

## Research Article

# Computational Simulation of Tumor Surgical Resection Coupled with the Immune System Response to Neoplastic Cells

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Numerous mathematical and computational models have arisen to study and predict the effects of diverse therapies against cancer (e.g., chemotherapy, immunotherapy, and even therapies under research with oncolytic viruses) but, unfortunately, few efforts have been directed towards development of tumor resection models, the first therapy against cancer. The model hereby presented was stated upon fundamental assumptions to produce a predictor of the clinical outcomes of patients undergoing a tumor resection. It uses ordinary differential equations validated for predicting the immune system response and the tumor growth in oncologic patients. This model could be further extended to a personalized prognosis predictor and tools for improving therapeutic strategies.

## 1. Introduction

The most recent mathematical models are relegating Gompertzian growth curves out of tumor growth modeling. Gompertzian growth strongly depends on time [1], and it can be demonstrated that this leads to artifacts in tumor growth models working with external perturbations, that is, any given therapy. Thus, ordinary differential equations (ODEs) that resemble more the behavior of perturbed tumors [2–4] also share more similarities with the ODEs from the Lotka-Volterra predator-prey model and with the logistic curve described by Verhulst. These ODEs are less time-dependent and focus on interactions among different populations and the carrying capacity of the system [5]. Other approaches for modeling tumor growth use complexity models [6, 7] or physically based models [8, 9], although they have been applied less on therapeutic models than ODEs.

Metastasis, the spread of the malignant cells through the body, causes the degeneration of different body functions, depending on the systems affected. Some of the computational models for metastasis are (a) those belonging to the field of complexity—where discrete models based on single cell interactions have been developed [10]—and (b) models

with ODEs [11, 12]. These models are useful for predicting outcomes for patients under antimetastatic drugs therapies.

Another important factor affecting the dynamics of the tumor is the immune system. De Pillis et al. developed a model that includes as input some features of natural killer cells (NK) and T CD8+ cells (TCD8), as well as the tumor growth rate. NK and TCD8 cells mediate most of the immune response against tumor growth. This model was incorporated into another one that was able to predict clinical outcomes in patients receiving immunotherapy. Interestingly, this model neglects metastasis but obtains clinically significant data [13].

Tumor resection, although a traditional treatment for cancer that is still applied as a treatment for some types of cancer, is a therapy whose mathematical modeling has not been fully developed. Remarkably, a biophysical model correlates histopathology findings with nutrient diffusion of tumor cells, thus permitting a prediction of the required tumor surgical resection for enhancing the probability of total remission [14]. Also, some studies in the field of probability predict the necessity of radiotherapy in postsurgical oncologic patients [15]. However, there are no models with ODEs or in the field of complexity, even though much clinical data have been recollected about tumor resection. It is well known that

many tumor surgeries lead to recurrence, and the most accepted mechanism for this is that resections are not always complete, so that negative surgical margins are critical for ensuring a better resection [16]. Also, deliberated partial resections are common, particularly when the tumor is located in organs whose function's maintenance is necessary (e.g., kidney, brain) [16, 17].

In this study, De Pillis et al. ordinary differential equations were coupled with a computational model of tumor resection to observe if the response of the immune system could be modified by a resection of a massive percentage of the tumor. This is a novel study using ODEs for modeling the immune system and tumor partial resection as perturbations on a tumor.

## 2. Methodology

Using Python 2.7 a program was developed to integrate the ODEs describing the immune system, the tumor, and their interactions. From De Pillis et al.,

$$\begin{aligned} \frac{dT}{dt} &= aT(1 - bT) - cNT - D, \\ \frac{dN}{dt} &= \sigma - fN + \frac{gT^2}{h + T^2}N - pNT, \\ \frac{dL}{dt} &= -mL + \frac{jD^2}{k + D^2}L - qLT + rNT, \end{aligned} \quad (1)$$

where

$$D = d \frac{(L/T)^\lambda}{s + (L/T)^\lambda} T, \quad (2)$$

where  $t$  is time,  $T$  is the number of tumor cells,  $N$  is the number of NK cells,  $L$  is the number of TCD8 cells, and  $D$  is the fractional cell kill. The other terms are constants describing the characteristics of the immune system and tumor cells and are better defined in the article from the group of De Pillis, although a brief description of them is given in Table 1.

The parameters that predict whether the immune systems response is either competent (i.e., an immune system capable of defeating a malignant tumor) or incompetent (i.e., the opposite, an immune system whose response is not sufficient and would be overwhelmed by a malignant tumor) against the tumor growth were extracted from the same reference and are given in Table 1.

