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The asynchronous exponential growth property in a model for the kinetic heterogeneity of tumour cell populations

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Abstract

A continuous cell population model, which represents both the cell cycle phase structure and the kinetic heterogeneity of the population following Shackney's ideas [J. Theor. Biol. 38 (1973) 305–333], is studied. The asynchronous exponential growth property is proved in the framework of the theory of strongly continuous semigroups of bounded linear operators.

Keywords: Cell population dynamics; Cell kinetic heterogeneity; Asynchronous exponential growth

1. Introduction

Populations of proliferating cells are characterized by cell-to-cell variability of the cell cycle kinetic parameters. Even cell populations growing in vitro, that is in a homogeneous environment, exhibit different cell cycle times because of the intrinsic variabilities in the

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✠ This paper is dedicated to the memory of our dear friend Ovide Arino, who passed away before the work was completed.

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machinery of cell cycle progression. Both experimental and clinical tumours, as demonstrated since the early studies using ^{3}H-thymidine labeling [14], show a larger extent of kinetic heterogeneity due to the possible presence of genetic heterogeneity, and to the different conditions of nutrition and oxygenation in the cell microenvironment, related to the tumour vascularization.

In the framework of deterministic models, the kinetic heterogeneity has been mainly represented by means of age-structured population models [1,2,4,15]. The age formalism, indeed, allows a simple representation of cell populations with variable (but uncorrelated) cell cycle times. Denoting by a ($a \geqslant 0$) the cell age and by $n(a,t)$ the cell density with respect to age, that is, $n(a,t)\,da$ is the number of cells with age between a and $a + da$ at time t, the basic model is given by

$$\frac{\partial n}{\partial t}(a,t) + \frac{\partial n}{\partial a}(a,t) = -\big[\beta(a) + \mu(a)\big]n(a,t),$$
$$n(0,t) = 2\int_0^{+\infty} \beta(a)n(a,t)\,da,$$

where $\beta(a)$ is the age-dependent division rate coefficient, which is related to the distribution of cell cycle duration, and $\mu(a)$ represents cell loss. More complex models, involving age-structured subpopulations, are required to take into account the different cell cycle phases [5].

Another approach to represent the kinetic heterogeneity was proposed by Lebowitz and Rubinow [9], considering the cell population as composed by a continuous spectrum of subpopulations each characterized by a given cell cycle transit time τ. The population is thus described by the cell density $n(a,\tau,t)$ ($a \in [0,\tau]$, $\tau > 0$), such that $n(a,\tau,t)\,da\,d\tau$ denotes the number of cells with age between a and $a + da$ and cell cycle time between τ and $\tau + d\tau$ at time t. The model is given by

$$\frac{\partial n}{\partial t}(a,\tau,t) + \frac{\partial n}{\partial a}(a,\tau,t) = -\mu(a,\tau)n(a,\tau,t),$$
$$n(0,\tau,t) = 2\int_0^{+\infty} \Theta(\tau,\tau')n(\tau',\tau',t)\,d\tau',$$

where $\Theta(\tau,\tau')$ is a transition kernel such that $\Theta(\tau,\tau')\,d\tau$ yields the probability that a cell originated from a cell with cycle time τ' will have cycle time between τ and $\tau + d\tau$. We note that the dependence of Θ on τ' introduces a partial heredity of the cell cycle transit time between mother and daughter cells. The model in [9], through the variable transformation $x = a/\tau$, can be written in terms of the cell maturity x and distributed cell maturation rates. Because the cell maturity, as defined by Rubinow [11], is a variable ranging from 0 to 1 which marks the progression through the cell cycle, the maturity formalism readily represents the cell cycle phases by assigned maturity intervals. It is easy to see that the preceding model implies a strict relationship among the transit times of the cell cycle phases. We remark that both the above models exhibit the asynchronous exponential growth property, that is, the population asymptotically shows an exponential growth with a steady distribution with respect to the structure variables, irrespective of the initial condition [15,16].

A different model for representing the proliferative heterogeneity of in vivo tumour cell populations was proposed by Shackney [12] and recently reconsidered by Shackney and Shankey [13]. This model, which is substantially based on the concept of cell maturity, introduces the idea of *growth retardation*: that is, it is assumed that cells change their rate of progression towards mitosis during their life-span, by moving from tracks with faster rate to tracks with slower rate. Whereas in [9] the cell cycle time and the phase transit times are determined at birth, now the transit times also depend on the random transitions occurring during cell life. Yet, this mechanism produces correlated transit times in cell cycle phases. From the biological viewpoint, the idea of growth retardation focuses on the microenvironmental origin of the tumour kinetic heterogeneity, and reflects the migration of cells from regions close to the vascular supply, to regions where worse conditions of microenvironment are prevailing and slow proliferation and/or cell arrest occur.

The model proposed by Shackney [12] was originally formulated as a discrete model. In [3] we propose a continuous cell population model, based on Shackney's ideas, which represents both the cell cycle phase structure and the kinetic heterogeneity of the population (see Section 2). In the present paper we will prove for this model the asynchronous exponential growth property, which guarantees that the cell population can desynchronize, as it is experimentally observed. The proof is developed in Sections 3 and 4, and is based on the theory of operator semigroups.

2. Formulation of the model

We start by describing, for the reader's convenience, the model presented in [3]. Let us consider a cell population in which cells are characterized by two state variables: the maturity x, $0 \leqslant x \leqslant 1$, with $x = 0$ at birth and $x = 1$ at division, and a state variable T, $0 < T_{\min} \leqslant T \leqslant T_{\max} < +\infty$, which identifies the rate of maturation $w(x, T)$, i.e., the local rate of progression through the cell cycle, in a suitable class of functions. For T the following relation holds:

$$\int_0^1 \frac{dx}{w(x,T)} = T$$

so that, if T does not change during cell life, the cell cycle duration is just given by T. The definition of T implies that, if T increases, the maturation rate will decrease.

Hypothesis 1. *The function $w(x, T)$ satisfies the following*:

(i) $w \in C^1([0,1] \times [T_{\min}, T_{\max}])$.
(ii) $\forall (x, T) \in [0,1] \times [T_{\min}, T_{\max}]$, $\frac{\partial w}{\partial T}(x, T) < 0$.
(iii) *There exists a constant $w^* > 0$ such that,* $\forall x \in [0,1]$, $w(x, T_{\max}) \geqslant w^*$.

Note that if w is independent of x, $w(x,T) = 1/T$ (and Hypothesis 1 is satisfied). Moreover, in view of Hypothesis 1, the progression rate cannot vanish at any point of the cell cycle and complete cell cycle arrest at some definite values of x is excluded.

During their life span, cells can change T at random by jump transitions to T values *larger* than the starting value (growth retardation), while conserving at each jump the maturity x. In this way, cells having the same value of T at birth may reach division following different tracks on the (x,T) plane and then with different cell cycle transit times. The transitions are governed by the transition rate $\lambda(x,T)$ and by the kernel $K(T,\tau,x)$, $T \geqslant \tau$, $T_{\min} \leqslant \tau \leqslant T_{\max}$, such that $K(T,\tau,x)\,dT$ represents the probability that the transition brings into $[T, T+dT]$ a cell with state variables x and τ. Therefore,

$$\int_{\tau}^{T_{\max}} K(T,\tau,x)\,dT = 1. \tag{1}$$

Because no transition is assumed to occur when $T = T_{\max}$, it is $\lambda(x, T_{\max}) = 0$.

When x attains the value $x = 1$, cells divide into two daughter cells. The daughters of cells that divide with $T = \tau$ will have at birth a value of T distributed around τ according to a given dispersion kernel $\Theta(T,\tau)$ which satisfies

$$\int_{T_{\min}}^{T_{\max}} \Theta(T,\tau)\,dT = 1.$$

This dispersion reflects phenomena, such as the unequal division of cells at mitosis, which contribute to the intrinsic variability of the duration of cell cycle. Finally, the population is affected by random cell loss according to a loss rate $\mu(x,T)$, which may represent cell death as well as an irreversible transition into a quiescent state.

The cell population will be described by the density function $n(x,T,t)$, such that $n(x,T,t)\,dx\,dT$ is the number of cells having $(x,T) \in [x, x+dx] \times [T, T+dT]$ at time t. As shown in [3], the following governing equation can be obtained:

$$\begin{aligned}
&\frac{\partial n}{\partial t}(x,T,t) + \frac{\partial}{\partial x}\big[w(x,T)n(x,T,t)\big] \\
&\quad = -\big[\lambda(x,T) + \mu(x,T)\big]n(x,T,t) + \int_{T_{\min}}^{T} \lambda(x,\tau)K(T,\tau,x)n(x,\tau,t)\,d\tau.
\end{aligned} \tag{2}$$

Equation (2) has to be complemented by the boundary condition

$$w(0,T)n(0,T,t) = 2\int_{T_{\min}}^{T_{\max}} \Theta(T,\tau)w(1,\tau)n(1,\tau,t)\,d\tau \tag{3}$$

and by the initial condition

$$n(x,T,0) = n_0(x,T). \tag{4}$$

By identifying the cell cycle phases, G1, S, G2 and M, with the maturity intervals (x_{i-1}, x_i), $i = 1,\ldots,4$, with $x_0 = 0$ and $x_4 = 1$, the integral of the density $n(x,T,t)$ over these maturity intervals (and all the values of T) gives the number of cells in the corresponding phases at time t. We note that the model here proposed becomes equivalent, when $\lambda(x,T)\equiv 0$, to the cell population model proposed by Lebowitz and Rubinow in [9], in the case of a finite range of cycle transit time.

