ASTES

Advances in Science, Technology and Engineering Systems Journal
Vol. 5, No. 6, 01-08 (2020)
www.astesj.com
Special Issue on Multidisciplinary Innovation in Engineering Science & Technology

ASTES Journal
ISSN: 2415-6698

Qualitative Properties of a Cell Proliferating Model with Multi-phase Transition and Age Structure

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ARTICLE INFO

Article history:
Received: 30 August, 2020
Accepted: 18 October, 2020
Online: 08 November, 2020

Keywords:
Semigroup
Dual semigroup
Asynchronous exponential growth

ABSTRACT

In this paper we study a cell division cycle modeled by a system of partial differential equations with an age structure. This model translates the many regulatory mechanisms within the cell cycle where it introduces the notion of phases. The individual cell can be either in I phases where the transition between theses phases are ordered and unidirectional. The model is related to the suns and stars caluculus via the dual semigroups of operators that are considered as solution of an abstract integral equation equivalent to a Volterra type equation of the form $w(t) = \Phi(w_t)$. We will determine the core operator Φ and prove that the semigroup solution of the model possesses the asynchronous exponential property. The model permits different types of controls where the provided framework allows better control on the model parameters and yields the characterization of the intrinsic rate of natural increase through properties of the core operator Φ. Finally, we demonstrate that the asymptotic behavior of the model is governed by the simple dominant eigenvalue and its associated eigenvector, that leads to the dispersion of the cell structure through the future generations.

1 Introduction

This paper is considered as an extension of the work originally presented in 2019 International Conference of Computer Science and Renewable Energies ICCSRE [1], that represents more refined work where we investigated the long time behavior of a cell cycle model using a well founded mathematical theory.
The cell cycle is an ordered set of molecular events that a cell undergoes until it divides into two daughter cells. It has been recognized that the cell cycle can be divided into two major phase: The interphase and the mitosis phase denoted by M. The interphase is commonly composed of three phases : G_1, S, and G_2. It is the longest part of the cell cycle and is devoted to duplication of the cell's component. During the S phase, the chromosomes are duplicated. It is known that throughout the M phase, the cell split, producing two daughter cells [2]. In each phase the progression in the division cycle is reglemented by a serial of molecular regulation events which are ordered, directional and punctuated by checkpoints. These latter make use of some protein dephosphorylation and degradation where they are under control of the molecular circadian clocks. In fact, several animal experiments showed that the role of these clocks are essential to exert a rhythmic regulating control of each step [3], [4]. These steps are intracellular cascades which ensures the smooth conduct of the proliferation. The extracellular factors such growth factors play an important role in the controling strategy which ensures the environmental requirements are adapted to the proliferation of the cell. Thus, the regulation of the cell cycle is a crucial process to the survival of the cell. It is known that there exists two key classes of regulatory molecules: cyclins (regulatory subunits) and cyclin dependent kinases (catalytic subunits) denoted by CDKs where through phosphorylation activates or inactivates target proteins to permit entry in the next phase of the cell cycle.

Through the cell cycle, there exists different restriction points. The first one is called start checkpoint. It regulates the progression in the G1 phase. The transition from G_1 to S is regulated by CDK4/cyclin D and CDK6/cyclin D where CDK is expressed in cells and cyclin D is synthesized due to the growth factors. Various cyclins are produced at each phase: S, G_2 and M, resulting in the periodic formation of distinct combinations of cyclin-CDK complexes that trigger the cell cycle events [2, 5].

These various mechanisms of regulation are showed to be inefficient in cancer cells. In addition, the disruption of circadian clocks is showed to enhance the tumour growth [6]–[8]. In fact, the circadian rhythms play an important role in the cell cycle control where they contribute to the cell cycle regulation by the synchronisation of the

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control system. However, these dynamics have still to be understood and investigated. Further, various speculation tried to explain this phenomenon which give rise to the concept of synchronisation, that is, to the speculation that less synchronised phases are within cell population, the faster is proliferation. It is known that circadian proteins control CDKs and theses latter control phase transitions. In the following, we want to investigate the question if circadian clocks control the proliferation of the cell population.

The paper is concerned with a system of partial differential equations (PDE) describing the case of a multi transition phases cycle [9] in which cells can transit from one phase to the next one. The cell cycle is assumed to be divided into I different phases where the individual cell can be distinguished from one another according to their age a. These cells can growth, die and transit to the next phase where the rates describing the associated physiological process depend only on the cell's age. Then, the model read as follows (see figure 1)

$$\begin{aligned} &\frac{\partial}{\partial t}p_i(t,a)+\frac{\partial}{\partial a}p_i(t,a)=-\mu_i(a)p_i(t,a)-\mathcal{K}_{i\to i+1}(a)p_i(t,a)\\ &p_i(t,0)=\int_0^\infty \mathcal{K}_{i-1\to i}(a)p_{i-1}(t,a)da \quad \text{for } 2\le i\le I \\ &p_1(t,0)=2\int_0^\infty \mathcal{K}_{I\to 1}(a)p_I(t,a)da \end{aligned} \tag{1}$$

Here $p_i(t,a)$ is the density of the population of cells at the i^{th} phase of age a at the instant t, that is, $\int_{a_1}^{a_2} p_i(t,a)da$ is the number of cells at the i^{th} phase with an age in the interval (a_1,a_2) at the instant t. The transition from the state i to the state j is given by the rate $\mathcal{K}_{i\to j}(a)$, that is $\mathcal{K}_{i\to j}(a)dt$ is the probability that a cell having an age a at instant t in the phase i transit in the time interval $(t,t+dt)$ to the phase j, in which they start with age 0, the last phase when $i=I$ refer to mitosis as it is expressed by the boundary conditions in (1). At the i^{th} state, the cells go to apoptosis at the rate $\mu_i(a)$, that is $\mu_i(a)dt$ is the probability that a cell having age a at instant t die in the time interval $(t,t+dt)$ in the phase i. Since the effective separation of the mother cell into two daughter cells, that is, since the cell birth, the individual cell can quantitated by a continuous variable corresponding to cell age.

