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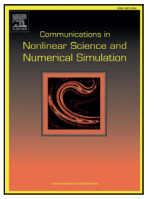

Research paper

Predicting the effectiveness of chemotherapy using stochastic ODE models of tumor growth

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ABSTRACT

Ordinary differential equation (ODE) models of cancer growth are often used to predict tumor growth and form the basis for more complex models used in personalized medicine. Unfortunately, ODE models provide predictions of the average behavior of the cell population neglecting the fact that cells are discrete objects subject to discrete events. This kind of stochasticity can dramatically change the time course of tumor growth, particularly when the cell population is small. Here, we investigate stochastic versions of seven common ODE models of cancer growth to determine the role of stochasticity in eradicating tumors via chemotherapy. We find that stochasticity leads to differences in predictions among the different models of both the level of chemotherapy needed to cure a tumor and the time it takes to achieve a cure. Our results highlight the need for more investigation of which model provides the best description of cancer growth.

1. Introduction

Despite significant investment and research effort, cancer remains a leading cause of death [1,2]. While new treatment strategies, such as immunotherapy [3,4], oncolytic viruses [5,6], and nanoparticles [7,8] are also being developed, chemotherapy of some kind remains a primary therapy [9,10]. Thus techniques for predicting the effectiveness of chemotherapy are valuable tools that can help guide clinicians when treating patients. Mathematical models in particular are increasingly being used to guide treatment regimens [11] and even to personalize treatment to individual patients [12–14].

While mathematical models attempting to make personalized predictions can be quite complicated, including spatial dynamics [15,16] and immune responses [17–19], such models can be difficult to parameterize [20–22] and are often analytically intractable. While not patient-specific, insight into cancer development and treatment can often be gained from simpler models. The simplest mathematical models of tumor development are ordinary differential equation (ODE) models that describe the replication of cancer cells. Several such models have been proposed [23–25] and are commonly used as the basis for more complex models. Unfortunately, there is no consensus on which of these models best describes tumor growth [26–29], although several studies have indicated that choice of growth model can significantly affect model predictions of both tumor growth and treatment effectiveness [24,25,30].

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Table 1
ODE models of tumor growth.

Model	Equation
Exponential	$\dot{N} = aN$
Mendelsohn	$\dot{N} = aN^b$
Logistic	$\dot{N} = aN\left(1 - \frac{N}{b}\right)$
Linear	$\dot{N} = \frac{aN}{(N+b)}$
Surface	$\dot{N} = \frac{aN}{(N+b)^{\frac{1}{3}}}$
Gompertz	$\dot{N} = aN \ln \frac{b}{(N+c)}$
Bertalanffy	$\dot{N} = aN^{\frac{2}{3}} - bN$

ODE models are also limited in that they describe the average behavior of the population and assume that the number of tumor cells is a continuous variable. However, cancer cells are discrete objects and the cell population changes when the discrete events of cell replication or cell death occur. Further, experiments show that cancer cell populations grow differently even when cell cultures are maintained under the same experimental conditions [31,32]. Using ODE models, cell populations growing in identical conditions should be described by the same model parameters and would therefore have identical growth curves, so ODE models are clearly limited in their ability to reproduce experimental results. Stochastic simulations of the ODE models can be used to address some of these limitations and will help to give insight into the variability seen in experiments and in patients [33].

While stochastic mathematical models have previously been used to model tumor development, they typically take the form of agent-based models [34–36] which often include spatial heterogeneity, the immune response, and other external factors, making it difficult to assess the influence of stochasticity alone. There are also a number of delay differential equation (DDE) and ODE based models of cancer growth that include stochastic noise terms [37–40] where the stochastic terms represent fluctuations in external factors such as intermittent treatment or changes in temperature. As of yet, there is no study of the variability of cancer growth and treatment response due solely to the discreteness of cancer cells and the events involved in cancer growth.

In this paper, we examine stochastic versions of seven commonly used ODE models to assess their predictions of how often tumors of various sizes are cured with different amounts of chemotherapy. We use the ODE models to formulate continuous time Markov chain (CTMC) models and analyze the extinction probability for a cancer cell. We also use computer simulations to examine the effect of chemotherapy when applied to the different growth models. Our simulations indicate that different models disagree on how much chemotherapy is needed to eradicate a tumor and how long it will take for chemotherapy to be effective, suggesting that more work is needed to identify which models best describe tumor growth.

