A generalization of Gompertz law compatible with the Gyllenberg-Webb model for tumour growth.

Alberto d'Onofrio
Department of Experimental Oncology, European Institute of Oncology, Milan, Italy
Antonio Fasano[1]
Department of Mathemaitcs U. Dini, University of Florence, Florence, Italy
Bernardo Monechi
Department of Physics, University of Florence, Florence, Italy

Abstract. We present a new extension of Gompertz law for tumour growth and ant-tumour therapy. After discussing its qualitative and analytical properties, we show, in the spirit of (Kozusko and Bajzer, 2003), that, like the standard Gompertz model, it is fully compatible with the two-population model of Gyllenberg and Webb, formulated in (Gyllenberg and Webb, 1989) in order to provide a theoretical basis to Gompertz law. Comparisons with some experimental data confirm the practical applicability of the model. Numerical simulations about the method performance are presented.

1 Introduction

In 1825 B. Gompertz (Gompertz, 1825) formulated his model for the mortality rate of a population, which later became one of the most frequently used laws to describe tumour growth (it is currently applied in other contexts, both in biology and in economics).
Gompertz differential law can be written for instance in the form

$$\dot{N} = N(a - b\ln N)\,,\ a>0,\ b>0\,, \tag{1.1}$$

where $N(t)$ represents either the number of individuals in the population or any quantity associated with its size (for instance the volume). The requirement $a>b$ must be fulfilled, if it has to express growth. Clearly a has to be interpreted as proliferation rate, while b is sometimes called the growth retardation factor. Of course the physical meaning of the parameters has to be adapted to the one assumed for N.
Adopting the normalization $N(0) = 1$, the integral of (1.1) is

$$N(t) = \exp\left[\frac{a}{b}\left(1 - e^{-bt}\right)\right]\,. \tag{1.2}$$

with a typical double exponential structure. The normalized *carrying capacity* is $N_\infty = e^{a/b}$, and the coefficient b determines the rate of convergence to it.
Gompertz law belongs to the large class of *phenomenological* growth models based on the competition of two terms, one representing production and the other associated with death. The number of such models is amazingly large, including the ubiquitous *logistic law* (with N replacing

[1] **CORRESPONDING AUTHOR. Email: fasano@math.unifi.it**

ln N in (1.1)) and the *generalized logistic* (the same term being now a power of N), the *von Bertalanffy* law (von Bertalanffy, 1957) with its generalizations, etc. A survey of many classical models, supplemented with an interesting comparative analysis, is due to M. Marusic (Marušić, 1996) (see also (Marušić and S. Vuk-Povlović, 1993),(Marušić et al., 1994)). The more recent paper by one of us (d'Onofrio, 2005), on modelling tumours and immune system interaction, also describes several growth models developed in recent years. Collecting a complete list of growth models seems however to be a hopeless task. In the paper (Marušić et al., 1994) fourteen models are tested on two specific sets of experimental data. In (Mombach et al., 2002) for logistic and Gompertz laws and in (d'Onofrio, 2009) for the general family $\dot{N} = f(N)N$ it has been showed how phenomenological models may be linked to inter-cellular inhibitory interactions.
Among the models reviewed in (Marušić, 1996) one can find the so-called *hyper-Gompertz* law:

$$\dot{N} = N(a - b\ln N)^{1+p}, \tag{1.3}$$

proposed in (Turner et al., 1976) as a limit case of a general class of three-parameter power-law models, which includes also the so-called *hyper-logistic* law (just put N in place of its logarithm in (1.3)). In (Laird, 1964) and (Turner et al., 1976) readers can find many more details and references.
Another interesting extension of the Gompertz law is the so called *generalized Gompertz*:

$$\dot{N} = N^{q}(a - b\ln N), \tag{1.5}$$

Note that same name is attributed to an extension of (1.2) in which e^{-bt} is replaced by the exponential of a polynomial in t up to the 3rd degree (Amorim et al. , 1993).

An extremely important question is whether Gompertz-like or logistic-like models are preferable. Quite opposite statements can be found in the literature and both the quoted surveys (as well as (Marušić and S. Vuk-Povlović, 1993),(Marušić et al., 1994)) deal with this delicate issue. Although we will not enter deeply such a debate, we make here some observations. First, it is not surprising that models of cancer growth can be so diversified, since apparently populations of cancer cells of different types and/or in different conditions may behave very differently. Indeed any macroscopic growth law has to mirror a set of phenomena occurring at the cellular scale, like metabolic processes and inter-cellular interactions that may vary considerably from case to case, as recently stressed by (Mombach et al., 2002) and by d'Onofrio (d'Onofrio, 2009). Second, as pointed out by (Steel, 1977 ; Wheldon, 1988; d'Onofrio, 2005), all growth laws producing a relative growth rate $\dot{N}/N$ tending to infinite as N (as volume or density) tends to zero (as for instance (1.1), (1.3), (1.5) for $\alpha<1$) are not adequate to describe the growth of small aggregate of tumours, since the doubling time is a quantity related to a complex set of biological processes such as cell division cycle and apoptosis and it cannot be arbitrarily small. Moreover, these laws are in contradiction with the possibility of immune surveillance (d'Onofrio, 2005).

The above observations on the doubling time led T.E. Wheldon (Wheldon, 1988) to propose an important modification of (1.1) the so called *Gomp-ex* law:

$$\dot{N} = \begin{cases} (a - b\ln(C))N & if \quad 0 < N < C \\ N(a - b\ln N) & if \quad N > C \end{cases} \tag{1.6}$$

In this way Gompertz law (1.1) comes into play only for sufficiently large populations, but below some critical size one just has a simple exponential growth. Even if we identify N with the number of cells, the switch to (1.6) is motivated by the requirement of stabilizing the ratio $\dot{N}/N$ for small populations.
Finally, the parallel history between Gompertz and logistic models has produced also the *Generalized-ex* model (Mombach et al. , 2002) which borrows from the *Gomp-ex* system the initial exponential growth, followed by generalized logistic.

The aim of the present paper is twofold.
First we discuss a generalization of Gompertz law different from the ones reviewed in (Laird, 1964) and (Marušić et al., 1994), namely

$$\dot{N} = N\left(a - b\left(\ln\left(\frac{N}{d} \right) \right)^{1/m} \right), \tag{1.7}$$

where d, m are positive numbers (clearly the choice d=1 m=1 reproduce (1.1)). The role of the parameter d is to discriminate populations which are large enough to be governed by (1.7), in the sense that we consider (1.7) to be valid when N exceeds some critical value $C >= d$. If instead $0<N<C$, (1.7) should be replaced by

$$\dot{N} = A(N)N , \tag{1.8}$$

where $A(N)$ is a bounded continuous function defined in $[0,C]$ and of course such that

$$A(C) = a - b\left(\ln\left(\frac{C}{d} \right) \right)^{1/m} .$$

Remark 1.1. The switch from (1.7) to (1.8) is in the spirit of the *Gomp-ex* model and has the aim of stabilizing the ratio N'/N for small populations. However, we must say that the choice of both C and d is not so critical, just meaning that (1.7) is to be used only for sufficiently large populations. Moreover, it should be emphasized that it is not quite appropriate to describe the behaviour of too small populations by means of differential laws, because in that case the discrete nature of the system prevails and the continuum approach may become defective. Thus the extension of the model to really small populations should in any case be taken with some reservation.

