Customized cancer therapy based on the dynamic analysis of the Tumor-Immune-Drug System interaction

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Introduction

Cancer is a serious a public health problem.It is becoming a trending topic to design dosing treatments based on mathematical models.Customized chemotherapy that consider Tumor-Immune-Drug (T-I-D) interaction minimize the side effects of chemotherapy and improve the quality of life, thereby greatly reducing the social medical burden.

This project intends to focus on mathematical modeling on tumor and Individualized immune status, using the parameters fitting and optimization of the mathematical model to make the model more accurately reflect the actual situation, providing theoretical guidance for the customization and optimization of tumor treatment, which could be integrated into clinical trials. We consider a mathematical model for dynamic programming of the Tumor-Immune-Drug system interaction to optimize cancer therapy. In section 1, we analyzed the dynamic scenarios of the 5 distinct models in the recent publications and then built the master mathematical model which cover the dynamic characters of the 5 models in the previous publications. In section 2, we analyzed the characters of the master model such as temporal evolution and phase plot of the system. In section 3, The master mathematical models are numerically verified in "Numerical simulations" section. Finally, we made discussions and conclusions of our mathematical findings.

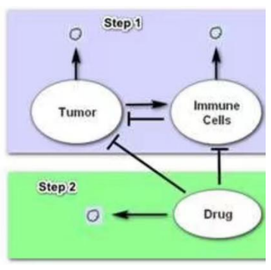

Figure 1. Illustration of Tumor-Immune-Drug network.

Model Establishment

We summarized 5 distinctive models from recent publications. In each model, T (t) is the tumor cell biomass, I (t) is the immune cell biomass and D(t) is the amount (or concentration) of chemotherapeutic drug in the bloodstream at time t.

Based on the above five model assumptions, their applicable scenarios, and their dynamics,we concatenate all five distinct equations into a master equation sets to capture all possible tumor-immune-drug relationship.(See Figure 2)

The master equations is:

$$\frac{dT}{dt} = r_1 T\left(1-\frac{p_1 T}{growth}\right) - \underbrace{\mu_1 IT\frac{I^{n1}}{g+I^{n1}}\frac{T^{n0}}{g12+T^{n0}}}_{repression\ term} - \underbrace{d_{11}TD}_{drug effect}$$

$$\frac{dI}{dt} = v_2 + \rho_2 T + \underbrace{r_2 I\left(1-\frac{p_2 I}{growth}\right)}_{} + \underbrace{\mu_2\frac{T^n}{h+T^n}}_{promotion} + \mu_{22}T(1-\beta T)I - d_{22}TI - \underbrace{d_2 I}_{death} - d_{21}ID$$

$$\frac{dD}{dt} = v(t) - d_3 D$$

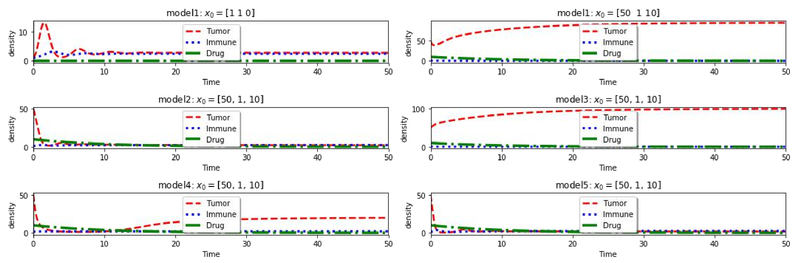

Figure 2. Dynamic scenarios of the master equation capturing dynamics in five distinctive published TID models.

Temporal evolution of the system without drug

we consider a few arbitrarily chosen sets of the (μ1, μ2) parameters and solve the system numerically in Mathematica.

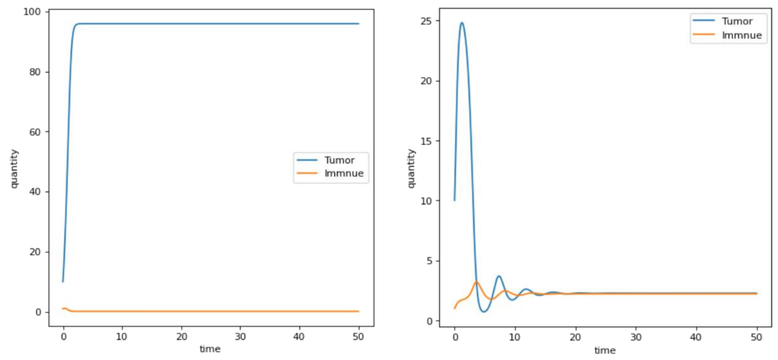

Figure 3. (left) time series of tumor and immune cell at μ1=1.5, μ2=3.5;
(right) time series of tumor and immune cell at μ1=2.2, μ2=4.2.

