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Mathematical Modeling of Tumor-Immune Interactions: Methods, Applications, and Future Perspectives

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Abstract. Mathematical oncology is a rapidly evolving interdisciplinary field that uses mathematical models to enhance our understanding of cancer dynamics, including tumor growth, metastasis, and treatment response. Tumor-immune interactions play a crucial role in cancer biology, influencing tumor progression and the effectiveness of immunotherapy and targeted treatments. However, studying tumor dynamics in isolation often fails to capture the complex interplay between cancer cells and the immune system, which is critical to disease progression and therapeutic efficacy. Mathematical models that incorporate tumor-immune interactions offer valuable insights into these processes, providing a framework for analyzing immune escape, treatment response, and resistance mechanisms. In this review, we provide an overview of mathematical models that describe tumor-immune dynamics, highlighting their applications in understanding tumor growth, evaluating treatment strategies, and predicting immune responses. We also discuss the strengths and limitations of current modeling approaches and propose future directions for the development of more comprehensive and predictive models of tumor-immune interactions. We aim to offer a comprehensive guide to the state of mathematical modeling in tumor immunology, emphasizing its potential to inform clinical decision-making and improve cancer therapies.

AMS subject classifications: 92C42, 92B05, 92B10

Key words: Tumor immunology, mathematical oncology, tumor-immune interaction, mathematical model, computational simulation.

1 Introduction

Cancer, often described as a malignant tumor, represents a complex and dynamic ecosystem [12, 51, 66]. This ecosystem, known as the tumor microenvironment (TME) (Fig. 1),

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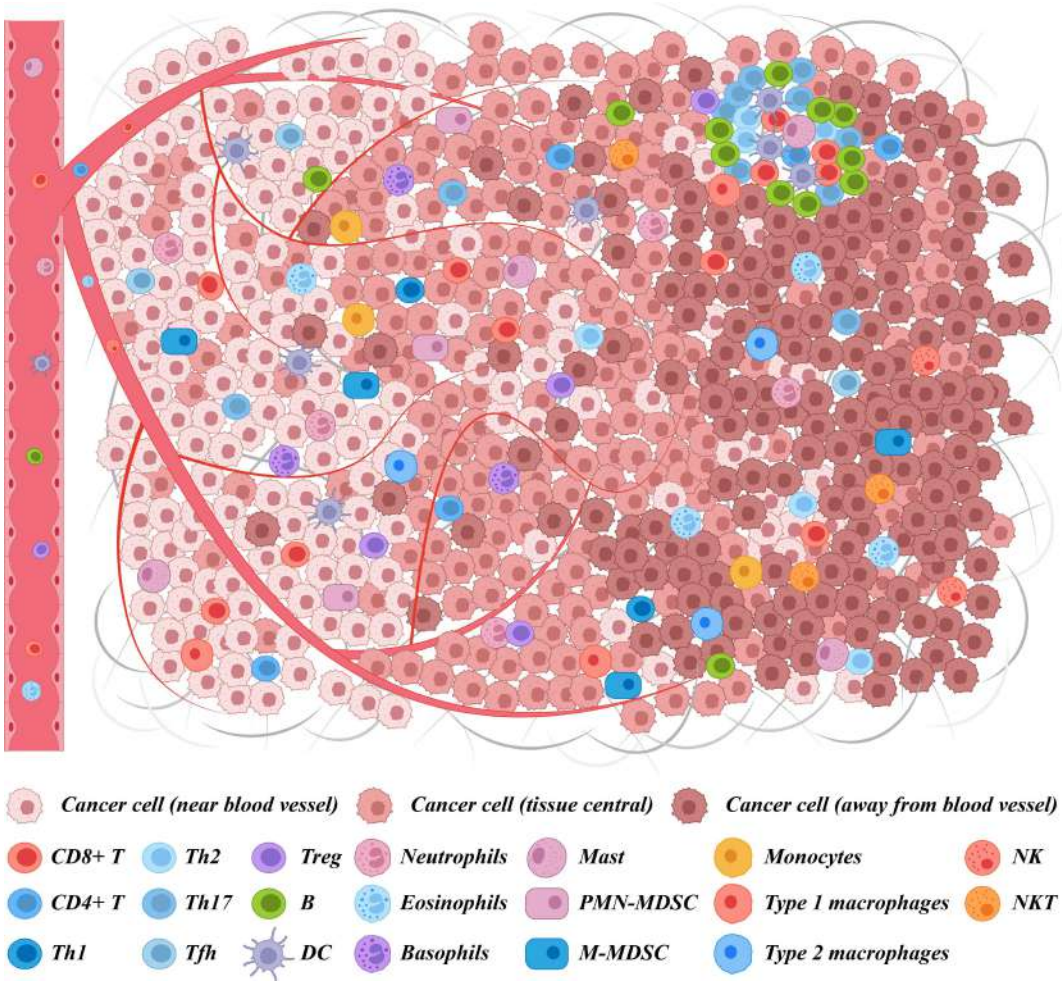

Figure 1: A global map of the tumor microenvironment.

comprises not only malignant tumor cells capable of rapid proliferation and metastasis but also includes various non-cancerous components such as immune cells, stromal cells, fibroblasts, and vascular endothelial cells [12, 66, 89, 119]. The TME plays a pivotal role in the processes of tumor growth, progression, metastasis, and drug resistance [66, 89, 119, 204, 239]. Within this environment, tumors actively shape conditions favorable to their survival and proliferation through mechanisms such as the secretion of cytokines, immune-modulating factors, and the expression of immune checkpoint molecules [133,240]. Meanwhile, immune cells infiltrate tumor tissue via migration, chemotaxis, and recruitment, influencing tumor development [133, 218, 227].

Tumor-immune system interactions are marked by a dynamic and complex interplay of mutual promotion, competition, and adaptation [93, 236]. These interactions not only influence tumor growth, metastasis, and regression but also modulate the immune sys-

tem's composition, function, and responsiveness [76–78,265]. Recent advances in single-cell sequencing and other biotechnological tools have significantly enhanced our understanding of these tumor-immune interactions [138,244,316]. However, the inherent complexity of these interactions poses challenges that experimental techniques alone cannot fully address, necessitating the use of mathematical modeling as a powerful complementary approach to uncover underlying patterns and mechanisms.

Mathematical models provide a framework for describing and simulating complex biological systems, allowing researchers to abstract and quantify interactions with the tumor-immune landscape [7,9,42,94,250]. These models offer several key advantages in studying tumor-immune dynamics:

(1) Quantitative description. Mathematical models enable the quantitative analysis of tumor-immune interactions through differential equations and algorithms, offering new perspectives on the complex processes underlying these interactions.

(2) Systematic analysis. By modeling tumor-immune interactions as integrated systems, these approaches capture feedback loops and multicomponent interactions, providing insights into the regulation of tumor growth, immune evasion, and immune cell dynamics.

(3) Multi-scale simulation. Mathematical models can simulate biological processes across multiple scales, from molecular and cellular to tissue levels, facilitating a comprehensive understanding of the dynamic nature of tumor-immune interactions.

(4) Treatment predictions. These models are also valuable tools for predicting the effects of various treatment strategies, aiding in the design of personalized therapies, and supporting clinical decision-making through the simulation of therapeutic outcomes.

Despite their potential, mathematical models of tumor-immune interactions face significant challenges [41,55,154,209]. The complexity of tumor-immune dynamics involves multiple time scales, diverse cellular components, and intricate regulatory networks, requiring an interdisciplinary approach that integrates knowledge from applied mathematics, computational science, tumor immunology, and clinical medicine. Additionally, the acquisition and processing of multi-source data are critical yet challenging aspects of model development, necessitating robust data integration and validation methods to ensure model reliability. Finally, interpatient variability in tumor types and immune characteristics adds another layer of complexity, underscoring the need for adaptable modeling approaches that can account for individualized tumor behavior and biomarker variability.

In this review, we comprehensively analyze the current landscape of mathematical models in tumor immunology, focusing on their methodologies, applications, and impact on understanding tumor dynamics and treatment responses. In Section 2, we discuss key immunological mechanisms and recent research. Section 3 delves into modeling

approaches and regulatory networks of tumor-immune interactions. In Section 4, we explore the application of these models to various cancer treatment strategies. Finally, we discuss current limitations and propose future directions for the advancement of mathematical models in the study of tumor-immune systems.

2 Biological background of immunological mechanisms

2.1 Hallmarks of cancer

The hallmarks of cancer define the fundamental characteristics that drive cancer development and progression (Fig. 2) [110–112]. In 2000, Hanahan and Weinberg [111] identified six original hallmarks: self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis. In 2011, four additional hallmarks were introduced: avoiding immune destruction, tumor-promoting inflammation, genome instability and mutation, and deregulating cellular energetics [112]. By 2022, four more hallmarks were recognized: unlocking phenotypic plasticity, non-mutational epigenetic reprogramming, polymorphic microbiomes, and the influence of senescent cells [110].

These hallmarks provide a comprehensive framework for understanding the progression and evolution of cancer. Recently, Bull and Byrne [36] proposed the "hallmakers" of mathematical oncology, which define how mathematical models can help elucidate the

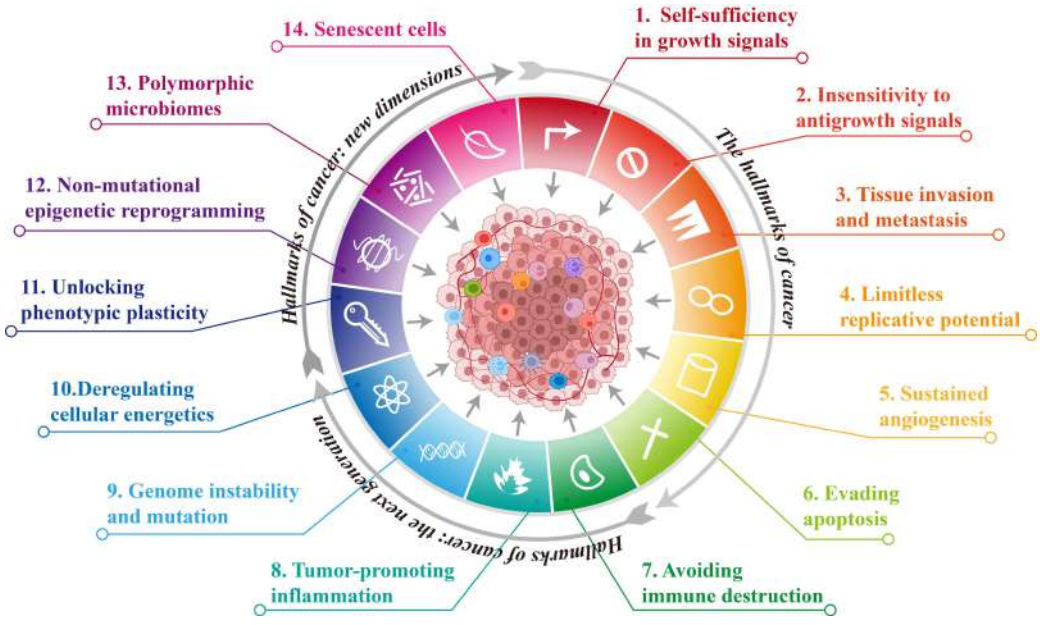

Figure 2: The hallmarks of cancer [110–112].

complex processes of tumor initiation and progression. The integration of mathematics, oncology, and immunology is driving new advances in cancer research.

The hallmarks of cancer emphasize the unique distinctions between tumor cells and normal cells, many of which are closely linked to the immune system. For example, immunosuppressive cells and tumor-associated fibroblasts contribute to the formation of pre-metastatic niches, facilitating tumor invasion and metastasis [66, 111]. Tumor-promoting inflammation is driven by the infiltration of inflammatory cells and cytokines, which significantly impact tumor-immune interactions [104, 112]. The interplay between polymorphic microbiomes, tumors, and the immune system forms a cancer-immune-microbiome axis that influences tumor progression and therapeutic response [110, 322]. Mathematical modeling of tumor-immune interactions is central to mathematical oncology, providing quantitative insights into the dynamics of cancer development and progression.

2.2 Immune cells

The immune system is a complex and highly coordinated defense network that safeguards the body against infections, diseases, and abnormal cells, including cancer [68, 230]. It consists of various cells, tissues, and organs that collaborate to identify and eliminate harmful pathogens as well as damaged or malignant cells. The system's core consists of immune cells, primarily lymphocytes and myeloid cells [68, 89, 230] (Fig. 3). Lymphocytes, which originate from lymphoid organs, are key players in the adaptive immune response against tumors. They are further classified based on their distinct functions and surface markers into T lymphocytes, B lymphocytes, natural killer (NK) cells, and natural killer T (NKT) cells. Myeloid cells, a crucial component of innate immunity, include granulocytes, myeloid-derived suppressor cells (MDSCs), dendritic cells (DCs), monocytes, and macrophages, all of which play vital roles in the body's immediate response to threats.

T lymphocytes are primarily involved in cellular immunity, recognizing and binding to specific antigens to initiate immune responses [307]. Due to their robust tumor-killing abilities, T cells have become a central focus in contemporary tumor immunology research. Naive T cells can differentiate into effector T cells under the influence of various cytokines, resulting in distinct subtypes such as helper T cells (Th), regulatory T cells (Treg), and cytotoxic T lymphocytes (CTL) [225, 330, 331].

Th cells are a subset of T lymphocytes that play a crucial role in regulating and coordinating the immune response by aiding in the activation and function of other immune cells through the secretion of specific cytokines. They are further divided into subtypes, including Th1, Th2, Th17, and follicular helper T cells (Tfh), based on their transcription factors and cytokine profiles:

- Th1 cells differentiate from naive CD4+ T cells under the influence of IL-12 and primarily secrete IL-2, IFN-γ, and TNF-α [185, 225, 330, 331]. Th1 cells enhance CTL

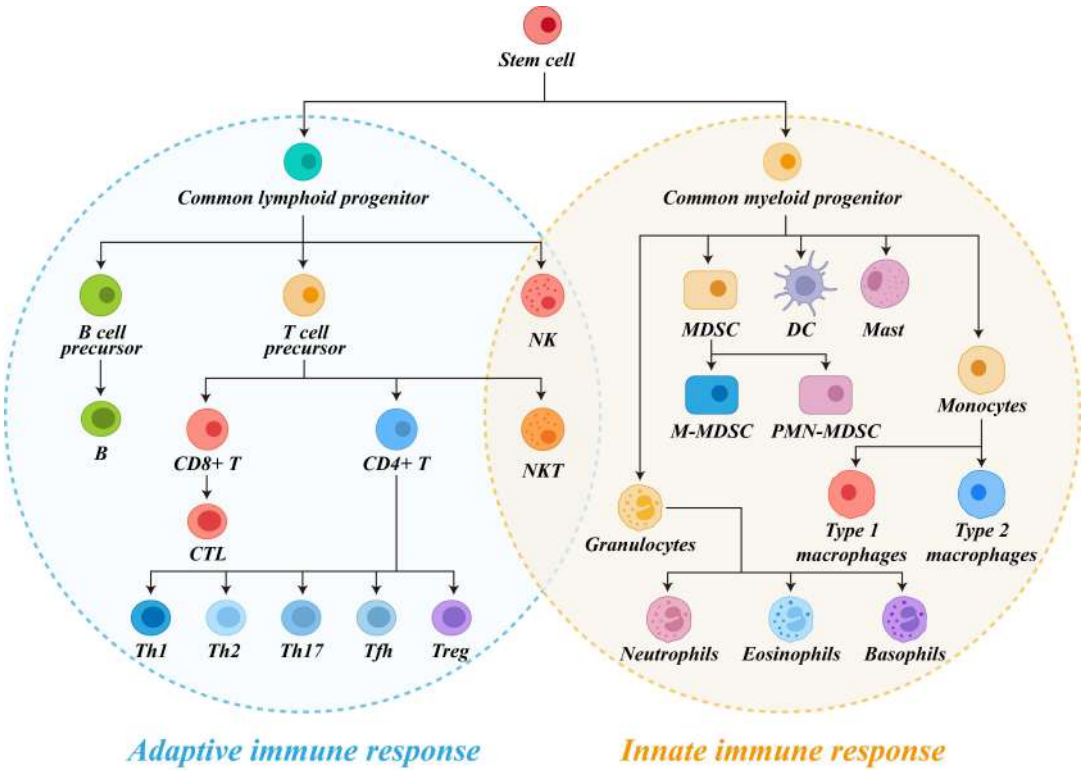

Figure 3: Immune cell lineage.

expansion through IL-2 and exert direct anti-tumor effects by secreting IFN-γ and TNF-α, which contributed to the killing of cancer cells.

