Modeling Immune-Mediated Tumor Growth and Treatment

Lisette de Pillis and Ami Radunskaya

Abstract The immune response is an important factor in the progression of cancer, and this response has been harnessed in a variety of treatments for a range of cancers. In this chapter we develop mathematical models that describe the immune response to the presence of a tumor. We then use these models to explore a variety of immunotherapy treatments, both alone and in combination with other therapies.

Keywords Tumor-immune interactions • Effector cell kill rate • Therapy optimization • Agent-based models • Immune response kinetics

1 Introduction

The simplest model of tumor growth assumes that cells undergo mitosis at a constant rate, resulting in a tumor population that grows exponentially. However, it is quickly apparent that this model is not consistent with clinical observation. As a thought experiment, consider a breast cancer cell, which is approximately 20 microns in diameter. If we assume a doubling time of two days, then after 26 doublings or 52 days, this single cell will have produced a mass of approximately 67 million cells, with a diameter of 8 mm—in other words a detectable tumor mass. After another 18 doublings or 88 days after the single cancer cell started dividing, the mass would be the size of a beach ball (of radius 25 cm).

Clinicians knew from experience that, in general, this was not a correct description of tumor growth, even in the absence of treatment. Tumor growth could be limited by many factors, an obvious one being a limited supply of nutrients, and several early mathematical models were proposed that account for the slowing

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of tumor growth as a result of limits on the ability of the vasculature to deliver nutrients [10, 42, 55]. There was also ample evidence that the immune system plays a significant role in the containment of tumors.

The exact role of the immune system in fighting cancer is not known, although as early as 1908, scientists proposed that the immune system could prevent the progression of many cancers. In particular, in that year, Nobel laureate Paul Ehrlich deduced that, without the immune system's intervention, there would be many more cases of cancer than we observe [25]. Throughout the past century, the "immunosurveillance" hypothesis was tested and retested, with experimental results sometimes supporting the hypothesis, sometimes rejecting it [24]. In the past two decades, the overwhelming majority of evidence is in favor of Ehrlich's hypothesis, and researchers are now seeking ways to enhance the ability of the immune system to stop the progression of the disease [26].

One of the earliest attempts to harness the immune system's response was made by an oncologist, William B. Coley, in the late 1800s, who noticed that some of his patients with what he thought was incurable cancer would improve when they simultaneously had an infection. He manufactured a mixture of dead bacteria, and experimentally administered the brew, known as "Coley's toxins," to patients with inoperable tumors. This treatment was successful enough to encourage other doctors to follow suit throughout the following decades [56]. Other immunotherapy treatments for cancer include stem cell transplants, introduced in the 1950's, and the administration of immune-stimulating cytokines. A stem cell transplant involves harvesting immune cells from the bone marrow of healthy individuals and transferring them to patients with leukemia. The administration of immune-stimulating cytokines is a technique that was pioneered and developed by Dr. Steven Rosenberg to treat patients with melanoma [50]. For an excellent review of cancer immunotherapies, see [3].

The role of the immune response in the control of cancerous cells also caught the interest of the mathematical community. Over the past twenty years, physicists and applied mathematicians have developed mathematical models that describe the interactions between tumor cells and immune cells in an attempt to understand the mechanisms behind observed behavior and to help clinicians design effective treatments. The earlier models consider tumor cells and immune cells at the population level [33, 36, 44, 52]. For an excellent survey of these early models see the book [1]. Later models include spatial effects [4, 5, 41] or focus on optimization of specific immunotherapy treatments [6, 35]. General frameworks have been developed from a systems perspective that are applicable to a variety of specific situations [19, 20]. This chapter is not intended to be an overview of this impressive body of work; the interested reader is referred to the texts cited here and the references therein. Rather, we follow our own trajectory of investigation and discovery, presenting several models of tumor–immune interactions that illustrate a variety of approaches to understanding the progression of the disease and to harnessing the immune response in the context of treatment.

