A Validated Mathematical Model of Cell-Mediated Immune Response to Tumor Growth by L.G. de Pillis et al.: an expository review

Yeting Li, Jonathan Zhu

December 16, 2021

Abstract

A Validated Mathematical Model of Cell-Mediated Immune Response to Tumor Growth [2] by L.G. de Pillis et al. is an article of original research in mathematical biology published in 2005 in the journal *Cancer Research*. A team of 3 co-authors develop a model for the immune response to tumor growth. The model is original in that it introduced a new functional form for the $CD8^+$-tumor kill term. Using data from two previous studies [3, 4], the authors build a mechanistic model that accounts for the relationships between tumor cells, Natural Killer cells, and $CD8^+$ T cells. Three first order ordinary differential equations (one per type of cell) describe the immune system mechanism in response to tumor cells. The authors determine the parameters by fitting the equation to data using a least-squares method and numerical differential equations solver. The results highlight the importance of $CD8^+$ T cell activation in cancer therapy. The article has been cited 314 times to date and has been used for further research on tumor-immune system interactions.

1 The journal and authors

The article *A Validated Mathematical Model of Cell-Mediated Immune Response to Tumor Growth* [2] is an article of original research in the field of mathematical biology. It was published in September 2005 in the journal *Cancer Research*, a peer-reviewed journal that publishes original and review articles on all aspects of cancer. Particular emphasis is given to the pathobiological foundations of cancer, as well as the translational study of cancer to inform public health action. The journal publishes biweekly and has one volume per year. It has an impact factor of 12.701 (2020).

The article is co-authored by two biomathematicians and one oncologist. The first author is Dr. Lisette G. de Pillis. She holds a Ph.D in mathematics from the University of California at Los Angeles in the United States. Her research interests include applications of math to solve real-life problems in biology with a focus on cancer and HIV. Dr. de Pillis is currently a Mathematics Professor at Harvey Mudd College.

The other 2 co-authors are:

- Dr. Ami E. Radunskaya, biomathematician,
- Dr. Charles L. Wiseman, oncologist.

2 The article

2.1 Background, purpose, scope

The article *A validated Mathematical Model of Cell-Mediated Immune Response to Tumor Growth* is in the field of biomathematics, a field of research that uses mathematical models to study biology. The

authors assume that readers are familiar with the following terms used in biology:

- **Tumor.** An abnormal mass of tissue that results from excessive cell division that is uncontrolled and progressive.
- **Natural killer cell (NK cell.)** Lymphocytes of the innate immune system that circulate in the body seeking out infected and cancerous cells. When they encounter an abnormal cell, natural killer cells secrete cytotoxic granules to destroy the cell and limit the spread of infection or disease in the body.
- **CD8$^+$ T cell.** Part of the adaptive immune system that attacks invading pathogens and infected host cells after recognition of abnormal cells.
- **Lysis** The destruction of cell via breakdown of its plasma membrane.

The scope of the research is twofold:

1. Describe tumor-immune interactions with focus on the role of NK cells and CD8$^+$ T cells.
2. Use a system of differential equations to present tumor immune growth, response, and interaction rates, as well as associated variables.

2.2 Literature review and originality

This article is not the first attempt to mathematically model tumor growth and treatment. A number of researchers using a variety of models over the past decades approach the dynamics of tumor growth under treatment. The authors specifically cite the following models, which they used to build their own, improved model:

- In 1986, Coldman AJ and Goldie JH published an article titled *A Stochastic Model for the Origin and Treatment of Tumors Containing Drug Resistant Cells* [1], where they use a stochastic model to understand the dynamics of tumor growth under chemotherapy, particularly focusing on the presence of drug-resistant mutants and their influence on eventual treatment outcomes.
- In 2001, de Pills L and Radunskaya A published an article titled *A Mathematical Tumor Model with Immune Resistance and Drug Therapy: an optimal control approach* [2] where they model tumor growth under chemotheraphy and an immune system response. Furthermore, it shows that optimal control therapy is able to drive the system into a desirable basin of attraction, whereas traditional pulsed chemotherapy is not.
- In 2004, Lin AH published an article *A Model of Tumor and Lymphpcyte interaction* [6], where she uses the predator-prey model to analysis the tumor growth and immune system response. The model accounts for many observed tumor behaviors: regions of uncontrolled tumor growth, tumor extinction in finite time, and irreversible lymphocyte decline.

