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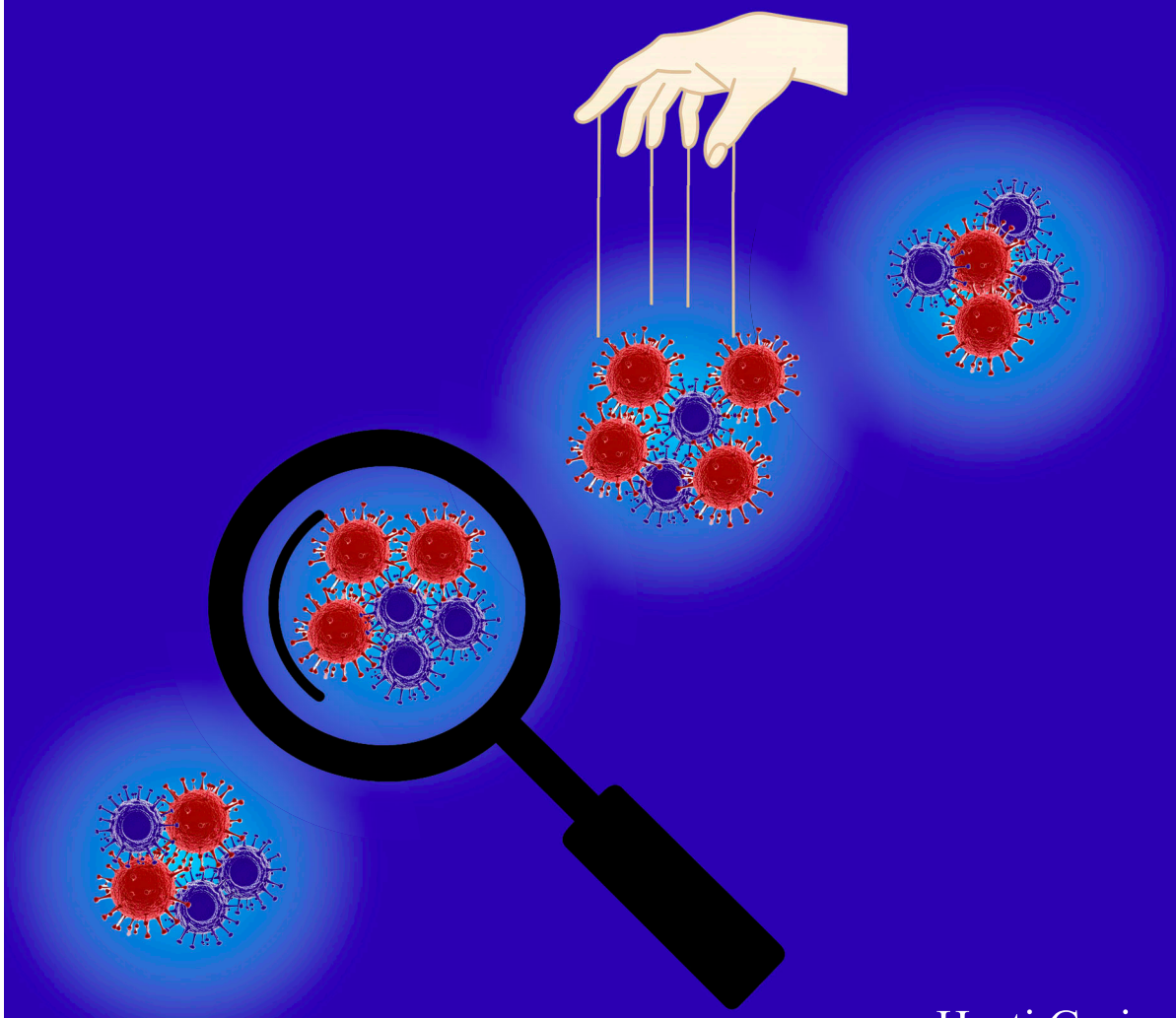

Hasti Garjani

Game Theory and Cancer: Modeling Cancer Dynamics and Optimizing Treatments

GAME THEORY AND CANCER: MODELING CANCER DYNAMICS AND OPTIMIZING TREATMENTS

Dissertation

for the purpose of obtaining the degree of doctor
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by

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CONTENTS

SUMMARY

Stackelberg Evolutionary Game (SEG) theory frames interactions between a rational leader and evolving followers, who play an evolutionary game among themselves. This framework has applications in managing evolving populations, including fisheries management, pest control, and cancer treatment. To manage an evolving system in question, in the standard practice, the leader usually adopts a constant aggressive strategy, with the aim to either preserve (e.g., fisheries management) or eradicate (e.g., pest control) the evolving system. However, adopting an aggressive constant strategy ignores the evolving nature of the population in question.

In this thesis, we identify leader's Nash and Stackelberg strategies in the game, assuming that the evolutionary followers have reached their eco-evolutionary equilibrium. We show that the constant aggressive strategy yields the least favorable outcome for the leader compared to the Nash and Stackelberg strategies. Furthermore, we show that the Stackelberg strategy consistently provides equal or better outcomes for the leader compared to the Nash strategy, as measured by the value of the leader's objective function.

We further explore the SEG framework in cancer treatment, where the followers are treatment-sensitive and treatment-resistant cancer cell populations. The resistant population develops treatment-induced resistance as a quantitative trait. We investigate how a physician as the leader can optimize treatment strategies to maximize patient's quality of life by anticipating the cancer cells' treatment-induced response. Three treatment strategies are compared: maximum tolerable dose (MTD), which is commonly used as the standard of care; the Nash strategy; and the Stackelberg strategy. The physician uses the Nash strategy when they take the cancer cells' ecological equilibrium point into account. However, the physician uses the Stackelberg strategy when they take the eco-evolutionary response of cancer cells into account. Our results demonstrate that the Stackelberg strategy achieves the best outcomes, including reduced treatment-induced resistance, lower drug dosage, and improved patient's quality of life. We show that the quality of life achieved with the Stackelberg strategy is at least as high as that of the Nash strategy, which typically outperforms the MTD approach.

The best strategy for the leader will depend on our understanding of the underlying eco-evolutionary dynamics of the evolutionary followers. To understand what the best evolutionary game for modeling cancer under treatment is, we fit various models to non-small cell lung cancer (NSCLC) *in-vitro* data analyzed earlier by *Kaznatcheev et al.* and *Soboleva et al.*. These experiments measure cell counts of Alectinib-sensitive and Alectinib-resistant cancer cells in environments with and without Alectinib and the presence or absence of cancer-associated fibroblasts (CAFs). We compare logistic, Gompertz, and von Bertalanffy growth models, along with Norton-Simon, linear, and ratio-dependent treatment efficacy terms. We also examine how Alectinib and CAFs influence model parameters and, subsequently, the interactions between cancer cells. For monoculture data, our results indicate that the logistic model with ratio-dependent treatment

efficacy provides the best fit. We derive inter-type competition coefficients for co-culture data using growth rate and carrying capacity estimates from monoculture. Statistical tests reveal that growth rate and carrying capacity parameters remain largely unaffected by the presence of CAFs. However, cell interactions in co-cultures vary significantly across environments due to changes in competition coefficients and drug efficacy. Specifically, we show that CAFs enable the coexistence of sensitive and resistant cells, whereas Alectinib favors the outcompetition of sensitive cells by resistant ones.

This PhD thesis furthers Stackelberg evolutionary games to frame interactions between a rational leader and evolutionary followers. We integrate SEG theory with empirical cancer growth modeling, highlighting the potential of game-theoretic approaches to enhance cancer treatment outcomes. We also discuss the challenges and future opportunities for applying this framework to other domains where managing evolving systems is essential.

SAMENVATTING

Stackelberg Evolutionaire Speltheorie (SEG) wordt gebruikt voor het modelleren van interacties tussen een rationele leider en evoluerende volgers, die een evolutionair spel spelen met elkaar. Dit theoretisch kader heeft toepassingen in het modelleren van evoluerende populaties, bijvoorbeeld visserijmanagement, ongediertebestrijding en de behandeling van kanker. Om een evoluerend systeem te sturen speelt de leider vaak een agressieve rol om het systeem te behouden (visserijmanagement) of uit te roeien (ongediertebestrijding). Deze agressieve rol neemt daarentegen niet de evoluerende eigenschappen van de populatie in rekening.

In deze thesis identificeren we de Nash- en Stackelberg strategieën die de leider kan hanteren in een SEG, ervan uitgaande dat de evolutionaire volgers hun eco-evolutionair evenwicht bereiken. We tonen aan dat een constante agressieve strategie het minst gunstige resultaat oplevert voor de leider in vergelijking met de Nash- en Stackelberg strategieën. Verder bewijzen we dat de Stackelberg-strategie consequent gelijke of betere uitkomsten oplevert voor de leider dan de Nash-strategie, gemeten aan de hand van de waarde van de objectieve functie van de leider.

Daarnaast verkennen we het SEG-kader binnen de behandeling van kanker, waarbij de volgers bestaan uit de behandelingsgevoelige en de behandelingsresistente kankercelpopulaties. De resistente populatie ontwikkelt resistentie in een mate die wordt geïnduceerd door de behandeling. We onderzoeken hoe een arts als leider de behandelingsstrategieën kan optimaliseren om de levenskwaliteit van een patiënt te maximaliseren door te anticiperen op de door de behandeling geïnduceerde respons van de kankercellen. Drie behandelingsstrategieën worden vergeleken: de maximaal getolereerde dosis (MTD), die vaak als standaardzorg wordt gebruikt; de Nash-strategie; en de Stackelbergstrategie. De arts gebruikt de Nash-strategie wanneer hij/zij het ecologische evenwichtspunt van de kankercellen kent. De arts gebruikt echter de Stackelberg-strategie wanneer hij/zij de eco-evolutionaire respons van de kankercellen meeneemt in de behandeling. Onze resultaten tonen aan dat de Stackelberg-strategie de beste uitkomsten oplevert, waaronder een verminderde door de behandeling geïnduceerde resistentie, een lagere medicatiedosering en een verbetering in de levenskwaliteit van de patiënt. We laten zien dat de levenskwaliteit die wordt bereikt met de Stackelberg-strategie minstens even hoog is als die bij de Nash-strategie, die doorgaans weer beter presteert dan de MTD-strategie.

Om een beter inzicht te krijgen in het modelleren van kanker tijdens de behandeling als een evolutionair spel, passen we twee-populatiemodellen toe op data van niet-kleincellige longkanker (NSCLC) uit in-vitro-experimenten gepresenteerd door Kaznatcheev et al. Hier worden de populaties van Alectinib-gevoelige en Alectinib-resistente kankercellen in omgevingen met en zonder Alectinib en met of zonder de aanwezigheid van met kanker-geassocieerde-fibroblasten (CAFs) gemeten. We vergelijken logistische, Gompertz- en von Bertalanffy-groeimodellen, samen met Norton-Simon-, lineaire en verhouding-afhankelijke behandelresultaat termen. We onderzoeken daarnaast hoe

Alectinib en CAFs invloed hebben op de modelparameters en op de interacties tussen kankercellen.

Voor monocultuurdata geven onze resultaten aan dat het logistieke model met ratio-afhankelijke behandelresultaten de beste fit biedt. We leiden intertype- competitiecoëfficiënten af voor co-cultuurdata door gebruik te maken van groeisnelheid- en draagkrachtinschattingen uit de monoculturen. Statistische tests tonen aan dat de groeisnelheid- en draagkracht-parameters grotendeels onaangetast blijven door de aanwezigheid van CAFs. De interacties tussen cellen in co-culturen variëren daarentegen echter sterk tussen omgevingen, dit is het gevolg van veranderingen in competitiecoëfficiënten en de effectiviteit van het medicijn. Specifiek tonen we aan dat CAFs het gelijktijdig bestaan van gevoelige en resistente cellen mogelijk maken, terwijl Alectinib de verdringing van gevoelige cellen door resistente cellen bevordert.

In deze PhD thesis worden Stackelberg evolutionaire spellen verder ontwikkeld om interacties te kaderen tussen een rationele leider en evolutionaire volgers. We integreren SEG-theorie met empirische modellen van kankergroei en benadrukken het potentieel van een speltheoretische benaderingen om behandeluitkomsten bij kanker te verbeteren. We bespreken ook de uitdagingen en toekomstige mogelijkheden voor het toepassen van dit kader in andere domeinen waarin het beheer van evoluerende systemen essentieel is.

1

INTRODUCTION

1.1. RESEARCH MOTIVATION

Cancer is one of the leading causes of mortality and is expected to become increasingly common as life expectancy increases (Shah et al., 2024). Chemotherapy, either combined with surgery, laser therapy, and immunotherapy or as an independent treatment, is one of the most frequently administered therapies for cancer. Therefore, it is essential to enhance the efficacy of chemotherapy drugs. Studies demonstrate that cancer cells can develop drug resistance, leading to treatment failure, especially in metastatic cancers (Dong et al., 2019; Gottesman et al., 2002). Numerous studies indicate that previous treatment strategies focused on eliminating the maximum quantity of cancer cells as fast as possible with the maximum tolerable drug dosage require reevaluation (Gad, 2014; Gatenby, Silva, et al., 2009; Takimoto, 2009).

Mathematical models can offer insights and solutions to the aforementioned challenges regarding the effect of maximum tolerable dose and resistance to drugs by forecasting the behavior of cancer cells over time, both in the presence and absence of drugs. Extensive research has been conducted to identify representative dynamics through the application of ODE and PDE models (Page and Nowak, 2002). Insights from population dynamics, such as density dependence suggesting an asymptotic state in population growth (Pearl and Reed, 1920; Solomon, 1958), have contributed to the development of more biologically informed cancer growth models. Furthermore, the concept of frequency dependence from evolutionary game theory (Maynard Smith, 1982), which considers the influence of the ratios of various population types, has enhanced these models.

Evolutionary games represent a category of mathematical models capable of reflecting the evolving nature of cancer cell behavior (Gatenby, Brown, and Vincent, 2009; Gatenby and Vincent, 2003). We consider a well-mixed population and homogeneity in the population; however, (Gallaher et al., 2018; You et al., 2017) show that spatial properties could also be important.

Researchers employ evolutionary games to model the interactions between drug-sensitive and drug-resistant cells, proposing treatment strategies that maximize the elim-

ination of cancer cells while minimizing the development of a fully resistant population. A recent effort incorporates resistance as a variable in the mathematical model and uses Darwinian dynamics to model the resistance (Pressley et al., 2021; Vincent and Brown, 2012). A representative model forecasts the response of cancer cells to drugs and provides the opportunity to develop optimized model-based therapies.

Recognizing the necessity for better treatment strategies, Staňková et al. (2019) conceptualized the treatment as a leader-follower (Stackelberg) game. Current treatment methodologies primarily rely on the assessment of the cancer's condition at the time of the treatment. This deprives the physician of the opportunity to tailor treatment according to the disease's response to medication. Identifying an evolutionary game that accurately reflects cancer cell behavior, and framing treatment procedure as a Stackelberg evolutionary game, requires additional exploration to realize the potential of this methodology.

1.2. PROJECT OBJECTIVE AND RESEARCH QUESTIONS

Considering the importance of managing drug resistance in cancer treatment, we develop the Stackelberg evolutionary game framework. We employ Darwinian dynamics as the evolutionary game where we have a fitness-generating function that accounts for populations and their strategies. We examine the leader's Nash and Stackelberg strategies and compare them to the naive strategy. Furthermore, we analyze the applications of this game and its potential for managing evolving systems. In the application of cancer treatment, cancer cells use resistance as their strategy, while the physician's strategy is the drug dose. Furthermore, we estimate the parameters of an evolutionary game theory model using *in-vitro* dataset of non-small cell lung cancer. Our research investigates the following questions:

1. **How can we use Stackelberg evolutionary games for managing evolving systems, and what are the applications?**

   Human intervention imposes selective pressures that drive evolutionary changes. Harvesting large fish reduces their average size, pests develop pesticide resistance, and cancer cells become resistant to drugs. Yet, aggressive confrontation remains a commonly used, naive strategy. We model populations' growth and strategy variations using evolutionary games. The Stackelberg evolutionary game framework introduces a rational leader who strategically guides eco-evolutionary dynamics for better outcomes. By comparing Nash and Stackelberg equilibria, we demonstrate that the latter consistently leads to superior outcomes, and both are superior to the naive strategy.

2. **What treatment approach should a physician select if cancer can be stabilized?**

   Studies show that in many metastatic cancer cases complete tumor eradication is unachievable. In these cases, tumor containment and managing cancer as a chronic condition is beneficial. We present an evolutionary game theory model for cancer involving two population types and a resistance trait. Furthermore, we determine the Nash and Stackelberg equilibria of the Stackelberg evolutionary game. In this context, the physician acts as a leader, seeking solutions that increase the

patients' quality of life instead of just applying the maximum tolerable dosage of medication, which is the standard therapeutic method.

3. **Which evolutionary game represents the interactions between drug-sensitive and drug-resistant cancer cell populations across different microenvironments?**

   Population models usually assume some structural properties, including growth dynamics and drug efficacy. Logistic, Gompertz, and von Bertalanffy growth models are thoroughly analyzed in the literature. Norton-Simon, linear, and ratio-dependent models are additionally introduced for the modeling of drug efficacy. We determine the suitable structure and estimate parameters of the evolutionary game for the non-small cell lung cancer data derived from an *in-vitro* experiment. We investigate how interactions among cancer cells change as their microenvironment varies.

1.3. CHAPTERS OVERVIEW

Chapter 2 presents an introduction to game theory and the necessary preliminaries for this research. In Chapter 3, we present mathematical formulations of evolutionary games with Darwinian dynamics and investigate how they can be managed. We also present three applications that can be described through Darwinian dynamics. This chapter contains the results from the first published article (Stein et al., 2023). In Chapter 4, we model cancer proliferation and its response to therapy as an evolutionary game between two cell types, one of which can evolve resistance as a quantitative trait. In this game, the dynamic variables are the fully treatment-sensitive cancer cell population, the treatment-resistant cell population, and an evolving resistance trait. Additionally, the physician is the leader in a Stackelberg evolutionary game who maximizes the patient's quality of life. This chapter presents the results from my second published article (Salvioli, Garjani, et al., 2024). In Chapter 5, we investigate the representability of evolutionary games by fitting various evolutionary game models to a dataset derived from an *in-vitro* experiment on non-small cell lung cancer. Furthermore, we analyze structural properties such as growth dynamics and drug efficacy. We also estimate model parameters and investigate how different microenvironments change the game between cancer cells. This chapter presents results that were first made available on BioRxiv (Garjani et al., 2025) and are currently under revision for publication in PLOS ONE. In Chapter 6, we present the conclusions of this research and the prospects of this work.

2

BACKGROUND AND FUNDAMENTALS

2.1. GAME THEORY

We typically use mathematical optimization when a single decision-maker has a specific objective or when a centralized problem formulation considers the objectives of every individual involved. In contrast, Game Theory examines scenarios - known as games - involving multiple interacting decision-makers (referred to as players in game-theoretic terminology) (Intriligator, 1971), where each individual's outcome depends not only on their own actions or traits but also on those of others. Von Neumann's paper on the minimax theorem for two-player zero-sum games laid the mathematical foundations of game theory (von Neumann, 1928), which were later formalized and expanded by von Neumann and Morgenstern in their seminal book "Theory of Games and Economic Behavior" (von Neumann and Morgenstern, 1944).

Games can be classified according to several attributes, such as the number and type of players, the game form, the information structure and its availability, the nature of interactions among players, and the form of their payoff functions. In this chapter, we also present the Nash and Stackelberg solution concepts of a game, which differ in their degree of game symmetry arising from the extent of information shared among players.

2.1.1. ELEMENTS OF A CLASSIC GAME

A classic game involves two or more decision-makers whose actions influence not only their own outcomes but also those of others. Such interactions are typically represented in normal form, where each player's available actions and associated payoffs are listed explicitly:

- Players:
  Decision makers participating in the game.
- Strategies:

Actions (or plans of action) that players choose rationally to maximize their own benefit.

- Payoffs:
  Quantitative outcomes (benefits or costs) that each player receives as a result of the chosen combination of strategies. A player's payoff generally depends on both their own strategy and the strategies chosen by others.

One of the simplest forms of a game is a two-player bi-matrix game, where each player has a discrete set of strategies and receives a discrete payoff. A typical representation is shown below.

		Player 2	
		C	D
Player 1	A	x_1, y_1	x_2, y_2
	B	x_3, y_3	x_4, y_4

In this two-player matrix game, Player 1 chooses between strategies A and B, and Player 2 between C and D. Each cell of the matrix corresponds to a pair of payoffs (x_i, y_i), representing the outcomes for Players 1 and 2, respectively. For instance, if Player 1 selects B and Player 2 selects D, the resulting payoffs are (x_4, y_4).

2.1.2. EVOLUTIONARY GAMES

Evolutionary game theory (EGT) extends non-cooperative game theory to explain how strategic interactions shape the evolution of traits within populations. It provides a framework for studying how the frequencies of different strategies - interpretable as genetic, phenotypic, or behavioral traits - change over time under selection pressures (Grodwohl and Parker, 2023; Maynard Smith, 1982). Rooted in the principles of non-cooperative game theory developed for rational decision-makers (von Neumann and Morgenstern, 1944), EGT replaces rational optimization with natural selection, where the success of a strategy is determined by its reproductive success, known also as fitness (Maynard Smith, 1982). This shift led to the concept of an evolutionarily stable strategy (ESS), a strategy that, when adopted by a population, cannot be invaded by strategies of rare mutants (Maynard Smith, 1974; Maynard Smith and Price, 1973).

In the standard EGT framework, the players are individual members of a population (or subpopulations) that interact according to fixed behavioral strategies. The state of the population is described by the relative frequencies of these strategies, which evolve over time as more successful strategies - those conferring higher fitness - become more common. When interactions occur randomly in a large, well-mixed population, the game can be represented by a symmetric payoff matrix.

	Population type 1	Population type 2
Population type 1	a, a	a', b'
Population type 2	b', a'	b, b

In this two-type example, individuals of type 1 interacting with type 2 receive a payoff of a', while type 2 individuals receive b'. In evolutionary games, such payoffs are interpreted as measures of reproductive success, which are fitness values determining how the frequencies of strategies change over time.

