A Survey of Simple ODE Models of Tumor Growth

Yuqi Liu, Ziyu Ou, Liqi Kong, and Yijian Li

Abstract

WHO (World Health Organization) declared that cancer is the second leading cause of death worldwide, with an estimated 9.6 million deaths, or one in six, in 2018. Here, we will describe how logistic, generalized logistic, Gompertz, and Bertalanffy models can model tumor growth and their predictions of chemotherapy dose and carrying capacity.

1 Introduction

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. The burden of cancer continues to grow globally, putting enormous physical, emotional strain on and financial impact on individuals, families, communities, and health systems. Large numbers of cancer patients worldwide lack access to timely quality diagnosis and treatment. Mathematical models can aid in understanding and treating cancer. Models give insight into how cancer grows and develops. In addition to optimizing or personalizing current treatment regimens, they can also predict the efficacy of new treatments or combinations of various therapies and give insight into the development of resistance to treatment [6].

Numerous ODE (Ordinary Differential Equation) growth models have been developed to predict tumor growth. Among these models, we focus on four of them: logistic, generalized logistic, Gompertz, and Bertalanffy models. We will analyze their description and prediction results and highlight their predictions of chemotherapy dose and carrying capacity. In anticipating the progression of cancer and its treatment outcomes, we hope that the results presented in this paper will inspire further research into the effect of choice of cancer growth model on predicted treatment outcomes and that researchers will consider more than just the most suitable fit [6].

2 Tumor growth models

In this section, we introduce the tumor growth models analyzed in this study. In each equation, a, b and c are model parameters, t is time, V is the volume of tumor, and V_{ini} is the initial value of tumor size.

2.1 Logistic

2.1.1 Idea inspiration

In "Differential Equations and Their Applications(fourth edition): Population Model (1.5)", Braun presents an ode model of population growth [2]. At the beginning of modeling, Braun uses a simple ode model with merely one parameter to initiate a relationship between the human population on earth with the time of change. However, that model cannot be applied because it does not take the number of diminished people on earth into account, leading to the predicted population density being much greater than the theoretically capable density of the planet [2]. Then, Braun modifies the model by adding a new negative parameter and retraining the rate of population growth, which enables him to predict the human population more precisely.

The population model shares the same theory as the tumor size model. Generally, we aim to design a model with an increasing size but decreasing growth rate. The magnitude of tumor size is hard to predict due to cancer cells dividing irregularly over time. Moreover, the difference of cancer cells respecting time can not only be determined by how many cancer cells grew; the number of dead cancer cells should also be considered [7]. Based on this idea, the difference of cancer cells respecting time depends on the number of cancer cells that grew and died in a specific time interval. We use V to represent the number of cancer cells in a tumor:

$$\frac{dV}{dt} = \gamma V - \delta V \tag{1}$$

We can simplify the equation by reducing the number of parameters by combining γV - δV into a single term, where a is a constant that represents the net population growth rate [2]:

$$\dot{V} = aV \tag{2}$$

2.1.2 Model

Also, same as Braun's population model, cancer cells inside the tumor exponentially grow at the beginning because they robbed plenty of nutrition from the human body. Then the growth rate decelerates as it grows larger, representing that the growth of tumor size depends on the tumor itself [7]. So we can substitute LHS of ode with $\dot{V}/V$. Consequently, equation (2) is generalized to a nonlinear first-order that incorporates growth deceleration:

$$\frac{\dot{V}}{V} = F(V), \text{ where F(V) is an appropriate function of V.} \tag{3}$$

The issue is that F(V) is with a constraint because the magnitude of the tumor will not expand to infinity. Instead, it will reach a maximum capacity when people die.

Let's set this host carrying capacity as a variable b. The aim is to design a function that can show the tumor growth rate continuously slows down with time. So, a corresponding equation that can reflect this trend is determined[6]:

$$\dot{V} = aV(\frac{b-V}{b}) = aV(1-\frac{V}{b}) \tag{4}$$

The solution of logistic model is given by:

$$V(t) = \frac{be^{at}}{b+e^{at}-1} \tag{5}$$

2.2 Generalized logistic

The generalized logistic model is defined by [1]:

$$\dot{V} = cV(1-(\frac{V}{a})^b) \tag{6}$$

where a is the carrying capacity. This model is between logistic and Gompertz: when $b = 1$, it is logistic, and when b goes to 0, it converges to Gompertz [1].

