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# A Comprehensive Review of Game Theory Applications in Modeling Cancer Progression and Treatment Strategies

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Abstract. Cancer is a major medical challenge, and mathematical modeling plays a key role in understanding its dynamics and improving treatments. Various modeling techniques have been developed, including differential equations, cellular automata, agent-based models, and game theory. While differential equations are widely used to simulate tumor growth and treatment responses, they often rely on simplified assumptions. Cellular automata capture spatial behaviors but may oversimplify biological mechanisms, and agent-based models can be computationally intensive. Game theory, by contrast, offers a strategic framework to study tumor evolution and resistance, enabling the design of adaptive therapies. This research provides a comprehensive review of recent advances in game theory-based cancer modeling. Cancer progression can be conceptualized as an evolutionary competition among various cell types. By employing game theory-based models, it is possible to predict the evolutionary dynamics of cancer. These models facilitate the development of evolutionary treatment strategies that guide the patient's condition towards more favorable outcomes. The investigation of tumor progression using game theory offers significant medical implications, as it bridges the gap between experimental findings and mathematical modeling. This approach not only enhances our understanding of cancer dynamics but also contributes to the design of more effective therapeutic interventions.

**Keywords:** Cancer, Game Theory, Cancer Treatment, Evolutionary Game, Prisoner's Dilemma Game, Stackelberg Game, Hawk-Dove Game, Public Goods Game



## 1. Introduction

Cancer originates from mutations in cellular DNA that disrupt normal regulatory mechanisms, resulting in uncontrolled proliferation. As shown in Figure 1, tumor cells exhibit hallmark capabilities that drive disease progression, including persistent proliferative signaling, resistance to growth inhibition and cell death, replicative immortality, angiogenesis, and metastasis [1]. These behaviors facilitate rapid clonal expansion and

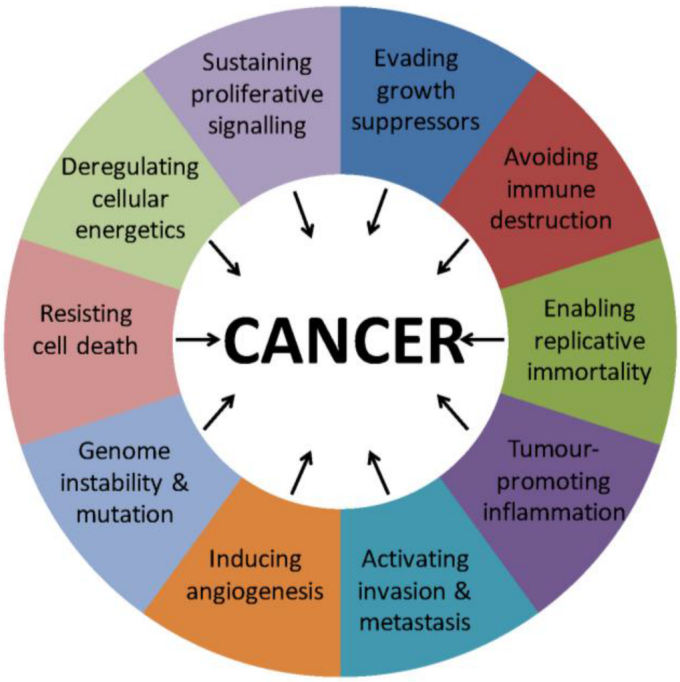


FIGURE 1. Characteristics of cancer disease [1].

contribute to additional mutations within the tumor population. To capture the underlying dynamics of cancer, various modeling frameworks have been proposed, such as cellular automata [2], [3], differential equations [4], [5], agent-based simulations [6], and more recently, game-theoretic models [7], [8]. Game theory, originally introduced by von Neumann and Morgenstern, has evolved from economic analysis to a powerful tool for modeling adaptive behavior across biological systems [9].

Its application to cancer research has gained momentum through evolutionary game theory, which draws on principles of Darwinian selection to explore competitive and cooperative strategies among cells [10]. Population-level dynamics are commonly analyzed using replicator equations, which model frequency changes based on fitness differentials. If a strategy yields higher fitness than the population average, it becomes more prevalent; conversely, inferior strategies diminish over time.

Key solution concepts in this context include Nash Equilibrium (NE) and Evolutionarily Stable Strategy (ESS). While NE identifies strategy configurations resistant to unilateral change, ESS further ensures resilience against invasion by mutant strategies under natural selection [11]. Static analysis of cancer populations often centers on identifying such stable configurations, whereas dynamic analysis tracks their evolution through time.

Game theory, a mathematical tool for analyzing biological problems, has recently been applied to explore the complexity of cancer. Various methods, such as the hawk-dove game [12], the prisoner's dilemma [13], coordination games [14], multiple public goods games, and the volunteer dilemma [15], have been utilized in recent years to analyze cancer. The hawk-dove game examines the interactions between two cancer cells within the same tumor, where they adopt either an invasion (hawk) or passive (dove) strategy.

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Each cell's role is determined by the type of opponent it encounters, as it lacks knowledge of its own type. This game aims to identify evolutionary stable strategies (ESS) within the population under study. An increase in fitness, reflected by a higher payoff and an enhanced cell reproduction rate, serves as a direct measure of tumor invasion. Within the game, cells may either cooperate or compete, but their behavior consistently aligns with the ESS of the group.

Using the hawk-dove game, researchers [12], [16] have proposed a model to examine the interaction between two distinct phenotypes in prostate cancer, where survival is influenced by their reliance on the microenvironment. Pathologically, this model contrasts stromogenic low-grade prostate adenocarcinoma with non-stromogenic high-grade prostate adenocarcinoma. The findings suggest that the hawk-dove game underscores the significance of the microenvironment in the prognosis and progression of prostate cancer.

The prisoner's dilemma, a well-known game theory model, has been extensively applied in political science and economics, and more recently in cancer research [13]. This game presents a scenario where two prisoners must decide whether to cooperate, knowing that cooperation is beneficial to both. In the context of cancer, this model can be used to analyze interactions between two cell populations. Group A represents non-tumor cells, while Group B represents tumor cells. Importantly, cells in Group A are unaware of the strategies of cells in Group B and vice versa, although both groups understand that cooperation yields the highest benefit. Additionally, both cell types recognize that if neither cooperates, they will receive minimal benefit, and if only one group cooperates, the other group will gain the benefit.

The Prisoner's dilemma, a paradigmatic game for analyzing interactions between selfish individuals, typically results in non-cooperation with minimal payoff for both players. However, in certain biological contexts, such as cancer, the outcome may differ. For instance, in the case of colon adenocarcinoma metastasizing to the liver, liver cells inherently cooperate due to their programming. This cooperation benefits metastatic colon cancer cells, enhancing their fitness and promoting the invasive nature of cancer [17].

Coordination games investigate mechanisms to promote uniformity within a group, where any deviation by an individual results in reduced payoffs for the entire group. This principle operates on various levels. For instance, pure coordination games require absolute positive uniformity to achieve the best collective payoff, while absolute negative uniformity results in a lower payoff, and any divergence in uniformity among individuals leads to zero payoff. The choosing-sides game exemplifies this concept, offering an all-or-none payoff: maximum profit is achieved only if all participants, such as drivers, choose the same side of the road, with any other choice yielding zero profit. A simpler type of coordination games is the stag hunt game, where lack of coordination among individuals results in minimal profit, whereas coordination yields higher profit. By modifying the Lotka-Volterra competitive model, coordination games have been proposed to enhance current cancer treatments. This approach involves comparing two different treatment strategies: one that increases the death rate of tumor cells and another that increases the mutation rate of tumor cells [14].

The volunteer dilemma, a prime example of N-player public goods games, models social dilemmas across various biological communities, including unicellular organisms (such as bacteria and amoeba), vertebrates [18], [19], and cancer cell communities. This dilemma occurs when certain individuals in a society volunteer to incur a cost to produce a public good, while others benefit without contributing. The absence of the public good is also detrimental to the population, leading to a stable equilibrium between cooperators and

defectors as long as the population size remains constant. However, the dilemma intensifies when the group size changes, as the overall payoff for the population decreases with an increasing number of members, especially in groups with a low probability of volunteers. Archetti's research has identified the optimal group size in social dilemmas as the size that maximizes the likelihood of producing a public good. An illustrative scenario of the volunteer dilemma involves a group of deer in Africa facing the threat of hunters [18]. In this context, the payoff for the deer is survival, while the cost to the volunteer is the accepted risk of being hunted first. The individual's dilemma is whether to alert the group to imminent danger. It's a choice that puts the animal at risk, or the entire group if it chooses not to cooperate. Interestingly, defectors can sometimes benefit the group under specific conditions. Thus, a mix of cooperators and defectors can create an ideal situation for the group's survival against a common threat.

The concept of a social dilemma has been employed to investigate the interactions between tumor cells and immune system cells, with tumor cells being likened to deer and immune cells to hunters [20]. Under experimental conditions, this model effectively demonstrates that the presence of defectors facilitates the tumor's ability to evade the immune system's effects.

Numerous studies have utilized the Stackelberg game to model cancer treatment. Stackelberg's evolutionary game theory (SEG) integrates classical and evolutionary game theory to analyze interactions between a rational leader and evolving followers, with the physician acting as a player in the game. The analysis of these models aids in the design of treatment strategies. Additionally, significant advancements in evolutionary graph theory over the past two decades have emphasized the importance of spatial considerations in modeling.

**1.1. Contributions.** This review establishes a timely and necessary synthesis of game theory applications in cancer modeling, addressing a research gap that persists despite the availability of previous surveys. While earlier studies have examined individual game-theoretic models in isolation, this work distinguishes itself by offering a guideline-driven framework designed to orient researchers across disciplines mathematics, biology, and clinical oncology toward both the conceptual foundations and translational potential of these models.