- Th2 cells can promote tumor growth by secreting cytokines such as IL-4, IL-5, and IL-10 [185, 225, 330, 331]. The differentiation of naive CD4+ T cells into the Th2 subtype is driven by IL-4, produced by granulocytes, mast cells, and already differentiated Th2 cells.
- Th17 cells are a subpopulation of effector CD4+ T cells known for secreting IL-17. Recent research indicates that TGF-β, IL-6, and IL-23 promote the differentiation of naive CD4+ T cells into the Th17 cells, whereas IFN-γ and IL-4 inhibit this process [281, 331].
- Tfh cells are primarily located in peripheral immune organs and play a crucial role in the formation of germinal centers [57].

Tregs are a subset of T cells with potent immunosuppressive functions, known for secreting high levels of immunosuppressive cytokines such as IL-10 and TGF-β [25, 333]. Tregs can be classified into two main types: naturally occurring Treg (nTreg) derived from the thymus, and induced adaptive Treg (iTreg). Within the TME, Tregs predominantly refer to iTreg, which facilitates tumor immune evasion, suppresses anti-tumor

immune responses, and contributes to the establishment of an immunosuppressive microenvironment.

CTLs are derived from naive CD8+ T cells and are central to the anti-tumor immune response. CTLs specifically recognize cancer cells through the interaction of their T cell receptors (TCRs) with major histocompatibility complex (MHC) expressed on the surface of cancer cells [307]. CTLs directly induce tumor cell death via the FasL-Fas signaling pathway and can also trigger apoptosis indirectly by secreting granzymes and perforin [21]. However, recent studies have shown that intratumoral CTLs often display an exhausted phenotype, marked by impaired immune function [203, 312]. Addressing CTL exhaustion presents a significant therapeutic opportunity in cancer treatment.

B cells primarily contribute to humoral immunity. Within the tumor-immune system, plasma cells derived from B cells secrete antibodies that recognize and bind to tumor antigens, facilitating the immune system's ability to target and eliminate cancer cells [269]. Additionally, B cells act as antigen-presenting cells (APCs), presenting tumor antigens to other immune cells and thereby initiating immune responses. Recent studies have shown that B cells support the maintenance of secondary lymphoid organ structures and promote the formation of intratumoral tertiary lymphoid structures (TLS) [86, 266]. TLS are clusters of immune cells that develop in non-lymphoid tissues and are typically found in chronically inflamed areas of cancers. Their presence is often associated with better survival outcomes for patients [86, 266].

NK cells are the archetypal innate immune cells, capable of recognizing and destroying tumor cells in a non-specific manner. NK cells eliminate cancer cells by releasing cytolytic mediators such as perforin and granzyme [53, 86]. Another typical function of NK cells is their ability to kill tumor cells by CD16 receptor-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) [53, 86]. Although they are traditionally considered part of the innate immune system, some NK cells display adaptive-like traits, including clone specificity and memory. Additionally, activated NK cells can secrete a range of cytokines and chemokines, further regulating the immune response [53, 86].

DC cells, as the most potent professional APCs, play a crucial role in mediating innate immune responses and inducing adaptive immunity [82, 307]. They are central to initiating, regulating, and sustaining anti-tumor immune responses. Immature DCs efficiently capture, process, and present tumor-associated antigens (TAAs) released by cancer cells. Once activated, DCs upregulate MHC molecules, which present antigens to T cell receptors (TCRs) on naive T cells, providing the first signal required for T cell activation. Simultaneously, DCs deliver the second activation signal through costimulatory molecules. Moreover, activated DCs secrete chemokines that promote T cell recruitment and cytokines such as IL-12, which drive the differentiation of Th1 and CTLs, providing the third signal for effective immune responses [82, 307]. Together, these mechanisms orchestrate a robust anti-tumor immune response.

Tumor-associated macrophages (TAMs) are classified into two main types, M1 and M2, based on their functional roles and activation states within the TME [28]. The differentiation of macrophages into these phenotypes is known as polarization. M1 macro-

phages are generally considered anti-tumor, as they secrete pro-inflammatory cytokines like IL-12, IFN-γ, and TNF-α [28,91,223]. On the other hand, M2 macrophages are linked to tumor progression, producing anti-inflammatory cytokines such as IL-4, IL-6, and CCL7 [28, 91, 223]. Macrophage polarization demonstrates significant plasticity: factors like M-CSF and TGF-β promote the transition of TAMs from the M1 to the M2 phenotype, while TNF-α and IL-12 drive the reverse transition from M2 to M1 [22, 28, 91, 223]. Understanding this bidirectional polarization is crucial for unraveling the complexities of tumor-immune interactions and their regulatory mechanisms.

Neutrophils, the most abundant granulocytes, serve as the body's first line of defense against infections. Within the TME, neutrophils can adopt distinct phenotypes [99, 257, 272]. N1 neutrophils exhibit anti-tumor properties, while N2 neutrophils promote tumor progression [99, 257, 272]. TGF-β is a key driver of neutrophil polarization towards the tumor-promoting N2 phenotype [257], while type I interferons facilitate polarization towards the anti-tumor N1 phenotype [257]. N1 neutrophils combat tumors by releasing reactive oxygen species (ROS) to kill cancer cells, and by promoting T cell activation and macrophage recruitment [99,257,272]. In contrast, N2 neutrophils contribute to tumor growth through angiogenesis, suppression of NK cell activity, and recruitment of Tregs [99,257,272].

MDSCs are a heterogeneous group of myeloid cells with strong immunosuppressive capabilities [117]. They are categorized into two major subtypes: polymorphonuclear MDSCs (PMN-MDSCs), which resemble neutrophils, and monocytic-MDSCs (M-MDSCs), which are more akin to monocytes [105]. In the TME, MDSCs exert potent protumor and immunosuppressive effects through various mechanisms, including the introduction of immunosuppressive cells, inhibition of lymphocyte trafficking, production of reactive oxygen species, and expression of immune checkpoint molecules [105, 117, 177]. Emerging evidence suggests that MDSCs are a hallmark of malignant tumors and represent a promising target of cancer immunotherapy [105, 117, 177].

2.3 Cancer immunoediting

Cancer immunoediting describes the dynamic interplay between tumors and the immune system, evolving across three distinct phases: elimination, equilibrium, and escape (Fig. 4) [76–78, 265]. These phases capture the dynamic struggle between tumor growth and immune surveillance, highlighting the interactions between the immune system and cancer progression.

The elimination phase marks the onset of immune surveillance, where the immune system identifies and attacks developing tumors (Fig. 4). DCs detect TAAs released by tumor cells and present them to T lymphocytes, initiating an immune response [307]. Upon antigens recognition, naive T cells differentiate into effector T cells, which target and destroy tumor cells by engaging specific antigens on the tumor surface. In addition, innate immune cells such as NK cells contribute to this phase by directly identifying and eliminating cancer cells using their inherent cytotoxic abilities [106]. This phase is charac-

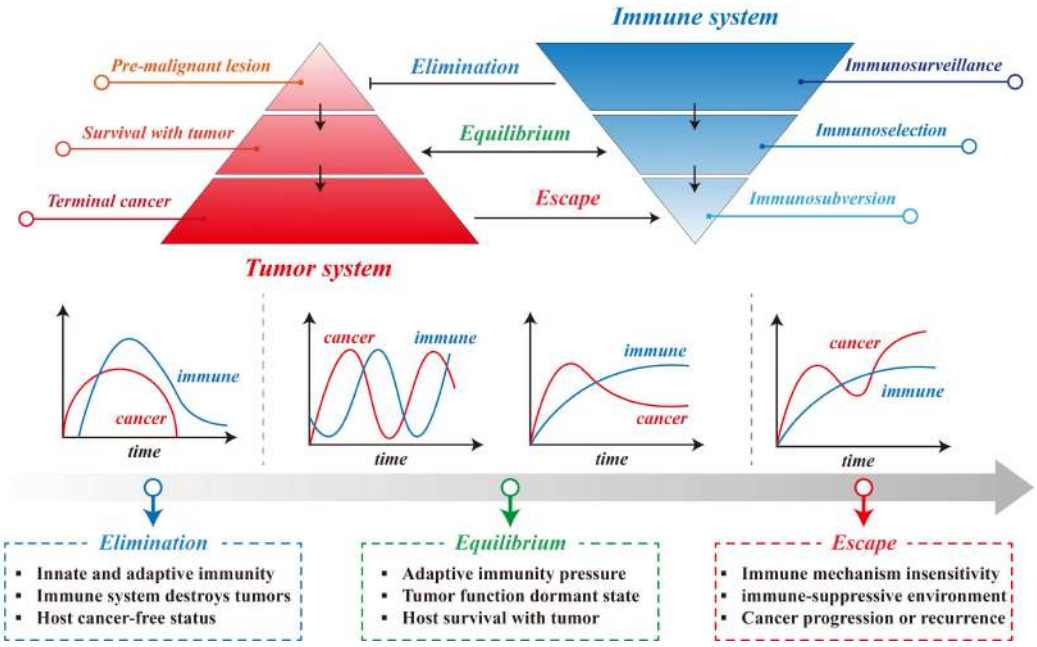

Figure 4: Mechanistic framework and dynamic perspectives on cancer immunoediting [106, 137, 332].

terized by the coordinated actions of both innate and adaptive immune systems, aiming to eliminate tumor cells at an early stage. While successful completion of this phase can result in the clearance of tumors, factors such as tumor heterogeneity, the complexity of the TME, and immune system limitations often allow for the survival of residual cancer cells [106, 137, 332].

The equilibrium phase is a critical stage in cancer immunoediting marking a prolonged standoff between the tumor and immune system (Fig. 4). This phase is characterized by a sustained balance, where tumor cells enter a dormant state to evade immune detection and destruction [106, 137, 332]. During equilibrium, tumors continue to evolve, accumulating mutations that promote immune escape and modulate tumor antigen expression [3, 199, 258]. Although the immune system persists in eliminating detectable tumor cells, only the most immunogenic subsets are cleared. If this phase is prolonged, tumors may accumulate enough genetic alterations to evade immune control, setting the stage for eventual immune escape and recurrence [106, 137, 332]. Under this continuous immune pressure, the tumor evolves through mutation and selection, progressively developing traits that enable immune evasion.

The escape phase is the final stage of cancer immunoediting (Fig. 4). At this point, the tumor gains the ability to evade immune destruction, leading to clinical progression and malignancy. Tumor immune escape is driven by two main mechanisms [106, 137, 332]. First, tumors reduce their immunogenicity by downregulating antigen expression, allowing them to slip past immune surveillance. Second, tumors enhance immune suppression

by upregulating immune checkpoints, which induces T cell apoptosis or impairs their function, weakening immune attacks. Tumor cells also secrete cytokines and chemokines to limit lymphocyte infiltration into the TME, while promoting the recruitment of MDSCs and Tregs. This creates an immune-privileged niche that supports tumor growth and survival.

2.4 Cancer-immunity cycle

The cancer-immunity cycle is a mechanistic model that outlines the sequential events between tumors and the immune system, providing a framework for understanding tumor immunology [48, 205]. This cycle consists of seven key steps, each contributing to the initiation and amplification of the immune response against cancer (Fig. 5):

(1) Release of cancer antigens. Genetic alterations in cancer cells lead to the production of TAAs, which are immunogenic proteins specific to the tumor [173]. As tumors grow and undergo apoptosis, these antigens are released into the TME, serving as signals to initiate a tumor-specific immune response (Step 1 in Fig. 5).

(2) Cancer antigen presentation. APCs capture and process TAAs, displaying them on their surface via MHC molecules. These APCs then travel through the lymphatic system to tumor-draining lymph nodes, where antigen presentation occurs, initiating an immune response (Step 2 in Fig. 5) [307]. This step is crucial for triggering a T-cell response against the tumor.

(3) Priming and activation of T cells. In the tumor-draining lymph nodes, naive T cells recognize the peptide-MHC complexes on APCs through their TCRs. This recognition activates the T cells, causing them to differentiate into effector T cells capable of targeting tumor cells (Step 3 in Fig. 5) [307]. The priming and activation of T cells are critical to the immune system's ability to fight the tumor.

(4) Trafficking of T cells to tumors. Once activated, effector T cells exit the lymph nodes and travel the bloodstream towards the tumor site, guided by various chemotactic signals (Step 4 in Fig. 5) [66, 239].

(5) Infiltration of T cells into tumors. Effector T cells infiltrate the tumor tissue in response to chemokine signals, dispersing throughout the TME to locate tumor cells (Step 5 in Fig. 5) [133, 218, 227].

(6) Recognition of cancer cells by T cells. Effector T cells identify tumor cells by recognizing specific antigens on their surface via their TCRs (Step 6 in Fig. 5) [89]. This recognition step is essential for the immune system to selectively target and destroy cancer cells.

(7) Killing of cancer cells. After recognizing the tumor cells, T cells release cytotoxic molecules such as granzyme and perforin, which induce apoptosis in the tumor cells (Step 7 in Fig. 5). The death of tumor cells releases additional antigens, which continue to fuel the cancer-immunity cycle, creating a feedback loop (Step 1 in Fig. 5) [48, 205].

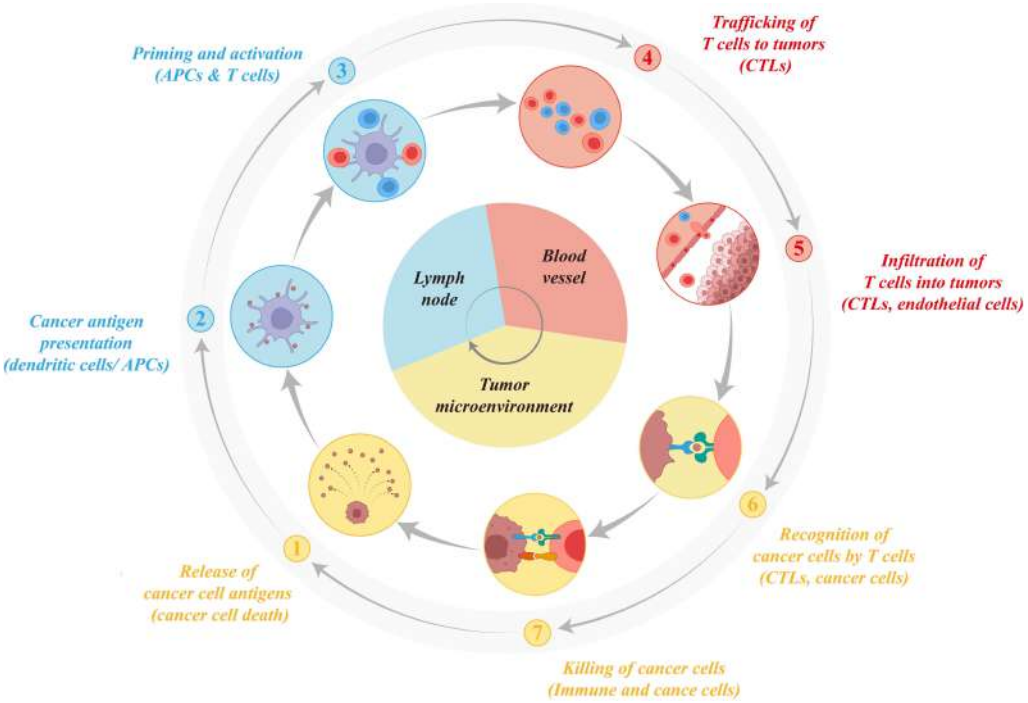

Figure 5: Cancer-immunity cycle [48].

