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Review

Mathematical modeling of tumor-immune cell interactions

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ABSTRACT

The anti-tumor activity of the immune system is increasingly recognized as critical for the mounting of a prolonged and effective response to cancer growth and invasion, and for preventing recurrence following resection or treatment. As the knowledge of tumor-immune cell interactions has advanced, experimental investigation has been complemented by mathematical modeling with the goal to quantify and predict these interactions. This succinct review offers an overview of recent tumor-immune continuum modeling approaches, highlighting spatial models. The focus is on work published in the past decade, incorporating one or more immune cell types and evaluating immune cell effects on tumor progression. Due to their relevance to cancer, the following immune cells and their combinations are described: macrophages, Cytotoxic T Lymphocytes, Natural Killer cells, dendritic cells, T regulatory cells, and CD4+ T helper cells. Although important insight has been gained from a mathematical modeling perspective, the development of models incorporating patient-specific data remains an important goal yet to be realized for potential clinical benefit.

1. Introduction

1.1. Immune system cell types

The human immune system has two main components that interact with each other to defend organisms from pathogens: the innate and the adaptive components. The innate response provides a general defense mechanism that can be quickly mounted. Cells that belong to this response include macrophages, Natural Killer (NK) cells, and neutrophil leukocytes. Monocytes circulate in the peripheral blood and are recruited to tissues following infection or injury, where they differentiate into either pro- or anti-inflammatory macrophages, based on cues in the local microenvironment. NK cells are regulators of the immune response and have the capability to target stressed or cancerous cells. Neutrophils circulate in the blood and migrate through tissue to destroy bacteria and other pathogens.

The adaptive response takes longer (up to 7 days) to mount a defense, but unlike the innate response, its targeting is highly customized to particular pathogens. The adaptive response maintains a memory of pathogens encountered, for quick re-activation of the defense if needed in the future. Cells of the adaptive component include B lymphocytes, T lymphocytes, and dendritic cells (DCs). During the course of fighting an infection, B lymphocytes produce antibodies specialized to a particular pathogen, while T lymphocytes develop into specialized cells, including Cytotoxic T Lymphocytes, T regulatory cells, T helper cells, and T memory cells. Dendritic Cells are antigen-presenting cells that initiate the adaptive response, traveling to secondary lymphoid organs upon exposure and uptake of pathogens to activate naïve T cells.

Cytotoxic T Lymphocytes (CTLs), also known as CD8+ T Cells or Killer T Cells, express a unique antigen-binding molecule (T-Cell Receptor) enabling them to kill any cell not recognized as belonging to the host organism. Their activity is tightly regulated by other immune cells. CD4+ T cells are commonly classified into T regulatory cells (Tregs) and T helper (Th) cells. Tregs regulate the Th cells, thus controlling the immune response. The Th cells control adaptive immunity against pathogens and cancer by activating other effector immune cells. The Th cells are activated on the surface of antigen-presenting cells, and in turn they activate macrophages to destroy ingested microbes, B cells to secrete antibodies, and CTLs to kill infected target cells.

1.2. Immune system surveillance

Tumor progression to malignancy depends critically upon escape from immunosurveillance, the process by which the immune system detects and eliminates cancerous cells. Prior to malignancy

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and metastasis, precancerous tumors may remain in a dormant state for years (Aguirre-Ghiso, 2007). Dormancy may not necessarily result from a lack of sufficiently stacked tumorigenic adaptations required for rapid replication, i.e., the persistence of safeguards that prevent unchecked growth. Dormancy may also result from a balance of oncotic growth kept in check by immunosurveillance. Through various mechanisms, both the innate and adaptive immune systems counteract growth by inducing apoptosis and/or cell cycle arrest (Dunn et al., 2004; Mittal et al., 2014). Natural Killer cells, Cytotoxic T Lymphocytes, CD4+ T helper cells, and B Lymphocytes regularly survey and prevent propagation of mutated cells (Nicholson, 2016). It is when the balance of growth and targeting is upset by evolutionary pressures in favor of tumors capable of immune evasion or immunoediting that malignancy may occur. In effect, the immune system's ability to prevent development of tumors can also create tumors undetectable by it.

1.3. Mathematical modeling

Mathematical modeling of cancer has traditionally been classified as continuum, discrete, or a (hybrid) combination of both, based on the physical representation of the relevant biological components, and has been extensively reviewed in the past decade (Alfonso et al., 2017; Anderson and Maini, 2018; Baldock et al., 2013; Byrne, 2010; Chaplain, 2011; Cristini et al., 2008; Deisboeck et al., 2011; Edelman et al., 2010; Enderling and Chaplain, 2014; Frieboes et al., 2011; Hatzikirou et al., 2012; Kreeger and Lauffenburger, 2010; Michor et al., 2011; Osborne et al., 2010; Palladini et al., 2010; Rejniak and McCawley, 2010; Szymańska et al., 2018; Vineis et al., 2010; Wang et al., 2015a,b). Whereas continuum formulations allow for more efficient representation of tissue-scale phenomena, discrete models are well-suited for representing individual cells and their interactions. Systems with only time as the independent variable typically present with ordinary differential equation (ODE) formulations, while those that include multiple spatial dimensions yield partial differential equation (PDE) systems of equations.

Models can also be classified in terms of their scale of interest, as to whether they represent phenomena at molecular, cellular, tissue/organ, or patient scales. Although tumor-immune dynamics occur at various scales, models have traditionally focused on one of these scales due to the complexities involved. In particular, a prey-predator approach is commonly used to describe numerous biological processes and is suited for representing the actions of individual cells (d'Onofrio et al., 2010; Letellier et al., 2013; Rocha et al., 2018; Singh et al., 2017). For example, a cell-by-cell approach may be useful for strategies in which Natural Killer cells or Cytotoxic T Lymphocytes "prey" on tumor cells. A strategy to represent multiple scales also taking into account the microenvironment is to represent the tumor itself as a semi-homogeneous aggregate of cells with strata of oxygenation controlling rate of proliferation (Owen and Sherratt, 1998). This allows intra-tumor dynamics such as development of hypoxic regions to be modeled. Blending of multiple scales can be computationally intensive, and has not yet been widely adopted (Rejniak and Anderson, 2011).

Recent comprehensive reviews have included evaluation of modeling the cancer-immune response to therapy (de Pillis et al., 2014), an assessment of tumor-immune non-spatial models (Eftimie et al., 2011), and an overview of multiscale agent-based and hybrid modeling of the tumor immune microenvironment and cancer immune response (Norton et al., 2019). This review encompasses continuum models developed in the last decade, highlighting spatial models, and focusing on the interactions of particular immune cell types with tumors and their microenvironment. In addition to tumor-immune cell dynamics, some models have explored the effects of immunotherapy, chemotherapy, and their combinations on tumor progression; some of these models are mentioned for illustrative purposes.

2. Modeling of tumor-immune cell interactions

2.1. Macrophages

Macrophages are the majority immune cell type in the tumor microenvironment (Nielsen and Schmid, 2017), and can have significant effects on tumor growth (Chanmee et al., 2014; Guo et al., 2013; Guo et al., 2014; Tripathi et al., 2014) and treatment response (De Palma and Lewis, 2013; Squadrito and De Palma, 2011). Macrophage phenotype and lineage vary (Italiani and Boraschi, 2014; Laoui et al., 2011), producing both tumorigenic and tumoricidal effects (Chanmee et al., 2014) (Roca et al., 2009), influenced by cytokines secreted by the tumor-associated tissue and stroma. The phenotype may be sorted into a spectrum, with the M1 inhibiting tumor growth by migrating to the tumor site and secreting cytotoxic compounds such as NO, and the M2 promoting cancer via recruitment to the tumor site and release of growth-promoting cytokines (Yao et al., 2018; Yuan et al., 2015). The phenotypes are fluid, with macrophage activation and M1 and M2 functions shared to various degrees depending on environmental cues.

In early work, Owen and Sherratt (1998, 1999) presented mathematical models to evaluate the effects of macrophage presence, influx, and ability to selectively kill tumor cells in avascular tumors. Subsequent modeling evaluated the ability of macrophages engineered to target tumor cells (Byrne et al., 2004) or deliver drug (Owen et al., 2004), finding that such approaches are non-intuitively sensitive to tumor and therapy parameters. These findings were further explored in Webb et al. (2007), showing that effective targeting of hypoxic tumor cells by macrophages would benefit from limited-diffusivity or non-cell-cycle dependent drugs.

