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# A Mathematical Investigation of a Dynamical Model for the Growth and Size Distribution of Multiple Metastatic Tumors

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**Abstract**

Recently, Iwata, Kawasaki and Shigesada proposed a dynamical model for the growth and size distribution of multiple metastatic tumors [*J. theor. Biol.*, **203**, 177–186 (2000)]. The model is based on von Foerster's equation for the colony size distribution $\rho(t,x)$ together with appropriate initial and boundary conditions. The parameters of the growth and colonization rates are fitted against clinical data obtained from X–Ray CT images and the model shows a very good agreement with these data.

In the present work we use the method of characteristics to derive solutions for the colony size distribution $\rho(t,x)$. We show that the boundary condition can be transformed into a linear Volterra integral equation of second kind, such that an existence result follows from the standard theory of integral equations and quasilinear first order PDE's. In particular we show that the solutions are in general discontinuous along a particular characteristic ground curve.

For a simple expression of the tumor growth rate we show how to derive explicit solutions using the method of characteristics and the resolvent kernel method for Volterra equations. The asymptotic behaviour of the discontinuity when using Gompertzian's growth rate is investigated and we propose a modified boundary conditions which ensures the existence of continuous solutions.

## 1 Introduction

The mathematical modeling of tumor growth has a long history in life sciences and applied mathematics. The most simple approach is to describe the growth of a single tumor by models from population dynamics. If the number of cells in the tumor is small, one may introduce statistical or stochastic models and more complicated models are necessary to include metastatic processes.

The present work deals with a mathematical investigation of a model to describe the growth and size distribution of multiple metastatic tumors recently proposed by Iwata, Kawasaki and Shigesda in [1]. The model is based on von Foerster's equation [2, 3], a first order partial differential equation, which models the dynamic behaviour of the colony size

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distribution $\rho(t,x)$ of metastatic tumors with cell number $x \geq 1$ at time $t$. The model is closed by the homogeneous initial condition $\rho(0,x) = 0$, which means that initially no metastatic tumors exists and an integral boundary conditions, which relates the value $\rho(t,1)$ to the values $\rho(t,x)$ with $1 < x < \infty$. The parameters of the growth and colonization rates are fitted against clinical obtained from X–Ray CT images and the authors obtained representation formulas of solutions of the model using Laplace's transformation in the time variable $t$. In particular, when assuming the Gompertzian growth rate, see 2.5 in Section 2, the solution can be expressed in terms of an infinite series and the solution shows a good agreement with clinical data.

The aim of the present work is give a global existence result, which is obtained using the method of characteristic for quasilinear first order PDE's. The assumptions on the growth and colonization rates need in the theorem are in particular satisfied by the expressions used in [1]. Because the boundary condition $\rho(t,1)$ is not given explicitly in the model, one should ensure that nevertheless the condition defines the solution at the boundary in a unique manner. Here, we show that the boundary condition can rewritten as a linear Volterra equation of second kind, which can be treated by standard methods from linear integral equations.

The paper is organized as follows. Following reference [1] we formulate in Section 2 the mathematical model proposed by the authors and indicate how explicit solutions are derived applying Laplace's transformations. In Section 3 we interpret von Foerster's equation as a quasilinear first order PDE and use the method of characteristics to derive representation formulas for solutions of the model. Using these formulas we show that the boundary condition given in [1] can be rewritten as a linear Volterra integral equation of second kind, which has a unique continuous solution under appropriate assumptions on the integral kernel.

Combining this result with the method of characteristics we formulate an existence result, which states that in general solutions will be only piecewise continuous with a discontinuity along a characteristic curve, which describes the number of cells in the primary tumor. This is due to some incompatibility of the initial and boundary conditions used in [1]. We show how explicit solutions are obtained from the method of characteristics and the kernel resolvent method for the Volterra integral equation. Moreover, we study the asymptotic behaviour of the discontinuity and propose a modified boundary condition, which yields a continuous solution. Section 4 contains the conclusions of the paper.

