Journal of Biological Systems, Vol. 7, No. 3 (1999) 285–306

STABLE SIZE DISTRIBUTION IN A MATHEMATICAL MODEL FOR TUMOR CELL POPULATION GROWTH DURING CHEMOTHERAPEUTICAL TREATMENT WITH TWO NON-CROSS RESISTANT DRUGS

HAMILTON F. LECKAR
Department of Applied Mathematics, UFF,
Rua Mário Santos Braga s/n,
24020-140 Rio de Janeiro, Brazil
E-mail: gmahafl@vm.uff.br

LAÉRCIO L. VENDITE
Department of Applied Mathematics, UNICAMP,
13081-970 São Paulo, Brazil
C. P. 6065
E-mail: vendite@ime.unicamp.br

Received 8 January 1998
Revised 15 February 1999

ABSTRACT

A size-structured model is developed to study the growth of tumor cell populations during chemotherapeutic treatment with two non-cross resistant drugs, $\mathcal{D}_0$ and $\mathcal{D}_1$. The cells reproduce by fission. Four types of cells are considered: sensitive cells to both $\mathcal{D}_0$ and $\mathcal{D}_1$, cells that are resistant to $\mathcal{D}_0$ only, cells that are resistant to $\mathcal{D}_1$ only, and cells that are resistant to both $\mathcal{D}_0$ and $\mathcal{D}_1$. Resistant cells arise by spontaneous genetic mutation from sensitive cells and are selected during the growth of the mixed population. The model consists on a system of linear partial differential equations describing the size-density of each type of cells. That corresponds to chemotherapeutic treatment on a given time sequence intervals such that, we continuously apply $\mathcal{D}_0$ at a first interval and next we apply $\mathcal{D}_1$ at a second interval, and so forth. We obtain a stable size-distribution theorem for this case.

Keywords: Size structure, tumor cell population, cellular resistance, evolution operator.

1. Introduction

Our aim in this paper is to describe a stable size-distribution theorem for a mathematical model developed to study the cellular resistance in tumor cell populations during alternated chemotherapeutic treatment with two non-cross resistant antiblastic drugs, $\mathcal{D}_0$ and $\mathcal{D}_1$.

We have considered the size-structure to describe the cellular resistance problem in tumor cell populations because antiblastic drugs are phase-specific, which means that they only act on a determined sensitivity phase of the cells.

It is also incorporated in the model the concept of spontaneous genetic mutation from sensitivity to resistance independent from the selection agent as previously demonstrated in the classical observations of Luria and Delbruck.

In a previous work [15], we have extended the result of stable size-distribution for a size-structured mathematical model for the growth of a cell population reproducing by binary fission into two exactly equal parts given in [8, Corollary 7.3]. We have considered an extension of that model for a tumor cell population in which two distinct subpopulations is considered: sensitive and resistant. We have shown the existence of stable size-distribution for each tumor cell subpopulation in two cases of only one drug treatment on sensitive cells: (a) a non-stop treatment, and (b) an instantaneous drug action on prescribed times.

For case (a), the model is given by the linear system:

$$\begin{cases} \dfrac{\partial s}{\partial t}(t,x) + \dfrac{\partial}{\partial x}(g(x)s(t,x)) \\ \quad = -(\mu(x) + \mu_F(x) + b(x))s(t,x) + 4(1-\alpha)b(2x)s(t,2x) \\ \dfrac{\partial r}{\partial t}(t,x) + \dfrac{\partial}{\partial x}(g(x)r(t,x)) \\ \quad = -(\mu(x) + b(x))r(t,x) + 4b(2x)r(t,2x) + 4\alpha b(2x)s(t,2x) \end{cases}$$

where t denotes the time, x denotes the *size* of an individual cell, $s = s(t,x)$ denotes the cell size density of sensitive cells at time t, $r = r(t,x)$ denotes the cell size density of resistant cells at time t, α is the constant mutation rate from sensitive into resistant tumor cells and, $g(x)$ is the size-specific individual growth rate; $\mu(x)$ is the size-specific per capita death rate, μ_F is the drug-kill rate for sensitive cells per capita per unit of time and, $b(x)$ is the size-specific probability of fission per unit of time.

The last term of each equation contains the factor $4 = 2 \times 2$ due to the fact that a cell divides into 2 parts and the second factor 2 is due to the fact that the size of daughters cells at $(x, x+dx)$ comes from the size of mothers cells at $(2x, 2x+2dx)$. Added to this, considerations at the level of the population individual cells lead to an evolution problem that generates a strongly-continuous semigroup.

The asymptotic behavior of this semigroup heavily depends on the functional relationship between the cell growth and its size x described by the size-dependent individual growth rate g. In supposing $g(2x) < 2g(x)$ for all relevant x, i. e., *the time that a cell needs to grow from size x to size $2x$ increases with their size x*, a stable size-distribution theorem for this problem is given in [15, Theorem 3]:

There exist a Malthusian parameter λ_1, a stable size-distribution $s_{\lambda_1}(x)$ for sensitive cells, and a Malthusian parameter λ_2 which has a correspondent stable size-distribution, $r_{\lambda_2}(x)$, for resistant cells, such that, as $t \to \infty$,

$$e^{-\lambda_1 t} s(t,x;\phi) \sim C_1 s_{\lambda_1}(x)$$
$$e^{-\lambda_2 t} r(t,x;\phi) \sim C_2 r_{\lambda_2}(x)$$

where $\lambda_1 < \lambda_2$, C_1 only depends on the first coordinated function of the initial condition ϕ and C_2 only depends on ϕ.

The model analyzed in this paper is an extension of the above model. It is formulated as the time-dependent evolution problem (2.6) below, arising from Eq. (2.1) to Eq. (2.4). In Corollary 3.1 we will state the correspondent result of stable size-distribution.

Roughly its statement is the following.

There exist real parameters $\lambda_1^i < \lambda_2^i < \lambda_3^i < \lambda_4$ $(i = 0, 1)$ and, for sufficiently large T, there exist non-negative bounded linear operators $\hat{s} = \hat{s}(T;\cdot)$, $\hat{r}_1 = \hat{r}_1(T;\cdot)$, $\hat{r}_2 = \hat{r}_2(T;\cdot)$ and $\hat{r}_d = \hat{r}_d(T;\cdot)$ such that, for all initial condition ϕ, as $n \to \infty$,

$$\begin{aligned} e^{-nT(\lambda_1^0+\lambda_1^1)} \quad s(2nT;\phi) &\to \hat{s}(T;\phi) \\ e^{-nT(\lambda_3^0+\lambda_2^1)} \quad r_1(2nT;\phi) &\to \hat{r}_1(T;\phi) \\ e^{-nT(\lambda_2^0+\lambda_3^1)} \quad r_2(2nT;\phi) &\to \hat{r}_2(T;\phi) \\ e^{-2nT\lambda_4} \quad r_d(2nT;\phi) &\to \hat{r}_d(T;\phi) \end{aligned}$$

where

$T > 0$ *is the duration time for each drug;*
$s(t,\phi)$ *is the size-density for cells that are sensitive to both $\mathcal{D}_0$ and $\mathcal{D}_1$ drugs at time t;*
$r_1(t,\phi)$ *is the size-density for cells that are resistant to $\mathcal{D}_0$ at time t;*
$r_2(t,\phi)$ *is the size-density for cells that are resistant to $\mathcal{D}_1$ at time t;*
$r_d(t,\phi)$ *is the size-density for cells that are resistant to both $\mathcal{D}_0$ and $\mathcal{D}_1$ at time t.*

In this case, a stable size-distribution becomes a uniform limit of projections that depends on a convenient choice of the drug duration time $T > 0$.

As a consequence, each subpopulation has a stable size distribution in the following sense: *for all sufficiently large n, the ratio of the number of cells of any subpopulation of tumor cells in a given size-interval by the total number of cells of this subpopulation is time independent.*

2. The Model and Its Interpretation

We consider four different types of tumor cells:

s-cells: cells sensitive to the action of $\mathcal{D}_0$ and $\mathcal{D}_1$ antiblastic drugs;
r_1-cells: cells that are resistant to the action of $\mathcal{D}_0$ and sensitive to the action of $\mathcal{D}_1$;
r_2-cells: cells that are resistant to the action of $\mathcal{D}_1$ and sensitive to the action of $\mathcal{D}_0$;
r_d-cells: cells that are resistant to both $\mathcal{D}_0$ and $\mathcal{D}_1$ actions.

The cells grow, die and reproduce by binary fission into two identical daughters. Any r_d-cell produces two identical r_d-cells, under division. An s-cell can produce two identical s-cells, two identical r_1-cells or two identical r_2-cells, under division.

Any r_1-cell can produce two identical r_1-cells or two identical r_d-cells, under division, and, an r_2-cell can produce two identical r_2-cells or two identical r_d-cells, under division. It is assumed that any cell of the population is characterized and distinguished from each other by an appropriate physically conserved quantity denoted by x, called the *size* of a cell of the population. We can interpret the size of a cell as its volume or mass.

Let $J_0, J_1, J_2, \cdots$ denote a sequence of intervals where it will occur continuous applications of the non-cross-resistant anti-blastic drugs $\mathcal{D}_0$ and $\mathcal{D}_1$.

Thus,

At J_n, for n even, only drug $\mathcal{D}_0$ acts continuously over the subpopulations of s-cells and r_2-cells;

At J_n, for n odd, only drug $\mathcal{D}_1$ acts continuously over the subpopulations of s-cells and r_1-cells.