This chapter is organized as follows. In Sect. 2 we develop the simplest model of the immune response, which uses two ordinary differential equations to describe two competing populations: the immune cells and the tumor cells. We add chemotherapy

to this simple model to illustrate the complexity in the resulting dynamics and to demonstrate *in silico* the importance of including the immune response in the design of treatment strategies. We add more realism to the model in Sect. 3 by distinguishing between the innate and the adaptive immune responses and describe several types of modeling techniques that can be used to explore this distinction. In the final section of the chapter, Sect. 4, we discuss immunotherapies, and give several examples of mathematical models that can be used to investigate immunotherapeutic protocols.

2 The Immune Response as One Population of Effector Cells

The immune system is a complex network of interacting cells, proteins and chemicals. This network consists of excitatory and inhibitory connections, positive and negative feedback loops, and delays. In the simplest mathematical model of tumor-immune interactions, we only consider those immune cells that have the ability to destroy antigen, or foreign cells. These include natural killer (NK) cells, cytotoxic T-cells (CTL) such as $CD8^+$ cells, macrophages, and other scavenger cells. As a first model, we lump all of these killer cells into one population called **effector cells**. We imagine that we are considering a small volume of tissue containing a tumor, we consider the tumor to be one homogeneous population of cells, and we assume that the interaction between tumor and effector cells can be described as an *average* affect. If the number of cells in each of the populations is large, we can describe the population as a continuum, and we can describe the evolution of the average using differential equations. We also include a population of normal host cells in this model, as a proxy for overall "well-being." Since a tumor cannot grow without bound, we assume that, in the absence of an immune response, the tumor will grow to some maximum size determined by the available nutrients. We assume the same for the normal cells. Several functional forms are used to model self-limiting growth in the literature, for example, logistic, Gompertz, or von Bertalanffy. In this formulation we use a logistic growth law for both normal and tumor cells. We note, however, that other growth laws produce qualitatively similar results. Further details of this model and an analysis of its long-term behavior can be found in [14] and [15].

We let $I(t)$ denote the number of effector immune cells at time t, $T(t)$ the number of tumor cells at time t, and $N(t)$ the number of normal, or host, cells at time t. A graphical representation of the model interactions is shown in Fig. 1.

The source of the immune cells is considered to be outside of the system, and we let s denote the constant influx of innate effector cells that would be present in the absence of a tumor. Furthermore, in the absence of any tumor, the cells will die off at a per capita rate d_1, resulting in a long-term population size of s/d_1 cells. Thus, immune cell proliferation will never suffer from crowding.

The presence of tumor cells stimulates the immune response, represented by the dashed arrow in the diagram. For biological realism, we assume here a saturation

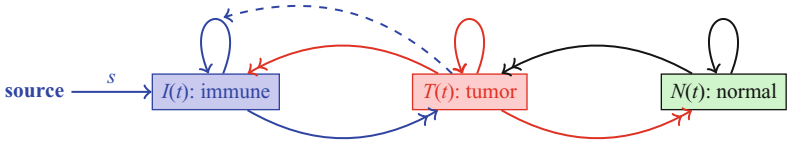

Fig. 1 A graphical representation of a population model of tumor-immune interactions, with three populations: immune effector cells (I), tumor cells (T), and normal cells (N). *Solid lines* indicate direct interactions, and *dashed lines* indicate indirect interactions. *Single arrow heads* denote a positive interaction, while double arrow heads denote an inhibitory interaction

limited effect. Furthermore, the reaction of immune cells and tumor cells can result in either the death of tumor cells or the inactivation of the immune cells, represented by two double-headed arrows.

The closed loop arrows on the tumor and normal cell population nodes represent normal growth and decay, which follows a logistic law. In addition there are two terms representing the competition between tumor and host cells, shown also as double-headed arrows in the diagram. Putting all the terms together gives the following system of ordinary differential equations:

$$\begin{aligned} \dot{N} &= r_2 N(1 - b_2 N) - c_4 TN, \\ \dot{T} &= r_1 T(1 - b_1 T) - c_2 IT - c_3 TN, \\ \dot{I} &= s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I. \end{aligned} \tag{1}$$

As shown in [15], this system has one "tumor-free" equilibrium at $(1/b_2, 0, s/d_1)$ and two "dead" equilibria, where the normal cell population is zero. Furthermore, the system can have one, two, or three "co-existing" equilibria, where all of the cell populations are nonzero, depending on the values of the parameters. Thus, in some parameter regimes, the system is *multistable*, where several stable equilibria exist at the same time, so that the long-term behavior of the system is determined by the initial conditions. We note that the concept of multistability is one of the few new ideas that biomathematics was able to offer the biomedical research community.

