



HAL
open science

Mathematical and numerical analysis for a model of growing metastatic tumors

Dominique Barbolosi, Assia Benabdallah, Florence Hubert, Federico Verga

► **To cite this version:**

Dominique Barbolosi, Assia Benabdallah, Florence Hubert, Federico Verga. Mathematical and numerical analysis for a model of growing metastatic tumors. 2008. hal-00262335v1

HAL Id: hal-00262335

<https://hal.science/hal-00262335v1>

Preprint submitted on 11 Mar 2008 (v1), last revised 25 May 2008 (v3)

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Mathematical and numerical analysis for a model of growing metastatic tu- mors

Dominique Barbolosi ^{*} — Assia Benabdallah ^{**} — Florence
Hubert ^{**} — Federico Verga ^{**}

^{*} *Université de la Méditerranée - UPRES EA 3286 - IFR 125 Physiopathologie
Humaine de Marseille*

27, boulevard Jean Moulin, 13385 Marseille Cedex 5, France.

^{**} *Université de Provence, LATP (UMR CNRS 6632),*

39 rue F. Joliot Curie, 13453 Marseille Cedex 13, France

{assia,fhubert,verga}@latp.univ-mrs.fr, dominique.barbolosi@neuf.fr

Abstract. In cancer diseases, the appearance of metastases is a very pejorative forecast. Chemotherapies are systemic treatments which aims at the elimination of the micrometastases produced by a primitive tumour. The efficiency of chemotherapies closely depends on the protocols of administration. Mathematical modeling is an invaluable tool to help in evaluating the best treatment strategy. Iwata and al [11] proposed a partial differential equation (PDE) that describes the metastatic evolution of an untreated tumour. We conducted in this article, a thorough mathematical analysis of this model. Particularly, we provide an explicit formula for the growth rate parameter, as well as a numerical resolution of this PDE. By increasing our understanding of the existing mode, this work is crucial for further extension and refinement of the model. It settle down the framework necessary for the consideration of drugs administration effects on tumour developpment.

Keywords: Von Foerster equation, semigroup approach, asymptotic behaviour, characteristic scheme, metastatic tumors

1. Introduction

Optimal management of cancer chemotherapy requires today a throughout and upgraded understanding of cancer cell kinetic and biochemistry. In order to manage most available information at the same time, since several years, numerous authors attempted by using mathematical modeling to optimize cancer therapy. Particularly, modelling is all the more useful with combined use today both cytotoxic agents and biologic agents (for example, such as trastuzumab (Herceptin) and antiangiogenesis agents). In the cancer disease, evidence for the existence of occult micrometastases at the time of diagnosis is overwhelming

[10] ; it is clear that a systemic therapy is the only treatment which may have an impact on the problem of disseminated tumors [9]. Dose-dense schedules may have an advantage over conventional schedules of drug administration [12] and we have already developed in [3] a mathematical model able to calculate the densified administration protocols in order to minimize the size of primary tumours while limiting the toxicity effects [3]. Recently, this methodology was applied to the metastatic breast cancer in phase I trial [7].

In order to improve the efficacy of adjuvant chemotherapy to prevent disseminating tumors, it seems interesting to develop a mathematical model describing the number of tumors which the size is below the detection threshold, and predicting the behaviour of metastases in patients. An interesting work was done by Iwata and al [11] which gives a partial differential equation (PDE), with initial and boundary conditions, which from a primary tumour with one cell, calculates the colony size distribution $v(x, t)$ of metastatic tumors without treatment. Here x is the tumour size, t the time and $v(x, t)$ the number of cells of size x at time t . In their paper the authors manage to obtain an analytical solution of their PDE using the Laplace transformation method, however such solutions are not numerically tractable.

Aiming to prevent the emergence of the micrometastases, anti-tumor agents must be used. Accordingly, the Iwata's model has to be modified to incorporate the effect of chemotherapy in order to detect which is the best protocol which will minimize the number of metastases, by using the method of optimization developed in [7]. The so obtained new PDE being analytically nonsolvable, it appears essential to us to have appropriate numerical schemes of resolution, it is why in this paper we propose first to begin by giving a thorough mathematic analysis of Iwata's model.

Reader's guide

We precise in section 2 the model under study: a Von Foerster equation with Gompertzian growth. It is a linear transport equation with a *non local* boundary condition combined with a singular source. The mathematical analysis of such an equation is developed in section 3. We in particular derive the asymptotic behaviour of the solution. We exhibit a *Malthus* parameter λ_0 that gives the growth rate of metastatic sites. This explicit formalae that gives this parameter shows a deep dependance on clinical characteristic data of the patient. We propose in section 4 an algorithm to approximate the solutions of such an equation. We give a theoretical validation of the numerical model for long time intervals. We finally give in section 4 some numerical results. Ours results are first compare to the one of [11]. Numerical simulations also confirm the theoretical asymptotic growth of the number of metastases. We conclude this section by a sensibility analysis with respect to the clinical characteristic data of the patient.

2. Presentation of the model

We present in this section the mathematical model describing the dynamics of the metastatic colony size distribution introduced in [11]. In this model we suppose that the primary tumor is generated by a single cell at $t = 0$ and grows with the rate $g(x)$ per unit time where x is the tumor size represented by the number of cells in the tumor. The growing tumor emits metastatic cells with the rate $\beta(x)$. Each metastatic cell develops into a new tumor, which also grows at rate $g(x)$ and emits new nuclei of metastasis just as the primary tumor does. Let $v(x, t)$ represent the colony size distribution with cell number x at time t , actually $v(x, t)dx$ means the number of metastatic tumors whose sizes range from x and $x + dx$ at time t . In the case considered here we suppose that the nuclei of colonization are located far enough from each other so that their ranges do not overlap for a long time period. The dynamics of the colony size distribution is given by the following Mac-Kendrick Von Foerster equation:

$$\begin{cases} \frac{\partial}{\partial t}v(x, t) + \frac{\partial}{\partial x}[g(x)v(x, t)] = 0, & x \in [1, b), t \geq 0 \\ g(1)v(1, t) = \int_1^b \beta(x)v(x, t)dx + \beta(x_p(t)), & \\ v(0, x) = 0. & \end{cases} \quad (1)$$

We have to deal with a transport equation with a non local boundary condition and an initial data equals to zero which supposes that there is no metastatic tumor at time $t = 0$. The boundary condition means that the number of metastatic cells newly created per unit time at time t is the total rate of occurrences of metastases due to metastatic tumors (corresponding to the integral term) and the primary tumor.

In the Iwata's model the data x_p , g and β are precised as follows.

1) The number of cells $x_p(t)$ in the primary tumor at time t is the solution of the Cauchy problem:

$$\begin{cases} \frac{d}{dt}x_p(t) = g(x_p(t)) \\ x_p(0) = 1. \end{cases} \quad (2)$$

2) A Gompertzian growth rate g is adopted:

$$g(x) = ax \ln \left(\frac{b}{x} \right), \quad (3)$$

where a denotes a **growth rate constant** and $b > 1$ the **maximum tumor size**.

We can solve explicitly the equation (2) which gives:

$$x_p(t) = b^{1-e^{-at}}. \quad (4)$$

3) The colonization rate $\beta(x)$ is chosen as:

$$\beta(x) = mx^\alpha, \quad (5)$$

where m is the **colonization coefficient** and α is the **fractal dimension** of blood vessels infiltrating the tumor. The parameter α expresses how the blood vessels geometrically distribute in or on a tumor. If the vascularity is superficial the fractal dimension α is assigned to be $2/3$ because we suppose that the tumor has the shape of a sphere hence the surface area is proportional to $2/3$. Else if the vascularization is homogeneously distributed in the whole tumor, α is supposed to be equal to 1.

3. Mathematical analysis of the Von Foerster equation with Gompertzian growth

We are now interested by mathematical analysis of the equation (1). We study in this section the existence and uniqueness of solutions as well as the long time behaviour of these solutions.

We consider the equation (1) in a more general case where the initial condition is non zero:

$$\begin{cases} \frac{\partial}{\partial t}v(x,t) + \frac{\partial}{\partial x}[g(x)v(x,t)] = 0, & x \in (1,b), t \geq 0 \\ g(1)v(1,t) = \int_1^b \beta(x)v(x,t)dx + f(t), & t > 0 \\ v(x,0) = v_0(x). \end{cases} \quad (6)$$

3.1. Existence of solutions

In the sequel, we suppose that g is given by (3), β by (5) and $f(t) = \beta(x_p(t))$ where x_p the number of cells in primary tumor is defined in (4). In particular, we have

$$\int_1^b \frac{\beta(x)}{g(x)} dx = +\infty. \quad (7)$$

Let us introduce the operator A and its domain:

$$A = -\partial_x(g(x)\cdot),$$

$$D(A) = \left\{ v \in L^1(1,b), gv \in W^{1,1}(1,b), \lim_{x \rightarrow b^-} (gv)(x) = 0, (gv)(1) = \int_1^b \beta(x)v(x) dx \right\}.$$

In order to prove the existence of solutions for the considered equation (6), we first need to state with some spectral properties of the operator A .

3.1.1. Spectral properties of A

We derive in this section some properties of the point spectrum $\sigma_p(A)$, the set of the eigenvalues of $(A, D(A))$.

Theorem 1. *There exists a unique **real** eigenvalue $\lambda_0 \in]0, +\infty[$ of the operator $(A, D(A))$. Moreover there exists $\varepsilon > 0$ such that*

$$\sigma_p(A) \subset \{0 < \operatorname{Re} \lambda < \lambda_0 - \varepsilon\} \cup \{\lambda_0\}.$$

Proof.