2. Methods

2.1. Mathematical models

We investigated seven commonly used ODE models of tumor growth [25] whose equations are given in Table 1. In the equations, N represents the number of cells in the tumor, and a, b, and c represent model parameters. The exponential and Mendelsohn models assume continuous division of all cells. While these models often capture early cancer cell replication well, they predict infinitely large tumors. The linear and surface models limit the number of cells that replicate at each time step leading to tumors that grow slower than those predicted by the exponential and Mendelsohn models, but still result in infinitely large tumors. The logistic, Gompertz, and Bertalanffy models reduce the effective growth rate of tumors as the tumors become large, resulting in predicted tumors that reach some maximum size. The effect of chemotherapy was incorporated into each model by including the term $-C_0N$, where C_0 represents a constant concentration of drug delivered to the tumor [30].

In this paper, we formulate the probabilistic counterpart of the ODE models, a continuous-time Markov chain (CTMC) model of tumor growth and treatment that will account for stochastic variability particularly when the number of cancer cells is small. This model incorporates fluctuations in replication and death of tumor cells. In these equations, there are two possible events: a replication event leading to an additional cancer cell, or death of a cancer cell. The probability of each of these events is given by the rate in the corresponding term (positive or negative) in the ODE. Events and probabilities for each of the models is given in Table 2. The time course of the CTMC is constructed using the Gillespie algorithm [41]. The Gillespie algorithm includes two random processes: (a) the size of the time step is chosen from an exponential distribution with a mean dependent on the sum of the rates of both events, and (b) the particular event that occurs at that time step is randomly chosen from all possible events with probability proportional to the relative rate of the event.

Parameter values for the models are taken from Murphy et al. [25] who fit these models to data from a GI-101A xenograft in nude mice [42]. Note that in Murphy et al. [25], tumor size is measured by tumor volume (mm^3) and for stochastic

Table 2
Event probabilities for each CTMC model.

Model	Event	Rate
Exponential	$N \to N+1$	a
	$N \to N-1$	C_0
Mendelsohn	$N \to N+1$	aN^{b-1}
	$N \to N-1$	C_0
Logistic	$N \to N+1$	a
	$N \to N-1$	$\frac{aN}{b}+C_0$
Linear	$N \to N+1$	$\frac{a}{(N+b)}$
	$N \to N-1$	C_0
Surface	$N \to N+1$	$\frac{a}{(N+b)^{\frac{1}{3}}}$
	$N \to N-1$	C_0
Gompertz	$N \to N+1$	$a\ln\left(\frac{b}{c}\right)$
	$N \to N-1$	$a\ln\left(\frac{N}{c}+1\right)+C_0$
Bertalanffy	$N \to N+1$	$aN^{-\frac{1}{3}}$
	$N \to N-1$	$b+C_0$

simulations, we need to convert our equations to number of cells. Total tumor volume is given by the number of cells multiplied by the volume of a cell, $V = V_{cell}N$. This means parameters that include some measure of size (mm or mm^3) need to be converted by dividing by the volume of a cell. We use $V_{cell} = 1760\mu m^3$, as found in Wagner et al. [43] for MCF-7 breast cancer cells. Parameter values used for simulations are given in Table 3.

3. Results

3.1. Calculation of extinction probability

When tumors are large, the time course is largely driven by the average descriptions given by the ODEs. That is, if the decay terms are larger than the growth terms, the tumor will die off; if growth terms are larger than decay terms, then the tumor will continue growing. Stochastic effects are most relevant when the number of cancer cells is small, where small random fluctuations could lead to extinction of the tumor. Under these conditions, the CTMC model becomes a multi-type branching process that describes the dynamics of a population of individual cells undergoing birth and death independently. If a time-homogeneous CTMC is a branching process, the only absorbing state is $\vec{0}$. For this model we define the probability to reach this state from state $\vec{m}$ as $\xi(\vec{m})$. This probability is referred to as the extinction probability. Biologically, the extinction probability gives the probability that the cancer is eliminated. Once a transition occurs, the current state $\vec{m}$ is incremented by one of the transition vectors given below.