The effects of macrophage repolarization on tumor growth were recently evaluated by den Breems and Eftimie (2016). M1 macrophage density x_{M1} is described as:

$$\frac{dx_{M1}}{dt} = (a_s x_{Ts} + a_{m1} x_{Th1}) x_{M1}\left(1 - \frac{x_{M1} + x_{M2}}{\beta_M}\right) - \delta_{m1} x_{M1} - k_{12} x_{M1} x_{M2} + k_{21} x_{M1} x_{M2},$$

where x_{M2} is the density of M2 macrophages, x_{Ts} is the density of immunogenic tumor cells recognized by immune cells, a_s is the activation rate of x_{M1} in the presence of x_{Ts} tumor-specific antigens, a_{m1} is the activation rate of x_{M1} in the presence of x_{Th1} type-I cytokines, x_{Th1} is the density of Th1 helper cells, β_M is the carrying capacity of M1 and M2 cells, δ_{m1} is the death rate of x_{M1} cells, k_{12} is the rate at which x_{M1} become x_{M2}, and k_{21} is the rate at which x_{M2} become x_{M1}. M2 macrophage density x_{M2} is described as:

$$\frac{dx_{M2}}{dt} = (a_n x_{Tn} + a_{m2} x_{Th2}) x_{M2}\left(1 - \frac{x_{M1} + x_{M2}}{\beta_M}\right) - \delta_{m2} x_{M2} + k_{12} x_{M1} x_{M2} - k_{21} x_{M1} x_{M2},$$

where x_{Tn} is the density of non-immunogenic tumor cells, a_n is activation rate of x_{M2} mediated by cytokines and growth factors produced by x_{Tn}, x_{Th2} is the density of Th2 helper cells, a_{m2} is the activation rate of x_{M2} by type-II immune response cytokines produced by x_{Th2}, and δ_{m2} is the death rate of x_{M2} cells. This study showed that type-II immune responses, characterized by large numbers of M2 and Th2 cells, are associated with tumor growth, and that the rates describing macrophage repolarization from M1 to M2 (and viceversa) determine the delay in tumor growth and the tumor size.

Clinically, a larger population of macrophages at a tumor lesion site is generally associated with poor patient outcomes, with a high M2/M1 ratio generally correlated with poor

prognosis (Lan et al., 2013). The effects of macrophages on triple-negative cancer were evaluated in an agent-based model in Norton et al. (2018), finding that although overall tumor growth is generally promoted by macrophages, excessive infiltration may not necessarily lead to substantial growth and could even promote tumor regression.

In Mahlbacher et al. (2018), M1, M2, and Tie2 expressing (TEM) macrophage variants were integrated into a spatio-temporal model of tumor growth representing a metastatic lesion in a highly vascularized organ such as the liver. TEMs are a macrophage subtype arising from a monocyte precursor distinct from the M1 and M2 subtypes. Their phenotype is similar to the M2, but unlike M2s, they are also critical for the support and maturation of neovascular sprouts (De Palma et al., 2005), and must be present for the tumor to progress (De Palma et al., 2005). Behaviors simulated by the model (described in further detail below) included M1 release of cytotoxic nitric oxide, M2 release of growth-promoting factors, and TEM facilitation of angiogenesis via Angiopoietin-2 and promotion of monocyte differentiation to M2 via IL-10. The results showed that M2 presence led to larger tumor growth regardless of TEM effects, implying that TEM ablation as an immunotherapeutic strategy may fail to restrain growth when the M2 represents a sizeable population. As TEM pro-tumor effects are less pronounced and on a longer time scale than M1-driven tumor inhibition, a more nuanced approach to influence monocyte differentiation taking into account the tumor state (e.g., under chemotherapy) may be desirable. The results highlighted the dynamic interaction of macrophages within a growing tumor, and evaluated the feasibility of a mathematical framework that could longer term help to optimize cancer immunotherapy.

A cornerstone of current cancer treatment is chemotherapy. In addition to cytotoxic effects on tumor cells, the effects on surrounding tissues and the immune system are still being elucidated. Some effects are synergistic; chemotherapy may cause cancerous cells to be more visible to the immune system, or upregulate the immune response directly or indirectly (Bracci et al., 2014). However, chemotherapy may also induce release of factors from nearby cells to promote tumor growth (Sun et al., 2012). Dosage and timing may have a variety of effects on immunosurveillance and tumoral resistance, suggesting a nuanced approach that also considers the effects of chemotherapy on the immune system to achieve better patient outcomes (Kareva et al., 2015).

Potential tumorigenic effects of macrophages, modeling the effect of macrophage presence and response to standard chemotherapy, and the role of the chemical tumor environment on tumor growth were examined in Chen et al. (2014). The tumor cell density c is modeled as follows:

$$\frac{\partial c}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 c v\right) = \lambda_c(w, C_{\text{ROS}})c\left(1 - \frac{c}{c^*}\right) - \mu_{c1}(w)c - \mu_{c2}c, \quad 0 < r < R(t),$$

where r is tumor radius, v is radial velocity, λ_c is proliferation rate, w is oxygen level, C_{ROS} is intracellular concentration of reactive oxygen species, μ_{c1} is necrosis rate, and μ_{c2} is apoptosis rate, assumed constant for non-treated tumors. In chemotherapy-treated tumors, the apoptosis term changes:

$$\tilde{\mu}_{c2} = \theta_4 \mu_{c2} \eta(w)$$
$$\eta(w) = \frac{w_0}{w},$$

where θ is the fraction of the volume occupied by cells and w_0 is the threshold for normoxia. Macrophages contribute to the chemical environment by expression of hypoxia inducible factors (HIF) which in turn influence levels of intracellular glutathione, a regulator of redox activity. The macrophage density m is modeled as:

$$\frac{\partial m}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 m v\right) = -\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 k_p m \frac{\partial p}{\partial r}\right), \quad 0 < r < L.$$

A system of ordinary and partial differential equations was used to describe the dynamics of intracellular glutathione as well as oxygen levels and pH. The modeling results suggest that macrophage HIF expression may contribute to tumor cell drug resistance via glutathione. Simulation results agreed with experimental observations of mouse mammary tumors *in vivo*, and the model was used to propose treatments by varying tissue oxygen, acidity, fast reducing rate (redox), and intracellular glutathione concentration.

In addition to being one the most prevalent immune cells in tumors, macrophages are natural phagocytic cells, which seek the hypoxic interior of tumor lesions in a natural healing response. This behavior makes them an attractive target for active drug delivery into tumor tissue. The hypoxia-seeking and tumor infiltration properties of macrophages were explored in Owen et al. (2011), finding that the combination of conventional and macrophage-based therapies could be synergistic. Macrophages were genetically modified to express an enzyme that activates the prodrug cyclophosphamide and were also loaded with magnetic nanoparticles. A magnetic field was applied to the tumor lesion, acting on the nanoparticles in the macrophages, and significantly enhancing their migration to the tumor interior. The probability of macrophage extravasation at location $\mathbf{x}$ from a vessel under the magnetic field is modeled as follows:

$$\Pr{}^{mac}_{extra}(x,t) = \Delta t 2\pi R(\mathbf{x},t)L(\mathbf{x},t)M_{blood}(\mathbf{x},t)\frac{V(\mathbf{x},t)}{A_v + V(\mathbf{x},t)} \times (\alpha_m + \beta_m|\mathbf{v}_{mag}\cdot\mathbf{n}(x,t)|)$$
$$M_{blood}(\mathbf{x},t) = k_M \frac{H(\mathbf{x},t)}{H_{in}} e^{-k_{mac}(t-T_{mac})},$$

where $R(\mathbf{x}, t)$ is vessel radius, $L(\mathbf{x}, t)$ is length of the vessel segment, M_{blood} is macrophage level in the vessel after a single macrophage injection, $V(\mathbf{x}, t)$ is VEGF concentration at site $\mathbf{x}$, A_v is VEGF concentration at half of its max, $\alpha_m$is baseline extravasation rate, β_m is increase in extravasation due to magnetic effects, $\mathbf{v}_{mag}$ is macrophage velocity due to the magnetic field, $H(\mathbf{x}, t)$ is hematocrit in the vessel, and H_{in} is the reference inflow of hematocrit. These mechanics were integrated in a complex multiscale model building on work in Owen et al. (2009), in which vascular growth, drug, oxygen, and VEGF diffusion, tissue growth, and cell movement are modeled at different timescales.

Recent work by Leonard et al. (2017, 2016) considered macrophages as both immune actors and vehicles for chemotherapeutic compound delivery. This model simulates macrophages as described in Mahlbacher et al. (2018), in which the tumor tissue itself is divided into hypoxic, necrotic and proliferating regions based on oxygen availability (Macklin et al., 2009; Wu et al., 2013) coupled with a dynamically evolving vascular system (McDougall et al., 2006). In Leonard et al. (2017, 2016), experiments were performed with macrophages uptaking a silicon-based multistage vector (MSV) loaded with the chemotherapeutic agent albumin-bound paclitaxel (nab-PTX). Drug and macrophage effects were evaluated in the tumor model calibrated to the *in vitro* experimental data. In the model, monocytes extravasate from the vasculature and migrate semi-stochastically along chemokine gradients secreted from the hypoxic and normoxic tissue regions. Contact with M1- or M2-favoring chemokines causes differentiation to macrophages, upon which they take an active role in the model (Mahlbacher et al., 2018). The tumor boundary velocity $\boldsymbol{v}_c$ as a function of the change in overall tumor tissue proliferation

rate $\lambda_p$is defined as (Macklin et al., 2009):

$$\nabla \cdot \boldsymbol{v}_c = \lambda_p.$$

The proliferation rate is dependent on oxygen availability, macrophage effects, and drug effects detailed below. Due to the short diffusion distance of NO, the anti-tumor activity λ_{M1} of M1 macrophages relies on an immediate-range effect λ_{NO}at the location of each macrophage (1_{M1}):

$$\lambda_{M1} = \lambda_{NO}\ 1_{M1}.$$

λ_{M2} is the proliferation-stimulating effect of M2, dependent on the effect λ_F and the diffusion of secreted growth factor F. The effect of λ_{M2} is additive with the native tumor proliferation rate λ_M:

$$\frac{d\lambda_{M2}}{dt} = \lambda_F F(1 - (\lambda_M + \lambda_{M2})).$$

The overall tumor proliferation rate λ_p is defined according to oxygen concentration σ: normoxic proliferating tumor region Ω_P, quiescent hypoxic tumor region Ω_H, and necrotic tumor region Ω_N:

$$\lambda_p = \begin{cases} non\ tumoral: & 0 \\ \Omega_P: & (\lambda_M + \lambda_{M2})\sigma\left(1-\bar{\lambda}_{effect}s\right)-(\lambda_A+\lambda_{M1}) \\ \Omega_H: & \lambda_{M2}\sigma\ -(\lambda_A+\lambda_{M1}) \\ \Omega_N: & -G_N \end{cases}.$$

The drug effect $\bar{\lambda}_{effect}$ at concentration s acts only on the proliferating tissue due to the cell-cycle targeting mechanism of nab-PTX. The tumor tissue native apoptosis rate is λ_A, and the rate of volume reduction in the necrotic region is G_N.

