Mathematical Model of Tumor-Immune Surveillance

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Abstract

We present a novel mathematical model involving various immune cell populations and tumor cell populations. The model describes how tumor cells evolve and survive the brief encounter with the immune system mediated by natural killer (NK) cells and the activated CD8⁺ cytotoxic T lymphocytes (CTLs). The model is composed of ordinary differential equations describing the interactions between these important immune lymphocytes and various tumor cell populations. Based on up-to-date knowledge of immune evasion and rational considerations, the model is designed to illustrate how tumors evade both arms of host immunity (i.e. innate and adaptive immunity). The model predicts that: (a) An influx of an external source of NK cells might play a crucial role in enhancing NK-cell immune surveillance; (b) The host immune system alone is not fully effective against progression of tumor cells; (c) The development of immunoresistance by tumor cells is inevitable in tumor immune surveillance. Our model also supports the importance of infiltrating NK cells in tumor immune surveillance, which can be enhanced by NK cell-based immunotherapeutic approaches.

Keywords: Mathematical model, Immune surveillance, Tumor escape, Immunotherapy

1 Introduction

Cancer is still one of the major causes of death worldwide. According to the World Health Organization (WHO), the number of new cancer cases is expected to increase by 70% over the next two decades [1]. Despite substantial advances in the treatment of certain types of cancer over the last few years, a definite cure for cancer is still difficult to find. Of particular importance is the immune system's ability to destroy cancer cells before they can cause harm to the body, a function known as immune surveillance. Studies show that the host immune system can recognize and eliminate cancerous cells [2–7], and that immunosurveillance mainly acts as a component of a more general process of cancer immunoediting through which neoplastic progression may be inhibited [2, 8]. Research also indicates that, despite immune surveillance, tumors do develop in the presence of a functioning immune system [9–12]. Additionally, studies suggest that tumor cells quickly acquire various mechanisms to “*escape*” immune surveillance and successfully grow into clinically apparent neoplasms [2, 8, 13–16]. Recent findings also report that tumor escape mechanisms from host immune surveillance present a major impediment for successful immunotherapy [17–22].

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1.1 Tumor-Immune Interactions

The Natural Killer (NK) cells are part of the innate immune-effector cells that provide a first line of defense in the body against pathogens, and crucially contribute to the immunosurveillance of tumors [2, 23, 24]. The NK cells have different cytotoxic properties and cytokine-production capacities that enable them to eliminate transformed cells (i.e, tumor cells and viral-infected cells). The NK cells can lyse tumor cells in a variety of distinct ways by exocytosis of perforin, subsequent binding of perforin to the target tumor cell membrane and formation of lytic pores or even by cytokine secretion [25, 26]. Some NK cells can also lyse tumor cells through the expression of the death-inducing ligands Fas ligand (FasL) and tumor necrosis factor (TNF)-related apoptosis inducing ligand (TRAIL). These ligands can induce tumor-cell apoptosis by binding to respective receptors, Fas and TRAILR on the tumor cell surface [27–31]. Tumor cells could also be killed by TNF- α produced by NK cells [9, 32]. Moreover, some natural killer cells, particularly the natural killer T (NKT) cells [33], secrete various pro-inflammatory cytokines, such as interferon (IFN)- γ and nitric oxide (NO) which act as danger signals, to inhibit tumor development and growth [33–35]. Natural killer cells can also lyse tumor cells through antibody-dependent cellular cytotoxicity (ADCC) which involves binding of antibodies to the Fc γ RIIIa receptor (CD16) on the NK cells [36, 37].

As part of the adaptive immunity, the activated CD8⁺ Cytotoxic T Lymphocytes (CTL) play a crucial role in controlling the development of tumor cells. Activation of T cells occurs when the T cell receptors bind to the antigen peptides, on the major histocompatibility complex (MHC) class molecules, presented to them by the antigen presenting cells, such dendritic cells or macrophages [38–41]. Upon recognition of antigen peptides on MHC class I molecules, the activated CTLs can directly kill tumor cells via death cell ligands such as TRAIL or by secreting cytotoxic granules such as perforin or granzyme [34, 42, 43]. The success of immune surveillance in controlling tumor development and growth may also depend on the number of cytotoxic T lymphocytes primed to combat the target cancerous cell. Therefore, another type of T cells called CD4⁺ T cells become activated and secrete cytokines, such as interleukin-2 (IL-2), which help in the clonal expansion of the cytotoxic T lymphocytes [44–46]. The more the cytotoxic T lymphocytes are produced, the better are the chances of immune surveillance of tumors [44]. Additionally, experimental studies by Gulubova et al. [47] suggest that a low NK cell number could be attributed to escape of metastatic cancer cells from the mechanisms of immune surveillance. Thus, the number of immune cells during the evolution of tumor cells may determine if the host immune system can effectively control tumor growth [44–47].

In this study, we are interested in the long-time dynamics between tumor cells and the host immune cells, and only consider the interplay of a tumor cells with natural killer (NK) cells and cytotoxic T lymphocytes (CTLs). In our modeling framework, we propose that the tumor cells that survived (through genetic mutations or epigenetic changes) a brief attack by either NK or CTLs, or both, have higher chances of acquiring resistance to future attacks by one or both types of immune cells. In fact, a tumor that has survived a lethal encounter with immune cells, usually develops a variety of defensive mechanisms to avoid future destruction by immune cells [3, 4, 10]. In turn, after surviving each encounter with either a NK or CTL, tumor apoptotic resistance to immune system control increases further via secretion of chemicals that diminish effectiveness of immune cells in the subsequent attacks [3], or by developing mechanisms that down-regulate or inactivate pro-apoptotic molecules, and up-regulate anti-apoptotic molecules [10, 48]. Tumor cells that escaped the initial interactions with immune cells are “wild-type” tumor cells because they are aware of the lethal presence of the immune effectors, and as such, they possess some defensive mechanism from the immune cell types that attacked them [9, 10, 38, 49, 50]. Therefore, after a finite number of encounters with either NK or CTL, or both, a complete or maximal

resistance to NK-CTL based immunity is acquired [13].

1.2 Previous Mathematical Models

Several mathematical models of tumor-immune system interactions have been developed by various researchers over the past decades [51–56]. For a comprehensive review of these models, the reader is referred to excellent review articles in [57–61].

Here, we review some of the key papers in the mathematical modeling of tumor-immune interactions. We focus specifically on these papers because we have used them in our model since they mathematically model evasion of tumors from immunosurveillance.

In [52], de Pillis et al. proposed a cancer immunosurveillance model system that considered different immune responses of innate and adaptive immunities to tumors recognition: the natural killer (NK) and $CD8^+$ T cells responses. The model tracked the different roles played by NK and $CD8^+$ T cells on tumor destruction. Based on experimental data, authors developed an innovative functional form to represent the interaction between tumor cells and the $CD8^+$ T cells. This functional form represents a percentage lysis of $CD8^+$ T cells to tumor cells. Their model did indeed set the stage for the cancer immunosurveillance modeling. Details of the hypothesis, such as why the functional form did not work for the natural killer dynamics was kind of lacking. Since in our model we assume that the tumour cells survive an attack by $CD8^+$ CTLs, we have not used this functional form in [52]; instead, we follow the dynamics of binding/detachment of $CD8^+$ CTLs to tumor cells, which lead to tumor escape from immune system, as in [13,62,63].

Webb et al. [64] proposed a mathematical model that represented tumor cell-lymphocyte interactions and the cell surface expression of Fas and FasL. The model was based upon the fact that certain types of human cancers produce functional FasL and hence can introduce an apoptosis on activated lymphocytes in vitro. This model by Webb et al. [64] showed how tumor cells evade immune surveillance using the FasL/Fas system and their secreted soluble forms (i.e. the matrix metalloproteinase (MMP) catalyzed soluble degradation product of the ligand (sFasL)); however it did not show how tumor cells escape from one or both arms of immune system (i.e. adaptive and innate immunity) and how tumor cells evolve after evading one or both arms of the host immune system. These shortcomings from Webb et al. [64] models are of particular interest to our model because tumors need to circumvent either one or both arms of immunity to maintain progressive growth [2]. More importantly, our proposed model considers the fact that the innate and adaptive immunities perform complementary functions. One of the most common mechanism by which tumors evade the host immune surveillance is by loss of MHC class I molecule expression on their cell surfaces. This mechanism only renders T cell responses ineffective. However, evidence shows that tumor cells that evade the $CD8^+$ T cell-mediated killing by down-regulation of MHC class I molecules become potential targets for NK cell-mediated killing [65,66] via “missing self” signals [67]. If the NK cell is unable to bind to MHC class I on the target cell, then NK-cell killing signal is triggered [67–69]. Therefore, it is important to show how tumor cells evolve and survive from both cytotoxic arms of immune system.

