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A Mathematical Investigation on Tumor-Immune Dynamics: The Impact of Vaccines on the Immune Response

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Abstract

Mathematical models analyzing tumor-immune interactions provide a framework by which to address specific scenarios in regard to tumor-immune dynamics. Important aspects of tumor-immune surveillance to consider is the elimination of tumor cells from a host's cell-mediated immunity as well as the implications of vaccines derived from synthetic antigen. In present studies, our mathematical model examined the role of synthetic antigen to the strength of the immune system. The constructed model takes into account accepted knowledge of immune function as well as prior work done by de Pillis et al. All equations describing tumor-immune growth, antigen presentation, immune response, and interaction rates were numerically simulated with MATLAB. Here, our work shows that a robust immune response can be generated if the immune system recognizes epitopes that are between 8 to 11 amino acids long. We show through mathematical modeling of how synthetic tumor vaccines can be utilized to mitigate a developing cancer.

Keywords: Tumor-immune dynamics; Immune response; T lymphocytes

Introduction

One effective way to cure disease is to prevent the development of it all together. One modality to combat disease is cancer vaccines that would "program" an individual's immune system to recognize foreign antigens by stimulating cytotoxic T lymphocytes (CTL) to attack cancer cells expressing a certain tumor antigen [1-5]. Current vaccine strategies to combat cancer include vaccines consisting of lymphocytes, which include: helper T lymphocytes (Th), dendritic cells (DC), macrophages, or reprogrammed oncolytic viruses [1,2]. Such vaccines may help deter cancer growth through stimulation of an individual's immune system or by directly attacking a cancer growth [1]. Important questions arise when dealing with the idea of preventative cancer vaccines such as the practicality of utilizing vaccines to prevent the development of cancer as well as how many memory CTL's need to be produced to provide a sentinel within an individual [1,6,7]. Cancer poses many issues to the vaccine development process as it displays the ability of antigen mimicry, a process by which tumor cells produce antigens with specific patterns of the host that can help cancer evade immune processing and development. Tumor antigen mimicry with self-antigen occurs since tumor-specific antigens (TSA) and tumor-associated (TAA) antigens are either mutated or overexpressed self-proteins, respectively (P53 and CEA). This results in active Th cells having a difficult time selecting for self from non-self. In addition, cancer growth displays variation; it may more rapid or slower than that of other disease processes. Such properties can result in a weak immune response. The multitude of complexities associated with cancer as well as its ability to deter host defenses has challenged researchers to seek for alternative therapies to chemotherapeutics due to their harmful side effects upon a host. One approach to treating cancer began in 1909 when the German scientist Paul Ehrlich proposed the "cancer immunosurveillance" hypothesis, which is the idea that the immune system can suppress an overwhelming number of carcinomas [4,8]. This approach was not tested until the 1950's when the field of Immunology advanced. Experiments attempting to show support

utilized mice that were inoculated with chemically-induced cancer cells; such cells lacked the capability to metastasize within a host. Over time, this led to the development of cancer-specific immunity in the recipient mice. This discovery provided the evidence needed for Ehrlich's hypothesis. Such experiments demonstrated that it is essential to have the presence of an antigen to elicit an immune response in the host, because if no distinctive structures exist, then no recognition would be established [9]. F. Macfarlane Burnet and Lewis Thomas, well-known immunologists during the 20th century, hypothesized that for immunosurveillance to exist, lymphocytes would need to act aggressively akin to sentinels to recognize and eliminate a cancer threat. The cancer immunosurveillance theory revolves around three transitions states, denoted as "E's" [9]:

- Elimination- The establishment of a strong cancer surveillance network by both the innate and adaptive immune system that seeks to eliminate cancer populations.
- Equilibrium- The long-term process of combat between a cancer population and a host's immunosurveillance network.
- Escape- The overpowering of cancer surveillance network by strong tumor variants, which results in host death.

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This hypothesis served as a foundation for a previous project inspired by de Pillis et. al. which studied the interactions of cancer and the immune system utilizing mathematical biology [9]. Mathematical Biology is a field of research that draws aspects from both mathematics and the biological sciences to represent, model, and analyze complex biological processes through techniques such as numerical simulations or phase plane analysis [7,10-13]. Mathematical modeling provides insight and validity to a complex biological system for clinical research without the utilization of human or animal models, entirely bypassing ethics boards completely [7,10,12]. Generated data can have similar validity to that of data obtained from human or animal experiments. Describing systems in qualitative and quantitative manners means that behaviors can be simulated and new behaviors that aren't evident to human/animal experimentation can be discovered. Differential equations, for example, can predict how populations can behave by analyzing variables such as time (ordinary differential equations-ODE) or space (partial differential equations) [11,13]. The probability of events can also be utilized within mathematical models through Monte-Carlo Simulations [14-18]. The development of such mathematical models has a wide range of implications including the possibility of discovering hidden behaviors within systems and determining long-term goals of a system. For the scope of this paper, we attempt to illustrate how mathematical modeling can be utilized to predict the strength of a host's immune response to lung cancer using a coupled Monte-Carlo/ordinary differential equation model. Our work is an expanded mathematical model that is based on a previous validated by a prior mathematical model by de Pillis et al. [9]. Her prior work explored the dynamics of tumor rejection, the roles NK and CD8+ T cells, as well as the development of protective immunity to subsequent tumor re-challenges. Her model was validated through comparison of mouse and human data to determine tumor growth and lysis rates. Her model further underwent a sensitivity analysis to determine sensitive aspects that could be patient specific that could be applied to a clinical setting. Her variable analysis suggests which patients could respond to treatment. Our model expands through the incorporation of additional cellular lines; macrophages are introduced to complete the innate immune system perspective and humoral immunity has been expanded upon through the introduction of CD4+, CD8+, and CD4+ T regulatory cell lines in both their dormant and active transitional states. In addition, Interleukin-2 is introduced to see how cytokines impact the immune response. Antigen presenting cells, such as dendritic cells, have also been introduced to see how antigen presentation plays a role in cancer immunosurveillance. While B cells play an important part in the adaptive immune response, this cell line has been excluded for the purposes of this model due to the focus on T cell response and the complexity of the model. We also show how this model can be utilized in a clinical setting to predict the long-term consequences of a patient's cancer status if injected with a vaccine composed of different lung cancer tumor epitopes [13,17,18]. The development of this model focused on first on establishing conditions in which the cancer immunosurveillance hypothesis "exists" through parameter estimations and bifurcation diagrams relating certain parameter families. For details on this work, please refer to the references section. This model then focused on validating which cell lines were the principal cell line in the innate immune, antigen presentation, and cell-mediated responses; of which, NK cells, dendritic cells, and CD8+ cells were key in the immune response against cancer. While not much insight present, validation of theoretical knowledge confirms that the development of the model is the right step. The next step of the model was to introduce "randomization" of the immune response via the introduction of Monte-Carlo simulation processes. Two variables of