The solution of this model is:

$$V(t) = \frac{V_{ini}a}{(V_{ini}^b + (a^b - V_{ini}^b)e^{-cbt})^{\frac{1}{b}}} \tag{7}$$

2.3 Gompertz

$$\dot{V} = (a - b\ln\frac{V}{V_{ini}})V \tag{8}$$

This model was first created by Benjamin Gompertz to explain human mortality curves [3]. After Anna Laird's success in using it to fit the growth of 19 tumor cell lines, it becomes popular in cancer literature [5, 10].

The solution of Gompertz model is [11]:

$$V(t) = V_{ini}e^{\frac{a}{b}(1-e^{-bt})} \tag{9}$$

From this equation, we can see that the volume predicted by Gompertz converges to a carrying capacity $V_{ini}e^{\frac{a}{b}}$.

2.4 Bertalanffy

According to equation(1), the difference of cancer cells in a specific time can be represented by aV - bV, where V is the number of cell numbers. But it can not show

the trend of tumor size growth very well. So, the parameters should be changed so that satisfying this condition.

Since the trend of tumor growth is consciously decelerating [7], the power of parameter growth should be reduced. In this situation, the coefficient of the diminished parameter will be less than the one of the dead, aiming to ensure an exponential increase at the beginning of the tumor size growth. Therefore, the equation of Bertalanffy is [6, 13]:

$$\dot{V} = aV^{\frac{2}{3}} - bV \tag{10}$$

The solution of Bertalanffy is [1]:

$$V(t) = (\frac{a}{b} + (V_{ini}^{\frac{1}{3}} - \frac{a}{b})e^{-\frac{b}{3}t})^3 \tag{11}$$

3 Methods

3.1 Dynamical analysis

To see the long term prediction of each model, we find the fixed points of them. A fixed point is defined by [9]

$$\dot{V}(t) = 0 \tag{12}$$

Those fixed points can give us information about the boundary between the growth and decay of the tumor [6].

3.2 Parameter estimation

We use the Python built-in function *scipy.optimize.curve_fit* to find parameters with the minimum sum of squared residuals (SSR) [12]. The formula of SSR is:

$$SSR = \sum_i (x_i - m_i)^2 \tag{13}$$

where x_i is the data point, and m_i is the predicted model value [6].

However, SSR has a bias towards models with more free parameters, because they have more freedom to fit the data. To correct such bias, we also use Aikaike's information criterion with a correction for small samples (AIC_C), which penalizes models with more parameters [6], to compare models' goodness of fit. The formula of AIC_C is given by:

$$AIC_C = nln\left(\frac{SSR}{n}\right) + \frac{2(K+1)n}{n-K-2} \tag{14}$$

where n is the number of data points and K is the number of parameters.

3.3 Data

The data set is obtained from Vaghi et al. [11], which consists of 66 samples of breast data measured by volume, 8 samples of breast data measured by fluorescence, and 20 samples of lung data measured by volume. We only work with the breast data measured by volume and the lung data, which are shown in Figure 1. The number of cells injected at the initial time t_{ini} was 10^6, so the initial volume V_{ini} in the whole dataset is $1mm^3$.

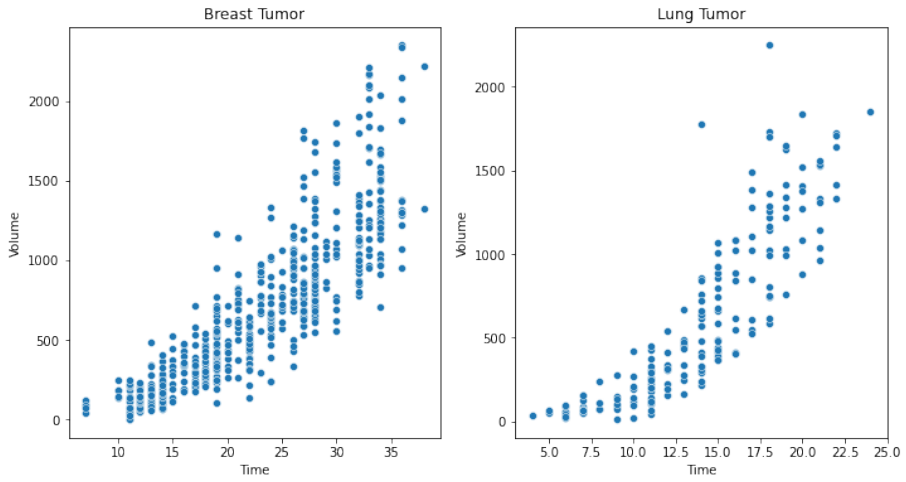

Figure 1: Dataset

4 Results

4.1 Descriptive power

To compare the descriptive power of the models, we first fit those models to our data sets by minimizing their SSR, and then calculate the SSR and AIC_C of them (Methods).

