

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 ([13](#)) 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 (14) 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 (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 [?].” 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 (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 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 (15)). 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

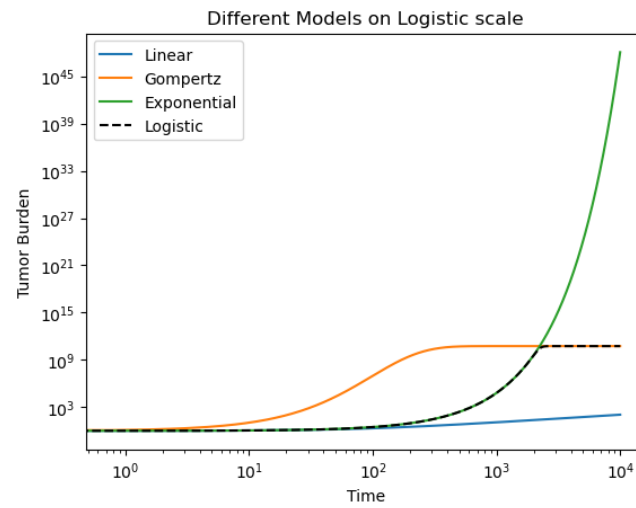


FIGURE 1. Tumor Burden for various growth functions

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 basis of our immune system modeling comes from a published paper in Cancer Research Volume 65 Issue 17 titled, "A Validated Mathematical Model of Cell-Mediated Immune Response to Tumor Growth"(Pillis, Radunskaya, Wiseman) This paper focuses on the interaction between cancer cells, NK cells, and CD8+ T cells(See appendix). While the interaction between cancer cells and tumors goes far beyond the influence of these two types of cells, according to the NIH, these are the two cell types that "... directly act on the breast cancer cells and promote antitumor immunity through destroying the cells"(Amens, Jensen N et al.) This paper models the populations of Tumor cells, effective CD8+ T cells, and effective NK cells(see appendix) with the following Differential Equations:

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

$$(5) \quad \frac{dN}{dt} = \sigma - N_dN + \frac{gT^2}{h + T^2}N - pNT$$

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

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

Here we provide an explanation of each component of the differential equations, where the constants are defined in the appendix.

In equation (??) the term $aT(1 - b)$ is the logistic growth of the tumor. The term cNT is the number of tumor cells killed in the interaction between tumor cells and NK cells. And D is the number of tumor cells killed in the interaction between CD8+ cells and tumor cells.

In equation (??) the term σ is the constant inflow of NK cells, the term fN is the number of NK cells that naturally die every day, The term $\frac{gT^2}{h+T^2}N$ is the number of NK cells that are recruited to fight the tumor, and the term pNT is the number of NK cells deactivated by the tumor cells.

In equation (??) the term mL is the number of CD8+ cells that naturally die. The term $\frac{jD^2}{k+D^2}L$ is the number of CD8+ cells recruited to fight cancer. The term qLT is the number of CD8+ cells deactivated by tumor cells. The term rNT is the number of CD8+ cells produced after NK cells die to Tumor cells.

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.

$$(8) \quad \frac{dT}{dt} = k_g T \ln\left(\frac{T_{\max}}{T}\right) - f\mu e^{-\gamma t} - n_{kr}NT - D$$

$$(9) \quad \frac{dN}{dt} = \sigma - n_d N + \frac{gT^2}{h + T^2}N - pNT - Nf\mu e^{-\gamma t}$$

$$(10) \quad \frac{dL}{dt} = -mL + \frac{jD^2}{l_r + D^2}L - qLT + rNT - Lf\mu e^{-\gamma t}$$

$$(11) \quad D = d \frac{(L/T)^\lambda}{s + (L/T)^\lambda} T$$

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

3. RESULTS

Here we have a forward Euler numerical method approximating the tumor burden with and without a single session of chemotherapy. We see that without chemotherapy the cancer grows exponentially. On the other hand, after a session of chemo, we see a sharp decline followed by a continuation of exponential growth.

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.