The mathematical structure of the model builds on earlier modeling from previous studies that are mentioned above. The new model describes the immune-tumor interaction, focusing on the role of NK cells and CD8$^+$ T cells. Based on the previous studies, the authors extend earlier mathematical model from the work of de Pillis et al. [2, 5] to lower-dimensional models. In other words, the authors consider the factor that different cell populations interact with each other. Furthermore, in the process of building the model, the authors need to determine the fractional cell kill dynamics. It is assumed that the fractional cell kill term for the immune cells is proportional to the size of the immune cell population. However, the authors discover that the assumption could be applied to NK cells, whereas

it is not consistent with the data for tumor-specific $CD8^+$ T cells. The authors identify the problem and introduce a new functional form for the $CD8^+$ T cell-tumor kill term, represented by D in the equation, which will be explained further in subsection 2.4.3.

2.3 Data

The data used to develop the model was taken from mouse data collected in a publication by Diefenbach et al. [3]. The mouse data was the rejection of tumors mediated by NK cells and $CD8^+$ T cells in syngeneic mice. The authors also used the human data collected in a publication by Dudley et al. [4] to validate the efficacy of the model. The human data was collected with patients who had metastatic melanoma and were treated with tumor-infiltrating lymphocytes. One example of the patient data is demonstrated in Figure 1.

The authors borrowed some parameter values used in this paper and estimated others from these data using MATLAB6 optimization software. They also used data from this publication on specific lysis rates of RMA cells (a cell commonly used in lab experiments) by ligand- and non-ligand-transduced NK and $CD8^+$ T cells, with ligand-transduced cells being cells with large specific biomolecules on their outer membrane.

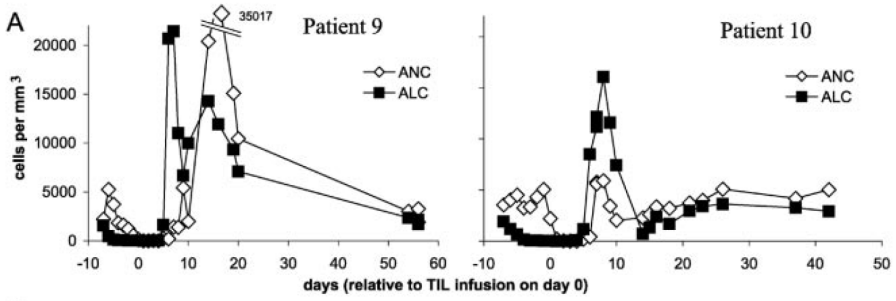

Figure 1: Example Human data from [4] that two patients exhibited a profound lymphocytosis after treatment. ALCs and absolute neutrophil counts are plotted overtime.

2.4 Methods

The authors build a mechanistic model to describe the dynamics of tumor growth with NK cells and $CD8^+$ T cells. The model consists of 3 first-order ordinary differential equations.

2.4.1 Model Description

The model divides the dynamic of tumor growth into 3 compartments. Individuals belongs to one of the 3 compartments, according to their relationship to the tumor. The 3 compartments are:

- Tumor cells (T): the growth of the tumor cells,
- NK cell (N): the growth of the population of the Natural Killer cells.
- $CD8^+$ T cell (L):the growth of the population of the $CD8^+$ T cell.

The relationship diagram between tumor cells, NK cells, and the $CD8^+$ T cell in Figure 2. Three differential equation (one per type of cells) describe the mechanisms of the growth growth with immune system response.

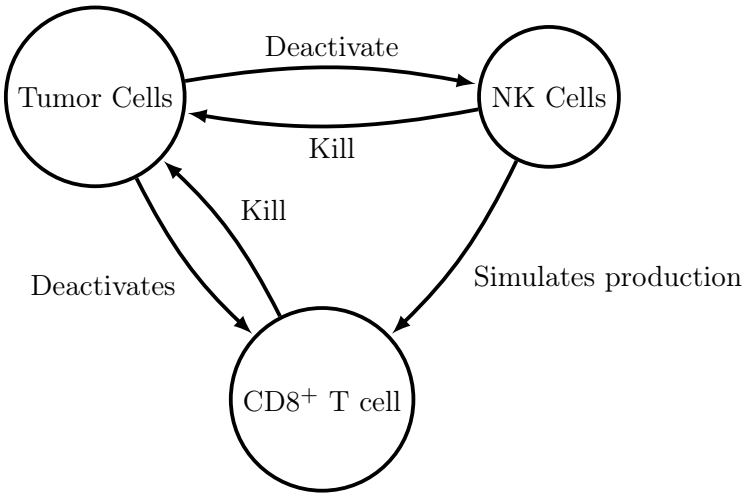

Figure 2: Relation diagram between tumor cells and immune cells.

