Modeling Cancer Evolution

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We develop some compartmental models of cancer evolution. Starting with a basic model consisting of single compartment, we develop different type of models of cancer undergoing chemotherapeutic treatments, including a model where cancer cells acquire resistance against chemotherapy. Through the modeling of amount of resistance acquired, we try to analyse the benefits/requirements of further chemotherapeutic treatments.

INTRODUCTION

Cancer is globally causing a large number of deaths every year. Even having treatments like chemotherapy does not always have a cure of disease, but may increase life expectancy of the patent. So understanding the evolution of cancer and the effects of treatments at cellular levels is becoming essential. Cancer is made up of a variety of cell types making the modeling more complex. Different set of cell types having different set of assumptions for behaviour of rest of the cells can form a lot of models. The report contains models for cancer evolution, treatment of chemotherapy and resistance acquired against chemotherapy. First, we report the necessary biological information, then we focus on developing the models, and lastly deriving results and analysis of how the developed models can be used.

CANCER EVOLUTION AND CHEMOTHERAPY UNDERSTANDING

During the life cycle of a cell, a cell has to pass some *checkpoints* to ensure integrity of the DNA. Upon failure of passing these checkpoints, the cell either gets repaired or destroys itself (also called *apoptosis*). But upon failure of these checkpoint mechanisms, the result may lead to a *malignant* cell which is *mutated* from a regular cell and become a cancerous cell which can replicate itself in large numbers and lead to developing of cancer. A *malignant* cell cannot spread its *mutation* to other normal cells. But at the end of life cycle, when a cell is divided into two daughter cells, the *mutation* is forwarded to daughter cells . A sufficiently large amount of cancer cells create tumor, and further growth(more than 10^{12} cells) cause death of the patient.

Cancer cells can be classified into compartments according to their proliferation capabilities. The cells active in cell division make up the proliferating or growth fraction. Those cells which have potential to grow into growth fraction, but currently does not proliferate are sectioned in clonogenic compartment.These cells are in resting phase currently and will naturally become active again by entering in growth fraction. Cells which are not capable of further division are called end cells. A proliferating cell does not convert into clonogenic but after a cell division, daughter cells may go to any of the compartments depending upon aggressiveness of cancer. Aggressive cancers have higher probability of daughter cells remaining in the proliferating fraction while slow developing cancers have higher probability of producing clonogenic cells.

A chemotherapeutic treatment is application of a cytotoxic agent which cause cells to undergo *apoptosis*(death of a cell). It also causes migrations from clonogenic to growth fraction.Chemotherapy is cyclic treatment. A Cycle specific agents can only destroy proliferating cells. This treatment causes a clonogenic cell to be converted into a proliferating cell and then destroying proliferating cells, thus decreasing total amount of cancer cells(also called *cancer burden*). With each treatment, system acquires a better resistance to the treatment, so generally multiple types of cytotoxic agents are treated. Our work includes modeling using only one type of cytotoxic agent. After the modeling of our problem, we will be able to say, after a certain acquirement of drug resistance,a further treatment is beneficial or not for the patient.

DEVELOPMENT OF MODELS

Some models have only one type of cancer cells, which sometimes incorporate drug resistance. Basic model for drug resistance in cancer is developed by Tomasetti [3]. Also a two compartmental model is developed by Panetta [2]. Using different types of cells help in better modeling of cancer. We develop a four compartmental model reducing the simplicity of previous ones. The models of the report are referred from westman et al [4].

HOMOGENEOUS CANCER MODELS

Homogeneous cancer models consist of a single cell type with all of the cells in the proliferating compartment. The main strength of this method is that we can easily select the parameters so that we get the consistent result with the clinical data we have and it can be used

to gain insight in the real problem. However, this model is an oversimplification of the actual phenomenon.

