Modeling The Effect On Tumor Growth Using Combination Of Chemotherapy And Immunotherapy

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Abstract

Analyzing a mathematical model from the article *Mixed Immunotherapy and Chemotherapy of Tumors: Modeling, Application and Biological Interpretations* by Dr. de Pillis, Gu, and Radunskaya, we are able to conduct different treatment plans to see the effects on tumor cells. Using a system of ordinary differential equations and human parameters extracted from a patient who was treated for melanoma we can conduct theoretical treatment plans that can help eradicate tumor cells and consider the quality of life. With treatment plan of chemotherapy, immunotherapy, or combination of both it can be shown that the number of tumor cells can be successfully decreased whereas without treatment it will otherwise grow. We will illustrate how the differences in the timing of the drug deliveries plays an important part in the effect on the number of tumor cells in the body.

Introduction / Background

We are able to make a multiple simulation of different treatment plans with immunotherapy, chemotherapy, and a mixer of both. There are assumptions in our model that should be noted:

1) A tumor grows logistically in the absence of an immune response
2) Both NK and $CD8^+T$ cells are capable of killing tumor cells
3) Both NK and $CD8^+T$ cells responds to tumor cells by expanding and increasing cytolytic activity
4) NK cells are normally present in the body, even when no tumor cells are present, since they are part of the innate immune response.
5) As part of the specific immune response, active tumor-specific $CD8^+T$ cells are only present in large numbers when tumor cells are present.
6) NK and $CD8^+T$ cells become inactive after some number of encounters with tumor cells

Ordinary Differential Equations

The model describes the kinetics of four populations, tumor cells and three types of immune cells, as well as two drug concentratiosn in the bloodstream. The populations at time t are denoted by:

1. $T(t)$, tumor cell population
2. $N(t)$, total NK cell population
3. $L(t)$, total $CD8^+T$ cell population
4. $C(t)$, number of circulation lymphocytes
5. $M(t)$, chemotherapy drug concentration
6. $I(t)$, immunotherapy drug concentration

$$
\begin{aligned}
\frac{dT}{dt} &= aT(1-bT) - cNT - DT - K_T(1-e^{-M})T \\
\frac{dN}{dt} &= eC - fN + \frac{gT^2N}{h+T^2} - pNT + K_N(1-e^{-M})N \\
\frac{dL}{dt} &= -mL + \frac{jD^2T^2L}{k+D^2T^2} - qLT + (r_1N + r_2C)T - \\
&\quad uNL^2 - K_L(1-e^{-M})L + \frac{p_ILI}{g_I+I} + v_L(t) \\
\frac{dC}{dt} &= \alpha - \beta C - K_C(1-e^{-M})C \\
\frac{dM}{dt} &= -\gamma M + v_M(t) \\
\frac{dI}{dt} &= \mu_I I + v_I(t) \\
&\text{where } D = \frac{d(\frac{L}{T})^l}{s+(\frac{L}{T})^l}
\end{aligned}
$$

Here $V_m(t)$, and $V_I(t)$ are chemotherapy treatment plan, and immunotherapy treatment plan respectively, and both are functions of time. $V_L(t)$ is the tumor infiltration lymphocyte (TIL) drug intervention term in which the immune cell levels are boosted by the addition of antigen specific cytolytic immune cells, which is also a function of time. Parameters are represented by lower case letters and state variables are represented by upper case letters.

Methods

Treatment Functions

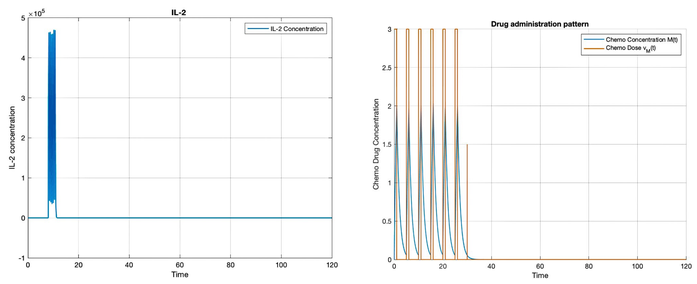

Figure 1: *(Left) immunotherapy square function(6 pulses from day 8 to day 11 at concentration $v_I(t) = 5 \times 10^5$ per pulse) and (right) the chemotherapy square function.(6 pulses from day 0 to day 30 once every 5 days with concentration $v_M(t) = 3$)*

Figure 1 is an example of how our treatment function looks like. For example, in figure 1 (right) we have our chemotherapy treatment where the red graph represent a square function indicating which days we inject our "chemotherapy treatment" and for how long. The blue graph represent the chemo concentration or the amount of time that our chemotherapy stays inside the body. Figure 1 (left) represent our "immunotherapy treatment plan" which is 6 pulses from day 8 to day 11 at concentration $v_I(t) = 5 \times 10^5$ per pulse. Similar to figure 1 it is a square function with respect to time.