2.4.2 Modeling assumptions

The authors make several modeling assumption to define the variables and write the differential equations:

1. The tumor cells grow logistically in the absence of an immune response.
2. Both NK cells and $CD8^+$ T cell can kill tumor cells.
3. Both NK cells and $CD8^+$ T cell respond to tumor cells by increasing metabolic activity and releasing various lymphokines.
4. As part of innate immunity, NK cells are always present and active in the system, even in the absence of tumor cells.
5. As part of specific immunity, $CD8^+$ T cells are recruited once tumor cells are present.
6. Each NK cell and $CD8^+$ T cell will eventually become inactivated after some number of encounter with tumor cells.

2.4.3 Model Equations

The first equation modeling the growth of the tumor is given as follows:

$$\frac{dT}{dt} = aT(1 - bT) - cNT - D$$

where

- T is the number of tumor cells at a given time,
- $aT(1 - bt)$ represents the logistic growth of the tumor given no immune response (assumption 1),
- $-cNT$ represents the tumor cells killed by NK cells (assumptions 2 and 3),
- D represents the fractional cell kill term by $CD8^+$ T cells (assumptions 2 and 3), given as

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

The rational form of this term is part of the originality of this model; previous models utilized a power form kill term, but the authors found that the rational kill form fits the experimental data better than the power form. Secondly, the equation modeling the growth of the NK cell population is given as follows:

$$\frac{dN}{dt} = \sigma - fN + \frac{gT^2}{h + T^2}N - pNT.$$

The equation consists of two linear terms: σ, the constant source of NK cells (assumption 4), and $-fN$, the NK cells that die. The meaning of the other terms are defined below:

- $-pNT$ is a mass-action interaction, or a constant product of two variables; it represents the inactivated NK cells (assumption 6).
- $\frac{gT^2}{h+T^2}N$ is of the Michaelis-Menten form and represents the newly recruited NK cells. It details the rate of a reaction given the concentration of tumor cells (T^2) and the maximum recruitment rate of NK cells (g). This term approaches an asymptote, which represents full saturation of a mediating enzyme (a catalyst that speeds up the recruitment of NK cells).

Finally, the equation modeling the growth of the $CD8^+$ T cell population is given as follows:

$$\frac{dL}{dt} = -mL + \frac{jD^2}{k + D^2} - qLT + rNT.$$

The equation similarly consists of

- $-mL$, the linear term , the number of T cells that die;
- $\frac{jD^2}{k+D^2}$, the Michaelis-Menten term , the newly recruited $CD8^+$ T cells (assumption 5);
- $-qLT$, the two mass-action interaction terms , the $CD8^+$ T cells that are inactivated (assumption 6);
- rNT, the newly-produced tumor-specific T cells.

2.4.4 Solution Methods

A large portion of the model was solved using a least-squares solver and computational software; exact details on how the model was solved were not fleshed out given that the journal is a primarily biological journal and its readers would not be as interested in reading in-depth how the model was solved.

2.5 Results and Discussion

2.5.1 Model Validation

Firstly, the authors determine the efficacy of the NK model in Figure 3. They compare the predictions of the model to experimental data for the lysis rates of RMA cells (a type of experimental cell usually used in lab studies) by NK cells, both ligand- and non-ligand-transduced; the experimental data matches well with the model's predictions, thus affirming its efficacy.

