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

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Abstract

Cancer is a serious public health problem. Despite its subsequent worrying side effects, chemotherapy plays a vital role in cancer therapies. Customized chemotherapy considering Tumor-Immune-Drug (T-I-D) interaction could minimize the side effects and improve the quality of life. Clinically, doctors usually administer chemotherapy at the highest dose that cancer patients can safely tolerate, which often leads to serious side effects and drug resistance. Oncologists believe that therapy adapted to the patient's condition and response may be more effective. The establishment of mathematical models will shed light on the biological evolution of cancer and formulate optimal cancer treatment strategies, guiding clinical trials of adaptive therapy according to the patient's current state. So far, most of the AT policies were developed based on outlier cases that can not be generalized. The problem of optimizing an individual's appropriate schedule and drug dosage remains unresolved.

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 reflect the actual situation more accurately, providing theoretical guidance for the customization and optimization of tumor treatment.

I have settled a master mathematical model for dynamic programming of the Tumor-Immune-Drug System Interaction to optimize cancer therapy. I first analyzed all publications about TID model after 2010, and summarized five most representative models that can cover all the models in recent publications. I thoroughly studied the model assumptions and systematic dynamics for all five published models, then built a master model that can cover the dynamic characters of all previously summarized five models. Regardless of the initial model assumption, we can solely use the master equation to describe various TID dynamics and use the master equation to design optimized drug treatment.

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. Under this model, regardless of the control parameters: $\mu 1$, the repression factor from immune cells on tumor; $\mu 2$, the promotion factor from tumor on immune cells; the system always settles into a stable solution. But these two parameters will determine the type of steady state. Despite the complexity of the model equations, only two types of behavior are possible – stable spirals and stable nodes. From the dynamic analysis of the model, model are not sensitive to initial conditions, no matter where the tumor or immune cells starts, they will eventually reach a stable state (node/spiral).

Knowing the dynamic of the tumor-immune system is important and instructive for designing future drug treatment. In this project, I have also developed a matrix for determining an effective and less painful treatment plan for patients, as well as how the master model can be applied to design optimal drug treatment.

Keywords: Customized cancer therapy / dynamic analysis / Tumor-Immune-Drug System interaction

1. Introduction

Cancer is a serious a public health problem. It was estimated by the International Agency for Research on Cancer (IARC) that 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020[1]. Chemotherapy is a necessary part of the cancer treatment, slowing down the reproduction of tumor cells, but also resulting in toxic and side effects such as myelosuppression, immunosuppression, mucositis, alopecia[2]. It has been an increasingly trending topic to design dosing treatments based on mathematical models [6]. Most of the modeling guidance projects have focused on the correlation between drugs and tumor growth to find the most appropriate drug dosage treatment[7]. But even for patients in the same stage of tumors, their responses to drugs vary [8]. Chemotherapy has a certain degree of damage or inhibition to the immune system. The efficacy of chemotherapy varies among individuals with different immune states [11]. Factors like microenvironment and immune status can significantly influence the disease progression and response to treatment of patients suffering from the same cancer. Therefore, customized chemotherapy[12][13] 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.

A tumor is caused by abnormal proliferation of tissues, which usually arises from genetic mutations[14]. The most important feature of a tumor is that it is more invasive and fast-growing compared to other tissues. Our bodies have their own immune system to defend against those mutant cells or invasions from outside, sometimes the immune system can be successful in fighting cancer[15]; however, often the abnormal cells' growth rate is greater than immune cells which causes uncontrollable growth [16].

There are many types of immune cells in our body system to defend from both infectious diseases and foreign materials[17]. The reason why the immune system can detect the presence of abnormal cells or foreign material is that those abnormal cells (e.g tumor) will generate very specific antigens, which are different from normal cells, and only immune cells can detect and take action[18]. Usually, when tumor cells generate the antigen and disperse into the host, a cytokine will link to this antigen as a result of a chemical reaction. This complex will bind to a dendritic cell precursor, taken into the precursor cells, then make dendritic cells mature and infuse back to host. T cells are distributed in blood vessel and are able to bind with mature dendritic cells. Because of the dendritic cells display of the tumor antigen, even more immune cells divide and then attack the tumor cells. The system network can be simplified in Fig. 1. Tumor and immune cells have the ability to divide, and also die after certain time[19]. The main interaction in this network is the stimulation of immune cell proliferation by tumor cells, and the repression of tumor proliferation by immune cells. Even there is negative feedback effect from immune system on tumor, in fact, the tumor has higher growth rate than immune cells, so it is very possible to have tumor cells growth out of control [20]. Also according to the literature, a tumor will take 44 month to reach its half life cycle, while immune cells take 0.76 day to decay [21].

Clinically, changes in white blood cell (WBC) count are used to regulate the use of drugs in chemotherapy [22]. Doctors usually administer chemotherapy at the highest dose that cancer patients can safely tolerate, which often leads to serious side effects. In addition, under long-term treatment, this method usually results in drug resistance in the surviving cancer cells, increasing the difficulty of further treatment, leading to recurrence. Maximum tolerated doses (MTD) -based chemotherapy kills cells that are sensitive to chemotherapy and chemorefractory cells eventually dominate it, leading to inevitable exhaustion of patients[23]. Therefore, for cancer patients, a standardized treatment plan is a cruel and helpless choice. They often have to make many detours to find the correct treatment plan. When they find it, there is probably not much time left. At present, many oncologists believe that adaptive therapy (AT) is adapted to the patient's condition and response[24], and that treatments aimed at "controlling" cancer may be more effective than trying to "cure" cancer. On the basis of the patient's current state and the expected evolutionary changes (trajectory), the implementation of mathematical models can guide clinical trials of AT for intermittent administration, reducing chemotherapy toxicity and delaying resistance, improving patient prognosis and predicting subsequent responses.