In [70], de Pillis et al. proposed a mathematical model that tracks the effect of multiple immune cells, $CD8^+$ T and NK cells, on tumor regression. The model focused on the interaction of the $CD8^+$ T and NK cells with various tumor cell lines: NKG2D ligand transduced and control-transduced (non-ligand) tumor cells. From the simulations, it was shown that ligand

transduced cells can stimulate protective immunity against tumor growth, while the control-transduced tumor cells can escape immune surveillance. Additionally, it was shown that the immune system provide better protection against tumors if it is primed with ligand-transduced cells than with non-ligand tumor cells. These simulations were in agreement with experimental data by Diefenbach et al. [71] which provided information on mouse immune response to the presence of a tumor. This model by de Pillis et al. [70] provided a baseline framework for our model. In comparison to our proposed model, ligand transduced tumor cells can be described as those tumor cells which are attacked by activated $CD8^+$ cytotoxic T lymphocytes (CTLs) (i.e. tumor cells with high expression of MHC class I molecules in attempt to hide from NK cell-mediated killing [72, 73]) and the control-transduced tumor cells can be described as those tumor cells which are potential targets for NK cells (i.e. tumor cells with down-regulated MHC class I molecules on their cell surfaces in attempt to evade the $CD8^+$ T cell-mediated killing [65, 66]).

Despite major advances in the fight against cancer, the mechanisms by which tumors escape the immune system’s recognition and control are still not well understood. Our aim in this work is to gain insight into these dynamics of tumor-immune surveillance via a mathematical model employing a system of nonlinear ordinary differential equations. To the best of our knowledge, this is the first attempt to mathematically model how tumor cell populations escape and acquire resistance to multiple immune cell populations resulting from their several cell-cell encounters. In this paper, we extend recent literature on tumor-immune surveillance [52, 64, 70] and present a unique study that proposes a predictive understanding of how tumor cells elude key immune system cells that provide robust host immune surveillance.

The paper is organized as follows. In section 2, we formulate our mathematical model that describes how tumor cells evolve and survive the brief encounter with immune system mediated by natural killer (NK) cells and the activated $CD8^+$ cytotoxic T lymphocytes (CTLs). In section 3, we carry out model analysis and numerical simulations. In section 4, we perform a sensitivity analysis on the model parameters to determine which parameters have the greatest impact on model outcomes. Finally, in section 5, we discuss the significance of the results and suggest future directions for enhance immune surveillance of tumors.

2 Model Formulation

2.1 Model Description

To describe how some immunogenic tumors (i.e. tumors that can be recognized by immune-effector cells), escape from the host immune surveillance, we first differentiate between the distinct interaction kinetics between natural killer (NK) cells, and the activated $CD8^+$ cytotoxic T lymphocytes (CTLs) with immunogenic tumors. Since both NK cells and CTLs can employ similar apoptosis mechanisms, we consider Fas/FasL binding between either type of immune system with the tumor cell. Fas is a 45-kDa type I membrane protein, and Fas-ligand (FasL) is a 37- to 40-kDa type II membrane protein which are members of the tumor necrosis factor receptor and ligand families [74, 75].

A Fas ligand (FasL) is present on cell surface of either an NK cell [27, 28, 31] or an activated $CD8^+$ CTL [76]. When an immune cell employs a Fas/FasL binding mechanism to lyse tumor cell, the FasL binds with its cell surface-bound receptor Fas on tumor cell [77]. This binding results in a complex through which apoptosis signals are sent into the target tumor cell.

The attachment and detachment between tumor and NK cells via Fas/FasL binding are depicted in Figure 1.

Figure 1: A schematic view of the binding and detachment of a tumor cell to a natural killer (NK) cell.

The formed complex enables the NK cell or CTL to induce the apoptosis signals to the bound tumor cell. Binding of Fas on a tumor cell with FasL triggers a cascade of sub-cellular events that result in apoptosis [78,79]. Some tumors, however, avoid the apoptosis through several mechanisms, including down-regulation of death receptors [10,80,81] or expression of anti-apoptosis proteins like B7-H1 [82,83], Phosphatidylinositol 3'-kinase (PI3 K) and Akt (protein kinase B) [84] on their cell surface. The evolution of these mechanisms may ultimately lead to tumor evasion from immune surveillance mediated by either natural killer cells or activated CD8⁺ cytotoxic T lymphocyte [2,72,85].

A partial schematic interaction dynamics which lead to tumor escape are depicted in Figure 2.

Figure 2: A schematic diagram of the interactions between tumor cells, natural killer cells and the activated CD8⁺ cytotoxic T lymphocytes. Parameters and variables appearing on this schematic diagram are summarized in Tables 1 & 2.

Figure 2 indicates the interaction dynamics between a population of natural killer cells, denoted by N , the population of activated CD8^+ cytotoxic T lymphocytes, denoted by L , and the population of “naïve” tumor cells (i.e. tumor cells that have not yet developed any

escape mechanism to immune cells), denoted by T^0 , and the population of tumor cells that have escaped immune surveillance once, T_N^1 and T_L^1 , or twice T_{NL}^1 . Note, the superscript 0 appearing in T^0 denotes “naiveness” (i.e. tumor cells that have not yet developed any escape mechanism to immune cells), while the superscript 1 appearing in T_N^1 , T_L^1 and T_{NL}^1 denotes “wildness” of tumor cells (i.e. tumor cells that can hide from the specific immune attack, and develop resistance to that specific immune cell). The subscripts, N , L and NL appearing in T_N^1 , T_L^1 and T_{NL}^1 , respectively denote the type of immune cell that interacted with the tumor cell.

Accumulating evidence indicates that tumor cells, after surviving an immune attack, they can either mount a “counter-attack” or develop resistance to immune cells [2, 22, 86]. Our model does not account for a direct tumor counterattack, as was done in [62, 63]. In our model, upon surviving their brief encounter with the tumor cells, the immune cells die to natural cell death, not as a consequence of tumor counterattack. In Matzavinos et al. [62] a spatio-temporal model of the interactions between tumor cells and tumor-infiltrating cytotoxic lymphocytes (TICLs) was proposed. The model included the spatial motility of both TICLs and tumor cells via a combination of random motility and chemotactic motion of the TICLs in response to the presence of chemokines. Authors focused mainly on the role of the immune system in determining dormant states of the tumor. Similar to our model, the TICLs are assumed to migrate into the tumor site and interact with the tumor cells in such a way that TICL-tumor cell complexes are formed. The outcome of these complexes was two fold: the death of the tumor cells or the inactivation (sometimes even the death) of the immune lymphocytes. The direct tumor counterattack was attributed to the death of the immune lymphocytes, TICLs. In Joshi et al [63], a mathematical model of immunotherapy and cancer vaccination was proposed. The model focused on the role of antigen presentation and co-stimulatory signaling pathways in cancer immunology. The direct tumor counterattack against effector immune cells was ascribed by the death of effector immune cells as one of the outcomes of the effector-tumor cell complexes. Counter-intuitively to these models, our model accounts for the development of resistance to immune cell-mediated killings as a result of one or multiple encounters of tumor cells with certain immune cells, as was done in [13]. In Al-Tameemi et al [13], a mathematical model that describes a solid tumor growth in the presence of the immune system response was presented. The model focused on the spatio-temporal interactions of the immunogenic tumor cells and cytotoxic T-lymphocytes (CTLs) in the presence of chemokines and “chemorepellents”. In [13], as well as in our model, tumor cells and CTLs are assumed to interact in such a way that CTL-tumor cell complexes are formed. After some time, the formed CTL-tumor cell complex breaks up. This break-up of complex can lead to a situation in which both the tumor cell and the CTL are alive, and either the CTL or the tumor cell survives their brief encounter [13].

In order for the adaptive immunity to mount a specific anti-tumor response, there has to be a variety of alarming activities from innate immune response that activate the adaptive immunity [12, 87]. We, however, have not included this step in our model since the focus is on the interaction dynamics of the activated $CD8^+$ cytotoxic T lymphocytes with tumor cells.

The kinetic parameters α_N^+ and β_L^+ represent respective initial rates of attachment of NK cells and CTLs to naive tumor cells. Rates of tumor escape following its first brief encounter with NK or CTL, with no damage on the cells, are denoted by α_N^1 and β_L^1 , respectively. Since the interaction between tumor cells and immune cells may inactivate some immune cells, we consider only the immune cells that possess a certain effector fitness (i.e. immune cytotoxic capacity similar to the one immune cells possess prior to their entanglement with tumor cells) after their interaction with tumor cells. The quantities, p_N and p_L , represent the respective proportions of NK cells and CTLs that are detached, with no damage on the cells, from complexes formed when tumor cells bound with NK cells and CTLs. Similarly, the quantities, π_N and ζ_L , denote the respective proportions of NK cells and CTLs that are detached, with no damage on the

cells, from complexes formed when “wild-type” tumors, T_N^1 and T_L^1 , bound with NK cells and CTLs.

It is known that almost all kinds of tumor cells express Fas [78], and some may express a Fas ligand, FasL, which might bind with its receptor, Fas, on the activated immune cell [88]. Through this engagement of Fas receptor with its ligand FasL, tumor cell may directly lyse the immune cell [4, 10, 64, 84, 89]. Thus, the quantities p_T and q_T represent the proportions of tumor cells that escaped (i.e. via tumor “counterattack”) from the surveillance mediated by NK cells and CTLs, respectively. Therefore, the Fas/FasL complex constitutes an important role in controlling survival or growth of tumor cells [78, 90].

Tumor cells interact with NK cell or CTL in such a way that complexes are formed as shown in Figure 1. The complex resulting from binding of natural killer cell or activated CD8⁺ cytotoxic T lymphocytes to naive tumor cell is denoted by C_N and C_L , respectively. If a tumor has survived a brief encounter with either a NK cell or CTL then such tumor develops, via mutations or epigenetic changes, a variety of mechanisms that might enable it to avoid future attacks by the encountered type(s) of immune system [13].

