

The Model Muddle: In Search of Tumor Growth Laws

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Abstract

In this article, we will trace the historical development of tumor growth laws, which in a quantitative fashion describe the increase in tumor mass/volume over time. These models are usually formulated in terms of differential equations that relate the growth rate of the tumor to its current state and range from the simple one-parameter exponential growth model to more advanced models that contain a large number of parameters. Understanding the assumptions and consequences of such models is important, as they often underpin more complex models of tumor growth. The conclusion of this brief survey is that although much improvement has occurred over the last century, more effort and new models are required if we are to understand the intricacies of tumor growth. *Cancer Res*; 73(8); 2407–11. ©2013 AACR.

The growth patterns exhibited by tumors have gathered the interest of scientists since the early days of cancer research, and despite almost a century of inquiry there are still uncertainties regarding the precise growth rate, or rather growth pattern, that solid tumors exhibit. This is in part due to the shift in scientific focus from the macroscopic increase in tumor size, to the (sub)microscopic workings of signal transduction pathways, and the impact of specific genetic alterations. However, a lot can still be gained from an advance in our knowledge of tumor growth, not least in the clinic, where established growth curves may help to determine optimal time period between mammography screening (1), and may be used, as part of more complex models, for calculating appropriate doses in radio- and chemotherapy (2).

The increase in size of a neoplasm caused by the upregulation of cell division among malignant cells is one of the most basic observations to be made when studying cancer (3). A natural question to ask is then how the size of the tumor increases over time as the disease progresses. What seems like a very simple question has, however, turned out to be immensely difficult to answer, and the reasons why have only become evident in the last couple of decades, when many of the complex processes underlying tumor progression have been discovered.

It was early on established that if cancer cells divide in a completely unconstrained fashion, and hence every cell in the tumor continuously passes through the cell cycle and gives rise to two daughter cells at regular intervals, then the number of cancer cells and therefore the volume and mass of the tumor would increase exponentially with time. The geometric

increase then implies that the time one has to wait for the tumor to double in size is constant over time. This picture of exponential growth has been shown to match the early stages of tumor growth, but, in all known cases, the doubling time eventually increases and continues to do so for the remainder of the disease. This can occur if either the average cell-cycle time increases or if there is a loss of dividing cells due to quiescence or cell death. We will discuss both these possibilities later on, but, for now, we simply note that other mechanisms need to be invoked.

The paradigm of exponential growth is thus unable to explain growth dynamics of tumors in the longer term, and one has to look beyond the simple idea of unconstrained cell division to explain the observed data. This was indeed done in the first half of the 20th century through pioneering work by Mayenord (4) and Schreck (1936; ref. 5) among others, who considered models in which the growth rate is retarded. However, to fully appreciate this advance, it is necessary to resort to mathematical notation. Exponential growth is described by the differential equation

$$\frac{dV(t)}{dt} = rV(t) \quad (1)$$

that equates the rate of increase in volume dV/dt to the current volume $V(t)$ times the growth rate r , assumed to be constant. This means that within an infinitesimal time interval, dt , the increase in volume dV is proportional to the current size of the tumor. The solution of this equation is $V(t) = V_0 e^{rt}$, where V_0 is the volume of the tumor at time $t = 0$ when measurements started, and e is the base of the natural logarithm. Eq. (1) can however be viewed as a special case of a more general equation

$$\frac{dV(t)}{dt} = rV(t)^b \quad (2)$$

that was introduced by Mendelsohn (6), where now the rate of increase is proportional to the volume raised to the power b , which can take on any value. Now if $b = 1$ the solution is the

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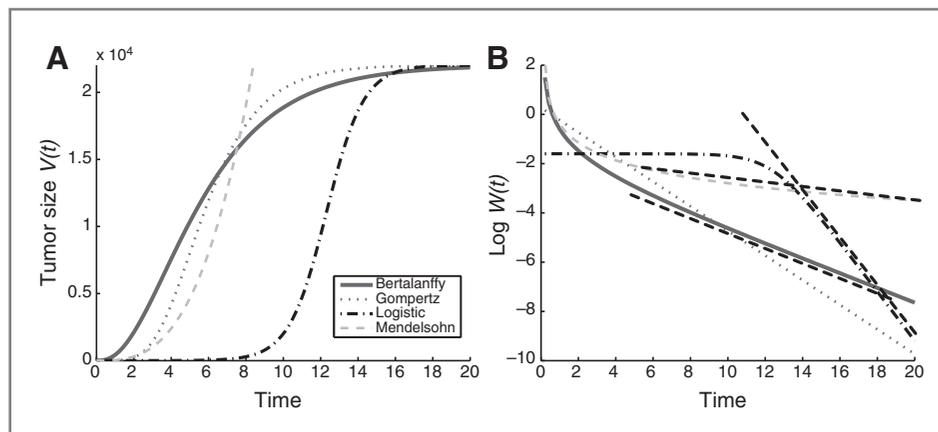


