From the Mendelsohn model to the Gompertz and logistic growth law

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Abstract

The *Gompertz* and logistic function in oncology is a popular method for modelling the empirical growth curves of avascular and vascular tumours in the early stage. However, these phenomenological models are purely descriptive and biological vindication is missing. The purpose of this article is to provide possible biological substantiation of the *Gompertz* and logistic function when used in relation to tumour growth.

Keywords: *Gompertz* function, logistic function, sigmoid function, ODE tumour growth models

1 Introduction

A great number of mathematical models for tumour growth have been proposed in the past to increase the understanding of the tumour growth process. Already in 1932 it was proposed by *C. P. Winsor* that the *Gompertz* and logistic curve possess similar properties which make them useful for the empirical representation of growth phenomena.*Laird* showed 1964 that the growth of a variety of tumours of the mouse, rat and rabbit, whether transplanted or primary, is well described by a *Gompertz* equation. The *Gompertz* equation was primarily used in a quite different context, as a model for the increase in mortality rate with age in a human population. *Benjamin Gompertz* (5 March 1779 – 14 July 1865), a British self-educated mathematician and actuary, worked out a new series of tables of mortality for the Royal Society, which led in 1825 to his law of human mortality. The law rests on an *a priori* assumption that a human's resistance to death decreases as the age increase. The model can be written as $\frac{\mathrm{d}N(t)}{\mathrm{d}t} = a \cdot N(t) - b \cdot N(t) \cdot \ln\left(N(t)\right) = -b \cdot N(t) \cdot \ln\left(\frac{N(t)}{K}\right)$, where $N(t)$ represents the number of individuals at time t, a and b are constants and $K = e^{\frac{a}{b}}$.

The logistic equation was discovered by *Pierre Francois Verhulst*, a Belgian mathematician and a doctor in number theory. In 1838 he published the equation $\frac{\mathrm{d}N(t)}{\mathrm{d}t} = r \cdot N(t) \cdot \left(1 - \frac{N(t)}{K}\right)$, where $N(t)$ represents number of individuals at time t, r the intrinsic growth rate and K the maximum number of individuals that the environment can support. 7 years later *Verhulst* published a paper, where he called the solution to this the logistic function, and the equation is

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now called the logistic equation. *Raymond Pearl* and *Lowell Reed* rediscovered the model in 1920 and promoted its use. Also the logistic differential equation has been intensively used to model the growth of tumours, for example by *V. G. Vaidya* and *F. J. Alexandro*.

Nevertheless the phenomenological models that we have introduced in this section are still of limited use on their own, because they are merely descriptive rather than explanatory. *Nicholas F. Britton* raises a question in his book *Essential Mathematical Biology*: The *Gompertz* equation... '*provides an excellent fit to empirical growth curves for avascular and vascular tomours in their early stage, often much better than the more intuitive von Bertalanffy equation, but why should this be so? Interpretations in terms of* $-\log\left(\frac{N}{K}\right)$ *as the proliferative fraction of cells in the tumour cell population and derivations in terms of the entropy of the system have been proposed, but a satisfactory answer to the question has yet to be found*'.

We will provide a possible answer to this question in the next section, approximating a tumour-biology based model by series representations to derive the *Gompertz* and logistic equation.

2 Model Derivations

We will first assume a spherical tumour. We will further assume that the growth of the tumour is limited by nutrients and/or oxygen which enter through the surface. If V is the sphere volume, A is the sphere surface and r is the sphere radius, $V^{\frac{2}{3}} \propto A$ applies, which can be demonstrated easily:

$$V^{\frac{2}{3}} = \left(\frac{4}{3}\cdot\pi\cdot r^3\right)^{\frac{2}{3}} = \frac{2\cdot\sqrt[3]{\frac{2}{\pi}}}{3^{\frac{2}{3}}}\cdot\pi\cdot r^2. \tag{1}$$

A well-known tumour model is the *Mendelsohn* model with the tumour volume $V(t)$ and the proportionality constant a:

$$\frac{\mathrm{d}V(t)}{\mathrm{d}t} = a\cdot\underbrace{\frac{V(t)^{\frac{2}{3}}}{V(t)}}_{\text{A/V ratio}}\cdot V(t) = a\cdot V(t)^{\frac{2}{3}}. \tag{2}$$

The *Mendelsohn* model describes unlimited growth. However, a tumour in the early stage has a sigmoid growth curve, meaning that we cannot follow this model further, but must make a modification by approximating the A/V ratio. We will use the following series for this:

$$x^{-k} = \sum_{n=0}^{\infty}\frac{(-k\cdot\ln(x))^n}{n!}. \tag{3}$$

Proof. We make use of the *Maclaurin* series $e^x = \sum_{n=0}^{\infty}\frac{x^n}{n!}$ for $-\infty < x < \infty$. We rewrite $x^{-k} = e^{-k\cdot\ln(x)}$ and replacing x by $-k\cdot\ln(x)$ in the *Maclaurin* series of e^x. Hence $x^{-k} = \sum_{n=0}^{\infty}\frac{(-k\cdot\ln(x))^n}{n!}$. □

To find where the series (3) converges, we use the ration test and compute:

$$\lim_{n\to\infty}\left|\frac{a_{n+1}}{a_n}\right| = \lim_{n\to\infty}\left|\frac{\frac{(-k\cdot\ln(x))^{n+1}}{(n+1)!}}{\frac{(-k\cdot\ln(x))^{n}}{n!}}\right| = \lim_{n\to\infty}\left|\frac{k\cdot\ln(x)\cdot n!}{(n+1)!}\right| = 0.$$

Thus the domain is all real numbers.

