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On the Application of Mathematical Models in Tumor Growth and Treatment

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Abstract

Mathematical models have been employed for a significant period to replicate dynamic biological processes. In more recent years, quantitative methods have gained widespread use in cancer research. Over the past century, modelers have characterized and examined tumor growth kinetics, resulting in a diverse range of models that encompass simple empirical ones as well as complex functional models considering cell cycle kinetics, cell-cell interactions, cell age distribution, and microenvironmental factors. Nonetheless, these models are seldom verified with experimental tumor growth data due to limited suitable data availability. Increasingly, techniques from mathematics, physics, computational science, and engineering are being utilized to comprehend how cancer populations react to clinical treatments. This article delves into the essential principles of mathematical modeling in tumor growth and tumor-host interactions while emphasizing crucial approaches vital for cancer research.

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1. Introduction

Mathematical modeling is a powerful tool to test hypotheses, confirm experiments, and simulate the dynamics of complex systems[1]. In addition to helping understand the mechanistic underpinnings of dynamical systems, mathematical models simulate complex systems relatively quickly without the enormous costs of laboratory experiments and the corresponding biological variations[2]. For oncology, in particular, such models can be calibrated using experimental or clinical data[3] and competing hypotheses of tumor progression can be evaluated and treatment options thoroughly analyzed before clinical intervention[4-6]. Techniques for quantitative modeling are plentiful, and many theoretical approaches are successfully applied to cancer biology[7]. Differential equation models and individual-based cell models paved the way into quantitative cancer biology about two decades ago[8]. In this paper, we will outline the process of developing these models and discuss their important use in simulating both tumor growth and its response to treatment. Furthermore, we will explore various models, evaluating their validation and predictive capabilities within the realm of cancer biology.

The process of estimating the quantity of cancer cells within a tumor poses considerable difficulties because of the ever-changing and dynamic nature of cell behavior throughout time. Tumor cells exhibit characteristics such as proliferation, entering into a quiescent state, or undergoing cellular death, making it complex to define their numerical growth pattern accurately. A deeper and more comprehensive understanding of the tumor, along with accurate prediction, can significantly aid in tackling cancer and identifying the most effective treatment approaches. Mathematical modelling, dynamic systems and differential equations can help on this treatment method[9].

2. Differential equation for modelling of tumor growth

Living systems exhibit characteristic processes related to the birth and death of cells. The fluctuations in the quantity of living cells occur through cell proliferation and mortality, resulting in a net change equal to the difference between new cell births and cell deaths over a specific time

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interval. The rate of new cell proliferation and cell death is subject to the temporal variations.

For a cancerous cell with a 24-hour cycle, we can estimate that the likelihood of a new cell emerging through division in one day is very high, approaching 100%. Even without understanding the present phase of cell division, it is reasonable to estimate that within one hour, the probability of this process occurring is approximately 1/24. This concept can be applied to the entire population, even when precise information about the precise quantity of cells within a tumor population is unavailable. For an unsynchronized cell population with a 24-hour cell cycle length, it can be presumed that all cells divide once during this time interval. Likewise, if the time interval (*dt*) is set at 1 hour, it can be expected that only about $1/24^{th}$ of the cells within the population will divide. Therefore, if $N(t)$ denotes the cell population and $\frac{dN(t)}{dt}$ represents the change in $N(t)$ as t increases:

$$\frac{dN(t)}{dt} = b\,N(t) - d\,N(t) \tag{2.1}$$

Here, *b* is the function of newly form cell, which is called the rate of birth, and *d*, the function of dying cells, known as the rate of death. Here, the quantity $N(t)$ rises as new cells are generated while simultaneously other cells perish. Consequently, there is an anticipated increase in cell count after a proliferative event and a decrease following instances of cell death. The mathematical expression presented as eqn. (2.1) is commonly known as an Ordinary Differential Equation (ODE).

Initially when *t* = 0, suppose we start with one million cells, denoted as $N(0) = 10^6$. The dynamics of population growth can lead to only one of the possible results:

(a) When the rate of births is equivalent to the rate of deaths i.e. *b* = *d*, then $\frac{dN(t)}{dt} = 0$. In this situation, the population size remains constant and the tumor enters a dormancy state. The dormancy state of a tumor is significantly influential in determining the progression and treatment of cancer. During dormancy, the tumor cells remain inactive, marked by minimal division activity. This can make the tumor less sensitive to traditional cancer treatments, such as chemotherapy, which often target proliferative cells. On the other hand, when $b = d > 0$, we can say that the cell proliferation is balanced by cell death[10,11].

(b) If the birth rate is greater than the death rate, then $\frac{dN(t)}{dt} > 0$ and the cellular population is steadily increasing, with the higher rates of $b - d$ resulting in faster growth. Several factors, such as nutrient availability and environmental conditions, influence the growth rate of the cell population and genetic makeup of the cells. In a favorable environment, where nutrients are abundant and the conditions are optimal, the cells will multiply at a faster rate.

(c) On the contrary, if the birth rate is lower than the death rate i.e. $\frac{dN(t)}{dt} < 0$ the population will steadily decline. In such a scenario, with the birth rate being lower than the death rate, the population will continue to decrease over time.

However, combining the terms $b\,N(t) - d\,N(t)$ simplifies eqn. (2.1) into a single-parameter problem into the unified term $(b-d)N(t)$, and by introducing a function, $r = b - d$, which represents the net population growth rate and proves pivotal in overseeing the regulation of cell population expansion. This function is closely linked to factors like nutrient accessibility and available space. Consequently, differential equation that characterizes variation in cell population over time is simplified to:

$$\dot{N}(t) = r\,N(t) \tag{2.2}$$

Then, if the rate $r(t)$ is less than zero, the population experiences a decrease; but when $r(t) = 0$, the population is a constant, or $r(t) > 0$, the population increases respectively. As *r* assumes values greater than 0, less than 0, or equal to 0, the population experiences an increase, decrease, or remains constant, respectively.