## 2 The Model of Iwata, Kawasaki and Shigesada

The model proposed by the authors in [1], which will be called for simplicity in the remainder of the paper the IKS–model, is the following. Let $\rho(t,x)$ be the colony size distribution of metastatic tumors with cell number $x$ at time $t$, i.e. $\rho(t,x)dx$ denotes the number of metastatic tumors at time $t$ with size in the interval $[x, x+dx]$. Assuming that tumors are not eliminated by some therapeutical treatment or natural death and that the nuclei of the colonization are located far enough from each other, the dynamical behavior is given by the so–called von Foerster's equation [2, 3]

$$\frac{\partial \rho(t,x)}{\partial t} + \frac{\partial}{\partial x}\left(g(x)\rho(t,x)\right) = 0 \tag{2.1}$$

with initial condition

$$\rho(0,x) = 0 \tag{2.2}$$

and boundary condition

$$g(1)\rho(t,1) = \int_1^\infty \beta(x)\rho(t,x)\,dx + \beta(x_p(t)) \tag{2.3}$$

The functions $g(x)$ and $\beta(x)$ appearing in (2.1) and (2.3) are the growth and colonization rates, respectively. Moreover, $x_p(t)$ denotes the number of cells in the primary tumor at time $t$ and is given by the solution of the ordinary differential equation

$$\frac{dx_p}{dt} = g(x_p), \quad x_p(0) = 1 \tag{2.4}$$

In [1] the authors mainly focus on the so–called Gompertzian growth rate $g(x)$, where

$$g(x) = ax\ln\left(\frac{b}{x}\right), \tag{2.5}$$

and $a$ and $b$ denote the constant growth rate and the tumor size at the saturated level, respectively. Several other expressions can be found in the literature, see, e.g., the references given in [1]; two of them are studied in more detail by Iwata et al. The linear growth rate, i.e.

$$g(x) = ax \tag{2.6}$$

which yields an exponential growth of $x_p(t)$ in time, as well as the power–law growth rate given by

$$g(x) = ax^{1-\gamma} \quad \text{for } 0 \le \gamma \le 1 \tag{2.7}$$

The colonization rate $\beta(x)$ is given by the expression

$$\beta(x) = mx^\alpha \tag{2.8}$$

where $m$ is the colonization coefficient and $\alpha$ the fractal dimension of blood vessels infiltrating the tumor, see the literature given in [1].

Using Laplace's transformation with respect to $t$ in (2.1) together with the initial condition (2.2) the authors obtained the parameter–dependent ordinary differential equation

$$s\tilde{\rho}(x,s) + \frac{\partial}{\partial x}(g(x)\tilde{\rho}(x,s)) = 0 \tag{2.9}$$

Substituting the general solution of (2.9) into the boundary condition (2.3), they derived explicit solutions or infinite series expansion of the solution, depending on the complexity of the growth rate $g(x)$. E.g., for the linear growth rate defined in (2.6), the explicit solution given in [1] reads

$$\rho(t,x) = \frac{m}{a}x^{-\alpha-(m/a)-1}e^{(a\alpha+m)t} \tag{2.10}$$

One should be a bit careful, because the expression given in (2.10) is only valid for points $(t,x)$ with $t > 0$ and $1 \le x < x_p(t)$. Due to initial condition (2.2), the solution vanishes for $(t,x)$ with $x \ge x_p(t)$, see Section 3.

In particular, solutions of the IKS–model are discontinuous along the curve defined by $x_p(t)$, because the boundary condition given by (2.3) is incompatible with the initial condition (2.2): in the limit $t \to 0$, Eq. (2.3) reads

$$g(1)\rho(1,0) = \int_0^\infty \beta(x)\rho(x,0)\,dx + \beta(x_p(0))$$

and from (2.2) and $x_p(0) = 1$ we obtain the condition

$$\beta(1) = 0$$

which obviously yields a contradiction with the prescribed form of $\beta(x)$ as given by (2.8) as long as $m \neq 0$.

# 3 The IKS–model revisited

Eq. (2.1), which we rewrite for convenience in the form

$$\frac{\partial \rho(t,x)}{\partial t} + g(x)\frac{\partial \rho(t,x)}{\partial x} = -g'(x)\rho(x,t), \tag{3.1}$$

is a hyperbolic quasilinear equation and the solution theory is based on the method of characteristics, see [4].

The characteristic system of (2.1) reads

$$\dot{x} = g(x), \quad x(s) = x_0 \tag{3.2}$$

$$\dot{w} = -g'(x)w, \quad w(s) = w_0 \tag{3.3}$$

where the trajectories given by (3.2) are the so–called characteristic ground curves. A particular ground curve is defined by (2.4), which describes the number of cells in the primary tumor and separates the $(t,x)$–plane into two different regions, like shown in Fig. 1.