Our goal is to show the asynchronous exponential growth (AEG) property of the solutions of (2)–(4). To this end, the above equations can be rewritten as

$$\begin{aligned} &\frac{\partial n}{\partial t}(x,T,t)+w(x,T)\frac{\partial n}{\partial x}(x,T,t)\\ &\quad = a(x,T)n(x,T,t)+\int_{T_{\min}}^{T_{\max}} b(x,\tau,T)n(x,\tau,t)\,d\tau, \end{aligned} \tag{5}$$

$$n(0,T,t)=\int_{T_{\min}}^{T_{\max}} \tilde{C}(T,\tau)n(1,\tau,t)\,d\tau, \tag{6}$$

$$n(x,T,0)=n_0(x,T), \tag{7}$$

where we have introduced the notations

$$\begin{aligned} a(x,T) &:= -\left[\lambda(x,T)+\mu(x,T)+\frac{\partial w}{\partial x}(x,T)\right],\\ b(x,\tau,T) &:= \lambda(x,\tau)K(T,\tau,x)H(T-\tau),\\ \tilde{C}(T,\tau) &:= \frac{2}{w(0,T)}\Theta(T,\tau)w(1,\tau), \end{aligned}$$

and H is the Heaviside function: $H(t)=0$ if $t<0$, $H(t)=1$ if $t>0$.

Let us introduce a new unknown function defined by

$$u(x,T,t):=\xi(x,T)n(x,T,t),\qquad \xi(x,T):=\exp\left(-\int_0^x \frac{a(s,T)}{w(s,T)}\,ds\right).$$

Multiplying both sides of Eqs. (5) and (6) by $\xi(x,t)$, straightforward calculations lead to the following formulation of the problem, for $0\leqslant x\leqslant 1$, $0<T_{\min}\leqslant T\leqslant T_{\max}<+\infty$, $t>0$:

$$\frac{\partial u}{\partial t}(x,T,t)+w(x,T)\frac{\partial u}{\partial x}(x,T,t)=\int_{T_{\min}}^{T_{\max}} B(x,\tau,T)u(x,\tau,t)\,d\tau, \tag{8}$$

$$u(0,T,t)=\int_{T_{\min}}^{T_{\max}} C(T,\tau)u(1,\tau,t)\,d\tau, \tag{9}$$

$$u(x,T,0)=u_0(x,T), \tag{10}$$

where

$$B(x,\tau,T):=\frac{b(x,\tau,T)\xi(x,T)}{\xi(x,\tau)},\qquad C(T,\tau):=\frac{\xi(0,T)\tilde{C}(T,\tau)}{\xi(1,\tau)}.$$

Recalling Eq. (1), we observe that $K(T, \tau, x)$ becomes unbounded for $\tau \to T_{\max}$. Thus, to guarantee that the integral in the right-hand side of (2) remains finite, we will require that $\lambda(x, \tau)K(T, \tau, x)$ be bounded. Therefore, we suppose that

Hypothesis 2. $B \in L^\infty([0, 1] \times [T_{\min}, T_{\max}]^2)$, $C \in L^\infty([T_{\min}, T_{\max}]^2)$.

3. The pure maturation problem

Here we start studying the associated *pure maturation* problem (obtained by setting to zero the right-hand side of Eq. (8)), which will be formulated in the framework of semigroup theory. Let us consider the problem, for $0 \leqslant x \leqslant 1$, $0 < T_{\min} \leqslant T \leqslant T_{\max} < +\infty$, $t > 0$,

$$\frac{\partial u}{\partial t}(x, T, t) + w(x, T)\frac{\partial u}{\partial x}(x, T, t) = 0, \tag{11}$$

$$u(0, T, t) = \int_{T_{\min}}^{T_{\max}} C(T, \tau)u(1, \tau, t)\, d\tau, \tag{12}$$

$$u(x, T, 0) = u_0(x, T). \tag{13}$$

After integrating along the characteristic lines, we will show that the solutions of this problem define a strongly continuous semigroup of bounded linear operators (C_0-semigroup). The infinitesimal generator and the resolvent of this semigroup will be also obtained.

3.1. Solution of the pure maturation problem along the characteristic lines

Considering T as a parameter, the differential system of characteristic lines associated to (11) is

$$\frac{dx}{ds} = w(x(s), T), \quad \frac{dt}{ds} = 1, \quad x(0) = x_0, \quad t(0) = t_0,$$

whose solution is $x_T(s) = \Phi(s, x_0, T)$, $t_T(s) = s + t_0$.

For each $x_0 \in (0, 1)$, let $J_T(x_0) \subset \mathbf{R}$ be the maximal open interval of definition of the solution $\Phi(\cdot, x_0, T)$ which, as a consequence of Hypothesis 1(iii), is a bounded interval, and let us define $\Omega_T := \{(s, x) \in \mathbf{R} \times (0, 1);\ s \in J_T(x)\}$. Then, bearing in mind some well-known properties of the flow Φ we have

Lemma 1. *Let us define*

$$W := \big\{(s, x_0, T);\ (s, x_0) \in \Omega_T,\ T \in [T_{\min}, T_{\max}]\big\}.$$

Under Hypothesis 1 *we have,* $\forall (s, x_0, T) \in W$*,* $s > 0$*,*

$$\frac{\partial \Phi}{\partial s}(s, x_0, T) > 0, \quad \frac{\partial \Phi}{\partial x}(s, x_0, T) > 0, \quad \frac{\partial \Phi}{\partial T}(s, x_0, T) < 0.$$

Proof. The first two inequalities follow immediately by inspection of the flow map. For the third one, since $\frac{\partial \Phi}{\partial s}(s, x_0, T) = w(\Phi(s, x_0, T), T)$, we have

$$\frac{\partial}{\partial s}\left(\frac{\partial \Phi}{\partial T}\right)(s, x_0, T) = D_1 w\big(\Phi(s, x_0, T), T\big)\frac{\partial \Phi}{\partial T}(s, x_0, T) + D_2 w\big(\Phi(s, x_0, T), T\big).$$

Hence, bearing Hypothesis 1 in mind, for $s > 0$,

$$\frac{\partial \Phi}{\partial T}(s, x_0, T) = \int_0^s \left[e^{\int_\sigma^s D_1 w(\Phi(k, x_0, T), T)\, dk}\right] D_2 w\big(\Phi(\sigma, x_0, T), T\big)\, d\sigma < 0$$

and the lemma is proved. □

Coming back to the problem of constructing the solution to (11)–(13) along the characteristic lines, let $(x_0, t_0) \in (0, 1) \times \mathbf{R}_+$ be fixed and let $(x_T(s), t_T(s))$, $s \in J_T(x_0)$, be the characteristic line such that $x_T(0) = x_0$, $t_T(0) = t_0$. Defining $\bar{u}_T(s) := u(x_T(s), T, t_T(s))$, Eq. (11) gives

$$\frac{d}{ds}\bar{u}_T(s) = 0 \quad \Rightarrow \quad u\big(x_T(s), T, t_T(s)\big) = u\big(x_T(0), T, t_T(0)\big) = u(x_0, T, t_0).$$

With the aim of obtaining an expression for $u(x, T, t)$, let $x = \Phi(t, 0, T) := \Psi_T(t)$ be the characteristic line corresponding to the initial condition $x_T(0) = t_T(0) = 0$. This curve is defined for $t \in [0, t_T^*]$, where $t_T^* := \sup J_T(0) < +\infty$ and $\Psi_T(t_T^*) = 1$.

Let us denote by $\tilde{\Psi}_T$ the extension of Ψ_T to $\mathbf{R}_+$ defined by

$$\tilde{\Psi}_T(t) := \begin{cases} \Psi_T(t), & \text{if } t \in [0, t_T^*], \\ 1, & \text{if } t \geqslant t_T^*. \end{cases} \tag{14}$$

The solution in a point (x, t) with $x > \tilde{\Psi}_T(t)$ can be written in terms of the initial condition $u(x, T, t) = u(\Phi(-t, x, T), T, 0) = u_0(\Phi(-t, x, T), T)$.

At a point (x, t) with $x \leqslant \tilde{\Psi}_T(t)$ the solution is given in terms of the boundary condition $u(x, T, t) = u(0, T, t - \Psi_T^{-1}(x))$.

Then, for $x \geqslant \tilde{\Psi}_T(t)$, the problem is reduced to an integral equation for $u(0, T, t)$. To calculate $u(1, \tau, t)$ with $\tau \in [T_{\min}, T_{\max}]$, we have to distinguish two situations: $1 = \tilde{\Psi}_\tau(t)$ and $1 > \tilde{\Psi}_\tau(t)$. Let us define $t_{\min} := \Psi_{T_{\min}}^{-1}(1)$, $t_{\max} := \Psi_{T_{\max}}^{-1}(1)$.