2.1 Population Growth Law

It was observed that Solid tumors initially grow rapidly, but growth decelerates as tumors grow bigger[12-14]. Since access to nutrients and space availability control the cell proliferation and death, the coefficients $b(t)$ and $d(t)$ is taken as nonlinear function of $N(t)$ leading to a self-contained equation[13]. For this purpose, we take into account the non-linear $N : R$ function. This is commonly referred to as the bulk growth rate and eqn. (2.2) transforms accordingly:

$$\dot{N}(t) = R(N(t))N(t) \tag{2.3}$$

If *r* represents the natural birth rate in environments with abundant space and nutrients, then *R* needs to satisfy one of two conditions:

1) When $\lim_{N\to\infty} R(N) = 0$, we must have $R(0) = r$ which is positive; provided $R'(\cdot)$ is negative.

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2) But when $R(0) = r$ which is positive; provided $R'(\cdot)$ is negative and $R(K) = 0$. Here, K represents the carrying capacity, which signifies the maximum size a tumor would reach without treatment, ultimately leading to mortality. This concept is pivotal for comprehending the dynamics and forecasting population growth patterns.

Both scenarios indicate that $R'(\cdot)$ is negative, signifying that R is a decreasing function.

2.2 Verhulst equation

If t_2 represents the tumor doubling time, eqn. (2.2) can be represented as:

$$\frac{dN(t)}{dt} = g_e N(t) \quad \text{where} \quad N(0) = N_0 \tag{2.4}$$

where N_0 represents the initial cell population, which is used to model growth over time t, and $g_e = \frac{\ln 2}{t_2}$ denotes the constant rate of tumor development.

An example of the rate of tumor growth dependent on tumor size relative to the host carrying capacity K is given by the logistic model[12]:

$$\dot{N} = rN\left(1 - \frac{N}{K}\right) \tag{2.5}$$

Here, the non-constant growth rate denoted by r, is associated with logistic growth and can be adjusted to reflect the growth rate in the exponential scenario at population size N_0 using the relation:

$$r = g_e\left(1 - \frac{N_0}{K}\right)^{-1}$$

From eqn. (2.5), we see that when the tumor size c is significantly smaller than the carrying capacity K, then $\left(1 - \frac{N}{K}\right) \approx 1$ such that the population growth, as described by equation (2.4), appears to be almost exponential. As the population nears the carrying capacity K, it is evident that further growth will be limited and eventually cease when $\left(1 - \frac{N}{K}\right) \to 0$.

From eqns. (2.3) and (2.5), we can express Verhulst equation as[14]:

$$R(N) = r\left(1 - \frac{N}{K}\right); \qquad K > 0 \tag{2.6}$$

Verhulst introduced the logistic model, proposing that the population growth rate is not constant but diminishes as the population size nears its maximum capacity, K. The parameter r defines the growth rate and the Verhulst equation can be extended as follows[5]:

$$R(N) = r\left[1 - \left(\frac{N}{K}\right)^a\right] \qquad a > 0, \quad K > 0 \tag{2.7}$$

2.3 Gompertz Equation

Various researchers had studied the numerous dynamic growth rate functions with the potential application with reference to the tumor growth[13,15]. The Gompertz curve[16] has been shown to reproduce biological growth that decelerates with population size[17] and is therefore applicable to observed tumor growth slowdown with tumor size[10,11,18]. The growth rate is determined by taking the negative logarithm of the current population size divided by the carrying capacity, serving as a significant indicator of population dynamics[18]:

$$\dot{N} = bN \log\left(\frac{K}{N}\right) \tag{2.8}$$

where the rate of growth is adjusted by a factor $b = g_l \ln\left(\frac{K}{N_0}\right)^{-1}$. Gompertz's concept was that the growth rate ought to diminish exponentially over time in order to accurately describe the entire growth curve. Here, it is clear that $\lim_{N\to\infty} R(N) = 0$ which means if the cell population is decreasing, the growth rate becomes unbounded. The rate of growth is constrained by the duration of the entire cell cycle, indicating a positive assumption for a large number of cells.

Proposition 1. *Gompertz law represents the asymptotic condition of the logistic power law when* $a \to 0$ *and* $b = ra$.

Proof. Initially, by replacing $b = ra$ in $b\log\left(\frac{K}{N}\right)$. As both functions N and K become equal, they are both equal to 0. Hence, we assume that they are not equal such that,

$$\lim_{a\to 0} \frac{1 - \left(\frac{N}{K}\right)^a}{a \log\left(\frac{K}{N}\right)}$$

which is indeterminate and since the two functions are both differentiable functions, L'Hôpital rule can be applied. Then:

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$$\lim_{a\to 0}\frac{\left(-\frac{N}{K}\right)^{a}\log\left(\frac{N}{K}\right)}{\log\left(\frac{K}{N}\right)}=1$$

Proposition 2. *When* $R(N)=bN^{-a}$, $a=\frac{1}{3}$ *in eqn. (2.3), the solution corresponds to the linear expansion of the radius, specifically* $N(T)\approx \bar{r}\,t^3$, *where* $\bar{r}=\frac{1}{3}b$ *as t approaches infinity, and* $t_0=0$.