2.5 Cancer immunotype

The term "cancer immunotype" refers to the distinct patterns of interaction between tumors and the immune system [75, 218]. One of the most common ways to classify cancer immunotypes is by distinguishing between "cold" and "hot" tumors (Fig. 6) [75,189,326]. Cold tumors are characterized by weak or absent immune responses, with three defining features: (1) minimal immune cell infiltration, (2) low expression of immune checkpoint molecules, and (3) poor response to treatment. In contrast, hot tumors exhibit strong immune activity, with high levels of immune cell infiltration and immune checkpoint expression. These tumors generate a robust anti-tumor immune response, often leading to more favorable treatment outcomes. The primary difference between cold and hot tumors lies in the degree of immune system engagement.

Based on the biological mechanisms of the cancer-immunity cycle, tumors can also be classified into three categories: immune-desert, immune-excluded tumors, and immune-inflamed (Fig. 6) [8, 49, 146, 205]. Immune desert tumors lack immune cell infiltration in the TME, resulting in minimal response. Immune-excluded tumors display immune cells that surround the tumor but fail to penetrate its interior, leading to ineffective immune surveillance and action. Immune-inflamed tumors feature substantial immune cell infiltration, particularly T cells, which are crucial for anti-tumor responses. These tumors are associated with elevated IFN-γ signaling and high tumor mutational burden, both

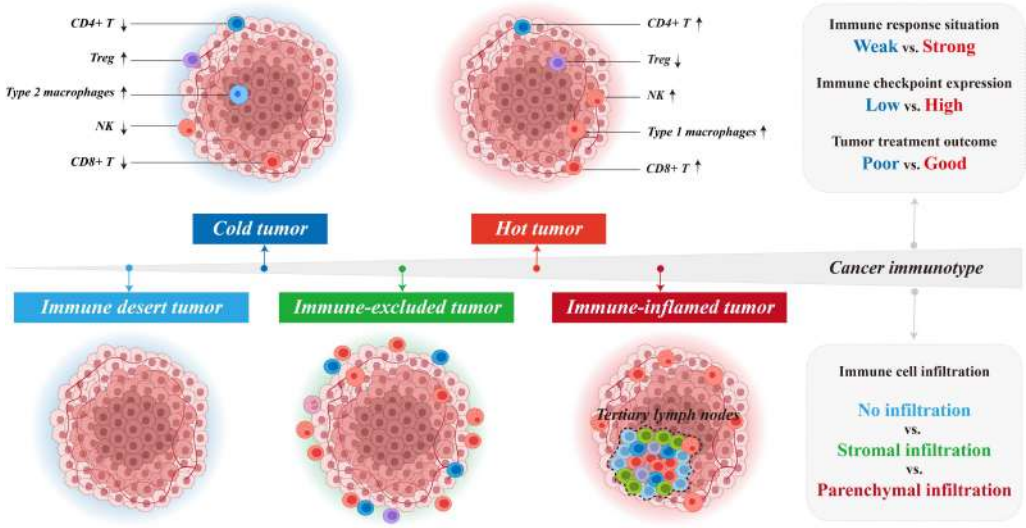

Figure 6: Cancer immunotype [49].

of which enhance immune activity against the tumor. Additionally, immune-inflamed tumors often develop TLS within the TME, which are linked to better clinical outcomes for patients [86, 266].

3 Mathematical formulations of tumor-immune interactions

Mathematical oncology is an emerging interdisciplinary field (Fig. 7) that leverages foundational knowledge in tumor immunology and real clinical data to explore cancer dynamics. By applying mathematical models and computational methods, it investigates key aspects of cancer such as tumor evolution, metastasis, drug resistance, prognosis prediction, and optimized treatment strategies [7, 9, 42, 94, 250]. This approach provides valuable insights into cancer behavior, helping to refine therapeutic approaches and enhance patient outcomes.

Mathematical models of tumor-immune interactions offer powerful tools and analytical frameworks for exploring key dynamics in tumor-immune systems [15, 81, 198]. In this review, we present two primary categories of modeling approaches for mathematically representing these interactions. The first category is equation-based models (EBMs), which use differential equations to capture the temporal and spatial dynamics of genes, cells, and molecules. These models are grounded in principles such as mass action laws, enzyme reaction kinetics, and fluid dynamics. EBMs, which are typically continuous models, include various formulations: ordinary differential equations (ODEs), delayed differential equations (DDEs), stochastic differential equations (SDEs), partial differential equations (PDEs), integral differential equations (IDEs), and quantitative systems pharmacology (QSP). The second category is rule-based models (RBMs), also known as agent-

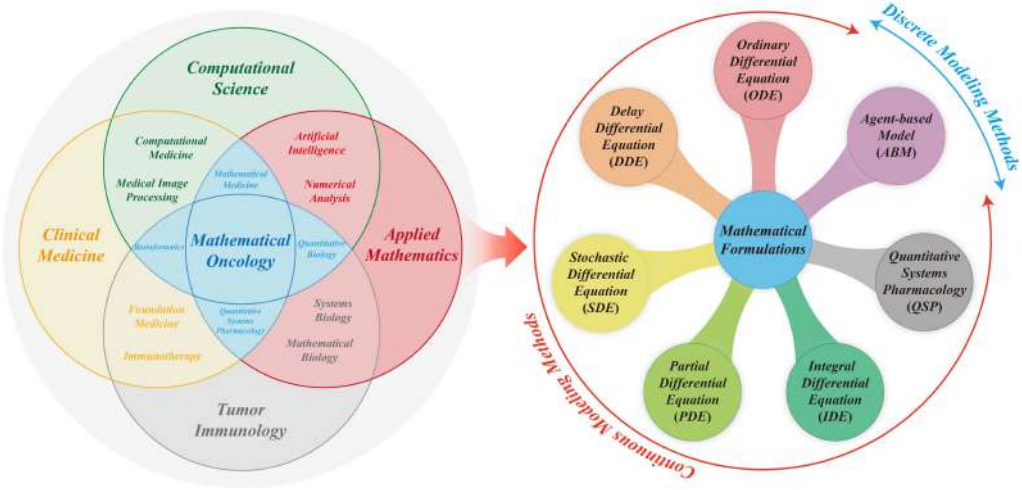

Figure 7: Venn diagrams and related professional keywords of interdisciplinary and intersectional research methods in the field of mathematical oncology.

based models (ABMs). These models describe system dynamics by simulating interactions between individual entities, such as protein molecules or cells, with rules derived from experimental data and biological mechanisms. ABMs are generally discrete models. While continuous models focus on the macroscopic interactions between tumors and the immune system, discrete models emphasize the stochasticity and uncertainty present at the microscopic level.

3.1 Ordinary differential equation model

The ODE model is a fundamental mathematical tool for describing tumor cell interactions with the immune system, providing a strong framework for analyzing tumor dynamics over time. By applying ODEs, researchers can thoroughly explore how tumors interact with various immune system components, such as immune cells, receptors, and cytokines. In this review, we present a unified framework for the ODE model of the tumor-immune system, represented as

$$\frac{\mathrm{d}X_i(t)}{\mathrm{d}t} = G_i + \sum_{j=1}^{n} F_{i,j}\big(\mathbf{X}(t);\Theta\big) + D_i, \tag{3.1}$$

where $\mathbf{X} = (X_1, X_2, \ldots, X_n)$ represents the cell numbers of different components in the tumor immune system, $F_{i,j}$ captures the interactions between components j and i, $\Theta = (\theta_1, \theta_2, \ldots, \theta_m)$ denotes the set of parameters. Additionally, G_i and D_i represent the dynamic behaviors of cell growth and death, respectively.

The growth rate term G_i in Eq. (3.1) can be expressed using several well-known growth models, classified into six types: exponential, power law, logistic, Hill function,

Gompertzian, and von Bertalanffy models [23,95,167,259,291]. These models are detailed below:

- Exponential model. The simplest form, $G_i = r_i X_i$, assumes that cells grow at a constant rate, often used to describe tumor growth where tumor size is assumed to increase proportionally to its current size over time.
- Power law model. This generalization of the exponential is given by $G_i = r_i X_i^{\alpha_i}$, where the growth rate is proportional to the current cell population raised to the power of α.
- Logistic model. In this model,

$$G_i = r_i \left(1 - \frac{X_i}{K_i}\right) X_i,$$

  growth slows as the cell population approaches its carrying capacity, K_i. A variant based on evolutionary game theory, the competitive logistic model,

$$G_i = r_i \left(1 - \frac{1}{K_i} \sum_{j=1}^{n} a_{ij} X_j\right) X_i,$$

  describes competition among different cell subtypes [309]. The logistic model can be generalized further to

$$G_i = r_i \left(1 - \left(\frac{X_i}{K_i}\right)^{\alpha_i}\right) X_i,$$

  providing more flexibility in describing growth dynamics.
- Hill model. Here, growth is expressed as a Hill model

$$G_i = \frac{r_i}{1 + (X_i/K_i)^{\alpha_i}} X_i,$$

  where K_i represents the half effective inhibitory concentration. The Hill model is often used to model growth regulated by cytokines in the microenvironment [24, 167].
- Gompertzian model. This model,

$$G_i = r_i \log\left(\frac{K_i}{X_i}\right) X_i,$$

  describes tumor growth with an exponentially decreasing rate, commonly applied to model tumor vascular growth [108, 222].
- von Bertalanffy model. A lesser-known model,

$$G_i = a_i {X_i}^{\alpha_i} - b_i X_i,$$

  which describes tumor growth in a form known as "type II growth" [310].

These models provide various mathematical formulations for cell growth and are used in literature to describe different cell types within the tumor-immune interaction framework.

The mathematical form of the remaining terms in Eq. (3.1) varies depending on the specific biological mechanisms and modeling objectives, offering flexibility to capture the complexity of tumor-immune interactions.

A growing number of mathematical models have been developed to explain the complex regulatory mechanisms between tumors and the immune system, based on the principles of ODE model construction [15, 81, 198]. This review focuses on summarizing the applications of these mathematical models in describing tumor-immune regulatory networks, as well as providing an overview of the development of ODE models in tumor-immune interactions modeling over the past three decades (Fig. 8).

The Lotka-Volterra model, traditionally used to describe predator-prey dynamics in ecological systems, has been adapted to many mathematical models. In the 1990s, Kuznetsov and Makalkin [157] applied the Lotka-Volterra model principles to tumor-immune interactions (Fig. 8a), highlighting how tumor growth stimulates immune responses and the phenomenon of tumor dormancy. Later, Kirschner and Panetta [150] expanded this research by incorporating the role of IL-2, a cytokine that enhances T cell proliferation and function, in tumor-immune interactions (Fig. 8b). This model has been instrumental in exploring adoptive cellular immunotherapy and analyzing behaviors such as short-term oscillations and long-term tumor recurrence. Wei *et al.* [308] further performed bifurcation analyses of the key parameters in [150], providing insights into their biological significance. Arciero *et al.* [16], building on Kirschner's model, incorporated the immunosuppressive and growth-promoting effects of TGF-β in tumor immunology (Fig. 8c). Their model predicted that increasing the production rate of TGF-β could enhance tumor growth and its ability to evade immune surveillance.

Pillis *et al.* [65] introduced an analytical framework to investigate the roles of NK cells and CD8+ T cells in tumor-immune surveillance (Fig. 8d), introducing a new functional form for tumor cell killing by CD8+ T cells, which emphasized the different dynamics between NK and CD8+ T cells in tumor immunity. However, this model did not account for immune suppression. Subsequently, Pillis *et al.* [63, 64] extended their model to include circulating lymphocytes, further exploring the effects of chemotherapy and immunotherapy on tumor evolution (Fig. 8e), marking one of the early efforts to study optimal control in drug treatment. Similarly, Castiglione *et al.* [45, 46] established a population dynamics model of tumor-immune competition (Fig. 8f) and used optimal control theory to identify the optimal dosing strategies for immunotherapy.

Tumor-immune interactions are exceedingly complex. While no single model can encompass all cell types and signaling molecules, overly simplified models fail to capture the intricate dynamics observed in experiments and clinical settings. Building on models involving IL-2 [150], TGF-β [16], effector cells [65], and Tregs [171], Robertson-Tessi *et al.* [248] developed a comprehensive mathematical model of tumor-immune interactions (Fig. 8g). This model introduced an immune suppression mechanism, incorporating

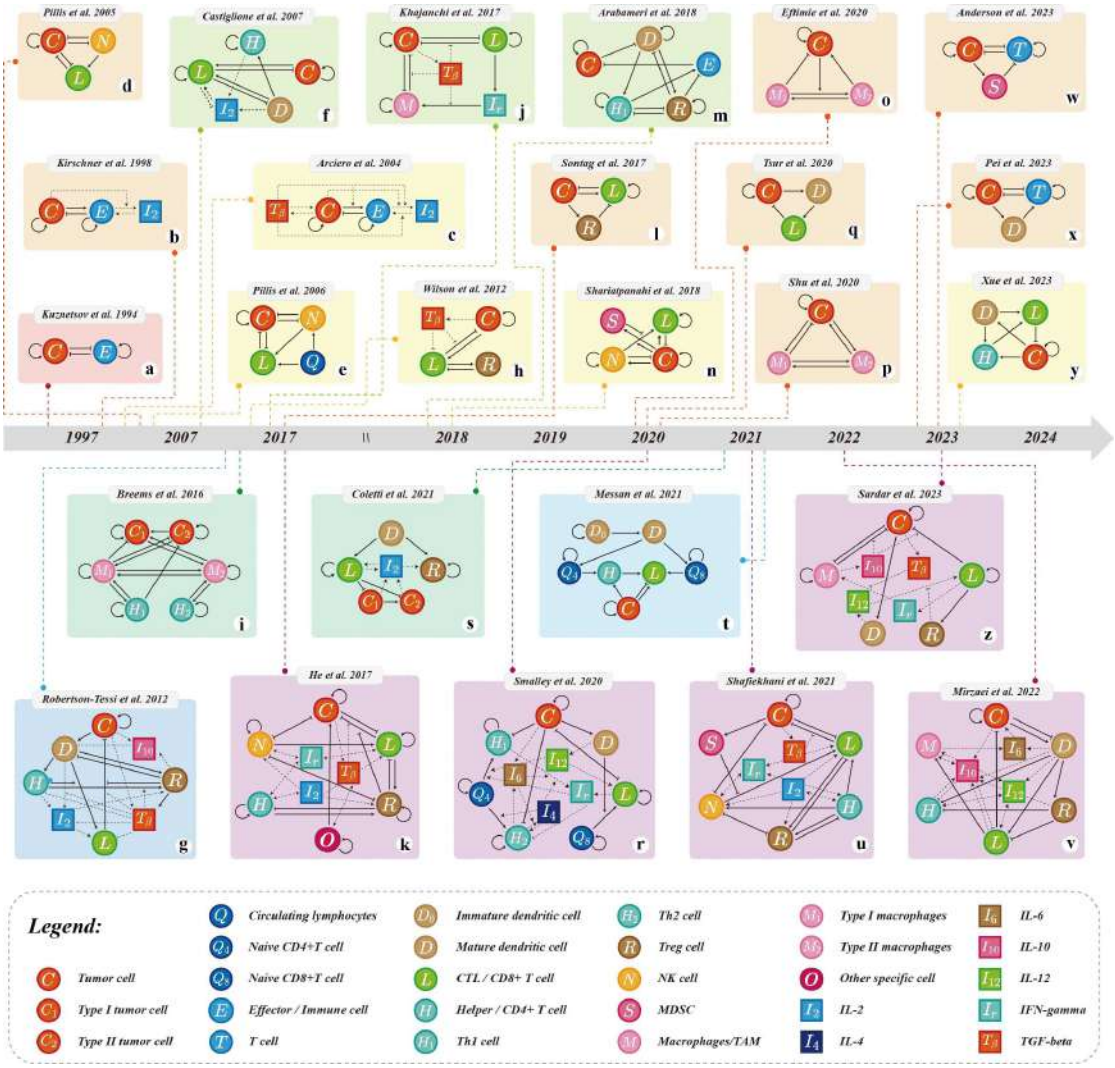

Figure 8: Application of ODE models in the description of tumor-immune regulatory networks. The content in the grey box indicates article information, with serial numbers corresponding to references. Solid lines represent cellular-level mechanisms, while dashed lines represent cytokine-level interactions. Arrows indicate proliferation or activation, and blocking arrows represent killing or inhibitions.

a negative feedback loop in the activation of the immune system. It suggested that tumors not only activate immune responses but also regulate immune suppression, weakening T cell function. Robertson-Tessi *et al.* [249] later extended this model to capture the interactions between tumors, the immune system, and chemotherapy. Soto-Ortiz *et al.* [278] built on these models, developing one that couples anti-angiogenic therapy targeting the tumor vasculature with immunotherapy targeting the tumor.

