

Lecture 2, Th., Jan., 18, 2007

Reading homework: Chapter 2, p13-26, reference 1

This course will focus on formulation and analysis of differential equations based mathematical models in medicine. In addition to possessing the highly desirable predictive power, these differential equations based models allow researchers to test and generate important and complicated biological hypothesis.

As in the case of mathematical ecology, we will cover some ODE based models first. Naturally, we shall start with the simplest group of such models: the one dimensional ODE tumor models. It is easy to image that there are many such models in the literature. Limited by time and space, we will cover only the three most well known scalar tumor models.

1. Logistic and von Bertalanffy Models for Tumor Growth. In the beginning, a tumor often grows in approximately a spherical form. If the tumor fails to produce enough signaling proteins such as vascular endothelial growth factor (VEGF) for angiogenesis, then the tumor can only grow to a certain size with available nutrient supplies. Indeed, most tumors exhibit a sigmoid growth curve in the early stage. For this reason, many modelers simply employ the well-known logistic equation

$$(1.1) \quad dN/dt = rN(1 - N/K) = rN - rN^2/K$$

as a simplistic model for tumor growth. Here N is the size of the tumor, usually measured as a number of cells or as a volume. r is the growth rate while rN/K can be interpreted as the density dependent death rate. The tumor size is an increasing function that tends to the carrying capacity K .

Generalizing the logistic model, von Bertalanffy (1957) introduced the equation

$$(1.2) \quad dN/dt = f(N) = \alpha N^\lambda - \beta N^\mu, \quad \lambda < \mu.$$

to represent tumor growth. This is often referred as the (generalized) von Bertalanffy tumor model. The tumor size is an increasing function that tends to the carrying capacity $(\alpha/\beta)^{1/(\mu-\lambda)}$.

Tumors tend to approach a steady state size in the nutrient-limited growth phase when nutrient is supplied only by diffusion. A particular case of the von Bertalanffy equation is the surface rule model (Bertalanffy, 1941), which states that growth is proportional to surface area ($\lambda = 2/3$) since nutrient have to enter through the surface, while death is proportional to the size ($\mu = 1$). In this special case, β is the death rate.

Notice that, the birth rate of logistic model and the death rate of the von Bertalanffy model (when $\mu = 1$) are constant. While these models have intuitively meaningful parameters, neither considered the typical three layer structure manifested by most multicellular tumor spheroid in their later phase.

Matlab file for generating figure (1.1).

```
-----  
t = 0:0.01:2*pi;  
x1 = 2.5*cos(t);  
y1 = 2.5*sin(t);  
x2 = 3.5*cos(t);  
y2 = 3.5*sin(t);
```

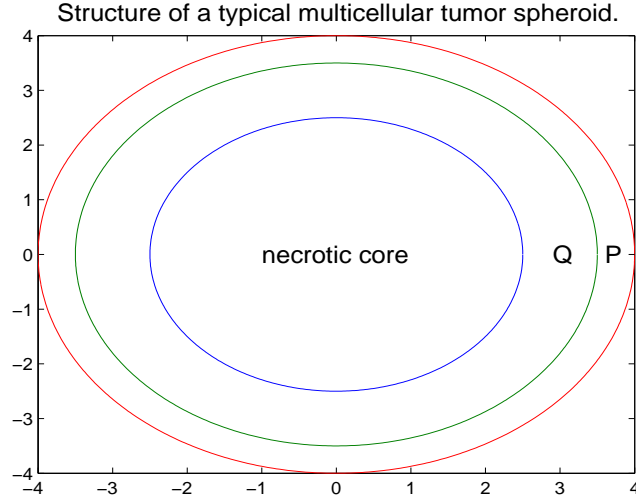


FIG. 1.1. *Structure of a typical multicellular tumor spheroid.* Q =quiescent layer, P =proliferating layer.

```
x3 = 4*cos(t);
y3 = 4*sin(t);
plot(x1,y1, x2, y2, x3, y3)
text(-1,0,'necrotic core','FontSize',14)
text(2.9,0,'Q','FontSize',14)
text(3.6,0,'P','FontSize',14)
title('Structure of a typical multicellular tumor spheroid.',
'FontSize',14)
```

2. Gompertz Model for Tumor Growth. Gompertz model is arguably the most important and celebrated tumor model. Many researchers reported that Gompertz model provided surprisingly good fit to their experimental data on various tumor growths. The key assumption embodied in the Gompertz model is that the cell growth rate decrease exponentially as a function of time.