The study in Leonard et al. (2016) found that a single dose could dampen and delay lesion growth, but that a repeated regimen may be indicated for remission. These results agreed with experiments of breast cancer metastasis to the liver in a mouse model. Additionally, the model simulated the MSV-nab-PTX treatment acting synergistically with macrophage polarization to the M1 tumor-growth inhibiting phenotype, as observed in *in vitro* experiments (Leonard et al., 2017) in which M2 were repolarized to the M1 phenotype by their uptake of nab-PTX.

Interestingly, it was found that the presence of M2 in addition to M1 might lead to a stronger tumor drug response than when only M1 were active, due to the M2 macrophages favoring tumor tissue proliferation and thus increasing tumor sensitivity to the cell-cycling action of nab-PTX.

2.2. Cytotoxic T Lymphocytes

Cytotoxic T Lymphocytes (CTLs) have been a leading focus of onco-immunology in recent years (Fremd et al., 2013), being well known for antitumor activity by inducing apoptosis in an infected or cancerous cell with high specificity (Maher and Davies, 2004). Thus, CTLs are a frequent cell type represented in tumor-immune interaction models. Kirschner and Panetta (1998) was one of the first theoretical studies to investigate the role that CTLs may have on tumor growth and regression. The interactions between populations of effector cells E, tumor cells T, and IL-2 I_L are modeled as follows:

$$\frac{dE}{dt} = cT - \mu_2 E + \frac{p_1 E I_L}{g_1 + I_L} + s_1, \quad E(0) = E_0$$
$$\frac{dT}{dt} = r_2(T)T - \frac{aET}{g_2 + T}, \quad T(0) = T_0$$
$$\frac{dI_L}{dt} = \frac{p_2 E T}{g_3 + T} - \mu_3 I_L + s_2, \quad I_L(0) = I_{Lo},$$

where E is the effector cell population, c is the tumor's antigenicity, s_1 is an external source of effector cells, T is the tumor cell population, $1/\mu_2$ is the effector cells' natural lifespan, $r_2(T)$ is the tumor growth term, a is the immune response strength, I_L is the concentration of IL-2 at a single tumor-site, μ_3 is the IL-2 degradation, and s_2 is external input of IL-2. An in-depth review of this model was presented in Eftimie et al. (2011).

Many models have implemented a prey-predator approach, modeling immune cells as the predator population and tumor cells as the prey population. The Kuznetsov model is a classical representation of this approach (Kuznetsov et al., 1994):

$$\frac{dE}{dt} = s + \frac{pET}{g+T} - mET - dE$$
$$\frac{dT}{dt} = aT(1 - bT) - nET,$$

where E is effector cells that enter the system with constant rate s, are recruited at rate $\frac{pET}{g+T}$, and are killed or inactivated by tumor cells T at rate m. Tumor cells grow at a logistic rate $aT(1-bT)$ with carrying capacity $\frac{1}{b}$, and are killed by effector cells at rate n. The non-dimensionalized Kuznetsov model is given as:

$$\frac{dx}{dt} = \sigma + \frac{\rho xy}{\eta + y} - \mu xy - \delta x$$
$$\frac{dy}{dt} = \alpha y(i - \beta y) - xy$$
$$x = \frac{E}{E_0},\ y = \frac{T}{T_0},\ \sigma = \frac{s}{nE_0T_0}, \rho = \frac{\rho}{nT_0}, \eta = \frac{g}{T_0},$$
$$\mu = \frac{m}{n},\ \delta = \frac{d}{nT_0},\ \alpha = \frac{a}{nT_0}, \beta = bT_0,\ \bar{t} = nT_0 t.$$

Khajanchi and Banerjee (2014) incorporated a discrete time delay τ into the Kuznetsov model to simulate the interval in which the effector cells (such as CTLs) are recruited to the area but not yet acting against the tum

$$\frac{dx}{dt} = \sigma + \frac{\rho x(t-\tau)y(t-\tau)}{\eta + y(t-\tau)} - \mu xy - \delta x$$
$$\frac{dy}{dt} = \alpha y(1 - \beta y) - xy.$$

Through this model, the established behavior of "sneaking through," in which larger tumors are eliminated but smaller ones remain and grow, is observed. Further, the results show that the presence of stable limit cycles means that the immune system and the tumor undergo oscillations. For tumors with low antigenicity these cycles may be relatively long, with the tumors in a dormant state for most of the time.

Kiran and Lakshminarayanan (2013), basing their model on the Kuznetsov model, applied multi-objective optimization and post-Pareto-optimality analysis to model the immune interaction with chemotherapy against a growing tumor:

$$\frac{dE}{dt} = s + \frac{pET}{g+T} - mET - d_1E + s_1 - J(M)E$$
$$J(M) = K_l\left(1 - e^{-M}\right)H_1(M - M_{max})$$
$$\frac{dT}{dt} = aT(1 - bT) - nET - L(T, M)$$
$$L(T, M) = k(M - M_{th})H(M - M_{th})T$$
$$\frac{dM}{dt} = u - \gamma M,$$

where E is the number of effector cells, T is the number of tumor cells, M is the concentration of doxorubicin (Dox). H is the Heaviside function, s is effector cell natural flow rate to the tumor, s_1 is the input rate of externally administered effector cells. and p and g are Michaelis–Menten parameters pertaining to accumulation of effector cells due to stimulation by cytokines released by effector cells in contact with tumor cells. Effect cell degradation

due to their interaction with tumor cells and their natural lifetime is given by mET and d_1E, respectively. Additionally, a is maximal tumor growth rate, $1/b$ is the tumor carrying capacity, u is the rate of Dox input and γ is the rate of Dox decay. The study found that the combination of both chemotherapy and immunotherapy to be more effective than either individually. Further, there exists a threshold of immunotherapeutic interventions that yields maximum tumor response; more than four interventions may not yield further benefit.

Moghtadaei et al. (2013) implemented a discretized version of the Kuznetsov model, with the simulation results illustrating the chaotic dynamics and periodic oscillations that characterize the case of long term tumor relapse. The performance of the Kuznetsov model in representing effector and tumor cell interactions in early-stage cancer was compared to agent-based modeling in Figueredo et al. (2013).

Kaur and Ahmad (2014) built upon the prey-predator model of El-Gohary (2008) by introducing Michaelis–Menten dynamics to the stimulation of resting CTL cells in the presence of tumor cells. Accordingly, the equation governing the rate of change of hunting cells, $\frac{dR}{dt}$, has an additional Michaelis–Menten term added:

$$\frac{dt}{dt} = q + r_1 T\left(1 - \frac{T}{k_1}\right) - \alpha_1 TH$$
$$\frac{dh}{dt} = \beta HR - d_1 H - \alpha_2 HT$$
$$\frac{dR}{dt} = r_2 R\left(1 - \frac{R}{k_2}\right) - \beta HR - d_2 R + \frac{\rho TR}{T+\eta},$$

where T is the tumor cell concentration, H is concentration of hunting CTL cells, and R is resting CTLs. The carrying capacities k prevent unbounded population growth. β is the rate of conversion from R to H, ρ is the proliferation rate of R, and η is the Michaeles–Menten K_M equivalent. Apoptotic or natural cell death rates are d_1 and d_2, α_1 is the rate of tumor cell death by H, and α_2 provides the uncommon dynamic of H death by tumor cells. The results showed that the addition of the Michaelis–Menten function achieved stability in the system with increased rate of growth of inactive resting CTL cells.