Step 1: The eigenvectors are given by $V(x) = \frac{g(1)V(1)}{g(x)} e^{-\int_1^x \frac{\lambda}{g(y)} dy}$ and $\sigma_p(A) \subset \mathbb{R}^+$.

We recall that $\lambda \in \sigma_p(A)$ if and only if there exists, $V \neq 0$ such that

$$\begin{cases} V \in D(A) \\ AV = \lambda V, \text{ in } (1, b) \end{cases}$$

The solution of

$$A = \partial_x(g(x)V) = -\lambda V, \text{ in } (1, b)$$

are given by:

$$V(x) = \frac{g(1)V(1)}{g(x)} e^{-\int_1^x \frac{\lambda}{g(y)} dy}. \quad (8)$$

The boundary condition

$$g(1)V(1) = \int_1^b \beta(x) V(x) dx$$

then reads

$$g(1)V(1) = \int_1^b g(1)V(1) \frac{\beta(x)}{g(x)} e^{-\int_1^x \frac{\lambda}{g(y)} dy} dx$$

First of all, notice that the function gV defined in (8) is in $W^{1,1}(1, b)$ and $\lim_{x \rightarrow b^-} (gV)(x) = 0$ if and only if $\operatorname{Re} \lambda > 0$. Moreover, direct computations show that

$$e^{-\lambda \int_1^x \frac{dy}{ay \ln \frac{b}{y}}} = \left(\frac{\ln \frac{b}{x}}{\ln b} \right)^{\frac{\lambda}{a}},$$

and therefore

$$V(x) = \frac{V(1)}{x} \left(\frac{\ln \frac{b}{x}}{\ln b} \right)^{\frac{\lambda}{\alpha} - 1}.$$

Thus $V \in L^1(1, b)$ if and only if $\operatorname{Re} \lambda > 0$. Therefore, to be in the spectrum of $(A, D(A))$, $\operatorname{Re} \lambda$ has to be greater than 0.

We can remark that if $V(1) = 0$ then $V = 0$, so $V(1) \neq 0$ and $\dim \operatorname{Ker}(A - \lambda I) = 1$.

We have:

$$g(1)V(1) = g(1)V(1) \int_1^b \frac{\beta(x)}{g(x)} e^{-\int_1^x \frac{\lambda}{g(y)} dy} dx.$$

We deduce that $\lambda \in \mathbb{C}$ is an eigenvalue of $(A, D(A))$ if and only if $\operatorname{Re} \lambda > 0$ and:

$$F(\lambda) := \int_1^b \frac{\beta(x)}{g(x)} e^{-\int_1^x \frac{\lambda}{g(y)} dy} dx = 1. \quad (9)$$

Let us introduce:

$$G(x) = \int_1^x \frac{dy}{g(y)}. \quad (10)$$

Thanks to the properties of g the function G is strictly increasing, C^1 and one to one from $(1, b)$ to $(0, +\infty)$. As $G'(x) \neq 0, \forall x \in (1, b)$, G is a C^1 diffeomorphism. We can write $F(\lambda)$ as follows:

$$F(\lambda) = \int_0^\infty \beta(G^{-1}(x)) e^{-\lambda x} dx.$$

Then, setting $\theta = \beta \circ G^{-1}$, we remark that:

$$F(\lambda) = \int_0^{+\infty} \theta(y) e^{-\lambda y} dy.$$

F is the Laplace transform of the function $\theta = \beta \circ G^{-1} \in L^\infty(0, \infty)$, we deduce that F is well defined and **holomorphic** (Laplace transform property) in the complex half plane $\Omega = \{\lambda \in \mathbb{C}, \operatorname{Re} \lambda > 0\}$. Thus the solutions of the equation $F(\lambda) = 1$ are all isolated. We have:

$$V(G^{-1}(x)) = g(1)V(1)G'(G^{-1}(x))e^{-\lambda x} \text{ for all } x \in (0, +\infty).$$

Step 2:

There exists a unique real eigenvalue λ_0 of $(A, D(A))$. Moreover, its algebraic

multiplicity is 1.

We will look at the solutions of (9) on the real line. Remark that F is continuous and strictly decreasing on \mathbb{R}^+ with $F(0) > 1$ thanks to (7) and:

$$\lim_{\lambda \rightarrow +\infty} F(\lambda) = 0.$$

Therefore by the intermediate value theorem, (9) admits a unique solution $\lambda_0 \in \mathbb{R}^+$.

As $\lambda_0 > 0$, we prove in the last step that $\ker(A - \lambda_0 I) = \mathbb{R}V$ for V defined by (8). In the sequel, we fix $V(1) > 0$.

Let us now show $\ker(A - \lambda_0 I)^2 = \ker(A - \lambda_0 I) = \mathbb{R}V$. A function $\varphi \in \ker(A - \lambda_0 I)^2$ if and only if $\varphi \in D(A)$ and there exists $c \in \mathbb{R}$ such that:

$$\begin{cases} A\varphi = \lambda_0\varphi - cV, & \text{in } (1, b) \\ g(1)\varphi(1) = \int_1^b \beta(x) \varphi(x) dx \end{cases} .$$

As previously this system is equivalent to:

$$\partial_x(g(x)\varphi) = -\lambda_0\varphi + cV, \text{ in } (1, b) \quad (11)$$

$$g(1)\varphi(1) = \int_1^b \beta(x) \varphi(x) dx \quad (12)$$

Solving the differential equation (11) we obtain for φ :

$$\varphi(x) = \frac{g(1)\varphi(1)}{g(x)} e^{-\int_1^x \frac{\lambda_0}{g(y)} dy} + \frac{c}{g(x)} \int_1^x e^{-\int_\tau^x \frac{\lambda_0}{g(y)} dy} V(\tau) d\tau.$$

One can deduce (since $F(\lambda_0) = 1$):

$$\int_1^b \beta(x) \varphi(x) dx = g(1)\varphi(1) + c \int_1^b \frac{\beta(x)}{g(x)} \int_1^x e^{-\int_\tau^x \frac{\lambda_0}{g(y)} dy} V(\tau) d\tau dx$$

In order to fulfill the condition (12) the condition:

$$c \int_1^b \frac{\beta(x)}{g(x)} \int_1^x e^{-\int_\tau^x \frac{\lambda_0}{g(y)} dy} V(\tau) d\tau dx = 0$$

is required. As β, g, V are positive functions on $[1, b)$ we deduce that $c = 0$ and:

$$\varphi(x) = \frac{g(1)\varphi(1)}{g(x)} e^{-\int_1^x \frac{\lambda_0}{g(y)} dy} = \delta V(x),$$

with $\delta = \frac{\varphi(1)}{V(1)}$, the conclusion follows. Therefore the algebraic multiplicity of λ_0 is 1.

Step 3:

There is a unique eigenvalue whose real part is equal to λ_0 .

Let λ_0 the real solution of $F(\lambda_0) = 1$. If $\lambda = \lambda_0 + i\alpha$, $\alpha \in \mathbb{R}$, is an eigenvalue of $(A, D(A))$ since $\theta = \beta(G^{-1})$ is real valued we have:

$$F(\lambda) = 1 \text{ if and only if } \begin{cases} \int_0^\infty \theta(x)e^{-\lambda_0 x} \cos(\alpha x) dx = 1 \\ \int_0^\infty \theta(x)e^{-\lambda_0 x} \sin(\alpha x) dx = 0 \end{cases}$$

Since $F(\lambda_0) = 1$, one can deduce that:

$$\int_0^\infty \theta(x)e^{-\lambda_0 x} (1 - \cos(\alpha x)) dx = 0.$$

Considering that $\theta > 0$ almost everywhere, this can be true if and only if $1 - \cos(\alpha x) = 0$, for all $x \in \mathbb{R}$. Therefore $\alpha = 0$.

Step 4:

There is no eigenvalue whose real part is bigger than λ_0 .

Indeed if $\lambda \in \{Re \lambda > \lambda_0\}$ then $|F(\lambda)| < F(\lambda_0) = 1$ and then $\lambda \notin \sigma_p(A)$.

Step 5:

There is at most a finite number of eigenvalues of real part in a compact of $(0, \lambda_0)$ and there exists $\varepsilon > 0$ such that $\sigma_p(A) \setminus \{\lambda_0\} \subset \{0 < Re \lambda \leq \lambda_0 - \varepsilon\}$.

Let $\lambda = a + ib$ with $0 < a < \lambda_0$,

$$F(\lambda) = 1 \text{ if and only if } \begin{cases} \int_0^\infty \theta(x)e^{-ax} \cos(bx) dx = 1 \\ \int_0^\infty \theta(x)e^{-ax} \sin(bx) dx = 0 \end{cases}.$$

According to the Riemann-Lebesgue theorem, we have:

$$\int_0^\infty \theta(x)e^{-ax} \cos(bx) dx \xrightarrow{b \rightarrow +\infty} 0,$$

uniformly in a on any compact of $\{z \in \mathbb{C}; Re(z) \in (0, \lambda_0)\}$.

As the eigenvalues are isolated, there can exist only a finite number over each compact of $\{0 < Re \lambda < \lambda_0\}$. Consequently:

$$\exists \varepsilon > 0; F(\lambda) = 1 \text{ and } \lambda \neq \lambda_0 \Rightarrow \operatorname{Re} \lambda \notin]\lambda_0 - \varepsilon, \lambda_0[.$$

Thus $\sigma_p(A) \setminus \{\lambda_0\} \subset \{0 < \operatorname{Re} \lambda \leq \lambda_0 - \varepsilon\}$.

Proposition 2 (see [2]).

1) The domain $D(A)$ is dense in $L^1(1, b)$.