The proposed size-structured model for the evolution of the tumor cells of the population is described by a nonautonomous linear system, given by following equations (2.1) to (2.4):

Equation for sensitivity:

$$\begin{cases} \dfrac{\partial s}{\partial t}(t,x) + \dfrac{\partial}{\partial x}(g(x)s(t,x)) \\ \qquad = -(\mu(x) + b(x) + (\mu_{\mathcal{D}_0} + \mu_{\mathcal{D}_1})(t,x))s(t,x) \\ \qquad\quad + 4b(2x)s(t,2x) - \alpha_1 \cdot 4b(2x)s(t,2x) - \alpha_2 \cdot 4b(2x)s(t,2x) \end{cases} \tag{2.1}$$

where $s(t,x)$ denotes the size-dependent density of s-cells at time t;

Equation for resistance to $\mathcal{D}_0$ and sensitivity to $\mathcal{D}_1$:

$$\begin{cases} \dfrac{\partial r_1}{\partial t}(t,x) + \dfrac{\partial}{\partial x}(g(x)r_1(t,x)) \\ \qquad = -(\mu(x) + b(x) + \mu_{\mathcal{D}_1}(t,x))r_1(t,x) \\ \qquad\quad + 4b(2x)r_1(t,2x) + \alpha_1 \cdot 4b(2x)s(t,2x) - \alpha_2 \cdot 4b(2x)r_1(t,2x) \end{cases} \tag{2.2}$$

where $r_1(t,x)$ denotes the size-dependent density of r_1-cells at time t;

Equation for resistance to $\mathcal{D}_1$ and sensitivity to $\mathcal{D}_0$:

$$\begin{cases} \dfrac{\partial r_2}{\partial t}(t,x) + \dfrac{\partial}{\partial x}(g(x)r_2(t,x)) \\ \qquad = -(\mu(x) + b(x) + \mu_{\mathcal{D}_0}(t,x))r_2(t,x) \\ \qquad\quad + 4b(2x)r_2(t,2x) + \alpha_2 \cdot 4b(2x)s(t,2x) - \alpha_1 \cdot 4b(2x)r_2(t,2x) \end{cases} \tag{2.3}$$

where $r_2(t,x)$ denotes the size-dependent density of r_2-cells at time t;

Equation for resistance to $\mathcal{D}_0$ and $\mathcal{D}_1$:

$$\begin{cases} \dfrac{\partial r_d}{\partial t}(t,x) + \dfrac{\partial}{\partial x}(g(x)r_d(t,x)) \\ \qquad = -(\mu(x)+b(x))r_d(t,x) \\ \qquad\quad + 4b(2x)r_d(t,2x) + \alpha_1 \cdot 4b(2x)r_2(t,2x) + \alpha_2 \cdot 4b(2x)r_1(t,2x) \end{cases} \tag{2.4}$$

where $r_d(t,x)$ denotes the size-dependent density of r_d-cells at time t.

The coefficients $\alpha_1, \alpha_2, g, b, \mu, \mu_{\mathcal{D}_0}, \mu_{\mathcal{D}_1}$ are such that:

α_1 is the *mutation rate* constant for s-cells into r_1-cells and for r_2-cells into r_d-cells;
α_2 is the *mutation rate* constant for s-cells into r_2-cells and for r_1-cells into r_d-cells;
g is the *individual size growth rate* per unit of time,

$$\frac{dx}{dt} = g(x); \tag{2.5}$$

b is the *probability of division* per capita per unit of time;
μ is the *death rate* per capita per unit of time;
$\mu_{\mathcal{D}_i}$ $(i = 0, 1)$ is the $\mathcal{D}_i$ *-drug-kill rate* time dependent per capita per unit of time, given for all $x \in \Omega$ by

$$\mu_{\mathcal{D}_i}(t,x) = \begin{cases} \mu_i(x) & (t \in J_{2k+i}) \\ 0 & (otherwise) \end{cases} \quad (k = 0, 1, 2, \cdots)$$

where μ_i is the $\mathcal{D}_i$-drug-kill rate per capita per unit of time.

In order to state the evolution problem, we consider:

1. The size x of the cells is normalized with $x \le x_{max} = 1$.
2. A given cell can divide itself only if its size is greater than a certain fixed threshold size $x = a > 0$ and all cells of the population have to divide themselves if their size x tends to the maximal size $x = 1$.
3. At division, an individual cell of size $x > a$ produces two daughters cells, each of them having the size $\dfrac{x}{2}$.

From these considerations it follows:

(*) there are no cells in the population with size less or equal to $\dfrac{a}{2}$;

(**) in Eq. (2.1) – Eq. (2.4) the terms involving the $2x$ argument should be considered equal to zero if $x \ge \dfrac{1}{2}$.

We arrive at the following **evolution problem**

$$\begin{cases} \dfrac{\partial u}{\partial t} = -\dfrac{\partial}{\partial x}(g(x)u(t,x)) - N_{\mathcal{D}}(t,x)u(t,x) & \\ \qquad\qquad\qquad + N_{\alpha_1,\alpha_2}(x)u(t,2x) & (t > 0, x \in \Omega) \\ u(t, \frac{a}{2}) = 0 & (t > 0) \\ u(0,x) = u^0(x) & (x \in \Omega) \end{cases} \tag{2.6}$$

where

$$0 \le \alpha_1, \alpha_2 \le \alpha_1 + \alpha_2 < 1;$$

$$N_{\mathcal{D}} = \begin{pmatrix} \mu + b + \mu_{\mathcal{D}_0} + \mu_{\mathcal{D}_1} & 0 & 0 & 0 \\ 0 & \mu + b + \mu_{\mathcal{D}_1} & 0 & 0 \\ 0 & 0 & \mu + b + \mu_{\mathcal{D}_0} & 0 \\ 0 & 0 & 0 & \mu + b \end{pmatrix};$$

$$N_{\alpha_1,\alpha_2}(x) = 4 \begin{pmatrix} (1-\alpha_1-\alpha_2)b(2x) & 0 & 0 & 0 \\ \alpha_1 b(2x) & (1-\alpha_2)b(2x) & 0 & 0 \\ \alpha_2 b(2x) & 0 & (1-\alpha_1)b(2x) & 0 \\ 0 & \alpha_2 b(2x) & \alpha_1 b(2x) & b(2x) \end{pmatrix}.$$

We recall that $N_{\alpha_1,\alpha_2}(x)u(t,2x) \equiv 0 \ \ (x \in \Omega_1)$.

Abstract Evolution Problem

Now, we intend to study the solutions of the problem (2.6) considering its time-dependent evolution. As we can see, the solution operator of problem (2.6) does not consist on a semigroup of operators. In fact, it is a *periodic* evolution operator.

In order to simplify the notation we will denote $\Omega = \left[\frac{a}{2}, 1\right]$, $\Omega_0 = \left[\frac{a}{2}, \frac{1}{2}\right]$ and $\Omega_1 = \left[\frac{1}{2}, 1\right]$.

We make some technical assumptions:

(I) g is a continuous, strictly positive function on Ω.

(II) b is continuous on $\left[\frac{a}{2}, 1\right)$, identically zero on $\left[\frac{a}{2}, a\right]$, strictly positive on $(a,1)$ and $\lim_{x\uparrow 1} \int_a^x b(\xi)d\xi = +\infty$.

(III) μ, μ_0, μ_1 are integrable functions such that, $0 \le \mu, \mu_0, \mu_1 \le 1$ on Ω, almost everywhere.

We can have the function $G(x) := \int_{a/2}^{x} \frac{d\xi}{g(\xi)}$ from Eq. (2.5) interpreted as the time that a cell needs to grow from the minimal size $\frac{a}{2}$ to the size x.

Let F_i and $\mathcal{F}_i$ $(i = 0, 1)$ be defined on Ω by:

$$F_i(x) := \exp\left(-\int_{a/2}^{x} \frac{\mu_i(\xi)}{g(\xi)} d\xi\right), \ \mathcal{F}_i(x) := \exp\left(-\int_{a/2}^{x} \frac{(\mu + b + \mu_i)(\xi)}{g(\xi)} d\xi\right) \quad (2.7)$$

and

$$E(x) := \frac{\mathcal{F}_i(x)}{F_i(x)} = \exp\left(-\int_{a/2}^{x} \frac{\mu(\xi) + b(\xi)}{g(\xi)} d\xi\right). \quad (2.8)$$

We have

$E(x)$ is the probability of a size $\dfrac{a}{2}$ cell to reach the size x without dying or being divided;

$F_i(x)$ is the probability of a size $\dfrac{a}{2}$ cell to reach the size x without being killed by $\mathcal{D}_i$ drug ;

$\mathcal{F}_i(x) = E(x)$ for any r_i-cell of size x.

By applying a transformation of dependent variables defined by means of the above functions to the problem (2.6) we have the abstract Cauchy problem (A.1) in the Appendix A.

After that we consider the semigroups $\{e^{t\mathcal{A}_i}\}_{t\geq 0}$ for $i = 0, 1$ on a Banach cartesian product space X^4 of continuous functions, generated by the unbounded linear operator $\mathcal{A}_i$ that correspond to the case of non-stop treatment with the drug $\mathcal{D}_i$.

Then from the fact that these semigroups do not commute, we define the weak solution of the abstract evolution problem (A.1) corresponding to (2.6) by composing in a sequence the semigroup $\{e^{t\mathcal{A}_0}\}$ on J_0 then the semigroup $\{e^{t\mathcal{A}_1}\}$ on J_1 and so on.

We give more details about the above considerations in the Appendix A.

Remark. The condition $g(2x) < 2g(x)$ for $x \in \Omega_0 = \left[\dfrac{a}{2}, \dfrac{1}{2}\right]$ implies the compacity in the semigroup $e^{t\mathcal{A}_i}(i = 0, 1)$ and the analysis of their asymptotic behavior as $t \to \infty$ becomes easier. The same conclusion follows in the case of the biologically unrealistic assumption $g(2x) > 2g(x)$ for $x \in \Omega_0$ and the compacity is lost in case of $g(2x) = 2g(x)$ for $x \in \Omega_0$. See [1, Example 4].