Building on work by Gatenby (1995) and instituting discrete and continuum time variations, Gurcan et al. (2014) presented the following model with Lotka–Volterra-like prey-predator interactions:

$$\frac{dx}{dt} = r_1 x(t)\left(1 - \frac{x(t)}{k_1}\right) - \alpha_1 x(t) y([\![t]\!]) + \alpha_2 x(t) y([\![t-1]\!])$$
$$\frac{dy}{dt} = r_2 x(t)\left(1 - \frac{y(t)}{k_2}\right) - \alpha_1 x(t) y([\![t]\!]) + \alpha_2 y(t) x([\![t-1]\!]) - d_1 y(t),$$

where t is the integer portion of $t \in [0, \infty)$. r_1 is growth rate of tumor cells, α_1 is their decay rate due to competition between tumor and CTL cells, population density of tumor cells is $x(t)$, the carrying capacity of the tumor cells population is k_1, $y(t)$ is the population density of CTLs, r_2 their growth rate, k_2 their carrying capacity, α_2 their decay rate due to competition between tumor and CTL cells, and d_1 their death rate. It was found that r_2 and α_1, or the CTL growth rate and tumor cell decay rate, were the most effective parameters in achieving tumor stability or remission.

Other studies that analyze CTLs as the primary immune effector cells include (Chakrabarty and Banerjee, 2010; Maher and Davies, 2004), and more recently (Serre et al., 2016; Wilkie and Hahnfeldt, 2013). In particular, Serre et al. (2016) presented a discrete-time pharmacodynamics model of the combination of radiotherapy with inhibitors of the PD1–PDL1 axis or the CTLA4 pathway. The ability to forecast pharmacodynamics endpoints was retrospectively validated by checking that the model could describe data from experimental studies that investigated the combination of immune checkpoint inhibitors with radiotherapy.

Two approaches were presented in Wilkie and Hahnfeldt (2013) to study the observed decline in CTL predation efficacy due to cancer dormancy time. The first approach takes into account the observed decay trend for the CTL predation strength in a model of cancer-immune interactions to predict the resulting dynamics and possible escape from dormancy. The second approach selectively prunes a heterogeneous cancer cell population to transform a mostly sensitive population into a mostly resistant population, while still maintaining the dormant state. The cancer cell C and immune cell I populations are assumed to vary in time but not in space:

$$\frac{dC}{dt} = \alpha C\left(1 - \frac{C}{K}\right) - a_0 CI, \mathrm{C}(0) = \mathrm{C}_0,$$

where α is the proliferation rate and K is the carrying capacity of the cancer population. Assuming that the only recruitment of immune cells occurs through cancer-initiated increases in the carrying capacity, the immune population is assumed to follow:

$$\frac{dI}{dt} = \gamma I\left(1 - \frac{I}{I_e + \mu CI}\right), I(0) = I_e,$$

where γ is the proliferation rate and $I_e + \mu CI$ is the recruitment due to cancer-immune interactions. These basic equations were then modified to account for the emergence of immuno-resistant cancer cell populations R with proliferation rate β:

$$\frac{dC}{dt} = \alpha C\left(1 - \frac{C+R}{K}\right) - a_0 CI, \mathrm{C}(0) = \mathrm{C}_0$$
$$\frac{dR}{dt} = \beta R\left(1 - \frac{C+R}{K}\right) - b_0 RI, R(0) = R_0$$
$$\frac{dI}{dt} = \gamma I\left(1 - \frac{I}{I_e + \mu(C + 0.001R)I}\right), I(0) = I_e.$$

The results suggest that delaying cancer growth via the targeted removal of immune-sensitive subpopulations may actually induce the immune response to advance the cancer to a more aggressive state.

A model evaluating purely CTL effects in the microenvironment was presented in Ramos et al. (2013). In this mesoscopic model, the role of a gradient of factors released from the tumor that are able to attract CTLs to the area is evaluated. The tumor grows according to nutrient availability,

$$\gamma\left(\vec{i}\right) = \gamma_\infty\left[1 - e^{-\Gamma p\left(\vec{i}\right)}\right]$$

where $p(i)$ is local nutrient concentration absorbed with affinity Γ. If nutrient content is sufficient, the tumor grows with cancerous cells $c(\vec{i})$ replacing a fraction fi,j of healthy cells $h(\vec{i})$:

$$f_{i,j} = h\left(\vec{i}\right) + \left[r_M c\left(\vec{i}\right) - h\left(\vec{i}\right)\right]\Theta\left[r_M c\left(\vec{i}\right) - h\left(\vec{i}\right)\right],$$

where Θ is the Heaviside unit step function and $r_M$is a constant.

A chemical messenger $m(\vec{r}, t)$ arising from the tumor cells at rate K, diffusing at rate α_m, binding lymphocytes $l(\vec{r}, t)$ at rate G, and decaying at rate τ_m is modeled as:

$$\frac{\partial m(\vec{r}, t)}{\partial t} = -\frac{m(\vec{r}, t)}{\tau_m} + \alpha_m \nabla^2 m(\vec{r}, t) - Gm(\vec{r}, t) l(\vec{r}, t) + Kc(\vec{r}, t).$$

Lymphocytes move according to messenger $m(\vec{r}, t)$ concentration with migration α_l and decay with rate of τ_l as follows:

$$\frac{\partial l(\vec{r}, t)}{\partial t} = -\frac{l(\vec{r}, t)}{\tau_l} + \alpha_l \nabla^2 l(\vec{r}, t) - \nabla \cdot [l(\vec{r}, t) \nabla m(\vec{r}, t)].$$

The attacking of cancer cells $c(\vec{r}, t)$ by lymphocytes is described as:

$$\frac{\partial c(\vec{r}, t)}{\partial t} = -bl(\vec{r}, t) c(\vec{r}, t),$$

where b is a constant describing the ability of the CTL to kill, and is not reduced by multiple interactions with tumor cells. The results suggest that killing cancer cells may not be a sufficient therapeutic strategy to prevent recurrence. Efficient killing of cancer cells should be complemented by treatments that either enhance containment of active tumor regions by clustering of CTLs or otherwise inhibit cancer cell migration.

A model wherein CTLs undergo immunoediting by tumor cells was presented in Al-Tameemi et al. (2012). The system included the situation in which tumor cells that survive an initial encounter with immune cells are more likely to survive subsequent attacks, thus modeling an approximation of the development of cancer cell resistance. The model further evaluated the spatiotemporal effects on the CTL and tumor cell populations. The tumor cells that have not yet encountered CTLs, referred to as "naïve" cells, are represented as follows:

$$\frac{\partial T_0}{\partial t} = D_{T_0}\nabla^2 T_0 + r_1 T_0\left(1-\beta_1\sum_{j=0}^{N} T_j\right) - k_0^+ E T_0 + \left(k^- + k(1-\theta_0)(1-p_0)\right)C_0,$$

where T_0 are the naïve tumor cells, $D_{T_0}\nabla^2 T_0$ describes the cells' random motion, D_T being the diffusion coefficient, r_1 is the baseline exponential growth of the tumor, β_1 is the inverse of the tumor carrying capacity in the absence of immune reactions, C_0 are the of CTL-tumor cell complexes, k_0^+ is the formation rate of C_0, E is the spatiotemporal dynamics of the CTL, k^- is the C_0 unbinding rate, k is the rate of lethally hit tumor or CTL cells, θ_0 is the probability of transition of tumor cells to the T_0 state, and p_0 is the death probability of naïve tumor cells. In combination, $r_1 T_0(1-\beta_1\sum_{j=0}^{N} T_j)$ describes the cells' logistic growth and $k_0^+ E T_0 + (k^- + k(1-\theta_0)(1-p_0))C_0$ describes the local kinetics. After encountering CTLs, the tumor cells become "non-naïve" and develop resistance to future encounters; the cells' spatiotemporal dynamics change as follows:

$$\frac{\partial T_i}{\partial t} = D_i\nabla^2 T_i + r_1 T_i\left(1-\beta_1\sum_{j=0}^{N} T_j\right) - k_i^+ E T_i + \left(k^- + k(1-\theta_i)(1-p_i)\right)C_i + k\theta_{i-1}(1-p_{i-1})C_{i-1},$$

where T_i are the non-naïve tumor cells, $i=1,\ldots,N$, and r_1 is the baseline exponential tumor growth rate, $D_i\nabla^2 T_i$ describes the cells' random motion, $r_1 T_i(1-\beta_1\sum_{j=0}^{N} T_j)$ describes the logistic growth, and $(k^- + k(1-\theta_i)(1-p_i))C_i + k\theta_{i-1}(1-p_{i-1})C_{i-1}$ describes the non-naive cells' local kinetics. Spatiotemporal dynamics E of the CTLs themselves are modeled including both random and chemotactic motion as well as negative movement in response to a repellant ρ by non-naïve tumor cells:

$$\frac{\partial E}{\partial t} = D_E\nabla^2 E - \chi(\alpha)\nabla.(E\nabla\alpha) + A(\rho).(E\nabla\rho) + sh(x) + \frac{f\sum_{j=0}^{N} q_j C_j}{g+\sum_{j=0}^{N} T_j} - d_1 E - E\left(\sum_{j=0}^{N} k_j^+ T_j\right) + \left(\sum_{j=0}^{N} k^- T_j\right) + \left(\sum_{j=0}^{N} k p_j C_j\right)$$

where D_E is the diffusion coefficient driving random motility, χ is the chemotaxis coefficient, α is the chemoattractant, q_j is the rate constant, $sh(x)$ is the CTL external reflux of CTLs, d_1 is the CTL baseline death rate, and f and g are constants. In combination, $A(\rho).(E\nabla\rho)$ represents chemorepulsion, $\frac{f\sum_{j=0}^{N} q_j C_j}{g+\sum_{j=0}^{N} T_j}$ represents proliferation, and the last three summation terms represent the local kinetics. The results showed that the process of cancer cell immunoevasion may result from interactions between CTLs and tumor cells, in which lymphocyte-tumor cell complexes are formed. Thus, tumor cells that survive the formation of these complexes can develop an increased probability of surviving further attacks by CTLs, counter-acting immunotherapies aiming to maintain a tumor in a dormant state.