The mechanism of cancer occurrence and metastasis is complex, varying from patient to patient. The establishment of mathematical models that simulates the growth process of tumors will shed light on the biological evolution of cancer[25]. Therefore, we could formulate optimal cancer treatment strategies and predict disease trends. The combination of mathematical models and biological data will turn cancer research into a quantitative and predictable science, linking micro-level information with a specific patient's tumor. Mathematical models researches of tumors provide meaningful references for the optimizing cancer therapy, including analyzing the behaviors of tumors, maximizing the effect of treatment, reducing harm, predicting prognosis, calculating the best customized drug combination and treatment plan such as dosage and frequency of medication. The appropriate frequency and dosage of treatment can reduce the side effects of the drug while shrinking the tumor, improving the quality of life of patients.

Regarding the research on the internal mechanism of tumor development and its comprehensive treatment, many professionals have constructed different types of mathematical models based on different professional theories[26][27], including analysis of tumor gene expression characteristics, testing different drug combination and understanding of the resistance to chemotherapy drugs:

- Through the analysis of tumor gene expression characteristics, it is possible to find the best targeted treatment approach and develop a new type of customized chemotherapy treatment for cancer. The chemotherapeutic methods for patients are ranked based on the gene expression characteristics of tumors. This ranking not only considers the effectiveness of fighting cancer, but also takes into account the degree of pain of patients caused by the drugs. Mathematical models are then applied to guide clinical trials of adaptive therapies and provide more customized treatment options to improve the feasibility of patient prognosis. This ability to learn from early treatment cycles and predict subsequent responses adds essential customization and flexibility to cancer treatment plans.
- Powerful tools are provided for cancer biologists and clinical oncologists to test different drug combination and determine the optimal treatment plan. Mathematical and computational models provide a fast and cost-effective way to test different drug combination and other assumptions.
- One of unresolved challenges is the frequent relapse of tumor in chemotherapy and the emergence of medication resistance. The mathematical model allows us to quickly identify the most effective drug combination for cancer patients. They also deepen our understanding of the resistance of cancer cells to chemotherapy drugs.
- Mathematical models are used to predict the development trend of cancer.

Ordinary Differential Equations (ODE) are the classic example of deterministic models. ODE-based tumor models are analyzed and optimized through computer simulation. It can be applied to tumor chemotherapy and immunotherapy evaluation. Sameen S. et al. further refined it and applied it to the analysis of drug resistance characteristics of colorectal cancer based on KRAS mutations [29]. Researchers like Roberto applied the ODE model to explore the theoretical basis of the interaction between cancer and obesity and the immune response [30]. Other researchers effectively used the basic characteristics of the ODE model and combined the inherent characteristics of different tumors to construct some unique models[28].

The current standard treatment process often leads to irreversible failure of the patient. Most of the AT policies were developed based on outlier cases that can not be generalized. So far, the results of clinical trials are unstable and lack support while some of the AT therapies share similarity with standard ones to a great extent.

The results of latest clinical trials showed that drug dosage and schedule had played important roles in reducing drug toxicity and enhancing effectivity of therapy. However, the problem of optimizing an individual's appropriate schedule and drug dosage remains unresolved.

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 reflect the actual situation more accurately, 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. In order to simplify the model, we assume infinite abundance of the nutrient in the vessel and an equal effect of the nutrient on both the tumor and immune cell. One thing worth mentioning is that usually a tumor can cause part of the tissue to swell, but in our model, we assume the tumor and immune cells are both constrained in certain volume of the tissue, so it is expected that their size will eventually reach a plateau.

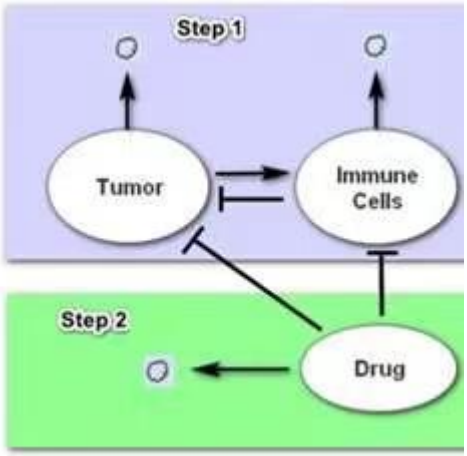


Figure 1. Illustration of Tumor-Immune-Drug network

2. Model Establishment

I summarized 5 distinctive models from recent publications [31]. The distinctiveness are mainly in the cell growth function, the interactive between tumor cells and immune cells. 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.

2.1. Model 1 [31-36]

Equations:

$$\begin{aligned}\frac{\mathrm{dT}}{\mathrm{dt}} &= r_1 T(1-p_1 T) - \underbrace{\mu_1 IT}_{\substack{\text{repression}\\ \text{term}}} - \underbrace{d_{11} TD}_{\text{drugeffect}} \\ \frac{dI}{dt} &= v_2 + \underbrace{\mu_2 \frac{IT^n}{h+T^n}}_{\text{promotion}} - d_{22} TI - \underbrace{d_2 I}_{\text{death}} - d_{21} ID \\ \frac{dD}{dt} &= v(t) - d_3 D\end{aligned} \tag{1}$$

The parameter used in the model is recorded in Table1.

The assumption of the model is:

- In the absence of foreign drugs and immune cells, tumor cells grow logistically. The growth term of tumor already considered tumor cells apoptosis, represented by $r_1 T(1-p_1 T)$.
- The repression from immune cells to tumor cells is proportional to the multiply of immune cells and tumor cells, represented by $\mu_1 IT$.
- Tumor cells can reduce immune cells cytotoxicity, represented by $\mathrm{d}_{22} TI$.
- The increase rate is dictated by the influx rate of immune cells in the bloodstream, v_2.
- The tumor cells stimulate the immune response, and the immune cells produce $\frac{\mu_2 T^{\mathrm{n}} I}{h+T^n}$; this leads to the promotion of immune cells.
- Chemotherapy drugs have damaging effects on tumor cells and immune cells. Represented by $\mathrm{d}_{11} TD$ and $\mathrm{d}_{21} ID$, respectively.
- The growth of chemotherapeutic Drug is dictated by the dose of the drug and its natural decay, represented by $v(t) - d_3 D$.

