BREAST CANCER MODEL WITH CHEMOTHERAPY AND IMMUNOLOGICAL RESPONSE

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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." [RR19] 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. Secondarily, 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. [ADvHJ+19]

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 (13) is characterized by an infinite growth as t increases which does not reflect the fact that a tumor

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can have a maximum size, even when considering a death rate. Moreover, the logistic model (14) converges too fast to the max size, $T_{\max}$, a tumor can be. [SBtTCRT23] 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 *neoadjuvent* or *adjuvent* (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 [Nav22]. 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 (17).

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. (16)). 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 19 or 18, 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 [dER14]." 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 [ABZ21]. 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 immunocomprimising 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 [AR20]. 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 for a specific cancer that exhibits the known interactions and behaviors that a tumor should exhibit when facing the immune system and chemotherapy as previously outlined.

We decided to specifically focus on breast cancer seeing that the National Cancer Institute records it as having the most number of cases as of 2024. For the immunological response, we also focused specifically on the response given by NK and $CD8^+$ cells. As per the chemotherapy, our focus was that of neoadjuvent therapy specific to one drug. Lastly, our tumor growth modeling focused on a sigmoidal relationship given by the Gompertz ODE.

2. Modeling

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

$$\frac{\mathrm{d}T}{\mathrm{d}t} = k_g T \ln\left(\frac{T_{\max}}{T}\right), \tag{1}$$

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 (14), 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 what a tumor can have with available nutrients. Figure 1 shows how the Gompertz model differs from that of other models used for tumor growth.

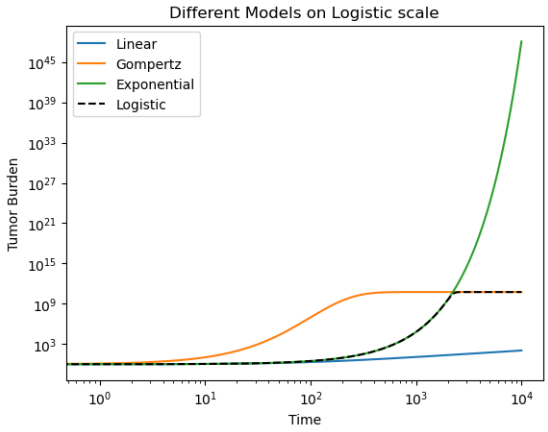


Figure 1. The uninhibited growth of various ODE models

Notice how the Gompertz model slows its growth first and more significantly than a logistic model while still converging towards the carrying capacity. The logistic growth, on the other hand, is much more aggressive after its inflection point. For the Gompertz model, take the derivative of (1) and set it equal to 0, this 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. As stated earlier, we wanted a model that exhibits an exponential growth but also has a slow

convergence to the carrying capacity. This is why the Gompertz is a better modeling choice than other given models [LAI64].

For chemotherapy effects, seeing that models are derived as exponential decays of the drug-dose and are dependent on 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 (15)). The chemotherapy differential expression is

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

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 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, with respect 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 decaying off (hence the decay) and thereby the proportion of tumor cells killed also decreases. 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

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

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

Having now considered chemotherapy, we opted to also include the influence of the immune system on the tumor burden of a patient. The basis of our immune system modeling comes from an already published model which focuses on the interaction between cancer cells, NK cells, and $CD8^+$ T-cells [dPRW05]. While there are many more cells that influence tumor burden, these are the two cells that act directly on breast cancer cells [ABZ21]. In the following differential equations, T is the tumor cell population, N is the NK cell population, and L is the $CD8^+$ T-cells population. The changes of these populations are modeled as

$$\frac{\mathrm{d}T}{\mathrm{d}t} = aT(1 - bT) - N_{KR}NT - D \tag{4}$$

$$\frac{\mathrm{d}N}{\mathrm{d}t} = \sigma - N_d N + \frac{gT^2}{h + T^2}N - pNT \tag{5}$$

$$\frac{\mathrm{d}L}{\mathrm{d}t} = -mL + \frac{jD^2}{L_R + D^2}L - qLT + rNT \tag{6}$$