Proof. Assuming that $R(N)=bN^{-a}$, we have

$$\frac{dN}{dt}=NbN^{-a}$$

$$\Rightarrow \quad N^{a-1}.dN=b.dt$$

Integrating, we get

$$\Rightarrow \quad \int_{N_0}^{N} N^{a-1}dN=\int_{0}^{t} bdt$$

$$\Rightarrow \quad \left[N^{a}\right]_{N_0}^{N}=a\times bt$$

$$\Rightarrow \quad N=\left(abt+N_0^{a}\right)^{1/a}$$

We assume that $a=\frac{1}{3}$, which gives

$$\lim_{t\to\infty} N(t)\approx \frac{1}{3}bt^3=\bar{r}\,t^3$$

Theorem 1. *Consider a continuous function* $h: I\to \mathbf{R}$ *within the interval I and the differential equation* $\frac{dN}{dt}=h(N)$. *Assuming that a set of isolated zeros of h is distinct and for each zero* z_0, *given that* $\int_{N_0}^{N} h^{-1}(N)dN$ *is divergent (z in proximity to* z_0*); then, the required solution for* $\frac{dN}{dt}=h(N)$ *corresponding to the initial condition* (t_0,N_0), *there exists a unique solution.*

Proof. If *N* is not a point of singularity such that $h(N)\neq 0$. We have,

$$\frac{dN}{dt}=h(N)$$

$$\Rightarrow \quad h^{-1}(N)dN=dt$$

Integrating, we get

$$\int_{N_0}^{N} h^{-1}(N)dN=\int_{t_0}^{t} dt$$

$$\Rightarrow \quad \int_{N_0}^{N} h^{-1}(N).dN=t-t_0$$

$$\Rightarrow \quad \left[H\right]_{N_0}^{N}=t-t_0$$

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Here, H is the antiderivative of $\frac{1}{h(N)}$. It can be inferred that $N = t - t_0$, H^{-1} exists as $\frac{1}{h} \neq 0$ and this shows that $H^{-1} \neq 0$ and thus H is a monotonic function. Consequently, the function $N(t)$ exists. For any value of N_0, the integral will be convergent, which implies that $\int_{N_0}^{N} \frac{dN}{h(N)}$, representing the time it takes for N_0 to reach N, is finite.

3. Mathematical Model for Cytotoxic and Cytostatic drugs

A tumor originates from mutated cells that undergo rapid proliferation, surpassing the normal growth rate of cells. But, not all tumor cells exhibit the same growth pattern and it is necessary to differentiate between at least two types of cells: those that proliferate (growing rapidly) and those that are quiescent (either growing slowly or in a dormant state). If they did, a 24-hour cell cycle would lead to the formation of a tumor comprising a million cells in a month, resulting in an unmanageable size of 10 cm. Therefore, it is essential to differentiate between these distinct cell types within the tumor.

Let $F(P)$ describes the proliferative cells growth. Within a tumor, there exists a layer of quiescent cells, speculated in transitioning into proliferating cells upon nutrient deprivation. Likewise, quiescent cells undergo death after an extended period of nutrient deficiency, denoted by the term $-dQ$ representing the death rate. Additionally, quiescent cells can transition back to proliferating state as $(bP - cQ)$ where bP represents the transitioning to quiescence and $-cQ$ denotes transitioning back to a proliferative state. The same dynamics apply to proliferative cells necessitating addition of $(-bP + cQ)$ in the equation representing evolution of proliferative cell population $\frac{dP}{dt}$.

Hence, a logistic model for interaction between proliferative and quiescent, expressing both would be (McAneney and O'Rourke, 2007):

$$\left.\begin{aligned} \frac{dP}{dt} &= F - bP + cQ && \text{for proliferative cells} \\ \text{and,}\quad \frac{dQ}{dt} &= bP - (c+d)Q && \text{for quiescent cells} \end{aligned}\right\} \tag{2.9}$$

such that the size of the tumor can be expressed as,

$$N = P + Q$$

Considering that proliferating cells have the most significant impact on the growth of N, numerous therapies concentrate on these cell populations through two primary strategies:

- ***Cell Transition Control:*** This strategy revolves around the regulation of cell transition. The idea is to maintain cells in a quiescent state, effectively halting their continuous growth. This is achieved through the use of cytostatic drugs, denoted as c_{stat} in our model. These drugs target specific proteins known as cyclins, which play a pivotal role in hindering the proliferation of cells.
- ***Direct Destruction of Proliferative Cells:*** Another approach involves directly targeting proliferative cells for destruction using cytotoxic drugs, referred to as c_{tox}. These treatments fall under the category of chemotherapies. This approach is commonly associated with chemotherapy, where the goal is to eliminate rapidly dividing cells. Cytotoxic drugs disrupt the cell cycle and induce cell death in actively proliferating cells.

We, now, introduce our model, which incorporates these dynamics and considerations, as:

$$\left.\begin{aligned} \frac{dP}{dt} &= F - (b + c_{stat})P + cQ - c_{tox}P, && \text{for proliferative cells} \\ \text{and,}\quad \frac{dQ}{dt} &= (b + c_{stat})P - (c+d)Q && \text{for quiescent cells} \end{aligned}\right\} \tag{2.10}$$

where $F = P.R = rP\left[\frac{K^a - |P|^a}{K^a}\right]; (c + d)r < bd$ and all r, K a, b, c and d are positive. To assist in the examination of the model, we make the assumption that:

$b_1 = b + c_{stat} + c_{tox}$ is positive.

also, $b_2 = b + c_{stat}$ is positive.

However, the results are presented in relation to eqn. (2.10).

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$$\left.\begin{aligned} &\frac{dP}{dt} = F - b_1 P + cQ, && \text{for proliferative cells} \\ \text{and,}\quad &\frac{dQ}{dt} = b_2 P - (c+d)Q && \text{for quiescent cells} \end{aligned}\right\} \tag{2.11}$$

Lemma 1. *The dynamical equation (2.5) maintains positivity i.e.* P^0 *and* Q^0 *are positive which implies that* $P(t)$ *and* $Q(t)$ *will be positive for all positive values of t.*

Proof. In this context, we find a triangle that remains invariant to demonstrate that the solutions are valid for all $t > 0$. Similarly, the objective is to determine the slope $m\ (0,\infty)$ of line $Q = L - mP$, along with the conditions for $L \in (0,\infty)$. This involves establishing the dynamics of this line, which acts as a transversal to the model, ensuring its trajectory remains within the confines of the rectangle.