Given different initial conditions, we have the tumor cells, immune cells and drug density dynamics scenarios from Model 1 as:

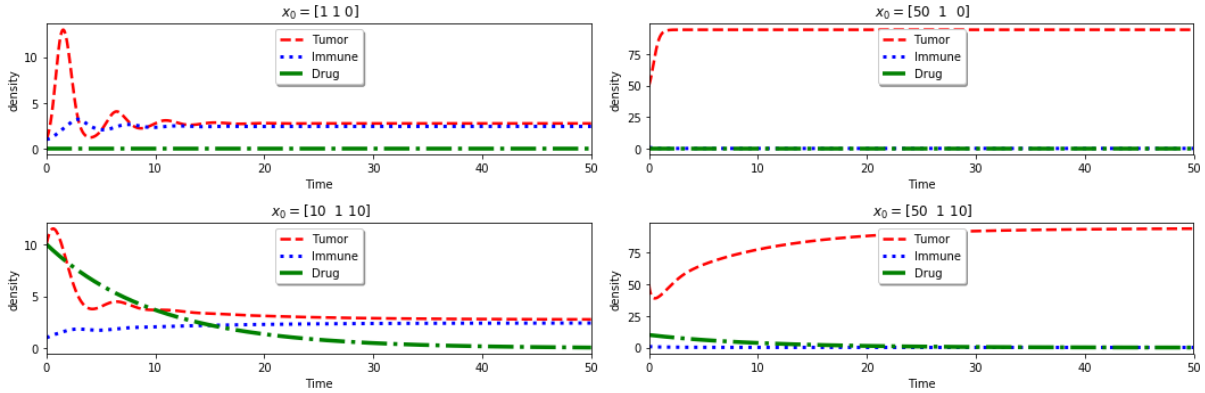


Figure 2. Four dynamic scenarios from Model 1 presented in publications [31].

a) TID dynamic when initial condition T=1, I=1, D=0. The density of tumor cells first increases and then decreases, maintaining a density (approximately 3) similar to that of immune cells, without drug.

b) TID dynamic when initial condition T= 50, I=1, D=0. Tumor cell density rapidly increases to the plateau stage (approximately 100), and immune cell density is always low without drug.

c) TID dynamic when initial condition T= 10, I=1, D=10. With the addition of the drug, the tumor cell density decreases from a high position until it maintains a density (approximately 3) similar to that of immune cells.

d) TID dynamic when initial condition T= 50, I=1, D=10. The tumor cell density gradually rises to the plateau high (approximately 100), the drug loses its effect, and the immune cell density remains low.

It shows only a small amount of tumor cells stimulate the immune response and finally reached a balance between tumor and immunity (Figure 2a). When the amount of tumor cells are very large, the immune response is suppressed and tumor cells grow out of control (Figure 2b). If the amount of tumor cells increases to a certain extent, chemotherapy drugs can inhibit tumor cells, stimulate immune response and finally achieve a balance between tumor and immunity (Figure 2c). . If the amount of tumor cells is too large, even chemotherapy drug can not inhibit tumor growing out of control (Figure 2d)

2.2. Model 2 [37]

Equations:

$$\frac{\mathrm{dT}}{\mathrm{dt}} = \underbrace{r_1 T(1-p_1 T)}_{growth} - \underbrace{\mu_1 \frac{TI^{n1}}{g+I^{n1}}}_{\substack{repression \\ term}} - \underbrace{d_{11}TD}_{drugeffect}$$

$$\frac{dI}{dt} = \rho_2 T + \underbrace{\mu_2 \frac{IT^n}{h+T^n}}_{promotion} - d_2 TI - \underbrace{d_2 I}_{death} - d_{21}ID \qquad (2)$$

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

The assumption of the model 2 is:

- Non-self antigenicity of the tumor cause he increase of the immune cells, represented by $\rho_2 T$.
- The immune cells repress the tumor growth, and the repression term can be expressed as $\mu_1 \frac{TI^{n1}}{g+I^{n1}}$.
- Antigenicity of the tumor cells.
- All other terms have been described in model 1.

Given different initial conditions, we have the tumor cells, immune cells and drug density dynamics scenarios from Model 2 as:

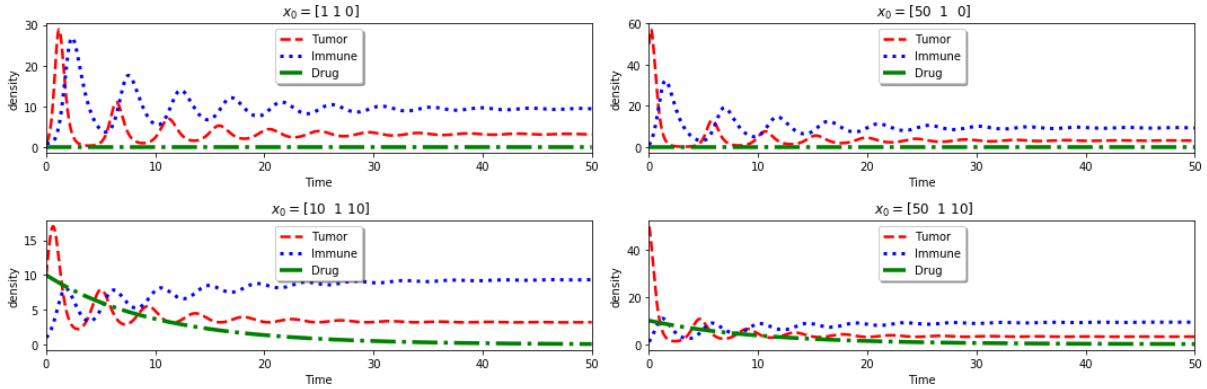


Figure 3. Four dynamic scenarios from Model 2 presented in publications [37].

a) and b) TID dynamic when initial condition (T=1, I=1, D=0) and (T= 50, I=1, D=0). Without drug, tumor cell density fluctuates with immune cell density. When the immune cells are high, the tumor cells are low; when the immune cells are depleted to a low density, the tumor cell dengsity increases again.

c) and d) TID dynamic when initial condition (T= 10, I=1, D=10) and (T= 50, I=1, D=10) . With the addition of the drug, Initially, the immune response is suppressed to a certain extent. Later the density of subsequent tumor cells fluctuates with the density of immune cells. Finally the four groups reach the balance between tumor and immune cells (approximatel density 5 and 10).

