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

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Introduction: The problam of cancer treatment

- Cancer is a serious a public health problem.
- Chemotherapy is vital for cancer treatment., but chemotherapy is Double-edged sword.
- Serious side effects and drug resistance arise from clinically maximum tolerated doses (MTD) -based chemotherapy.
- Adaptive therapy (AT) is adapted to the patient's condition and response, reducing chemotherapy toxicity, more effective.
- Mathematical models help us understand the biological evolution of cancer and formulate optimal cancer treatment.

So far, Most of the adaptive treatment policies in the past are special cases and temporary. The results of clinical trials are not stable.

The problem of optimizing an individual's appropriate schedule and drug dosage remains unresolved.

Introduction:

This project focus on

- Mathematical modeling on tumor and individualized immune status.
- Using the parameters exploration and optimization of the mathematical model.
- To make the model reflect the actual situation more accurately.
- providing theoretical guidance for the customization of tumor treatment.

Methods and Results

- **Section 1. Summarize representative dynamics of models in publications, then build up the master mathematical model capturing the dynamic characters of the previous models.**
- **Section 2. analyze the characters of the master model such as temporal evolution and phase plot of the system without drug.**

  In order to gain some qualitative insight into the possible solutions of the system before classifying them in a systematic and exhaustive way, I consider a few arbitrarily chosen sets of the model parameters, namely the repression term from immune cells to tumor growth, and stimulation term from tumor cells to immune system, and solve the system numerically in Python.
- **Section 3. The master mathematical models would be numerically verified.**

  I investigate how to design the best drug treatment to eliminate the tumor in the shortest time frame.

  It is assumed that the chemotherapeutic drug is given to the patient as a continuous Dirac Delta Function.
- **Finally, conclusions of the mathematical findings would be made.**

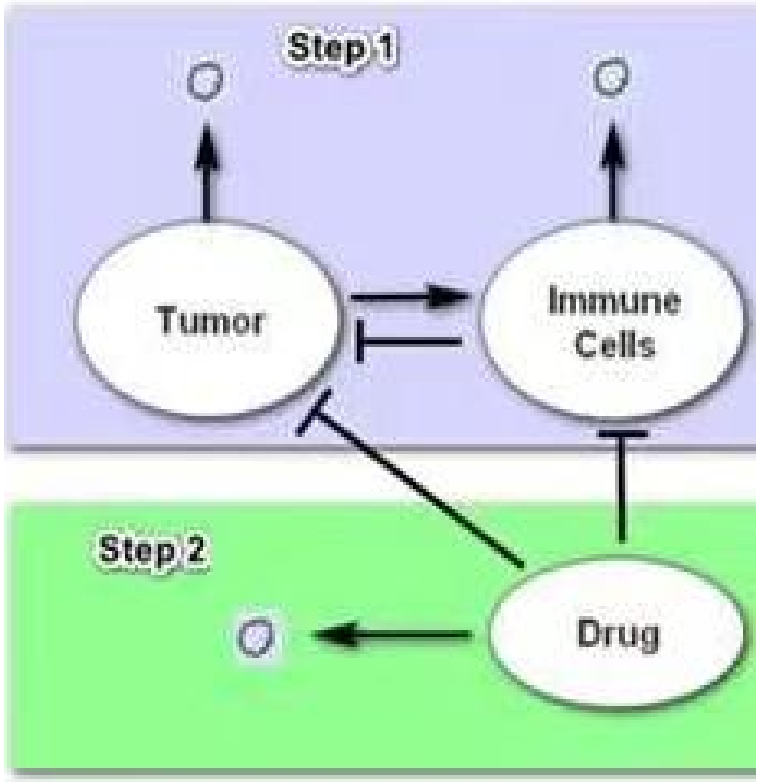

Figure 1. Illustration of Tumor-Immune-Drug network.