Equation (1.7) seems to provide a new generalization (at least within the literature consulted by the authors), somehow completing the already rich scenario of the Gompertz models, and it has some interesting features that will be illustrated in Sect.2. An appropriate name for it could be *log-power-Gompertz*, but in the sequel it will be referred to just as (1.7). Its interest is not just limited to filling a hole in the collection of Gompertz-like models, since it can be at least as useful as the other generalizations of (1.1), if not better.

Of course one could combine some of the extensions above in various ways, but the price to pay is the increase of the number of parameters. For example, it would be possible to replace the factor N in (1.7) by some power N^{α}. We will not deal with such multi-parameter laws, though they may have some theoretical interest.

The second objective we want to pursue is to show that the two-population model by Gillenberg-Webb (Gyllenberg and Webb, 1989) (in the sequel referred to as G-W model) is always fully

compatible with (1.7). In doing so we shall extend the analysis of Kozusko and Bajzer (Kozusko and Bajzer, 2003) who addressed this same issue with reference to the standard law (1.1), completing the former study of (Gyllenberg and Webb, 1989) in this direction, whose aim was actually to provide a theoretical support to Gompertz law. Under this respect too (1.7) proves to be different e.g. from hyper-Gompertz (1.3). Indeed, while the procedure of (Kozusko and Bajzer, 2003) applies to (1.3) in a straightforward way, a different technique is generally required for (1.7). It is interesting to note that in the paper (Kozusko and Bajzer, 2003) the way of deriving the parameter *b* in (1.1) is based on a slightly incorrect argument, although the result is certainly correct. Therefore it will be appropriate to reconsider the whole question of the compatibility of the two models. In Section 3. we will discuss the question of the compatibility of the G-W model with a general kinetic law of the form $\dot{N} = f(N)N$. Then in Sect. 4 we analyze more specifically the relationship between G-W and (1.7) In order to check the practical applicability of (1.7) we have carried out the fitting of some set of experimental data (Sect. 6), showing that the method performs better than the standard model (1.1).

Though we will not work out the whole analysis, we remark (Sect. 5) that the theory exposed by Kozusko and Bourdeau in (Kozusko and Bourdeau, 2007) concerning the compatibility with von Bertalanffy and Gompertz model of a two-population model (proliferating and quiescent cells) with an exchange rate between compartments depending only on the proliferating/total fraction, can agree with (1.7) too.

Finally, we shall easily show that model (1.7) can be compatible with a constraint proposed in (d'Onofrio, 2009) for the compatibility between macroscopic phenomenological laws of cellular growth and microscopic laws of interaction between cells.

2 Qualitative and quantitative properties of the solutions of (1.4).

2.1 Some basic qualitative properties of the solutions

The asymptotic value of the population is easily deduced from (1.7):

$$(2.1)\quad \lim_{t\to+\infty} N(t) = N_\infty = d\exp\left(\left(\frac{a}{b}\right)^m\right).$$

Note that in a unperturbed in vivo and in vitro tumour the asymptotic size N_∞ is of course very large so that $N_\infty > N(0)$ and is in the range of applicability of (1.7). According to the role assigned to the coefficient *d*, we expect that the exponential factor in (2.1) is large. Therefore a minimal requirement on the parameters is

$$a>b,$$

which will be tacitly assumed in the sequel, unless when dealing with tumours under continuous infusion therapy. In the latter case we may have $N_\infty < N(0)$. Our model can be easily adapted to describe a constant continuous infusion therapy with *log*-kill rate θ :

$$(2.2)\qquad \dot{N} = N\left(a_0 - \theta - b\left(\ln\left(\frac{N}{d}\right)\right)^{1/m}\right),$$

where a_0 refers to the unperturbed case. Let us define $a = a_0 - \theta$. If $a>0$, i.e. if the level of therapy is low or moderate, the behaviour is the same as the unperturbed case, provided the ratio a/b is large enough to keep the solution in the Gompertz regime. If $a<0$ it follows that:

$$\dot{N} = N\left(a_0 - \theta - b\left(\ln\left(\frac{N}{d} \right) \right)^{1/m} \right) < 0,$$

and in a finite time $N(t)$ would drop below the applicability range of (2.2).

Finally, in (d'Onofrio, 2009) it has been shown that a general law of growth $\dot{N} = f(N)N$ is compatible with the hypothesis of inter-cellular inhibitory interactions if and only if $f''(N)>0$, a constraint that, for example, is fulfilled by Gompertz, von Bertanlaffy and also by generalized logistic law $f(N) = N(1 - cN^{\alpha})$, provided that $\alpha<1$. The same constraint in model (1.7) reads:

$$f''(N) = \frac{b\left(\ln(\frac{N}{d}) \right)^{-2+1/m} \left(-1 + m + m\ln(\frac{N}{d}) \right)}{mN^2} > 0\,,$$

As a consequence, the growth of a tumour having initial size $N(0)$ and following our model is compatible with the hypothesis of inter-cellular inhibitory interactions (d'Onofrio, 2009) if

$$m > \frac{1}{1 + \ln\left(\frac{N(0)}{d} \right)}. \tag{2.3}$$

More in general, since $N>C$, if we choose

$$m > \frac{1}{1 + \ln\left(\frac{C}{d} \right)},$$

which is a mild restriction in case $C>>d$. E.g. if $C = 10\,d$ the above constraint reads $m > 0.302$.

1.1 *Analytical properties of the solutions*

We start supposing that we are dealing with an unperturbed tumour or with a tumour to which a moderate therapy is delivered (modelled by (2.2)), so that $a>0$. In this case, by means of the transformations

$$u = \frac{b^m}{a^m} \ln\left(\frac{N}{d} \right), \quad \tau = \frac{b^m}{a^{m-1}} t \tag{2.4}$$

we may rewrite equation (1.7) as follows:

$$\frac{du}{d\tau} = 1 - u^{\frac{1}{m}}(\tau), \quad u(0) = \frac{b^m}{a^m} \ln\left(\frac{N(0)}{d} \right) \tag{2.5}$$

Remark 2.1. Note that $u(\tau) < 1$ for untreated tumours. If $u(0)>1$, as it may happen in presence of moderate therapy ($a>0$), the solution will be decreasing.