It indicates that, regardless of the initial density, tumor cells stimulate the immune response and in turn immune cells inhibit tumor growth, representing a wave-like dynamic process. The final immune cell density is higher than the tumor cell density, forming a steady state (Figure 3a, 3b). The addition of drugs inhibited the immune response to a certain extent. However, in the dynamics of the system, tumor cell density still fluctuates with immune cell density. Eventually a balance of tumor cell density lower than immune cell density is formed (Figure 3c, 3d).

2.3. Model 3 [38]

Equations:

$$\frac{\mathrm{dT}}{\mathrm{dt}} = \underbrace{r_1 T(1-p_1 T)}_{growth} - \underbrace{\mu_1 \frac{IT^{n1}}{g+T^{n1}}}_{repression\ term} - \underbrace{d_{11} TD}_{drugeffect}$$

$$\frac{dI}{dt} = v_2 + \underbrace{\mu_2 \frac{IT^{n}}{h+T^{n}}}_{promotion} - d_{22} TI - \underbrace{d_2 I}_{death} - d_{21} ID \qquad (3)$$

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

The assumption of the model is:

- Immune cells inhibit tumor growth, the term is $\mu_1 \frac{IT^{n1}}{g+T^{n1}}$. Notice this repression term is different with the rest of the models.
- All other terms have been described in model 1.

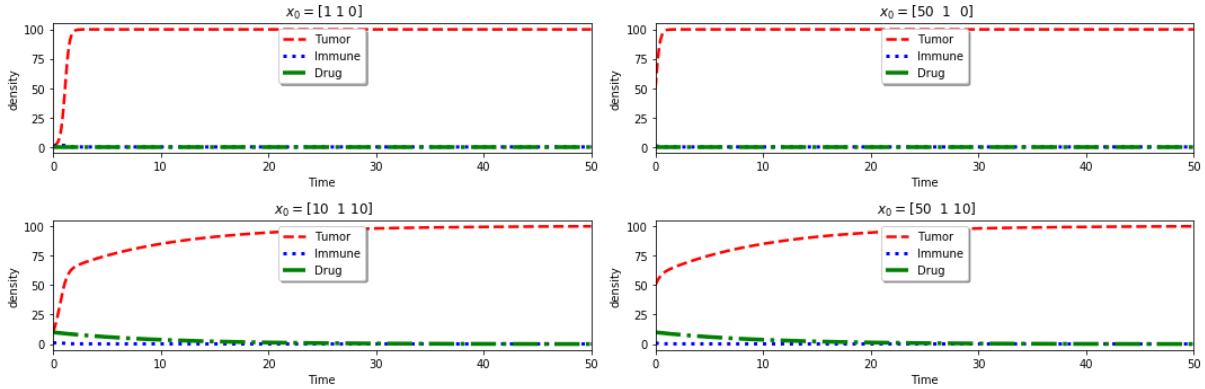


Figure 4. Four dynamic scenarios from Model 3 presented in publications [38].

a) and b) TID dynamic when initial condition (T=1, I=1, D=0) and (T= 50, I=1, D=0). Without drug, tumor cells grow rapidly out of control (approximate density 100) and the density of immune cells is always low.

c) and d) TID dynamic when initial condition (T= 10, I=1, D=10) and (T= 50, I=1, D=10). With the addition of drug, the tumor cells grow slightly at the initial stage, gradually grow to a high plateau (approximate density 100), out of control.

It shows that, regardless of the initial tumor cell density, without drug, tumor grows rapidly out of control and fails to stimulate the immune response. Addition of Drug initially can inhibit tumor growing to a certain degree, but gradually fail and tumor grows out of control.

2.4. Model 4 [39]

Equations:

$$\frac{\mathrm{dT}}{\mathrm{dt}} = r_1 T(1-p_1 T) - \underbrace{\mu_1 IT}_{\substack{repression\\ term}} - \underbrace{d_{11} TD}_{drugeffect}$$

$$\frac{dI}{dt} = r_2 I(1-p_2 I) - d_{21} ID \qquad (4)$$

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

The assumption of the model is:

- The Immune cell growth restriction can be simulated by a logistic model, represented by $r_2 I(1-p_2 I)$.
- All other terms have been described in model 1.

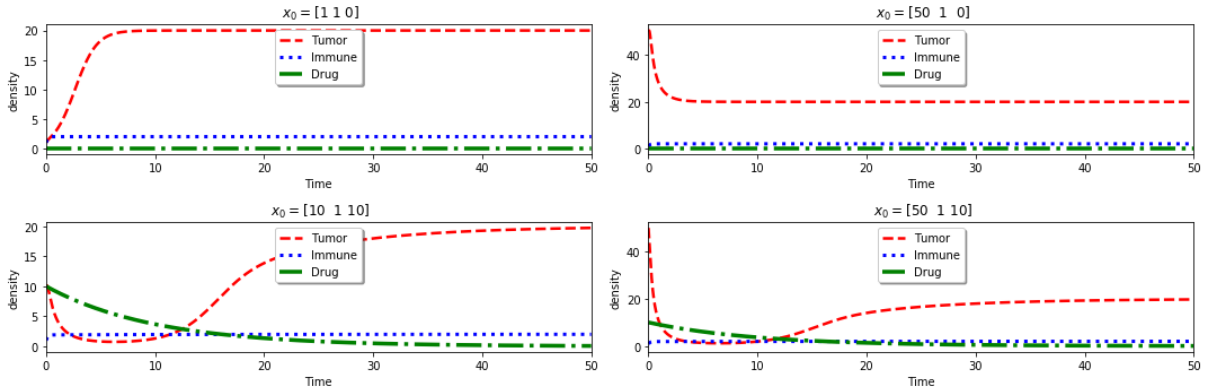


Figure 5. Four dynamic scenarios from Model 4 presented in publications [39].

a) TID dynamic when initial condition T=1, I=1, D=0. Tumor grows fast to plateau period (approximate density 20).

b) TID dynamic when initial condition T= 50, I=1, D=0. The initial density of tumor cells are much higher (higher than 40), growing drop to the density of plateau period(approximate density 20).

c) TID dynamic when initial condition T= 10, I=1, D=10. Initially drug can inhibit the density of tumor (approximate density 1), but gradually tumor grows to the the density of plateau period(approximate density 20).

d) TID dynamic when initial condition T= 50, I=1, D=10. The initial density of tumor cells are much higher (higher than 40), initially drug can inhibit the density of tumor (approximate density 1), but gradually tumor grows to the the density of plateau period(approximate density 20).