Substituting now x by V in (3) and adding the proportionality constant a yields

$$a\cdot V^{-k} = a\cdot\sum_{n=0}^{\infty}\frac{(-k\cdot\ln(V))^{n}}{n!}. \tag{4}$$

Truncating the series expansion of series (4) and keeping only the terms of degree less than or equal to $n=1$, it follows that

$$a\cdot V^{-k} \approx -a\cdot k\cdot\ln(V) + a. \tag{5}$$

We define $a\cdot k = b$, $\frac{1}{k} = c$ and $K = e^{c}$. K will always be designated as the carrying capacity below. Therefore equation (5) becomes

$$a\cdot V^{-k} \approx -b\cdot\ln\left(\frac{V}{K}\right). \tag{6}$$

Substituting $a\cdot\frac{V(t)^{\frac{2}{3}}}{V(t)}$ of equation (2) by $-b\cdot\ln\left(\frac{V}{K}\right)$ of equation (6) yields

$$\frac{\mathrm{d}V(t)}{\mathrm{d}t} = -b\cdot V(t)\cdot\ln\left(\frac{V(t)}{K}\right). \tag{7}$$

This is the *Gompertz* differential equation after the growth model of the same name.

A general differential equation can be obtained from (4):

$$\frac{\mathrm{d}V(t)}{\mathrm{d}t} = a\cdot V(t)\cdot\sum_{n=0}^{i}\frac{k^{n}\cdot(-\ln(V(t)))^{n}}{n!}. \tag{8}$$

For $i=0$ we get the exponential growth law, for $i=1$ as shown the *Gompertz* growth law and for $i=\infty$ the *Mendelsohn* model.

A second series representation of x^{-k} is given by

$$x^{-k} = \sum_{n=0}^{\infty}\binom{-k}{n}\cdot(x-1)^{n} \tag{9}$$

Proof. An extension of the Binomial Theorem states, that if k is any number and $|x|<1$, then $(1+x)^{k} = \sum_{n=0}^{\infty}\binom{k}{n}\cdot x^{n}$. Hence $(1+x)^{-k} = \sum_{n=0}^{\infty}\binom{-k}{n}\cdot x^{n}$. Replacing x by $x-1$ in the binomial series yields $x^{-k} = \sum_{n=0}^{\infty}\binom{-k}{n}\cdot(x-1)^{n}$. □

We use again the ration test to find where the series (9) converges. Assuming k, n and x are positive:

$$\lim_{n\to\infty}\left|\frac{\binom{-k}{n+1}\cdot(x-1)^{n+1}}{\binom{-k}{n}\cdot(x-1)^{n}}\right| = \lim_{n\to\infty}\frac{|x-1|\cdot(k+n)}{n+1} = |x-1|\,.$$

Therefore series (9) converges when $|x-1|<1$, and we obtain a further general differential equation:

$$\frac{\mathrm{d}V(t)}{\mathrm{d}t} = a\cdot V(t)\cdot\sum_{n=0}^{i}\binom{-k}{n}\cdot(V(t)-1)^{n}\,. \tag{10}$$

The result for $i=1$ is the *Bernoulli* differential equation of the logistic growth model. We define $a\cdot k = b$ and $1+\frac{1}{k} = K$, which immediately results in the following:

$$\frac{\mathrm{d}V(t)}{\mathrm{d}t} = b\cdot V(t)\cdot(K-V(t))\,. \tag{11}$$

For $i=0$ we get again the exponential growth law and for $i=\infty$, we of course obtain the *Mendelsohn* model.

3 Discussion

As we have shown in the previous section that the *Gompertz* and logistic equation are able to approximate the *Mendelsohn* model for some small V if the constants are accordingly chosen. As the *Gompertz* and logistic equation provide an excellent fit to empirical growth curves of tumours we can assume that a tumour at least in the early stage follows the surface/volume model, but then changes its behavior latest at the point it can not uptake enough nutrients by its surface anymore. The tumour enters then the vascular stage by stimulating blood-vessel formation. Beside the improved nutrient supply the tumour is now able to spread (metastases). Using the series (3) and (9) respectively the general differential equations (8) and (10) we can approximate the *Mendelsohn* model more accurately and over a wider interval as the *Gompertz* and logistic equation can do. As the radius of convergence of series (9) is restricted, series (3) respectively equation (8) is more applicable to obtain new tumour growth models. The big drawback is that the differential equation solutions become more and more complicated.

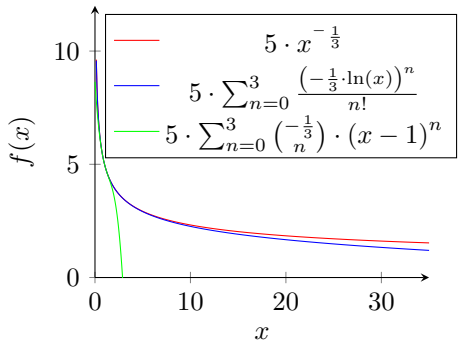

Fig. 1 Approximations of $f(x) = 5\cdot x^{-\frac{1}{3}}$ using the series (3) and (9)

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