Initial Conditions:
$T(0) = 2 \times 10^7$ $N(0) = 1 \times 10^3$ $L(0) = 6 \times 10^8$ $C(0) = 6 \times 10^8$
$M(0) = 0$ $I(0) = 0$

Model Outputs

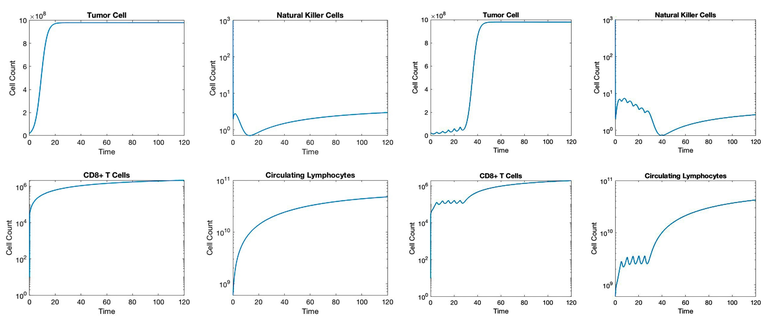

Figure 2: *(Left) our model outputs with no treatment plans and (right) our model outputs with just chemotherapy .*

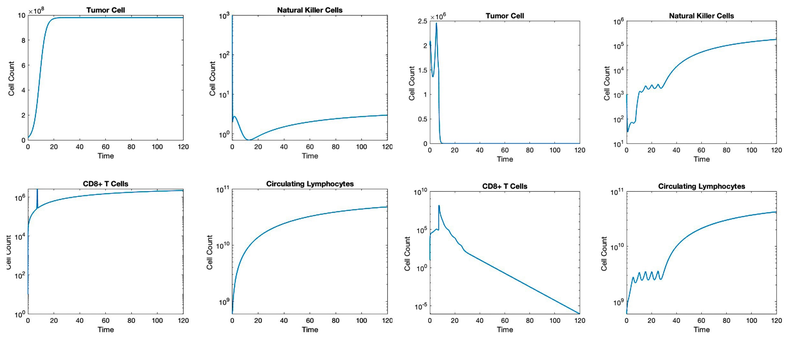

Figure 3: *(Left) our model outputs with just immunotherapy and (right) our model outputs with combination of both.*

We wanted to run multiple simulations to see how well our treatment plan will go. Looking at figure 2 (left), this is the results with no treatment plan, and so we can see that the tumor cells grows to dangerous level, we denote this as "not successful". In figure 2 (right) we implemented just chemotherapy treatment which can be seen in figure 1 (right) and still the model suggests this as not successful. The same result can be shown in figure 3 (left) which is the result of our model with just immunotherapy treatment, which can be seen in figure 1 (left). It is not until the combination of both treatment plans that we see a "successful" results. By running multiple simulation with multiple treatment plans we can see a pattern emerging that can be beneficial in the medical community.

Conclusion

In Conclusion, after conducting multiple simulations, we notice that there are patterns that repeat given certain conditions. We have noticed that there are multiple situations where using just immunotherapy or just chemotherapy is not enough to have a "successful" output from our model. However, it is the combination of these treatment plans that outputs the results that we desire, just as we have seen from the previous example. There are situations where chemotherapy is enough to have a "successful" output, however most of the time we will need very high doses or an initial condition for the amount of tumor cells to be very low, where it is considered non threatening. The figure below is an example of a "successful" output given a chemotherapy plan of high doses.

Initial Conditions:
$T(0) = 2 \times 10^7$ $N(0) = 1 \times 10^3$ $L(0) = 6 \times 10^8$ $C(0) = 6 \times 10^8$
$M(0) = 0$ $I(0) = 0$

Model Outputs

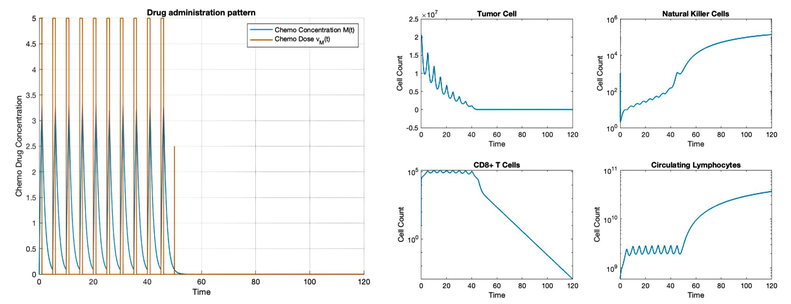

Figure 4: *(Left) chemotherapy square function (right) outputs from our model.*

There are also situations where immunotherapy gives a "successful" result, but just like chemotherapy, oftentimes we will need an initial condition of tumor cell to be very low.

Future Work

Some future work that we consider doing is to use different parameters from different patients to see if the same treatment plan will work on them. We want to see if our theoretical treatment plan will work on them as well or that we have to come up with a different treatment plan all together.The parameters that we use are from patient number 10 which can be read in [4]. We also want to look into patients with different kinds of cancer, which can give different types of parameters to work with and then come up with new types of theoretical treatment plans.

Acknowledgements & References

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