2) For $\operatorname{Re} \lambda \in \{\lambda \in \mathbb{C}, \operatorname{Re} \lambda \in]\lambda_0 - \varepsilon, \lambda_0[\} \cup \{\lambda \in \mathbb{C}; \operatorname{Re} \lambda > \lambda_0\}$, the range $R(\lambda I - A) = L^1(1, b)$ and

$$\{\lambda \in \mathbb{C}, \operatorname{Re} \lambda \in]\lambda_0 - \varepsilon, \lambda_0[\} \cup \{\lambda \in \mathbb{C}; \operatorname{Re} \lambda > \lambda_0\} \subset \rho(A).$$

As $D(A)$ is dense in $L^1(1, b)$, one can define $(A^*, D(A^*))$, the adjoint of $(A, D(A))$:

$$\begin{aligned} A^*w(x) &= g(x)\partial_x w(x) - \beta(x), \\ D(A^*) &= \{w \in L^\infty(1, b), g\partial_x w \in L^\infty(1, b)\}. \end{aligned}$$

Moreover, one has

Proposition 3. *There exists a unique triplet $(\lambda_0, \phi, V) \in]0, +\infty[\times D(A^*) \times D(A)$ such that*

$$\begin{cases} AV = \lambda_0 V, & A^* \phi = \lambda_0 \phi \\ \phi \geq 0, \phi(1) = 1, \text{ and } \int_1^b V(x)\phi(x)dx = 1. \end{cases}$$

More precisely, as $\beta(x) = mx^\alpha$ then

$$\phi \in C^0([1, b)), 1 \geq \phi \geq \frac{mb^\alpha}{\lambda_0} > 0. \quad (13)$$

Proof. We solve $A^* \phi = \lambda_0 \phi$ and get

$$\phi(x) = e^{\lambda_0 G(x)} \left(\int_x^b \frac{\beta(y)}{g(y)} e^{-\lambda_0 G(y)} dy \right)$$

with G defined in (10). Recall that $\theta = \beta(G^{-1})$, one deduces

$$\phi(x) = e^{\lambda_0 G(x)} \left(\int_{G(x)}^{+\infty} \theta(z) e^{-\lambda_0 z} dz \right) > 0 \quad (14)$$

Moreover,

$$\phi \in C^0([1, b)), \phi \geq \frac{mb^\alpha}{\lambda_0} > 0.$$

We finally choose $V(1)$ such that $\int_1^b V(x)\phi(x)dx = 1$.

3.1.2. The homogeneous problem via a semigroup approach

Consider

$$\begin{cases} \frac{\partial}{\partial t}v(x,t) + \frac{\partial}{\partial x}[g(x)v(x,t)] = 0, & x \in (1,b), t \geq 0. \\ g(1)v(1,t) = \int_1^b \beta(x)v(x,t)dx & t > 0 \\ v(x,0) = v_0(x). \end{cases} \quad (15)$$

We recall at first some properties about semigroups, let $(X, \|\cdot\|)$ a Banach space (see [8] for more details):

Definition 4. An operator $(A, D(A))$ on a Banach space X is said to be dissipative if:

$$\|(\lambda I - A)x\| \geq \lambda \|x\|,$$

Actually we have a more practical criterion in order to establish the dissipativity of an operator. For all $x \in X$, we define the dual set of x by:

$$J(x) = \{x' \in X'; \langle x, x' \rangle_{X, X'} = \|x\|^2 = \|x'\|^2\},$$

and we are going to use the following result:

Proposition 5. $(A, D(A))$ is dissipative if and only if for all $x \in D(A)$, there is $j(x) \in J(x)$ such that:

$$\operatorname{Re}\langle Ax, j(x) \rangle_{X, X'} \leq 0. \quad (16)$$

Let us show now the main theorem

Theorem 6. The operator $(A, D(A))$ generates a semigroup on $L^1(1, b)$.

The theorem 6 is a consequence of the following theorem:

Theorem 7 ([8]). Let $(A, D(A))$ a dissipative operator on a Banach space X such that there exists $\lambda > 0$ such that $(\lambda I - A)$ is onto, then the restriction of A to $\overline{D(A)}$ generates a contraction semigroup on $\overline{D(A)}$.

In particular:

$$\left. \begin{array}{l} \overline{D(A)} = X \\ \forall \lambda > 0, R(\lambda I - A) = X \\ \exists \omega \in \mathbb{R}; (A - \omega I) \text{ is dissipative} \end{array} \right\} \Rightarrow (A, D(A)) \text{ generates a semigroup on } X.$$

The first two points come from Proposition 2. We just have to check the dissipativity condition:

Proposition 8. For all $\omega \geq \|\beta\|_{L^\infty}$, $A - \omega I$ is dissipative.

Proof. Let $v \in L^1(1, b)$ and $E = \{x \in (1, b); v(x) = 0\}$. The function $j(v) = \frac{v}{|v|} \mathbf{1}_{E^c} \|v\|_{L^1(1, b)}$ belongs to $J(v)$. We have $j(v) \in L^\infty$ with $\|j(v)\|_{L^\infty} \leq \|v\|_{L^1}$. In addition:

$$\langle v, j(v) \rangle_{L^1(1, b), L^\infty(1, b)} = \int_1^b \frac{v^2}{|v|} \mathbf{1}_{E^c} \|v\|_{L^1(1, b)} = \|v\|_{L^1(1, b)}^2 = \|j(v)\|_{L^\infty(1, b)}^2.$$

Furthermore,

$$\begin{aligned} \langle Av - \omega v, j(v) \rangle_{L^1(1, b), L^\infty(1, b)} &= - \int_1^b j(v) \partial_x (gv) dx - w \int_1^b v j(v) dx \\ &= - \int_1^b j(v) \partial_x (gv) dx - w \|v\|_{L^1(1, b)}^2. \end{aligned}$$

We use now lemma 24 proved in the appendix and we get:

$$\langle Av - \omega v, j(v) \rangle_{L^1(1, b), L^\infty(1, b)} = g(1) \|v\|_{L^1(1, b)} |v(1)| - \omega \|v\|_{L^1(1, b)}^2$$

Using the boundary condition ($v \in D(A)$), we get

$$\begin{aligned} \langle Av - \omega v, j(v) \rangle_{L^1(1, b), L^\infty(1, b)} &= \|v\|_{L^1(1, b)} \left| \int_1^b \beta(x) v(x) dx \right| - \omega \|v\|_{L^1(1, b)}^2 \\ &\leq \left(\|\beta\|_{L^\infty(1, b)} - \omega \right) \|v\|_{L^1(1, b)}^2. \end{aligned}$$

It is sufficient to choose $\|\beta\|_{L^\infty(1, b)} \leq \omega$ in order to obtain (16). Hence we have proved that $(A, D(A))$ generates a semigroup denoted e^{tA} .

Let us recall some definitions of semigroup solutions (see [13] for more details).

Definition 9. Let X a Banach space and $(A, D(A))$ a generator of a C^0 -semigroup on X , denoted e^{tA} . Let

$$\begin{cases} y'(t) = Ay(t), & t \in (0, T) \\ y(0) = x \end{cases}. \quad (17)$$

We call

– **weak solution** (mild solution) of (17), a function $y \in \mathcal{C}([0, +\infty[; X)$ given by

$$y(t) = e^{tA} x. \quad (18)$$

– **strong solution** (classical solution) of (17) a function $y \in \mathcal{C}([0, +\infty]; X) \cap \mathcal{C}^1((0, +\infty]; X)$ given by (18) such that $y(t) \in D(A)$ for all $t \in (0, +\infty[$ and satisfying (17) in $[0, +\infty[$.

Moreover one has

Theorem 10. [13] Let e^{tA} a C_0 -semigroup on X of generator $(A, D(A))$. Then:

- for all $x \in X$ (17) has a unique weak solution,
- for all $x \in D(A)$ (17) has a unique strong solution.

Therefore we have the main result of this subsection :

Theorem 11.

- For any $v_0 \in D(A)$ and $T > 0$ there exists an unique strong solution $v \in \mathcal{C}([0, T], D(A)) \cap \mathcal{C}^1([0, T], L^1(1, b))$. It satisfies the system (15) in $L^1(1, b)$
- For any $v_0 \in L^1(1, b)$ and $T > 0$, there exists an unique weak solution $v \in \mathcal{C}([0, T], L^1(1, b))$ such that (15) is verified in the distribution sense.

This ends the existence of solutions of the homogenous problem associated to (6). In the next subsection we will construct a solution (weak) of (6) for zero initial data. Then we conclude by noticing that the unique solution of (6) is the sum of the the homogenous and this previous.

3.1.3. The non homogeneous problem via a fixed point argument

Consider

$$\begin{cases} \partial_t v + \partial_x (gv) = 0, & x \in (1, b), t > 0, \\ g(1)v(1, t) = \int_1^b \beta(x)v(x, t)dx + f(t), & t > 0, \\ v(x, 0) = 0 \end{cases} \quad (19)$$

We define

Definition 12. We call a **strong solution** on $[0, T]$ of system (19) a function $v \in \mathcal{C}^1([0, T]; L^1(1, b))$ such that $gv \in \mathcal{C}([0, T]; W^{1,1}(1, b))$, $\lim_{x \rightarrow b^-} (gv)(x, t) = 0$ for all $t \in [0, T]$ and v satisfies (19). This function v can be viewed as a linear function \mathcal{T} of the source term $v = \mathcal{T}f$.

One has

Theorem 13. For any $f \in \mathcal{C}^1([0, +\infty[)$ such that $f(0) = 0$ there exists a unique strong solution of system (19). Moreover, the operator \mathcal{T} defined on $\{f \in \mathcal{C}^1([0, +\infty[); f(0) = 0\}$ satisfies the positivity property:

$$f \geq 0 \Rightarrow \mathcal{T}f \geq 0.$$

Proof. We are going to construct the strong solution by a fixed point argument. As we have to use a bootstrap argument in time, we have to consider a more general initial data than 0.