Since we are considering the tumor-immune interactions under immune surveillance, tumor cell that has once survived its encounter with NK cell is still susceptible to further attacks by CTLs, and vice-versa. Since “wild-type” tumor cells usually develop immune resistance to a type of immune cell that it has encountered [13], in this study, we assume that subsequent interactions between that particular “wild-type” tumor with the same type of immune cell is unlikely. Thus, we are only considering susceptibility of such tumor cell to other different types of immune cell to illustrate how tumors may ultimately elude overlapping attacks of distinct immune cells participating in tumor surveillance.

Tumors do indeed develop complex mechanisms to evade various activities of immune system recognition and control [2]. Here, we denote by C_{NL}^N and C_{NL}^L complexes formed from the interaction of such “wild-type” tumor cells with NK cell and CTLs, respectively. Rate of binding of NK cells to “wild-type” tumor cell that escaped from CTL surveillance is denoted by α_L^+ , and the rate of detachment of NK cells from the complex C_{NL}^N formed with such tumor cell is denoted by α_L^- . Similarly, the respective rates of binding and detachment of CTLs from “wild-type” tumor cell that escaped from NK-cell surveillance are denoted by β_N^+ and β_N^- .

The parameters and variables described in this section are summarized in Tables 1 & 2.

2.2 Model Assumptions

We make the following assumptions for our model based on the discussion above and the scientific literature on the immune system [13, 48, 65, 66, 70, 91–96]:

- (i) All tumors are immunogenic to trigger an immune response, and grow logistically in the absence of immune response [70].
- (ii) If a tumor has escaped from NK-cell surveillance, then the tumor resistance to NK-mediated killing increases after its brief encounter with NK cell; the same analogy is also true for the CTL surveillance. This resistance to NK-mediated killing is considered to occur as a result of up-regulation of MHC class I molecules [48]. Consequently, up-regulation of these MHC class I molecules renders tumor cells more susceptible to CTL-mediated killing [65, 66, 92, 93, 96]. Thus, phenotypically, the “wild-type” tumors are different from the naive tumor cells.

- (iii) The probability of “wild-type” tumor cell, that escaped NK-mediated killing, being recognized and also of forming a complex with a NK cell (implicitly embedded in the parameter α_L^+) is small or zero. The same assumption applies to “wild-type” tumor cell that escaped CTL-mediated killing [13].
- (iv) As part of the innate system, natural killer cells (N) are always present [70, 91] in the host immune system, but cytotoxic T lymphocytes (L) are only present when tumor is present [70].
- (v) Both NK cells and activated $CD8^+$ CTLs eventually become less effective after the first encounter with tumor cells [70, 95].
- (vi) Both NK and CTLs can lyse tumor cells [70, 94].

2.3 Terms Used for Growth, Death and Recruitment

We adapt a logistic growth for naive tumor cell, $aT^0(1 - bT^0)$, as well as wild-type tumor cells that have survived the encounter with immune cells, $aT_j^i(1 - bT_j^i)$ with $j = N, L, NL$ and $i = 1$. The rate of tumor growth is denoted by a , which includes both cell multiplication (mitosis) and death, and the maximum carrying capacity of the tumor cells is represented by the parameter b . Since we have assumed that CTLs are only present in the host immune system only when the tumor is present, the growth term for the activated $CD8^+$ CTLs consists only of natural cell death. Thus, we have $\mu_2 L$ as the growth term for the activated $CD8^+$ CTLs. The NK cells are produced from an external source, s , as in [70]. The constant parameter, s , accounts for the fact that NK cells, as part of the innate immune, are always present in the host body, even when no tumor is present. We assume that NK cells and CTLs die at different constant rates μ_1 and μ_2 , respectively.

The recruitment term, $f(C, T)$ where $C = (C_L, C_{NL}^L)$ and $T = (T^0, T_N^1)$, denotes proliferation function of CTLs due to signals, such as released cytokines, produced in an autocrine manner by the CTLs in CTL-tumor cell complexes [62, 97]. The function f reaches some saturation at certain point since the immune system cannot produce activated $CD8^+$ CTLs indefinitely. Thus, the function f can be written as $f(C, T) = r_1 C_L / (g + T^0) + r_2 C_{NL}^L / (g + T_N^1)$, where r_1 and r_2 are constant rates at which CTLs are recruited due to the formation of the complexes with “naive” and “wild-type” tumor cell populations, respectively. Note $r_1 \geq r_2 \geq 0$ because after each brief encounter with immune cells, the tumor cell develops some resistance towards subsequent interaction or potential killing of each type of immune system encountered. Model variables are summarized in Table 1.

Table 1: Model Variables

Variables	Description
L	Activated CD8 ⁺ cytotoxic T lymphocytes (CTLs)
N	Natural killer (NK) cells
T^0	Naive tumor cells
T_N^1	Wild-type tumor cells that escaped from NK cells
T_L^1	Wild-type tumor cells that escaped from activated CD8 ⁺ CTLs
T_{NL}^1	Wild-type tumor cells that escaped from both NK cells and activated CD8 ⁺ CTLs
C_N	Complex formed by NK cell and naive tumor cell
C_L	Complex formed by CTL and naive tumor cell
C_{NL}^N	Complex formed by NK cell and wild-type tumor cell that escaped from activated CD8 ⁺ CTLs
C_{NL}^L	Complex formed by CTL and wild-type tumor cell that escaped from NK cells

2.4 Model Equations

Assuming mass action kinetics, the model describing the interactions between various immune cells and tumor cells is given by the following system of nonlinear ordinary differential equations:

$$\frac{dN}{dt} = \underbrace{s}_{\text{supply}} - \underbrace{\mu_1 N}_{\text{natural death}} - \underbrace{\alpha_N^+ N T^0 + p_N \alpha_N^- C_N}_{\text{local kinetics, with } T^0} - \underbrace{\alpha_L^+ N T_L^1 + \pi_N \alpha_L^- C_{NL}^N}_{\text{local kinetics, with } T_L^1} \quad (1)$$

$$\frac{dL}{dt} = \underbrace{f(C, T)}_{\text{recruitment}} - \underbrace{\mu_2 L}_{\text{natural death}} - \underbrace{\beta_L^+ L T^0 + q_L \beta_L^- C_L}_{\text{local kinetics, with } T^0} - \underbrace{\beta_N^+ L T_N^1 + \zeta_L \beta_N^- C_{NL}^L}_{\text{local kinetics, with } T_N^1} \quad (2)$$

$$\frac{dT^0}{dt} = \underbrace{a T^0 (1 - b T^0)}_{\text{logistic growth}} - \underbrace{\alpha_N^+ N T^0}_{\text{local kinetics, with } N} - \underbrace{\beta_L^+ L T^0}_{\text{local kinetics, with } L} \quad (3)$$

$$\frac{dT_N^1}{dt} = \underbrace{a T_N^1 (1 - b T_N^1)}_{\text{logistic growth}} + \underbrace{p_T \alpha_N^- C_N}_{\text{escaped, from } N} - \underbrace{\beta_N^+ L T_N^1}_{\text{local kinetics, with } L} \quad (4)$$

$$\frac{dT_L^1}{dt} = \underbrace{a T_L^1 (1 - b T_L^1)}_{\text{logistic growth}} + \underbrace{q_T \beta_L^- C_L}_{\text{escaped, from } L} - \underbrace{\alpha_L^+ N T_L^1}_{\text{local kinetics, with } N} \quad (5)$$

$$\frac{dT_{NL}^1}{dt} = \underbrace{a T_{NL}^1 (1 - b T_{NL}^1)}_{\text{logistic growth}} + \underbrace{\zeta_T \beta_N^- C_{NL}^L}_{\text{escaped, from } L} + \underbrace{\pi_T \alpha_L^- C_{NL}^N}_{\text{escaped, from } N} \quad (6)$$

where

$$f(C, T) = \underbrace{\frac{r_1 C_L}{(g + T^0)}}_{\text{Proliferation of CTLs in response to the naive tumors}} + \underbrace{\frac{r_2 C_{NL}^L}{(g + T_N^1)}}_{\text{Proliferation of CTLs in response to the wild-type tumors}} \quad (7)$$

The parameters $\alpha_N^+, \alpha_N^-, \alpha_L^+, \alpha_L^-, \beta_L^+, \beta_L^-, \beta_N^+, \beta_N^-, \pi_T, \pi_N, \zeta_T, \zeta_L, p_N, p_T, q_L, q_T, r_1, r_2, s, r_1, r_2, g, \mu_1$ and μ_2 , summarized in Table 2, are all positive constants. Note, $f(C, T)$ denotes activation of the CTLs due to signals from binding of the activated CD8⁺ CTLs with the tumor

cells. Here, p_T and q_T denotes the proportions of initial tumor cell populations that escaped the local interactions with NK cells and CTLs, respectively. Similarly, π_T and ζ_T represent the proportions of the “wild-type” tumor cell populations that escaped local interactions with NK cells and CTLs, respectively.