The paper advocates for a dedicated survey that does more than catalog existing approaches; it contextualizes them within the biological complexities of cancer. Specific attention is paid to underexplored domains such as spatial dynamics, social dilemmas in tumor microenvironments, and gene expression analysis via microarray modeling, each of which presents unique challenges and opportunities. To facilitate practical application and future development, this review articulates a coherent set of research questions aimed at identifying existing advancements, methodological gaps, and open challenges, including heterogeneity, evolutionary adaptation, and therapeutic resistance.

Nonetheless, current modeling frameworks exhibit critical limitations. Many rely on static payoff structures, overlooking the temporal dynamics of tumor evolution and treatment response. The spatial complexity of the tumor microenvironment and heterogeneous cell–cell interactions are often simplified or ignored. Furthermore, most models are restricted to a single biological scale whether molecular, cellular, or tissue-level missing critical cross-scale dependencies that shape tumor behavior.

These guidelines inform the organization of the paper, which is structured around six

modeling paradigms: evolutionary games, public goods dilemmas, classical strategic interactions, spatially informed models, microarray-based strategies, and game theory-driven therapeutic frameworks.
Foundational concepts in both cancer biology and strategic modeling are clarified at the outset, enhancing accessibility for interdisciplinary readers. In doing so, the review not only serves as a resource for theoretical exploration but also provides a translational scaffold linking mathematical abstractions to clinical insight ultimately fostering more informed and adaptive approaches to cancer treatment. This study explores the strategic behavior of cancer cells under both treated and untreated conditions through the lens of game theory. Leveraging a range of methodologies, we examine foundational principles in cancer modeling and evolutionary dynamics, then delve into specific frameworks including public goods games, Hawk-Dove scenarios, and the Prisoner's Dilemma to analyze cooperative and competitive interactions among cellular populations. Spatial game theory is employed to highlight how tumor topology influences strategic outcomes, while microarray-based models address gene expression variability. We also investigate therapy optimization using game-theoretic strategies and present experimental case studies demonstrating practical implementations. The final sections synthesize these approaches, offering conclusions and future directions for advancing interdisciplinary cancer research.

## 2. Basic Concepts

To establish a consistent foundation for the subsequent sections, this review introduces two key domains of knowledge: cancer biology and game theory. These concepts form the basis for interpreting and evaluating various modeling approaches throughout the article.

**2.1. Cancer Concepts and Definitions.** Cancer originates from mutations in the DNA of cells that disrupt normal regulatory mechanisms. These alterations trigger uncontrolled proliferation, a hallmark of malignancy. As shown in Figure 1, cancer cells exhibit distinct traits that collectively define the disease and shape its clinical behavior [1].
**Loss of Regulatory Control:** Mutated cells no longer respond to signals that suppress growth or promote cell death. This dysregulation underpins their persistent division and survival.
**Avoidance of Apoptosis:** Unlike healthy cells that undergo programmed cell death when damaged, cancer cells resist apoptosis, enabling continued survival under adverse conditions.
**Autonomous Growth Pathways:** Through carcinogenesis, cancer cells develop independence from external growth factors, allowing unchecked expansion.
**Angiogenesis and Nutrient Access:** To support their high metabolic demands, cancer cells stimulate new blood vessel formation. This vascular remodeling not only ensures nutrient supply but also facilitates metastasis.
**Resistance to Growth Inhibition:** Despite the presence of growth-suppressing signals whether intracellular or environmental cancer cells persist in dividing, highlighting their escape from standard tissue controls.
**Metastatic Potential:** Cancer progression includes detachment of cells from the primary tumor and colonization of distant tissues via the bloodstream, forming secondary tumors.
**Asexual Proliferation and Mutation Cascade:** Rapid cell division amplifies the cancer cell population and fosters conditions that encourage further mutations, fueling tumor evolution.
These features are central to developing therapeutic strategies aimed at targeting the

vulnerabilities of cancer cells, particularly within adaptive and game-theoretic treatment frameworks.

**2.2. Game Theory Concepts and Definitions.** Game theory is a mathematical framework used to analyze strategic interactions between agents whose decisions affect one another's outcomes. In the context of cancer modeling, it provides a versatile lens for representing cellular behaviors, competition for resources, and responses to treatment. The following core concepts form the foundation for game-theoretic approaches in oncology:
**Players and Strategies:** Key players include cancer cells, stromal cells, immune cells, and therapy agents. Each player can adopt strategies such as proliferation, invasion, cooperation, immune evasion, or treatment response.
**Payoff Functions:** Strategies yield payoffs quantified by outcomes like reproductive success, survival probability, or treatment sensitivity. These payoffs represent the fitness advantage conferred by each decision.
**Nash Equilibrium and Evolutionarily Stable Strategy (ESS):** A Nash equilibrium is a strategic configuration where no player benefits from unilateral deviation. An ESS, building upon this concept, resists invasion by mutant strategies and reflects stability under evolutionary dynamics.
**Replicator Dynamics:** These differential equations track changes in population shares of competing strategies over time, depending on their relative fitness. They help model tumor heterogeneity and the rise or fall of cellular phenotypes.
**Public Goods and Social Dilemmas:** Tumor cells often face trade-offs between individual fitness and collective benefit. Public goods models illustrate how cooperation (e.g., angiogenesis or immune suppression) can emerge or fail within cancer cell populations.
**Stackelberg Games:** These hierarchical models simulate interactions where a leader (e.g., physician) optimizes a strategy in anticipation of the adaptive responses of the followers (cancer cells). Stackelberg evolutionary games offer a promising route for designing treatment protocols based on dynamic cancer behavior.
**Adaptive Therapy Frameworks:** Rooted in game-theoretic reasoning, adaptive therapy treats cancer as a responsive opponent. Rather than aiming for total eradication, treatment strategies are adjusted over time to maintain tumor control and prevent resistance, optimizing patient outcomes while minimizing adverse effects.

## 3. The Evolutionary Game Theory in Cancer

Game theory provides a robust framework for modeling strategic interactions in complex biological systems, including cancer. Over recent decades, game-theoretic models have significantly advanced our understanding of cancer dynamics, therapeutic responses, and the development of effective treatment strategies. One pioneering model that explores cancer cell behavior through fitness matrices and replicator dynamics is the "Go-vs-Grow" game introduced by Basanta et al. [21]. A critical milestone in tumor progression is metastasis, defined as the spread of cancer to non-adjacent organs. According to Basanta et al., this transformation requires cells to shift from a purely proliferative phenotype to a motile one—an adaptation that entails a biological cost, as represented in the benefit matrix provided.
The model considers two phenotypes: proliferative and motile. Their interactions are captured in Table 1, which presents the payoff matrix. Here, the benefit associated with any interaction is denoted by b, while the cost of cellular movement is marked as c, relative to the baseline benefit. Basanta et al. subsequently expanded this model to include

TABLE 1. Payoff matrix for the Go-vs-Grow game.

| Phenotype | Proliferative Strategy | Mobile Strategy |
|---|---|---|
| **Proliferative Strategy** | $\frac{1}{2}$ | $b - c$ |
| **Mobile Strategy** | $b$ | $b - \frac{c}{2}$ |

the influence of glycolysis, introducing three distinct cancer cell types: invasive (Go), autonomous growth (Grow), and glycolytic (GLY) phenotypes. The analysis emphasized how changes in matrix parameters affect game properties and the evolutionarily stable strategies (ESSs) [22].

Building on this, further studies investigated tumor–stroma interactions and their influence on cancer invasiveness [23]. Sartakhti et al. explored tumor-stromal dynamics specifically in multiple myeloma [24], [25], while Dingli et al. focused on stromal dominance over tumor cells [26]. In [27], an evolutionary game-theoretic model was introduced to study cancer invasion via interactions between MMP and TIMP molecules. The model effectively captures extracellular matrix degradation and suggests potential therapeutic approaches for impeding invasion.

Another application of evolutionary game theory involves modeling cancer–immune system interactions [28]. This work addressed dynamics among proliferative, quiescent, and immune cells, using algebraic stability analysis to assess equilibrium conditions that represent tumor homeostasis.

In [29], You et al. introduced an agent-based, two-dimensional, continuous-space model that simulates interactions among cancer cells with respect to their proximity to blood vessels. Applied to metastatic castration-resistant prostate cancer (mCRPC), the model analyzes the population dynamics of three phenotypes: exogenous testosterone-dependent ($T^+$), testosterone-producing ($T^P$), and testosterone-independent ($T^-$) cells. The tumor microenvironment is divided into five zones (0–4), with decreasing carrying capacity as distance from the vessel increases. Zone 0 represents the vessel itself, while Zone 4 lies too far to support proliferation. In Zones 1–3, proliferation is determined by spatially defined payoff matrices, illustrated schematically in Figure 2. Multiple studies have mod-

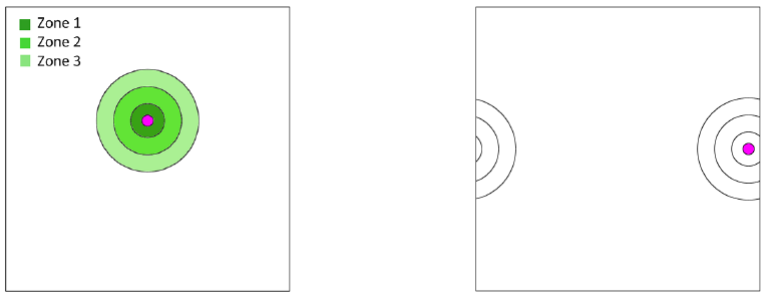


FIGURE 2. Schematic representation of a blood vessel and surrounding regions. Region 0 contains the vessel; regions 1 to 3 radiate outward with decreasing proliferation support, and region 4 lies beyond viable nutrient range [29].

eled cell–cell and tumor–environment interactions using Lotka–Volterra (LV) equations and their extensions [30]. While initially designed for two-species systems, LV dynamics

have been expanded to accommodate n cancer cell types. By transforming the fitness matrix into a competition matrix and maintaining equilibrium, the replicator dynamics for n types can be recast into an LV model with n-1 types, and vice versa. This ESS equivalence is detailed in [31]. Models by Zhang et al. [30], which use replicator dynamics as noted in [32], demonstrate conservation of ESS across transformations. Cunningham et al. [33] extended these concepts to optimize abiraterone treatment using control theory, minimizing total tumor burden variance.