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

Due to the complexity and number of constants, we define and quantify them in Appendix B, but we will break down the contribution of each component. In equation (4), the tumor cell population increases by a single component, $aT(1-b)$, which is the logistic growth of the tumor. The remaining two terms $N_{KR}NT$ and D signify number of tumor cells killed by NK cells and CD8$^+$ cells, respectively. In equation (5), the NK cell population increases due to two components. One is the constant inflow of cells independent from tumor influence, denoted σ. And the other is the increase of NK cells due to the tumor's presence. This term takes the form of a Michaelis-Menten kinetics equation, and is denoted $\frac{gT^2}{h+T^2}N$. The remaining two terms of this equation are decreases in NK cell population. The first being natural NK cell death, denoted N_dN, and the last one being he number of NK cells deactivated by tumor cells, denoted pNT. For equation (6) we again have two components which are loses in CD8$^+$ T-cells population, the terms mL and qLT. The first of which is the number of naturally dying cells, and the second is the number deactivated by tumor cells. We also find two components contributing to an increase in CD8$^+$ T-cells, the first of which being $\frac{jD^2}{k+D^2}L$, the number of CD8$^+$ cells recruited to fight cancer, again in the form of a Michaelis-Menten kinetics equation. Lastly, the term rNT models the phenomenon where CD8$^+$ cells are produced after an NK cell is killed by a tumor cell.

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, mainly being inhibited in their ability to kill cancerous cells [RGct]. 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. As such, we introduced a term in the differential equations for both CD8$^+$ cells and NK cells that seeks to replicate the natural inhibition CD8$^+$ and NK cells experience. Specifically, the term kills[1] of in proportion to their interactions with the chemotherapy drug. In their Chemotherapy for Breast Cancer page, the American Cancer Society states that typically chemotherapy will be around 3-6 months which gives about 8-12 treatment

[1]We thought of this with an analogy 20 workers where only 5 are actively working, so that 15 workers are "dead" at work. While this is a very naïve assumption, it does help exhibit inhibition.

cycles (see A). Hence to properly show inhibition, we altered the parameter at the end of (9) and (10) until simulations prediction at least 5 rounds of chemotherapy before *remittance* (see A). This results in the following system of equations.

$$\frac{\mathrm{d}T(t)}{\mathrm{d}t} = k_g T(t)\ln\left(\frac{T_{\max}}{T(t)}\right) - f\mu e^{-\gamma t} - n_{kr}N(t)T(t) - D \tag{8}$$

$$\frac{\mathrm{d}N(t)}{\mathrm{d}t} = \sigma - n_d N(t) + \frac{g(T(t))^2}{h+T^2}N - pN(t)T(t) - N(t)f\mu e^{-\gamma t} \tag{9}$$

$$\frac{\mathrm{d}L(t)}{\mathrm{d}t} = -mL(t) + \frac{jD^2}{l_r+D^2}L(t) - qL(t)T(t) + rN(t)T(t) - Lf\mu e^{-\gamma t} \tag{10}$$

$$D = d\frac{\left(\frac{L(t)}{T(t)}\right)^{\lambda}}{s+\left(\frac{L(t)}{T(t)}\right)^{\lambda}}T(t) \tag{11}$$

The constants and form of the equation should be familiar, as they are taken directly from the above equations.

To begin modeling, we called $t_o = t = 0$ to be the time when a tumor should be of sufficient size that a person, medical practice, or immune system should be able to identify or detect the cancer. While it is unknown why cancer can go undetected completely from the immune system or medicine, there are estimates for a tumor burden that should be detectable. Specifically, Caley and Jones stated that when cancer is detectable there are about 10^8 to 10^9 tumor cells in the body [CJ12]. Since it was part of our interest to examine whether our model would show a tumor growing to its $T_{\max}$ without much immunological intervention, we begun with an initial tumor burden of $T_o = 9 \times 10^8$ (number of cells) as shown in Figure 2.

For the chemotherapy, we opted to start the treatment at 45 days from t_o to account for the time a patient has between waiting for biopsy results, further lab tests, and the actual start of the chemotherapy.

In the paper of Sopik and Narod, they estimated the probability of dying from breast cancer as a function of the size of the tumor and found that, while some primary tumor sizes can be as big as $150mm$ in diameter, the mortality probability plateaus starting with tumors with a diameter of $91mm$ [SN18]. Specifically, the mortality probability of tumors with a diameter of $150mm$ is about 64.1% whereas tumors with a diameter of size ranging from $91 - 100mm$ exhibited a 60% mortality probability. Thus, there is not much of an increase in chance of death with a bigger tumor size. Hence, our $T_{\max}$ became the number of cells found in a tumor of mm in diameter. Larsen et al found that, on average and in a highly dense colorectal carcinoma, there is about $35mm^2$ of tumor tissue [LGB14].