Figure 1. Tumor growth curves. A, the growth curves for 4 different models of tumor growth. The Gompertz (dotted), Bertalanffy (solid), and Logistic (dash-dotted) tend to an asymptotic value, whereas the Mendelsohn model (dashed) gives rise to unconstrained growth. B, the quantity $\log \log V(t)/V(t-1)$ plotted for the different tumor growth models. This quantity decreases linearly for the Gompertz model and is used as a means to determine the parameters of the model. However, the other models also exhibit an approximately linear decrease, suggesting that these may explain data that is fitted to the Gompertz model.

above exponential growth curve, but for $b \neq 1$ the solution is given by

$$V(t) = ((1-b)(rt+C))^{-\frac{1}{b}} \quad (3)$$

where C is a constant related to the initial condition (see Fig. 1A). By fitting growth curves from mouse mammary tumors to this equation, Dethlefsen and colleagues (7) were able to show that many tumors grow according to Eq. 3 with $b \approx 2/3$. This value of b was in fact already suggested by Mayenord in 1932 (4), and can be derived from simple physical considerations: Assuming that the tumor is spherical in shape with volume V , its surface area scales as $V^{2/3}$. If we further assume that the growth of the tumor is limited by nutrients and/or oxygen which enter through the surface, then the growth rate of the tumor should be proportional to its surface area, that is, $V^{2/3}$. In this case ($b = 2/3$) the solution is given by $V(t) \sim t^3$, or in terms of the of the tumor radius $R(t) = \sqrt[3]{V(t)} \sim t$.

In other words, the radius of the tumor grows linearly with time, and this behavior can also be explained by assuming that only a thin layer of cells at the surface of the tumor are in fact dividing. This suggestion was, at the time, highly disputed (8–10), and results from animal models suggested that the whole tumor was mitotically active. In fact, for subexponential growth to occur, it is not sufficient for a constant fraction of the tumor cells to be quiescent, but an ever increasing fraction of cells must become mitotically inactive as the growth progresses. This seemed an unlikely scenario, given that tumors actually grow at a considerable rate, but we now know that this is the general mode of growth of solid tumors, at least before vascularization: Tumors contain a proliferating region of roughly constant width, and, hence, an ever diminishing fraction of active cells.

Despite the improvement in describing tumor growth curves, the above model could not account for the longer term reduction in growth rate often associated with later stages of the disease. This problem was addressed in a seminal paper by Laird (11), who suggested a fundamentally different model for

explaining tumor growth, namely the Gompertz model, whose unexpected origin deserves a mention. It was put forward by Benjamin Gompertz in 1825 (12) as a means to explain human mortality curves. Gompertz had made the observation that "If the average exhaustions of a man's power to avoid death were such that at the end of equal infinitely small intervals of time, he lost equal portions of his remaining power to oppose destruction. . . ." then the number of living humans at age x would be given by

$$L(x) = ke^{-e^{-bx}} \quad (4)$$

where k , a and b are constants, of which k and b are necessarily positive.

The main motivation for the model was actuarial, as a practical means of determining the value of life insurances, and only later was it proposed as a model for biologic growth. This was done by the geneticist Sewall Wright in 1926 (13), who observed that "the average growth power, as measured by the percentage rate of increase, tends to fall at a more or less uniform percentage rate." Or in other words, the growth rate of an organism or organ tends to decrease at a constant rate. The model was first applied by Davidson (14), for describing the growth of cattle, who also gave the following derivation of the equation, which formalizes what Wright had put in words.