The tumor-immune interactions resulting in cell-complexes are governed by the kinetics derived in Figure 2. Therefore, the equations for the complexes are given by:

$$\frac{dC_N}{dt} = \underbrace{\alpha_N^+ NT^0}_{\text{Complex formation between } N \& T^0} - \underbrace{\alpha_N^- C_N}_{\text{Complex detachment between } N \& T^0} \quad (8)$$

$$\frac{dC_L}{dt} = \underbrace{\beta_L^+ LT^0}_{\text{Complex formation between } L \& T^0} - \underbrace{\beta_L^- C_L}_{\text{Complex detachment between } L \& T^0} \quad (9)$$

$$\frac{dC_{NL}^N}{dt} = \underbrace{\alpha_L^+ NT_L^1}_{\text{Complex formation between } L \& T_L^1} - \underbrace{\alpha_L^- C_{NL}^N}_{\text{Complex detachment between } N \& T_L^1} \quad (10)$$

$$\frac{dC_{NL}^L}{dt} = \underbrace{\beta_N^+ LT_N^1}_{\text{Complex formation between } L \& T_N^1} - \underbrace{\beta_N^- C_{NL}^L}_{\text{Complex detachment between } N \& T_N^1} \quad (11)$$

In this model, if either the tumor cell or attacking immune cell does not posses a ligand, then the variables $C_N(t)$, $C_L(t)$, $C_{NL}^N(t)$ and $C_{NL}^L(t)$ are zero because the formation of complexes requires the ligand to be present. The initial conditions for the model are:

$$\begin{aligned} N(0) &= N_0, \quad L(0) = L_0, \quad T^0(0) = T_0, \quad T_N^1(0) = T_L^1(0) = T_{NL}^1(0) = 0, \\ C_N(0) &= C_L(0) = C_{NL}^N = C_{NL}^L = 0. \end{aligned} \quad (12)$$

For simplicity, we do not model successive multiple encounters between one immune cell type and the same tumor cell that survived the first brief encounter. We only consider the case where the target tumor cells have evaded the NK and/ or CTL surveillance once. This is to illustrate how tumors acquire resistance to immune surveillance, and ultimately proliferate without bound or get to equilibrium state of immunoediting as suggested by Dunn et al. [2]. This model (1) – (11) can easily be extended to the setup of n tumor escapes from immune surveillance mediated by NK cells and CTLs. Thus we have omitted this case in this study. We now present a detailed explanation of each term involved in each model equation.

In equation 1, the first term, s , represents a constant background source rate for natural killer cells. The second term, $-\mu_1 N$, represents natural cell death of the NK cell population. The third term, $(-\alpha_N^+ NT^0 + p_N \alpha_N^- C_N)$, represents the local interaction dynamics between NK cells and naive tumor cells, resulting in binding of NK cells to naive tumor cells, $-\alpha_N^+ NT^0$, and detachment of NK cells from tumor cells, $p_N \alpha_N^- C_N$, without damaging cells. Here, we assume that the NK cells that are detached from NK cell-tumor complex maintained a high level of effectiveness as before the interaction with tumor cells. This assumption is usually made when there is no cell damage resulting from detachment of cells from the complexes [13]. Similarly, the fourth term, $(-\alpha_L^+ NT_L^1 + \pi_N \alpha_L^- C_{NL}^N)$, represents the local interaction kinetics between NK cells and the wild-type tumor cells that survived their brief encounters with the CTLs. The term $-\alpha_L^+ NT_L^1$ represent binding of NK cells to tumor cells, while the term $\pi_N \alpha_L^- C_{NL}^N$ represents detachment of NK cells from the NK cell-tumor complex. Recently, it has been shown that

NK/CTLs can rapidly attack other target cells after their detachment from tumor cells [98]. This later interaction of NK cells and wild-type tumors may be important and is therefore included in the model.

In equation 2, the first term, $f(C, T)$, denotes recruitment of CTLs in response to the presence to tumor cells. That is, $r_1 C_L / (g + T^0)$, represents CTL proliferation in response to naive tumor cells, and $r_2 C_{NL}^L / (g + T_N^1)$ represents the CTL proliferation in response to wild-type tumor cells that escaped their brief encounter with the natural killer cells. This functional form is borrowed from the simplified activated CD8⁺ T-cell recruitment term from de Pillis et al [99]. Moreover, this CTL recruitment has been used by Matzavinos et al. [62] and Joshi et al [63]. This functional form is usually employed when one assumes that the recruitment of CTLs is due to signals, such as released cytokines (signaling molecules that mediate and regulate immune system), produced by immune cells in tumor-CTL complexes [62, 63]. The second term, $-\mu_2 L$, represents natural death of the activated CD8⁺ CTLs, as in de Pillis et al [57, 70, 91]. Since we have assumed that activated CD8⁺ CTLs are only present when the tumor is present, then the activated CD8⁺ CTLs do not have an intrinsic growth. This third term, $(-\beta_L^+ LT^0 + q_L \beta_L^- C_L)$, represents binding $-\beta_L^+ LT^0$, of activated CD8⁺ CTLs to the naive tumor cells, and detachment, $q_L \beta_L^- C_L$, of activated CD8⁺ CTLs from the naive tumor cells. Similar to NK cell, activated CD8⁺ CTLs are susceptible to interactions with the wild-type tumor. Hence, the last term, $(-\beta_N^+ LT_N^1 + \zeta_L \beta_N^- C_{NL}^L)$, represents the local interactions of the activated CD8⁺ CTLs with the wild-type tumors that escaped from NK cell surveillance. The term $-\beta_N^+ LT_N^1$ represents binding of the activated CD8⁺ CTLs to wild-type tumor cells, and $\zeta_L \beta_N^- C_{NL}^L$ represents detachment of the activated CD8⁺ CTLs from wild-type tumor cells.

In equation 3, the intrinsic growth dynamics of the naive tumor cells is represented by logistic growth, $aT^0(1 - bT^0)$. The logistic growth laws are consistent with models fitted to real tumor growth data [52, 57, 70]. Since naive tumor cells are immunogenic to all immune cells, the local interactions of the naive tumour cells with NK cells and activated CD8⁺ CTLs is represented by $-\alpha_N^+ NT^0$ and $-\beta_L^+ LT^0$, respectively.

In equation 4, similar to equation (3), the first term represents a logistic growth of the wild-type tumor cells which survived and escape their brief encounters with the NK cells. The number of escaped tumor cells are represented by the second term, $p_T \alpha_N^- C_N$. However, since tumor cells which evade NK cell surveillance (i.e. tumor cells with up-regulated expression of major histocompatibility complex (MHC) class I molecules [48]) are susceptible to CTL-mediated killing [65, 66, 92, 93, 96], their local interaction with the activated CD8⁺ CTLs is represented by the last term, $-\beta_N^+ LT_N^1$.

In equation 5, the equation for wild-type tumor cells discussed is similar to the above equation. The first term, $aT_L^1(1 - bT_L^1)$, represents logistic growth of the wild-type tumor cells that survived and escaped their brief encounter with activated CD8⁺ CTLs. The second term, $q_T \beta_L^- C_L$, represents tumor cells that escaped CTL surveillance (i.e. tumor cells with down-regulated MHC class I molecules). Down-regulation of MHC class I molecule is known to be one of the escape mechanisms of tumor cells to evade CTL-mediated killing [65, 66, 92, 93, 96]. However, down-regulation of these MHC class I molecules renders tumor cells more susceptible to NK cell-mediated killing [65, 66]. Furthermore, evidence shows that NK cells can recognize tumors that might evade the activated CD8⁺ CTL-mediated killing by aberrant human leukocyte antigen (HLA) expression [100].

In equation 6, the first term represents logistic growth of the wild-type tumor cells that are resistant to immune surveillance mediated by both NK cell and activated CD8⁺ CTLs. We note that these tumor cells are “*multi-immunoresistant*” to both cytotoxic immune cells, and therefore present a major impediment to successful immunotherapy [17–21].

2.5 The Reduced Model

The intrinsic growth of tumors involves multiple time scales: the proliferation of tumor cells normally occurs on a time interval of months to years *in vivo*, while *in vitro* takes weeks to months [101]. A complex formed between a NK cell or CTL and tumor cell occurs on a small time scale (i.e. from several minutes to a few hours [97]). Moreover, the recruitment of CTLs as well as the influx of NK cells to a tumor site usually occurs on a much slower time scale (i.e. tens of hours [97]). In order to account for these differences in the time scales, we adopt a quasi-steady-state analysis on the cell complexes (i.e. $\frac{dC_N}{dt} = \frac{dC_L}{dt} = \frac{dC_{NL}^N}{dt} = \frac{dC_{NL}^L}{dt} \approx 0$). More importantly, we are interested in the interaction between tumor cell populations and the immune system; hence we simplify the model’s equations (1) – (11), by using quasi-steady-state approximations for the complexes. By this approach, we obtain the following relations for the cell complexes:

$$C_N = \left(\frac{\alpha_N^+}{\alpha_N^-} \right) NT^0; \quad C_L = \left(\frac{\beta_L^+}{\beta_L^-} \right) LT^0; \quad (13)$$

$$C_{NL}^N = \left(\frac{\alpha_L^+}{\alpha_L^-} \right) NT_N^1; \quad C_{NL}^L = \left(\frac{\beta_N^+}{\beta_N^-} \right) LT_N^1. \quad (14)$$