Methods and Results

Model 1
Equations:

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

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

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

The assumption of the model is:

1. 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 $r_1 T(1 - p_1 T)$
2. The repression from immune cells to tumor cells is proportional to the multiply of immune cells and tumor cells, represented by $\mu_1 IT$
3. tumor cells can reduce immune cells cytotoxicity, represented by $d_{22} TI$
4. The increase rate is dictated by the influx rate of immune cells in the bloodstream, v_2
5. The tumor cells stimulate the immune response, and the immune cells produce $\frac{\mu_2 T^n I}{h + T^n}$; this leads to the promotion of immune cells.
6. Chemotherapy drugs have damaging effects on tumor cells and immune cells. Represented by $d_{11} TD$ and $d_{21} ID$, respectively
7. The growth of chemotherapeutic Drug is dictated by the dose of the drug and its natural decay, represented by $v(t)$- $\underbrace{d_3 D}$

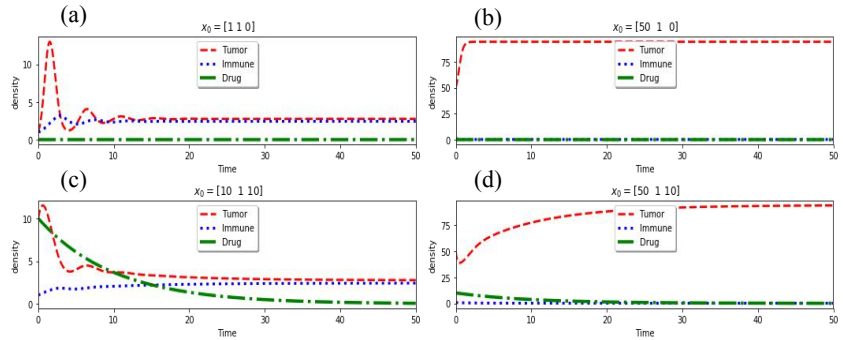

Figure 2. Four dynamic scenarios from Model 1 presented in publications.

(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.

Methods and Results

Model 2
Equations:

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

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

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

The assumption of the model 2 is:

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

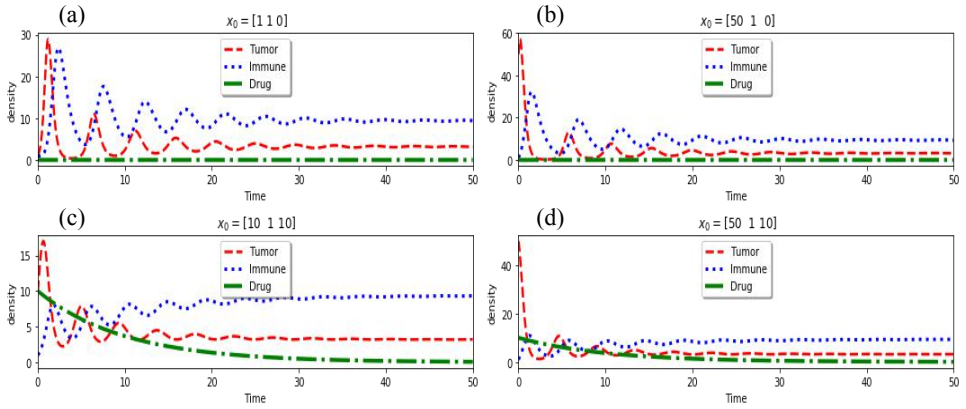

Figure 3. Four dynamic scenarios from Model 2 presented in publications

(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).

Methods and Results

Model 3
Equations:

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

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

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

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.

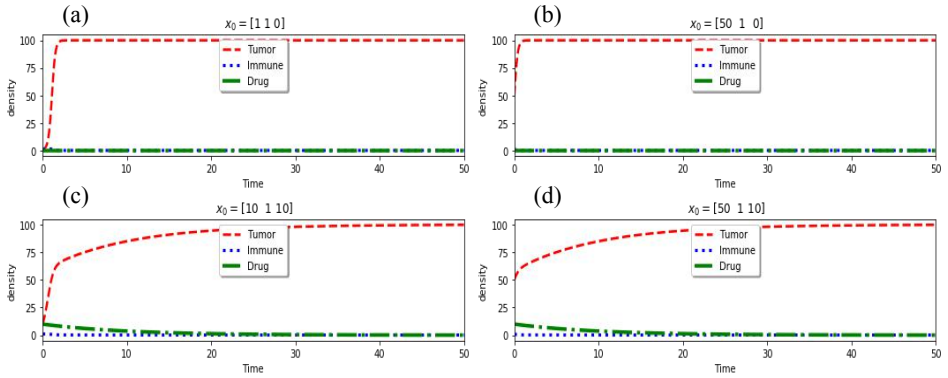

Figure 4. Four dynamic scenarios from Model 3 presented in publications .