Above the curve defined by $x_p(t)$ the solution of (2.1) only depends on the initial condition prescribed along the points $(0,x)$ with $x \geq 1$, below the curve the solution is generated by the boundary condition given at the points $(t,1)$ with $t > 0$. Hence, denoting the solutions of (3.2) and (3.3) by $X_{t,s}(x_0)$ and $W_{t,s}(x_0,w_0)$, respectively, one can derive the solution $\rho(x,t)$ in the form

$$\rho(t,x) = W_{t,0}(T_t^{-1}(x), \rho(0,T_t^{-1}(x))) \tag{3.4}$$

if $x \geq x_p(t)$ and

$$\rho(t,x) = W_{t,s}(1, \rho(s,1)), \quad s = T_t^{-1}(x) \tag{3.5}$$

if $x < x_p(t)$, where the function $T_t$ in (3.4) is defined by

$$T_t(x_0) = X_{t,0}(x_0)$$

whereas in (3.5) one has

$$T_t(s) = X_{t,s}(1)$$

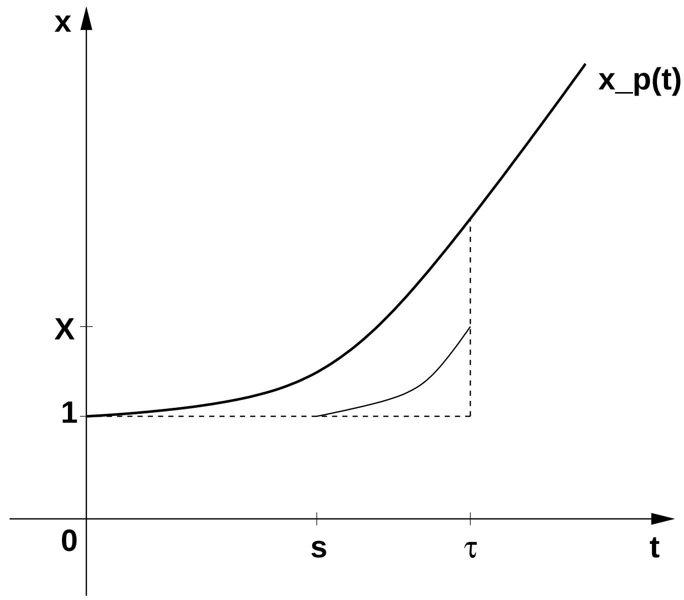


Figure 1: Characteristic curve $x_p(t)$ separates the $(t, x)$–plane into two regions.

The boundary value $\rho(s, 1)$ in (3.5) is not given explicitly in the IKS–model, but defined by the boundary condition (2.3). To obtain the boundary value $\rho(\tau, 1)$ for some fixed $\tau > 0$, one has to integrate the expression $\beta(x)\rho(\tau, x)$ along the vertical line starting from $(\tau, 1)$ up to the point $(\tau, x_p(\tau))$, see Fig. 1. Hence, we should investigate in the following in more detail the integral expression in (2.3).

Let the point $(\tau, X)$ with $1 < X < x_p(\tau)$ be fixed. If we assume that there exists a characteristic ground starting at some $0 < s < \tau$ at the point $x_0 = 1$, which is running through $(\tau, X)$, we have from (3.5) the expression

$$\rho(\tau, X) = W_{\tau,s}(1, \rho(s, 1))$$

Then the integral in (2.3) can be transformed to an integral along the line $(s, 1)$ with $0 < s < t$, i.e.

$$g(1)\rho(t, 1) = \int_0^t \beta(T_t(s))W_{t,s}(1, \rho(s, 1)) \left| \frac{dT_t(s)}{ds} \right| ds + \beta(x_p(t)) \tag{3.6}$$

Integrating (3.3) yields

$$W_{t,s}(1, \rho(s, 1)) = \rho(s, 1) \exp\left( -\int_s^t g'(X_{\tau,s}(1))\, d\tau \right) \tag{3.7}$$

and substituting (3.7) into (3.6) one has

$$g(1)\rho(t, 1) = \int_0^t \beta(T_t(s)) \exp\left( -\int_s^t g'(T_\tau(s))\, d\tau \right) \left| \frac{dT_t(s)}{ds} \right| \rho(s, 1)\, ds + \beta(x_p(t)) \tag{3.8}$$

Assuming $g(1) \neq 0$, Eq. (3.8) represents a linear Volterra integral equation of second kind, which we write in the more compact form

$$v(t) - \mu \int_0^t K(t,s) v(s)\, ds = f(t) \tag{3.9}$$

with $\mu = 1/g(1)$ and

$$\begin{aligned} f(t) &= \mu \beta(x_p(t)) \\ K(t,s) &= \beta(T_t(s)) \exp\left( - \int_s^t g'(T_\tau(s))\, d\tau \right) \left| \frac{dT_t(s)}{ds} \right| \end{aligned}$$

### 3.1 An existence result for the IKS–model and explicit solutions

Using the standard theory of linear integral equations, like given in the textbook [5], one has the following existence result for Eq. (3.9).