It indicates that, without drug, tumor grows rapidly out of control and fails to stimulate the immune response. However, even the initial density of tumor cells are much higher, tumors growing drop to the density of plateau period(approximate density 20). Drug initially can inhibit tumor growing but subsequently grows to the density of plateau period, out of control, regardless of the initial density of tumor cells. The immune response is not stimulated.

2.5. Model 5 [40]

Equations:

$$\frac{\mathrm{dT}}{\mathrm{dt}} = -r_1 T \ln\left(\frac{T}{T_\infty}\right) - \underbrace{\mu_1 IT}_{\substack{repression \\ term}} - \underbrace{d_{11} TD}_{drugeffect}$$

$$\frac{dI}{dt} = v_2 + \mu_2 T(1-\beta T)I - \underbrace{d_2 I}_{death} - d_{21} ID \tag{5}$$

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

The assumption of the model is:

- Assuming that there is a fixed limited bearing capacity, the immune response pair can reduce the tumor volume.
- The Immune system's response to tumors is state-dependent: small tumors stimulate the proliferation of immune cells, while large tumors inhibit the activity of the immune system. Represented by $\mu_2 T\ (1-\beta T)\ I$.

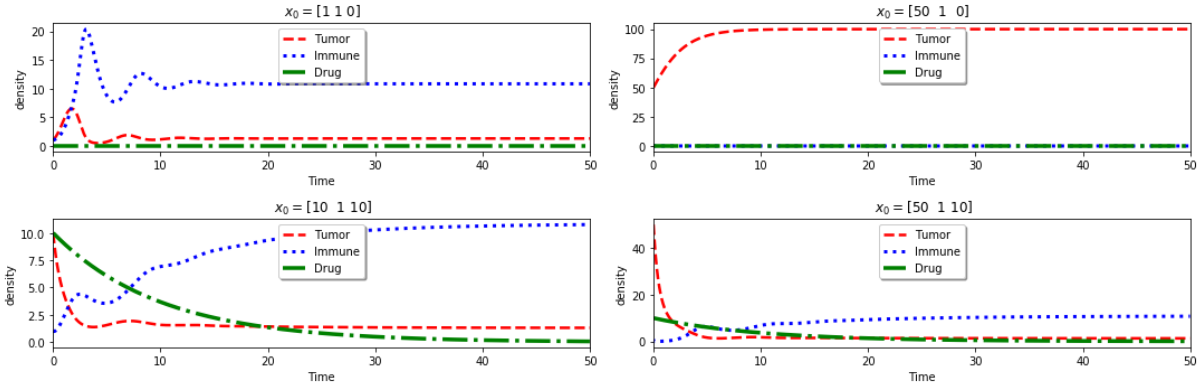


Figure 6. Four dynamic scenarios from Model 5 presented in publications [40].

a) TID dynamic when initial condition T=1, I=1, D=0. Tumor stimulate immune response and immune cells inhibit tumor growing, finally reaching to the balance (immune 10 and tumor 1).

b) TID dynamic when initial condition T= 50, I=1, D=0. Tumor at the initial density 50 grows fast to plateau period (density 100),out of control.

c) TID dynamic when initial condition T= 10, I=1, D=10. Drug inhibit initial immune response, finally reaching to the balance (immune 10 and tumor 1).

d) TID dynamic when initial condition T= 50, I=1, D=10. Drug inhibit initial immune response and tumor at the initial density 50, finally reaching to the balance (immune 10 and tumor 1).

It shows that small amount of tumor cells stimulate a strong immune response and reached a balance between tumor and immunity. When the amont of tumor cells are very large, the immune response is suppressed and tumor cells grow out of control. If the amount of tumor cells increases to a certain extent, chemotherapy

drugs can promote stronger immune response and finally achieve a balance between tumor and immunity. If the amount of tumor cells is large, chemotherapy drug can inhibit tumor growing and immune response, finally reaching a balance between tumor and immunity.

Table 1. Parameters used in five distinctive models

Constant	**Description**	**Value**	**Applied in**
	Innate growth rate of tumor cells	5	Model 1,2,3,4,5
	mutual carrying capacity for tumor cells	0.01	Model 1,2,3,4
	constant influx rate of immune cells	1	Model 1,2,3,5
	regression term from immune to tumor	10	Model 1,4,5
	regression term from immune to tumor	20	Model 2,3
	loss of the immune cells due to tumor	0.1	Model 1,3
	promotion term from tumor to immune	0.5	Model 1,2,5
	steepness coefficient of the immune cell recruitment curve by tumor cells.	10	Model 1,2,3
	per capita decay rate of immune cells without tumor cells	1	Model 1,2,3.5
	decay rate of the drug.	0.1	Model 1,2,3,4,5
	the dose of drug given.	0	Model 1,2,3,4,5
	response to the drug for tumor cells	0.2	Model 1,2,3,4,5
	response to the drug for immune cells	0.05	Model 1,2,3,4,5
	The antigenicity of the tumor	0.1	Model 2
	constant	10	Model 2,3
	Immune cells grow rate	6	Model 4
	the carrying capacity of B cells	0.2	Model 4
	constant	0.00264	Model 5

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.

The master equations is:

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

$$\frac{dI}{dt} = v_2 + \rho_2 T + r_2 I(1-p_2 I) + \underbrace{\mu_2 \frac{IT^n}{h+T^n}}_{promotion} + \mu_{22} T(1-\beta T)I - d_{22}TI - \underbrace{d_2 I}_{death} - d_{21}ID \tag{6}$$

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

The assumption of the master equation is the combination of all above five model assumptions.