Other models that evaluate CTL-tumor interactions include Frascoli et al. (2014), which investigated oscillatory and unbounded eradicative growth patterns in an avascular tumor in a hybrid partial differential and agent based model, and (Rozova and Bratus, 2016), which accounted for negative chemotherapy effects on both tumor cells and CTLs. The infiltration of CTLs into small, avascular multicellular tumor spheroids was modeled in Matzavinos et al. (2004). Recruitment of CTLs to the site of melanoma lesion in mice was examined with an agent-based model in Pappalardo et al. (2011). In this case, antibody treatment upregulates the C137 receptor of tumoral endothelial cells, enhancing CTL migration to the area and achieving tumor elimination. Some models have explored the interaction of tumor and effector immune cells in the context of chaos (Itik and Banks, 2010) and noise (Bose and Trimper, 2011).

The synergistic effects of radiotherapy and cytotoxic T cells were examined in Chappell et al. (2015) with a system of four main variables: S (tumor volume), T (density of T cells in tumor and microenvironment, I (concentration of the immune agent), and C (radioactivity):

$$\frac{dS}{dt} = f_1(S) - f_2(S,T,C)$$
$$\frac{dT}{dt} = f_3(S,T,I,C) - f_4(S,T,C)$$
$$\frac{dI}{dt} = f_5(S,I)$$
$$\frac{dC}{dt} = f_6(S,C),$$

where the various $f_1 \ldots f_6$ functions respectively denote tumor logistic growth, tumor death, T cell activation. T cell death and inactivation, immunotherapy decrease, and radiotherapy decrease. The model was able to reproduce the *in vivo* observations of tumor volume and activated T cell number by Deng et al. (2014), with the simulation results showing that tumor clearance is achieved with both irradiation and presence of T cells, but not with each alone. Additionally, the prevalence of activated T cells capable of killing cancer cells is higher with radiation therapy, suggesting a combined approach to treatment.

2.3. Cytotoxic T Lymphocytes and Natural Killer cells

Identifying infected or cancerous cells with abnormal or absent surface presentations, Natural Killer cells (NKs) eliminate cancerous cells as part of the innate immune response. In many cancer patients, NKs are found to be deficient or abnormal, with curtailed cytokine release profiles and antitumor activities (Guillerey et al., 2016). Models in Kiran and Lakshminarayanan (2013) and de Pillis et al. (2009) considered the effects of both chemotherapy and adoptive cell transfer of CTLs. They were modeled in de Pillis et al. (2009) as follows:

$$\frac{dT}{dt} = aT(1-bT) - cNT - DT - K_T\left(1-e^{-\delta_T M}\right)T$$
$$\frac{dN}{dt} = f\left(\frac{e}{f}C - N\right) - pNT + \frac{p_N NI}{g_N + I} - K_N\left(1-e^{-\delta_N M}\right)N$$
$$\frac{dL}{dt} = \frac{\theta mL}{\theta + I} + j\frac{T}{K+T}L - qLT + (r_1 N + r_2 C)T - \frac{\mu L^2 CI}{\kappa + I} - K_L\left(1-e^{-\delta_L M}\right)L + \frac{p_I LI}{g_I + I} + \upsilon_L(t)$$

$$\frac{dC}{dt} = \beta\left(\frac{\alpha}{\beta} - C\right) - K_C\left(1 - e^{-\delta_C M}\right)C$$
$$\frac{dM}{dt} = -\gamma M + \upsilon_M(t)$$
$$\frac{dI}{dt} = -\mu_1 I + \phi C + \frac{\omega LI}{\zeta + I} + \upsilon_I(t),$$

where T is the tumor cell population, N is the concentration of NK cells, L is the CTL concentration, C is the concentration of other lymphocytes, M is the concentration of chemotherapeutic drug (here doxorubicin), I is the concentration of IL-2, υ_L is concentration per time of CTLs injected, υ_M is the concentration per time of drug injected, and υ_I is the rate and concentration per time of IL-2 administered.

The first term on the right hand side in the equation for T represents logistic growth, the second is NK-induced tumor death, the third is CTL-induced tumor death, and the fourth is drug-induced tumor death. Here, $D = d\frac{(L/T)^l}{s+(L/T)^l}$, where d and l are immune system strength and immune system scaling coefficients, respectively, and s is the value of $(L/T)^l$ required for half-maximal CTL toxicity. In the equation for N, eC is production of NK cells from circulating lymphocytes and fN is NK turnover, the second term is NK death by exhaustion of tumor-killing resources, the third term is the IL-2 stimulatory effect on NK cells, and the fourth term is NK cells death due to drug toxicity. In the equation for L, the first term is CTL turnover, the second is CTL stimulation by tumor debris from CTL-induced death, the third CTL death by exhaustion of tumor-killing resources, the fourth includes CTL stimulation by tumor debris from NK-induced death and activation of naïve CTL cells, the fifth is breakdown of surplus CTL in the presence of IL-2, the sixth is death of CTL cells due to drug toxicity, and the seventh is the stimulatory effect of IL-2 on CTLs. In the equation for C, the first term includes lymphocyte creation and turnover, and the second represents lymphocyte death due to drug toxicity. In the equation for M, the first term encapsulates drug elimination and excretion. In the equation for I, the first term is IL-2 decay, the second is IL-2 production by naïve CTL and T helper cells, and the third term is IL-2 production by activated CTL cells.

The model parameters were carefully calibrated to patient-specific data. The immune recruitment is presented in Michaelis–Menten form, which is useful in providing a saturation effect regarding increasing presence of immune effector cells (Kirschner and Panetta, 1998). The effectiveness of immune therapy in conjunction with chemotherapy and IL-2 administration was shown to be heavily reliant on CTL tumor-targeting ability. This model was later updated in de Pillis et al. (2014) to incorporate variations of immune vaccine and chemotherapy treatments.

In a model based on de Pillis and Radunskaya, (2003), Mahasa et al. (2016) took the novel step of incorporating into the tumor cell population immune resistance against NKs and CTLs, highlighting the importance of an inadequate NK population in facilitating tumor escape. The interaction between NK cells N, activated CTLs L, naïve tumor cells T^0, and wild-type tumor cells that escaped surveillance by (i) NK cells T_N^1, (*ii*) activated CTLs T_L^1, or (*iii*) both NK and activated CTLs T_{NL}^1, is given by:

$$\frac{dN}{dt} = s - \mu_1 N + \left(p_N\alpha_N^- C_N - \alpha_N^+ N T^0\right) + \left(\pi_N\alpha_L^- C_{NL}^N - \alpha_L^+ N T_L^1\right)$$
$$\frac{dL}{dt} = \left[r_1 C_L/(g+T^0) + r_2 C_{NL}^L/\left(g+T_N^1\right)\right] + \left(q_L\beta_L^- C_L - \mu_2 L - \beta_L^+ L T^0\right) + \left(\varsigma_L\beta_N^- C_{NL}^L - \beta_N^+ L T_N^1\right)$$
$$\frac{dT^0}{dt} = aT^0(1 - bT^0) - \alpha_N^+ N T^0 - \beta_L^+ L T^0$$
$$\frac{dT_N^1}{dt} = aT_N^1(1 - bT_N^1) + p_T\alpha_N^- C_N - \beta_N^+ L T_N^1$$
$$\frac{dT_L^1}{dt} = aT_L^1(1 - bT_L^1) + q_T\beta_L^- C_L - \alpha_L^+ N T_L^1$$
$$\frac{dT_{NL}^1}{dt} = aT_{NL}^1(1 - bT_{NL}^1) + \varsigma_T\beta_N^- C_{NL}^L + \pi_T\alpha_L^- C_{NL}^N,$$

where C_N, C_L, C_{NL}^N, and C_{NL}^Lrespectively represent the complex formed by NK and naïve tumor cells, CTL and naïve tumor cells, NK and wild-type tumor cells that escaped surveillance from active CTLs, and CTL and wild-type tumor cells that escaped surveillance from NK.

In the equation for N, the first term on the right hand side represents the source of NK cells, the second term is NK natural death, the third represents the local interaction between NK and naïve tumor cells, and the fourth is the local interaction between NK and wild-type tumor cells. In the equation for L, the first term is CTL recruitment, the second is activated CTL natural death, the third represents binding and detachment of activated CTL from naïve tumor cells, and the fourth is the binding and detachment of activated CTL from wild-type tumor cells that escaped NK cell surveillance. In the equations for the naïve and wild-type tumor cells, the first term represents logistic growth. For naïve tumor cells T^0, the second term represents interactions with NK cells and the third term denotes interactions with activated CTLs. For the three wild-type tumor cell equations, the second terms represents tumor cells that have escaped surveillance by NK, activated CTL, or both types of cells, respectively, while the third terms represent the local interactions with these respective immune cells.