By substituting these expressions into the system equations (1) – (6), we obtain the following simplified system for the tumor-immune dynamics:

$$\frac{dN}{dt} = s - \mu_1 N - (1 - p_N) \alpha_N^+ NT^0 - (1 - \pi_N) \alpha_L^+ NT_N^1 \quad (15)$$

$$\begin{aligned} \frac{dL}{dt} = & \frac{r_1 \beta_L^+ LT^0}{\beta_L^- (g + T^0)} + \frac{r_2 \beta_N^+ LT_N^1}{\beta_N^- (g + T_N^1)} - \mu_2 L - (1 - q_L) \beta_L^+ LT^0 \\ & - (1 - \zeta_L) \beta_N^+ LT_N^1 \end{aligned} \quad (16)$$

$$\frac{dT^0}{dt} = aT^0(1 - bT^0) - \alpha_N^+ NT^0 - \beta_L^+ LT^0 \quad (17)$$

$$\frac{dT_N^1}{dt} = aT_N^1(1 - bT_N^1) + p_T \alpha_N^+ NT^0 - \beta_N^+ LT_N^1 \quad (18)$$

$$\frac{dT_L^1}{dt} = aT_L^1(1 - bT_L^1) + q_T \beta_L^+ LT^0 - \alpha_L^+ NT_L^1 \quad (19)$$

$$\frac{dT_{NL}^1}{dt} = aT_{NL}^1(1 - bT_{NL}^1) + \zeta_T \beta_N^+ LT_N^1 + \pi_T \alpha_L^+ NT_L^1 \quad (20)$$

Followings are the positive initial conditions of the system:

$$N(0) = N_0, \quad L(0) = L_0, \quad T^0(0) = T_0, \quad T_N^1(0) = T_L^1(0) = T_{NL}^1(0) = 0, \quad s(0) = s_0. \quad (21)$$

The system of equations (15) – (20) along with the initial conditions (21) constitute a reduced model of the immune surveillance of tumors that we use to explain how tumor cells evade immune surveillance in the next section.

3 Model Simulations and Results

In this section, we discuss the numerical simulations of our mathematical model and give plausible explanations of the proposed model results. The model enables us to simulate tumor evasion based on various influx of the NK cells and the activated $CD8^+$ CTLs. An enhanced understanding of how tumors evade immune surveillance may help to identify which components of host immune-effector forces that need to be augmented to boost natural protection against tumors [2]. The major goal of this computational study is to quantitatively elucidate how tumor cells escape from immune surveillance based on the findings by Dunn et al. [2]:

- (i) The immune system has capacity to recognize and destroy nascent transformed cells (Elimination phase (immunosurveillance)).
- (ii) Some tumor cells may survive immune destruction and become dormant (Equilibrium phase (i.e. the phase where immuno-editing occurs)).
- (iii) After some time, selected tumor cell variants from the equilibrium phase can now grow into clinically detectable tumors.

Of particular interest to our model framework is to elucidate how tumor cells most likely circumvent either one or both arms of host immunity (i.e. innate and adaptive immunity) in order to maintain progressive growth. A thorough understanding of plausible escape mechanisms employed by tumor cells is a first necessary step towards the development of successful strategies for immunotherapy [17, 88, 102].

3.1 Model Baseline Parameters

To quantitatively analyze our model, we first need to determine the model baseline parameter values or at least a reasonable physiological range for them. We use data from the available literature where possible and for other parameters we consider different value ranges and their impact on the model outputs. A summary of the parameter descriptions and their numerical values is given in table 2. We used most of the baseline parameter values reported in [13, 62, 63, 70, 91, 97].

We now outline our approach to estimating numerical values for each model parameter. To date, there is still a lack of quantitative data for Fas/FasL system between tumor cells and immune system. We determined our model parameter estimates based on a variety of approaches. First, we sourced all available parameter values from biological literature, particularly parameter values related to activated $CD8^+$ CTLs. To the best of our knowledge, most of the available estimates of Fas/FasL system is based on the interactions of activated $CD8^+$ CTLs with tumor cells. However, since the engagement of Fas/FasL system in activated $CD8^+$ CTLs is similar to NK cells [103], we held most of the unknown parameter estimates of binding and detachment of NK cells to tumor cells same as those of activated $CD8^+$ CTLs with tumor cells. Second, for some parameters, there is no relevant information available regarding their numerical ranges, we chose parameter values which confirmed the model's behavior with biological realism.

Even though the parameter estimates provided in this section are baseline estimates taken from a variety of sources, model sensitivity to changes in parameter values has been explored (see Section 4). In the following sections, we discuss in detail how numerical values for each model parameter were estimated.

3.1.1 The natural killer cells

For numerical ranges of source of NK cells, s , we used values within biological ranges stated in [97]. The death rate of NK cells, $\mu_1 = 4.12 \times 10^{-2} \text{ cell}^{-1} \text{ day}^{-1}$, is obtained from de Pillis et al. [91]. We use same rate of binding of NK cells to tumor, $\alpha_N^+ = 1.3 \times 10^{-7} \text{ day}^{-1}$, as activated CD8⁺ CTLs binding rate reported in [13, 63]. The proportion of NK cells that survived from NK-naive tumor complex and maintained high level of effectiveness, $p_N = 0.94$, is an *ad hoc* value and has been chosen to give biologically feasible outcomes. The value of this proportion is not available in the literature. The formed complexes between NK cells and tumor cells, may result in inactivation of some the NK cells and consequently further chances of survival of the tumor cells [13, 62]. Since there is no information in the literature on the proportion of NK cells that survived from NK-tumor complex formed with wild-type tumor cell that escaped from CTL and maintained high level of effectiveness, we chose a value of $\pi_N = 0.80$ in order to obtain a biologically relevant outcome from the model. The binding rate of NK cells to tumor cell that escaped from CTLs, $\alpha_L^+ = 1.2 \times 10^{-9} \text{ day}^{-1} \text{ cells}^{-1}$, is also an *ad hoc* value that is chosen to give the biologically reasonable model results. Since the NK cells are capable of lysing tumor cells via Fas/FasL system [27–31], the chosen value of α_L^+ was motivated from the magnitude of the values of CTL Fas/FasL binding as considered in [63]. The Fas/FasL system is in the same family as tumour necrosis factor (TNF) and the extracellular domains of members of the TNF family are known to be well conserved [64]. That means, the order of magnitude of the values of Fas/FasL system should not change very much as of those values of TNF family.

3.1.2 The activated CD8⁺ Cytotoxic T Lymphocytes

The rate of activated CD8⁺ CTLs recruitment due to signals resulting from CTL-naive tumor interaction, $r_1 = 0.2988 \times 10^8 \text{ day}^{-1} \text{ cells}$, is left unchanged from Al-Tameemi et al [13], Matzavinos et al [62] and Joshi et al [63]. The rate of binding of activated CD8⁺ CTLs to naive tumor cells, $\beta_L^+ = 1.3 \times 10^{-7} \text{ day}^{-1} \text{ cells}^{-1}$, and rate of detachment of CTLs from naive tumor cells, $\beta_L^- = 24 \text{ day}^{-1}$, are taken from Al-Tameemi et al [13] and Joshi et al [63]. The constant appearing in recruitment function of the activated CD8⁺ CTLs, g , is obtained from Al-Tameemi et al [13], Matzavinos et al [62] and Joshi et al [63].

The recruitment rate of activated CD8⁺ CTLs recruitment due to the presence of wild-type tumor cells is given by $r_2 = 0.2755 \times 10^6 \text{ day}^{-1} \text{ cells}$. Since there is no data measuring the relevant recruitment kinetics of activated CD8⁺ CTLs to wild-type tumor cells, this value is chosen to maintain model consistency with biological expectations. Since the activated CD8⁺ CTLs binds to tumor cells via the Fas/FasL system, we used same binding and detachment rates of activated CD8⁺ CTLs to/from wild-type tumor cells as those of CTL-naive tumor interactions: $\beta_N^+ = 1.3 \times 10^{-7} \text{ day}^{-1} \text{ cells}^{-1}$, and $\beta_N^- = 24 \text{ day}^{-1}$, respectively. This was motivated by the fact that the Fas/FasL system is in the same family as tumour necrosis factor (TNF) and the extracellular domains of members of the TNF family are known to be well conserved [64].

The natural death of the activated CD8⁺ CTLs, $\mu_2 = 2.0 \times 10^{-2} \text{ cell}^{-1} \text{ day}^{-1}$, is taken from de Pillis et al. [91]. The proportion of activated CD8⁺ CTLs that survived from CTL-naive tumor complex and maintained high level of effectiveness, $q_L = 0.94$, as well as the proportion of activated CD8⁺ CTLs that survived from CTL-tumor complex formed with “wild-type” tumor cell that escaped from NK cells and maintained high level of effectiveness, $\zeta_L = 0.85$, are *ad hoc* values that are chosen to obtain the model consistency with biological expectations.

3.1.3 The naive tumor cells

The tumor growth rate, $a = 0.5822 \text{ day}^{-1}$, and the inverse of the tumor carrying capacity, $b = 2.33 \times 10^{-8} \text{ cells}^{-1}$, were left unchanged from the values found by the de Pillis et al. [70], who derived them by using MATLAB's *least-squares distance* to tumor growth data in mice from Diefenbach et al. [71]. Interestingly, these same values from de Pillis et al. [70] provide a best fit to our model for naive tumor cell population, equation (15), in the presence of weak immune system. The fitting was done by minimizing the sum of square errors between observed data points and values of model solutions using the MATLAB function *lsqnonlin*, and obtained Figure 3. Other parameters, α_N^+ and β_L^+ , were discussed above.

