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Unique estimation of Gompertzian breast cancer growth rate parameter

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Abstract

Finding formulas to predict the growth of tumors has been of interest since the early days of cancer research. Many models have been proposed, but there is still no consensus about the growth patterns that solid tumors exhibit. This is an important problem because an accurate model of tumor growth is needed for evaluating screening strategies, optimizing radiation treatment protocols, and making decisions about patient treatment. The pattern of growth of human breast cancer is important theoretically and clinically. In this paper we estimate the growth rate parameter of Gompertz breast cancer growth model and prove the uniqueness theorem.

Keywords Gompertz model, breast cancer, tumour growth rate, estimation, uniqueness.

Introduction

Breast cancer is cancer that develops from breast tissue. It is a cancer that forms in the cells of the breasts. Breast cancer can occur in women and rarely in men. Breast cancer is the second most common cancer in women after skin cancer. Breast cancer, like other cancers, occurs because of an interaction between an environmental (external) factor and a genetically susceptible host. Normal cells divide as many times as needed and stop. They attach to other cells and stay in place in tissues. Cells become cancerous when they lose their ability to stop dividing, to attach to other cells, to stay where they belong, and to die at the proper time.

The pattern of growth of human breast cancers is clinically important, specifically for estimating the duration of pre-diagnosis silent growth and for the design of an optimal post-surgery chemotherapeutic schedule. The theoretical study of breast cancer growth patterns has been the subject of considerable debates and controversy among mathematical oncologists for over two

decades.In 1984, Speer et al. proposed a stochastic numerical model of breast cancer growth wherein all individual tumors are assumed to grow with identical Gompertzian parameters but subsequently develop kinetic heterogeneity by random time-dependent processes [4].

Speer et al. estimated that the average time for the tumor burden to increase from 1 cell to detection was on average 8 years. Their model also derived quantitative relationships between the likelihood of remission versus number of years after mastectomy, and the number of metastatic sites versus number of positive nodes in an in silico cancer-positive cohort. This approach to modeling breast cancer growth kinetics allows for the generation of individual growth curves, rather than averaged, population-based cancer growth dynamics.

In contrast to the Speer et al. model, Norton et al. demonstrated in 1988 that the deterministic Gompertz equation provided the best fit when used to relate clinical breast cancer tumor sizes and rates of regression post-therapy [2]. Norton generated a hypothetical survival curve fitting the classical Gompertzian growth model to the percentage of surviving patients per year after diagnosis. He estimated the probability distribution function of the growth decay parameter to be log-normal and dependent on the current number of tumor cells, in contrast to the stochastic nature of the equivalent parameter used by Speer et al [3,4]. While the model proposed by Norton fits clinical data on untreated breast cancer, it is unclear whether Gompertzian kinetics (or a variant of it) also applies to the disease progression during or post therapy.

Estimation of parameters

An exact mathematical description of our model of breast cancer cell proliferation is given by

$$N(t) = N_0 e^{\frac{a}{b}(1-e^{-bt})} \qquad (1)$$

where $N_(t)$ is the cell number at time t; N_0 is the starting size at time $t = 0$. a and $b(> 0)$ are the Gompertz growth parameters. The Gompertz model presents a doubling time which depends only on b. Solving equation ([two]) for cells rate doubling gives

$$CRD = -\frac{1}{b} ln \left[1 - \frac{b}{a} ln 2\right]. \qquad (2)$$

Benjamin Gompertz (1825) [1] proposed that the growth of tumour volume increased exponentially with time for all tumours. Various subsequent researchers, especially in biology and gerontology, have viewed Gompertz observation as a law that describes the process of senescence in almost all type of tumours at any time after the onset of growth. As a rough approximation at initial growth, Gompertz exponential formula does capture the rise in growth in a great variety of tumours. Equation (1) gives

$$\frac{a}{b} = \frac{ln[N^*(t)]}{(1-e^{-bt})} \qquad (3)$$

where $N^*(t) = \frac{N(t)}{N_0}$ and

$$N(t_i) = N_0 e^{\frac{a}{b}(1-e^{-bt_i})} \qquad (4)$$

(where t_i is the time at which tumor size had reached a lethal tumor size N_i at some time less than or equal to t). After a few algebraic manipulations we get

$$t_i = -\frac{1}{b} ln \left[1 - \frac{b}{a} ln \left[\frac{N(t_i)}{N_0}\right]\right]. \qquad (5)$$

