A Stochastic Modeling of Lung Cancer Cells

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Abstract:

Targeted therapies represent an alternative drug-based and less invasive method of combating various forms of cancers. However, these methods often eventually fail, as they lead to a development over time of cancer cell populations that are rendered resistant to drugs used in such targeted therapies. As a result, in order to optimize the length of time during which a patient may utilize such therapies in relative comfort, it is useful to measure and track just how these cancer cell populations change over time and in response to various conditions. This project employs the use of stochastic (random) processes to create a basic model of how these populations grow over time in response to varying environments, including different initial populations, birth rates, death rates, and levels of treatment. By combining various factors into a workable model, predictions concerning the results of various treatments can be made, resulting in a more optimized dosage pattern tailored to the various characteristics of a given case. Although the model created in the scope of this project does not capture all potentially important factors of a cancer cell population, the results suggest that further research and a more complex model could yield highly useful results in the field of cancer cell targeted therapies.

Mathematical Modeling-A Process

When examining a particular aspect of the world around us, we are often faced with a limitation in the amount of data we can collect and process. Mathematical modeling is a method of examining and mathematically interpreting these results in the form of a model, which may in turn predict a larger range of results than were originally obtainable through data. According to Daniel Maki and Maynard Thompson of Indiana University, modeling begins the identification of some real world problem, in this case the acquired resistance to erlotinib therapies of lung cancers. After data is combined and interpreted, mathematical concepts and abstractions formulate an extended mathematical model, expanding upon the original data. In this case, data concerning lung cancer cell populations held in isolation involving different environments and treatments are expanded upon through the formulation of equations relating these factors. Once the mathematical model is created, predictions and conclusions it makes are compared with real data in a continuing process of refining and updating the model; in this way, more insightful and accurate predictions can be made.

Birth/Death Process and Cell Populations

To evaluate the effectiveness of a targeted therapy over time, we establish a birth/death process to model the population's size. Before any models can be made, several assumptions are made:

- We assume that the birth/death process is Markovian; that is, the current state of the population is the only information used in calculating the next transition in the system.
- We summarize all sources of population increase and decrease with rates referred to as the birth and death rates of the system. All reasons for cell birth and death are to be summarized by these rates.
- We do not take into account any systems other than the cancer cell population itself. This omits the interaction of the population with the rest of the body as well as any external mutations. The model is based off of cancer cell populations held in isolation, thus creating this assumption.

After these assumptions are made, a cell population is initially modeled by a continuous birth-death process. To simulate this, the model uses the current cell population alongside accompanying birth and death rates to generate the time p until the next "event," which is defined as a positive or negative change in the population. So, with cell population Z, birth and death rates b and d, and starting time t=0, we establish a basic birth-death process with function $p=(-\ln(1-x)/(d+b))$, where x is a randomly generated number in the interval (0,1). Once the time until the next event is generated, time is updated to $t=t+p$ and another random number y in (0,1) is generated. If $y<(b/(b+d))$, then we say that a cell birth occurred; otherwise, a cell has died. The population is then updated accordingly. This process continues until some predetermined time, and a simple birth-death process results. This, it turns out, is insufficient. However, it lays a framework for the rest of the model.

Carrying Capacity

Although the simple birth/death process does capture the exponential nature of cell growth, environmental constraints places a limit on population. In this particular case, cell populations were grown in isolation to create this limitation. For this model, we label N as the carrying capacity of the environment. We then redefine birth rate in terms of the carrying capacity as $b=c*Z*(N-Z)$, where c is a constant. Thus, as population rises, birth rate rises as well until the population nears capacity, at which point birth rate slows until it flattens at the capacity itself. The result is the familiar S-shaped curve in Figure 1, which models an individual cell population without treatment:

Figure 1

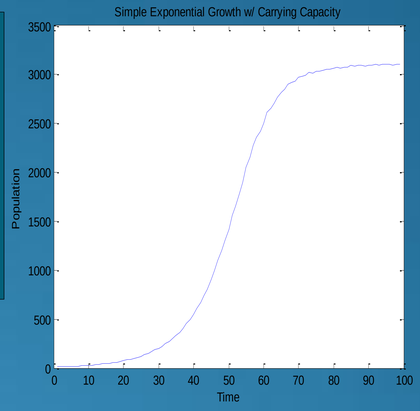
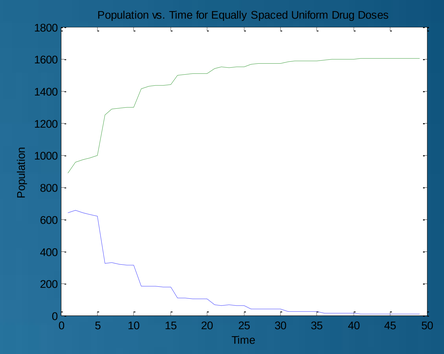


