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Research on the application of mathematical modeling in tumor immunology in the context of chemotherapy

Jiaming Zhou

Beijing No.80 High School, Beijing, China, 100102

km134997@163.com

Abstract. Cancer is not only a highly detrimental disease but also a particularly grave health concern. Moreover, the current incidence and mortality rates in our country are far from encouraging, making the prevention and control situation very challenging. Therefore, identifying the most scientific and effective treatment methods has become one of our primary research focuses. This paper, building upon previous models and incorporating resistance factors, categorizes tumor cells into those that are sensitive to chemotherapy drugs and those that become resistant. Using MATLAB, we have adjusted various sensitivity parameters in the model to simulate the number of tumor cells over 40 days. This simulation aims to analyze the sensitivity levels of tumor cells to different parameters upon the inclusion of resistance factors. The initial data used for the simulation were derived from the original paper. Ultimately, our findings indicate that tumor cells are most sensitive to the chemotherapy drug's killing rate for normal tumor cells and the decay rate of the chemotherapy drug. Due to the drug resistance factor, the sensitivity of different parameters is influenced. For parameters related to chemotherapy drugs, the final results, when incorporating this factor, may deviate significantly from those of previous models without this factor. For instance, the decay rate of chemotherapy drugs might result in a larger total number of tumor cells or a steeper trend compared to previous findings.

Keywords: Tumor, Chemotherapy, Drug-resisitence

1. Introduction

As technological advancements increasingly deepen our understanding of tumor drug resistance, the corresponding academic research has likewise matured. This progress is evident in studies investigating the influence of the intratumoral microenvironmenton on drug treatment sensitivity [1], as well as research probing the underlying causes for chemotherapy resistance in tumors, frequently attributed to the limited penetration of anti-cancer medications into tumor tissues [2]. In response, academia has pioneered various strategies to tackle this drug resistance, such as employing multifunctional nanocarriers to counteract tumor drug resistance [3]. Alternatively, mathematical models are being used to simulate the likelihood of overcoming drug resistance via personalized treatment plans [4]. This paper focuses on optimizing a mathematical model that elucidates tumor immunity under chemotherapy[5]. Although the model's architecture initially incorporated assumptions about drug resistance, it failed to express its tangible impact on other variables within the model and lacked consideration in the final parameter sensitivity analysis. To address these gaps, this study augments the foundational model with variables accounting for drug-resistant mutations in tumor cells and includes the effects of drug

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resistance on other parameters in the final sensitivity analysis. This enriches the model, allowing for a more precise determination of which parameters exert the greatest influence on tumor cell dynamics.

2. Research Method

The original model established a mathematical model representing tumor growth, immune response, and the impact of chemotherapy drugs on the tumor. It considered T(t) signifies the count of tumor cells at the moment t, N(t) is used to specify the number of NK cells present at a given time t.L(t) denotes the quantity of CTLs cells at a given moment t, and u(t) to signify the concentration of chemotherapy drugs at the location of the tumor when t occurs. The model was built based on the following assumptions:

(1) Both immunological agents and chemotherapeutic treatments can reduce the number of tumor cells.

(2) Due to degradation, counteraction against the tumor, and the effects of chemotherapy drugs, the number of immune effector cells will decrease.

(3) Chemotherapeutic agents can dynamically act on tumor cells and immune response cells through the principles of mass-action kinetics.