Bayer [34] proposed an evolutionary coordination game to simulate cancer initiation and progression. Despite their analytical complexity, coordination games offer high potential for modeling frequency-dependent interactions and informing therapeutic design. Bayer modeled two species using ordinary differential equations and applied LV dynamics to describe growth constraints and cooperation dynamics.

In [35], Zheng et al. predicted tumor–stroma dynamics using an evolutionary game model. Their approach transitioned from mean field theory (MFT) which assumes population homogeneity to interacting particle systems (IPS), better suited to discrete spatial cell populations. Durrett and Levin [36] have shown that spatially discrete models yield behaviors often starkly different from those predicted by MFT. Alternatives to MFT include reaction–diffusion equations, patch-based models, and IPS, all of which help capture localized interactions.

The evolutionary context of cancer presents extensive challenges, requiring models that reflect rapid, disturbance-induced evolution. Notable examples include drug resistance in tumor cell lines [37], fishing-induced phenotype shifts [38], mating behavior adaptations [39], and climate-driven trait variation [40]. In these domains, the G-function fitness-generating approach offers a unified method for modeling both population dynamics and strategic evolution through differential equations linked to Darwinian principles. Pressley et al. [41] utilized game-theoretic modeling to compare progression timelines under maximum tolerated dose (MTD) and adaptive therapy. The adaptive protocol, which pauses treatment when tumor burden falls below half and resumes upon relapse, was shown to outperform MTD in delaying resistance—especially in two-cell populations (sensitive vs. resistant). Resistance is treated as a quantitative trait, and the dynamics are governed by G-function formalism [42].

Swierniak et al. [43] proposed the Multidimensional Spatial Evolutionary Games (MSEG) framework, wherein cells can express mixed phenotypes across a spatial grid. This modeling approach enables populations to exhibit biologically realistic diversity and better reflect actual tissue heterogeneity.

Finally, tumorigenesis is inherently evolutionary, driven by genetic alterations. Gene-centric models have helped define the biological logic of cancer, while computational methods offer opportunities to translate evolutionary theory into clinical control strategies. The importance of these methods is emphasized in [44].

The research on cancer modeling using evolutionary game theory is summarized in Table 2 and compared based on the evaluated features.

## 4. Cancer Modeling with Public Goods Game Theory

The public goods game serves as a well-established framework for analyzing collective behavior and has been applied across diverse domains, including economics, microbial cooperation, human societies, and animal populations. Its application to cancer modeling, however, represents a relatively recent development. Similar to pairwise evolutionary game theory, the public goods game has been utilized to examine various aspects of tumor

TABLE 2. A review of models with evolutionary game theory.

| Ref. No. | Model Type | Purpose of the Model | Success Evaluation | Key Notes |
|---|---|---|---|---|
| [21] | Go-vs-Grow Game | Study motility emergence via competition | Conditions favoring motile phenotypes | Fitness matrix and replicator dynamics for spatial competition |
| [22] | Evolutionary Game | Role of glycolysis in glioma invasion | Glycolytic cells promote invasiveness | Interaction among AG, GLY, and INV cells |
| [23] | Evolutionary Game | Tumor–stroma interactions in prostate cancer | Stromal co-option drives progression | Stromagenic vs. stromal-independent phenotypes |
| [24], [25] | Evolutionary Game | Tumor–stroma dynamics in myeloma | Thresholds for plasma cell extinction | Pairwise vs. collective interactions; nonlinear benefits in [25] |
| [26] | Evolutionary Game | Normal vs. malignant cell interactions | Coexistence and dominance scenarios | Replicator dynamics for phenotype stability |
| [27] | Evolutionary Game | MMP–TIMP dynamics in invasion | Conditions for invasive equilibrium | Payoff matrices for protease-inhibitor dynamics |
| [28] | Evolutionary Game | Cancer immunoediting phases | Immune–tumor dynamics modeled | Strategies: proliferative, quiescent, immune cells |
| [29] | Agent-Based Game Theory | Vasculature in mCRPC modeling | Spatial dynamics of $T^+$, $T^p$, $T^-$ cells | Agent-based modeling in continuous space |
| [34] | Coordination Game | Cancer initiation via coordination dynamics | Coordination failures in evolution | Coordination game theory for cell decisions |
| [35] | Evolutionary Game | Cancer–stromal dynamics via particles | Spatial patterns and heterogeneity | Interacting particle systems for cell interactions |
| [41] | Evolutionary Game | Resistance under therapies | Adaptive therapy delays resistance | Replicator equations for treatment modeling |
| [43] | MSEG | Cancer evolution under interventions | Mixed phenotypes and spatial heterogeneity | Realistic tumor population framework |

biology, though the number of such models remains limited.

Archetti was among the first to employ public goods theory in cancer research, focusing on the dynamics of growth factor production specifically, angiogenic signals produced by tumor cells [45]. His model incorporated a non-linear sigmoid benefit function, demonstrating that frequency-dependent interactions can result in the stable coexistence of growth factor-producing and non-producing phenotypes. Archetti identified five distinct dynamical regimes in his model, each emerging based on parameters such as the cost of factor production, diffusion rate, and the collective benefit conferred to tumor cells. One key insight from Archetti's work is the role of collective interactions in maintaining tumor heterogeneity, a property strongly linked to therapeutic resistance. His findings revealed that anti-angiogenic therapies, which aim to suppress growth factor production, are often transiently effective. Eventually, tumor populations adapt by upregulating these factors. In a subsequent study, Archetti applied this framework to insulin-like growth factor II

(IGF-II) in pancreatic cancer, illustrating how variations in production capacity can shift the population equilibrium and influence tumor growth rates [46]. This model also explored how diffusion levels affect phenotype coexistence and population stability.
Further extending this line of inquiry, Archetti developed a public goods model to investigate the Warburg effect, which describes cancer cells' preference for anaerobic glycolysis over oxidative metabolism [47]. He modeled the cooperation between cells that produce acidifying byproducts such as lactic acid and protons and those that do not. In a follow-up study, the model was expanded to encompass four phenotypes: aerobic (OXI), anaerobic (GLY), invasive (INV), and anaerobic–invasive (GLY-INV) [48]. GLY and GLY-INV were defined as cooperators contributing to environmental acidification, while the other two acted as defectors. Archetti showed that the Warburg effect functions as a non-linear public good, sustaining tumor heterogeneity and enabling GLY-potent cell populations to coexist.
Importantly, this work highlighted how acidity-targeted treatments may be effective when they raise the metabolic cost of cooperation specifically, the cost of producing acid in oxygen-rich conditions. However, these strategies were shown to lose efficacy when combined with anti-angiogenic therapies, suggesting a need for more nuanced treatment combinations.
Complementary research by Salimi et al. [27] introduced an evolutionary multi-impure public goods game model to describe myeloma cell invasion, focusing on MMP and TIMP dynamics. This study captured extracellular matrix degradation as a function of cooperative molecule production and proposed treatment strategies to counteract invasion. Their framework allowed players to simultaneously engage in producing multiple growth factors. Moreover, they developed a structured public goods game to model angiogenesis, demonstrating that evolutionary forces, combined with spatial and structural constraints, can facilitate the expansion of angiogenic clones within a tumor.
The collective body of research in this area is systematically summarized in Table 3, which reviews cancer models based on public goods game theory. The table compares model architectures, evaluated features, and biological assumptions. Through this synthesis, the review aims to clarify current achievements and limitations in applying public goods theory to cancer modeling.

## 5. Modeling Cancer with the Hawk-Dove Game and the Prisoner's Dilemma Game

Several studies have applied the Hawk-Dove game to model interactions among cancer cells [50], [51], [52], [53], [54]. Laruelle et al. [55] specifically utilized this game-theoretic approach to investigate the dynamics between tumor cell populations. Their research explored tumor heterogeneity by simulating scenarios with two or three distinct cell types, calculating the evolutionary stable strategies and associated fitness values. The mathematical results suggest that tumors with lower intratumoral heterogeneity tend to exhibit more invasive behavior compared to those with higher heterogeneity a conclusion supported by histological and genomic data from renal carcinoma studies.
The differentiation and mutation capacity of leukocytes, which leads to leukemia development, plays an important role in ecological modeling. In [56], the dynamics of leukemia are examined using the Hawk-Dove game. This model captures the interactions between malignant leukocytes and healthy leukocytes (leu), addressing the patient's condition both before and after diagnosis and treatment.
Clear cell renal cell carcinomas (CCRCCs) are characterized by dynamic cell populations.

TABLE 3. A review of public goods game theory models used in cancer research

| Ref. No. | Model Type | Purpose of the Model | Success Evaluation | Key Notes |
|---|---|---|---|---|
| [27] | EGT, Public Goods Game | Analyze MMP–TIMP interactions in cancer invasion | Aligns with in vitro data; identifies invasion suppression strategies | Reveals equilibria and proposes two therapeutic approaches |
| [45] | Conceptual/ Mathematical | Explain high glycolysis in cancer | Offers evolutionary insight; lacks experimental validation | Acidic microenvironment proposed as evolutionary advantage |
| [46] | Nonlinear Public Goods Game | Maintain IGF-II heterogeneity in pancreatic cancer | Lab confirms advantage for non-producers | Explains equilibrium coexistence among cancer subtypes |
| [47] | Nonlinear Public Goods Game | Understand Warburg effect as cooperation issue | Predicts stable glycolysis via group selection | Nonlinear benefits stabilize glycolytic behavior |
| [48] | Multiplayer Public Goods Game | Explore invasive subclones under Warburg effect | Strong theory; limited empirical support | Invasive phenotypes adapt to acidity changes under treatment |
| [49] | Theoretical Review | Apply public goods theory to disease evolution | Adaptable model for cancer and infections | Suggests public goods dynamics for treatment and epidemic modeling |

Their developmental trajectory—from early homogeneity to pronounced intratumoral heterogeneity (ITH), followed by secondary clonal and subclonal diversity has been modeled using the Hawk-Dove framework [57].