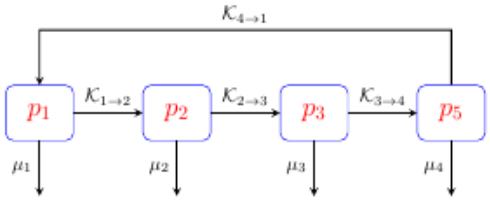

Figure 1: Flow chart of the model describing the evolution of cells along each phase of the cycle and the transition to the next phase between the cell densities. Here I=4, this corresponds to G1-S-G2-M.

It is known that cells transit through the cell cycle with variability in intermitotic times which correspond to different biological processes such the proteic (G_1 phase) or DNA (S phase) or microtuble (M phase) synthesis . As contrary to the model given in [9], the progression speed is assumed to be constant, that is one does not take into account the external growth factors. Indeed, the progression speed can be enhanced by the external growth factors in the early of the G_1 phase.

The authors in [9]–[16] considered a partial differential equations modeling a proliferating cell population with taking into consideration their external controls which can be hormonal, circadian, pharmacological . . . that leads to investigate the consequences of a periodic control on these models. Their results assert that the effect of circadian control on tumour proliferation is indirect.

Here, the death rates are supposed only age dependent. However, the case time-periodic death rates studied in [10, 11], using the Floquet theory, had shown a higher first eigenvalue and thus enhanced proliferation of the population.

For the one phase cell transition model [16, 17], it has been proved that if we influence the cell cycle with some control of a periodic function, we obtain that cells with cell cycle duration slightly lower than the control function period are selectively more advantageous, in addition, they hypothetize that the effect of disruption of circadian rhythms on tumour growth enhancement is indirect. The model for I phases was first introduced in [9], where the authors studied the long time behaviour of this model with the effect of a circadian control using an entropy method. Their results show that it imposes a circadian rythm to the cell cycle.

Mathematical cell cycle models have been treated since the 1960s by authors such as Fredrickson, Bell, Sinko and Streifer. These models were traditionally formulated as partial differential equations for the age and/or size distribution of the cell population. Diekmann et al. [18] used semigroup methods to give conditions for when there is, and also when there is not, asynchronous exponential growth of the population in a constant environment. More recently, Diekmann and coworkers have argued in favour of using (abstract) integral equations for the birth rate instead of PDE, also, and in particular, for the nonlinear models resulting from interaction via the environment.

The purpose of this paper is to create a mathematical framework for the analysis of this type of models by using the theoretically well established semigroup method based on the suns and stars calulcus using the perturbed dual semigroups of operators on the spaces of the form $\mathcal{E}:=L^1((-h,0),\mathcal{F})$. These semigroups are solutions of the integral equation [19]–[21] of the type :

$$p(t)=P_0(t)f+\int_0^t P_0^{\odot *}(t-\tau)\Phi(p(\tau))d\tau, \quad \text{for } t\ge 0 \tag{2}$$

where $h>0$, $\mathcal{F}$ is a Banach space and $\Phi:\mathcal{E}\to\mathcal{Z}$ and $\mathcal{Z}$ is some bigger Banach space. It has been proved that this method is well suited for applications, in particular in the field of cell biology models [22, 23].

In the following, the main result is to provide necessary and sufficient conditions on the parameters building the cell division cycle model (1) in order to yield the property of asynchronous exponential growth.The asynchronous exponential property is explained mathematically by the fact that a simple dominant eigenvalue govern the spectrum of the infinitesimal generator of the semigroup solution of the model. In the context of the semigroup theory, this operator will be the associated infinitesimal generator. We can say that the asynchronous exponential growth occurs when the following estimate $\|e^{-\lambda_0 t}p(t,\cdot)-\mathcal{P}p_0\|$ decreases to 0 exponentially as t tends to infinity, where the vector population is defined by $p(t,a)=(p_i(t,a))_{1\le i\le I}^{tr}$ and $p_0(a)$ is the initial given distribution of the population. This latter

means that when the cell population is multiplied by an exponential factor, know an asymptotic stabilization around a unidimensional projection. It is noted that this projection is only dependent on the initial structure of the concerned population.
We will use the theory developed in the works [19]–[21] to exhibit the link between the solutions of the model and the perturbed dual semigroups. First, we determine the operator Φ. Secondly, we derive different results, only based on the properties of the operator Φ ranging from existence to qualitative properties and particulary give a characterization of the Malthusian parameter as a spectral radius of some bounded operator.
Throughout this paper, the two parameters $\mathcal{K}_{i\to j}(a)$ and $\mu_i(a)$ are supposed to satisfy the assumption

$\left(\mathbf{H}_{\mathcal{K},\mu}\right)$: (1) The rates $\mathcal{K}_{i\to j}, \mu_i$ defined from $(0,\bar{a})$ to $\mathbb{R}$ are continuous.
(2) $\mathcal{K}, \mu \in L^\infty((0,\bar{a}),\mathbb{R})$ such that there exists $0 < \bar{\mathcal{K}} < \infty$ where $0 < \mathcal{K}_{i\to j}(a) \le \bar{\mathcal{K}}$ and$\mathcal{K} \not\equiv 0$ in addition there exists $\bar{\mu} > 0$ such that $0 \le \mu_i \le \bar{\mu}$