Equation (2.5) has the following implicit solution:

$$u(\tau) \cdot G\left(u(\tau)^{1/m}; m\right) = u(0) \cdot G\left(u(0)^{1/m}; m\right) + \tau \ , \tag{2.6}$$

where *G(z,m)* is the Gauss hypergeometric function ${}_2F_1(p_1, p_2, p_3, z)$ (Abramowitz and Stegun, 1972) evaluated at (1, *m*, *m*+1, *z)*, and is the sum of the series

$$G(z;m) = \sum_{k=0}^{+\infty} \frac{m}{k+m} z^k \ .$$

Thus:

$$u(\tau) = Q\left(u(0) \cdot G\left(u(0)^{1/m}; m\right) + \tau ; m\right), \tag{2.7}$$

where *Q(u; m)* is the inverse of the function $H(u;m) := uG\left(u^{1/m}; m\right)$.
Finally, coming back to the original variables *N*, *t*, we find

$$N(t) = d \exp\left(\frac{a^m}{b^m} Q\left(\frac{b^m}{a^m} \ln\left(\frac{N(0)}{d} \right) G\left(\left(\frac{b^m}{a^m} \ln\left(\frac{N(0)}{d} \right) \right)^{1/m}; m \right) + \frac{b^m}{a^{m-1}} t; m \right) \right) \tag{2.8}$$

Note that the above results suggest that the parameter *b* enters the solution just through the ratio *a/b*. More precisely it will be convenient to use the triple

$$\rho = \left(\frac{a}{b} \right)^m = \ln\left(\frac{N_\infty}{d} \right) > 1, \ a, \ m \ , \tag{2.9}$$

so that (2.8) reads:

$$N(t) = d \exp\left(\rho \ * Q\left(\rho \ \ln\left(\frac{N(0)}{d} \right) G\left(\left(\rho \ \ln\left(\frac{N(0)}{d} \right) \right)^{1/m}; m \right) + \frac{t}{a\rho}; m \right) \right) \ . \tag{2.10}$$

Now, let us suppose that the tumour is undergoing a continuous infusion therapy with θ sufficiently large to have $a<0$. We may still adopt a similar procedure, but the transformation replacing (2.5) is now

$$v = \frac{b^m}{|a|^m} \ln\left(\frac{N}{d} \right) \ , \quad \tau = \frac{b^m}{|a|^{m-1}} t \tag{2.11}$$

bringing (1.7) to the form

(2.12) $$\frac{dv}{d\tau} = -\left(1 + v^{\frac{1}{m}}(\tau)\right), \quad v(0) = \frac{b^m}{|a|^m}\ln\left(\frac{N(0)}{d}\right).$$

Thus $\frac{dv}{d\tau} < 0$ and in a finite time τ_C the solution takes the value $v(\tau_C) = \frac{b^m}{|a|^m}\ln\left(\frac{C}{d}\right)$ leaving the applicability range of (1.7). However, for $0 < t \le \tau_C$, we may still express the solution implicitly by means of the Gauss hypergeometric function:

(2.13) $$v(\tau)\cdot G\left(-v(\tau)^{1/m}; m\right) = v(0)\cdot G\left(-u(0)^{1/m}; m\right) - \tau .$$

2.3 *Assessing the influence of the three parameters on the solutions*

In this section we shall shortly assess, both analytically and graphically, the influence of the various parameters. We shall show that our mathematical model correctly describes the biology of the growth phenomena. Indeed, from a biological point of view the parameter *a* is the net rate of growth in absence of inter-cellular competition, thus the solutions of (1.7) have to be increasing with *a*. The parameter *b* is somehow related with self-competition within the population. The increased apoptotic rate due to that competition is

$$\varphi(N) = b\left(\ln\left(\frac{N}{d}\right)\right)^{\frac{1}{m}}.$$

Thus, remembering that the Gompertz-like law (1.7) is valid for $N >> \delta$, an increase of *b* makes the apoptosis rate increase, that, while an increase of *m* implies a lower apoptosis rate. Hence we expect solutions to be decreasing in *b* and increasing both with respect to *a* and to *m*. Let us prove it.

Proposition 2.1. The solutions of (2.5) are increasing in *a*, *m* and ρ (whereas they are decreasing in *b*). The same is true for the solutions of the model with continuous infusion therapy (with *a* now including the term $-\theta$).

Proof. Let us consider a tumour with free rate *a* and another population with $a_1 > a$. Then

$$\dot{N} = N\left(a - \theta - b\left(\ln\left(\frac{N}{d}\right)\right)^{1/m}\right) < N\left(a_1 - \theta - b\left(\ln\left(\frac{N}{d}\right)\right)^{1/m}\right)$$

which, applying the elementary properties of differential inequalities, implies that:

$$N(t, N(0), a, b, m, \theta) < N(t, N(0), a_1, b, m, \theta)$$

Similarly one can proof the same kind of monotone dependence with respect to *m*. On the contrary, considering the parameter *b*:

$$\dot{N} = N\left(a - \theta - b\left(\ln\left(\frac{N}{d}\right)\right)^{1/m}\right) < N\left(a - \theta - b_1\left(\ln\left(\frac{N}{d}\right)\right)^{1/m}\right)$$

$$\Rightarrow$$

$$N(t, N(0), a, b, m, \theta) > N(t, N(0), a, b_1, m, \theta)$$

and similarly for the parameter θ.

Finally, concerning ρ, which is defined in absence of therapy via $a = b\rho^{\frac{1}{m}}$, and also for moderate therapies replacing a by $a-\theta$, rewriting (1.7) as follows:

(2.14) $$\dot{N} = Nb\left(\rho^{\frac{1}{m}} - \left(\ln\left(\frac{N}{d}\right)\right)^{1/m}\right)$$

and again applying differential inequalities, our claim easily follows.

The next proposition points out the role of the parameter m, which is characteristic of model (1.7).

Proposition 2.2. Let us confine with the case $a>0$. The parameter m can be selected so to obtain a prescribed exponential convergence of N to its asymptotic limit N_∞.

Proof.

Given $a>0$ and the carrying capacity N_∞, let us impose that for large t

$$N(t) = N_\infty(1 - \varepsilon(t)),$$

with $\varepsilon(t) \approx e^{-\lambda t}$, $\lambda>0$. It is easily seen that, in combination of (1.7), the latter condition implies

$$\dot{\varepsilon} \approx -\frac{a}{m}\left(\frac{b}{a}\right)^m \varepsilon,$$

to the first order in ε. Therefore we obtain the desired value of m

$$m = \frac{a}{\lambda \ln N_\infty},$$

and of course b has to be chosen accordingly:

$$b = a(\ln N_\infty)^{-(\lambda \ln N_\infty)/a}.$$

Conversely, λ can be deduced from m.

A classical analysis of the solutions of Gompertz-like models is concerned with the inflection points. Let us look for the inflection points of the solutions of (1.7). We confine to the case $a>0$ and $N>C$ (Gompertz regime).

Proposition 2.2. As long as they stay in the Gompertz-like regime, the solutions of (1.7) may have at most one inflection point.

Proof.