Lemma 1 implies that, $\forall \tau \in [T_{\min}, T_{\max}]$ and $t \geqslant 0$, we have $\tilde{\Psi}_{T_{\max}}(t) \leqslant \tilde{\Psi}_\tau(t) \leqslant \tilde{\Psi}_{T_{\min}}(t)$ and $0 < t_{\min} < t_{\max}$. Therefore

(a) $t \in [0, t_{\min}]$ ($\Rightarrow$ $\Psi_\tau(t) < 1$), $u(1, \tau, t) = u_0(\Phi(-t, 1, \tau), \tau)$.
(b) $t \in [t_{\max}, +\infty)$ ($\Rightarrow$ $\tilde{\Psi}_\tau(t) = 1$), $u(1, \tau, t) = u(0, \tau, t - \Psi_\tau^{-1}(1))$.
(c) $t \in [t_{\min}, t_{\max}]$. In this case there exists a unique $\tau^*(t) \in [T_{\min}, T_{\max}]$ such that $\Psi_{\tau^*(t)}(t) = 1$, so that

$$u(0, T, t) = \int_{T_{\min}}^{\tau^*(t)} C(T, \tau) u(1, \tau, t)\, d\tau + \int_{\tau^*(t)}^{T_{\max}} C(T, \tau) u(1, \tau, t)\, d\tau.$$

The first integral corresponds to values of τ such that $1 = \tilde{\Psi}_\tau(t)$, and then $u(1,\tau,t) = u(0,\tau,t-\Psi_\tau^{-1}(1))$, while in the second one it is $1 > \Psi_\tau(t)$ and therefore $u(1,\tau,t) = u_0(\Phi(-t,1,\tau),\tau)$.

Summarizing,

$$u(0,T,t) = \begin{cases} \int_{T_{\min}}^{T_{\max}} C(T,\tau)u_0(\Phi(-t,1,\tau),\tau)\,d\tau, & \text{if } t \in [0,t_{\min}], \\ \int_{T_{\min}}^{\tau^*(t)} C(T,\tau)u(0,\tau,t-\Psi_\tau^{-1}(1))\,d\tau & \\ \quad + \int_{\tau^*(t)}^{T_{\max}} C(T,\tau)u_0(\Phi(-t,1,\tau),\tau)\,d\tau, & \text{if } t \in [t_{\min},t_{\max}], \\ \int_{T_{\min}}^{T_{\max}} C(T,\tau)u(0,\tau,t-\Psi_\tau^{-1}(1))\,d\tau, & \text{if } t \in [t_{\max},+\infty). \end{cases}$$

Let us observe that the first line in the formula above provides the function $u(0,T,t)$ for $t \in [0,t_{\min}]$ in terms of the initial data u_0. Henceforth we have an explicit formula for the solution of the pure maturation problem in the interval $t \in [0,t_{\min}]$,

$$u(x,T,t) = \begin{cases} u_0(\Phi(-t,x,T),T), & \text{if } x > \Psi_T(t), \\ \int_{T_{\min}}^{T_{\max}} C(T,\tau)u_0(\Phi(-t+\Psi_T^{-1}(x),1,\tau),\tau)\,d\tau, & \text{if } x < \Psi_T(t). \end{cases}$$

3.2. Semigroup associated to the pure maturation problem

We are going to define a family of operators $\{S_0(t)\}_{t\geqslant 0}$ on the Banach space $X := L^1([0,1]\times[T_{\min},T_{\max}])$ with the usual norm.

(i) $t \in [0,t_{\min}]$, $u_0 \in X$,

$$\big(S_0(t)u_0\big)(x,T) := \begin{cases} u_0(\Phi(-t,x,T),T), \quad \text{if } x > \Psi_T(t), \\ \int_{T_{\min}}^{T_{\max}} C(T,\tau)u_0(\Phi(-t+\Psi_T^{-1}(x),1,\tau),\tau)\,d\tau, \\ \quad \text{if } x < \Psi_T(t). \end{cases}$$

(ii) $t > t_{\min} \Rightarrow t = kt_{\min} + \tilde{t}$, with $k \in \mathbf{N}$ and $\tilde{t} \in [0,t_{\min})$. Then

$$S_0(t) := \big[S_0(t_{\min})\big]^k S_0(\tilde{t}).$$

Our next goal is to show that $\{S_0(t)\}_{t\geqslant 0}$ is a C_0-semigroup on X.

Proposition 1. *The family of operators $\{S_0(t)\}_{t\geqslant 0}$ satisfies*

$$\forall t_1,t_2 \geqslant 0, \quad S_0(t_1+t_2) = S_0(t_1)S_0(t_2).$$

Proof. *Step* 1. Let $t_1,t_2 \geqslant 0$ be such that $t_1+t_2 \leqslant t_{\min}$.

Introducing the notation $u_1(x,T) := (S_0(t_1)u_0)(x,T)$, we have

$$\begin{aligned} \big(S_0(t_2)(S_0(t_1)u_0)\big)(x,T) &= \big(S_0(t_2)u_1\big)(x,T) \\ &= \begin{cases} u_1(\Phi(-t_2,x,T),T), & \text{if } x > \Psi_T(t_2), \\ \int_{T_{\min}}^{T_{\max}} C(T,\tau)u_1(\Phi(-t_2+\Psi_T^{-1}(x),1,\tau),\tau)\,d\tau, & \text{if } x < \Psi_T(t_2). \end{cases} \end{aligned}$$

Step 1.1. In the case $x > \Psi_T(t_2)$ we have

- For $\tilde{x} := \Phi(-t_2, x, T) > \Psi_T(t_1)$,

$$u_1(\tilde{x}, T) = u_0\big(\Phi(-t_1, \tilde{x}, T), T\big) = u_0\big(\Phi\big(-t_1, \Phi(-t_2, x, T), T\big), T\big)$$
$$= u_0\big(\Phi(-t_1 - t_2, x, T), T\big) = \big(S_0(t_1 + t_2)u_0\big)(x, T).$$

In the last equality we have used

$$\begin{cases} x > \Psi_T(t_2), \\ \Phi(-t_2, x, T) > \Psi_T(t_1) \end{cases} \quad \Rightarrow \quad x > \Psi_T(t_1 + t_2),$$

which can be proved easily: with the notation $x^* := \Phi(t_1, 0, T)$, we have $\tilde{x} > x^* \;\Rightarrow\; \Phi(t, \tilde{x}, T) > \Phi(t, x^*, T)$ and then

$$\Phi(t_2, \tilde{x}, T) = x > \Phi(t_2, x^*, T) = \Phi\big(t_2, \Phi(t_1, 0, T), T\big) = \Psi_T(t_1 + t_2).$$

- For $\tilde{x} < \Psi_T(t_1)$, we have $x < \Psi_T(t_1 + t_2)$ and then

$$x = \Phi(t_2, \tilde{x}, T) < \Phi(t_2, x^*, T) = \Psi_T(t_1 + t_2).$$

From the definition of $S_0(t)$ for $t \in [0, t_{\min}]$, we have

$$\big(S_0(t_1 + t_2)u_0\big)(x, T) = \int_{T_{\min}}^{T_{\max}} C(T, \tau)u_0\big(\Phi\big(-t_1 - t_2 + \Psi_T^{-1}(x), 1, \tau\big), \tau\big)\, d\tau$$

and also

$$\big(S_0(t_2)u_1\big)(x, T) = \int_{T_{\min}}^{T_{\max}} C(T, \tau)u_0\big(\Phi\big(-t_1 + \Psi_T^{-1}\big(\Phi(-t_2, x, T)\big), 1, \tau\big), \tau\big)\, d\tau.$$

Equating the two expressions, our goal is to check the equality $-t_1 - t_2 + \Psi_T^{-1}(x) = -t_1 + \Psi_T^{-1}(\Phi(-t_2, x, T))$ which is equivalent to $\Phi(-t_2, x, T) = \Psi_T(-t_2 + \Psi_T^{-1}(x))$. Since $x = \Phi(\Psi_T^{-1}(x), 0, T)$, the last equality holds.

