Glioblastoma Cell Count Approximation through Mathematical Modeling

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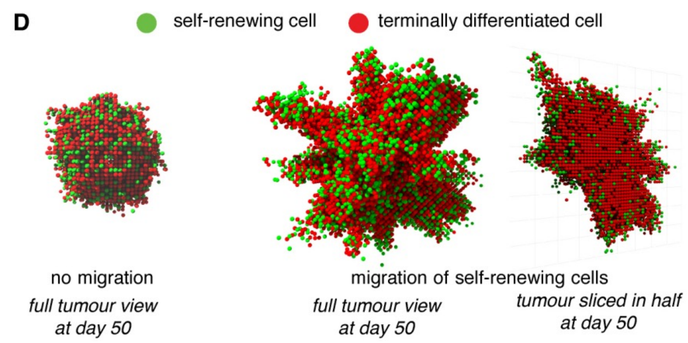
Abstract

This study develops mathematical models to predict tumor sizes in glioblastoma multiforme (GBM), a notably aggressive brain tumor. It critiques existing estimation methods and presents a new model grounded in empirical data and mathematical fundamentals. The analysis is based on three assumptions: uniform cell composition, spatial independence, and minimal external impact on growth. It outlines GBM growth phases: rapid expansion, steady progression, and eventual saturation. The models elucidate the complex dynamics of GBM growth and aim to enhance tumor size prediction in clinical settings. Future work will focus on refining these models to determine optimal surgery timing for GBM patients.

Background

- Glioblastomas consit of glial cells with an average size of 12 to 14 μm. The average final, or fatal, volume of a glioblastoma in vivo is 160 mL, approximately 7.2% of the total brain volume, which is about 2200 mL. This fatal size translates to approximately 7.28 x 10^11 cells, while the average number of cells at diagnosis is 1.53 x 10^11 cells.
- At the time of diagnosis, tumors typically have a diameter of about 4 cm. Simpson et al. (1993) observed in a study of 645 patients that 38% had tumors with diameters smaller than 5 cm, 56% had tumors between 5 and 10 cm, and 6% had tumors larger than 10 cm.
- The Gompertz model, an early growth estimation model, uses the equation $V(t)=V_0 e^{K(1-e^{(-rt)})}$ to describe tumor growth. Here, $V(t)$ is the tumor volume at time t, V_0 is the initial volume, and K is the natural logarithm of the ratio of maximum tumor volume to the initial volume. The parameter r has no direct biological meaning; accordingly, the saturation point estimated by the Gompertz model cannot be used practically, especially for forecasting.

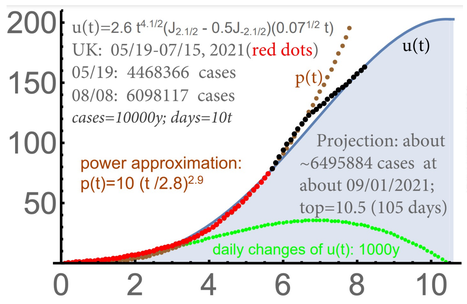


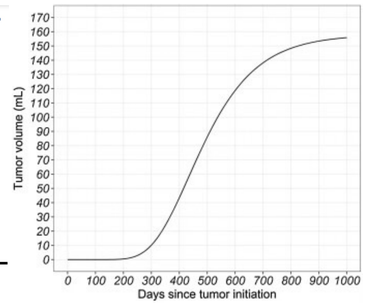
How Tumors Grow

1. The tumor initially grows from a single cell in a near-exponential pattern, which we'll call stage 1, rapid growth.
2. After this, it transitions into a steady, linear progression, marked by symptoms like headaches, vomiting, and seizures, where it's often detected via medical imaging. This is stage 2.
3. In stage 3, or the protection stage, growth slows as the body's immune response, involving T cells and apoptosis, begins to combat the tumor.

Ultimately, the tumor reaches a "carrying capacity," a peak cell count where growth stagnates, and cell death occurs.