In (2.14) set

$$M = N/d, \quad y = \ln M, \quad Y = y^{\frac{1}{m}}.$$

The asymptotic value of Y is a/b.
Then it easy to see that

(2.15) $$\ddot{M} = \dot{M}aF(Y) \text{ , with } F(Y) = 1 - \frac{1}{c}Y - \frac{1}{mc}Y^{1-m},$$

where $c = \frac{a}{b} = \rho^{\frac{1}{m}}$.

For m=1 the only zero of F is Y=c–1, meaning $N = \frac{d}{e}N_\infty$.

For m<1 the function F is decreasing from $F(0)$=1 to $F(c)$=$-(mc^m)^{-1}$. Therefore it vanishes only once for some Y=Y*. If we conjecture that we may write Y^*=$c(1-\eta)$, with η<<1 and we use in (2.15) the first order approximation in η, then we find $\eta = \left(1 - m + mc^m\right)^{-1}$. This expression is consistent with η<<1, provided m is not too small. Indeed, its analysis reveals that the condition for η to be small is that $m^2 \ln c >> 1$ (remember that c is large).
For m>1 the function F tends to –∞ at the origin, keeping the same value as above for Y=c.
We compute

$$F'(Y) = \frac{m-1}{mc}Y^{-m} - \frac{1}{c}, \qquad F''(Y) = -\frac{m-1}{c}Y^{-m-1}.$$

The first derivative vanishes for Y=$Y_m = \left(1 - \frac{1}{m}\right)^{\frac{1}{m}}$. Therefore F takes its maximum there. If the maximum is positive there will be two inflection points, which become coincident when the maximum is zero. However, we remark that Y_m takes values between 0 (m↓1) and 1 (m→∞). This corresponds to values of N/d between 1 and e. Thus the smaller inflection point is certainly outside the Gompertz range. In order to check whether the other inflection point Y* may or may not be observable we may argue as follows. First compute the maximum of F, namely $F(Y_m) = 1 - \frac{1}{c}\left(\frac{m}{m-1}\right)^{\frac{m-1}{m}}$, which in our conditions is positive, since the factor multiplying $\frac{1}{c}$ is at most $e^{\frac{1}{e}}$, and c is supposed to be large. Next observe that for Y> Y_m we have $0 < F''(Y) < F''(Y_m)$, so that a lower estimate of Y* is obtained by taking the largest zero of the function $F(Y_m) + \frac{1}{2}F''(Y_m)(Y - Y_m)^2$. After some algebra we deduce that $(Y^* - Y_m)^2 > \frac{2(c-1)}{m}\left(\frac{m-1}{m}\right)^{\frac{1}{m}}$.
Remembering that c>>1, we see that the inflection point is observable unless m is very close to 1. The latter restriction can be removed using exactly the same argument as for the case m<1, i.e. looking for Y*=$c(1-\eta)$, with η<<1.

3 On the compatibility of a general law $\dot{N} = f(N)N$ with the Gillenberg-Webb model.

In (Gyllenberg and Webb, 1989) the following two-population model has been proposed for the evolution of a tumour

$$\dot{P} = [\beta - \mu_P - r_o(N)]P + r_i(N)Q \tag{3.1}$$

$$\dot{Q} = r_o(N)P - [r_i(N) + \mu_Q]Q \tag{3.2}$$

$$N = P + Q \tag{3.3}$$

where P and Q denote the number of proliferating and of quiescent cells, respectively. The initial conditions are such that $P_0 + Q_0 = 1$.

In (3.1) β is the proliferation rate, μ_P, μ_Q are death rates, and the functions $r_o(N), r_i(N)$ express the rates of the respective transitions $P \to Q$, $Q \to P$.

The aim of this section is to show that model (1.7) is compatible with the Gyllenberg-Webb model, meaning that it is possible to find two meaningful function $r_o(N)$ and $r_i(N)$ such that the evolution of the total population $N(t)$ is ruled by our model.

Before proceeding, we will illustrate some interesting results related to the compatibility with the G-W model of a general tumour growth law $\dot{N} = f(N)N$, where f is a continuous function for $N>0$ and such that the product $f \cdot N$ tends to zero as N tends to zero. The null point ($P=0, Q=0$) is in all cases an equilibrium for the system (3.1)-(3.3). Moreover, note that adding (3.1) to (3.2) one obtains:

$$\dot{N} = (\beta - \mu_P)P - \mu_Q Q . \tag{3.4}$$

As a consequence, by applying the LaSalle's invariance principle it holds that:

Lemma 3. 1. If $\beta \le \mu_P$ then the cellular population is decreasing and will tend to zero and as a consequence (P,Q) will tend to $(0,0)$, i.e. the null equilibrium is globally asymptotically stable.

Moreover, it is immediate to prove:

Lemma 3.2. If $\beta > \mu_P$ then it exists a non trivial equilibrium (P_∞, Q_∞) such that:

$$P_\infty = \frac{r_i(N_\infty) + \mu_Q}{r_i(N_\infty) + \mu_Q + r_0(N_\infty)} N_\infty \tag{3.5}$$

where the rates $r_o(N), r_i(N)$ have to satisfy

$$\mu_Q r_o(N_\infty) = (\beta - \mu_P)(\mu_Q + r_i(N_\infty)) \tag{3.6}$$

Before starting our compatibility analysis, it is convenient to eliminate the Q variable, so we shall study the system:

$$\dot{P} = [\beta - \mu_P - r_o(N) - r_i(N)]P + r_i(N)N \tag{3.7}$$

$$\dot{N} = (\beta - \mu_P + \mu_Q)P - \mu_Q N . \tag{3.8}$$

We begin with the following generic properties that have to hold for the general model $\dot{N} = f(N)N$ to make it compatible with (3.7), (3.8).

Lemma 3.3 If $\beta > \mu_P$ then in order that system (3.7), (3.8) may be compatible with a generic model of he form $\dot{N} = f(N)N$, it is necessary that

(3.9) $$f(N) < (\beta - \mu_P).$$

Proof. By inserting the relationship $\dot{N} = f(N)N$ in (3.8) it yields that:

(3.10) $$\frac{P}{N} = \frac{\mu_Q + f(N)}{\beta - \mu_P + \mu_Q},$$

and since for all N it must be $P/N<1$ our claim follows easily.

Evaluating (3.8) at time $t=0$ we find

(3.11) $$N'(0) = (\beta - \mu_P)P_0 - \mu_Q Q_0 = \gamma P_0 - \mu_Q N(0),$$

with $\gamma = \beta - \mu_P + \mu_Q$, it follows that:

Lemma 3.4. If the initial data are such that

(3.12) $$\frac{\mu_Q N(0)}{\gamma} < P_0 \le N(0)$$

then the tumour grows asymptotically to equilibrium.

Remark 3.1. The obvious biological interpretation of Lemma 3.2 is that we must start with enough proliferating cells to allow a growth regime to set in.