2 Well posedness

In this section, the mathematical analysis of the multi phases proliferating cell cycle model will be provided using the theory developed for the perturbed dual semigroups [24]–[27] associated to the equation of Volterra type :

$$p(t) = \phi(p_t) \tag{3}$$

where the Hale notation $p_t(s) := p(t+s)$ is used (see [28]–[35]), and the operator $\phi : \mathcal{E} := L^1((-h,0),\mathcal{F}) \to \mathcal{F}$. Our construction will permit to link the solutions of the model (1) to the solutions of the integral equation

$$p(t) = P_0(t)f + j^{-1}\left(\int_0^t P_0^{\odot *}(t-s)\Phi(p(s))ds\right) \tag{4}$$

where P_0 satisfies the properties of a semigroup of bounded linear operators on $\mathcal{E}$ with $\mathcal{E}^\odot \subset \mathcal{E}^*(\subset$ stands as the linear subspace) on which P_0^* yields the strong continuity, that is,

$$\mathcal{E}^\odot = \{f^* \in \mathcal{E}^* : \lim_{t\downarrow 0}\|P^*(t)f^* - f^*\| = 0\}$$

It can be shown that this subspace is closed in the norm topology of $\mathcal{E}^*$ and weak* dense subspace on $\mathcal{E}^*$ [24]. In addition, the semigroup on $\mathcal{E}^\odot$ is denoted by $P_0^\odot := P_0^*|_{\mathcal{E}^\odot}$. It is obvious that this restriction build a semigroup that is strongly continuous on the subspace $\mathcal{E}^\odot$. Since we consider an element of $\mathcal{E}$ as a bounded linear functional on $\mathcal{E}^\odot$. We can embed $\mathcal{E}$ into $\mathcal{E}^{\odot *}$ via the map q of $\mathcal{E}$ into $\mathcal{E}^{\odot *}$ defined by :

$$< f^\odot, qf >=< f, f^\odot >, \qquad \text{for } f \in \mathcal{E}, f^\odot \in \mathcal{E}^\odot$$

It is obvious that $q(\mathcal{E}) \subset \mathcal{E}^{\odot\odot}$. When $q(\mathcal{E}) = \mathcal{E}^{\odot\odot}$ then $\mathcal{E}$ is said to be $\odot$-reflexive with respect to $P(t)$.

Go back to the study of the model (1). The state space considered is $\mathcal{E} := L^1([0,\tilde{a}],\mathbb{R}^I)$. The parameter $\tilde{a} > 0$ is the maximal age that an individual cell can attain. This space is endowed with norm

$$\|f\|_{\mathcal{E}} = \int_0^{\tilde{a}} \|f(a)\|_{\mathbb{R}^I} da, \qquad f \in \mathcal{E}$$

Next, we introduce the operator $\chi(a)$ that yields the equation

$$\begin{aligned} \chi'(a) &= -\chi(a)\mathcal{M}(a) \\ \chi(0) &= Id(\text{ stands for identity}) \end{aligned} \tag{5}$$

with

$$\mathcal{M}(a) = \mathrm{Dg}\,(m_{i,i}(a))_i \qquad 1 \le i \le I \tag{6}$$

where Dg stands for the diagonal matrix and the entries of the matrix $\mathcal{M}$ hold

$$m_{i,j}(a) := \begin{cases} \mu_i(a) + \psi_{i\to i+1}(a) & \text{if } i = j \\ 0 & \text{else} \end{cases} \tag{7}$$

The aim of the introduction of this transformation is to demonstrate that $\{P(t)\}_{t\ge 0}$ the semigroup solution of the model (1) is equivalent to $(P_\phi(t))_{t\ge 0}$ the semigroup solution of (4). Thus, via this machinery and under the properties of the operator ϕ, we will establish the asynchronous exponential property only by handling with the equivalent semigroup and go back to the original one by using the cited transformation.
Before going to give the main results, we need some settings. First, let set $p(t,a) := (p_i(t,a))_{1\le i\le I}^{tr}$. So via this vector, our initial model (1) can be reformulated as an vector type Mckendrick Von Foerster model

$$\frac{\partial}{\partial t}p(t,a) + \frac{\partial}{\partial a}p(t,a) = -\mathcal{M}(a)p(t,a) \tag{8}$$

with the boundary condition at age 0

$$p(t,0) = \int_0^{\tilde{a}} \mathcal{B}(a)p(t,a)da \tag{9}$$

The matrix $\mathcal{M}$ is given above by (6) and (7) and the matrix $\mathcal{B}$ is given by

$$B(a) = \begin{pmatrix} 0 & 0 & 0 & \cdots & 0 & 2K_{I\to 1} \\ K_{1\to 2} & 0 & 0 & \cdots & 0 & 0 \\ 0 & K_{2\to 3} & 0 & \cdots & 0 & 0 \\ \vdots & 0 & \ddots & \ddots & \vdots & \vdots \\ \vdots & & \ddots & \ddots & 0 & \vdots \\ 0 & \cdots & \cdots & 0 & K_{I-1\to I} & 0 \end{pmatrix}$$

After we gave a compact form to the original model (1). Now, we consider the transformation

$$m(t,.) := \Gamma p(t,.) \tag{10}$$

where $(\Gamma g)(a) := \chi(a)g(a)$ with $a \in (0,\bar{a})$ and the operator χ satisfies the first order differential equation (5). Via this latter, we arrive at the equivalent system where it is more easily to handle than the original one (8). The model is formulated as given

$$\begin{aligned} \frac{\partial}{\partial t}m(t,a) + \frac{\partial}{\partial a}m(t,a) &= 0 \\ m(t,0) &= \int_0^{\tilde{a}} \theta(a)m(t,a)da \end{aligned} \tag{11}$$

The kernel θ is given by

$$\theta(a) = \mathcal{B}(a)\chi^{-1}(a), \quad \text{for } a \in (0,\tilde{a}) \tag{12}$$

The diagonal matrix χ^{-1} is given by

$$\chi^{-1}(a) = \mathrm{Dg}\left(\tilde{z}_{i,i}(a)\right)$$
$$\tilde{z}_{i,j} := \begin{cases} e^{-\int_0^a m_{i,i}(\tau)d\tau} & \text{if } i = j \\ 0 & \text{else} \end{cases} \tag{13}$$

