



Mathematical Model of Colorectal Cancer with Monoclonal Antibody Treatments

L.G. dePillis^{*1}, H. Savage² and A.E. Radunskaya³

¹Department of Mathematics, Harvey Mudd College, Claremont, California, USA

²Graduate Group in Immunology, University of California, Davis, Davis, California, USA

³Department of Mathematics, Pomona College, Claremont, California, USA

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Abstract

We present a new mathematical model of colorectal cancer growth and its response to monoclonal-antibody (mAb) therapy. Although promising, most mAb drugs are still in trial phases, and the possible variations in the dosing schedules of those currently approved for use have not yet been thoroughly explored. To investigate the effectiveness of current mAb treatment schedules, and to test hypothetical treatment strategies, we have created a system of nonlinear ordinary differential equations (ODEs) to model colorectal cancer growth and treatment. The model includes tumor cells, elements of the host's immune response, and treatments. Model treatments include the chemotherapy agent irinotecan and one of two monoclonal antibodies - cetuximab, which is FDA-approved for colorectal cancer, and panitumumab, which is still being evaluated in clinical trials. The model incorporates patient-specific parameters to account for individual variations in immune system strength and in medication efficacy against the tumor. We have simulated outcomes for groups of virtual patients on treatment protocols for which clinical trial data are available, using a range of biologically reasonable patient-specific parameter values. Our results closely match clinical trial results for these protocols. We also simulated experimental dosing schedules, and have found new schedules which, in our simulations, reduce tumor size more effectively than current treatment schedules. Additionally, we examined the system's equilibria and sensitivity to parameter values. In the absence of treatment, tumor evolution is most affected by the intrinsic tumor growth rate and carrying capacity. When treatment is introduced, tumor growth is most affected by drug-specific PK/PD parameters.

Keywords: Colorectal cancer; Mathematical model; Monoclonal antibody; Immunotherapy; Mixed chemo-immunotherapy; Simulated cohort study; In silico tumor growth;

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^{*}Corresponding author: E-mail: depillis@hmc.edu

1 Introduction

According to the American Cancer Society, colorectal cancer is the third most commonly diagnosed cancer and the third leading cause of cancer death in both women and men in the United States [1]. Monoclonal antibodies have been explored as an adjuvant treatment for colorectal cancer, but there are still many unanswered questions about their effectiveness and optimal use. The goal of this work is to contribute to the understanding of how best to incorporate monoclonal antibodies into colorectal cancer treatment. We present a system of nonlinear ordinary differential equations (ODEs), that models the growth of a colorectal tumor, its interactions with the host's immune system, and the effects of three treatment options: the chemotherapy drug irinotecan, and two monoclonal-antibody (mAb) treatments, cetuximab and panitumumab. We use this model to run clinical trial simulations over cohorts of virtual patients with varying response rates. After validating our outcomes against published clinical trial data, we then explore alternate hypothetical treatment scenarios.

Colorectal Cancer

Monoclonal antibody therapies, which are targeted cancer therapies, are being tested in clinical trials to address colorectal tumors that are chemotherapy-refractory. Monoclonal antibodies are small antibodies that are manufactured to bind to specific proteins. Multiple protein targets can be used, but epithelial growth factor receptor (EGFR) is a common and useful choice. EGFRs are found in cell membranes in cells all over our body, and circulating epithelial growth factor (EGF) binds to this receptor and signals a cascade in the cell, resulting in cell proliferation. The increased growth rate in tumor cells is usually caused by multiple mutations, but a common mutation upregulates the number of EGFRs [2–5]. Monoclonal antibodies targeting EGFRs are considered promising since many cancerous cells have the EGFR-upregulating mutation.

Cetuximab and panitumumab, both monoclonal antibodies that bind to EGFR and block EGF from binding, are two monoclonal antibodies that have been shown to have some degree of effectiveness against colorectal cancer. Cetuximab, used with or without the chemotherapy drug irinotecan, has been shown to improve survival times and quality of life [4]. It is an IgG1 antibody, a subclass of antibodies that is able to elicit antibody-dependent cellular cytotoxicity (ADCC) from Natural Killer (NK) cells, thus increasing the NK cells' cytotoxicity [4]. Panitumumab is a newer drug and has undergone fewer clinical trials. It has been shown to decrease tumor

Acronyms: mAb: monoclonal antibody, ODE: ordinary differential equation, NK:Natural Killer cell, CD8⁺:cytotoxic T-cell, CTL:cytotoxic T-lymphocyte (often equivalent to CD8⁺ T-cell), ADCC:antibody-dependent cellular cytotoxicity, EGF:endothelial growth factor, EGFR:endothelial growth factor receptor, CDC:complement-dependent cytotoxicity

growth rate, but clinical trials have not yet been able to confirm that it increases overall survival time [4]. Both cetuximab and panitumumab are able to activate the cascade known as complement dependent cytotoxicity (CDC), and both increase chemotherapy's toxicity to tumor cells by hindering their ability to reproduce [5]. There are three main pathways for mAb induced tumor death (see Figure 1): interactions between mAbs, NK cells, and tumor cells; interactions between mAbs, chemotherapy and tumor cells; and interactions only between mAbs and tumor cells, resulting in growth rate reduction, complement activation, and possibly other mechanisms for tumor death.

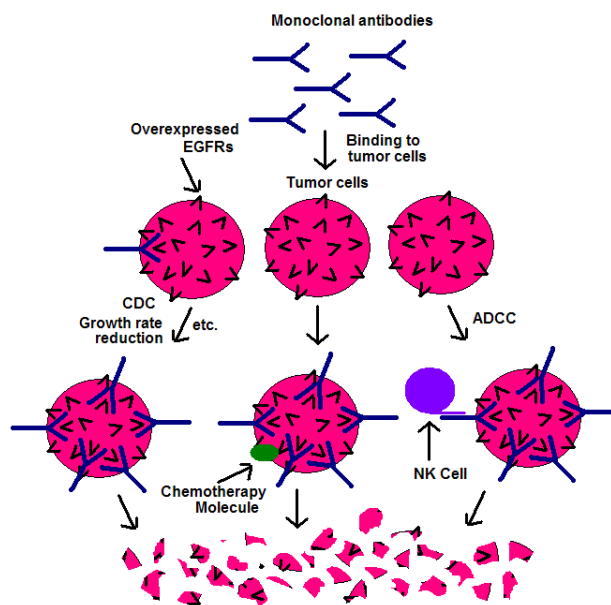


Figure 1: **Three methods of mAb-induced tumor cell death are represented in this model.** If an NK cell is present then the cell can undergo ADCC, if a chemotherapy molecule is present then the cell will increase death from the chemotherapy drug, and otherwise, the mAb molecule will cause tumor cell death on its own, through a variety of mechanisms.

Currently, monoclonal-antibody treatments are mainly used in patients with metastatic cancer, particularly when no other treatment has worked [4]. However, it is possible that with positive results from current clinical trials, monoclonal antibodies may become a more significant part of colorectal-cancer treatment. The model presented here can shed further light on monoclonal antibody treatments by simulating clinical trials.

Previous Models

A variety of approaches has been taken to the mathematical modeling of colorectal cancer growth and treatment. These include ODE models, spatial models, and statistical models. A nice review can be found in [6], where mechanistic models and phenomenological cell population models are discussed. The primary focus of this review is to explore published models that include chemotherapy, with the end goal of optimizing therapy regimens. In particular, in [7] a PK-PD model of irinotecan (CPT11) is combined with a compartment model to describe a whole-body physiologically based model for colon cancer in mice. In the model presented in this paper, we include immunotherapy in addition to chemotherapy, using a phenomenological cell population model.

In [8], Johnston *et al.* considered two different approaches to the modeling of cells in a colonic crypt. They first consider an age-structured model which tracks the locations, properties, and ages of stem cells, transit cells, which move up the wall of the crypt to the surface, and differentiated cells. The resulting model was then simplified using a continuous approximation. They found that the resulting ODE system provided a good approximation for the growth rate produced by the age-structured model for a sufficiently large time scale. This work, which shows that an ODE system can be used to represent a 3D structure in the colon, motivated our choice of model for a colorectal tumor. However, the use of ODEs requires the simplifying assumption that the tumor is spatially homogeneous, and only tracks tumor population changes over time. Since the measure of overall tumor size is used to indicate the strength of a patient's response to treatment in the clinic, it is reasonable to use tumor size as a measure of treatment efficacy in our model as well.

Other mathematical models of colonic cancer focus on the initiation of the disease. For example, in [9] a mathematical model is developed that supports the hypothesis that two types of genetic instability can lead to tumorigenesis in individuals with colorectal cancer. More recently, Lo *et al.* [10] proposed a mathematical model of the initiation of colorectal cancer that explores a possible link with colitis.