Lemma 14. *For any $v_0 \in L^1(1, b)$ such that $gv_0 \in W^{1,1}(1, b)$, $\lim_{x \rightarrow b^-} (gv_0) = 0$ and for all function $f \in \mathcal{C}^1([0, +\infty[)$ such that $f(0) = g(1)v_0(1) - \int_1^b \beta(y)v_0(y)dy$, there exists a unique strong solution v of*

$$\begin{cases} \partial_t v + \partial_x(gv) = 0 \\ g(1)v(1, t) = \int_1^b \beta(y)v(y, t)dy + f(t) \\ v(\cdot, 0) = v_0. \end{cases}$$

Proof.

For $0 \leq T_0 < T$, and $u \in L^1(1, b)$ let us define

$$X_T^{T_0}(u) = \{w \in \mathcal{C}^1([T_0, T]; L^1(1, b)); w(\cdot, T_0) = u(\cdot)\}.$$

and

$$X_T^0(v_0) = \{w \in \mathcal{C}^1([0, T]; L^1(1, b)); w(\cdot, 0) = v_0(\cdot)\} = X_T.$$

We endow the set X_T with the distance associated by :

$$\|v\|_{X_T} = \sup_{t \in [0, T]} \|v\|_{L^1(1, b)} + \sup_{t \in [0, T]} \|\partial_t v\|_{L^1(1, b)}$$

Thus X_T is a complete metric space. Define $\mathcal{T}_{v_0, f}(w) = v$ by:

$$v(x, t) = \begin{cases} \frac{1}{g(x)} \left(\int_1^b \beta(y)w(y, t - G(x)) dy + f(t - G(x)) \right), & G(x) < t \\ \frac{1}{g(x)}(gv_0)(G^{-1}(G(x) - t)), & G(x) > t, \end{cases}$$

where we recall that $G(x) = \int_1^x \frac{dy}{g(y)}$. Direct computations show that

$$\|v(t)\|_{L^1(1, b)} \leq t \|\beta\|_{L^\infty(1, b)} \sup_{t \in [0, T]} \|w(t)\|_{L^1(1, b)} + T \sup_{t \in [0, T]} |f(t)| + \|v_0\|_{L^1(1, b)},$$

and

$$\lim_{x \rightarrow b^-} (gv)(x, t) = 0. \quad (20)$$

Moreover we observe that v is continuous on $[1, b) \times [0, T] \setminus \{t = G(x)\}$ and from the hypothesis on w we deduce that for all $x_0 \in [1, b)$:

$$\begin{aligned} \lim_{\substack{G(x) < t \\ (x, t) \rightarrow (x_0, G(x_0))}} (gv)(x, t) &= \lim_{\substack{G(x) < t \\ (x, t) \rightarrow (x_0, G(x_0))}} \left(\int_1^b \beta(y)w(y, t - G(x)) dy + f(t - G(x)) \right) \\ &= \left(\int_1^b \beta(y)w(y, 0) dy + f(0) \right). \end{aligned}$$

By the compatibility conditions satisfied by $v_0, f, w(\cdot, 0)$, one gets

$$\lim_{\substack{G(x) < t \\ (x,t) \rightarrow (x_0, G(x_0))}} (gv)(x, t) = (gv_0)(1).$$

Besides, one has as $gv_0 \in W^{1,1}(1, b)$

$$\begin{aligned} \lim_{\substack{G(x) < t \\ (x,t) \rightarrow (x_0, G(x_0))}} (gv)(x, t) &= \lim_{\substack{G(x) < t \\ (x,t) \rightarrow (x_0, G(x_0))}} (gv_0)(G^{-1}(G(x) - t)) \\ &= (gv_0)(G^{-1}(0)). \end{aligned}$$

Recall that $G^{-1}(0) = 1$, so one deduces

$$\lim_{\substack{G(x) > t \\ (x,t) \rightarrow (x_0, G(x_0))}} (gv)(x, t) = (gv_0)(1).$$

Therefore $gv \in \mathcal{C}([1, b] \times [0, T])$ and $v(\cdot, 0) = v_0$. Furthermore, as $w \in X_T$ and $gv_0 \in W^{1,1}(1, b)$, we have for $x < b$

$$\partial_t v(x, t) = \begin{cases} \frac{1}{g(x)} \left(\int_1^b \beta(y) \partial_t w(y, t - G(x)) dy + f'(t - G(x)) \right), & \text{if } G(x) < t \\ -\frac{1}{g(x)} (g(G(x) - t)) \partial_x (gv_0)(G^{-1}(G(x) - t)), & \text{if } G(x) > t \end{cases}$$

and

$$\partial_x (gv)(x, t) = \begin{cases} -\frac{1}{g(x)} \left(\int_1^b \beta(y) \partial_t w(y, t - G(x)) dy + \partial_t f(t - G(x)) \right), & \text{if } G(x) < t \\ \frac{1}{g(x)} (g(G(x) - t)) \partial_x (gv_0)(G^{-1}(G(x) - t)), & \text{if } G(x) > t \end{cases}$$

We have

$$\partial_t v, \partial_x (gv) \in \mathcal{C}([0, T]; L^1(1, b)), \quad (21)$$

and

$$\partial_t v + \partial_x (gv) = 0. \quad (22)$$

So $v \in X_T$. Moreover, we note

$$\begin{aligned} &(\mathcal{T}_{v_0, f}(w_1) - \mathcal{T}_{v_0, f}(w_2))(x, t) \\ &= \frac{1}{g(x)} \left(\int_1^b \beta(y) (w_1 - w_2)(y, t - G(x)) dy \right) \mathbf{1}_{G(x) \leq t}, \end{aligned}$$

and

$$\begin{aligned} & \partial_t(\mathcal{T}_{v_0,f}(w_1) - \mathcal{T}_{v_0,f}(w_2))(x, t) \\ &= \frac{1}{g(x)} \left(\int_1^b \beta(y) \partial_t(w_1 - w_2)(y, t - G(x)) dy \right) \mathbf{1}_{G(x) \leq t}, \end{aligned}$$

what gives

$$\|\mathcal{T}_{v_0,f}(w_1) - \mathcal{T}_{v_0,f}(w_2)\|_{X_T} \leq T \|\beta\|_\infty \|w_1 - w_2\|_{X_T}.$$

Consequently, for $T < \frac{1}{\|\beta\|_\infty}$, the considered application is a contraction on X_T and has therefore a unique fixed point. Define $T_1 = \frac{1}{2\|\beta\|_\infty}$. Let us denote by v this unique fixed point on $[0, T_1]$. It satisfies $\mathcal{T}_{v_0,f}(v) = v$ on X_{T_1} . One has that $f(T_1) = g(1)v(1, T_1) - \int_1^b (\beta(y)v(y, T_1)) dy$, so one can define the operator $\mathcal{T}_{v(\cdot, T_1), f}$ on $X_{2T_1}^{T_1}(v(\cdot, T_1))$ and, as T_1 depends only on $\|\beta\|_\infty$, the same arguments show that it has a unique fixed point on $[T_1, 2T_1]$. We can iterate the procedure in any interval of length T_1 and therefore in $[0, +\infty[$. This ends the proof of the lemma.

The positivity property is a direct consequence of the fact that $w \geq 0$ and, $f \geq 0$ implies that $\mathcal{T}_{0,f}(w) \geq 0$. This ends the proof of the theorem.

Proposition 15. *For any $T > 0$, \mathcal{T} is a linear continuous map from the space $\{f \in \mathcal{C}^1([0, T]); f(0) = 0\}$, endowed with the $L^1(0, T)$ norm, to $\mathcal{C}([0, T]; L^1(1, b))$.*

Proof. By theorem 13, \mathcal{T} is defined from $\{f \in \mathcal{C}^1([0, +\infty)); f(0) = 0\}$ to $\mathcal{C}([0, T], L^1(1, b))$ by $\mathcal{T}f = v$ where v is the solution constructed above. Moreover from (21), one can apply lemma 24, and as v satisfies (20), (22), we get that

$$0 = \langle \partial_t v + \partial_x(gv), j(v) \rangle_{L^1, L^\infty}.$$

thus,

$$\partial_t \int_1^b |v(x, t)| dx - \left| \int_1^b \beta(y)v(y, t) dy + f(t) \right| = 0.$$

So

$$\|v(t)\|_{L^1(1,b)} \leq \|\beta\|_{L^\infty(1,b)} \int_0^t \|v(s)\|_{L^1(1,b)} ds + \int_0^t |f(s)| ds.$$

Therefore, by Gronwall lemma, we have

$$\|v(t)\|_{L^1(1,b)} \leq e^{t\|\beta\|_{L^\infty(1,b)}} \int_0^t |f(s)| ds, \quad \forall t \leq T.$$

Thus one gets

$$\|\mathcal{T}f\|_{\mathcal{C}([0,T];L^1(1,b))} \leq e^{T\|\beta\|_{L^\infty(1,b)}} \|f\|_{L^1(0,T)}. \quad (23)$$

Now we are able to construct a weak solution of system (19).