**Theorem 1** *Let $\Delta = \{(t,s) \in [0,\infty)^2 : x \in [0,\infty), t \in [0,x]\}$ and assume that $K : \Delta \to \mathbb{R}$ is a continuous functions, i.e. $K \in \mathcal{C}(\Delta)$. Then Eq. (3.9) has for all $\lambda \neq 0$ and every $f \in \mathcal{C}([0,\infty))$ a unique solution $v \in \mathcal{C}([0,\infty))$.*

The theorem above ensures, that the boundary condition (2.3) yields a continuous function $v(t) = \rho(t,1)$ for $t \in (0,\infty)$, which we need to extend the method of characteristics to the region below the curve $x_p(t)$, as shown in Fig. 1. Using Theorem 1 we can formulate the following existence result for Eq. (2.1) together with initial and boundary condition (2.2) and (2.3), respectively.

**Theorem 2** *Let $g \in \mathcal{C}^2([1,\infty))$ be a positive function with $g(1) \neq 0$ and $\beta \in \mathcal{C}([1,\infty))$. Then, if $\beta(1) = 0$, Eq. (2.1) together with the initial and boundary conditions (2.2) and (2.3), respectively, has a solution $u \in \mathcal{C}([0,\infty) \times [1,\infty))$.*

*If $\beta(1) \neq 0$, the system has a solution, which is piecewise continuous and has a jump along the curve defined by $x_p(t)$ with jump height $h(t)$ given by*

$$h(t) = \beta(1) \exp\left( - \int_0^t g'(x_p(\tau))\, d\tau \right) \tag{3.10}$$

**Proof** The assumption $g \in \mathcal{C}^2$ ensures that the characteristic system defined by (3.2) and (3.3) has global unique solutions in time. Moreover, the trajectory $X_{t,s}(x_0)$ as defined above is continuously differentiable with respect to all arguments $t, s$ and $x_0$.

Because $g$ is positive, the trajectories $X_{t,s}(x_0)$ are monotonically increasing in $t$ for all $s \geq 0$ and $x_0 \geq 1$, will not interact due to uniqueness and cover the whole region $t \geq 0$ and $x \geq 1$ of the $(t,x)$–plane. Hence the method of characteristics will work globally in time.

From $g(1) \neq 0$, we know that the boundary condition (2.3) defines a linear Volterra integral equation of second kind and because $\beta \in \mathcal{C}([1,\infty))$ and

$$\frac{\partial X_{t,s}(x_0)}{\partial s} \in \mathcal{C}([0,\infty)^2 \times [1,\infty))$$

Theorem 1 ensures that there exists a function $v(t) = \rho(t, 1) \in \mathcal{C}([0, \infty)$, which defines the necessary boundary condition for (2.1).

Finally, due to (2.3) we have

$$\lim_{t \to 0} v(t) = \beta(1)$$

and therefore the solution is continuous along the curve defined by $x_p(t)$ as long as $\beta(1) = 0$. If $\beta(1) \neq 0$, Eq. (3.10) directly follows from (3.7), which completes the proof.

It remains to show how to derive explicit solutions using the method of characteristics and analytical techniques for linear Volterra integral equations of second kind. For simplicity we will restrict ourselves in the following to the case of a linear growth rate and assume $\alpha = 1$ in (2.8), i.e. blood vessels are homogeneously distributed in the whole tumor.

Assuming $g(x) = ax$ the characteristic system reads

$$\begin{aligned} \dot{x} &= ax, \quad x(s) = x_0 \\ \dot{w} &= -aw, \quad w(s) = w_0 \end{aligned}$$

and therefore

$$X_{t,s}(x_0) = x_0 e^{a(t-s)} \tag{3.11}$$

$$W_{t,s}(w_0) = w_0 e^{a-(t-s)} \tag{3.12}$$

Then

$$T_t(s) = X_{t,s}(1) = e^{a(t-s)}, \quad \frac{dT_t(s)}{ds} = -ae^{a(t-s)}$$

and with $\beta(x) = mx$, we obtain the integral equation

$$v(t) - m \int_0^t e^{a(t-s)} v(s)\, ds = \frac{m}{a} e^{at},$$

i.e. the kernel $K(t, s)$ of the integral equation is given by

$$K(t, s) = e^{a(t-s)} \tag{3.13}$$

From the theory of Volterra equations of second kind it is known that the solution of (3.9) can be represented in terms of the resolvent kernel method, i.e. one has

$$v(t) = f(t) + \mu \int_0^t R(t, s; \mu) f(s)\, ds \tag{3.14}$$

where $R(t, s; \mu)$ denotes the resolvent kernel given by

$$R(t, s; \mu) = \sum_{k=1}^{\infty} \mu^{k-1} K^{(k)}(t, s) \tag{3.15}$$

and the $K^{(k)}$'s are obtained from the successive approximation method by

$$\begin{aligned} K^{(1)}(t, s) &:= K(t, s) \\ K^{(k+1)}(t, s) &:= \int_s^t K(t, \tau) K^{(k)}(\tau, s)\, d\tau \end{aligned}$$