If the tumor-free equilibrium is stable, then small tumors will be eradicated by the immune system. A linearized stability analysis shows that this occurs when the *resistance coefficient* is larger than the intrinsic growth rate of the tumor, i.e., when

$$\frac{c_2 s}{d_1} + c_3 > r_1.$$

If a patient has a detectable tumor that is progressing, then we can assume that the tumor-free equilibrium is unstable. Two bifurcation diagrams are shown in Fig. 2.

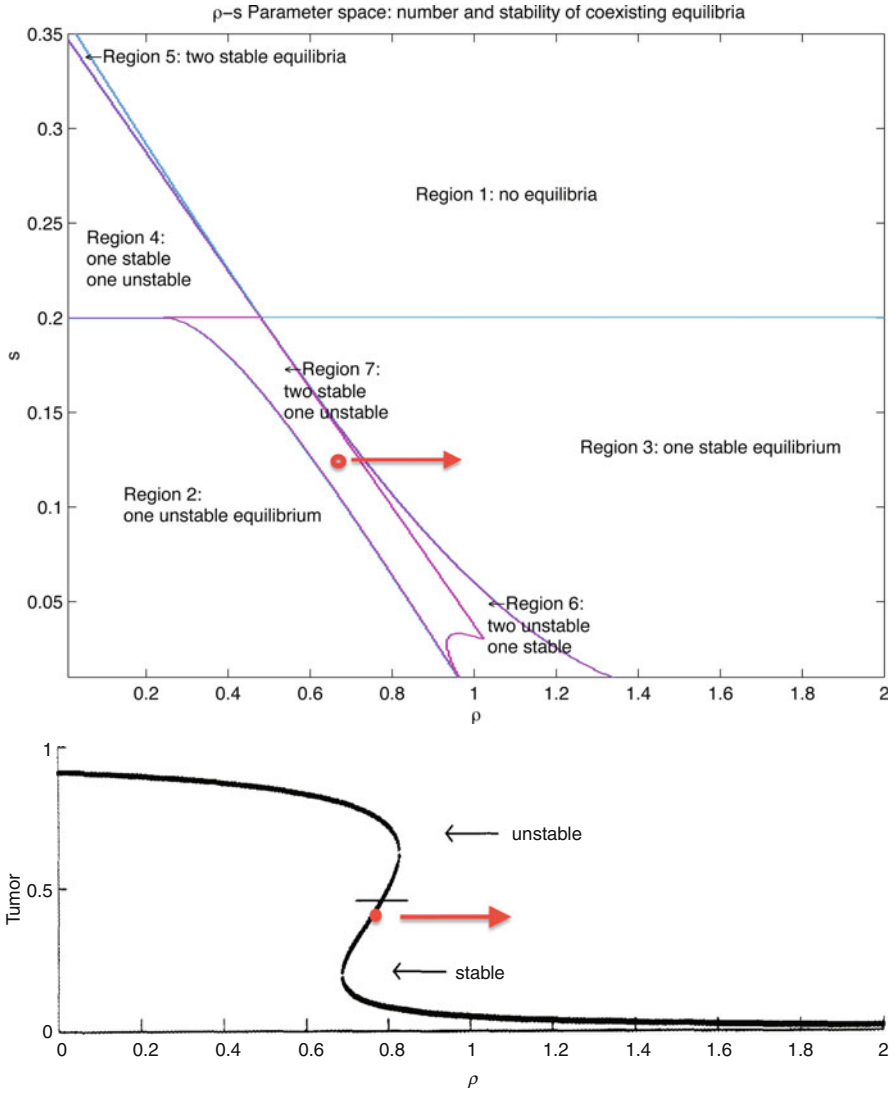

Fig. 2 Bifurcation diagram showing how changes in the immune source (s) and recruitment (ρ) parameters affect the number and stability of equilibria with nonzero tumor values. Note that the tumor-free equilibrium is not shown here: it is assumed to be unstable if there is a tumor. The red arrow indicates movement through the diagram as a result of a hypothetical treatment that enhances the immune response, such is the administration of interleukin 2 (IL2). Upper graph: Number and type of co-existing equilibria as a function of source rate, s, and immune response, ρ. Lower graph: Tumor cell populations at the equilibria as a function of the immune response rate, ρ. Stability of equilibria is indicated. Movement is from Region 2 through Regions 7 and 6 and finally into Region 3: as ρ increases from 0.1 to 2.0. Source rate $s = .12$, tumor populations as fraction of carrying capacity. See [15] for details

We can interpret these diagrams in the context of immunotherapy treatments as follows: treatment should move the system into a regime where it is attracted to a small, presumably harmless, tumor. If a patient has a detectable tumor that is progressing, we can assume that it is *not* in the basin of attraction of a stable, small-tumor equilibrium. Suppose the system is in Region 7, where it will be attracted to a relatively large tumor equilibrium (the dot in both graphs in Fig. 2). By administering cytokines that increase the immune response or by giving a vaccine that increased the immunogenicity of the tumor, the parameter ρ could be increased, moving the system to the right in the bifurcation diagrams (denoted by the arrows in both graphs). The system would then be in the basin of attraction of a relatively small tumor equilibrium, and the tumor would regress without further treatment.