the model were introduced as extra equations in the model to simulate the strength of a tumor epitope vaccine that influences the strength of the immune response based on the size of the epitope. The randomness of the model can eventually be utilized in a clinical setting to allow clinicians to prognosticate the long-term health status of a patient after a tumor vaccine is utilized. We developed a mathematical model of tumor dynamics in response to a vaccine injection composed of lung cancer epitopes (Survivin, Kita-Kyushu lung cancer antigen 1 (KKLC1), and epidermal growth factor receptor (EGFR)) of different fragment sizes (8-12 amino acids (aa) long) with the goal of determining which epitopes produce a strong immune response.

Methods

The dynamics of the mathematical model, as well as parameter values, are borrowed from assertions, prior mathematical models, as well as through parameter estimation through numerical simulations. Our model is based on a previous model published by de Pillis et al. [9], but expanded to include simplified T cell development and more cell populations to better depict the immune response to cancer. No patient data was integrated into this model yet as this model is in its infancy; a literature review shows no prior model with an integrated Monte-Carlo simulator. Generated data now is theoretical but has applicability to the clinical setting. The basis for the model is listed below.

Model development

In this study, we developed a mathematical model of tumor dynamics in response to a vaccine injection composed of lung cancer epitopes of different fragment sizes (8-12 amino acids (aa) long) with the goal of determining which epitopes produce a strong immune response [9,13,19,20]. The biological assumptions are taken into consideration during the development of the model, with prior work done by de Pillis et al. [9], and accepted the knowledge of immune function, including the following [21,22]:

- 1) Tumor cells grow in a myriad of ways if there is an absence of an immune response. This assumption is based on previous studies that considered population growth models such as logarithmic, Gompertzian, exponential, etc. Gompertzian growth will be utilized for this model as this correlates with the cancer immunosurveillance hypothesis [1,11,12,23].
- 2) Natural Killer (NK) and CTLs can kill tumor cells [4,11,21,22].
- 3) Tumor cells can elicit endogenous defenses in primed cells [4,11,21,22].
- 4) NK cells are abundant and constantly circulate in the immune system in their non-primed state.
- 5) For cell-mediated immunity, T cells are abundant in their naïve stage and differentiate into CD4, CD8, and CD4 regulatory cells through simplification of the maturation process in the thymus. This model assumes a linear transitional state from the naïve to mature states [1,19,22].
- 6) The activation of cell-mediated immunity (CMI) is regulated by professional antigen presenting cells (APC) such as Langerhans's, B cells, and macrophages [22].
- 7) Activation of naïve T cells is dependent on Michaelis-Menten kinetics.
- 8) IL-2 is secreted by mature T cells to activate and recruit circulating effector cells. The process of recruitment is based upon IL-2

secreted by Th cells that stimulate inactive Th cells, leaving a chemical trail for newly activated ones to return to a site where an infectious process began. There are a finite number of receptors on the cellular surface of a naïve T cell and an IL-2 molecule can be only be bound to one receptor at a time. The model assumes an overabundance of circulating IL-2 molecules [2,11]. For this model, we assume only IL-2 is the principal cytokine abundant in circulation and we opt to ignore the presence of other cytokines.

9) Regulatory T cells (Tregs) are present to decrease the activity of effector and helper T cells. This cell population is minute compare other T cell populations as only a certain subset express CD25 and FoxP3. This population is only present up to 5%. Our model accounts for this fact and incorporates it as a valid assumption [2].

10) Two variables (R_c and M_a) will undergo a Monte-Carlo simulation to simulate possible responses from lung cancer epitopes. A Monte-Carlo simulation was necessary to incorporate into the model since it considers a probabilistic input (tumor antigen size) and turns it into a deterministic output (immune response). Multiple simulations can be run and can determine possible outcomes of an individual's immune profile [2,10,11,12].

11) All immunological recruitment terms are assumed to be of Michaelis-Menten kinetics as they are commonly used in mathematical tumor models that include immune components; a saturation effect is achieved because of this assumption. Here, we assume there are finite cellular receptors for IL-2 and for cellular signaling to transition naïve immune cells to their primed state.