Subsequent research generalized these ideas to continuous population dynamics. Building on Maynard Smith's ESS concept, Taylor and Jonker introduced the replicator equation, linking ESS conditions to asymptotically stable equilibria of the corresponding dynamical system (Taylor and Jonker, 1978). Hofbauer and Sigmund later provided a comprehensive analysis of replicator and other evolutionary dynamics, elucidating their stability properties and long-term behavior (Hofbauer and Sigmund, 2003).

2.1.3. NASH STRATEGY

In a non-cooperative game with rational players, a Nash strategy refers to the strategy chosen by an individual player as part of a Nash equilibrium. A Nash equilibrium is a combination of strategies, one for each player, such that no player can increase their payoff by unilaterally changing their own strategy while the others keep theirs fixed. Each player's Nash strategy is therefore their best response to the Nash equilibrium strategies of all other players.

Nash's work on non-cooperative games (Nash, 1951), Harsanyi's analysis of games with incomplete information, and Selten's contributions to economic applications led to major breakthroughs in game theory during the 1950s (Erickson, 2015). The applications of non-cooperative games in social sciences, political sciences, and economics have since driven further developments in the field.

A Nash equilibrium thus represents a stable outcome of strategic interaction among rational decision-makers, where each player optimizes their payoff given the choices of others, and no one can benefit from deviating alone.

2.1.4. STACKELBERG STRATEGY

The Stackelberg strategy is named after Heinrich von Stackelberg, an economist, who first analyzed games involving asymmetric decision-makers (von Stackelberg, 1934). In his book published in 1934, "Marktform und Gleichgewicht" (von Stackelberg, 1934), he extended the classical Cournot duopoly model - originally a symmetric game, meaning that both firms have identical strategy sets and payoff structures and move simultaneously - to study situations with asymmetry between players (Hicks and von Stackelberg, 1935).

Stackelberg distinguished three possible cases: (1) The Cournot solution, in which each producer assumes the other's output is fixed and convergence occurs iteratively; (2) the asymmetric, or Stackelberg, solution, in which one producer (the leader) anticipates the other's (the follower's) reaction and optimizes strategically; and (3) the simultaneous Cournot case, in which both producers act as if the other's choice were fixed from the outset. Besides the descriptive definitions, Stackelberg also presented arithmetic, algebraic, and geometric analyses of equilibrium behavior (Hicks and von Stackelberg, 1935).

Initially, the Stackelberg framework was applied mainly to static models of market competition (Intriligator, 1971; von Stackelberg, 1934). Since the 1970s, the concept has

been generalized to dynamic settings and applied across many fields, including engineering and biology (Başar and Olsder, 1999; Caruso et al., 2019; Simaan and Cruz, 1973).

In a two-player Stackelberg game, one player acts as the leader and the other as the follower. The leader commits to a strategy first, anticipating how the follower will respond. The follower, upon observing or being affected by the leader's choice, selects the best response that maximizes their own payoff given the leader's decision. The leader, in turn, chooses a strategy that maximizes their own payoff, taking into account the follower's best-response behavior. Importantly, the Stackelberg formulation reflects a hierarchy of information or commitment rather than a strict sequence in time. The leader is assumed to commit to a strategy in the sense that the follower optimizes given this fixed choice, but this commitment need not correspond to a physical order of moves. Even if both players act simultaneously, the player capable of anticipating the other's best response effectively plays the role of the leader. The resulting Stackelberg equilibrium is therefore a pair of strategies in which the follower's choice maximizes their payoff given the leader's decision, and the leader's choice maximizes their payoff given the follower's best-response behavior.

Alternative formulations of the Stackelberg equilibrium appear in the literature. As summarized by Rasmusen (Rasmusen, 2007), the term may refer to (1) equilibria in sequential extensive-form games where players act in order; (2) games in which one participant moves first; or (3) strategies chosen sequentially, where each player selects the optimal response to the already-chosen actions of earlier movers and anticipates the likely responses of later ones. Here, we adopt the definition of the Stackelberg equilibrium proposed by Simaan and Cruz (Simaan and Cruz, 1973) and summarized in the book by Başar and Olsder (Başar and Olsder, 1999), which provides the basis for our subsequent analysis.

2.1.5. APPLICATIONS OF GAME THEORY IN CANCER MODELING

Efforts to mathematically model the behavior of cancer cells and predict their responses to treatments such as chemotherapy date back several decades (Aroesty et al., 1973). Early tumor growth models described tumor expansion using exponential and Gompertz functions in terms of tumor weight or volume. Laird (1965) demonstrated that the Gompertz growth model accurately represents tumor weight growth in mice, rats, and rabbits. Others have compared different growth laws for modeling tumor volume dynamics, including exponential, logistic, and von Bertalanffy models (Ghaffari Laleh et al., 2022; Marušic et al., 1994; Murphy et al., 2016).

More recent research has shown that cancer cell heterogeneity is a key factor that must be considered when modeling tumor behavior (Marusyk et al., 2014; Zhang et al., 2014). Researchers have investigated differences among cancer cell subpopulations and how heterogeneity influences treatment outcomes (Gallaher et al., 2018; Greene et al., 2015; Guo et al., 2023). Insights from population ecology have also shaped cancer modeling approaches, for instance, through the use of density-dependent growth terms that capture competition for limited resources. Odum (1971) associated the carrying capacity with the asymptote of the logistic curve (Chapman and Byron, 2018).

To better understand the complex ecological and evolutionary interactions among cancer cells, researchers began to employ game theory (Grodwohl and Parker, 2023).

Evolutionary game theory, introduced by Maynard Smith and Price (1973), accounts for frequency-dependent selection in populations containing multiple interacting types. This framework soon became influential in cancer research and has been applied to the analysis of tumor cell dynamics and treatment responses (Gatenby and Vincent, 2003; Pressley et al., 2021; Wölfl et al., 2022).

Further extensions of evolutionary game theory have incorporated continuous strategies and Darwinian dynamics to capture gradual evolutionary adaptation. Brown and Vincent (1987) and Vincent and Brown (2012) developed theoretical foundations for such continuous-strategy evolutionary games, in which populations evolve toward states of higher fitness within their ecological environment. Gatenby, Brown, and Vincent (2009), Gatenby and Vincent (2003), and Vincent and Gatenby (2005) applied these frameworks to model cancer cell interactions and evolutionary dynamics under treatment.

2.1.6. STACKELBERG GAMES FOR DESIGNING TREATMENT

Besides modeling the behavior of cancer cells, game theory is also valuable in the formulation of treatment strategies (Wölfl et al., 2022; Zhang et al., 2017). Chen and Cruz (1972) extended the static economic competition to the case of dynamic games, in which the information structure is asymmetric, giving one player an informational advantage over the other. In such games, the strategies and the state of the system can change over time and influence the objective function (Chen & Cruz, 1972; Simaan & Cruz, 1973). Since then, researchers developed and applied the Stackelberg game theory in various contexts (Başar and Srikant, 2002; Moon and Başar, 2018; Zheng et al., 1984).

More recently, several studies have proposed using the Stackelberg framework to design cancer treatments (Salvioli, Garjani, et al., 2024; Staňková et al., 2019; Stein et al., 2023; Wölfl et al., 2022). In this approach, referred to as the Stackelberg evolutionary game (SEG), the evolving cancer cell populations engage in an evolutionary game, while the physician acts as a rational leader who anticipates their evolutionary response and adjusts treatment accordingly. The physician aims to steer the tumor's eco-evolutionary dynamics toward a desired outcome, such as minimizing tumor burden or maximizing patient quality of life, by exploiting the leader-follower hierarchy formalized in Stackelberg game theory. This concept is now being extended to managing complex Darwinian systems involving vector-valued strategies and life-history traits (Kleshnina et al., 2023).

2.2. PRELIMINARIES

In this section, we illustrate the key game-theoretic concepts introduced above through a representative mathematical example. This example illustrates how the concepts of best response, Nash equilibrium, and Stackelberg equilibrium are derived and interpreted. The focus here is on building intuition rather than providing complete mathematical derivations. Furthermore, we outline preliminary information regarding the model and framework employed in this research.

2.2.1. A TWO-PLAYER NON-COOPERATIVE GAME WITH CONTINUOUS STRATEGIES

In the third and fourth chapters of this thesis, we consider a game that is essentially a generalization of the following example. Assume two players F as the follower and L as the leader with strategies u_F and u_L, respectively. The strategies $u_F \in \mathbb{R}$ and $u_L \in \mathbb{R}$ are continuous in the sense that they can take infinitely many possible values, rather than being limited to discrete choices. This type of game is introduced and discussed as a continuous-kernel or an infinite game (Başar & Olsder, 1999).

We first consider the simultaneous-move situation where each player may know both payoff functions and the other's strategy set, but they choose their strategies simultaneously and do not observe the other's choice at the time of decision. Let the follower and leader choose $u_F, u_L \in \mathbb{R}$. The payoff functions are given by $J_F(u_F, u_L)$ in equation 2.1 and $J_L(u_F, u_L)$ in equation 2.2:

$$J_F(u_F, u_L) = 10 - 2(u_L - 2)^2 - 3(u_F - 1)^2 - 2u_L u_F, \tag{2.1}$$

$$J_L(u_F, u_L) = 10 - 2u_L^2 - 3u_F^2 + u_L u_F. \tag{2.2}$$

The best response of each player is a curve that maximizes the payoff of that player for any strategy of the other player, as follows:

$$u_F^*(u_L) = \arg\max_{u_F} J_F(u_F, u_L),$$

$$u_L^*(u_F) = \arg\max_{u_L} J_L(u_F, u_L).$$

Here, the payoff function of each player is smooth and concave with respect to the player's strategy. The best response of each player is the strategy that maximizes that player's payoff for any given strategy of the other player. In general, this best-response function can take different forms depending on the structure of the payoff functions. In this example, because both payoff functions are quadratic and concave with respect to each player's own strategy, the best responses are linear functions that can be obtained by setting the partial derivative of each payoff with respect to that player's own strategy to zero (holding the opponent's strategy fixed):

$$u_F^*(u_L) = \frac{6 - 2u_L}{6}, \quad u_L^*(u_F) = \frac{u_F}{4}.$$

In this quadratic example the best responses are linear and intersect in a single point, which is the Nash equilibrium: $(u_F^N, u_L^N) = \left(\frac{12}{13}, \frac{3}{13}\right)$.

Now assume that player L (the leader) anticipates player F's best-response function $u_F^*(u_L) = \frac{6-2u_L}{6}$. The Stackelberg solution is obtained by maximizing the leader's payoff subject to this response,

$$u_L^S = \arg\max_{u_L} J_L(u_F^*(u_L), u_L).$$

The Stackelberg solution here is $(u_F^S, u_L^S) = (\frac{13}{16}, \frac{9}{16})$. In this quadratic example, the leader's payoff at the Stackelberg solution is $J_L(u_F^S, u_L^S) = 7.8$, which exceeds its payoff at the Nash equilibrium $J_L(u_F^N, u_L^N) = 7.5$. In general, however, this advantage is not guaranteed. The leader guarantees Nash or better payoffs when the follower's best response

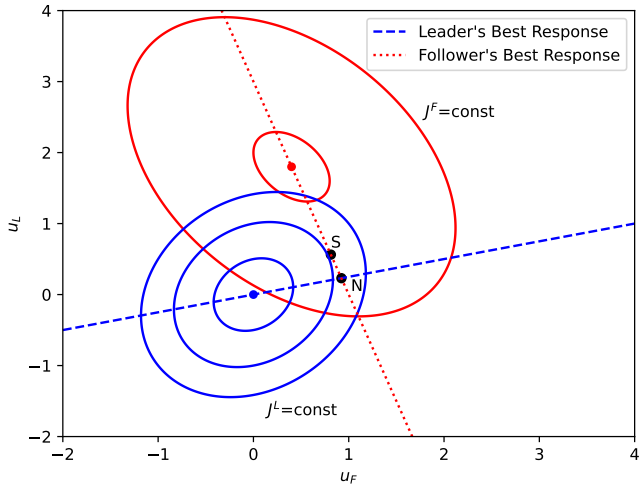

Figure 2.1: Level curves of the objective functions of player L (leader) and Player F (follower) are illustrated in blue and red solid lines, respectively. The best response lines of player L and F are illustrated in dashed blue line ($u_L^*(u_F) = \frac{u_F}{4}$) and dotted red line ($u_F^*(u_L) = \frac{6-2u_L}{6}$), respectively. Point N, which illustrates the Nash solution, lies at the intersection of the best responses. Point S illustrates the Stackelberg solution and lies on the tangent of the best response line of the follower and one of the leader's level curves.

to a fixed action of the leader is single-valued (especially at u_L^N), action sets are compact/convex, and payoffs are continuous, with J_F strictly concave in u_F; then choosing u_L^N reproduces Nash, and optimizing cannot do worse (Başar & Olsder, 1999; Simaan & Cruz, 1973). In this quadratic example, the follower's payoff at the Stackelberg solution is $J_F(u_F^S, u_L^S) = 4.8$, and at the Nash equilibrium $J_F(u_F^N, u_L^N) = 3.2$. Even though the follower receives an advantage in this example, that is not always the case. In figure 2.1, the level curves of both objective functions, the best response curves, the Nash solution, and the Stackelberg solution are illustrated. The Nash equilibrium is the intersection of the two best-response curves (red dotted for F, blue dashed for L). In this quadratic example these curves are lines. The Stackelberg solution lies at the tangency point between a level curve of the leader's payoff (blue) and the follower's best-response curve (red).

2.2.2. DARWINIAN DYNAMICS

Darwinian dynamics describe how populations and heritable traits change over time under selection. Following the fitness-generating function (G-function) framework (Brown and Vincent, 1987; Vincent and Brown, 2012), let

$$G(v, \mathbf{u}, \mathbf{x})$$

denote the per-capita growth rate (fitness) of a rare focal type expressing trait value v in an environment determined by the resident traits $\mathbf{u}$ and resident abundances $\mathbf{x}$. Evaluating at the resident trait $v = u_i$ gives the ecological growth rate of resident type i.

The coupled eco-evolutionary dynamics for two resident types (extensions are analogous) are

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = x_i\, G(v,\mathbf{u},\mathbf{x})\Big|_{v=u_i}, \qquad i=1,2, \tag{2.3}$$

$$\frac{\mathrm{d}u_i}{\mathrm{d}t} = \sigma\, \frac{\partial G(v,\mathbf{u},\mathbf{x})}{\partial v}\Big|_{v=u_i}, \qquad i=1,2. \tag{2.4}$$

Here $\mathbf{u} = (u_1,u_2)^\top$ and $\mathbf{x} = (x_1,x_2)^\top$. The parameter $\sigma > 0$ scales evolutionary change and can be interpreted as a measure of heritability and additive genetic variance (Vincent and Brown, 2012). Equation (2.3) captures ecological dynamics (abundance change driven by current fitness), whereas (2.4) states that traits move along the local selection gradient (the fitness derivative with respect to the expressed trait).

An ecological equilibrium satisfies $G(u_i,\mathbf{u},\mathbf{x}) = 0$ for all resident types i. An evolutionary singular point satisfies $\frac{\partial G}{\partial v}|_{v=u_i} = 0$ for all i. Local evolutionary stability (ESS in this gradient setting) requires a negative second derivative with respect to v (fitness decreases for nearby mutants), while convergence stability requires that the selection gradient points toward the singular point under the induced ecological feedback (Vincent and Brown, 2012). We refer the reader to the cited sources for full conditions and proofs.

When traits are discrete strategies and abundances are normalized to frequencies, (2.3) reduces to the replicator form with payoffs interpreted as fitness (Hofbauer and Sigmund, 2003; Taylor and Jonker, 1978). Thus the G-function framework recovers classical frequency-dependent selection as a special case while accommodating continuous traits and environmental feedbacks.

2.2.3. STACKELBERG EVOLUTIONARY GAME FOR CANCER TREATMENT

In this thesis, we consider the quality of life of the patient as the physician's objective. The population of cancer cells, their resistance to therapy, and treatment dose influence the physician's objective function, and the physician uses treatment dose u_L as a strategy to maximize this objective. Cancer cells have a fitness-generating function $G(v,\mathbf{u},\mathbf{x},u_L)$ and their abundances and resistance traits evolve according to (2.3)–(2.4); that is, abundances change with current fitness and traits move along the local selection gradient. The physician anticipates these eco-evolutionary responses when choosing u_L. Table 2.1 summarizes the players, objectives and strategies of this game between the physician and cancer cells.

Players	**Objective**	**Strategies**
Physician	Quality of life	Treatment dose
Cancer cells	Fitness	Therapy resistance

Table 2.1: Basic elements of a Stackelberg evolutionary game in cancer

3

STACKELBERG EVOLUTIONARY GAME THEORY: HOW TO MANAGE EVOLVING SYSTEMS

Stackelberg Evolutionary Game (SEG) theory combines classical and evolutionary game theory to frame interactions between a rational leader and evolving followers. In some of these interactions, the leader wants to preserve the evolving system (e.g. fisheries management), while in others, they try to drive the system to extinction (e.g. pest control). Often the worst strategy for the leader is to adopt a constant aggressive strategy (e.g. overfishing in fisheries management or maximum tolerable dose in cancer treatment). Taking into account the ecological dynamics typically leads to better outcomes for the leader and corresponds to the Nash equilibria in game-theoretic terms. However, the leader's most profitable strategy is to anticipate and steer the eco-evolutionary dynamics, leading to the Stackelberg equilibrium of the game. We show how our results have the potential to help in fields where humans try to bring an evolutionary system into the desired outcome, such as, among others, fisheries management, pest management and cancer treatment. Finally, we discuss limitations and opportunities for applying SEGs to improve managing evolving biological systems[1].

3.1. INTRODUCTION

Evolutionary game theory reveals the logic behind adaptations when evolution by natural selection is frequency-dependent (Broom & Rychtář, 2013; Brown, 2016; Hofbauer & Sigmund, 1998). Accordingly, an individual's fitness depends not only on her own trait, but also on the densities of traits in the population. These traits may be simple animal behaviors as suggested by the Prisoner's Dilemma (PD), Hawk-Dove (HD) and Rock-Scissors-Paper games (Broom & Rychtář, 2013; Hofbauer & Sigmund, 1998). The

[1] This chapter is based on previously published work (Stein et al., 2023).

former two games represent social dilemmas where everyone benefits most when all Cooperate (PD) or all play Dove (HD). Yet, the outcome of natural selection in the PD is Defect (unless one adds iterative plays of the game or non-random interactions), and the HD game generally results in the coexistence of the two strategies. The genius behind Maynard Smith and Price (1973) involved their evolutionarily stable strategy (ESS) definition (Maynard Smith & Price, 1973). While Defect in the PD was not a group optimum, it was a strategy which, when common in the population, could not be invaded by any rare alternative strategies. And, while the mixed strategy of the HD game fails the group, it does illustrate what happens when a rare strategy H (or D) can invade a population where D (or H) are common. Neither H nor D are resistant to invasion. The RSP game revealed how the Nash equilibrium (in this case $(1/3, 1/3, 1/3)$) was not attainable if one included strategy dynamics (a key component of evolving systems). An enduring point of the last c. 50 years of evolutionary game theory is that ESSs, while not always attainable, are more often than not the outcome of evolution by natural selection.

Game-theoretic thinking on natural selection precedes 1973. Lewontin (1961) proposed game theory from the perspective of organisms playing against their physical environments (Lewontin, 1961). In some ways a prescient thought, in that life can be seen as entities that game the laws of physics and chemistry, and then go on to evolve further adaptations to game conspecifics, competitors, predators and prey. For instance, Fisherian sex ratios where parents invest essentially equal effort into female and male offspring (most notably the 50:50 sex ratio) follow from game-theoretic logic (Charnov, 1973, 1976). Height in trees is an outcome of evolutionary arms race, and managers in forestry and silviculture consider this when thinning and spacing trees (Falster & Westoby, 2003; Hawkins, 1926; Woodhead, 1934). Similarly, evolutionary game theory provides the logic behind the evolution of radical male adornments across many animal species, Batesian mimicry, cannibalism in flour beetles, as well as the evolution of cooperation and mutualisms. All topics noted as frequency-dependent prior to 1973 (Emlen, 1968; L. T. Evans, 1938; Janzen, 1966; Park et al., 1968).

The outcomes of evolutionary games are driven by natural selection involving both changes to population size (ecological dynamics) and the frequency of heritable traits (evolutionary dynamics). Not necessarily so for games involving humans. First, humans are rational and can base their decisions on a variety of goals that do not necessarily involve life and death (Başar & Olsder, 1999; Maschler et al., 2020). Second, payoffs can involve diverse tangibles and intangibles such as monetary profit, utility, pleasure or aesthetics (von Neumann & Morgenstern, 1944). Despite differences in the ways humans and nature plays games, they do come together as bio-economic or bio-sociologic games, in which the actions of humans influence the eco-evolutionary dynamics of pest species, pathogens, commercially or recreationally harvested species, and species of conservation interest. One of the first examples of this dates back to King James I of Scotland. It was brought to his attention that the size of cod seemed smaller than before (Davis, 1989). This is an early record of how size-selective harvesting of fish causes notable evolutionary changes in size at first reproduction, fecundity, and other life history traits. Similarly, a scientist from the United States Department of Agriculture noted in the early 1900s how various agricultural pests were evolving resistance to various biocides (Melander, 1914). Starting in the 1950s, it was recognized how various forms of

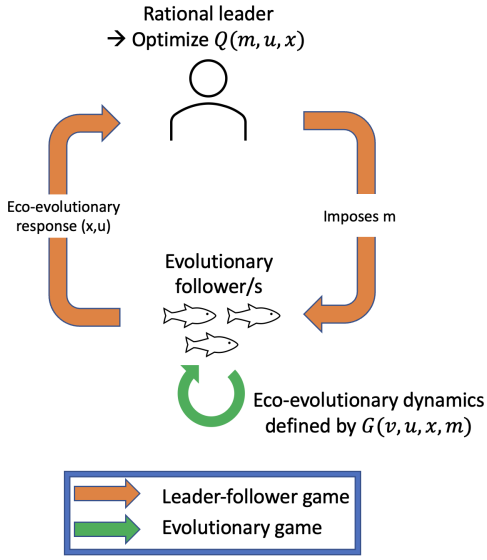

Figure 3.1: Illustration of the Stackelberg evolutionary game. It combines two types of games: (i) the leader-follower (Stackelberg) game between the rational leader and evolutionary followers, and (ii) the evolutionary game between the followers. The Stackelberg strategy of the leader anticipates the eco-evolutionary response (x,u), whereas the Nash strategy anticipates the ecological response x only.

weed control selected for crop ecotypes of weeds that had adjusted their seedling phenology in response to hand weeding, their seed size in response to sorting techniques, and maturation timing to match harvesting regimes (Forgash, 1984; Radosevich et al., 2007). Throw into this antibiotic resistant strains of bacteria (Conlin et al., 2014) and the evolution of therapy resistance within cancer patients (Staňková, 2019), and it is clear that managing evolving species, be they pests, resources, diseases or species of conservation interest, poses unique challenges.