Step 1.2. In the case $x < \Psi_T(t_2)$, we also have $x < \Psi_T(t_1 + t_2)$ and then

$$\big(S_0(t_1 + t_2)u_0\big)(x, T) = \int_{T_{\min}}^{T_{\max}} C(T, \tau)u_0\big(\Phi\big(-t_1 - t_2 + \Psi_T^{-1}(x), 1, \tau\big), \tau\big)\, d\tau.$$

On the other hand

$$\big(S_0(t_2)u_1\big)(x, T) = \int_{T_{\min}}^{T_{\max}} C(T, \tau)u_1\big(\Phi\big(-t_2 + \Psi_T^{-1}(x), 1, \tau\big), \tau\big)\, d\tau,$$

where

$$u_1\big(\Phi\big(-t_2 + \Psi_T^{-1}(x), 1, \tau\big), \tau\big) = \big(S_0(t_1)u_0\big)\big(\Phi\big(-t_2 + \Psi_T^{-1}(x), 1, \tau\big), \tau\big).$$

Since $t_1 + t_2 < t_{\min} < \Psi_\tau^{-1}(1) \;\Rightarrow\; -t_2 + \Psi_T^{-1}(x) + \Psi_\tau^{-1}(1) > t_1 + \Psi_T^{-1}(x) > t_1$, we have

$$\begin{aligned}\Phi\bigl(-t_2+\Psi_T^{-1}(x),1,\tau\bigr) &= \Phi\bigl(-t_2+\Psi_T^{-1}(x)+\Psi_\tau^{-1}(1),0,\tau\bigr)\\ &> \Phi(t_1,0,\tau)=\Psi_\tau(t_1)\end{aligned}$$

and then

$$\begin{aligned}&\bigl(S_0(t_1)u_0\bigr)\bigl(\Phi\bigl(-t_2+\Psi_T^{-1}(x),1,\tau\bigr),\tau\bigr)\\ &\quad = u_0\bigl(\Phi\bigl(-t_1,\Phi\bigl(-t_2+\Psi_T^{-1}(x),1,\tau\bigr),\tau\bigr),\tau\bigr)\\ &\quad = u_0\bigl(\Phi\bigl(-t_1-t_2+\Psi_T^{-1}(x),1,\tau\bigr),\tau\bigr).\end{aligned}$$

This proves that $S_0(t_2)S_0(t_1)=S_0(t_1+t_2)$.

Step 2. Let $t_1,t_2\geqslant 0$ be such that $t_1+t_2>t_{\min}$. We can write $t_i=k_it_{\min}+\tau_i$, with $k_i\in\mathbf{N}$, $\tau_i\in[0,t_{\min})$, $i=1,2$, and then $t_1+t_2=(k_1+k_2)t_{\min}+\tau_1+\tau_2$.

Step 2.1. Suppose that $\tau_1+\tau_2\in[0,t_{\min})$. Then

$$\begin{aligned}S_0(t_1+t_2) &= \bigl[S_0(t_{\min})\bigr]^{k_1+k_2}S_0(\tau_1+\tau_2)=\bigl[S_0(t_{\min})\bigr]^{k_1}S_0(\tau_1)\bigl[S_0(t_{\min})\bigr]^{k_2}S_0(\tau_2)\\ &= S_0(t_1)S_0(t_2).\end{aligned}$$

Step 2.2. If $\tau_1+\tau_2>t_{\min}$, we can write $t_1+t_2=(k_1+k_2+1)t_{\min}+(\tau_1-\beta t_{\min})+(\tau_2-(1-\beta)t_{\min})$, where β has been chosen so that

$$\begin{cases}\tau_1-\beta t_{\min}>0,\\ \tau_2-(1-\beta)t_{\min}>0\end{cases}\quad\Leftrightarrow\quad 1-\frac{\tau_2}{t_{\min}}<\beta<\frac{\tau_1}{t_{\min}}.$$

Then

$$\begin{aligned}S_0(t_1+t_2) &= \bigl[S_0(t_{\min})\bigr]^{k_1+k_2+1}S_0(\tau_1-\beta t_{\min})S_0\bigl(\tau_2-(1-\beta)t_{\min}\bigr)\\ &= \bigl[S_0(t_{\min})\bigr]^{k_1}S_0(\beta t_{\min})S_0(\tau_1-\beta t_{\min})\\ &\quad\times\bigl[S_0(t_{\min})\bigr]^{k_2}S_0\bigl((1-\beta)t_{\min}\bigr)S_0\bigl(\tau_2-(1-\beta)t_{\min}\bigr)\\ &= \bigl[S_0(t_{\min})\bigr]^{k_1}S_0(\tau_1)\bigl[S_0(t_{\min})\bigr]^{k_2}S_0(\tau_2)=S_0(t_1)S_0(t_2).\qquad\square\end{aligned}$$

Bearing this proposition in mind we can now establish the following theorem.

Theorem 1. *Under Hypotheses* 1 *and* 2, *the family of operators* $\{S_0(t)\}_{t\geqslant 0}$ *is a strongly continuous semigroup of bounded linear operators on the space* X.

Proof. It is evident that each $S_0(t)$ is a linear operator and that $S_0(0)=\mathrm{Id}$.

Next, we prove that for each $t>0$, $S_0(t)\in\mathcal{L}(X)$, i.e., $S_0(t)$ is a bounded linear operator. It suffices to make the proof for $t\in[0,t_{\min}]$. Let $u_0\in X$ be fixed. Then

$$\begin{aligned}\bigl\|S_0(t)u_0\bigr\|_X &\leqslant \int_{T_{\min}}^{T_{\max}}\left[\int_0^{\Psi_T(t)}\left(\int_{T_{\min}}^{T_{\max}}C(T,\tau)\bigl|u_0\bigl(\Phi\bigl(-t+\Psi_T^{-1}(x),1,\tau\bigr),\tau\bigr)\bigr|\,d\tau\right)dx\right]dT\\ &\quad+\int_{T_{\min}}^{T_{\max}}\left(\int_{\Psi_T(t)}^{1}\bigl|u_0\bigl(\Phi(-t,x,T),T\bigr)\bigr|\,dx\right)dT\\ &:= I_1(t)+I_2(t).\end{aligned}$$

Recalling Hypothesis 2, we have

$$I_1(t) \leqslant \|C\|_\infty \iiint\limits_{V(t)} \left|u_0\big(\Phi\big(-t+\Psi_T^{-1}(x),1,\tau\big),\tau\big)\right| dx\,dT\,d\tau, \tag{15}$$

where

$$V(t) := \big\{(x,T,\tau);\ 0 \leqslant x \leqslant \Psi_T(t),\ (T,\tau)\in[T_{\min},T_{\max}]^2\big\}. \tag{16}$$

We perform in (15) the change of variables defined by

$$\sigma := \Phi\big(-t+\Psi_T^{-1}(x),1,\tau\big), \quad \eta := \tau, \quad \xi := T, \tag{17}$$

under which, $V(t)$ is transformed into

$$\tilde V(t) = \big\{(\sigma,\eta,\xi);\ \Phi(-t,1,\eta) \leqslant \sigma \leqslant 1,\ (\eta,\xi)\in[T_{\min},T_{\max}]^2\big\}. \tag{18}$$

The Jacobian of this change of variables is given by

$$J = w\big(\Phi\big(-t+\Psi_T^{-1}(x),1,\tau\big),\tau\big)\frac{1}{w(x,T)}$$

hence, from Hypothesis 1 we have $J^{-1} \leqslant \frac{\|w\|_\infty}{w^*}$. Therefore,

$$I_1(t) \leqslant \|C\|_\infty \frac{\|w\|_\infty}{w^*} \iiint\limits_{\tilde V(t)} \left|u_0(\sigma,\eta)\right| d\sigma\,d\eta\,d\xi \leqslant M\|u_0\|_X, \tag{19}$$

where

$$M := \|C\|_\infty \frac{\|w\|_\infty}{w^*}(T_{\max}-T_{\min}) > 0. \tag{20}$$

We also have

$$I_2(t) = \iint\limits_{W(t)} \left|u_0\big(\Phi(-t,x,T),T\big)\right| dx\,dT \tag{21}$$

with $W(t) := \{(x,T);\ \Psi_T(t) \leqslant x \leqslant 1,\ T\in[T_{\min},T_{\max}]\}$.

To estimate the integral in (21) we choose the new set of variables $\sigma := \Phi(-t,x,T)$, $\eta := T$ and then, straightforward calculations lead to

$$I_2(t) = \iint\limits_{\tilde W(t)} \left|u_0(\sigma,\eta)\right|\left|D_2\Phi(t,\sigma,\eta)\right| d\sigma\,d\eta,$$

where $\tilde W(t) := \{(\sigma,\eta);\ 0 \leqslant \sigma \leqslant \Phi(-t,1,\eta),\ \eta\in[T_{\min},T_{\max}]\}$. Since

$$\begin{cases} \frac{\partial}{\partial s}\big(\frac{\partial \Phi}{\partial x}\big)(s,x,T), = D_1 w(\Phi(s,x,T),T)\frac{\partial\Phi}{\partial x}(s,x,T), \\ \frac{\partial\Phi}{\partial x}(0,x,T) = 1, \end{cases}$$

we have, for $s \geqslant 0$,

$$\frac{\partial\Phi}{\partial x}(s,x,T) = \exp\left(\int_0^s D_1 w\big(\Phi(r,x,T),T\big)\,dr\right)$$

which provides the estimate $\sup_{(\sigma,\eta)\in[0,1]\times[T_{\min},T_{\max}]} |D_2\Phi(t,\sigma,\eta)| \leqslant \exp(t\|D_1 w\|_\infty)$.

Therefore

$$I_2(t) \leqslant e^{t\|D_1 w\|_\infty} \iint\limits_{\tilde{W}(t)} \big|u(\sigma,\eta)\big|\, d\sigma\, d\eta \leqslant e^{t\|D_1 w\|_\infty} \|u_0\|_X. \tag{22}$$

Putting (19) and (22) together, we have $\|S_0(t)u_0\|_X \leqslant M^*(t)\|u_0\|_X$ with

$$M^*(t) := \|C\|_\infty \frac{\|w\|_\infty}{w^*}(T_{\max} - T_{\min}) + e^{t\|D_1 w\|_\infty} > 0,$$

which proves that $S_0(t)$ is a bounded linear operator on X with uniform bound on bounded subsets of t.