(4) A higher sustained drug dosage will lead to a rise in tumor cell counts and depletion of immune response cells and exhaustion of the immune effector cells.

$$N'(t) = aN(t)\big(1 - bN(t)\big) - \alpha_1 N(t)T(t) - k_N u(t)N(t), \tag{1}$$

$$L'(t) = eN(t)T(t) - \mu L(t) - \beta_1 L(t)T(t) - k_L u(t)L(t), \tag{2}$$

$$T'(t) = cT(t)\big(1 - dT(t)\big) - \alpha_2 N(t)T(t) - \beta_2 L(t)T(t) - k_T u(t)T(t), \tag{3}$$

$$u'(t) = v - \omega u(t). \tag{4}$$

Upon examining the original model, it is noticeable that the fourth assumption suggests a higher continuous drug dosage input might result in a rise in tumor cell counts and depletion of immune response cells. Is implies the potential development of drug resistance in tumor cells. However, in equation (3)T(t) merely represents the intrinsic growth term of the tumor cells and their elimination by the chemotherapeutic drug and effector cells. The equation does not account For the group of tumor cells resistant to drugs that arise due to exposure to the chemotherapeutic drug. Given that these drug-resistant tumor cells would have a substantially lower death rate when exposed to chemotherapy compared to the non-resistant tumor cells, a portion of these cells would not be eliminated, which isn't reflected in the equation. This omission suggests that the derived T(t)would be an underestimation of the actual scenario. Such discrepancies could lead to significant errors in subsequent sensitivity analyses of parameters.

In light of these shortcomings in the original model, this paper has made appropriate optimizations. This research divided the tumor cells into two categories: one portion representing the normal, non-mutated tumor population Tn(t), and the other part representing the drug-resistant mutated population Td(t). The assumptions remain consistent with those mentioned above.

$$N'(t) = aN(t)\big(1 - bN(t)\big) - \alpha 1 N(t)\big(Tn(t) + Td(t)\big) - k_N\, u(t)N(t), \tag{5}$$

$$L'(t) = eN(t)T(t) - \mu L(t) - \beta_1 L(t)\big(Tn(t) + Td(t)\big) - k_L u(t)L(t), \tag{6}$$

$$Tn'(t) = r_1 Tn(t)\left(1 - \frac{Tn(t) + Td(t)}{Tmax}\right) - rTn(t) - \alpha_2 N(t)Tn(t) - \beta_2 L(t)Tn(t) - \quad k_1 u(t)Tn(t), \tag{7}$$

$$Td'(t) = r_1 Td(t)\left(1 - \frac{Tn(t) + Td(t)}{Tmax}\right) + rTn(t) - \alpha_2 N(t)Td(t) - \beta_2 L(t)Tn(t) - \quad k_2 u(t)Tn(t), \tag{8}$$

$$u'(t) = v - \omega u(t). \tag{9}$$

The initial conditions are $N(0) = N_0 \geq 0, L(0) = L_0 \geq 0, T(0) = T_0 \geq 0, u(0) = u_0 \geq 0.$

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The third equation illustrates the activity patterns of typical tumorr cells. The premise here is that it follows a logistic growth, $r_1 Tn(t)(1-\frac{Tn(t)+Td(t)}{Tmax})$, where Tmax stands for the carrying capacity of the two types of tumor cells. This paper assumes that drug-resistant tumor cells are derived from mutations in tumor cells, with a respective constant mutation rate denoted by r. The number of normal tumor cells should be reduced by the population of drug-resistant tumor cells post-mutation, denoted as $-rTn(t)$. After interactions between both types of immune cells and tumor cells, part of them becomes inactive, represented by $-\alpha_2 N(t)Tn(t)$and respectively. Following the effects of chemotherapy drugs, they also become inactive, with the inactivation term denoted as $k_t u(t)Tn(t)$.

In order to simplify the model, The study set up dimensionless state variables according to Model 1.1 and proceeded with the nondimensionalization.

$$\bar{N}=\frac{\alpha 2}{\mu}N,\bar{L}=\frac{\alpha 1\alpha 2}{h\mu}L,\bar{T}_N=\frac{1}{T_{max}}T_N\ \bar{T}_D=\frac{1}{T_{max}}T_D,u=\frac{K_n}{\mu},dt=\frac{1}{\mu}d\tau.$$