Utilizing the 10 assumptions from above, the system can be described as 13 coupled differential equations (11 coupled equations and 2 "stand-alone" equations) where each equation gives the rate of change of a cell population in terms of growth, death, cell-cell kill, cell recruitment, or cell inactivation. Previous versions of this model studied different aspects of the immune response; for example, CTL's are the primary cell in cell mediated immunity and dendritic cells are the principal cell that bridges the innate and adaptive immune responses [1,7]. This model, now, has been modified further to introduce the addition of lung cancer "vaccines" using Monte-Carlo processes to simulate an antigen stimulation response to different HLA epitopes [9,13,19]. The strength of binding will depend on the generated values of two variables from the Monte-Carlo process. The model is as follows:

$$\frac{dc}{dt} = R_c C \log C - k_1 T_e C - k_3 MC \quad (1)$$

$$\frac{dN}{dt} = B_n - D_n N + \frac{R_n NC}{M_n + C} - L_n Nc \quad (2)$$

$$\frac{dT_n}{dt} = b_t - d_t T_n - \frac{m_a T_n A_p}{mt + A_p} \quad (3)$$

$$\frac{dT_e}{dt} = \frac{m_a T_n A_p}{mt + A_p} - D_t T_e + r_T I_2 T_e - i_H R_e T_e \quad (4)$$

$$\frac{dH_n}{dt} = b_h - d_h H_n - \frac{m_a H_n A_p}{mt + A_p} \quad (5)$$

$$\frac{dH_e}{dt} = \frac{m_a H_n A_p}{mt + A_p} - D_h H_e + r_T I_2 H_e - i_H R_e H_e \quad (6)$$

$$\frac{dI_2}{dt} = C_i I_2 - d_i I_2 - i_H I_2 T_e - i_H I_2 H_e - r_T I_2 R_e \quad (7)$$

$$\frac{dA_p}{dt} = r_a C - d_a A_p \quad (8)$$

$$\frac{dR_n}{dt} = b_r - d_r R_n - \frac{m_a R_n A_p}{mt + A_p} \quad (9)$$

$$\frac{dR_e}{dt} = \frac{m_a R_n A_p}{mt + A_p} - D_h R_e + r_T I_2 R_e \quad (10)$$

$$\frac{dM}{dt} = r_a C - d_n M - l_n MC \quad (11)$$

$$\frac{dr_c}{dt} = 0 \quad (12)$$

$$\frac{dm_a}{dt} = 0 \quad (13)$$

Equation #1 describes the change in the population of a cancerous pathology in which the state variable is C . Cancer populations propagate (r_c) at a fixed rate and die off due to cell-to-cell interactions between NK cells (k_1), CTL's (k_2), and macrophages (k_3).

Equation #2 describes the change of NK cell populations in which the state variable of this equation is (N). NK cells are born at a fixed rate (B_n) and die off (D_n) in proportion to population levels. In addition, NK cells are recruited in response to cancer antigen presentation at a fixed rate (R_n and M_n) as well as die off due to cell-cell interactions with cancer (L_n).

Equation #3 describes the change of naïve CD8 populations in which the state variable of this equation is (T_n). Naïve CD8 populations are born at a fixed rate (B_t) and die off (D_t) in proportion to population levels. Such cells then transition from the naïve to primed states due to cancer antigen acquisition (M_a) by antigen presenting cells at a fixed rate (m_a), which then present the processed cancer antigen to naïve populations.

Equation #4 describes the change of primed CD8 populations in which the state variable of this equation is (T_e). Naïve CD8 populations are primed with cancer antigen transition from their naïve to primed states to combat cancer (first term) and die off (D_e) in proportion to population levels. Primed CTL populations are then influenced due to memory cell recruitment by interleukin-2 (r_T) and are inhibited (i_H) by T regulatory cells.

Equation #5 describes the change of naïve CD4 populations in which the state variable of this equation is (H_n). Naïve CD4 regulatory populations are born at a fixed rate (B_h) and die off (D_h) in proportion to population levels. Such cells then transition from the naïve to primed states due to cancer antigen acquisition (M_a) by antigen presenting cells at a fixed rate (m_a), which then present the processed cancer antigen to naïve populations.

Equation #6 describes the change of primed CD4 populations in which the state variable of this equation is (H_e). Naïve CD8 populations are primed with cancer antigen transition from their naïve to primed states to combat cancer (first term) and die off (D_e) in proportion to population levels. Primed CTL populations are then influenced due to memory cell recruitment by interleukin-2 (r_T) and are inhibited (i_H) by T regulatory cells.

Equation #7 describes the change of interleukin-2 concentration in which the state variable of this equation is (I_2). IL-2 is produced at a constant rate (C_i) by primed immune cells, mainly of HTL lineage, and is consumed in varying proportions (R_h , R_p and R_r) to recruit circulating memory cells to combat cancer populations. In addition, IL-2 denatures (D_i) in proportion to population levels.

Equation #8 describes the change of antigen presenting cells in which the state variable of this equation is (A_p). APC populations are primed (R_a) in direct proportion to cancer antigen and die off (d_a) in proportion to population levels.

Equation #9 describes the change of naive CD4 regulatory populations in which the state variable of this equation is (R_n). Naive CD4 regulatory populations are born at a fixed rate (B_r) and die off (D_r) in proportion to population levels. Such cells then transition from the naive to primed states due to cancer antigen acquisition (M_a) by antigen presenting cells at a fixed rate (M_i), which then present the processed cancer antigen to naive populations.