Using (3.13) in the successive approximation method one obtains

$$K^{(k)}(t,s) = \frac{1}{(k-1)!}(t-s)^(k-1)e^{a(t-s)}$$

and the resolvent kernel in (3.8) is given by

$$R(t,s;m) = \sum_{k=1}^{\infty} m^{k-1}\frac{1}{(k-1)!}(t-s)^{k-1}e^{a(t-s)(\alpha-1)} = e^{(a+m)(t-s)}$$

From (3.14) we finally get the explicit boundary values $\rho(t,1)$ in the form

$$\rho(t,1) = v(t) = \frac{m}{a}e^{at} + \frac{m^2}{a}\int_0^1 e^{(a+m)(t-s)}e^{as}\,ds = \frac{m}{a}e^{(a+m)t} \tag{3.16}$$

Using (3.5) in combination with (3.12) we get the solution for $1 < x < x_p(t)$ in the form

$$\rho(t,x) = \rho(s,1)e^{a(t-s)} \tag{3.17}$$

and using (3.11) yields

$$s = t - \frac{1}{a}\ln x \tag{3.18}$$

such that from (3.17) with (3.16) and (3.18) one has for $1 < x < x_p(t)$ the solution

$$\rho(t,x) = \frac{m}{a}x^{-2-m/a}e^{(a+m)t}$$

and the complete solution of the IKS-model is

$$\rho(t,x) = \begin{cases} 0 & : \quad t \geq 0,\ x \geq e^{at} \\ \frac{m}{a}x^{-2-m/a}e^{(a+m)t} & : \quad t > 0,\ 1 < x < e^{at} \end{cases} \tag{3.19}$$

which coincides with the result given in [1].

If we assume that the characteristic system is explicitly solvable, but no analytical solution can be obtained from the resolvent kernel method, the new formulation of the boundary condition (2.3) as Volterra integral equation is anyway helpful, because one may combine numerical methods for the Volterra equation with the method of characteristics.

## 3.2 Asymptotic behaviour of the discontinuity in the IKS–model

The IKS–model shows an interesting asymptotic behaviour when applying the Gompertzian growth rate and the parameter set given in [1]. In the following we study in more detail the behaviour of the discontinuity along the curve $x_p(t)$, given by (3.10) in Theorem 2.

Assuming (2.5) for the growth rate, the trajectory $x_p(t)$ is given by

$$x_p(t) = be^{-e^{-at}\ln b} \tag{3.20}$$

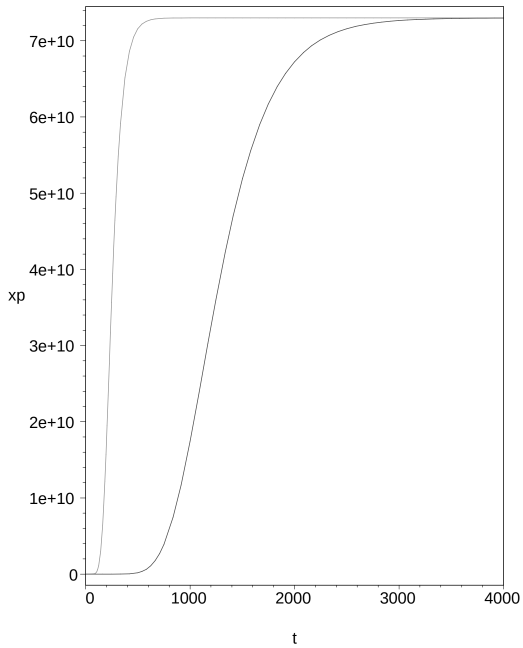


Figure 2: Trajectory $x_p(t)$ reaches for $t \to \infty$ the saturated level $b = 7.3 \cdot 10^{10}$. The values for $a$ are $a = 0.0143$ (left curve) and $a = 0.00286$ (right curve).