Assume that a growth process is governed by

$$\frac{dV(t)}{dt} = r(t)V(t) \quad (5)$$

where $V(t)$ is the mass or volume of an organism. This equation is similar to the equation of exponential growth (Eq. 1), but with the growth rate $r = r(t)$ now being time dependent. We now assume that $r(t)$ decreases in proportion to its current value at a constant rate ρ , that is,

$$\frac{dr(t)}{dt} = -\rho r(t). \quad (6)$$

The solution of these two coupled equations now yields the Gompertz curve in its more familiar shape

$$V(t) = V_0 e^{\frac{r_0}{\rho}(1-e^{-\rho t})} \quad (7)$$

where r_0 is the growth rate at time $t = 0$, and V_0 is the initial volume of the animal. This equation has successfully been fit to biologic growth in a wide variety of contexts ranging from the growth of internal organs (15), whole organisms (16), and entire populations (17). In contrast to the exponential and Mendelsohn model, the growth curve generated by the Gompertz equation (Eq. 7) is sigmoidal in shape, and reaches a constant value, or asymptote, as $t \rightarrow \infty$ with $V_\infty = V_0 e^{r_0/\rho}$ (see Fig. 1A).

The previous success in describing biologic growth is probably what motivated the application of the Gompertz equation to tumor growth, but Laird also gives some justification in terms of tumor biology. In arguing in favour of the Gompertz model, Laird notes that if only a constant fraction of the tumor cells were cycling then this would still give rise to exponential growth, albeit with a smaller growth rate. The observed exponential decrease in overall growth rate coupled with experimental observations suggesting that almost all cancer cells in a tumor are passing through the cell cycle (11) was instead readily explained by a model in which all cells cycled, but with an ever diminishing speed.

A suggested mechanism of action was growth retarding factors, whose effects increases during growth according to an exponential function, and one candidate was an accelerated immunologic response (11). We now know that quite the opposite is true; large parts of solid tumors are quiescent, and the cells that are actually dividing do this at a rate comparative to the one at early stages of progression (18). This means that the decaying growth rate in Eq. 6 cannot be given any natural biologic meaning, because it represents, not a single process, but the joint effect of many confounding factors, the total sum of which is negative. In addition, the doubling times required to match the early phases of tumor growth sometimes take on unrealistically small values (<10 hours; ref. 19), suggesting fundamental problems with the modeling approach. Despite these drawbacks, the Gompertz equation has proven to be a useful tool when describing tumor growth curves. It has been applied and varied in many different ways, for example, to capture the effects of radiation (20) and antiangiogenic therapy (21). The latter variation is interesting as it makes use of the notion of a variable maximal volume or "carrying capacity", imposed by some environmental limitation such as nutrients. To grasp this concept we need view the Gompertz equation in a different, but completely equivalent, form

$$\frac{dV(t)}{dt} = \rho V(t) \log \frac{K(t)}{V(t)}, \quad (8)$$

where $K(t)$ is the carrying capacity of the tumor at time t , which in the previous time-independent equation would equal V_∞ . When $V(t) = K(t)$ we have $\log K(t)/V(t) = \log 1 = 0$, and the growth rate is equal to zero. Hahnfeldt and colleagues (21) coupled the carrying capacity to the angiogenic response by formulating a separate differential equation for $K(t)$, which

takes into account the influence of the tumor mass on the dynamics of the vasculature. They could show that the model accurately describes the growth dynamics both in untreated tumors and those exposed to antiangiogenic factors such as angiostatin.

The Gompertz model is, however, not the only model that can capture a decrease in tumor growth rate over time and an asymptotic mass, and at least two other models have been put forward as plausible candidates. The logistic (or Pearl-Verhulst) equation given by

$$\frac{dV(t)}{dt} = rV(t) \left(1 - \frac{V(t)}{K}\right). \quad (9)$$

was first formulated by Pierre Francois Verhulst in 1838 (22) as a means of describing the dynamics of a population with an intrinsic growth rate r , whose total size is limited by a carrying capacity K (see Fig. 1A). It has since then become a mainstay of biomathematics and has successfully been applied to a large number of biologic phenomena, ranging from bacterial populations to algae and mammals (23). Whereas the Gompertz equation assumes an exponentially decreasing growth rate, the logistic equation instead assumes that the growth rate falls off linearly with the size, until it becomes equal to zero when it reaches the carrying capacity $V(t) = K$. In terms of matching actual growth curves, the logistic and Gompertz equation are quite similar (24), with the main difference being that the Gompertz curve is asymmetric, with the point of inflection (the time point where the growth rate is maximal) occurring after 37% of the final size has been reached, whereas for the logistic this occurs after half of the growth has occurred. The logistic equation can be derived by considering a spatially extended population where reproduction is constrained by available space. Although the competition for space plays an important role in tumor growth, this derivation ignores many other important factors, such as limited nutrients, that also influence the process. This leaves the model hanging in a phenomenological void, also inhabited by the Gompertz model, with the possible advantage that it has a mechanistic derivation.