No treatment Model

General form for the evolution of cell population is:

$$\frac{dp(t)}{dt} = p(t)f(p(t),t) \tag{1}$$

where $p(t)$ is the population and $f(p(t),t)$ is the growth rate. The way that the population will evolve depends on the form of the growth rate, $f(p(t),t)$. The following 3 forms of the growth are used in various studies.

$$f(p,t) = \begin{cases} c_1 & ExponentialGrowth \\ c_2(1-p/K) & LogisticGrowth \\ c_3 log(K/p) & GompertzGrowth \end{cases}$$

where c_i and K are positive constants that represent the leading order exponential growth and the carrying capacity, respectively. For small population sizes the growth is exponential but as the population becomes larger it cannot keep on increasing exponentially. The unbounded growth is clearly not realistic for cancer in a finite host. The logistic growth exhibits a more realistic sigmoid curve which captures the exponential growth rates for small population sizes and limits the population to an appropriate carrying capacity to approximate over-crowding effects. Logistic growth under controlled conditions is almost as aggressive as exponential growth, except near the tumor carrying capacity, so it might be a good model for extremely aggressive cancers. The Gompertz growth, like the logistic, is also sigmoid in shape but differs in that the solution to equation 1 is an exponential of an exponential with saturation. It is a type of mathematical model for a time series, where growth is slowest at the end of a time period. So it is more sensitive to the saturation effect compared to logistic growth for same initial condition. There is a lot of literature taking Gompertz function to model growth of cance cell,one can be found here [1].

Treatment Model

In treatment models understanding the way the drug interacts with the human body is the most important part. This entails many different concepts such as the mode by which the drug is to be administered, the effects of toxicity, the way in which the drug exits the system, and the development of resistance to the drug. Here we have assumed that the drug administrations and the effects of chemotherapy are instantaneous. In the model time scale of one day the majority of effects of the treatment will be affected in one time unit so our assumption is justified to some extent albeit not completely realistic. In this model we assume that maximum allowed dose of the drug is administered to kill as many cells as possible. We define time impulse function Δ_i as follows:

$$\Delta_i(t) = \begin{cases} 1, t = t_i \\ 0, otherwise \end{cases}$$

Effects of treatments are introduced in the model using this impulse. Let us consider m treatment cycles where each cycle consists of n treatments. So total $N = m \times n$ treatments are given. The effect of these N treatments can be incorporated in the model(1) as follows:

$$\frac{dp(t)}{dt} = (f(p(t),t) - \delta(p(t),t) - \sum_{i=1}^{N} \Delta_i k_i(t))p(t) \tag{2}$$

Here i takes the values from 1 to N denoting individual treatments given at time t_i. k_i represents the kill rate for treatment i which represents the fraction of cells killed. The $\delta(p(t),t)$ represents the natural cell death rate. This homogeneous model does not contain any information about the types of cells involved in the treatments or the development resistance against the drug administered so the scope of this model is quite limited.

HETEROGENEOUS CANCER MODELS

Heterogeneous cancer models consist of multiple cell types which are proliferating and clonogenic in our case. We extend the model to four compartments which will help to reduce simplicity of models and make it more realistic.

No Treatment Model

Let Proliferating and clonogenic compartments be $P(t)$ and $C(t)$. The first *malignant* cell has to be in growth fraction(proliferating ell) at the time of birth. So initial conditions will be, $P(0) = 1$ and $C(0) = 0$. This condition also restricts further parameters to fulfill condition $P(t) \geq 0$ for all $t \geq 0$. Following model describes heterogeneous cancer without any treatment. Growth rate of compartment, i.e., $f(P,C,t)$ is of Gompartzian relative rate of change form, depending on total population.

$$f(P,C,t) = \lambda * log(\frac{K}{P+C})$$

where, λ is growth rate and K is carrying capacity. The total cell population being the carrying capacity, we consider that only proliferating cells undergo division(make

new cells) and we directly multiply this rate f to P(t) because all of them are active in the division. Death rates are δ_p and δ_c, accounting for cell death(apoptosis) and conversion to end cells. $\alpha(P,C,t)$ is probability at which a daughter cell becomes clonogenic after cell division which makes probability of a daughter cell staying in growth fraction $1-\alpha(P,C,t)$. Cells migrating naturally from clonogenic to growth fraction have probabily of migrating $\beta(P,C,t)$. The final equations look like,

$$\frac{dP}{dt} = (1-\alpha(P,C,t))f(P,C,t)P + \beta(P,C,t)C - \delta_p P$$

$$\frac{dC}{dt} = \alpha(P,C,t)f(P,C,t)P - \beta(P,C,t)C - \delta_c C \quad (3)$$