The incompetent immune system was perturbed during tumor growth with a sudden removal of tumor cells at an arbitrary time. It was then observed whether the immune response remained insufficient against the tumor. The time of the surgery and its extent were deliberately changed in different simulations. Thus, the surgery is evidently an algorithm, not an ODE in this model.

## 3. Results

The data from De Pillis et al. for competent and incompetent immune system responses against tumors were reproduced.

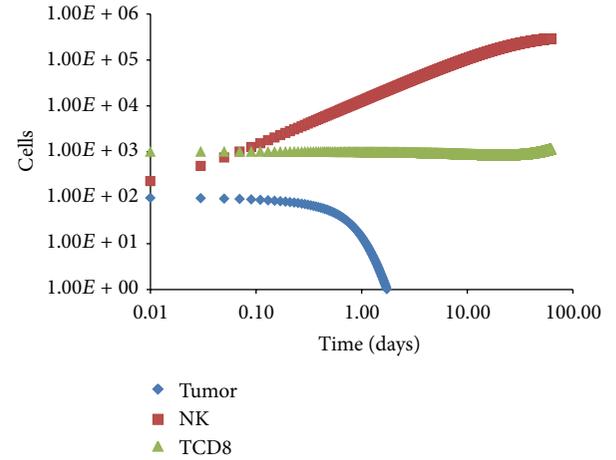


FIGURE 1: Competent immune system versus tumor. NK cell number increase of about 3 orders of magnitude. TCD8 cell increment is less marked, but necessary for an efficient response.

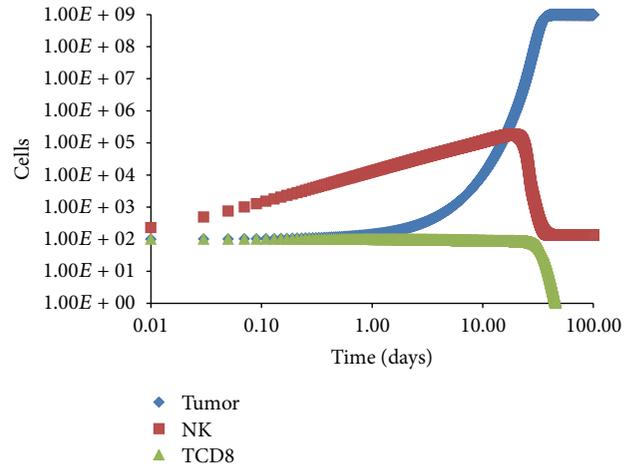


FIGURE 2: Incompetent immune system overwhelmed by a tumor.

The parameters used for the simulations are described in Table 1. When the immune system is overwhelmed by the tumor, a marked decrement of its response is observed, an effect that does not happen in competent immune systems, as shown in Figures 1 and 2. In Figure 1, NK cells exhibit a rapid growth that leads to tumor extinction; interestingly, TCD8 cells number is not modified at a large extent. Nonetheless, TCD8 cell stability is essential for attacking the tumor, as may be seen in Figure 2, where tumor growth elicits a rapid response, at first primarily dependent on NK cells, but with entire collapse of the immune system occurring at around day 20.

Remarkably, when the incompetent immune system is perturbed with a partial but important surgery, an inflection in the remaining tumor cells is observed with practically the same immune response, which does not modify (Figure 3). However, the immune system collapse observed in Figure 2 is not reproduced when the surgery is performed. The key

TABLE 1: Parameters defining a competent and an incompetent immune system for a given tumor (modified from [13]).