The cumulative tumour size of the Gompertz model equation (1) is given by

$$N_c = \int_0^{\infty} N^*(t)dt. \qquad (6)$$

Finally the eatimation for b is given by

$$-b = \frac{1}{N_c} e^{-\frac{a}{b}} \int_{-\frac{a}{b}}^{\infty} \frac{e^{-y}}{y} dy, \qquad (7)$$

where $y = -\frac{a}{b} e^{-bt}$ In this article we estimate b, as it is the key parameter to calculate the rate doubling time or half - life ($t_{\frac{1}{2}} = \frac{ln2}{b}$).

Existence of the parameter

The integral in the equation (7) exists if $b < 0$. If $b > 0$, then $\frac{e^{-y}}{y}$ has a pole at $y = 0$. Hence we take the principal value of the integral and prove its existence.

Principal value of the integral $\int_{-\frac{a}{b}}^{\infty} \frac{e^{-y}}{y} dy$ exists, if $b > 0$.

Proof: Now,

$$\int_{-\frac{a}{b}}^{\infty} \frac{e^{-y}}{y} dy = \int_{-\frac{a}{b}}^{-\epsilon} \frac{e^{-y}}{y} dy + \int_{-\epsilon}^{\epsilon} \frac{e^{-y}}{y} dy + \int_{\epsilon}^{\infty} \frac{e^{-y}}{y} dy.$$

Consider the middle term on the right hand side of the above integral

$$\begin{aligned} \lim_{\epsilon \to 0} \int_{-\epsilon}^{\epsilon} \frac{e^{-y}}{y} dy &= \lim_{\epsilon \to 0} \left[\int_{-\epsilon}^{0} \frac{e^{-y}}{y} dy + \int_{0}^{\epsilon} \frac{e^{-y}}{y} dy \right] \\ &= \lim_{\epsilon \to 0} \left[-\int_{0}^{\epsilon} \frac{e^{-y}}{y} dy + \int_{0}^{\epsilon} \frac{e^{-y}}{y} dy \right] \\ &= 0 \end{aligned}$$

Hence the principal value of the above integral exists, if $b > 0$. The basic equation (7) is transcendental, involving an exponential integral. Hence, its solution may not be unique and so it is necessary to prove the uniqueness of b.

Uniqueness of the parameter

3.1 Uniqueness theorem

Note:

It may be observed that $\frac{1}{N_c}$ cannot exceed a, as $\frac{1}{N_c}$ represents contributions from a and b.

Proof:

$$-b = \frac{1}{N_c} e^{-\frac{a}{b}} \int_{-\frac{a}{b}}^{\infty} \frac{e^{-y}}{y} dy$$

$$-b \leq \frac{1}{N_c} e^{-\frac{a}{b}} e^{\frac{a}{b}} (-\frac{b}{a})$$

which implies that $\frac{1}{N_c} \leq a$.

The equation (7) has a unique solution if $\frac{2t_i}{N_c} < 1$ for $b > 0$.

Proof:
Let b_1 and b_2 be two distinct positive solutions of (7). Then

$$-b_1 = \frac{1}{N_c} e^{-\frac{a}{b_1}} \int_{-\frac{a}{b_1}}^{\infty} \frac{e^{-y}}{y} dy$$

$$-b_2 = \frac{1}{N_c} e^{-\frac{a}{b_2}} \int_{-\frac{a}{b_2}}^{\infty} \frac{e^{-y}}{y} dy$$

Using (3) we have

$$-b_1 = \frac{1}{N_c} e^{-\frac{lnN^*(t)}{(1-e^{-b_1 t_i})}} \int_{-\frac{lnN^*(t)}{(1-e^{-b_1 t_i})}}^{\infty} \frac{e^{-y}}{y} dy$$

$$-b_2 = \frac{1}{N_c} e^{-\frac{lnN^*(t)}{(1-e^{-b_2 t_i})}} \int_{-\frac{lnN^*(t)}{(1-e^{-b_2 t_i})}}^{\infty} \frac{e^{-y}}{y} dy$$