$$d\vec{m}_1 = (+1) \text{ for } N \to N+1$$
$$d\vec{m}_2 = (-1) \text{ for } N \to N-1.$$

If the rate of the i^{th} reaction is defined as a_i with the a_i given for the various models in Table 2 then the probability that the i^{th} reaction is the next reaction is given by

$$P_i(\vec{m}) = \frac{a_i(\vec{m})}{Z(\vec{m})} \quad i = 1, \ldots, n_{max}$$
$$\text{where } Z(\vec{m}) = \sum_{i}^{n_{max}} a_i(\vec{m}),$$

and $n_{\max}$ is the number of transitions involved in the model (2 in this case). The time of the next reaction is a random variable with distribution $Z(\vec{m})\exp(-Z(\vec{m})t)$ with mean $\frac{1}{Z(\vec{m})}$ (according to the Gillespie algorithm). The probability that a tumor containing N cells eventually evolves to extinction, given by the extinction coefficient, $\xi(\vec{m})$, is

$$\xi(\vec{m}) = \sum_i P_i(\vec{m})\xi(\vec{m} + d\vec{m}_i), \vec{m} \neq \vec{0}, \tag{1}$$
$$\xi(\vec{m}) = 1 \text{ when } \vec{m} = \vec{0}.$$

So the extinction coefficient for these models, which have two possible events (birth and death of cells), is

$$\xi(\vec{m}) = \frac{a_1(\vec{m})}{Z(\vec{m})}\rho^{N+1} + \frac{a_2(\vec{m})}{Z(\vec{m})}\rho^{N-1}, \tag{2}$$

Table 3
Model parameters.

Model	a	b	c
Exponential	0.0262 /day		
Mendelsohn	0.286 /day	0.616	
Logistic	0.0370 /day	1.14×10^{9}	
Linear	3.34×10^{7} /day	9.60×10^{8}	
Surface	0.0502 /day	2.88×10^{8}	
Gompertz	0.279 /day	7.90×10^{9}	6.82×10^{9}
Bertalanffy	0.0580 /day	0.0119 /day	

Table 4
Single-cell extinction probabilities for ODE models of tumor growth.

Model	Extinction Probability
Exponential	$\frac{a+C_0}{2a}\left[1-\sqrt{1-\frac{4aC_0}{a+C_0}}\right]$
Mendelsohn	$\frac{a+C_0}{2a}\left[1-\sqrt{1-\frac{4aC_0}{a+C_0}}\right]$
Logistic	$\frac{a+\frac{a}{b}+C_0}{2a}\left[1-\sqrt{1-\frac{4a\left(\frac{a}{b}+C_0\right)}{a+\frac{a}{b}+C_0}}\right]$
Linear	$\frac{a+bC_0}{2a}\left[1-\sqrt{1-\frac{4aC_0}{a+bC_0}}\right]$
Surface	$\frac{a+b^{1/3}C_0}{2a}\left[1-\sqrt{1-\frac{4aC_0}{a+b^{1/3}C_0}}\right]$
Gompertz	$\frac{a\ln(bc)+C_0}{2a\ln(b)}\left[1-\sqrt{1-\frac{4a\ln(b)[a\ln(c)+C_0]}{a\ln(bc)+C_0}}\right]$
Bertalanffy	$\frac{a+b+C_0}{2a}\left[1-\sqrt{1-\frac{4a(b+C_0)}{a+b+C_0}}\right]$

where ρ is the extinction probability for a single cell.

The CTMC assumption of independent events means that this equation can be reduced to an algebraic expression where the extinction probability from a given state is the product of the extinction probabilities from each of the constituents of that state [44], so we can write

$$\xi(\vec{m}) = \rho^N = \frac{a_1}{Z}\rho^{N+1} + \frac{a_2}{Z}\rho^{N-1} \tag{3}$$

where ρ^N is the probability that N cells initiate a process that results in extinction. This assumption allows us to solve for the extinction probability ρ,

$$\rho = \frac{Z}{2a_1} \pm \frac{Z}{2a_1}\sqrt{1-\frac{4a_1a_2}{Z}}$$

Note that since probabilities must be less than one, we use the negative root (the positive root leads to $\rho > 1$). Formally, the extinction probability is the lesser of the above expression and 1. For the ODE tumor models of Table 1, the extinction probabilities are given in Table 4. Using the parameters from Table 3, these expressions all lead to very similar dependence of the extinction probability on the amount of chemotherapy (Fig. 1). The extinction probability approaches 1 as $C_0 \to 1$. It is not surprising that the differing expressions lead to the same curve since the particular parameters used here were all estimated from fits to a particular data set and the models all essentially agree on early time dynamics when the extinction probability applies.