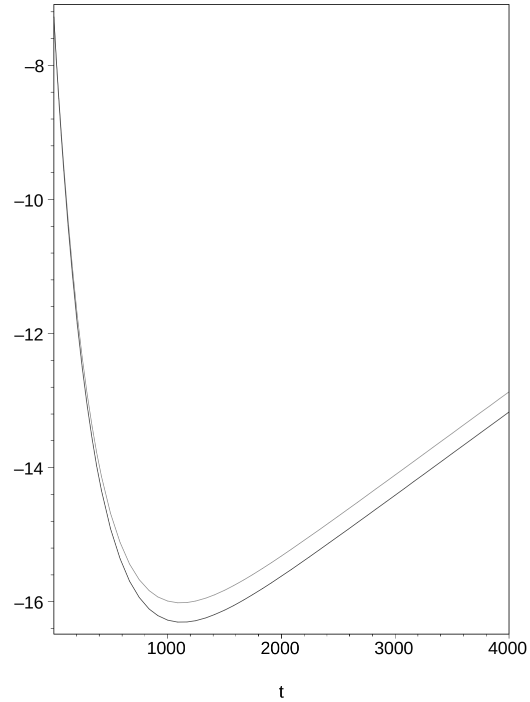


Figure 3: Dynamic behaviour of the jump height $h(t)$. Shown is $\log_{10}(h(t))$ for two different saturated levels, namely $b = 7.3 \cdot 10^{10}$ (lower curve) and $b = 3.65 \cdot 10^{10}$ (upper curve) with $a = 0.00286$.

In the limit $t \to \infty$ the curve $x_p(t)$ reaches the value $b$, which defines the tumor size at the saturated level, see Fig. 2 for two different values of $a$.

Substituting (3.20) into (3.10) and using $\beta(1) = m$, we get

$$h(t) = m e^{at} b^{-e^{-at}-1} \tag{3.21}$$

The behaviour of $h(t)$ is driven by two competing terms, namely an exponential growth with rate $a$ as well as an exponentially fast decay to $1/b$, expressed by the last term on the right hand side of (3.21). The exponential growth dominates the large time behaviour, the exponential decay describes the jump height for small times.

Fig. 3 shows the behaviour of $h(t)$ with $a = 0.00286$ and two different values for the saturated tumor size, namely $b = 7.3 \cdot 10^{10}$ and $b = 3.65 \cdot 10^{10}$, like used in [1]. Because $h(t)$ varies by several orders of magnitude along the time interval $[0, 4000]$, the quantity given in the figure is $\tilde{h}(t) = \log_{10}(h(t))$. The influence of the parameter $b$ with respect to the global behaviour of $h(t)$ is obviously quite small.

Changing the parameter $a = 0.00286$ to $a = 0.0143$ yields the result shown in Fig. 4. Again the influence of the saturated tumor size $b$ is small, but the exponential decay to a minimal value of $h(t)$ runs much more faster then in the previous case and therefore the exponential growth starts much more early. The graph of Figs. 3 and 4 looks quite similar but the length of the time interval in Fig. 4 is only one fourth of the one in Fig. 4. A comparison for the two different values of $a$ and fixed $b = 7.3 \cdot 10^{10}$ on the interval $[0, 4000]$ is given in Fig. 5.

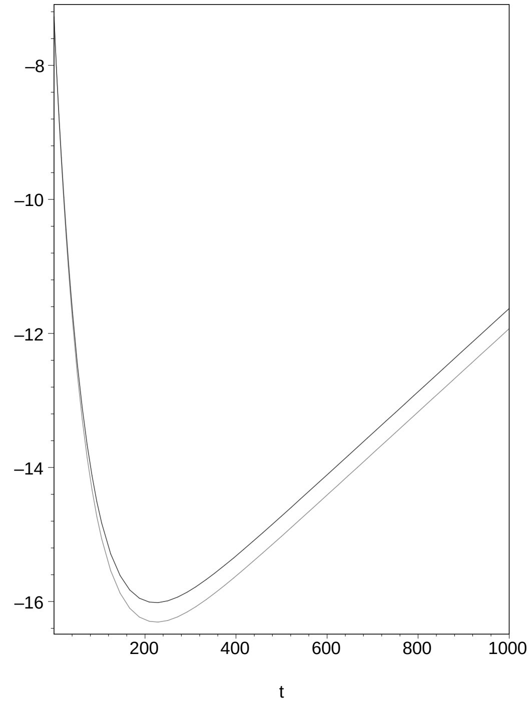


Figure 4: Dynamic behaviour of the jump height $h(t)$. Same values as in Fig. 3, but now with $a = 0.0143$ and time interval $[0, 1000]$.