A second candidate, which has received considerably less attention, is the Bertalanffy equation

$$\frac{dV(t)}{dt} = \alpha V(t)^{2/3} - \beta V(t) \quad (10)$$

whose instigator was the founder of general systems theory Ludwig von Bertalanffy. It was put forward as a model for organism growth (25), and its derivation is similar to the above model by Mendelsohn (6), Eq. 2, that is, growth occurs proportional to surface area, with the additional assumption that the loss of tumor mass due to cell death occurs in proportion to the volume of the tumor with a constant β , related to the commonly used cell loss factor. The solution of Eq. 10 is also sigmoidal in shape, and tends to a fixed volume as time increases, where the growth and loss term balance each other out (see Fig. 1A). The striking thing about the Bertalanffy equation is that it both matches experimental tumor growth curves well, and in addition, has a derivation with biologically meaningful parameters. In a review of different tumor growth

models, it was in fact shown that the Bertalanffy model gave a better fit than both the Gompertz and Logistic model in 7 of 10 cases (26).

Despite this fact, the Gompertz model has remained the most applied models when it comes to describing tumor growth curves (see, for example, Norton; ref. 27). How can this be the case? We believe the reasons are twofold, one theoretical and one practical.

The former reason is related to the nature and purpose of modeling. Do we formulate and apply a model in an effort to understand a system, or to predict its future behavior? The answer is rarely clear cut, but, if one leans towards prediction, then a model that is disconnected from reality in terms of mechanisms and dynamics is acceptable, as long as it does the job of predicting. If one, on the other hand, has a yearning for understanding the system at hand, then the model has to be derived from, and based on, real mechanisms and entities within the system. Since the purpose of growth curves is often to predict the future size of the tumor, it is not surprising that the phenomenological Gompertz model has dominated.

The second reason is of a more practical nature, and connected to the method with which one fits experimental data to the Gompertz model. To find the parameters of the model, one forms the quantity $W(t) = \log V(t) - \log V(t-1)$, which decays exponentially with time according to $W(t) = Ae^{-\rho t}$, where $A = r_0/\rho(e^\rho - 1)$. Thus, to find the parameters of the model, one plots the quantity $\log W(t) = \log A - \rho t$ as a function of time, and by applying some regression method, such as least squares, finds ρ as the (negative) slope and $\log A$ as the intercept. In this process, we essentially take the logarithm of the tumor volume $V(t)$ twice, suppressing any deviations from the Gompertz model, and thus making it quite easy to fit the model to data that follows a completely different growth law. This fact is illustrated in Figure 1B, which shows four different growth curves (Gompertz, Logistic, Mendelsohn, and Bertalanffy) and the quantities $\log W(t)$ plotted over time. It is evident that even though the growth curves $V(t)$ look quite different, the plots of $\log W(t)$, at least for longer times, are very close to being straight lines, which is consistent with the Gompertz model. In

the case of real tumor data with its inherent experimental error, and in some cases late detection, this distinction is even harder to make, and in one sense the Gompertz model is poised to win the race.

In my opinion, these are the two main reasons why the Gompertz model has held a dominating position for nearly half a century. However, the ease with which a model can be fitted to data should not determine its use over other, more accurate models, and also the latter methodological consideration we find worth scrutinizing. A model that is grounded in the actual biology (which the Gompertz model is not) can not only provide predictions, but also give insight into the underlying dynamical process of tumor growth. By comparing the parameter values obtained from different patients or cell lines, one might be able to draw conclusions about the basis of growth and its dynamics. Among the candidates we have reviewed here, it seems that the Bertalanffy equation of tumor growth is the most suitable candidate. It produces growth curves that are nearly indistinguishable from the well-known Gompertz model, but has the advantage of being biologically motivated.

However, more research is needed in this field, which for a long time has remained dormant. A notable exception to this is the model by Herman and colleagues (28), which takes into account the tumor vascular network and its interface with the cardiovascular system of the host. This comprehensive model relates tumor vascularization and growth to metabolic rate, and gives predictions for tumor properties. These include growth rates, metabolic rates, degree of necrosis, blood flow rates, and vessel sizes, all of which are clinically relevant variables, and show that models such as this one are helpful in our future inquiry into the dynamics of tumor growth.

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