The model presented here is an extension of the work of de Pillis *et al.* [11], in which a tumor-cell population, immune-cell populations, and drug concentrations are modeled with a system of nonlinear ODEs. The model by de Pillis *et al.* also includes patient-specific parameters representing the strength of the patient's immune system, and has been validated with published studies on mice and humans [12]. It has successfully demonstrated the need for immunotherapy in addition to chemotherapy to prevent the tumor from growing again after drug therapies have been completed, and was used to study the importance of the patient-specific parameters in the effectiveness of immunotherapy treatment [11, 13]. The new model includes terms for monoclonal-antibody treatment and its effects on the cell populations. Parameter values have been adjusted to reflect dynamics specific

to colorectal cancer.

2 Mathematical Model

The goal of this mathematical model is to describe tumor growth, immune response, and treatments, including chemotherapy and monoclonal antibody (mAb) treatments. Our model tracks the following populations and quantities:

- Cell Populations

$T(t)$ the total tumor cell population (cells);

$N(t)$ the concentration of NK cells per liter of blood (cells/L);

$L(t)$ the concentration of cytotoxic T lymphocytes ($CD8^+$) per liter of blood (cells/L);

$C(t)$ the concentration of lymphocytes per liter of blood, not including NK cells and active $CD8^+$ T cells (cells/L).

- Medications and Cytokines

$M(t)$ the concentration of chemotherapy per liter of blood (mg/L);

$I(t)$ the concentration of interleukin per liter of blood (IU/L);

$A(t)$ the concentration of monoclonal antibodies per liter of blood (mg/L);

The specific treatments that we will explore are the chemotherapeutic drug irinotecan (CPT11), and mAbs cetuximab or panitumumab.

- Treatments:

$v_M(t)$ the amount of irinotecan injected per day per liter of blood (mg/L per day);

$v_A(t)$ the amount of monoclonal antibodies injected per day per liter of blood (mg/L per day).

In the following section, we give a description of the equations describing the evolution of each population. In Section 3, examples of the evolution of simulated cell populations over time are presented, and treatments and clinical trials are simulated. Finally, we present a parameter sensitivity analysis and discuss the results. Details of the parameter estimation, a discussion of equilibria and their stability and further sensitivity analyses are given in the Research Supplement.

Equations

The full system of ODEs of the model is given below. The equations are based on the model proposed in [11], with additions necessary to describe mAb and combination treatments. These additional terms are shown in bold face. A summary of the purpose of each model term can be found in Tables 1-6.

$$\frac{dT}{dt} = aT(1 - bT) - (c + \xi \frac{\mathbf{A}}{\mathbf{h}_1 + \mathbf{A}})NT - DT - (K_T + \mathbf{K}_{AT}\mathbf{A})(1 - e^{-\delta_T M})T - \psi \mathbf{A}T \quad (2.1)$$

$$\frac{dN}{dt} = eC - fN - (p + \mathbf{p}_A \frac{\mathbf{A}}{\mathbf{h}_1 + \mathbf{A}})NT + \frac{p_N NI}{g_N + I} - K_N(1 - e^{-\delta_N M})N \quad (2.2)$$

$$\frac{dL}{dt} = \frac{\theta mL}{\theta + I} + j \frac{T}{k + T}L - qLT + (r_1 N + r_2 C)T - \frac{uL^2 CI}{\kappa + I} - K_L(1 - e^{-\delta_L M})L + \frac{p_I LI}{g_I + I} \quad (2.3)$$

$$\frac{dC}{dt} = \alpha - \beta C - K_C(1 - e^{-\delta_C M})C \quad (2.4)$$

$$\frac{dM}{dt} = -\gamma M + v_M(t) \quad (2.5)$$

$$\frac{dI}{dt} = -\mu_I I + \phi C + \frac{\omega LI}{\zeta + I} \quad (2.6)$$

$$\frac{d\mathbf{A}}{dt} = -\eta \mathbf{A} - \lambda \mathbf{T} \frac{\mathbf{A}}{\mathbf{h}_2 + \mathbf{A}} + \mathbf{v}_A(t) \quad (2.7)$$

where

$$D = d \frac{(L/T)^l}{s + (L/T)^l} \quad (2.8)$$

Model Terms Describing Growth and Interactions

Each of Equations (2.1) - (2.7) describes the time evolution of one of the eight system variables. Each equation contains a growth, or source, term, and a decay term. Most of the equations also contain interaction terms that describe how one population of cells or molecules affects another. For example, in Equation (2.1), the tumor is assumed to grow logistically in the absence of other cells or antibodies. The competition term between tumor and NK cells follows a mass action law, where the effectiveness of the NK cells in killing tumor cells, or the *per cell* kill rate, is enhanced by the presence of monoclonal antibodies (see also the discussion

below). The interaction between cytotoxic T lymphocytes (CTLs) and tumor cells is described by a *ratio-dependent* law, articulated in Equation (2.8). The derivation of this term is described in detail in [12].

A recruitment term is included for the tumor-specific CD8⁺ T cells, as well as a production term in Equation (2.6) that reflects the increased presence of IL-2 when CTLs are present. Interleukin, whose concentration is denoted by the variable $I(t)$, activates the production of NK cells and CD8⁺ cells, indicated by the positive saturating terms in Equations (2.2) and (2.3). However, IL-2 can also aid in the inactivation of CD8⁺ cells. From Abbas *et al.* [14], we find that the deactivation of CD8+T cells occurs through a pathway that requires IL-2 and the action of CD4+T cells (found in the circulating lymphocytes). Moreover, it occurs only at high concentrations of activated CD8+T cells. This deactivation is represented by the term $-\frac{uL^2CI}{\kappa+I}$ in Equation (2.3).

Also described in the model are the effects of a cytotoxic drug such as irinotecan. This drug is assumed to have a detrimental effect on all of the cell populations. For more details on the derivation of these terms see [11] and [15], and for parameter values, sources, and derivations see the Research Supplement.

Discussion of Terms Describing Treatment

In this section we give details on terms in the model that were added to the one proposed in [11]. In Equation (2.1), three terms represent the three pathways of mAb-induced tumor-cell death (see Figure 1).

- The term $-\xi \frac{A}{h_1+A} NT$ represents the rate of tumor-cell death caused by ADCC. Some monoclonal antibodies have protein structures which, when bound to a tumor cell, allow them to simultaneously activate NK cells and to direct them to the invader [5]. Thus, when a mAb/tumor-cell complex and NK cell meet, the tumor cell is more likely to be killed than when an NK cell meets an unbound tumor cell. Kurai and colleagues [16] found that cetuximab has a threshold concentration above which ADCC activity no longer increases. So, we assume that ADCC activity increases with mAb concentration until it becomes saturated, and we model this with a sigmoid function.
- The term $-K_{AT}A(1 - e^{-\delta_T M})T$ represents the rate of chemotherapy-induced death of tumor cells, assisted by monoclonal antibodies. When tumor cells are not able to proliferate, they are much more susceptible to chemotherapy-induced death [5]. So, when mAbs are bound to tumor cells, blocking their EGFRs and thus inhibiting tumor cell proliferation, they increase the tumor-cell death caused by chemotherapy.
- The term $-\psi AT$ accounts for the rate of tumor-cell death caused directly by tumor cell interactions with mAbs. This term includes tumor-cell death from

CDC, from a reduction in EGF binding and thus tumor-growth rate, [5].

The term $-p_A \frac{A}{h_1+A} NT$ in Equation (2.2) represents the rate of NK-cell death due to ADCC interactions with tumor cells and monoclonal antibodies. We assume that ADCC activity increases with mAb concentration until it becomes saturated. As with the term $-pNT$, it is assumed that NK cells experience exhaustion of tumor-killing resources after multiple interactions with tumor cells [17]. We note that we chose not to incorporate mAb interactions in Equations (2.3), (2.4) and (2.5), since the literature suggests that effects of mAbs are specific to tumor cells [2–5, 18].

The evolution of the monoclonal antibody population is described in Equation (2.7). The term $v_A(t)$ represents mAb treatments. Because mAbs are not produced naturally in the body, no additional growth terms are included. The term $-\eta A$ represents the natural degradation of the mAb protein in the body. The term $-\lambda T \frac{A}{h_2+A}$ represents the loss of available mAbs as they bind to tumor cells. MAbs have a very strong binding affinity for their target growth-factor receptors, and there are many growth factor receptors on every cell, so we assume that many mAbs are lost with each tumor cell. Since our model describes targeted monoclonal antibodies, we assume that the mAbs are formulated so as to bind tightly to the targeted antigen, with a very low dissociation constant. Therefore, we assume that the growth factor receptors are fully saturated when the mAb concentration is significantly higher than the growth factor receptor concentration. That is, we can approximate the number of mAbs lost with each tumor cell as the number of growth-factor receptors on that cell, as long as mAb concentration is not close to zero.