To finish this preliminary part, simple computations yield that:

Lemma 3.5 The condition (in addition to (3.9)) for a general growth law $\dot{N} = f(N)N$ to be compatible with the G-W model is that the functions $r_o(N), r_i(N)$ satisfy

(3.13) $$r_i(N)[\beta - \mu_P - f(N)] - r_o(N)[\mu_Q + f(N)] = [\mu_Q + f(N)][f(N) - \beta + \mu_P] + Nf'(N)f(N).$$

Note that (3.13) reduces to (3.6) when $f=0$, i.e. $N=N_\infty$.

Now, let us go back to model (1.7). In the standard Gompertz case ($m=1$, $d=1$) the functions $r_o(N), r_i(N)$ can be just supposed to be continuous for $1 \le N \le N_\infty$, but when we address the issue of compatibility with (1.7) we are forced to consider a larger class. Indeed for (1.7) we have

(3.14) $$f(N) = a - b\left(\ln\frac{N}{d}\right)^{\frac{1}{m}}, \quad f'(N)N = -\frac{b}{m}\left(\ln\frac{N}{d}\right)^{\frac{1}{m}-1}$$

and for $m>1$ the last term in (3.13) becomes singular if N is allowed to approach d.

Remark 3.2. Even though in principle we have excluded that N can approach d, we remark two things: (i) from the modelling point of view there is a large flexibility in the way of performing the transition from (1.7) to (1.8), which amounts to the choice of d and C: one possibility would be to just identify the two constants (in the sense that d is increased to C) and this would bring the above singularity in the admissible range; (ii) the G-W model does not include any critical size of the population, so one could look for a global identification extrapolating the Gompertz regime to small populations. In the spirit of (i) we can just consider the equation for the rescaled quantity N/d, which amounts to setting d=1 in (1.7). If we want to follow the strategy (ii) we may look at N as the number of cells and let it take values including N=1. Once more this is achieved by setting d=1 in (1.7). *For this reason in the next section we shall use the simplified version of (1.7) with d*=1.

4 Making model (1.7) compatible with the Gyllenberg-Webb model.

According to the last remark, in this section we use (1.7) in the form

(4.1) $$\dot{N} = N\left(a - b(\ln N)^{\frac{1}{m}}\right)$$

where N is meant as a rescaled quantity.
In (Kozusko and Bajzer, 2003) conditions are found to make the G-W model compatible with the standard Gompertz law, a question already considered in (Gyllenberg and Webb, 1989), but only for the case $r_o(N) = 1 + \ln N$. As we said, the same procedure applies with minor modification to the hyper-Gompertz but it does not in general for (1.7). Moreover, in (Kozusko and Bajzer, 2003) the equation proposed for calculating b is presented as a new piece of information but indeed it duplicates another equation previously derived. Therefore the whole matter is a bit confused and we prefer to fully reconsider the question of compatibility of (1.7) with the Gillenberg-Webb system (3.7), (3.8), so to clarify even these details. Of course our analysis will include the standard Gompertz law as a particular case.
In the previous section we have seen that we must require conditions (3.9), (3.13) where we now put $f = a - b(\ln N)^{\frac{1}{m}}$.

Let us look for more conditions with the aim of identifying the coefficients a, b.

Proposition 4.1. The coefficients a, b in (4.1) can always be identified in terms of the data of the G-W model.
Proof.
One very simple relationship is

(4.2) $$f(N_0) = a - b(Ln(N_0))^{1/m} = \gamma\frac{P_0}{N_0} - \mu_Q, \text{ with } \gamma = \beta - \mu_P + \mu_Q,$$

deducible from $\dot{N}(0) = N_0 f(N_0)$ and from (3.11). Thus the first relationship between *a* and *b is expressed in terms of the initial data of the G-W model*. Note that P_0 is subjected to condition (3.12).

Concerning the parameter *b*, in (Kozusko and Bajzer, 2003) the authors deduce it for the standard case m=1 from the computation of $\ddot{N}(0)$, but their procedure has a defect that we are going to illustrate.
Proceeding as in (Kozusko and Bajzer, 2003), we compute $\ddot{N}(t)$ from (3.7), (3.8), (3.10), and $\dot{N}/N = f(N)$ obtaining

$$\ddot{N}/N = (\beta - \mu_P - r_o - r_i)(\mu_Q + f) + \gamma r_i - \mu_Q f, \tag{4.4}$$

At the same time, from (4.1) we have

$$\ddot{N}/N = f(f + Nf'). \tag{4.5}$$

In (Kozusko and Bajzer, 2003) the authors observe that (4.5), with t=0, can be used to get the coefficient *b* (since in the standard case $Nf' = -b$), and therefore *b* is obtained by equating the right hand sides of (4.5) and of (4.4). However the equation coming out from this procedure is not a new piece of information. Indeed it can be checked that the equality

$$(\beta - \mu_P - r_o - r_i)(\mu_Q + f(N)) + (\beta - \mu_P - \mu_Q) r_i - \mu_Q f(N) = f(N)(f(N) + Nf'(N)) \tag{4.6}$$

(written for any *t*) is nothing but the compatibility condition (3.13). We conclude that using (4.6) for t=0 is the same as using (3.13). It means that all information we may get on *b* is already contained in (3.13), namely

$$-\left(\gamma \frac{P_0}{N_0} - \mu_Q\right) \frac{(Ln(N_0))^{(-1+1/m)}}{m} b = \gamma \left(1 - \frac{P_0}{N_0}\right)\left(r_i(N_0) + \gamma \frac{P_0}{N_0}\right) - \gamma \frac{P_0}{N_0} r_o(N_0) \tag{4.7}$$

In the standard case the left hand side is simply *ab* and of course the result of (Kozusko and Bajzer, 2003) is eventually correct.

4.1 The case N(0)=1

It is worthwhile to note that if *N(0)=1* (i.e. in term of dimensional variables if the initial tumor burden is equal to *d*) for the model (4.1) then the l.h.s. of (4.7) vanishes when m<1, while for m>1 it is not defined since f' is singular for $N \to 1$. Thus, in this interesting case, the procedure fails for $m \neq 1$. Nevertheless, we can still take advantage of (4.6), i.e. (3.13), to retrieve some information on *b*. For instance, suppose that $\frac{1}{m} = n > 1$ is an integer. If we differentiate (3.14) with respect to *N* and taking in account *N(0)=1* we get

$$-Nff'' = 3ff' + Nf'^2 + (r_o' + r_i')(\mu_Q + f) - (\beta - \mu_P - \mu_Q - r_o - r_i) f' - \gamma r_i' \tag{4.8}$$

Therefore, if n=2 the left hand side evaluated for N=1 is $2ab$ and, since $f(1) = a, f'(1) = 0$, we get

(4.9) $$2ab = (r_o'(1) + r_i'(1))(\mu_Q + a) - \gamma r_i'(1)$$

If $n>2$, we differentiate until we can isolate the term $-Nff^{(n)}$, whose limit as $N\to 1$ is $n!ab$, so that once more we can solve for b. Of course we are now supposing that $r_o(N), r_i(N)$ are n times continuously differentiable for $1 \le N \le N_\infty$.
The situation is very different when $n<1$, because at least one of the transition functions $r_o(N), r_i(N)$ has to be singular, according to (4.6), which we recall to be the same as (3.13). Thus we write