3. Asymptotic Behavior of the Solutions

In the first half of this section we describe the asymptotic behavior for large time of $e^{t\mathcal{A}_0}$ and $e^{t\mathcal{A}_1}$ in Theorems 3.1 and 3.2, respectively. These are stable size-distribution theorems that respectively correspond to a chemotherapeutical treatment with a time continuous $\mathcal{D}_0$ action on s-cells and r_1-cells and, time continuous $\mathcal{D}_1$ action on s-cells and r_1-cells alternately for a same period of time T. After that, by combining these results, we obtain the asymptotic behavior for large n of $(e^{T\mathcal{A}_1}e^{T\mathcal{A}_0})^n$ in Corollary 3.1 for $T > 0$. From that we deduce a stable size-distribution theorem for problem (2.6).

Notation. Let we represent any $\phi \in X^4$ by a column consisting of four coordinate functions ϕ_1, ϕ_2, ϕ_3 and ϕ_4 belonging to the space X. Following columns are associated with a such ϕ:

$$\phi^{(3)} := \begin{pmatrix} \phi_1 \\ \phi_2 \\ \phi_3 \end{pmatrix}, \quad \phi^{(2)} := \begin{pmatrix} \phi_1 \\ \phi_2 \end{pmatrix} \quad \text{and} \;, \quad \widetilde{\phi^{(2)}} = \begin{pmatrix} \phi_1 \\ 0 \\ \phi_3 \end{pmatrix}.$$

Next developments are based on the assumption

(A) $g(2x) < 2g(x)$ for all $x \in \Omega_0 = \left[\frac{a}{2}, \frac{1}{2}\right]$

and also on the following

(B) $a \geq 1/2$ and the functions $\mu_0 \geq 0$, $\mu_1 \geq 0$ are continuous, not identical to zero on $\Omega = \left[\frac{a}{2}, 1\right]$.

Cases of Treatment with Only One Drug

If the mutation rates satisfies the inequalities

$$0 < \alpha_2 \leq \alpha_1 < 1/2\,,$$

the asymptotic behavior of the semigroup $e^{t\mathcal{A}_0}$, is given by:

Theorem 3.1. *Suppose $g(2x) < 2g(x)$, for all $x \in \Omega_0$. There exist real numbers $\lambda_1^0 < \lambda_2^0 < \lambda_3^0 < \lambda_4$ and non-negative functions $S_{\lambda_1^0}, R_{1\lambda_3^0}, R_{2\lambda_2^0}$ and $R_{d\lambda_4}$ such that for any $\phi \in X^4$, there exist real constants $C_0^{(1)}(\phi_1), C_0^{(2)}\left(\widetilde{\phi^{(2)}}\right)$, $C_0^{(3)}\left(\phi^{(3)}\right)$ and $C_0(\phi)$ so that for any $t \geq 0$ we can write*

$$e^{t\mathcal{A}_0}\phi = \begin{pmatrix} e^{t\lambda_1^0} C_0^{(1)}(\phi_1) S_{\lambda_1^0} \\ e^{t\lambda_3^0} C_0^{(3)}\left(\phi^{(3)}\right) R_{1\lambda_3^0} \\ e^{t\lambda_2^0} C_0^{(2)}\left(\widetilde{\phi^{(2)}}\right) R_{2\lambda_2^0} \\ e^{t\lambda_4} C_0(\phi) R_{d\lambda_4} \end{pmatrix} + \begin{pmatrix} z_1(t, \phi_1) \\ z_2\left(t, \phi^{(3)}\right) \\ z_3\left(t, \widetilde{\phi^{(2)}}\right) \\ z_4(t, \phi) \end{pmatrix}$$

where for the $z_i\,(i = 1, \ldots, 4)$ we have:

$$\begin{aligned} \lim_{t\to+\infty} e^{-t\lambda_1^0} z_1(t, \phi_1) &= 0 \\ \lim_{t\to+\infty} e^{-t\lambda_3^0} z_2\left(t, \phi^{(3)}\right) &= 0 \\ \lim_{t\to+\infty} e^{-t\lambda_2^0} z_3\left(t, \widetilde{\phi^{(2)}}\right) &= 0 \\ \lim_{t\to+\infty} e^{-t\lambda_4} z_4(t, \phi) &= 0\,. \end{aligned}$$

It results that there exists a stable size-distribution for each cell subpopulation in the tumor cell population under a non-stop treatment with $\mathcal{D}_0$.

Next, we have a similar result of existence of a stable size-distribution for each cell subpopulation in the tumor cell population under a non-stop treatment with $\mathcal{D}_1$.

If the mutation rates satisfies the inequalities

$$0 < \alpha_1 \leq \alpha_2 < 1/2\,,$$

the asymptotic behavior of the semigroup $e^{t\mathcal{A}_1}$ is given by the following theorem.

Theorem 3.2. *Suppose $g(2x) < 2g(x)$, for all $x \in \Omega_0$. There exist real numbers $\lambda_1^1 < \lambda_2^1 < \lambda_3^1 < \lambda_4$ and non-negative functions $S_{\lambda_1^1}$, $R_{1\lambda_2^1}$, $R_{2\lambda_3^1}$ and $R_{d\lambda_4}$ such that for any given $\phi \in X^4$ there exist real constants $C_1^{(1)}(\phi_1)$, $C_1^{(2)}(\phi^{(2)})$, $C_1^{(3)}(\phi^{(3)})$, $C_1(\phi)$ so that for any $t \geq 0$ we can write*

$$e^{t\mathcal{A}_1}\phi = \begin{pmatrix} e^{\lambda_1^1 t} C_1^{(1)}(\phi_1) S_{\lambda_1^1} \\ e^{\lambda_2^1 t} C_1^{(2)}(\phi^{(2)}) R_{1\lambda_2^1} \\ e^{\lambda_3^1 t} C_1^{(3)}(\phi^{(3)}) R_{2\lambda_3^1} \\ e^{\lambda_4 t} C_1(\phi) R_{d\lambda_4} \end{pmatrix} + \begin{pmatrix} z_1(t,\phi_1) \\ z_2(t,\phi^{(2)}) \\ z_3(t,\phi^{(3)}) \\ z_4(t,\phi) \end{pmatrix}$$

where

$$\lim_{t\to\infty} e^{-\lambda_i^1} z_i = 0 \quad (i = 1,2,3) \text{ and } \lim_{t\to\infty} e^{-\lambda_4 t} z_4 = 0.$$

Theorems 3.1 and 3.2 can be proved by means of arguments similar to those given in the proof to Corollary 3.1 in Appendix C.

Alternate Treatment

Finally we consider the situation where each treatment is applied alternately for a same period of time T. First, $\mathcal{D}_0$-treatment is applied during the interval of time $J_0 = [0, T]$ to kill sensitive and r_2-cells and so $\mathcal{D}_1$-treatment is applied during the interval of time $J_1 = [T, 2T]$ to kill sensitive and r_1-cells and so on.

We combine the results of both theorems above by considering that the mutation rates are equals, that is to say, satisfies the relations

$$0 < \alpha_2 = \alpha_1 = \alpha < 1/2$$

to give the asymptotic behavior of $\left(e^{T\mathcal{A}_1} e^{T\mathcal{A}_0}\right)^n$, as n tends to infinity.

Corollary 3.1. *Suppose $g(2x) < 2g(x)$, for all $x \in \Omega_0$. For a convenient choice of $T > 0$, there exist non-negative bounded linear operators $\overline{S} = \overline{S}(T,\cdot), \overline{R}_1 = \overline{R}_1(T,\cdot), \overline{R}_2 = \overline{R}_2(T,\cdot), \overline{R}_d = \overline{R}_d(T,\cdot)$ from X^4 to X, such that, for all $\phi \in X^4$, as $n \to \infty$,*

$$\begin{aligned} e^{-nT(\lambda_1^0+\lambda_1^1)}[(e^{T\mathcal{A}_1} e^{T\mathcal{A}_0})^n \phi]_1 &\to \overline{S}(T,\phi)\,, \\ e^{-nT(\lambda_3^0+\lambda_2^1)}[(e^{T\mathcal{A}_1} e^{T\mathcal{A}_0})^n \phi]_2 &\to \overline{R}_1(T,\phi)\,, \\ e^{-nT(\lambda_2^0+\lambda_3^1)}[(e^{T\mathcal{A}_1} e^{T\mathcal{A}_0})^n \phi]_3 &\to \overline{R}_2(T,\phi)\,, \\ e^{-2nT\lambda_4}[(e^{T\mathcal{A}_1} e^{T\mathcal{A}_0})^n \phi]_4 &\to \overline{R}_d(T,\phi)\,. \end{aligned}$$

Proof. The sketch of the proof of this result is given in Appendix C.

Remark

1. Malthusian parameters for each kind of cell subpopulation in consideration are given in Appendix B.
2. For K and ε we have:

$$K = \max\{K_i, K_i^{(j)} : i = 0, 1; j = 1, 2, 3\}$$

and

$$\varepsilon = \min\{\varepsilon_i, \varepsilon_i^{(j)} : i = 0, 1; j = 1, 2, 3\},$$

from Eq. (B.8), Eq. (B.11) and Eq. (B.12) in the Appendix B. Then we take

$$T > \frac{1}{\varepsilon} \ln K \, .$$

3. Theorem 3.1 gives the stable size-distribution for the case $\mu_0 \equiv \mu_1 \equiv 0$ which corresponds to the situation where there is no treatment.