3.1.4 The wild-type tumor cells

Estimation of most the parameters in these tumor cell populations was discussed in the previous sub-sections, except for the proportion of tumor cells that survived from NK/CTL-tumor complex and maintained high level of effectiveness: $p_T = 0.05$ from a complex between NK cells, N , and naive tumor cells, T^0 ; $q_T = 0.05$ from the complex formed by activated CD8^+ CTLs, L , and naive tumor cells, T^0 ; $\zeta_T = 0.13$ from the complex between activated CD8^+ CTLs, L , and wild-type tumor cells that escaped from NK cell surveillance, T_N^1 , and $\pi_T = 0.18$ from the complex formed between NK cells, N , and the wild-type tumor cells that escaped from NK cell surveillance, T_L^1 . These parameter values are chosen to ensure that the model operates within a biologically reasonable regime.

Table 2: Tumor-Immune Model Baseline Parameters: Their Definition and Sources

Parameter	Definition	Value	Source
s	External influx of NK cells	$3.2 \times 10^3 - 3.2 \times 10^4 \text{ day}^{-1} \text{ cells}$	[97]
μ_1	per capita death rate of NK cells	$4.12 \times 10^{-2} \text{ cell}^{-1} \text{ day}^{-1}$	[91]
μ_2	per capita death rate of CTLs	$2.0 \times 10^{-2} \text{ cell}^{-1} \text{ day}^{-1}$	[91]
a	The per capita growth rate of tumor cells	0.5822 day^{-1}	[70]
b	The reciprocal carrying capacity of the tumor cells	$2.33 \times 10^{-8} \text{ cells}^{-1}$	[70]
α_N^+	Rate of binding of NK cells to naive tumor cell	$1.3 \times 10^{-7} \text{ day}^{-1} \text{ cells}^{-1}$	Estimate
α_N^-	Rate of detachment of NK cells from NK-tumor cell complex	24 day^{-1}	Estimate
β_L^+	Rate of binding of CTLs to naive tumor cell	$1.3 \times 10^{-7} \text{ day}^{-1} \text{ cells}^{-1}$	[13, 63]
β_L^-	Rate of detachment of CTLs from CTL-tumor complex	24 day^{-1}	[13, 63]
α_L^+	Rate of binding of NK cells to tumor cell that escaped from CTL	$1.2 \times 10^{-9} \text{ day}^{-1} \text{ cells}^{-1}$	Estimate

α_L^-	Rate of detachment of NK cells from tumor cell that escaped from CTL	24 day^{-1}	Estimate
β_N^+	Rate of binding of CTLs to tumor cell that escaped from NK cell	$1.3 \times 10^{-7} \text{ day}^{-1} \text{ cells}^{-1}$	[13, 63]
β_N^-	Rate of detachment of CTLs from tumor cell that escaped from NK cells	24 day^{-1}	[13]
p_N	Proportion of NK cells that survived from NK-naive tumor complex & maintained high level of effectiveness	0.94	Estimate
p_T	Proportion of naive tumor cells that survived from NK-naive tumor complex & maintained high level of effectiveness	0.05	Estimate
q_L	Proportion of CTLs that survived from CTL-naive tumor complex & maintained high level of effectiveness	0.94	Estimate
q_T	Proportion of naive tumor cells that survived from CTL-naive tumor complex & maintained high level of effectiveness	0.05	Estimate
π_N	Proportion of NK cells that survived from NK-tumor complex formed with “wild-type” tumor cell that escaped from CTL & maintained high level of effectiveness	0.80	Estimate
π_T	Proportion of “wild-type” tumor cells that escaped from NK cells	0.18	Estimate
ζ_L	Proportion of CTLs that survived from CTL-tumor complex formed with “wild-type” tumor cell that escaped from NK cells & maintained high level of effectiveness	0.85	Estimate
ζ_T	Proportion of “wild-type” tumor cells that escaped from CTLs	0.13	Estimate

r_1	Rate of CTLs recruitment due to CTL-“naive” tumor complex	$0.2988 \times 10^8 \text{ day}^{-1} \text{ cells}$	[13, 62, 63]
r_2	Rate of CTLs recruitment due to CTL-“wild-type” tumor complex	$0.2755 \times 10^6 \text{ day}^{-1} \text{ cells}$	Estimate
g	Maximum CTL recruitment by immunogenic tumor cells	$2.02 \times 10^7 \text{ cells}$	[13, 62, 63]

3.2 Simulations and Results

The numerical solutions of our model equations (15) – (20), along with the initial conditions (21) are carried out using MATLAB *ode23s*. This stiff ODE solver, *ode23s*, was used in this simulation in order to appropriately handle the differing time scales in the system. In this simulation, the initial value set for strong immune system consists of 10^5 NK cells and 10^2 activated CD8^+ lymphocytes as considered by Mamat et al [104]. The low influx of natural killer (NK) cells, is $s = 3.2 \times 10^3 \text{ day}^{-1} \text{ cells}$ [97] and the low recruitment of activated CD8^+ cytotoxic T lymphocytes (CTLs), is $r_1 = 0.2988 \times 10^8 \text{ day}^{-1} \text{ cells}$ [13, 62, 63] and $r_2 = 0.2755 \times 10^6 \text{ day}^{-1} \text{ cells}$ - estimate.

3.2.1 Comparing with previous studies

Using key model parameters, we started our simulation by comparing our results to a previously published model by de Pillis et al. [70] who also investigated the interactions of the NK and CD8^+ cells with various tumor cell lines. It is important to emphasize here that the study in [70] is based on assuming that tumor cells are a homogeneous population, while in this study tumor cells are considered to be a heterogeneous (i.e. different tumor cell lines: naive and wild-type tumors) population. This is motivated by the evidence that tumor cells develop certain immunoresistance to a specific immune cell after surviving their brief encounters [13]. During tumor cell development, tumor cells mutate in such a way that they are not all identical [105]. This usually results in heterogeneous tumor cell sub-populations [105, 106]. Recent evidence shows that tumors cells that survive immune surveillance usually develop complex mechanisms that enable them to evade the immune system [107]. By considering different tumor cell populations, our model shows that tumor escape from immune surveillance may be attributed to evolution and development of these heterogeneous tumor cell populations. In addition, this model successfully indicates the advantage of following different tumor populations to reduce tumor escape from immune surveillance.

Figure 3 indicates that naive tumor cells grow logistically in the presence of a weak immune response, not only in the absence of the immune response as done in [70]. More importantly, since NK cells are always present in the body [70, 91], this figure shows that the fact that tumor cells develop and grow in the presence of functioning immune surveillance [12].

Figure 3: Plot shows fitting of naive tumor cell population of the model (15) – (20) to the real data of tumor growth used by De Pillis et al [70].

3.2.2 Investigating the effects of the weak immune system on tumor evasion

The simulations, as indicated in Figure 4 suggest that the model, with the parameter assumptions and values we used, is capable of reproducing tumor escape from immune surveillance in a biologically realistic time frame.

Figure 4: Plots indicating the growth of the tumor cell populations and immune cells over time in the instance where there is low influx of natural killer (NK) cells, $s = 3.2 \times 10^3 \text{ day}^{-1} \text{ cells}$ and low recruitment of activated CD8^+ cytotoxic T lymphocytes (CTLs), $r_1 = 0.2988 \times 10^{-8} \text{ day}^{-1} \text{ cells}$ and $r_2 = 0.2755 \times 10^{-8} \text{ day}^{-1} \text{ cells}$. The plot shows that all the “wild-type” tumors, T_N^1 , T_L^1 and T_{NL}^1 , are capable of evading the immune system.

It is known that the immune system is capable of recognising and eradicating small tumors, though some tumor cells can slip through the immune system net [10, 12, 108, 109]. Figure 4

indicates that tumor cells usually escape immunosurveillance when the immune system is depleted [70]. Here, by depleted immune system we mean the case when there are few cytotoxic immune cells at the tumor site. More apparent growth dynamics of each cell population are given in Figure 5(a) – 5(b).

(a) Immune cells.

(b) tumor cells.

Figure 5: Plots of individual tumor and immune cell populations when there is low influx of natural killer (NK) cells and low recruitment of activated $CD8^+$ cytotoxic T lymphocytes (CTLs). Figure 5(a) indicates a natural response of NK cells to the presence of the tumor, followed by decline to a non-zero level of NK cells. Figure 5(b) shows how each tumor sub-population is growing over time in the case when the immune system is weak.

The results in Figure 5(a) could describe a case where immune system cells are out-competed by tumor cells in the search of necessary nutrients required to maintain their survival. Note

that the CTLs are continually declining because we have assumed that they are only present when the tumor is present, hence they have a negative growth rate. Thus, we observe in Figure 5(b) that all tumor populations are growing when the immune system is weak (i.e. when there is low influx of natural killer (NK) cells, $s = 3.2 \times 10^3 \text{ day}^{-1} \text{ cells}$ and low recruitment of activated CD8^+ cytotoxic T lymphocytes (CTLs), $r_1 = 0.2988 \times 10^{-8} \text{ day}^{-1} \text{ cells}$ and $r_2 = 0.2755 \times 10^{-8} \text{ day}^{-1} \text{ cells}$).

However, if the immune system is strong (i.e., when there are 10^5 NK cells and 10^2 activated CD8^+ lymphocytes), and high influx of NK cells, $s = 3.2 \times 10^4 \text{ day}^{-1} \text{ cells}$, we obtain Figure 6.