3 Results

Clinical Trial Simulations for Common Treatment Regimens

We used the model to explore expected responses to treatment at a population level. In particular, we simulated response to treatment for patients with a range of immune “strengths”. The effectiveness of the CD8⁺ T-cells is described in the model by the term D described in Equation (2.8). In order to describe a group of patients with different immune strengths, we allow the three parameters in Equation (2.8) to take on one of four values taken from a biologically reasonable range, [11]. These three patient-specific parameters are d , the maximum kill-rate by effector cells; s , the steepness of the effector-cell response to the presence of tumor; and l , a measure of the non-linearity of the response. Table 1 lists the specific values used. Using four different values for each of the three parameters yields 64 virtual patient types, each with a different immune system.

To account for variation between patients in tumor response to therapy, we also varied the values of the parameters K_T , the rate of tumor-cell death from

chemotherapy, and ψ , the rate of cell death induced by mAb agents. For each simulation, the values of these parameters were randomly sampled from a distribution given by the density function

$$p(x) = \frac{1}{3x_{max}}(1 - x/x_{max})^{-2/3}, 0 \leq x < x_{max},$$

where x_{max} is the maximum value of each parameter, either K_{max} or ψ_{max} . (See Table 1.)

In these clinical trial simulations, we assume that the simulated patients have slightly compromised immune systems after already having been through other immuno-depleting therapies. MAb therapy is currently used mainly as a last resort, after other treatments have been attempted unsuccessfully, so we expect the tumor population size to initially be large. Initial values for the state variables reflect this, with a large initial tumor size, $T(0) = 10^9$ cells, and relatively low levels of NK and CD8⁺ lymphocytes. All initial values are given in the Research Supplement. Simulated treatments were administered to each patient, represented by $v_M(t)$ and $v_A(t)$ in model equations (2.5) and (2.7).

Clinical trial simulations were run over the set of 64 virtual patients multiple times. Final tumor size and lymphocyte counts were recorded for each patient. Lymphocyte count was used as a marker for patient health—if the lymphocyte count dropped low enough for the patient to be considered grade 4 leukopenic, the treatment was considered to be too harsh and not useful. This minimum lymphocyte count was determined to be 1.4×10^8 , based on the WHO criteria of grade 4 leukopenia being less than 10^9 total white blood cells per liter (see reference [19], and see also the discussion of the parameter K_C in the Research Supplement). Final simulated tumor sizes were categorized as a “Complete Response” (CR), “Partial Response” (PR), or “No Response” (NR). Tumors that continue to grow are categorized as NR, and any tumor smaller than ≈ 2.2 mm in diameter is categorized as CR. This value was chosen since it is significantly below the clinical detection level of 5 mm in diameter, [20]. In our analysis, we assume a spherical, homogeneous tumor, so that 2.2 mm in diameter corresponds to 2^7 cells. Finally, those tumors that don’t continue to grow, but are larger than 2×10^7 cells, are categorized as PR.

We compare the results of the simulated trials to those reported in [2, 5, 21–23]. See Table 1 for a summary of these clinical trial outcomes. Note that the published clinical trial results for cetuximab and panitumumab that we used for comparison reported results as “Response” or “No Response” almost exclusively, so for our clinical trial simulations of the commonly used treatments, we group PR and CR together under “Response”. This facilitates comparison between our simulation results and the results of reported clinical trials.

Monotherapy clinical trial simulations were performed for each of the three drugs used in our model. An irinotecan monotherapy clinical trial was simulated, using a

common treatment regimen, and results were compared with clinical data. (The treatment details can be found in the “Treatments” section of the Research Supplement). Irinotecan monotherapy simulations resulted in a total response of 18.7%, (15.6% PR, 3.1% CR), versus an overall reported response rate of 30% (see Figure 2(A)). This is consistent with practice, since patients getting mAb treatments are often not very responsive to chemotherapy. Cetuximab and panitumumab clinical trials were also simulated, using the common treatment regimens found in “Treatments”, to verify that the desired response rate was achieved. Parameter calculations for each mAb drug involved choosing a value for ψ that resulted in accurate clinical trial results for the mAb monotherapies, but verification of these values is important. Cetuximab monotherapy simulations matched the expected results with a total response rate of 10%, (10% PR, 0% CR), versus an overall reported response rate of approximately 10% (see Figure 2(B)), and panitumumab monotherapy simulations matched the expected results with a total simulation response rate of 12.15% (10.9% PR, 1.25% CR), versus an overall reported response rate of 10-13% (see Figure 2(C)). Combination therapies, using either irinotecan and cetuximab or irinotecan and panitumumab, were also simulated. These simulations used the common treatments for each drug and gave the two treatments simultaneously.

We do not currently have a way to adjust severity classification for the tumor based on patient health. A smaller tumor in a very sick patient can be just as dangerous as a larger tumor in healthier patient. Therefore, when examining monotherapies, which do not have particularly damaging effects on the immune system, we measured responses after one week in order to capture the less dramatic and potentially transient effects, which could still be helpful to patients whose immune systems have not been severely compromised by treatments. However, in the case of combination treatments, we chose to wait longer after treatment before measuring results. The clinical trial studies summarized in Table 1 did not report when tumor was measured after the last treatment, so we chose to measure tumor size four weeks after the final treatment for all simulations. Although many more patients experienced an initial drop in tumor size as a result of the combination treatments, this drop was frequently unhelpful to the patient because of the additional loss of immune strength associated with the harsher combination treatments.

Our simulations match reported clinical trial results fairly closely (see Figure 3). The results from these simulations are also provided in Table 1, along with the associated clinical trials data.

Impact of Patient Specific Response Parameters on Treatments

We also ran the model to simulate individual patients, using set values for the patient-specific parameters, to examine how the tumor and immune system interact with strong or weak responses to the medications. The results from these simulations were plotted as cell populations/concentrations versus time. In Figure 4, we

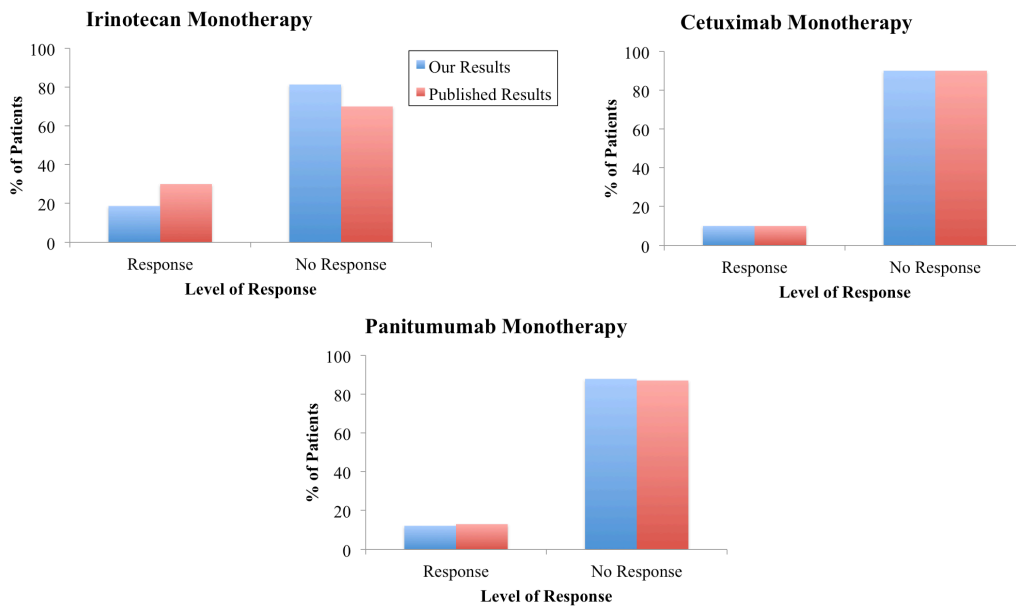


Figure 2: **Our clinical trial simulations compared to reported clinical trial results for irinotecan monotherapy (A), cetuximab monotherapy (B), and panitumumab monotherapy (C).** Our simulation results closely match published results for both cetuximab and panitumumab monotherapies. For irinotecan monotherapies, the reduced response seen in our simulations is intended, since the patients receiving mAb therapy are often not as responsive as most patients to other treatments.

first see how the initial tumor size determines whether the tumor ultimately shrinks or grows to carrying capacity in the absence of treatment. In our remaining simulations that include treatment, we ensure that the initial tumor size is chosen to be sufficiently large (10^9 cells) so that it would grow to carrying capacity in the absence of treatment.

