Modeling pulsed drug treatment with a constant drug in cancer growth models

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Background

- Cancer is a leading cause of death worldwide, causing around one in every six deaths.
- Models can help predict how different treatments affect cancer cell growth in hopes of determining which will effectively kill a tumor.
- Realistic pulsed drug treatments can be computationally expensive and difficult to analyze mathematically.
- It's computationally easier to simulate constant drug treatment, so we examined whether pulsed treatment could be approximated by a constant drug simulation.

Methods

- We stimulated cancer growth curves under different treatment regimens (different doses, different timings) simulated by a pharmacokinetic model.
- They were then fitted with a growth curve assuming a constant drug concentration. Fitting is done by minimizing the sum of square residuals,

$$\mathrm{SSR} = \sum_{i=1}^{n} \left(y_i - f(t_i;\theta)\right)^2,$$

- The estimated constant drug dose was determined as a function of the applied drug dose and the dose timing.
- All code was written using python.

Modeling drug effect

The pharmacokinetic model of a drug treatment is

$$D(t) = \frac{D_{\mathrm{app}} \cdot k_a}{(k_a - k_e)} \left[\frac{[1-\exp(-nk_e\tau)]\,\exp(-k_e t)}{1-\exp(-k_e\tau)} - \frac{[1-\exp(-nk_a\tau)]\,\exp(-k_a t)}{1-\exp(-k_a\tau)} \right]$$

where D_{app} is the dose of the pill administered in units of mg, τ is the time between doses, k_a and k_e are the drug absorption and elimination rates, respectively, and n is the number of doses administered. Time, t, is measured from the n^{th} dose. The dose is used to calculate the drug efficacy through the $\mathrm{E_{max}}$ model,

$$\varepsilon = \frac{\varepsilon_{\max} D}{IC_{50} + D},$$

where $\varepsilon_{\max}$ is the maximum possible effect of the drug, IC_{50} is the drug dose at which you achieve half the maximum effect, and D is the applied dose of the drug. Drug efficacy is used to reduce the growth rate of cancer by multiplying the parameter a by $(1-\varepsilon)$.

Tumor Growth Models

We assess seven different models of tumor growth.

Exponential model:

$$\dot{V} = aV$$

Mendelsohn model:

$$\dot{V} = aV^b$$

Logistic model:

$$\dot{V} = a\left(1 - \frac{V}{b}\right)$$

Linear model:

$$\dot{V} = \frac{aV}{(V+b)}$$

Surface model:

$$\dot{V} = \frac{aV}{(V+b)^{\frac{1}{3}}}$$

Bertalanffy model:

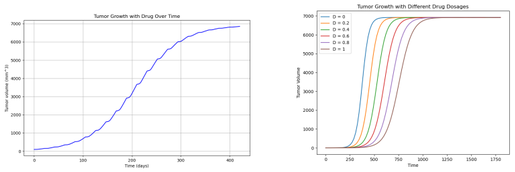
$$\dot{V} = V^{\frac{2}{3}} - bV$$

Gompertz model:

$$\dot{V} = aV \ln\left[\frac{b}{V+c}\right]$$

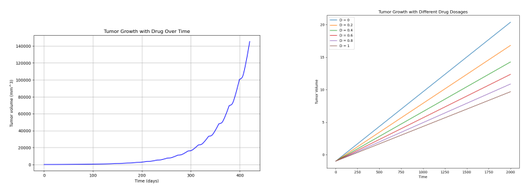
V is the volume of the tumor, and a, b, and c are parameters.

Logistic Model



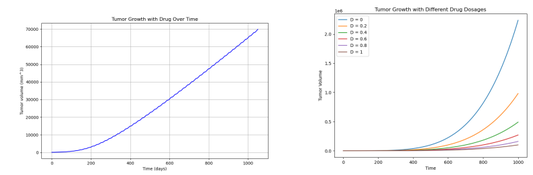
The logistic model assumes that all cells regularly divide until resources such as space or nutrients become limited.

Exponential Model



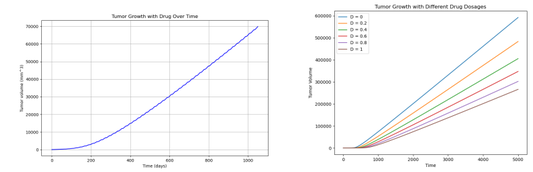
The exponential model assumes that all cells divide regularly.

Mendelsohn Model



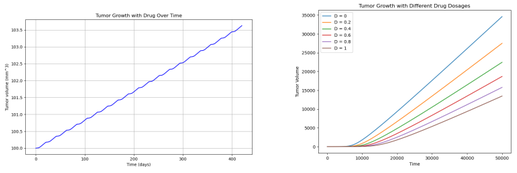
The Mendelsohn model assumes that some cells divide regularly while others are in a dormant state.

Linear Model



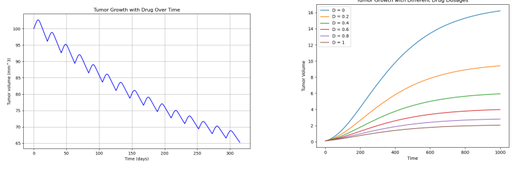
The linear model assumes that the number of new cells added remains constant at all times.

Surface Model



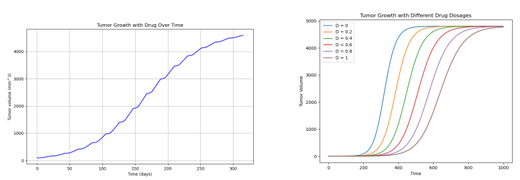
The surface model assumes that only the cells on the surface of a spherical tumor divide.

Bertalaffany Model



The Bertalanffy model assumes that cells near the surface of a spherical tumor divide and cells in the interior die.

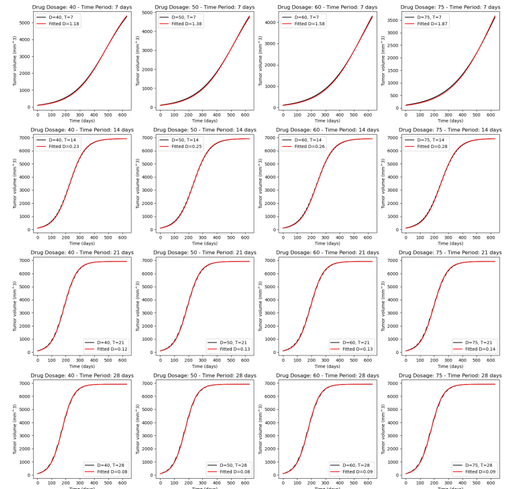
Gompertz Model



The Gompertz model assumes that cells are less likely to divide as they age.

Tumor Fitting

- With every model of tumor growth, we fitted a treated growth curve with a growth curve assuming a constant drug concentration. Below is an example of a fitted model of the Logistic curve.



Conclusions

- Different growth models exhibit varying rates of tumor volume reduction, with some models, like the Bertalanffy model, showing a more pronounced decrease in tumor volume over time.
- The selection of a growth model significantly impacts the final count of cancerous cells.
- In all cases, we are able to find a constant applied drug dose that reproduces the effect of a pharmacokinetic drug.