Equation #10 describes the change of primed CD4 regulatory populations in which the state variable of this equation is (R_c). Naive CD4 regulatory populations are primed with cancer antigen transition from their naive to primed states to combat cancer (first term) and die off (D_c) in proportion to population levels. Primed CTL populations are then influenced due to memory cell recruitment by interleukin-2 (R_i).

Equation #11 describes the change of macrophage populations in which the state variable of this equation is (M). NK cells are primed at a rate (R_a) in proportion to cancer antigen and die off (D_n) in proportion to population levels as well as interactions with cancer cells (L_n).

Equations #12 and #13 act as placeholder equations for two variables (R_c and M_a)—that act as the Monte-Carlo Simulator via a pseudo-number generator that affects the output of the other eleven equations.

A Monte-Carlo simulator was added to the previous version of this model to account for the random strengths of an individual's immune system when an APC encounters a tumor antigen. Selected antigens from the database include EGFR1 and Survivin [18]. Tumor antigens, obtained from Harvard University's TANTAGEN epitope database, are processed via an MHC class I pathway and are random sizes (8-11) amino acids long. In addition, cancer growth rates, although slow, vary from individual to individual [18]. Thus, a simulator (random number generator for both R_c and M_a) was utilized to vary the response of an individual's immune system when exposed to a tumor vaccine or model the immune system once lung cancer is detected. Each tumor antigen selected from TANTAGEN would be simulated through the "Monte-Carlo" simulator on MATLAB and such results would be incorporated into final graphs. Parameters for the model were either estimated or incorporated from another source [20] (Table 1). The above model was then subjected to MATLAB, an open source math modeling program, was utilized to simulate the model, estimate parameter values, as well as determine scenarios in which tumor vaccines produce varying immune responses. Below is a table of all parameters and estimated values.

Results

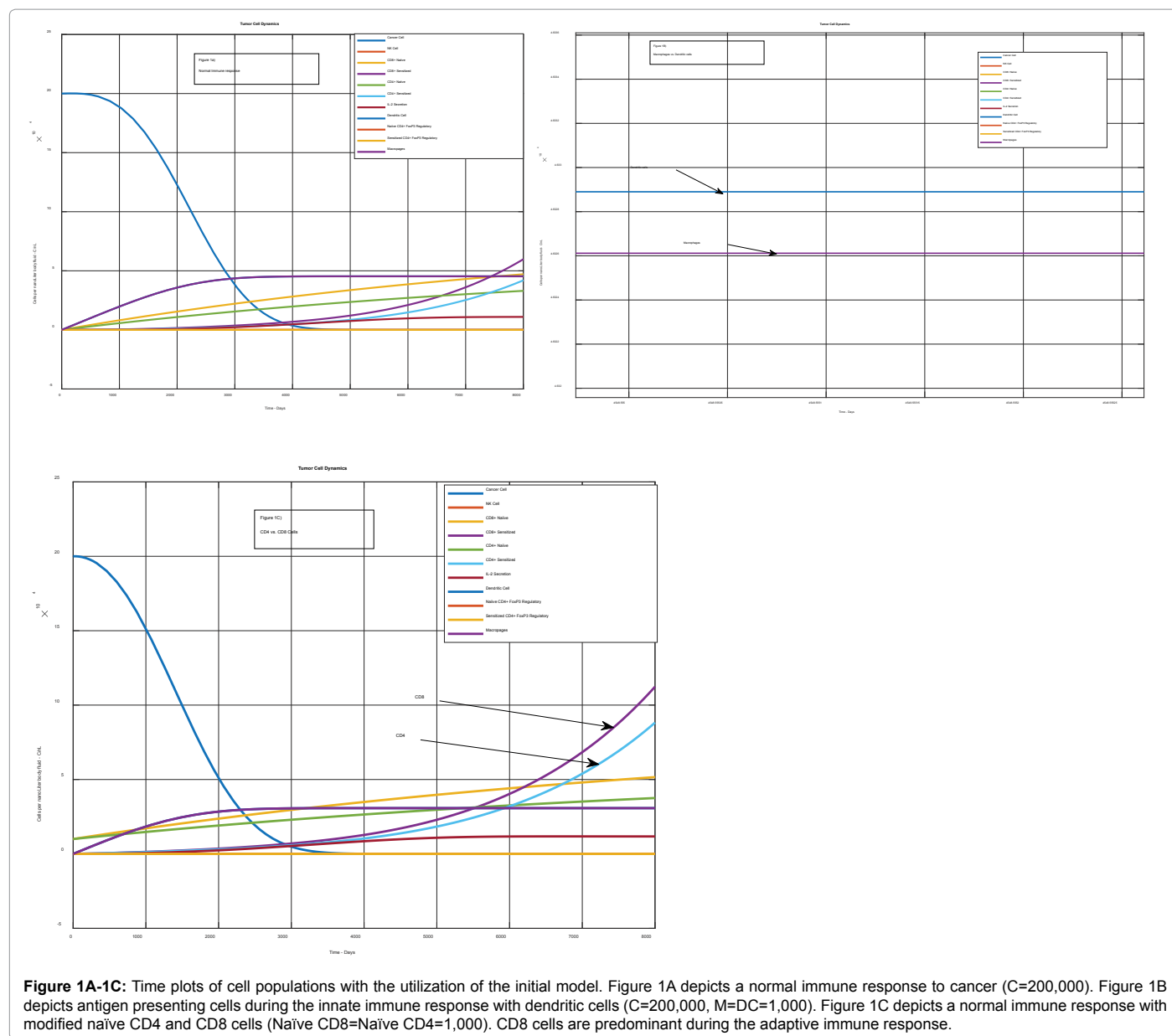
The above model can be utilized to simulate the strength of a host's immune response after he or she is inoculated with a lung cancer vaccine. Results from the model are *in silico*, meaning that results from this model can be applied to a clinical setting, but not to 100% accuracy. Here, the term "injected vaccine" will reference refers to