In Figure 5, we simulate irinotecan/cetuximab combination therapy, and can see how a modification in an individual's CD8+T cell response to tumor, via response function D , affects treatment outcomes. We also simulated the tumor response to irinotecan/panitumumab combination therapy (figure not shown) with $l = 1.6$ and $s = 7 \times 10^{-3}$, resulting in a moderate response D , and with $l = 1.3$ and $s = 4 \times 10^{-3}$, resulting in a high response D . With the moderate D , the tumor will increase to carrying capacity with the cessation of treatment, but the stronger D allows the patient's immune response to eradicate the tumor.

In Figure 6, we observe how individual tumor sensitivity to either chemotherapy or mAb therapy affects tumor size. In particular, we simulate four possible combi-

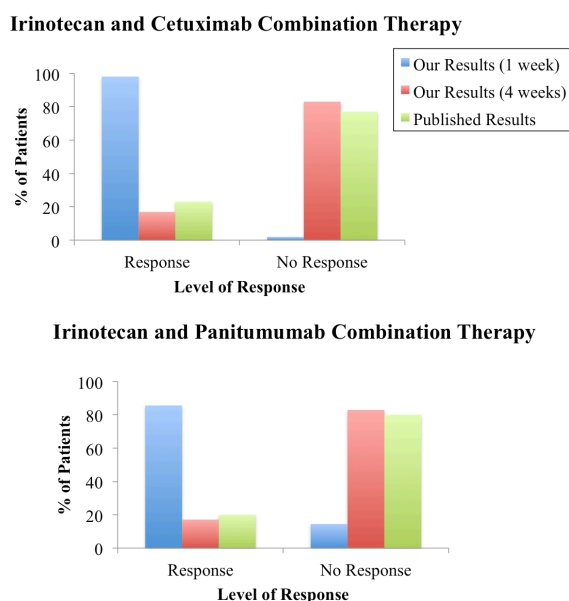


Figure 3: **Our clinical trial simulations compared to reported clinical trial results for irinotecan and cetuximab combination therapy (A) and irinotecan and panitumumab combination therapy (B).** If simulation results are measured one week post-treatment, they do not replicate published results for combination therapies. However, if simulation results are measured four weeks post-treatment, our results are very similar to published results.

nations: a strong response to both chemo and mAb therapy (A), a weak response to both chemo and mAb (B), a strong response to chemo but a weak response to mAb (C), and a strong response to mAb but a weak response to chemo (D).

In order to explore which patient-specific parameters play a role in whether a patient will respond to treatment, the effect of the variable parameters, d , l , s , K_T , and ψ , was also examined. d , l , and s were fixed at three sets of values from the set of patient-specific parameters used for clinical trial modeling, a “weak D” ($d = 1.3$, $l = 2$, $s = 4 \times 10^{-2}$); “moderate D” ($d = 1.6$, $l = 1.4$, $s = 8 \times 10^{-3}$); and “strong D” ($d = 2.1$, $l = 1.1$, $s = 5 \times 10^{-3}$) response. The variables K_T and ψ were then varied over their range of 0 to their maximum values, using cetuximab as the mAb drug, and the model was run for 28 days with each pair of values. Figure 9(A) shows that a patient with a weak inherent immune system cannot have a complete response, even with a full-strength response by the tumor to the chemotherapy and mAb treatments. A strong response by the tumor to either treatment will result in a partial response for the tumor overall. Figure 9(B) shows that a patient with a moderately strong

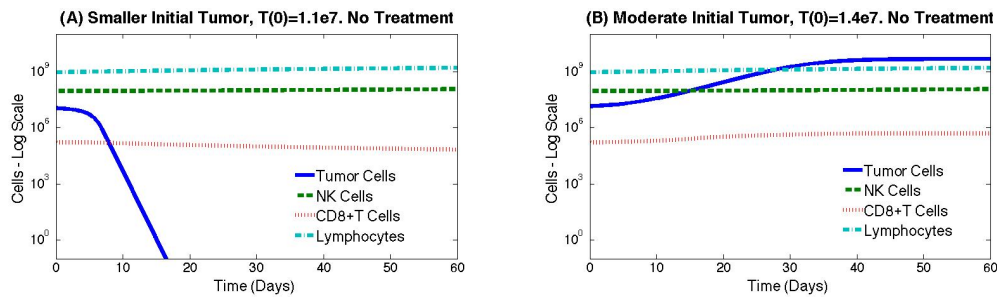


Figure 4: **Patients can end up at either the *no tumor equilibrium* or the *large tumor equilibrium*.** In (A) $T(0) = 1.1 \times 10^7$ cells, in (B) $T(0) = 1.4 \times 10^7$ cells. A tumor with a small initial size will quickly shrink toward zero, a tumor with a larger initial size will quickly grow to the carrying capacity of the system. All other initial values are the same in both simulations.

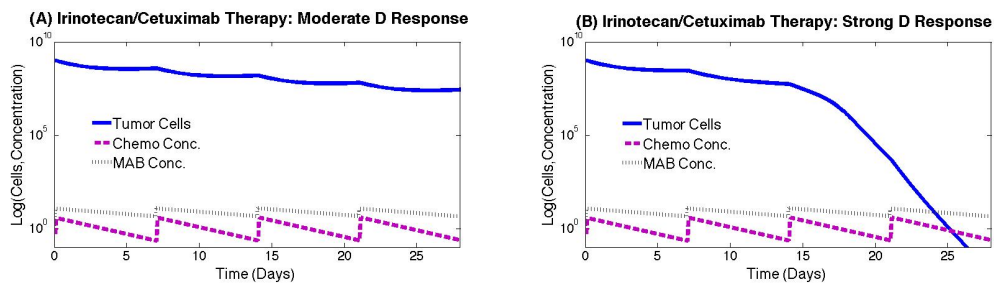


Figure 5: **Effect of patient-specific immune response function D on tumor response to irinotecan/cetuximab treatment.** Tumor response to irinotecan/cetuximab combination therapy with $l = 1.6$ and $s = 7 \times 10^{-3}$ (A), resulting in a moderate response D , and with $l = 1.3$ and $s = 4 \times 10^{-3}$ (B), resulting in a stronger response D . With the moderate D , the tumor will increase to carrying capacity with the cessation of treatment, but the stronger D allows the patient's immune response to eradicate the tumor.

immune system has a chance of overpowering the tumor and obtaining a complete result, with strong tumor responses by the tumor to both the chemotherapy and mAb drugs. The patient is more likely however to have a partial overall response, resulting from a strong response by the tumor to only one medication, or to have no response. Figure 9(C) shows that a patient with a strong immune system has a good chance for a complete overall response, with a strong response by the tumor to either the mAb or chemotherapy treatments. However, the patient will still

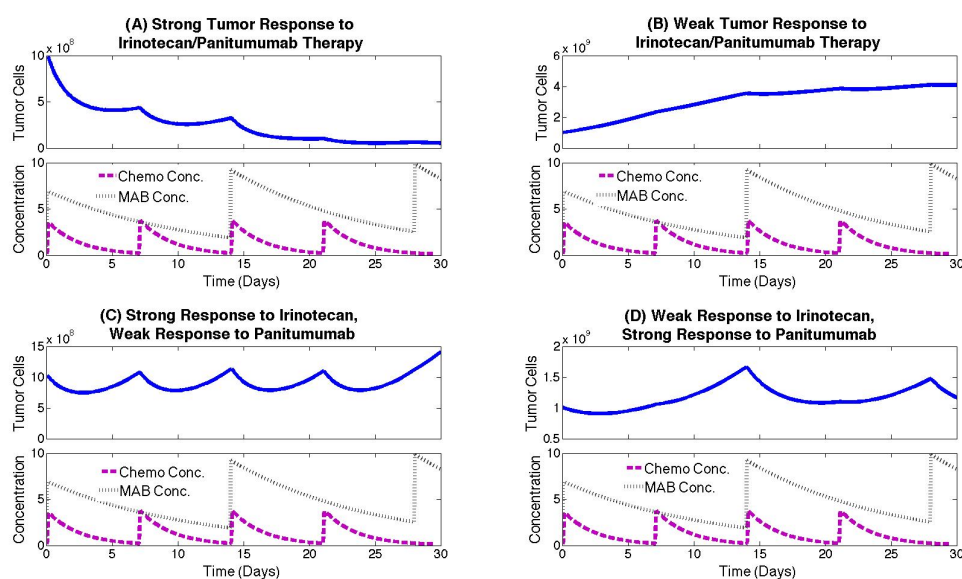


Figure 6: **Tumor responses to combination therapy with irinotecan and panitumumab.** When the tumor has a strong response (high K_T and ψ , 100% strength) to both medications (A), the tumor shrinks during the course of the treatment. When the tumor has a weak response (low K_T and ψ , 10% strength) to both medications (B), the tumor grows toward the carrying capacity. When the tumor has either a strong response to irinotecan and a weak response to panitumumab (C) or a weak response to irinotecan and a strong response to panitumumab (D), the tumor will fluxuate in size, but will stay approximately the same size overall during the treatment course.

not respond to the treatment if the tumor is only weakly affected by both of the medications.