3.2. Stochastic simulations

We ran simulations of the CTMC models both with and without treatment, as shown in Fig. 2. There are some differences in the untreated time courses — after 25 days the model predictions of tumor size range from as little as 300 cells (Bertalanffy) to 1000 cells (exponential). There is very little variability in the time course for untreated cancer for the majority of the models, the exception being the Bertalanffy model, which consistently has about 50 cells for the 10 simulations shown in Fig. 2.

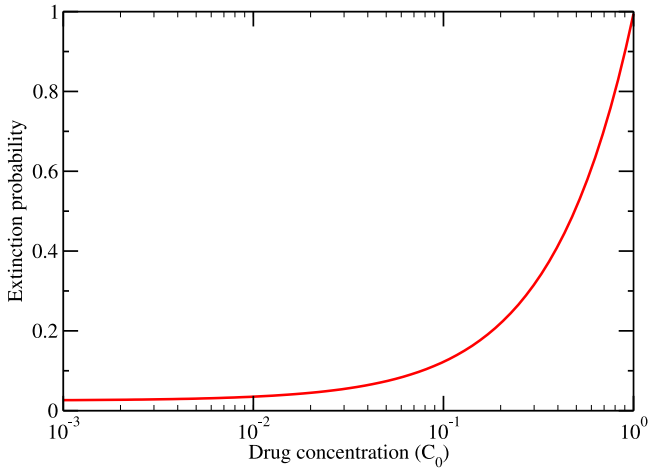

Fig. 1. Extinction probability of a single cell as a function of the chemotherapy dose. We find the same curve for all growth models.