(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.

Methods and Results

Model 4
Equations:

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

$$\frac{dI}{dt} = \underbrace{r_2 I(1 - p_2 I)}_{\text{growth}} - d_{21} ID$$

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

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.

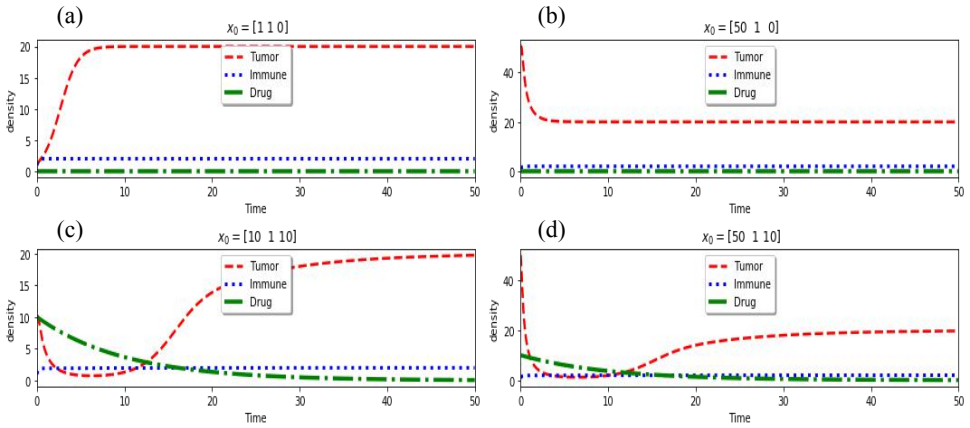

Figure 5. Four dynamic scenarios from Model 4 presented in publications.

(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).

Methods and Results

Model 5

Equations:

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

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

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

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 $\mu_2 T(1-\beta T)I$

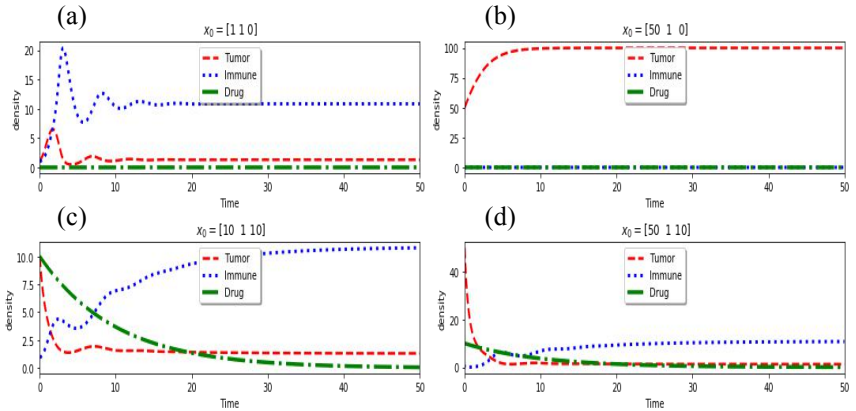

Figure 6. Four dynamic scenarios from Model 5 presented in publications.

(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).

Methods and Results

The master equations is:

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

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

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

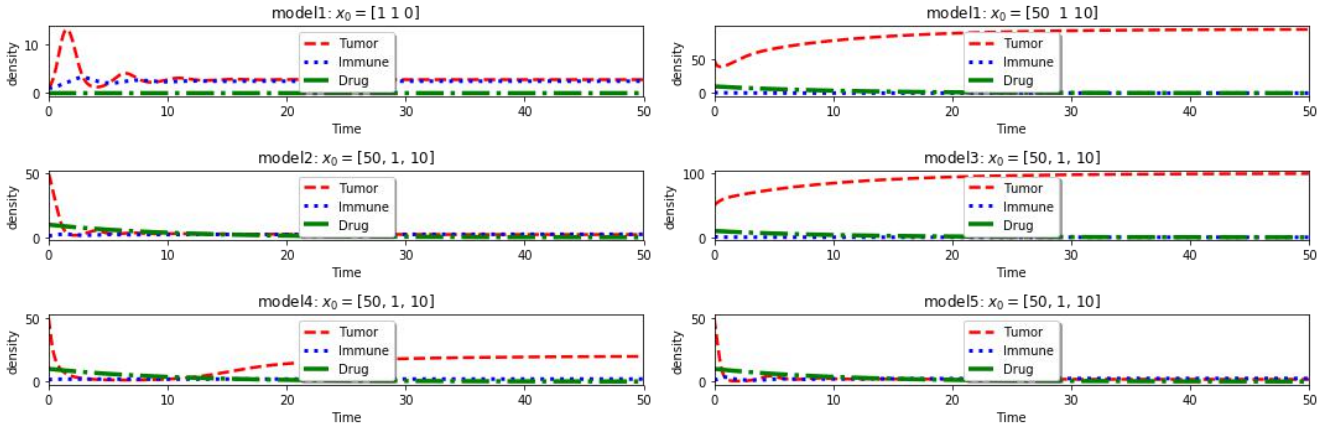

Figure 7. Master equation to capture dynamics in five distinctive published TID models.

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.

Methods and Results

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.

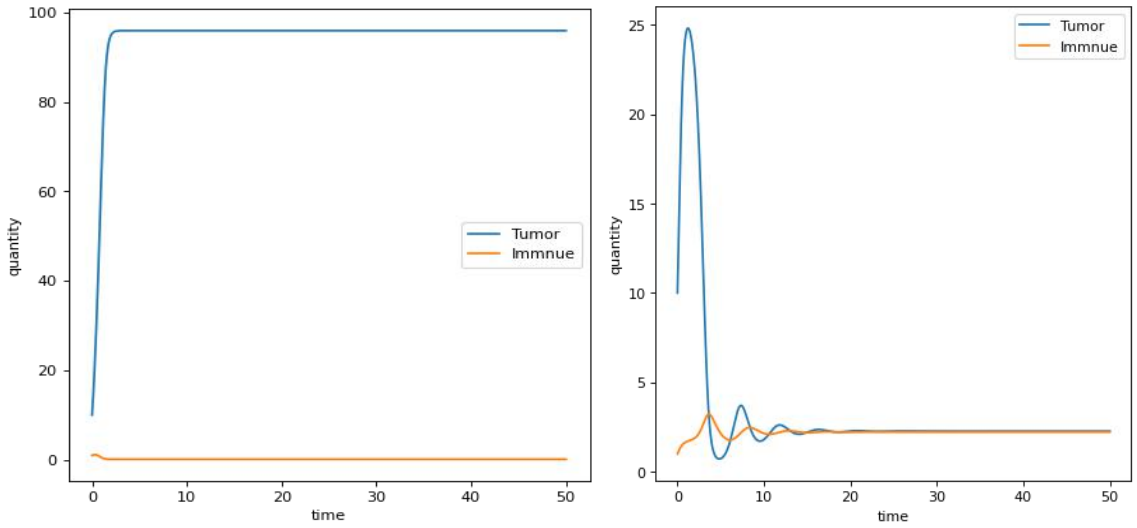

Figure 8 (left) time series of tumor and immune cell at μ1=1.5, μ2=3.5; (right) time series of tumor and immune cell at μ1=2.2, μ2=4.2

Phase portrait

In order to determine the effect of the initial conditions on the behavior of the system, a phase portrait was drawn in Fig.4(left).Fig.4(right) 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.