Clinical Trial Simulations for Hypothetical Treatments

Clinical trial simulations with hypothetical treatment combination regimens were also performed. We explored various timings and dosing levels of irinotecan in combination with cetuximab, and separately, irinotecan in combination with panitumumab. Many of the combination treatments we experimented with, which used different doses, dosing frequencies, and different start times for each medication, were not as successful at shrinking the tumor as the current standard treatments. However, we did find some treatment regimens which appear to result in a smaller final tumor size, one with each of the mAb medications. These results are shown

in Figure 7. For comparison, we include one set of simulation results for tested treatments that can also be found in Table 1, as well as the results of the two separate hypothetical dosing schedules. In Figure 7, top panel, we compare population responses to three different combination doses of irinotecan combined with panitumumab, and in the bottom panel, we compare irinotecan combined with cetuximab.

Hypothetical Treatment 1: One hypothetical treatment improvement can be seen when using irinotecan combined with panitumumab, required no change in dosing levels, but a change in the timing of the dose administration. In this case, we dose first with panitumumab, and then wait four days to begin irinotecan doses. Irinotecan is then continued every 7 days for the remainder of the treatment, while panitumumab continues to be administered once every two weeks, as with a standard dosing schedule. This treatment decreased the total number of patients who did not respond to treatments from 14.4% to 8.4%, although it also decreased the number of patients who demonstrate a complete response from 18.1% to 11.4%. Simulation results can be seen in Figure 7, top panel. Since the medications are not being given at the same time, the patient may experience fewer simultaneous side effects with this treatment schedule. However, the treatment also requires the patient to make extra trips to the hospital for treatment administration.

Hypothetical Treatment 2: In Figure 7, top panel, we also show a second hypothetical treatment, in which the doses of both irinotecan and panitumumab are increased: The irinotecan dose is 2.8 times the standard dose, and panitumumab is 1.5 times the standard dose. However, dosing frequency is decreased to once every three weeks for both medications. This results in a slightly higher complete response rate of 12.2%, and a partial response rate of 71.3%.

Hypothetical Treatment 3: In the third hypothetical scenario, shown in Figure 7, bottom panel, we look at irinotecan combined with cetuximab. In this case, we modify the dose timing only, and leave dose amounts at standard levels. We dose first with irinotecan, and follow up with a cetuximab dose four days later. This strategy was not particularly successful. The complete response rate was only 12.2%, as opposed to the 17.2% achieved by the standard dosing schedule.

Hypothetical Treatment 4: Treatment option 4 combines a higher dose of irinotecan and a higher dose of cetuximab, both administered less frequently than standard treatment would require. Results are pictured in Figure 7, bottom panel. Irinotecan is administered once every three weeks, and cetuximab is administered once every two weeks. Treatment lasts nine weeks, so the individual receives three irinotecan doses, and four cetuximab doses. The use of these drugs at the higher doses, at least as monotherapies, has been reported in the literature [2, 21, 24]. The higher dosed irinotecan/cetuximab combination increases the overall response rate from 98.9% for the standard treatment to 100%, and increases the complete response rate from 17.2% to 60.9%.

Of all four hypothetical treatments presented, the high-dose irinotecan/cetuximab combination appears to be the most effective. In our simulations, the lymphocyte

count stayed above a specified minimum, which is one way to measure the degree of immune system damage from the chemotherapy. With this treatment schedule, the medications are not always given in the same weeks, which has the benefit of the tumor population being kept low with frequent medications, while side effects for the patient may be reduced. However, this treatment schedule also requires that the patient receive medication every week, which may be an inconvenience (versus, for example, the treatment with irinotecan and panitumumab being given only every 3 weeks).

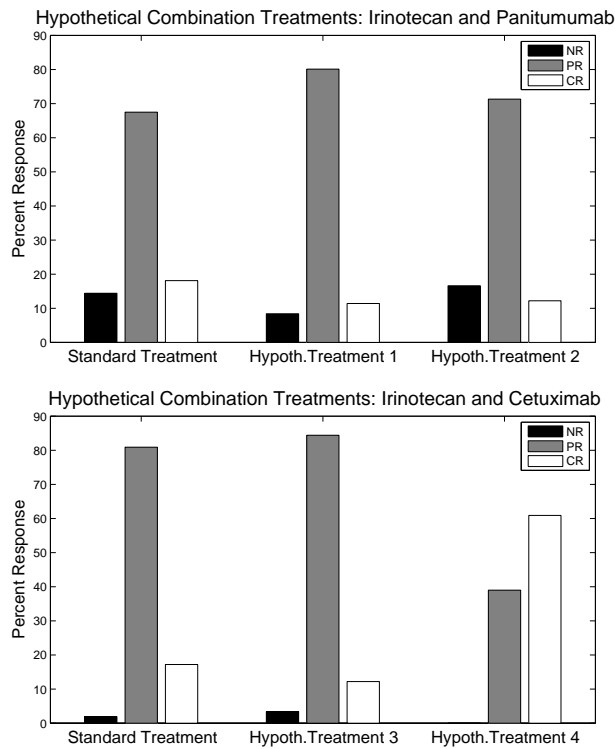


Figure 7: **Response rates from clinical trial simulations, comparing standard treatment to two experimental treatment schedules.** Top panel is irinotecan and panitumumab. Bottom panel is irinotecan and cetuximab. NR, No Response. PR, Partial Response. CR, Complete Response. 320 individuals simulated. Dosing details in Table 2.

Sensitivity to Parameters

Parameter sensitivity analysis was performed to determine which model parameters have the greatest effect on tumor size, both in the absence of treatment and with different treatments. We found seven parameters that significantly affected tumor size in our simulations. In order to separate short term and long term effects, we looked at tumor size seven days after initiation of the simulation, and again at twenty eight days after initiation. In most cases, parameters that had a significant impact on tumor size at day seven were also significant at day twenty eight. A full description of the parameters and their values can be found in the Research Supplement, and in Tables 1-6, but we will briefly explain here the parameters found to be most significant.

Each parameter value was individually increased and decreased by 5% while all other parameter values were held constant. Tumor size was measured at 7 days, when the tumor is still growing very quickly in our model, and at 28 days, when it is close to its maximum volume in our model. First, we analyzed parameter sensitivity in simulations with no treatments given, so treatment-related parameters did not affect simulation outcomes. Results for parameters with the most significant impact on outcomes are shown in Figure 8(A) and (B) at days 7 and 28. Note that, while b (which represents the inverse of the carrying capacity) is by far the most important parameter in determining final tumor size, a (the intrinsic tumor growth rate) is important in determining how quickly the tumor reaches its maximum volume. The parameter l , which affects the functional form of the CTL kill rate, has the most significant effect on non-medicated initial tumor growth of all the immune system parameters.

A sensitivity analysis with treatment-related parameters was then performed. For chemotherapy irinotecan treatment parameters, the final tumor size was found to be very sensitive to K_T and δ_T , which determine the model's response to the chemotherapy drug, and to γ , which represents the excretion of the chemotherapy drug (see Figure 8(C), (D)). Tumor regrowth between treatments was much more dependent on γ than was the decrease in tumor size following treatments. This makes sense, because when the chemotherapy remains in the body longer, it will be more effective at maintaining lower tumor volumes between treatments.

We next tested the monoclonal antibody therapies, cetuximab and panitumumab, separately. Dose timings for cetuximab and panitumumab are different, so we measured parameter sensitivity according to the different lengths of a standard course of treatment for each treatment type. For cetuximab, we consider one course of treatment to be on days 0, 7, 14 and 21 (four treatments total, once per week over four weeks), whereas for panitumumab, one course of treatment is on days 0, 14, and 28 (three treatments total, once every other week for three weeks). We then measured tumor size one week after the last dose of the treatment course. Therefore, long term sensitivity for cetuximab treated tumors was measured at day 28,

and for panitumumab at day 35. In both cases, the final tumor size was found to be sensitive to ψ , the strength of the tumor's response to mAb drugs, and to η , the mAb turnover rate (see Figure 8(E-H)). This is reasonable, since the main anti-tumor activity of mAb medications is through interference with the ability of EGF to bind to EGFR on the tumor cell surface, an activity which is included in the term ψ [5]. In the short term, cetuximab also shows some sensitivity to ξ and p_A , which are the parameters that determine the strength of ADCC activity.

We note that a five percent change in all the remaining parameters negligibly affected final tumor size. In particular, the parameter K_{TA} , which represents the increase in effectiveness of chemotherapy when it is used in conjunction with mAb therapy, had very little effect on final tumor size. In this case, the final tumor size after 28 days changed by less than 0.5 percent with a five percent change in K_{TA} (figure not shown).

