

THE EFFECT OF CHEMOTHERAPY AND IMMUNOLOGICAL RESPONSE ON BREAST CANCER GROWTH

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ABSTRACT. Place abstract here. The abstract summarizes in one paragraph the main question and conclusions draw from your investigation.

1. BACKGROUND/MOTIVATION

Mathematical oncology is field of oncology, the study of cancer, that employs math to study cancer and its behavior. In the words of Dr. Rockne and MD Scott, “it [serves] as a bridge between . . . the biologist, and the practicing clinician.” One of the biggest application of mathematical modeling in oncology is tumor growth modeling. In mathematical oncology, tumor growth modeling seeks to understand and model the characteristics and dynamics that govern general cancer growth. Moreover, it seeks also to understand and model the relationship between cancer and the systems that fight against it as well as the response of the cancer itself to these systems.

The primary main purpose of tumor growth modeling is to first develop a general tumor growth model in the absence of any intervention. Secondly, it seeks to model the response to external factors such as immunological response or treatment. And thirdly, the modeling will then add tumor resistance and active fighting against any form of treatment be it from the immune system or other treatments. In the absence of any intervention, several models have been made to try to show the growth of a tumor, measured by *tumor burden*, denoted T , (see [A](#) for definitions), as a function of time t . The models range from simple ODEs such as linear growth, or logistic growth, to more complicated models employing stochastic differential equations and algebraic differential equations. The main hope of these general growth models is to be able to use these models to develop more personable treatment to individuals facing the plight of cancer [?].

The more commonly used models due to their simplicity are linear, exponential, and logistic models (see [B](#) for equations). However, these do not accurately reflect the full and overall growth of observed cancers with the exception of a few cancer scenarios. That is, they fail to generalize to the dynamics a cancer will exhibit: primarily that it has slow exponential rate and a maximal size. In particular, the exponential model (9) is characterized by an infinite growth as t increases which does not reflect the fact that a tumor can have a maximum size, even when considering

a death rate. Moreover, the logistic model (10) converges too fast to the max size, T_{\max} , a tumor can be [?]. As such, a need for a model that can firstly exhibit a slow exponential rate and then a slow convergence to the carrying capacity is preferred to others that only exhibit one of these two characteristics.

When it comes to treatment, most cancers typically use a combination for surgery, chemotherapy, and radiation therapy for treatment. In breast cancer, surgery is the primary treatment which is not well suited for math modeling. Surgery removes as much as the cancer as possible so that any modeling growth would just have a sudden vertical drop in tumor burden at the time the surgery is removed causing discontinuities in the modeling. For breast cancer, chemotherapy, be it neoadjuvant or adjuvant (see A), is the most common treatment supplement to surgery, being the primary treatment.

Most models for tumor growth in response to chemotherapy are primarily based on chemotherapy affecting cells at specific cell-cycles but mainly seeking to model the resistance of a specific tumor to the given drug or drugs. Moreover, they also focus on the effects after one dose and not on a treatment plan that incorporates the frequency of the treatment. Ophir Nave did describe that whenever chemotherapy is introduced into a model the drug would interact with both the immune system and cancer itself [?]. Moreover, it should also be some sort of summation of the dosage effects that wanes through the passage of time but may perhaps have a sudden and rapid change in the tumor growth as modeled by Nave in (13).

Most models employ a sort exponential decay of the administered drug to the patient to get the rapid effect that a chemotherapy drug has on the tumor burden (e.g. (12)). These are also specific to a certain phase of the cell state, but despite their specificity, at times ignore the negative effects on the immune system. Further, the effect the drug has on the tumor burden is usually also attributed to only the drug itself and the effects, while at times minimal, of the immune system fighting the cancer is omitted. Given these characteristics, it is of interest to find an expression for the effect of chemotherapy that has a rapid change in tumor burden and either on all cells or at specific cell-states but also has an effect on the immune system.