Macrophage polarization and transformation are typical biological phenomena where cancer cells remodel the TME. Breems *et al.* [69] developed a model of macrophage po-

larization (Fig. 8i), which integrated interactions between two types of tumor cells, two subsets of Th cells, and two types of macrophages. Their results showed that tumor growth is strongly correlated with the Type II immune response characterized by Th2 and M2. Similarly, Shu *et al.* [273] proposed a model describing the interactions between tumor cells, M1 and M2 macrophages (Fig. 8p), demonstrating that cancer evolution depends not only on tumor-induced activation of M1 and M2 macrophages but also on transitions between these macrophage states. Eftimie [79] explored the impact of M1-to-M2 transformation driven by tumor cells (Fig. 8o), analyzing how macrophage phenotype conversion influences tumor growth, control, and decay. Additionally, Eftimie *et al.* [80] investigated the role of transitional macrophages in tumor evolution. Analogous to M2 macrophages, MDSCs also exert potent immunosuppressive effects in the TME. Shariatpanahi *et al.* [271] developed a model examining the interactions between tumors, CTLs, NK cells, and MDSCs (Fig. 8n), assessing the impact of anti-MDSC drugs on tumor growth and immune system restoration. More recently, Anderson *et al.* [11] proposed an ODE model that provides insights into the tumor, T cell, and MDSC interactions (Fig. 8w), and suggested combining immune checkpoint inhibitors (ICIs) with MDSC inhibitors as a therapeutic strategy.

Sontag [277] proposed an immune recognition model (Fig. 8l) incorporating systems biology mechanisms such as negative feedback, incoherent feedforward loops, and bistability. This model captured the complex interactions among tumors, CTLs, and Tregs, using mathematical theory to elucidate key biological mechanisms. In recent years, significant research has focused on applying mathematical methods to tumor immunology models involving the regulation of three interacting elements. Tsur *et al.* [293] developed a model (Fig. 8q) incorporating tumors, CTLs, and DCs to predict the efficacy of ICIs in melanoma and analyze the system's local and global dynamics. Pei *et al.* [231] established a model (Fig. 8x) incorporating tumors, T cells, and DCs to analyze the combined effects of RNA interference and ICIs in breast cancer, using machine learning methods to optimize treatment strategies.

Wilson *et al.* [313] explored the synergistic effects of anti-TGF-β and vaccine therapies by dividing the tumor immune response into four modules: tumor, CTLs, Tregs, and TGF-β (Fig. 8h). Building on this, Khajanchi *et al.* [142] integrated the interactions between tumors, macrophages, CTL, TGF-β, and IFN-γ to examine tumor control through immunotherapy (Fig. 8j). Coletti *et al.* [56] developed a model (Fig. 8s) incorporating two types of tumor cells, DCs, Tregs, CTLs, and IL-2, using bistability to explain the heterogeneity of tumor evolution. He *et al.* [114] proposed a model of the regulatory mechanisms within the TME (Fig. 8k), demonstrating that combined therapies reduce Tregs and improve patient survival. Arabameri *et al.* [14] created a mathematical model of tumor-immune interactions, focusing on DC mechanisms (Fig. 8m), which highlighted the role of DC vaccines in tumor progression. More recently, Sardar *et al.* [260] developed a nine-dimensional tumor immune dynamical system (Fig. 8z) and employed a quasi-steady-state approximation to reduce it to a four-dimensional ODE model, capturing tumor immunity dynamics in response to various cytokines. Similarly, Xue *et al.* [317] es-

tablished a four-dimensional ODE model of tumor immunity (Fig. 8y), conducting Hopf bifurcation analysis and evaluating the combined therapeutic efficacy. This body of work, combining theoretical analysis with numerical simulations, provides a foundation for future studies in mathematical oncology.

T cell activation is crucial in the tumor-immune response, directly impacting the body's ability to mount an effective anti-tumor immune reaction. Smalley *et al.* [276] constructed a tumor-immune interaction network (Fig. 8r) to investigate the activation processes of CD4+ and CD8+ T cells, as well as their involvement in anti-tumor immune responses, using computer simulations to model dynamic responses to anti-PD-1 therapies. Messan *et al.* [206] developed a mathematical model for cancer vaccine treatment (Fig. 8t), focusing on DC activation, antigen presentation, and T cell-mediated immune attack on tumor cells. Similarly, Mirzaei *et al.* [212] constructed a mathematical model (Fig. 8v) that encompasses T cell activation and explores the intricate regulatory interactions between cells and cytokines. Shafiekhani *et al.* [270] further examined the combined efficacy of chemotherapy and immunotherapy by developing a mathematical model driven by both cellular and cytokine interactions (Fig. 8u).

3.2 Delay differential equation model

Time delays are an essential aspect of biological processes in the mathematical modeling of tumor-immune systems. These delays arise from various processes such as molecular production, cell proliferation and differentiation, tumor recognition and phagocytosis by the immune system, and the migration of cells between different tissues–each requiring a certain amount of time. Therefore, incorporating discrete time delays into mathematical oncology models helps improve the understanding of the dynamic interactions between tumors and the immune system. Based on Eq. (3.1), we can generalize the DDE model of the tumor-immune system in a unified form as

$$\frac{\mathrm{d}\vec{X}(t)}{\mathrm{d}t}=\vec{F}\big(\vec{X}(t),\vec{X}(t-\tau_1),\vec{X}(t-\tau_2),\ldots,\vec{X}(t-\tau_k);\Theta\big), \tag{3.2}$$

where τ_1, τ_2, …, τ_k represent the time delays. This review highlights several representative DDE models of tumor-immune interactions developed over the past two decades, with a particular focus on the biological mechanisms governed by discrete time delays. The regulatory networks and time-delay factors incorporated in these DDE models are visualized in Fig. 9.

Villasana *et al.* [297] were pioneers in developing a DDE model (Fig. 9a) that described interactions between tumor cell subpopulations in the interphase and mitotic phases with the immune system, examining the influence of cycle-specific drugs on tumor growth. Their theoretical and numerical analyses demonstrated that periodic solutions can arise through Hopf bifurcations. Additionally, Yafia [318] expanded the work of Kuznetsov *et al.* [157] by introducing a two-dimensional DDE model (Fig. 9b) of tumor-immune interactions, with a time delay representing the immune system's response time following

tumor cell recognition. This model revealed that system dynamics are largely governed by the delay parameter, with Hopf bifurcations in this parameter predicting the emergence of limit cycles from non-trivial steady states. Similarly, Banerjee *et al.* [19] extended the model by Sarkar *et al.* [262] to a three-dimensional DDE model framework (Fig. 9c) by incorporating biologically relevant mechanisms and delays related to the conversion of resting cells to effector cells.

Bi and Ruan [26] developed a two-dimensional tumor-immune model with two delays (Fig. 9d), deriving general formulas to assess the direction, period, and stability of both codimension-one and codimension-two bifurcation periodic solutions. Building on this, Bi *et al.* [27] advanced a similar two-dimensional model with three delays (Fig. 9e), with each delay representing tumor proliferation, tumor-stimulated effector cell growth, and effector cell differentiation, respectively. Concurrently, Dong *et al.* [73] introduced a three-dimensional DDE model with two delays (Fig. 9f), focusing on the immune activation delay of effector cells and the activation delay of Th cells. In computational modeling, Qomlaqi *et al.* [238] developed a comprehensive nine-dimensional DDE model with three delays (Fig. 9g), effectively illustrating the dynamic evolution of the tumor-immune interactions.

Khajanchi *et al.* [140, 141, 143–145] proposed a series of influential DDE models for tumor-immune systems. Initially, Khajanchi *et al.* [141] incorporated a discrete delay into the recruitment term for effector cells based on the model by Kuznetsov [157], deriving explicit expressions for the direction of Hopf bifurcation and periodic solution stability using normal form theory and the center manifold theorem. Subsequently, Khajanchi *et al.* [143] introduced a five-dimensional DDE model with four nonlinear delay terms (Fig. 9h), demonstrating the influence of multiple delays on tumor-immune interactions. In [145], they also proposed a three-dimensional model depicting the interaction between tumors, effector cells, and healthy host cells (Fig. 9i), which explores how tumor cells persist despite transient immune responses. Further models by [144] and [140] focused on interactions between tumors, CTLs, and Th cells (Fig. 9l), incorporating delays associated with Th cell-mediated CTL activation. Recently, Sardar *et al.* [261] developed an advanced tumor-immune interaction model with three discrete delays (Fig. 9o), reducing a nine-dimensional ODE model to a four-dimensional DDE model through a quasi-steady-state approximation of cytokine levels. Their study extensively examined the model's foundational properties, including existence, uniqueness, positivity, boundedness, and uniform persistence.

Das *et al.* [59, 61, 62] have made notable contributions to advancing DDE models in tumor-immune dynamics. In [59], they introduce a DDE model featuring Monod-Haldane response dynamics (Fig. 9j), capturing the interactions among tumors, effector cells, and IL-2. Further expanding this framework, [62] and [61] developed a more comprehensive DDE model (Fig. 9m) involving tumors, effector cells, Th cells, and IL-2, incorporating cytokine-mediated cell signaling with time delays to coordinate immune responses. Additionally, [61] explored an optimal control approach for combined immunotherapy and chemotherapy.

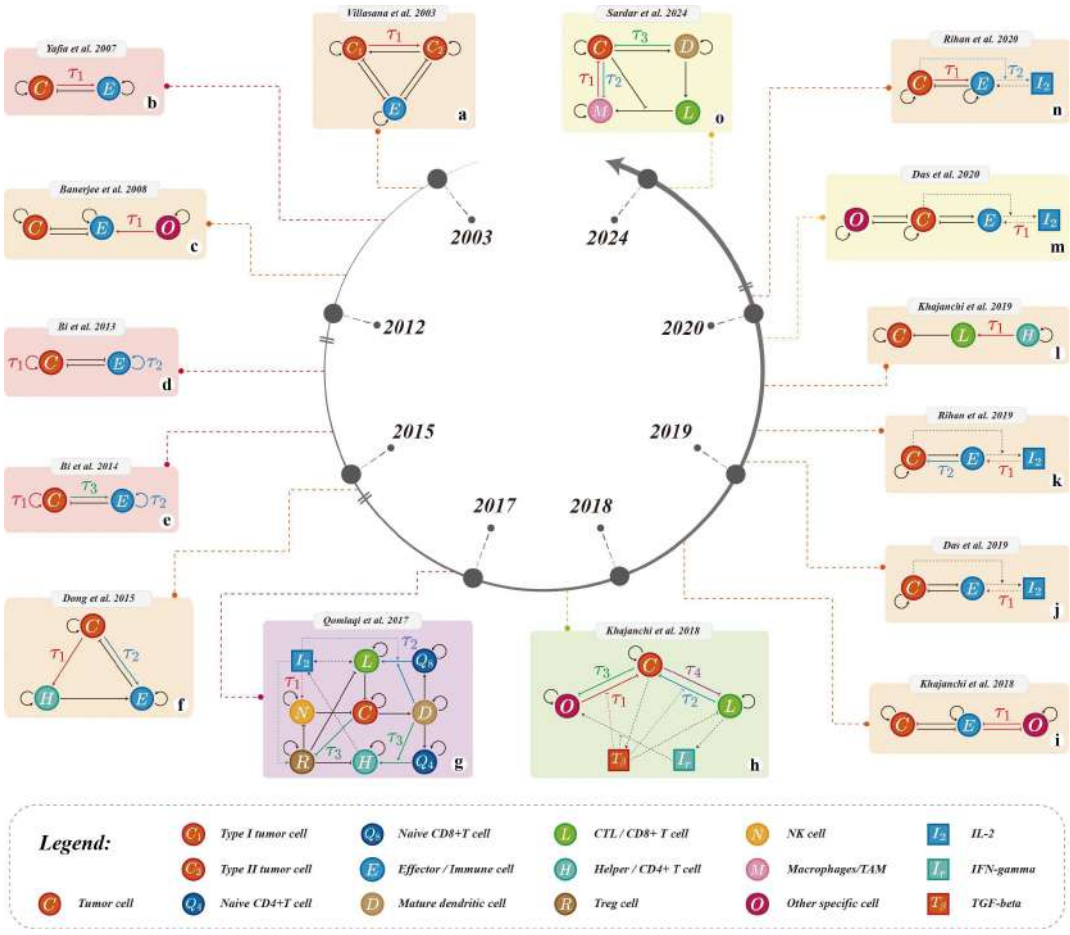

Figure 9: Application of DDE models in describing tumor-immune regulatory networks. The grey box contains article information, with serial numbers corresponding to the references. Solid lines represent cellular-level mechanisms, while dashed lines represent cytokine-level mechanisms. Sharp arrows indicate proliferation or activation, and blocked arrows indicate killing or inhibition. Red, blue, green, and purple lines correspond to the 1st, 2nd, 3rd, and 4th time delays, respectively.

Rihan *et al.* [245–247] have also contributed groundbreaking work to the field of DDE models of tumor-immune systems. Based on the foundational models in [150] and [59], Rihan *et al.* [246] introduced a model with two delay processes (Fig. 9k), examining tumor-immune dynamics and optimal control under immunochemotherapy. Building on this, [247] introduced a fractional-order DDE model (Fig. 9n) that analyzed conditions for stability and Hopf bifurcations with two distinct delays. More recently, Rihan *et al.* [245] developed a DDE model incorporating stochastic noise, demonstrating that stochastic fluctuations can suppress tumor cell growth and that white noise can potentially lead to tumor dormancy or eradication.

Recently, more biologically detailed DDE models have been formulated. Among them, Dickman and Kuang [71, 72] presented a two-compartment DDE model that dis-

tinguishes the peripheral blood from the TME and integrates key mechanisms, including DC maturation and CTL cell activation. This work marks a substantial evolution from single-compartment to multi-compartment DDE models. Additionally, Wang *et al.* [306] introduced a DDE model featuring two specific delays to represent the dynamics between tumors and the lymphatic system, characterizing tumor proliferation and the maturation process of T lymphocytes.