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

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

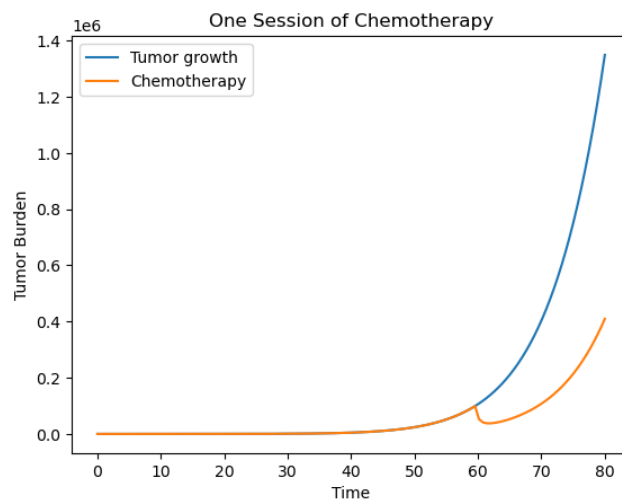


FIGURE 2. Tumor burden with vs without chemo session

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

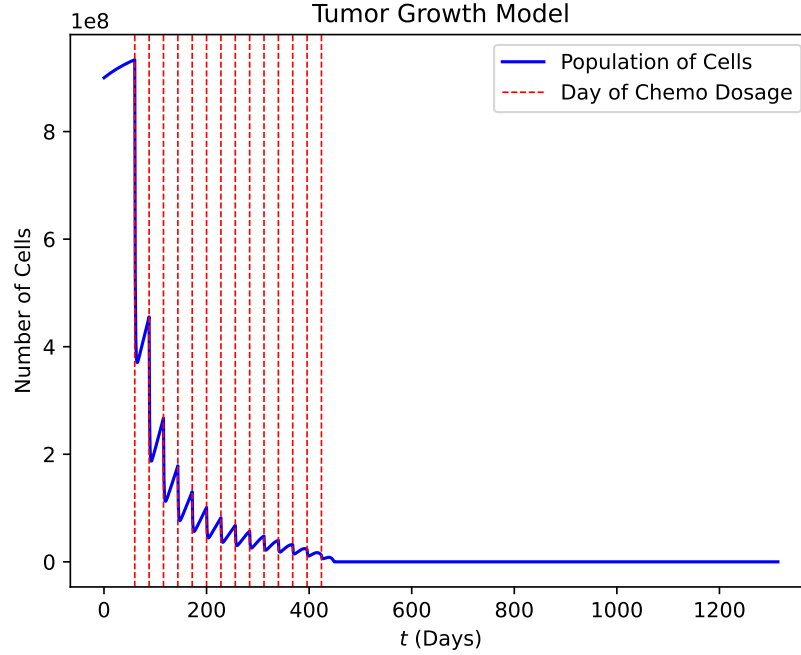


FIGURE 3. The growth of breast cancer growth as modeled by

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.

The overall model has some unique strengths and weaknesses as well. As shown above, it predicts that after a certain number of chemotherapy treatments the cancer will die out due to the immune response overwhelming the trace amounts of cells. It also accurately show that if not enough chemotherapy treatments are given, the tumor burden returns to high levels rather quickly.

While it does not break down after 1 month like the immune model it does, however, show a concerning dependence on initial conditions. With a large initial tumor burden, the model shows that the burden will decrease under effects of the immune system alone, which runs counter to what is observed.

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.

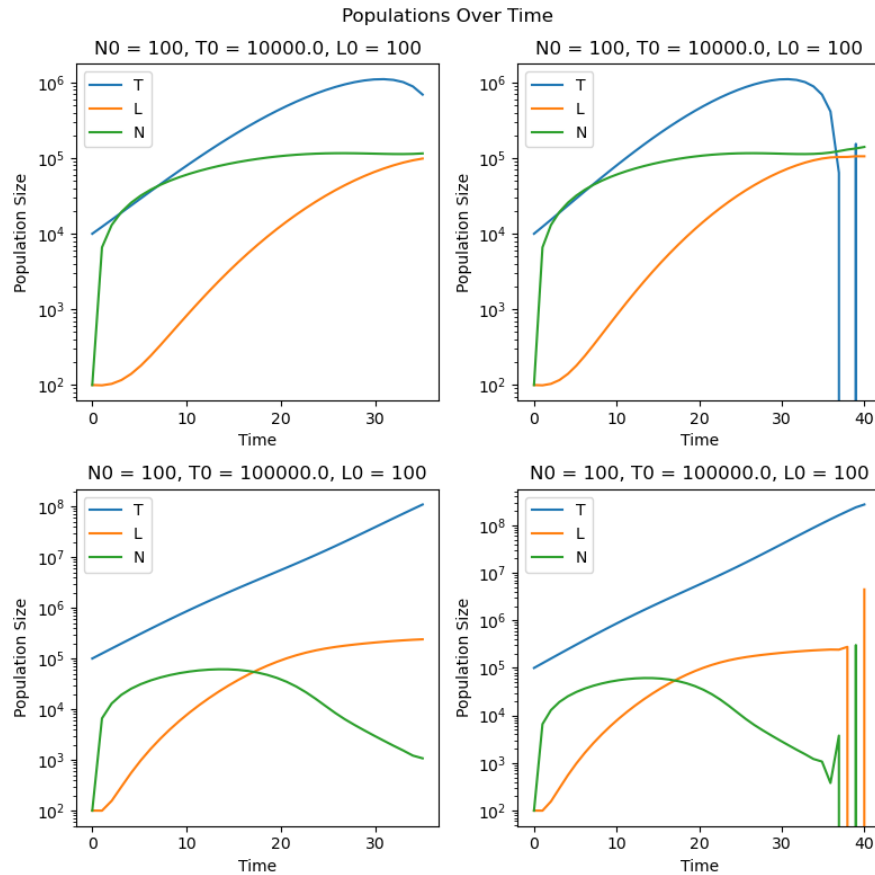


FIGURE 4. Various plots of the populations for different initial values

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
 - 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 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 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:

$$(12) \quad \frac{dT}{dt} = k,$$

where k is the growth rate

- Exponential Growth:

$$(13) \quad \frac{dT}{dt} = kT$$

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

- Logistic Growth:

$$(14) \quad \frac{dT}{dt} = kT \left(1 - \frac{T}{T_{\max}} \right),$$

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

$$(15) \quad G_M = -\gamma M,$$

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

$$(16) \quad g(t) = h e^{-\gamma(t-n-\tau)},$$

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

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

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

- Immunological Response Models:

- 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 $cells day^{-1}$ 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):

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

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

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

- 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.

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