The immune system naturally patrols the body in search of foreign bodies to kill and prevent diseases. The patrolling and immediate responses are given by the innate immune system and helper response to anything missed by the immediate response as well as targeted response is handled primarily by the adaptive immune system (see A). This patrolling is not just for foreign bacteria but also abnormal cells such as cancer cells. Majority of models, like those in 15 or 14, look at these two parts of the immune system as a whole and its interaction with the tumor and normal cells. That is, they do not look at the specific immune cells interacting with the cancer other than the collective response of the immune system on tumor growth. But as mentioned by de Pillis et. al, “in some applications, it is not sufficient to represent the immune response with a single homogeneous population of effector killer cells [?].” Thus, a good model, depending on the cancer, should have a more specific interaction between the immune cells that deal with that cancer in particular and the cancer itself. If it is general, it suffices to show the interaction as whole.

The modeling for tumor-immunological response typically look at relationship between natural killer cells (NK) and cytotoxic T-cells ($CD8^+$) (see [A](#)) and how they affect tumor growth. Although there are many other cells which contribute to an immune response, NK cells and CD8 cells are the only ones which directly kill the cancer cells in breast cancers [?]. The $CD8^+$ cells are recruited to kill the cancer by the NK cells, and from this interaction arises a relation between the populations of the NK, $CD8^+$, and cancer cells. Unfortunately, many of the models which examine the relationship between cancer and the immune system do not include analysis of the interactions which occur once chemotherapy has begun. Because of the immunocompromising effects of radiation and chemotherapy, the body's ability to fight tumors naturally will decrease, leading to interesting dynamics of the cell populations. Thus, we expect to see some description showing how the NK or $CD8^+$ cells become inhibited or die off as chemotherapy is introduced.

One important term that is used in modeling the interactions between the immune system and the tumor comes from the biochemistry equation for enzymatic reaction rates known as *Michaelis-Menten kinetics*. Specifically, the Michaelis-Menten kinetics model the rate at which an enzyme acts upon some molecule to form a complex and then act in such a way so as to produce a new product and regenerate the original enzyme. In the context of tumor modeling, the Michaelis-Menten kinetics model the interaction between abnormal cells and the immune system, immune system and tumor cells, and tumor-tumor cell interactions. The former describes the rate of the immune system responding to the growth of abnormal cells that could potentially become cancer. The latter specifically considers the rate of how tumors induce other cells to become tumor cells, and the middle interaction would look at seeing specifically the rate of change between the immune system being affected by the tumor but as well as affecting the tumor itself [?]. Hence, any model looking into the interaction of a tumor with the immune system should consider similar interactions or those modeled by Michaelis-Menten.

Given all of these characteristics for modeling tumor growth in general, as well the intricacies of chemotherapy, and then adding the difficulties of modeling immune-tumor interactions, we can gain an understanding why there is much difficulty in getting an overall general model that works for any cancer and any form of chemotherapy. Thus, our attempt is to bring forth a model that can work in a generalized setting with the current limitations and known interactions and behaviors that a tumor-growth model should exhibit. To aid with the difficulty of making a generalized model, we decided to specifically focus on breast cancer seeing that is National Cancer Institute records it as having the most number of cases as of 2024. Moreover, we also focused specifically on the immunological response given by NK and $CD8^+$ cells as well as adding the aid that comes from chemotherapy. Lastly, our tumor growth modeling focused on a sigmoidal relationship given by Gompertz.

2. MODELING

In solving the original Gompertz model, finite difference methods were used because of their simplicity yet relative accuracy. The local truncation error for Forward Euler can be found as follows $\tau_i = |T'(t_i) - \frac{T(t_i+h) - T(t_i)}{h}|$ where $T(t_i)$ is the actual solution at time i . Using Taylor Series, we can expand this to $|T'(t_i) - \frac{T(t_i) + hT'(t_i) + \frac{h^2}{2}T''(t_i) + \frac{h^3}{6}T'''(t_i) + O(h^4) - T(t_i)}{h}|$ which simplifies to $|-hT''(t_i) - \frac{h^2}{2}T'''(t_i) + O(h^3)| = O(h)$. So although quick to code and compute, there is a relatively large error term.