From Figure 2 and 3, and Table 2 and 4, we can see that logistic model cannot describe both breast data and lung data well. The other three models give a reasonable fit to both data sets, with Bertalanffy slightly better on breast data, and generalized logistic and Gompertz performing better on lung data. The descriptive power of generalized logistic and Gompertz is very close when both adjusting (AIC_C) and not adjusting (SSR) parameter number. This can be explained by the value estimated for the parameter b of generalized logistic, which is very small, and generalized logistic converges to Gompertz when b goes to 0 (Tumor growth models).

	logistic	generalized logistic	Gompertz	Bertalanffy
a	3.02×10^{-1}	2.61×10^{3}	5.97×10^{-1}	1.31
b	1.48×10^{3}	1.58×10^{-4}	7.59×10^{-2}	6.05×10^{-2}
c	–	5.78×10^{7}	–	–

Table 1: Parameters estimated on the breast data set

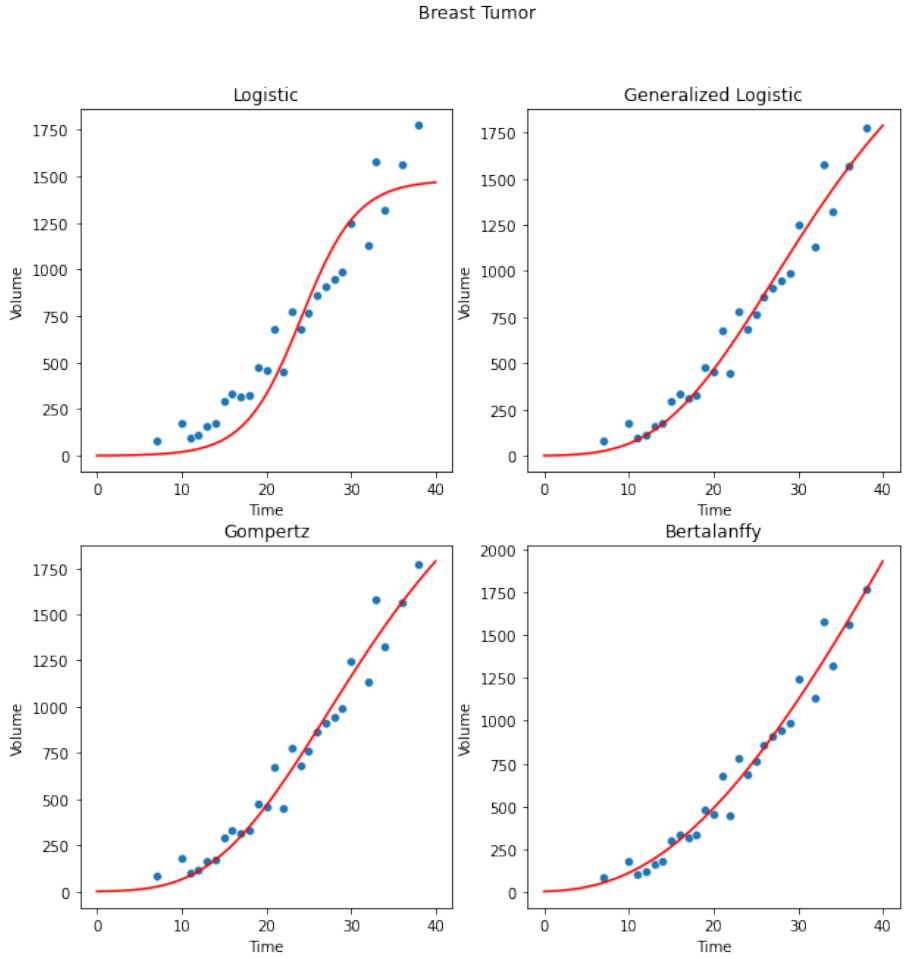

Figure 2: Models fit to the breast data set

	logistic	generalized logistic	Gompertz	Bertalanffy
SSR	6.81×10^{5}	2.15×10^{5}	2.15×10^{5}	1.83×10^{5}
AIC_c	281	252	250	245