Treatment Model

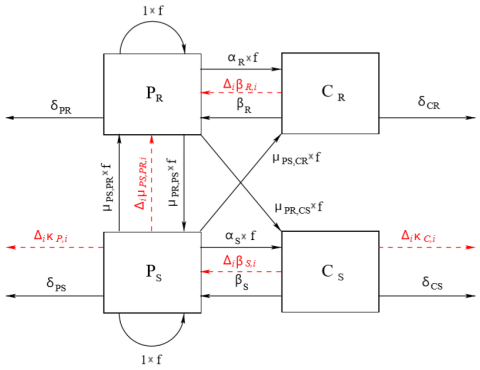

FIG. 1. Diagram representing treatment resistance model with four compartments

Using same initial conditions as no treatment model, this model employs treatment with same characteristics as in homogeneous model such as instantaneous effects and discrete cyclic application. Most important effect of chemotherapy is showed by $\Delta_i\beta_i$ which is transfer coefficient of cells migrating from clonogenic to growth fraction. This recruitment is because of the loss of proliferating cells due to treatment. Co-efficients $\Delta_i k_{C,i}$ and $\Delta_i k_{P,i}$ stand for the cells killed in each section during the treatment. As described in above section, for cycle specific cytotoxic agents(e.g. chemotherapy), $k_{C,i} = 0$. Following are the system of equations,

$$\frac{dP}{dt} = (1-\alpha(P,C,t))f(P,C,t)P + \beta(P,C,t)C - \delta_p P - \sum_{i=1}^{N}\Delta_i(k_{p,i}P - \beta_i C)$$

$$\frac{dC}{dt} = \alpha(P,C,t)f(P,C,t)P - \beta(P,C,t)C - \delta_c C - \sum_{i=1}^{N}\Delta_i C(k_{c,i}+\beta_i) \quad (4)$$

Treatment Resistant Model

The previous model does not incorporate capability of resistance of cells towards treatment. We make compartments of susceptible(towards treatment) and resistant cells, denoted by S and R respectively. Resistance may be intrinsic or acquired. But the resistance can be lost after mitosis(cell division) due to mutation of DNA of the daughter cells. Upon each treatment, a small fraction of proliferating susceptible cells will acquire resistance and a small fraction dies. Because the chemotherapy does not affect clonogenic cells, susceptible clonogenic does not migrate to resistant directly, they just migrate to corresponding growth fraction. The drug resistance is assumed to be complete(only binary value). Initially, $P_S(0) = 1$ $P_R(0) = 0$ $C_R(0) = 0$ $C_S(0) = 0$. $f(P_R,P_S,C_R,C_S,t)$ and system of equations are as follows.

$$f(P_R,P_S,C_R,C_S,t) = \lambda log(\frac{K}{P_R(t)+P_S(t)+C_R(t)+C_S(t)})$$

$$\frac{dP_R}{dt} = [(1-\alpha_R-\mu_{PR,CS}-\mu_{PR,PS})P_R+\mu_{PS,PR}P_S]f+\beta_R C_R - \delta_{PR}P_R + \sum_{i=1}^{N}\Delta_i(\mu_{PS,PR,i}P_S + \beta_{R,i}C_R)$$

$$\frac{dP_S}{dt} = [(1-\alpha_S-\mu_{PS,CR}-\mu_{PS,PR})P_S+\mu_{PR,PS}P_R]f+\beta_S C_S - \delta_{PS}P_S + \sum_{i=1}^{N}\Delta_i(-\mu_{PS,PR,i}P_S + \beta_{S,i}C_S - k_{P,i}P_S)$$

$$\frac{dC_R}{dt} = [\alpha_R P_R + \mu_{PS,CR}P_S]f - \beta_R C_R - \delta_{CR}C_R - \sum_{i=1}^{N}\Delta_i\beta_{R,i}C_R$$

$$\frac{dC_S}{dt} = [\alpha_S P_s + \mu_{PR,CS}P_R]f - \beta_S C_S - \delta_{CS}C_S - \sum_{i=1}^{N}\Delta_i(\beta_{S,i}+k_{C,i})C_S \quad (5)$$

where, $\alpha, \beta, \delta_p, \delta_c$ coefficients are subscripted with corresponding R and S. The fact that a cell division can cause both R and S type of cell, forms new parameters defined as $\mu_{i,j}$, where i denotes parent compartment and j denotes daughter compartment. Again, $\Delta_i k_{C/P,i}$ is loss due to chemotherapy. Both compartments have *back migration* transfer constants $\Delta_i \beta_{R,i}$ and $\Delta_i \beta_{S,i}$. Acquired resistance is shown by $\Delta_i \mu_{PS,PR,i}$. Now number of compartments grow exponentially, as more cytotoxic agents are given. Total 2^{M+1} compartments will be made if M number of cytotoxic agents are given.

