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

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Appendix A. 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.

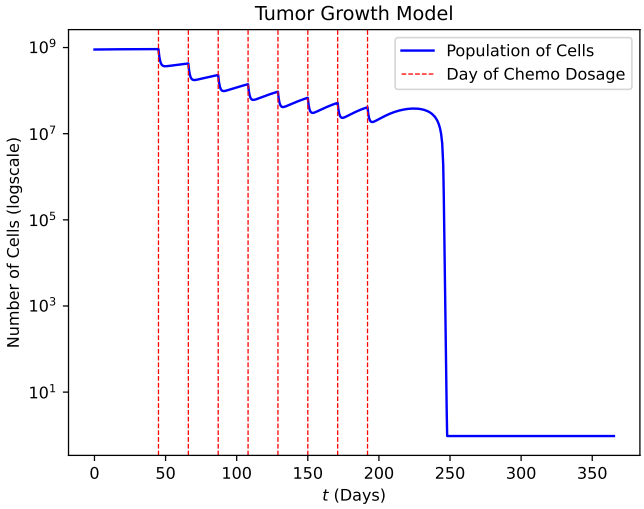

Figure 1. The growth of breast cancer, in a semilog scale for T, as modeled by (**??**). Compare to Figure **??**. This graph helps us appreciate the actual death of cancer to near zero.

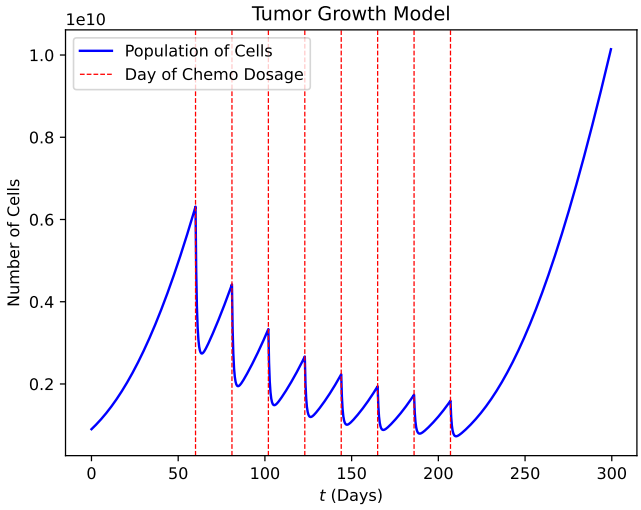

FIGURE 2. Abnormal growth given by an abnormally big tumor capacity of size at least 91mm in diameter.

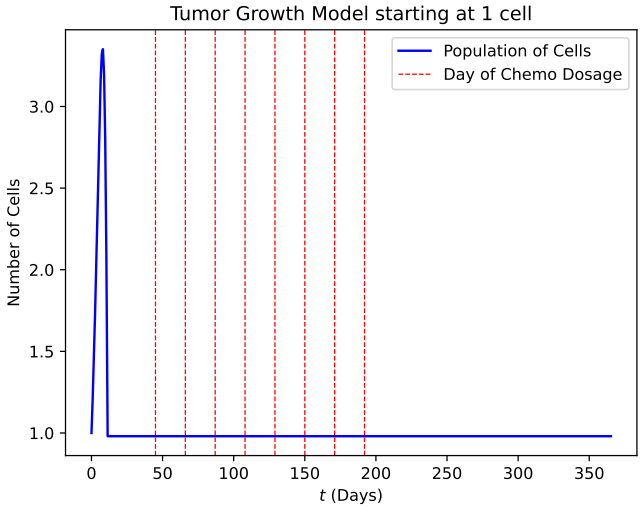

FIGURE 3. Tumor growth starting from 1 cell.

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.