3. Results

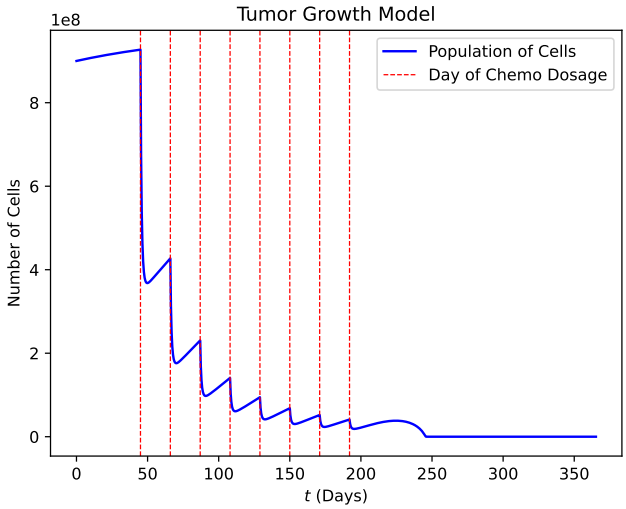


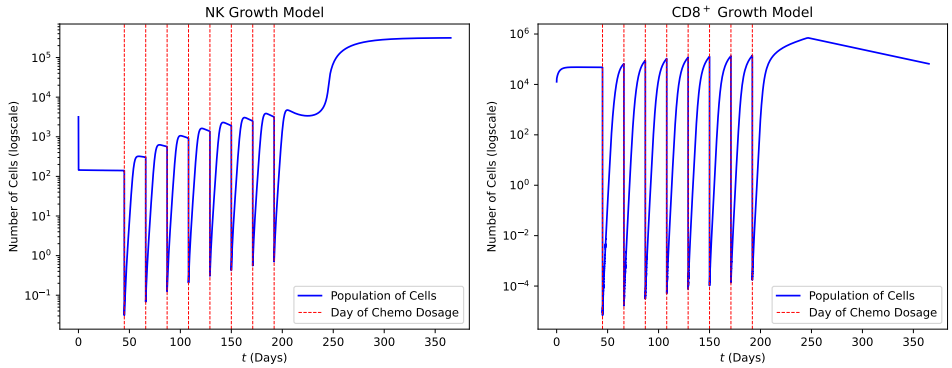
Figure 2. The growth of breast cancer as modeled by (8) for 8 cycles with each one occurring every 3 weeks for $T_o = 9 \times 10^8, T_{\max} = 9 \times 10^9$.

As mentioned earlier, starting at (t_o, T_o), we can see in Figure 2 that our model exhibits growth for an amount that should, in theory, not yet be detectable. Thus, initially our model does well in describing the dynamics that tumor burden should exhibit on the premise the immune system has not fully detected. That is, the characteristics are that the tumor remains undetectable for the most part with perhaps some interactions with the immune system but not to the degree the immune system recruits heavily to attack cancer.

Another important aspect of our model as displayed in Figure 2 is the successful remission of cancer. In Figure 5 (see in Appendix C), we can more fully appreciate the death of cancer to tumor burden levels that are near zero. This seems

The fully integrated cancer model with both chemotherapy and immune cells predicts unreasonable results for chemotherapy without additional adjustments. For reasonable initial tumor sizes, one or two rounds of chemotherapy almost immediately kill the tumor. In practice, patients undergo 5-8 rounds of chemotherapy on average before showing signs of remission. Such problematic behavior is likely a result of the immune model, which as presented in a previous paper does not generalize well past 30 days. Thus, we tweaked our initial full model to produce qualitatively sound results.

To solve the equation given by (8), we used



(A) NK cells. (B) $CD8^+$ cells.

FIGURE 3. The growth of immune cells in relation to the tumor of Fig 2.

`scipy.integrate.solve_ivp`

that use the explicit Runge-Kutta method of order 5(4) which assumes an accuracy of the fourth-order but takes steps using a fifth-order accurate formula.