4 Discussion

We have extended the mathematical model presented in [11] to include monoclonal antibody treatment. We have tuned the parameter values of the model to make them specific to colorectal cancer, the chemotherapy treatment irinotecan, and the monoclonal antibody treatments cetuximab and panitumumab. Two stable equilibrium states were found numerically, a *no tumor equilibrium* and a *large tumor equilibrium*. Tumors can be driven to either of these states in simulations, depending on the relative strength of the patient's immune system and the treatments given.

Colorectal tumors can have a wide variety of mutations, and some of these mutations limit a medication's ability to function fully. The parameters K_T and ψ represent a range of different tumor responses to the same chemotherapy and mAb treatments. At the beginning of a simulation for an individual, values for these parameters can be chosen randomly from within proscribed biological ranges. Use of these randomly chosen variables allows us to replicate the population level results seen in clinical trials.

A clinical study can be simulated by numerically solving the model multiple times to represent each individual outcome in the study. In our simulations, we solved the model with 64 different combinations of patient parameters. When simulating individuals receiving mAb monotherapy, the resulting population level response rates are quantitatively very close to the reported rates from clinical trials.

The simulation response rates for irinotecan chemotherapy was lower than the response rates reported in [5]. We intentionally chose model parameters to yield this outcome. This is because we are assuming that our cohort of 64 individuals have already had chemotherapy with less success than would be seen in a general population, and are therefore in need of additional mAb therapy [22]. On

the other hand, the cohort in [5] was from the general population.

For combination therapies, our tumor population responded too well to the medication short term, although in the long term, our simulated responses matched experimental response rates well. The short-term over-responsiveness could be caused by inaccuracies in the model parameters or by time frame differences in the reported response rates. One possible inaccuracy in the model is that the variability in tumor responses to medication may not be accurately represented by the random variables. Tumors cells that aren't destroyed by one medication may be less likely to respond to another medication as well, such as cells in the center of the tumor, to which the medications would have limited access. Because mAbs and chemotherapy drugs generally have very different targets and mechanisms, a mutation causing the tumor to be refractory to one medication won't necessarily cause it to be refractory to the other, but it is possible. If that were the case, one model improvement might be to use one random variable to represent the tumor's response to both medications, instead of two variables. Most response rates are not actually reported with a time frame, so the response rates found with this model from four weeks post-treatment may be more consistent with real life measurements than the response rates from one week post-treatment. The model parameters reported here give a reasonable fit to response rates for combination therapies reported at four weeks post treatment. In future work, we will refine the model to take into account spatial effects, including tumor heterogeneity and the obstacles to drugs infiltrating the interior of the tumor. With these refinements, in addition to coupling the probabilities of response to different medications, we believe that the model could give a more accurate description of the response to medication early in the post-treatment period.

Reported clinical trials for the dual treatments also often did not specify irinotecan dosing, whether the patients previously received treatment, or how long the treatment was given, so this may be responsible for part of the difference in response rates as well. Overall, our model gives a qualitatively good prediction of likely results for various dosing schedules.

In many of the experimental treatments, particularly in the high-dose treatments, the simulated individual's immune system was also greatly weakened by the treatments, particularly by irinotecan. Thus, although the tumor cell population was greatly reduced by the treatments, the individual's immune system was still unable to destroy the remaining tumor cells. Although we did not find much information about the use of CD8+T-cell treatments for colorectal cancer in the literature, the addition of this treatment during the chemotherapy and mAb drug courses could help to bolster the immune system and allow the patient's immune response to lyse tumor cells more effectively. This model, with the addition of a CD8+T cell treatment component, could be used to test this treatment hypothesis.

The parameter sensitivity analysis yielded results that were intuitively reasonable. The analysis also serves to highlight which parameters could be possible

targets for reducing tumor size. For example, if we can get a better sense of biologically how to influence l , a parameter that affects the functional form of the CTL kill rate, a large decrease in l would result in an immune system that is able to conquer the tumor much more easily than the immune system resulting from a change in the other immune system parameters.

In the future, two modifications to this model could yield even more realistic outcomes. First, we could tailor the parameters K_T and ψ to have a more specific biological meaning. For example, the KRAS mutation is known to be present in about 40% of all colorectal tumors, and is known to reduce the effectiveness of mAb treatment to almost zero [25, 26]. Information such as the EGFR counts on the tumor cells and the presence or absence of the KRAS mutation in an individual's tumor could allow for more personalized and specific parameter values, chosen from a smaller distribution based on features of the tumors cells, instead of from a larger random distribution. Second, an equation representing patient well-being could be very useful for predicting effective treatments. Although using lymphocyte count allows us to determine that the patient's immune system has not been completely destroyed by the medication, it doesn't take into account factors such as the inconvenience of frequent treatments, or the fact that high doses of cytotoxic medication may result in side effects harmful to cells of the body other than immune cells (such as those of the stomach lining).

There are several notable clinical observations that are important in informing the next stages of model development. One of these is that tumor cells become resistant to chemotherapeutic drugs, making disease progression very sensitive to the timing and dosing used in treatments [6]. The expansion of the model to include a tumor population resistant to a particular drug would allow *in silico* testing of a variety of treatment scenarios. Another aspect of treatment to bear in mind is the effect of an individual's circadian fluctuations on the tumor's susceptibility to cytotoxic agents. These periodic fluctuations can be captured in our model by allowing time-varying parameters or by introducing delays into the model. Some models of colon cancer that do include circadian rhythms are discussed in [6] and in the references therein.

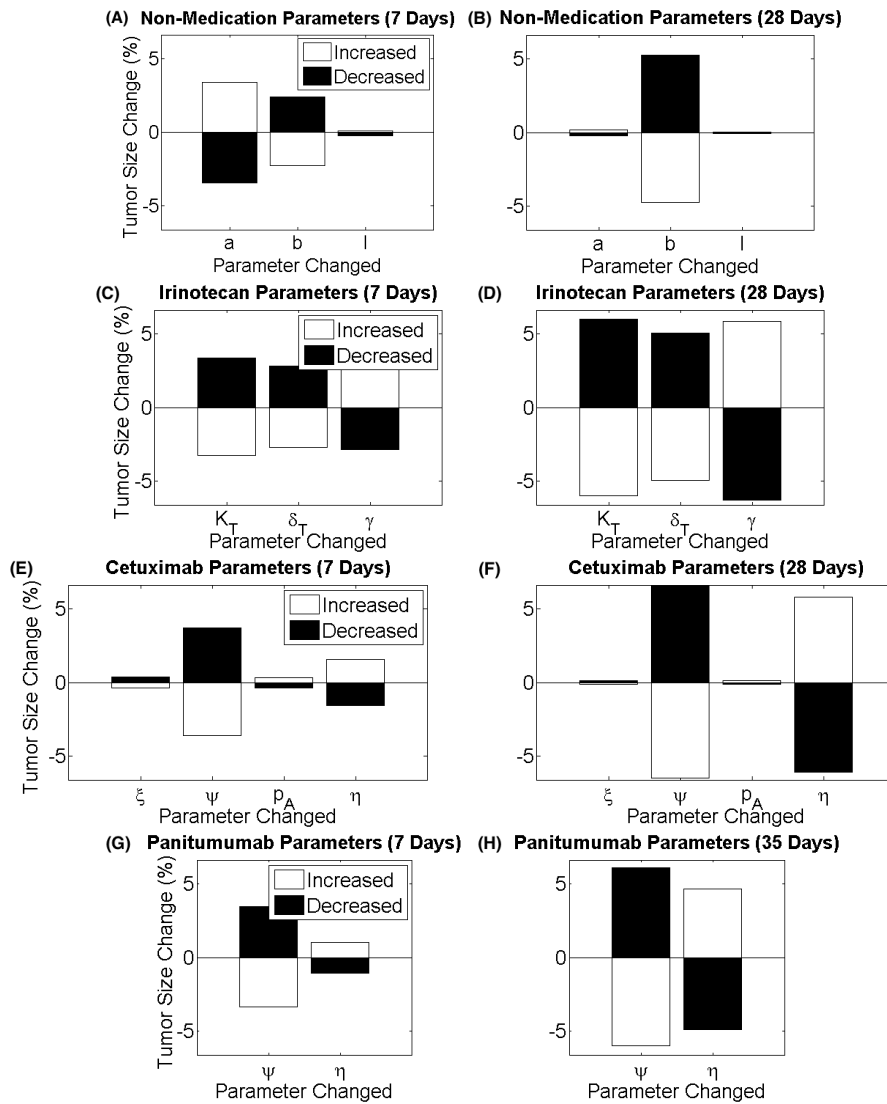


Figure 8: **Sensitivity of final tumor size to a 5% change in parameters.** Final tumor size measured at day 7 to capture short-term sensitivity, and at day 28 (for no medication, irinotecan, and cetuximab parameters) or day 35 (for panitumumab parameters) to capture sensitivity after treatments are completed. No medication: final tumor size most sensitive to exponential growth rate (a) and carrying capacity (b) at day 7 (A), and to carrying capacity (b) at day 28 (B). Irinotecan: final tumor size most sensitive to irinotecan-induced tumor cell death rate (K_T), efficacy (δ_T), and elimination rate (γ) at both 7 and 28 days (C), (D). Cetuximab: final tumor size most sensitive to rate of cetuximab-induced tumor death (ψ) and elimination rate (η) at both 7 and 28 days (E), (F). Panitumumab: final tumor size most sensitive to panitumumab-induced tumor death rate (ψ) at 7 days (G) and both (ψ) and elimination rate (η) at 35 days (H). Parameters resulting in $<0.05\%$ change in final tumor size with a 5% change are not shown. 3121