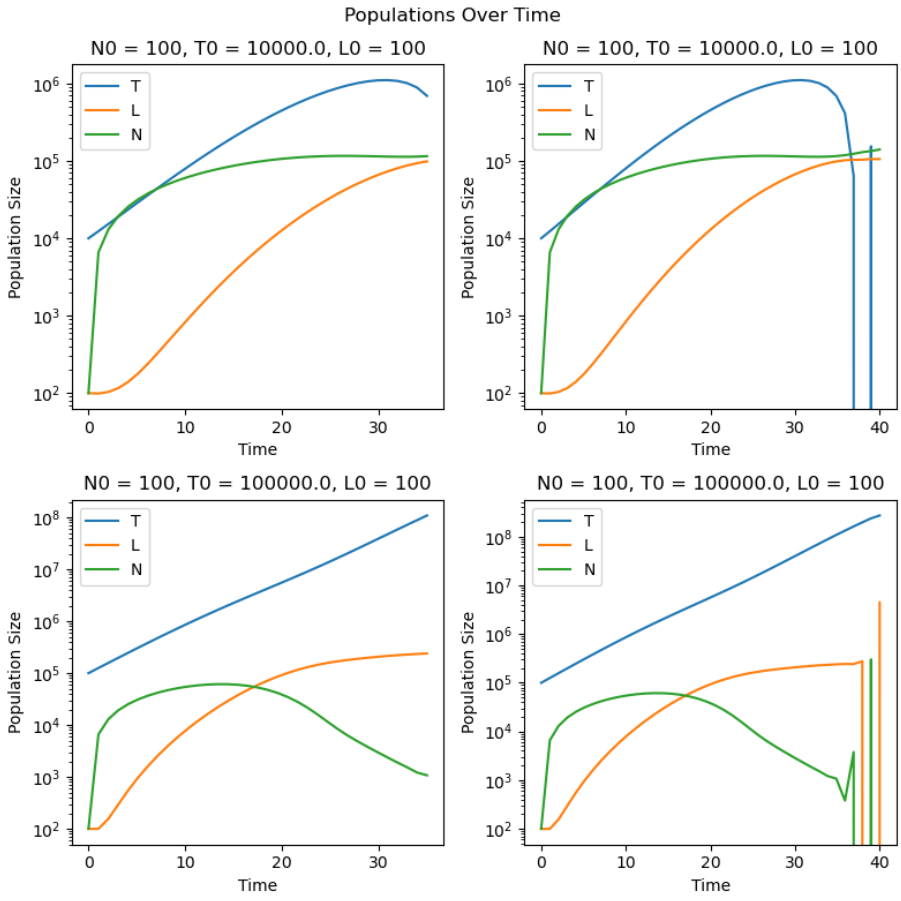

FIGURE 4. Various plots of the populations for different initial values

Appendix B. 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 C. Models

In this section, we describe and give equations we have referenced throughout our work.

- Tumor Growth Models:
  - Linear growth:

$$\frac{\mathrm{d}T}{\mathrm{d}t} = k, \tag{1}$$

    where k is the growth rate
  - Exponential Growth:

$$\frac{\mathrm{d}T}{\mathrm{d}t} = kT \tag{2}$$

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

$$\frac{\mathrm{d}T}{\mathrm{d}t} = kT\left(1 - \frac{T}{T_{\max}}\right), \tag{3}$$

    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

$$G_M = -\gamma M, \tag{4}$$

    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

$$g(t) = he^{-\gamma(t-n-\tau)}, \tag{5}$$

    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

$$\mathscr{F} = \sum_{k=0}^{n} q(t-mk)\mathscr{H}(t-mk)e^{\frac{t-mk}{0.5}}, \tag{6}$$

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):

$$\begin{aligned} \frac{\mathrm{d}N}{\mathrm{d}t} &= rN(1-\beta_1 N) - \eta NI - \gamma NT \\ \frac{\mathrm{d}T}{\mathrm{d}t} &= \alpha_1 T(1-\alpha_2 T) + \beta_2 NT - \alpha_3 T1 \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \sigma - \delta I \tfrac{\rho NI}{m+N} + \frac{\rho_1 TI}{m_1+T} - \mu NI - \mu_1 TI \end{aligned} \tag{7}$$

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

$$\begin{aligned} \frac{\mathrm{d}T}{\mathrm{d}t} &= a_1 T(1-b_1 T) - c_2 ET - c_3 NT - k_2(1-e^{-u}) \\ \frac{\mathrm{d}N}{\mathrm{d}t} &= a_2(1-b-2N) - c_4 NT - k_3(1-e^{-u}) \end{aligned} \tag{8}$$

- 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.

$$\begin{aligned} \frac{\partial N}{\partial t} &= r_2 N(1-b_2)N - c_4 TN - a_3(1-e^U)N + D_N \frac{\partial^2 N}{\partial x^2} \\ \frac{\partial T}{\partial t} &= r_1 N(1-b_1 T) - c_2 IT - c_3 TN - a_2(1-e^{-U})T + D_T \frac{\partial^2 T}{\partial x^2} \\ \frac{\partial I}{\partial t} &= s + \frac{\rho IT}{\alpha+T} - c_1 IT - d_1 I - a_1(1-e^{-U})I + D_I \frac{\partial^2 I}{\partial x^2} \\ \frac{\partial U}{\partial t} &= v(t) - d_2 U + D_U \frac{\partial^2 U}{\partial x^2} \end{aligned} \tag{9}$$

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