Definition 16. *We say that v is a weak solution of system (19) if there exists a sequence $(f_n \subset \mathcal{C}^1([0, +\infty))$ such that $f_n(0) = 0$ that converges to f in $L^1(0, T)$ for any $T > 0$ and $(\mathcal{T}f_n)$ converges to v in $\mathcal{C}([0, T]; L^1(1, b))$.*

Therefore by proposition 15, one has

Proposition 17. *For any $f \in L^1_{loc}(0, +\infty)$ there exists a unique weak solution. We still denote \mathcal{T} the extension of \mathcal{T} to $L^1_{loc}(0, +\infty)$.*

Proof. It suffices to notice that if $f \in L^1_{loc}(0, +\infty)$ there exists a sequence $f_n \in \mathcal{C}^1([0, +\infty[)$ such that $f_n(0) = 0$ that converges toward f in $L^1_{loc}(0, +\infty)$ and to use (23).

3.1.4. Application to Von Foerster equation with Gompertzian growth

From the last subsections one can deduce an existence and uniqueness result for the global problem (6) :

Theorem 18. *For any $v_0 \in L^1(1, b)$ and $f \in \mathcal{C}([0, +\infty[)$, there exists an unique weak solution $v \in \mathcal{C}([0, +\infty[; L^1(1, b))$ of system (6) given by*

$$v(t) = e^{tA}v_0 + \mathcal{T}f(t). \quad (24)$$

Moreover if $v_0 \in D(A)$ and if $f \in \mathcal{C}^1([0, +\infty[)$ such that $f(0) = 0$, there exists a unique strong solution v , still given by (24), such that $f(t) = g(1)v(1, t) - \int_1^b \beta(y)v(y, t)dy$, for all $t \in [0, +\infty[$.

3.2. Asymptotic behaviour of weak solutions

3.2.1. The homogeneous problem

We start considering the homogeneous problem (15). What follows is an adaptation of ideas, that can be found in [14]. Let us decompose the space $L^1(1, b)$ into :

$$L^1(1, b) = \mathbb{R}V \oplus (\mathbb{R}\phi)^\perp,$$

where

$$(\mathbb{R}\phi)^\perp = \left\{ u \in L^1(1, b), \langle u, \phi \rangle_{L^1, L^\infty} = \int_1^b u\phi = 0 \right\}.$$

and ϕ is the eigenfunction defined in proposition 3. Actually let $L^1_\phi(1, b)$ be the space:

$$L^1_\phi(1, b) = L^1((1, b); \phi dx)$$

endowed with the norm $\|u\|_\phi := \int_1^b |u(x)| \phi(x) dx$. Any $u \in L^1(1, b)$, can be decomposed into

$$u = \langle u, \phi \rangle_{L^1, L^\infty} V + (u - \langle u, \phi \rangle_{L^1, L^\infty} V)$$

Thanks to the proposition 3, $\|\cdot\|_\phi$ defines a norm equivalent to the L^1 norm. We state the asymptotic behaviour of the weak solutions in the space L^1_ϕ .

We state now an important proposition giving some properties of the weak solutions:

Theorem 19. *For any initial data in $L^1(1, b)$, the weak solution of the homogeneous problem (15) satisfies*

1) *Decreasing of the norm $L^1_\phi(1, b)$*

$$\|v(t)\|_{L^1_\phi(1, b)} \leq e^{\lambda_0 t} \|v_0\|_{L^1_\phi(1, b)}. \quad (25)$$

2) *Conservation of the mean value in $L^1_\phi(1, b)$*

$$\int_1^b e^{-\lambda_0 t} v(t) \phi(x) dx = \int_1^b v_0(x) \phi(x) dx, \forall t \geq 0. \quad (26)$$

3) *Comparison principle*

$$v_{0,1} \leq v_{0,2} \Rightarrow v_1(t) \leq v_2(t).$$

Proof. Let $v_0 \in D(A)$ and $\tilde{v}(t) = e^{-\lambda_0 t} v(t)$, we have

$$\begin{cases} \partial_t \tilde{v} + \partial_x (g(x) \tilde{v}) + \lambda_0 \tilde{v} = 0, & x \in (1, b), t > 0, \\ g(1) \tilde{v}(1, t) = \int_1^b \beta(x) \tilde{v}(x, t) dx, & t > 0, \\ \tilde{v}(x, 0) = v_0(x). \end{cases} .$$

But ϕ satisfies

$$\begin{cases} -g(x) \partial_x \phi(x) + \lambda_0 \phi(x) = \beta(x), & x \in (1, b), \\ \phi > 0, \phi(1) = 1, \text{ and } \int_1^b V(x) \phi(x) dx = 1. \end{cases}$$

Therefore we have

$$\partial_t (\tilde{v} \phi)(x, t) + \partial_x (g \tilde{v} \phi)(x, t) = -\beta \tilde{v}(x, t), \quad x \in (1, b), t > 0. \quad (27)$$

One can remark that $\tilde{v} \in \mathcal{C}([0, +\infty[; D(A)) \cap \mathcal{C}^1([0, +\infty[; L^1(1, b))$ and so as for $\tilde{v}\phi$. Using this fact, and Lemma 24 we obtain

$$\frac{d}{dt} \int_1^b |\tilde{v}| \phi dx + \int_1^b \partial_x (g |\tilde{v}\phi|) dx = - \int_1^b \beta |\tilde{v}(x, t)| dx, \quad t > 0.$$

Integrating by parts and taking into account the boundary condition on \tilde{v} , we get

$$\frac{d}{dt} \int_1^b |\tilde{v}| \phi dx - \left| \int_1^b \beta \tilde{v}(x, t) dx \right| = - \int_1^b \beta |\tilde{v}(x, t)| dx, \quad t > 0, \quad (28)$$

hence

$$\frac{d}{dt} \int_1^b |\tilde{v}| \phi dx = \left| \int_1^b \beta \tilde{v} dx \right| - \int_1^b \beta |\tilde{v}| dx \leq 0, \quad \text{as } \beta > 0.$$

Integrating in time we get:

$$\| e^{-\lambda_0 t} v(t) \|_{L^1_\phi(1, b)} \leq \| v_0 \|_{L^1_\phi(1, b)}, \quad \forall t \geq 0, \forall v_0 \in L^1(1, b).$$

Hence the inequality (25) follows immediately for any $v_0 \in D(A)$. By density of $D(A)$ in $L^1(1, b)$ we deduce that (25) holds for any initial data in $L^1(1, b)$. In order to get (26) one integrates (27) with respect to x

$$\frac{d}{dt} \int_1^b \tilde{v}\phi dx + \int_1^b \partial_x (\tilde{v}\phi g) dx = - \int_1^b \beta \tilde{v}(x, t) dx.$$

Using the boundary condition, we finally obtain:

$$\frac{d}{dt} \int_1^b \tilde{v}\phi dx = 0.$$

Let us show the positivity property:

We start again from the equation (27). We first prove that if $v_0 \leq 0$ then $v(t) \leq 0, \forall t \geq 0$, for $v_0 \in D(A)$. Let us consider the function

$$\text{sgn}^+(v) = \frac{\max(v, 0)}{|v|} \mathbf{1}_{E^c}.$$

As in lemma 24 one gets:

$$\int_1^b \partial_x (gv) \text{sgn}^+(v) dx = -g(1) \|v\|_{L^1(1, b)} v_+(1)$$

We multiply now the equation (27) by $\text{sgn}^+(\tilde{v})$ and we obtain:

$$\frac{d}{dt} \int_1^b \tilde{v}^+ \phi dx \leq 0,$$

integrating in time we have

$$\int_1^b \tilde{v}^+(x, t) \phi(x) dx \leq \int_1^b v^+(x, 0) \phi(x) dx,$$

and as $v^+(x, 0) = 0$, we derive

$$\int_1^b \tilde{v}^+ \phi dx = 0, \forall t \geq 0.$$

As we have already shown that $\phi \geq \frac{mb^\alpha}{\lambda_0}$, one gets

$$\tilde{v}^+(x, t) = 0, \forall t \geq 0, \text{ or } v(t) \leq 0.$$

Thus we have proved the monotony property for all initial data in $D(A)$ and then by density for any initial data in $L^1(1, b)$.

We state now our principal result concerning the asymptotic behaviour in the case of the model. As in [14], one has

Theorem 20. *There exists $\gamma > 0$ such that $\beta(x) \geq \gamma\phi(x), \forall x \in [1, b]$. Moreover for ant $v_0 \in (\mathbb{R}\phi)^\perp$, one has*

$$\|e^{-\lambda_0 t} e^{tA} v_0\|_{L_\phi^1(1, b)} \leq e^{-\gamma t} \|v_0(t)\|_{L_\phi^1(1, b)}.$$

Therefore for any $v_0 \in L^1(1, b)$ we have:

$$\lim_{t \rightarrow +\infty} e^{(-\lambda_0 + \gamma')t} \left\| e^{tA} v_0 - e^{-\lambda_0 t} \langle v_0, \phi \rangle_{L^1, L^\infty} V \right\|_{L_\phi^1(1, b)} = 0, \forall \gamma' < \gamma.$$

Proof. From the definition of ϕ (see (14)) direct computations show that there exists $\gamma \geq m$ such that $\beta(x) \geq \gamma\phi(x), \forall x \in [1, b]$. Let $v_0 \in (\mathbb{R}\phi)^\perp$, as $v(t) = e^{-\lambda_0 t} e^{tA} v_0$ has zero mean value in $L_\phi^1(1, b)$, from (28) one can deduce

$$\begin{aligned} \frac{d}{dt} \int_1^b |v(t)| \phi dx &= \left| \int_1^b \beta v(x, t) dx \right| - \int_1^b \beta |v(x, t)| dx \\ &= \left| \int_1^b (\beta - \gamma) v(x, t) dx \right| - \int_1^b \beta |v(x, t)| dx \\ &\leq \int_1^b |(\beta - \gamma\phi)v(t)| dx - \int_1^b \beta |v(x, t)| dx \\ &\leq \int_1^b (\beta - \gamma\phi) |v(x, t)| dx - \int_1^b \beta |v(x, t)| dx \\ &\leq -\gamma \int_1^b |v(x, t)| \phi dx, \end{aligned}$$

therefore

$$\int_1^b |e^{-\lambda_0 t} e^{tA} v_0| \phi dx \leq e^{-\gamma t} \int_1^b |v_0| \phi dx. \quad (29)$$