We can also learn something about the effects of uncertainty in the environment by looking at the bifurcation diagram. For example, suppose the system is near the right boundary of Region 7 in Fig. 2, for example, near the point $s = .17$, $\rho = .6$. In this case, small fluctuations in the parameter s, the influx rate of effector cells in the absence of a tumor, could cause the system to move into Region 3. A reverse saddle-node bifurcation occurs where one stable equilibrium and one unstable equilibrium disappear, and the system would move towards the one remaining stable equilibrium. In this case, this would be beneficial, since the remaining equilibrium is at a point in state space with a small tumor population. The effect of stochastic fluctuations in the parameters has been discussed in the context of tumor–immune models in, for example, [7], and the effects of random fluctuations on resistance to chemotherapy is treated nicely in [21].

2.1 The Immune Response and Chemotherapy

In a scenario known as "Jeff's phenomenon," it has been clinically observed that tumors treated with cytotoxic chemotherapy can respond in a non-intuitive way. For some patients, after one treatment the tumor will shrink, and after another it might continue to grow, resulting in a temporal oscillation that is asynchronous with the chemotherapy. This phenomenon is reported in [59], where it is argued that this asynchronicity cannot be explained solely by acquired drug resistance. We hypothesize that it is the interaction of the chemotherapy with the immune response that could explain Jeff's phenomenon and test the hypothesis by adding a chemotherapeutic term to the model.

We assume that the rate of change of the concentration of drug at the tumor site, $u(t)$, can be described by a time-varying input function, $v(t)$, representing the administration of the drug, and by an elimination rate, d_1. We also assume that the drug kills all three types of cells in the model at a saturating rate, but that it acts preferentially on the more quickly dividing tumor cells and immune cells than on the normal host cells. A graphical representation of the system is shown in Fig. 3, with edges terminating in open circles denoting an inhibitory (killing) effect.

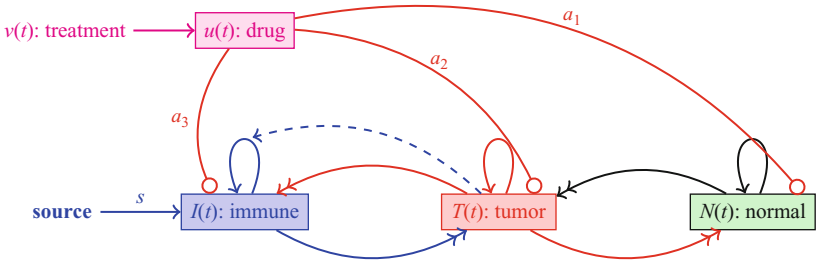

Fig. 3 A graphical representation of the model with chemotherapy. *Solid lines* represent direct interactions, with single arrowheads representing cooperative interactions, double arrowheads representing competitive interactions, and open circles representing a killing effect. *Dashed lines* represent interactions that affect the rate of another interaction