After simplification, The study can obtain the following model:

$$\bar{N}'(\tau)=\frac{a}{\mu}\bar{N}(\tau)(1-\frac{b\mu}{\alpha_2}\bar{N}(\tau))-\bar{N}(\tau)(\bar{T}_N(\tau)+\bar{T}_D(\tau)-\bar{u}(\tau)\bar{N}(\tau), \quad (10)$$

$$\bar{L}'(\tau)=\bar{N}(\tau)\left(\bar{T}_N(\tau)+\bar{T}_D(\tau)\right)-\bar{L}(\tau)-\frac{\beta_1}{\alpha_1}\bar{L}(\tau)\left(\bar{T}_N(\tau)+\bar{T}_D(\tau)\right)-\bar{u}(\tau)\bar{L}(\tau), \quad (11)$$

$$\bar{T}_N'(\tau)=\bar{T}_N(\tau)\left(1-\bar{T}_N(\tau)-\bar{T}_D(\tau)\right)-\frac{r}{r_1}\bar{T}_N(\tau)-\bar{N}(\tau)\bar{T}_N(\tau)-\frac{h\beta_2}{\alpha_1\alpha_2}\bar{L}(\tau)\bar{T}_N(\tau)-\frac{k_1}{k_n}\bar{u}(\tau)\bar{T}_N(\tau), \quad (12)$$

$$\bar{T}_D'(\tau)=\bar{T}_D(\tau)\left(1-\bar{T}_N(\tau)-\bar{T}_D(\tau)\right)+\frac{r}{r_1}\bar{T}_N(\tau)-\bar{N}(\tau)\bar{T}_D(\tau)-\frac{h\beta_2}{\alpha_1\alpha_2}\bar{L}(\tau)\bar{T}_D(\tau)-\frac{k_2}{k_n}\bar{u}(\tau)\bar{T}_D(\tau), \quad (13)$$

$$\bar{u}'(\tau)=\frac{k_n\sigma}{\mu^2}-\frac{\omega}{\mu}\bar{u}(\tau). \quad (14)$$

Redefine $\bar{N},\bar{L}$, $\bar{T}_N$, $\bar{T}_D$, $\bar{u}$ as N, L, T_N,T_D, u respectively. After substituting the respective steady-state variables into the model, The research obtains the following equation (10)-(14)

$$N'(t)=pN(t)(1-1.8\times10^{-2}N(t))-N(t)(T_N(t)+T_D(t)-u(t)N(t), \quad (15)$$

$$L'(t)=N(t)\left(T_N(t)+T_D(t)\right)-L(t)-3.42\times10^{-3}L(t)\left(T_N(t)+T_D(t)\right)-u(t)L(t), \quad (16)$$

$$T_N'(t)=T_N(t)\left(1-T_N(t)-T_D(t)\right)-5.6\times10^{-3}\bar{T}_N(t)-\bar{N}(t)T_N(t)-6.02\times10^3L(t)T_N(t)-k_su(t)T_N(t), \quad (17)$$

$$T_D'(\tau)=T_D(t)\left(1-T_N(t)-T_D(t)\right)+5.6\times10^{-3}T_N(t)-N(t)T_D(t)-6.02\times10^3L(t)T_D(t)-k_du(t)T_D(t), \quad (18)$$

$$u'(t)=s-fu(t). \quad (19)$$

Which $p=\frac{a}{\mu}$, $k_s=\frac{ks}{kn}$ $k_d=\frac{kd}{kn}$, $s=\frac{k_n\sigma}{\mu^2}$, $f=\frac{\omega}{\mu}$, $\frac{b\mu}{\alpha_2}=1.8\times10^{-2}$, $\frac{\beta_1}{\alpha_1}=3.42\times10^{-3}$, $\frac{r}{r_1}=5.6\times10^{-3}$, $\frac{r\beta_2}{\alpha_1\alpha_2}=6.02\times10^3$.