(4.10) $$r_j(N) = \rho_j(N) + \chi_j(N)(\ln N)^{n-1}, \qquad j=o,i$$

where the ρ_j and the χ_j's are continuous and bounded functions. In the limit $N\to 1$ we obtain from (4.6)

(4.11) $$nab = (\chi_o(1) + \chi_i(1))(\mu_Q + a) - \gamma\chi_i(1),$$

thus determining b.
This same result shows how to complete our analysis by examining the case $n>1$ *not integer*. For instance if n is between 1 and 2 we may go back to (4.8), where f'' is singular like $(\ln N)^{n-2}$, and we realize that we have to attribute the same singularity to the first derivatives of the transition functions $r_o(N), r_i(N)$. In general we must differentiate (4.6) $[n]$ times ($[n]$ is the largest integer less than n) and let the $[n]$-th derivatives of $r_o(N), r_i(N)$ possess the singularity $(\ln N)^{n-[n]-1}$. In this way we can always identify b, just by matching the singular terms in (4.6).

4.2 Behaviour of the population P and Q

We may add some considerations concerning the behaviour of the populations P, Q for a model compatible with (4.1). It suffices to deal with P.

Proposition 4.2. The function P(t) may be strictly increasing or have a maximum when m<1. For m>1 it may be strictly decreasing or have one minimum and one maximum before tending to its asymptotic limit.
Proof. The asymptotic limit of P is easily deduced from (3.10):

(4.12) $$P_\infty = \frac{\mu_Q}{\gamma} e^{c^m}.$$

Again from (3.10) we calculate the time derivative

(4.13) $$\gamma\dot{P} = Nf(N)\left(\mu_Q + f(N) + Nf'(N)\right)$$

Proceeding as in the proof of Proposition 2.2, we set $y^{\frac{1}{m}} = Y \in [0,c]$, thus writing the expression in brackets in the form

(4.14) $$G(Y) = \mu_Q + a - bY - \frac{b}{m}Y^{1-m}$$

For $m<1$ this function decreases from $\mu_Q + a$ to

$$\boldsymbol{Z}=\mu_Q - \frac{b}{m}c^{1-m}.$$

Hence P has exactly one maximum when $Z<0$, otherwise it is always increasing.
When $m>1$, G tends to $-\infty$ as $Y\to 0$ and $G(c)=Z$. Moreover

$$G' = -b + b\frac{m-1}{m}Y^{-m}$$

vanishes at $Y = \left(1 - \frac{1}{m}\right)^{\frac{1}{m}}$, i. e. the quantity Y_m already introduced in the proof of Proposition 2.2, and $G'' < 0$. Thus we may distinguish the following cases:

(a) $Z \geq 0 \Rightarrow$ P has exactly one maximum occurring before Y_m

(b) $Z < 0$ and $G(Y_m) \leq 0 \Rightarrow$ P is monotone decreasing

(c) $Z < 0$ and $G(Y_m) > 0 \Rightarrow$ P has a minimum and a maximum occurring before and after Y_m, respectively.

5 The Kozusko-Bourdeau model

In this short section, we briefly deal with the relationship of (4.1) with the two population model considered by Kozusko and Bourdeau in (Kozusko and Bourdeau, 2007). In the latter the proliferating and the quiescent cells evolve according to the system

(5.1) $$\dot{P} = (\beta - \mu_P)P - N\Psi\left(\frac{P}{N}\right),$$

(5.2) $$\dot{Q} = N\Psi\left(\frac{P}{N}\right) - \mu_Q Q.$$

The initial conditions are still $P_0 + Q_0 = 1$. The authors investigate the compatibility of the above model with standard Gompertz and with von Bertanlaffy models.
Let us show how (5.1), (5.2) relates with any model of the form $\dot{N} = f(N)N$.

Proposition 4.3. When *f(N)* is a continuously differentiable invertible function it is always possible to express the transition rate function Ψ in model (4.15), (4.16) in terms of the inverse function of *f*.
Proof. It is convenient to introduce $\rho = P/N$, whose asymptotic limit in our notations is $\rho_\infty = \mu_Q/\gamma$
Note that (5.1) implicitly introduces the constraint $\Psi(\rho_\infty) = \rho_\infty(\beta - \mu_P)$. From (Kozusko and Bourdeau, 2007) we recall that as a consequence of the equations above the total population evolves according to

(5.3) $$\frac{\dot{N}}{N} = \gamma(\rho - \rho_\infty).$$

By comparison with $\dot{N} = f(N)N$ we deduce that

(5.4) $$f(N) = \gamma(\rho - \rho_\infty).$$

Hence, with the assumption $f'(N) \neq 0$ we may define the inverse function $N = G(\rho)$ and differentiating w.r.t. ρ we obtain

(5.5) $$f'(N) = \frac{\gamma}{G'(\rho)},$$

from which we deduce that

(5.6) $$Nf'(N) = \gamma\left(\frac{d}{d\rho}\ln G(\rho)\right)^{-1}$$

Differentiating (5.4) w.r.t. t and using (5.3), (5.6) we get

(5.7) $$\dot{\rho} = \gamma(\rho - \rho_\infty)\left(\frac{d}{d\rho}\ln G(\rho)\right)^{-1}.$$

On the other hand (5.1), (5.2) imply

(5.8) $$\dot{\rho} = (\beta - \mu_P)\rho - \Psi(\rho) - \gamma\rho(\rho - \rho_\infty)$$

and by comparison we deduce the desired link between the transition rate function Ψ in the model (5.1), (5.2) and the function G:

(5.9) $$\Psi(\rho) = (\beta - \mu_P)\rho\gamma(\rho - \rho_\infty)\left\{1 + \left(\frac{d}{d\rho}\ln G(\rho)\right)^{-1}\right\}.$$

In the specific case of (4.1), from (5.4) we get immediately

(5.10) $$G(\rho) = \exp\left[\frac{a - \gamma(\rho - \rho_\infty)}{b}\right]^m.$$