Now

$$\begin{aligned} b_1 - b_2 &= -\frac{1}{N_c}\left[\int_{z_1}^{\infty} \frac{e^{-y+z_1}}{y} dy - \int_{z_2}^{\infty} \frac{e^{-y+z_2}}{y} dy\right] \\ &= -\frac{1}{N_c}\int_0^{\infty} e^{-w}\left[\frac{1}{w+z_1} - \frac{1}{w+z_2}\right] dw \end{aligned} \quad (8)$$

where $z_j = -\frac{lnN^*(t)}{(1-e^{-b_j t_i})}$ for $j = 1,2$ and $w = (y - z_j)$ for $j = 1,2$. Also, $e^{-w} \geq 1, \forall w \leq 0$. Hence we obtain

$$\begin{aligned} |b_1 - b_2| &\leq \frac{1}{N_c}|z_1 - z_2| \int_0^{\infty} \frac{dw}{(w+z_1)(w+z_2)} \\ &= \frac{1}{N_c} ln\left[\frac{z_1}{z_2}\right]. \end{aligned}$$

Therefore we get

$$\begin{aligned} |b_1 - b_2| &\leq \frac{1}{N_c}|ln\left[\frac{1-e^{-b_2 t_i}}{1-e^{-b_1 t_i}}\right]| \\ &= \frac{1}{N_c}|ln|\left[\frac{e^{-b_2 t_i}(e^{-b_2 t_i}-1)}{e^{-b_1 t_i}(e^{-b_1 t_i}-1)}\right]| \\ &= \frac{1}{N_c}\left|ln\left[\frac{e^{-b_2 t_i}}{e^{-b_1 t_i}}\right] + ln\left[\frac{e^{-b_2 t_i}-1}{e^{-b_1 t_i}-1}\right]\right| \\ &= \frac{1}{N_c}|[b_1 t_i - b_2 t_i] + ln[e^{b_2 t_i}-1] - ln[e^{b_1 t_i}-1]|. \end{aligned}$$

Applying mean value theorem, we obtain

$$\begin{aligned} |b_1 - b_2| &= \frac{1}{N_c}[|b_1 t_i - b_2 t_i| + ln|e^{-b_2 t_i} - e^{-b_1 t_i}|] \\ &= \frac{1}{N_c}[|b_1 - b_2| t_i + |b_1 - b_2| t_i] \\ &= \frac{2t_i}{N_c}|b_1 - b_2|. \end{aligned}$$

which gives

$$\left(\frac{2t_i}{N_c} - 1\right)|b_1 - b_2| \geq 0.$$

But $\frac{2t_i}{N_c} < 1$. Hence the above inequality implies that $b_1 \equiv b_2$, for $b > 0$.

3.2 Necessary Condition for Uniqueness

The necessary condition to have a unique solution for equation (7) is that $\frac{t_i}{N_c ln[N^*(t)]} < 1$ for $b > 0$.

Proof:
Let b_1 and b_2 be two distinct positive solutions of ([fi]). Then from ([sev]) we have

$$\begin{aligned} b_1 - b_2 &= -\frac{1}{N_c}(z_2 - z_1)\int_0^\infty \frac{e^{-w}}{(w + z_1)(w + z_2)}dw \\ &= -\frac{1}{N_c}\left(\frac{1}{1 - e^{-b_2 t_i}} - \frac{1}{1 - e^{-b_1 t_i}}\right)(1 - e^{-c_1 t_m})(1 - e^{-c_2 t_m}) \\ &\times \int_0^\infty \frac{e^{-y ln[N^*(t)]}}{(1 + y(1 - e^{-b_1 t_i}))(1 + y(1 - e^{-b_2 t_i}))}dy. \end{aligned}$$