In simple words, our objective is to establish criteria that enable the line's movement to remain inside the specified rectangle:

$$\left\langle \left(\frac{dP}{dt}, \frac{dQ}{dt}\right), (m,\ 1) \right\rangle < 0$$

which results in,

$$\begin{aligned} g(P) &= \left\langle \left(\frac{dP}{dt}, \frac{dQ}{dt}\right), (m,1) \right\rangle \\ &= -(c+d-cm)L + b_2 P\ -(b_1 - c - d + cm)mP\ + mF(P) \end{aligned}$$

so that,

$$g(0)\ = -[c+d-\ mc]L$$

Here,

$$-[c+d-\ mc]L < 0$$

which is true if and only if,

$$m < \frac{(c+d)L}{cL}$$

$$\Rightarrow \qquad m < 1 + \frac{d}{c}$$

Here, we see that when $d = 0$, we get the minimum for the function $1+\frac{d}{c}$ which is 1. Based on this evidence, we can deduce that $m \in (0, 1)$, we choose the most suitable option for m as 0.5.

Lemma 2. *Consider*

$$L_0 = \frac{2P_*}{c+2d}\left(-\frac{b_1}{2} + b_2 + \frac{c}{4} + \frac{d}{2} + \frac{r}{2} - \frac{r}{2}\left(\frac{P_*}{K}\right)^a\right) > 0$$

where $P_* = K\left(\frac{-b_1 + b_2 + \frac{c}{2} + d + r}{r(1+a)}\right)^{\frac{1}{a}}$. *Therefore, for all values of* $L > L_0$, *and* $P \in (0, 2L)$ *given that* $Q = \left(L - \frac{P}{2}\right)$;

$\left\langle \left(\frac{dP}{dt}, \frac{dQ}{dt}\right), \left(m, \frac{1}{2}\right) \right\rangle$ *is always negative.*

Proof. We are given that $Q = \left(L - \frac{P}{2}\right)$; such that

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$$\left\langle\left(\frac{dP}{dt},\frac{dQ}{dt}\right),\left(m,\frac{1}{2}\right)\right\rangle=\left\langle\left[F-b_1P+cQ,b_2P-(c+d)Q\right],\left(\frac{1}{2},1\right)\right\rangle$$

$$=-\left(\frac{c}{2}+d\right)L-\left[\frac{b_1}{2}-b_2-\frac{c}{4}-\frac{d}{2}-\frac{r}{2}+\frac{r}{2}\left(\frac{P}{R}\right)^a\right]P$$

Let us denote *B(P)* as the above expression. Our objective is to determine if *B* has a maximum value.

$$B'(P)=-\left[\frac{b_1}{2}-b_2-\frac{c}{4}-\frac{d}{2}-\frac{r}{2}+\frac{r}{2}\left(\frac{P}{R}\right)^a(1+a)\right]$$

For maxima or minima,

$$B'(P)=0$$

which is true if and only if,

$$P_*=K\left(\frac{-b_1+b_2+\frac{c}{2}+d+r}{r(1+a)}\right)^{\frac{1}{a}}.$$

This represents the highest maximum limit. Again,

$$B''(P)=-\left[\frac{\left(\frac{ar}{2}\left(\frac{P}{K}\right)^a\right)+\left(\frac{a^2r}{2}\left(\frac{P}{K}\right)^a\right)}{P}\right]$$

which shows that $B''(P)$ is negative i.e. $B''(P_*)$ is negative. Therefore, *B(P)* has a maxima at P_*. Now, we have

$$B(P_*)=-\left(\frac{c}{2}+d\right)L-\left[\frac{b_1}{2}-b_2-\frac{c}{4}-\frac{d}{2}-\frac{r}{2}+\frac{r}{2}\left(\frac{P}{R}\right)^a\right]P_*$$

and when $B(P_*)$ is negative,

i.e. $$B(P_*)<0\Leftrightarrow L=\frac{2P_*}{c+2d}\left(-\frac{b_1}{2}+b_2+\frac{c}{4}+\frac{d}{2}+\frac{r}{2}-\frac{r}{2}\left(\frac{P_*}{K}\right)^a\right)$$

which is clearly positive.

Lemma 3*. There is a stable equilibrium at the point (0, 0). And when* $c(r-c_{tox})+rd>(b+c_{stat}+c_{tox})d$ *, another steady state is located at*

$$(\bar{P},\bar{Q})=\left[K\left(1-\frac{(c+d)c_{tox}+(b+c_{stat})d}{r(c+d)}\right)^{\frac{1}{a}},\frac{(b+c_{stat})K}{c+d}\left(1-\frac{(c+d)c_{tox}+(b+c_{stat})d}{r(c+d)}\right)^{\frac{1}{a}}\right]$$

which lies in the first quadrant.