As we have seen before, we can write $L^1(1, b) = \mathbb{R}V \oplus (\mathbb{R}\phi)^\perp$ and consequently we can also write that:

$$v_0 = \langle v_0, \phi \rangle_{L^1, L^\infty} V + (v_0 - \langle v_0, \phi \rangle_{L^1, L^\infty} V)$$

so

$$e^{tA} v_0 = \langle v_0, \phi \rangle_{L^1, L^\infty} e^{\lambda_0 t} V + e^{tA} (v_0 - \langle v_0, \phi \rangle_{L^1, L^\infty} V).$$

Then we have:

$$e^{-\lambda_0 t} e^{tA} v_0 = \langle v_0, \phi \rangle_{L^1, L^\infty} V + e^{-\lambda_0 t} e^{tA} (v_0 - \langle v_0, \phi \rangle_{L^1, L^\infty} V)$$

Therefore, taking the norm and using (29), we obtain

$$\|e^{-\lambda_0 t} e^{tA} v_0 - \langle v_0, \phi \rangle_{L^1, L^\infty} V\|_{L_\phi^1(1, b)} \leq e^{-\gamma t} \|v_0 - \langle v_0, \phi \rangle_{L^1, L^\infty} V\|_{L_\phi^1(1, b)}$$

which implies that

$$e^{-\lambda_0 t} \|e^{tA} v_0 - e^{\lambda_0 t} \langle v_0, \phi \rangle_{L^1, L^\infty} V\|_{L_\phi^1(1, b)} \leq e^{-\gamma t} \|v_0 - \langle v_0, \phi \rangle_{L^1, L^\infty} V\|_{L_\phi^1(1, b)}$$

and concludes the proof of the theorem.

3.2.2. The non homogeneous problem

We focus now on the asymptotic behaviour of the weak solutions for the non homogeneous problem.

Theorem 21. *For all initial data $v_0 \in L^1(1, b)$ and $f \in \mathcal{C}([0, +\infty[)$ the unique weak solution of (19) satisfies for all $t \geq 0$:*

$$\int_1^b e^{-\lambda_0 t} \mathcal{T} f(x, t) \phi(x) dx - \int_0^t e^{-\lambda_0 \tau} f(\tau) d\tau = 0.$$

Moreover,

$$\|\mathcal{T} f(t)\|_{L_\phi^1(1, b)} \leq e^{\lambda_0 t} \int_0^t e^{-\lambda_0 \tau} |f(\tau)| d\tau, \quad \forall t \geq 0.$$

Proof. Consider $f_n \in \{\mathcal{C}^1[0, +\infty[; f_n(0) = 0\}$ such that $f_n \rightarrow f$ in $L_{loc}^1(0, +\infty)$. From (21), one has

$$\frac{d}{dt} \left(\int_1^b e^{-\lambda_0 t} \mathcal{T} f_n(x, t) \phi(x) dx - \int_0^t e^{-\lambda_0 \tau} f_n(\tau) d\tau \right) = 0.$$

Integrating in time and passing to the limit and taking into account the continuity of \mathcal{T} , we deduce the first item.

Besides, still by (21) one can apply lemma 24 to $e^{\lambda_0 t} \mathcal{T} f_n$:

$$\int_1^b \phi e^{-\lambda_0 t} |\mathcal{T} f_n(x, t)| dx \leq \int_0^t e^{-\lambda_0 \tau} |f_n(\tau)| d\tau.$$

Once again, passing to the limit we obtain the second item. This ends the proof of the theorem.

We can deduce now the principal result:

Theorem 22 (Asymptotic behaviour of weak solutions).

i) For any $v_0 \in (\mathbb{R}\phi)^\perp$, the unique weak solution of (19) verifies

$$\lim_{t \rightarrow +\infty} e^{-\lambda_0 t} \|v(t)\|_{L_\phi^1(1, b)} \leq \lim_{t \rightarrow +\infty} \int_0^t e^{-\lambda_0 \tau} |f(\tau)| d\tau.$$

ii) There exists $\gamma > 0$ such that for any $v_0 \in L_\phi^1(1, b)$

$$\left\| e^{-\lambda_0 t} v(t)(t) - \langle v_0, \phi \rangle_{L^1, L^\infty} V \right\|_{L_\phi^1(1, b)} \leq e^{-\gamma t} \|v_0\|_{L_\phi^1(1, b)} + \int_0^t e^{-\lambda_0 \tau} |f(\tau)| d\tau$$

Proof. Recall that $v(t) = e^{tA} v_0 + \mathcal{T} f(\cdot, t)$. From theorem 20 and theorem 21, one deduces the two items.

3.2.3. Application to Von Foerster equation with Gompertzian growth

In the model of growing metastatic tumors we have $v_0 = 0$ and $f > 0$, the unique solution of (1) is nonnegative and we have:

$$\|v(t)\|_{L_\phi^1(1, b)} = e^{\lambda_0 t} \int_0^t e^{-\lambda_0 \tau} f(\tau) d\tau = e^{\lambda_0 t} \int_0^t e^{-\lambda_0 \tau} \beta(x_p(\tau)) d\tau.$$

The source $f(t)$ is equal to $mx_p^\alpha(t) = mb^{\alpha(1-e^{-at})}$. We define now an interesting quantity for clinical applications. For a clinician, a useful data to know is without a doubt the total number N_1 of metastases and in particular the number of large size metastases that is to say for example the tumors whose size is larger than 10^9 cells, which correspond approximately to a tumor of 30g.

$$N_{b_{min}}(t) = \int_{b_{min}}^b v(x, t) dx. \quad (30)$$

We can give an estimate of N_1 . By (13) we have $\phi \geq \frac{mb^\alpha}{\lambda_0}$ and $\phi \leq 1$. Therefore, as

$$\frac{1}{\max \phi} \|v\|_{L^1_\phi} \leq N_1(t) = \int_1^b \frac{1}{\phi(x)} v(x,t) \phi(x) dx \leq \frac{1}{\min \phi} \|v\|_{L^1_\phi}$$

we get

$$mb^\alpha e^{\lambda_0 t} \int_0^t e^{-\lambda_0 \tau} b^{-\alpha e^{-a\tau}} d\tau \leq N_1(t) \leq \lambda_0 e^{\lambda_0 t} \int_0^t e^{-\lambda_0 \tau} b^{-\alpha e^{-a\tau}} d\tau$$

We derive that for all $t \geq 0$,

$$mb^{\alpha-1} \frac{e^{\lambda_0 t} - 1}{\lambda_0} \leq N_1(t) \leq e^{\lambda_0 t}. \quad (31)$$

We can bring this to light in next section, with the numerical simulations.

An interesting fact to observe is that if we neglect the effect of the growth due to the metastases itself for small times, that is to say:

$$\begin{cases} \frac{\partial}{\partial t} \rho(x,t) + \frac{\partial}{\partial x} (g(x)\rho(x,t)) = 0, \forall x \in [1, b], \forall t \geq 0 \\ g(1)\rho(1,t) = \beta(x_p(t)), \forall t \geq 0, \\ \rho(0,x) = 0, \forall x \in [1, b]. \end{cases},$$

one obtains:

$$N_\rho(t) := \int_1^b v(x,t) dx = \int_0^t \beta(x_p(\tau)) d\tau = m \int_0^t b^\alpha \left(\frac{1}{b}\right)^{\alpha e^{-a\tau}} d\tau.$$

We will see in the numerical simulations that $N_1(t)$ does not exceed 1 while more than one year and that the influence of the emission of metastases by metastases itself is also long to appear.

4. Numerical analysis

We propose in this section a numerical approximation of problem (1) for data coming from clinical observations of a metastatic hepatocarcinoma, (see [11]):

$$a = 0.00286, b = 7.3 \times 10^{10}, \alpha = \frac{2}{3}, m = 5.3 \times 10^{-8}.$$

4.1. A characteristics scheme

Due to various scales imposed by the clinical data, we observed that classical upwind finite volume schemes require a very fine discretization in order to be stable for long time. That is why we preferred to use a different approach using the behaviour of the solution of (1) along the characteristic curves. Such methods have been investigated in [1] for more general growth speed g but for space intervals of length 1. In the case of Gompertz growth, the scheme derivation is made easier, by the explicit expression of the solutions of the characteristics (2).

Let k be a constant time step discretization, $k = \frac{T}{N}$ on this interval $[0, T]$:

$$0 = t_1 < \dots < t_n = (n-1)k < \dots < T_{N+1} = T.$$

The spatial discretization can be restricted to the interval $[1, x_p(T)]$, since we saw in the section 3.1.3 that the solution vanishes for (t, x) , $x \geq x_p(T)$. Let $x_n = x_p(t_n)$ this discretization:

$$1 = x_1 < x_2 < \dots < x_N < x_{N+1} = x_p(T).$$

We then denote by v_i^n an approximation of the solution v of problem (1) at the point (x_i, t_n) .