The Warburg effect, in which cancer cells adopt a glycolytic phenotype even in oxygen-rich environments, involves strategic metabolic interactions. Glycolytic cells are believed to influence aerobic cells by releasing lactic acid, a glycolytic byproduct that creates an acidic microenvironment around the tumor, often harmful to healthy cells. This interaction is modeled in [58] using the Prisoner's Dilemma: while cooperative behavior enhances competitiveness for the population as a whole, individual cells lack incentives to modify their own metabolic strategies unilaterally.

In [58], cancer metabolism and resource allocation are framed as a strategic game between aerobic and anaerobic (glycolytic) cells. Aerobic cells require less glucose to generate ATP, while glycolytic cells consume far more resources to produce the same energy yield, with lactic acid as a byproduct [59]. Thus, aerobic metabolism represents the "non-cooperative strategy," which emerges as the evolutionarily stable approach in the Prisoner's Dilemma. Initially considered a "passenger process" in tumor ecology, lactic acid accumulation may later become a "stimulator process" reshaping the tumor's microenvironment and population composition to facilitate a previously inaccessible "cooperator" strategy. This study evaluates natural selection through the lens of game theory.

Research leveraging the Hawk-Dove game and the Prisoner's Dilemma to model cancer is thoroughly summarized in Table 4. These frameworks provide powerful tools for analyzing

strategic interactions between cancer cells and their surrounding environment, ultimately contributing to the development of more effective therapeutic approaches.

TABLE 4. A review of models in cancer research using the Hawk-Dove game and the Prisoner's Dilemma game

| Ref. No. | Model Type | Purpose of the Model | Success Evaluation | Key Notes |
|---|---|---|---|---|
| [51] | Hawk-Dove Game | Explore interactions between malignant and normal cells in multiple myeloma | Altering fitness shifts equilibrium toward healthy cells | Fitness reduction in malignant cells restores balance |
| [52] | Hawk-Dove & Prisoner's Dilemma | Analyze selection between competing games in cancer dynamics | Game dominance shifts with population and strategy fitness | Framework for selecting between games, not just strategies |
| [54] | Hawk-Dove Game | Assess spatial dependencies using 3D simulations | 3D models better reflect population dynamics | Spatial structure affects stability and tumor behavior |
| [55] | Hawk-Dove Game | Investigate tumor heterogeneity effects on progression | Lower heterogeneity leads to aggressive tumors | Supported by histological/genomic data from renal carcinoma |
| [56] | Hawk-Dove Game | Compare predator-prey vs. game-theoretic models in leukemia | Insights into patient condition pre/post treatment | Models cell interactions and stem cell transplant scenarios |
| [57] | Hawk-Dove Game | Model early evolution of CCRCC | Transition from homogeneity to clonal/subclonal diversity | Linked to pathological and genomic evidence |
| [58] | Prisoner's Dilemma Game | Model metabolic interactions: glycolytic vs. aerobic cells | Glycolytic cooperation enhances competitiveness | Lactic acid secretion creates hostile microenvironment |
| [60] | Prisoner's Dilemma Game | Analyze metabolic trade-offs in cancer | Differential resource usage and ATP yield | Highlights cooperation and competition in tumor evolution |

## 6. Considering the Role of Space in Cancer Modeling with Game Theory

Any comprehensive model of cancer progression must account for spatial effects [61], as cells are confined within anatomical structures and interact with neighboring cells. These interactions influence cell fitness based on their location within the tissue structure, affecting the probability of mutation depending on where it initially appears in the tumor. The interplay between spatial factors and survival strategies in evolutionary game theory (EGT) has been studied for over 30 years. This was first described in the 1992 study by Novak and May [62], which demonstrated how complex population structures of cooperators and defectors can evolve or decline when arranged on a two-dimensional grid [63]. In this context, Lieberman et al. [64] have made significant contributions by introducing

the field of evolutionary graph theory, which examines evolution on graphs of structured populations. In their study, mutations are characterized by a constant relative fitness r. The paper discusses two specific structures, the directional line and the star (illustrated in Figures 3 and 4, respectively), which are relevant to cancer progression. In a directed line arrangement, cells can only reproduce at the node to their right. Consequently, a mutation becomes fixed, irrespective of its impact on reproductive fitness, if and only if it occurs at the leftmost node. The directed line model eliminates selection pressure, a property

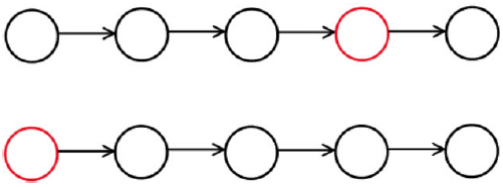

FIGURE 3. In a directed line, each vertex propagates to its adjacent right vertex. Mutations arising at the bottom (leftmost) node can potentially replace all other cells, whereas mutations occurring elsewhere (top) cannot propagate leftward and eventually disappear.

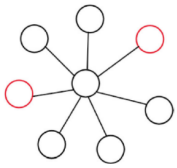

FIGURE 4. A star graph features multiple peripheral nodes linked to a central hub, with unidirectional connections. Substitution can occur from periphery to center or vice versa. In systems with many peripheral nodes, stable mutation fixation requires replication to the center followed by propagation to another peripheral node. The probability of central occupancy without replacement becomes negligible.

experimentally validated in colorectal crypts, which exhibit one-dimensional replication dynamics [65]. Star-like configurations used to model pancreatic and colon cancers [61] require mutations to replicate twice to stably propagate within the network [66]. A key distinction in graph-based models lies in the directionality of edges. In directed graphs, an edge from vertex $v_i$ to $v_j$ signifies that the offspring of $v_i$ may replace the resident of $v_j$, but not vice versa. In undirected graphs, replacement can occur in either direction. Weighted graphs extend this framework by introducing edge-specific probabilities $w_ij$, representing the likelihood that residents of $v_j$ are replaced, given that resident $v_i$ is selected for reproduction.

To represent epithelial tissues, regular graphs are often employed, in which every node has the same number of neighbors (k). Ohtsuki et al. [67] formulated a Prisoner's Dilemma model on such graphs, demonstrating that cooperation is favored if the benefit-to-cost ratio b/c exceeds k. Therefore, the probability of encountering a cooperator or defector depends solely on the strategies adopted by neighboring nodes [68].

Another critical metric in evolutionary graph theory is the structure coefficient $\sigma$, which

reflects how graph topology and update rules affect strategic success under weak selection. For a general two-player game, the corresponding payoff matrix is shown in equation (1).

| | A | B |
|---|---|---|
| A | $\alpha$ | $\beta$ |
| B | $\gamma$ | $\delta$ |

(1)

Strategy A is favored if the inequality $\sigma\alpha+\beta > \gamma+\sigma\delta$ holds. As $\sigma$ increases, self-interaction payoffs ($\alpha$ and $\delta$) become more influential in determining evolutionary stability.
In Prisoner's Dilemma games, cooperation becomes advantageous when $\frac{b}{c} > \frac{\sigma+1}{\sigma-1}$. In infinite populations ($\sigma = 1$), cooperation cannot evolve. These relationships hold for both birth–death and death–birth update mechanisms. More complex structures, such as star graphs, show $\sigma$ values dependent on update methods. For example, a star with N nodes has $\sigma = 1$ under birth–death updates, but under death–birth updates, $\sigma = \frac{(N^3-4N^2+8N-8)}{(N^3-2N^2+8)}$.
Structure coefficients have also been adapted for multiplayer games [69] and multi-strategy models [70], and are instrumental in incorporating spatial structures into adaptive dynamics [71].
To formally account for spatial effects, EGT must include structural corrections to replicator equations. In regular graphs, depending on the game's payoff matrix and update rule, an additional term modifies the definition of evolutionary stability [72].
Spatial effects on epithelial layers have been modeled using Voronoi lattices introduced over a century ago to represent cell nucleus distributions in tissue samples [73], [74]. Voronoi nodes typically have six neighbors, rarely fewer than four or more than eight. These networks simulate mechanical forces exerted by neighboring cells, influencing nuclear movement and spatial reorganization. Archetti [75] applied a public goods game with a sigmoid benefit function on Voronoi lattices, using local updates where births and deaths occur among adjacent nodes—allowing benefits to diffuse beyond immediate contacts.
Studies by Kaveh et al. [76] and Rychtář & Taylor [77] showed that spatial variation in fitness suppresses stability within invasive populations. In contrast, Ashcroft et al. [78] and Dean et al. [79] proposed that time-dependent selection fluctuations promote heterogeneity. Mehdipour et al. [80] further suggested that environmental variability can stabilize previously non-viable mutant strains.
Spatial influences can also be approximated in cancer models using pseudo-space formulations. By constructing replicator equations based on hypothetical payoff matrices and assuming fixed cell locations, interactions among different phenotypes can be modeled without explicit graph structures. Flach et al. [81] employed this approach to analyze melanoma–fibroblast interactions. Fibroblasts stabilize freely migrating cancer cells, converting them into fixed cells, which in turn divide and produce blocked cells trapped within the tumor mass.
In this model, three cell types were treated as separate populations with distinct growth dynamics. A similar pseudo-spatial method was used by Qian et al. [82] to explore cooperator and defector dynamics, where cancer cells actively modify their microenvironment to enhance survival. Other techniques for incorporating space in EGT include patch models where cell populations are subdivided into discrete groups and reaction–diffusion models, as outlined by Durrett and Levin [83], [84]. These approaches, along with recent efforts [85], [86], highlight the transformative impact of spatial realism on cancer modeling, producing more accurate and biologically consistent population dynamics.
The role of spatial structure in game-theoretic cancer modeling is summarized in Table 5.

Integrating these spatial dimensions enables deeper insights into tumor growth dynamics, treatment resistance, and the design of spatially informed therapeutic interventions.