Table 2: SSR and AIC_c when fitting to the breast data set

	logistic	generalized logistic	Gompertz	Bertalanffy
a	4.62×10^{-1}	2.60×10^{3}	8.74×10^{-1}	1.83
b	1.64×10^{4}	1.44×10^{-1}	1.08×10^{-1}	5.77×10^{-2}
c	–	1.06	–	–

Table 3: Parameters estimated on the lung data set

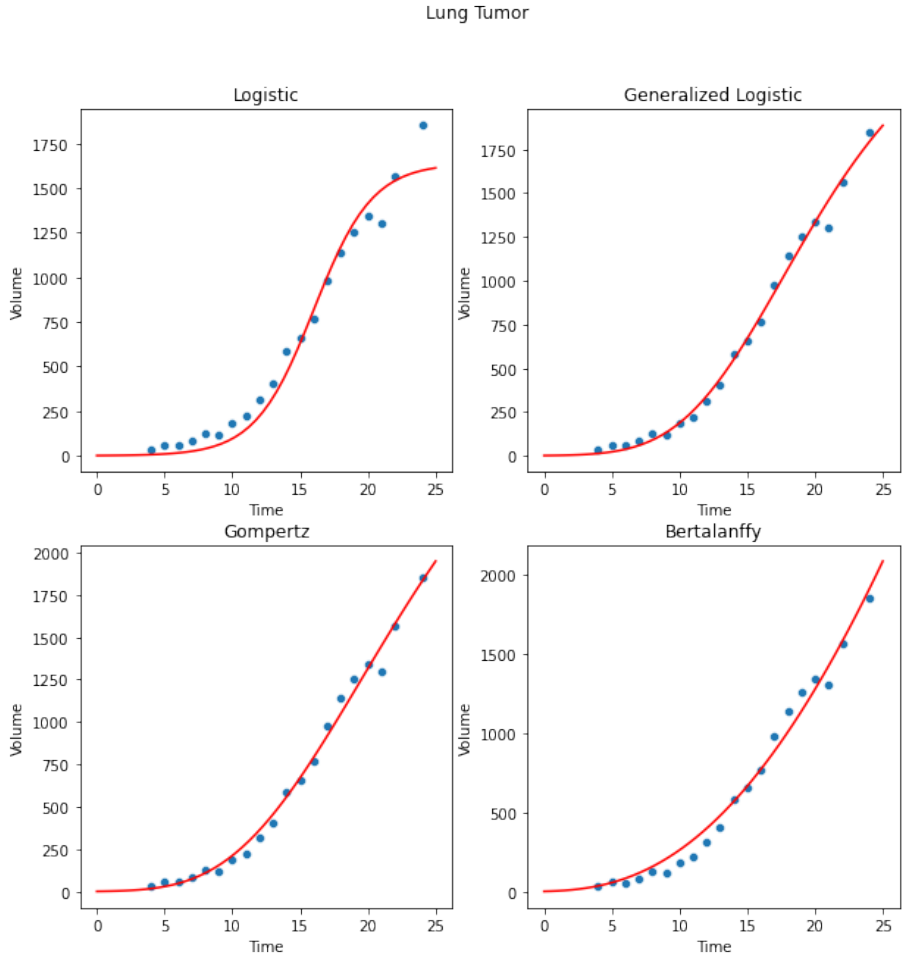

Figure 3: Models fit to the lung data set

	logistic	generalized logistic	Gompertz	Bertalanffy
SSR	1.74×10^{5}	4.91×10^{4}	5.46×10^{4}	1.03×10^{5}
AIC_c	244	212	213	230

Table 4: SSR and AIC_c when fitting to the lung data set

4.2 Predictive power

Apart from descriptive power, we also care about predictive power. To this end, we estimate parameters on the first one, two, and three quarter(s) of each data set, which are the first 7, 14, and 21 time points for breast data, and 5, 10, and 15 time points for lung data.

Prediction results on breast data are shown in Figure 4 and Table 5. Bertalanffy gives the best prediction for breast tumor growth in all three cases, and logistics always underestimates the tumor size. When the data set used for prediction is enough, generalized logistic and Gompertz can have comparable predictive power as Bertalanffy.