The key point of the construction of this scheme is that the points (x_i, t_n) and (x_{i+1}, t_{n+1}) belong to the same characteristic for any $n \geq 0$ and $i \geq 0$. For all $n \geq 0$, we solve explicitly the transport equation on the time interval $[t_n, t_{n+1}]$ and we use a first order quadrature method to take into account the boundary condition. Computing the characteristics between the point (t_n, x_{i-1}) and (t_{n+1}, x_i) , we obtain the following scheme:

$$\left\{ \begin{array}{l} v_1^0 = \frac{1}{g(1)}\beta(x_p(0)), v_i^0 = 0, 2 \leq i \leq N+1 \\ v_i^{n+1} = v_{i-1}^n e^{ak} f_{i-1}(k), i = 2, \dots, N+1, n = 1, \dots, N \\ v_1^{n+1} = \frac{1}{g(1)}\beta(x_p(t_{n+1})) + \frac{1}{g(1)} \sum_{i=2}^N h_i \beta(x_i) v_i^{n+1}, n = 1, \dots, N \end{array} \right. \quad (32)$$

where $f_i(k) = \left(\frac{x_i}{b}\right)^{1-e^{-ak}}$ and $h_i = x_i - x_{i-1}$.

4.2. Convergence analysis

We show in this section the convergence of the characteristics scheme. We denote $e_i^n = v(x_i, t_n) - v_i^n$ the error of the scheme. Remarking that if one starts

from the exact solution at the points (x_i, t_n) then the scheme is exact at the points (x_i, t_{n+1}) :

$$v(x_i, t_{n+1}) = v(x_{i-1}, t_n) f_{i-1}(k) e^{ak}$$

we derive

$$\begin{cases} e_i^{n+1} = e_{i-1}^n f_{i-1}(k) e^{ak} \\ e_1^{n+1} = \frac{1}{g(1)} \sum_{i=2}^N h_i \beta_i e_i^{n+1} + r^{n+1} \\ e_i^0 = 0 \end{cases}$$

The truncation error only comes from the quadrature error; one can estimate r^n as soon as the function βv is smooth:

$$|r^n| \leq h_n (x_p(t_n) - 1) |\partial_x(\beta v)(\eta_i, t_n)|, \text{ for } \eta_i \in [x_{i-1}, x_i]$$

We have the following result:

Theorem 23 (Error estimates). *Let $\Omega_T = \{(x, t) \in [1, b] \times [0, \frac{T}{a}]; x \leq x_p(t)\}$ and $v \in C^1(\Omega_T)$. There exists $C_T = C(T, \beta, v)$ such that*

$$\|e^n\|_1 \stackrel{\text{def}}{=} \sum_{i=1}^N h_i |e_i^n| \leq C_T F_n(k) e^{\lambda_0 t_n},$$

with $F_n(k) \xrightarrow[k \rightarrow 0]{} 0$ uniformly in n such that $t_n \in \Omega_T$.

Note that the weak solution of the problem (1) fullfills the assumptions of this theorem and thus the convergence of the characteristic scheme (32) is proved for the problem (1) for long time intervals.

Proof. We have

$$\begin{aligned} \|e^{n+1}\|_1 &= h_1 |e_1^{n+1}| + e^{ak} \sum_{i=2}^N h_i |e_{i-1}^n| f_{i-1}(k) \\ &= h_1 |e_1^{n+1}| + e^{ak} \sum_{i=1}^{N-1} h_{i+1} |e_i^n| f_i(k) \end{aligned}$$

with

$$\begin{aligned} h_1 |e_1^{n+1}| &\leq \frac{h_1}{a \ln b} \sum_{i=2}^N h_i \beta_i |e_i^{n+1}| + h_1 |r^{n+1}| \\ &\leq \frac{h_1}{a \ln b} \sum_{i=1}^{N-1} h_{i+1} \beta_{i+1} e^{ak} f_i(k) |e_i^n| + h_1 |r^{n+1}|. \end{aligned}$$

Hence we obtain

$$\|e^{n+1}\|_1 \leq h_1|r^{n+1}| + \sum_{i=1}^{N-1} h_i|e_i^n|e^{ak}f_i(k)\frac{h_{i+1}}{h_i} \left(1 + h_1\frac{\beta_{i+1}}{a\ln b}\right). \quad (33)$$

Remark that:

- There exists k_0 such that for all $k \leq k_0$

$$\frac{h_1\beta_i}{a\ln b} \leq 2kmb^\alpha.$$

This is a corollary of the mean value theorem:

$$h_1 = x_p(k) - 1 = b^{1-e^{-ak}} - 1 \leq ak\ln(b)e^{-\ln(b)(1-e^{-x})} \leq 2ak\ln(b)$$

as soon as $k \leq k_0$ where $k_0 = \frac{1}{a}\ln\left(\frac{1}{1-\frac{\ln(2)}{\ln(b)}}\right) \sim 0.98$.

- For any $k > 0$ and any $i \geq 0$,

$$f_i(k)\frac{h_{i+1}}{h_i} \leq 1$$

Indeed, we can write

$$\begin{aligned} h_i &= e^{\ln(b)(1-e^{-aik})} \left(1 - e^{\ln(b)e^{-aik}(1-e^{-ak})}\right) \\ h_{i+1} &= e^{\ln(b)(1-e^{-aik})} \left(e^{\ln(b)e^{-aik}(1-e^{-ak})} - 1\right) \end{aligned}$$

Hence,

$$\begin{aligned} f_i(k)\frac{h_{i+1}}{h_i} &= e^{-\ln(b)e^{-aik}(1-e^{-ak})} \frac{e^{\ln(b)e^{-aik}(1-e^{-ak})} - 1}{1 - e^{\ln(b)e^{-aik}(1-e^{-ak})}} \\ &= \frac{1 - z^{e^{-ak}}}{1 - z} \end{aligned}$$

with $z = e^{-\ln(b)e^{-aik}(e^{ak}-1)} \leq 1$ and then $1 - z^{e^{-ak}} \leq 1 - z$.

The estimate (33) becomes for $k \leq k_0$:

$$\begin{aligned} \|e^{n+1}\|_1 &\leq 2ak\ln(b)(x_p(t_n) - 1)h_n\|\partial_x(\beta v)\|_\infty + \|e^n\|_1 e^{ak} (1 + 2kmb^\alpha) \\ &\leq 2ak\ln(b)(x_p(t_n) - 1)h_n\|\partial_x(\beta v)\|_\infty + \|e^n\|_1 e^{k(a+2mb^\alpha)}. \end{aligned}$$

Using a discrete Gronwall lemma we get:

$$\|e^n\|_1 \leq 2ak\ln(b)\|\partial_x(\beta v)\|_\infty \sum_{l=0}^{n-1} h_l(x_p(t_l) - 1)e^{(n-1-l)k(a+2mb^\alpha)}.$$

$$\begin{aligned} \|e^n\|_1 &\leq 2ak \ln(b) \|\partial_x(\beta v)\|_\infty (x_p(t_n) - 1) h_n \frac{e^{(a+2mb^\alpha)t_n} - 1}{e^{(a+2mb^\alpha)k} - 1}, \\ &\leq 2ak \ln(b) \|\partial_x(\beta v)\|_\infty h_n (x_p(t_n) - 1) \frac{e^{(a+2mb^\alpha)t_n} - 1}{(a + 2mb^\alpha)k} \end{aligned}$$

Now remark that $2mb^\alpha \leq \lambda_0$, we obtain for $t_n \leq \frac{T}{a}$

$$\|e_n\|_1 \leq 2 \ln(b) e^T \|\partial_x(\beta v)\|_\infty h_n (x_p(t_n) - 1) e^{\lambda_0 t_n}.$$

We conclude using the fact that $F_n(k) = h_n(x_p(t_n) - 1)$ converges towards 0 uniformly on $n \leq \frac{T}{ak}$ as k tends to 0.

4.3. Numerical results

4.3.1. Influence of the production of metastases by metastases previously created

The figure 1 and figure 2 gives some comparisons between $N_{b_{min}}$ and N_ρ (see (30) for their definition) for different times. We observe that the influence of the previously created metastases, that is to say the influence of the integral term in the boundary condition, is hardly visible before almost three years, as we could expect.

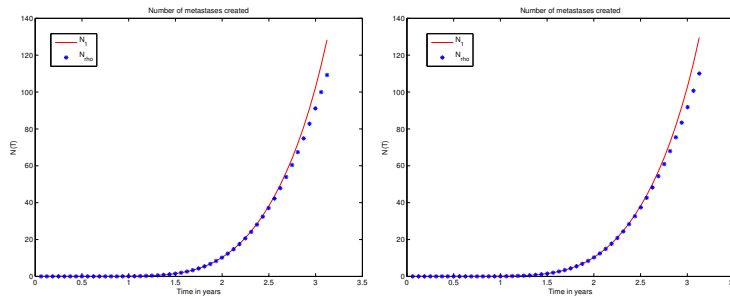


Figure 1. Number of metastases after 3 years with $k = 2$ hours (left) and $k = 1$ hours. (right)

4.3.2. Evolution of the metastases number following the tumor size

We compare the evolution of the metastases number for large size tumors. The figure 3 shows that before three years, there are very few metastases greater than 10^8 cells. In the figure 4, we compare the number of metastases N_{10^8} and N_{10^9} . In these figures the time step is $k = 1$ hour.

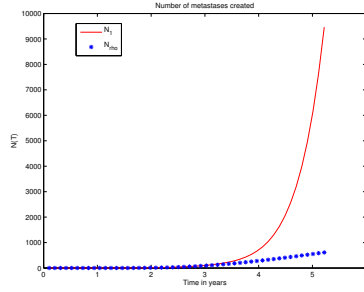


Figure 2. *Number of metastases after 5 years*

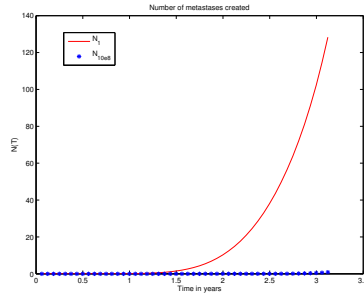


Figure 3. *Comparison of the total number of metastases and the number of metastases larger than 10^8 cells after 3 years*

4.3.3. Asymptotic behaviour of N_1 and comparison with theoretical results

We compare in table 1 the values of $N_1(T)$, that we obtain with the one obtained in [11]. We observed a good agreement between our results.