Definition 2.1 *The strongly continuous semigroup $\{P(t)\}$ is said to be a translation semigroup on $L^1((-r,0),\mathcal{F})$ with $r > 0$ and $\mathcal{F}$ is a Banach space if the following $(P(t)f)(x) = f(x+t)$ is satisfied when $x + t < 0$.*

Diekmann et al. have demonstrated in [20] that the space $\mathcal{E}$ is $\odot$-reflexive with respect to P_0, where the operator P_0 is defined as the translation semigroup to the right and 0 on $\mathbb{R}^+$. Its generator $\mathcal{A}_0$ is given by

$$\mathcal{D}(\mathcal{A}_0) = \{f \in \mathcal{E} : f \in AC \text{ and } f(0) = 0\}$$
$$\mathcal{A}_0 f = -f'$$

where AC stands for the absolutely continuous space. We have the following identification (see [19] and [20])

$$L^1([0,\bar{a}],\mathbb{R}^I)^{\odot} \to C_0((-\tilde{a},0],\mathbb{R}^I)$$
$$L^1([0,\bar{a}],\mathbb{R}^I)^{\odot *} \to \mathrm{NBV}([0,\tilde{a});\mathbb{R}^I)$$

The semigroup $P_0^{\odot *}$ is the translation to the right and 0 on $\mathbb{R}^+$. Its generator $\mathcal{A}_0^{\odot *}$ is given by

$$\mathcal{D}(\mathcal{A}_0^{\odot *}) = \{f^{\odot *} \in \mathcal{E}^{\odot *} : f^{\odot *}(a) = \int_0^a g(s)ds \text{ and } g \in \mathcal{E}^{\odot *}\}$$
$$\mathcal{A}_0^{\odot *} f^{\odot *} = -f^{\odot *} = g$$

Using integration and the natural embedding q from $\mathcal{E}$ into $\mathcal{E}^{\odot *}$ and taking into account the boundary condition, we arrive at

$$m(t) = P_0(t)g + q^{-1}\int_0^t P_0^{\odot *}(t-s)\Phi(m(s))ds \tag{14}$$

where the core operator Φ defined from $\mathcal{E}$ to $\mathcal{E}^{\odot *}$ is given as a perturbation with finite dimensional range

$$\Phi(g) = \phi_1(g)\mathcal{H}_1 + \phi_2(g)\mathcal{H}_2 + \ldots + \phi_I(g)\mathcal{H}_I \tag{15}$$

The Heaviside function $\mathcal{H}_i$ is given by $\mathcal{H}_i(a) = e_i$ if $a \in (0,\tilde{a})$ else $\mathcal{H}_i(a) = 0$ where $\{e_1, e_2, \ldots, e_I\}$ is the canonical basis of $\mathbb{R}^I$. The canonical injection q is defined by $(qx)(a) = \int_0^a x(s)ds,\ s \in [0,\tilde{a})$ where the inverse is clearly differentiation.
The operator given in (11) is defined from $\mathcal{E}$ to $\mathbb{R}^I$ and it is given by the integral formula

$$\Phi g = \int_0^{\tilde{a}} \theta(s)g(s)ds \tag{16}$$

the kernel θ is given by (12). In the following, we adopt the following Hale notation

$$m_t(a) := m(t-a), \quad \text{for all } a \in [0,\tilde{a}]$$

with

$$m_0(a) = g(a) \qquad a \in [0,\tilde{a}] \tag{17}$$

In fact, the solutions of the formulation given by the integral equation (14) is proven to be equivalent to the solutions of the renewal equation [20]

$$\begin{aligned} m(t) &= \Phi(m_t), \quad \text{for } t > 0 \\ m_0(a) &= g(a), \quad a \in [0,\tilde{a}] \end{aligned} \tag{18}$$

where the latter generates a translation semigroup [28] given by

$$\mathcal{T}_\Phi g(a) = \begin{cases} g(a-t) & \text{if } a - t > 0 \\ \Phi(\mathcal{T}_\Phi(t-a)g) & \text{if } a - t \le 0 \end{cases}$$

The following result gives us the existence and uniqueness of the perturbed semigroup solution of the abstract integral equation (14)

Theorem 2.2 *Since the assumption $(\mathbf{H}_{\mathcal{K},\mu})$ holds. We obtain that $\phi \in \mathcal{L}(\mathcal{E},\mathcal{F})$. Then for the initial data $g \in \mathcal{E}$, the equation (14) has unique solution $m(t)$ on $[0,T)$ for some positive real number T where the operator $\mathcal{A}_\phi$ characterized as the following*

$$\begin{aligned} \mathcal{D}(\mathcal{A}_\phi) &= \{\varphi \in W^{1,1}((0,\bar{a}),\mathbb{R}^I), \varphi(0) = \phi\varphi\} \\ \mathcal{A}_\phi\varphi &= -\varphi', \qquad \varphi \in \mathcal{D}(\mathcal{A}_\phi) \end{aligned} \tag{19}$$

is the inifinitesimal generator of the semigroup P_ϕ on $\mathcal{E}$.

Proof. The hypothesis given by $(\mathbf{H}_{\mathcal{K},\mu})$ allows to us to obtain the first assertion about the boundedness of ϕ. Then, by using regular arguments on contraction mapping theory, we obtain the existence of the perturbed semigroup $(P_\phi(t))_{t\ge 0}$ solution of (14) on $\mathcal{E}$. □

3 Compactness and irreducibility

It is known that the eventual compactness result is often used to determine the asymptotic behavior of semigroups. In fact, it implies that the growth bound of the semigroup denoted by $\omega(T(t))$ equals the spectral bound denoted by $s(A)$, where

$$\omega(T) = \inf\{w : \|T(t)\| \le Me^{wt}, M \ge 0\}$$

and

$$s(A) = \begin{cases} \sup\{\Re e\lambda : \lambda \in \sigma(A)\} & \text{if } \sigma(A) \ne \emptyset \\ -\infty & \text{if } \sigma(A) = \emptyset \end{cases}$$

Definition 3.1 *We say that the semigroup $\{P(t)\}_{t\ge 0}$ is eventually compact if for some $t_0 \ge 0$ the operators $P(t)$ are compact for all $t \ge t_0$.*

We will give a criterion to obtain the compactness of the semigroup.