Figure 4: Doses taken at regular times



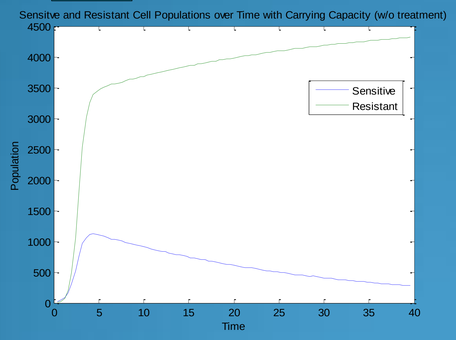
Sensitive and Resistant Cells

The development of cells resistant to targeted therapy treatment is the primary cause of their eventual failure; as such, the growth of these cells must be incorporated in the model. To do this, we introduce a second population Z_2 with separate birth and death rates b_2 and d_2. Its population and accompanying rates are then used in the new determination of p. Now, whenever an event occurs, one of a few potential outcomes occurs:

- A sensitive cell (in population Z) divides.
- A sensitive cell dies.
- A sensitive cell mutates (at rate m) and becomes resistant (Z_2 increases).
- A resistant cell (in population Z_2) divides.
- A resistant cell dies.

This creates a two-population birth-death process with a minor gain in overall fitness to the resistant cell population. Note that no treatment has yet been included in the model. Figure 2 illustrates these two populations.

Figure 2



Dosing Strategies

The ultimate question to be answered by the model is how drugs should be administered to a patient in order to prolong their effectiveness. Thus, different methods of administering these targeted therapies may yield different patterns in the populations of sensitive and resistant cells. Figures 4-6show two possible dose strategies.

Figure 5: Decreasing doses taken at regular times

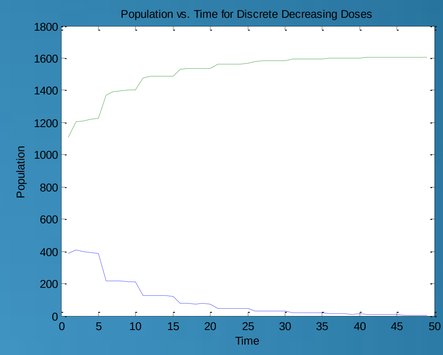


Figure 6: Continuous Increasing Dose

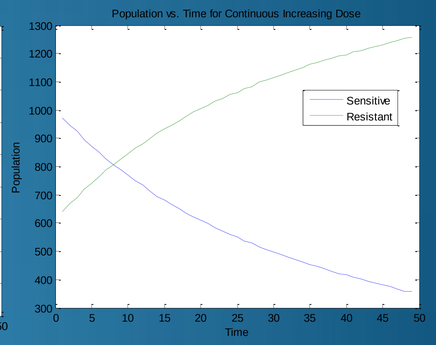
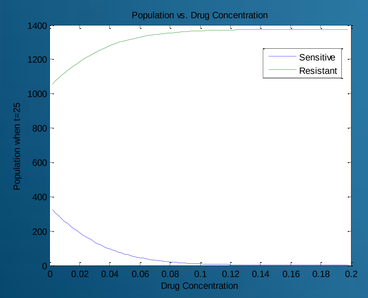


Figure 3



Introduction of Treatment

The goal of targeted therapies is to limit the growth of a cancer cell population for as long as possible. We introduce a treatment factor into the model as some drug concentration of erlotinib, a treatment for lung cancer limiting overactive EGFR (a cell growth factor receptor which, when overactive, may result in the excessive division of cancerous cells). This treatment is modeled as a reduction in each cell's birth rate based upon drug concentration. However, as Figure 3 indicates, the model reflects the corresponding increase in concentration over time of cells resistant to erlotinib. This increase becomes more pronounced as drug concentration increases, due to the relative increase in cell fitness.

Conclusion/Further Research

This model, while far from complete, gives some indication of the nature of these cancer populations and corresponding treatment patterns. By comparing these predicted results with future data, we are able to refine the process and gain further insight on the nature of these populations. Therefore, we conclude that further data will be necessary as part of an ongoing process of incorporating new information, updating the model, and comparing its predicted values with actual data. Further research on this topic in this emerging field is available in a variety of different forms, such as the 2011 American Chemical Society article *Evolutionary Modeling of Combination Treatment Strategies To Overcome Resistance to Tyrosine Kinase Inhibitors in Non-Small Cell Lung Cancer* by S. Mumenthaler, J. Foo, et. Al. or other such articles.

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