3.3 Stochastic differential equation model

Stochastic perturbations accompany nearly all living processes, encompassing intrinsic noise arising from molecular-level fluctuations and external noise stemming from environmental changes [292, 324]. Integrating stochastic terms into models to capture these influences – such as intercellular communication and protein perturbations – on tumor-immune interactions is essential. Stochastic models can be constructed by introducing stochastic processes or parameters, providing a robust framework to study how randomness affects tumor-immune dynamics. SDE models allow for analysis of tumor-immune system behavior under stochastic perturbations, including asymptotic and stability analyses, periodic solutions, and tumor heterogeneity evolution. This review describes a general SDE model of the tumor-immune system as

$$\mathrm{d}\vec{X}_t = \vec{\mu}(t,\mathbf{X}_t;\Theta)\mathrm{d}t + \vec{\sigma}(t,\vec{X}_t;\Theta)\mathrm{d}\vec{W}_t, \tag{3.3}$$

where $\vec{X}_t$ represents the stochastic state variable, $\vec{\mu}(t,\vec{X}_t;\Theta)$ is the drift term modeling the trend of changing, $\vec{\sigma}(t,\vec{X}_t;\Theta)$ is the diffusion term reflecting stochastic fluctuations, and $\vec{W}_t$ is a Wiener process capturing stochastic disturbances.

Mukhopadhyay *et al.* [217] developed an SDE model for tumor-immune interactions, simulating white noise perturbations around system boundaries and equilibrium points– a standard method for adding stochastic perturbations to deterministic models. Caravagna *et al.* [44] extended the [150] model to a hybrid stochastic framework, combining stochastic processes to capture cellular dynamics and differential equations for interleukin dynamics. Xu *et al.* [315] investigated stochastic bifurcations in the tumor-immune system under symmetric non-Gaussian Lévy noise, linking bifurcation patterns with noise intensity and stability. Li *et al.* [176] adapted a simplified tumor-immune ODE model to an SDE framework with Gaussian white noise, providing insights into the stochastic dynamics of tumor growth, immune response, and immunoediting.

Subsequently, Caravagna *et al.* [44] examined the effects of stochastic shocks on tumor suppression, while Deng *et al.* [70] developed a pulsed stochastic tumor-immune model with mode transitions, emphasizing the link between stochastic and pulsed perturbations on system behavior. Liu *et al.* [188] constructed a continuous time Markov chain model based on the branching processes theory to characterize the dynamics of tumor-immune interactions. Li *et al.* [50, 179] extended the classical two-dimensional tumor-immune ODE model [157] to an SDE framework, utilizing stochastic Lyapunov analysis, comparison theorem, and strong ergodicity theorem to explore the system's asymptotic

properties. Yang *et al.* [320] introduced a stochastic model for pulsatile therapy, examining the impact of fluctuations and combined immunotherapy and chemotherapy on treatment outcomes. Han and Hao *et al.* [109, 113] studied the most probable trajectories of the proposed stochastic tumor-immunity model.

Recently, several three-dimensional SDE models have emerged to model tumor-immune interactions more accurately [6, 31, 60, 121, 234, 319]. For example, Bose *et al.* [31] investigated an SDE model involving tumors, effector cells, and tumor-detecting cells, showing that noise correlation parameters strongly influence tumor-immune dynamics. Phan *et al.* [234] developed an SDE model to simulate viral therapy, while Yang et al. [319] introduced a pulsed SDE model to describe interactions between the tumor, Th cells, and CTLs. Alsakaji *et al.* [6] proposed a stochastic delay differential model to simulate the tumor-immune system under white noise and treatment.

More recently, Lai *et al.* [162] developed an SDE model that characterizes the clinical course of chronic myeloid leukemia (CML) patients achieving treatment-free remission post-therapy. By modeling feedback interactions between leukemic stem cells and the bone marrow microenvironment, they identify early relapse and long-term remission as typical clinical manifestations following treatment cessation. This model suggests that the leukemic cell proportion in blood and the TME index could be important for TFR outcomes, representing a recent clinical application of SDE models in oncology.

3.4 Partial differential equation model

PDE models effectively describe the spatiotemporal dynamics of tumors and immune cells, capturing changes in tumor-immune interactions. Recent research has highlighted the complex interactions among immune cells in the TME during tumor progression. In this review, we summarize mathematical models using reaction-diffusion equations to characterize tumor-immune interactions. The following unified framework describes the spatiotemporal dynamics of the tumor-immune system:

$$\frac{\partial X_i}{\partial t}+\nabla\cdot(\vec{u}_i\, X_i)-\delta_i\nabla^2 X_i=f_i(X_1,\cdots,X_n),\quad \vec{X}=(X_1,\cdots,X_n)\in\Omega(t) \tag{3.4}$$

where

$$\nabla=\left(\frac{\partial}{\partial x},\frac{\partial}{\partial y},\frac{\partial}{\partial z}\right),\quad \nabla^2=\frac{\partial^2}{\partial x^2}+\frac{\partial^2}{\partial y^2}+\frac{\partial^2}{\partial z^2}.$$

Here, $\vec{u}_i$ denotes the advective velocities, $\delta_i>0$ are diffusion coefficients. The components X_i can denote different cells or molecules, each exhibiting unique advective velocities and diffusion rates. Notably, in modeling molecular-scale dynamics, the convection term $\nabla\cdot(\vec{u}_i X_i)$ can be set to zero (i.e. $\vec{u}_i=\vec{0}$) to reflect the negligible effect of intercellular pressures on smaller molecules, distinguishing it from cellular-scale dynamics. The tumor is represented by $\Omega(t)\subset\mathbb{R}^3$ and is subject to a moving boundary condition.

To simplify the model, it is often assumed that the tumor is spherical, with all variables radially symmetric. Consequently, the variables depend only on time t and radial

distance r, where $r=|\vec{x}|$. The velocity and bounded region are expressed as $\vec{u}=u(r,t)\vec{x}/|\vec{x}|$ and $\Omega(t)=\{r<R(t)\}$, respectively. In spherical coordinates, Eq. (3.4) becomes

$$\frac{\partial X_i}{\partial t}+\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2uX_i\right)-\delta_{X_i}\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial X_i}{\partial r}\right)=f_i(X_1,\ldots,X_n). \tag{3.5}$$

The free boundary $r=R(t)$ moves with the speed of the cellular population, hence [163]

$$\frac{\mathrm{d}R(t)}{\mathrm{d}t}=u\big(R(t),t\big), \tag{3.6}$$

where the velocity u is derived from pressure exerted by proliferating cancer cells. If we assume a constant total cell density, such that $\sum_{i=1}^{m}X_i(r,t)=X_0$. Integrating the cell dynamic equations allows for the derivation of $u(r,t)$, satisfying

$$\frac{1}{r^2}\frac{\partial}{\partial r}(r^2u)=\sum_{i=1}^{m}f_i. \tag{3.7}$$

One notable study on a PDE model for combination therapy in breast cancer is by Lai *et al.* [163], which integrates eight cellular-level dynamic behaviors and fourteen molecular-level elements to assess therapeutic efficacy using evaluation indices. Their results demonstrate a positive correlation between BET inhibitors and CTLA-4 inhibitors in breast cancer, showing that tumor volume decreases as dosages increase for each drug. In a subsequent model, Lai *et al.* [160] explored breast cancer treatment by combining anti-angiogenic agents with chemotherapy. Given the antagonistic interaction observed between bevacizumab and docetaxel, the model examines various dosing strategies, suggesting that non-overlapping regimens may yield superior outcomes.

The BRAF mutation is one of the most commonly prevalent in melanoma patients. Lai *et al.* [159] developed a PDE model for combined targeted therapy using BRAF inhibitors and ICIs in melanoma. This study reveals that the drugs have a synergistic effect at low doses, whereas high doses lead to antagonism. Thus, identifying these antagonistic regions early through animal studies or initial clinical trials is crucial to optimizing dosing in clinical applications. Similarly, Friedman *et al.* [88] established a PDE model to investigate the efficacy of combining BRAF inhibitors with anti-CCL2, anti-PD-1, and anti-CTLA-4 antibodies, aiming to identify strategies that mitigate resistance induced by BRAF inhibition. Additionally, Liao *et al.* [182] introduced a PDE model that incorporates both proinflammatory and anti-inflammatory effects of IFN-γ for melanoma treatment using ICIs.

PDE models are frequently employed to explore the biological mechanisms underlying tumor evolution. Szomolay *et al.* [290] constructed a model to examine the role of GM-CSF in promoting vascular endothelial growth factor (VEGF) inactivation, which in turn slows tumor growth. Lee *et al.* [165] used a chemotaxis-reaction-diffusion model to analyze the interactions between tumor cells and neutrophils that drive tumor invasion. Kim *et al.* [147] coupled this model with receptor dynamics to elucidate the dual

role of cellular senescence in cancer progression. In other studies, Friedman *et al.* [87,274] developed a PDE model to study tumor-immune interactions, focusing on the role of exosomes–extracellular vesicles containing mRNA, microRNA, and proteins–as predictive biomarkers for tumors. Jacobsen *et al.* [129] created a PDE model to investigate the impact of CNN1, an extracellular matrix protein, on oncolytic virus therapy in gliomas, finding that CCN1 limits therapeutic efficacy by enhancing the activation and migration of pro-inflammatory macrophages.

In recent years, numerous PDE models have emerged to study the dynamic evolution of cancer under combination therapies. Lai *et al.* [161] developed a model explaining the effects of combined radiotherapy and anti-PD-L1 treatment. Their findings indicate that patients receiving concurrent therapy benefited more than those on weekly alternating schedules. Siewe *et al.* [275] presented a PDE model for dual immunotherapy combining anti-PD-1 and anti-CSF-1. Kim *et al.* [148] also contributed a model analyzing the role of NK cells in treating primary glioblastoma with oncolytic viruses (OV) and protease inhibitors, finding that NK cells exhibit significant anti-tumor effects, which increase when exogenous NK cells are injected into the tumor.

PDE models have also been used to quantify cancer immunoediting. Li *et al.* [178] developed a PDE model that encapsulates the interactions among tumor cells, immune cells, cancer-associated fibroblasts, and angiogenic cells, describing the phases of cancer evolution: Elimination, Equilibrium, and Escape. The model demonstrates how immune cells and cancer-associated fibroblasts facilitate transitions between these states, offering new insights into how changes in the TME influence cancer immunoediting.

3.5 Integral differential equation model

Tumor cells are generally viewed as cells with malignant proliferative potential, resulting from genetic mutations that arise during the prolonged self-renewal processes of stem cells. In the 1970s, the G0 cell cycle model was introduced to describe the regenerative dynamics of homogeneous stem cells (Fig. 10a) [40, 197]. Lei *et al.* [170] were the first to incorporate epigenetic factors into models of stem cell regeneration, with the aim of exploring how genetic and epigenetic regulation interact in stem cell renewal. Building on this, to further characterize the regeneration dynamics of heterogeneous tumor stem cells (Fig. 10b), Lei [167, 168] proposed an IDE model framework. This framework provides a general mathematical description of tumor stem cell regeneration dynamics with epigenetic transitions

$$\begin{aligned}\frac{\partial Q(t,\vec{x})}{\partial t} &= -Q(t,\vec{x})\big(\beta(c,\vec{x})+\kappa(\vec{x})\big)\\ &\quad +2\int_\Omega \beta\big(c_{\tau(\vec{y})},\vec{y}\big)Q\big(t-\tau(\vec{y}),\vec{y}\big)\mathrm{e}^{-\mu(\vec{y})\tau(\vec{y})}p(\vec{x},\vec{y})\mathrm{d}\vec{y}, \qquad (3.8)\\ c(t) &= \int_\Omega Q(t,\vec{x})\zeta(\vec{x})\mathrm{d}\vec{x}.\end{aligned}$$

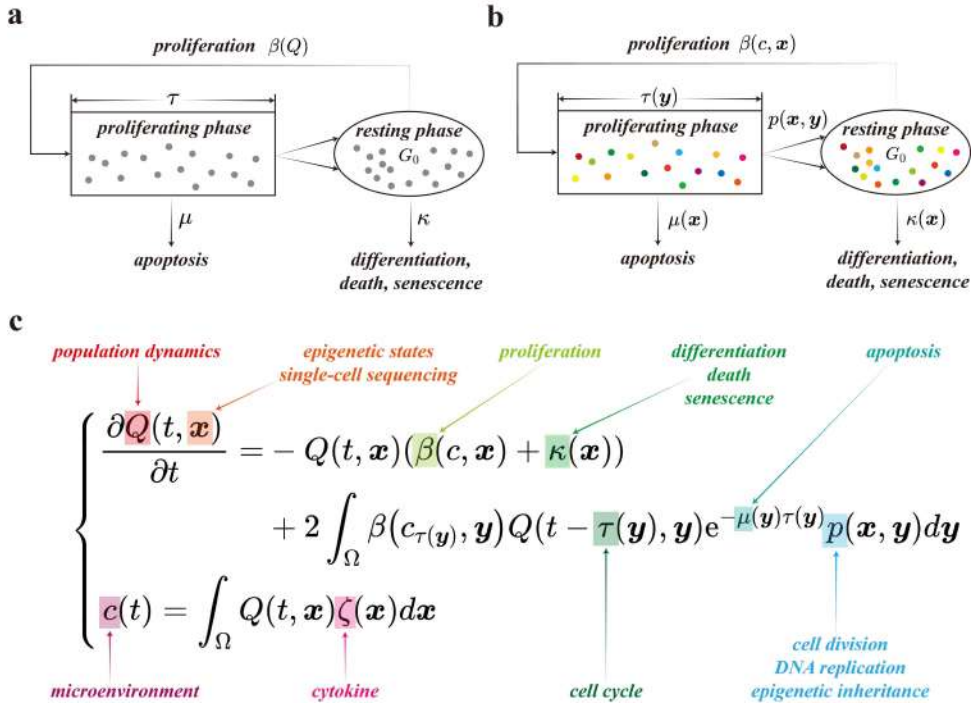

Figure 10: Mechanism illustration and general mathematical framework for stem cell regeneration dynamics. a. Mechanistic diagram of homogeneous stem cell regeneration dynamics. b. Mechanism diagram of heterogeneous stem cell regeneration dynamics. c. The framework of the mathematical model for heterogeneous stem cell regeneration. Here, Q denotes the number of stem cells in the resting phase; $\vec{x}$ represents epigenetic status; Ω is the space encompassing all possible epigenetic states; β represents the rate at which resting-phase cells return to the proliferating phase; κ is the clearance rate (including differentiation, death, and senescence) of cells in the resting phase (G_0); τ denotes the cell cycle duration; μ is the apoptosis rate; $p(\vec{x},\vec{y})$ represents the probability that a daughter cell in state $\vec{x}$ originates from a mother cell in state $\vec{y}$ after division; c is the effective concentration of growth-inhibitory cytokines; and $\zeta(\vec{x})$ is the rate of cytokine secretion by a cell in state $\vec{x}$.

This equation extends the G0 cell cycle model to include stem cell heterogeneity and plasticity and can be applied to describe biological processes associated with stem cell regeneration, including development, aging, and tumor evolution [167,168,181,325].

In modeling the dynamic mechanisms underlying tumor evolution, Eq. (3.8) connects various components: epigenetic states $\vec{x}$, tumor dynamics ($\beta(c,\vec{x})$, $\kappa(\vec{x})$, $\mu(\vec{x})$), cell cycle duration $\tau(\vec{x})$, cytokine secretion ($\zeta(\vec{x})$), and the inheritance probability of epigenetic states $p(\vec{x},\vec{y})$ (Fig. 10c). The functions $\beta(c,\vec{x})$, $\kappa(\vec{x})$, $\mu(\vec{x})$, and $\tau(\vec{x})$, which describe cell cycle kinetics, are collectively termed the cell's kinetotype as proposed in [167].

The inheritance function $p(\vec{x},\vec{y})$ in Eq. (3.8) is essential for capturing cell plasticity during the cell cycle. Although determining the exact form of $p(\vec{x},\vec{y})$ biologically is challenging due to the complexity of biochemical processes involved in cell division, it can be considered as a conditional probability density

$$p(\vec{x},\vec{y}) = P(\text{state of daughter cell} = \vec{x} \,|\, \text{state of mother cell} = \vec{y}).$$

This allows us to focus on the epigenetic states before and after cell division, bypassing the intermediate processes. Huang *et al.* [122–124] developed a computational model based on epigenetic mechanisms, specifically, histone modifications, showing that inheritance probabilities can be described using a conditions Beta distribution.