Proof. Here, we get a stable equilibrium only if,

$$\frac{dP}{dt}=0$$

which is possible if and only if,

$$P\left[\frac{cb_2}{c+d}+r\left(1-\frac{P}{R}\right)^a-b_1\right]=0$$

$$\Rightarrow \quad P=0 \text{ or } \bar{P}=\left[K\left(1+\frac{c(b_2-b_1)-b_1d}{r(c+d)}\right)^{\frac{1}{a}}\right]$$

and, $$\frac{dQ}{dt}=0$$

which is true if and only if,

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$$Q = \frac{b_2 P}{c+d}$$

Hence, (*0, 0*) is a point of stable equilibrium. Again, when $1 - \frac{b_1 d - c(b_2 - b_1)}{r(c+d)}$ is positive, we get the other equilibrium point $\left(\bar{P}, \frac{b_2 \bar{P}}{c+d}\right)$ which is possible if and only if,

$$b_1 d > \left[r + (b_2 - b_1)\right]c + rd$$

Lemma 4. *If the equilibrium point* (*0, 0*) *is an attracting node, then we have*

$$c(r - c_{tox}) + rd < (b + c_{stat} + c_{tox})d$$

Proof. The linear equation at the point (*0, 0*) can be expressed as,

$$\begin{bmatrix} \frac{dP}{dt} \\ \frac{dQ}{dt} \end{bmatrix} = \begin{bmatrix} r - b_1 & c \\ b_2 & -(c+d) \end{bmatrix} \begin{bmatrix} P \\ Q \end{bmatrix}$$

Therefore, the characteristic polynomial is given by $x^2 + (b_1 + c + d - r)x - (r - b_1)(c+d) - b_2 c$. Thus, the eigenvalues will be:

$$\alpha = \frac{1}{2}\left((r - b_1 - c - d) - \sqrt{(r - b_1 - c - d)^2 + 4\left[(r - b_1)(c+d) + b_2 c\right]}\right)$$

$$\beta = \frac{1}{2}\left((r - b_1 - c - d) + \sqrt{(r - b_1 - c - d)^2 + 4\left[(r - b_1)(c+d) + b_2 c\right]}\right)$$

Here, we observed that when the discriminant is positive, then the eigenvalues will be real. Now, we can examine the sign of α and β,

$$(r - b_1)(c+d) + b_2 c = cr + dr + b_2 c - b_1 c - b_1 d$$
$$= \left[r + (b_2 - b_1)\right]c + (r - b_1)d$$

Here, $\left[r + (b_2 - b_1)\right]c + (r - b_1)d$ is negative, only if

$$b_1 d > \left[r + (b_2 - b_1)\right]c + rd$$

Similarly, $\left[r + (b_2 - b_1)\right]c + (r - b_1)d$ is negative, only if

$$4\left[\left\{r + (b_2 - b_1)\right\}c + (r - b_1)d\right] < 0$$

$$\Rightarrow \quad \sqrt{(r - b_1 - c - d)^2 + 4\left[\left\{r + (b_2 - b_1)\right\}c + (r - b_1)d\right]} < |b_1 + c + d - r|$$

Again, if $\left[r + (b_2 - b_1)\right]c + (r - b_1)d$ is negative, we have

$$r < \frac{b_1 d - (b_2 - b_1)c}{(c+d)}$$

$$\therefore \quad r - b_1 - c - d = b_1 + c + d - \frac{b_1 d - (b_2 - b_1)c}{(c+d)}$$

$$= \frac{b_1(c+d) + (c+d)(c+d) - b_1 d + (b_2 - b_1)c}{(c+d)}$$

$$= \frac{(c+d)^2 + b_2 c}{(c+d)} > 0$$

As a result, it can be deduced that

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$$r-b_1-c-d>\sqrt{(r-b_1-c-d)^2+4\left[\{r+(b_2-b_1)\}c+(r-b_1)d\right]}>0$$

i.e. β is negative. Thus, if $b_1 d>\left[r+(b_2-b_1)\right]c+rd$ and both α and β will be negative, so the zero equilibrium point becomes an attractive node. This dynamic is shown in Figure 2.1.

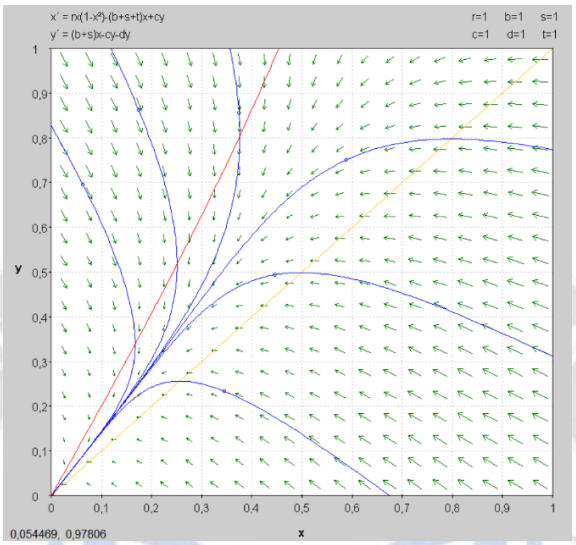

Figure 2.1 Illustration showing (*0, 0*) is an attracting node

Lemma 5. *If* $c(r-c_{tox})+rd>(b+c_{stat}+c_{tox})d$, *the zero steady state is a critical point and its equilibrium manifold is not located in the first quadrant. Additionally, the another equilibrium point* $(\bar{P},\ \bar{Q})$ *acts as an attracting node.*

Proof. In accordance with the expression in the preceding lemma, we have

$$\alpha=\frac{1}{2}\left((r-b_1-c-d)-\sqrt{(r-b_1-c-d)^2+4\left[\{r+(b_2-b_1)\}c+(r-b_1)d\right]}\right)$$

$$\beta=\frac{1}{2}\left((r-b_1-c-d)+\sqrt{(r-b_1-c-d)^2+4\left[\{r+(b_2-b_1)\}c+(r-b_1)d\right]}\right)$$

We can follow a similar approach as outlined in the preceding lemma. Here, $\{r+(b_2-b_1)\}c+(r-b_1)d$ is negative if and only if

$$b_1 d>\{r+(b_2-b_1)\}c+rd$$

Similarly, $\{r+(b_2-b_1)\}c+(r-b_1)d$ is negative, only if

$$4\left[\{r+(b_2-b_1)\}c+(r-b_1)d\right]<0$$

$$\Rightarrow \quad \sqrt{(r-b_1-c-d)^2+4\left[\{r+(b_2-b_1)\}c+(r-b_1)d\right]}<|r-b_1-c-d|$$

Then, we will consider two different scenarios:

(i) When $r-b_1-c-d$ is positive: This condition is true if and only if,

$$\sqrt{(r-b_1-c-d)^2+4\left[\{r+(b_2-b_1)\}c+(r-b_1)d\right]}>(r-b_1-c-d)$$

$$\Rightarrow \quad \beta>0$$

Here, $\alpha<0$.