The *Gompertz* model is a logistic model that was created to describe the growth of human mortality in 1825 by Benjamin Gompertz. In particular, the ODE is given by

$$(1) \quad \frac{dT(t)}{dt} = k_g T \ln\left(\frac{T_{\max}}{T}\right),$$

where k_g is a growth constant of the tumor, T is the total number of cancer cells, and t is days. The solution to the ODE is of sigmoidal nature. Like the logistic growth model (10), the Gompertz model starts off with a quasi-exponential growth at the beginning that is short lived. However, unlike the logistic model, the Gompertz model slowly converges to the carrying capacity of that a tumor can have with available nutrients. That is, the Gompertz model slows its growth first and more significantly than a logistic model while still converging, slowly, towards the carrying capacity. Getting the derivative of (1) and setting it equal to 0, gives us that the inflection point of the Gompertz model is at $\frac{T_{\max}}{e}$. This is the point when 36.8% of the carrying capacity has been reached compared to the inflection point of the logistic model that occurs at half the carrying capacity. Given these characteristics, the Gompertz model is a popular and good choice for modeling tumor growth.

For chemotherapy effects, seeing that models are derived as exponential decays of the drug-dose and are dependent on the type of the type of drug administered as well as the percentage of cancer killed at a specific cell-state, we opted to work with the model proposed by Bethge et al (which is similar to the one given by de Pillis and Radunskaya (11)). The chemotherapy differential expression is

$$(2) \quad f\mu c(t)T, c(t) = e^{-\gamma t},$$

where μ represents the drug sensitivity of cells (thereby implying drug effectiveness), $c(t)$ is the concentration of the given drug with a rate modeled by a decay constant $\gamma = \frac{\ln 2}{t_{1/2}}$ after the half-life of the drug, and f is the proportion of cells that are in specific cell-cycle such that chemotherapy affects those cells specifically. If the given drug affects all cells equally irrespective of cell cycle, then f is equal to 1.

The chemotherapy differential expression specifically models the rate of change in respect to time of the death or removal of tumor cells by the given drug. At $t = 0$, we would expect a high number of cells to be killed off, and as time continues, we would expect to see that the effectiveness of the drug levels off (hence the decay).

Moreover, depending on how good or strong the drug is, we would expect to have a different rate of change which is the purpose of the half life in γ and the f constant. Adding (2) to our growth in (1) gives

$$(3) \quad \frac{dT(t)}{dt} = k_g T \ln\left(\frac{T_{\max}}{T}\right) - f\mu c(t) = k_g T \ln\left(\frac{T_{\max}}{T}\right) - f\mu e^{-\gamma t}.$$

For our purposes, we chose to go with a chemotherapy treatment plan of one dose every two weeks for a total of 14 doses.

The combination of the two models requires some thought. The Gompertz-Chemo integrated model for tumor burden can be added in place of the logistic growth factor in the immune system model, but the effects of the chemotherapy on the immune cells cannot be ignored. Although sources were inconclusive on whether the chemotherapy directly killed the NK and CD8+ cells, it is known that all cells are negatively affected by the therapy. We make the assumption that the number of NK and CD8+ cells affected by the chemotherapy is proportional to (2) and the number of NK and CD8+ cells. This results in the following system of equations.

$$(4) \quad \frac{dT}{dt} = aT(1 - bT) - cNT - D$$

$$(5) \quad \frac{dN}{dt} = \sigma - fN + \frac{gT^2}{h + T^2}N - pNT - Nf\mu e^{-\gamma t}$$

$$(6) \quad \frac{dL}{dt} = -mL + \frac{jD^2}{k + D^2}L - qLT + rNT$$

$$(7) \quad D = d \frac{(L/T)^\lambda}{s + (L/T)^\lambda} T$$

The primary aspect of the project is the modeling of the chosen phenomenon. If your group's repeated attempts resulted in abject failure, or your group succeeded, detail them in this section. Be sure to account for the various attempted models and why they were not appropriate. Include numerical simulations for each attempted model. Reference figures and plots, like Figure 1.