These assumptions result in the following system of equations (see [15] for parameter values and more details):

$$\begin{aligned}
\dot{N} &= r_2 N(1 - b_2 N) - c_4 TN - a_1(1 - e^{-u})N, \\
\dot{T} &= r_1 T(1 - b_1 T) - c_2 IT - c_3 TN - a_2(1 - e^{-u})T, \\
\dot{I} &= s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I - a_3(1 - e^{-u})I, \\
\dot{u} &= v(t) - d_1 u.
\end{aligned} \tag{2}$$

where $a_1 < a_3 < a_2$. A simulation of this model demonstrating Jeff's phenomenon is shown in Fig. 4. Thus, the immune response could play a role in the delayed response of some patients to cytotoxic chemotherapy. This simple model also suggests that a close monitoring of the state of the cellular immune response could help in designing more effective treatment protocols.

With the relatively simple model given by Equation 2, we can attempt to answer the question: what is the best treatment regimen for a patient with a specific parameter set? As a first step, we must define what we mean by "best." One criterion might be "the one that minimizes tumor size at the end of treatment" and another might be "the one that is least toxic." Once the criteria are settled, optimization techniques can be applied to the system to propose effective treatment protocols. For example, suppose we wish to minimize the tumor burden after 45 days of treatment, while keeping the tumor population as low as possible and keeping the

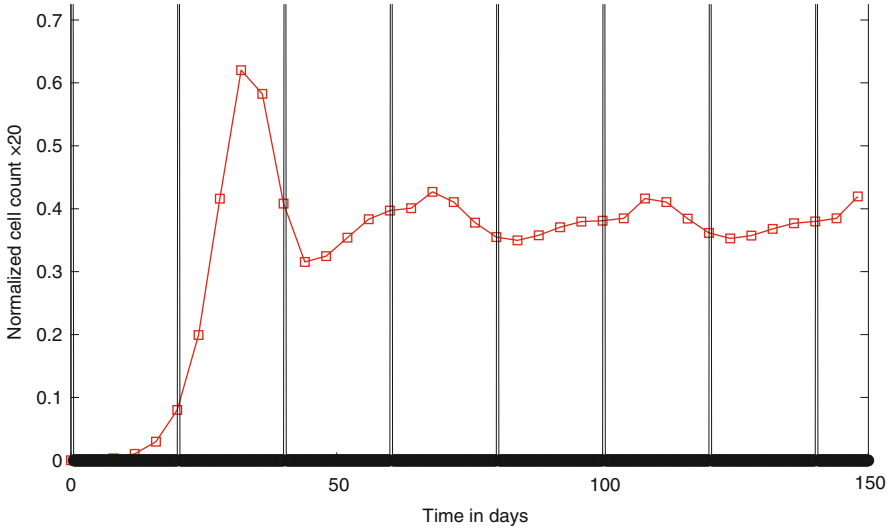

Fig. 4 Simulation of the model in system 2 demonstrates a possible role of the immune response in an asynchronous response to chemotherapy. Vertical lines show the simulated bolus injections of the drug, administered every 21 days

level of normal cells above 75 % of their normal value (a measure of toxicity). In terms of an optimization problem, we want to find the function $v(t)$, representing the administration of the drug, that minimizes the following *cost* function, where t_f is the total time of treatment.

$$J(v(t)) = w_1 T(t_f) + w_2 \int_0^{t_f} T(t)dt + w_3 \max_{t\in(t_0,t_f)} T(t), \tag{3}$$

where w_i are weighting constants. Note that three terms were required in the cost function: the first reflects our desire to minimize the tumor at the end of treatment, t_f. The second reflects our desire to minimize the total tumor present over the course of treatment, and the third term puts a penalty on any treatment that results in a large tumor at any point. The omission of either of the final two terms yields solutions with tumor populations that grow very large for a short period of time. The weighting of the three terms also yields qualitatively different results. For the set of experiments we present here, we set $w_1 = 1500, w_2 = 150, w_3 = 1000$, but other weightings might be preferred, depending on the type of tumor.