TABLE 5. A review of models considering spatial effects in cancer modeling with game theory.

| Ref. No. | Model Type | Purpose of the Model | Success Evaluation | Key Notes |
|---|---|---|---|---|
| [67] | Prisoner's Dilemma on Graphs | Condition for cooperation on structured populations | Cooperation favored when $b/c > k$ across networks | Compared update rules; applies to regular graphs and social networks |
| [72] | Evolutionary Game on Graphs | Stability and invasion on graph-structured populations | Extra term in replicator equation; stability conditions derived | Extended uninvadability to regular and heterogeneous graphs |
| [75] | Public Goods Game on Voronoi Network | Localized public-good interactions among tumor cells | Coexistence regimes and spatial clustering via sigmoid benefit | Benefit diffusion beyond neighbors; network heterogeneity emphasized |
| [78], [79] | Evolutionary Game with Fluctuating Environments | Temporal fluctuations in selection and heterogeneity | Variability increases heterogeneity; fixation probabilities shift | Moran process with stochastic fitness; mutation effects included |
| [81] | Pseudo-Spatial Approach | Melanoma–fibroblast interactions in growth and resistance | Predicted fibroblast-enhanced melanoma survival | Paracrine loops modeled; stromal targeting suggested |
| [82] | Pseudo-Spatial Multi-Population Model | Competition and niche construction by metastatic subclones | Subclones alter carrying capacity and invasion dynamics | Three cell types modeled; niche feedback incorporated |
| [83], [84] | Patch and Reaction–Diffusion Game | Spatial discreteness and local interaction effects | Structure stabilizes coexistence; invasion thresholds shift | Patch-based and reaction–diffusion models compared |
| [87] | Hawk–Dove Game with Resource Fluctuations | Resource-driven strategic interactions and heterogeneity | Stable mixed strategies under resource variability | Resources added to payoffs; mean-field and lattice analyses used |

## 7. Microarray Game Theory for Gene Expression Analysis

Microarray technology, a relatively recent innovation, enables the simultaneous quantification of gene expression levels (i.e., mRNA abundance) for thousands of genes. Through gene expression microarrays, researchers can continually generate matrices of gene expression data, where each row represents a gene and each column corresponds to a sample or experiment (e.g., multiple patients with a genetic disorder), thus capturing observable biological effects.

Various analytical models have been developed to infer gene functions, interactions, and

dynamic behaviors under different biological conditions from these matrices (see [88], for example). One such method, based on coalition games, is introduced in [89]. A key advantage of this approach lies in its ability to assign numerical indices such as association indices that reflect the extent to which each gene is associated with a given condition (e.g., a tumor), while accounting for the expression patterns of other genes.
In [89], the association frequency of all gene subsets with specific conditions is represented using a coalition game framework, referred to as the microarray game. Within this model, the association index of each gene is computed using the Shapley value [90], resulting in a unique relational metric that satisfies a set of properties described in [89]. A higher Shapley value for a gene within a given microarray game indicates a stronger association between that gene and the genomic mechanisms underlying the studied condition [91].

## 8. Modeling Cancer Treatment with Game Theory

A widely accepted principle in cancer treatment involves administering the highest possible drug dose in the shortest feasible time frame known as maximum dose strategies. The concept of the Maximum Tolerated Dose (MTD) has long been a cornerstone of cancer therapy and serves as the basis for clinical evaluation in most drug trials. However, it has not been universally adopted as a suitable strategy for all cancer types [92].
A major limitation of this approach lies in the assumption that resistant cancer cell populations do not exist prior to treatment. From an evolutionary standpoint, this assumption is problematic. Administering high-dose treatments to eliminate the maximum number of cancer cells can inadvertently promote the growth of resistant populations. Conversely, delivering lower doses at optimized intervals may reduce toxicity and stimulate the immune response. Although MTD-based strategies often yield initial success, they frequently fail over time, leading to treatment relapse. Gatenby and Frieden modeled the impact of such treatments on tumor progression using mathematical equations [93].
Their analysis demonstrated that continuous treatment with a fixed chemotherapy dose effectively eliminates drug-sensitive cells, but allows a small population of resistant cells to survive and proliferate unchallenged. This phenomenon, known as Competitive Release, is illustrated in Figure 5-A. To address this issue, alternative scheduling methods such as metronomic chemotherapy have been proposed. This approach involves alternating periods with and without drug administration, offering a potential improvement over constant MTD therapy [94].
However, the effectiveness of metronomic therapy remains inconsistent. Some in silico studies suggest it may outperform MTD-based protocols [95], but other research indicates that while metronomic therapy can extend survival, it still fosters resistance in various forms. Moreover, preclinical and clinical investigations, particularly involving metastatic melanoma, have not consistently demonstrated superiority over MTD-based treatment.
A core limitation of both MTD and metronomic strategies is their reliance on fixed dosing schedules, despite the tumor's high sensitivity to therapeutic variation. Adaptive therapy strategies based on the competition between sensitive and resistant cancer cells have emerged as the most successful evolution-informed approaches to cancer treatment. Within tumors, cancer cells compete with stromal cells for essential nutrients, space, and survival signals. Drug-resistant cells may evade apoptosis due to these competitive dynamics.
An alternative therapeutic perspective advocates maintaining a sizable population of drug-sensitive cells during treatment, thereby limiting tumor growth to a manageable level. In this framework, the optimal drug dose should be the minimum necessary to trigger a

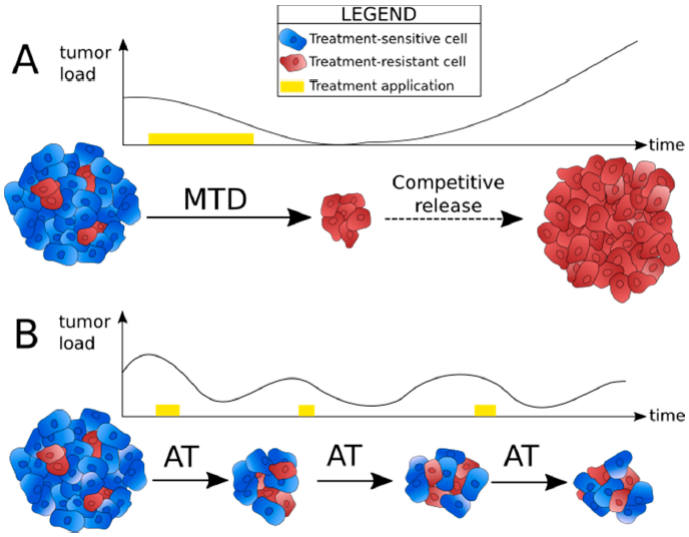


FIGURE 5. Principle of Adaptive Therapy. (A) Under MTD strategy, continuous treatment with a fixed dose (yellow band) leads to competitive release, relapse, and treatment failure. (B) Adaptive Therapy (AT) adjusts drug dosage and timing based on tumor progression (yellow bars), aiming to reduce tumor burden with maximal inhibition cycles [96].

therapeutic response. Once the tumor shrinks to an acceptable size, treatment should be paused. Although regrowth may occur, the dominant cell population will be sensitive, allowing for re-initiation of treatment cycles (Figure 5-B).

The first mathematical model of adaptive therapy, introduced by Gatenby et al. [97], used equations to simulate competition among tumor cell subpopulations. This model was applied to analyze responses to MTD, metronomic, and adaptive strategies across tumors with varying resistance profiles. Both theoretical interpretations and simulations indicate that adaptive therapy can significantly improve survival compared to conventional approaches. Supporting experimental evidence from xenografted ovarian cancer treated with carboplatin confirmed the practicality of adaptive therapy, showing that tumors could be managed using progressively lower drug doses and extended intervals compared to MTD protocols.

This foundational model has inspired the development of new frameworks designed to optimize adaptive strategies, better understand tumor ecology, and expand their applicability across diverse cancer types. Recent clinical trials have further shown that adaptive drug regimens can outperform traditional treatments based on continuous MTD use. Unlike rigidly planned therapies, adaptive protocols dynamically adjust dosage in response to the tumor's evolving state.

In [98], Martinez analyzed a dataset comprising 590 non-small cell lung cancer patients who had received either chemotherapy or immunotherapy. The study aimed to compare a game theory–based model incorporating the evolution of treatment resistance with classical mathematical approaches. The population growth functions examined included exponential, logistic, general Gompertz, Gompertz, Bertalanffy, and classical Bertalanffy models. Notably, this research marked the first application of Stackelberg game theory to cancer modeling using a large clinical cohort. Cancer cell responses to treatment were modeled

as an evolutionary game, consistent with approaches presented in [41]. The physician's decision variable (m) represented the dose of either docetaxel (a chemotherapy drug) or a PD-1 immune checkpoint inhibitor (MPDL3280A).
Since no patient in the dataset received both treatments concurrently, a single model was employed to describe both therapeutic options. In chemotherapy, the dose rate (m) could vary continuously from 0 to 1, where m = 1 corresponds to the maximum tolerated dose (MTD) and m = 0 signifies no treatment. By contrast, immunotherapy decisions were binary: either treatment was administered (m = 1) or withheld (m = 0), as reviewed in [9]. The model assumes a constant dose for both treatments unless chemotherapy is delivered intermittently, in which case m can fluctuate between 0 and 1.
The biological-evolutionary dynamics of cancer were represented by a population vector $x$, where treatment resistance was modeled as a continuous trait $u \in [0, 1]$. Here, $u = 0$ denotes full sensitivity to treatment, and $u = 1$ indicates complete resistance. Population and trait dynamics were described using the fitness-generating function G [99]. The per capita growth rate of cancer cells, expressed as $G(u, x, m)$, defined the population dynamics via equation (2):

$$\dot{x} = xG(u, x, m) \tag{2}$$

The evolution of the resistance trait was modeled by equation (3):