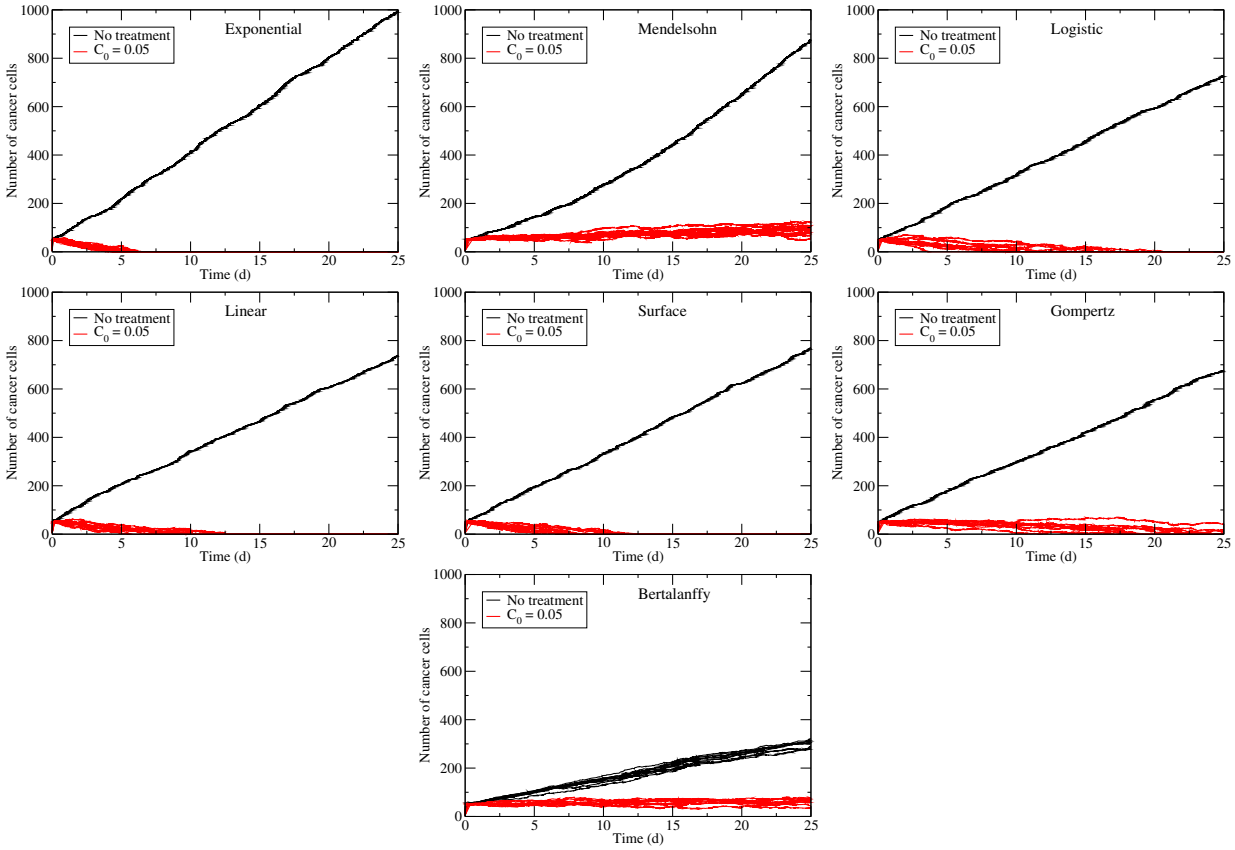

Fig. 2. Time course of 10 simulations of untreated (black) and treated (red) cancer growth for all models. Simulations were started with 50 cancer cells; model parameters are given in Table 3.

The models also have different predictions for the effect of chemotherapy on the growth of cancer cells. The Bertalanffy and Mendelsohn models appear to require a higher level of chemotherapy than the other models to eradicate the cancer. In these two models, the amount of chemotherapy used shrinks the number of cancer cells, but does not fully eliminate all of them. In the remaining models, the time to completely eliminate the tumor varies from 5 days (exponential) to about 25 days (Gompertz). There is also more variability in the predicted time courses for each model which is to be expected since treatment decreases the number of cancer cells and stochasticity has more of an effect in small populations.