Lemma 3.2 *Since $\Phi \in \mathcal{L}(\mathcal{X},\mathbb{R}^I)$ is with finite Range. The semigroup $\{P(t)\}_{t\ge 0}$ given by (14) is eventually compact.*

Proof. The core operator Φ is spanned by the linearly independent set $\{\mathcal{H}_i\}_{1\le i\le I}$ in $\mathcal{X}^{\odot *}$, that is, Φ is with Range$(\Phi) < \infty$, where the core operator Φ takes the form given by (15). We know that there exists $\Phi_i^* \in L^\infty([-\tilde{a},0],\mathbb{R}^I)$ such that :

$$\Phi_i(\zeta) = \int_0^{\tilde{a}} < \zeta(a), \Phi_i^*(-a) > da, \qquad \forall \zeta \in \mathcal{X}$$

We conclude that :

$$\Phi(\zeta) = \sum_{i=1}^{n} \int_0^{\tilde{a}} < \zeta(a), \Phi_i^*(-a) > \mathcal{H}_i da, \qquad \forall \zeta \in \mathcal{X}$$

Let $t > 2\tilde{a}$, we have $\forall \tau, \tau' \in [0, \tilde{a}],\ \tau' < \tau$ for all f in the unit ball of $\mathcal{X}$. Then,

$$\begin{aligned}
&\|[P(t)\zeta](\tau) - [P(t)\zeta](\tau')\|_{\mathbb{R}^n} \\
&= \|q^{-1} \int_0^t P_0^{\odot *}(t-s) \left\{ (\Phi(P(s)\zeta)ds)(\tau) - (\Phi(P(s)\zeta)ds)(\tau') \right\} \|_{\mathbb{R}^n} \\
&= \|q^{-1} \left(- \int_{t-\max\{t,\tau\}}^{t} \Phi(P(s)\zeta)ds + \int_{t-\max\{t,\tau'\}}^{t} \Phi(P(s)\zeta)ds \right) \|_{\mathbb{R}^n} \\
&= \|q^{-1} \left(\int_{t-\max\{t,\tau'\}}^{t-\max\{t,\tau\}} \Phi(P(s)\zeta)ds \right) \|_{\mathbb{R}^n} \\
&= \|q^{-1} \left(\sum_{i=1}^{n} \int_0^{\tilde{a}} \int_{t-\max\{t,\tau'\}}^{t-\max\{t,\tau\}} < P(s)\zeta(a), \Phi_i^*(-a) > \mathcal{H}_i ds\, da \right) \|_{\mathbb{R}^n} \\
&= \|q^{-1} \left(\sum_{i=1}^{n} \int_0^{\tilde{a}} \int_{t-\max\{t,a+\tau'\}}^{t-\max\{t,a+\tau\}} < \Phi(P(s)\zeta), \Phi_i^*(-a) > \mathcal{H}_i ds\, da \right) \|_{\mathbb{R}^n}
\end{aligned}$$

Let $\alpha_1 = t - \tau$ and $\alpha_2 = t - \tau'$

$$\begin{aligned}
&\|[P(t)\zeta](\tau) - [P(t)\zeta](\tau')\|_{\mathbb{R}^n} \\
&= \|q^{-1} \left(\sum_{i=1}^{n} \int_{\alpha_1}^{\tilde{a}+\alpha_1} \int_0^a < \Phi(P(s)\zeta), \Phi_i^*(\alpha_1 - a) > \mathcal{H}_i ds\, da \right. \\
&\left. - \sum_{i=1}^{n} \int_{\alpha_2}^{\tilde{a}+\alpha_2} \int_0^a < \Phi(P(s)\zeta), \Phi_i^*(\alpha_2 - a) > \mathcal{H}_i ds\, da \right) \|_{\mathbb{R}^n} \\
&= \|q^{-1} \left(\sum_{i,j=1}^{n} \int_{\alpha_1}^{\tilde{a}+\alpha_1} \int_0^a < \Phi_j(P(s)\zeta)\mathcal{H}_j, \Phi_i^*(\alpha_1 - a) > \mathcal{H}_i ds\, da \right. \\
&\left. - \sum_{i,j=1}^{n} \int_{\alpha_2}^{\tilde{a}+\alpha_2} \int_0^a < \Phi_j(P(s)\zeta)\mathcal{H}_j, \Phi_i^*(\alpha_2 - a) > \mathcal{H}_i ds\, da \right) \|_{\mathbb{R}^n} \\
&= \|q^{-1} \left(\sum_{i,j=1}^{n} \int_0^a \left\{ \int_{\alpha_2}^{\tilde{a}+\alpha_2} < \Phi_j(P(s)\zeta)\mathcal{H}_j, \Phi_i^*(\alpha_1 - a) - \Phi_i^*(\alpha_2 - a) > \right. \right. \\
&\mathcal{H}_i da + \int_{\alpha_1}^{\alpha_2} < \Phi_j(P(s)\zeta)\mathcal{H}_j, \Phi_i^*(\alpha_2 - a) > \mathcal{H}_i da \\
&\left. \left. + \int_{\tilde{a}+\alpha_1}^{\tilde{a}+\alpha_2} < \Phi_j(P(s)\zeta)\mathcal{H}_j, \Phi_i^*(\alpha_2 - a) > \mathcal{H}_i da \right\} ds \right) \|_{\mathbb{R}^n} \\
&\leq \sup_{1 \leq i,j \leq n} \|\mathcal{H}_i\| \|\mathcal{H}_j\| \sum_{i,j=1}^{n} \left(\sup_{0 \leq s \leq 2\tilde{a}} |\Phi_j(P(s))\zeta)| \times \right. \\
&\left\{ \int_{\alpha_2}^{\alpha_2+\tilde{a}} |\Phi_j^*(\alpha_1 - a) - \Phi_j^*(\alpha_2 - a)| da + \int_{\alpha_1}^{\alpha_2} |\Phi_i^*(\alpha_2 - a)| da \right. \\
&\left. \left. + \int_{\tilde{a}+\alpha_1}^{\tilde{a}+\alpha_2} |\Phi_i^*(\alpha_2 - a)| da \right\} \right)
\end{aligned}$$