Since

$$\frac{e^{-y ln[N^*(t)]}}{(1 + y(1 - e^{-b_1 t_i}))(1 + y(1 - e^{-b_2 t_i}))} \leq 1,$$

we get

$$\begin{aligned} b_1 - b_2 &\leq -\frac{1}{N_c}\left(\frac{1}{1 - e^{-b_2 t_i}} - \frac{1}{1 - e^{-b_1 t_i}}\right)(1 - e^{-b_1 t_i})(1 - e^{-b_2 t_i})\int_0^\infty e^{-y ln[N^*(t)]}\, dy \\ &= -\frac{1}{N_c}\left(\frac{1}{1 - e^{-b_2 t_i}} - \frac{1}{1 - e^{-b_1 t_i}}\right)(1 - e^{-b_1 t_i})(1 - e^{-b_2 t_i})\frac{1}{ln[N^*(t)]}. \end{aligned}$$

Hence,

$$|b_1 - b_2| \leq \frac{1}{N_c ln[N^*(t)]} |(1 - e^{-b_1 t_i}) - (1 - e^{-b_2 t_i})|$$
$$= \frac{1}{N_c ln[N^*(t)]} \left| (b_1 t_i) \frac{(1 - e^{-b_1 t_i})}{b_1 t_i} - (b_2 t_i) \frac{(1 - e^{-b_2 t_i})}{b_2 t_i} \right|$$
$$= \frac{1}{N_c ln[N^*(t)]} \left| \frac{b_1 t_i}{\left(\frac{b_1 t_i}{1 - e^{-b_1 t_i}}\right)} - \frac{b_2 t_i}{\left(\frac{b_2 t_i}{1 - e^{-b_2 t_i}}\right)} \right|.$$

Thus

$$|b_1 - b_2| \leq \frac{t_i |b_1 - b_2|}{N_c ln[N^*(t)] max \left(\frac{b_1 t_i}{1 - e^{-b_1 t_i}}, \frac{b_2 t_i}{1 - e^{-b_2 t_i}}\right)}.$$

Suppose we have a unique solution of ([fi]), it follows from ([ei]) that

$$\frac{t_i}{N_c ln[N^*(t)] max \left(\frac{b_1 t_i}{1 - e^{-b_1 t_i}}, \frac{b_2 t_i}{1 - e^{-b_2 t_i}}\right)} < 1.$$

Since $\frac{bt_i}{1 - e^{-bt_i}} \geq 1, \forall bt_i \geq 0$, from ([ni]) we get

$$\frac{t_i}{N_c ln[N^*(t)]} < min \left(\frac{b_1 t_i}{1 - e^{-b_1 t_i}}, \frac{b_2 t_i}{1 - e^{-b_2 t_i}}\right) < max \left(\frac{b_1 t_i}{1 - e^{-b_1 t_i}}, \frac{b_2 t_i}{1 - e^{-b_2 t_i}}\right)$$
$$1 \leq min \left(\frac{b_1 t_i}{1 - e^{-b_1 t_i}}, \frac{b_2 t_i}{1 - e^{-b_2 t_i}}\right) \leq max \left(\frac{b_1 t_i}{1 - e^{-b_1 t_i}}, \frac{b_2 t_i}{1 - e^{-b_2 t_i}}\right)$$

Note that $\frac{bt_i}{1 - e^{-bt_i}}$ attains 1 only if $bt_i = 0$. Hence the above inequalities implies that $\frac{t_i}{N_c ln[N^*(t)]} < 1$ for $b > 0$. Thus, to have a unique solution of equation (7) it is necessary that $\frac{t_i}{N_c ln[N^*(t)]} < 1$ for $b > 0$.

Remark: From theorem 5.1, the condition of unique b does not depend on $N^*(t)$, but from theorem 5.2 the necessary condition for unique b depends on $N^*(t)$. Hence theorem 5.2 is more useful than theorem 5.1.

Conclusion

The purpose of this discussion is to provide an unique estimation for the parameter in terms of Gompertz growth rate model. This estimation method is necessary when attempting to estimate the growth rate in a Gompertzian breast cancer growth rate model, at their maximum lifespan. The estimation formulated in this work can be used for future clinical trails. More research is needed for further applications and will be addressed in near future.

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