$$(2.1) \quad \frac{dN}{dt} = r(t)N(t), \quad \frac{dr}{dt} = -ar(t).$$

Notice that

$$(2.2) \quad \frac{d(\ln(N))}{dt} = \frac{1}{N} \frac{dN}{dt} = r(t) = \frac{-1}{a} \frac{dr}{dt}.$$

From which we obtain that for some constant b ,

$$(2.3) \quad \ln(N) = (-r(t) + b)/a.$$

Which is equivalent to say that $r(t) = b - a \ln(N)$. This gives us an alternative and more popular form of the Gompertz model

$$(2.4) \quad \frac{dN}{dt} = bN - a \ln(N)N = N(b - a \ln(N)).$$

Note that this function is not defined for $N = 0$, so we must assume that the tumor has a certain size before applying this model. Again, the tumor size is an increasing function that tends to the carrying capacity $K = e^{a/b}$. Using the substitution $u = \ln(N/K)$, we can solve the Gompertz equation with initial condition $N(0) = N_0$. We obtain that $N(t) = Ke^{-AB}$, where $A = -\ln(N_0/K)$ and $B = e^{-bt}$.

Simpson-Herren and Lloyd (1970) studied the growth of a number of tumors. One tumor they studied was the C3H Mouse Mammary tumor, which is stimulated by a provirus. They were able to find the growth rate for these tumors. Figure 2.2 is a graph showing the experimental data of the tumor sizes and the tumor growth rate as a function of its size. The figure includes the curve for the Gompertz model. It is not surprising that there is a number of mathematical models that can closely match the growth of this particular tumor. Laird (1964) showed that this tumor growth satisfies the Gompertz model particularly well. The growth function is given by the equation

$$G(N) = N(b - a \ln(N)),$$

where N are the number of tumor cells and a and b are constants that are matched to the data measuring the growth of a tumor. For the data above, the best fit curve is given by

$$G(N) = N(0.4126 - 0.0439 \ln(N)).$$

When the growth of the tumor stops, the tumor is at its maximum size supportable with the available nutrient and space supply. We would also like to know when the tumor is growing most rapidly. This will occur when the derivative is zero. The equilibrium is found when

$$G(N) = N(b - a \ln(N)) = 0.$$

Since $N > 0$, this occurs when $b - a \ln(N) = 0$. This is equivalent to $\ln(N) = b/a$. Thus, $N^* = \exp(b/a)$ is the unique equilibrium and is similar to the carrying capacity in the logistic model. For the specific data given above, the

$$N^* = e^{0.4126/0.0439} = e^{9.399} = 12,072,$$

which matches the P-intercept on the graph above.