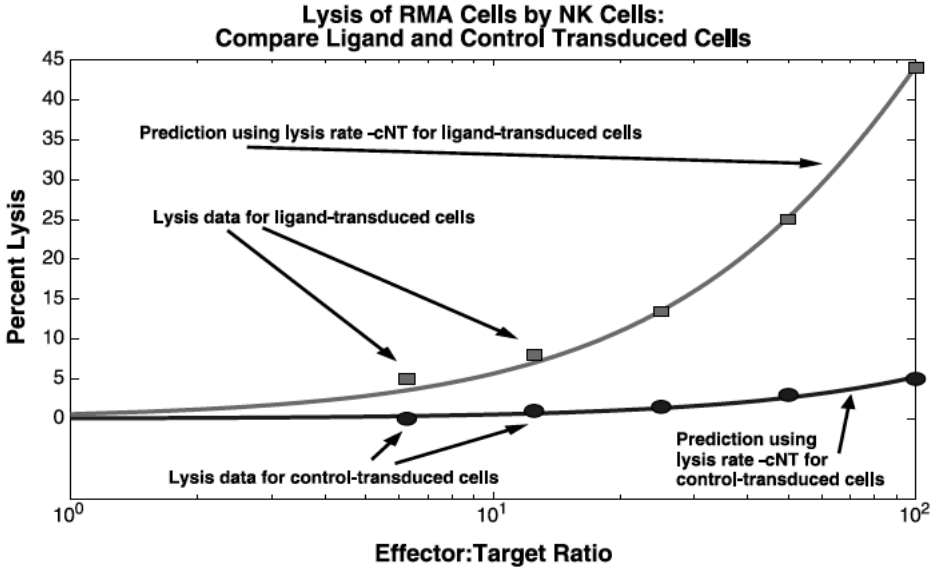

Figure 3: Comparison of the model predictions to experimental data for the lysis of experimental RMA cells by NK cells for both ligand-transduced and non-ligand-transduced cells. From dePillis et al., A Validated Mathematical Model of Cell-Mediated Immune Response to Tumor Growth (2005), Cancer research, 65(17), 7950-7958.

2.5.2 Functional Form

Similarly, the authors determine the efficacy of the $CD8^+$ T cell model's rational kill term (D). To do this, they similarly plotted the model's predictions with experimental data (Figure 4), both for previous power law models and their new rational kill law, as well as for both non-ligand-transduced and ligand-transduced. There is a noticeably better fit for experimental data with ligand-transduced cells with the rational kill law, supporting it as a more effective model.

Further supporting the efficacy of the rational kill law are an error analysis and a comparison between the model and human data. The error analysis shows high error levels between the power law predictions and experimental data for ligand-transduced cells, while the comparison to the human data shows that the rational law matches the human data, further supporting the efficacy of the model.

2.5.3 Sensitivity Analysis

Next, the authors conduct a sensitivity analysis. By changing each of the parameters in each of the model's equations by small amounts, the authors analyze which small change has the most substantial effect on the tumor's size. The full sensitivity analysis is given in Figure 5; the authors found a (tumor growth rate) and λ (exponent of the fractional cell kill by $CD8^+$ T cells) to be the most significant parameters in determining the size of the tumor.

2.5.4 Simulation of Human Data

Finally, the authors simulate cancer treatments with their model. These treatments consist of cells (both ligand- and non-ligand-transduced cells) being injected into simulated systems, with non-ligand-transduced cells injected into both systems after 10 days. These simulations show that with

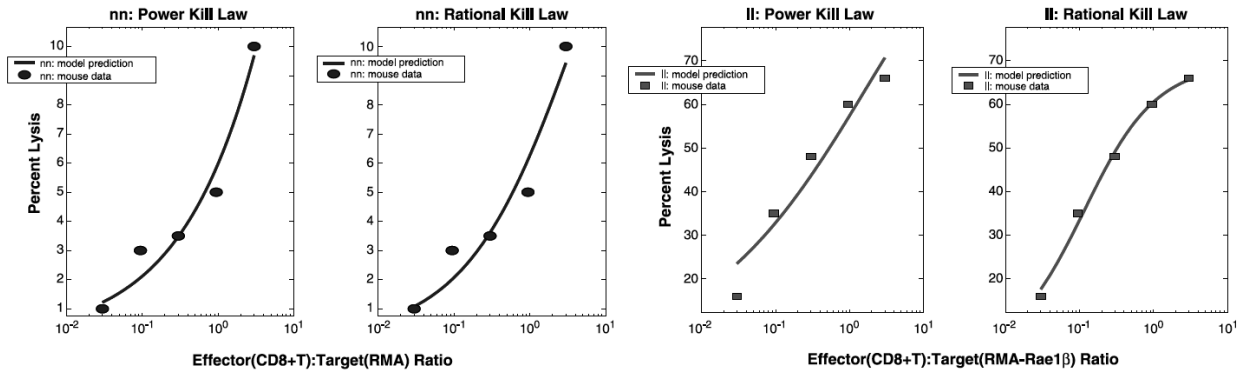

Figure 4: Comparison of the model predictions to experimental data for the tumor cell kill by $CD8^+$ T cells, for previously used power law models (far left and middle right) and the original rational law model (middle left and far right) as well as for both non-ligand-transduced (far left and middle left) and ligand-transduced (middle right and far right) cells. From dePillis et al., A Validated Mathematical Model of Cell-Mediated Immune Response to Tumor Growth (2005), Cancer research, 65(17), 7950-7958.

ligand-transduced cells, the tumor size is effectively reduced to zero. Similarly, the authors simulate treatments with only NK cells, only $CD8^+$ T cells, and with both present to determine the maximum tumor size each type of cell could support on their own. They find that while $CD8^+$ T cells alone can remove a larger tumor than NK cells alone, both working in tandem produces the most powerful immune response.