6 Data Fitting

An essential feature of a mathematical model is its ability of reproducing not only qualitatively but also quantitatively the dynamics of the phenomenon that is described by it. This is particularly relevant in applications of mathematics to biology. Thus, in order to assess the performance of our

model in replicating the growth of tumours, we present in this section the result of fitting the parameters of (1.7) to some data on the growth of the experimental, although *in vivo*, murine mammary carcinoma EMT6/R0 of athymic mice. These data regards the volume of the tumours, thus here N deniotes the volume. The measure units are cubic millimeters for the volume (i.e. for *N* and for *d*), and days for the time. Note that, for the ske of the notation simplicity, we set to 0 the instant of the first measurement.
We shall also fit the parameters of the classical Gompertz model to these data, with the aim of comparing our enhanced model with that venerable model.
The EMT6/R0 data were used as test case in the paper (Marušić et al., 1994b), where an interesting comparison between various model of growth was proposed, and the problem of the fitting models of growth to data was in depth faced. In fact, based on the observations on the nature of the measurement errors affecting this kind of data, that are characterized by standard errors that are proportional to the measured volume (Marušić et al., 1994b), Marusic and coworkers suggested that the method of least squares should not directly be applied to the data of tumour size, but to the logarithmically transformed data. In fact in the transformed data the standard error becomes constant since logarithm transforms multiplicative error into an additive error.
As a consequence the lest-squares objective function (i.e. the square of the Euclidean norm of the vector of residuals) to be minimized is:

$$LSSE(a,b,m,d,N(0)) = \sum_{i=1}^{n} \left(Log(N_i) - Log(N(t_i,a,b,m,d,N(0)))\right) \tag{6.1}$$

equivalently written as:

$$LSSE(a,b,m,d,N(0)) = \sum_{i=1}^{n} \left(y_i - f(t_i,a,b,m,d,N(0))\right)^2 \tag{6.2}$$

where $y_i = Log(N_i)$ and:

$$f(t,a,b,m,d,N(0)) = Log(N(t,a,b,m,d,N(0))) = Log(d) + \left(\frac{a}{b}\right)^m fu\left(a^{1-m}b^m t, \left(\frac{b}{a}\right)^m Log\left(\frac{N(0)}{d}\right), m\right)$$

where $fu(\tau, u(0), m)$ is determined, for each datum and value of the parametric vector, by solving the following equation in the variable *u*:

$$uG\left(1,m,m+1,u^{1/m}\right) - u(0)G\left(1,m,m+1,u(0)^{1/m}\right) = \tau \quad \text{(eqinv)}$$

Thus, independently from the minimization algorithm one can choose, at each evaluation of *f(t,a,b,m,d,N(0))* one has also to numerically solve *n* times (in our case *n=32*) the equation (eqinv). Moreover, the minimization of *LSSE(a,b,m,d,N(0))* is subject to some constraints. The first is the positivity of both the parameters (*a>0,b>0,m>0,d>0, N(0)>0)* and of the argument of the logarithm that implies:

$$d \le N(0)$$

Moreover, since we aim at investigating data on the growth of a untreated tumour it must also hold that:

$$N(0) < N(\infty)$$

implying the nonlinear constraint:

(6.3) $$Log\left(\frac{N(0)}{d}\right) < \left(\frac{a}{b}\right)^m$$

We performed the constrained minimization by using the Nelder-Meade Algorithm with penalty functions. To get initial guesses for the parameters, we performed two preliminary linear fittings based on the first 8 and on the last 8 data.
We obtained the following minimizing values:

$$a_{\min} = 0.70349,\ b_{\min} = 0.177355,\ m_{\min} = 0.60815,$$
$$d_{\min} = 0.148136, N(0)_{\min} = 3.9848$$

to which it corresponds the minimal value *0.4996* for LSSE. The corresponding asymptotic value is 2243. Note that, for these values of the parameters and of the initial condition, constraint (2.3) holds since it reads 0.60815 > 0.231. Corresponding to these optimal values we assessed the normality of the residuals:

$$r_i = y_i - Log(f(t,a,b,m,d,N(0)))$$

by means of the Bera-Jarque test (Jarque and Bera, 1980) whose null hypothesis *Ho* is : the data are normal. We obtained as p-value *p=0.4856*>0.5 that confirms *a posteriori* the hypothesis of normality of the errors in the logarithmic transform of data.

In order to calculate the asymptotic standard error and confidence intervals, we calculated the covariance matrix of the function *LSSE* at the optimal vector of parameters, but unfortunately the problem seems badly conditioned so that the asymptotic standard errors were huge and the confidence intervals included negative values. Numerical approximate algorithms, such as bootstrap, to obtain trustable (and non-asymptotic) confidence intervals might be used, but this was outside the aims of this work.

Then we minimized, by using the same method, the Gompertz model:

$$y_G(t,b,y^\infty,y(0)) = y^\infty - (y^\infty - y(0))Exp(-bt)$$

where $y_G(t,\beta,y(0)) = Log(N(t))$ and $y^\infty = (a/b)$,
so that we had to minimize:

$$J(b,y^\infty,y(0)) = \sum_{i=1}^{n} \left(y_i - y_G(t_i,b,y^\infty,y(0))\right)^2$$

by obtaining that the minimum occurs at:

$$b_{\min} = 0.112169,\ y^{\infty}{}_{\min} = 7.6228,$$
$$y(0)_{\min} = 1.20817 \Rightarrow\ N(0)_{\min} = 3.3471$$

and the minimum of J is is equal to 0.689594. The corresponding asymptotic value for N is 2043.

In figure (1) we plotted, for the parameters estimated in this section, in the left panel the logarithm of Gompertz model and the logarithmic data; in the right panel the log of model (1.7) and the logarithmic data.

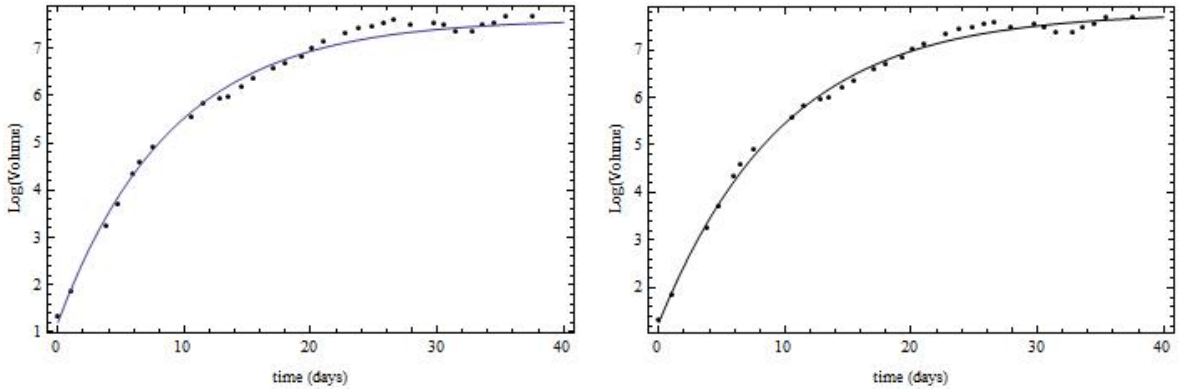

Figure 1. Experimental data taken from (Marušić et. Al, 1994) with logarithmic transform. Comparison with
logarithm of standard Gompertz (left panel), and with model (1.7) (right panel).