Hence, we obtain that $\{P(t)\zeta\}_{t\geq 0}$ is equicontinuous since $|\alpha_2 - \alpha_1|$ tends to zero uniformly for ζ in the unit ball of $C([0, \tilde{a}], \mathbb{R}^n)$. The rest of the proof is due to applying a famous result of Arzela-Ascoli, we obtain then that $\{P(t)\}_{t\geq 0}$ is eventually compact. □

Proposition 3.3 *Let assume that* $(\mathbf{H}_{\mathcal{K},\mu})$ *is satisfied. Then the strongly continuous semigroup P and* $\mathcal{T}_\Phi$ *are eventually compact.*

Proof. The core operator Φ given by the formula (15) is a perturbation of finite rank. Then by using the following result [35, Proposition 4], we obtain the eventual compactness of the semigroup solution $\{T_\Phi(t)\}_{t\geq 0}$. The perturbed semigroup $\{W(t)\}_{t\geq 0}$ is eventually compact by applying the result in Lemma3.2. □
In the follwing we define the family $(\tilde{\Psi}_\lambda)_{\lambda\in\mathbb{C}}$ of operators such that their entries are defined by

$$\tilde{\Psi}_{\lambda,i,j} := < \nabla_{\lambda,j}, \nabla_i^* >, \quad \lambda \in \rho(\mathcal{A}_0) \tag{20}$$

with

$$\nabla_{\lambda,i} = q^{-1} R(\lambda, \mathcal{A}_0^{\odot *}) \nabla_i^{\odot *}, \quad \lambda \in \rho(\mathcal{A}_0)$$
$$\{\nabla_i^{\odot *}\}_{1\leq i\leq I} \text{ is a linearly independent set in } \mathcal{X}^{\odot *}$$

If we adopt this formulation to the integral equation given by (14) such that

$$\begin{aligned}
\nabla_i^{\odot *} &= \mathcal{H}_i \\
\nabla_{\lambda,j} &= \left(q^{-1} R(\lambda, \mathcal{A}_0^{\odot *}) \mathcal{H}_j \right)(s) = e^{\lambda s} e_j \\
\nabla_i^* &= \Theta_{i,j}
\end{aligned}$$

where Θ is given by

$$\begin{pmatrix}
0 & 0 & \cdots & 0 & 2\psi_{I\to 1}\bar{z}_{I,I} \\
\psi_{1\to 2}\bar{z}_{1,1} & 0 & \cdots & \cdots & 0 \\
0 & \psi_{2\to 3}\bar{z}_{2,2} & \ddots & & \vdots \\
\vdots & \ddots & \ddots & \ddots & \vdots \\
0 & \cdots & 0 & \psi_{I-1\to I}\bar{z}_{I-1,I} & 0
\end{pmatrix}$$

Therefore we obtain

$$\tilde{\Psi}_\lambda x = \Phi(e^{\lambda \cdot} \otimes x) \quad \text{for } x \in \mathbb{R}^I$$

where the relation $\otimes$ is defined by

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

Next we will give a characterization of the spectrum of the infinitesimal generator $\mathcal{A}_\Phi$ associated to the perturbed semigroup W_Φ by using the family of operators defined above. This characterization permits to show that the spectrum is a point spectrum and there exists a characteristic equation, the roots of which are the eigenvalue of the infinitesimal generator of the associated perturbed semigroup. Furthemore, we will give a criterion which assure the simplicity of these eigenvalues.

Proposition 3.4 *λ belongs to $\sigma(\mathcal{A}_\Phi)$ if and only if λ belongs to $\sigma_p(\mathcal{A}_\Phi)$ if and only if*

$$\prod_{i=1}^{I} \int_0^{\tilde{a}} \exp\left(- \int_0^x \lambda + m_i(\tau) d\tau \right) \mathcal{K}_{i\to i+1}(x) dx = \frac{1}{2} \tag{21}$$

Proof. By transforming the integral equation (14) using the Laplace transformation, we obtain the following resolvent equation

$$(I - q^{-1} R(\lambda, \mathcal{A}_0^{\odot *})\Phi) R(\lambda, \mathcal{A}) = R(\lambda, \mathcal{A}_0), \text{ for } \lambda \in \rho(\mathcal{A}_0)$$

Then it is clear that λ belongs to the spectrum of $\mathcal{A}_\Phi$ if and only if the operator $I - q^{-1} R(\lambda, \mathcal{A}_0^{\odot *})\Phi$ is not invertible. By straightforward computation it is turn out that it is satisfied if and only if $\det(\mathbb{I} - \tilde{\Psi}_\lambda) = 0$ that is equivalent to the assertion (21) since the term $q^{-1} R(\lambda, \mathcal{A}_0^{\odot *})\Phi$ is bounded and $\sigma(\mathcal{A}_0) = \emptyset$. By the eventual compactness of the semigroup the spectrum of $\mathcal{A}_\Phi$ is ponctual. □