Phase portrait of the system without drug

In order to determine the effect of the initial conditions on the behavior of the system, a phase portrait was drawn in Figure 4a for μ1=1.5, μ2=3.5, the immune cells being eventually knocked down by tumor cells. Figure 4b shows the other phase portrait for μ1=2.2, μ2=4.2, there being a final balance between tumor cells and the immune cells.

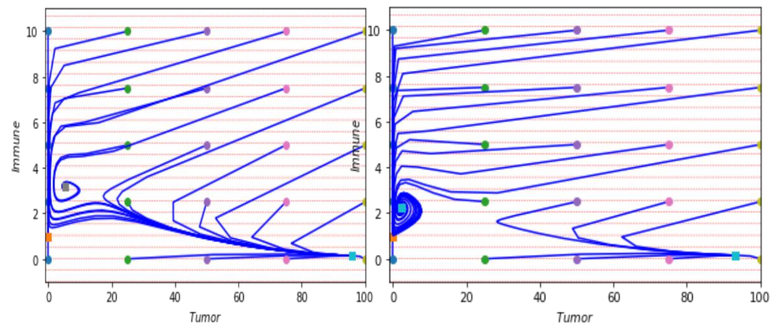

Figure 4. (left) phase portrait of network at μ1=1.5, μ2= 3.5; (right) phase portrait of network at μ1=2.2, μ2=4.2.

Numerical simulation of the TID model

After establishing the master equation, we can investigate how can we design the best drug treatment to eliminate the tumor in the shortest timeframe.As figure 5 shows,we assume the chemotherapeutic drug is given to the patient as a continuous Dirac Delta Function.

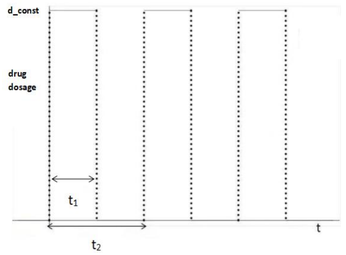

Figure 5. taking drug effect function.

Figure 6 shows the situation when the initial condition of TID is fixed at T=50, I=1, D=10. We are varying t_1,t_2 and D_{const}.Interestingly, we see when the drug influx rate is too small, the tumor growth slowed down, but still increasing. When t_1=1,D_{const} =10, the tumor growth is significantly slowed down, but occurs as an oscillation. While when t_1=2,D_{const} =10 the tumor cell can be eliminated from the system in within 3 drug cycles.

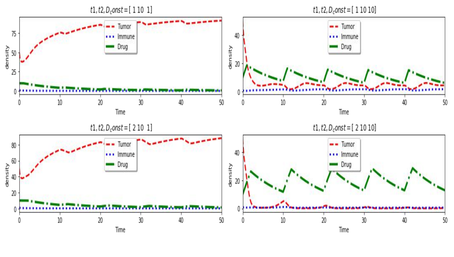

Figure 6. Effect from Drug influx rate to TID dynamic.

In order to conduct a more precise search, we searched thousands of different combinations of t_1,t_2 and D_{const} . As we see in Figure 7, despite the drug influx parameters in Figure 7, first row can all eliminate the tumor, last subfigure of the second row (red boxed image) is preferred treatment. Because is long, while is relatively in smaller dose.

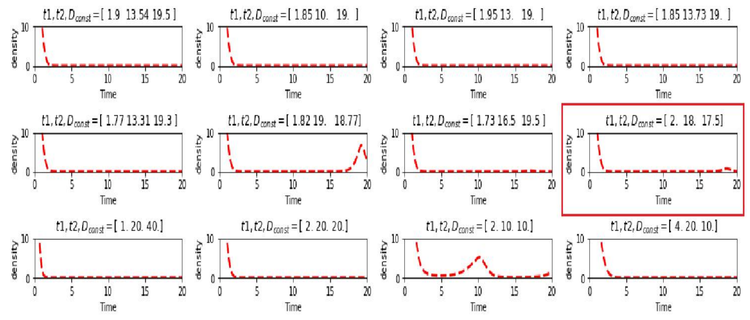

Figure 7. TID system dynamic under various drug treatment.

Conclusion

I have settled a master mathematical model for the Tumor-Immune-Drug System Interaction，capturing the dynamic characters of all five distinct models in the previous publications.

To better understand the dynamic of master TID model, I studied the temporal evolution and phase plot of the tumor-immune interaction without adding the drug.

I have developed a matrix for deciding the treatment plan is effective and painless for patient, as well as how the master model can be applied to design optimal drug treatment.