Stackelberg Evolutionary Game Theory (SEG) provides a framework for modelling and managing such evolving systems (Salvioli et al., 2021). Its main idea is straightforward. Humans, as managers, stakeholders, or simply as concerned citizens, take actions that directly or indirectly influence the population sizes (ecological dynamics) and evolutionary characteristics (evolutionary dynamics) of species of interest. The species of interest follow the dictates of natural selection and evolutionary game theory. Based on the manager's actions, there will be changes in the abundance of the species, as well as in their evolutionary traits (Figure 3.1).

Managers and stakeholders can take several approaches. First, they may simply take actions based on the current disposition of the species with respect to the species' abundance and trait values. In this case, simply weed away without forethought of the eventual consequences. Second, they may consider the ecological consequences of their actions, such as aiming to maintain a sustainable stock of fish while ignoring evolutionary consequences. Thirdly, the manager may anticipate and steer both the ecological and evolutionary consequences of various management strategies for the species of interest.

In the first case, the manager is neither ecologically nor evolutionarily enlightened, the second represents an ecologically but not evolutionarily enlightened manager, and the third is both ecologically and evolutionarily enlightened. This third case corresponds to leader's Stackelberg strategy in the SEG game. SEGs are characterized by a rational leader and evolutionary followers playing an evolutionary game among themselves (Salvioli et al., 2021; Staňková et al., 2019; von Stackelberg, 1934). The manager has the potential to leverage their advantages, as they play first in terms of implementing a set of actions and as they are rational. Based on the manager's actions, the evolving species evolve to a new ESS (if it exists), according to their eco-evolutionary dynamics. The opportunity here is to promote choices by humans that are both ecologically and evolutionarily enlightened when dealing with the other denizens of our planet. There is already an existing tradition of using evolutionary game theory to solve such bioeconomic games going back to Law and Grey (1989), when they present the Evolutionarily Optimal Harvest Strategy for managing commercially valuable species, such as fisheries (Law & Grey, 1989). Our goal here is to offer a general framework for SEGs that can be applied broadly. In what follows, we 1) formalize the notation and framework for SEGs and establish the conditions under which the Stackelberg solution (both ecologically and evolutionarily enlightened) is either the same or different and superior to the Nash solution (ecologically but not evolutionarily enlightened), 2) establish conditions under which the actions of the manager may either decrease or increase the strategies that coexist at the ESS, 3) consider applications to fisheries, cancer and pest management. We conclude with a prospectus for what needs to be done regarding the theory and application of SEGs in various domains.

3.2. FORMALIZING THE GAME AMONG EVOLUTIONARY FOLLOWERS

Let $\mathbf{x}(t) = (x_1(t), \dots, x_n(t))^T$ define population sizes of evolutionary followers with types in $\Theta = \{1, \dots, n\}$ at time t. The fitness of a follower of type $i \in \Theta$ may depend on both the densities and traits of all followers and the actions of the leader. Consequently, the ecological dynamics of followers of the i-th type are given by

$$\frac{\mathrm{d}x_i(t)}{\mathrm{d}t} = x_i(t) \cdot H_i(\mathbf{U}(t), \mathbf{x}(t), \mathbf{m}(t)). \tag{3.1}$$

Here, $\mathbf{U}(t) = \left(u_{ij}(t)\right)$ is the trait matrix at time t, where u_{ij} denotes the value of trait $j \in \Theta = \{1, 2, \dots, p\}$ of a follower of type i, and the vector $\mathbf{m}(t) = (m_1(t), \dots, m_q(t))^T$ describes the intensities of the q possible actions of the leader. Finally, $H_i(\mathbf{U}(t), \mathbf{x}(t), \mathbf{m}(t))$ is the *per capita* growth rate of follower of type i at time t. It may give rise to both density and frequency-dependent dynamics, as it depends on $\mathbf{x}$ explicitly.

The evolutionary dynamics may be described through a *fitness generating function*, or G-function (Vincent & Brown, 2012). Such a function describes the fitness $G(\mathbf{v}, \mathbf{U}, \mathbf{x}, \mathbf{m})$ of a single individual of type $\mathbf{v} = (v_1, \dots, v_p)^T$ when the current types, their densities, and the actions of the leader are described by $\mathbf{U}$, $\mathbf{x}$, and $\mathbf{m}$, respectively. In particular, replacing v_j in the G-function with u_{ij} for each $j \in \Theta$ yields the fitness of a follower of type i. Thus,

$$G(\mathbf{v}, \mathbf{U}, \mathbf{x}, \mathbf{m})|_{\mathbf{v}=(u_{i1}, \dots, u_{ip})} = H_i(\mathbf{U}, \mathbf{x}, \mathbf{m}), \tag{3.2}$$

and equation (3.1) may be rewritten as

$$\frac{\mathrm{d}x_i(t)}{\mathrm{d}t} = x_i(t) \cdot G(\mathbf{v}(t), \mathbf{U}(t), \mathbf{x}(t), \mathbf{m}(t))|_{\mathbf{v}(t)=(u_{i1}(t),\ldots,u_{ip}(t))}. \tag{3.3}$$

Followers with a higher *per capita* growth rate will persist in the population. Therefore, the dynamics of trait j of a follower of type i are given as

$$\frac{\mathrm{d}u_{ij}(t)}{\mathrm{d}t} = \sigma_{ij} \frac{\partial G(\mathbf{v}(t), \mathbf{U}(t), \mathbf{x}(t), \mathbf{m}(t))}{\partial v_j(t)}\Big|_{\mathbf{v}(t)=(u_{i1}(t),\ldots,u_{ip}(t))}. \tag{3.4}$$

Here, σ_{ij} defines the evolutionary speed and is a measure of heritability and additive genetic variance, in line with Fisher's fundamental theorem of natural selection (Fisher, 1930; Okasha, 2008). This speed may be influenced by many other factors, like mutation rates, population size, population structure and the underlying genetics of inheritance. In *adaptive dynamics*, σ_{ij} increases linearly with population size, but is stochastic with respect to other variables (canonical equation of adaptive dynamics (Dieckmann & Law, 1996; Geritz et al., 1998; Hastings & Gross, 2012; J. Metz et al., 2016; J. A. Metz et al., 1995)). For the sake of simplicity, when modeling (3.4), it is often assumed that σ_{ij} is the same constant for all i and j, while one could easily imagine that σ_{ij} varies in time and may be a (likely nonlinear) function of $x_i(t)$, as suggested by adaptive dynamics. In the remainder of this paper, we will not write out the time-dependence explicitly. Thus we shall use $\mathbf{U}$, $\mathbf{x}$ and $\mathbf{m}$ instead of $\mathbf{U}(t)$, $\mathbf{x}(t)$ and $\mathbf{m}(t)$, respectively. Equations (3.3) and (3.4) constitute the Darwinian dynamics, describing the eco-evolutionary dynamics of evolutionary followers in response to a vector-valued action $\mathbf{m}$ of the leader.

If the ecological dynamics (3.3) converge to a stable equilibrium $\mathbf{x}^* \geq 0$, we call $\mathbf{x}^*$ an *ecological equilibrium*. Each combination of followers' evolutionary traits and leader's strategies $(\mathbf{U}, \mathbf{m})$ may have an associated vector of stable population sizes $\mathbf{x}^*$, with $\mathbf{x}_i^* \geq 0 \quad \forall i \in \{1, 2, \ldots, n\}$. A generic $\mathbf{U}$ may correspond to no, one or more values of $\mathbf{x}^*$, depending on the G-function. Moreover, even if we assume that the ecological equilibrium exists for any choice of $\mathbf{U}$ and $\mathbf{m}$, only a subset of possible values of $\mathbf{U}$ and $\mathbf{m}$ will correspond to positive equilibrium population sizes, where for other values some types of followers will go extinct (Halloway et al., 2019).

Solved together with left-hand side set to zero, equations (3.3)–(3.4) often determine an eco-evolutionary equilibrium solution, a pair composed of followers' equilibrium population size and trait values, which we will denote by $\mathbf{x}^*(\mathbf{m}, \mathbf{U}^*(\mathbf{m}))$ and $\mathbf{U}^*(\mathbf{m})$. It is also possible that none or only one of the dynamics (3.3)–(3.4) are at equilibria. We will discuss that situation as well.

The non-zero equilibrium values of $x_i^*(\mathbf{m})$ and their associated strategies $(u_{i1}^*(\mathbf{m}), \ldots, u_{ip}^*(\mathbf{m}))$ form a 'coalition' of strategies. If for a particular choice of $\mathbf{m}$, these strategies resist invasion by mutant strategies, they are called Evolutionarily Stable Strategies (ESSs) with respect to action $\mathbf{m}$ (Hofbauer & Sigmund, 1998). A necessary condition for an ESS is that it maximizes G with respect to v_i for those $x_i^*(\mathbf{m})$ that are positive. This implies that the fitness of a mutant strategy is not larger than the fitness at the ESS (Vincent & Brown, 2012). Further stability properties of the ESS can be analyzed (e.g., convergence stability or neighborhood invasion stability (NIS) (Apaloo, 1997; Apaloo et al., 2009); the extension to the matrix evolutionary traits is straightforward).

3.3. FORMALIZING THE STACKELBERG EVOLUTIONARY GAME

Here we will formalize the situation where we include a rational player to the evolutionary game. This additional player (leader) can choose $\mathbf{m}$ in order to optimize their objective, while the followers' eco-evolutionary dynamics are described by (3.3)–(3.4). Since the followers are evolutionary players within the structure of a leader-follower (Stackelberg) game (Başar & Olsder, 1999; Hicks & von Stackelberg, 1935), we call these games *Stackelberg evolutionary games* (SEGs), in accordance with recent research on this topic (Salvioli, 2020; Salvioli, Garjani, et al., 2024; Salvioli et al., 2021; Staňková et al., 2019; Wölfl et al., 2022). The leader, as the only rational player in this SEG, is assumed to be able to anticipate and steer the eco-evolutionary responses of the followers defined by (3.3)–(3.4), while followers can only adapt to the actions already taken by the leader.

We will first briefly discuss the situation when neither ecological nor evolutionary equilibria are achieved (yet) (Section 3.3.1) or when the transient dynamics towards equilibria are considered important. Subsequently, we will focus on the most studied case where the eco-evolutionary equilibria are reached and where the strategies of the leader and followers are scalar-valued (Section 3.3.2).

3.3.1. STACKELBERG EVOLUTIONARY GAME IN TRANSIENT DYNAMICS

We introduce a rational leader selecting a strategy $\mathbf{m}(\cdot) \overset{\text{def}}{=} [\mathbf{m}(t)]_{t\in[0,T]}$, where the eco-evolutionary dynamics of the followers are defined through (3.3)–(3.4). Here $T \in \mathbb{R}^+_\infty = \mathbb{R}^+ \cup \{+\infty\}$ and can also be defined as the first time an ecological and/or evolutionary equilibrium is reached. The objective Q of the leader varies with $\mathbf{m}(\cdot)$, where $\mathbf{U}(\cdot) \overset{\text{def}}{=} \{[\mathbf{U}(t)]_{t\in[0,T]}; \mathbf{U}(0) = \mathbf{U}_0\}$ and $\mathbf{x}(\cdot) \overset{\text{def}}{=} \{[\mathbf{x}(t)]_{t\in[0,T]}; \mathbf{x}(0) = \mathbf{x}_0\}$. In such a situation, the leader's goal is to find the optimal $\mathbf{m}^*(\cdot)$ that maximizes such an objective, i.e., find

$$\mathbf{m}^*(\cdot) = \arg\max_{\mathbf{m}(\cdot)} Q(\mathbf{m}(\cdot), \mathbf{U}(\cdot), \mathbf{x}(\cdot)), \tag{3.5}$$

subject to (3.3)–(3.4) and the initial conditions $\mathbf{U}(0) = \mathbf{U}_0$ and $\mathbf{x}(0) = \mathbf{x}_0$. The problem defined by (3.5) with respect to (3.3)–(3.4) is an optimal control problem. Thus we could utilize open-loop, closed-loop or feedback strategies to solve it (Başar & Olsder, 1999). However, we will focus on the variant of the problem when an ecological equilibrium of the followers have been reached and when the leader's objective depends only on traits and population size at that equilibrium.

3.3.2. SIMPLIFIED VARIANT OF THE PROBLEM

One can consider variants of the problem from Section 3.3.1 where either the ecological dynamics (3.3), the evolutionary dynamics (3.4), or both reach equilibria. The former two cases occur due to time-scale separation of the ecological and evolutionary dynamics (Cortez & Ellner, 2010; Yamamichi et al., 2011), an assumption considered realistic for many eco-evolutionary dynamic systems. When the eco-evolutionary dynamics are very fast or when the transient dynamics are not that important for the problem at hand, one can assume that the eco-evolutionary equilibrium has been reached, while the objective function Q can also depend on the transient dynamics leading to this equilibrium. In such a case, T may be defined as the first time when the eco-evolutionary equilibrium

of (3.3)–(3.4) is reached.

In the next section of this work (Section 3.4), we will analyze the simplest possible version of the problem (3.5) with respect to (3.3)–(3.4). We will assume the following:

A1. As opposed to the vector or matrix-valued dynamics (3.3)–(3.4), the evolutionary and ecological traits of the followers are scalar, and their population is monomorphic, with the eco-evolutionary dynamics defined as

$$\frac{\mathrm{d}x}{\mathrm{d}t} = x \cdot G(v,u,x,m)|_{v=u}, \tag{3.6}$$

$$\frac{\mathrm{d}u}{\mathrm{d}t} = \sigma \frac{\partial G(v,u,x,m)}{\partial v}\Big|_{v=u}. \tag{3.7}$$

A2. The leader searches constant m maximizing $Q(m,u,x)$.

A3. The objective of the leader $Q(m,u,x)$ is differentiable and defined at the ecological equilibrium of the system $x^*(m,u)$.

Given A1-A3, we will consider different assumptions regarding the leader's knowledge of the eco-evolutionary equilibria of (3.6)-(3.7) when optimizing their objective, which will lead to different outcomes of this leader's optimization.

Most of the results we will present in the next section can be extended to the more generic cases when these assumptions are relaxed. When discussing different applications of Stackelberg evolutionary games (Section 3.5), we will consider both the simplest and more generic forms of the game, with followers' eco-evolutionary dynamics defined by (3.3)–(3.4).

3.4. PROPERTIES OF STACKELBERG EVOLUTIONARY GAMES AT ECOLOGICAL EQUILIBRIUM $x^*(m,u)$

3.4.1. EVOLUTIONARY RESPONSE OF FOLLOWERS AT $x^*(m,u)$

Let us assume that for a fixed m and u, the population reaches an equilibrium $x^* = x^*(m,u)$ (ecological equilibrium) where $x^*(m,u)$ is defined by $G(v,u,x^*(m,u),m)|_{v=u} = 0$ when $x^*(m,u)$ is positive. The ESS strategy $u^*(m)$ of the followers in response to the leader's strategy m maximizes G:

$$u^*(m) = \arg\max_v G\left(v,u^*(m),x^*(m,u^*(m)),m\right) \tag{3.8}$$

The $u^*(m)$ represents the best response of the followers, in accordance with the dynamic game theory literature (Başar & Olsder, 1999). While we assume that the followers' evolutionary strategy will reach (3.8) and that the system is at ecological equilibrium $x^*(m,u)$, the leader may or may not consider these pieces of information. That brings us to the possible strategies of the leader.

3.4.2. LEADER'S POSSIBLE STRATEGIES AT $x^*(m,u)$

The leader can be naive, ecologically enlightened, or evolutionary enlightened. There are two possible interpretations of a naive strategy by the leader: (i) either the leader maximizes their objective with respect to m, while not taking eco-evolutionary dynamics into account, or (ii) the leader plays an a priori constant action, which in practice often corresponds to the maximum possible action, in the belief that this is the best possible action to play, not optimizing anything. In this paper, we will assume that these two actions coincide. If the leader takes the ecological dynamics into account, they will maximize $Q(m,u,x^*(m,u))$. As explained in the supplementary information, this eventually leads us to the Nash equilibrium (formally defined below). Finally, if the leader additionally takes the followers' evolutionary dynamics (3.8) into account, they will maximize $Q(m,u^*(m),x^*(m,u^*(m)))$ leading to the Stackelberg equilibrium.

The three possible strategies of the leader can be formalized as follows:

Naive strategy: The leader plays a constant and aggressive strategy $m = m_{\max}$, ignoring followers' ecological and evolutionary dynamics.

Ecologically enlightened strategy corresponding to the Nash strategy: The best response of the manager to the followers is

$$m^*(u) = \arg\max_m Q(m,u,x^*(m,u)), \tag{3.9}$$

the followers respond by their ESS $u^*(m)$ given by (3.8). A Nash equilibrium (m^N,u^N) is defined as a pair of strategies which correspond to best responses of the leader and followers to each other, which is given by an intersection of the curves $m = m^*(u)$ and $u = u^*(m)$. At Nash equilibrium, no player can improve their outcome by unilaterally changing their strategy.

Evolutionarily enlightened leader's strategy corresponding to the Stackelberg strategy: With this strategy, the leader anticipates $u^*(m)$ and $x^*(m,u^*(m))$ and, therefore, can include them both into their objective Q before maximizing it with respect to their action m. The leader's Stackelberg strategy is thus:

$$m^S = \arg\max_m Q(m,u^*(m),x^*(m,u^*(m))) \tag{3.10}$$

In all three cases, we assume that the followers are bound to their ESS strategy $u^*(m)$. At the equilibrium, the evolutionarily enlightened leader can never perform worse than an ecologically enlightened leader. Similarly, the ecologically enlightened leader typically performs better than the naive leader. Of interest is when the Nash and Stackelberg strategies of the leader coincide. The following theorem elucidates that.

Theorem 3.4.1 *If leader's Nash and Stackelberg strategies are characterized by first-order optimality conditions, then they coincide in the following cases:*

a) *If* $\frac{\mathrm{d}u^*(m)}{\mathrm{d}m} = 0$.

b) *If* $\frac{\partial Q}{\partial u}(m, u^*(m), x^*(m, u^*(m))) = 0$ *and, moreover,*

$$\frac{\partial Q}{\partial x}(m, u^*(m), x^*(m, u^*(m))) = 0$$

or

$$\frac{\partial x^*}{\partial u}(m, u^*(m)) = 0.$$

Proof 1 *The first-order optimality condition for the leader's strategy to be a Nash strategy is*

$$\frac{\partial Q}{\partial m} + \frac{\partial Q}{\partial x}\frac{\partial x^*}{\partial m}(m, u^*(m)) = 0, \tag{3.11}$$

while the first-order optimality condition for the leader's strategy to be a Stackelberg strategy is

$$\frac{\partial Q}{\partial m} + \frac{\partial Q}{\partial x}\frac{\partial x^*}{\partial m}(m, u^*(m)) + \frac{\mathrm{d}u^*(m)}{\mathrm{d}m}\left(\frac{\partial Q}{\partial u} + \frac{\partial Q}{\partial x}\frac{\partial x^*}{\partial u}(m, u^*(m))\right) = 0, \tag{3.12}$$

where in both (3.11) *and* (3.12)*, all partial derivatives of* Q *are evaluated at* $(m, u^*(m), x^*(m, u^*(m)))$*. It follows that if conditions a) or b) are satisfied,* (3.11) *and* (3.12) *coincide.*

Remark 3.4.1 Case a) would arise if the leader's strategy does not affect the evolution of the trait (at least for relevant values of m). There is then no loss in not taking this evolution into account, so it suffices for the leader to be ecologically enlightened.

Case b) would arise if the following conditions are satisfied: First, the objective function is independent of u (the leader only cares about the population size and not the trait of the species), so that $\partial Q/\partial u = 0$. Second, competition among followers is purely density-dependent, so that $G(v, u, x, m) = \hat{G}(v, x, m)$, with $\hat{G}$ non-increasing in x. As shown below, this implies that at the eco-evolutionary equilibrium, the partial derivative of x with respect to u cancels: $\frac{\partial x^*}{\partial u}(m, u^*(m)) = 0$, thus conditions b) are met.

To see why this derivative cancels, note that at the eco-evolutionary equilibrium $(u^*(m), x^*(m, u^*(m)))$, the fitness of a mutant trait is no larger than the fitness of the resident. Moreover, at any (positive) ecological equilibrium $x^*(m, u)$, the fitness of trait u is zero. Therefore, for any trait v,

$$G(v, u^*(m), x^*(m, u^*(m)), m) \le G(u^*(m), u^*(m), x^*(m, u^*(m)), m) = 0 = G(v, v, x^*(m, v), m) \tag{3.13}$$

Since $G(v, u, x, m) = \hat{G}(v, x, m)$, it follows that $\hat{G}(v, x^*(m, u^*(m)), m) \le \hat{G}(v, x^*(m, v), m)$. Since $\hat{G}$ is non-increasing in x, this implies that $x^*(m, u^*(m)) \ge x^*(m, v)$. That is, $u^*(m)$ maximizes the population size $x^*(m, u)$. Therefore $\frac{\partial x^*}{\partial u}(m, u^*(m)) = 0$, hence the result.

3.5. APPLICATIONS OF STACKELBERG EVOLUTIONARY GAMES

SEG theory can be used in any situation when a rational party (leader) wants to save, contain or eliminate a biological system responding to the leader's action according to the principles of natural selection. Here we provide examples of research that has framed such interactions through SEGs and highlight opportunities for further applications of game theory to these domains.

3.5.1. FISHERIES MANAGEMENT

In (Salvioli et al., 2021), a SEG between a fisheries manager as a rational leader and a fish stock as evolutionary followers was considered. In this model the leader selects the harvesting rate m and the fish respond by evolving their body size at maturation u to maximize the fitness. The leader aims at maximizing their net profit $Q(m,u,x)$, which is a function of the strategies of the players and the population size of the fish x.