The model results indicate that increasing the number of NK cells might be crucial to enhance NK-mediated immune surveillance. Further, the results show that the immune system alone may be incapable of thwarting tumor growth, while the development of tumor immunoresistance may be an unavoidable outcome of tumor-immune surveillance.

The antitumor effects of IL-21, focusing on NK, and CTL immunity, were evaluated in (Cappuccio et al., 2006):

$$\dot{u} = input - \mu_1 u,$$

where *input* is proportional to the total number of genetically engineered tumor cells n, u is the concentration of IL-21 and μ_1 is the clearance rate.

$$\dot{x} = r_1 x\left(1 - \frac{x}{h_1(u)}\right)$$
$$h_1(u) = \frac{p_1 u + p_2}{u + q_1},$$

where x is the NK population within the spleen, r_1 the growth rate of the NK population, h_1 is the carrying capacity the NK cells, p_1 is the minimum value of x, and p_2 and q_1 are varying parameters for the carrying capacity following $x_0 = \frac{p_2}{q_1}$.

$$\dot{y} = r_2 y\left(1 - \frac{y}{h_2(m)}\right)$$
$$h_2(m) = h_2(0) + \frac{\sigma m}{1 + \frac{m}{D}}$$
$$\dot{m} = au - \mu_2 m,$$

where y is the tumor-specific CD8$^+$ T subset in the lymph nodes, r_2 the growth rate of the CD8$^+$ T population, h_2 the carrying capacity of CD8$^+$ T cells, σ relates the growth of the carrying capacity to the memory factor, m is an IL-21 dose-dependent product, a is m's proportionality constant, and μ_2 is the reciprocal of the duration of the CD8$^+$ T response.

$$\dot{p} = \frac{b_1 u}{b_2 + u} - \mu_3 p$$
$$\dot{n} = g(n) - k_1 pxn - k_2 pyn,$$

where p is a general protein, b_1 and b_2 are variables of the function, and μ_3 is the natural degradation of the protein p, n is tumor mass, g describes the tumor dynamics, k_1 is the cytotoxic, protein mediated, antitumor interaction between tumor and NK cells, and k_2 is the interaction between tumor and $CD8^+$ T cells. The simulation results were compared to data from fibrosarcoma and melanoma tumors grown in mice. It was found that the effectiveness of IL-21 therapy to achieve tumor reduction was highly dependent on antigenicity and size of the tumor lesion. This system was later expanded and examined in the context of a pharmacokinetic/pharmacodynamic model validated by murine data (Elishmereni et al., 2011).

The interactions of CTLs and NK cells with a tumor growing in avascular conditions were studied with a two-dimensional stochastic agent-based model in Pourhasanzade et al. (2017). The effects of hypoxia were modeled including mutant and non-mutant proliferative cancer cells. The simulations illustrate the effect of the microenvironment on tumor growth and on the immune system, and the potential of the model to evaluate these effects under various immune and tumor conditions.

A model that examined NK cells alone, and the effect of antibody therapy is Hoffman et al. (2018). Antibodies bind to cancer cells, marking them for killing by NK cells. The multi-timescale model evaluated the rate of antibody binding to cancer cells, and the rate of tumor cell kill by activated NKs, taking the novel step of making the rate of cell kill dependent on the amount of antibody bound to cancer cells:

$$\begin{aligned}
\frac{dA}{dt} &= -k_{on}(\rho_T S - RS)A + k_{off}RS, A(0) = A_0\\
\frac{dR}{dt} &= k_{on}(\rho_T - R)A - k_{off}R, R(0) = R_0\\
\frac{dS}{dt} &= -f(R)C, S(0) = T_0\\
\frac{dC}{dt} &= \beta_{on}(N_0 - C)(S - C) - \beta_{on}C - f(R)C, C(0) = 0,
\end{aligned}$$

where antibodies A bind reversibly with rate k_{on} to unbound tumor receptors and dissociate from them with rate k_{off}, R is the number of antibody-receptor complexes per cancer cell, S is total concentration of cancer cells, and C are cellular conjugates of NK and tumor cells, binding with rate β_{on} and dissociating with rate β_{off}. The total concentration of target receptors is proportional with constant ρ_T to the total concentration of cancer cells. NK cells kill the cancer cells to which they bind with rate $f(R) = f_K^* R/(R + R_K)$, where f_K^* is the maximum rate of killing and R_K is the value of R for which the killing rate is half-maximal. The simulations reveal that the system evolves in a fast timescale, during which antibodies bind to tumor cell surface receptors and complexes of NK cells with cancer cells are formed, and also in a slower timescale, during which the tumor cells are killed by the NK cells.

2.4. Cytotoxic T Lymphocytes and dendritic cells

Dendritic cells are antigen-presenting cells, serving as a bridge between the innate and adaptive immune systems by assisting in the activation, differentiation and maturation of CTLs. It has been observed that their maturation and response may be hindered and altered by factors released from tumor cells (Markov et al., 2016).

de Pillis et al. (2013a) expanded upon prior work modeling interactions of dendritic cells with activated and memory CTLs (Ludewig et al., 2004). The model represents the spleen, the blood, and the tumor as separate compartments. The effect of additional doses of DCs and activated CTLs on a logistic-growth tumor was fit to experimental murine data. The model accounts for the trafficking of immune cells between the three compartments. In particular, the equations of the model regarding interactions between activated CTLs (E^a_{tumor}), tumor-infiltrating DCs (D_{tumor}), and tumor cells T in the tumor compartment are as follows:

$$\begin{aligned}
\frac{dE^a_{tumor}}{dt} &= \mu_{BTE}(T)E^a_{blood} - a_{E_aT}E^a_{tumor} - cE^a_{tumor}T\\
\frac{dT}{dt} &= rT\left(1 - \frac{T}{k}\right) - \mathscr{D}T\\
\frac{dD_{tumor}}{dt} &= \frac{mT}{q+T} - (\mu_{TB} + a_D)D_{tumor} + \nu_{tumor}(t),
\end{aligned}$$

where μ are flow rates between compartments, E^a_{blood} are activated CTLs in the blood compartment, a_{E_aT} is death rate of activated CTLs, c is rate of inactivation of CTLs by tumor cells, r is tumor growth rate, m is maximum DC recruitment rate to tumor site, q is value of T required for half-maximal DC recruitment, μ_{TB} is rate of transfer of DCs from tumor to blood, a_D is DC natural death rate, and $\nu_{tumor}(t)$ allows to inject DCs intratumorally to compare treatment protocols. The term $\mathscr{D}$ describes the ratio:

$$\mathscr{D} = d\frac{(E^a_{tumor})^l}{s + \left(E^a_{tumor}\right)^l},$$

where d represents maximum fractional tumor kill by CTLs and s is the value of $(E^a_{tumor}/T)^l$ required for half-maximal activated CTL toxicity. The simulation results analyzing intratumoral

DC injections to intravenous DC injections of various dosages and schedules fell within the experimental measurements obtained with mice implanted with melanoma tumors and treated with DC injections (Lee et al., 2007). Overall, the results of the model imply that more effective immunotherapy treatment protocols could be achieved by modifying the injection location and schedule.

Macfarlane et al. (2018) presented a spatially structured model of tumor-immune competition taking into account the difference in movement between activated and inactive immune cells. The model is able to capture the shift in movement that occurs with CTLs and DCs as they become activated by tumor antigens. Both CTL and DC cell movement becomes more restricted than in a pre-activation state (Boissonnas et al., 2007; Engelhardt et al., 2012). Inactive immune cells are modeled with a Lévy walk mechanism, where cells move in just one direction over a span of time, thus covering a large area. The number of time steps s that inactivated cells move in that singular direction is given by the Lévy-Distribution:

$$P(s) = s^{-(\alpha+1)},$$

where α is the walk exponent, as described in Harris et al. (2012). The movement of activated cells is modeled via Brownian motion. To confirm that using a Lévy walk and a change to Brownian motion upon activation is a sensible approach for modeling the movement of immune cells, the simulations qualitatively replicated the experimental data of Boissonnas et al. (2007). The study found that an increase in the number of DCs may lead to overcrowding and thus longer tumor removal times. A crucial parameter in tumor removal was found to be the ratio between the killing rate of tumor cells by CTLs and the tumor cell proliferation rate. The simulations further showed that an increase in activation rates of either CTLs or DCs had little effect on tumor removal.

2.5. T Regulatory cells

T Regulatory cells (Tregs) modulate the immune response, helping to prevent potential autoimmune action by other lymphocytes such as CTLs (Kondelkova et al., 2010). They are generally recruited and upregulated to the tumor site, and provide negative feedback on immune system activation, preventing autoimmune disease and maintaining immune homeostasis. Higher numbers of Tregs both

in the tumor microenvironment and the vasculature are associated with poorer patient outcomes.

Building on and incorporating the model in de Pillis et al. (2009, 2013b) examined the effect of Tregs in combination with CTLs, NKs, and CD4+ cells in the context of treatment with the tyrosine kinase inhibitor sunitinib, which has shown better tumor response than treatment with IL-2. The tumor cell population T is modeled as:

$$\frac{dT}{dt} = aT(1-bT) - ce^{-\lambda_T R}NT - DT,$$

where the first term represents logistic tumor growth, the second term incorporates Treg-inhibited NK tumor cell kill, and the third term includes $D = d\frac{(L/T)^l}{s+(L/T)^l}$, which describes tumor cell kill by CTLs.