Proposition 3.5 *The spectral bound of $\mathcal{A}_\Phi$ equal to the growth bound of W_Φ, that is,*

$$s(\mathcal{A}_\Phi) = \omega(W_\Phi)$$

such that there exists a real dominant eigenvalue $\tilde{\lambda}$ of $\mathcal{A}_\Phi$ solution of

$$\tilde{\lambda} = s(\mathcal{A}_\Phi)$$
$$\prod_{i=1}^{I} \int_0^{\tilde{a}} \exp\left(-\int_0^x \lambda + m_i(\tau)d\tau\right)\mathcal{K}_{i\to i+1}(x)dx = \frac{1}{2} \qquad (22)$$

Proof. Since our semigroup solution of (14) is eventually compact, the result given in [20, Theorem 2.7] provides to us that $s(\mathcal{A}_\phi) = \omega(W_\phi)$. The map given by the spectral radius of the operator $\tilde{\Psi}_\lambda$ is continuous. In addition, the operator $\tilde{\Psi}$ decreases and it satisfies

$$r(\tilde{\Psi}_\lambda) \text{ tends to } +\infty \quad \text{as } \lambda \text{ tends } -\infty$$
$$r(\tilde{\Psi}_\lambda) \text{ tends to } 0 \quad \text{as } \lambda \text{ tends } +\infty$$

Then there exists a unique real root $\tilde{\lambda}$ that holds (22) where $\tilde{\lambda}$ is an eigenvalue of $\mathcal{A}_\phi$. Using the fact that the spectral radius of $\tilde{\Psi}$ is monotone, we have the result

$$\tilde{\lambda} = \sup\{\Re e\lambda : \lambda \in \sigma(\mathcal{A}_\phi)\} = s(\mathcal{A}_\phi)$$

Finally, since the semigroup is eventually compact, the real eigenvalue $\tilde{\lambda}$ solution of (22) is dominant.□

We can say from the above result that less control on the transition and mortality rates, the higher the growth rate, that is the proliferation is faster within cells with less synchronised phases.

Proposition 3.6 *The operator $\tilde{\Psi}_\lambda$ is irreducible such that $\tilde{\lambda}$ is a pole of order 1.*

Proof. The irreducibility is a strong positivity property for the semigroup that provides to us a convenient criterion about the simplicity of the poles. Let $g, g^* \in \mathbb{R}^I$ we have

$$< \tilde{\Psi}_\lambda g, g^* >= \int_0^{\tilde{a}} \exp(-\lambda a) \sum_{i=1}^{I-1} \mathcal{K}_{i\to i+1} g_{i+1}^* \bar{z}_{i,i} g_i + 2\mathcal{K}_{I\to 1} g_1^* \bar{z}_{I,I} g_I da > 0$$

□

Next, we investigate the behavior in the long term of the perturbed semigroup solution of (14), where we show that the property of asynchronous exponential property is fufilled

Theorem 3.7 *The solution semigroup $\{P_\phi(t)\}_{t\geq 0}$ of* (14) *holds*

$$\|\exp(-\lambda_0 t)P_\phi(t) - Q\| \leq \beta e^{-\gamma t} \text{ for } \gamma > 0, \beta \geq 1, \forall t \geq 0$$

such that Q given by

$$Qg = \alpha(g)(e^{\lambda_0 \cdot} \otimes \varphi_{\lambda_0})$$

and

$$\alpha(g) = \frac{< \psi_{\lambda_0}^*, \phi(\theta \mapsto \int_0^\theta \exp(\lambda_0(\theta - s))g(s)ds >}{< \psi_{\lambda_0}^*, \phi(\theta \mapsto \theta \exp(-\lambda_0\theta) \otimes \psi_{\lambda_0} >}, \quad \psi \in \mathcal{E} \qquad (23)$$

where $\psi_{\lambda_0} > 0$ ($\psi_{\lambda_0}^* > 0$) is the eigenvector of $\tilde{\Psi}_{\lambda_0}$ (respectively of $\tilde{\Psi}_{\lambda_0}^*$) such that $< \psi_{\lambda_0}^*, \psi_{\lambda_0} >= 1$.

Proof. Our state space $\mathcal{X}$ can be decomposed as the following

$$\mathcal{X} = N_{\tilde{\lambda}} \oplus R_{\tilde{\lambda}}$$

where

$$\begin{cases} N_{\tilde{\lambda}} = \ker(\mathcal{A}_\Phi - \tilde{\lambda}I) = e^{\tilde{\lambda}\cdot} \otimes \ker(I - \tilde{\Psi}_{\tilde{\lambda}}) \\ \quad = \{\alpha e^{\tilde{\lambda}\cdot} \otimes \psi_{\tilde{\lambda}} : \alpha \in \mathbb{R}\} \\ R_{\tilde{\lambda}} = \text{Range}(\mathcal{A}_\Phi - \tilde{\lambda}\mathbb{I}) \end{cases}$$

where $\varphi_{\tilde{\lambda}}$ is the positive eigenvector of $\tilde{\Psi}_{\tilde{\lambda}}$ associated to the eigenvalue $\tilde{\lambda}$ solution of (22). The projection of g on the subspaces $N_{\tilde{\lambda}}$ and $R_{\tilde{\lambda}}$ gives us

$$g = \alpha(g)\exp(-\tilde{\lambda}.) \otimes \psi_{\tilde{\lambda}} + \rho$$

Then our semigroup solution of (14) can be rewritten as

$$P_\Phi(t)g = \alpha(g)\exp(-\tilde{\lambda}(t - .))\psi_{\tilde{\lambda}} + (P_\Phi(t)|_R)(\rho)$$

Using the fact that $\omega(P_\Phi(t)|_R) < \tilde{\lambda}$. Then we obtain that

$$P_\Phi(t)g = \alpha(g)\exp(-\tilde{\lambda}(t - .))\psi_{\tilde{\lambda}} + o(\exp(\tilde{\lambda}t))$$