To reflect our desire to avoid excessive toxicity, we introduce a *constraint* function:

$$N(t) \geq 0.75, \quad 0 \leq t \leq t_f, \tag{4}$$

where the host cell population, $N(t)$, is scaled to a fraction of its normal value. Additional constraints are that all state variables must satisfy Equation 2 and that both the rate of drug input and the total amount of drug administered are bounded: $0 \leq v(t) \leq \max_v$, $0 \leq \int_0^{t_f} v(t)\,dt \leq v_{TOT}$.

This optimization problem can be solved using a variety of available techniques. In Fig. 5 we compare simulations using a traditional, "pulsed" protocol, where the drug is administered over short (12 h) periods, repeated every 2 days for 40 treatments (so the last treatment ends midday on Day 80). In this experiment, we simulate a patient with a relatively weak initial immune system ($I(0) = .1$) and the simulation shows that the traditional pulsed treatment is ineffective in the long term: once treatment stops, the tumor continues to grow, and the disease progresses. In the right panel of Fig. 5 we show a solution obtained using a direct collocation method, DIRCOL [57]. We required that the total amount of drug administered be no more than the total in the traditional case, so $v_{TOT} = \sum_{n=1}^{40} \int_0^{.5} 1\,dt = 20$. The optimized protocol suggests that the drug be administered over longer periods of time, on the order of days, with irregularly spaced treatments. In fact, it suggests one very short pulse of chemo at Day 125. With this treatment the tumor burden is driven to near zero by Day 70, and it remains there for the duration of the simulation. It is worth emphasizing that the only difference between the two treatments is the *timing* of the doses: the total amount of drug, and the maximum drug given are the same.

There are many possible optimization questions that could be asked in this setting. For example, it is possible that, by adding the total amount of drug used to the cost functional, one could find treatment protocols that are equally effective but that use less drug. Or it might be desirable to introduce a penalty term that curbs the destruction of the immune population. In Sect. 4 we will explore other optimization techniques and results in the context of designing cancer vaccines.

3 The Innate and Adaptive Immune Response

The human body has a huge army of defender cells, generally known as *white blood cells* (WBC) or *leukocytes*. It creates approximately a billion of these cells each day. A subset of these leukocytes are *lymphocytes*, which comprise 20–30 % of the WBC. In this section we will focus on two types of lymphocytes: the natural killer (NK) lymphocytes and the cytotoxic T lymphocytes (CTLs). Both of these cells are *cytotoxic*, meaning that they kill antigen or "nonself" cells. However, they belong to two different arms of the immune response: NK cells belong to the *innate* immune system. They form part of the immune system's regular patrol, and they are activated to *lyse*, or kill, cells that they encounter when that cell does not have a high expression level of certain molecules known as MHC I (major histocompatibility complex class I). The CTLs are part of the *adaptive* immune system. These cells originate from stem cells that then migrate to the thymus (hence the "T").