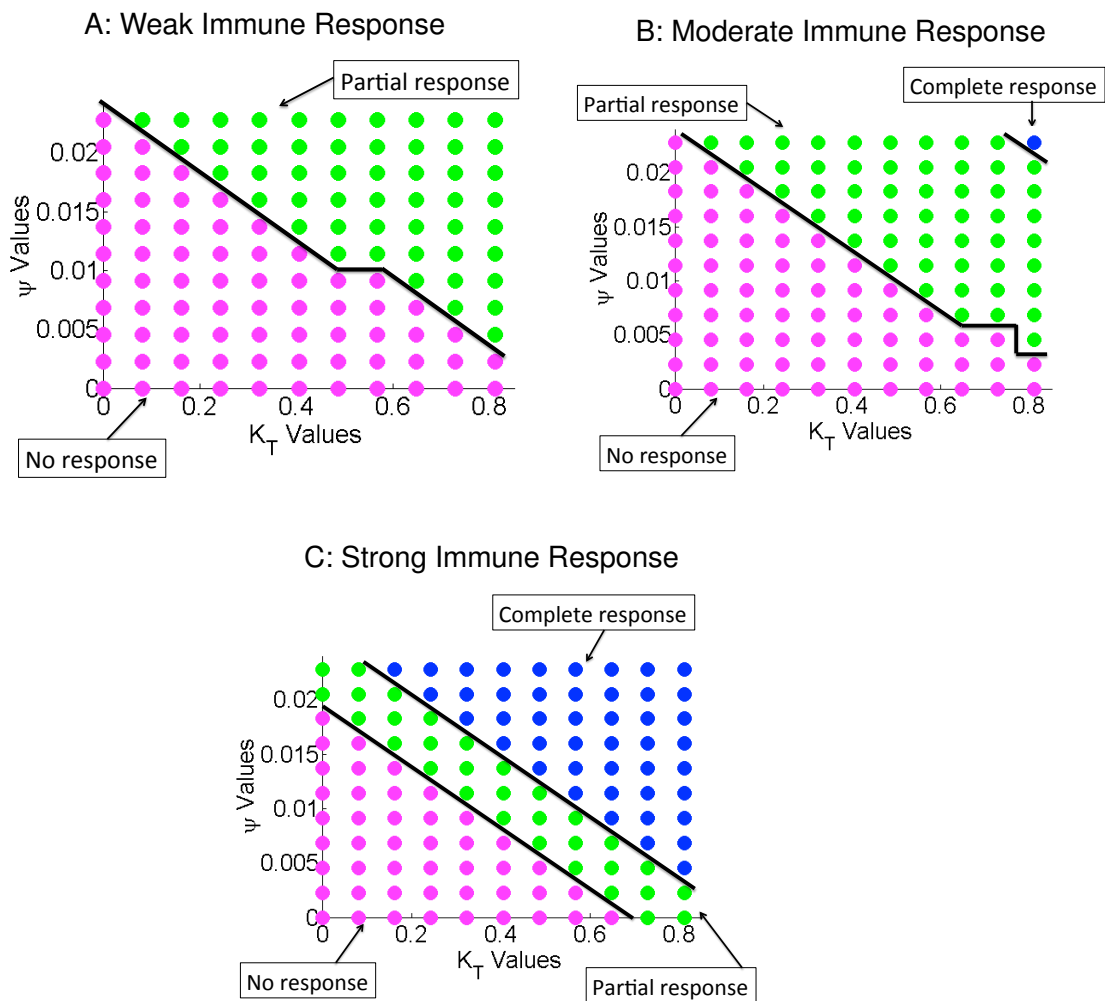


Figure 9: **Sensitivity to the strength of ψ ($\in 0 - 2.28 \text{ L mg}^{-1} \text{ Day}^{-1}$, examined for cetuximab only) and K_T ($\in 0 - 0.81 \text{ Day}^{-1}$), for a patient with a weak (A), moderate (B), and strong (C) immune response . Blue means complete response to medication, green means partial response to medication, magenta means no response to medication. In a patient with a weakened immune system, the medications will not be able to completely remove the tumor, even when the tumor cells have a maximal response to both medications. However, a patient with a strong immune system has a good chance of eliminating the tumor, as long as the patient's tumor cells have some response to the medications. Parameter values used for the immune kill rate, D are as follows. Weak response: $d = 1.3, l = 2, s = 4 \times 10^{-2}$; moderate response: $d = 1.6, l = 1.4, s = 8 \times 10^{-3}$; strong response: $d = 2.1, l = 1.1, s = 5 \times 10^{-3}$.**

5 Tables

Table 1: Tumor Equation Terms and Parameters.

Term	Param	Description and Value (Units)	Source
$aT(1 - bT)$	a	Logistic tumor growth Growth rate of tumor 2.31×10^{-1} (Day ⁻¹)	[27]
	b	Inverse of carrying capacity 2.146×10^{-10} (Cells ⁻¹)	[28]
$-cNT$	c	NK-induced tumor death Rate of NK-induced tumor death 5.156×10^{-14} (L Cells ⁻¹ Day ⁻¹)	[11]
$-\xi \frac{A}{h_1+A} NT$	ξ	mAb-induced tumor death from NK cell interactions Rate of NK-induced tumor death through ADCC 6.5×10^{-10} (L Cells ⁻¹ Day ⁻¹) ^a 0 (L Cells ⁻¹ Day ⁻¹) ^b	[16] [23]
	h_1	Concentration of mAbs for half-maximal increase in ADCC 1.25×10^{-6} (mg L ⁻¹) ^a 0 (mg L ⁻¹) ^b	[16] [23]
	d	CD8 ⁺ T cell-induced tumor death Immune-system strength coefficient {1.3, 1.6, 1.9, 2.1}, (Day ⁻¹)	[11]
$-DT$	l	Immune-system strength scaling coefficient {1.1, 1.4, 1.7, 2.0}, (-)	[11]
	s	Value of $(\frac{L}{T})^l$ necessary for half-maximal CD8 ⁺ T-cell effectiveness against tumor { 4×10^{-3} , 7×10^{-3} , 9×10^{-3} , 3×10^{-2} }, (L ⁻¹)	[11]
	K_T	Chemotherapy-induced tumor death Rate of chemotherapy-induced tumor death $0 - 8.1 \times 10^{-1}$ (Day ⁻¹)	[29]
$-K_{AT}A(1 - e^{-\delta_T M})T$	δ_T	Medicine efficacy coefficient 2×10^{-1} (L mg ⁻¹)	[29]
	K_{AT}	mAb-induced tumor death from increase in chemotherapy effectiveness	
		Additional chemotherapy-induced tumor death due to mAbs 4×10^{-4} (L mg ⁻¹ Day ⁻¹) ^a 4×10^{-4} (L mg ⁻¹ Day ⁻¹) ^b	<i>ad hoc</i> value <i>ad hoc</i> value

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Table 1 – continued from previous page			
Term	Param	Description and Value (Units)	Source
$-\psi AT$		mAb-induced tumor death	
	ψ	Rate of mAb-induced tumor death	
		$0 - 2.28 \times 10^{-2} \text{ (L mg}^{-1}\text{Day}^{-1})^a$	[5]
		$0 - 3.125 \times 10^{-2} \text{ (L mg}^{-1}\text{Day}^{-1})^b$	[5]

Descriptions of the biological relevance of each term and parameter and the parameter values in $T(t)$, which tracks the tumor cell population.

^a For cetuximab.

^b For panitumumab.

Table 2: NK Cell Equation Terms and Parameters.