4. Conclusion

In the case of prolonged treatment we found that each cell subpopulation considered has an intrinsic Malthusian parameter and an intrinsic stable size-distribution. In this direction, Corollary 3.1 essentially explains the fact that for appropriate choice of T and for large n each cell subpopulation has their own stable size distribution: *"for all n sufficiently large, the ratio of the size distribution of any subpopulation of tumor cells in a given size-interval, by the total subpopulation, is constant, independent of the time"*.

In this work as in the previous one [15], we did need a different kind of extension of the stable size-distribution notion than the one given in [1,8,21]. They only refer to a population of individuals of the same species. Notice that if one applies directly the results found in the literature, the asymptotic behavior of the sensitive cell subpopulations is completely lost.

Toxicity problems in human chemotherapeutic treatments lead us to think that these theoretical results may have some experimental relevance.

Appendix A. Abstract Evolution Problem

Transformation of Variables

Let H_0 and H_1 denote the matrix operators which corresponds respectively to the following formal transformations of dependent variables

$$S = g\,\frac{s}{\mathcal{F}_0}\,, \; R_1 = g\,\frac{r_1}{E}\,, \; R_2 = g\,\frac{r_2}{\mathcal{F}_0}\,, \; R_d = g\,\frac{r_d}{E}\,,$$

and

$$S = g\,\frac{s}{\mathcal{F}_1}\,, \; R_1 = g\,\frac{r_1}{E}\,, \; R_2 = g\,\frac{r_2}{\mathcal{F}_1}\,, \; R_d = g\,\frac{r_d}{E}\,,$$

with g , F_i and $\mathcal{F}_i\,(i = 0, 1)$ and E defined respectively by (2.5), (2.7) and (2.8).

Substituting in (2.6) the formal transformation

$$U(t,x) = Hu(t,x) = \begin{cases} H_0\, u(t,x) & (t \in J_{2k}) \\ H_1\, u(t,x) & (t \in J_{2k+1}) \end{cases}$$

we have the following transformed problem:

$$\begin{cases} \dfrac{\partial U}{\partial t} = -g(x)\dfrac{\partial U}{\partial x}(t,x) + M_{\alpha_1,\alpha_2}(t,x)U(t,2x) & (t > 0, x \in \Omega) \\ U\left(t, \dfrac{a}{2}\right) = 0 & (t > 0) \\ U(0,x) = U^0(x) & (x \in \Omega) \end{cases} \tag{A.1}$$

with

$$M_{\alpha_1,\alpha_2}(t,x)U(t,2x) \equiv 0, \text{ for all } t \geq 0, \text{ if } x \in \Omega_1,$$

where

$$M_{\alpha_1,\alpha_2}(t,x) = \begin{cases} M^0_{\alpha_1,\alpha_2}(x) & (t \in J_{2k}) \\ \\ M^1_{\alpha_1,\alpha_2}(x) & (t \in J_{2k+1}) \end{cases}$$

for

$$M^0_{\alpha_1,\alpha_2}(x) = \begin{pmatrix} (1-\alpha_1-\alpha_2)k_0(x) & 0 & 0 & 0 \\ \alpha_1 k_0^0(x) & (1-\alpha_2)k(x) & 0 & 0 \\ \alpha_2 k_0(x) & 0 & (1-\alpha_1)k_0(x) & 0 \\ 0 & \alpha_2 k(x) & \alpha_1 k_0^0(x) & k(x) \end{pmatrix},$$

$$M^1_{\alpha_1,\alpha_2}(x) = \begin{pmatrix} (1-\alpha_1-\alpha_2)k_1(x) & 0 & 0 & 0 \\ \alpha_1 k_1(x) & (1-\alpha_2)k_1(x) & 0 & 0 \\ \alpha_2 k_1^0(x) & 0 & (1-\alpha_1)k(x) & 0 \\ 0 & \alpha_2 k_1^0(x) & \alpha_1 k(x) & k(x) \end{pmatrix},$$

$$k(x) = 4g(x)\,\frac{b(2x)}{g(2x)}\,\frac{E(2x)}{E(x)},$$

$$k_i(x) = 4g(x)\,\frac{b(2x)}{g(2x)}\,\frac{\mathcal{F}_i(2x)}{\mathcal{F}_i(x)} = k(x)\,\frac{F_i(2x)}{F_i(x)}$$

and

$$k_i^0(x) = 4g(x)\,\frac{b(2x)}{g(2x)}\,\frac{\mathcal{F}_i(2x)}{E(x)} = k(x)F_i(2x).$$

Abstract Cauchy Problem

In order to get to the solution of (A.1), we consider for $i = 0, 1$ the unbounded linear operators $\mathcal{A}_i$ on X^4, where $X = \{\phi \in C(\Omega) : \phi(a/2) = 0\}$ with the sup-norm, defined by

$$D(\mathcal{A}_i) = \Big\{U \in (X \cap C^1(\Omega \setminus \{\tfrac{1}{2}\}))^4 : U'(a/2) = 0, \lim_{x \downarrow \frac{1}{2}} [-g(x)U'(x)]$$
$$\text{and } \lim_{x \uparrow \frac{1}{2}} [-g(x)U'(x) + M^i_{\alpha_1,\alpha_2}(x)U(2x)] \text{ exist and are equal } \Big\},$$

$$(\mathcal{A}_i U)(x) = -g(x)U'(x) + M^i_{\alpha_1,\alpha_2}(x)U(2x)\ (x \in \Omega, U \in D(\mathcal{A}_i)).$$

One can demonstrate, using arguments similar to those given in [8], the following result.

Theorem A.1. $\mathcal{A}_i$ $(i = 0, 1)$ *is closed densely defined linear operator on* X^4 *which generates a linear* C_0*-semigroups* $\{e^{t\mathcal{A}_i}\}_{t \geq 0}$ *on* X^4.

If $g(2x) < 2g(x)$ *for* $x \in \Omega_0$, *then* $e^{t\mathcal{A}_i}$ *is a compact operator for* $t \geq G(1)$.

The solution of (A.1) is given by composition of the solution operators $\{e^{t\mathcal{A}_1}\}_{t \geq 0}$ and $\{e^{t\mathcal{A}_0}\}_{t \geq 0}$.

Results in Theorem A.1 have correspondents in the initial problem (2.6), *i. e.*, weak solutions of problem (2.6) are given by a sequence of composition of the following semigroups

$$H_0^{-1} e^{t\mathcal{A}_0} H_0 u^0 \quad \text{and} \quad H_1^{-1} e^{t\mathcal{A}_1} H_1 u^1 \ \ (t \geq 0)$$

where, the transformation H_i $(i = 0, 1)$ is an isomorphism from Banach space X_0^4 onto X^4 with $X_0 = \{\phi \in X : \phi/E \text{ is bounded }\}$ and $\|\phi\|_0 = \|\phi/E\|_\infty$.

Appendix B. Spectral Properties of $\mathcal{A}_i$ (and $e^{t\mathcal{A}_i}$)$(i = 0, 1)$

In this section, we will follow the results contained in [8] and [20]. We also refer the reader to [16,11].

The Spectrum of $\mathcal{A}_i (i = 0, 1)$, Case $a \geq \dfrac{1}{2}$

Suppose $a \geq \dfrac{1}{2}$ (i.e., the maximal size of a daughter cell is less than the minimal size of a mother cell). For a detailed study of the general case, see [12, Chapter II]. We make use of the above condition to study U solutions of the equation $\lambda U - \mathcal{A}_i U = f$ for $\lambda \in \mathbb{C}$ and $f \in X^4$. By doing so, we conclude that $x \in \Omega_0$ implies in $2x \in \Omega_1$ and then we first integrate on Ω_1 and on Ω_0 afterwards. Explicitly we have:

In Ω_1,

$$U(x) = e^{\lambda(G(\frac{1}{2}) - G(x))} U\left(\frac{1}{2}\right) + \int_{1/2}^{x} e^{\lambda(G(\xi) - G(x))} f(\xi) \frac{d\xi}{g(\xi)}. \tag{B.1}$$

In Ω_0,

$$U(x) = e^{\lambda(G(\frac{1}{2}) - G(x))} \hat{\pi}_{M^i_{\alpha_1,\alpha_2}}(\lambda, x) U\left(\frac{1}{2}\right) + \hat{\zeta}_{M^i_{\alpha_1,\alpha_2}}(\lambda, f, x) \tag{B.2}$$

where

$$\hat{\pi}_{M^i_{\alpha_1,\alpha_2}}(\lambda,x)=\int_{a/2}^{x}e^{\lambda(G(\xi)-G(2\xi))}M^i_{\alpha_1,\alpha_2}(\xi)\frac{d\xi}{g(\xi)}$$

and

$$\hat{\zeta}_{M^i_{\alpha_1,\alpha_2}}(\lambda,f,x)$$
$$=\int_{a/2}^{x}e^{\lambda(G(\xi)-G(x))}\left[f(\xi)+M^i_{\alpha_1,\alpha_2}(\xi)\left(\int_{1/2}^{2\xi}e^{\lambda(G(\eta)-G(2\xi))}f(\eta)\frac{d\eta}{g(\eta)}\right)\right]\frac{d\xi}{g(\xi)}.$$