Finally, we have to show that, $\forall u_0 \in X$, $\lim_{t\to 0_+} \|S_0(t)u_0 - u_0\|_X = 0$. It is enough to prove continuity for each $u_0 \in C([0,1]\times[T_{\min}, T_{\max}])$, since this space is a dense subspace of X. We have

$$\begin{aligned}
&\big\|S_0(t)u_0 - u_0\big\|_X \\
&\quad = \int\limits_{T_{\min}}^{T_{\max}} \left(\int\limits_0^{\Psi_T(t)} \left(\left| \int\limits_{T_{\min}}^{T_{\max}} C(T,\tau) u_0\big(\Phi\big(-t + \Psi_T^{-1}(x), 1, \tau\big), \tau\big)\, d\tau \right.\right.\right. \\
&\qquad \left.\left.\left. - u_0(x,T) \right| \right) dx \right) dT + \int\limits_{T_{\min}}^{T_{\max}} \left(\int\limits_{\Psi_T(t)}^{1} \big|u_0\big(\Phi(-t,x,T),T\big) - u_0(x,T)\big|\, dx \right) dT \\
&\quad := (I) + (II).
\end{aligned}$$

Since $\forall t \geqslant 0$ we have $\Psi_T(t) \leqslant \Psi_{T_{\min}}(t)$, we can write

$$(I) \leqslant \big(1 + \|C\|_\infty (T_{\max} - T_{\min})\big)\|u_0\|_\infty (T_{\max} - T_{\min})\Psi_{T_{\min}}(t) \to 0 \quad (t \to 0_+).$$

On the other hand, using the uniform continuity of u_0, for each $\varepsilon > 0$ there exists $\delta(\varepsilon) > 0$ such that

$$\big|\Phi(-t,x,T) - x\big| \leqslant \delta(\varepsilon) \quad \Rightarrow \quad \big|u_0\big(\Phi(-t,x,T),T\big) - u_0(x,T)\big| \leqslant \varepsilon$$

and taking into account that $\lim_{t\to 0_+} \Phi(-t,x,T) = x$ uniformly on x, there exists $\eta(\delta(\varepsilon)) > 0$ such that

$$0 < t < \eta\big(\delta(\varepsilon)\big) \quad \Rightarrow \quad \sup_{x\in[0,1]} \big|\Phi(-t,x,T) - x\big| \leqslant \delta(\varepsilon).$$

Therefore, for $0 < t < \eta(\delta(\varepsilon))$,

$$(II) \leqslant \varepsilon \int\limits_{T_{\min}}^{T_{\max}} \big[1 - \Psi_T(t)\big]\, dT \leqslant \varepsilon(T_{\max} - T_{\min}).$$

This completes the proof of the theorem. □

Some standard but lenghtly calculations lead to the following result for the infinitesimal generator of the semigroup.

Proposition 2. *The infinitesimal generator of the semigroup* $\{S_0(t)\}_{t\geqslant 0}$ *is the operator* A_0 *defined by*

$$(A_0\varphi)(x,T) := -w(x,T)\frac{\partial\varphi}{\partial x}(x,T)$$

with domain

$$D(A_0) := \left\{\varphi \in X;\ \frac{\partial\varphi}{\partial x} \in X,\ \varphi(0,\cdot) = \int_{T_{\min}}^{T_{\max}} C(\cdot,\tau)\varphi(1,\tau)\,d\tau\right\}.$$

3.3. The resolvent of A_0

We are going to obtain the resolvent of the generator A_0, that is, the operator $(\lambda I - A_0)^{-1}$. For each given $f \in X$, we have to solve the equation $(\lambda I - A_0)\varphi = f$.

We consider: (i) the homogeneous equation $(\lambda I - A_0)\varphi = 0$,

$$\frac{\partial\varphi}{\partial x}(x,T) = -\frac{\lambda}{w(x,T)}\varphi(x,T) \quad\Rightarrow\quad \varphi_H(x,T) = \varphi(0,T)e^{-\lambda\int_0^x \frac{ds}{w(s,T)}},$$

(ii) the particular solution of the complete equation $(\lambda I - A_0)\varphi = f$. We look for a solution $\varphi_P(x,T) := m(x,T)e^{-\lambda\int_0^x \frac{ds}{w(s,T)}}$, where $m(x,T)$ should be calculated. Straightforward calculations lead to

$$\varphi_P(x,T) = \int_0^x \frac{f(s,T)}{w(s,T)}e^{-\lambda\int_s^x \frac{d\sigma}{w(\sigma,T)}}\,ds.$$

Now, we impose on $\varphi := \varphi_H + \varphi_P$ the condition $\varphi \in D(A_0)$,

$$\varphi(0,T) = \int_{T_{\min}}^{T_{\max}} C(T,\tau)\left(\varphi(0,\tau)e^{-\lambda\int_0^1 \frac{ds}{w(s,\tau)}} + \int_0^1 \frac{f(s,\tau)}{w(s,\tau)}e^{-\lambda\int_s^1 \frac{d\sigma}{w(\sigma,\tau)}}\,ds\right)d\tau. \tag{23}$$

For each $\lambda \in \mathbf{C}$ we define the two operators

(i) $L_\lambda : L^1(T_{\min},T_{\max}) \to L^1(T_{\min},T_{\max})$,

$$L_\lambda(h)(T) := \int_{T_{\min}}^{T_{\max}} C(T,\tau)e^{-\lambda\int_0^1 \frac{ds}{w(s,\tau)}}h(\tau)\,d\tau,$$

(ii) $S_\lambda : X \to L^1(T_{\min},T_{\max})$,

$$S_\lambda(f)(T) := \int_{T_{\min}}^{T_{\max}} C(T,\tau)\left(\int_0^1 \frac{f(s,\tau)}{w(s,\tau)}e^{-\lambda\int_s^1 \frac{d\sigma}{w(\sigma,\tau)}}\,ds\right)d\tau,$$

which allows us to write Eq. (23) as $(I - L_\lambda)(\varphi(0,\cdot)) = S_\lambda(f)$. Since

$$\left\|L_\lambda(h)\right\|_{L^1} = \int_{T_{\min}}^{T_{\max}} \left| \int_{T_{\min}}^{T_{\max}} C(T,\tau) e^{-\lambda \int_0^1 \frac{ds}{w(s,\tau)}} h(\tau)\, d\tau \right| dT$$
$$\leqslant \|C\|_\infty (T_{\max} - T_{\min}) \|h\|_{L^1} e^{-\lambda \int_0^1 \frac{ds}{w(s,T_{\min})}} \to 0 \quad (\lambda \to +\infty),$$

there exists $\lambda_0 > 0$ such that $\|L_\lambda\| < 1$ for $\lambda \geqslant \lambda_0$. This implies $[\lambda_0, +\infty) \subset \rho(A_0)$ (resolvent set of A_0) and also that $(I - L_\lambda)^{-1}$ exists for $\lambda \geqslant \lambda_0$, which yields

$$\varphi(0,\cdot) = (I - L_\lambda)^{-1}\big(S_\lambda(f)\big).$$

The resolvent of A_0 is, for $\lambda > \lambda_0$,

$$\big((\lambda I - A_0)^{-1} f\big)(x,T) = e^{-\lambda \int_0^x \frac{ds}{w(s,T)}} (I - L_\lambda)^{-1}\big(S_\lambda(f)\big)(T) + \int_0^x \frac{f(s,T)}{w(s,T)} e^{-\lambda \int_s^x \frac{d\sigma}{w(\sigma,T)}}\, ds. \tag{24}$$

Our next goal is to show one of the main results of this paper, which will be an essential piece in the proof of the AEG property for the model. This result involves the measure of noncompactness α. We refer the reader to [15] for the general theory.

Theorem 2. *The α-growth bound of the semigroup $\{S_0(t)\}_{t \geqslant 0}$ satisfies that*

$$\omega_1(A_0) := \lim_{t \to +\infty} \frac{\log(\alpha(S_0(t)))}{t} = -\infty.$$

To prove the theorem, we need some preliminary results.

Let us consider for each $t \in [0, t_{\min}]$, the two linear bounded operators $N(t), K(t) : X \to X$ such that $S_0(t) = N(t) + K(t)$. $N(t)$ and $K(t)$ are defined by

$$\big(N(t)u_0\big)(x,T) = \begin{cases} u_0(\Phi(-t,x,T),T), & \text{if } x > \Psi_T(t), \\ 0, & \text{if } x < \Psi_T(t), \end{cases}$$
$$\big(K(t)u_0\big)(x,T) = \begin{cases} 0, & \text{if } x > \Psi_T(t), \\ \int_{T_{\min}}^{T_{\max}} C(T,\tau) u_0(\Phi(-t + \Psi_T^{-1}(x), 1, \tau), \tau)\, d\tau, & \text{if } x < \Psi_T(t). \end{cases}$$

We state now some properties of these operators.