Parameter and units	Parameter description	Parameter value	Reference or Estimation
R_c (1/day)	Cancer Propagation	$1 \times 10^{-10} < x < 1 \times 10^{-4}$	Estimation
K_1, K_2, K_3, L_n (Cell/day \times nL)	Interaction between cancer, NK, CD8, and Macrophages	3.50×10^{-12}	de Pillis et al. in 2005
		4.60×10^{-7}	
		7.50×10^{-12}	
		1.00×10^{-13}	
B_n (cell/day \times nL)	Birth (fixed) and death rates of NK cells/Macrophages	1.30×10^{-2}	de Pillis et al. in 2005
D_n (1/day)		4.12×10^{-8}	
R_n (1/day)	Recruitment of circulating NK cells	2.50×10^{-8}	de Pillis et al. in 2005
M_n (cell ² /nL)		20.2	
M_a (1/day)	Antigen Presentation	$1 \times 10^{-7} < x < 1 \times 10^{-3}$	Estimation
B_i (cell/nL \times day)	Birth and death rates of naive CD4 cells	8.55	Kim et al. in 2007
D_i (1/day)		3.00×10^{-8}	
D_i (1/day)	Death rates of CD4, CD8, and CD4 regulatory cells	2.00×10^{-8}	Kim et al. in 2007
D_h (1/day)		4.00×10^{-8}	
D_r (1/day)		1.00×10^{-9}	
R_i (cell/nL \times day)	Recruitment rates of CD4, CD8, and CD4 regulatory cells	3.75×10^{-8}	de Pillis et al. 200
R_h (cell/nL \times day)		1.88×10^{-9}	
R_r (cell/nL \times day)		3.75×10^{-8}	
I_i (1/day)	Inhibition of CD4/CD8 Activity by CD4 Regulatory cells.	5.00×10^{-7}	de Pillis et al. 2005
I_n (1/day)			
B_n (cell/nL \times day)	Birth and death rates of naive CD8 cells	6	Kim et al. in 2007
D_n (1/day)		3.00×10^{-8}	
B_r (cell/nL \times day)	Birth and death rates of naive CD4 regulatory cells	4.50×10^{-5}	Kim et al. in 2007
D_r (1/day)		3.00×10^{-8}	
C_i (1/nL \times day)	Production and degradation of IL-2	1.00×10^3	Kim et al. in 2007
D_i (1/day)		1.00×10^{-7}	
R_a (1/day)	Antigen production and death of APCs	1.00×10^{-4}	Kim et al. in 2007
D_a (1/day)		3.00×10^{-8}	

A list of parameters used for the model. Parameter values are indicated to be utilized from another paper or estimated from computer simulations.

Table 1: Parameter descriptions and values.

a computerized simulation of a host's immune response after he or she is inoculated with a vaccine, and then subsequently encounters a tumor antigen once discovered. All images depicted in this section run on an arbitrary time scale rather than a 24-hour day. This timescale is utilized to provide the basis for how the model can be applied to a clinical setting. Previous versions of this model focused on the "cancer immunosurveillance" hypothesis as well as confirming prior knowledge of established immunological knowledge. A previous version of the model, for example, did not have equations #11-13. The output of previous models, first using GNU Octave, then MATLAB, depicted cancer being eliminated over time coming from a powerful immunological response. With such results and confirmations in mind, the model then focused on the application of vaccines to the immunological host. This model can be used to simulate the relative strength of the immunological response to a cancer population within a host after a tumor vaccine is injected into a host. Relevant parameters to consider that help determine the strength of the immune response include R_c (cancer propagation) and M_a (Antigen presentation) as both variables are important to utilize in the Monte-Carlo Simulator. During the experiment's course, biologically relevant parameter ranges were estimated through multiple simulations with MATLAB. This was necessary to determine what range of values for both variables have



applicability to the clinical setting. Figures 1A-1C establish the basis of the model without the application of a Monte-Carlo simulator. Our model, before the Monte-Carlo simulation was added, was valid through confirmation of prior immunological knowledge; our model demonstrated, for example, that macrophages played more of an active role during the innate immune phase as this cellular population not only could deter cancer to a limited degree but also has the role of acting as a professional Antigen Presenting Cell (APC) along with dendritic (DC) and B cells. Our model also confirmed that the main cell population that bridges between the innate and adaptive immune system is APCs, but the major cellular population involved is DCs. Our model also confirmed that the principal cell that can eliminate cancer is Cytotoxic T-Lymphocytes (CTLs). Such confirmations establish that the model has a basis for the clinical setting. A previous version of this model was also utilized to establish the basis the cancer immunosurveillance hypothesis.