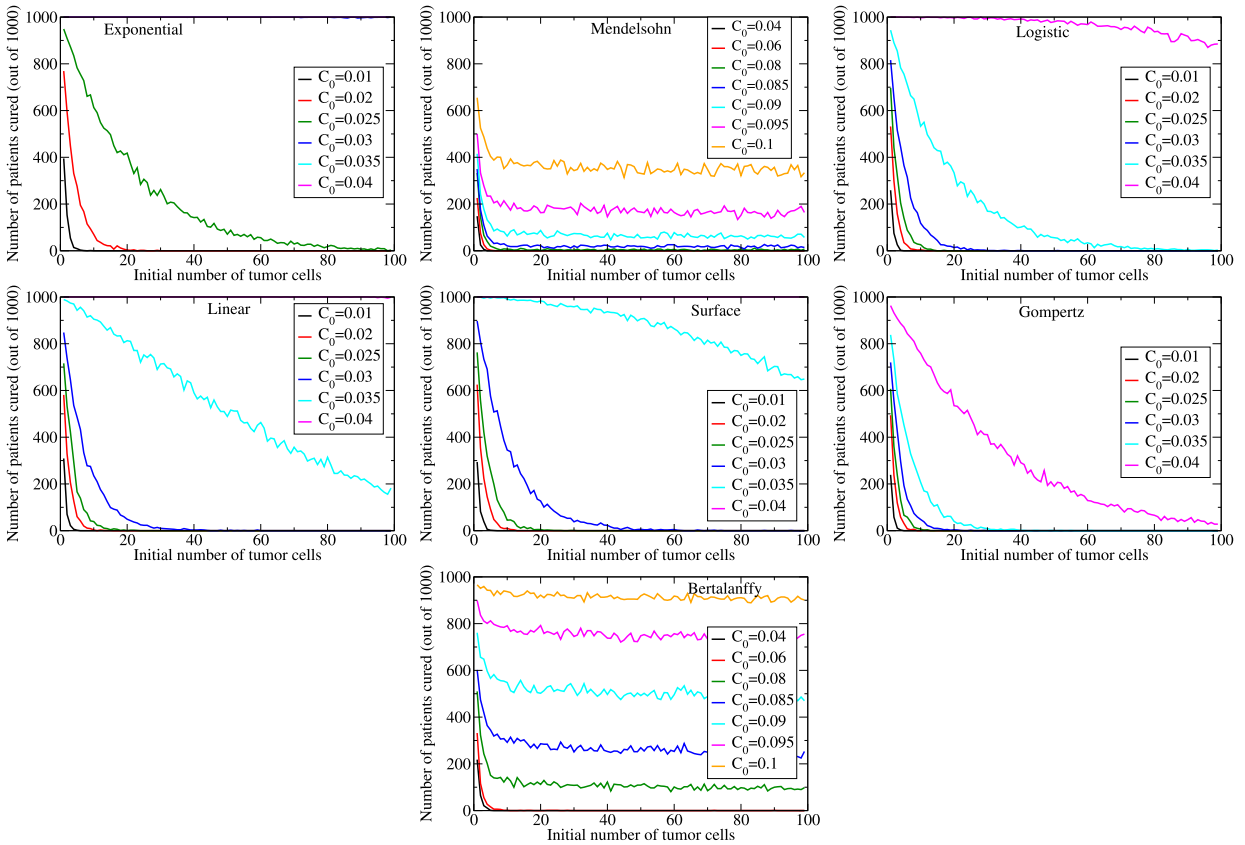

Fig. 3. Predicted cure rate as a function of the initial size of the tumor for different doses of chemotherapy. We simulated 1000 patients using different levels of chemotherapy and examined how many tumors were eradicated. Note that the Mendelsohn and Bertalanffy models use different amounts of chemotherapy than the remaining models.

3.3. *Effectiveness of treatment*

While tumors might start with the appearance of a single cell, they are often not noticed until they are bigger. At large sizes, the effective dose of chemotherapy can be derived from the ODEs [25], but once the tumor starts shrinking, the final steps towards complete elimination are again driven by stochastic processes. We use simulations of the stochastic models to study the model predictions of effectiveness of chemotherapy on this final elimination process by examining the probability of elimination for different sizes of small tumors.

Fig. 3 shows the model predictions of the number of patients cured (out of 1000) for various levels of chemotherapy and different initial tumor sizes. As noted in Fig. 2, the Bertalanffy and Mendelsohn models require higher levels of chemotherapy to achieve a cure. Even with $C_0 = 0.1$ (more than twice the effective dose for most of the remaining models), the Mendelsohn model predicts that only 40% of patients will be cured. The Bertalanffy model predicts about 90% of patients will be cured with this dose. For both these models, the predicted number of patients cured is largely independent of the initial size of the tumor. The remaining models predict that larger tumors need larger doses of chemotherapy to cure patients. There is also variability in the models' predictions of the amount of chemotherapy needed to cure 100% of patients with the exponential model needing as little as $C_0 = 0.03$ to achieve a cure for tumor sizes up to 100 cells.

When treating patients, we are not just interested in how many will be cured given a certain dose of chemotherapy, but also in how long we will need to treat patients to achieve a cure. Fig. 4 shows the predicted mean time to cure for each of the models, based on 1000 simulations for each level of chemotherapy and initial tumor size. The Mendelsohn and Bertalanffy models are again outliers predicting on average about a year of treatment at high levels of chemotherapy for those who achieve a cure. The remaining models require less than 50 days of treatment at the highest level of chemotherapy we simulated to cure tumors of 100 cells. The models also predict that larger tumors will take longer to cure, with a roughly linear dependence at high doses of chemotherapy predicted by all models except the Mendelsohn and Bertalanffy models.

Note that the smallest value of C_0 is not quite high enough to fully suppress cancer growth in the deterministic version of the models [25], so we are depending entirely on stochasticity to drive the cancer cells down to 0. As the initial number of tumor cells becomes larger, this becomes more difficult. Not only does it take longer, but the time at which it occurs