Lung data prediction results are in Figure 5 and Table 6. Bertalanffy still gives the best prediction when we only use the first quarter of the whole data set, however, it overestimates tumor size when more data is used for prediction. Generalized logistic and Gompertz have the smallest SSR with the first half data, and they have similar predictive power as logistic when predicting on the first 3/4 data set.

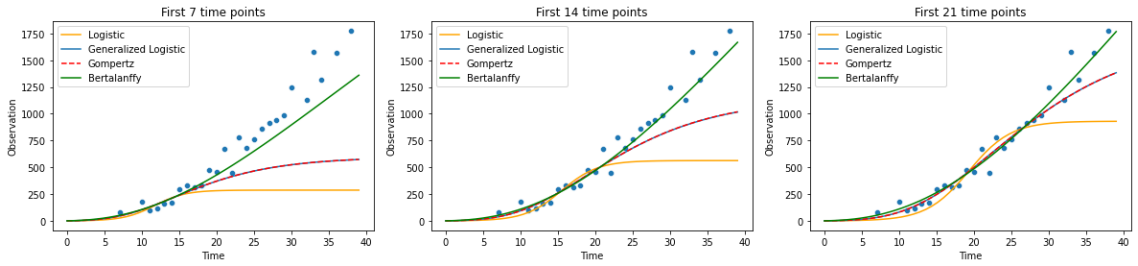

Figure 4: Prediction results of breast data

	logistic	generalized logistic	Gompertz	Bertalanffy
1/4	1.08×10^7	6.11×10^6	6.11×10^6	1.05×10^6
1/2	5.61×10^6	1.96×10^6	1.96×10^6	2.91×10^5
3/4	2.02×10^6	5.48×10^5	5.47×10^5	2.00×10^5

Table 5: Prediction SSR of breast data

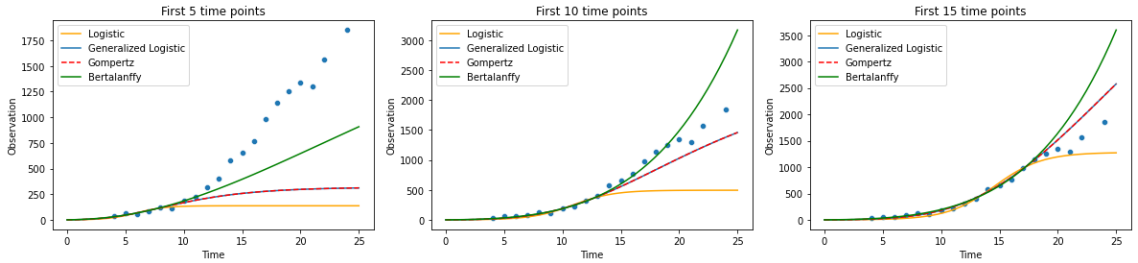

Figure 5: Prediction results of lung data

	logistic	generalized logistic	Gompertz	Bertalanffy
1/4	1.17×10^7	8.76×10^6	8.76×10^6	3.76×10^6
1/2	5.78×10^6	7.66×10^5	7.65×10^5	1.30×10^6
3/4	5.16×10^5	6.14×10^5	6.15×10^5	2.62×10^6

Table 6: Prediction SSR of lung data

4.3 Clinically important measurements prediction

The variances in predictions can make great differences in decision making. Here, we present two quantitative examples that are of clinical interest: carrying capacity and chemotherapy.

4.3.1 Carrying capacity

Carrying capacity is the maximum tumor size predicted, and it is determined by the non-zero fixed point of each model [6]. Some previous studies show that using the ratio of tumor volume and carrying capacity can fit historical radiation response data accurately [8].

The predicted results are shown in Table 7 and Figure 6. The predictions given by three models show large variation, with the prediction of Bertalanffy 4 times larger than that of Gompertz and generalized logistic and 7 times larger than that of logistic.