The following is the meaning of the formula parameters:

a(/day): Intrinsic growth rate of NK cell;

b(/cell): Inverse of the maximum environmental carrying capacity of NK cells, 3.17×10^{-6}[5];

β_2(/cell/day): Death rate of tumors induced by CTLs, 3.5×10^{-7}[5];

r(/day): Mutation rate from normal tumor cells to drug-resistant tumor cells, $10\times10^{-4.5}$[6];

ω(/day): Decay rate of chemotherapy drugs, 9.0×10^{-1}[6];

k_N, k_L(/day): Rate at which chemotherapy drugs kill immune cells, 6.0×10^{-1}[6];

k_1(/day): Rate at which chemotherapy drugs kill normal tumor cells, 8.0×10^{-1}[6];

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μ(/day): Natural death rate of CTLs, 2.0×10^{-2}[7];

h(/cell/day): Activation rate of CTLs by lytic fragments of tumor cells killed by NK cells, 1.1×10^{-7}[7-8];

r_1 (/day): Intrinsic growth rate of both types of tumor cells, 1.8×10^{-1}[9];

T_{max}(/cell): Maximum environmental carrying capacity for both types of tumor cells, 1.0×10^{9}[9]

α_1 (/cell/day): Deactivation rate of NK cells due to tumor interaction, 1.0×10^{-7}[9];

α_2(/cell/day): Death rate of tumors induced by NK cells, 3.23×10^{-7}[9-10];

β_1 (/cell/day): Deactivation rate of CTLs due to tumor interaction, 3.42×10^{-10}[11];

$\mathcal{V}$(dose): Constant input of chemotherapy drugs;

k_2(/day): Rate at which chemotherapy drugs kill drug-resistant tumor cells, 3.0×10^{-1}

e(/cell/day): Activation rate of CTLs by tumor cell fragments lysed by NK cells,1.1×10^{-7}[12-13];

3. Findings

In the equation (17)-(19) , the paper sets the parameter $k_s = 0.2, k_d = 0.1, f = 0.1, s = 10$,p to range from 0 to 1, with an interval of 0.01. The study then utilized MATLAB to simulate the tumor cell count on the 40th day, denoted as curve (a), taking the initial values of 1×10^5NK cells, 1×10^2CTLs cells, 1×10^5 regular tumor cells, 1×10^5 drug-resistant tumor cells, and a drug concentration of 10. Analyzing curve (a), the paper observed that as the value of parameter p increases, the overall count of tumor cells demonstrates a declining trend. However, within this trajectory, there are substantial fluctuations in the tumor cell count, and the eventual outcome remains relatively stable. This suggests that while NK cells do have a cytotoxic effect on tumor cells, their kill rate isn't particularly high. Moreover, it underscores the role of NK cells as the body's first line of defense; they do possess a certain level of cytotoxicity, but it's not sufficient to completely eliminate the tumor cells.

Subsequently, by setting the parameter$k_d = 0.1, f = 0.1, s = 10, p = 20, k_s$ to range between 0.3 and 0.8 with an interval of 0.05, the paper once again employed MATLAB to simulate the count of regular tumor cells on the 40th day, depicted as a curve (b). Analyzing this curve, it's clear that as the parameter $k_s$value escalates, the count of regular tumor cells decreases drastically. Eventually, the number of tumor cells is reduced to zero. This suggests that even minor variations in this parameter $k_s$can lead to significant fluctuations in the tumor cell count, even potentially eradicating them entirely. Thus, the tumor cells are extremely sensitive to this particular parameterk_s. Consequently, when treating tumor cells, chemotherapy can be considered a primary therapeutic intervention, taking into account these findings.

Similarly, this paper sets the parameter $f = 0.1, s = 10, p = 20, k_s = 0.2, k_d$to range from 0.3 to 0.55, with an interval of 0.05. Using MATLAB, the paper simulated the number of drug-resistant tumor cells on the 40th day, as shown in Figure (c). Upon analyzing the graph, it is evident that with a rising value, the study observes a decrement in the number of tumor cells. However, in contrast to the killing rate of normal tumor cells k_s, the trend in Figure (c) is more gradual. This indicates that once the tumor develops drug resistance, the cytotoxic effect of chemotherapy drugs on it diminishes. The emergence of drug resistance significantly undermines the therapeutic efficacy of chemotherapy, marking it one of the crucial challenges in cancer treatment.