$$\dot{u} = \sigma \frac{\partial G}{\partial u} \tag{3}$$

where the parameter $\sigma$ controls the rate of evolutionary change and may be affected by factors such as genetic variance or mutation rate.
To effectively apply game-theoretic principles to cancer treatment design, detailed knowledge of both the tumor's biological composition and its evolutionary responses to therapy is essential. In [100], Gaska et al. investigated how transcriptional data could be used as input for game theory models to forecast glioblastoma organoid responses to radiation therapy. They used both supervised and unsupervised learning approaches to extract cellular compositions and identify the proportions of cancer cell subtypes in patients treated with radiation. Replicator equations were then employed to model transient dynamics and identify evolutionarily stable states within these organoids. This methodology offers a promising avenue for designing evolution-informed cancer therapies.
While shifts in population-level characteristics such as cell density or size pertain to biological dynamics, changes in trait distribution (quantitative or qualitative) reflect evolutionary dynamics. Since the total cell population in the studied organoids was constant, only evolutionary aspects were analyzed. Replicator dynamics, a foundational tool in evolutionary game theory, remain widely used to model processes such as natural selection and genetic variation.
In recent years, evolutionary game theory (EGT) has gained traction in oncology as a means to inform personalized treatment strategies. Rather than aiming to eliminate all tumor cells, EGT-based approaches seek to reduce tumor cell fitness relative to normal cells, thereby managing tumor burden. In metastatic cancer, treatment strategies should consider lesion count, timing of lesion emergence, and biological heterogeneity. For oligometastatic patients, combining systemic and local interventions—such as interventional oncology—may offer superior outcomes. Notably, targeting a single lesion may trigger an immune response against others, a phenomenon known as the abscopal effect, which has been examined and modeled in [101].
To explore pediatric sarcoma treatment, Reed et al. introduced a G-function defined as

follows [102] (equation4):

$$G = r\left((1-v_1)(1-v_2)(1-v_3) - \frac{x}{K}\right) - \mu_1(v_1) - \mu_2(v_2) - \mu_3(v_3) \tag{4}$$

Here, $v_i$ denotes the resistance to treatment $i \in \{1,2,3\}$, $r$ is the intrinsic growth rate, and $\mu_i(v_i) = \dfrac{m_i}{k_i + b_i v_i}$ represents the death rate induced by treatment $i$. Parameters $m_i$, $k_i$, and $b_i$ describe the strength of the treatment, intrinsic resistance, and benefits of resistance, respectively. In this equation, $K$ represents the carrying capacity of the tumor environment. It defines the maximum population size (denoted by $x$) that the system can sustain under given biological and environmental constraints. This function ($G$) offers a framework for assessing therapeutic protocols, including adaptive strategies for metastatic prostate cancer, as detailed in [103].

In [104], Salvioli et al. modeled two cell populations: sensitive and resistant. The goal was to identify conditions under which tumor burden could be stabilized. Using a Stackelberg evolutionary game framework, the physician acted as the leader, selecting dosing strategies to maximize a quality-of-life–based objective function incorporating tumor size, resistance level, and treatment intensity. A complementary model was proposed in [105], where simulations confirmed the strategy's efficacy and potential clinical utility.

In [106], Liu et al. found that combining Chinese herbal medicine with chemotherapy improved therapeutic outcomes. When tumors exhibited aggressive growth, chemotherapy doses were increased after reaching a critical threshold in Chinese medicine efficacy. Conversely, during slower tumor progression, both therapies were simultaneously adjusted after threshold activation. Using Steinberg game theory, the authors proposed coordinated strategies for minimizing toxicity and enhancing efficacy.

Mahmoodifar and Newton [107] applied an evolutionary rock-paper-scissors game framework to model cancer–immune interactions among healthy cells, T-cells, and cancer cells. Chemotherapy and immunotherapy dosing schedules were modeled as control functions. Results suggested that optimal chemotherapy duration aligns with one-quarter of the cancer–immunity cycle, while immunotherapy should span half a cycle and precede chemotherapy for maximum efficacy.

While therapeutic strategies aiming to rapidly reduce tumor volume often correlate with clinical response, they frequently foster treatment resistance. Evolution-informed approaches seek to delay resistance and preserve intratumoral heterogeneity. Recent trials have shown encouraging outcomes, with empirical data guiding parameter selection and treatment design. A major consequence of resistance-driven dynamics is "competitive release," where resistant clones expand following aggressive treatment. This effect can be mitigated by tailoring drug dosage and adjusting the initial population composition.

Tumor heterogeneity plays a central role in resistance evolution. Kaznatcheev et al. [108] developed a method to quantify effective evolutionary games in cultures of non-small cell lung cancer—specifically comparing cells sensitive and resistant to the ALK inhibitor alectinib. Although focused on cancer cell interactions, this method is applicable to broader studies of microscopic evolutionary systems.

While extensive research has focused on single-drug therapies, clinical treatment often involves multidrug protocols. Optimizing these strategies is challenging due to combinatorial complexity, cellular interactions, and dosing schedules. Nevertheless, evolutionary game theory presents a powerful framework for designing dynamic, adaptive therapies that respond to tumor evolution and enhance long-term clinical outcomes.

The study [109] investigates evolutionary strategies in two-drug cancer therapies, introducing an approach in which therapeutic agents are categorized into primary and secondary roles. The primary drug is selected based on its superior efficacy and/or minimal toxicity, whereas the secondary drug is deployed specifically to target subpopulations of cancer cells that exhibit resistance to the primary agent. Mathematical simulations demonstrate that this primary–secondary approach prolongs time to progression (TTP) and patient lifespan compared to conventional therapies that do not account for evolutionary dynamics. Furthermore, the study presents a clinical trial model for abiraterone-adaptive therapy in metastatic castration-resistant prostate cancer. Simulation results indicate that the co-administration of docetaxel during abiraterone treatment substantially enhances TTP.

Recent clinical trials have shown that adaptive therapies—those which adjust treatment regimens based on tumor response can outperform standard therapies that follow the maximum tolerated dose (MTD) protocol. Unlike fixed dosing strategies, adaptive therapies modify dosage in real-time according to tumor status. In [110], a framework for optimizing adaptive treatment policies is proposed, utilizing an evolutionary game theory model of cancer. Based on predefined therapeutic goals, the study employs dynamic programming to determine optimal treatment strategies. Specifically, total drug dosage and recovery time are optimized via the Hamilton–Jacobi–Bellman equation. Comparative analysis reveals that adaptive treatment policies significantly reduce total drug usage relative to MTD-based strategies. The findings underscore the utility of optimal control theory in guiding the development of adaptive treatment protocols and support their integration into clinical trial design.

In the context of Metastatic Clear Cell Renal Cell Carcinoma (mCCRCC), recent treatment strategies have markedly improved patient survival rates. Many patients receive sequential treatments outside of clinical trial frameworks. Voog et al. recently reported that a substantial subset of patients those with favorable or intermediate prognoses retains the capacity for further therapeutic interventions even after two lines of treatment, thereby extending survival. According to data from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), overall survival spans 57 months for patients with good or intermediate prognoses, compared to 19 months for those with poor prognoses [111].

Tumor heterogeneity remains a central factor influencing drug resistance and disease progression. Advances in sequencing and single-cell technologies have only recently enabled detailed characterization of intra-tumoral genetic diversity. These datasets are essential for the construction of molecular models that explain tumor development, evolutionary adaptation, and therapeutic response. Recent efforts in this domain have resulted in mathematical models that aim to predict treatment outcomes and resistance trajectories in cancer [112].

Research into game theory–based cancer treatment models is comprehensively reviewed and synthesized in Table 6. This summary provides a comparative analysis of various modeling approaches, offering researchers insights into current limitations, opportunities for refinement, and directions for developing more effective therapeutic strategies.

TABLE 6. A Review of Game Theory Models in Cancer Treatment Research.

| Ref. No. | Model Type | Purpose of the Model | Success Evaluation | Key Notes |
|---|---|---|---|---|
| [97] | Evolutionary replicator–game model | Simulate tumor response to chemo types; validate with xenografts | Adaptive therapy prolonged progression vs. MTD/metronomic | Three-strategy game; dose modulation; supported by OVCAR experiments |
| [98] | Game-theoretic NSCLC resistance model | Fit clinical tumor trajectories with evolving resistance | GT model outperformed standard fits; captured U-shaped responses | Models resistance as trait; first large clinical dataset application |
| [100] | Replicator dynamics + transcriptomics | Predict GBM organoid response to radiotherapy | Matched hypoxia-driven dynamics; fitted cell proportions over time | RNA-seq data processed to infer cell types; replicator-based forecasting |
| [101] | Conceptual EGT framework | Guide interventional oncology in oligometastatic patients | Proposed delay of systemic shifts; abscopal effects; pending validation | Combines local ablation with systemic IO; EGT leadership dynamics |
| [103] | G-function eco-evolutionary model | Model clonal competition and therapy sequencing in sarcomas | Reproduced tumor stages; identified stable/cyclic equilibria | Uses fitness-generating functions; recommends timing for chemo/immuno |
| [104] | Stackelberg evolutionary game | Optimize dose strategy for tumor stabilization | Evolution-aware therapy improved QoL, minimized dose/resistance | Physician as leader; compares MTD, ecology-only, full control |
| [105] | Stackelberg eco-evolutionary control | Steer tumor dynamics via resource manipulation | Resource control shifted tumor to desired phenotype | Adds patch/resource dimensions; formal control setup; leader adjusts environment |
| [106] | Steinberg game (doctor vs tumor) | Model chemo–Chinese medicine synergy | Timing guidelines for dual treatment; reduced toxicity | Doctor chooses chemo; tumor adapts; Chinese medicine as modulator |
| [107] | RPS evolutionary game | Align chemo/immuno timing with tumor–immune cycles | Optimal chemo $\approx \frac{1}{4}$ cycle, immuno $\approx \frac{1}{2}$; immuno→chemo best control | Models cells as RPS game; schedules as time-dependent controls |
| [108] | In vitro game assay | Measure CAF/drug impact on NSCLC cell fitness | Switch from Leader to Deadlock game under conditions | Tagged cells co-cultured; growth $\beta$ fitness $\beta$ payoff matrix; first empirical assay |
| [109] | Primary– secondary Stackelberg EGT | Design two-drug protocol with role separation | Delayed progression; docetaxel benefit during abiraterone cycles | Combines selection, resistance fitness, QoL; guides timing decisions |
| [110] | Dynamic programming + EGT | Compute optimal adaptive therapy policies | Reduced drug use; expanded recoverable tumor states; trade-offs analyzed | Solved HJB PDE; derived feedback dosing; compared control strategies |
| [111] | Observational cohort study | Evaluate systemic agents post-VEGFR- TKI in RCC | Median OS 57 mo (good risk) vs 19 mo (poor); $\geq 4$ lines tolerated | IVOIRE study supports TKI rechallenge; improved survival with sequential therapy |

## 9. Experimental Case Studies Using Game Theory in Cancer Research

Recent advances in mathematical oncology have demonstrated the practical utility of game-theoretic models through experimental validation and clinical application. Several studies have successfully bridged theoretical frameworks with biological data, confirming the relevance of strategic modeling in cancer dynamics and treatment optimization.