Following (Brown & Parman, 1993), the profit is given by the difference between the value of harvested fish biomass and the cost of fishing, with the harvest coming from two sources: harvesting of adult fish and harvesting of juvenile fish that are larger than the net size, which can be considered as a second decision variable of the manager.

Figure 3.2 compares two management strategies of the fisheries manager: ecologically enlightened (Nash) and evolutionarily enlightened (Stackelberg), showing their impact on the fish size and on the profit of the manager. The Nash equilibrium is reached where the best response curve (ESS) of the fish intersects with that of the manager (Figure 3.2A). At this point the fish are evolutionarily stable (as no individual can increase its fitness by unilaterally changing its size) and ecologically stable (as their expected per capita growth rate is 0 at x^*). For the manager this is a no regret strategy: given the size of the fish, the manager has no incentive to change the harvesting rate m^N. Conversely, the Stackelberg equilibrium is not a point on the manager's best response curve, but a point on the fish ESS curve where profit is maximized (Figure 3.2A).
In practice, the difference between the two management strategies lies in the assumptions. The ecologically enlightened manager recognizes the effects of harvesting on the population size of the fish, but sees the adult size of the fish as fixed, and therefore does not take evolution into account. In order to determine the optimal harvesting rate m^N, this manager considers the effect of m and x^*, but maximizes the profit function Q holding u constant (Figure 3.2B). Conversely, the evolutionarily enlightened manager anticipates that the fish will evolve in response to harvesting, incorporates both the ecological and the evolutionary consequences ($x^*(m,u^*(m))$ and $u^*(m)$) of harvesting into the profit function Q, and selects the harvesting rate m^S that maximizes the profit with this in mind (Figure 3.2B). The profit curve for this management strategy intersects the profit curve for the ecologically enlightened management strategy at its maximum (Nash outcome), meaning that the Nash outcome is achievable for the Stackelberg manager but not vice versa. Overall, with the Nash approach, the manager tends to adopt a high harvesting rate that eventually leads to smaller fish (Figure 3.2A). With the Stackelberg approach, the manager scales back the harvesting rate, which leads to bigger fish size and higher profit.

In (Salvioli et al., 2021), each choice of the fisheries manager (m) corresponded to a unique ESS ($u^*(m)$) of the fish. However, the manager's actions may change not only the exact value of the follower's ESS but also the number of strategies comprising the ESS, possibly due to a speciation event (see also (Landi et al., 2015)). To see how a biological system with multiple ESS can occur and what it means for the leader's best strategies, let us consider another example, with eco-evolutionary dynamics of the fish in the form of (3.6)–(3.7). The eco-evolutionary dynamics are defined through G-function

$$G(v,u,x,m) = r\left(1-\frac{x}{K(v)}\right) - H(v,m), \tag{3.14}$$

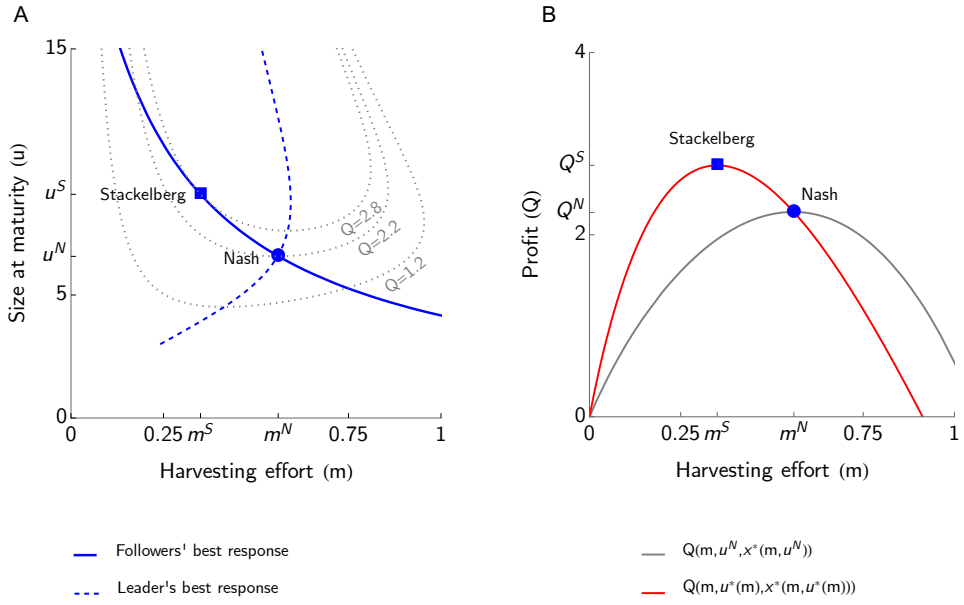

Figure 3.2: **A)** The best response curve (ESS) of the fish (solid line) and the best response curve of the fisheries manager (dotted line). The Nash equilibrium lies at the intersection of the fish's ESS curve and the best response curve of the manager, while the Stackelberg equilibrium lies on the ESS curve of the fish but not on the best response curve of the manager. This is because the latter one is obtained by maximizing the profit over the best response of the followers. With the Stackelberg approach, the manager adopts a lower harvesting effort, which leads to bigger fish size. **B)** The effect of the harvesting effort on the profit for the ecologically enlightened strategy (Nash) and evolutionarily enlightened strategy (Stackelberg). The ecologically enlightened manager considers the size of fish at maturation as fixed ($u = u^N$) and selects the harvesting rate which maximizes the profit with this in mind (grey curve). The evolutionary enlightened manager assumes that the size of fish at maturation is the ESS ($u^*(m)$) and selects a harvesting rate that maximizes the profit accordingly (red curve). The evolutionarily enlightened approach leads to higher profits with a lower harvesting rate than the ecologically enlightened one. Adapted from (Salvioli et al., 2021).

where $K(v) = K_{\max} e^{-v^2/\sigma_K^2}$ is the carrying capacity. Here $H(v,m) = me^{-v^2/\sigma_H^2}$ defines the harvesting rate with harvesting effort m and u is the fish's evolutionary trait related to their catchability. If there is no harvesting ($m = 0$), the population follows a logistic growth and eventually adopts trait $u = 0$ to maximize the carrying capacity. Increasing the harvesting effort ($m > 0$) leads to reduction of the growth rate by the harvesting rate $H(v,m)$. The manager's profit is defined as

$$Q(m,u,x) = H(u,m)x - cm, \tag{3.15}$$

where the first term defines the harvested amount of fish and the second term defines the cost of harvesting. In this model, we assume there is some intermediate strategy that maximizes the fish's access to resources, and we normalize this to $u = 0$. This strategy might be habitat choice, seasonal movements, other foraging strategies, or morphology, all important for determining fish abundance. Hence $u = 0$ maximizes carrying capacity. Furthermore, we assume that investment in fishing gear, fishing boats and fishing regu-

lations have been adjusted and fixed over time to be maximally efficient at catching fish with trait $u = 0$. Therefore, both the carrying capacity of the fish and their catchability are maximized when $u = 0$, and both decline as the fish's strategy deviates either above or below this value.

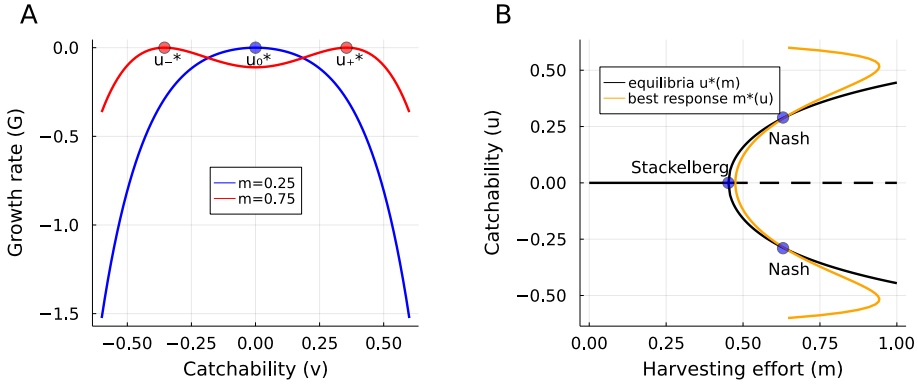

Figure 3.3: Bifurcation of an ESS of the fish with respect to harvesting rate. **A)** G-function at the eco-evolutionary equilibrium for fixed m. At $m = 0.25 < m_c$, there is one ESS (u_0^*), while for $m = 0.75 > m_c$, there are two ESS ($u_\pm^*$). **B)** A pitchfork bifurcation in ESS at $m_c \approx 0.45$. The leader's best response curve is depicted in orange. Parameter values: $r = 1.0$, $K_{\max} = 10000$, $\sigma_K = 0.55$, $\sigma_H = 0.50$, and $c = 500$.

The fish are under stabilizing selection to maximize their carrying capacity in the absence of harvesting and under disruptive selection to avoid harvesting. For small harvesting efforts m, we find a unique ESS $u_0^* = 0$ that maximizes $G(v, u, x, m)$ (see Figure 3.3A, blue line). As m increases, the disruptive selection can turn the convergent stable maximum $u_0^* = 0$ into a convergent stable minimum, thus creating a bifurcation in the ESS into an evolutionarily stable set (ESSet) with two coexisting strategies u_+^* and u_-^* (see Figure 3.3, red line). The corresponding bifurcation diagram is depicted in Figure 3.3B. With the given parameters, the harvesting effort at which the bifurcation occurs is $m_c = 0.45$. We see that for $m < 0.45$ the ESS is given by $u_0^* = 0$. At $m = 0.45$, the ESS splits into two branches u_+^* and u_-^* that further diverge from each other as m increases.

Next, we analyse the Nash and Stackelberg strategies of the game. We calculate the Nash equilibrium (m^N, u^N) and the Stackelberg equilibrium (m^S, u^S). First, we consider the case where $m^*(0) \leq m_c$. In this case, the Nash strategy m^N falls below the critical harvesting effort m_c and the corresponding trait value is $u^N = 0$. We find that the Stackelberg strategy coincides with the Nash strategy, which goes in agreement with Theorem 3.4.1 as $\frac{du^*(m)}{dm} = 0$ when $m < m_c$. When $m^*(0) > m_c$, the best response $m^*(u)$ intersects with both u_+^* and u_-^* such that $m^N > m_c$ and $u^N \neq 0$. This leads to a change in trait u and potentially speciation of the fish. In contrast to the previous case, the Stackelberg equilibrium does not coincide anymore with the Nash equilibrium. Rather, the Stackelberg strategy m^S is equal to the critical harvesting effort m_c, thus harvesting as much as possible while keeping the carrying capacity maximized with $u^S = 0$, as illustrated in Figure 3.3B. Mathematical details and calculations can be found in the supplementary information, and Mathematica code is provided online.

3.5.2. CANCER TREATMENT

Applications of game theory to understanding cancer and improving treatment were summarized in a review paper (Wölfl et al., 2022) and in multiple publications on this topic (Ardévol Martinez et al., 2023; Farrokhian et al., 2022; M. A. R. Strobl et al., 2022; Zhang et al., 2022). To describe how the SEG theory can be useful in improving cancer treatment, let us consider a SEG of cancer treatment between a physician and a polymorphic population of cancer cells consisting of resistant and sensitive cells. This game is based on a model presented by Pressley et al. (2021). We extend it by including competition among cancer cells (Salvioli, Garjani, et al., 2024). This inclusion likely makes the model more realistic (Freischel et al., 2021) and the eco-evolutionary dynamics more stable (Satouri et al., 2025). The sensitive and resistant cells have population x_S and x_R, respectively, and resistance traits u_S and u_R, respectively, while m represents the drug dosage of a single drug. Here $m = 0$ corresponds to no dose and $m = 1$ corresponds to the maximum tolerable dose (MTD). As in (Pressley et al., 2021), the sensitive cancer cells remain drug-sensitive (u_S is always 0), while the resistant subpopulation has a resistance trait that evolves in response to the dose m of the drug applied by the physician. The eco-evolutionary dynamics of the cancer cells for each cancer subpopulation $i \in \{R, S\}$ is a simplified case of (3.3)–(3.4) where we have a vector $\mathbf{u}$ instead of the matrix $\mathbf{U}$.

In this model, σ_i is the evolutionary speed of the populations $i \in \{R, S\}$, with $\sigma_S = 0$. The eco-evolutionary dynamics are defined using G-function

$$G(v, \mathbf{u}, \mathbf{x}, m) = r(v)\left(1 - \frac{\sum_{j\in\{R,S\}} \alpha_{ij} x_j}{K}\right) - d - \frac{m}{k + bv},$$

where $r(v) = r_{\max} e^{-g v}$ is the growth rate carrying a cost of resistance regulated by g, α_{ij} defines the competitive effect of type j on type i, K is the carrying capacity and d the natural death rate. Parameter k defines the innate resistance that may be present before drug exposure and b the benefit of the evolved resistance trait in reducing therapy efficacy (Pressley et al., 2021). Our model assumes that depending on the population size at the equilibrium ($x^* = x_S^*(m, u_S) + x_R^*(m, u_R)$), there are three possible outcomes: (i) Extinction ($x^* \leq 0$) where cancer is cured, (ii) progression (x^* larger than a certain fraction of the carrying capacity $\delta\ K$) where the disease progresses, and (iii) stabilization ($0 < x^* \leq \delta K$) where the cancer can be stabilized as a chronic disease with no or little side-effects related to the tumor burden. The best evolutionary response of the followers is $u_S^* = 0$ for the sensitive cancer population at all times, while it is calculated through (3.8) for the resistant cancer population. This is also illustrated in Figure 3.4.

The physician optimizes the constant treatment dose $m \in [0, 1]$, in order to maximize patient's quality of life

$$Q(m, u_R, x^*) = Q^{\max} - c_1\left(\frac{x^*}{K}\right)^2 - c_2\, u_R^2 - c_3\, m^2, \tag{3.16}$$

where $Q^{\max}$ is the maximum quality of life and weights c_1, c_2, and c_3 indicate the extent by which quality of life decreases with the tumor burden, rate of resistance, and drug toxicity, respectively. [2]MTD, commonly applied as the standard of care, leads extinction

[2]This sentence is adjusted based on an error fixed in Figure 3.4. Prior calculations showed MTD resulted in

of sensitive cells and a lower quality of life. When disease stabilization is feasible, we compare the physician's ecologically enlightened and evolutionarily enlightened treatment strategies. The physician's best response is calculated through (3.9). Figure 3.4 illustrates that for the considered parametrization, both Nash and Stackelberg solutions stabilize the tumor burden and succeed over MTD, which leads to extinction of sensitive cells. As illustrated in Figure 3.4A, the evolutionarily enlightened (Stackelberg) strategy corresponds to both a lower treatment dose/toxicity and a lower treatment-induced resistance than the ecologically enlightened (Nash) one. Furthermore, the Stackelberg strategy leads to the best result in terms of patient quality of life, followed by the Nash strategy, and MTD. Figure 3.4B demonstrates a situation when the quality of life function does not include treatment resistance, condition b) of Theorem 3.4.1 is satisfied, and therefore the Nash and Stackelberg equilibria coincide.

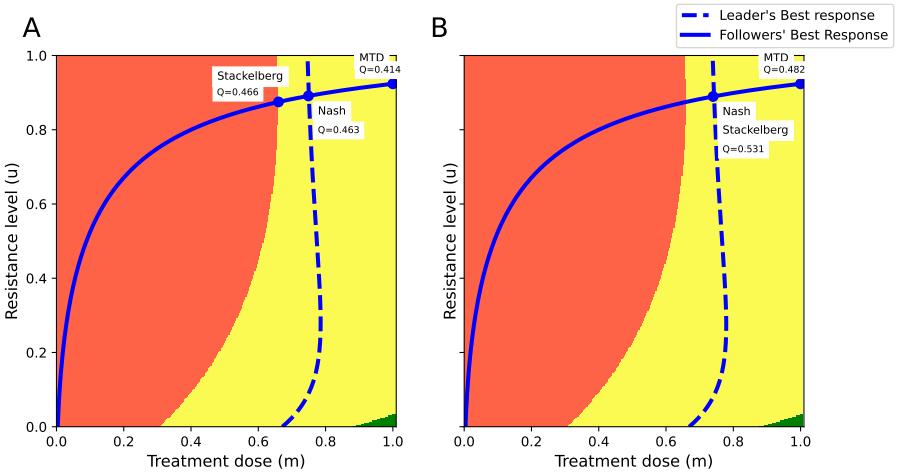

Figure 3.4: The outcomes of the maximum tolerable dose (MTD)), ecologically enlightened (Nash) strategy, and evolutionary enlightened (Stackelberg) strategy of the physician, when playing a SEG against cancer: The yellow and red areas represent tumor stabilization ($0 < x^* \leq \delta K$) and progression ($x^* > \delta K$) regions, respectively (Salvioli, Garjani, et al., 2024). **A)** The Nash and Stackelberg outcomes differ when Q defined by (3.16) is an explicit function of u. **B)** The Nash and Stackelberg outcomes coincide when $c_2 = 0$. Parameterization: $\delta = 0.7$, $r_{\max} = 0.45$, $g = 0.8$, $K = 10000$, $d = 0.01$, $k = 2$, $b = 10$, $\alpha_{SS} = \alpha_{RR} = 1$, $\alpha_{SR} = 0.1$, $\alpha_{RS} = 0.9$, $\sigma_S = 0$, $\sigma_R = 1$, $C = 1$; **A)** $c_1 = 0.54$, $c_2 = 0.21$, $c_3 = 0.25$, **B)** $c_1 = 0.68$, $c_2 = 0$, $c_3 = 0.32$.

Other examples in cancer treatment where SEG theory could be useful exist. A special case of cancer is transmissible cancer, i.e. cancer that can be transmitted from one individual to another one. While such cancers are currently rare, it is possible that they were much more common during the evolutionary history of life on earth and that over time, the species evolved prevention and suppression mechanisms (Aktipis, 2020; Dujon et al., 2021; Ujvari et al., 2016a, 2016b). Tasmanian devils' facial tumors and clam leukemia represent examples of such cancers. While it is possible to model cancer spread within one host through our equations (3.3)–(3.4), to frame transmissible cancers within the

disease progression at the equilibrium point, however, adjusted equilibrium points led to MTD in the stabilization region.

SEG framework, one needs to include the possibility of cancer transmission from host to host. Spatially implicit or explicit modelling may need to be included in (3.3)–(3.4) for this purpose.

3.5.3. PEST MANAGEMENT

For over 100 years, it has been recognized that insect pests evolve pesticide resistance. More recently, managers have advocated for resistance management plans, including a restrained use of pesticides, crop rotation, a strategic timing of multiple pesticides, and pesticide-free sanctuaries (Consortium et al., 2013; Cunningham, 2019; Peshin & Dhawan, 2009). Stackelberg evolutionary game theory provides a conceptual framework for targeting pests' resistance strategies in response to control strategies of the pest manager and the subsequent selection for the best control strategies. The SEG theory can help to replace the currently utilized ecologically enlightened application of pesticides with evolutionarily enlightened strategies, which will lead to a higher chance for pest containment (Brown & Staňková, 2017). Future research can focus on including vector-valued strategies of the pest manager. Those correspond to multiple pesticides and other possible strategies, while the trait strategies should be matrix-valued as in (3.4) if multiple pests are considered.

3.5.4. OTHER APPLICATIONS

Stackelberg evolutionary games frame situations where one tries to control evolving biological systems. There are plenty of examples from the literature where a SEG philosophy is already considered, even if the underlying SEG dynamics are not framed in game-theoretic (or any other mathematical) terms and the leader's strategies are not explicitly optimized. For instance, the strategy of stabilization of an incurable disease has been successfully applied when treating human immunodeficiency virus (HIV) infection (Blumenthal et al., 2018; Deeks et al., 2013; Mahungu et al., 2009) and diabetes (Chun et al., 2019; Wilson et al., 2007). It has been recognized that when biomedical interventions fail in curing a disease, it may be better to aim for its control/stabilization. Iwasa et al. (2003) quantified the probability of disease escape from biomedical interventions, such as vaccines or therapy (Iwasa et al., 2003). Here a more formal usage of SEGs could help to find better strategies targetting the disease.

Conservation biology, where the goal is the survival of species in deteriorating habitats, is another field where SEGs could be utilized to achieve better outcomes. Klausmeier et al. (2020) formulated eco-evolutionary dynamics similar to (3.3)–(3.4) and its extension to the SEG framework is straightforward. Optimizing available conservation strategies by defining a proper objective for the human as a leader in this game is a natural next step.

The idea that the conservation of species is a problem complementary to eradicating species is not novel. The phenomenon of species' adaptation to its environment where this adaptation leads to its survival (which is not always wished for) is referred to as evolutionary rescue (Alexander et al., 2014).

SEGs have the potential to be extended and applied in situations leading to global threats to human health, such as preventing antibiotic resistance or containing viral diseases, such as Covid-19 (Hiltunen et al., 2017; Lashley et al., 2020). When targeting an-

tibiotic resistance, one could consider the objective function defining a treatment success with the given drug while avoiding the treatment-induced resistance. The human influence on the evolution of antibiotic resistance has been studied in (Hiltunen et al., 2017) and has the potential to be solved through the SEG theory. The ongoing threat of Covid-19 demonstrates the importance of understanding the ecology and evolution of infectious diseases and subsequent design of appropriate containment strategies (Hodcroft et al., 2021). Humans influence the eco-evolutionary dynamics of infectious diseases in multiple ways. (Rogalski et al., 2017) Framing the problem as a SEG may lead to better therapeutic and non-therapeutic interventions and overall higher quality and quantity of life.