Subsequently, setting the parameter$k_s = 0.2, k_d = 0.1, f = 0.1, p = 20$, and letting s range from 0 to 100, at intervals of 10, the paper employed MATLAB to simulate the tumor cell count on the 40th day, as illustrated in Figure (d). From the study analysis of Figure (d), it's clear that altering the concentration of chemotherapy drugs doesn't substantially affect the final tumor cell count. Upon incorporating the drug-resistance factor, the sensitivity of s to the number of tumor cells has been further reduced. This means that the resultant change in the number of tumor cells will become increasingly smaller, leading to a trend where the graph becomes more and more gradual. Therefore, merely adjusting the drug concentration not only fails to achieve therapeutic outcomes against tumors but can also inflict harm on effector cells or native body cells. There's even the potential risk of tumor relapse.

Lastly, setting the parameter $k_s = 0.2, k_d = 0.1, p = 20, s = 10,$ this research sets the parameter f to range from 0.5 to 1.2, with an interval of 0.1. The paper then used MATLAB to simulate the tumor

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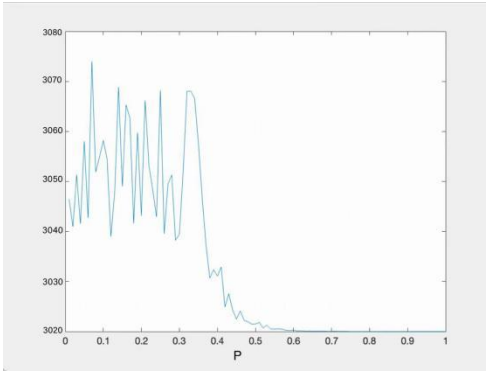
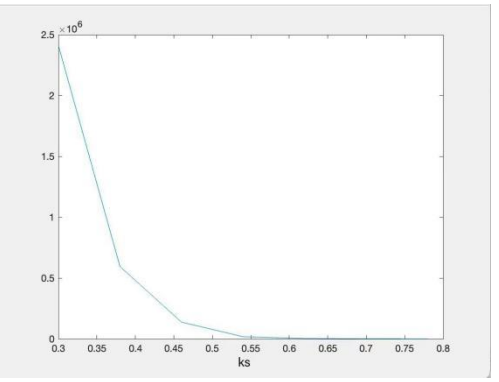
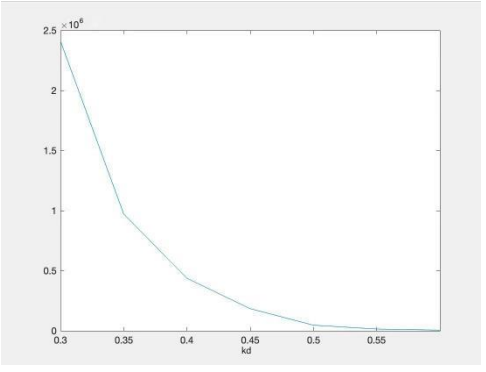
cell count on the 40th day, denoted as curve (e). By analyzing the graph (d), it is discernible that as the decay rate of the chemotherapy drug accelerates, the number of tumor cells in the host increases continuously. After incorporating the drug-resistance factor, as the decay rate of chemotherapeutic drug increases, the number of tumor cells correspondingly rises. Due to the insensitivity of the drug-resistant tumor cells to the chemotherapy, the rate of increase of these tumor cells will be faster compared to before, and the corresponding number will also be greater than when this factor was not considered. Correspondingly, to enhance the efficacy of chemotherapy, the paper can reduce the decay rate of the drug within the host.