(ii) When $r-b_1-c-d$ is negative: This condition is true if and only if,

$$\sqrt{(r-b_1-c-d)^2+4\left[\{r+(b_2-b_1)\}c+(r-b_1)d\right]}<(r-b_1-c-d)$$

$$\Rightarrow \quad \alpha<0$$

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Here, $\beta > 0$.

In general, if $b_1 d > \left[r + (b_2 - b_1)\right]c + rd$: when $\alpha < 0$ and $\beta > 0$; the zero equilibrium point functions as a critical point. Hence, the eigenvector of α, serving as the stable manifold (since λ is less than 0), can be characterized as:

$$\left[\frac{r - b_1 - c - d - \sqrt{(r - b_1 - c - d)^2 + 4\left[\{r + (b_2 - b_1)\}c + (r - b_1)d\right]}}{2b_2}\right], 1 = (u, v)$$

The negativity of *u* indicates that the eigenvector is not located in the first quadrant.

$$u = \frac{r - b_1 - c - d - \sqrt{b_1^2 - 2b_1c + 4b_2c - 2b_1d - 2b_1r + c^2 + d^2 + r^2 + 2cd + 2cr + 2dr}}{2b_2}$$

$$= \frac{(-b_1 + c + d + r) - \sqrt{4b_2c + b_1^2 - 2(c + d + r)b_1 + (c + d + r)^2}}{2b_2}$$

$$= \frac{(-b_1 + c + d + r) - \sqrt{4b_2c + (-b_1 + c + d + r)^2}}{2b_2}$$

Here, we can see that $(r - b_1 - c - d) < \sqrt{4b_2c + (-b_1 + c + d + r)}$, which means that the above expression is negative. Now, it will become evident that the non-zero equilibrium point functions as an attracting node if $b_1 d > \left[r + (b_2 - b_1)\right]c + rd$. The equation can be linearized with respect to $(\bar{P}, \bar{Q})$ as follows:

$$\begin{bmatrix} \frac{dP}{dt} \\ \frac{dQ}{dt} \end{bmatrix} = \begin{bmatrix} \left(\frac{1+a}{c+d}\right)\{b_1(d+c) - b_2c\} - ar - b_1 & c \\ b_2 & -(c+d) \end{bmatrix} \begin{bmatrix} P & -\bar{P} \\ Q & -\bar{Q} \end{bmatrix}$$

$$\Rightarrow \quad \begin{bmatrix} \frac{dP}{dt} \\ \frac{dQ}{dt} \end{bmatrix} = M \begin{bmatrix} P & -\bar{P} \\ Q & -\bar{Q} \end{bmatrix}$$

Now, let us denote that:

$$tr\ M = \left(\frac{1+a}{c+d}\right)\{b_1(d+c) - b_2c\} - (ar + b_1 + c + d)$$

and,
$$det\ M = -\left[\left(\frac{1+a}{c+d}\right)\{b_1(d+c) - b_2c\} - ar - b_1\right](c+d) - cb_2$$

$$= a\left[r(c+d) + b_2c - b_1(c+d)\right]$$

The characteristic polynomial associated with *M* is:

$$x^2 - (tr\ M)x + det\ M$$

Therefore, the eigenvalues can be written as,

$$\lambda = \frac{tr\ M + \sqrt{(tr\ M)^2 - 4det\ M}}{2}$$

and,
$$\mu = \frac{tr\ M - \sqrt{(tr\ M)^2 - 4det\ M}}{2}$$

Here, the eigenvalues are real because since the discriminant will always be positive. In addition, *det M* wil take on positive value if and only if,

$$det\ M > a\left[r(c+d) + b_2c - b_1(c+d)\right] > 0$$

$$\Rightarrow \quad b_1 d > \left[r + (b_2 - b_1)\right]c + rd$$

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Again, when *det M* is positive, we should have

$$\sqrt{(tr\ M)^2 - 4\ det\ M} < |tr\ M|$$

Moreover, it is essential that when $b_1 d > \left[r + (b_2 - b_1)\right]c + rd$, the value of *tr M* should be negative. In addition, *det M* will be positive and we have

$$tr\ M = \left(\frac{1+a}{c+d}\right)\{b_1(d+c) - b_2 c\} - (ar + b_1 + c + d) < -\left(\frac{cb}{c+d} + c + d\right)$$

which is clearly negative. Thus, $\sqrt{(tr\ M)^2 - 4\ det\ M} < |tr\ M| < \lambda$ which is negative. Similarly, since *tr M* is negative, $-\sqrt{(tr\ M)^2 - 4\ det\ M}$ should also be negative i.e. μ is also negative.

Additionally, if $b_1 d > \left[r + (b_2 - b_1)\right]c + rd$, λ and μ should be negative, which implies that the non-zero stable point is an attracting node. The dynamics of the system is illustrated in Figure. 2.2.

