}h(x,\xi(\tau,\sigma))\gamma(\tau,\sigma)f(s,\sigma)ds\,d\sigma\,d\tau\,dx}{\int_0^A\int_0^{\tilde{\theta}}\int_0^A\mu^*(x)e^{\lambda_0\tau}h(x,\xi(\tau,\sigma))\gamma(\tau,\sigma)\mu(\sigma)d\sigma\,d\tau\,dx}$$

## 4. Conclusion

In this paper we showed that the theory developed for translation semigroups provides a strong mathematical framework for the analysis of the cell cycle model formulated by equation (1). This is a cell population model with unequal division where cells transit through the cell cycle with variability in intermitotic times. The equation of this model which relies on a branching process approach to describe the mechanisms of the evolution in cell populations is to be considered as a delay integral equation. The analysis of this model using translation semigroups theory has not been considered before and the provided framework allows a better control of key factors related to such an analysis.

The focus of the provided framework was on relating the analysis of the model to the study of properties of its associated core operator $\phi$ in order to get concise biological insights about evolution in cell populations. Under assumptions related to the core operator $\phi$ the framework allowed us to conclude that the cell population asymptotically shows an exponential growth and to give a characterization of associated Malthusian parameter in terms of $\phi$. Contrary to many analysis methods, the framework allows us therefore to better guide such analysis using minimal assumptions. No assumptions on the semigroup are made, but instead only assumption on the core operator or on the derived operators $\widetilde{\phi}_\lambda$ from $\phi$. Indeed it is the characterization of the solution semigroup in terms of the core operator $\phi$ that allowed us to dig deeply in the analysis process to find out the sufficient properties that yield such conclusion about the asymptotic behavior.

Notice that translation semigroups tools have shown to be very useful for the study of various models from population dynamics. In separate papers that are in preparation we are interested in the application of such translation semigroups tools to the mathematical analysis of dynamics of other multidimensional models from cell population and epidemiology that are based on a partial differential equations approach for the modeling of the dynamics of associated population densities.

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