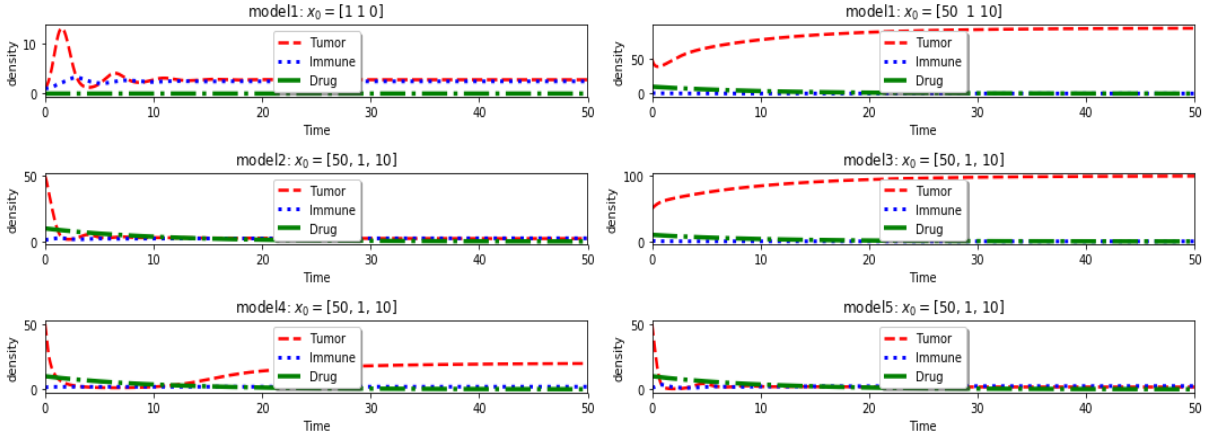


Figure 7. Dynamic scenarios of Master equation capturing dynamics in five distinctive published TID models.

a) TID dynamic when initial condition T=1, I=1, D=0. The dynamic of tumor, immune cells, and drug is similar to model 1 in the same initial condition (Figure 2a)

b) TID dynamic when initial condition T= 50, I=1, D=10. System dynamic is similar to model 1 in the same initial condition (Figure 2d).

c) TID dynamic when initial condition T= 50, I=1, D=10. System dynamic is similar to model 2 in the same initial condition (Figure 3d).

d) TID dynamic when initial condition T= 50, I=1, D=10. System dynamic is similar to model 3 in the same initial condition (Figure 4d).

e) TID dynamic when initial condition T= 50, I=1, D=10. System dynamic is similar to model 4 in the same initial condition (Figure 5d).

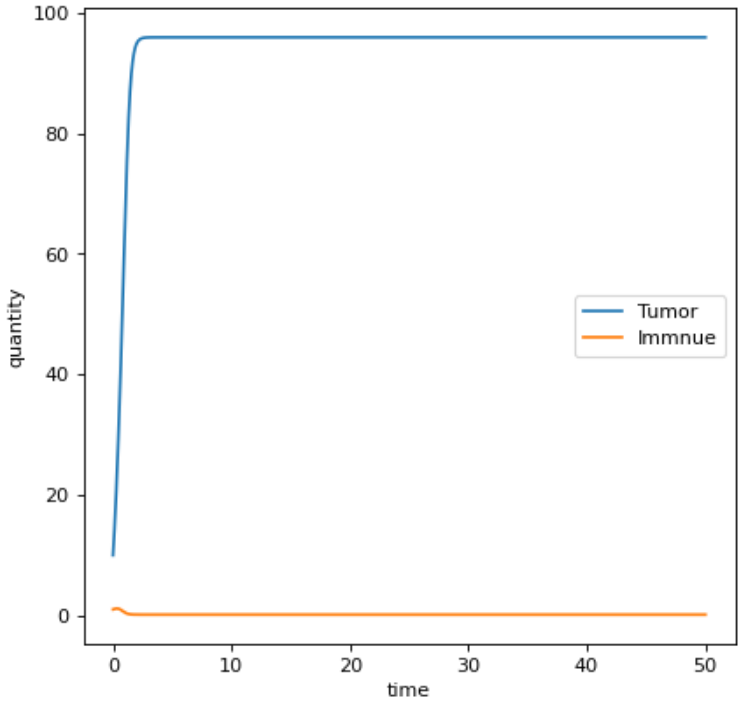
f) TID dynamic when initial condition T= 50, I=1, D=10. System dynamic is similar to model 5 in the same initial condition (Figure 6d).

As Figure 7 shows, the master equation can capture the dynamic of five distinctive published TID systems. This means the master equation is not heavily assumption based. One can imagine, before the master model, to make customized chemotherapy treatment plan, one needs to determine which TID model describes the patient situation the best, then design the treatment using that particular model. Right now, regardless of the initial model assumption, we can solely use the master equation to describe various TID dynamics and use the master equation to design optimized drug treatment.

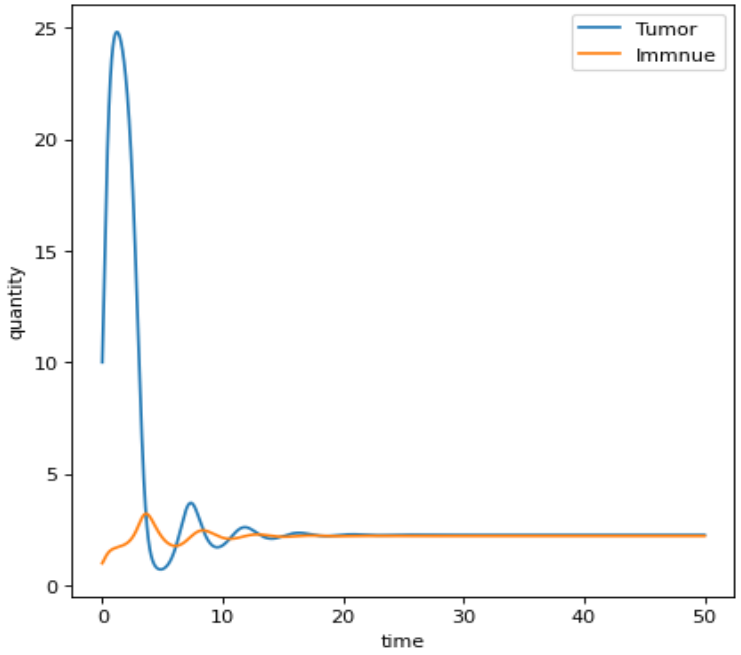
3. Temporal evolution of the system without Drug