For instance, Archetti et al. [46] experimentally validated a public goods game model in neuroendocrine pancreatic cancer, showing that IGF-II production heterogeneity is maintained through frequency-dependent selection. Similarly, Gatenby et al. [97] applied an evolutionary game model to ovarian cancer xenografts, demonstrating that adaptive therapy prolongs tumor control compared to conventional dosing strategies.

Kaznatcheev et al. [108] introduced an empirical "game assay "by co-culturing sensitive and resistant non-small cell lung cancer (NSCLC) lines, quantifying payoff matrices and revealing a shift in game class under drug pressure. Gaska et al. [100] integrated transcriptomic data from glioblastoma organoids into replicator dynamics, predicting treatment-induced resistance trajectories.

Clinical datasets have also supported game-theoretic predictions. Martinez et al. [98] showed that models incorporating resistance evolution outperform classical growth models in fitting tumor trajectories of NSCLC patients. Zhang et al. [121] and West et al. [109] applied evolutionary strategies to metastatic prostate cancer, guiding adaptive therapy protocols that delay resistance and improve patient outcomes.

In a separate study, Liu et al. introduced a Steinberg game framework to optimize chemotherapy regimens by incorporating Chinese medicine as a dynamic and adaptive component [113]. Their experimental results highlighted that strategically coordinating herbal treatments with chemotherapy can minimize drug toxicity and enhance therapeutic outcomes, particularly in tumors exhibiting aggressive proliferation.

Leither et al. developed an agent-based modeling approach leveraging spatial statistics to infer game-theoretic interactions between drug-sensitive and drug-resistant cancer cells [114]. The study revealed that spatial patterns in tumor cell distributions encode underlying ecological dynamics, allowing treatment strategies to be tailored using single time-point imaging without requiring full temporal tracking.

Li et al. presented an optimal control framework for adaptive cancer therapy rooted in evolutionary game theory and pharmacokinetics [115]. Their simulations demonstrated that maintaining ecological balance between sensitive and resistant populations helps suppress overall tumor burden and extend survival, outperforming conventional treatment strategies. These experimental case studies underscore the translational relevance of game theory in oncology not only in advancing conceptual models but also in guiding clinical decision-making, refining treatment schedules, and shaping next-generation adaptive therapy designs.

## 10. Discussion

This research presents a comprehensive overview of recent advances in cancer modeling through the lens of game theory. Within tumors, cells simultaneously engage in competition for space and resources and cooperate by secreting factors that promote tumor growth and invasion. These interactions between cancer cells and their microenvironment play a crucial role in cancer progression.

Cooperation among cancer cells underpins several hallmarks of cancer and is facilitated by diffusible factors that influence both cancer and stromal cells. Various molecules, genes,

and signaling pathways are involved in these processes. In cooperative environments, mutant cells that stop producing growth factors can still benefit from those secreted by neighboring cells, thus avoiding the metabolic cost of production. These mutants gain a fitness advantage and may proliferate more rapidly. Over time, subclones originating from such non-producing cells may outcompete and potentially eliminate the original growth factor-producing subclones. These dynamics highlight the intricate interplay between cooperation and competition in tumor evolution and underscore the significance of understanding these mechanisms to develop effective cancer therapies.

A recent study [116] identified possible altruistic behavior in breast cancer cells, where a small subpopulation increases the overall tolerance to the chemotherapeutic agent taxane. This subpopulation is characterized by high expression of the noncoding RNA miR-125b, and it secretes proteins that activate PI3K, thereby offering survival benefits to neighboring cells during taxane exposure.

Under evolutionary game theory [117], the notion of profit aligns with Darwinian principles. The players are proliferating cells including cancer, stromal, and peripheral cells while strategies represent phenotypes arising from mutations, distinguishing different subclones within the population. Optimization occurs via natural or clonal selection, which adjusts strategy frequencies in proportion to their fitness over time. Although game theory does not offer new insights into hallmarks that are not frequency-dependent such as genome instability or the unlimited replicative potential of cancer cells it is particularly useful for analyzing interactions that are frequency-dependent. These include self-sufficiency in growth signals, evasion of apoptosis and the immune system, neoangiogenesis, and metastasis. Such hallmarks rely on interactions among cancer cells or between cancer cells and stromal cells.

Evolutionary game theory offers a structured approach to dissect these interactions, enhancing our understanding of the forces driving cancer progression and therapy resistance. Modeling these dynamics helps reveal how phenotypes compete and cooperate within the tumor microenvironment, which could guide the development of more effective treatment strategies.

The Prisoner's Dilemma (PD) is one of the simplest games illustrating the challenge of cooperation. Widely discussed in evolutionary biology and economics, PD shows how cooperation can emerge over time through mechanisms like genetic relatedness or repeated interactions. In cancer research, game theory has also been applied through variants such as the chicken game [118], [119]. PD serves as a foundational model for exploring the evolution of cooperative behaviors.

Subsequent cancer studies [120], [121], [122], [123] largely applied pairwise game models. While valuable, such models fall short of capturing the full complexity of cancer. In reality, most cooperative behaviors in cancer are better explained through multiplayer games, where payoffs stem from collective interactions among many cells. This is especially relevant given the role of diffusible factors—such as releasable growth factors [124], [125] in these processes.

Multiplayer game models offer a richer framework for understanding the dynamics of cancer cell interactions. These models reflect the collective behaviors that underpin tumor growth and progression. For example, when cancer cells produce and diffuse growth factors, they generate a supportive microenvironment that fosters development and therapy resistance. Modeling these interactions as multiplayer games reveals how cancer cells cooperate to maximize survival and proliferation.

Furthermore, such models help pinpoint therapeutic targets by exposing critical interactions that sustain tumor growth. Disrupting the production or diffusion of growth factors, for instance, could break down cooperative networks and make cancer cells more vulnerable to treatment. By integrating multiplayer game theory into cancer research, scientists gain deeper insight into tumor biology and uncover new strategies for effective therapy.
Experimental validation of game theory in cancer began with studies on insulin-like growth factor II (IGF2), focusing on cell proliferation and apoptosis evasion in pancreatic neuroendocrine tumors. Other applications include research on isocitrate dehydrogenase 1 (IDH1) mutant cells in secondary glioblastoma progression, the response of prostate cancer to intermittent androgen suppression therapy [126], and metabolic exchanges between hypoxic and oxygenated cancer cells—often mediated by lactic acid production [126] along with studies by Varzhenis [127], [128], [129].
Interactions between tumor cells and stromal cells can also be viewed through a cooperative lens. For example, tumors recruit and activate normal fibroblasts, transforming them into cancer-associated fibroblasts (CAFs). These CAFs then secrete growth factors and cytokines that promote tumor progression [130]. While some may interpret this recruitment as coercion, cancer cells also demonstrate cooperation by producing diffusible factors that attract and activate fibroblasts.
These growth factors further support tumor expansion through neoangiogenesis or immune system modulation—either by stimulating or suppressing different immune cell types. Across all these scenarios, cancer cells cooperate by releasing factors that prompt stromal cells to build a more favorable environment. Game theory has been invaluable for interpreting these complex tumor-stroma dynamics, especially in the context of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), which are central to prostate cancer progression and the behavior of multiple myeloma [131], [132].
A notable case of intratumoral cooperation is the Warburg effect [133], which also hinges on diffusible factors. Under hypoxic conditions, some glycolytic cancer cells produce lactate, which neighboring cancer cells then use as an alternative energy source [134].
The Warburg effect is not solely an adaptive response to hypoxic conditions; it can also manifest under normoxic environments. Its principal role may involve acidification of the tumor microenvironment via the release of diffusible metabolites. This acidification contributes to the induction of normal cell death, facilitates tumor invasion, promotes immunosuppression, and enhances the secretion of growth factors [135], [136]. The inherently cooperative nature of the Warburg effect is evident in its collective benefits to the tumor. Although glycolysis is energetically less efficient than oxidative phosphorylation in terms of ATP yield, it offers strategic advantages by modifying the microenvironment to favor tumor progression. The lactate and other metabolites produced by glycolytic cancer cells create a hostile niche for healthy cells while concurrently supporting tumor expansion and invasion.
Cancer cells may also trigger a similar metabolic shift in adjacent cancer-associated fibroblasts (CAFs), a phenomenon termed the "reverse Warburg effect" [137]. In this scenario, CAFs secrete metabolites that are readily utilized by cancer cells, thereby amplifying their growth and metastatic capabilities [138], [139]. Understanding both the Warburg effect and its cooperative dimensions is essential for developing targeted therapies. Disrupting these metabolic symbioses may present viable strategies for inhibiting tumor progression and metastasis. Game theory offers a powerful framework for modeling and manipulating such interactions, facilitating more informed and strategic therapeutic interventions.

Cooperation among cancer cells is exemplified by the action of diffusible molecules operating through autocrine and paracrine signaling mechanisms. These signals significantly influence cell survival and proliferation. Growth factors produced by cancer cells not only stimulate proliferation and angiogenesis but also aid in circumventing programmed cell death and immune surveillance. This network of interactions extends beyond tumor cells and includes reciprocal exchanges with stromal components.