Term	Param	Description and Value (Units)	Source
eC		Production of NK cells from circulating lymphocytes	
	$\frac{e}{f}$	Ratio of NK cell synthesis rate with turnover rate	
		$\frac{1}{9} (-)$	[11]
$-fN$	f	NK turnover	
		Rate of NK cell turnover	
		$1 \times 10^{-2} \text{ (Day}^{-1})$	Modified from [11]
$-pNT$	p	NK death by exhaustion of tumor-killing resources	
		Rate of NK cell death due to tumor interaction	
		$5.156 \times 10^{-14} \text{ (L Cells}^{-1}\text{Day}^{-1})$	[11]
$-p_A \frac{A}{h_1+A} NT$	p_A	Additional NK death by exhaustion of tumor-killing resources from mAb interactions	
		Rate of NK cell death due to tumor-mAb complex interaction	
		$6.5 \times 10^{-10} \text{ (L Cells}^{-1}\text{Day}^{-1})^a$	[16]
		$0 \text{ (L Cells}^{-1}\text{Day}^{-1})^b$	[23]
$\frac{p_N NI}{g_N + I}$	p_N	Stimulatory effect of IL-2 on NK cells	
		Rate of IL-2 induced NK cell proliferation	
		$5.13 \times 10^{-2} \text{ (Day}^{-1})$	[11]
	g_N	Concentration of IL-2 for half-maximal NK cell proliferation	
		$2.5036 \times 10^5 \text{ (IU L}^{-1})$	[11]

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Table 2 – continued from previous page

Term	Param	Description and Value (Units)	Source
$-K_N(1 - e^{-\delta_N M})N$		Death of NK cells due to chemotherapy toxicity	
	K_N	Rate of NK depletion from chemotherapy toxicity 9.048×10^{-1} (Day ⁻¹)	[30]
	δ_N	Chemotherapy toxicity coefficient 2×10^{-1} (L mg ⁻¹)	[29]

Descriptions of the biological relevance of each term and parameter and the parameter values in $N(t)$, which tracks the concentration of NK cells.

^a For cetuximab.

^b For panitumumab.

Table 3: CD8+ T Cell Equation Terms and Parameters.

Term	Param	Description and Value (Units)	Source
$\frac{\theta m L}{\theta + I}$	θ	CD8 ⁺ T-cell turnover Concentration of IL-2 to halve CD8 ⁺ T-cell turnover 2.5036×10^{-3} (IU L ⁻¹)	[11]
	m	Rate of activated CD8 ⁺ T-cell turnover 5×10^{-3} (Day ⁻¹)	Modified from [11]
$j \frac{T}{k+T} L$	j	CD8 ⁺ T-cell stimulation by CD8 ⁺ T cell-lysed tumor-cell debris Rate of CD8 ⁺ T-cell lysed tumor cell debris activation of CD8 ⁺ T cells 1.245×10^{-4} (Day ⁻¹)	Modified from [11]
	k	Tumor size for half-maximal CD8 ⁺ T-lysed debris CD8 ⁺ T activation 2.019×10^7 (Cells)	[11]
$-qLT$	q	CD8 ⁺ T-cell death by exhaustion of tumor-killing resources Rate of CD8 ⁺ T-cell death due to tumor interaction 5.156×10^{-17} (Cells ⁻¹ Day ⁻¹)	Modified from [11]
$r_1 NT$	r_1	CD8 ⁺ T-cell stimulation by NK-lysed tumor-cell debris Rate of NK-lysed tumor cell debris activation of CD8 ⁺ T cells 5.156×10^{-12} (Cells ⁻¹ Day ⁻¹)	[11]

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Table 3 – continued from previous page			
Term	Param	Description and Value (Units)	Source
r_2CT		Activation of naive CD8 ⁺ T cells in the general lymphocyte population	
	r_2	Rate of CD8 ⁺ T-cell production from circulating lymphocytes 1×10^{-15} (Cells ⁻¹ Day ⁻¹)	Modified from [11]
$-\frac{uL^2CI}{\kappa+I}$		Breakdown of surplus CD8 ⁺ T cells in the presence of IL-2	
	u	CD8 ⁺ T-cell self-limitation feedback coefficient 3.1718×10^{-14} (L ² Cells ⁻² Day ⁻¹)	[11]
	κ	Concentration of IL-2 to halve magnitude of CD8 ⁺ T-cell self-regulation 2.5036×10^3 (IU L ⁻¹)	[11]
$-K_L(1 - e^{-\delta_L M})L$		Death of CD8 ⁺ T cells due to chemotherapy toxicity	
	K_L	Rate of CD8 ⁺ T-cell depletion from chemotoxicity 4.524×10^{-1} (Day ⁻¹)	[30]
	δ_L	Chemotherapy toxicity coefficient 2×10^{-1} (L mg ⁻¹)	[29]
$\frac{p_I LI}{g_I + I}$		Stimulatory effect of IL-2 on CD8 ⁺ T cells	
	p_I	Rate of IL-2 induced CD8 ⁺ T-cell activation 2.4036 (Day ⁻¹)	[11]
	g_I	Concentration of IL-2 for half-maximal CD8 ⁺ T-cell activation 2.5036×10^3 (IU L ⁻¹)	[11]

Descriptions of the biological relevance of each term and parameter and the parameter values in $L(t)$, which tracks the concentration of CD8+ T cells.

Table 4: Lymphocyte Equation Terms and Parameters.

Term	Parameter	Description and Value (Units)	Source
α		Lymphocyte synthesis in bone marrow	
	$\frac{\alpha}{\beta}$	Ratio of rate of circulating lymphocyte production to turnover rate 3×10^9 (Cells L ⁻¹)	[31]
$-\beta C$		Lymphocyte turnover	
	β	Rate of lymphocyte turnover 6.3×10^{-3} (Day ⁻¹)	[11]

Table cont'd on next page.

Table 4 – continued from previous page

Term	Parameter	Description and Value (Units)	Source
$-K_C(1 - e^{-\delta_C M})C$		Death of lymphocytes due to chemotherapy toxicity	
	K_C	Rate of lymphocyte depletion from chemotherapy toxicity	
		5.7×10^{-1} (Day ⁻¹)	[30]
	δ_C	Chemotherapy toxicity coefficient	
		2×10^{-1} (L mg ⁻¹)	[29]

Descriptions of the biological relevance of each term and parameter and the parameter values in $C(t)$, which tracks the concentration of other lymphocytes.

Table 5: Interleukin-2 Equation Terms and Parameters.

Term	Parameter	Description and Value (Units)	Source
$-\mu_I I$		IL-2 turnover	
	μ_I	Rate of excretion and elimination of IL-2	
		11.7427 (Day ⁻¹)	[11]
ϕC		Production of IL-2 due to naive CD8 ⁺ T cells and CD4 ⁺ T cells	
	ϕ	Rate of IL-2 production from CD4 ⁺ /naive CD8 ⁺ T cells	
		1.788×10^{-7} (IU Cells ⁻¹ Day ⁻¹)	[11]
$\frac{\omega I I}{\zeta + I}$		Production of IL-2 from activated CD8 ⁺ T cells	
	ω	Rate of IL-2 production from CD8 ⁺ T cells	
		7.88×10^{-2} (IU Cells ⁻¹ Day ⁻¹)	[11]
	ζ	Concentration of IL-2 for half-maximal CD8 ⁺ T-cell IL-2 production	
		2.5036×10^3 (IU L ⁻¹)	[11]

Descriptions of the biological relevance of each term and parameter and the parameter values in $I(t)$, which tracks the concentration of interleukin-2.

Table 6: Medication Equations Terms and Parameters.

Term	Parameter	Description and Value (Units)	Source
Chemotherapy		Excretion and elimination of chemotherapy	
$-\gamma M$		Rate of excretion and elimination of chemotherapy drug	
	γ		

Table cont'd on next page.

Table 6 – continued from previous page			
Term	Parameter	Description and Value (Units)	Source
		4.077×10^{-1} (Day ⁻¹)	[30]
mAb Therapy			
$-\eta A$	η	Excretion and elimination of mAbs Rate of mAb turnover and excretion 1.386×10^{-1} (Day ⁻¹) ^a 9.242×10^{-2} (Day ⁻¹) ^b	[23] [23]
$-\lambda T \frac{A}{h_2+A}$	λ	Loss of mAbs due to tumor-mAb binding Rate of mAb-tumor cell complex formation 8.9×10^{-14} (mg Cells ⁻¹ L ⁻¹ Day ⁻¹) ^a 8.6×10^{-14} (mg Cells ⁻¹ L ⁻¹ Day ⁻¹) ^b	[32] [32]
	h_2	Concentration of mAbs for half-maximal EGFR binding 4.45×10^{-5} (mg L ⁻¹) ^a 4.3×10^{-5} (mg L ⁻¹) ^b	[32] [32]

Descriptions of the biological relevance of each term and parameter and the parameter values in $M(t)$ and $A(t)$, which track the concentration of chemotherapy and mAb therapy, respectively.

^a For cetuximab.

^b For panitumumab.

Competing interests

The authors declare that no competing interests exist.

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