We also notice that

$$\hat{\pi}_{M^0_{\alpha_1,\alpha_2}}=\begin{pmatrix}(1-\alpha_1-\alpha_2)\pi_0(\lambda,x) & 0 & 0 & 0\\ \alpha_1\pi_0^0(\lambda,x) & (1-\alpha_2)\pi(\lambda,x) & 0 & 0\\ \alpha_2\pi_0(\lambda,x) & 0 & (1-\alpha_1)\pi_0(\lambda,x) & 0\\ 0 & \alpha_2\pi(\lambda,x) & \alpha_1\pi_0^0(\lambda,x) & \pi(\lambda,x)\end{pmatrix}$$

and

$$\hat{\pi}_{M^1_{\alpha_1,\alpha_2}}=\begin{pmatrix}(1-\alpha_1-\alpha_2)\pi_1(\lambda,x) & 0 & 0 & 0\\ \alpha_1\pi_1(\lambda,x) & (1-\alpha_2)\pi_1(\lambda,x) & 0 & 0\\ \alpha_2\pi_1^0(\lambda,x) & 0 & (1-\alpha_1)\pi(\lambda,x) & 0\\ 0 & \alpha_2\pi_1^0(\lambda,x) & \alpha_1\pi(\lambda,x) & \pi(\lambda,x)\end{pmatrix}$$

with

$$\pi(\lambda,x)=\int_{a/2}^{x}e^{\lambda(G(\xi)-G(2\xi))}k(\xi)\frac{d\xi}{g(\xi)},\ \pi_i(\lambda,x)=\int_{a/2}^{x}e^{\lambda(G(\xi)-G(2\xi))}k_i(\xi)\frac{d\xi}{g(\xi)}$$

and

$$\pi_i^0(\lambda,x)=\int_{a/2}^{x}e^{\lambda(G(\xi)-G(2\xi))}k_i^0(\xi)\frac{d\xi}{g(\xi)},\ (i=0,1).$$

The continuity for $x=\dfrac{1}{2}$ gives the following condition from equations (B.1) and (B.2)

$$(Id-\hat{\pi}_{M^i_{\alpha_1,\alpha_2}}(\lambda))U\left(\frac{1}{2}\right)=\hat{\zeta}_{M^i_{\alpha_1,\alpha_2}}(\lambda,f)\quad(i=0,1)\tag{B.3}$$

where we use the notation for $i=0,1$

$$\pi_i\left(\lambda,\frac{1}{2}\right):=\pi_i(\lambda),\ \ \pi_i^0\left(\lambda,\frac{1}{2}\right):=\pi_i^0(\lambda),$$

$$\hat{\pi}_{M^i_{\alpha_1,\alpha_2}}\left(\lambda, \frac{1}{2}\right) := \hat{\pi}_{M^i_{\alpha_1,\alpha_2}}(\lambda) \quad \text{and} \quad \hat{\zeta}_{M^i_{\alpha_1,\alpha_2}}\left(\lambda, f, \frac{1}{2}\right) := \hat{\zeta}_{M^i_{\alpha_1,\alpha_2}}(\lambda, f).$$

If $det(\hat{\pi}_{M^i_{\alpha_1,\alpha_2}}(\lambda) - Id) \neq 0$, we can solve $U\left(\frac{1}{2}\right)$ in Eq. (B.3) and the resolvent operator for $\mathcal{A}_i$ is given by

$$U(x) = U_\lambda(x) = ((\lambda Id - \mathcal{A}_i)^{-1} f)(x)$$

$$= \begin{cases} e^{\lambda(G(\frac{1}{2})-G(x))} U_\lambda\left(\frac{1}{2}\right) + \int_{1/2}^{x} e^{\lambda(G(\xi)-G(x))} f(\xi) \frac{d\xi}{g(\xi)} \ (x \in \Omega_1) \\ e^{\lambda(G(\frac{1}{2})-G(x))} \hat{\pi}_{M^i_{\alpha_1,\alpha_2}}(\lambda, x) U_\lambda\left(\frac{1}{2}\right) + \hat{\zeta}_{M_i}(\lambda, f, x) \quad (x \in \Omega_0)\,. \end{cases}$$

Then, $\lambda \in \rho(\mathcal{A}_i)$. This resolvent operator is compact.

If $det(Id - \hat{\pi}_{M^i_{\alpha_1,\alpha_2}}(\lambda)) = 0$ then, by solving Eq. (B.3) with $f \equiv 0$, we can find non trivial eigenfunctions for $\mathcal{A}_i$. So $\lambda \in \sigma(\mathcal{A}_i)$.

Notation. For $i = 0, 1$ let λ^i_1, λ^i_2, λ^i_3 and λ_4 denote the real eigenvalues of $\mathcal{A}_i$. We recall that they satisfy:

$$\pi_0(\lambda^0_1) = \frac{1}{1-(\alpha_1+\alpha_2)}, \ \pi_0(\lambda^0_2) = \frac{1}{1-\alpha_1}, \ \pi(\lambda^0_3) = \frac{1}{1-\alpha_2} \ \text{ and } \ \pi(\lambda_4) = 1\,,$$

$$\pi_1(\lambda^1_1) = \frac{1}{1-(\alpha_1+\alpha_2)}, \ \pi_1(\lambda^1_2) = \frac{1}{1-\alpha_2}, \ \pi(\lambda^1_3) = \frac{1}{1-\alpha_1} \ \text{ and } \ \pi(\lambda_4) = 1\,.$$

Localization of the Eigenvalue for $\mathcal{A}_i (i = 0, 1)$

In this section we suppose each function μ_i $(i = 0, 1)$ to be continuous and non identical to zero on Ω. This technical condition is sufficient, for instance, to prove Lemma B.1 below.

The analyticity and monotonicity, of $\pi(\lambda)$ and $\pi_i(\lambda)$ when restricted to real λ, imply the following results in this section which extend their correspondent results in [8, Sec. 6] and [20, Sec. 3.4].

Lemma B.1. *For $i = 0$ or $i = 1$: $\pi_i(\lambda) < \pi(\lambda)$, for all $\lambda \in \mathbb{R}$.*

Eigenvalues of $\mathcal{A}_0$

Suppose $0 < \alpha_2 \leq \alpha_1 < \frac{1}{2}$. Then, we have:

Corollary B.1. *If $g(2x) < 2g(x)$ for $x \in \Omega_0$, then there exists $\varepsilon > 0$, such that, $\lambda \in \sigma(\mathcal{A}_0)$ implies $Re(\lambda) \leq \lambda_4 - \varepsilon$.*

Eigenvalues of $\mathcal{A}_1$

Suppose $0 < \alpha_1 \leq \alpha_2 < \frac{1}{2}$. Then, we have:

Corollary B.2. *If $g(2x) < 2g(x)$ for $x \in \Omega_0$, then there exists $\varepsilon > 0$, such that, $\lambda \in \sigma(\mathcal{A}_1)$ implies $Re(\lambda) \leq \lambda_4 - \varepsilon$.*

In particular we have the following corollary.

Corollary B.3. *If $0 < \alpha_1 = \alpha_2 = \alpha < \frac{1}{2}$, then*

(i) $\lambda_1^0 < \lambda_2^0 < \lambda_3^0 < \lambda_4$.
(ii) $\lambda_1^1 < \lambda_2^1 < \lambda_3^1 < \lambda_4$.

If in addition $\mu_0 \equiv \mu_1$, then $\pi_0 = \pi_1$, $\pi_0^0 = \pi_1^0$, $\lambda_1^0 = \lambda_1^1$, $\lambda_2^0 = \lambda_2^1$ and $\lambda_3^0 = \lambda_3^1$.

Spectral Decompositions related to $\mathcal{A}_i$ and $e^{t\mathcal{A}_i}\,(i = 0, 1)$

For details about the basic results used in this section we refer to [11, Sec. 4.2, Appendix 2.4].

Consider $a \geq \frac{1}{2}$, $0 \leq \alpha_1 = \alpha_2 = \alpha < \frac{1}{2}$ and $g(2x) < 2g(x)$ for $x \in \Omega_0$. So,

$$\lambda_1^i < \lambda_2^i < \lambda_3^i < \lambda_4, \quad \text{for } i = 0, 1. \tag{B.4}$$

We have a direct sum decomposition

$$X^4 = \mathcal{N}(\lambda_4 Id - \mathcal{A}_i) \oplus \mathcal{R}(\lambda_4 Id - \mathcal{A}_i) \tag{B.5}$$

with spectral projection $P_i : X^4 \to \mathcal{N}(\lambda_4 Id - \mathcal{A}_i)$ given by

$$P_i \phi = C_i(\phi) U_{\lambda_4} \tag{B.6}$$

where the first three components of U_{λ_4} are equal to zero and its fourth component is

$$R_{d\lambda_4}(x) = \begin{cases} e^{-\lambda_4 G(x)} & (x \in \Omega_1) \\ e^{-\lambda_4 G(x)} \pi(\lambda_4, x) & (x \in \Omega_0) \end{cases}. \tag{B.7}$$

P_i is the residue at $\lambda = \lambda_4$ in the Laurent development for the resolvent operator $(\lambda Id - \mathcal{A}_i)^{-1}$. Functions $C_i(\phi)$ are not the same for $i = 0, 1$.

Remark. $e^{t\mathcal{A}_i}$ $(i = 0, 1)$ is eventually compact C_0-semigroup.

Then, for all $t \geq 0$,

(a) $\sigma(e^{t\mathcal{A}_i}) \subset \{0\} \cup e^{t\sigma_P(\mathcal{A}_i)}$.
(b) $\mathcal{N}(\lambda_4 Id - \mathcal{A}_i)$ is invariant for $e^{t\mathcal{A}_i}$ and $e^{t\mathcal{A}_i} P_i \phi = e^{t\lambda_4} P_i \phi$.
(c) There exist real numbers $K_i \geq 1$ and $\varepsilon_i > 0$ such that, for all $t \geq 0$,

$$\|e^{t\mathcal{A}_i}(Id - P_i)\| \leq K_i e^{t(\lambda_4 - \varepsilon_i)} \|Id - P_i\|. \tag{B.8}$$

Notation. (i) $[\phi]_k$ represents the k^{th} component of $\phi \in X^4$.
(ii) $\mathcal{A}_i^{(j)}$ (resp. $e^{t\mathcal{A}_i^{(j)}}$) represents for $i = 0$ and $j = 1, 3$, or $i = 1$ and $j = 1, 2, 3$ the principal order j square sub-matrix operator of $\mathcal{A}_i$ (resp. $e^{t\mathcal{A}_i}$) acting on X^j. In cases $i = 0$ and $j = 2$, $\widetilde{\mathcal{A}_0^{(2)}}$ (resp. $e^{t\widetilde{\mathcal{A}_0^{(2)}}}$) represents the principal order 3 square sub-matrix operator of $\mathcal{A}_0$ (resp. $e^{t\mathcal{A}_0}$) having zero entries in their second row and second column as well as, acting on $Z = X \times \{0\} \times X$.