(a) $N(t)$ is a nilpotent operator. For each $u_0 \in X$, we have

$$\operatorname{support}\big(N(t)u_0\big) \subset \big\{(x,T);\ \tilde{\Psi}_T(t) \leqslant x \leqslant 1,\ T \in [T_{\min}, T_{\max}]\big\}$$

and also

$$\begin{aligned} (x,T) \in \operatorname{support}\big(N^2(t)u_0\big) \quad &\Rightarrow \quad \Phi(-t,x,T) > \Phi(t,0,T) \\ &\Rightarrow \quad \Phi\big(t, \Phi(-t,x,T), T\big) > \Phi\big(t, \Phi(t,0,T), T\big) \\ &\Rightarrow \quad x > \Phi(2t,0,T). \end{aligned}$$

Therefore $\operatorname{support}(N^2(t)u_0) \subset \{(x,T);\ \tilde{\Psi}_T(2t) \leqslant x \leqslant 1,\ T \in [T_{\min}, T_{\max}]\}$ and, so on

$$\operatorname{support}\big(N^p(t)u_0\big) \subset \big\{(x,T);\ \tilde{\Psi}_T(pt) \leqslant x \leqslant 1,\ T \in [T_{\min}, T_{\max}]\big\}, \quad p = 3, \ldots.$$

Since $\Psi_{T_{\max}}(t_{\max}) = 1$, there exists $p_0 > 1$ such that $\tilde{\Psi}_T(p_0 t) \geqslant \tilde{\Psi}_{T_{\max}}(p_0 t) = 1$. Hence

$$\forall (x, T) \in [0, 1] \times [T_{\min}, T_{\max}], \quad \big(N^{p_0}(t)u_0\big)(x, T) = 0,$$

and then $\forall p \geqslant p_0$, $N^p(t) = 0$, that is, $N(t)$ is a nilpotent operator.

(b) There exists $t^* \in (0, t_{\min})$ such that $\forall t \in (0, t^*)$, $K^2(t) = 0$. In fact, for each $u_0 \in X$, we have

$$\big(K^2(t)u_0\big)(x, T) = \begin{cases} 0, & \text{if } x > \Psi_T(t), \\ \int_{T_{\min}}^{T_{\max}} C(T, \tau)(K(t)u_0)(\Phi(-t + \Psi_T^{-1}(x), 1, \tau), \tau)\, d\tau, \\ \quad \text{if } x < \Psi_T(t), \end{cases}$$

and also, using the notation $x_\tau(t) := \Phi(-t + \Psi_T^{-1}(x), 1, \tau)$,

$$\big(K(t)u_0\big)\big(x_\tau(t), \tau\big) = \begin{cases} 0, & \text{if } x_\tau(t) > \Psi_\tau(t), \\ \int_{T_{\min}}^{T_{\max}} C(T, \tau)C(\tau, \sigma)u_0 \\ \quad \times(\Phi(-t + \Psi_\tau^{-1}(x_\tau(t)), 1, \tau), 1, \sigma), \sigma)\, d\sigma, \\ \quad \text{if } x_\tau(t) < \Psi_\tau(t). \end{cases}$$

We can choose $t^* > 0$ small enough such that $\Phi(-t^*, 1, T_{\min}) > \Phi(t^*, 0, T_{\min})$ and then since the functions of τ, $\Phi(-t^*, 1, \tau)$ and $\Phi(t^*, 0, \tau)$ are respectively increasing and decreasing, we have $\forall t \in (0, t^*)$,

$$\forall \tau \in [T_{\min}, T_{\max}], \quad x_\tau(t) > \Psi_\tau(t).$$

Therefore $(K(t)u_0)(x_\tau(t), \tau) = 0$, which implies $K^2(t)u_0 = 0$. Let us notice that t^* satisfies $\Phi(2t^*, 0, T_{\min}) < 1$, and hence $2t^* < t_{\min}$.

(c) Choosing $t = \alpha t_{\min}$, $\alpha \in (0, 1/2)$, then the natural number p_0 such that $N^{p_0}(t) = 0$, satisfies

$$p_0 \geqslant \frac{t_{\max}}{t} = \frac{1}{\alpha} \frac{t_{\max}}{t_{\min}}.$$

Next, we will define the operator $K_p(t) := K(t)N^p(t)$ for each natural number p with $1 \leqslant p < (1/\alpha)(t_{\max}/t_{\min}) \leqslant p_0$.

For each $u_0 \in X$, we have

$$u_p(x, T) := \big(N^p(t)u_0\big)(x, T) = \begin{cases} u_0(\Phi(-pt, x, T), T), & \text{if } (x, T) \in \mathcal{S}_p, \\ 0, & \text{if } (x, T) \notin \mathcal{S}_p, \end{cases}$$

where $\mathcal{S}_p := \text{support}(N^p(t))$. Then,

$$\big(K_p(t)u_0\big)(x, T) = \big(K(t)u_p\big)(x, T) = H\big(\Psi_T(t) - x\big) \int_{T_{\min}}^{T_{\max}} C(T, \tau)u_p\big(x(\tau), \tau\big)\, d\tau,$$

where we have introduced the notation $x(\tau) := \Phi(-t + \Psi_T^{-1}(x), 1, \tau)$. Since $u_p(x(\tau), \tau) = H(x(\tau) - \Psi_\tau(pt))u_0(\Phi(-(p+1)t + \Psi_T^{-1}(x), 1, \tau), \tau)$, we have

$$\begin{aligned} &\big(K_p(t)u_0\big)(x, T) \\ &\quad = H\big(\Psi_T(t) - x\big) \int_{\tau_p^*(x,T)}^{T_{\max}} C(T, \tau)u_0\big(\Phi\big(-(p+1)t + \Psi_T^{-1}(x), 1, \tau\big), \tau\big)\, d\tau, \end{aligned}$$

where $\tau_p^*(x,T)$ is the unique solution of the equation $\Phi(-t+\Psi_T^{-1}(x),1,\tau)=\Psi_\tau(pt)$, that is $\Phi((p+1)t-\Psi_T^{-1}(x),0,\tau)=1$.

The following lemma establishes an essential result for the proof of Theorem 2.

Lemma 2. *Let us consider $t=\alpha t_{\min}$, $\alpha\in(0,1/2)$, and let p,q be two natural numbers such that $1\leqslant p,q\leqslant(1/\alpha)(t_{\max}/t_{\min})$. Then, the operator $K_p(t)K_q(t)$ is a compact operator on X.*

Proof. For each $u_0\in X$, let us introduce the notation $\tilde u_p(x,T):=(K_p(t)u_0)(x,T)$. Then,

$$\begin{aligned}\big(K_q(t)K_p(t)u_0\big)(x,T)&=\big(K_q(t)\tilde u_p\big)(x,T)\\&=H\big(\Psi_T(t)-x\big)\int_{\tau_q^*(x,T)}^{T_{\max}}C(T,\tau)\tilde u_p\big(x_q(\tau),\tau\big)\,d\tau,\end{aligned}$$

where $x_q(\tau):=\Phi(-(q+1)t+\Psi_T^{-1}(x),1,\tau)$. Since

$$\begin{aligned}\tilde u_p(x_q(\tau),\tau)&=H\big(\Psi_\tau(t)-x_q(\tau)\big)\\&\quad\times\int_{\tau_p^*(x_q(\tau),\tau)}^{T_{\max}}C(\tau,w)u_0\big(\Phi\big(-(p+1)t+\Psi_\tau^{-1}(x_q(\tau)),1,w\big),w\big)\,dw,\end{aligned}$$

we have $\tilde u_p(x_q(\tau),\tau)=0$, $\forall\tau\in[\tilde\tau_q(x,T),T_{\max}]$, where $\tilde\tau_q(x,T)$ is the solution to $\Phi(-(q+1)t+\Psi_T^{-1}(x),1,\tau)=\Phi(t,0,\tau)$, that is, $\Phi((q+2)t-\Psi_T^{-1}(x),0,\tau)=1$.

