Effect of the Hill coefficient on estimates of drug efficacy

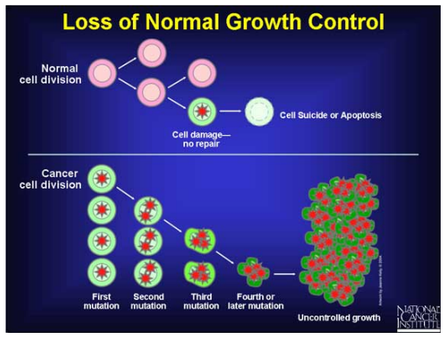
Gabriel McCarthy and Hana M. Dobrovolny

Department of Physics and Astronomy, Texas Christian University, Fort Worth, TX, USA

Background

- Cancer is one of the leading causes of death in the U.S.
- The estimated national expenditures for cancer in 2017 were 147.3 billion dollars in cancer care in the United States.
- According to the American Cancer Society, men have a 39.66% probability of getting the disease in their lifetime and women have a 37.65% chance of getting the disease.
- The primary treatment for cancer is chemotherapy. A large variety of drugs are already in use and more are constantly being tested.
- It is important that a drug's effectiveness is properly characterized before trying the drug in patients.

What is cancer?



Cancer is a group of illnesses caused by the uncontrolled growth of mutated cells that can group together and form a tumor.

ODE mathematical model

We use the logistic model of cancer growth

$$\frac{dV}{dt} = rV\left(1 - \frac{V}{k}\right)$$

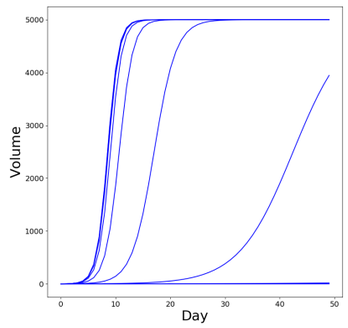
- The tumor's growth increases at rate r.
- The volume is divided by the carrying capacity k, so when the volume is equal to the carrying capacity this term is equal to one. That means that there is no more growth as the volume gets large since the slope changes to zero.

Modeling ϵ_{max} and IC_{50}

We model the effectiveness of the drug with

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

- ϵ_{max} is the drug's maximum efficacy, IC_{50} is the dose at which the drug is at 50% effectiveness, and m is the Hill coefficient.
- The Hill coefficient is a measure of the interaction between drug and binding site.
- If the drug changes a tumor's growth rate, increasing dose gives slower-growing tumors.

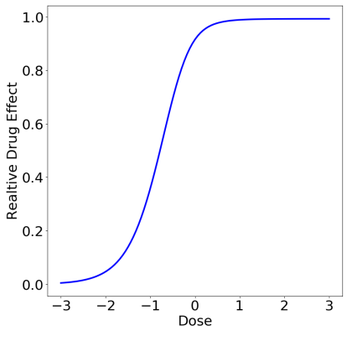


Relative drug effect

The relative drug effect is found by

$$\mathrm{RD} = 1 - \frac{V_{\mathrm{treated}}}{V_{\mathrm{untreated}}}$$

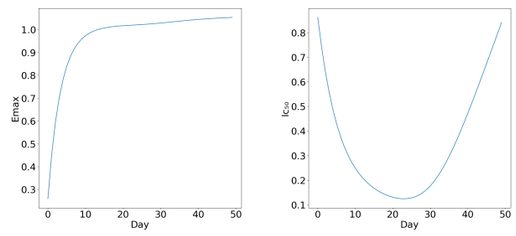
where volume measurements are made on a single specified day. A dose response curve plots the relative drug effect as a function of dose.



For each measurement day there is a different dose response curve. This gives us the ability to measure the change in ϵ_{max} and IC_{50} over each day.

Change in ϵ_{max} and IC_{50} with measurement time

We assume that ϵ_{max}, IC_{50} and m are equal to 1 and use our model to see what values of ϵ_{max} and IC_{50} would be measured on different days.

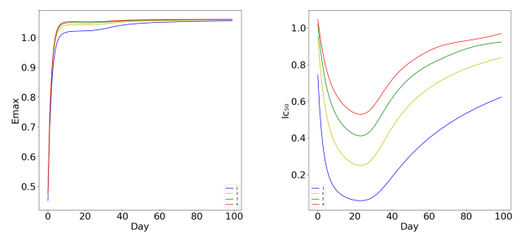


- ϵ_{max} eventually equals one, but IC_{50} never equals 1.
- We underestimate the maximum effectiveness of the drug and underestimate the doses needed to see an effect.
- IC_{50} starts high, but quickly drops and then recovers, whereas the ϵ_{max} grows and then plateaus.

Effect of the Hill coefficient

A Hill coefficient bigger than one means that drug binding at one site makes it easier for drugs to bind at other sites. We modeled the change in IC_{50} and ϵ_{max} with the change in the Hill coefficient.

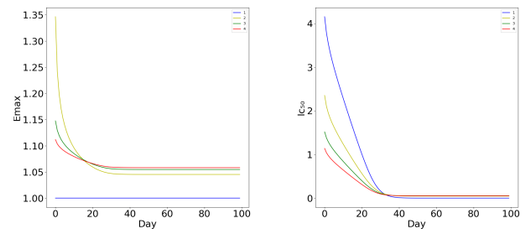
$$\frac{dV}{dt} = \left(1 - \frac{\epsilon_{max} D^m}{IC_{50}^m + D^m}\right) rV\left(1 - \frac{V}{k}\right).$$



- Changing the Hill coefficient doesn't have much effect on the measurement of ϵ_{max}.
- Increasing the Hill coefficient increases the measured values of IC_{50} making them closer to the real value.

Drug affecting carrying capacity

When we put the Hill coeffiecnt on the carrying capacity it is effecting or limiting how much room or capacity there is for the tumor to grow.



- The IC_{50} greatly increases and is on a logarithmic scale whilst the ϵ_{max} remain in the same range.
- Both the IC_{50} and ϵ_{max} start high and plateau quickly.

Conclusions

- When we add the the Hill coefficient we observe that both the ϵ_{max} and IC_{50} estimates differ from their real values.
- The Hill coefficient changes the IC_{50} and ϵ_{max} in different ways — it has a bigger impact on estimates of IC_{50}.

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Cancer is one of the leading causes of death in the U.S and over 147 billion dollars are spent on it every year. Cancer is the uncontrolled growth of mutated cells, and around one out of three people get it. Cancer is a serious health risk to the world. Drugs are one of the common treatments of cancer and need to be studied in the lab before being used in humans. We used mathematical models to look at how the effectiveness of a drug changes as its ability to bind to proteins changes.