There exist direct sum decompositions for $i = 0, 1$

$$X^j = \mathcal{N}(\lambda_j^i Id - \mathcal{A}_i^{(j)}) \oplus \mathcal{R}(\lambda_j^i Id - \mathcal{A}_i^{(j)}) \quad (j \neq 2, \text{ if } i = 0). \tag{B.9}$$

$P_i^{(j)} : X^j \to \mathcal{N}(\lambda_j^i Id - \mathcal{A}_i^{(j)})$ $(j \neq 2,$ if $i = 0)$ denotes a spectral projection.
For $i = 0$, $j = 2$, we have

$$Z = X \times \{0\} \times X = P_0^{(2)} Z \oplus (Id - P_0^{(2)}) Z, \quad \text{where } P_0^{(2)} Z = \mathcal{N}(\lambda_2^0 Id - \widetilde{\mathcal{A}_0^{(2)}}). \tag{B.10}$$

In all of the above-mentioned cases, we have that $e^{t\mathcal{A}_i^{(j)}}$ (resp. $e^{t\widetilde{\mathcal{A}_0^{(2)}}}$) are C_0-semigroups generated by $\mathcal{A}_i^{(j)}$ (resp. $\widetilde{\mathcal{A}_0^{(2)}}$) and the following lemma.

Lemma B.2. *There exist* $K_i^{(j)} \geq 1$, $\varepsilon_i^{(j)} > 0$ *such that, for all* $t \geq 0$*,*

$$\|e^{t\mathcal{A}_i^{(j)}}(Id - P_i^{(j)})\| \leq K_i^{(j)} e^{t(\lambda_j^i - \varepsilon_i^{(j)})} \|Id - P_i^{(j)}\| \tag{B.11}$$

and

$$\|e^{t\widetilde{\mathcal{A}_0^{(2)}}}(Id - P_0^{(2)})\| \leq K_0^{(2)} e^{t(\lambda_2^0 - \varepsilon_0^{(2)})} \|Id - P_0^{(2)}\|. \tag{B.12}$$

Appendix C. Proofs of the Main Results

Proof of Corollary 3.1

We have $\lambda_1^0 < \lambda_2^0 < \lambda_3^0 < \lambda_4$ and $\lambda_1^1 < \lambda_2^1 < \lambda_3^1 < \lambda_4$ from Corollary B.3 where $\pi(\lambda_4) = 1$, $\pi(\lambda_3^0) = \dfrac{1}{1-\alpha} = \pi(\lambda_3^1)$ which implies $\lambda_3^0 = \lambda_3^1$. We have also $\pi_0(\lambda_2^0) = \dfrac{1}{1-\alpha}$, $\pi_0(\lambda_1^0) = \dfrac{1}{1-2\alpha}$, $\pi_1(\lambda_2^1) = \dfrac{1}{1-\alpha}$, $\pi_1(\lambda_1^1) = \dfrac{1}{1-2\alpha}$. Moreover,

$$\sigma(\mathcal{A}_0) \cap \mathbb{R} = \{\lambda_1^0, \lambda\,{}_2^0, \lambda_3^0, \lambda_4\} \text{ and } \quad \sigma(\mathcal{A}_1) \cap \mathbb{R} = \{\lambda_1^1, \lambda_2^1, \lambda_3^1, \lambda_4\}.$$

From (B.4) the real number λ_4 is the strictly dominating eigenvalue of $\mathcal{A}_0$ and $\mathcal{A}_1$ (satisfies respectively the Corollaries B.1 and B.2) and U_{λ_4} given in (B.6)(B.7) satisfies $\mathcal{A}_0 U_{\lambda_4} = \lambda_4 U_{\lambda_4}$, $\mathcal{A}_1 U_{\lambda_4} = \lambda_4 U_{\lambda_4}$ and we have from $Nucl(\mathcal{A}_0 - \lambda_4 Id) = Nucl(\mathcal{A}_1 - \lambda_4 Id) = \mathbb{R} \cdot \{U_{\lambda_4}\}$ and (B.5):

$$X^4 = \mathbb{R} \cdot \{U_{\lambda_4}\} \oplus Im(\mathcal{A}_0 - \lambda_4 Id) \text{ and } X^4 = \mathbb{R} \cdot \{U_{\lambda_4}\} \oplus Im(\mathcal{A}_1 - \lambda_4 Id).$$

We remark that the functions $P_0, P_1 : X^4 \to \mathbb{R} \cdot \{U_{\lambda_4}\}$ are not the same because in general $C_0(\phi) \neq C_1(\phi)$.

Given $\phi \in X^4$, we can write

$$(e^{T\mathcal{A}_1} e^{T\mathcal{A}_0})^n \phi = \left\{ \sum_{j=1}^{n} (e^{2(n-(j-1))\lambda_4 T} P_0 + e^{(2(n-(j-1))-1)\lambda_4 T} P_1 \delta_0)(\delta_1\delta_0)^{j-1} \right\} \phi + (\delta_1\delta_0)^n \phi \tag{C.1}$$

and

$$(\delta_1\delta_0)^n \phi = \begin{pmatrix} 0 \\ 0 \\ 0 \\ [(\delta_1\delta_0)^n \phi]_4 \end{pmatrix} + \begin{pmatrix} (e^{T\mathcal{A}_1^{(3)}} e^{T\mathcal{A}_0^{(3)}})^n \phi^{(3)} \\ 0 \end{pmatrix} \tag{C.2}$$

where we are using the notation: $\delta_1 := e^{T\mathcal{A}_1}(Id - P_1)$ and $\delta_0 := e^{T\mathcal{A}_0}(Id - P_0)$. Taking into account (B.8) we have from (C.1)

$$\begin{aligned} &\left\| e^{-2nT\lambda_4} \left(e^{T\mathcal{A}_1} e^{T\mathcal{A}_0} \right)^n \right\| \\ &\quad \leq \left\{ 1 + K_0 e^{-T\lambda_4} \right\} \sum_{j=1}^{n} \left(K_1 K_0 e^{-T(\varepsilon_0 + \varepsilon_1)} \right)^{j-1} + \left(K_1 K_0 e^{-T(\varepsilon_0+\varepsilon_1)} \right)^n . \end{aligned} \tag{C.3}$$

Notation

$$\begin{aligned} \delta_0^{(3)} &= e^{T\mathcal{A}_0^{(3)}}(Id - P_0^{(3)}) & \delta_1^{(3)} &= e^{T\mathcal{A}_1^{(3)}}(Id - P_1^{(3)}) \\ \widetilde{\delta_0^{(2)}} &= e^{T\widetilde{\mathcal{A}_0^{(2)}}}(Id - P_0^{(2)}) & \delta_1^{(2)} &= e^{T\mathcal{A}_1^{(2)}}(Id - P_1^{(2)}) \\ \delta_0^{(1)} &= e^{T\mathcal{A}_0^{(1)}}(Id - P_0^{(1)}) & \delta_1^{(1)} &= e^{T\mathcal{A}_1^{(1)}}(Id - P_1^{(1)}) \end{aligned}$$

We observe by direct calculation that the following hold

- $P_1^{(3)} P_0^{(3)} = P_0^{(3)} P_1^{(3)} \equiv 0$.
- $(P_1^{(3)}\psi)^{(2)} = 0$ and $\left((P_0^{(3)}\psi)^{(2)} \right)^{\sim} = 0$.
- $\delta_0^{(3)} P_0^{(3)} = \delta_1^{(3)} P_1^{(3)} = 0$.

These relations imply

$$e^{T\mathcal{A}_0^{(3)}} \phi^{(3)} = e^{T\lambda_3^0} P_0^{(3)} \phi^{(3)} + e^{T\mathcal{A}_0^{(3)}}(Id - P_0^{(3)})\phi^{(3)} = e^{T\lambda_3^0} P_0^{(3)} \phi^{(3)} + \delta_0^{(3)} \phi^{(3)}.$$

We can also deduce the following

$$e^{T\mathcal{A}_1^{(3)}}e^{T\mathcal{A}_0^{(3)}}\phi^{(3)} = \begin{pmatrix} e^{T\mathcal{A}_1^{(1)}}e^{T\mathcal{A}_0^{(1)}}\phi_1 \\ 0 \\ 0 \end{pmatrix} + \begin{pmatrix} 0 \\ \left[e^{T\mathcal{A}_1^{(2)}}\left(\delta_0^{(3)}\phi^{(3)}\right)^{(2)}\right]_2 \\ 0 \end{pmatrix}$$
$$+ e^{T\lambda_3^0}\begin{pmatrix} 0 \\ \left[e^{T\mathcal{A}_1^{(2)}}\left(P_0^{(3)}\phi^{(3)}\right)^{(2)}\right]_2 \\ 0 \end{pmatrix}$$
$$+ e^{T\lambda_3^1}P_1^{(3)}e^{T\widetilde{\mathcal{A}_0^{(2)}}}\widetilde{\phi^{(2)}} + \begin{pmatrix} 0 \\ 0 \\ \left[\delta_1^{(3)}e^{T\widetilde{\mathcal{A}_0^{(2)}}}\widetilde{\phi^{(2)}}\right]_3 \end{pmatrix}. \tag{C.4}$$