Moreover, we chose to go with a chemotherapy treatment plan of one dose every four weeks (i.e. 28 days) for a total of 14 doses. Specifically, those doses started about 60 days after the initial discovery of tumor. The results are shown in Figure 2. These results seem to be on par with the estimates given by Mayo Clinic where for advanced breast cancer, treatment is beyond that of six months.

Here we plot the differential equations of the immune system. We get our initial values from a plot in the paper where we got the differential equations. In the paper published, the populations only go to about 35 days. Below we've created similar plots, but as we increase the time beyond 35 days, we start to see some problems, which we will address in the analysis/conclusions section.

4. Analysis/Conclusions

Weakness: cannot model properly for bigger Tmax anything from 50mm on

One of the hard aspects was that for certain values our modeling would show quite the decline. ADD TODO graph in supplemental information. These would

Our initial numerical method approximating the tumor burden with and without chemo showed the sharp decline that a chemo session causes in the tumor cell population. On a long enough time scale we would see a plateau in the chemo population growth as it reaches its carrying capacity. The challenge with this dynamic is that this only models a single chemo session,

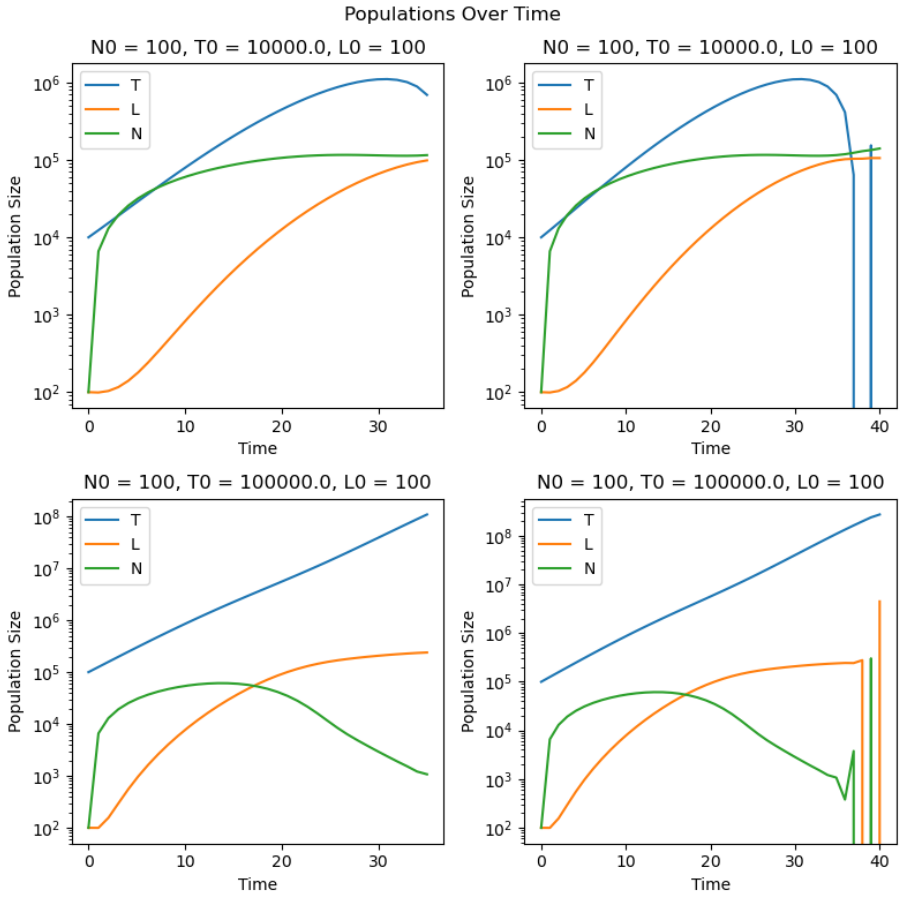


FIGURE 4. Various plots of the populations for different initial values

while we would expect many round of several sessions each in the treatment of cancer.

In modeling the immune system alone, we had some success, but the dynamics we were able to capture don't work well on a long enough time

scale. Specifically, after about 35 days we start to see negative populations and discontinuous changes in population. While we may be able to gain some insight on the interaction between cancer cells, Natural Killer cells, and CD8+ cells, we have an unreasonably short time scale that our model works on.