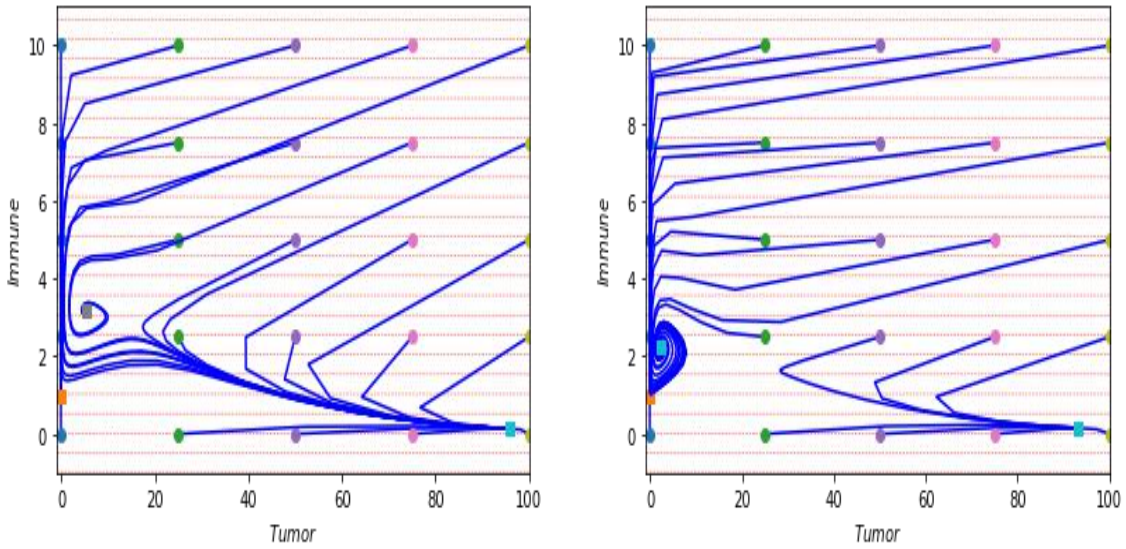

Figure 9 (left) phase portrait of network at μ1=1.5, μ2= 3.5; (right) phase portrait of network at μ1=2.2, μ2=4.2

Methods and Results

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. We assume the chemotherapeutic drug is given to the patient as a continuous Dirac Delta Function .