Time in years	$N_1(T)$ [11]	$N_1(T)$ authors
$T = 3$	135	134
$T = 3.4$	263	260
$T = 3.6$	396	396
$T = 3.8$	712	718

Table 1. *Comparative results of $N_1(T)$*

Let us now check the lower bound of N_1 given in (31). We choose two different values of a (see [11]) and we compute the associated theoretical λ_0 using the results obtained in [11]. In the figure 5, we observe that the function

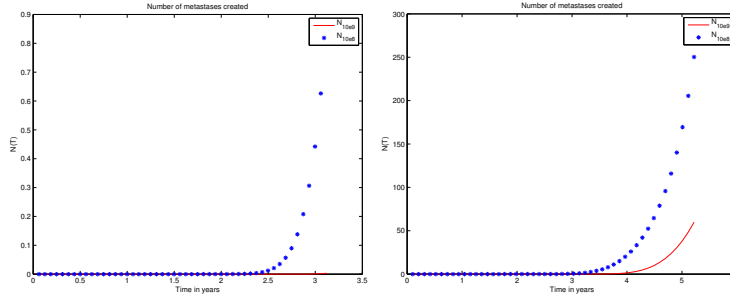


Figure 4. Comparison of the number of metastases larger than 10^8 cells and larger than 10^9 cells after 3 and 5 years

$\ln(N_1(t))$ becomes linear after some time. Using (31) the slope s of the straight line is given by:

$$s = p \times \lambda_0 \quad (34)$$

where the number p is such that $a = \frac{p}{365}$. These slope gives an very good approximation of λ_0 , as shown in Table 2:

a	Theoretical λ_0	λ_0 obtained with (34)
$a = .00286$	2.03	2.02
$a = .0143$	1.41	1.43

Table 2. Comparative results of λ_0

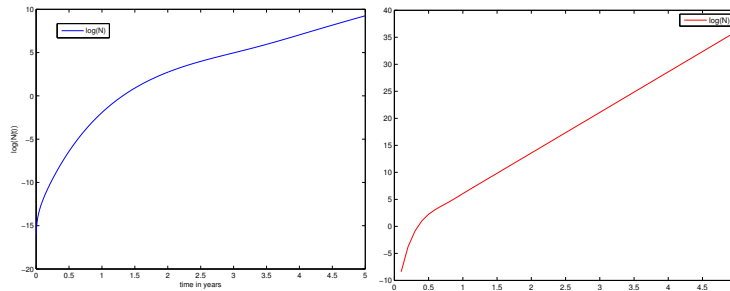


Figure 5. Log of the number of metastases after 5 years with $a = .00286$ (left) and $a = .0143$ (right)

In figure 6, we compare the solution obtained by the characteristics scheme and the theoretical profile given in [6] and [11]:

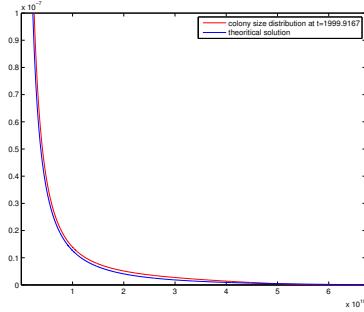


Figure 6. Comparison of the approximate solution and the theoretical solution after 2000 days with $\lambda_0 = 2.02995$

$$v(x, t) \simeq \frac{a}{mb^\alpha \ln b} e^{\lambda_0 t} \left(1 - \frac{\ln x}{\ln b}\right)^{\lambda_0 - 1} \frac{1}{c(\lambda_0)}, \quad x \in [1, x_p(t)]$$

where

$$c(\lambda_0) = \sum_{n=0}^{\infty} \frac{(-\alpha \ln b)^n}{n!(\lambda_0 + n)^2}.$$

For $\alpha = .4$, we observed in figure 7 the "U-shaped" profile claimed in [11].

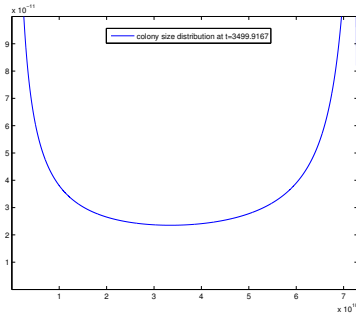


Figure 7. Solution with $\alpha = .4$

5. Conclusion

Even if this model is a simplification of a more complicated phenomena, its asymptotic gives interesting informations about the evolution of metastatic sites. In particular it shows that for large time, the exponential growth of the density of metastases is given by a parameter λ_0 . The knowledge of this parameter is therefore fundamental. As its definition shows (see (9)), λ_0 depends

on a, b, α, m . An interesting problem would be to identify these coefficients by suitable observations on the patient. The first question could be: can we find a one to one correspondance between clinical observations and the parameters a, b, α, m that we use in the model? This leads to a mathematical uniqueness problem that we plan to investigate. The minimization of λ_0 with respect to the parameters a, b, α, m is another important question that can give informations on the target of therapies.

6. Appendix

We finally give in this section the proof of a technical result that we previously used:

Lemma 24. *For any function $v \in L^1(1, b)$ such that $gv \in W^{1,1}(1, b)$, we have:*

$$\int_1^b \partial_x(gv)j(v)dx = -g(1)\|v\|_{L^1(1,b)}|v(1)|.$$

Proof. Let us consider the following sequence:

$$\Gamma_n(s) = \begin{cases} 1 & \text{if } s \geq \frac{1}{n} \\ -1 & \text{if } s \leq -\frac{1}{n} \\ ns & \text{otherwise} \end{cases},$$

For any function $v \in D(A)$, we have $g\partial_x v \in L^1(1, b)$ and $g\partial_x v\Gamma'_n(v) \in L^1(1, b)$. Furthermore $\{x \in (1, b); \Gamma'_n(v(x)) \neq 0\} = \{|v| \leq \frac{1}{n}\}$. Hence $vg\partial_x v\Gamma'_n(v) \in L^1(1, b)$ and

$$\int_1^b \partial_x(gv)\Gamma_n(v) = -\int_1^b vg\partial_x v\Gamma'_n(v)dx - g(1)v(1)\Gamma_n(v(1)).$$

By Lebesgue's theorem, one can deduce:

$$\partial_x(gv)\Gamma_n(v) \xrightarrow{n \rightarrow +\infty} \partial_x(gv) \frac{j(v)}{\|v\|_{L^1(1,b)}}$$

and moreover

$$\Gamma_n(v(1)) \xrightarrow{n \rightarrow +\infty} |v(1)|.$$

Moreover, as $g\partial_x v \in L^1(1, b)$, we conclude that

$$g(\partial_x v)v\Gamma'_n(v) \xrightarrow{n \rightarrow +\infty} 0 \text{ in } L^1(1, b).$$

References

- [1] O. Angulo and J. C. Lopez-Marcos. Numerical scheme for size-structured populations equations. *Mathematical Biosciences*, 157:169–188, 1999.
- [2] H. T. Banks and F. Kappel. Transformation semigroups and l^1 approximation for size structured population models. *Semigroup Forum*, 38, 1989.
- [3] D. Barbolosi and A. Iliadis. Optimizing drug regimens in cancer chemotherapy by an efficacy-toxicity model. *Computer and Biomedical Research*, 33, 2000.
- [4] K.B. Bischoff, K.J. Himmelstein, R.L. Dedrick, and D.S. Zaharko. Pharmacokinetics and cell population growths models in cancer chemotherapy. *Chem. Eng. Med. Biol*, 118:47–64, 1973.
- [5] J. Clairambault, B. Laroche, S. Mischler, and Perthame B. A mathematical model of the cell cycle and its control. Technical Report 4892, INRIA, France, July 2003.
- [6] A. Devys, T. Goudon, and P. Lafitte. A model describing the growth and the size distribution of multiple metastatic tumors. *Preprint*, 2007.
- [7] Post-Meeting Edition, editor. *A mechanistic model predicting hematopoiesis and tumor growth to optimize docetaxel + epirubicin (ET) administration in metastatic breast cancer (MBC): Phase I trial*, volume 25 (18S). ASCO Annual Meeting Proceedings, 2007, June 20 Supplement.
- [8] K.J. Engen and R. Nagel. *One parameter Semigroups for Linear Evolution Equations*. Springer, 2000.
- [9] Early Breast Cancer Trialists Collaborative Group. Systemic treatment of early breast cancer by hormonal, systemic or immune therapy: 133 randomized trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet*, 339:71–85, 1992.
- [10] J. Harris, M. Morrow, and L. Norton. Malignant tumors of the breast. In Jr VT DeVita, S Hellman, and SA Rosenberg, editors, *Cancer: Principles and Practice of Oncology (5th Edition)*, pages 1557–1602, Philadelphia: Lippincott-Raven, 1997.
- [11] K. Iwata, K. Kawasaki, and N. Shigesad. A dynamical model for the growth and size distribution of multiple metastatic tumors. *J. Theor. Biol*, 203:177–186, 2000.
- [12] L. Norton. Theoretical concepts and the emerging role of taxanes in adjuvant therapy. *The Oncologist*, 6(suppl3):30–35, 2001.
- [13] A. Pazy. *Semigroups of Linear Operators and Applications to Partial Differential Equations*. Springer, 1983. Applied mathematical sciences.

- [14] B. Perthame. *Transport Equations on Biology*. Birkhäuser, 2007. Frontiers in Mathematics.