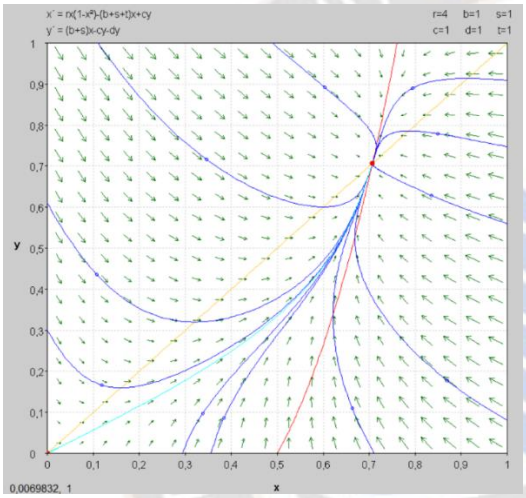

Figure 2.2 $c(r - c_{tox}) + rd > (b + c_{stat} + c_{tox})d$.

Observation 1. *The transformation of non-zero equilibrium states into zero equilibrium states occurs when* $(b + c_{stat} + c_{tox})d = (r - cc_{tox})c + rd$. *Additionally, when* $\lambda = 0$ *and* $\mu < 0$, *the equilibrium state loses its hyperbolic property. This emphasizes the significance of parameter values in influencing the behavior and stability of the system. The dynamic behavior of the system under different parameter conditions is illustrated in Figures 2.3.*

Figures 2.1, 2.2, and 2.3 illustrate the transition between different parameter states and showcase the behavior in each situation; equilibrium points are denoted by red dots, trajectories are shown with blue lines, green arrows indicate tangents to the trajectories, while red and orange signify nullclines. It is clear that the system's behavior is highly sensitive to the parametric values and from these figures, it is evident that periodic orbits cannot exist based on the nullclines.

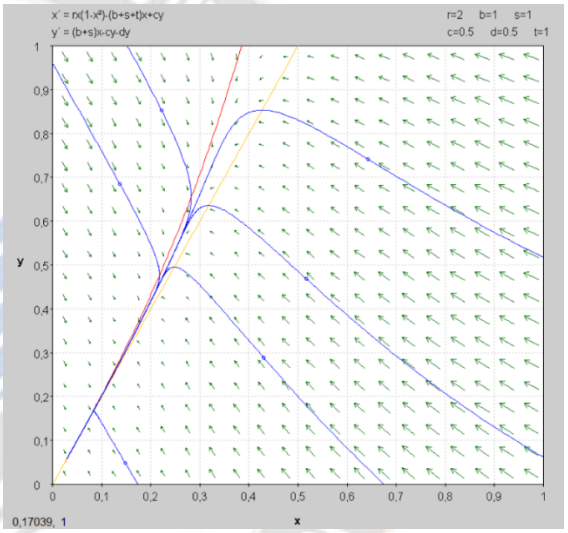

Figure 2.3 $(b + c_{stat} + c_{tox})d = (c + d)r - cc_{tox}$

Lemma 6. *The system does not exhibit any periodic trajectories.*

Proof. Here, let us examine two scenarios:

(1) $b_1 d \geq \{r + (b_2 - b_1)\}c + rd$

We only have a solitary equilibrium point in the first quadrant, and this zero equilibrium point operates as an attracting node. As mentioned previously, the impossibility of a periodic orbit around this point leads to the conclusion that there are no periodic trajectories in the first quadrant. Upon further analysis, it becomes evident that the absence of periodic orbits in the first quadrant aligns with our initial assessment. This finding contributes to a better understanding of the system's behavior in this specific region. Moving forward, we can direct our focus to other aspects of the system to gain a more comprehensive perspective.

(2) $b_1 d < \{r + (b_2 - b_1)\}c + rd$

Lemma 4.5 implies the existence of two stable states. According to the Poincarè-Bendixon criterion, it is clear that

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a periodic trajectory can only exist in the region where the sign of divergence changes. Therefore, our primary focus is to pinpoint the curve at which the divergence equals zero. This will allow us to determine the critical point and analyze the behavior of the trajectories emanating from it. To establish the lemma, it is imperative to demonstrate that the dynamics of *P* are positive.

$$\nabla = \frac{d\dot{P}}{dP} + \frac{d\dot{Q}}{dQ} = F'(P) - b_1 - c - d = r - b_1 - c - d - (1+a)r\left(\frac{P}{K}\right)^a$$

We can differentiate between two cases:

(a) When $r - b_1 - c - d \le 0$, we have $\nabla < 0$ which lies in the first quadrant.

(b) When $r - b_1 - c - d > 0$, we have

$$\nabla = 0 \text{ if } P_1 = K\sqrt[a]{\frac{r - b_1 - c - d}{(1+a)r}}$$

We can analyze the overall dynamics of the points $(P_1,\ Q)$ where *Q* and *a* are positive.

$$\frac{dP}{dt} = F(P_1) - b_1 P_1 + cQ$$

$$\Rightarrow \quad \frac{dP}{dt} = P_1\left[r\left\{1 - \left(\frac{P_1}{K}\right)^a\right\} - b_1\right] + cQ$$

$$\Rightarrow \quad \frac{dP}{dt} = P_1\left[r\left(1 - \frac{r - (b_1 + c + d)}{(1+a)r}\right) - b_1\right] + cQ$$

$$\Rightarrow \quad \frac{dP}{dt} = P_1\left[\left(\frac{(1+a)r - r + (b_1 + c + d)}{(1+a)}\right) - b_1\right] + cQ$$

$$\Rightarrow \quad \frac{dP}{dt} = P_1\left[\frac{(1+a)r - r + (b_1 + c + d) - b_1(1+a)}{(1+a)}\right] + cQ$$

$$\Rightarrow \quad \frac{dP}{dt} = P_1\left[\frac{a(r - b_1)r + c + d}{(1+a)}\right] + cQ > P_1(c+d) + cQ > 0$$

$$\Rightarrow \quad \frac{dP}{dt} = P_1\left(\frac{a(r - b_1) + c + d}{(1+a)}\right) + cQ > P_1(c+d) + cQ$$

which is clearly positive as $r - (b_1 + c + d) > 0$. Thus, $\frac{dP}{dt}$ is also positive. Hence, we can say that the trajectories is non-periodic orbit as it does not cross the line $(P_1,\ Q)$ when *Q* is positive.