3.6. DISCUSSION

Starting in 1973, the subdiscipline of evolutionary game theory began to expand rapidly (Brown, 2016; Maynard Smith & Price, 1973). It initially did so quite independent of the larger field of "classical" game theory that has been applied to economics, sociology, military sciences, engineering, diplomacy, political sciences and more (Başar & Olsder, 1999). This larger domain of game theory beyond EGT included diverse solution concepts and ways to frame the strategy sets, payoffs and objectives (such as utility, profit, well-being, various societal metrics, tactical or strategic level military or conflict outcomes). Initially, EGT centered around the ESS as a likely outcome of evolution by natural selection. It is well established that an ESS needs to be a Nash equilibrium that is additionally uninvadable (Hofbauer & Sigmund, 1998, 2003). EGT has expanded solution concepts to include convergence stability, neighborhood invader strategy, and mutual invasibility (Apaloo, 1997; Apaloo et al., 2009; Brännström et al., 2013). All developed concepts derive from the ecological and evolutionary dynamics that drive changes in strategy frequencies, in contrast to the rational choice of the classical games (J. A. J. Metz et al., 2008; Vincent & Brown, 2012). Here we draw on the Nash and Stackelberg solutions from classical game theory and the associated eco-evolutionary dynamics and ESS to formalize games between a rational leader and evolving followers termed Stackelberg Evolutionary Game (SEG) Theory in earlier work (Salvioli, 2020; Salvioli et al., 2021). The need for such formalization begins with the long-term recognition that human management strategies impact not only the distribution and abundance of species (ecological dynamics) but also the evolutionary trajectories of pest species, harvested species, species of conservation interest, and diseases. The need is even greater as we see rapid evolution continuing to occur with additional responses to urbanization (evolution of urban eco-types) and climate change (acclimation followed by adaptation of many affected species). Starting with Law and Grey, EGT has been applied to these human-nature games in a manner we would term SEGs (Law & Grey, 1989). Humans can act as rational players in line with classical game theory, and nature responds to human actions in accord with EGT. Prior SEG-like models have been applied to fisheries management, pesticide management, antibiotic resistance, and increasingly in managing therapy resistance when treating cancer (Brown & Staňková, 2017; Salvioli et al., 2021; Staňková et al., 2019). Here we begin a unified modelling framework for considering SEGs that can apply to prior, present and future applications. In a SEG, a manager or stakeholder selects an action that aims to maximize their objective in terms of benefiting from a valued

species or controlling an undesirable one.

This leads to three management strategies: naive, ecologically enlightened, and evolutionarily enlightened. The naive manager takes the current population size and trait value of the species as fixed and bases their choice on what ever are their current values. This tends to lead to overfishing, maximum tolerable dosing in cancer, and generally an extreme strategy by the manager, particularly when the objective is monotonic with respect to the manager's action. The ecologically enlightened manager considers in advance the consequences of their actions on the species' population size and adjusts their strategy accordingly. Such a strategy forms the basis of most maximum sustainable harvest style strategies for harvesting species or the individual-level desire to use antibiotics or pesticides. This strategy leads to a Nash equilibrium between the manager's strategy and the species' ESS. The evolutionarily enlightened manager considers the eco-evolutionary consequences of their strategy on the species' ESS. This leads to a Stackelberg solution.

The three management strategies will be the same if the manager's action does not affect on the species' strategy or population size – unlikely in virtually all real life scenarios. Furthermore, in most cases, the naive manager will lead to the most extreme management choices (this can be seen in certain fisheries management strategies that include overharvesting followed by no harvesting at all upon the fisheries' collapse). The Nash and Stackelberg solutions of the ecologically and evolutionarily enlightened managers, respectively, will be the same if 1) the manager's actions have no evolutionary effects on the species, or 2) the species trait has no effect on the manager's objective, and the species population size does not influence the manager's objective or the effect of the species strategy on its population size cancels at the ESS. Otherwise, the Stackelberg solution deviates from the Nash. This is likely the case in most realistic scenarios, as the manager's actions do influence the traits of the species, the species' trait likely influences its population size, and the manager's objective likely includes caring about the species trait and population size.

It seems in the models to date that the Stackelberg solution results in a more moderate management strategy than the Nash in terms of harvesting effort, pesticide application or drug therapy (be it in the context of cancer or infectious diseases). Increasingly more knowledge of the system is required in going from naive to ecologically enlightened to evolutionarily enlightened management. In order to anticipate and steer the eco-evolutionary response of a biological system, we need to improve our ability to estimate population size and composition prior to intervention. In order to estimate and optimize the model parameters a continuous surveillance is required. A sufficient technology for identifying, quantifying and monitoring the evolving strategy distribution in heterogeneous populations is not yet available. This presents one limit to achieving a Stackelberg solution – though pest management and especially cancer therapies are moving in that direction, with the advent of liquid biopsies, radiomics, organoids and xenografts (Bruna et al., 2016; Gatenby et al., 2013; Lianidou et al., 2014; Verduin et al., 2021).

Another impediment to implementing a Stackelberg solution includes disagreement and lack of knowledge regarding the speed of evolution and even what trait might evolve. For instance, the cancer cells may have more than one resistance mechanism for a given

cancer and therapy. Which will actually evolve in response to therapy, and will it be the same for each patient? This suggests that management strategies might begin with an ecologically enlightened approach as a probe to see in what direction and how quickly the evolutionary traits of the species evolve. Other issues arise when the trait may be qualitative rather than quantitative. For cancer, qualitative resistance might be a result of genetic mutations (Dagogo-Jack & Shaw, 2018; Turajlic et al., 2019). The management of a preexisting mutant population was for example studied in (Viossat & Noble, 2021). However, additional resistance and driver mutations can emerge during therapy leading to more aggressive cancers. The risk of acquiring additional driver mutations is higher if the tumour burden is high. This needs to be considered for future studies and could be taken into account by implementing a penalty term for high tumour burden in the objective function.

As shown in Section 3.5 for the fisheries management example, the way to the Nash and Stackelberg solutions is not always straightforward, as the followers may speciate into two or more types with distinct strategies. While the discussion about speciation and its impact on finding the Nash and Stackelberg equilibria has just started, it becomes natural to look in the direction of adaptive dynamics as a natural extension to our work (Brännström et al., 2013; Diekmann, 2002). For instance, a fitness minimum may represent an evolutionary branching point of adaptive dynamics (Dieckmann & Doebeli, 1999; Doebeli & Dieckmann, 2000; Geritz et al., 1998), leading to different eco-evolutionary responses in the followers than those which we defined.

Our presentation of SEG theory is just a beginning and invites more expansive models, theorems, and applications. We touched upon but did not formalize the solutions for cases where the manager and/or the species under consideration have vector-valued traits. We note how the manager's strategy may alter the number of coexisting strategies within the ESS. A manager's harvest strategy of keeping medium sized adults while releasing smaller (juvenile or young adults) and larger (high reproductive potential) such as occurs in lobster fisheries could select for two species of lobster where there had been one - a species that only breeds below the lower threshold and one that waits to breed until above (Acheson & Knight, 2000). We did not consider all of the important stability properties associated with convergence stability, NIS and mutual invasibility that might influence the speed and possibility of the species achieving its ESS once subjected to the manager's strategy. The examples investigated in this paper do not explicitly account for spatial structures or constraints. It remains for future studies to investigate how spatial structures, as for example studied in (Bocedi et al., 2021) and (M. A. R. Strobl et al., 2022), can be included in the SEG framework.

Finally, in terms of the applications discussed here we did not consider the manager's utility derived from the transient dynamics, or whether permanently aiming for transients would be the best strategy such as strategies of applying or withholding a pesticide or cancer therapy when the abundance of the pest is above or below some threshold. SEGs can and should be extended to differential games where time dependent, optimal control strategies become an option for the manager. An important context for extending SEGs concerns cases where there are multiple stakeholders each with different objectives and perhaps access to different strategies. The SEG now includes a game among the stakeholders in addition to their intentional and collateral effects

on the species ESS. Along this line, there may be a diversity of different species within the community under management. For instance, there is mounting evidence that harvesting fish in coastal fisheries may be releasing octopus (a different G-function) from predation or competition, thus increasing their numbers and inviting the expansion of octopus harvesting (Hart et al., 2019; Sauer et al., 2021). SEGs with multiple stakeholders and multiple G-functions among the species of interest may be quite frequent.

In conclusion, 50 years saw EGT grow into a substantial body of models, theories and applications that are now central to studies of evolutionary ecology. In bioeconomic games of managing evolving resources and pests, we see the emergence of Stackelberg Evolutionary Game Theory. And while some of us may not be alive to see what happens in the next 50 years, we believe that SEG theory will be an essential body of mathematics vital for managing humanities relationship with nature.

4

STACKELBERG EVOLUTIONARY GAMES OF CANCER TREATMENT: WHAT TREATMENT STRATEGY TO CHOOSE IF CANCER CAN BE STABILIZED?

We present a game-theoretic model of a polymorphic cancer cell population where the treatment-induced resistance is a quantitative evolving trait. When stabilization of the tumor burden is possible, we expand the model into a Stackelberg evolutionary game, where the physician is the leader and the cancer cells are followers. The physician chooses a treatment dose to maximize an objective function that is a proxy of the patient's quality of life. In response, the cancer cells evolve a resistance level that maximizes their proliferation and survival. Assuming that cancer is in its ecological equilibrium, we compare the outcomes of three different treatment strategies: giving the maximum tolerable dose throughout, corresponding to the standard of care for most metastatic cancers; an ecologically enlightened therapy, where the physician anticipates the short-run, ecological response of cancer cells to their treatment, but not the evolution of resistance to treatment; and an evolutionarily enlightened therapy, where the physician anticipates both ecological and evolutionary consequences of the treatment. Of the three therapeutic strategies, the evolutionarily enlightened therapy leads to the highest values of the objective function, the lowest treatment dose, and the lowest treatment-induced resistance. Conversely, in our model, the maximum tolerable dose leads to the worst values of the objective function, the highest treatment dose, and the highest treatment-induced resistance[1].

[1] This chapter is based on previously published work (Salvioli, Garjani, et al., 2024).

4.1. INTRODUCTION

Metastatic cancer, characterized by the spread of malignant cells from its original site to other parts of the body, remains largely incurable, with cancer death rates declining by only 1.5 percent per year between years 2001 and 2017 (Henley et al., 2020; Jemal et al., 2017; O'Sullivan et al., 2015). This lack of progress in metastatic cancers is, in part, due to the standard of care in metastatic cancers, which typically applies a drug or drug combination at maximum tolerable dose (MTD), either continuously or in predefined treatment cycles (Enriquez-Navas et al., 2016; Frei et al., 1998; Gad, 2014; Gatenby, 2009; Takimoto, 2009). The same regimen continues until there is unacceptable toxicity, unambiguous evidence of tumor progression, or cure. However, in metastatic cancers, cure is rare (Dong et al., 2019; Savage et al., 2009; Sledge Jr, 2016).

The goal of killing as many cancer cells as fast as possible may be evolutionarily unwise (Dujon et al., 2021; C. P. Evans, 2018; Gatenby, 2009; Staňková, 2019; Staňková et al., 2019; West et al., 2023). This is because MTD imposes a very strong selection pressure for the evolution of treatment-induced resistance, which subsequently leads to treatment failure (Aguadé-Gorgorió et al., 2024; Dujon et al., 2021; C. P. Evans, 2018; Greaves & Maley, 2012; Jemal et al., 2017; Merlo et al., 2006; Pressley et al., 2021; Viossat & Noble, 2021; Werner et al., 2011; Zhang et al., 2017).

Evolutionary cancer therapies (also known as adaptive therapies) provide an alternative to the standard of care (Gatenby, Silva, et al., 2009; Gatenby, 2009; Lin-Rahardja et al., 2023; Natterson-Horowitz et al., 2023; Staňková, 2019; Staňková et al., 2019). Evolutionary therapies aim to manage treatment-induced resistance in cancer cells by anticipating and steering their ecological and evolutionary dynamics. Such therapies integrate mathematical models, known cancer biology, and patient-specific data to improve care. Different therapy goals lead to different types of evolutionary therapy:

- Delaying progression or tumor burden stabilization: In situations where curative therapies are too risky or unavailable, evolutionary therapies strive to prolong the time to progression (clinical trials NCT02415621, NCT03511196, NCT05393791, NCT03543969, and NCT03630120) or, when possible, to stabilize the tumor burden by maintaining a tumor burden that is viable for the patient (clinical trial NCT05080556). In all named trials, the goal of treatment has shifted from "treat to eradicate" to a less ambitious but more attainable "treat to delay progression" or "treat to contain" (Alvarez & Viossat, 2024; Cunningham et al., 2020; Masud & Kim, 2024; Viossat & Noble, 2021; West et al., 2023). The strategy of stabilization of an incurable disease has been motivated by the success of similar strategies outside of oncology, for instance, when treating human immunodeficiency virus (HIV) (Blumenthal et al., 2018; Deeks et al., 2013; Mahungu et al., 2009) and diabetes (Chun et al., 2019; Wilson et al., 2007).

- Cure: Recently, there have been attempts to cure metastatic cancers through extinction (or first strike – second strike) evolutionary therapy (clinical trials NCT04388839, and NCT04343365). This therapy aims at cure by applying a "first strike" treatment to decrease the tumor burden below a critical threshold, followed by "second strike" treatments aiming at cancer eradication (Gatenby & Brown, 2020; Gatenby et al., 2019, 2020).

The first and most well-known trial based on evolutionary therapy is Zhang *et al.*'s trial (NCT02415621), which aimed at delaying cancer progression. In this trial, patients with metastatic Castrate-Resistant Prostate Cancer (mCRPC) were given abiraterone until their Prostate Specific Antigen (PSA, a blood biomarker of tumor burden) dropped below 50% of its initial value (Zhang et al., 2022; Zhang et al., 2017). At this point, the abiraterone treatment was stopped and re-administered only when the PSA returned to its initial value. Then a new therapy cycle started. This led to cycles on and off abiraterone in response to the patients' PSA levels. While Zhang *et al.*'s protocol eventually fails and progression occurs, it happens much later than with the standard of care (Zhang et al., 2022; Zhang et al., 2017). As of the time of writing, 12 of 16 patients have progressed (median time to progression of about 30 months compared to about 14 months for the standard of care), though after six years, four patients continue to cycle without any indication of disease progression (Zhang et al., 2022). Zhang *et al.*'s adaptive protocol is currently repeated in trial NCT05393791, with nearly 200 patients.

Despite the success of Zhang *et al.*'s trial, theory tells us that one could do even better for this target group of patients. Cunningham et al. (2020) demonstrated with a variant of Zhang et al. (2017)'s model that stabilization of the tumor burden may be possible in mCRPC. Further, they showed that even when it is unclear at what tumor burden one should stabilize, it is often possible to reach this stable tumor burden by gradually decreasing the dose whenever the tumor burden is decreasing, starting from the maximum tolerable dose (Gatenby, 2009). Such a dose reduction therapy is currently being tested in patients with relapsed Platinum-sensitive High-Grade Serous or High-Grade Endometrioid Ovarian Cancer (clinical trial NCT05080556). In (Cunningham et al., 2020) and (M. A. Strobl et al., 2021) a potentially even more effective approach is explored, a dose titration protocol, where the treatment starts with a very low dose, which is gradually increased whenever the tumor burden grows and decreased whenever it decays. These theoretical results and the mentioned ongoing clinical trial in ovarian cancer provide motivation for our present work, where we analyze what the best constant treatment dose is if cancer cannot be cured but can be stabilized at a viable tumor burden.
To do so, we use an evolutionary version of the leader-follower games originally introduced in economics to conceptualize interactions with an imbalance in power between firms in oligopolistic markets by the German economist von Stackelberg (Hicks & von Stackelberg, 1935; von Stackelberg, 1934). Indeed, the physician and the cancer cells engage in a type of leader-follower game: The physician chooses a treatment dose to maximize an objective function expressing the patient's quality of life and the cancer cells adapt to this treatment, in a way that affects the physician's objective (Staňková et al., 2019). The difference with standard leader-follower games is that cancer cells are not modeled as rational players but as playing an evolutionary game that determines the cell types that emerge, their population size, and their evolutionary traits (Archetti & Pienta, 2019; Bayer et al., 2022; Dingli et al., 2009; Hummert et al., 2014; Tomlinson, 1997).

The combination of these two levels of interaction (between the physician and cancer cells and between the cancer cells themselves) results in a game that some of us have recently termed a Stackelberg evolutionary game (Kleshnina et al., 2023; Salvioli et al., 2021; Stein et al., 2023). Stackelberg evolutionary game theory applies to situations with a rational player (the physician in the case of cancer treatment) and evolutionary fol-

lowers, which can be a community of populations, species, or types that evolve by natural selection (cancer cells in the case of cancer treatment). In these games, the rational player can act as the leader and anticipate and steer the eco-evolutionary dynamics of the followers, who adapt to the actions of the leader, according to the principles of natural selection.

Here, we extend the cancer model of Pressley et al. (2021), who considered a polymorphic cancer cell population consisting of sensitive cells that do not evolve and resistant cells whose treatment-induced resistance is a quantitative evolving trait. Pressley *et al.* assumed only density-dependent selection of cancer cells. Motivated by in-vitro and in-vivo studies that demonstrated the cancer cells' frequency-dependent selection (Freischel et al., 2021; Kaznatcheev et al., 2017; Noble et al., 2021; Susswein et al., 2022; van Neerven et al., 2021; Zhang et al., 2022), here we assume direct competition between the two cancer cell types, leading to frequency dependence. Moreover, we assume that the sensitive cancer cells have a larger competitive effect on the resistant cells than vice-versa. Furthermore, as Pressley et al. (2021), we assume a cost of resistance in the growth rate of resistant cells, i.e., the growth rate of resistant cancer cells decreases with the resistance level.

Pressley *et al.* demonstrated that Zhang *et al.*'s adaptive therapy protocol prolonged the time to progression when compared to continuous therapy at maximum tolerable dose also in models with the treatment-induced resistance evolving as a quantitative trait. Here, we focus on a situation when cure is impossible, but the tumor burden can be stabilized at a viable level for the patient. For this case, we determine the optimal constant treatment dose maximizing the objective function of the physician, which is a function depending on the tumor burden, treatment toxicity, and the cancer cell's level of treatment-induced resistance. This objective function captures the patient's quality of life.

In what follows, we: 1) develop a model for the cancer's eco-evolutionary dynamics, 2) expand it into a Stackelberg evolutionary game of cancer treatment, and 3) compare three different strategies that the physician might use to treat the patient (maximum tolerable dose, an ecologically enlightened strategy, and an evolutionarily enlightened strategy), while assuming the tumor burden has reached its equilibrium size. We conclude by highlighting the main outcomes and their relevance for the field of (mathematical) oncology, discussing model limitations, and proposing future research directions.

4.2. METHODS

Following Pressley et al. (2021), we consider a model with two cancer cell types: sensitive cells, whose resistance to treatment is minimal, and (potentially) resistant cells, which may adapt to evolutionary pressures by becoming more or less resistant to treatment. However, in contrast to Pressley *et al.*, we allow for differing magnitudes of inter- and intra-type competition between the two types of cancer cells. Furthermore, we determine for which treatment doses and treatment-induced resistance levels the tumor burden can be stabilized at levels viable for the patient. Stabilization in this context refers to employing a constant treatment dose that keeps the tumor burden at a progression-free/viable equilibrium size. When the tumor burden can be stabilized, we adopt a Stackelberg (leader-follower) evolutionary game theory approach (Ardévol Martinez et

al., 2023; Salvioli et al., 2021; Staňková et al., 2019; Stein et al., 2023; Wölfl et al., 2022): The leader (physician) chooses a treatment dose with the aim of maximizing an objective function, which is a proxy for the patient's quality of life and depends on the tumor burden, resistance level of cancer cells, and the treatment dose.

The cancer cells adapt to treatment in two ways, which are easiest to conceptualize as a short-run and a long-run response (though, technically, our model does not assume a separation of time scales). In the short-run (ecological time scale), only the absolute and relative abundances of the two types of cancer cells evolve. In the longer-run (evolutionary time-scale), the resistance level of the resistant cells evolves as well. This resistance level may be seen as their (evolutionary) strategy. The function mapping a given treatment dose to the resistance level that evolves in response can be perceived as the cancer cells' evolutionary response function, which is somewhat analogous to the best-response function of the follower in a standard Stackelberg game, in that it defines the response of the followers maximizing their objective with respect to their strategy. Drawing on this analogy, we call this function the cancer cells' best-response function.

We consider three possible cases, leading to three potentially different therapeutic outcomes. In the first case, the physician just uses the maximum tolerable dose (MTD) of treatment. In the second case, the physician can observe the current resistance level of cancer cells. After a potential phase of "tatônnement", where the physician adjusts the treatment dose based on the actual resistance level of cancer cells and the cancer cells evolve resistance in response to this updated treatment dose, this is expected to lead to a stable situation: the resistance level of resistant cells is a best response to the current treatment dose, and this treatment dose is a best response to the resistant cells' current resistance level.

We refer to this stable situation as the (static) Nash equilibrium of the game. The corresponding strategy of the physician is called the Nash strategy.

In the third case, the physician also anticipates the evolutionary response of the cancer cells, meaning the physician knows in advance the best response of the cancer cells in terms of their resistance to all possible treatment doses that the physician can apply. This can lead to a stable outcome corresponding to a Stackelberg equilibrium of the leader-follower game, where the followers' strategy is at an eco-evolutionary equilibrium, with respect to their strategy and population size. The corresponding strategy of the physician is their Stackelberg strategy, in accordance with the literature on Stackelberg games and our recent work (Başar & Olsder, 1999; Kleshnina et al., 2023; Salvioli et al., 2021; Simaan & Cruz, 1973; Stein et al., 2023). The Stackelberg strategy fully exploits the leadership role of the physician and is, by construction, the leader's best strategy (Kleshnina et al., 2023; Staňková et al., 2019; Stein et al., 2023).

When the tumor may be stabilized, we compare the outcomes corresponding to these three strategies: maximum tolerable dose, the ecologically enlightened/Nash strategy, and the evolutionarily enlightened/Stackelberg strategy.