The above images (Figures 1A-1C) are a product of the old model

through expansion of de Pillis et al. model. Here, the model tells a complete story of the cancer immunosurveillance response through multiple perspectives, except for B cells. The ultimate result from all figures is the elimination of a cancerous population. Figure 1B depicts the principal cell that bridges the innate and adaptive immune responses, while Figure 1C depicts the major cell during the immune response; the CD8 response is augmented through CD4 assistance. The next step for this project is to show how it results can be applied to a clinical setting to determine the effectiveness of a cancer vaccine prior to a host developing cancer. For this part of the study, three processed antigens from the TANTIGEN database were utilized for the Monte-Carlo Simulator, which is: 1) Survivin, 2) Kita-Kyushu lung cancer antigen 1 (KKLC1), and 3) Epidermal growth factor receptor (EGFR) [24]. Most of these tumor antigens are processed via an MHC class I pathway which requires HLA (Human Leukocyte Antigen) –A and –B molecules to facilitate the immune recognition process. The size of the tumor antigen, too, plays a role in the strength of the immune

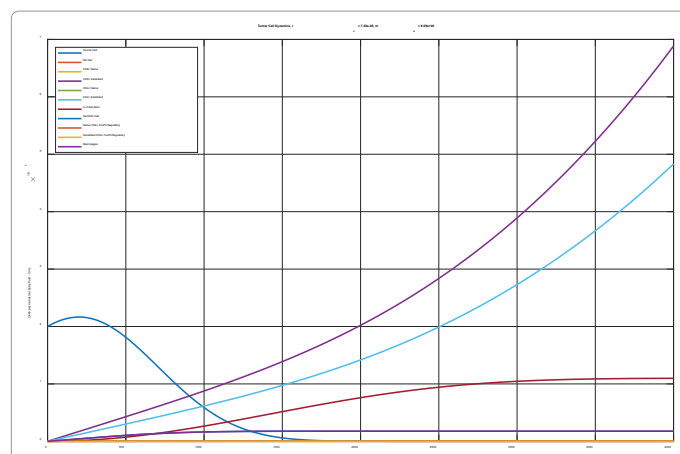


Figure 2: A time plot of cell populations with the utilization of the new model. This figure illustrates an immune response after an individual is injected with a tumor vaccine. Here, the patient is exposed to a tumor antigen (Survivin) of 11 amino acids long. Here, cancer is eliminated in 1750 days. C=20,000 cells.

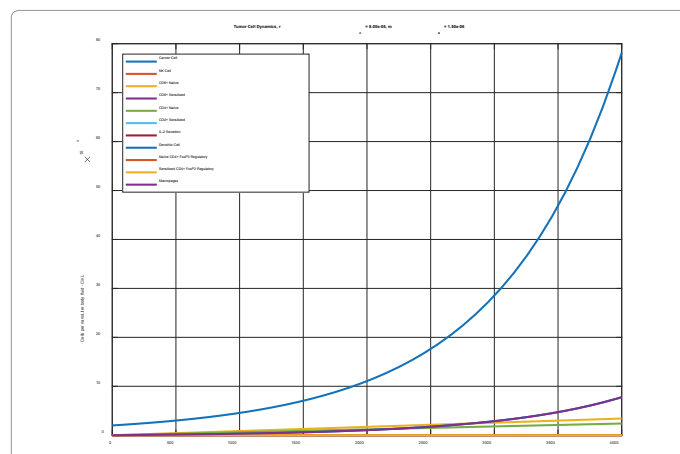


Figure 3: A time plot of cell populations with the utilization of the new model. This figure illustrates an immune response after an individual is injected with a tumor vaccine. Here, the patient is exposed to a tumor antigen (Survivin) of weak or no affinity to an MHC class I molecule. Here, cancer is not eliminated. C=20,000 cells.

response as certain sizes of each epitope interact with a specific HLA molecule. The model accounts for such interactions through the two Monte-Carlo simulators. Both Monte-Carlo simulators also account for the “randomness” of antigen size due to the variation of both R_c and M_a . Generated graphs for this project assumes that for each simulation, a patient was injected with a “cocktail” of vaccine epitopes of random sizes. The immune system recognizes an epitope that is between 8-11 aa long and produces a robust immune response. Any other size of an epitope will alter the immune response. Figure 2 shows an immune response after inoculation with a lung tumor vaccine; for example, a vaccine composed of synthetic survivin epitopes of random sizes.

For the above situation, the injected vaccine has a mix of synthetic survivin molecules with different fragment lengths of 5-11 amino acids. This situation illustrates the individual encountering a fragment of 10 aa long via an MHC class I pathway with a HLA-A molecule; HLA-A11:02 are the associated MHC class I molecule for survivin epitopes. Any other interaction with other HLA molecules (HLA-A24:02, etc.) may produce a weak response for the immune system due to the weak binding affinity between survivin and other HLA molecules (data not

shown). Here to note are several differences between Figures 1 and 2. With the addition of a tumor vaccine, cancer’s existence is cut down to 3/8 of its original lifespan. A cancer population lives up to about 1500 arbitrary days compared to 4,000 without a vaccine. In addition, the immune response is more robust. A reason for these observations is that with the addition of a tumor vaccine, more memory CTLs and HTLs are produced. A strong response has, in sense, been programmed and can be activated on a whim when a developing cancer is noticed. Another situation that can occur, there may times in which a tumor vaccine may be ineffective to an individual in that the tumor antigen may not have the proper associated HLA molecule or the processed peptide is too large or small for the immune system to recognize. After inoculation with a tumor vaccine, the immune system may fail to recognize a processed tumor antigen as the size of it may have weak recognition from the MHC class I pathway or a developing cancer population may have evolved its epitopes to avoid recognition all together. In this case, once active lung cancer is detected by an individual’s immune system, it must keep up with the growth rate of a specific lung cancer type to eliminate the growth, keeping in equilibrium, or allowing it to escape and predisposing the host to die. In this case, the figure below would suggest an escape situation whereby lung cancer would allow the host to succumb. Figure 3 shows an immune response after inoculation with a lung tumor vaccine:

Epitope size, ultimately determine the strength of the immune response. The tumor vaccine used for the above image may have epitope fragments less than 8-11 aa long. The small fragment size is mainly due to CTLs and DCs responding at a slow rate or a high cancer growth rate. In this case, cancer growth plays a major role in this situation as overgrowth results in less processing of cancer peptides. A tumor vaccine may be composed of peptide patterns that produce either strong, weak or no affinity to HLA-A11:02, depending on the fragment length. The pattern influences the binding affinity due to the amino acid sequence and shape. If a specific pattern cannot bind in a configuration that can be recognized by any HLA-A molecule, then the immune system will fail to respond to lung cancer and a patient will succumb.

Discussion

The above model incorporates tumor-immune interaction terms of a form that is qualitatively different from those commonly used in that Monte-Carlo randomization methods are utilized to depict multiple clinical scenarios of how a tumor vaccine influences an immune response. For this paper, three antigens (Survivin, Kita-Kyushu lung cancer antigen 1 (KKLC1), and Epidermal growth factor receptor (EGFR)) were selected for this model to predict how the immune system would respond to synthetic lung tumor vaccines. Our results illustrate that amino acid epitopes between 8-11 aa long will produce a robust immune response, while anything not in this estimated range will produce a non-robust immune response. Here, Figures 2 and 3 illustrate an immune response of an injected cocktail of survivin epitopes; the results inferred from this can be applied to epitope cocktails of KKLC1 and EGFR since both epitopes utilize the same MHC class I pathway. Synthetic survivin can also exist as fragment lengths of 9 or 11 aa long and can interact with molecules of the HLA-A family. We utilized the TANTIGEN database to look for possible pairings of epitopes to specific HLA molecules; from a TANTIGEN database search, an HLA molecule that can bind with the best affinity to Survivin molecules is HLA-A11:02 mainly due to the number of patterns that can bind to the molecule [24]. This model, although useful in predicting the long-term status of a patient, cannot

effectively predict which antigen epitopes and HLA combinations will produce a strong immune response due to the current nature of the model. As of now, the model can only foretell the immune system's response to a specific antigen. The current version of this model can only test three epitopes at this moment through variation of two parameters (cancer propagation and antigen presentation). With the addition of more epitopes over time, the model will need to be subjected to a hidden Markov model to determine the probability of the immune system strength as well as binding strength for sequences. Consequently, the current use of this model will involve prediction of the immunological efficiencies of each epitope in terms of generating a cancer-specific tumoricidal immune response. The strength of binding between processed antigen and an MHC molecule depends on how well the primary structure (amino acid) of processed antigen can bind to the groove of an MHC molecule (MHC class I and class II). Three isoforms of MHC class I molecules exist within the human immune system (HLA-A, HLA-B, and HLA-C), with HLA-A02 being the most common molecule. MHC class I molecules are designed to recognize peptide fragments of about eight to ten aa along with the maximum being 11. With the involvement of intracellular antigens for cancer, the selection of the right HLA gene complex depends on the sequence involved to activate the system. As mentioned previously, the primary structure of processed antigen must conform to the right configuration to elicit a response from a CD8 cell. We can infer from our results is that anything, not 8-11 aa long will produce an immune response, but affects the duration and strength. For this, antigen processing and recognition can be thought of as a randomized process.

Conclusion

One effective way to reduce morbidity and mortality of a disease in the first place is through vaccination. This process can be approached from multiple perspectives, such as clinical trials on humans and animals, but one unique way is through the lens of mathematical biology; mathematical simulations provides numerous benefits such as the non-reliance upon human/animal models as well as predicting future behaviors for a system [10,25]. Although mathematical modeling cannot portray life to complete accuracy, this process can find qualitative and quantitative hidden behaviors not seen in clinical trials. For the scope of this project, the aim was to generate an 11-differential equation model with a Monte-Carlo simulator that could predict the course of the immune system after injection with a synthetic cancer vaccine. The initial stages of development of this model confirmed prior knowledge of the innate and adaptive immune system; for example, CD8 cells are the principal cell-mediated immunity for cancer as well as dendritic cells being the principal cell during the innate immune response. Three antigens Survivin, KKL1, and EGFR [24] were utilized from the TANTIGEN database to predict an immune response once cancer was detected within an individual following utilization of a synthetic vaccine. In conclusion, we have for the first time applied mathematical modeling as a tool to depict the relative strength of a host's immune response after it has been subjected to a lung tumor vaccine. Here, we showed and can infer that if a synthetic epitope is not between 8-11 aa long, which can be substantiated by the TANTIGEN database, a host will produce an immune response, but that is not ideal to the elimination of cancer [26,27]. Studies are ongoing to elucidate the above perspectives by mathematical modeling through different means. In this regard, mathematical modeling of tumor immune dynamics through the perspective of vaccines may be highly important and useful to support the decision-making of how vaccines are synthesized and incorporated into a host. In addition, this model can

be utilized to serve clinicians and patients as a prognosticating tool to depict situations to facilitate a patient's decision process [28,29]. Future explorations of this model will aim at comparing generated data with data derived from clinical studies to substantiate the authenticity of this mathematical model in the prediction of clinical efficacy of various immune-therapeutic modules. Mathematical modeling is important tool researchers can utilize as it can also be applied to study other human disease processes such as cardiovascular, gastrointestinal, as well as auto-immune diseases.