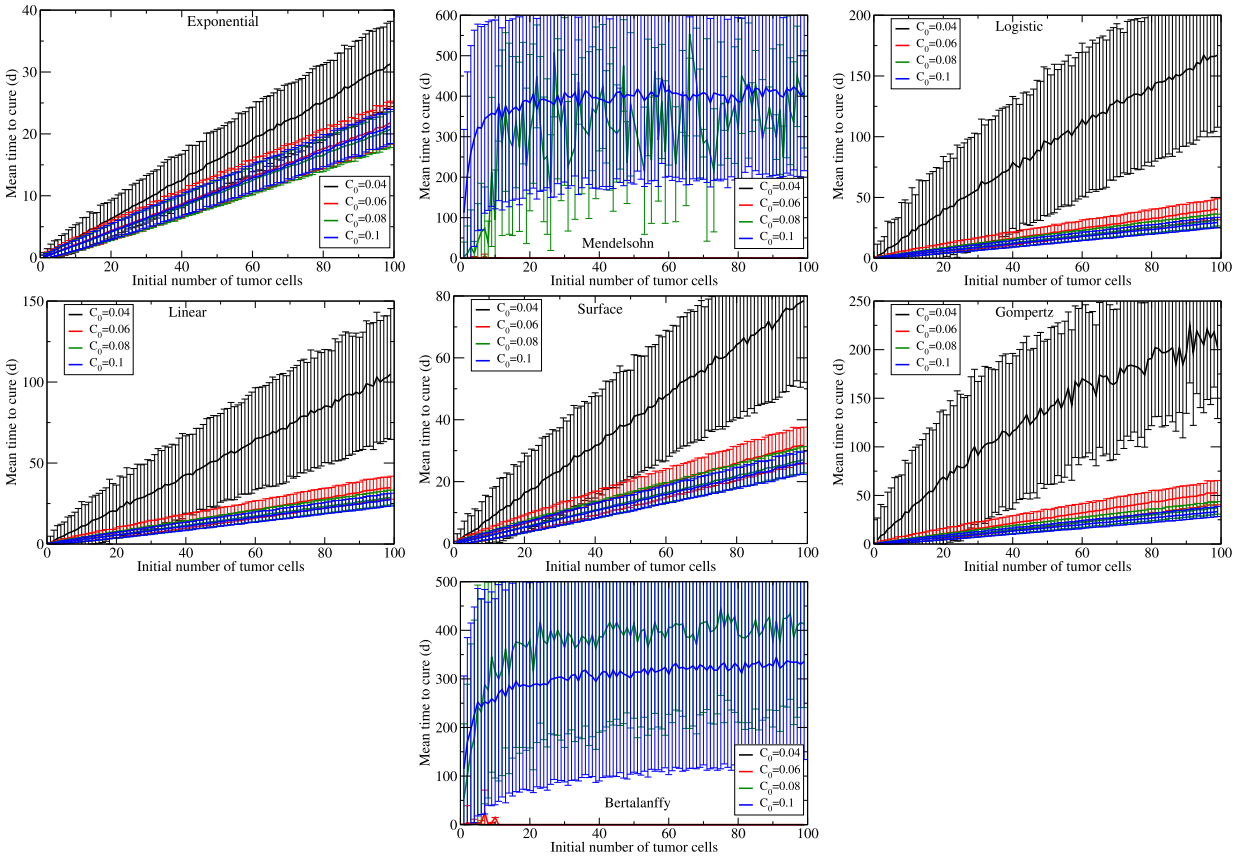

Fig. 4. Mean time to cure as a function of the initial size of the tumor. We simulated 1000 patients using different levels of chemotherapy and examined how long it took until the tumors were eradicated. Error bars indicate the standard deviation.

is more variable since the variability depends on $\sqrt{t_{\text{cure}}}$). An example of the increase in variability can be seen in Fig. 2 particularly for the Gompertz model where the treated curves run very close to $N = 0$, so some patients are cured relatively quickly while others have a few tumor cells linger for quite some time. For the Mendelsohn and Bertanlanffy models, the two lowest concentrations of chemotherapy actually don't ever cure the tumor. The higher concentrations start to sometimes cure the infection with the lower of those two doses occasionally curing the cancer and the highest concentration curing cancer more frequently. Thus it is always the concentration that is closest to the threshold concentration for cure that results in the most variable time to cure (longest error bars).