Our full model produces reasonable results, but the immune system component of the model remains a weak point. Qualitatively, our model performs as expected when we include chemotherapy. However, the immune system component remains too strong when left on its own. Only by including the effects of chemotherapy on the immune system did we keep the strength of the CD8 cells in check. If our model is to be useful, it needs to accurately predict tumor burden in the absence of chemotherapy.

If our model were accurate in predicting tumor burden alone, it might be useful to prescribe chemotherapy treatments to breast cancer patients. Given initial measurements of tumor burden and immune cells, doctors could verify whether a patient is in remission.

Unfortunately, on the other end of the table, results of treatment are not always positive. Our model might indicate whether chemotherapy is a viable cure to breast cancer of a certain size given immune system conditions. However, currently, our model does not predict negative outcomes well. Given more time, we might figure out constants for which certain initial conditions produce an overtake by cancer cell growth and thus an equilibrium solution representing a bad outcome.

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. $CB8^+$ 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
  - Neoadjuvent 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.
  - Adjuvent 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 or 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 effecive anticancer drugs it also shrinks by a constant fraction [Nor14] of itself
- Remission: A decrease in or disappearance of signs and symptoms of cancer. In partial remission, some, but not all, signs and symptoms of cancer have disappeared. In complete remission, all signs and symptoms of cancer have disappeared, although cancer still may be in the body.
- Treatment cycle: the regular and repeated interval of time between each new dose of a chemotherapy drug. A cycle comprises of a rest period to allow the body to heal from the effects until the new dose is given. This information was retrieved from the American Cancer Society and [CJ12].
- 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 cel

Appendix B. Models

- Tumor Growth Models:
  - Linear growth:

$$\frac{\mathrm{d}T}{\mathrm{d}t} = k, \tag{12}$$

    where k is the growth rate
  - Exponential Growth:

$$\frac{\mathrm{d}T}{\mathrm{d}t} = kT \tag{13}$$

    or with a death rate constant of d, $\frac{\mathrm{d}T}{\mathrm{d}t} = (k-d)T$
  - Logistic Growth:

$$\frac{\mathrm{d}T}{\mathrm{d}t} = kT\left(1 - \frac{T}{T_{\max}}\right), \tag{14}$$

    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

$$G_M = -\gamma M, \tag{15}$$

    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

$$g(t) = he^{-\gamma(t-n-\tau)}, \tag{16}$$

    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

$$\mathscr{F} = \sum_{k=0}^{n} q(t-mk)\mathscr{H}(t-mk)e^{\frac{t-mk}{0.5}}, \tag{17}$$

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

- Immunological Response Models:
  - Pillis, Radunskaya, Wiseman:
    $\frac{dT}{dt} = aT(1-bT) - cNT - D$
    $\frac{dN}{dt} = \sigma - fN + \frac{gT^2}{h+T^2}N - pNT$
    $\frac{dL}{dt} = -mL + \frac{jD^2}{k+D^2}L - qLT + rNT$
    $D = d\frac{(L/T)^\lambda}{s+(L/T)^\lambda}T$
    Where we define each constant:
    - a $= 5.14 \times 10^{-1}$ has units day^{-1} is the tumor growth rate
    - b $= 1.02 \times 10^{-9}$ has units cell^{-1} where $\frac{1}{b}$ is the tumor carrying capacity.
    - $N_{NR} = 3.23 \times 10^{-7}$ has units cell^{-1}day^{-1} is the fractional cell kill(see appendix) rate of NK cells against tumors.
    - $sigma = 1.3 \times 10^4$ has units cellsday^{-1} is the constant NK cells production.
    - $N_d = 4.12 \times 10^{-2}$ has units day^{-1} is the natural death rate of NK cells.
    - $g = 2.5 \times 10^-2$ has units day^{-1} is the max NK recruitment
    - $h = 2.02 \times 10^7$ has units cell^2 is the steepness coefficient of the NK recruitment curve.
    - $p = 1.00 \times 10^{-7}$ has units cell^{-1}day^{-1} is the rate at which tumors incapacitate NK cells
    - $m = 2.00 \times 10^{-2}$ has units day^{-1} is the natural death rate of CD8+ cells.
    - $j = 3.75 \times 10^{-2}$ has units day^{-1} is the max CD8+ recruitment rate, and the constant $k = 2 \times 10^7$ has units cell^2 is the steepness coefficient of the CD8+ recruitment curve.
    - $L_R = 2 \times 10^7$ has units cell^2 is the steepness coefficient of the CD8+ recruitment curve.
    - $q = 3.42 \times 10^{-10}$ has units cell^{-1}day^{-1} is the rate that tumors deactivate CD8+ cells.
    - $r = 1.1 \times 10^{-7}$ has units cell^{-1}day^{-1} is the rate at which those CD8+ cells are produced.
    - $d = 5.80$ has units day^{-1} is the saturation level of fractional tumor cell kill by CD8+ T cells