Figure 6: Plots indicating the growth of the tumor cell populations and immune cells over time in case where there is high influx of natural killer (NK) cells, $s = 3.2 \times 10^4 \text{ day}^{-1} \text{ cells}$. The plot indicates that immune system is capable of eliminating some “wild-type” tumor cells, particularly T_L^1 , or reducing growth of other “wild-type” tumor cells, T_N^1 and T_{NL}^1 .

Figure 6 demonstrates that the fact that an effective immune surveillance, mediated by NK cells and activated CD8^+ CTLs, is capable of controlling tumor growth [2]. We further investigate how tumor may evolve if the immune system is weak. Here, a weak immune system initially consists of 10^3 NK cells and 10 activated CD8^+ cytotoxic T lymphocytes for the same initial naive tumor cell of 10^4 cells. More interestingly, by following individual plots of each population, we obtain Figure 7(a) – 7(b).

(a) Immune cells.

(b) tumor cells.

Figure 7: Plots of individual tumor and immune cell populations when there is high influx of natural killer (NK) cells and high recruitment rate of activated $CD8^+$ cytotoxic T lymphocytes (CTLs). Figure 7(a) shows a rapid growth of NK cells in response to the presence of the tumors, followed by saturation because there cannot be an unbounded supply of NK cells in a realistic biological setting. Figure 7(b) shows how each tumor sub-populations eradicated or reduced over time.

Figure 7(a) – 7(b) indicates that even-though the immune system is able to eradicate or reduce some tumor sub-populations, an evolution of multi-immunoresistant tumors cells, denoted by T_{NL}^1 , that escaped from both arms of immune systems continue increasing. This simulation demonstrates the fact that tumors do develop in the presence of a functioning immune system [9–12].

4 Sensitivity Analysis

We now explore the sensitivity analysis of the model output to parameter values. We carry out two standard procedures of evaluating model sensitivity to changes in the parameter values, namely global sensitivity analysis (GSA) and local sensitivity analysis (LSA).

4.1 Global Sensitivity Analysis (GSA)

We performed a global sensitivity analysis (GSA), where all 22 model parameters are varied simultaneously, to investigate how variations in all model parameters influence the model outcome. In particular, we consider one of the most reliable and efficient types of global sensitivity analysis indexes, namely partial rank correlation coefficient (PRCC) [110]. PRCC measures the relationship (specifically monotonicity) between a model variable of interest and each model parameter. Results of PRCC help to identify which key input parameters contribute most to model variability. PRCC takes values between -1 and $+1$. The sign of PRCC indicates how the model variable of interest is qualitatively related to each model parameters. The absolute value of PRCC determines the degree of monotonicity between the model variable of interest and the specific parameter.

Using the weak immune system baseline conditions, (i.e. 10^3 NK cells and 10 activated $CD8^+$ CTLs), we first computed the time to equilibrium (tumor free equilibrium) before performing the global sensitivity analysis. Here, time to equilibrium is the time immune system requires to eradicate or at least bring the tumor to a controlled state without any treatment or boosting. For our model, time to equilibrium is 60 days. After 60 days, most of the naive tumor growth dynamics have already been established. That means, either the tumor has been eliminated by the immune system or escaped the immune surveillance. Of particular interest, are the intermediate time points prior to dynamical equilibrium. These time points may represent the time periods whose effect in tumor-immune interactions may be altered through specific immunotherapies to inhibit tumor escape or prolong immune system control on tumor populations.

We performed PRCC analyses for four different time points in order to investigate which parameters consistently influence each model cell population in time. The indexes are evaluated at the following time points 15, 30, 45 and 60 days prior to equilibrium state, and the model variable chosen for sensitivity analysis is natural killer cells (Equation (15)). For each of the four time points, denoted by 1, 2, 3 and 4, PRCC results are shown in Figure 8. From the PRCCs results presented in Figure 8, we conclude that the parameters for NK source, s , natural death of NK cells, μ_1 , and the binding rate, α_L^+ , of NK cells to the “wild-type” tumours, T_L^1 , account for most uncertainty for NK cell population.

Figure 8: PRCC results showing sensitivity indices of the model parameters with naive tumor cell population chosen as a baseline PRCC analysis variable.

Figure 8 indicates PRCC results which show how parameters s , μ_1 and α_L^+ are consistently significant and the most important parameters accountable for most of the variability NK cells. The PRCC results suggest that the NK cell population over time is mainly affected by variations in the parameters s , μ_1 and α_L^+ . PRCC scatter plots of the NK cell population versus each parameter have been obtained, but we provide only scatter plots of these three important parameters in Figure 9(a) – 9(c), where the strong correlations are confirmed. Note that although the scatter plot for the parameter α_L^+ shows weak correlation, parameter α_L^+ is found to be consistently significant with the PRCC analysis.

Figure 9: PRCC scatter plots of the most significant parameters s, μ_1 and α_L^+ (computed at the last time point, day 60). The title of each plot provides the PRCC value with the corresponding p-value. The results are significant at the 0.05 level.

In all figures in Figure 9(a) – 9(c), the axes indicate the residuals of the linear regression between the rank-transformed values of the NK cell population against the rank-transformed values of each the parameter. Note, Figure 9(a) and Figure 9(b) are statistically significant even at 0.001 level, while Figure 9(c) is significant at 0.05 level of significance. The source of NK cells has a strong positive, with PRCC of 0.92697, correlation with NK cell population, while the death rate of NK cells has a strong negative, with PRCC of -0.95583 , correlation with NK cell population. The absolute value of the PRCC value of 0.5 indicates no correlation between the input variable (i.e. parameters in this case) and the outcome variable (i.e. the NK cell population). Thus, from Figure 9(c) we note that the binding rate of NK cell to tumor cell has a moderate negative correlation, with the PRCC value of -0.10202 and a small p-values $0.022519 < 0.05$, with the NK cell population. The parameters with large absolute PRCC values, $PRCC > |0.5|$, with corresponding small p-values < 0.05 , are considered to be the most important parameters [111]. These scatter plots illustrate how significant is PRCC analysis in determining monotonic relationships between model variables and parameters using rank-transformation method.

Most interestingly, we performed PRCC analysis with regard to naive tumor cells in order to investigate which parameters have significant variations in naive tumor population. This

is important because parameters with high influence on naive tumor cell population may be accountable for tumor escape, leading to a new generation of wild-type tumor, $T_i^1, i = N, L, NL$. Identification of these parameters can help to design treatment strategies that specifically target those factors that augment tumor escape from immune surveillance. The results of the PRCCs are presented in Figure 10.

Figure 10: PRCC results showing sensitivity indices of the model parameters with “naive” tumor cell population chosen as a baseline PRCC analysis variable.

Figure 10 shows PRCC results over fourth different points: 15, 30, 45 and 60 days. In this analysis, different parameters become statistically significant in different time points. For instance, two parameters, the maximum CTL recruitment by immunogenic tumor cells, g , and the rate of CTLs recruitment due to CTL-“wild-type” tumor complex, r_2 , were statistically significant in the first time point. In the second time point, 30 days, CTLs recruitment due to CTL-“naive” tumor complex, r_1 and the binding rate of CTLs to naive tumor cells, β_L^+ , are most influential in determining the tumor escape ($|PRCC| > 0.5$) and are statistically significant (p-value < 0.05). In 45 days, only death of NK cells, μ_1 , and the proportion of NK cells that survived from NK-tumor complex formed with “wild-type” tumor cell that escaped from CTL and maintained high level of effectiveness, p_N , are most significant influential parameters. In the last in 60 days, an intrinsic tumor cell growth rate, a , the binding rate of NK cells to tumor cell that escaped from CTLs, α_L^+ , and recruitment rate of CTLs due to CTL-“wild-type” tumor complex are the only parameters that account for most variability in the model.

Despite a large number of parameters the model has, we note that it is significantly more sensitive to variations to few parameters. Interestingly, at later time points, it is highly sensitive to the intrinsic tumor growth rate a , as was the model by de Pillis et al. [99]. This is very interesting because given some tumor data sets these parameters can be easily estimated, as was done in de Pillis et al. [52, 70]. One of the most interesting finding in our analysis results is that the model reveals a higher degree of sensitivity to key parameters that could be targeted with specific immunotherapies. The NK-cell based immunotherapy can be used to enhance

immune surveillance against developing tumors [9]. Most interestingly, the fact that tumor-immune interactions can be observed experimentally [2, 112], our sensitivity analysis indicates that the model parameters, such as binding rate of NK cells to tumor cells or CTL recruitment, may be desirable targets for immunotherapy.

4.2 Local Sensitivity Analysis (LSA): Model implications for Immunotherapy

We now provide a brief local sensitivity analysis of our model, equations (15) – (20), in order to investigate how specific parameters of interest influence model behavior. Since the model has many parameters, we only performed sensitivity analysis of parameters that are associated with model implications for immunotherapy. In particular, we focused on how specific changes in the source of NK cells, s , affect the number of “wild-type” tumor cells, T_L^1 , that are susceptible to NK-cell mediated lysis after surviving their encounter with the CTLs. To perform sensitivity analysis of our model with respect to the source of NK cells, s , we assumed that the NK cell influx parameter can be uniformly increased within the range of $\pm 10\%$ or $\pm 20\%$ of the initial parameter baseline value.