4.2.1. MODEL OF CANCER ECO-EVOLUTIONARY DYNAMICS

We consider two distinct cancer cell populations: sensitive and resistant. We introduce frequency-dependent interactions between these two cell types by varying the intra- and inter-type competition coefficients. The treatment-induced resistance is modeled as a

quantitative trait, meaning that this resistance exists on a continuum, and the resistant cells can exhibit some level of resistance $u_R(t) \geq 0$ that evolves over time t in response to therapy. While we assume that the sensitive cells do not evolve resistance ($u_S(t) = 0$ for all t), we retain both u_S and u_R in our model, even though $u_S = 0$ in the current scenario. This is done to allow for future extensions of this model where u_S may reach different values. We model the eco-evolutionary dynamics of the cancer cells using a fitness-generating function, also known as a G-function (Vincent & Brown, 2012). The G-function defines how the fitness of a focal cancer cell using strategy v is influenced by the environment and the strategies and population sizes of the resident types. In particular, the G-function is crucial for determining the evolutionary dynamics for how the resistant strategy evolves over time. The resistance level evolves in the direction of the fitness gradient $\frac{\partial G}{\partial v}$, with respect to the focal individual's strategy v (Vincent & Brown, 2012). This derivative is then evaluated at the current resident strategy u_R, leading to an equation defining the evolutionary dynamics for the resident strategy itself (Pressley et al., 2021; Vincent & Brown, 2012). The rate at which the resistance strategy changes is scaled by an evolutionary speed term σ, which we assume constant for simplicity. The exact value of σ does not influence the equilibrium outcomes presented in this paper.

The eco-evolutionary dynamics of the two populations of cancer cells are as follows:

$$\frac{\mathrm{d}x_R}{\mathrm{d}t} = x_R\, G(v, \mathbf{u}, \mathbf{x}, m)\Big|_{v=u_R}, \tag{4.1}$$

$$\frac{\mathrm{d}u_R}{\mathrm{d}t} = \sigma\, \frac{\partial G(v, \mathbf{u}, \mathbf{x}, m)}{\partial v}\Big|_{v=u_R}, \tag{4.2}$$

$$\frac{\mathrm{d}x_S}{\mathrm{d}t} = x_S\left(r(u_S)\left(1 - \frac{\alpha_{SS}\, x_S + \alpha_{SR}\, x_R}{K}\right) - d - \frac{m}{k + b u_S}\right), \tag{4.3}$$

$$u_S = 0, \tag{4.4}$$

where we assume that the G-function has the following form:

$$G(v, \mathbf{u}, \mathbf{x}, m) = r(v)\left(1 - \frac{\alpha_{RS}\, x_S + \alpha_{RR}\, x_R}{K}\right) - d - \frac{m}{k + bv}, \tag{4.5}$$

and that the vectors $\mathbf{u} = (u_R, u_S)^\top$ and $\mathbf{x} = (x_R, x_S)^\top$ capture the resistance strategies and population sizes of the two cancer cell populations, respectively. Treatment-induced resistance may come at a cost (Staňková, 2019), which may make resistant cells less fit in the absence of treatment. In (4.5), we assume a cost of resistance in the intrinsic growth rate. More specifically, $r(v) = r_{\max} e^{-g\, v}$, where g determines the magnitude of the effect of resistance on the growth rate. The intra-type competition effects are given by α_{SS} and α_{RR}, while α_{RS} and α_{SR} are the inter-type competition coefficients. Parameter K denotes the carrying capacity of cancer cells, while parameter d is the natural death rate of cancer cells. In our model, we assume that the physician applies a treatment dose $m(t) \in [0, 1]$ at time $t \geq 0$, where $m(t) = 0$ corresponds to no dose and $m(t) = 1$ to MTD. We assume that drug efficacy increases with m and decreases with the focal cell's resistance strategy v, its innate resistance k, and the benefit b of the resistance level.

Parameter values, except the cost of resistance's magnitude g and inter-type competition coefficients α_{RS} and α_{SR}, are taken from (Pressley et al., 2021). The ratio of the

Variables	Meaning	Feasible values
x	Cancer cell population	$[0, K]$
x_S	Sensitive population	$[0, K]$
x_R	Resistant population	$[0, K]$
u_S	Resistance strategy of sensitive cells	0
u_R	Resistance strategy of resistant cells	$\mathbb{R}_0^+$
v	Resistance strategy (focal individual)	$\mathbb{R}_0^+$
m	Treatment dose	$[0, 1]$
Parameters		**Values**
$r_{\max}$	Intrinsic growth rate of the cancer cells	0.45
d	Intrinsic death rate	0.01
K	Carrying capacity	10000
g	Magnitude of cost of resistance	0.8
k	Innate cell immunity	2
b	Magnitude of resistance benefit	10
σ	Evolutionary speed of resistant cells	1
δ	Progression threshold (fraction of K)	0.7
α_{RS}	inter-type competition coefficient	0.9
α_{SR}	inter-type competition coefficient	0.15
α_{SS}	intra-type competition coefficient	1
α_{RR}	intra-type competition coefficient	1

Table 4.1: Variables and parameter values of the game (Pressley et al., 2021; Zhang et al., 2022).

inter-type competition coefficients is taken from (Zhang et al., 2022). Parameters and their values are summarized in Table 4.1.

4.2.2. VIABILITY ANALYSIS OF THE ECO-EVOLUTIONARY EQUILIBRIA OF CANCER DYNAMICS

The time to progression corresponds to the moment when the tumor burden exceeds a predefined fraction $\delta \in (0, 1]$ of the carrying capacity. We set this δ to 0.7 as in (Pressley et al., 2021). Our first objective is to identify treatment doses and treatment-induced resistance levels for which it is possible to maintain the tumor burden below the progression threshold δK.

The sizes of sensitive and resistant cancer cell populations at the ecological equilibria $x_R^*(m, u_R)$ and $x_S^*(m, u_R)$ at any given resistance level are found by solving $\frac{dx_R}{dt} = 0$ and $\frac{dx_S}{dt} = 0$, respectively. The tumor burden $x^*(m, u_R)$ is defined as $x^*(m, u_R) = x_R^*(m, u_R) + x_S^*(m, u_R)$. The extinction, stabilization, and progression regions are defined as follows:

- *Extinction region*: all (m, u_R)-pairs for which the cancer population eventually goes extinct, i.e., where the tumor burden at equilibrium $x^*(m, u_R)$ is zero (shown in green in Figure 4.1):

$$\mathcal{G} = \{(m, u_R) \in [0, 1] \times \mathbb{R}_+^0 : x^*(m, u_R) = 0\}.$$

- *Stabilization region*: all (m, u_R)-pairs for which the tumor burden at equilibrium $x^*(m, u_R)$ is positive, but does not exceed δK (shown in yellow in Figure 4.1):

$$\mathscr{Y}_\delta = \{(m, u_R) \in [0,1] \times \mathbb{R}^0_+ : 0 < x^*(m, u_R) \leq \delta K\}.$$

- *Progression region*: all (m, u_R)-pairs for which the tumor burden progresses, i.e., for which the tumor burden at equilibrium $x^*(m, u_R)$ is higher than the progression threshold δK (shown in red in Figure 4.1):

$$\mathscr{R}_\delta = \{(m, u_R) \in [0,1] \times \mathbb{R}^0_+ : x^*(m, u_R) > \delta K\}.$$

Figure 4.1 shows different values of the ecological equilibrium $x^*(m, u_R)$ for different m and u_R values, determining the three regions $\mathscr{G}$, Y_δ, and R_δ for the particular parametrization of the model. According to (4.2), the treatment-induced resistance u_R under a

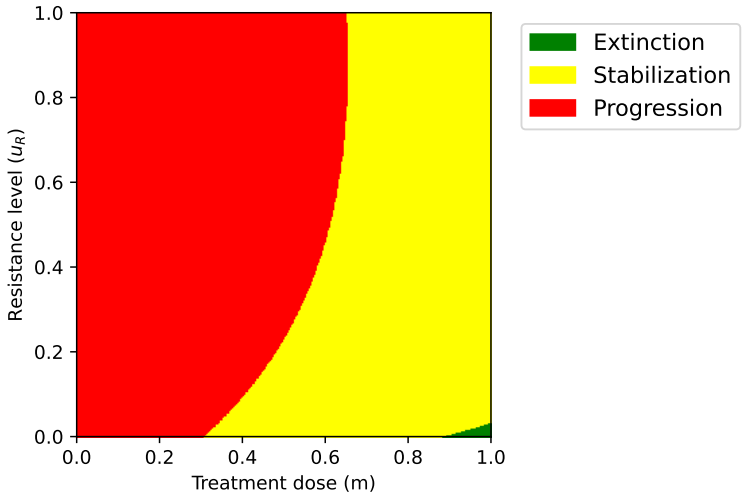

Figure 4.1: The equilibrium population size. We identify three possible regions: The green area $\mathscr{G}$ corresponds to combinations of m and u_R for which $x^*(m, u_R) = 0$, i.e., the region where cancer is cured; the red area $\mathscr{R}_\delta$ corresponds to combinations of m and u_R for which $x^*(m, u_R) > \delta K$, i.e., the region where the tumor burden is too high, and the disease progresses; the yellow area $\mathscr{Y}_\delta$ corresponds to combinations of m and u_R for which the tumor burden stabilizes at a nonzero but viable level, and the corresponding values of the objective function will matter. Parametrization: $\delta = 0.7$, $r_{\max} = 0.45$, $g = 0.8$, $K = 10000$, $d = 0.01$, $k = 2$, $b = 10$, $\alpha_{SS} = \alpha_{RR} = 1$, $\alpha_{SR} = 0.15$, $\alpha_{RS} = 0.9$.

particular treatment dose m eventually evolves towards an evolutionarily stable strategy (ESS) $u_R^* = u_R^*(m)$. At eco-evolutionary equilibrium, the cancer population is at its ecological equilibrium and $u_R = u_R^*$. By definition, when the population is at the eco-evolutionary equilibrium, the ESS strategy maximizes G (Apaloo et al., 2009; Vincent & Brown, 2012) and the first order condition applies:

$$\frac{\partial G(v, \mathbf{u}^*, \mathbf{x}^*, m)}{\partial v}\bigg|_{v=u_R^*} = 0, \tag{4.6}$$

whenever this derivative exists.

We assume that it is possible to cure or contain the disease with a constant treatment dose if values of m exist for which the pair $(m, u_R^*(m))$ lies in the extinction or stabilization region, respectively. Otherwise, progression under a constant treatment dose is inevitable.

4.2.3. EXPANDING THE MODEL INTO A STACKELBERG EVOLUTIONARY GAME

In the previous section, we introduced an evolutionary game between different types of cancer cells. Here we extend this game into a Stackelberg evolutionary game, where the physician as the leader maximizes the patient's quality of life through selecting a particular treatment dose. This quality of life is captured in an objective function, defined for treatment doses and resistance levels where cure is unachievable but stabilization is possible. By maximizing such an objective function with respect to the treatment dose, we determine which of the treatment strategies leading to a viable tumor burden is the most desirable for the patient. Our objective function depends on the cancer cell population, the toxicity due to the treatment dose, and the treatment-induced resistance of the cancer cells. We assume that the objective function decreases when the tumor burden increases, as the patient might experience pain or other side effects (Jalali & Dutta, 2012; Merker et al., 2014). Similarly, the objective function decreases with the treatment dose, because of the increased treatment-induced toxicity. Moreover, we assume that the objective function declines with cancer resistance level, as more resistant cells might give rise to secondary tumors and side effects (Mitola et al., 2021; Vasan et al., 2019), which decrease the patient's quality of life. Besides, the resistance level could be associated with the Warburg effect, which may alter the micro-environment to be more suitable for cancer cell proliferation (Liberti & Locasale, 2016). Here, we introduce the following objective function Q:

$$Q(m, u_R, x^*(m, u_R)) = \begin{cases} Q^{\max} - c_1\left(\frac{x^*(m,u_R)}{K}\right)^2 - c_2 u_R^2 - c_3 m^2, & (m, u_R) \in \mathscr{Y}_\delta, \\ \text{undefined}, & \text{elsewhere.} \end{cases} \tag{4.7}$$

In (4.7), $Q^{\max}$ represents the maximum value of the objective function, while the weights c_1, c_2, and c_3 (where $c_1 + c_2 + c_3 = 1$, $c_1, c_2, c_3 \in [0, 1]$) determine the impact of tumor burden, treatment-induced resistance level, and treatment toxicity on the patient's quality of life, respectively.

Figure 4.2 depicts the objective function (4.7) for a particular parametrization. In those cases where the tumor burden can be stabilized, but cure is impossible, we compare the following treatment strategies and their effects on the physician's objective function (see also Table 4.2):

- Ecologically enlightened strategy (or Nash strategy): The physician considers the ecological but not the evolutionary effects of treatment.

  For a fixed resistance level u_R, the best response of the physician would be the treatment dose:

$$m^*(u_R) = \arg\max_m Q(m, u_R, x^*(m, u_R)). \tag{4.8}$$

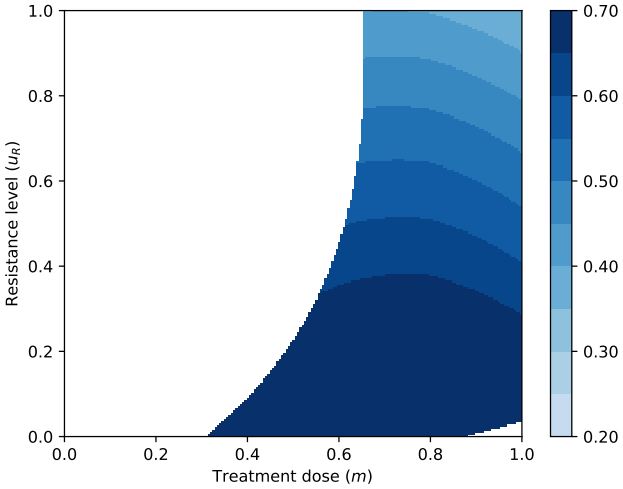

Figure 4.2: The physician's objective function as a function of the tumor burden, the treatment dose and the resistance level (4.7). The white space illustrates the region where the objective function is undefined. Parametrization: $\delta = 0.7$, $r_{\max} = 0.45$, $g = 0.8$, $K = 10000$, $d = 0.01$, $k = 2$, $b = 10$, $\alpha_{SS} = \alpha_{RR} = 1$, $\alpha_{SR} = 0.15$, $\alpha_{RS} = 0.9$, $\sigma = 1$, $Q^{\max} = 1$, $c_1 = 0.5$, $c_2 = 0.25$, $c_3 = 0.25$.

Besides, for a given treatment dose m, the cancer cells' resistance evolves to their ESS given by (4.6). We refer to the stable situation this may lead to as the Nash equilibrium of the game (meaning the Nash equilibrium of the underlying simultaneous-move game). It lies at the intersection of the cancer cells' evolutionary response (ESS strategy) curve $u_R^*(m)$ and the physician's best response curve $m^*(u_R)$. This Nash equilibrium is only meaningful if these curves intersect within the stabilization region. When this is the case, we denote by m_N the physician's Nash strategy and by $u_R^*(m_N)$ the cancer cells' Nash strategy.

- Evolutionarily enlightened strategy (or Stackelberg strategy): The physician anticipates the ecological and evolutionary response of the cancer cells to therapy. It is defined as

$$m_S = \arg\max_m Q(m, u_R^*(m), x^*(m, u_R^*(m))). \tag{4.9}$$

The cancer cells' strategy at the Stackelberg equilibrium is given by their ESS $u_R^*(m_S)$.

For some parametrizations of our model, the MTD, i.e., $m = 1$, can also stabilize the tumor burden. In such a case, the physician's objective function (4.7) is defined for $m = 1$ as well. If that is the case, we can compare the outcomes of ecologically and evolutionarily enlightened treatment strategies with the physician's objective function under MTD.

Ecological equilibrium	The populations of sensitive and resistant cancer cells are not changing ($\dot{x}_S = 0$ and $\dot{x}_R = 0$) given the current resistance level u_R and the current treatment dose m.
Eco-evolutionary equilibrium	The cancer cells are at the ecological equilibrium, and the resistance level of the resistant cells is not changing ($\dot{u}_R = 0$).
(static) Nash equilibrium	The cancer cells are at an eco-evolutionary equilibrium while the treatment dose is at the best response to the current resistance level.
Stackelberg equilibrium	Cancer cells are at an eco-evolutionary equilibrium, and the physician maximizes the objective function knowing the evolutionary response of cancer cells.

Table 4.2: Four notions of equilibria utilized in this paper

4.3. RESULTS

We first calculate the ecological equilibria of cancer cells. We then calculate the physician's Nash and Stackelberg strategies and the game's corresponding outcomes in terms of the objective function of the physician (4.7). When the equilibrium population size lies in the patient's stabilization region, we compare the MTD, Stackelberg and Nash outcomes of the game. In Appendix B.1, we illustrate the basins of attraction of these equilibria. Competition coefficients α_{SS} and α_{RR} are set to 1 as in (Pressley et al., 2021), which is a common assumption in the ecology literature (Berryman, 1992; Freischel et al., 2021; Iannelli & Pugliese, 2014; Vincent & Brown, 2012).

4.3.1. ECOLOGICAL EQUILIBRIA OF CANCER CELLS

The ecological equilibria of the cancer cells can be found by setting $\frac{\mathrm{d}x_R}{\mathrm{d}t}$ and $\frac{\mathrm{d}x_S}{\mathrm{d}t}$ to zero. With

$$\begin{aligned}\hat{x}_S(m,u_R) &\stackrel{\text{def}}{=} \frac{K}{r_{\max}(1-\alpha_{SR}\alpha_{RS})}\left(\frac{\alpha_{SR}\,m\,\mathrm{e}^{g\,u_R}}{k+b\,u_R}-\frac{m}{k}+\alpha_{SR}\,d\,\mathrm{e}^{g\,u_R}\right)\\ &\quad+\frac{K\,(r_{\max}-d-\alpha_{SR}\,r_{\max})}{r_{\max}(1-\alpha_{SR}\alpha_{RS})},\\ \hat{x}_R(m,u_R) &\stackrel{\text{def}}{=} \frac{K}{r_{\max}(1-\alpha_{SR}\alpha_{RS})}\left(-\frac{m\,\mathrm{e}^{g\,u_R}}{k+b\,u_R}+\frac{\alpha_{RS}\,m}{k}-d\,\mathrm{e}^{g\,u_R}\right)\\ &\quad+\frac{K\,(r_{\max}-\alpha_{RS}r_{\max}+\alpha_{RS}\,d)}{r_{\max}(1-\alpha_{SR}\alpha_{RS})},\end{aligned}$$

we obtain the following ecological equilibria $(x_S^*(m,u_R), x_S^*(m,u_R))$:

$$(x_S^*(m,u_R),x_R^*(m,u_R)) \stackrel{\text{def}}{=} \begin{cases} (0,0), & \text{if} \quad \hat{x}_S\le 0,\ \hat{x}_R\le 0,\\ (\max\{\bar{x}_S,0\},0), & \text{if} \quad \hat{x}_S\ge 0,\ \hat{x}_R\le 0,\\ (0,\max\{\bar{x}_R,0\}), & \text{if} \quad \hat{x}_S\le 0,\ \hat{x}_R\ge 0,\\ (\hat{x}_S,\hat{x}_R), & \text{if} \quad \hat{x}_S>0,\ \hat{x}_R>0, \end{cases} \tag{4.10}$$

with

$$\bar{x}_S = K\left(1 - \frac{d + \frac{m}{k}}{r_{\max}}\right),$$
$$\bar{x}_R = K\left(1 - \frac{d + \frac{m}{k+b\,u_R}}{r_{\max}} e^{g\,u_R}\right).$$

In Figure 4.3, we demonstrate the areas in the (m, u_R)-plane with different types of the ecological equilibria (4.10).

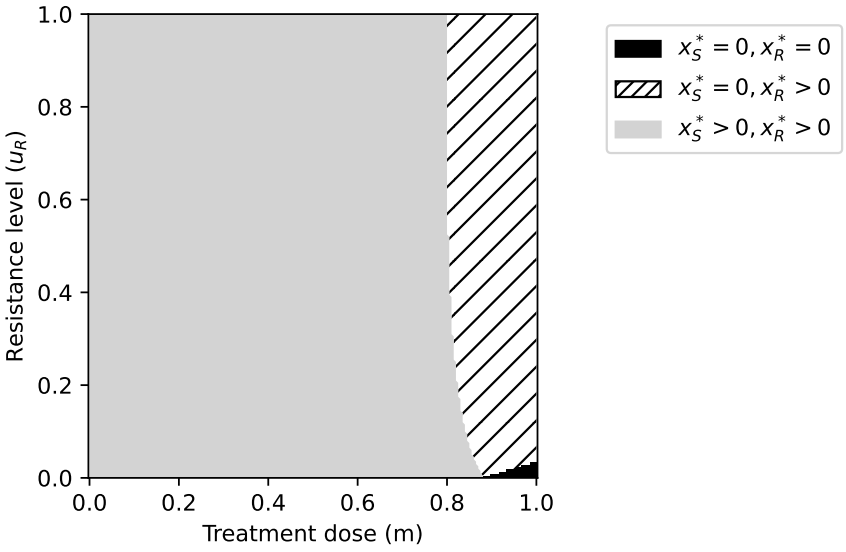

Figure 4.3: The $x_S^*(m, u_R)$ and $x_R^*(m, u_R)$ values corresponding to different m and u_R values. We identify three possible regions: The black area corresponds to $(m, u_R) \in [0,1] \times [0,1]$ where $x_S^*(m, u_R) = x_R^*(m, u_R) = 0$, the dashed area corresponds to $(m, u_R) \in [0,1] \times [0,1]$ where $x_S^*(m, u_R) = 0$, $x_R^*(m, u_R) > 0$, and the gray area indicates the region $(m, u_R) \in [0,1] \times [0,1]$ where both populations coexist, i.e., $x_S^*(m, u_R) > 0$, $x_R^*(m, u_R) > 0$. Parametrization: $\delta = 0.7$, $r_{\max} = 0.45$, $g = 0.8$, $K = 10000$, $d = 0.01$, $k = 2$, $b = 10$, $\alpha_{SS} = \alpha_{RR} = 1$, $\alpha_{SR} = 0.15$, $\alpha_{RS} = 0.9$.

Extending the Pressley *et al.*'s model to include competition coefficients creates a non-monotonic relation between the total population size at the ecological equilibrium and treatment dose. In Pressley *et al.*'s model, the total equilibrium population size decreases as the treatment dose increases, which means that lower constant treatment doses will also fail if MTD fails. Therefore, we consider the extended model more realistic for many cancers and treatments. The cell population is considered extinct in areas where $x_S^* = 0$ and $x_R^* = 0$.