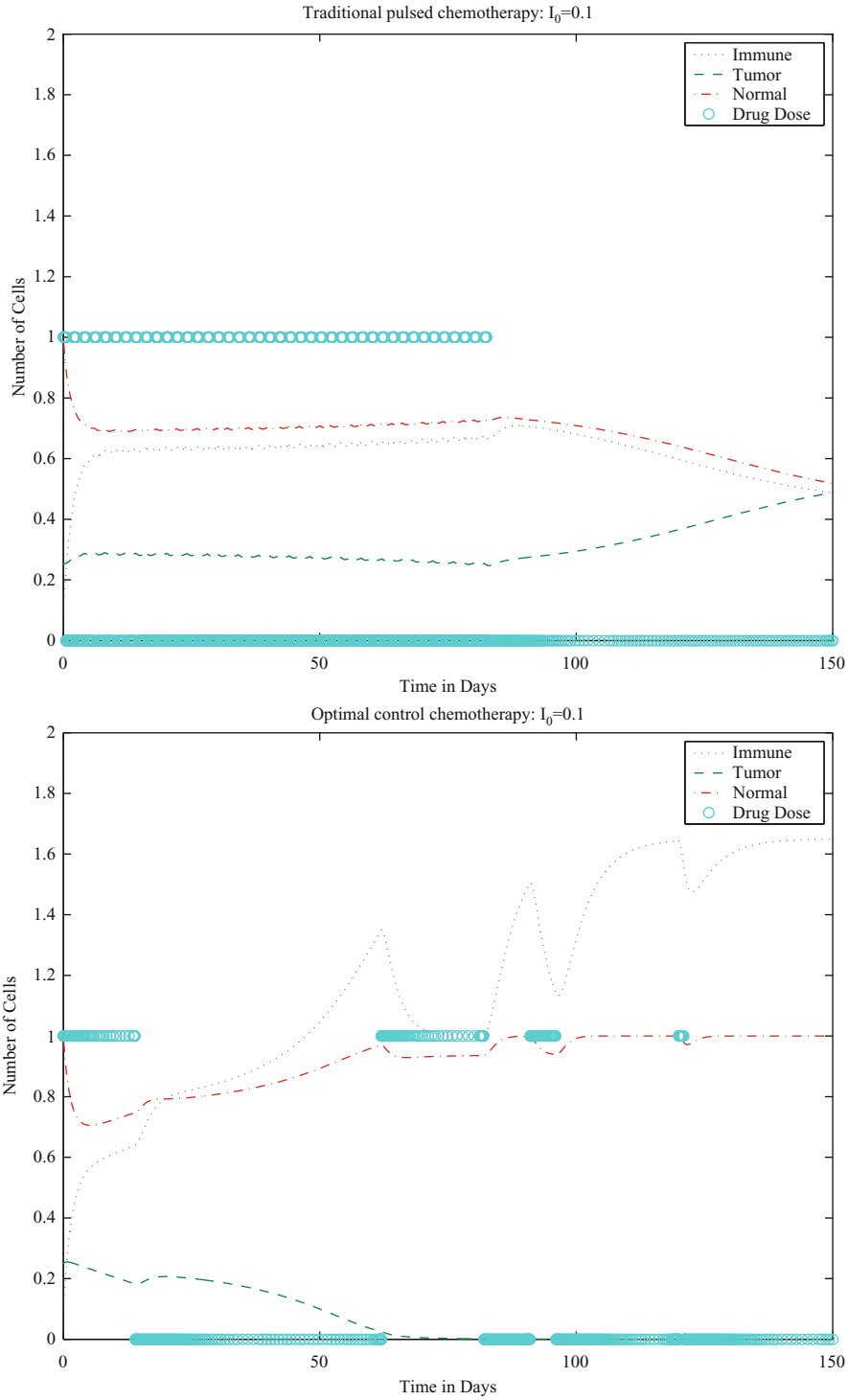

Fig. 5 (continued)

From there they are recruited to various lymph organs. When a nonself cell, or antigen, is encountered by a certain type of roving immune cells called *antigen-presenting* cells (APCs), they are engulfed, and pieces of the foreign cell are "presented" to the T-cells, activating them and causing them to proliferate into one population that can recognize and kill that particular type of foreign cell. Figure 6 gives a sketch of this process, where the antigen-presenting cell is a *macrophage*. Once the CTL is activated, it will seek out the specific antigen for which it is trained. Some activated CTLs will become memory cells, providing immunity for a second attack by the same foreign cells.

Note that other T-cells known as "helper T-cells" are also activated in this process, and these T-cells participate in the activation of the CTLs or "killer T-cells." Helper T-cells will appear in our models later, in Sect. 4.1. Helper T-cells also activate B-cells, which are key players in the *humoral response*, that part of the immune response that is mediated by antibodies. Another important class of APCs is the *dendritic cells* (DCs), which are now being used in the development of cancer vaccines. These will be discussed in Sect. 4.2. In terms of the body's fight against cancer, both NK cells and CTLs act like predators, but their methods of recognizing—and killing—their prey are different. As part of the innate immune system, natural killer cells are cytotoxic cells that are highly effective in lysing multiple (but specific) tumor cell lines [43]. Unlike cells of the specific immune system, which are drawn to a location due to the presence of antigen, the natural killer cells are constantly present guarding the body from infection and disease.