Straightforward calculations show that $\tilde\tau_q(x,T)>T_{\min}$ and $\tilde\tau_q(x,T)>\tau_q^*(x,T)$, henceforth

$$\begin{aligned}&\big(K_p(t)K_q(t)u_0\big)(x,T)\\&=H\big(\Psi_T(t)-x\big)\int_{\tau_q^*(x,T)}^{\tilde\tau_q(x,T)}C(T,\tau)\\&\quad\times\left(\int_{\tau_p^*(x_q(\tau),\tau)}^{T_{\max}}C(\tau,w)u_0\big(\Phi\big(-(p+1)t+\Psi_\tau^{-1}\big(x_q(\tau)\big),1,w\big),w\big)\,dw\right)d\tau\\&=H\big(\Psi_T(t)-x\big)\\&\quad\times\iint_{M(x,T,t)}C(T,\tau)C(\tau,w)u_0\big(\Phi\big(-(p+1)t+\Psi_\tau^{-1}\big(x_q(\tau)\big),1,w\big),w\big)\,dw\,d\tau,\end{aligned}$$

where

$$M(x,T,t):=\big\{(w,\tau);\ \tau_p^*\big(x_q(\tau),\tau\big)\leqslant w\leqslant T_{\max},\ \tau\in\big[\tau_q^*(x,T),\tilde\tau_q(x,T)\big]\big\}.$$

With the help of the change of variables $\sigma := \Phi(-(p+1)t + \Psi_\tau^{-1}(x_q(\tau)), 1, w)$, $\eta := w$, the expression above can be written as

$$\big(K_q(t)K_p(t)u_0\big)(x,T) = H\big(\Psi_T(t) - x\big) \iint\limits_{\tilde{M}(x,T,t)} \mathcal{C}(x,T,t,\sigma,\eta)u_0(\sigma,\eta)\,d\sigma\,d\eta$$

and making an extension by zero of the kernel to $[0,1] \times [T_{\min}, T_{\max}]$, we can express

$$\big(K_q(t)K_p(t)u_0\big)(x,T) = \iint\limits_{[0,1]\times[T_{\min},T_{\max}]} \mathcal{R}(x,T,t,\sigma,\eta)u_0(\sigma,\eta)\,d\sigma\,d\eta$$

which is a compact operator (see [7, Corollary 9.7.3]). □

Proof of Theorem 2. Let $t \in (0, t_{\min}/2)$ be such that $K^2(t) = 0$, and p_0 be the smallest integer such that $N^{p_0}(t) = 0$. The iterate $[S_0(t)]^p = [K(t) + N(t)]^p$ consists of the products $[K(t)]^{p_1}[N(t)]^{p_2}[K(t)]^{p_3}\ldots[N(t)]^{p_{2m}}$ with $p_1 + p_2 + \cdots + p_{2m} = p$, $p_i \geqslant 0$, $i = 1,\ldots,2m$. Some of these products are equal to zero if $p_{2j+1} \geqslant 2$ or $p_{2j} \geqslant p_0$. For p big enough ($p > 2p_0$) it can be seen that the only surviving terms are those containing the expression $K(t)[N(t)]^{p_{2k}}K(t)[N(t)]^{p_{2l}}$, with $1 \leqslant p_{2k}, p_{2l} < p_0$, which is a compact operator in view of Lemma 2.

Henceforth, for p big enough $\alpha([S_0(t)]^p) = 0$. Therefore

$$r_e\big(S_0(t)\big) := \lim\sup_{p\to\infty} \sqrt[p]{\alpha\big(\big[S_0(t)\big]^p\big)} = 0.$$

Since $\forall t \geqslant 0$, $r_e(S_0(t)) = e^{t\omega_1(A_0)}$, we can conclude that $\omega_1(A_0) = -\infty$. □

4. AEG property for the complete model

In this section we will show that the solutions to the problem (8)–(10) (the complete model) define a C_0-semigroup $\{S(t)\}_{t\geqslant 0}$, with infinitesimal generator A, which has the AEG property.

Let us remember that AEG property means that there exists $\lambda^* \in \mathbf{R}$ which is an eigenvalue of A and a strictly positive associated eigenfunction $\varphi^* \in X$ such that, for each $u_0 \in X$, $\lim_{t\to+\infty} e^{-\lambda^* t}S(t)u_0 = C_0\varphi^*$, where C_0 is a constant depending on the initial data u_0.

The *Malthusian parameter* λ^* satisfies that $\lambda^* = s(A) := \sup\{\operatorname{Re}\lambda;\ \sigma(A)\}$.

4.1. Semigroup associated to the model (8)–(10)

In the framework of semigroup theory, we will consider Eq. (8) as a perturbation of (11). To this end, let us define the operator $B_0 : X \to X$,

$$\forall\varphi \in X, \quad (B_0\varphi)(x,T) := \int_{T_{\min}}^{T_{\max}} B(x,\tau,T)\varphi(x,\tau)\,d\tau,$$

which, under Hypothesis 2 is linear bounded with $\|B_0\| \leqslant \|B\|_\infty$.

Then, $A := A_0 + B_0$ with domain $D(A) := D(A_0)$ is the infinitesimal generator of a strongly continuous semigroup on X, which will be denoted $\{S(t)\}_{t\geqslant 0}$. This semigroup satisfies a *variation of constants formula* [8],

$$\forall u_0 \in X, \quad S(t)u_0 = S_0(t)u_0 + \int_0^t S_0(t-s)B_0S(s)u_0\,ds. \tag{25}$$

We are going to give an explicit expression of this equality for $t \in [0, t_{\min}]$. First of all we introduce the notations

$$u(x,T,t) := \big(S(t)u_0\big)(x,T),$$

$$F(x,T,t) := \big(B_0S(t)u_0\big)(x,T) = \int_{T_{\min}}^{T_{\max}} B(x,\tau,T)u(x,\tau,t)\,d\tau.$$

For $0 \leqslant s \leqslant t \leqslant t_{\min}$, we have

$$\big(S_0(t-s)F(\cdot,\cdot,s)\big)(x,T) = \begin{cases} F(\Phi(s-t,x,T),T,s), \quad s > t - \Psi_T^{-1}(x), \\ \int_{T_{\min}}^{T_{\max}} C(t,\tau)F(\Phi(s-t+\Psi_T^{-1}(x),1,\tau),\tau,s)\,d\tau, \\ \quad s < t - \Psi_T^{-1}(x), \end{cases}$$

and then,

$$\big(S(t)u_0\big)(x,T) = \big(S_0(t)u_0\big)(x,T) + G(x,T,t) \tag{26}$$

with

$$G(x,T,t) := \begin{cases} \int_0^{t-\Psi_T^{-1}(x)} \Big(\int_{T_{\min}}^{T_{\max}} C(T,\tau)\Big[\int_{T_{\min}}^{T_{\max}} B(\Phi(s-t+\Psi_T^{-1}(x),1,\tau),w,\tau) \\ \quad \times u(\Phi(s-t+\Psi_T^{-1}(x),1,\tau),w,s)\,dw\Big]d\tau\Big)\,ds \\ \quad + \int_{t-\Psi_T^{-1}(x)}^{t} \Big(\int_{T_{\min}}^{T_{\max}} B(\Phi(s-t,x,T),\tau,T) \\ \quad \times u(\Phi(s-t,x,T),\tau,s)\,d\tau\Big)\,ds, \\ \quad \text{if } x \in [0,\Psi_T(t)], \\ \int_0^t \Big(\int_{T_{\min}}^{T_{\max}} B(\Phi(s-t,x,T),\tau,T)u(\Phi(s-t,x,T),\tau,s)\,d\tau\Big)\,ds, \\ \quad \text{if } x \in [\Psi_T(t),1]. \end{cases}$$

4.2. *Asymptotic behavior of the semigroup* $\{S(t)\}_{t\geqslant 0}$

In this section we will establish the main result of this paper: the semigroup $\{S(t)\}_{t\geqslant 0}$ has the AEG property. We will achieve this result using the following test for AEG [6].

Theorem 3. *If $\{S(t)\}_{t\geqslant 0}$ is an irreducible positive semigroup with infinitesimal generator A on a Banach lattice X and if $\omega_1(A) < \omega_0(A)$, then $\{S(t)\}_{t\geqslant 0}$ has the AEG property.*

Let us recall that $\omega_0(A)$ is the *growth bound* of the semigroup, defined by

$$\omega_0(A) := \lim_{t\to+\infty} \frac{\log\|S(t)\|}{t}.$$

Theorem 4. *The semigroup* $\{S(t)\}_{t\geqslant 0}$ *has the AEG property.*

Proof. (a) *Positivity*. Since the semigroup $\{S_0(t)\}_{t\geqslant 0}$ is positive and B_0 is a positive operator, we have positivity for the semigroup $\{S(t)\}_{t\geqslant 0}$.

(b) *Irreducibility*. Taking into account the variation of constants formula (25), it is enough to prove irreducibility of the semigroup $\{S_0(t)\}_{t\geqslant 0}$. Since

$$(\lambda I - A_0)^{-1} = \int_0^{+\infty} e^{-\lambda t} S_0(t)\,dt$$

and using the expression (24) for the resolvent $(\lambda I - A_0)^{-1}$, we have $\forall\varphi \in X$, $\forall\psi \in X^*$ (topological dual space of X), $\varphi \geqslant 0$, $\psi \geqslant 0$ and denoting $\langle\cdot\,,\cdot\rangle$ the usual product of duality in X,

$$0 < \bigl\langle \psi, (\lambda I - A_0)^{-1}\varphi \bigr\rangle = \int_0^{+\infty} e^{-\lambda t} \bigl\langle \psi, S_0(t)\varphi \bigr\rangle\,dt$$

which implies existence of $t_0 > 0$ such that $\langle \psi, S_0(t_0)\varphi\rangle > 0$.