Moreover, cooperativity encompasses the broader spectrum of releasable molecules, including metabolites resulting from the Warburg effect and various small biomolecules. Such compounds remodel the microenvironment to favor tumor survival and dissemination. One notable cooperative mechanism involves the secretion of factors that induce lipolysis in adjacent adipocytes, releasing free fatty acids. These fatty acids are then absorbed by cancer cells, providing essential energy for tumor growth [140]. Additionally, cancer cells reshape the metabolic landscape during metastatic colonization. For example, colorectal cancer cells secrete creatine kinase B-type, which interacts with hepatocyte-derived creatine to produce phosphocreatine. This compound is then taken up by metastatic cancer cells in the liver to fuel ATP generation and drive metastatic progression [141].

Tumor-derived exosomes further illustrate cooperative behavior, transmitting proteins, lipids, and nucleic acids that influence neighboring cells and sculpt a supportive niche for proliferation and metastasis [142]. These interactions can be conceptualized through public goods games, where individual cancer or stromal cells act as "players" contributing diffusible factors to a shared microenvironmental "pool." These contributions yield collective benefits such as increased proliferation, resistance to apoptosis, immune evasion, acidification, and enhanced invasiveness.

While some microenvironmental dynamics can be modeled via two-player games including the chicken game, the prisoner's dilemma, the hawk-dove game, and classical evolutionary games the architecture of tumors necessitates more complex modeling. In actual biological settings, cells interact with multiple neighbors; for instance, monolayer cultures typically contain about six adjacent cells, with extreme variations being uncommon [124]. These interactions become even more intricate within three-dimensional tumor structures. Thus, public goods models offer a more realistic and comprehensive means of describing tumor ecology by accounting for the cumulative effects of cell contributions to the microenvironment, including growth factors, metabolites, and other modulatory agents.

Game-theoretic models have also been extended to encompass interactions between medical professionals and tumors via Stackelberg's framework. Here, physicians act as strategic leaders, while cancer cells respond as followers, enabling sophisticated analysis of therapeutic decision-making. The emergence of anti-evolutionary therapies marks a pivotal shift toward sustainable cancer management. Conventional therapies frequently drive the evolution of resistant clones, leading to relapse. In contrast, treatments targeting the relatively stable stromal cells such as immunotherapies are less prone to resistance due to reduced mutational rates. Designing therapies that circumvent the evolutionary potential of cancer cells requires an integration of dynamic and equilibrium principles often overlooked in current regimens.

One innovative approach involves dose modulation to enhance competition among cancer subclones. By applying evolutionary principles, such strategies aim to exploit competitive cellular interactions to hinder resistance formation, aligning with the rationale behind Darwinian or evolutionary-informed therapies [143].

Traditionally, the standard of care (SoC) relies on the maximum tolerated dose (MTD), administering the highest dose a patient can endure to maximize tumor eradication. MTD

remains effective for certain aggressive cancers such as late-stage lung cancer [144]. However, this approach often triggers resistance and eventual treatment failure in other malignancies [143]. Adaptive therapy offers an alternative paradigm by adjusting drug dosages to sustain competition among sensitive and resistant clones, maintaining a dynamic equilibrium that delays dominance by resistant populations.

This strategy harnesses intratumoral evolutionary dynamics, promoting prolonged treatment efficacy while minimizing resistance. By eschewing blanket high-dose approaches in favor of strategic modulation, adaptive therapy represents a forward-thinking model that prioritizes sustainability and long-term disease control.

The application of adaptive therapy underscores the critical importance of incorporating evolutionary and ecological principles into cancer treatment design. By understanding and modulating the competitive dynamics within the tumor microenvironment, researchers and clinicians can develop more nuanced therapeutic strategies that enhance patient outcomes and minimize the risk of treatment failure. This innovative approach calls for sustained research efforts and clinical trials to refine and optimize adaptive therapy protocols across diverse cancer types.

Among the emerging strategies is the deliberate alteration of selection pressures within tumors to favor the proliferation of more benign or treatment-responsive subclones. Such tactics seek to harness intra-tumoral evolutionary dynamics, steering them toward less invasive phenotypes. Another promising avenue involves the use of synergistic combination therapies that adapt in real-time to cancer cell evolution, thereby improving overall therapeutic efficacy [145].

A particularly intriguing strategy involves the genetic engineering of tumor cells to eliminate genes encoding essential growth factors. When reintroduced into the native tumor, these modified cells gain a proliferative advantage by exploiting growth factors secreted by unmodified cells—a phenomenon referred to as the "autologous cell defect" [146]. Through clonal selection, these engineered cells may gradually dominate the tumor population. Eventually, the tumor may collapse due to the scarcity of essential growth factors, or at minimum, the deleterious effects of excessive cytokine production could be mitigated. These approaches illustrate the potential of leveraging both genetic engineering and evolutionary theory to design therapies that are simultaneously effective and resistant to relapse.

The challenge of fostering cooperation among inherently self-interested entities be they biological cells or individuals is nontrivial. Sustainable cooperation remains rare and fragile. In cancer, malignant transformation occurs in a limited subset of cells, which subsequently evolve cooperative mechanisms to promote tumor progression. Game theory offers a robust analytical framework for identifying and disrupting such cooperative behaviors and for inhibiting clonal expansion. By applying game-theoretic concepts, researchers can inform the design of anti-evolutionary therapies aimed at preventing the rise of drug-resistant cancer cell populations [147].

Recent research demonstrates that game theory can yield viable alternatives to the conventional maximum tolerated dose (MTD) strategy. Rather than relying exclusively on aggressive dosing, game theory-informed approaches focus on predicting and directing the evolutionary trajectories of tumors. This enables the development of adaptive therapies that anticipate and counteract the evolutionary responses of cancer cells [148].

Numerous game-theoretic models explaining cancer dynamics have been rigorously validated with empirical data [149], [150]. These validations reinforce the credibility and applicability of such models in elucidating tumor behavior. Crucially, interdisciplinary

collaboration between theorists and experimental scientists is essential for translating evolutionary therapy concepts into clinically effective treatments. Such synergy facilitates the development of personalized interventions that improve patient outcomes and potentially achieve curative results.

A growing domain for the application of game theory is machine learning. In a recent study [151], a novel framework integrated Shapley values with game-theoretic principles and Federated Learning (FL) to predict breast cancer outcomes. In this paradigm, multiple data holders collaboratively train a model while preserving privacy, with each participant acting as a strategic agent making decisions about engagement. Payoff functions were introduced to incentivize model optimization at the local level.

Graph Neural Networks (GNNs), which are widely employed for tasks such as node classification, graph classification, and link prediction, have recently been paired with game-theoretic methods for interpretability. These approaches treat model features as players in a cooperative game, calculating their importance based on marginal contributions to decision-making coalitions [152].

In a related study, Liu et al. [153] applied a Shapley Additive Explanation framework grounded in cooperative game theory to identify predictive factors in breast cancer recurrence. Using real-world data from 1,629 patients, they successfully uncovered key variables linked to disease outcomes.

Despite the promise of machine learning models, limitations in generalizability, interpretability, and reproducibility hinder their clinical adoption. Black-box models often yield high accuracy but lack the transparency required for clinical trust. To address these challenges, a recent study [154] proposed a hybrid framework combining Kolmogorov–Arnold Networks (KANs) with evolutionary game theory, enabling more interpretable and adaptable diagnostic models.

While there is growing interest in integrating game theory into machine learning particularly for cancer diagnosis and data-driven modeling this study specifically focuses on game-theoretic modeling of cancer cell behavior. Therefore, a comprehensive review of game theory applications in cancer identification and prediction via machine learning is beyond our scope.

## 11. Conclusions and Future Work

Game theory has been applied across a wide range of disciplines [155], [156]. This comprehensive review highlights the transformative potential of game theory, particularly evolutionary game theory, in advancing our understanding of cancer progression and treatment design. By modeling the strategic interactions among cancerous and non-cancerous cells, researchers have been able to simulate phenotypic competition, treatment-induced selection, and microenvironmental adaptation. These frameworks have yielded valuable insights into tumor heterogeneity, therapy resistance, and dynamic treatment optimization.

Despite the promising alignment with real-world cellular behavior, evolutionary game theory models face several challenges. One significant limitation is the comprehensive understanding required of all phenotypes and their interactions. As the number of phenotypes increases, the likelihood of achieving a stable state within the population diminishes. Additionally, many models simplify the payoffs for phenotype interactions, treating them as static and straightforward. However, in the dynamic environment of tumors, the payoffs are typically non-static and time-dependent. Moreover, not all cells experience the same payoffs in their interactions with other cells. Local effects and spatial considerations play

crucial roles in these interactions. The structure, texture, and type of cellular interactions significantly influence cellular fitness.

Another limitation of game theory models in cancer evolution is their single-scale focus. While this approach can be applied at various levels within the cell, between cells, and at the tissue level most models tend to examine only one of these levels at a time.

To address these gaps, future research should advance toward developing dynamic payoff structures that respond in real time to treatment effects, cellular adaptation processes, and environmental fluctuations. Enhancing spatial fidelity through agent-based modeling is equally crucial, allowing researchers to capture local cellular interactions, niche construction mechanisms, and diffusion dynamics within the tumor microenvironment. A comprehensive understanding of cancer progression further demands multiscale integration, where models connect intracellular signaling pathways with intercellular evolutionary games and tissue-level growth patterns. Moreover, incorporating both epigenetic and non-genetic sources of heterogeneity will be essential, as they underpin cancer cells' ability to switch strategies and evade therapy. Finally, grounding theoretical models in biological reality calls for robust empirical validation pipelines leveraging transcriptomic profiles, histological analyses, and medical imaging to tailor simulations to individual patient landscapes.

Promising new directions include hybrid frameworks that integrate game-theoretic logic with machine learning, real-time adaptation algorithms for personalized therapy scheduling, and spatial inference techniques using single time-point imaging to deduce strategic cell interactions.

In closing, the application of game theory to cancer research has matured from abstract modeling to biologically and clinically grounded frameworks. Overcoming existing limitations and extending model sophistication will be critical in designing adaptive, patient-tailored therapies ultimately moving from theoretical insight to therapeutic impact.

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