Figure 11 and Figure 12 show the effect of varying the source term in the NK cells, resulting in an increase for NK cell population and reduction of the “wild-type” tumor cells, particularly T_L^1 . The NK cell source is varied in a biologically relevant range presented in Table 2 in order to investigate the effect of NK cell influx on tumor regression. From Figure 11, it can be observed when there is low boosting of NK cells, NK cell density quickly reduces to zero. That means low-level boosting of NK cells, does not increase NK cell density for longer periods of time. For instance, from Figure 11, it can be seen that 50% boosting of NK cells continue producing elevated NK-cell density for up to 20 days. Thus, in this simulation, it seems likely that tumor cell evasion from NK-cell surveillance would occur after 20 days.

Figure 11: The plot showing the effect of varying the source term of NK cells in numerical solutions. Increasing the source term of NK cells leads increased cell density of NK cells for certain period of time. Other baseline parameters for these simulations are the same as in Table 2, but we have values of s as indicated on the graph.

From Figure 12, it can also be observed that high-level boosting of NK cells results in significant reduction of tumor cells that are potential targets for NK cell. The presence of a

high number of NK cells in tumors contributes significantly to the host's anti-tumor immune responses [113]. It is important to note that Figure 12 does not indicate tumor eradication within 40 days, but tumor control with different NK-cell boosting levels. This result indicates that the NK cell-based immunotherapy may be necessary (although perhaps not sufficient) to achieve an increased tumor regression or a delayed tumor growth.

Figure 12: The evolution of the “wild-type” tumor cells, T_L^1 , in numerical solutions of our model, indicating the effect of varying the source term of NK cells. By increasing the source term of the NK cells does not only decrease the number of tumor cell population but also reduce time for evolution of these cells. The baseline parameters for these simulation are given in Table 2, with values of the source of NK cells, s , as indicated on the graph.

The above results show that the number of immune cells at the tumor site plays a significant role in cancer immune surveillance. It is important to emphasize that at each time step in our simulations, the number of immune cells at the tumor site is characterized by the intent to interact with tumor cells and/ or carry out tumor lysis. When there are few immune cells at the tumor site, we assumed that other immune cells, which are not at the tumors site, are randomly attempting to migrate into immunogenic tumor site. As can be seen in Figure 11 and Figure 12, an increment in the source of NK cells, results in depleted number of tumor cells.

These results also suggest that an infiltration of NK cells can be used as one of the biological treatment options to boost immune surveillance. Recent evidence indicates that NK-cell infiltration into tumor tissues has been associated with positive prognosis in patients [9]. Moreover, studies from human cancers demonstrate that when there are few infiltrating NK cells into the tumor site, tumor elimination is not feasible [114,115]. Therefore, as shown in this study, NK-cell infiltration may be an important immunotherapeutic strategy to enhance immune surveillance against tumor cells.

5 Discussion

In this paper, we developed a novel mathematical model for the immune surveillance of tumors. The model describes how tumor cells evolve and survive the brief encounter with the immune system mediated by natural killer (NK) cells and the activated $CD8^+$ cytotoxic T lymphocytes (CTLs). To our knowledge, this is the first mathematical study of the tumor escape and acquisition of immune resistance to multiple immune cell populations. The key features of this model are:

- (a) *The development of immunoresistance by the tumor cells:* the model successfully demonstrates that an evasion of tumor cells from their brief encounters with specific immune cells may enable tumor cells to acquire an immune-resistant phenotype through genetic mutations or epigenetic changes. After surviving an immune attack, to support their growth, tumor cells either mount a “counter-attack” or develop resistance to immune cells [2, 22, 86].
- (b) *The inclusion of multiple tumor cell populations:* multiple tumor cell populations are included in this model, so that their respective evasion mechanisms can be quantified at different stages of tumor growth. To avoid CTL-mediated lysis, tumor cells usually down-regulate the major histocompatibility complex (MHC) class I molecules [65, 66, 92, 93, 96]. However, this down-regulation of MHC class I molecules renders tumor cells more susceptible to NK cell-mediated killing [65, 66]. Thus, the model qualitatively illustrates these dynamics of tumor hiding from immune cells.

The model predicts that the low NK cell number could be attributed to escape of cancer cells from the mechanisms of immune surveillance as shown in Figures 4 and 5(b). It also predicts that the development of immunoresistance by tumor cells is inevitable in tumor immune surveillance as shown in Figures 6 and 7(b). In addition to an important strategy of promoting tumor regression by focusing on increasing $CD8^+$ T cell activity [52] (i.e. to augment the negative CTL growth), our model supports boosting of NK cells. Most interestingly, an immune-boosting of NK cells may offer a better strategy for devising novel and more effective immunotherapies aimed at eliminating nascent tumor escape and reducing acquired immune resistance. Evidence from experimental studies indicates that insufficient NK cell recruitment leads to tumor progression [116]. Additionally, the model indicates that the host immunity can only effectively control tumor growth of certain cell populations if the immune system is strong, as can be seen in Figure 6, otherwise tumor growth progression would be uncontrollable. Recent progress in NK cell immunobiology indicates that tumor cells can be eradicated only when immune responses are adequate [9].

The major results from this model are highlighted as follows:

An influx of the external source of NK cells might play a crucial role in enhancing NK-cell immune surveillance. The numerical simulations indicate that an infiltration of the external source of NK cells might play a crucial role when there are insufficient NK cells in the body as seen in Figure 11 and Figure 12. Increasing the source term of NK cells leads to an increased number of NK cells and consequently a decrease in the number of tumor cell populations. This could be used as an adoptive cellular immunotherapy (ACI), a treatment in which the anti-tumor leukocytes, like activated $CD8^+$ cytotoxic T lymphocytes (CTLs) or activated NK cells, are activated and cultured in large numbers in a laboratory and transferred into tumor bearing host. Advances in anti-tumor treatments such as cytokine-based immunotherapy [117] and adoptive cellular therapy [118] indicated that NK-cell based immunotherapies provide a

better prognosis against tumors [9].

Immune system alone is not fully effective against progression of tumor cells. The model's simulations show that the immune system alone is not fully effective against progression of tumor cells. For example, Figure 6 elucidates the dynamics of tumor-immune interactions with a strong immune system, but the multi-immunoresistant tumor cell population continues to grow. It is also worthwhile to note that the NK cell population needs to be high enough, in the range of $1.0 \times 10^4 - 3.2 \times 10^4 \text{ day}^{-1} \text{ cells}$, for an effective anti-tumor response as shown in Figure 12. Recent evidence indicates that the presence of a high number of NK cells at the tumor site contributes significantly to the host's immune surveillance [113].

It has been suggested that low NK cell numbers in tumors increases chances of tumor escape from immune surveillance [9, 23, 47, 113, 114, 119]. This has been shown by our model as depicted in Figure 4 and Figure 5(a) – 5(b). In this scenario, all tumor cell populations grow uncontrollably within a short period of time. This demonstrates that the number of immune cells necessary for inhibition of tumor growth is of paramount importance [23]. The NK cells, as part of innate immunity, are the first immune effectors to attack developing tumor cells before the strong specific immunity comes into play [2, 68]. Evidence from clinical studies indicates that improved survival rate of patients with gastric carcinoma was significantly enhanced in patients with a high rate of NK infiltration than in those with a low level of NK infiltration [120]. Hence, the low number of NK cells at the tumor site, may give tumor cells a chance to evade immune surveillance.

More importantly, studies show that high levels of NK cells, particularly tumor infiltrating NK cells (TINKs), have demonstrated a favorable tumor regression in patients with colorectal carcinoma [121] and in squamous cell lung cancer [122]. This suggests that increasing NK-cell influx into tumor tissues could represent a positive prognostic outcome, as implicitly shown by the model's simulations in Figure 12.

Multi-immunoresistance. Finally, we note that while some tumor cell populations are decreased, naive tumor cells, T^0 , and wild-type tumors that escaped from activated $CD8^+$ CTLs, T_L^1 , in Figure 7(b), the multi-immunoresistant tumor population, T_{NL}^1 , is not altered significantly. Development of the multi-immunoresistant tumor cell population is a major problem in cancer immune surveillance [21, 22].

Recent evidence shows that even-though a NK cell immunity complements a $CD8^+$ cytotoxic T lymphocytes (CTLs) immunity, poor prognosis has been observed from patients with HLA-I-defective melanoma cells [123]. This indicates that tumors are capable of deploying complex mechanisms to evade NK cell immunosurveillance as well. Experimental studies of Gulubova et al. [47] indicate that low NK cell numbers at the tumor site could be attributed to escape of metastatic cancer cells from the mechanisms of immune surveillance. This is confirmed by our simulation as indicated in Figure 4.

More importantly, the model simulations, depicted in Figure 11 and Figure 12, support the importance of infiltrating NK cells in tumor immune surveillance, which can be enhanced by NK cell-based immunotherapeutic approaches like infiltration of autologous (patients' own) NK cells [9, 124].

An important drawback of the proposed model is that the multi-immunoresistant tumor population persists growing regardless of the presence of a high NK cell influx or a high recruitment of activated $CD8^+$ cytotoxic T lymphocytes (CTLs) to the tumor site. This problem can be avoided by combining immunotherapy, as indicated by external source of NK cells in our model, with other therapies like chemotherapy and/ or oncolytic virotherapy [125, 126].

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Conflict of Interest

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

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