NK cells N with baseline production eC from circulating lymphocytes, natural cell death fN, inactivation pNT of NK cells by tumor cells, and IL-2 induced NK cell proliferation $\frac{p_N NI}{g_N+I}$, are represented as:

$$\frac{dN}{dt} = f\left(\frac{e}{f}C - N\right) - pNT + \frac{p_N NI}{g_N + I}.$$

The CTL population L is described by:

$$\frac{dL}{dt} = -mL - qLT + (r_1 N + r_2 C)T + \frac{p_l LI}{g_l + I} - \frac{zL^2 RI}{\kappa + I} + j\frac{T}{\kappa + T}L,$$

with CTL turnover of mL, cytolytic potential qLT, CTL recruitment by debris of tumor cells lysed by NK $r_1 NT$, recognition of tumor presence proportional to the number of encounters between circulating CTLs and tumor cells $r_2 CT$, CTL activation via IL-2 $\frac{p_l LI}{g_l+I}$, breakdown of surplus CTLs in the presence of Tregs and IL-2 $\frac{zL^2RI}{\kappa+I}$, and accumulation of effector cells via CTL stimulation $j\frac{T}{\kappa+T}L$. The Treg population R is modeled as:

$$\frac{dR}{dt} = u\left(\frac{w}{u}C - R\right) + \frac{p_R RI}{g_R + I} - H_R\left(1 - e^{-\lambda_R S}\right)R,$$

with production wC, turnover uR, IL-2-induced proliferation $\frac{p_R RI}{g_R+I}$, and inhibition by sunitinib $H_R(1-e^{-\lambda_R S})R$. Production of lymphocytes C in bone marrow with rate α and turnover βC is:

$$\frac{dC}{dt} = \beta\left(\frac{\alpha}{\beta} - C\right).$$

IL-2 concentration is represented by I:

$$\frac{dI}{dt} = -\mu_1 I + \phi C + \frac{\omega LI}{\zeta + I},$$

with natural decay $-\mu_1 I$, IL-2 production ϕC by Treg and naïve CTLs, and IL-2 production $\frac{\omega LI}{\zeta+I}$ by activated CTLs. Sunitinib concentration S is calculated as:

$$\frac{dS}{dt} = -\eta S + \upsilon_S(t),$$

with secretion and elimination $-\eta S$, and dosing $\upsilon_S(t)$.

The simulation results reflected clinical outcomes to sunitinib treatment, including improved tumor control for sunitinib treatments following standard protocols, greater response rate for sunitinib treatments at double the standard dose, and improved responses to sunitinib treatment when the patient's immune strength scaling and the immune system strength coefficients parameters were low, implying a slightly stronger natural immune response.

2.6. CD4+ T Helper cells

CD4+ T Helper cells are critical to the activation of Cytotoxic T Lymphocytes, recruitment of macrophages, and the release of interleukins. They have been incorporated into models examining the effects of IL-2 and IL-21 on cancer growth and remission (de Pillis and Radunskaya, 2014; Dong et al., 2014; Nwabugwu et al., 2013). In particular, de Pillis and Radunskaya (2014) extensively explored a variety of immunotherapy treatments based on previous work modeling these tumor-immune interactions. In Dong et al. (2014), three populations of cells were represented, focusing on interactions between tumor, CTL, and T helper cells:

$$\frac{dT}{dt} = aT(1-bT) - nET$$
$$\frac{dE}{dt} = k_1 TE - d_1 E + pEH$$
$$\frac{dH}{dt} = s_2 + k_2 TH - d_2 H,$$

where T is the population of tumor cells, E is the population of effector (CTL) cells, H is the population of T helper cells, a is the maximal growth rate of T, b is the inverse of the carrying capacity to the tumors biological environment, n is the rate tumor cells are lost by effector cell interaction, k_1 is the effector cell stimulation rate by disintegrated tumor cell debris, d_1 is the inverse of the natural lifetime of effector cells, p is the activation rate of effector cells by T helper cells, s_2 is the birth rate of T helper cells in bone marrow, k_2 is T helper cell stimulation rate by the presence of tumor antigens, and d_2 is the inverse of natural lifespan of T helper cells. The study showed that T helper cells have a crucial role in the long term periodic oscillation behaviors observed with tumor-immune system interactions.

A comprehensive model was presented by Robertson-Tessi et al. (2015), in which T helper cells, T regulatory cells (Tregs), CTLs, and dendritic cells (DCs), along with interleukins and their effects on tumor cells, are modeled together with combinations of chemo- and immunotherapy. The model is based primarily on Robertson-Tessi et al. (2012), for which the evolution of tumor cells T is described as follows:

$$\dot{T} = \frac{T}{\left(\left(\frac{1}{\gamma_1}\right)^p + \left(\frac{T^{1-m}}{\gamma}\right)^p\right)^{\frac{1}{p}}} - \frac{r_0 T^*}{\left(1 + k_2\frac{T^*}{E}\right)} \cdot \frac{1}{\left(1 + k_3\frac{R}{E}\right)\left(1 + \frac{S}{S_1}\right)},$$
$$\gamma_1 = \gamma (T_1)^{m-1}$$
$$T^* = \frac{T}{\left(1 + \left(\frac{T^{1-n}}{k_1}\right)^p\right)^{\frac{1}{p}}}$$

where the first term on the right hand side (T equation) represents tumor growth and the second term specifies the tumor cell kill by CTLs, accounting for death in the absence of suppressive effects (first fraction) and the suppressive effects of TGF-β and Tregs on the tumor cell death (second fraction). Accordingly, E is the effector (CTL) cells, R is the Treg cells, γ is the growth coefficient, γ_1 is the exponential growth coefficient, m is the power law exponent, p sets the smoothness of transition between tumor growth modes, r_0 is the rate at which effector cells kill tumor cells, T^* is the number of tumor cells accesible by the immune system, and S is the suppression of cell activity. Dendritic cells evolution is modeled according to the following:

$$\dot{U} = \frac{aT^*}{\left(1 + \frac{I}{I_1}\right)\left(1 + \frac{R}{R_1}\right)} - \frac{\lambda U}{1 + \frac{U}{M_H}} - \delta_U U$$
$$\dot{D} = \frac{\lambda U}{a + \frac{U}{M_H}} - \delta_D D,$$

where U is the number of unlicensed dendritic cells and D is the number of licensed dendritic cells. The first term on the right hand side (U equation) represents dendritic cell maturation via encounter with tumor antigens, which is inhibited by IL-10 (I) and Treg cells (R), the second term represents the licensing of dendritic

cells via encounters with T helper cells M_H, and the third term is cell death with rate δ_U. The tumor antigenicity is a.

The three types of T cells in the model (CTLs, T helper cells, and Tregs) are initially activated with a high proliferation rate, and then they mature to fully functional cells. The effector (CTL) cells E are modeled as follows:

$$\dot{A}_E = \frac{\alpha_1 M_E}{1 + k_4 \frac{M}{D}} - \delta_A A_E$$

$$\dot{E} = \frac{\alpha_2 A_E C}{\left(1 + \frac{S}{S_2}\right)(C_1 + C)} - \delta_E E,$$

where the first term on the right hand side (equation for A_E, modeling the CTL activation), represents CTL activation via interaction with the mature licensed dendritic cells, and the second term represents CTL de-activation. The proliferative cytokine IL-2 is C.

The activation of T helper cells H is modeled similarly to the effector cells:

$$\dot{A}_H = \frac{\alpha_3 M_H}{1 + k_4 \frac{M}{(U+D)}} - \delta_A A_H$$

$$\dot{H} = \frac{\alpha_4 A_H C}{\left(1 + \frac{S}{S_2}\right)(C_1 + C)} - \frac{\alpha_7 H S}{S_3 + S} - \delta_H H,$$

where the activation can occur via both unlicensed and licensed dendritic cells. Further, T helper cells can convert into Tregs if TGF-β is present, as represented by the second term in the equation for H. Treg cells R and their activation A_R are modeled with a similar set of equations, in which the Treg proliferation is not suppressed by TGF-β:

$$\dot{A}_R = \frac{\alpha_5 M_R}{1 + k_4 \frac{M}{D}} - \delta_A A_R$$

$$\dot{R} = \frac{\alpha_6 A_R C}{(C_1 + C)} + \frac{\alpha_7 H S}{S_3 + S} - \delta_R R.$$

Modeling the complex interplay of the tumor cells with these immune cells yielded insights into treatments, such as the role of IL-2 as an adjunct therapy with adoptive T cell transfer (Robertson-Tessi et al., 2015). The inclusion of the immune response is predicted to significantly expand the region of tumor control for both cytotoxic and cytostatic chemotherapies. Opportunities for personalized medicine are suggested based on the type of immunotherapy, schedule of administration, and tumor characteristics. Importantly, it was shown that there exists an optimal antigenicity that maximizes the immune system response for a given tumor growth rate, and that increased antigenicity may decrease the tumor response (Robertson-Tessi et al., 2012).