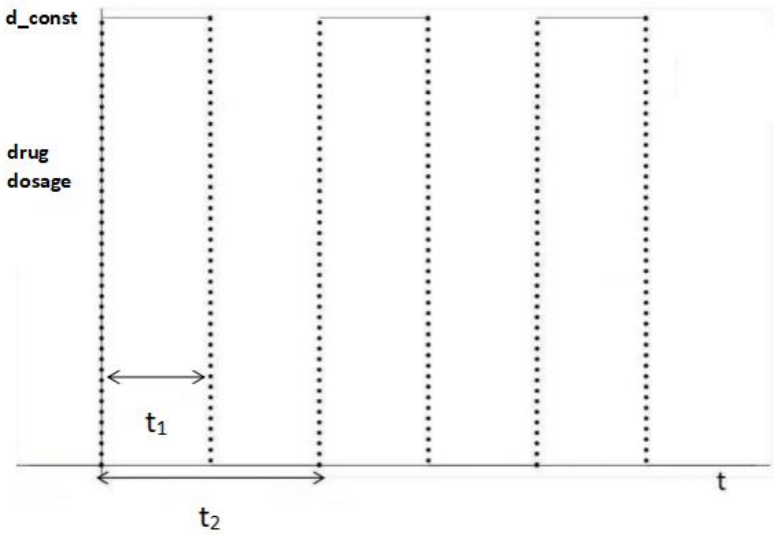

Figure 10 taking drug effect function

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

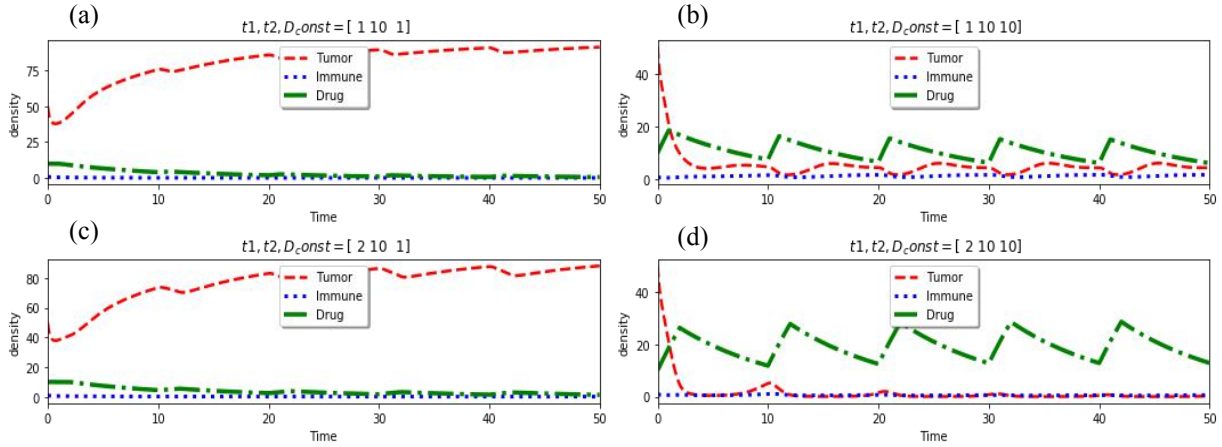

Figure 11 Effect from Drug influx rate to TID dynamic

Methods and Results

Numerical simulation of the TID model

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

- The minimum timeframe for tumor density to decrease under 0.01.
- The area of t_1 * D_{const} 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.

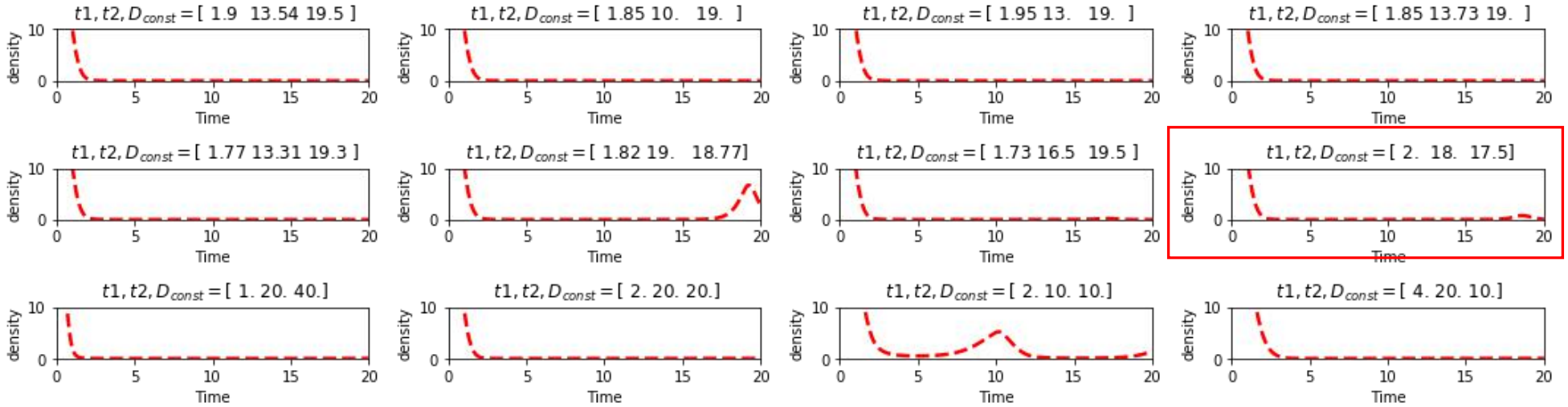

Figure 12: TID system dynamic under various drug treatment (selected 16 representative)

Despite the drug influx parameters in Figure 12, first row can all eliminate the tumor, last subfigure of the second row (red boxed image) is preferred treatment. Because t_2 is long, while D_const is relatively in smaller dose.

Conclusion

- Summarized five representative models in publications
- Built a master model that can cover the dynamic characters of previous five models.
- Studied the temporal evozlution and phase plot of the model.
- Developed a matrix for deciding the treatment plan is effective and painless for patient
- Studied how the master model can be applied to design optimal drug treatment.