Matlab file for generating figure (2.1).

```
-----
x = 0:0.005:1;
y1 = x.*(1-x);
y2 = x.^(2/3)-x;
y3 = -x.*log(x);
plot(x,y1, 'r:', x, y2, x, y3, 'k-.')
legend('logistic', 'von Bertalanffy', 'Gompertz', 1)
ylim([0 0.4]);
xlabel('N')
ylabel('tumor growth functions')
title('Plot of some tumor growth functions', 'FontSize', 12)
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```

Some researchers have also considered the following so-called generalized Gompertz model (Marui and Vuk-pavlovi 1993, Marui et al. 1994),

$$(2.5) \quad \frac{dN}{dt} = N^\alpha(b - a \ln(N)).$$

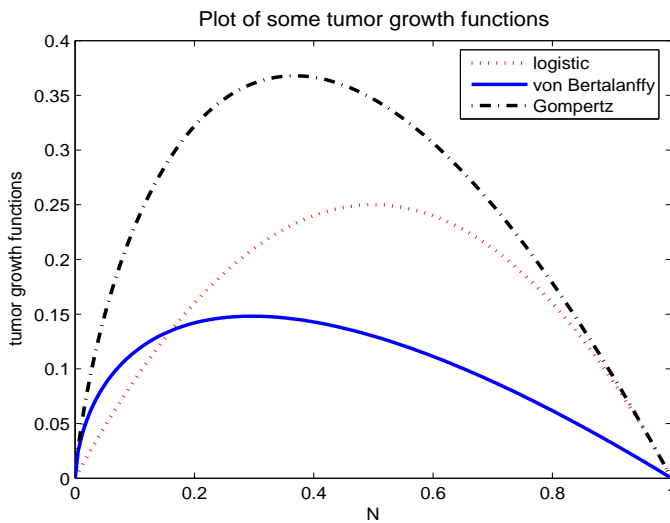


FIG. 2.1. Plot of some tumor growth functions: logistic $N(1 - N)$, von Bertalanffy $N^{2/3} - N$, Gompertz $-N \ln(N)$. Notice that the growth rate of logistic equation peaks late while that of von Bertalanffy model peaks early.

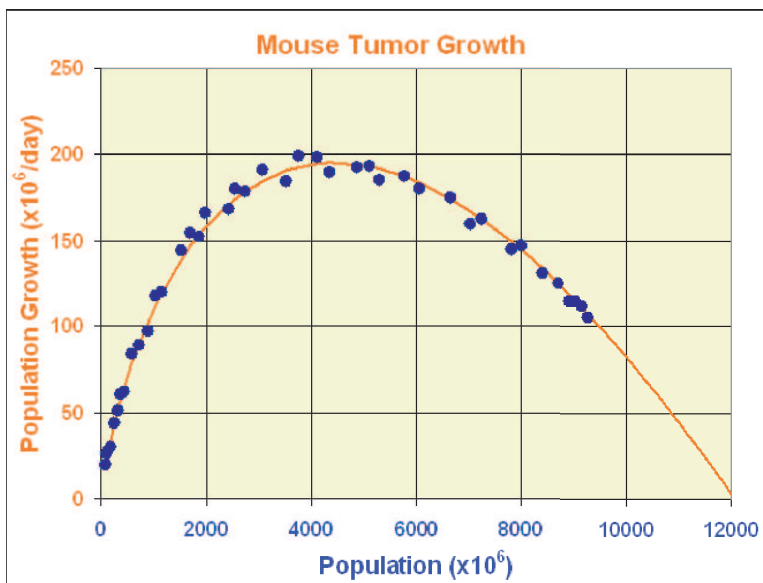


FIG. 2.2. Mouse tumor growth rate as a function of size. From http://www-rohan.sdsu.edu/jmahaffy/courses/s00a/math121/lectures/product_rule/product.html

Marui and Vuk-pavlovi (1993) compared the Gompertz model, the generalized Gompertz model, and a host of other one dimensional ODE tumor models to predict growth of multicellular tumor spheroids as paradigms of the prevascular phase of tumor growth. They reported that the Gompertz model is the model with the best prediction power. The generalized Gompertz model is ranked as the second most predictive model. Moreover, the ranking of models was not affected by the applied

minimization criteria of weighted least squares, unweighted least squares and fitting to logarithmically transformed data.

Marui et al. (1994) compared model fittings of the *in vivo* volume growth of two murine tumor cell lines. Fourteen one dimensional deterministic multicellular spheroid models were studied. The von Bertalanffy model and the logistic model were declared unfit for the data while Gompertz model provided the best fit. However, the authors concluded that more sophisticated models that incorporating fine tumor structures are needed and data collection methods can also be improved.

Benjamin Gompertz (1779 - 1865) applied the calculus to actuarial questions and he is best remembered for Gompertz's Law (function) of (human) Mortality. Gompertz, in 1825, observed that when death rates are plotted on a logarithmic scale with respect to age, a straight line known as the Gompertz function is obtained. It is the most informative actuarial function for investigating the ageing process. The slope of the Gompertz function line indicates the rate of actuarial ageing. His expertise in this area led to his being consulted by government, including giving evidence to the select parliamentary committees on friendly societies in 1825 and 1827, and he did important computational work for the army medical board. His insights have remained central to the study of human mortality. Gompertz was a founder member of the Royal Statistical Society in 1834.

EXERCISES

(1). This exercise provides a **problematic** attempt to show that Gompertz model can be viewed as a limiting case of the von Bertalanffy model (page 238, Britton 2003).
i). In the von Bertalanffy model (1.2), let $\mu = 1$, $b = \alpha - \beta$ and $a = \beta(\mu - \lambda)$. Show that the von Bertalanffy model can be written as

$$(2.6) \quad \frac{dN}{dt} = bN^\lambda - aN^\lambda \frac{N^{1-\lambda} - 1}{1 - \lambda}.$$

ii). In the above equation, take the limit as $\lambda \rightarrow 1^-$, show that it becomes the Gompertz model (2.4). Is this a valid argument? If not, where is the problem?

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