It follows from (B.11) and (B.12) the inequalities:

$$\left\|\left[e^{T\mathcal{A}_1^{(3)}}e^{T\mathcal{A}_0^{(3)}}\phi^{(3)}\right]_1\right\| \le e^{T\left(\lambda_1^0+\lambda_1^1\right)}\left\|\phi^{(3)}\right\|$$

$$\left\|\left[e^{T\mathcal{A}_1^{(3)}}e^{T\mathcal{A}_0^{(3)}}\phi^{(3)}\right]_2\right\| \le e^{T\left(\lambda_3^0+\lambda_2^1\right)}\left(1+K_0^{(3)}e^{-T\varepsilon_0^{(3)}}\right)\left\|\phi^{(3)}\right\|$$

$$\left\|\left[e^{T\mathcal{A}_1^{(3)}}e^{T\mathcal{A}_0^{(3)}}\phi^{(3)}\right]_3\right\| \le e^{T\left(\lambda_3^1+\lambda_2^0\right)}\left(1+K_1^{(3)}e^{-T\varepsilon_1^{(3)}}\right)\left\|\phi^{(3)}\right\| .$$

On other side, we can also use for $e^{T\mathcal{A}_0^{(3)}}$ and $e^{T\mathcal{A}_1^{(1)}}$ the following expressions

$$e^{T\mathcal{A}_0^{(3)}} = \begin{pmatrix} e^{T\mathcal{A}_0^{(1)}} & 0 & 0 \\ H(T) & e^{TA_{(1-\alpha)}} & 0 \\ e^{TA^0_{(1-\alpha)}} - e^{T\mathcal{A}_0^{(1)}} & 0 & e^{TA^0_{(1-\alpha)}} \end{pmatrix}$$

and

$$e^{T\mathcal{A}_1^{(3)}} = \begin{pmatrix} e^{T\mathcal{A}_1^{(1)}} & 0 & 0 \\ e^{TA^1_{(1-\alpha)}} - e^{T\mathcal{A}_1^{(1)}} & e^{TA^1_{(1-\alpha)}} & 0 \\ W(T) & 0 & e^{TA_{(1-\alpha)}} \end{pmatrix}$$

where

$$H(T)\psi = \alpha \int_0^T e^{(T-\mu)A_{(1-\alpha)}} C_0^0 \left(e^{T\mathcal{A}_0^{(1)}} \psi\right) d\mu, \text{ with } C_0^0(\varphi)(x) = k_0^0(x)\varphi(2x)$$

and

$$W(T)\psi = \alpha \int_0^T e^{(T-\mu)A_{(1-\alpha)}} C_1^0 \left(e^{T\mathcal{A}_1^{(1)}} \psi\right) d\mu, \text{ with } C_1^0(\varphi)(x) = k_1^0(x)\varphi(2x)$$

and from that

$$\left(e^{T\mathcal{A}_1^{(3)}} e^{T\mathcal{A}_0^{(3)}}\right)\phi^{(3)} = \begin{pmatrix} e^{T\mathcal{A}_1^{(1)}} e^{T\mathcal{A}_0^{(1)}} & 0 & 0 \\ H_1(T) & e^{TA^1_{(1-\alpha)}} e^{TA_{(1-\alpha)}} & 0 \\ W_1(T) & 0 & e^{TA_{(1-\alpha)}} e^{TA^0_{(1-\alpha)}} \end{pmatrix}$$

with

$$H_1(T) = \left(e^{TA^1_{(1-\alpha)}} - e^{T\mathcal{A}_1^{(1)}}\right) e^{T\mathcal{A}_0^{(1)}} + e^{TA^1_{(1-\alpha)}} H(T)$$

and

$$W_1(T) = W(T)\, e^{T\mathcal{A}_0^{(1)}} + e^{TA_{(1-\alpha)}} \left(e^{TA^0_{(1-\alpha)}} - e^{T\mathcal{A}_0^{(1)}}\right).$$

The operators $A^i_{(1-\alpha)}$ $(i = 0, 1)$ and $A_{(1-\alpha)}$ are represented by the operators L defined below for $k_L(x) = (1-\alpha)k_i(x)$ and $k_L(x) = (1-\alpha)k(x)$, respectively:

$D(L)$ given by

$$\Big\{ u \in X : U \in C^1(\Omega \setminus \{\tfrac{1}{2}\}),\quad \frac{du}{dx}(\frac{a}{2}) = 0,\quad \lim_{x\uparrow\frac{1}{2}}(-g(x)\frac{du}{dx}(x) + k_L(x)u(2x))$$

$$\text{and} \quad \lim_{x\downarrow\frac{1}{2}}(-g(x)\frac{du}{dx}(x)) \text{ exist and are equal} \Big\}$$

for all $u \in D(L)$,

$$Lu(x) = \begin{cases} -g(x)\dfrac{du}{dx}(x) + k_L(x)u(2x) & (x \in \Omega_0) \\ -g(x)\dfrac{du}{dx}(x) & (x \in \Omega_1)\ . \end{cases}$$

The following formula holds

$$e^{T\mathcal{A}_1^{(3)}} e^{T\mathcal{A}_0^{(3)}} \begin{pmatrix} \psi \\ 0 \\ 0 \end{pmatrix} = \begin{pmatrix} e^{T\mathcal{A}_1^{(1)}} e^{T\mathcal{A}_0^{(1)}} \psi \\ 0 \\ 0 \end{pmatrix} + \begin{pmatrix} 0 \\ \left[e^{T\mathcal{A}_1^{(2)}} \left(e^{T\mathcal{A}_0^{(3)}}\right)^{(2)} \begin{pmatrix} \psi \\ 0 \end{pmatrix} \right]_2 \\ 0 \end{pmatrix}$$

$$+ \begin{pmatrix} 0 \\ 0 \\ \left[e^{T\mathcal{A}_1^{(3)}} \widetilde{e^{T\mathcal{A}_0^{(2)}}} \begin{pmatrix} \psi \\ 0 \\ 0 \end{pmatrix} \right]_3 \end{pmatrix}$$

and from this we have expressions for

$$\left(e^{T\mathcal{A}_1^{(3)}}e^{T\mathcal{A}_0^{(3)}}\right)^2\phi^{(3)} \text{ and } \left(e^{T\mathcal{A}_1^{(3)}}e^{T\mathcal{A}_0^{(3)}}\right)^3\phi^{(3)}$$

and from (B.8), (B.11) (B.12) we have the estimations

$$\begin{aligned}&\left\|\left[\left(e^{T\mathcal{A}_1^{(3)}}e^{T\mathcal{A}_0^{(3)}}\right)^3\phi^{(3)}\right]_2\right\| \\ &\qquad \le e^{3T\left(\lambda_3^0+\lambda_2^1\right)}\left(e^{2T\left(\lambda_1^0+\lambda_1^1-\lambda_3^0-\lambda_2^1\right)}+1+K_0^{(3)}e^{-T\varepsilon_0^{(3)}}\right)\left\|\phi^{(3)}\right\|\end{aligned} \tag{C.5}$$

and

$$\begin{aligned}&\left\|\left[\left(e^{T\mathcal{A}_1^{(3)}}e^{T\mathcal{A}_0^{(3)}}\right)^3\phi^{(3)}\right]_3\right\| \\ &\qquad \le e^{2T\left(\lambda_3^1+\lambda_2^0\right)}\left(e^{2T\left(\lambda_1^0+\lambda_1^1-\lambda_3^1-\lambda_2^0\right)}+1+K_1^{(3)}e^{-T\varepsilon_1^{(3)}}\right)\left\|\phi^{(3)}\right\|.\end{aligned} \tag{C.6}$$

Following the same procedure, we can proof the analogous relations for $\left(e^{T\mathcal{A}_1^{(3)}}e^{T\mathcal{A}_0^{(3)}}\right)^n\phi^{(3)}$.

Finally, we have

$$e^{T\mathcal{A}_1^{(1)}}e^{T\mathcal{A}_0^{(1)}} = e^{T\lambda_1^0}e^{T\mathcal{A}_1^{(1)}}P_0^{(1)} + e^{T\mathcal{A}_1^{(1)}}e^{T\mathcal{A}_0^{(1)}}\left(Id - P_0^{(1)}\right). \tag{C.7}$$

From (C.7) we can write

$$\begin{aligned}&\left(e^{T\mathcal{A}_1^{(1)}}e^{T\mathcal{A}_0^{(1)}}\right)^2 \\ &\quad = e^{T\lambda_1^0}e^{T\mathcal{A}_1^{(1)}}P_0^{(1)}\left(e^{T\mathcal{A}_1^{(1)}}e^{T\mathcal{A}_0^{(1)}}\right) + e^{T\mathcal{A}_1^{(1)}}\delta_0^{(1)}\left\{e^{T\lambda_1^0}e^{T\mathcal{A}_1^{(1)}}P_0^{(1)} + e^{T\mathcal{A}_1^{(1)}}\delta_0^{(1)}\right\} \\ &\quad = e^{T\lambda_1^0}e^{T\mathcal{A}_1^{(1)}}P_0^{(1)}\left(e^{T\mathcal{A}_1^{(1)}}e^{T\mathcal{A}_0^{(1)}}\right) + e^{T\lambda_1^0}e^{T\mathcal{A}_1^{(1)}}\delta_0^{(1)}e^{T\mathcal{A}_1^{(1)}}P_0^{(1)} + \left(e^{T\mathcal{A}_1^{(1)}}\delta_0^{(1)}\right)^2\end{aligned}$$

and successively. Thus, we have an expression for $\left(e^{T\mathcal{A}_1^{(1)}}e^{T\mathcal{A}_0^{(1)}}\right)^4$ for which

$$\left\|\left(e^{T\mathcal{A}_1^{(1)}}e^{T\mathcal{A}_0^{(1)}}\right)^4\right\| \le e^{4T\left(\lambda_1^0+\lambda_1^1\right)}\sum_{j=0}^{4}\left(K_0^{(1)}e^{-T\varepsilon_0^{(1)}}\right)^j.$$

From this we can prove, by finite induction, the following estimate for arbitrary $n \ge 1$

$$\left\|\left(e^{T\mathcal{A}_1^{(1)}}e^{T\mathcal{A}_0^{(1)}}\right)^n\right\| \le e^{nT\left(\lambda_1^0+\lambda_1^1\right)}\sum_{j=0}^{n}\left(K_0^{(1)}e^{-T\varepsilon_0^{(1)}}\right)^j. \tag{C.8}$$

Finally, from $(C.3)$, $(C.5)\,(C.6)$ and $(C.8)$ by taking into account the condition $T > \frac{1}{\varepsilon}\ln K$, i. e., $Ke^{-T\varepsilon} < 1$, the proof of the Corollary 3.1 is completed.