Parameter	Units	Meaning	Competent	Incompetent
$a$	Day <sup>-1</sup>	Tumor growth rate	$5.14 \times 10^{-1}$	$5.14 \times 10^{-1}$
$b$	Cell <sup>-1</sup>	$1/b$ is tumor carrying capacity	$1.02 \times 10^{-9}$	$1.02 \times 10^{-9}$
$c$	Cell <sup>-1</sup> day <sup>-1</sup>	Fractional tumor cell kill by NK cells	$3.23 \times 10^{-7}$	$3.23 \times 10^{-7}$
$d$	Day <sup>-1</sup>	Saturation level of fractional tumor cell kill by TCD8 cells	5.8	5.8
$\lambda$	None	Exponent of fractional tumor cell kill by TCD8 cells	1.36	1.36
$s$	None	Steepness coefficient of the tumor-TCD8 cells competition	2.5	2.5
$\sigma$	Cells day <sup>-1</sup>	Constant source of NK cells	$1.3 \times 10^4$	$1.3 \times 10^4$
$f$	Day <sup>-1</sup>	Death rate of NK cells	$4.12 \times 10^{-2}$	$4.12 \times 10^{-2}$
$g$	Day <sup>-1</sup>	Maximum NK cell recruitment rate by tumor cells	$2.5 \times 10^{-2}$	$2.5 \times 10^{-2}$
$h$	Cell <sup>2</sup>	Steepness coefficient of the NK cell recruitment curve	$2.02 \times 10^7$	$2.02 \times 10^7$
$p$	Cell <sup>-1</sup> day <sup>-1</sup>	NK cell inactivation rate by tumor cells	$1.0 \times 10^{-7}$	$1.0 \times 10^{-7}$
$m$	Day <sup>-1</sup>	Death rate of TCD8 cells	$2.0 \times 10^{-2}$	$2.0 \times 10^{-2}$
$j$	Day <sup>-1</sup>	Maximum TCD8 cell recruitment rate	$3.75 \times 10^{-2}$	$3.75 \times 10^{-2}$
$k$	Cell <sup>2</sup>	Steepness coefficient of the TCD8 cell recruitment curve	$2.0 \times 10^7$	$2.0 \times 10^7$
$q$	Cell <sup>-1</sup> day <sup>-1</sup>	TCD8 cell inactivation rate by tumor cells	$3.42 \times 10^{-10}$	$3.42 \times 10^{-10}$
$r$	Cell <sup>-1</sup> day <sup>-1</sup>	Rate at which tumor-specific TCD8 cells are stimulated to be produced as a result of tumor cells killed by NK cells	$1.1 \times 10^{-7}$	$1.1 \times 10^{-7}$
$T(0)$	Cells	Initial number of tumor cells	100	100
$N(0)$	Cells	Initial number of NK cells	200	200
$L(0)$	Cells	Initial number of TCD8 cells	1000	100

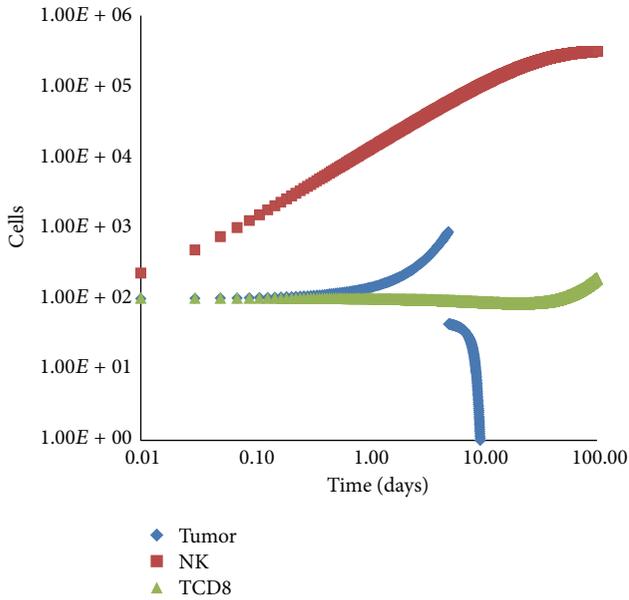


FIGURE 3: The same incompetent immune system depicted in Figure 2, plus a 95 percent resection at day 5; an inflection in the tumor growth curve is seen after the surgery.

finding is that this more vulnerable system is capable of reducing the remaining tumor cells.

In order to recognize the extent and the time of the surgery as important variables when a tumor surgical resection is performed, different percentages of tumor removal and

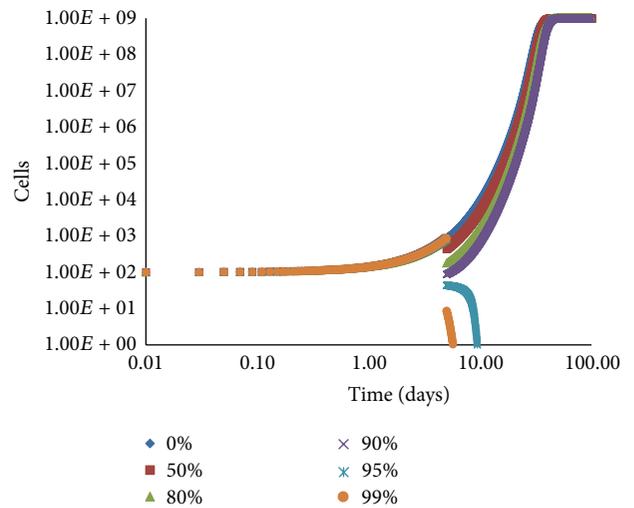


FIGURE 4: Tumor growth resulting from different percentages of tumor resection: 0, 50, 80, 90, 95, and 99% of the tumor, but with the same immune system as in Figure 2 and all of them at day 5.

times for surgery were tested (Figures 4 and 5, resp.). At day 5, and for the same immune system response seen in Figure 2, only surgeries that remove 95% or more of the tumor would cure the patient (assuming that no other intervention is performed) (Figure 4). On the other hand, a 95% resection would only cure the patient if it is performed earlier than day 10 (Figure 5).