4. Discussion

We examined seven stochastic models of tumor growth based on commonly used ODE models to compare their predictions of how much chemotherapy is needed to cure the disease. The ODE versions of the models were all fit to the same experimental data, so in the absence of any treatment and stochastic effects, they all make similar predictions of tumor growth [25]. However, the addition of stochasticity, even in the absence of treatment, creates differences in the predictions of cancer growth with models showing several hundred cell differences at 25 days. In contrast, the ODE model fits to data gave very similar predictions up to 60 days [25]. In the absence of treatment, many of these models do not include cell death, so they very quickly grow to sizes where stochastic effects are not important and there is little variability from one simulation to another. The only model in our simulations that showed simulation to simulation variability in the absence of treatment was the Bertalanffy model, indicating that the birth and death rates for this model are fairly similar, leading to less steady growth of the tumor and therefore more variability in predicted time courses.

When chemotherapy is added to the models, there are notable differences in the predicted efficacy of treatment. While the single cell extinction probability is the same for all models examined here, the Mendelsohn and Bertalanffy models need substantially higher doses of chemotherapy to achieve a cure than the remaining models when multi-cell initial tumors are considered. These two models also predict a substantially longer time to cure than the remaining models. This is consistent with analysis of the ODE versions of the different models [25] that also showed these two models required a larger amount of chemotherapy to eradicate the tumor.

The drastically different predictions produced by the models serve to highlight the need to determine which growth model best describes tumor growth. As previously noted, the Mendelsohn model suggests that treatment would be needed for at least a year to cure as little as 40% of patients. In contrast, the exponential model requires the same level of chemotherapy for as little 20 days to cure all patients. Since our model assumes continuous chemotherapy, the difference in the amount of drug delivered to the patient between these two extremes is substantial. Our study thus indicates that mathematical models must be chosen and calibrated with care before being used to make patient treatment recommendations. If the Mendelsohm model is used to guide patient treatment, we could be overestimating the dose and treatment regimen needed to cure the patient. Given the toxicity of most chemotherapy [45,46], this could be dangerous for the patient. At the other extreme, if we use the exponential model to guide patient treatment, we could be underestimating the dose and timing of treatment, leading to failure of chemotherapy, which also leads to an adverse outcome for the patient. Thus the recent push to start incorporating mathematical modeling in the development of treatment plans for cancer patients [47–51], must be undertaken with great care. Our results suggest that such personalization will not be possible unless we accurately describe the cancer growth kinetics for that patient. If we simply assume a standard model of cancer growth with some standard parameters, the recommended dosage and treatment time could be dangerously wrong.

While this study uses highly simplified models, these growth models often form the basis for more complex models that are used to help guide patient treatment decisions [51–54]. Our results clearly indicate that the choice of growth model can lead to significantly different predictions about treatment outcome, so it is clear that due consideration needs to be given to choice of growth model. Previous studies suggest that the most appropriate tumor growth model depends on cell type [26,27] as well as the local environment [55,56], so growth model selection is not a trivial problem. In fact, several studies have found differences in typical model selection criteria (AIC, BIC, etc.) are minimal when experimental data sets are taken over a short time span [25,26,57]. One possible solution, then, is to take experimental data over a longer period of time, although this can be costly and time-consuming. Another option is to leverage experimental data containing both control and treatment information to help determine which growth model is most appropriate. While this also involves more cost and effort, the additional data could also be used to constrain drug effect models.

Our study also uses a simplified implementation of chemotherapy, assuming that chemotherapy reduces the number of tumor cells at a constant rate. Our incorporation of chemotherapy does not allow for consideration of the mechanism of action of the drug [58], which can change the predicted effectiveness of chemotherapy [59]. Additionally, the dose of chemotherapy is time-dependent and is more accurately modeled by a pharmacodynamic model [60]. The effect of both of these is considered in the work of Albano et al. [61] who reconstruct drug effect time courses from treatment data.

In summary, we have shown that the addition of stochasticity to simple mathematical models of cancer growth produces differences in model predictions that can lead to poor guidance for patient treatment. The addition of stochasticity also provides insight into the variability in patient cure rate and time to cure. Our results highlight the need for further investigation to determine which growth model is most appropriate for use in personalized medicine applications.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Samara Sharpe: Software, Validation, Formal analysis, Writing - original draft, Writing - review & editing. **Hana M. Dobrovolny:** Conceptualization, Methodology, Validation, Writing - review & editing, Supervision, Project administration.

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