Because the values of the μ1 and μ2 parameters can be variable, we cannot get a unique solution of the system. In fact, as we shall see later in the discussion, the range of possible types of behavior is quite limited despite the large parameter space. In order to gain some qualitative insight into the possible solutions of the system before classifying them in a systematic and exhaustive way, we consider a few arbitrarily chosen sets of the (μ1, μ2) parameters and solve the system numerically in Mathematica.

Thus, one possible scenario, which occurs at (μ1=1.5, μ2=3.5) is shown on Figure 8a. Both the tumor and the immune system concentrations reach a steady state, with the tumor being a large positive quantity and the immune response close to zero. As it will become clear with the linearization analysis later, the fact that both variables reach a steady state is not simply a special case but rather the only scenario. This result has an important biological relevance because it suggests that neither the tumor, nor the immune cells can grow indefinitely. This is logical, as they are both bounded within the dimensions of the organism. What can change is the way the stable solutions are reached over time. As we see in Figure 8b with another example of control parameters (μ1=2.2, μ2=4.2), both variables show damped oscillations before arriving at the steady state. The oscillations are out of phase, with the tumor preceding the immune response by 1/3 of the period. Interestingly, oscillations in both tumor growth and immune response have been observed experimentally.



(a)

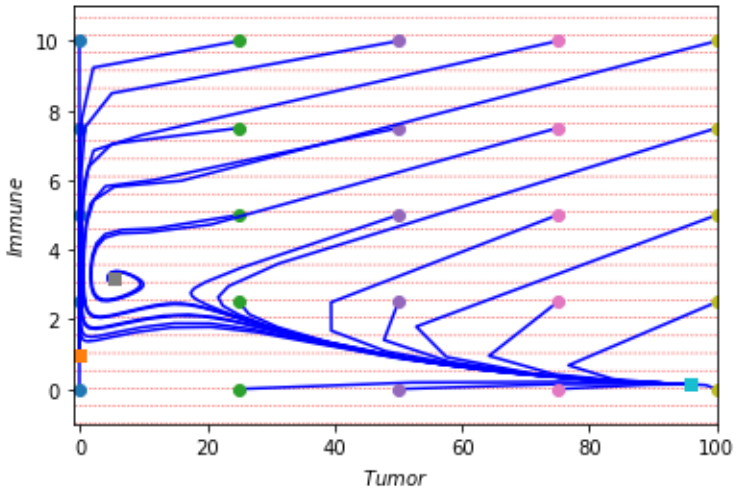


(b)

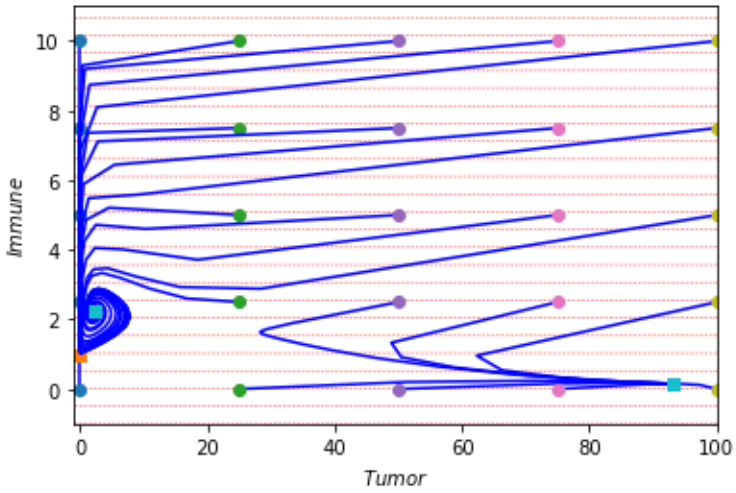
Figure 8.(a) time series of tumor and immune cell at μ1=1.5, μ2=3.5;
(b) time series of tumor and immune cell at μ1=2.2, μ2=4.2

4. Phase portrait

In order to determine the effect of the initial conditions on the behavior of the system, a phase portrait was drawn in Figure 9a for μ1=1.5, μ2=3.5. It shows that the immune cells will be eventually knocked down by tumor cells, and this is the usually the case when people get uncontrollable tumor. Figure 9b shows the other phase portrait for μ1=2.2, μ2=4.2. Mostly there would be a final balance between tumor and the immune cells. This describes the dynamic behavior of a stable node steady state, the curve comes to a fixed point in the case of the spiral.



(a)



(b)

Figure 9. (a) phase portrait of network at μ1=1.5, μ2= 3.5;
(b) phase portrait of network at μ1=2.2, μ2=4.2

5. 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. It is assumed that the chemotherapeutic drug is given to the patient as a continuous Dirac Delta Function (see Figure 10).

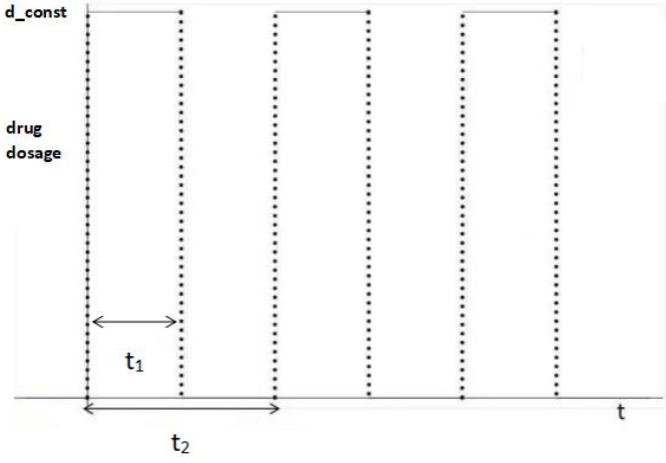


Figure 10. taking drug effect function

It shows the situation when the initial condition of TID is fixed at T=50, I=1, D=10 while t_1,t_2 and D_{const} are being varied. Interestingly, it is observed that when the drug influx rate is too small ($D_{\text{const}} = 1$), the tumor growth slowed down, but still increasing (Figure 11a, c). When $t_1 = 1$, $D_{\text{const}} = 10$, the tumor growth is significantly slowed down, but occurs as an oscillation (Figure 11b). While when $t_1 = 2$, $D_{\text{const}} = 10$, the tumor cell can be eliminated from the system in within 3 drug cycles (Figure 11d).