4.3.2. THE BEST RESPONSE CURVES OF CANCER AND THE PHYSICIAN

The best response curve of the resistant cancer cell population (ESS curve) is determined using (4.6). With $\hat{u}_R(m) \overset{\text{def}}{=} -\frac{k}{b} - \frac{m}{2bd} + \sqrt{\frac{m^2}{4b^2d^2} + \frac{m}{bdg}}$,

$$u_R^*(m) = \begin{cases} 0, & \text{if} \quad \hat{u}_R(m) < 0, \\ \hat{u}_R(m), & \text{otherwise.} \end{cases} \tag{4.11}$$

Note that $\hat{u}_R(m)$ increases with m. The best response curve $m^*(u_R)$ of the leader is determined by maximizing their objective function $Q(m, u_R^*(m), x^*(m, u_R^*(m)))$ with respect to m. Note that the objective function is differentiable and concave in m, and, therefore, $m^*(u_R)$ is calculated by setting the first derivative of the objective function to zero and projection to $[0,1]$ whenever the result falls outside of this interval[2]. Letting $A = \frac{(1-\alpha_{SR})e^{gu_R}}{k+bu_R} + \frac{1-\alpha_{RS}}{k}$ and

$$\hat{m}(u_R) \overset{\text{def}}{=} \frac{c_1 A\left(r_{\max}(2-\alpha_{RS}-\alpha_{SR}) - (1-\alpha_{RS})d - (1-\alpha_{SR})de^{gu_R}\right)}{c_1 A^2 + c_3 r_{\max}^2 (1-\alpha_{SR}\alpha_{RS})^2},$$

the leader's best response then reads as

$$m^*(u_R) = \begin{cases} 0, & \text{if} \quad \hat{m}(u_R) < 0, \\ \hat{m}(u_R), & \text{if} \quad \hat{m}(u_R) \in [0,1], \\ 1, & \text{otherwise.} \end{cases} \tag{4.12}$$

The parameter c_2 (determining the impact of treatment-induced resistance on the objective function) has no effect on the leader's best response curve and, therefore, does not influence the Nash solution. However, the parameter c_2 affects the Stackelberg solution.

4.3.3. IDENTIFYING THE NASH AND STACKELBERG EQUILIBRIA

The Nash equilibrium lies at the intersection of the best response curves of cancer cells and the physician, defined by (4.11) and (4.12), respectively. The Stackelberg equilibrium is calculated numerically through (4.9). It corresponds to the point on the cancer's best response curve that maximizes the physician's objective function.

Figure 4.4A shows a particular parametrization of the model for which the MTD and the Nash and Stackelberg equilibria all lie in the stabilization region. The physician's best response, calculated through (4.12), is shown as a dashed line. Figure 4.4B shows that for this parametrization, the evolutionarily enlightened (Stackelberg) strategy leads to the highest value of the objective function, followed by the ecologically enlightened (Nash) strategy, while MTD leads to the lowest value of the objective function. Moreover, the evolutionarily enlightened (Stackelberg) strategy corresponds to both a lower treatment dose/toxicity and lower treatment-induced resistance than the ecologically enlightened (Nash) strategy and MTD.

[2] Details on maximizing the quality of life function is in appendix B.2. This appendix is not part of the original paper.

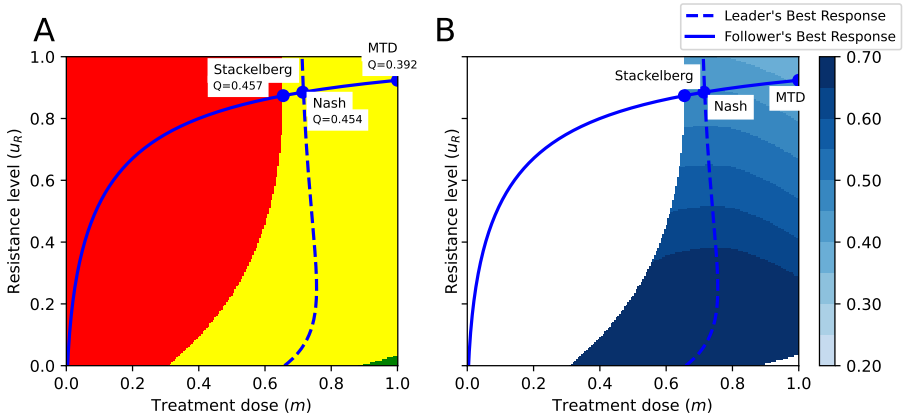

Figure 4.4: The outcomes of the MTD, ecologically enlightened (Nash), and evolutionarily enlightened (Stackelberg) strategies of the physician in the SEG against cancer: The yellow and red regions represent combinations of u_R and m leading to tumor stabilization and progression, respectively. **A)** Illustration of the outcomes of the Stackelberg, Nash, and MTD treatment strategies and corresponding values of the objective function. **B)** The level curves of the objective function and outcomes of the Nash, Stackelberg, and MTD treatment strategies. Parametrization: $\delta = 0.7$, $r_{\max} = 0.45$, $g = 0.8$, $K = 10000$, $d = 0.01$, $k = 2$, $b = 10$, $\alpha_{SS} = \alpha_{RR} = 1$, $\alpha_{SR} = 0.15$, $\alpha_{RS} = 0.9$, $Q^{\max} = 1$; $c_1 = 0.5$, $c_2 = 0.25$, $c_3 = 0.25$.

The Nash and Stackelberg equilibria of a Stackelberg evolutionary game can coincide under certain conditions, for instance, if the leader's strategy does not affect the evolution of the resistance level of the cancer cells, as proven by Stein et al. (2023).[3] Figure 4.5 illustrates the case where the Nash and Stackelberg solutions coincide, due to the fact that the objective function does not include treatment-induced resistance (Stein et al., 2023). However, even in this situation, the MTD results in a lower value of the objective function than the Nash and Stackelberg strategies. In appendix B.1, the local stability of the eco-evolutionary equilibria is determined through numerical analysis of the Jacobian matrix. Furthermore, in this appendix, we illustrate the domain of attraction of the Nash equilibrium.

4.4. DISCUSSION

Cancer treatment is a Stackelberg (or leader-follower) evolutionary game. Recent works, including those of Staňková et al. (2019), Wölfl et al. (2022), Stein et al. (2023), and Kleshnina et al. (2023), suggested that physicians should exploit the advantages of their leadership role in this game. This is because the physician, unlike the cancer cells, can anticipate and steer the cancer's eco-evolutionary response to treatment, while the cancer cells can only adapt to the current and past physician's actions. Staňková et al. (2019) proposed that in order to utilize their leadership role fully, the physician needs to (i) set the treatment goal, as different treatment goals will correspond to different treatment

[3] The analogy with a standard leader-follower game is that if the follower has a strictly dominant action, then the outcomes of the subgame perfect equilibrium of the leader-follower game and of the Nash equilibrium of the simultaneous move game coincide.

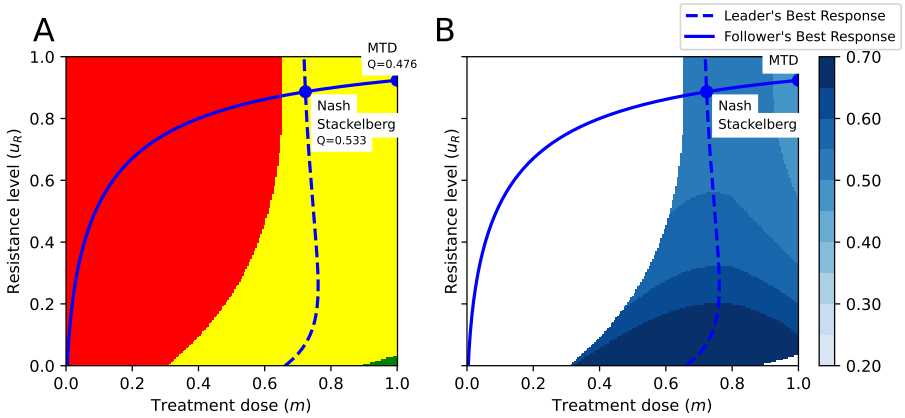

Figure 4.5: The outcomes of the MTD, ecologically enlightened (Nash) and evolutionarily enlightened (Stackelberg) strategies of the physician in the SEG against cancer: The yellow and red regions represent tumor burden stabilization at a safe level and progression, respectively. **A)** The Nash and Stackelberg strategies coincide. **B)** The values of the physician's objective function coincide with the Nash and Stackelberg strategies and are better than that of MTD. Parametrization: $\delta = 0.7$, $r_{\max} = 0.45$, $g = 0.8$, $K = 10000$, $d = 0.01$, $k = 2$, $b = 10$, $\alpha_{SS} = \alpha_{RR} = 1$, $\alpha_{SR} = 0.15$, $\alpha_{RS} = 0.9$, $Q^{\max} = 1$; $c_1 = 0.67$, $c_2 = 0$, $c_3 = 0.33$.

strategies, (ii) introduce a resistance management plan, and (iii) perform after-action reports, adjusting assumptions and parameters based on how different patients respond to the treatment (see also (Zhang et al., 2022)).

In this work, we focused on a specific treatment goal, finding the constant treatment dose maximizing the physician's objective function once the tumor burden can be stabilized at a level viable for the patient. We did so by utilizing the Stackelberg evolutionary game framework where cancer is modeled as an evolutionary game, extending the polymorphic cancer model by Pressley et al. (2021). In their paper, Pressley et al. (2021) compared the time to progression of Zhang et al. (2017)'s adaptive protocol to that of the maximum tolerable dose. They demonstrated that, while the adaptive protocol always extended the time to progression, in some cases, this improvement was rather small.

Rather than analyzing the transient phase of controlling the tumor burden and prolonging the time to progression (Cunningham et al., 2018; Cunningham et al., 2020; Gluzman et al., 2020; Pressley et al., 2021), here we have focused on finding a constant treatment dose maximizing the physician's objective function when the tumor burden can be stabilized (Basar et al., 2024). This physician's objective function depends on the tumor burden, treatment toxicity, and the treatment-induced resistance in cancer cells. The weights in this objective function can be adjusted to capture the importance of the tumor burden, resistance level, and treatment toxicity for each patient, in line with patient-centered care (Reynolds, 2009). Subsequently, we analyzed the impact of different treatment strategies in terms of this objective function: MTD, an ecologically enlightened therapy, and an evolutionarily enlightened therapy.

We have shown that the evolutionarily enlightened therapy leads to at least as high values of the objective function as the ecologically enlightened therapy, while the MTD

leads to the lowest objective function values. For most parametrizations, the ecologically enlightened therapy leads to a higher treatment dose than the evolutionarily enlightened therapy, while both are less toxic than MTD.

For some parametrizations, the evolutionarily enlightened treatment corresponding to the Stackelberg strategy of the Stackelberg evolutionary game of cancer treatment leads to an outcome that is at the boundary of the progression region (Figure 4.4). This means that a small deviation in estimating the cancer cells' response would lead to growth of the tumor burden. However, upon observation of this cancer growth, the treatment dose could be increased a little, and the cancer would be stabilized again; thus, aiming at the Stackelberg strategy is still the best option.

In general, reaching any equilibrium requires frequent measurements of the tumor volume and its composition and depends on many factors, such as the speed of the cancer's response to treatment. However, the physician may still be able to find the Stackelberg equilibrium by dose de-escalation, meaning starting from the MTD and applying small adjustments to the dose until the desired equilibrium is reached, as suggested by, among others, Enriquez-Navas et al. (2016) and Cunningham et al. (2020). Another effective strategy may be starting from a minimal effective dose and gradually increasing it until an equilibrium is reached, which seems even more effective in a model similar to that of Zhang et al. (2017). This strategy has not yet been tested in clinical trials but may have potential (Cunningham et al., 2020; M. A. Strobl et al., 2024).

The model that we studied included treatment-induced resistance as a quantitative trait. Another option is to model resistance as a qualitative trait (Archetti, 2016; Basanta et al., 2008; Bayer et al., 2018; Bayer et al., 2022; Gluzman et al., 2020; Kaznatcheev et al., 2017; Muros et al., 2017; Salvioli, Vandelaer, et al., 2024; Soboleva et al., 2025; You et al., 2017). Our model can be also extended to include several quantitative traits, evolving in response to multiple drugs and therapeutics (Kleshnina et al., 2023; Reed et al., 2020; Stein et al., 2023). Of interest in such models are cross-sensitivities (Yoon et al., 2018, 2021), co-resistance (Nichol et al., 2019), and more possible effective treatment strategies available in a multi-drug setting, such as evolutionary double bind therapy (Cunningham et al., 2011; Gatenby, Brown, & Vincent, 2009; Maley et al., 2004).

In our model, the cost of resistance is associated with the growth rate of the resistant cancer cell type. Alternatively, one could consider models where either the carrying capacity (Pressley et al., 2021) or the competition coefficients (Vincent & Brown, 2012) explicitly depend on the resistance level.

In accordance with some parametrizations of the model presented here, there are cancers for which MTD can effectively stabilize tumors (Ardévol Martinez et al., 2023; Ghaffari Laleh et al., 2022; Kaznatcheev et al., 2019). Also, there are metastatic cancers where we may be able to aim for a more ambitious treatment goal than tumor stabilization, namely for cure (Dujon et al., 2021; Gatenby et al., 2019). For example, in multiple myeloma, there is a discussion on when to aim for a cure instead of containment. Strategies for these two goals differ substantially (Dimopoulos et al., 2020; Rajkumar, 2011; Rajkumar & Kumar, 2020) and game-theoretic models fitted with patient data may help us to find a suitable treatment goal, corresponding evolutionary therapy, and predict the patient/tumor response to such therapy.

Our future research, therefore, will focus on the analysis of the properties of a wider

class of game-theoretical models based on classical dynamics (Ghaffari Laleh et al., 2022; Kuang et al., 2016), extended into a game-theoretic setting, and validating these models through in-vitro and in-vivo data, similarly to how it was done for other cancer models (Kaznatcheev et al., 2019; Soboleva et al., 2025; Spekking et al., 2024). The ultimate goal is to analyze multiple dynamics that fit the data well, evaluate alternative hypotheses and models, and propose suitable treatment goals and evolutionary therapies to improve patient quality of life and survival.

5

REPRESENTATIVE EVOLUTIONARY GAME MODELS OF NSCLC GROWTH: INSIGHTS FROM *in-vitro* EXPERIMENTS

Identifying representative mathematical models of cancer dynamics aids in understanding and predicting their behavior, enabling the development of more effective treatments. In this paper, we fit two-population models to the non-small cell lung cancer (NSCLC) data obtained from an *in-vitro* experiment presented by *Kaznatcheev et al.*. In this experiment, the populations of drug-sensitive and drug-resistant cells are measured in environments with and without Alectinib drug and in the presence or absence of cancer-associated fibroblasts (CAFs). We compare the logistic, Gompertz, and von Bertalanffy growth models, as well as Norton-Simon, linear, and ratio-dependent drug efficacy terms, by analyzing this dataset. In the context of population ecology, our model includes density independence through growth rate parameters, density dependence through carrying capacity parameters, and frequency-dependent interactions through inter-type competition coefficients. Furthermore, we employ these models to investigate how Alectinib and CAFs modify model parameters and, consequently, the interactions between cancer cells. We determine that the logistic model with ratio-dependent drug efficacy more accurately represents the mono-culture data compared to the aforementioned growth models and drug efficacies. Using the parameter estimates for growth rate and carrying capacity from mono-culture data, we derive the inter-type competition coefficients for co-culture data. Statistical tests demonstrate that the growth rate and carrying capacity parameters do not significantly change by the presence or absence of CAFs. Cell interactions in co-cultures, however, vary across different environments due to changes in competition coefficients and drug efficacy parameters. We demonstrate that in the presence of CAFs, both sensitive and resistant cells can coexist, while in the

presence of the drug, resistant cells outcompete sensitive ones[1].

5.1. INTRODUCTION

Lung cancer is one of the most common cancers diagnosed (Siegel et al., 2024), and it is the leading cause of cancer death (Kratzer et al., 2024). Despite advances in treating cancer, cures for metastatic cancers are rare (Dong et al., 2019; Gatenby & Brown, 2020; Savage et al., 2009), and mathematical modeling offers tools to help with innovative approaches. Mathematical oncology can quantify the agreements between mathematical models of cancer growth and experimental outcomes (Rockne et al., 2019; Sebastião et al., 2022), and help to develop more effective treatment strategies.

Increasingly, cancer progression and growth are viewed as an evolutionary game where the best strategy (heritable trait) of an individual cancer cell depends upon the strategies of its neighboring cancer cells and the therapy (Altrock et al., 2015; Bayer et al., 2022; Gatenby & Vincent, 2003; Wölfl et al., 2022). We can also assume cancer is involved in a leader-follower (Stackelberg) evolutionary game where the physician (leader) applies therapy to which the cancer cells (followers) respond (Kleshnina et al., 2023; Staňková et al., 2019; Stein et al., 2023). Cancer cells' interactions with their environment include competition for resources, co-opting of normal cells, responding to immune cells, and engaging in public goods games through angiogenesis and ecosystem engineering (Hanahan & Weinberg, 2011; Salimi Sartakhti et al., 2017; Zhang et al., 2022).

Competition within evolutionary games can be driven by three types of processes (Mueller, 2020; You et al., 2017). First, there can be density-independent processes where a cancer cell's survival and proliferation rate are (nearly) independent of other cells – this is typical of population growth at low population sizes when space and nutrients are abundant. Second, density-dependent processes. These occur when a cancer cell suffers lower fitness (prospects for survival and proliferation) as the density of cancer cells increases, typically occurring through lack of space or nutrients or build-up of toxins. Third, there are frequency-dependent interactions which occur when the fitness of a cell depends on its trait and the frequency of traits among the other cancer cells (Freischel et al., 2021).

In cancer, there is growing interest in competition assays and experiments where two (or sometimes more) cell lines are followed in mono- and co-cultures to see how the populations grow, interact, and do or do not coexist. Such experiments draw from a long tradition in ecology of competing single-celled protists such as Paramecium or yeast. This tradition goes all the way back to the seminal experiments of Gause in the 1920s and 30s (Gause, 1932). For cancer, such experiments can reveal the cost of resistance (competing a sensitive and resistant cell line under the presence or absence of drug therapy) (Madan et al., 2022), the role of glycolysis (competing highly glycolytic cell lines against highly oxidative phosphorylation cell lines) (Silva et al., 2012), effects of immune cells or fibroblasts (competing cell lines thought to differ in the costs and benefits associated with normal cells), effects of microenvironmental conditions (competing cells lines with differing responses to pH, nutrient deprivation, growth factors, etc.) (Kaznatcheev et al., 2019; Mayer et al., 2023; Parker et al., 2021), effects of different therapies singly or

[1] This chapter is published as a preprint (Garjani et al., 2025).

in combination (competing cell lines through having differing responses), and effects of gene knock-out experiments to discern metabolic pathways (competing knock-out cell lines against their sensitive cell line) (Zhong et al., 2024).

Considering the interactions between the cells as a game, there are roughly three ways to model the trajectory and outcome of competition experiments involving two cell lines. The simplest is to focus entirely on frequency-dependent interactions by using a 2×2 matrix game where the cell types represent two strategies, and they experience payoffs associated with intra-cell line and inter-cell line interactions. The outcomes can be determined by estimating entries of the payoff matrix and using the replicator equation to derive dynamics towards an equilibrium (Basanta et al., 2012). This approach subsumes any density-independent and density-dependent processes into the 4 elements of the payoff matrix. A more sophisticated version of the 2×2 matrix game occurs when the game is no longer bilinear, meaning that the success of an individual is no longer a linear weighted averaging of payoffs based on the two cell lines. Rather, payoffs can be a nonlinear (concave up or concave down) combination of payoffs from changing the frequency of cell types (Vincent & Brown, 2012). To model the trajectory and outcomes, one requires fitness functions based on these nonlinear relationships that can be used to directly derive frequency dynamics. Such a frequency-dependent model will produce trajectories that deviate somewhat from the replicator equation based on the degree of nonlinearities. A third approach uses ecological models of competition, such as Lotka-Volterra (L-V) competition equations. Such a model can include density-independence, ρ, density dependence via a carrying capacity, K, and frequency-dependent interactions via the inter-type competition coefficients, α_{ij}. The outcomes of and trajectories of such a model, like the L-V competition equations, are determined by these parameters. We use this model. Properly fitting such a model requires relatively large numbers of treatment combinations using initial conditions. Namely, co-cultures seeded at different frequencies of cell types and ideally at different total initial number of cells.

Here, we test for frequency- and density-dependent interactions between two cancer cell lines using data from Kaznatcheev et al. (2019). They measured the population of two cell lines using 12 initial ratios from zero to one, under four environmental conditions: all combinations of the presence and absence of cancer-associated fibroblasts (CAFs) and the presence and absence of the drug. In their study, Kaznatcheev et al. (2019) fit their data to the replicator equation, which only considers the frequency dynamics of the two cell types, not the dynamics of their population sizes.

Here, we expand their analyses by explicitly modeling the population dynamics. First, we fit the data to three models of population growth (Logistic, Gompertz, von Bertalanffy (Ghaffari Laleh et al., 2022; Murphy et al., 2016)) that are commonly applied to cancer. We extend the von Bertalanffy growth dynamics to consider competition between the two cell types in a manner similar to Logistic and Gompertz (Martin et al., 1992; Viossat & Noble, 2021). Second, we compare three ways of including drug efficacy (M. Strobl et al., 2023): Norton-Simon model (Norton & Simon, 1986), density-independent mortality (Norton & Simon, 1977), and density-dependent mortality (West & Newton, 2017). Third, we test how intrinsic growth rates (ρs as density-independent effects), carrying capacities (Ks as density-dependent effects), and competition coefficients (α_{ij}s as frequency-dependent effects) vary with cell type, presence and absence

of CAFs, and presence and absence of drug. Finally, we compare our model predictions for the outcomes of competition under the four environments to those of Kaznatcheev et al. (2019).