On the other hand, cytotoxic T lymphocytes are able either to lyse or to induce apoptosis in cells presenting *specific* antigens, such as tumor cells [43]. Unlike NK cells, CTLs are only able to recognize a specific antigen or tumor cell line. It is known, however, that these cells are able to destroy more than one tumor cell during their life cycle while a single natural killer cell generally kills very few [36]. After destroying the target cell, the CTLs move on in search of other antigen-presenting cells.

3.1 The dePillis–Radunskaya Law

In the fight against cancer, both the innate and the adaptive arms of the immune response are important. In fact, laboratory experiments show that without both NK cells and CTLs, tumors injected into mice will escape the immune surveillance

Fig. 5 *Left*: A patient with a relatively weak initial immune population ($I(0) = .1$ in normalized units) shows progressive disease after a series of pulsed chemotherapy treatments. The bolus treatments are simulated as injections at the maximum rate (normalized to $\max_v = 1$) for 12 h, repeated every 2 days for the course of the treatment. *Right*: A solution to the optimization problem given in Equation 3. The total amount of drug is the same in both the left (traditional treatment) and right (optimized treatment) simulations. The optimized treatment protocol is successful in eliminating the tumor

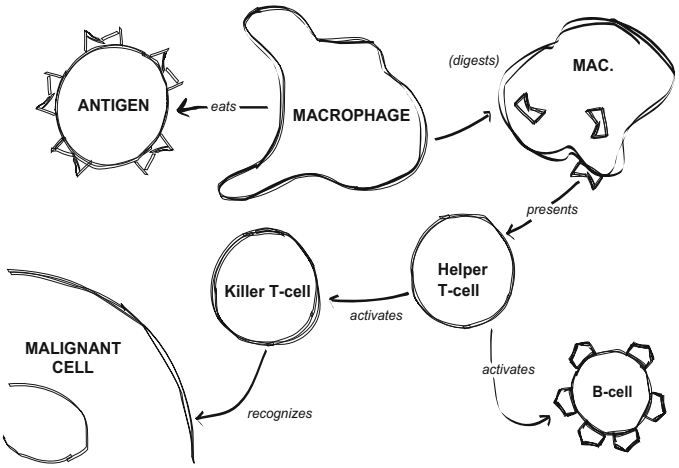

Fig. 6 A graphical representation of the activation of the adaptive immune response. A macrophage, a type of antigen-presenting cell (APC), recognizes a particular cell as "nonself" or antigen and engulfs it. The APC then presents bits of the engulfed, or "phagocytosed" cell to immature T-cells, which then begin to proliferate, activating other immune cells and, ultimately, the killer T-cells, or CTLs, and recognize and kill malignant cells of the same type as the initial antigen

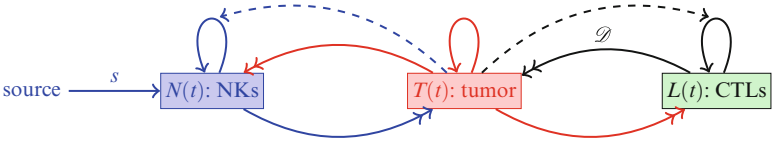

Fig. 7 Schematic of the model with two types of effector cells: natural killer cells (N), representing the innate immune response, and cytotoxic T lymphocytes (L), representing the adaptive immune response. As before, the solid lines represent direct interactions, with a single arrow-head denoting a cooperative interaction, and a double arrowhead denoting a competitive interaction. The dashed lines represent indirect interactions, where one population affects the *rate* of another interaction

(e.g., [18]). We therefore separate the effector cell population from the previous model into two subpopulations: the NK cells and the CTLs. Without the host cells, the model diagram becomes that shown in Fig. 7.

In developing the model, we assume again that the tumor grows logistically, that the NK cells, as part of the innate immunity, have a constant source, that immune cell proliferation is enhanced by the presence of the tumor, and that immune cells and tumor cells interact competitively. Furthermore, we know that the destruction of tumor cells by NK cells results in an increased uptake of antigen by antigen-presenting cells and, hence, an increase in the number of tumor-specific CTLs that are produced.

In the previous model given by System 1, competition between effector immune cells and tumor cells was represented by a mass action term of the form $-cIT$.