According to Nwabugwu et al. (2013) CD4+ T helper cells play a vital role in tumor senescence, especially in the absence of CD8+ T killer cells. Without this check on tumor growth, malignancy and relapse become more likely in individuals in which the CD4+ cell population is depleted. The model examined the CD4+ dependent macrophage response to senescent tumor cells, using a previously developed multi-state tumor model, This model was combined with the model of Robertson-Tessi et al. (2012), which was modified to include T helper cell-dependent macrophage recruitment. The model predicted that a lack of T helper cells in immunocompromised individuals would soon led to tumor relapse.

2.7. Generalization of immune cell types

Given the plurality of immune cell types and associated cytokines involved in tumor growth, the incorporation of each cell type and cytokine would be ideal, yet it may be computationally costly from a practical standpoint. An alternative approach is to provide an approximation of the major immune system components, generalizing them into tumoricidal and tumorigenic components.

In Wilkie and Hahnfeldt (2017), the cancer population C is assumed to follow logistic growth, limited by a carrying capacity K_C:

$$\frac{dC}{dt} = \frac{\mu}{\alpha}(1 + \Psi)C\left(1 - \left(\frac{C}{K_C}\right)^{\alpha}\right), \; C(0) = C_0,$$

where $\frac{\mu}{\alpha}$ is the unregulated growth rate, μ is the intrinsic growth rate, α is the reciprocal of how strongly the carrying capacity regulates the population. The predation Ψ of the cancer population by the immune system is:

$$\Psi = -\theta\left(\frac{I^{\beta}}{\phi C^{\beta} + I^{\beta}} + \epsilon \log_{10}(1 + I)\right).$$

The saturation kinetics of strong cytotoxic actions $\frac{I^{\beta}}{\phi C^{\beta} + I^{\beta}}$ is as described in de Pillis et al. (2005), while $\epsilon \log_{10}(1 + I)$ permits a gradual increase to this saturation based on a significant increase in the immune presence. The immune population I is governed by logistic growth:

$$\frac{dI}{dt} = \lambda(I + rC)\left(1 - \frac{I}{K_I}\right), I(0) = I_0,$$

where λ is unregulated growth rate, r is the cancer-induced recruitment parameter, and K_I is the carrying capacity.

The model is able to represent the complexity of tumor-immune responses, with some interactions initially appearing to assist tumorigenesis but longer term helping to establish dormancy. Consequently, treatments that stabilize the antitumor inflammatory environment and near term stimulate tumor growth may be preferable to those focused on immediate tumor regression. These results are consistent with Leonard et al. (2017), which found that short-term pro-tumor immune activity may sensitize the tumor tissue to drug treatment.

As one of the trademarks of cancer is the downregulation of the immune system to facilitate tumor escape, investigations into why this occurs and what trends may encourage upregulation have been subjects of modeling interest. A succinct 4-equation model was presented by Wilkie et al. (2016), wherein net tumor growth, predation by generalized immune effector cells, tumorigenic effects of immune cells, and cell sensitivity to environmental signals for apoptosis, proliferation, or quiescence were examined. The net growth and predation by generalized immune effector cells are the same as those described in Wilkie and Hahnfeldt (2017). An equation allowing the cancer to modify its own carrying capacity is added:

$$\frac{dK_C}{dt} = pC(t) - qK_C(t)C(t)^{\frac{2}{3}},$$

where K_C is the carrying capacity for the cancer population, p is the growth stimulation constant, and q is the inhibition constant. Several outcomes were obtained via this model, including tumor dormancy and escape. The model assumes that cell populations are homogeneous and therefore does not consider spatial differences.

Alternately to generalizing immune cell types or modeling only a single immune cell type, as focusing on a single immune cell type may have limited utility and biological relevance, some models strike a balance, incorporating several immune cell types with common stimuli or actions. For example, NK, CTL, and macrophages have a direct cell-mediated role in killing cancer cells (Kolev et al., 2005) and thus may be grouped as effector cells for simplicity, while CD4+ and B cells have a more adjunct role in secreting cytokines and influencing the behaviors of immune, cancerous, and normal cells, and thus can be broadly

grouped as secretory cells. López et al. (2014) used the model from de Pillis et al. (2005) to consider different cell populations for innate and specific immune responses, disregarding tumor-host interplay.

The immune response is integrated into a single effector cell population E, which combines the equations for both CTL and NK cells. Neglecting the recruitment and lysis of NK, which are more ineffective than CTLs in fighting tumor cells, the simplified model becomes:

$$\dot{E} = \sigma - d_3 E + g\frac{D^2(E,T)T^2}{h + D^2(E,T)T^2}E - a_{31}TE$$

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

where σ is the constant input of E, d_3 is the inactivation rate of effector cells, T is the tumor cell population, and a_{31} is related to the immune-tumor competition. Tumor T and host H cell populations are represented by:

$$\dot{T} = r_1 T\left(1 - \frac{T}{K_1}\right) - a_{12}HT - D(E,T)T$$

$$\dot{H} = r_2 H\left(1 - \frac{H}{K_2}\right) - a_{21}TH,$$

where r_1 and r_2 are the tumor and host cells' growth rates, respectively, a_{12} and a_{21} represent the competition of host cells and tumor cells, and viceversa, respectively, and K_1 and K_2 are the tumor host cells carrying capacity, respectively. The dynamical properties of the model were evaluated, providing for the capability to explain theoretical and experimental data of tumor progression. The simulation results of chemotherapy were in good agreement with previous experiments in mice (Hiramoto and Ghanta, 1974).

3. Discussion

The models reviewed herein strive to provide a means to analyze the complex interactions between tumor and immune cells, with the results showing that specific insights into these interactions are attainable via mathematical modeling. Yet the immune response in the cancer microenvironment is a highly complex and dynamic process that may extend beyond the practical reach of any single model. In addition to immune system components, there is still much tumor biology that is poorly understood, e.g., the debate regarding the concept of tumor dormancy as a steady or transient phenomenon (Wilkie and Hahnfeldt, 2017). Additionally, cancerous cells themselves display much variation in phenotype and genotype (Marusyk and Polyak, 2010), which has not yet been thoroughly modeled in a tissue-scale system. Other components of the tumor microenvironment require further investigation. It is known that macrophages affect and encourage the growth of tumoral vasculature (De Palma et al., 2005) but recent research suggests that irregular tumoral vasculature may in turn affect the immune response. For example, endothelial cells may act to block the recruitment and entry of T cells to the tumor site (Schaaf et al., 2018). Further, as more is understood about immunotherapy, its interactions with established treatment modalities, e.g., chemotherapy, would be of clinical interest. Applying modeling to fine-tune methods of combining chemotherapy, and its benefit of years of clinical application, with novel immunotherapies could be of practical application.

In the past ten years, the advent of –omic data has offered the potential to revolutionize the field of medicine. In particular for onco-immunotherapy, next generation sequencing (NGS) technology has enabled determining the genomic, transcriptomic, and metabolomic landscapes for immune, tumor and stromal cells. A major challenge is that the large size of these data and the complexity of its analysis preclude a simple process. Machine learning techniques including deep learning are being applied to help with this challenge, yet such techniques struggle to provide patient-specific conclusions (Grapov et al., 2018). Another challenge is that it may be clinically impractical to collect these data from individual tumors. Diagnostic evaluation of cancer patients typically includes imaging along with tissue biopsy if feasible. The biopsied tissue is histologically evaluated for confirmation of disease and staging. Few of these tissues are then further evaluated to obtain –omics information, although there have been efforts towards personalized medicine (Kakimi et al., 2017). Nevertheless, expanded interdisciplinary collaborations between modelers and clinicians may enable the development of models that could incorporate these data.

The challenge of collecting clinical information for mathematical model purposes represents an enormous barrier to the practical application of these models. Although this challenge has always been present for biological modeling in general, it is particularly acute when it comes to models of onco-immunology and onco-immunotherapy. The models reviewed here for the most part have limited input from clinically relevant data. One reason is the complexity of the information spanning tumor, immune, and organ systems across molecular, cellular, and tissue scales. Assuming that such information were available, it would still be difficult to include the information in terms of meaningful parameter values. Models would need to be constructed based on the availability of parameter values and their meaningful interpretation, which is a non-trivial task. Based on the types of data, a data-driven approach to the modeling may be suitable. Combinations of model systems may not necessarily yield the best answer, as what is needed are new ways of abstracting system information in order to obtain relevant results.

If patient-specific tumor system data were clinically collectable and models were constructed that could evaluate such data for prognostic value and for exploration of hypothetical treatments (e.g., chemotherapy, immunotherapy, and combinations thereof), the next challenge is to deliver meaningful predictions in a timely manner to clinicians. This challenge may be the most difficult of all, since the field of medicine is by nature conservative and slow to adopt new technologies, as it rightfully strives to maintain the welfare of patients as a top priority. The standard for a model to be validated for prognostic information is therefore high, as it should be. It will take years of work, including large amounts of patient data collection and analysis, to establish model prognostic credibility. Collaborations between modelers and clinicians will need to be nurtured long term in order to achieve this goal.

In spite of these challenges, the continued advance of biological knowledge of tumor-immune cell interactions has provided and is expected to continue offering opportunities for the application of mathematics towards model development. Coupled with the ever-expanding capabilities of computational tools, this advance suggests a hopeful future for the practical application of models of tumor-immune dynamics, with the ultimate goal of improving cancer patient outcomes.

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