	Logistic	generalized logistic	Gompertz	Bertalanffy
K	b	a	$e^{\frac{a}{b}}$	$(\frac{a}{b})^3$
Predicted K	1479	2608	2608	10209

Table 7: Carrying capacity

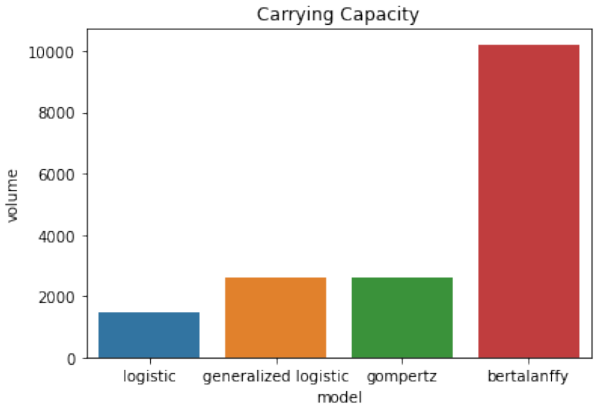

Figure 6: Carrying capacity predicted

4.3.2 Chemotherapy

Chemotherapy is a commonly used cancer treatment, and it is very important to determine the dose of it. When the dose is above the needed amount, the anti-tumor effect is not improved, but toxicity will increase, and when the dose is below standard, the effect is significantly reduced [4]. In this section, we use a simplified assumption to calculate the chemotherapy dose predicted by each model.

We assume that chemotherapy slows down the tumor growth rate by C_0V, so to get tumor growth models under chemotherapy, we subtract this term from the models discussed previously [6]. We are interested in finding the minimum dose of chemotherapy needed to stop tumor growth, so we treat C_0 as a variable and find the fixed point of each model when $V = V_{ini}$. Here, we present the logistic model as an example to show how we do such analysis.

Tumor growth rate with chemotherapy:

$$\dot{V} = aV(1 - \frac{V}{b}) - C_0V \tag{15}$$

To find the fixed point, we set $\dot{V}$ to 0:

$$aV(1 - \frac{V}{b}) - C_0V = 0 \tag{16}$$

We want V be V_{ini}, and in our case, it is 1, so

$$a(1 - \frac{1}{b}) - C_0 = 0 \tag{17}$$

Solve the expression of C_0:

$$C_0 = a - \frac{a}{b} \tag{18}$$

Table 8 and Figure 7 show the dose predicted by each model. The prediction of Bertalanffy is 2 times larger than Gompertz and generalized logistic, and 4 times larger than logistic.

	Logistic	generalized logistic	Gompertz	Bertalanffy
C_0	$a - \frac{a}{b}$	$c(1 - (\frac{1}{a})^b)$	a	$a - b$
Predicted C_0	0.302	0.60	0.60	1.25

Table 8: Chemotherapy

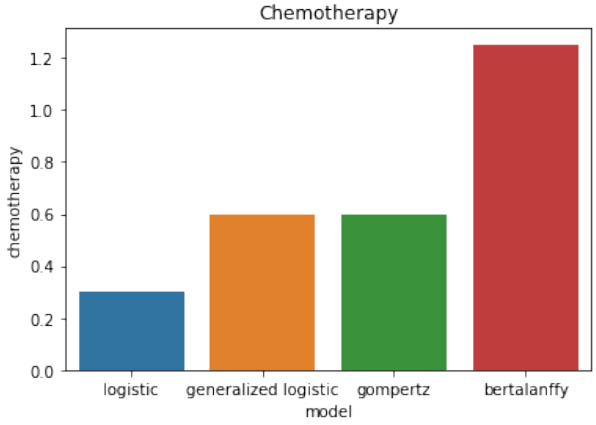

Figure 7: Chemotherapy predicted

5 Discussion

The purpose of this paper is to see how precise each model is in describing and predicting tumor growth, with the best hope to provide guidance in model selection. We focus on analyzing the results of four models: logistic, generalized logistic, Gompertz, and Bertalanffy, as well as highlighting their predictions of two clinically important measurements. The results of this study suggest that no one model can perform the best in all cases. Their performance depends both on the data set and the number of time points used for prediction.

Since we only use two data sets, and the model used to describe chemotherapy is highly simplified, the results may be not very generalizable. However, we do believe that our results emphasize a significant problem. The prediction differences are huge for those models. As a result, these inaccuracies could have significant impacts on patient outcomes like providing too much treatment, causing more severe side effects, or too little treatment, possibly resulting in continued growth of the tumor [6].

In future studies, we can consider some other more sophisticated models that can

describe the biological processes better. In addition, we can also use more data sets of other cancer types to see if there is a pattern for how to choose the prediction model.

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