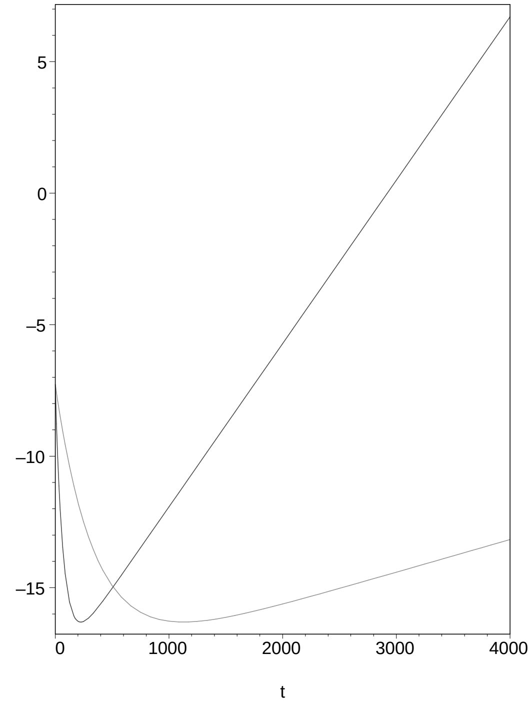


Figure 5: Dynamic behaviour of the jump height $h(t)$. Comparison between $a = 0.00286$ and $a = 0.0146$ with $b = 7.3 \cdot 10^{10}$.

The Gompertzian growth rate always attends its maximal value at $x = e^{-1}b$, independent of the parameter $a$. The particular curve $x_p(t)$ reaches this value at time $t = -\ln(\ln(b))/a$. Like can be seen in Figs. 3 and 4, this is approximately the time, when the behaviour of the jump height turns from the exponential decay to the exponential growth. This coincides with the behaviour of the right hand side of (3.3), which changes its sign exactly at $x = e^{-1}b$.

Due to the asymptotic behaviour of $h(t)$, like discussed above, one may expect that the IKS–model contains different time scales or regions, where methods from asymptotic analysis will help to obtain more treatable solution formulas, even for complicated expression of the growth and colonization rates. An asymptotic analysis should come along with a dimensionless form of the model in order to detect the characteristic scalings of the system.

### 3.3 A compatible boundary condition for the IKS–model

As formulated in Theorem 2, the solution of the IKS–model will be continuous, if $\beta(1) = 0$. Another possibility to overcome the incompatibility between (2.3) and (2.2), is to use a modified boundary condition, like, e.g.,

$$g(1)\rho(t,x) = \int_1^\infty \beta(x)\rho(t,x)\,dx + \beta(x_p(t)) - \beta(x_p(0)) \tag{3.22}$$

This condition has the same structure as (2.3), but now in the limit $t \to 0$ one has

$$g(1)\rho(0,1) = \int_1^\infty \beta(x)\rho(0,x)\,dx$$

which is satisfied by (2.2).

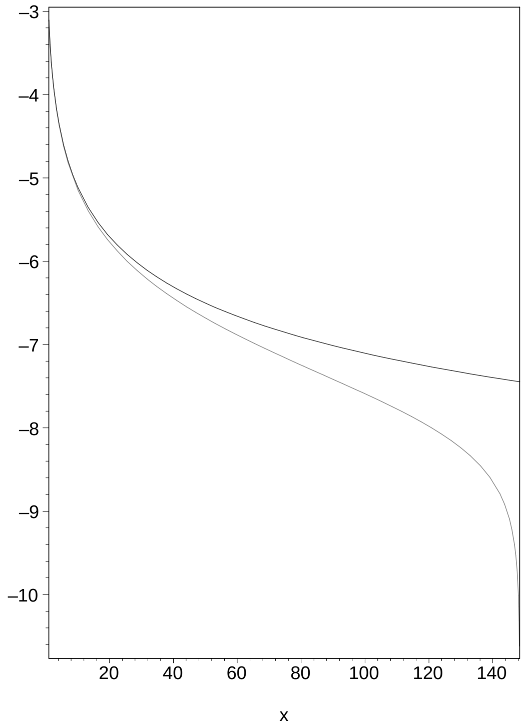


Figure 6: Profiles of the two solutions (3.19) and (3.23), respectively, at time $t = 500$. Shown is $\log_{10}(\rho(t,x)$ with $a = 0.01$ and $m = 5.3 \cdot 10^{-8}$. The continuous solution runs to zero as $x \to e^{at}$.