RESULTS

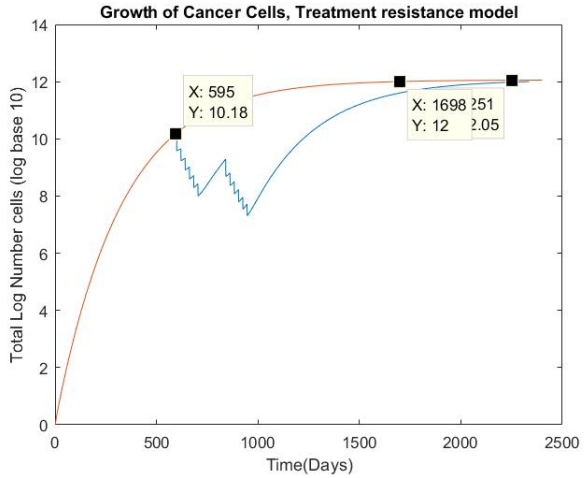

FIG. 2. Logarithm of total population size vs time of cancer growth for 2 treatment cycles

The blue curve in the figure 2 corresponds to the growth of the system having a single growth cell(i.e $P_S(0) = 1$) at $t = 0$. The red curve shows the growth if no treatment was introduced during the growth. The probabilistic rates are taken to be uniform for this example. For exact values of the rates refer to the code. The patient dies if the population of the cancer cells reaches 10^{12}. In the absence of treatment, it can be observed that the patient dies before 1700 days, where as with two treatment cycles the patient dies at 2336 days. Hence the treatment increases the life expectancy by approximately 39%. If the third treatment cycle is administered, the first treatment of the third cycle shows nominal effect and the rest of the treatments do not show any clinical benefits as can be seen from figure 3. This result can be explained by observing that the total population that can be effectively treated, at the start of a third treatment cycle, is of the same order of magnitude as the resistant populations. This additional treatment cycle may have adverse effects on quality of life of the patient and also possibly decrease the life expectancy of the patient.

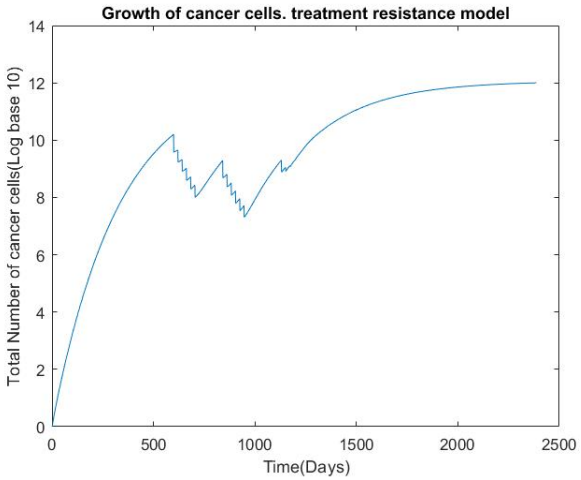

FIG. 3. Logarithm of total population size vs time of cancer growth for 3 treatment cycles

CONCLUSION

The growth of cancer is erratic in nature and cannot be accurately described in terms of a simple mathematical model since every cell at each time would need to be considered. Also various types of cancers have different effects on the cell and these effects may vary with each patient and other aspects. Due to lack of clinical data and erratic nature of cancer it is almost impossible to formulate an ideal model which can be used for all the patients. In this model for the development of cancer, we have focused on the heterogeneous nature of cancer and the effects of drug resistance which are necessary for understanding the effects of treatment. Even though this model only approximates the complex process, it can be used as a tool for clinicians to explore the development of cancer in the patient and the results of treatments, and can be used to weigh the benefits versus the side effects of the next treatment in order to determine whether or not the next treatment should be given.

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