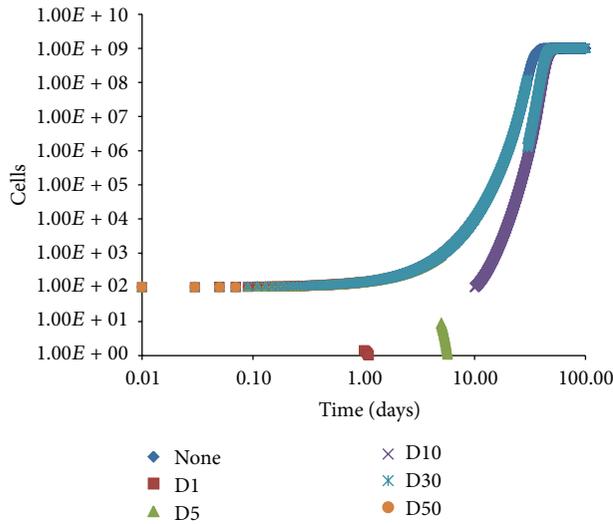


FIGURE 5: Tumor growth for resections at days 1, 5, 10, 30, and 50; the extent of the surgery was set at 95% and the immune system is the same as that shown in Figure 2.

#### 4. Discussion

A decline in tumor growth could not be elicited by the immune system in every case. In Figure 1, a sufficient immune response performed by a competent immune system leads to the inhibition of the tumor. However, a partial but sufficient surgery may reverse the overwhelming of the immune system response when otherwise it would be incompetent (e.g., Figures 2 and 3). When the surgery was implemented, the most important variables turned out to be (a) the tumor size at the time of the surgery, which is a variable dependent on the time of the surgery, as can be seen in Figure 5, where only resections performed before tumor growth reaches a significant inflexion point are curative; (b) the extent of the surgery: Figure 4 shows how resections reducing the number of tumor cells below a critical number (50 cells for this particular tumor interacting with this particular immune system) may lead to total remission; and (c) the immune system response at the time of the surgery, which was found to be equivalent to the number of cells in the immune system, which only defines a higher or lower critical tumor mass (data not shown). Interestingly, clinical data from a study with resection of different percentages of the tumor highly resembled this data: only resections spanning 90% or more of the tumor volume were likely to lead to a total remission of abdominal Burkitt's lymphoma; this can be seen in Figure 4 [18]. It must be noted that in the simulation depicted in Figure 5 the critical number of cells (a threshold that, if trespassed, will lead to a massive growth of the tumor) is consistent with that in Figure 4. This effect shows that the time of resection is not by itself a prognostic factor.

The assumptions taken by this model define its limitations. It does not take into account metastasis, adjuvant chemotherapy, or tumor angiogenesis. Nonetheless, studying a single variable in this case would be more reliable. Thus, this model would work better for predicting the behavior

of tumors in which angiogenesis and metastasis may be neglected. This is an evident limitation when predicting outcomes distant in time. Hence, this model would work better for predicting clinical events foreseen to occur soon when considering tumors that metastasize, since the possibility of distant metastasis increases with time. Although the timing of the interventions in this model is early, it must be taken into account that the patients from [13] had an advanced disease. This does not diminish the reliability of the model, as it may be personalized to every patient. On the other hand, it could be difficult to estimate the proportion of the tumor extracted. This problem may be avoided since a correlation exists between the volume of the tumor and the number of cells in the tumor, and computed tomography can estimate tumor volume accurately [19]. Diffusion-tensor magnetic resonance may even estimate brain tumor cellularity precisely [20].

This study was performed on a validated model of immune system against tumor growth and could be further developed to consider metastasis, chemotherapy, and any other therapy for every individual case. This will bring a more personalized health care and prognosis depending on more than population statistic variables, as in the prevalent prognosis calculation [21]. Besides this, it would be highly beneficial if surgeons could be aided with computer programs for improving the patients' follow-up and scheduling subsequent surgeries based on evidence.

#### 5. Conclusion

A novel computational model is hereby proposed, which predicts the interaction of tumors and immune system response and their behavior after a partial surgical resection using ordinary differential equations. It was shown that a partial but sufficient surgery could help the immune system defeat a tumor *in silico*. Otherwise, the immune system explored would have collapsed and been incapable of eradicating the neoplasm.

Further research is needed in order to improve prognostic tools and therapeutic strategies using computational models predicting clinical outcomes of patients with cancer. This computational model requires clinical validation, although it is based on a model of immune system that correlated well with the outcomes of patients with cancer. Moreover, ODEs should be tested, for example, against stochastic differential equations, in order to assess their reliability.

#### Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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