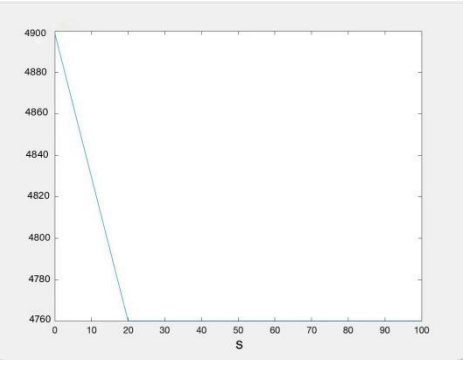
In summary, while there are numerous parameters in the model, the tumor's response to changes in a few specific parameters is much more pronounced compared to others. Based on the sensitivity analysis previously mentioned, it's evident that tumor cells are highly sensitive to the chemotherapy drug's induced death rate for regular tumor cells and the decay rate of the chemotherapy drugf. However, when mutation factors are introduced, new parameters emerge, like the chemotherapy drug's induced death rate for drug-resistant tumor cells k_d, and consequently, the chemotherapy drug's sensitivity to these cells decreases. Furthermore, as the decay rate of the chemotherapy drugf increases, the remaining number of tumor cells will be higher than in scenarios without any mutations. Then there are parameters like the growth rate of NK cells, denoted as p, and the constant input rate of the chemotherapy drug, denoted as "s". Originally, these parameters were relatively insensitive to tumor cells, and with the inclusion of mutation rates, their sensitivity only decreases further. Particularly, the constant input rate of the chemotherapy drugs becomes even less influential due to the implications of drug resistance. Thus, even with changes in the constant input rate of the chemotherapy drug, the final count of remaining tumor cells will hardly show any significant variations.





(a) sensitivity analysis graph of parameter p (b) sensitivity analysis graph of parameter k_s





(c) sensitivity analysis graph of parameter k_d (d) sensitivity analysis graph of parameter s

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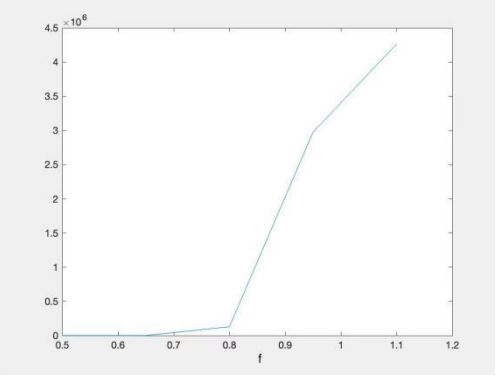

(e) sensitivity analysis graph of parameter f

Figure 1. The influence of various parameters on the total tumor cell count 40 days later

4. Conclusion

In this study, the mathematical model presented in the original paper has been refined to establish a set of ordinary differential equations (ODE) that describe tumor cell responses to the immune system under chemotherapy. Building on the foundation of the primary article, we have incorporated drug resistance factors and accounted for their influence on various variables. This research also delved into the sensitivity of the equation (17)-(19) parameters, discussing the ultimate impact of these five parameters k_s, k_d, f, p, s on tumor cell count. Notably, we found that the killing rate of chemotherapeutic drugs on conventional tumor cells k_s and the drug decay rate f exhibit pronounced sensitivity concerning tumor cell count. Simultaneously, it can be observed that the sensitivity Kd of chemotherapeutic drugs to drug-resistant tumor cells is less than the killing rate ks for conventional tumor cells. The introduction of this factor alters the sensitivity of the corresponding parameters to some extent. This model did not consider potential changes in the inactivation rate of drug-resistant tumor cells following their interaction with other effector cells. Therefore, future research focusing on the impact of drug-resistant tumor cells on respective effector cells holds significant importance. Furthermore, drug resistance remains a formidable challenge in the process of tumor treatment. Consequently, it would be prudent to integrate strategies specifically targeting drug resistance, such as the nanotechnology solutions to counteract resistance that we mentioned earlier, to mitigate its effects during chemotherapeutic drug treatment.

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