3. RESULTS

Clearly and succinctly state and describe the conclusions that you can draw from the model you have achieved (or the many failed attempts). Does your model(s) perform well quantitatively or qualitatively?

4. ANALYSIS/CONCLUSIONS

Discuss the appropriateness of the techniques/methods you employed in modeling. Did your group appropriately model the chosen phenomenon? If not, what different steps could you have taken if you had more time? What did you learn about the techniques/method that were used in the group project? If your model

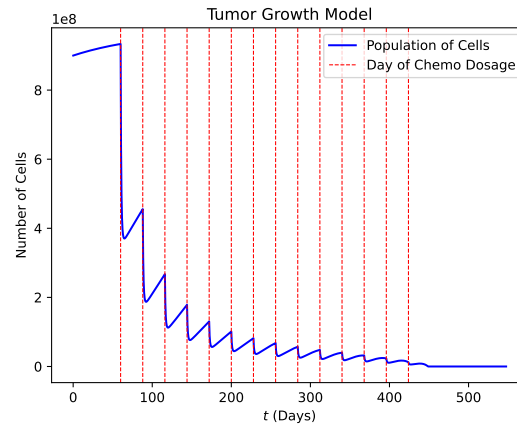


FIGURE 1. The growth of breast cancer growth as modeled by

was successful, what additional insight/conclusions could you obtain from it? For instance, if you had a successfully modified SIR model, how might it affect different government policy? If you had a successful model for the spread of inaccurate information on social media, how might it be implemented to help reduce the spread of inaccurate information?

This part should all be done before you get to *page 11*. The bibliography can spill on to page 11, but we won't read text that goes past page 10.

APPENDIX A. DEFINITIONS

The following definitions are derived from the National Cancer Institute, unless otherwise stated

- **Adaptive Immune System:** the part of the immune system that specifically targets the germs or foreign substances that are causing an infection. In order to do this, this system needs to first recognize the substance as such. Therefore, this system is slower and needs training. $CD8^+$ cells are part of this system.
- **Cancer:** a term for diseases in which abnormal cells divide without control and can invade nearby tissues
- **Chemotherapy:** a cancer treatment where drugs are used to kill cancer cells or stop them from dividing
 - **Neoadjuvant Chemotherapy:** chemotherapy administered before the primary treatment of the tumor is performed. Typically, surgery is the primary treatment. Its main goal is to shrink the tumor so that it is easier to remove.
 - **Adjuvant Chemotherapy:** Chemotherapy administered after primary tumor treatment is administered. Its intent is to lower the risk of the cancer returning.

- Cytotoxic/CD8⁺ T-cell: is a T-lymphocyte that kills infected cells or cells that are damaged in other ways. They are not natural killers and as such have to be trained to kill cancer. (Mayo clinic)
- Innate Immune System: the part of the immune system that is the first line of defense against intruders or unknown foreign cells in the body. It responds to all foreign substances in the same manner (National Library of Medicine). It can be thought of as "kill first, ask questions later." NK cells are part of this system.
- Log-kill Hypothesis: when growth of a cancer is exponential—increasing by a constant fraction of itself every fixed unit of time—then in the presence of effective anticancer drugs it also shrinks by a constant fraction [?] of itself
- Tumor: an abnormal mass of tissue that forms when cells grow and divide more than they should or do not die when they should. Tumors may be *benign* (not cancer) or *malignant* (cancer). For this project, defined the tumor burden as the number of cancer cells in the body.
- Tumor burden: the size of a tumor or number cancer cells. This is the total amount of cancer found in the body.
- Natural Killer Cell (NK Cell): A type of immune cell that has granules (small particles) with enzymes that can kill tumor cells or cells infected with a virus. A natural killer cell is a type of white blood cell

APPENDIX B. MODELS

- Tumor Growth Models:
 - Linear growth:

$$(8) \quad \frac{dT}{dt} = k,$$

where k is the growth rate

- Exponential Growth:

$$(9) \quad \frac{dT}{dt} = kT$$

or with a death rate constant of d , $\frac{dT}{dt} = (k - d)T$

- Logistic Growth:

$$(10) \quad \frac{dT}{dt} = kT \left(1 - \frac{T}{T_{\max}} \right),$$

where T_{\max} is the max size a tumor can be, which is equivalent to the carrying capacity.