REFERENCES

1. . Sung, H., et al., Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;0:1-41
2. .Tanay, M.A.L., Medications Used for Cancer, in Understanding Pharmacology in Nursing Practice, P. Hood and E. Khan, Editors. 2020, Springer International Publishing: Cham. p. 393-411.
3 . Epstein, R.S., et al., Patient Burden and Real-World Management of Chemotherapy-Induced Myelosuppression: Results from an Online Survey of Patients with Solid Tumors. Adv Ther, 2020. 37(8): p. 3606-3618.
4. .Morrison, V.A., Immunosuppression associated with novel chemotherapy agents and monoclonal antibodies. Clin Infect Dis, 2014. 59 Suppl 5: p. S360-4.
5. . Chaveli-López, B. and J.V. Bagán-Sebastián, Treatment of oral mucositis due to chemotherapy. J Clin Exp Dent, 2016. 8(2): p. e201-9.
6.. Glassman, P.M. and J.P. Balthasar, Physiologically-based modeling of monoclonal antibody pharmacokinetics in drug discovery and development. Drug Metab Pharmacokinet, 2019. 34(1): p. 3-13.
7. .Mould, D.R., et al., Developing Exposure/Response Models for Anticancer Drug Treatment: Special Considerations. CPT Pharmacometrics Syst Pharmacol, 2015. 4(1): p. e00016.
8. . .Abreu, S., et al., Patient-derived ovarian cancer explants: preserved viability and histopathological features in long-term agitation-based cultures. Sci Rep, 2020. 10(1): p. 19462.
9. . Urueña, C., et al., Evaluation of chemotherapy and P2Et extract combination in ex-vivo derived tumor mammospheres from breast cancer patients. Sci Rep, 2020. 10(1): p. 19639.
10. Palmer, A.C. and P.K. Sorger, Combination Cancer Therapy Can Confer Benefit via Patient-to-Patient Variability without Drug Additivity or Synergy. Cell, 2017. 171(7): p. 1678-1691.e13.
11. Eriksson, H. and K.E. Smedby, Immune checkpoint inhibitors in cancer treatment and potential effect modification by age. Acta Oncol, 2020. 59(3): p. 247-248.
12. Chan, C.W.H., et al., Novel Strategies on Personalized Medicine for Breast Cancer Treatment: An Update. Int J Mol Sci, 2017. 18(11).
13. Mosa, A.S.M., A.M. Hossain, and I. Yoo, A dynamic prediction engine to prevent chemotherapy-induced nausea and vomiting. Artificial Intelligence in Medicine, 2020. 109: p. 101925.
14. Kosianova, A., et al., Natural molecules as modulators of epigenetic silencing in human cells for cancer care and aging. Biological Communications, 2020. 65(4), 315–330. https://doi.org/10.21638/spbu03.2020.405
15. Lee-Six, H., et al., Population dynamics of normal human blood inferred from somatic mutations. Nature, 2018. 561(7724): p. 473-478.
16. Romero-Garcia, S., et al., Lactate contribution to the tumor microenvironment: mechanisms, effects on immune cells and therapeutic relevance. Front Immunol, 2016. 7: p. 52.
17. Pattanayak, S. Succulent biomedicines-an effective way of getting protection against diseases through immunomodulation. Explor Anim Med Res, Vol.10, Issue - 2, 2020, p. 112-123
18. Paludan, S.R., et al., Constitutive immune mechanisms: mediators of host defence and immune regulation. Nat Rev Immunol 21, 137–150 (2021). https://doi.org/10.1038/s41577-020-0391-5
19. Makaryan1, SZ,et al., Modeling immune cell behavior across scales in cancer. WIREs Syst Biol Med. 2020;12:e1484. https://doi.org/10.1002/wsbm.1484
20. Williams, J.B.,et al., Tumor heterogeneity and clonal cooperation influence the immune selection of IFN-γ-signaling mutant cancer cells. Nat Commun 11, 602 (2020). https://doi.org/10.1038/s41467-020-14290-4
21. Shields G, et al., Psychosocial Interventions and Immune System Function: A Systematic Review and Meta-analysis of Randomized Clinical Trials. JAMA Psychiatry. 2020;77(10):1031-1043. doi:10.1001/jamapsychiatry.2020.0431