Modeling Cancerous Growth





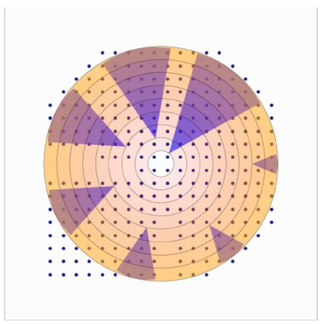
Let's start with an explanation of tumor growth. Let u_n represent the total number of cancerous cells at a given time, starting from the identification of the initial cancerous cell. We'll define n as the number of days since that point. The following equation describes the initial stage of this growth of cancerous cells over time

$$u_n = u_{n-1} + R_0 (u_{n-1} - u_{n-2}) , \ \lambda^2 = (1 + R_0) \lambda - R_0$$

Here R_0 is the average number of neighboring glial cells infected by any one glial cell. Then $\lambda_{1,2} = \frac{(1+Ra)}{2} \pm \frac{\sqrt{(1+R_0)^2}}{\sqrt{4-R_0}} = \{1, R_0\}$, and $u_n = C_1 + C_2 (R_0)^n$ for some $C_{1,2}$. If $C_2 \neq 0$ and $R_0 > 1$, the growth of the total number of cancerous cells will be exponential.

To ensure non-exponential growth at later stages R must approach 1, which is the resonance condition. However, R ≈ 1 leads to unstable linear growth, making it theoretically inadequate; long periods of linear growth are well-recognized in oncology. The key factor reducing the spread of cancerous cells is the presence of T cells or another immune response, which we will address as follows.

Basically, the spread of cancer is modeled as growing "combinatorial circles" of infected tissue in time; their growth is linear in this figure. These circles are conceptual rather than geometric. Immunity and treatment eliminates some clusters of cells, which prevents further growth of cells in the corresponding directions (sectors in the figure), akin to pruning a tree. Constant pruning inevitably stops the growth.



Generally, the circle of infected cells can be modeled as a ball with dimension c, where the number of cancerous cells u_n is proportional to n^c. The value of c varies: it may be around 2 for tumors in areas like the cerebrospinal fluid with non-interactive neighbors, but typically exceeds 2 for glioblastomas in the brain, given their spatial independence. Here, c is expected to be quite stable, unlike R, which fluctuates dramatically. The expectations are that c and a (below) can be reliably determined before the turning point. There is strong similarity of our curves with those modeling Covid-19 and similar processes in invasion ecology. We provide a sample curve (due to Ivan Cherednik). They are different from those of Gompertz-type and their parameters are very much meaningful biologically.

Bessel Function

The number of newly infected cells is mostly near the surface area of this ball. We present their number as $c \frac{u_{n-1}}{(n-1)}$ and arrive at $u_n - u_{n-1} = c \frac{u_{n-1}}{(n-1)}$. Next, we need to add our immunity response, natural or boosted by some treatment, chemotherapy, etc. The equation becomes a predator-pray model from invasion ecology. Switching to differential equations:

$$\frac{du(t)}{dt} = c\frac{u(t)}{t} - p(t), \ \frac{dp(t)}{dt} = a * u(t)$$

Here t is the time from the first infection, c is the tumor growth rate percentage, a is the intensity of the immunity, treatment and other protective mechanisms, represented (totally) by p(t). When a = 0 (no active protection), we obtain the power growth: $u(t) \sim Ct^c$. These parameters can be measured experimentally, presumably before the turning point. Any solution of the system above can be obtained as a linear combination of two basic solutions $u^1(t)$ and $u^2(t)$:

$$u^{1,2}(t) = t^{(c+1)/2} J_{\pm\frac{c-1}{2}}(\sqrt{a}t), \ J_a(x) = \sum_{m=0}^{\infty} \frac{(-1)^m (\frac{x}{2})^{2m+a}}{m!\,\Gamma(m+a+1)}$$

Bessel functions of the first kind, $J_a(x)$, are new in modeling the growth of cancerous cells. In this framework, $u^1(t)$, which includes a positive sign, is the primary solution reflecting tumor growth, while $u^2(t)$ is typically smaller and less significant. For our specific in vivo model, constants c and a are set to specific values. In contrast to the Gompertz model, where the parameters are frivolous, they have obvious biological-clinical meaning and can be used for forecasting.

The important property of Bessel-type formulas for tumor growth is that the saturation, the first maximum of u(t), is directly related to a (the intensity of our response). This is perfectly compatible with the picture of growing circles we provided. If c and a are known, we can estimate the final size of the tumor and the time before the saturation. This is of utmost importance!

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