The framework provided in Eq. (3.8) establishes a foundational model encompassing the key elements of stem cell regeneration, including cell cycling, heterogeneity, and plasticity. This model can be extended to account for gene mutations and cell lineage evolution [167]. However, stem cell systems in biological processes may need to be incorporated, such as gene networks within the cell cycle, cell-to-cell interactions within specific niches, and interactions between cells and the microenvironment. For further discussion, please refer to [169].

Utilizing the modeling mechanisms outlined by Lei *et al.* [170], Guo *et al.* [107] developed a multi-scale computational model to simulate the progression from inflammation to tumorigenesis. This model effectively reproduces the pathway of transformation from inflammation to cancer, comprising two primary stages: the transition from normal tissue to precancerous lesions and the progression from these lesions to malignant tumors. Computational results suggest that long-term, mild inflammation can initiate the development of precancerous lesions from a normal state, though it appears insufficient to drive full malignancy. In contrast, moderate and severe inflammation markedly enhances the progression from a precancerous state to tumor development.

Liang *et al.* [181] applied a generalized framework for heterogeneous stem cell regeneration to investigate the dynamics of epigenetic states in a one-dimensional context. The biological background of this study is to understand dynamic blood disorders, specifically fluctuations in blood cell counts. The model elucidates the influence of changes in cellular heterogeneity and plasticity on population dynamics, particularly cyclic and oscillatory behaviors. Results suggest that alterations in cellular heterogeneity and plasticity can affect conditions that give rise to oscillatory phenomena in stem cell regeneration systems.

In recent years, chimeric antigen receptor T (CAR-T) cell therapy has shown promising clinical benefits in treating B-cell acute lymphoblastic leukemia (B-ALL). Zhang *et al.* [325] combined biological experiments with a mathematical model to explore CAR-T-induced cellular plasticity leading to tumor recurrence. This study successfully replicates tumor evolution dynamics observed in biological models, predicting that CAR-T-induced cellular plasticity following CD19 CAR-T therapy could drive B-ALL recurrence. Both the model and experiments suggest that a combined CAR-T therapy targeting CD19 and CD123 at specific ratios may prevent disease relapse.

Ma *et al.* [196] recently developed a mathematical model based on Eq. (3.8) to evaluate how heterogeneous PD-L1 expression affects disease progression in cancer patients. This model attributes tumor cell heterogeneity to stemness and PD-L1 expression levels, while T-cell heterogeneity is influenced by PD-1 expression. Results show that during the early stages of anti-PD-L1 therapy, response rate and efficacy correlate with PD-L1 expression levels in virtual patients. For patients with high PD-L1 expression, anti-PD-L1 treat-

ment more effectively controls tumor growth. The model also reveals that a maximum-tolerated dose strategy offers superior survival benefits for PD-L1-positive esophageal cancer patients.

In addition, Su *et al.* [287] conducted theoretical research on Eq. (3.8), focusing on the eigenvalue problems and asymptotic behaviors of both monogenotypic and polygenotypic stem cell regeneration models with epigenetic transitions. They examined the long-term dynamical and steady-state solutions associated with the three classes of quasilinear nonlocal diffusion evolution equations derived from these models, providing explicit formulas for thresholds pertinent to tissue development, degeneration, and abnormal growth.

3.6 Quantitative systems pharmacology model

QSP is a methodology that leverages traditional pharmacokinetics, pharmacology, and systems biology to quantitatively describe interactions between drugs and patients (Fig. 11). QSP models focus on population characteristics, variability in drug response markers, and disease progression in drug analysis. In tumor-immune modeling, they highlight the mechanisms underlying tumor-immune interactions and the dynamic migration of immune cells across different compartments. The objective of QSP models is to provide quantitative descriptions of drug efficacy and predictive models for disease progression. In this review, we explore QSP models grounded in tumor-immune interactions and present recent advancements in the field.

Milberg *et al.* [210] developed a QSP model to predict the response of immune checkpoint blockade in melanoma treatment. This model examined the response of monotherapy, combination therapy, and sequential therapy with anti-PD-1, anti-PD-L1, and anti-CTLA-4, revealing the therapeutic variations among patients. Such models provide powerful tools for assessing the efficacy of immunotherapy and guiding clinical decisions. Similarly, Wang *et al.* [303] developed a QSP model to investigate the pharmacokinetics and pharmacodynamics of anti-PD-1, anti-PD-L1, and anti-CTLA-4 therapies individually and in combination. Ma *et al.* [194, 195] used QSP models to evaluate the efficacy of T-cell engager (TCE) monotherapy, anti-PD-L1 monotherapy, and combination therapy in colorectal cancer patients.

Wang *et al.* [304] created a QSP model to conduct virtual clinical trials and identify predictive biomarkers. Their model, designed to evaluate immune checkpoint blockade therapy combined with epigenetic modulators in HER2-negative breast cancer, explored immune cell migration across four compartments: central, peripheral, tumor, and lymph node. The study confirmed that epigenetic modulators enhance ICIs' effects, proposing that tumor mutational burden, tumor-infiltrating effector T cell density, and the effector-to-regulatory T cell ratio in the TME as potential biomarkers for clinical trials.

In another application, Wang *et al.* [302] used a QSP model to predict the effectiveness of ICIs and chemotherapy in triple-negative breast cancer, optimizing drug dosages and treatment regimens. Recognizing the importance of TAMs as critical immunosuppressive

cells, Wang *et al.* [305] expanded the QSP model to include TAM heterogeneity, examining their impact on tumor evolution within the TME.

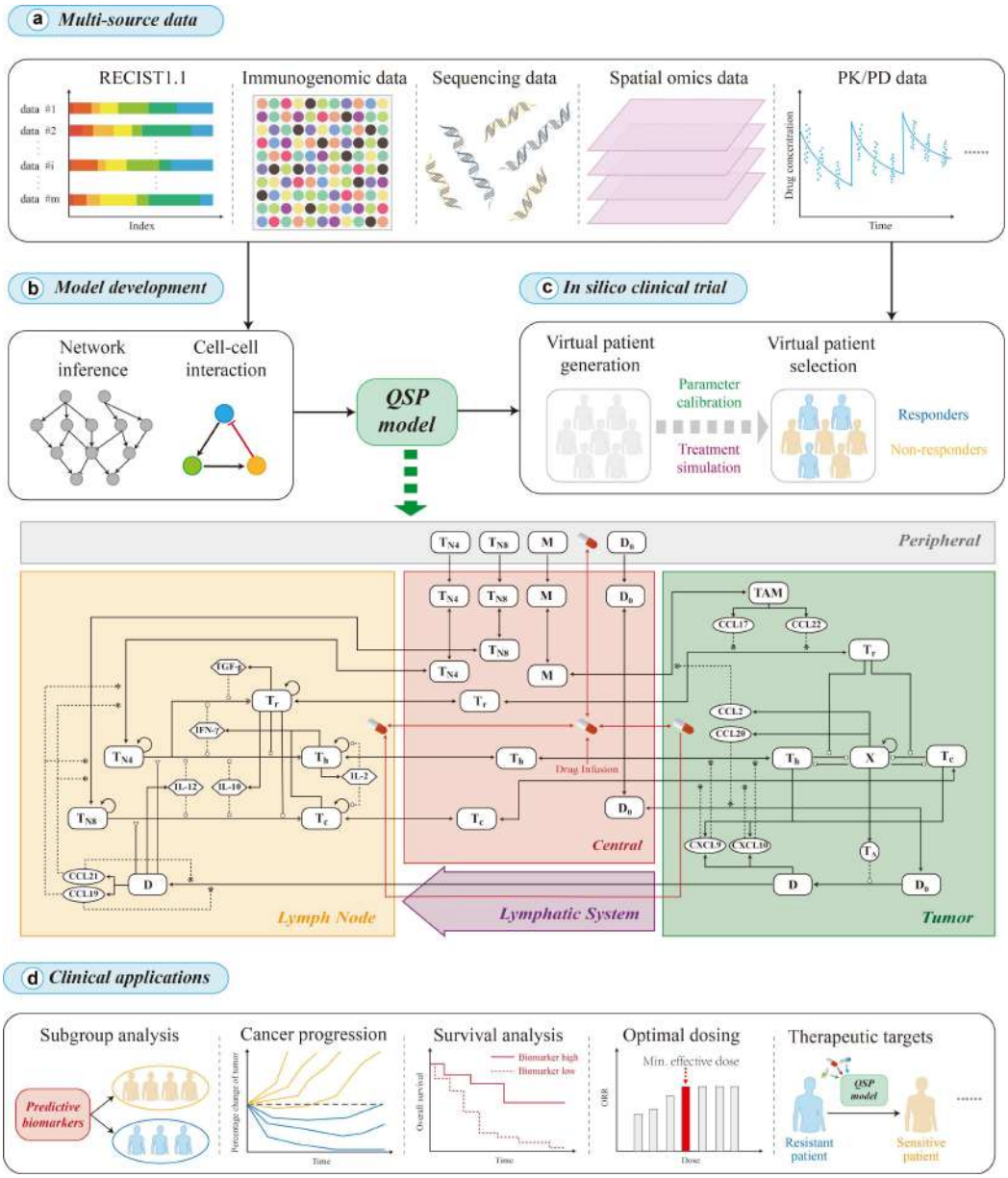

Figure 11: Schematic illustration of research methods integrating multi-source data with QSP models. a. Multi-source data help infer QSP model mechanisms and networks or guide the generation of effective virtual patients. b. A multi-compartmental QSP model is constructed based on tumor immunology's mechanisms and interaction networks. c. Calibration and simulation lead to selecting valid virtual patients for in silico clinical trials. d. QSP models can then be applied clinically to identify predictive biomarkers, project cancer progression, analyze survival, and optimize doses to enhance treatment sensitivity, especially in non-responders.

Sové *et al.* [279] developed a modular QSP platform for immuno-oncology (IO) research, which integrates essential tumor-immune interaction mechanisms. This modular approach allows for the creation of IO-QSP models with specific mechanisms to address targeted research questions. This work has facilitated and advanced the progress of QSP modeling research. Sové *et al.* [280] also used this framework to examine ICIs in hepatocellular carcinoma, predicting clinical trial outcomes using a random forest model. Ippolito *et al.* [126] leveraged an IO-QSP model to explore the potential of conditionally activated molecules, which can enhance anti-tumor responses while reducing systemic toxicity, for breast cancer immunotherapy. Recently, Wang *et al.* [300] focused on designing pharmacokinetic and pharmacodynamic modules within a QSP model to simulate the effects of targeted therapy combined with PD-L1 inhibitors in advanced non-small cell lung cancer.

With advancements in imaging technologies and spatial transcriptomics, tumor spatial data is increasingly critical in guiding QSP models for improved predictive accuracy. Gong *et al.* [103] and Nikfar *et al.* [221] developed a hybrid computational modeling platform, spQSP-IO, to simulate non-small cell lung cancer growth and immunotherapeutic responses based on spatial data, accounting for tumor heterogeneity and patient variability. Zhang *et al.* [327] used single-cell sequencing and the spQSP platform to predict immunotherapy outcomes in triple-negative breast cancer. Ruiz-Martinez *et al.* [253] extended the spQSP platform to analyze tumor growth dynamics across spatial and temporal scales.

Arulraj *et al.* [17] recently developed a transcriptome-informed QSP model to investigate metastasis in triple-negative breast cancer and predict PD-1 inhibitor efficacy. This model identified 30 key biomarkers, with Treg density variation within lymph nodes emerging as a promising indicator. Wang *et al.* [301] further developed an immunogenomic-driven QSP model to forecast PD-L1 inhibitor response in non-small cell lung cancer patients. By adjusting model parameters, this study generated virtual patient cohorts to predict clinical responses and identify potential biomarkers, examining the pharmacokinetics of PD-L1 inhibitors and using compressed latent parameterization to account for individual variations in drug response.

3.7 Agent-based model

Tumor growth and development is a complex, multi-scale biological process encompassing molecular, cellular, microenvironmental, and tissue-level interactions [9]. ABM is a computational approach that simulates complex systems by representing the behaviors of individual agents [1, 311]. ABM's capacity to model biological processes at the computational element level makes it an effective tool for simulating the multiscale nature of tumor development. Within ABMs, agents are entities with specific behaviors and functions, representing biological components like genes, proteins, blood vessels, or cells. In this review, we highlight ABM operational rules, available software packages, and primary applications in modeling tumor-immune system interactions.

Typically, cellular behaviors modeled in ABMs include migration, proliferation, differentiation, apoptosis, growth, morphological changes, secretion, and cell-cell interactions (Fig. 12a). ABM frameworks are generally divided into two main paradigms: lattice-based and off-lattice methods. Lattice-based models use either structured or unstructured meshes. Structured meshes are easier to implement programmatically but have limitations in visualizing data and representing complex biological mechanisms. Unstructured meshes, like the hexagonal grids often used for tumor-immune models, help overcome these limitations. Off-lattice methods, meanwhile, include center-based and boundary-based models.

Cellular Automata (CA) is one of the most foundational lattice-based approaches [294], where each grid cell can accommodate at most one biological cell (Fig. 12b). Operating within a discrete space-time framework, CA models update cell states based on predefined rules encompassing rest, movement (to adjacent sites), death (vacating a site), and division (placing daughter cells in adjacent grids). Another popular lattice-based ap-

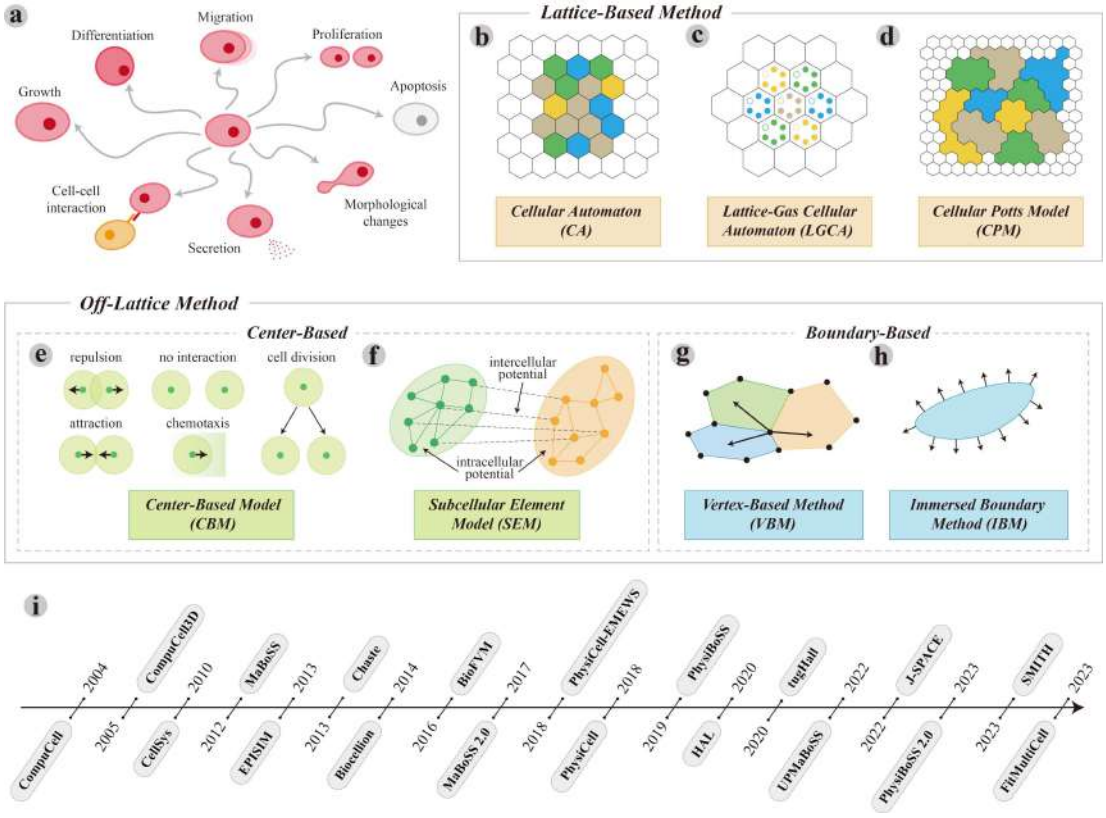

Figure 12: The biological mechanisms, modeling methods, and toolkits of ABMs for tumor-immune interactions. a. Biological mechanisms in ABMs. b. Cellular automaton method. c. Lattice-gas cellular automaton method. d. Cellular Potts method. e. Center-based method. f. Subcellular element method. g. Vertex-based method. h. Immersed boundary method. i. Toolkits of ABMs.

proach, the Lattice-Gas Cellular Automaton (LGCA), allows multiple cells to occupy the same grid space (Fig. 12c) [314]. LGCA models follow simple particle movement and collision rules based on physical principles, ensuring the conservation of mass, momentum, and energy. LGCA has proven useful in simulating the spread of tumor cells, including their infiltration into surrounding tissues and distant metastasis. These models capture cell population dynamics effectively without requiring detailed descriptions of individual cell morphologies. In contrast, the Cellular Potts Model (CPM) uses multiple lattice sites to represent a single cell, enabling detailed modeling of cell morphology and mechanical properties (Fig. 12d) [267]. Although CPM offers more detailed representations of cellular shape and behavior, it requires higher computational resources.

