Understanding the Effect of Measurement Time on Drug Characterization

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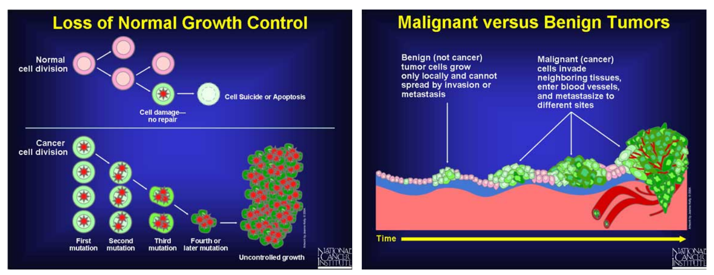
Cancer

- Cancer is a disease characterized by uncontrolled growth and spread of abnormal cells.
- Cancer is initiated with mutation of a gene that controls the cell cycle.
- The tumor rapidly mutates and can metastasize throughout the body.



Images from: http://www.web-books.com/eLibrary/Medicine/Cancer/04MB9.html

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Motivation

- There are two quantities that characterize the effect of a drug: $\epsilon_{\max}$ 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 $\epsilon_{\max}$ and IC_{50} time-dependent estimates.
- Objective: use mathematical modeling to test a new method for measuring $\epsilon_{\max}$ and IC_{50} that gives time-independent estimates.

Logistic Model

This model assumes that there is some resource that limits growth of the tumor.

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

where a is the growth rate, V is the volume of the tumor, and b is the carrying capacity.

Relative Drug Effect

$$R = 1 - \frac{V_{\text{drug}}}{V_{\text{no drug}}}$$

where V_{drug} is the number of cells after drugs are applied to the cells and $V_{\text{no drug}}$ is the number of cells when no drugs are applied to cells.

Implementing drug effect

- To understand how the drug affects the growth of tumor cells, we use the drug efficiancy, ϵ. ϵ is given by

$$\epsilon = \frac{\epsilon_{\max} D}{D + \mathrm{IC}_{50}}$$

where ϵ is the drug efficiency and D is drug concentration.

- If we assume that the drug decreases growth rate, we multiply a 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 b by $(1-\epsilon)$.

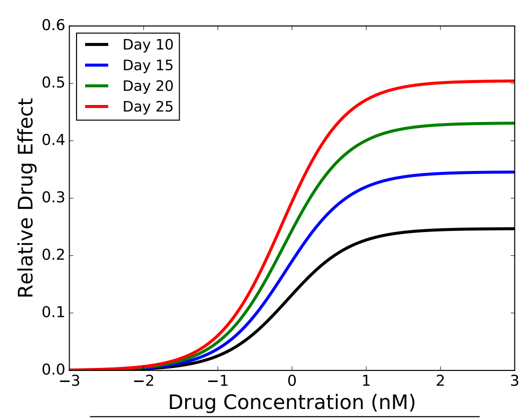
Methods

Fitting was performed by minimizing the sum of squared residuals (SSR),

$$\mathrm{SSR} = \sum_i (x_i - m_i)^2,$$

where x_i are the experimental data points, and m_i are the predicted model values at the same times.

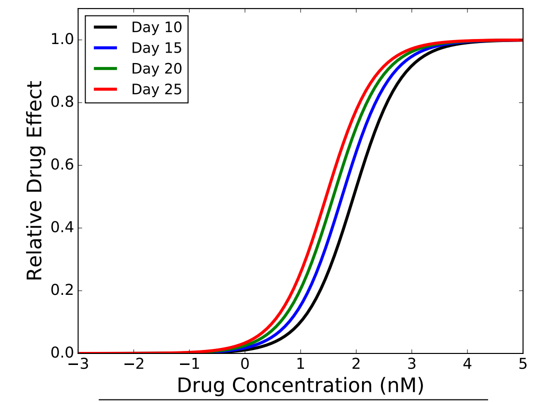
Drug Reducing a



Days	$\epsilon_{\max}$	IC_{50}
Day 10	0.247	0.873 nM
Day 15	0.346	0.817 nM
Day 20	0.431	0.767 nM
Day 25	0.504	0.720 nM

- $\epsilon_{\max}$ increase and IC_{50} decreases with measurement time.
- This is a problem because the day that is chosen to measure $\epsilon_{\max}$ and IC_{50} causes there to be a different recommended ideal dose.