Theorem.2*. In the first quadrant, if* $(b + c_{stat} + c_{tox})d \ge (r - c_{tox})c + rd$ *: the point (0, 0) serves as a global attractor with no periodic trajectory. If* $(b + c_{stat} + c_{tox})d < (r - c_{tox})c + rd$ *, the point* $(\bar{P},\ \bar{Q})$ *also acts as a global attractor without any periodic trajectories in the first quadrant.*

Proof*.* In the case where $(b + c_{stat} + c_{tox})d \ge (r - c_{tox})c + rd$, according to Lemma 5, $(P,\ Q)$ is the only fixed point in the first quadrant. We have also established, through Lemma 6, the absence of periodic trajectories. Combining these Lemmas, all the orbits are bounded within positively invariant triangles, implying the existence of an *ω*-limit set. Consequently, by the Poincaré-Bendixon criterion, there exists an *ω*-limit, and all the solutions converge towards this *ω*-limit, denoted as (*0, 0*).

For $(b + c_{stat} + c_{tox})d < (r - c_{tox})c + rd$, there are two steady states: (0, 0) and $(\bar{P},\ \bar{Q})$ using Lemma 4. Applying Lemma 5, we find that the point (*0, 0*) is linearly unstable, where the stable manifold is not located in the first quadrant. Additionally, Lemma 6 rules out the presence of a periodic orbits. Since $\phi(P^0,\ Q^0)$ exists for all positive values of *t* and is bounded, the dynamical system possesses an *ω*-limit set. In these conditions, the Poincaré-Bendixon criterion can be applied. As a consequence of this theorem, there is an ω-limit, represented as (*P, Q*), to which all solutions converge towards the attracting node. As a result, *ω* serves as a universal attractor in the first quadrant.

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Observation 1*. Biological inferences*

(1) $(b+c_{stat}+c_{tox})d \geq (r-c_{tox})c+rd$

When this scenario occurs, the point (*0, 0*) serves as a universal attractor. In simpler terms, both *P* and *Q* approach zero, resulting in:

$$N = P+Q = 0$$

This signifies the disappearance of the tumor. Research has shown that the phenomenon of global attractor is a promising development in the field of tumor dynamics. This behavior indicates a potential strategy for targeting the conditions that lead to the vanishing of the tumor. Understanding the underlying mechanisms behind this attraction to the origin point is crucial for developing effective therapies and interventions. Further investigation into the specific factors and processes involved in this phenomenon could provide valuable insights for the development of novel treatment approaches. If this situation happens, (0, 0) is a global attractor.

(2) $(b+c_{stat}+c_{tox})d < (r-c_{tox})c+rd$

Under this scenario, the model transitions to the non-zero equilibrium state.

$$(\bar{P},\bar{Q}) = \left(K\sqrt[a]{\frac{rc+(r-b-c_{stat})d+(c+d)c_{tox}}{r(c+d)}}, \left(\frac{b+c_{stat}}{c+d}\right)\bar{P} \right)$$

But, the transition is independent of the initial conditions. We know that $(b+c_{stat}+c_{tox})d < (r-c_{tox})c+rd$, which gives

$$\sqrt[a]{\frac{rc+(r-b-c_{stat})d+(c+d)c_{tox}}{r(c+d)}}, \left(\frac{b+c_{stat}}{c+d}\right) \in (0,1)$$

$$\Rightarrow \quad \bar{P} \in (0,\ K)$$

and, $$\bar{Q} \in \left(0, \left(\frac{b+c_{stat}}{c+d}\right)K\right)$$

Therefore,

$$\bar{N} = \bar{P}+\bar{Q}$$

$$\Rightarrow \quad \bar{N} = K\left(1-\frac{(b+c_{stat})d}{r(c+d)}-\frac{c_{tox}}{r}\right)^{1/a} \times \left(1+\left(\frac{b+c_{stat}}{c+d}\right)\right)$$

Hence, $$\bar{N} \in \left(0,\ K\left(1+\left(\frac{b+c_{stat}}{c+d}\right)K\right)\right)$$

It is evident that cytotoxic drugs consistently exhibit efficacy. This is attributed to the decrease in $\bar{N}$ as c_{tox} increases. Furthermore, an increase in either c_{stat} or $b+c_{stat}$ leads to an increase in $\bar{N}$; however, it is noteworthy that the cells that experience this increase are the quiescent ones. The parameter *c*, which governs changes in quiescent cells and the death rate (*d*) of quiescent cells, contributes to a decrease in $\bar{N}$. It is apparent that $\bar{N}$ also shows increments as *K*, representing the maximal tumor size grows larger. Furthermore, it becomes clear that $\bar{N}$ increases significantly when $\frac{d}{r} << 1$.

4. Conclusions

The field of cancer research has witnessed an expanding array of mathematical models being used in recent decades. The use of mathematical modeling has demonstrated its effectiveness as a valuable tool for comprehending the intricate nature of cancer and its advancement. Such models have offered valuable insights into factors such as growth of tumor, the dynamics of cancer cell populations, and the impact of different treatment methods. By using mathematical equations and simulations, researchers have been able to predict how tumors may respond to different therapies and identify optimal treatment strategies for individual patients. In this paper, we have showcased the application of simple models, and when compared with emperical data, illustrated their utility in simulating intricate biological processes. These models proficiently encapsulate the dynamics of tumor growth and the subsequent response to treatment. However, as the realm of cancer research progresses, more advanced mathematical models are being crafted to address the intricacies inherent in cancer biology. These advanced models consider genetic diversity, the tumor microenvironment, and interactions with the immune system,

offering a more comprehensive understanding of cancer progression and treatment outcomes.

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