Center-based Model (CBM) is an off-lattice approach that characterizes cell behaviors and interactions within a system [202]. In CBM, cells exert forces dependent on the distance from their neighbors, including repulsive forces when in close proximity, attractive forces when farther apart, and the chemokine-induced pulling force (Fig. 12e). Another off-lattice model, the Subcellular Element Model (SEM), focuses on the dynamics and interactions of subcellular structures within cells (Fig. 12f) [256]. SEM can simulate processes such as the binding of signaling molecules – like hormones, antigens, and neurotransmitters – to cell membrane receptors, triggering biochemical cascades within the cell. In drug discovery, SEM models simulate drug-target binding, aiding in predictions of mechanisms of action and potential side effects. Beyond CBM and SEM, boundary-based models, which simulate dynamic changes in complex systems, have gained prominence. The Vertex-based Method (VBM) represents cells as polygons or polyhedra and calculates forces on vertices to depict cell morphological changes (Fig. 12g) [85]. VBM is crucial for processing vertex data in mesh models and identifying key points in imaging. The Immersed Boundary Method (IBM), a biomechanical approach, models tissues as clusters of heterogeneous cells (Fig. 12h) [243], emphasizing biomechanical properties and cell-microenvironment interactions.

A range of open-source ABM software packages has emerged based on the principles of ABM construction [1, 311]. Here, we highlight toolkits valuable for studying tumor evolution and tumor-immune interactions (Fig. 12i). Initial studies focused on intracellular signaling pathways and gene networks in tumor growth, resulting in software packages like CompuCell [128], CompuCell3D [54], MaBoSS [285], MaBoSS 2.0 [283], tugHall [219], and UPMaBoSS [284]. As the importance of the TME was recognized, new toolkits emerged to analyze the TME and multicellular interactions, including CellSys [120], EPISIM [289], Chaste [211], Biocellion [135], PhysiCell [97], PhysiBoSS [172], PhysiBoSS 2.0 [235], and FitMultiCell [4]. These tools bridge molecular-level cellular signaling and gene networks with the TME, facilitating multi-scale integration. Concurrently, tools for mathematical oncology models in spatially complex systems such as BioFVM [96], HAL [34], and PhysiCell-EMEWS [228], have been developed. Emulating Darwinian evolution, cancer is seen as an evolving system with competing subpopulations. Consequently, toolkits like J-SPACE [13] and SMITH [286] focus on tumor branching evolution and heterogeneity.

Numerous multi-scale models have been developed to explore intricate tumor-immune interactions. Anderson *et al.* [10] pioneered a multi-scale cancer invasion model, enabling studies of how the microenvironment affects solid tumor growth and therapeutic responses. Building on this, Sun *et al.* [288] developed a multi-scale ABM to evaluate tyrosine kinase inhibitor (TKI) efficacy in brain tumors, incorporating biological and physical features such as blood flow and pressure from tumor growth. This model showed that tumor growth is influenced by the EGFR signaling pathway and cell cycle. Additionally, Liang *et al.* [180] employed multi-scale modeling to predict the synergistic effects of targeting both EGFR and VEGFR pathways in brain tumor treatment.

Recently, ABMs have advanced the study of tumor heterogeneity and drug resistance. Gong *et al.* [102] developed an ABM to model tumor-immune interactions, focusing on the effects of ICIs on tumor progression. This study categorized tumors as PD-L1$^+$ and PD-L1$^-$ and demonstrated decreasing T cell distribution over time in tumor sites, alongside spatial and temporal variations in cell type distributions. Jenner *et al.* [130] used ABM to assess locoregional gemcitabine treatment efficacy in pancreatic cancer, accounting for cancer cell sensitivity, drug resistance, and drug distribution. Genderen *et al.* [296] studied prostate TME with ABM, revealing spatial constraints on tumor growth and immune regulation.

ABMs have increasingly integrated machine learning, statistical techniques, and multi-modal imaging to enhance quantitative analyses of tumor-immune interactions. Cess *et al.* [47] combined ABM with neural networks to create a multi-scale model examining how macrophage-based immunotherapies may alter immune responses. Bull *et al.* [37] employed spatial autocorrelation and clustering methods to analyze ABM-generated data, quantifying spatial and phenotypic heterogeneity in simulated tumors, offering novel perspectives and approaches for comprehending the complexity and dynamics of tumor progression. Hickey *et al.* [118] integrated multi-modal imaging with multi-scale modeling, capturing intricate biological processes in tumors. This approach provides valuable tools for understanding tumor dynamics and enhancing cancer therapy development.

The fusion of hybrid modeling, multi-scale modeling, and machine learning in mathematical oncology has introduced innovative approaches to tumor research [127,282,309]. These interdisciplinary studies have advanced tumor immunology and offer theoretical and practical foundations for developing effective immunotherapies. With ongoing research and technological advancements, tumor immunotherapy continues to evolve, promising improved treatments and hope for cancer patients.

4 Mathematical models of cancer therapy approaches

Mathematical models are invaluable in cancer research, offering theoretical frameworks to decipher cancer's complexity, forecast disease progression, and assess treatment strategies. The immune microenvironment, biological characteristics, and treatment approa-

ches vary significantly across cancer types. Table 1 presents the most common cancer types and the corresponding mathematical modeling methods. Fig. 13 illustrates six primary categories encompassing 15 prominent cancer treatment modalities. The following section provides a concise overview of the biological mechanisms and mathematical models underlying various cancer therapies.

4.1 Chemotherapy and radiotherapy

Chemotherapy, a longstanding cancer treatment, utilizes chemical agents to kill or inhibit the proliferation of cancer cells. While it is crucial in preventing cancer spread and metastasis, chemotherapy can also damage normal tissues and immune cells within the tumor environment. Recently, researchers have developed mathematical models to examine metronomic chemotherapy approaches, which involve continuous low-dose regimens [295], as well as pulse chemotherapy, characterized by intermittent high-dose treatments [121, 319]. With the increasing success of combination therapies, mathematical models have also explored chemotherapy in conjunction with radiotherapy [20], immunotherapy [61, 63, 64, 270], or antiangiogenic therapy [160].

Radiotherapy remains one of the most widely used cancer treatments, benefiting nearly half of all cancer patients. This approach employs high-energy radiation to damage the DNA within tumor cells, thereby inhibiting their growth and replication to achieve therapeutic goals. While few mathematical models focused on radiotherapy in the past, recent research has led to models addressing standalone radiotherapy [229], chemoradiotherapy combinations [20], and radiotherapy paired with immunotherapy [161,268]. These developments underscore the growing role of mathematical modeling as an effective tool for studying and optimizing cancer treatments.

4.2 Targeted therapy

Targeted therapy is a precision-based approach in cancer treatment that disrupts specific molecular pathways essential for tumor growth and survival, contrasting with traditional chemotherapy that broadly affects both healthy and cancerous cells [158, 298]. This targeted inhibition of oncogenic pathways leverages unique or dysregulated proteins and genes within cancer cells, thereby improving treatment specificity.

Angiogenesis, essential for tumor nutrient supply, is a primary target in solid tumors, driven by factors such as VEGF. Anti-VEGF therapies inhibit blood vessel formation by blocking VEGF signaling, effectively starving the tumor. Mathematical models have been instrumental in understanding VEGF dynamics, evaluating anti-VEGF efficacy, and predicting resistance patterns. For example, Liang *et al.* [180] and Hutchinson *et al.* [125] developed multiscale models that capture VEGF signaling within the TME, simulating tumor growth inhibition through VEGF targeting. Additionally, pharmacokinetics/pharmacodynamics (PK/PD) models by He *et al.* [115] and Zheng *et al.* [329] predict optimal dosing and timing of anti-angiogenic therapies to improve clinical outcomes.

Table 1: Mathematical oncology models of various cancer types.

Type	**Research**	**Model**	**Treatment method**
Leukemia	Moore *et al.* [215]	ODE	–
	Lai *et al.* [162]	SDE	Tyrosine kinase inhibitor
	Zhang *et al.* [325]	IDE	CAR-T therapy
Brain cancer	Kogan et al. [152]	ODE	T cell infusion therapy
	Sun *et al.* [288]	ABM	Tyrosine kinase inhibitors
	Khajanchi *et al.* [142]	ODE	Immunotherapy
	Khajanchi *et al.* [143]	DDE	Immunotherapy
	Liang *et al.* [180]	ABM	anti-EGFR + anti+VEGFR
	Anderson *et al.* [11]	ODE	–
Bladder cancer	Bunimovich-Mendrazitsky *et al.* [39]	ODE	BCG vaccine
	Bunimovich-Mendrazitsky *et al.* [38]	ODE	BCG vaccine + IL-2 treatment
	Okuneye *et al.* [224]	ODE	Anti-FGFR + Immune checkpoint inhibitor
	Li *et al.* [174]	ODE	Anti-FGFR + Immune checkpoint inhibitor
Melanoma	Lai *et al.* [159]	PDE	BRAF inhibitor + Immune checkpoint inhibitor
	Tsur *et al.* [293]	ODE	Immune checkpoint inhibitor
	Friedman *et al.* [88]	PDE	BRAF inhibitor + Immune checkpoint inhibitor
	Dickman *et al.* [72]	DDE	DC vaccine
	Liao *et al.* [182]	PDE	Immune checkpoint inhibitor + IFN-γ treatment
	Milberg *et al.* [210]	QSP	Immune checkpoint inhibitor
	Xue *et al.* [317]	ODE	DC vaccine + Immune checkpoint inhibitor
	Ramaj *et al.* [241]	ODE	Oncolytic virotherapy
Prostatic cancer	Valle *et al.* [295]	ODE	Cancer vaccine + Chemotherapy
	Kogan *et al.* [153]	ODE	Immunotherapy
	Ji *et al.* [131]	ODE	–
	Coletti *et al.* [56]	ODE	DC vaccine + Anti-CTLA-4
	Genderen *et al.* [296]	ABM	Androgen deprivation therapy
Breast cancer	Lai *et al.* [163]	PDE	BET inhibitor + Immune checkpoint inhibitor
	Szomolay *et al.* [290]	PDE	GM-CSF treatment
	Lai *et al.* [160]	PDE	VEGF inhibitor + Chemotherapy
	Wang *et al.* [304]	QSP	Immune checkpoint inhibitor + epigenetic modulator
	Wang *et al.* [302]	QSP	Chemotherapy + Immune checkpoint inhibitor
	Pei *et al.* [231]	ODE	RNA interference + Immune checkpoint inhibitor
	Mirzaei *et al.* [212]	ODE	–
	Bitsouni *et al.* [29]	ODE	Anti-CD20 (Rituximab)
	Siewe *et al.* [274]	ODE	Anti-CD20 (Rituximab)
Head and neck cancer	Smalley *et al.* [276]	ODE	Immune checkpoint inhibitor
	Nazari *et al.* [220]	ODE	Anti-IL-6
	Pang *et al.* [229]	ODE	Radiotherapy
Pancreatic cancer	Shafiekhani *et al.* [270]	ODE	Anti-CD25 + Chemotherapy
	Louzoun *et al.* [193]	ODE	EGFR silencing + TGF-β silencing
	Jenner *et al.* [130]	ABM	Chemotherapy

Table 1: Mathematical oncology models of various cancer types (cont'd).

Type	Research	Model	Treatment method
Lung cancer	Eftimie *et al.* [80]	ODE	–
	Lourenco *et al.* [192]	ODE	–
	Wang *et al.* [301]	QSP	Immune checkpoint inhibitor
	Wang *et al.* [300]	QSP	Macrophage-targeted therapy + Immune checkpoint inhibitor
Colorectal cancer	Fletcher *et al.* [83]	ABM	–
	Sameen *et al.* [255]	ODE	EGFR inhibitor + Chemotherapy
	Lo *et al.* [190]	ODE	–
	Ma *et al.* [195]	QSP	TCE therapy + Immune checkpoint inhibitor
	Mirzaei *et al.* [213]	PDE	–
Myeloma	Koenders *et al.* [151]	ODE	–
	Gallaher *et al.* [90]	ODE	–
	Bouchnita *et al.* [32]	PDE	–
Thyroid cancer	Da *et al.* [58]	ODE	Radiotherapy
Liver cancer	Delitala *et al.* [67]	ODE	Radiotherapy
	Sové *et al.* [280]	QSP	Immune checkpoint inhibitor

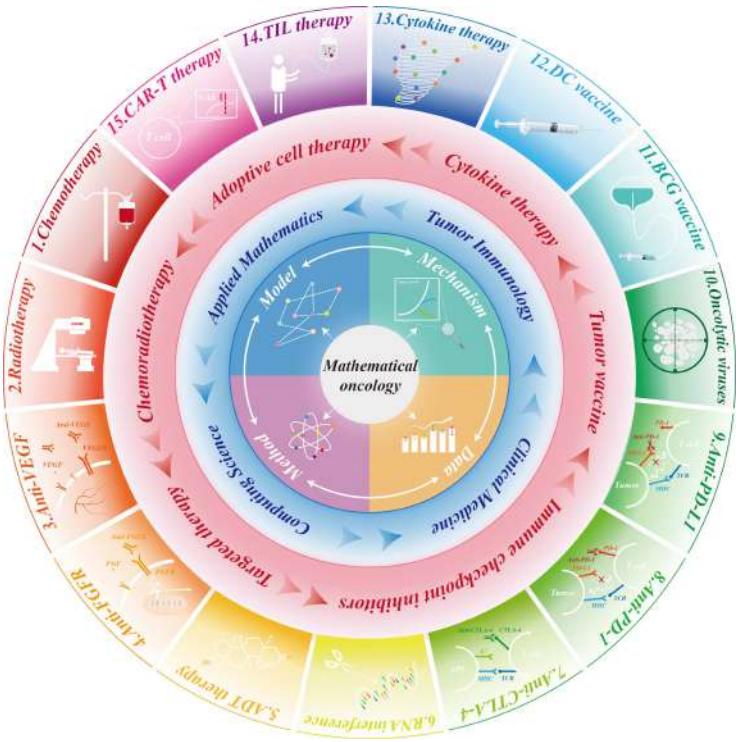

Figure 13: Mathematical models and mechanisms of cancer therapy methods.