Thus by simple eye inspection one might say that both the curves fit well the data. However, such an empirical comparison is not satisfactory. Thus, to compare the two models we performed the well known F-test based on the f statistics:

$$f = \frac{n - p_2}{p_1 - p_2} \frac{LSQ_1 - LSQ_2}{LSQ_2}$$

which follows approximately the F-distribution (for n sufficiently large, as in our case) and where n is the number of data, $p_1 > p_2$ are the number of parameters of two models "1" and "2" to be compared, and the symbol LSQ denotes the least-square functions. In our case "2" is our model and "1" is the Gompertz model. We obtained $f=+5.2246$ corresponding to a p-value $p=0.01<0.05$, which implies that the difference of the two models is statistically significantly different. In other words the positive difference between the two values of LSSE is not due to the chance, so that we may say that the ability of fitting the EMT6/R0 data of (Marušić et. Al, 1994) by our model is better than that of Gompertz model.
Finally, in in figure 2 we show the model (1.7), the Gompertz model and the non-transformed data. From this figure it is possible to better catch how the model (1.7) is better able to capture the tumour dynamics.

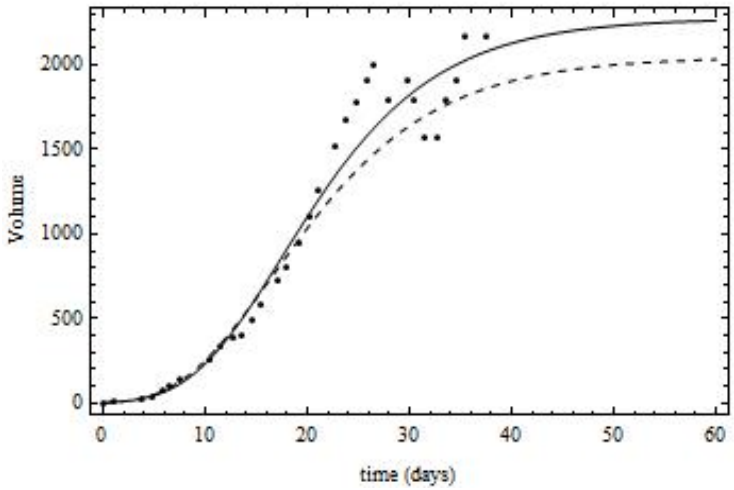

Figure 2. Experimental data taken from (Marušić et. Al, 1994) . Comparison with standard Gompertz model (dashed line), and with model (1.7) (solid line).

7 Conclusions

In this work we proposed a new model for describing the growth and response to therapy of macroscopic tumours that extends the well-known Gompertz model. The proposed model, which tends the Gompertz model, has some features that may be of interest both from the mathematical and from the biological point of view.
The model preserves some key features of the Gompertz model, including the fact that analytical solution can be calculated by means of inverse of the Gauss hypergeometric function, including in the case where a constant continuous infusion therapy is delivered.
Although it is a ode model based on a single scalar ODE, our model is fully compatible with finer bi-compartimental descriptions of tumour growth as (Gyllenberg and Webb, 1989: Kozusko and Bourdeau, 2007) that take in account that in all macroscopic tumours both proliferating and quiescent cells are present.
This compatibility is a sign of realism of the proposed model, which, indeed, well performed in the fitting of some relevant experimental data for murine mammary tumour, by giving results that are comparable, and slightly better, than the classical Gompertz model.
Finally, we have to stress that we well specified that the validity of our model and of the related biological inferences are focused on macroscopic tumours, whereas for the initial phases of growth we adopted a Gomp-Ex – like modelling, which allow to circumvent the major problems of the Gompertz-like models, namely the unboundedness of their relative growth rate.

References

M. Abramowitz and I.A. Stegun, I. A. (Eds.).Handbook of Mathematical Functions with Formulas, Graphs, and Mathematical Tables. New York: Dover, pp. 555-566, 1972.

L. Amorim, A. Bergamin Filho, B. Hau, *Analysis of progress curves of sugarcane smut on different cultivars using functions of double sigmoid pattern.* Phytopathology **83** (1993) 933-936.

A. d'Onofrio, *A general framework for modelling tumor-immune system competition and immunotherapy: Mathematical analysis and biomedial inferences.* Physica D **208** (2005) 202-235.

A. d'Onofrio, *Fractal growth of tumors and other cellular populations: Linking the mechanistic to the phenomenological modeling and vice vers*, Chaos Solitons and Fractals (2009)

J.P. Freyer, R.M. Sutherland. *Regulation of growth saturation and development of necrosis in EMT6/Ro mutlicellular spheroids by the glucose and oxygen supply.* Cancer Res. **46** (1986) 3504-3512.

B. Gompertz, *On the nature of the function expressive of human mortality and on a a new mode of determining the value of life contingencies.*. Phil. Trans. Roy. Soc. London **115** (1825) 513-585.

M. Gyllenberg, G. Webb, *Quiescence as an explanation of Gompertzian tumor growth.* Growth, Dev. Aging **53** (1989) 25-33.

F. Kozusko, Z. Bajzer, *Combining Gompertzian growth and cell population dynamics*. Math. Biosci. **185** (2003) 153-167.

(Kozusko and Bourdeau, 2007) F. Kozusko, M. Bourdeau. *A unified model of sigmoid tumour growth based on cell proliferation and quiescence.* Cell Prolif. 40 (2007) 824-834.

Jarque, C. M. and A. K. Bera. *Efficient tests for normality, homoscedasticity and serial independence of regression residuals* Economics Letters **6** (1980) 255–259

A.K. Laird, *Dynamics of tumor growth.* Brit. J. Cancer **18** (1964) 490-502.

M. Marušić, S. Vuk-Povlović, *Prediction power of mathematical models for tumor growth.* J. Biol. Systems **1** (1993) 69-78

M. Marušić Ž. Bajzer, S. Vuk-Povlović, J.P. Freyer, *Tumor growth in vivo and as multicellular spheroids compared by mathematical models*. Bull. Math. Biol. **56** (1994) 617-631.

M. Marušić Ž. Bajzer, J.P. Freyer and S. Vuk-Povlović. Analysis of growth of multicellular tumor spheroids by mathematical models. Cell Prolif. **27** (1994b) 73.

M. Marušić, *Mathematical models of tumor growth*. Lecture at the Mathematical Colloquium of the Croatian Math. Soc., Osijek (1996) 175-191.

J.C.M. Mombach, N. Lemke, B.E.J. Bodmann, M.A.P. Idiart. *A mean-field theory of cellular growth*. Europhys. Lett. **59** (2002) 923–928

G.G. Steel (1977) Growth Kinetics of Tumors. Oxford. Calrendon Press

M.E. Turner Jr., E.L. Bradley Jr., K.A. Kirk, K.M. Pruitt, *A theory of growth*. Math. Biosci. **29** (1976) 367-373.

L.von Bertalanffy, *Untersuchungen über die Gesetzlichkeit des Wachstums, VII, Stoffwechseltypen und Wachstumtypen.* Biol. Zentralblatt **61** (1941) 510-535.

L.von Bertalanffy, *Quantitative laws in metabolism and growth*. Q. Rev. Biol. **32** (1957) 217-231.

T. E. Wheldon (1988). Mathematical models in cancer research, Bristol and Philadelphia – Adam Hilger.