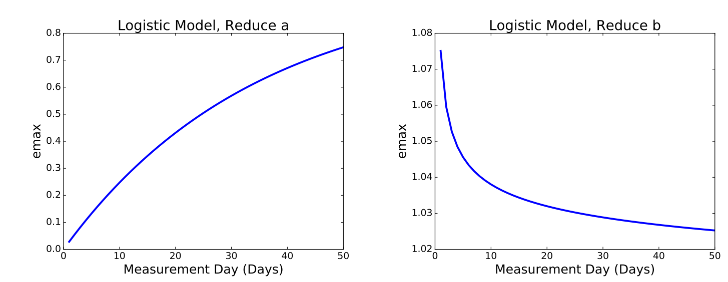
Drug Reducing b



Days	$\epsilon_{\max}$	IC_{50}
Day 10	1.038	5.722 nM
Day 15	1.034	3.765 nM
Day 20	1.032	2.848 nM
Day 25	1.030	2.477 nM

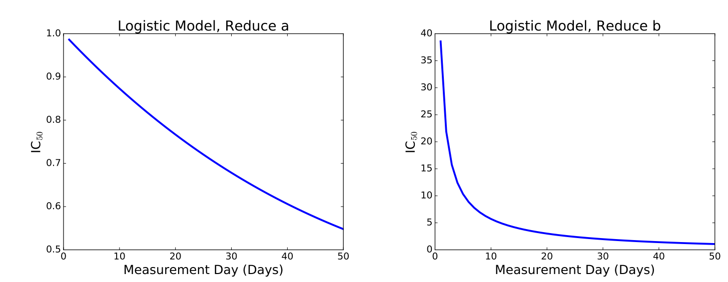
- IC_{50} decreases with increasing measurement time.
- $\epsilon_{\max}$ does not change much, but increases slightly with measurement time.

$\epsilon_{\max}$ for Relative Drug Effect



- When a drug acts on a, $\epsilon_{\max}$ increases steadily.
- There are little changes to $\epsilon_{\max}$ when a drug acts on b and the largest decrease happens during the first 10 days.

IC_{50} for Relative Drug Effect



- These figures show drastic differences in IC_{50} values when measurements are taken on different days.
- Predicted IC_{50} drastically decreases during the first 10 days for a drug that reduces b.

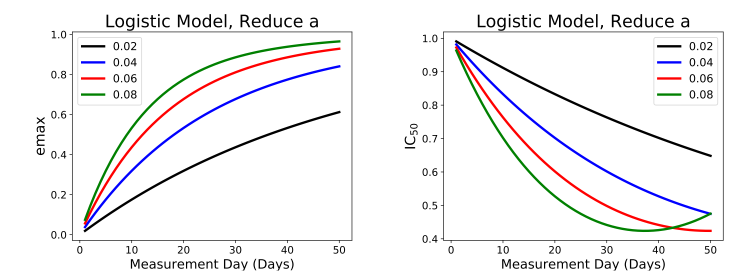
Sensitivity Analysis

Derivation of Sensitivity Analysis:

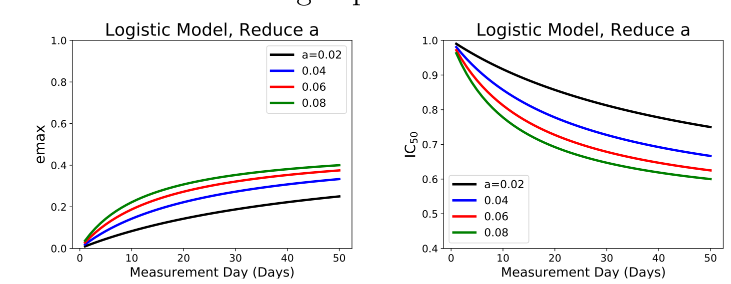
$$\epsilon_{max,measured} = \frac{\epsilon_{\max} a t_m}{2 + a t_m + \epsilon_{\max} a t_m}$$

$$\mathrm{IC}_{max,measured} = \frac{(2 + a t_m)\mathrm{IC}_{50}}{2 + a t_m + \epsilon_{\max} a t_m}$$

Computationally Modeled



Using Equation of Line



- These figures show a sensitivity analysis for parameter a to show how choice of initial conditions for growth rate changes the predicted $\epsilon_{\max}$ and IC_{50} values.
- We found the growth rate parameter caused the largest differences in the IC_{50} values.
- Differences in figures due to Taylor expansion.

Conclusions

- We used mathematical models to understand how IC_{50} and $\epsilon_{\max}$ change with measurement time.
- The largest difference between the relative drug effect on the growth rate and the relative drug effect on the carrying capacity is that $\epsilon_{\max}$ increases with time for growth rate, but $\epsilon_{\max}$ decreases with time for carrying capacity.
- For both drugs, IC_{50} decreases with measurement time.

Future Directions

- Develop more complex growth and drug models to better characterize drug treatments.
- Test model fitting on theoretical data by generating a fake data set, then see if we can get the correct predicted fit.