Characterizing the Efficiency of Anticancer Drug Treatment Using Mathematical Models

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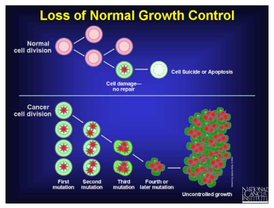
Cancer

- Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells.
- Cancer is initiated with mutation of a gene that controls the cell cycle.
- The mass of abnormal cells, a tumor, rapidly mutates and can metastasize throughout the body.
- Current treatments include surgery, radiation, and chemotherapy.



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Methods

- We used mathematical modeling to extract ϵ_{max} and IC_{50} for doxorubicin in a breast cancer cell line by combining a model for tumor growth with a model for the effect of a drug.
- We fit experimental data from Trebunova et. al. for 0 nM, 200 nM, 500 nM, 1000 nM of doxorubicin.
- I grow cells in a 12 well plate and I then count them in order to see how the cells grow. This data is then input into the computer in order to understand how much chemotherapy drugs will be needed to most effectively kill the tumor.

Tumor growth model

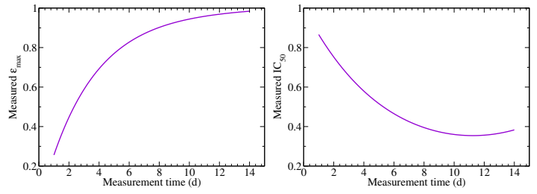
We use the logistic model,

$$\dot{V} = \lambda V\left(1 - \frac{V}{K}\right)$$

- where λ is the growth rate, V is the volume of the tumor, and K is the carrying capacity.
- This model assumes that there is some resource that limits growth of the tumor.

Motivation

- There are two quantities that characterize the effect of a drug: ϵ_{max} is the maximum possible effect from a drug and IC_{50} is the drug concentration where the effect diminishes by half.
- Current measurement techniques produce ϵ_{max} and IC_{50} estimates that depend on measurement time.
- Determining the effectiveness of drugs is determined by comparing the data for cells treated with chemotherapy drugs to cell data that is not treated with drugs. Meaning that determining ϵ_{max} and IC_{50} depends on when the control data measurement is taken for cells that are not treated with drugs.
- I want to fix this time dependence problem by finding a way of determining a time independent measurement of the effectiveness of the drug, using mathematical modeling.



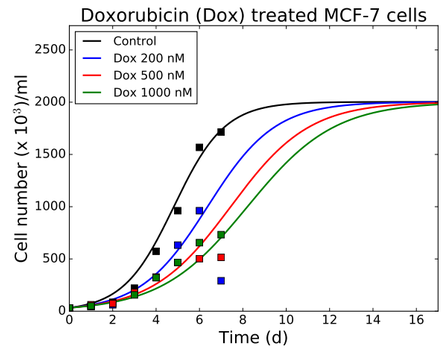
- The objective of my research is to use mathematical modeling to test a new method for measuring ϵ_{max} and IC_{50} that gives estimates independent of measurement time.

Implementing drug effect

$$\epsilon = \frac{\epsilon_{max} D}{D + IC_{50}}$$

- where ϵ is the drug efficiency and D is drug concentration.
- If we assume that the drug decreases growth rate, we multiply λ by $(1-\epsilon)$ to represent the effect of the drug in the model.
- If we assume that the drug decreases the carrying capacity, we multiply K by $(1-\epsilon)$ to represent the effect of the drug in the model.

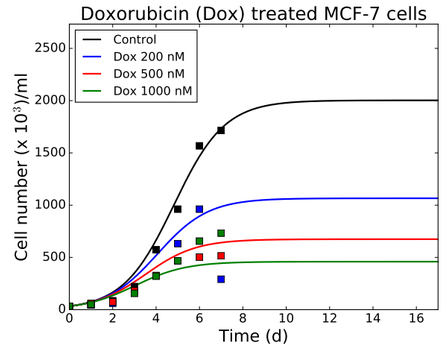
Drug effect on growth rate



λ	K	ϵ_{max}	IC_{50}
0.853 mL/s	2000 cell/mL	0.500	210 nM

- Our fits suggest that doxorubicin only lowers the growth rate of MCF-7 cells by 50%.
- About 210 nM is needed to achieve a 25% reduction in the growth rate.

Drug effect on carrying capacity

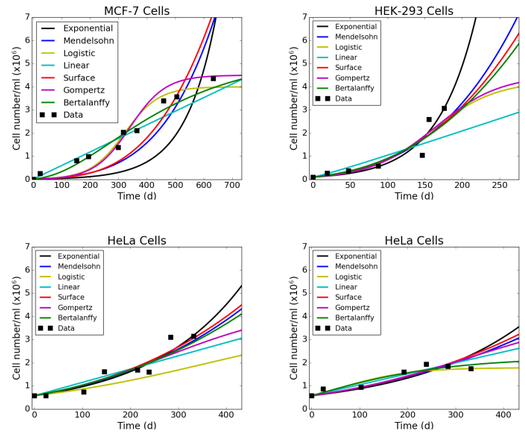


λ	K	ϵ_{max}	IC_{50}
0.853 mL/s	2000 cell/mL	0.919	193 nM

- Our fits suggest that doxorubicin can lower the carrying capacity of MCF-7 cells by 92%.
- ~190 nM of doxorubicin will reduce the carrying capacity of cells by 46%.

Experimental Work

- Other ODE models have been proposed to model cancer cell growth.
- We are in the process of counting HEK, HeLa, and MCF-7 cells for control data.
- We will test other growth models and models of drug action.



Conclusions

- We used mathematical models to extract measurement time independent estimates of ϵ_{max} and IC_{50}.
- We determined values for ϵ_{max} and IC_{50} assuming doxorubicin reduces growth rate or reduces the maximum number of cells.
- The IC_{50} was similar in both cases, but doxorubicin is better at reducing the maximum number of cells.
- This work is intended to characterize the efficacy of anticancer drug treatments and determine the correct doses before trying those in patients to get the most effective therapeutic treatment for patients.

Future Directions

- We will develop more complex growth and drug models to better characterize drug treatments.