Combination therapies are frequently pursued to counteract resistance associated with monotherapy. Hybrid models incorporating anti-VEGF with immunotherapies, such as checkpoint inhibitors, reveal enhanced immune cell infiltration and reduced immune evasion within the tumor [159]. Similarly, models combining anti-VEGF with chemotherapy illustrate the modulation of tumor sensitivity to chemotherapeutics, supporting strategies that maximize synergistic effects while minimizing toxicity [160].

Fibroblast growth factor receptor (FGFR) targeting is another avenue, especially in cancers where FGFR contributes to tumor progression and resistance. Mathematical models by Okuneye *et al.* [224] and Li*et al.* [174] explored the co-targeting of FGFR and VEGF pathways in bladder cancer, revealing that FGFR inhibition can mitigate resistance mechanisms against anti-VEGF therapy. Additionally, RNA interference (RNAi) therapies show promise in silencing oncogenes and resistance genes, with models developed by Arcieto *et al.* [16] and Pei *et al.* [231] helping predict gene silencing impacts on tumor progression.

In hormone-dependent cancers like prostate cancer, androgen deprivation therapy (ADT) plays a crucial role. Models developed by Coletti *et al.* [56] and West *et al.* [309] have elucidated androgen receptor dynamics, illustrating feedback mechanisms leading to resistance. Such models guide adaptive ADT strategies, aiming to sustain tumor sensitivity over prolonged treatment periods.

Beyond microenvironmental and hormonal targets, direct approaches to disrupt oncogenic drivers in cancer cells include TKIs, such as imatinib, which selectively targets the BCR-ABL fusion protein in CML [35,74], and EGFR-targeting TKIs in non-small cell lung cancer, like gefitinib and erlotinib, which significantly enhance outcomes by inhibiting tumor growth pathways [132]. PK/PD models for these TKIs help optimize dosing regimens to balance efficacy and minimize resistance and toxicity [33,162,251,288].

Some therapies aim to directly activate apoptotic pathways in cancer cells. BH3 mimetics, such as Venetoclax, inhibit the anti-apoptotic protein BCL-2, reactivating apoptosis in cancers like chronic lymphocytic leukemia (CLL) [233]. Models incorporating cell-death kinetics and pathway dynamics are used in predicting resistance and optimizing combination strategies with BH-3 mimetics [18,164].

Emerging multi-omics and patient-specific data, combined with machine learning, enhance the predictive power of mathematical models in targeted therapy [216]. Future research is expected to integrate real-time patient data, enabling adaptive dosing and personalized treatment adjustments, with the potential to further refine therapeutic responses and combat resistance effectively.

4.3 Immune checkpoint inhibitors

ICIs target key molecules that regulate immune responses by inhibiting T cell activity, primarily through pathways involving CTLA-4, PD-1, and PD-L1. CTLA-4 reduces T cell activation by binding to B7 molecules on APCs, while PD-1 on T cells and PD-L1 on tumor cells interact to enable immune evasion by tumors. Blocking these immune checkpoints

with ICIs enables a robust anti-tumor immune response, making a major breakthrough for patients with advanced cancers.

Mathematical models have evolved alongside the clinical use of ICIs, enhancing understanding of T cell dynamics, tumor progression, and therapy optimization. Models for anti-CTLA-4 [56,163,210,280,303,317], anti-PD-1 [17,159,182,195,210,231,276,280,317], and anti-PD-L1 [161,210,224,300,301,303] have been widely developed, aiming to simulate the effects of ICIs on T cell proliferation and tumor rejection in solid tumors. These models assist in identifying optimal dosing schedules, assessing TME variations, and exploring resistance mechanisms, thereby providing actionable insights for improved treatment protocols.

Recent studies have integrated ICIs with combination therapies to reflect current clinical strategies, pairing ICIs with chemotherapy [92, 334], radiotherapy [183], and anti-angiogenic agents [166]. Quantitative approaches using mathematical models to analyze such combinations must account for synergistic and antagonistic interactions among drugs to reflect real-world dynamics. Incorporating multiple layers of immune interactions, tumor heterogeneity, and drug effects, mathematical models of ICIs serve as a theoretical foundation for optimizing personalized ICI therapies and could significantly inform precision treatment strategies [174,175].

4.4 Adoptive cell therapy

Adoptive cell therapy (ACT) is a promising strategy in cancer immunotherapy that uses patients' own immune cells to target and eliminate tumor cells. The primary ACT methods currently utilized in clinical settings include tumor-infiltrating lymphocyte (TIL) therapy and CAR-T therapy. In TIL therapy, lymphocytes are extracted from a patient's tumor tissue, expanded in vitro, and reintroduced to the patient. These TILs are highly specific to the tumor, allowing them to recognize and effectively eliminate cancer cells within the TME. Kogan *et al.* [152] developed a mathematical model assessing the therapeutic impact of T-cell infusion, providing theoretical insights into outcomes for high-grade malignant gliomas. Similarly, Yang *et al.* [321] explored the therapeutic potential of pulsed IL-2 administration alongside ACT, demonstrating the cytokine's ability to enhance therapeutic efficacy.

CAR-T cell therapy, a transformative form of ACT, involves genetically modifying T cells to express chimeric antigen receptors that specifically target antigens on tumor cells. This approach has shown remarkable success in treating hematological cancers, with ongoing research expanding its potential applications to solid tumors [134]. Mathematical modeling has become instrumental in optimizing CAR-T therapy, providing insights into T cell proliferation dynamics, tumor-cell interactions, cytokine release, and patient-specific treatment protocols. Both deterministic and ABMs allow researchers to simulate CAR-T cell expansion and immune response and predict optimal dosing schedules, which also consider side effects like cytokine release syndrome [2,226,325].

To address the specific challenges CAR-T cells face in solid tumors, spatial and multi-scale models have been employed to explore barriers to CAR-T cell infiltration and inter-

actions within immunosuppressive TME. The models offer insights into immune evasion mechanisms and T cell exhaustion, both crucial for enhancing CAR-T efficacy in solid tumors [100, 136, 237, 254]. In addition, advanced machine learning and neural network methods have recently been applied to analyze CAR-T cell therapy, examining correlations between CAR-T cell subtype dynamics in vivo and therapeutic outcomes [149].

Mathematical modeling of ACT therapies has allowed researchers to simulate complex tumor-immune interactions and optimize various therapeutic parameters. These models play a critical role in identifying variables affecting treatment efficacy such as cell dosage, cytokine support, and immune-tumor interactions. Consequently, mathematical frameworks provide a foundational basis for refining ACT strategies, enhancing their effectiveness, and broadening their applicability to diverse cancer types.

4.5 Tumor vaccine

Cancer vaccines, a form of active immunotherapy, aim to activate or amplify the body's immune defenses to slow tumor progression or eradicate cancer cells. Common types include OV, Bacillus Calmette-Guérin (BCG) vaccines, and DC vaccines.

OV are genetically modified to effectively infect and destroy cancer cells. Jacobsen *et al.* [129] developed a mathematical model to explore how extracellular matrix protein CCN1 impacts OV efficacy in glioma treatment. Additionally, Kim *et al.* [148] proposed a framework evaluating NK cell activity in OV and Bortezomib therapy for glioblastoma, while Ramaj and Zhou [241] studied hypoxia's effect on OV outcomes, showing environmental factors can influence treatment success.

The BCG vaccine, derived from attenuated Mycobacterium bovis, is widely used to prevent tuberculosis and has applications in treating non-muscle-invasive bladder cancer. Bunimovich-Mendrazitsky *et al.* [38, 39] modeled BCG therapy, both alone and combined with IL-2, concluding that IL-2 does not enhance BCG's anti-tumor effects in bladder cancer, highlighting the need for precise treatment combinations.

As a promising approach in immunotherapy, DC vaccines present new avenues for cancer treatment with a potential for personalized medicine. Sardar *et al.* [260] examined the effects of pulsed DC vaccine therapy on immune response and tumor control, while Dickman *et al.* [72] used a compartmental model to analyze tumor elimination, control, and escape during DC therapy for melanoma. Importantly, DC vaccines reinforce personalized treatment by targeting specific tumor antigens, increasing therapeutic accuracy. The value of combination therapies has also been explored; Coletti *et al.* [56] and Xue *et al.* [317] investigated dual therapy with DC vaccines and immune checkpoint inhibitors, providing a theoretical basis for future preclinical trials in dual immunotherapy.

4.6 Cytokine inhibitor

Cytokine inhibitors serve a vital function in cancer therapy by regulating cytokine activity to affect tumor cell growth, metastasis, and invasion. Mathematical models enable the simulation of therapeutic effects for various doses, administration times, and

delivery methods, providing a scientific foundation for refining clinical treatment approaches. Wilson *et al.* [313] investigated the synergy between anti-TGF-β therapy and vaccine treatment, shedding light on combination therapies' impact on immune modulation. Yang *et al.* [321] further explored the efficacy of pulsed dosing of adoptive cell therapy with IL-2 in cancer treatment, while Ratajczyk *et al.* [242] developed a model combining TNF-α inhibitors with virotherapy, demonstrating the potential benefits of integrated approaches. Although monotherapy with cytokine inhibitors can have limited efficacy, combining them with other immunotherapies has shown synergistic effects. This integration highlights the importance of mathematical modeling in elucidating underlying biological mechanisms and optimizing treatment strategies.

5 Discussions

Mathematical models describing tumor-immune interactions are increasingly recognized as vital tools in understanding the complex dynamics between tumor evolution and immune response [15, 81, 198]. These models provide a quantitative framework for investigating tumor-immune interactions, predicting treatment outcomes, and optimizing therapeutic strategies, paving the way for individualized precision medicine. Despite notable progress, significant challenges remain.

Uncertainty in model parameters. Mathematical models of tumor-immune interaction require numerous biological variables and parameters to accurately represent complex system dynamics. This complexity, however, creates challenges in parameter estimation. Experimental limitations and the scarcity of precise biological data often hinder the direct measurement of these parameters. Moreover, many of these parameters are not static; they shift dynamically with changes in the tumor and immune environment, further complicating estimation. Addressing this issue will require a stronger emphasis on experimental data collection and analysis alongside the development of more sophisticated methods for parameter analysis and estimation [186, 200, 214]. Recently, specialized and efficient parameter estimation methods and tools have been proposed in computational systems biology. For example, Bayesian parameter estimation methods [184, 187], Monte Carlo methods [156], optimization methods [264], neural networks [98], SensSB [252], BioModels [101], and pyPESTO [263].

Discrepancies between simplified models and tumor-immune system complexity. To reduce complexity and enhance mathematical tractability, existing models often simplify the biological landscape of tumor-immune interactions. However, excessive simplification can overlook critical complexities inherent to real-world biology. Many models, for example, focus only on tumor-T cell interactions, often neglecting the roles of other immune cells and non-cellular components (e.g., oxygen, cytokines, or chemokines) that significantly influence tumor progression. Additionally, essential biological mechanisms, such as genetic mutations, tumor heterogeneity, and plasticity, are often excluded. Advancing model accuracy will require the integration of these crucial factors to better reflect tumor-immune dynamics [201, 208, 323]. Recently, mathematical models of the inter-

action between tumors, immunity, and microorganisms have been proposed to explore the role of microorganisms in tumor evolution dynamics [52]. Meanwhile, multi-scale models integrating molecules, cells, microenvironments, and tissues have also been developed [180].

Computational challenges in multiscale modeling. Modeling tumor-immune interactions requires capturing processes across multiple scales, from molecular to tissue levels, necessitating complex interscale connections and imposing high computational demands. This data exchange between scales consumes substantial resources, with specific regions often requiring high-precision models or algorithms to improve accuracy. However, higher precision amplifies computational complexity and strains power resources. Additionally, solving extensive multiscale models often entails prolonged simulation times, especially for interactive or long-term scenarios, which can increase costs and reduce modeling efficiency. Addressing these challenges will require innovative modeling approaches, optimized algorithms, and advancements in data processing and storage capabilities [84,116,299]. FitMultiCell has recently been developed for modeling, simulating, and parameterizing multi-scale multicellular processes [4]. PhysiBoSS offers simulations for complex events across various spatial and temporal scales [172,235]. These methods aid in modeling multi-scale tumor immune systems and enhance computational performance.

Mathematical oncology integrates tumor immunology, clinical medicine, applied mathematics, and computational science, forming a powerful approach to tackling complex challenges in tumor research [7, 9, 42, 94, 250]. As mathematical models advance, they promise greater precision, personalization, and integration with intelligent technologies. Future progression in this field will depend on multidisciplinary collaborations, allowing for the continuous evolution of mathematical approaches. Modeling tumor-immune interactions, a crucial core of this field, elucidates the immune system's role in tumor progression, dormancy, and immune evasion, informing broader models of cancer growth and treatment response. Building on recent developments, we highlight key research directions to guide future studies in the mathematical modeling of tumor-immune interactions.

Systematic modeling and quantitative analysis of the TME. Systematic modeling and quantitative analysis are essential for investigating the dynamic changes within the TME [7, 43, 139, 250, 323]. By developing detailed tumor-immune regulatory network models, researchers can quantitatively represent interactions between tumors and the immune system, which aids in identifying potential immune biomarkers predictive of tumor behavior. Quantitative metrics derived from these models provide theoretical foundations for understanding cancer immunoediting and classifying cancer immune phenotypes. Such metrics not only shed light on tumor-immune system evolution but also facilitate cancer subtyping. Furthermore, mathematical oncology models help reveal mechanisms behind TME-mediated drug resistance and recurrence. Ultimately, systematic modeling and quantitative analysis offer novel perspectives for cancer therapy, significantly supporting individualized treatment plans for patients.

Development of multiscale and multiphysics mathematical models. Multiscale modeling enables the integration of biological processes occurring across molecular, cellular, and tissue scales, allowing mathematical models to more accurately capture the complex dynamics of tumor progression [36, 43, 201, 250, 311]. This capability supports the exploration of drug diffusion and distribution by simulating anticancer drug mechanisms across different biological levels, thereby improving the prediction of therapeutic outcomes. Multiphysics models further enhance this by combining different physical fields to simulate tumor behavior in various environments. For example, mechanical fields can represent pressure gradients in the TME and model cell migration, while chemical fields can depict drug distribution and metabolic processes. The integration of multiscale and multiphysics modeling in oncology provides a powerful tool for understanding and predicting tumor growth, metastasis, and response to treatments.

Development of mathematical models integrating multisource data. Integrating multisource data into mathematical models offers an enriched understanding of tumor biology, immune responses, disease progression, and optimized treatment approaches [30, 41, 191, 250, 301, 328]. With the establishment of extensive public cancer databases such as SEER, TCGA, and NCDB, researchers have access to detailed clinical, biomarker, genomic, transcriptomic, and proteomic data. Translating this diverse data into formats compatible with mathematical models bridges a critical gap, enhancing model validation and addressing biases in predictive accuracy. Additionally, data-model integration enables the development of early warning systems for cancer progression. As data and models become more interoperable, this integration stands to be a major focus in advancing tumor research and predictive oncology.

Exploring the application of machine learning in mathematical oncology. Machine learning (ML) introduces new capabilities to model optimization, parameter estimation, and cancer classification [5, 155, 207, 232, 250]. Techniques like neural networks, support vector machines, and Gaussian mixture models enhance the predictive power of mathematical models and facilitate the creation of virtual cancer cohorts. Machine learning optimization techniques also facilitate model parameter adjustments, reducing prediction errors and boosting overall model performance. Recent research has also highlighted the promise of neural networks in solving differential equations, especially physics-informed neural networks (PINNs) and neural ODE approaches, which improve both solution accuracy and model generalization. Thus, machine learning integration into mathematical oncology not only enhances model precision and efficiency but also opens up new avenues for individualized cancer research and treatment planning.

In summary, mathematical models of tumor-immune interactions offer a robust framework for exploring tumor dynamics and informing clinical treatment strategies. While challenges remain, advancements in technology and interdisciplinary collaboration promise to elevate the role of mathematical models in tumor immunology research, promoting closer cooperation between mathematicians and immunologists to drive cross-disciplinary breakthroughs.

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