References

1. Abbas A, Lichtman A (2010) Cellular and molecular immunology. (6th edn). Elsevier Publications, Netherlands.
2. Ahmadzadeh M, Rosenberg SA (2006) IL-2 administration increases CD4 CD25 foxp3 regulatory cells in cancer patients. *Blood* 107: 2409-2414.
3. Baraka A, Borai M, Hesam M, Almalky M (2014) Study of T-regulatory cells in patients with acute, idiopathic thrombocytopenic purpura. *Egyptian J Haematol* 39: 37.
4. De Boer RJ, Hogeweg P, Dullens HF, De Weger RA, Den Otter W (1985) Macrophage T lymphocyte interactions in the anti-tumor immune response: A mathematical model. *J Immunol* 134: 2748-2758.
5. De Pillis LG, Radunskaya AE, Wiseman CL (2005) A validated mathematical model of cell mediated immune response to tumor growth. *Cancer Res* 65: 7950-7958.
6. Dunn GP, Old LJ, Schreiber RD (2004) The immunobiology of cancer immunosurveillance and immunoediting. *Annu Rev Immunol* 22: 329-360.
7. Eberhardt M, Lai X, Tomar N, Gupta S, Schmeck B, et al. (2016) Third-kind encounters in biomedicine: Immunology meets mathematics and informatics to become quantitative and predicative. *Methods Mol Biol* 1386: 135-179.
8. Edlstein-keshet E (2005) Mathematical models in biology. University of British Columbia, Vancouver, British Columbia, Canada
9. Forsy U (2002) Marchuk's model of immune system dynamics with application to tumour growth. *J Theor Med* 4: 85-93.
10. Isaeva OG, Osipov VA (2009) Different strategies for cancer treatment: Mathematical modeling. *Comput Math Methods Med* 10: 253-272.
11. Joshi B, Wang X, Banerjee S, Tian H, Matzavinos A (2009) On immunotherapies and cancer vaccination protocols: a mathematical modeling approach. *J Theor Biol* 259: 820-827.
12. Kim PS, Lee PP (2012) Modeling protective anti-tumor immunity via preventative cancer vaccines using a hybrid agent-based and delay differential equation approach. *PLoS Comput Biol* 8: 1-16.
13. Kim PS, Lee PP, Levy D (2007) Modeling regulation mechanisms in the immune system. *J Theor Biol* 246: 33-69.
14. Lin WW, Karin M (2007) A cytokine-mediated link between innate immunity, inflammation and cancer. *J Clin Invest* 117: 1175-1183.
15. Linton M (2008) Human Physiology. Kendall Hunt Publishing. Iowa, USA.
16. Margolin K (2008) Cytokine therapy in cancer. *Expert Opinion on Bio Therap* 8: 1495-1505.
17. Marusic M (1996) Mathematical models of tumor growth. *Mathematical Communications* 1: 2.
18. Murray JM (1993) Mathematical biology. (3rd edn) Springer. Germany.
19. Olsen LR, Tongchusak S, Lin H, Reinherz EL, Brusic V (2017): TANTIGEN: A comprehensive database of tumor T cell antigens. *Cancer Immunol Immunother* 66: 731-735.
20. Ozao-Choy J, Ma G, Kao J, Wang GX, Meseck M (2009) The novel role of tyrosine kinase inhibitor in the reversal of immune suppression and modulation of tumor microenvironment for immune-based cancer therapies. *Cancer Res* 69: 2514-2522.
21. Pappalardo F, Chiacchio F, Motta S (2012): Cancer vaccines: state of the art of the computational modeling approaches. *Biomed Res Int* 1-6.

22. Roederer M, Koup RA (2003) Optimized determination of T cell epitope responses. J Immunol Methods 274: 221-228.
23. Stevenson MM (2016) Non-small cell lung cancer treatment protocols. Medscape.
24. Tong JC, Tan TW, Ranganathan S (2004) Modeling the structure of bound peptide ligands to major histocompatibility complex. Protein Sci 13: 2523-2532.
25. Toussaint NC, Dönnès P, Kohlbacher O (2008) A mathematical framework for the selection of an optimal set of peptides for epitope-based vaccines. PLoS Comput Biol 4: 1-12.
26. Valzasina B, Guiducci C, Dislich H, Killeen N, Weinberg AD, et al. (2005) Triggering of OX40 (CD134) on CD4 CD25 T cells blocks their inhibitory activity: a novel regulatory role for OX40 and its comparison with GITR. Blood 105: 2845-2851.
27. Walker R, Enderling H (2016) From concept to clinic: Mathematically informed immunotherapy. Curr Probl Cancer. 40: 68-83.
28. Wares JR, Crivelli JJ, Yun CO, Choi IK, Gevertz JL (2015) Treatment strategies for combining immunostimulatory oncolytic virus therapeutics with dendritic cell injections. Math Biosci Eng 12: 1237-1256.
29. Zama L, Ponti C, Mirandola P, Gobbi G, Papa S (2002) NK Cells and Cancer. J Immunol 178: 4011-4016.