- Chemotherapy Models:
 - Exponential Decay: Pillis and Radunskaya modeled the mix of immunotherapy and chemotherapy on tumor growth. In particular, they modeled the drug as an exponential decay given by

$$(11) \quad G_M = -\gamma M,$$

where $M = M(t)$ is the concentration of the drug in the bloodstream at some time t .

- Panetta also used an exponential but considering the frequency between doses as

$$(12) \quad g(t) = he^{-\gamma(t-n-\tau)},$$

where $g(t)$ is the effects of the chemotherapy drug, γ is the decay of the drug, n is number of doses, and τ is the period between doses.

- Personalized treatment: Ophir Nave modeled a personalizable treatment plan as

$$(13) \quad \mathcal{F} = \sum_{k=0}^n q(t - mk) \mathcal{H}(t - mk) e^{\frac{t-mk}{0.5}},$$

where n is the duration of the treatment, m is the interval between treatments, and \mathcal{H} a unit step function.

- Immunological Response Models:
 - Alharbi & Sham Rambely: their modeling equations looked at the interaction of tumor cells and the immune system, I , as a whole as well as normal cells, N , (non-immune, non-tumor cells). They described the relationships by (using a logistic growth for tumor T):

$$(14) \quad \begin{aligned} \frac{dN}{dt} &= rN(1 - \beta_1 N) - \eta NI - \gamma NT \\ \frac{dT}{dt} &= \alpha_1 T(1 - \alpha_2 T) + \beta_2 NT - \alpha_3 T I \\ \frac{dI}{dt} &= \sigma - \delta I \frac{\rho NI}{m_1 + N} + \frac{\rho_1 TI}{m_1 + T} - \mu NI - \mu_1 TI \end{aligned}$$

- dePillis et. al: they modeled the primary interaction between effector cells, E , like $CD8^+$, and the tumor, T by using logistic growth and

$$(15) \quad \begin{aligned} \frac{dT}{dt} &= a_1 T(1 - b_1 T) - c_2 ET - c_3 NT - k_2(1 - e^{-u}) \\ \frac{dN}{dt} &= a_2(1 - b - 2N) - c_4 NT - k_3(1 - e^{-u}) \end{aligned}$$

- Growth-Chemo-Immune PDE System: Ansarizadeh, Singh, and Richards modeled tumor cells using a system of PDEs. Specifically, they used a logistic model for the normal cells N , tumor T , immune I , and the chemotherapeutic drug U . For them, the drug was only active for certain phases of the cell division cycle the expression $1 - e^{-U}$ was used to

denote the fraction of cells killed.

$$\begin{aligned}
 (16) \quad & \frac{\partial N}{\partial t} = r_2 N(1 - b_2)N - c_4 TN - a_3(1 - e^U)N + D_N \frac{\partial^2 N}{\partial x^2} \\
 & \frac{\partial T}{\partial t} = r_1 N(1 - b_1 T) - c_2 IT - c_3 TN - a_2(1 - e^{-U})T + D_T \frac{\partial^2 T}{\partial x^2} \\
 & \frac{\partial I}{\partial t} = s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I - a_1(1 - e^{-U})I + D_I \frac{\partial^2 I}{\partial x^2} \\
 & \frac{\partial U}{\partial t} = v(t) - d_2 U + D_U \frac{\partial^2 U}{\partial x^2}
 \end{aligned}$$

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REFERENCES

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