Evolution Problem (2.6)

Mathematically, the existence of stable size-distribution in the evolution problem (2.6) is given by the long time behavior of $\left(e^{TA_1}e^{TA_0}\right)^n\phi = (H_1^{-1}e^{T\mathcal{A}_1}H_1H_0^{-1}e^{T\mathcal{A}_0}H_0)^n\phi$ for large n. We have from Corollary 3.1 and their notations:

Corollary C.1. *Suppose $g(2x) < 2g(x)$, for all $x \in \Omega_0$. Then, for a convenient choice of T, we can find nonnegative linear operators $\hat{S} = \hat{S}(T,\cdot), \hat{R}_1 = \hat{R}_1(T,\cdot), \hat{R}_2 = \hat{R}_2(T,\cdot), \hat{R}_d = \hat{R}_d(T,\cdot)$ in $\mathcal{L}(X_0^4;X_0)$ such that, for all $\phi \in X^4$,*

$$\begin{aligned}
e^{-nT(\lambda_1^0+\lambda_1^1)}\ [(H_1^{-1}e^{T\mathcal{A}_1}H_1H_0^{-1}e^{T\mathcal{A}_0}H_0)^n\phi]_1 &\to \hat{S}(T,\phi)\,,\\
e^{-nT(\lambda_3^0+\lambda_2^1)}\ [(H_1^{-1}e^{T\mathcal{A}_1}H_1H_0^{-1}e^{T\mathcal{A}_0}H_0)^n\phi]_2 &\to \hat{R}_1(T,\phi)\,,\\
e^{-nT(\lambda_2^0+\lambda_3^1)}\ [(H_1^{-1}e^{T\mathcal{A}_1}H_1H_0^{-1}e^{T\mathcal{A}_0}H_0)^n\phi]_3 &\to \hat{R}_2(T,\phi)\,,\\
e^{-2nT\lambda_4}\ [(H_1^{-1}e^{T\mathcal{A}_1}H_1H_0^{-1}e^{T\mathcal{A}_0}H_0)^n\phi]_4 &\to \hat{R}_d(T,\phi)\,.
\end{aligned}$$

Proof. Let we consider for $(i=0,1)$ $(j=1,2,3)$ the following notations:

(a) $\overline{P_i} := H_i^{-1}P_iH_i$ and $\overline{\delta_i} := H_i^{-1}\delta_iH_i$
(b) $\left(H_i^{-1}\right)^{(j)} := H_i^{(-j)}$, $\overline{P_i^{(j)}} := H_i^{(-j)}P_i^{(j)}H_i^{(j)}$, $\overline{\delta_i^{(j)}} = H_i^{(-j)}\delta_i^{(j)}H_i^{(j)}$ and $e^{TA_i^{(j)}} := H_i^{(-j)}e^{T\mathcal{A}_i^{(j)}}H_i^{(j)}$.

By exploring the particular diagonal form of the operators H_i, and by using similar arguments that we are used in proof of the Corollary 3.1 we observe that

(i) $H_iP_j = H_i^{-1}P_j = P_j$, $\overline{P_i} = P_iH_i$; $\overline{\delta_i} = \delta_iH_i$, $\left[\overline{\delta_1}\ \overline{\delta_0}\right]_4 = [\delta_1\delta_0]_4$.
(ii) By changing in (C.1) P_0 by P_0H_0, $P_1\delta_0$ by $P_1H_1\overline{\delta_0}$ and $\delta_1\delta_0$ by $\overline{\delta_1\delta_0}$, we obtain another analogous formula to (C.1) and changing $(e^{T\mathcal{A}_1^{(3)}}e^{T\mathcal{A}_0^{(3)}})^n\phi^{(3)}$ by $(e^{TA_1^{(3)}}e^{TA_0^{(3)}})^n\phi^{(3)}$ in (C.2) we obtain an analogous formula to (C.2). Then, we have a analogous formula to (C.3) with K_1K_0 replaced by $\|H_0^{-1}\|\|H_0\|\|H_1^{-1}\|\|H_1\|K_1K_0$.

and so on, we obtain the proof of Corollary C.1.

References

[1] Arino O., Some spectral properties for the asymptotic behavior of semigroups connected to population dynamics, *SIAM Review* **34** (1992) pp. 445–476.

[2] Anderson E. C. and Bell G. I., Cell growth and division. I. A mathematical model with applications to cell volume distributions in mammalian suspension cultures, *Biophys. J.* **7** (1967) pp. 329–351.

[3] Bonazza M., Massi G. B. and Vendite L. L., Un modello matematico per lo studio della resistenza tumorale ai farmaci anti-neoplastici. I — Trattamento con uno solo farmaco. In *Atti del III Incontro Multidisciplinare "Pillola e Mammella"* (Editrice "Il Sedicesimo", Firenze, 1986) pp. 314–319 .

[4] Bonazza M., Massi G. B. and Vendite L. L., Un modello matematico per lo studio della resistenza tumorale ai farmaci anti-neoplastici. II — Trattamento con l'associazione dei due farmaci ugualmente attivi. In *Atti del III Incontro Multidisciplinare "Pillola e Mammella"* (Editrice "Il Sedicesimo", Firenze, 1986) pp. 320–328.

[5] Bonazza M., Mini E. and Vendite L. L., *Valutazione della resistenza tumorale ai farmaci anti-blastici attraverso l'elaborazione di un programa al calcolatore* Atti del LXIV Congresso Nazionale della Socità Italiana di Ginecologia e Ostetricia (Ed. "Monduzzi", Roma, 1987) pp. 1539-1546.

[6] Costa M. S., Boldrini J. L. and Bassanezi R. C., Chemotherapeutic treatments involving drug resistance and the level of normal cells as a criterion of toxicity, *Math. Biosci.* **125** (1995) pp. 211–228.

[7] Delbruck M. and Luria S., Mutations of bacteria from virus sensitivity to virus resistance, *Genetics* **28** (1943) pp. 491–511.

[8] Diekmann O., Heijmans H. J. A. M. and Thieme H. R., On the stability of the cell size distribution, *J. Math. Biol.* **19** (1984) pp. 227–248.

[9] Diekmann O. and Metz A. M. (eds.), *The Dynamics of Physiologically Structured Populations*, Lecture Notes in Biomath. **68** (Springer, New York, 1986).

[10] Diekmann O., Gyllenberg M., Thieme H. R. and Verduyn Lunel S. M., *A Cell-Cycle Model Revisited*, CWI Report AM-R 9305, 1993.

[11] Diekmann O., van Gils S.A. , Verduyn Lunel S.M. and Walther H. -O., *Delay Equations* (Springer-Verlag, New York, 1995).

[12] Heijmans H. J. A. M., *Dynamics of Structured Populations*, PhD. Thesis, University of Amsterdan, 1985.

[13] Heijmans H. J. A. M. , An eigenvalue problem related to cell growth, *J. Math. Anal. Appl.* **111** (1985) pp. 235–280.

[14] Leckar H. F., *Size-Structured Mathematical Models for Tumoral Cell Populations and Cellular Resistance Problem to Instantaneous Drug Action*, PhD. Thesis, University of Campinas, Brazil, 1996.

[15] Leckar H. F. and Vendite L.L., On the stable size distribution in a mathematical model for tumor cell growth reproducing by fission and the cellular resistance problem, in *Proceedings of the 4th International Conference on Mathematical Population Dynamics*, ed. by O. Arino, D. Axelrod and M. Kimmel, *Series in Mathematical Biology and Medicine* **6** (World Scientific Publishing, Singapore, 1997) pp. 207–222.

[16] Pazy A., *Semigroups of Linear Operators and Applications to Partial Differential Equations* (Springer, New York, 1983).

[17] Schappacher W., *Asymptotic Behavior of Linear C_0-Semigroups* (Lecture Notes, Quaderni, Bari, 1983).

[18] Sinko J. W. and Streifer W., A model for populations reproducing by fission, *Ecology* **52** (1971) pp. 330–335.

[19] Skipper H. E., The forty year old mutation theory of Luria and Delbruck and its pertinence to cancer chemotherapy, *Av. Cancer Res.* **40** (1983) pp. 331–363.

[20] Vendite L. L., *Mathematical Modeling for Tumoral Cell Populations Growth and Cellular Resistance Problem to Anti-Blastic Drugs*, PhD. Thesis, FEE–UNICAMP, 1988.

[21] Webb G. F., *Theory of Nonlinear Age-Dependent Population Dynamics* (Marcel Dekker, New York, 1985).