Then we obtain

$$\|\exp(-\tilde{\lambda}t)P_\Phi(t)g - Qg\|_{\mathcal{E}} \leq \beta\exp(-\delta t)\|g\|_{\mathcal{E}} \quad \text{for } \gamma > 0, \beta \geq 1, g \in \mathcal{E}$$

where $Qg = \alpha(g)\exp(-\tilde{\lambda}.)\psi_{\tilde{\lambda}}$. Then

$$\alpha(g) = \frac{< \psi_{\tilde{\lambda}}^*, \phi(\theta \mapsto \int_0^\theta \exp(\tilde{\lambda}(\theta - s))g(s)ds >}{< \psi_{\tilde{\lambda}}^*, \phi(\theta \mapsto \theta\exp(-\tilde{\lambda}\theta) \otimes \psi_{\tilde{\lambda}} >}, \quad g \in \mathcal{E}$$

such that $\psi_{\tilde{\lambda}}^*$ is a positive eigenvector of $\tilde{\Psi}_{\tilde{\lambda}}^*$ that yields the condition $< \psi_{\tilde{\lambda}}^*, \psi_{\tilde{\lambda}} >= 1$. □

Proposition 3.8 *The semigroup solution of* (1) *possesses the asynchronous exponential property.*

Proof. Using the relation $(\Gamma f)(s) = \chi(s)f(s), \forall s \in (0, \tilde{a})$ we obtain the similar semigroup

$$P(t)f = \Gamma^{-1}(P_\Phi(t)\Gamma f), \quad \forall f \in \mathcal{E}$$

Then by considering the formula $\tilde{Q}f = \Gamma^{-1}(Q(\Gamma f))$ we obtain the estimate

$$\begin{aligned} &\|\exp(-\tilde{\lambda}t)P(t)f - \tilde{Q}f\|_{\mathcal{E}} = \|\Gamma(\exp(-\tilde{\lambda}t)P(t)f - Qf)\|_{\mathcal{E}} \\ &\leq \|\exp(-\tilde{\lambda}t)(P_\Phi(t)\Gamma f) - (\alpha(\Gamma f)\exp(-\tilde{\lambda}.)\psi_{\tilde{\lambda}})\|_{\mathcal{E}} \\ &\leq \beta\exp(-\gamma t)\|f\|_{\mathcal{E}} \end{aligned}$$

We can conclude that the solution of (1) yields the asynchronous exponential property. □

As generations follow one another, the synchronisation between phases are less expressed within the evolving cell population, that is we observe a variability in the structure when a cell transition from the i^{th} phase to the $(i+1)^{th}$ phase, and becomes fully desynchronised. In the following a threshold phenomenon appear and it can be formulated as the spectral radius of some integral operator

Proposition 3.9 *Let $r(\tilde{\Psi}_\lambda)$ be the spectral radius of $\tilde{\Psi}_\lambda$ defined by* (20)*. Then the following holds :*

1. *If $\int_0^{\tilde{a}} \exp\left(-\int_0^x m_i(\tau)d\tau\right)\mathcal{K}_{i\to i+1}(x)dx < \frac{1}{2}$ the trivial equilibrium state is asymptotically stable.*
2. *If $\int_0^{\tilde{a}} \exp\left(-\int_0^x m_i(\tau)d\tau\right)\mathcal{K}_{i\to i+1}(x)dx > \frac{1}{2}$ the trivial equilibrium state is unstable.*

Proof. We have shown that $\tilde{\lambda} = s(\mathcal{A}_\phi)$. Due to the monotonicity of the operator $\tilde{\Psi}_\lambda$ we have that the spectral bound $s(\mathcal{A}_\phi) < 0$ if

$$r(\tilde{\Psi}_0) = \int_0^{\tilde{a}} \exp\left(-\int_0^x m_i(\tau)d\tau\right)\mathcal{K}_{i\to i+1}(x)dx < \frac{1}{2}$$

which corresponds to the trivial equilibrium state. Then, since from

$$\|P(t)f\|_\mathcal{E} \leq e^{\tilde{\lambda}t}\|f\|_\mathcal{E}$$

we have $\lim_{t\to\infty} P(t)f = 0$ and it is unstable when

$$\int_0^{\tilde{a}} \exp\left(-\int_0^x m_i(\tau)d\tau\right)\mathcal{K}_{i\to i+1}(x)dx > 1/2 \quad \square$$

4 Conclusion

The study of the cell population dynamics by taking into account the proliferation process and generations overlapping take an important part in the mathematical modeling and analysis. Various analytical and probabilist methods were performed to this aim. In particular, the semigroup method, that demonstrate it is theoretically well established combining between different theories such as operator theory, functional analysis, spectral theory ...

In this paper, the dual semigroup theory provide a useful framework to examine these processes. In particular, the context of the control of the cell cycle where many complex regulatory processes are involved where the structuration by age permits to us to track the individual cell position through the multiple generations. We proved the asynchronous exponential property that consists as an important trait within the cell populations. In fact, the synchronisation or desynchronisation is essential in tumour therapy in which drugs can synchronize cell phases and others can destroy cells in the same phases.

Here, we investigated the role of the circadian clock in the control of the proliferation within the cell population. Mathematically, we can conclude that the disruption of the circadian clock, in particular the desynchronisation between the transition from a phase to another one has a major effect on the proliferation of cells. In addition, we demonstrate that as time evolves, the cells are more desynchronised than the younger generations. In this context, natural questions arise about the differences in synchronisation between healthy and cancerous cells. This question is essential in order to understand the cell cycle and to use such knowledge to make optimisation methods for cancer therapy.

In this paper, we consider only age dependent parameter, in perspective we want to examine the effect of time dependent and different periodic controls on the cell proliferation and to compare theses controls between them.

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