(c) *Inequality* $\omega_1(A) < \omega_0(A)$. In fact, we will show that $\omega_1(A) = -\infty$. First of all, we analyze the expression of the semigroup $\{S(t)\}_{t\geqslant 0}$ in terms of $\{S_0(t)\}_{t\geqslant 0}$ given in (26). Let us consider the term

$$G_1(x,T,t) := \int_0^{t-\Psi_T^{-1}(x)} \left(\int_{T_{\min}}^{T_{\max}} C(T,\tau) \left[\int_{T_{\min}}^{T_{\max}} B\bigl(\Phi\bigl(s - t + \Psi_T^{-1}(x), 1, \tau\bigr), w, \tau\bigr) \times u\bigl(\Phi\bigl(s - t + \Psi_T^{-1}(x), 1, \tau\bigr), w, s\bigr)\,dw \right] d\tau \right) ds,$$

where $t \in [0, t_{\min}]$, $x \in [0, \Psi_T(t)]$, $T \in [T_{\min}, T_{\max}]$. With the help of the change of variables $\eta := w$, $\xi := \Phi(s - t + \Psi_T^{-1}(x), 1, \tau)$, $\sigma := s$, it can be written as

$$G_1(x,T,t) = \iiint_{\Omega(x,T,t)} \mathcal{K}(x,T,t,\xi,\eta,\sigma) u(\xi,\eta,\sigma)\,d\xi\,d\eta\,d\sigma,$$

where

$$\begin{aligned} \Omega(x,T,t) := \bigl\{(\xi,\eta,\sigma)\colon\ & \Phi\bigl(\sigma - t + \Psi_T^{-1}(x), 1, T_{\max}\bigr) \leqslant \xi \\ & \leqslant \Phi\bigl(\sigma - t + \Psi_T^{-1}(x), 1, T_{\min}\bigr), \\ & \sigma \in [0, t - \Psi_T^{-1}(x)],\ \eta \in [T_{\min}, T_{\max}]\bigr\}. \end{aligned}$$

Denoting by $\tilde{\mathcal{K}}$ the extension by zero of the kernel $\mathcal{K}$ to $Q^* \times Q^*$, with $Q^* := [0,1] \times [T_{\min}, T_{\max}] \times [0, t_{\min}]$, we can write $G_1(x,T,t) = \mathcal{H}(u)(x,T,t)$, where $\mathcal{H}\colon L^1(Q^*) \to L^1(Q^*)$ is the operator defined by

$$\mathcal{H}(u)(x,T,t) := \iiint_{Q^*} \tilde{\mathcal{K}}(x,T,t,\xi,\eta,\sigma) u(\xi,\eta,\sigma)\,d\xi\,d\eta\,d\sigma.$$

Hypothesis 2 implies that $\tilde{\mathcal{K}} \in L^\infty(Q^* \times Q^*)$, hence it is easy to prove that $\mathcal{H}$ is a compact operator (see [7, Corollary 9.7.3]).

Let us now consider the term

$$G_2(x,T,t) := \begin{cases} \int_{t-\Psi_T^{-1}(x)}^t \Big[\int_{T_{\min}}^{T_{\max}} B(\Phi(s-t,x,T),\tau,T) \\ \quad \times u(\Phi(s-t,x,T),\tau,s)\,d\tau\Big]\,ds, \\ \quad \text{if } x \in [0,\Psi_T(t)], \\ \int_0^t \Big[\int_{T_{\min}}^{T_{\max}} B(\Phi(s-t,x,T),\tau,T)u(\Phi(s-t,x,T),\tau,s)\,d\tau\Big]\,ds, \\ \quad \text{if } x \in [\Psi_T(t),1]. \end{cases}$$

Extending by zero the function B to $[0,1]\times[0,t]$, that is, introducing the function

$$H(x,T,t,\tau,s) := \begin{cases} B(\Phi(s-t,x,T),\tau,T), & \text{if } (x,s) \in (I), \\ 0, & \text{if } (x,s) \in (II), \end{cases}$$

with

$$(I) := \big\{(x,s);\ t-\Psi_T^{-1}(x) \leqslant s \leqslant 1,\ 0 \leqslant x \leqslant \Psi_T(t)\big\} \cup \big(\big[\Psi_T(t),1\big]\times[0,t]\big),$$
$$(II) := \big\{(x,s);\ 0 \leqslant s \leqslant t-\Psi_T^{-1}(x),\ 0 \leqslant x \leqslant \Psi_T(t)\big\},$$

we can define an operator $\mathcal{L}: L^1(Q^*) \to L^1(Q^*)$ by

$$\mathcal{L}(u)(x,T,t) := \iint\limits_{[T_{\min},T_{\max}]\times[0,t]} H(x,T,t,\tau,s)u\big(\Phi(s-t,x,T),\tau,s\big)\,d\tau\,ds$$

so that $\mathcal{L}(u)(x,T,t) = G_2(x,T,t)$.

Straightforward calculations show that $\mathcal{L}$ is a bounded linear operator with $\|\mathcal{L}\| \leqslant \|B\|_\infty\|w\|_\infty(T_{\max}-T_{\min})$. Moreover

$$\mathcal{L}\big(\mathcal{L}(u)\big)(x,T,t) = \int_0^t \Bigg(\iiint\limits_{[T_{\min},T_{\max}]^2\times[0,s]} H(x,T,t,\tau,s)H\big(\Phi(s-t,x,T),\tau,s,\sigma,w\big) \times u\big(\Phi\big(\sigma-s,\Phi(s-t,x,T),\tau\big),\sigma,w\big)\,d\tau\,d\sigma\,dw\Bigg)\,ds.$$

The change of variables $\lambda = \Phi(\sigma-s,\Phi(s-t,x,T),\tau)$, $\eta=\sigma$, $\xi = w$, transform the above integral into

$$\mathcal{L}\big(\mathcal{L}(u)\big)(x,T,t) = \int_0^t \Bigg(\iiint\limits_{N(x,T,t,s)} \mathcal{V}(x,T,t,s,\lambda,\eta,\xi)u(\lambda,\eta,\xi)\,d\lambda\,d\eta\,d\xi\Bigg)\,ds$$

with

$$\begin{aligned} N(x,T,t,s) = \big\{(\lambda,\eta,\xi):\ &\Phi\big(\sigma-s,\Phi(s-t,x,T),T_{\max}\big) \leqslant \lambda \\ &\leqslant \Phi\big(\sigma-s,\Phi(s-t,x,T),T_{\min}\big), \\ &\eta \in [T_{\min},T_{\max}],\ \xi \in [0,s]\big\}. \end{aligned}$$

Extending by zero the function $\mathcal{V}$ to $Q^* \times [0, t_{\min}] \times Q^*$, we have finally

$$\mathcal{L}\big(\mathcal{L}(u)\big)(x,T,t) = \int_0^t \left(\int\int_{Q^*}\int \tilde{\mathcal{V}}(x,T,t,s,\lambda,\eta,\xi)u(\lambda,\eta,\xi)\,d\lambda\,d\eta\,d\xi \right) ds.$$

This expression allows us to conclude without difficulty that the iterate $\mathcal{L}^2$ is a compact operator on $L^1(Q^*)$.

Summarizing, we have transformed (26) into $u = w + \mathcal{H}(u) + \mathcal{L}(u)$ with $u := S(\cdot)u_0$, $w := S_0(\cdot)u_0$, and since $\mathcal{L}(u) = \mathcal{L}(w) + \mathcal{L}(\mathcal{H}(u)) + \mathcal{L}(\mathcal{L}(u))$, we arrive at $u = w + \mathcal{L}(w) + \mathcal{H}(u) + \mathcal{L}(\mathcal{H}(u)) + \mathcal{L}(\mathcal{L}(u))$.

The composition of a compact operator with a bounded linear operator is also a compact operator, therefore we can write $S(t)u_0 = S_0(t)u_0 + \mathcal{L}(S_0(t)u_0) + \mathcal{U}(t)u_0$ with $\mathcal{U}(t)$ a compact operator. Hence $\alpha(S(t)) \leqslant \alpha(S_0(t)) + \alpha(\mathcal{L}(S_0(t))) \leqslant (1 + \|\mathcal{L}\|)\alpha(S_0(t))$ and then, taking into account Theorem 2,

$$\begin{aligned}\omega_1(A) := \limsup_{t\to+\infty} \frac{\log(\alpha(S(t)))}{t} &\leqslant \big(1 + \|\mathcal{L}\|\big) \limsup_{t\to+\infty} \frac{\log \alpha(S_0(t))}{t} \\ &= \big(1 + \|\mathcal{L}\|\big)\omega_1(A_0) = -\infty.\end{aligned}$$

From the results obtained in the previous section we can deduce easily that the semigroup $\{S_0(t)\}_{t\geqslant 0}$ is irreducible, positive and eventually compact, and then $\sigma(A_0) \neq \emptyset$, which implies that $\omega_0(A_0) > -\infty$ (see [10, Theorem 3.7, p. 311]). But the perturbation B_0 is a positive operator, so that $\omega_0(A) \geqslant \omega_0(A_0)$ (see [6, p. 231]), which proves that $\omega_0(A) > -\infty$. The theorem is thus proved. □

5. Conclusion

In this paper we have studied the basic property of asynchronous exponential growth in a cell population model in which cells are characterized by two state variables, the maturity and a state variable identifying the rate of maturation. Due to this structure, the model can represent both the cell cycle phases and the kinetic heterogeneity within the population. The key feature of the model is the incorporation of the concept of growth retardation [12,13], that reflects the kinetic consequences of the possible worsening of microenvironment during the life span of the cell. A partial heredity of the maturation rate of the mother cell by the daughter cells was also assumed, according to [9]. The assumption of nonstrict heredity was crucial for establishing the property of asynchronous exponential growth.

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