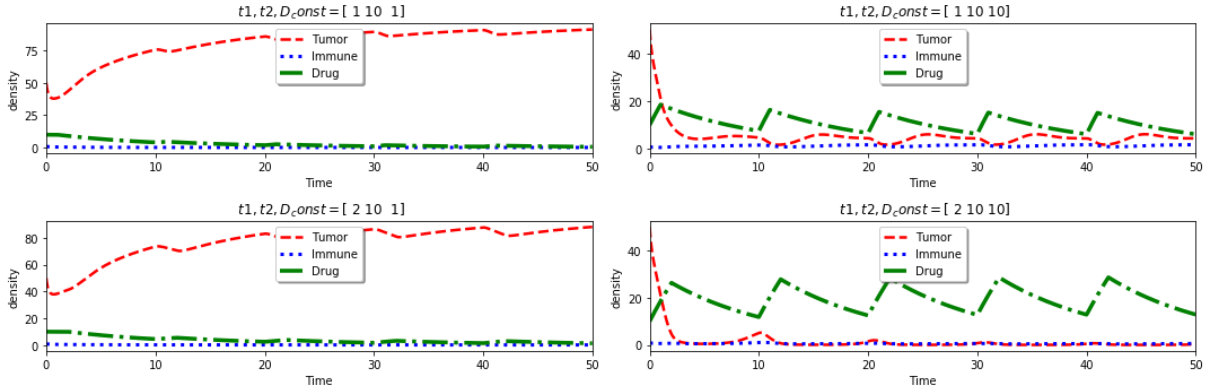


Figure 11. Effect from Drug influx rate to TID dynamic

In order to conduct a more precise search, we searched thousands of different combinations of t_1 , t_2 , and D_{const} . We set an initial range for the value of t_1 , t_2 , and D_{const} , e.g. $0 \le t_1 \le 2$, $10 \le t_2 \le 20$, and $0 \le D_{\text{const}} \le 20$. We look for

- The minimum timeframe for tumor density to decrease under 0.01.
- The area of $t_1 * D_{const} * number$ of drug cycles to eliminate tumor to 0.01 is minimum.
- t_1 and D_{const} should be as short and small as possible, t_2 should be as long as possible.

As we see in Figure 12, despite the drug influx parameters, first row of Figure 12 can all eliminate the tumor, last subfigure of the second row (red boxed image) is a preferred treatment. Because us short, is long, while is relatively in smaller dose.

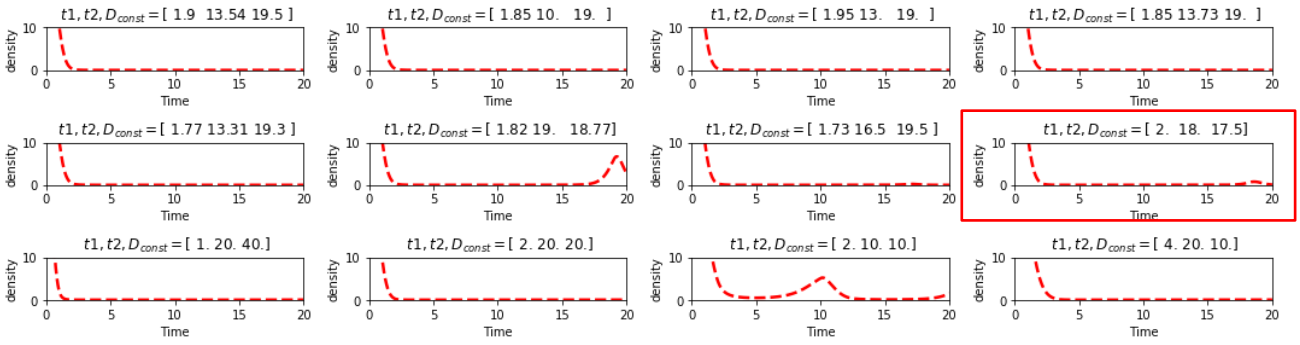


Figure 12: TID system dynamic under various drug treatment (selected 16 representative). , and value is listed on top of each subfigure. Red box shows the most optimized drug treatment.

6. Conclusion

In this project we have settled a master mathematical model for dynamic programming of the Tumor-Immune-Drug System Interaction to optimize cancer therapy. We first analyzed all publications about TID model after 2010, and summarized five most representative models that can cover all the models in recent publications. We thoroughly studied the model assumptions and systematic dynamics for all five published models. We then built a master model that can cover the dynamic characters of all five summarized models in the previous publications. We now have one single set of equations that can describe all TID model dynamics publications described after 2010, which is essential to design optimized and customized drug treatment plan.

To better understand the dynamic of master TID model, we studied the temporal evolution and phase plot of the tumor-immune interaction without adding the drug. Under this model, regardless of the control parameters: $\mu 1$, the repression factor from immune cells on tumor; $\mu 2$, the promotion factor from tumor on immune cells; the system always settles into a stable solution. But these two parameters will determine the type of steady state. Despite the complexity of the model equations, only two types of behavior are possible - stable spirals and stable nodes. From the dynamic analysis of the model, model is not sensitive to initial conditions, no matter where the tumor or immune cells starts, they will eventually reached to a stable state (node/spiral).

Knowing the dynamic of the tumor-immune system is important and instructive for designing future drug treatment. In this project, we have also 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 (Figure 12).

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