* $s = 2.5 \times 10^{-1}$ has no units, and is the steepness of the curve which determines the Tumor vs. CD8+ cell competition. Lastly,
* $\lambda = 1.36$ has no units.

– 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):

$$\begin{aligned} \frac{\mathrm{d}N}{\mathrm{d}t} &= rN(1-\beta_1 N) - \eta NI - \gamma NT \\ \frac{\mathrm{d}T}{\mathrm{d}t} &= \alpha_1 T(1-\alpha_2 T) + \beta_2 NT - \alpha_3 T1 \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \sigma - \delta I \tfrac{\rho NI}{m+N} + \frac{\rho_1 TI}{m_1+T} - \mu NI - \mu_1 TI \end{aligned} \tag{18}$$

– dePillis et. al: they modeled the primary interaction between effector cells, E, like CB8$^+$, and the tumor, T by using logistic growth and

$$\begin{aligned} \frac{\mathrm{d}T}{\mathrm{d}t} &= a_1 T(1-b_1 T) - c_2 ET - c_3 NT - k_2(1-e^{-u}) \\ \frac{\mathrm{d}N}{\mathrm{d}t} &= a_2(1-b-2N) - c_4 NT - k_3(1-e^{-u}) \end{aligned} \tag{19}$$

- 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.

$$\begin{aligned} \frac{\partial N}{\partial t} &= r_2 N(1-b_2)N - c_4 TN - a_3(1-e^U)N + D_N \frac{\partial^2 N}{\partial x^2} \\ \frac{\partial T}{\partial t} &= r_1 N(1-b_1 T) - c_2 IT - c_3 TN - a_2(1-e^{-U})T + D_T \frac{\partial^2 T}{\partial x^2} \\ \frac{\partial I}{\partial t} &= s + \frac{\rho IT}{\alpha+T} - c_1 IT - d_1 I - a_1(1-e^{-U})I + D_I \frac{\partial^2 I}{\partial x^2} \\ \frac{\partial U}{\partial t} &= v(t) - d_2 U + D_U \frac{\partial^2 U}{\partial x^2} \end{aligned} \tag{20}$$

Appendix C. Supplemental Graphs

In this section, we give more graphs that help our analysis as supplementary information to the main points and graphs given in the paper.

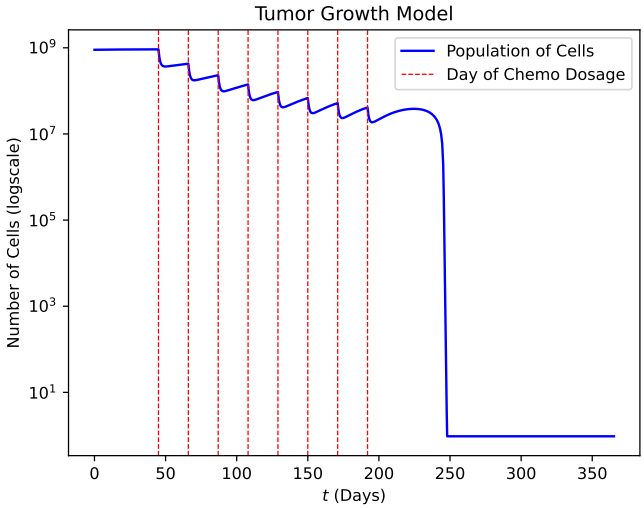


FIGURE 5. The growth of breast cancer, in a semilog scale for T, as modeled by (8). Compare to Figure 2. This graph helps us appreciate the actual death of cancer to near zero.

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