3 Conclusion

The model presented many strengths, including that it fit experimental data well. This was especially true with the new rational kill term D. In addition, it also agreed with previous models, and it highlighted the importance of researching the interactions of NK and $CD8^+$ T cells in investigating cancer treatments, especially since these were the main attackers of tumor cells in the model.

However, the authors posed some self-criticisms of their model, two of them being that it does not account for immune system self-regulation or down-regulation of immune responses. In other words, the authors did not take into account real-world immune system actions, which involve reaching a maximum response before reducing its response; instead, the authors assumed the immune system response to be theoretically infinite and always increasing.

Several suggestions for future research arise from this paper's discussion. One main suggesting is laboratory tests to further research the cell dynamics between NK and $CD8^+$ T cells, which is especially important not only in further supporting the efficacy of this model and future models but also in investigating cancer treatments. Secondly, the authors suggested that cancer treatments be developed specifically based on ligand-transduced $CD8^+$ T cells, as the presence of these cells in the model was shown to be highly effective at reducing the tumor's size to zero.

4 Impact

This article is a highly impactful article, with a citation count of 314 as of 2021. Many of the articles that cite this article were written fairly recently, with quite a few being written in 2021.

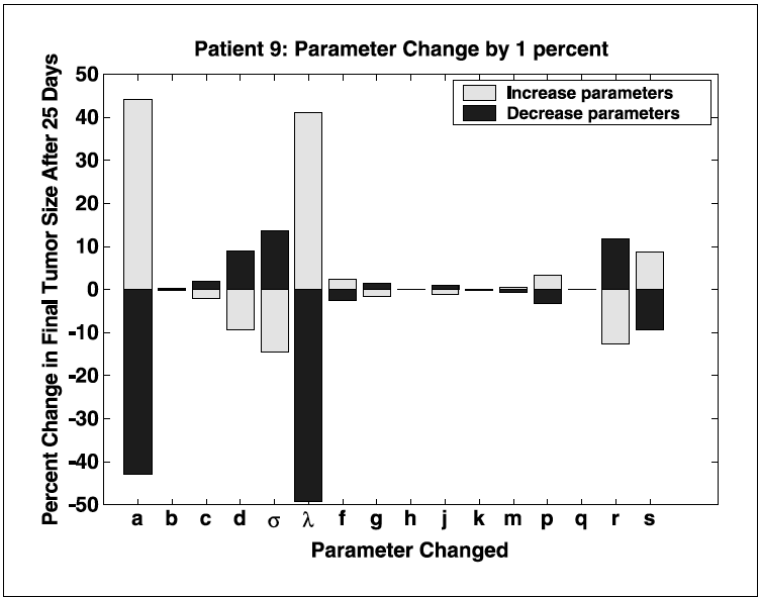

Figure 5: Results of the authors' sensitivity analysis of their model, where each parameter was changed by a small amount; the authors then analyzed the effects of these small changes on the final size of the tumor. The most significant parameters were found to be a (tumor growth rate) and λ (exponent of the fractional cell kill by $CD8^+$ T cells). From dePillis et al., A Validated Mathematical Model of Cell-Mediated Immune Response to Tumor Growth (2005), Cancer research, 65(17), 7950-7958.

- In 2021, Dehingia et al. expanded on this model to include the delayed immune response to the tumor in their article titled *Mathematical Analysis of a Cancer Model with Time-delay in Tumor-immune Interaction and Stimulation Processes* [7].
- In 2021, Trobia et al. make the model more specific to drug-senstitive brain tumor growth and include a chemotherapy aspect for the brain tumors in their article titled *Mathematical Model of Brain Tumor Growth with Drug Resistance* [9].
- In 2021, Ghanizadeh et al. expanded on this model to include different phases of cancer treatment in their article titled *Mathematical Modeling Approach of Cancer Immunoediting Reveals New Insights in Targeted-therapy and Timing Plan of Cancer Treatment* [8].

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