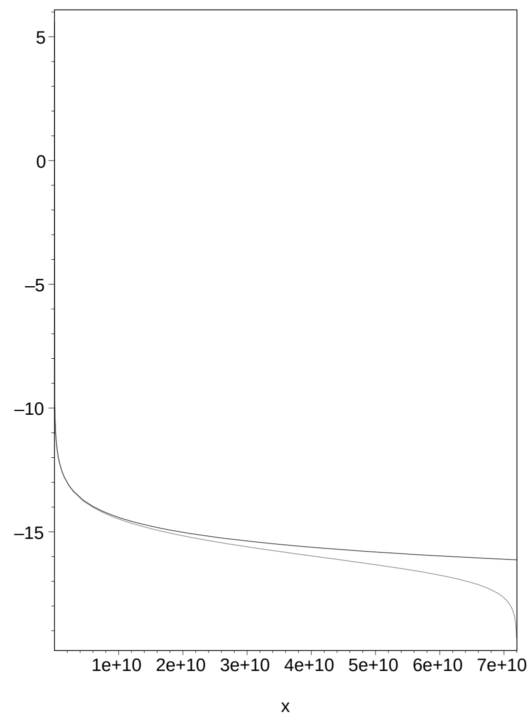


Figure 7: Profiles of the two solutions (3.19) and (3.23), respectively, at time $t = 2500$. Shown is $\log_{10}(\rho(t,x)$ with $a = 0.01$ and $m = 5.3 \cdot 10^{-8}$. The continuous solution runs to zero as $x \to e^{at}$.

Performing the same steps as above, one obtains for the solution of the Volterra integral equation the expression

$$v(t) = \frac{m}{a+m}\left(e^{(a+m)t} - 1\right)$$

and the solution of (2.1) with initial and boundary conditions (2.2) and (3.22) now reads

$$\rho(t,x) = \begin{cases} 0 & : \; t \geq 0,\, x \geq e^{at} \\ \dfrac{m}{a+m}\dfrac{1}{x}\left(x^{-1-m/a}e^{(a+m)t} - 1\right) & : \; t > 0,\, 1 < x < e^{at} \end{cases} \tag{3.23}$$

which satisfies the condition $\rho(t, x_p(t)) = 0$.

Assuming a linear growth rate $g(x) = ax$ it is trivial to obtain for the discontinuous solution given by (3.19) the asymptotic limit of $h(t)$ as $t \to \infty$,

$$h(t) = \beta(1)e^{-at},$$

i.e. the discontinuity will vanish exponentially fast with parameter $a$. On the other hand, from (3.16), we know that the function $v(t)$ grows exponentially fast in time. Hence, for large $t$ we can expect again some characteristic regions in the solution profiles of (3.19) and (3.23).

Figs. 6 and 7 show the profile of the solutions given by (3.19) and (3.23) at two different times, namely $t = 500$ and $t = 2500$. The parameter $a$ and $m$ are $a = 0.01$ and $m = 5.3 \cdot 10^{-8}$.

The continuous solution vanishes for $x \to x_p(t)$, whereas the discontinuous solution reaches the limit $h(t)$, which itself vanishes as $t \to \infty$. The scales at the vertical axis in Fig. 7 indicates that the value of $\log_1 0(\rho(2500, x))$ is about 5 for $x$ close to 1. This represents the exponential growth of $v(t)$, but the values drop down within a small boundary layer at $x = 1$. This behaviour again suggests to perform an asymptotic expansion method for a dimensionless form of the IKS–model.

# 4 Conclusion

In the present work we gave a mathematical investigation of a model to describe the growth and size distribution of multiple metastatic tumors recently proposed by Iwata, Kawasaki and Shigesada. Using the method of characteristics and an appropriate transformation of the integral boundary conditions we gave an existence result, which states that the solutions of the model in general will be discontinuous along a particular characteristic curve, which describes the number of cells in the primary tumor. This discontinuity is due to an incompatibility between the initial and boundary conditions used in the model. We proposed a modified boundary conditions which yields a continuous solution and shows a similar global behaviour like the original one.

The existence theorem relies on an appropriate transformation of the integral boundary condition using the method of characteristics, which yields a linear Volterra integral equation of second kind. This reformulation of the original boundary condition is even useful when no analytical solutions of the characteristic system or the Volterra integral equation are available, such that one should compute discrete approximations using numerical methods.

An investigation on the asymptotic behaviour of the discontinuity shows some interesting phenomena of the model, namely the existence of different time scales or regions as well as a boundary layer around $x = 1$. Hence, it seems to be worthwhile to use an asymptotic expansion technique for a dimensionless form of the model, in order to to derive more explicit representation formulas of solutions, even for more complicated expressions for the growth and colonization rates. Theses formulas might be useful when applying the model to some clinical data from individual patients. Moreover, a dimensionless form will give a better understanding on the characteristics scales of the model. Some work in this direction is currently under investigation.


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