22. Park, B., et al., Association of white blood cell count with breast cancer burden varies according to menopausal status, body mass index, and hormone receptor status: a case-control study. Sci Rep, 2019. 9(1): p. 5762.
23. Hazim A. et al., Relationship Between Response and Dose in Published, Contemporary Phase I Oncology Trials. J Natl Compr Canc Netw. 2020, 18, 4;
DOI: https://doi.org/10.6004/jnccn.2019.7375
24. Gluzman M, Optimizing adaptive cancer therapy: dynamic programming and evolutionary game theory. Proc. R. Soc. B. 2020,287:20192454. http://dx.doi.org/10.1098/rspb.2019.2454
25. Yan G. et al., Advances in mathematical models of the active targeting of tumor cells by functional nanoparticles, Computer Methods and Programs in Biomedicine,2020, Volume 184, 105106, https://doi.org/10.1016/j.cmpb.2019.105106.
26. Bozic, I., et al., Delineating the evolutionary dynamics of cancer from theory to reality. Nat Cancer 1, 580–588 (2020). https://doi.org/10.1038/s43018-020-0079-6
27. Robert A. Beckman R. et al., How Should Cancer Models Be Constructed? Cancer Control. 2020, 27: 1-12. DOI: 10.1177/1073274820962008
28. Abe et al., (2020). Flint: a simulator for biological and physiological models in ordinary and stochastic differential equations. Journal of Open Source Software, 5(53), 2331. https://doi.org/10.21105/joss.02331
29. Sameen S. et al., Mathematical modeling of drug resistance due to KRAS mutation in colorectal cancer. Journal of Theoretical Biology, 2016, 389: 263-273. https://doi.org/10.1016/j.jtbi.2015.10.019.
30. Ku-Carrillo R. et al., Effects of the obesity on optimal control schedules of chemotherapy on a cancerous tumor. Journal of Computational and Applied Mathematics. 2017, 309: 603-610. https://doi.org/10.1016/j.cam.2016.05.010
31. Sharma S.et al., Dynamical Behaviour of a Tumor-Immune System with Chemotherapy and Optimal Control. Journal of Nonlinear Dynamics. 2013, Volume 2013: Article ID 608598, 13 pages. http://dx.doi.org/10.1155/2013/608598
32. Sharma S.et al., Analysis of the Dynamics of a Tumor–Immune System with Chemotherapy and Immunotherapy and Quadratic Optimal Control. Differ Equ Dyn Syst. 2016, 24(2):149-171. DOI 10.1007/s12591-015-0250-1
33. I.Bashkirtseva, I. et al., Analysis of noise-induced phenomena in the nonlinear tumor-immune system. Physica A, 2020,549:123923
34. Zeng C. et al., Dynamic Analysis of a Tumor-Immune System under Allee Effect. Mathematical Problems in Engineering. 2020, Volume 2020, Article ID 4892938, 11 pages. https://doi.org/10.1155/2020/4892938
35. Das P. et al., Characterizing chaos and multifractality in noise-assisted tumor-immune interplay. Nonlinear Dyn. 2020, 101:675-685. https://doi.org/10.1007/s11071-020-05781-6
36. Yang H. et al.,Extinction and persistence of a tumor-immune model with white noise and pulsed comprehensive therapy. Mathematics and Computers in Simulation. 2021, 182: 456-470
37. Kirschner D. et al., Modeling immunotherapy of the tumor – immune. Interaction. J. Math. Biol. 1998, 37: 235-252
38. Arabameri A. et al., A structural methodology for modeling immune-tumor interactions including pro- and anti-tumor factors for clinical applications. Mathematical Biosciences.2018, 304:48-61
39. Dhar B. et al., A numerical approach of tumor-immune model with B cells and monoclonal antibody drug by multi-step differential transformation method. Math Meth Appl Sci. 2020;1-13. DOI: 10.1002/mma.7009
40. Ledzewicz U. et al., Optimal controls for a mathematical model of tumor-immune interactions under targeted chemotherapy with immune boost. Discrete and continuous dynamical systems series B. 2013,18(4):1031-1051.
doi:10.3934/dcdsb.2013.18.1031.

Thanks

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