5.2. METHODS

Kaznatcheev et al. (2019) conducted competition experiments in cell culture using two non-small cell lung cancer cell lines: one sensitive (parental) and the other resistant to the drug Alectinib. Experimental treatments consisted of all combinations of the presence or absence of cancer-associated fibroblasts (CAFs) and the presence or absence of Alectinib, and 8 seeding frequencies (0, 0.1, 0.2, 0.4, 0.6, 0.8, 0.9, and 1 ratios of sensitive to resistant cells). Each combination was replicated 6 times. To measure population dynamics, sensitive and resistant cell lines were labeled with green fluorescent protein and mCherry fluorescent proteins, respectively. Population sizes as measured by fluorescence intensity were recorded at intervals of 4 hours from time 0 to 120 hours. When present, Alectinib was introduced into wells as a single dose after 20 hours. Kaznatcheev et al. (2019), in evaluating the outcomes of competition, only considered the frequency-dynamics of cells within the wells, namely the ratio of sensitive cells to total population size. In what follows, we use their entire time series of the cancer cells' population sizes to fit models from population ecology. We investigate models that consider density independence, density dependence, and frequency dependence. We first evaluate how well the data fit three commonly used growth models of population dynamics, adjusted for two-species competitive interactions. Next, we determine the representative drug efficacy model. Then, focusing on the Lotka-Volterra competition models, we test how cell lines, fibroblasts, and the drug influence intrinsic growth rates, carrying capacities, and competition coefficients. Finally, we assess how these parameter variations impact interactions among different cell types.

5.2.1. LOGISTIC, GOMPERTZ, AND VON BERTALANFFY GROWTH MODELS

We look into two-population extensions of the Logistic, Gompertz, and von Bertalanffy models. The two population models with Logistic and Gompertz growth have been explored for cancer population growth in the literature (Freischel et al., 2021; Viossat & Noble, 2021). The general forms of these two-population models with Norton-Simon drug effects are presented in Equations 5.1 and 5.2, respectively.

$$\begin{aligned}\dot{S}(t) &= \rho_1\Big(1-\frac{S+\alpha_{SR}R}{K_1}\Big)(1-\lambda C(t))S(t)\\ \dot{R}(t) &= \rho_2\Big(1-\frac{\alpha_{RS}S+R}{K_2}\Big)R(t).\end{aligned} \tag{5.1}$$

$$\begin{aligned}\dot{S}(t) &= \rho_1 \ln\Big(\frac{K_1}{S(t)+\alpha_{SR}R(t)}\Big)(1-\lambda C(t))S(t)\\ \dot{R}(t) &= \rho_2 \ln\Big(\frac{K_2}{\alpha_{RS}S(t)+R(t)}\Big)R(t).\end{aligned} \tag{5.2}$$

The three variables $S(t)$, $R(t)$, and $C(t)$ show the sensitive to drug population, the resistant to drug population, and the amount of drug. We extend von Bertalanffy growth

dynamics (Ghaffari Laleh et al., 2022) to a two-population model in Equation 5.3.

$$\begin{aligned}\dot{S}(t) &= \rho_1\Big(1-\frac{\sqrt[3]{S+\alpha_{SR}R}}{K_1}\Big)(1-\lambda C(t))S^{\frac{2}{3}}(t)\\ \dot{R}(t) &= \rho_1\Big(1-\frac{\sqrt[3]{\alpha_{RS}S+R}}{K_2}\Big)R^{\frac{2}{3}}(t)\end{aligned} \tag{5.3}$$

These models consider density independence through ρ_1 and ρ_2, density dependence through K_1 and K_2, frequency dependence through α_{SR} and α_{RS}, and drug efficacy through λ. We fit the data to investigate how many and which of these parameters are supported by the dataset derived from the *in-vitro* experiment.

We fit each model to each repetition of the experiment individually to examine the variability in parameter estimates. The model simultaneously predicts values for resistant and sensitive cells, and given that, in most instances, one population type significantly outnumbers the other, we use a weighted sum of squared errors. The corresponding cost function for each well is denoted as:

$$J_w = \sum_{i\in\{S,R\}}\sum_{t=12}^{116}\Big(\frac{d_{it}^{measured}-d_{it}^{model}}{\max_t(d_i^{measured})}\Big)^2. \tag{5.4}$$

where $i \in \{S,R\}$ denotes the population type, and $t \in \{12,16,...,116\}$ is the time point in the series. The equation $\frac{d_{it}^{measured}-d_{it}^{model}}{\max_t(d_{it}^{measured})}$, presents the error value for cell of type i at time t. We start from $t = 12$ hour to let the cells settle in the well as suggested by Kaznatcheev et al. (2019). The $d_{it}^{measured}$ is the measured population at time t for population type i, $d_i^{measured}$ is the vector of the measured population of type i from time 12 to 116 (measured every four hours), and d_{it}^{model} is the predicted population size using the proposed model.

We use the Chi-square error ($\chi^2 = J_w$) and AIC ($N\ln(\frac{\chi^2}{N})+2N_{varys}$ where N_{varys} is the number of variables, and N is the number of data points) as our goodness of fit measures to compare the fit results in different wells.

We estimate the model parameters by minimizing the cost function Equation 5.4, considering the difference between the predicted data points from time 12 hours until time 116 hours and the measured data points. To fit the data to the two-population models, the initial values for the resistant and sensitive populations are set to the measured data values at 12 hours, as Kaznatcheev et al. recommended in their paper. Here, we fit the observations in each well to the model separately to ensure that the intra-subject variations are not averaged out. This helps in assessing whether significant variations occur because of differing experimental conditions, such as varying initial ratios or initial populations.

These models include a maximum of seven different parameters (ρ_1, ρ_2, K_1, K_2, α_{SR}, α_{RS}, and λ). First, we fit the data to a model with two unknown parameters (same growth rates and carrying capacities for both cancer cell types) in cases where the drug is not present and a model with three unknown parameters (same growth rates and carrying capacities for both cancer cell types and drug efficacy for the sensitive population) when the drug is present. We increase the number of unknown parameters to at most 5, as

seen in Table 5.1. To prevent overfitting, we increase the number of parameters gradually, considering equal ρ_1 and ρ_2 values, equal K_1 and K_2 values, and $\alpha_{SR} = \alpha_{RS} = 1$. We assume distinct growth rates for the two populations $\rho_1 \neq \rho_2$ for the second fit (Logistic 2 of Table 5.1). For the third and fourth fits, we assume that the model has the same growth rates and one competition coefficient equal to one and an unknown α_{SR} or α_{RS}, respectively. Finally, we fit the model with distinct competition coefficients and the same growth rates and carrying capacities for both populations. The models are illustrated in Table 5.1. We repeat the same stepwise increase in the number of unknown parameters

Logistic 1	$\dot{S}(t) = \rho\left(1 - \frac{S+R}{K}\right)(1 - \lambda C(t))S(t)$ $\dot{R}(t) = \rho\left(1 - \frac{S+R}{K}\right)R(t).$
Logistic 2	$\dot{S}(t) = \rho_1\left(1 - \frac{S+R}{K}\right)(1 - \lambda C(t))S(t)$ $\dot{R}(t) = \rho_2\left(1 - \frac{S+R}{K}\right)R(t).$
Logistic 3	$\dot{S}(t) = \rho\left(1 - \frac{S+\alpha_{SR}R}{K}\right)(1 - \lambda C(t))S(t)$ $\dot{R}(t) = \rho\left(1 - \frac{S+R}{K}\right)R(t).$
Logistic 4	$\dot{S}(t) = \rho\left(1 - \frac{S+R}{K}\right)(1 - \lambda C(t))S(t)$ $\dot{R}(t) = \rho\left(1 - \frac{\alpha_{RS}S+R}{K}\right)R(t).$
Logistic 5	$\dot{S}(t) = \rho\left(1 - \frac{S+\alpha_{SR}R}{K}\right)(1 - \lambda C(t))S(t)$ $\dot{R}(t) = \rho\left(1 - \frac{\alpha_{RS}S+R}{K}\right)R(t).$

Table 5.1: Models inspired by Logistic growth. Sensitive and resistant population growth follows the ODE model presented at each block. The unknown parameters in the Logistic 1 model are ρ, K, and λ. Unknown parameters in Logistic 2 are ρ_1, ρ_2, K, and λ. Unknown parameters in Logistic 3 are ρ, K, α_{SR}, and λ. Unknown parameters in Logistic 4 are ρ, K, α_{RS}, and λ. Unknown parameters in Logistic 5 are ρ, K, α_{SR}, α_{RS}, and λ.

for Equations 5.2 and 5.3. The tables containing these models are in the appendix (Table C.1 and Table C.2). In total, we fit 36 wells to 15 different models. We compare the error and AIC distribution of the different models to determine the appropriate models that fit our data.

5.2.2. DRUG EFFICACY IN THE TWO-POPULATION MODEL

In addition to growth dynamics, we analyze three models of drug efficacy: the Norton-Simon model, density-independent mortality, and density-dependent mortality. The three mentioned drug effects for the logistic model are illustrated in Equations 5.5 - 5.7.

1. Norton-Simon model:

$$\dot{S}(t) = \rho_1\left(1 - \frac{S}{K_1}\right)(1 - \lambda C(t))S(t) \tag{5.5}$$

2. Linear drug effect:

$$\dot{S}(t) = \rho_1\left(1 - \frac{S}{K_1}\right)S(t) - \lambda C(t) \tag{5.6}$$

3. Ratio-dependent drug effect:

$$\dot{S}(t) = \rho_1\left(1 - \frac{S}{K_1}\right)S(t) - \lambda C(t)S(t) \tag{5.7}$$

We determine the best drug efficacy model by fitting it to the monoculture data. Evidence suggests the model's structural characteristics (e.g., carrying capacity values, the representative growth model, or drug efficacy) for monoculture and co-culture are similar (Rodriguez Messan et al., 2021). Therefore, we use the parameter estimates of the monoculture to develop the two-population model.

5.2.3. IMPACT OF CELL TYPE AND THE PRESENCE OR ABSENCE OF CAFS AND DRUG ON MODEL PARAMETERS

By fitting data from each well to the model separately, we get replicate parameter estimates, which allow us to compare within-category variance and between-category variance. We use ANOVA (Analysis of Variance) to test the impact of CAFs and therapy on growth rates (density-independent parameters ρ) and carrying capacities (density-dependent parameters K).

First, we find the growth rate and carrying capacity of monoculture-sensitive and resistant cells in DMSO and CAF environments. Next, we use a two-way ANOVA test for the effects of population type (sensitive and resistant), environment (DMSO and CAF), and their interaction. Then, we use these estimates to estimate the drug efficacy term when the drug is present. The fitted one-population model of sensitive cells:

$$\dot{S} = \rho_1 S\left(1 - \frac{S}{K_1}\right) - \lambda SC(t) \tag{5.8}$$

The fitted one-population model of resistant cells:

$$\dot{R} = \rho_2 R\left(1 - \frac{R}{K_2}\right) \tag{5.9}$$

The co-culture experiment is also carried out in four distinct environments. We use the growth rate, carrying capacity, and drug effect parameters derived from the monoculture experiment to find the competition coefficients in the co-culture. This stepwise approach leverages our prior knowledge of the model in monocultures. The competition coefficients are the only variables that change while fitting the co-culture data.

5.2.4. EFFECT OF THE ENVIRONMENT ON THE INTERACTIONS AMONG THE CELLS

The experiment is conducted under four environmental conditions, accounting for the presence or absence of CAFs and the presence or absence of the drug. Kaznatcheev et al. (2019) only investigated frequency, not density-dependent dynamics. They used the replicator equation to forecast outcomes. They predicted the occurrence of a mixed equilibrium (where both sensitive and resistant cells coexist) only in an environment with the presence of CAFs, while anticipating the extinction of sensitive cells in all other

environments. We fit the data to a model that incorporates density dependence, density independence, and frequency dependence. We examine the influence of the environment on each parameter based on the values of the fitted parameters to gain more insight into the effect of the environment.

5.3. RESULTS

5.3.1. COMPARING LOGISTIC, GOMPERTZ, AND VON BERTALANFFY GROWTH MODELS

Our analysis demonstrates that fitting the two-population Logistic, Gompertz, and von Bertalanffy models outlined in Section 5.2.1 results in satisfactory fits for all models with at least three fitted parameters. We find AIC and error distributions for specific environments or a specific number of unknown parameters that suggest one growth model is better. Still, the superiority of each growth model has no consistency. This can be due to the high correlation among the parameters and the similarities of the models. The median error of the 15 models fit is illustrated in Fig 5.1. As shown in this figure, the median error is large when there are only two unknown parameters, such as in the model referred to as "Logistic 1" in Table 5.1. However, the difference between the error values for the rest of the models is very small, as presented in Fig 5.1. Comparisons based on the AIC align with the conclusions drawn from the error metric, as illustrated in Appendix Fig C.1.

Note that, allowing all the parameters to vary independently for each well results in overfitting, shown by minimal variations in error values as the number of parameters increases. There is insufficient variation in goodness of fit metrics for determining the best growth model. Therefore, we fitted the logistic model as it makes no assumptions regarding nonlinear density-dependence. Results from an ANCOVA provide additional support for this decision, as presented in the Appendix C.3.

5.3.2. DETERMINING DRUG EFFICACY TERM

We analyzed three treatment effects: Norton-Simon, linear, and ratio-dependent drug efficacies, introduced in Equations 5.5, 5.6, and 5.7, respectively. Among these three models, ratio-dependent drug efficacy was more representative of the data and led to smaller chi-square errors, as observed in Figure 5.2. Furthermore, ratio-dependent drug efficacy aligns with the accepted biological understanding of population growth in relation to resource scarcity, whereas the Norton-Simon model does not. Our model uses $C(t) = 1$ when the drug is administered, since the drug is administered in a constant dose (Kaznatcheev et al., 2019). Therefore, in the Norton-Simon model, for any $\lambda > 1$, if the population exceeds the carrying capacity K, the population derivative $\dot{S}$ becomes positive and can increase indefinitely. Furthermore, for $\lambda < 1$, the model is not representative of a decreasing population, indicating that this model does not accurately reflect the results of this experiment, where certain wells exhibit population decline.

5.3.3. PARAMETER VARIATIONS ACROSS CELL TYPES AND CAFS PRESENCE

We used the logistic growth and the ratio-dependent treatment effect determined in sections 5.3.1 and 5.3.2 to build the co-culture model. First, we fitted the sensitive and resis-

Figure 5.1: Chi-square error for the two-population model fits. Heatmap of the median of error values is for the proposed fifteen models in Tables 5.1, C.1, C.2 that account for Logistic, Gompertz, and von Bertalanffy growth models with different numbers of unknown parameters. The Logistic 1, Gompertz 1, and Von Bertalanffy 1 models have ρ, K, and λ as unknown parameters. The maximum number of unknown parameters in these models is five. Different growth models with more than three parameters yield insignificant variations in error. This means assuming more than four parameters leads to overfitting.

tant cell population in wells where only one cell type is present (monocultures) in DMSO and CAF environments. We found estimates for growth rates of sensitive and resistant cells (ρ_1 and ρ_2) and their carrying capacities (K_1 and K_2). We observed that the growth rate and carrying capacity values of sensitive and resistant cells were not influenced by the presence and absence of CAFs when the drug was not present (Figures 5.3 and 5.4).

Then, we fixed the sensitive population's growth rate and carrying capacity parameters at the median of their value in DMSO and CAF environments, to estimate the drug efficacy parameter (λ) in environments where Alectinib is present. ANOVA results supported our decision to fix the sensitive population's growth rate and carrying capacity at the median, showing that population type significantly affected these parameters, while CAFs presence had no significant effect.

We observed no changes in the resistant cells' population following drug administration in monoculture, observing the time series data. Therefore, we re-estimated the carrying capacity and growth rate parameters for resistant populations in environments containing only the drug and in those with both CAFs and the drug. The boxplots of carrying capacity for sensitive and resistant populations in Figure 5.3 demonstrate that population type has a more significant influence on the carrying capacity parameter than

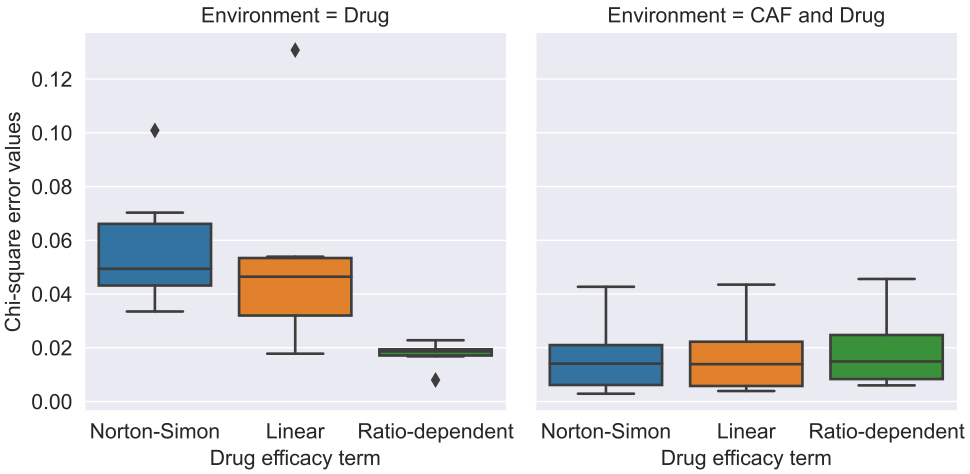

Figure 5.2: Chi-square error values for Norton-Simon, linear, and ratio-dependent drug efficacy (Equations 5.5, 5.6, 5.7) in the presence of drug. The ratio-dependent drug efficacy model leads to smaller errors compared to Norton-Simon and linear drug effects in environments when only the drug is present.

the presence or absence of CAFs and drug. The lines shown in environments where the drug is present for sensitive cell population correspond to boxplots for fixed values. The variation in carrying capacity estimates of resistant population in the presence of the drug is significantly higher than in other environments, perhaps due to more variations in the initial population in those wells. Although the initial ratio of sensitive and resistant populations is fixed at one and zero, respectively, the initial population size varies in different wells.

Figure 5.4 illustrates the boxplots of growth rate values. The growth rate estimates for both cancer cell types were not influenced by the environment. We fixed the growth rate of the sensitive population in DMSO and CAF environments and estimated the drug efficacy parameter (λ) in environments with Alectinib.

The boxplots for drug efficacy (λ) show that CAFs significantly decrease the effect of the drug on the sensitive cells' population (Figure 5.5). We used the median of $(\rho_1, K_1, \rho_2, K_2)$ parameters in all environments estimated from the monotypic cultures. However, considering that the presence of CAFs significantly influences the drug efficacy term (λ), we used the median of this term in the presence and absence of CAFs separately. Using the median of all other parameters, we estimated the competition coefficients (α_{SR} and α_{RS}) in wells where both populations were present with different initial ratios.

The consideration of carrying capacity, growth rate, and drug effect as varying parameters resulted in overfitting and increased the correlation among the various parameters. Utilizing the estimates derived from the monocultures to construct the two-population model addressed these challenges.

From the boxplots of the competition coefficients derived from 6 different initial ratios in four environments (Figure 5.6), we see that the presence of the drug increased the

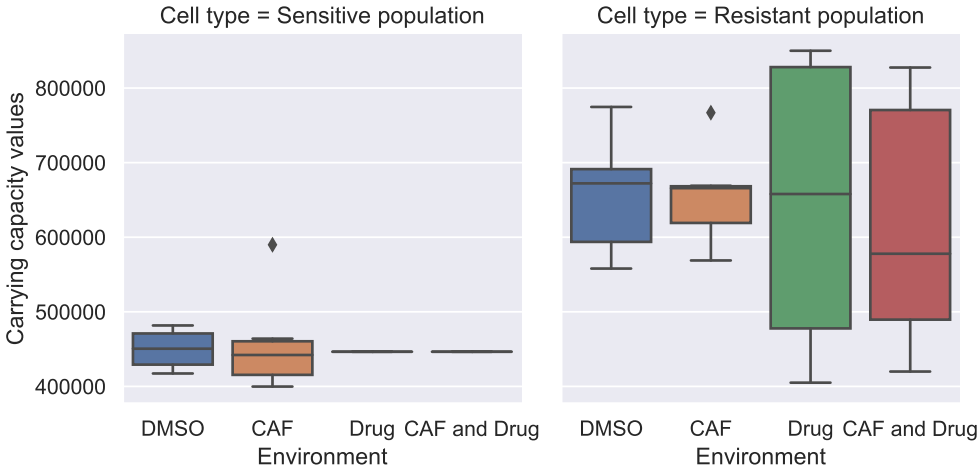

Figure 5.3: Carrying capacities (K_1 and K_2) in all environments. The boxplots of carrying capacity for sensitive and resistant populations illustrate the outcomes in different wells of the monotypic cultures. The carrying capacity of sensitive cells in the presence of the drug is fixed at the median of those parameters in DMSO and CAF environments. The cell type significantly affects carrying capacity, while the presence or absence of CAFs and drug results in minimal and non-significant variation.

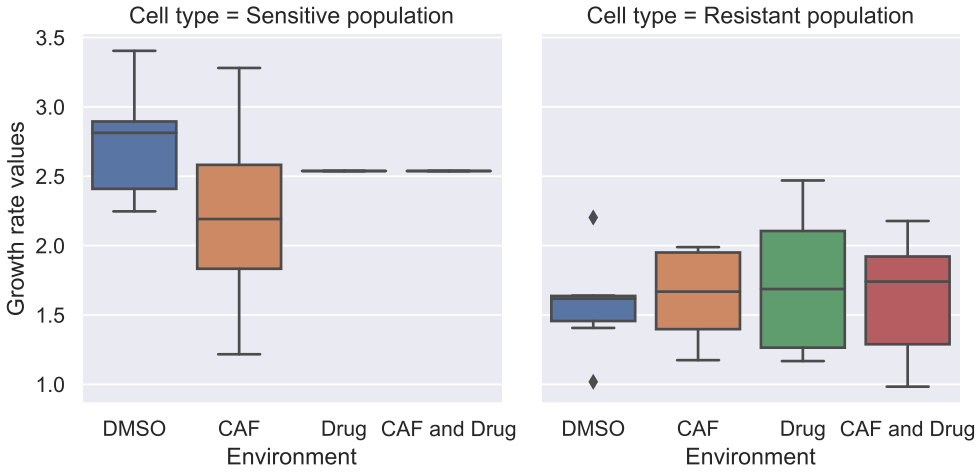

Figure 5.4: Growth rate parameters (ρ_1 and ρ_2) in all environments. The boxplots of growth rates for sensitive and resistant populations illustrate outcomes in different wells of the monotypic cultures. The growth rate of sensitive cells in the presence of the drug is fixed at the median of those parameters in DMSO and CAF environments. The cell types had significantly different growth rates, while the presence or absence of CAFs and drug resulted in minimal and non-significant variation.

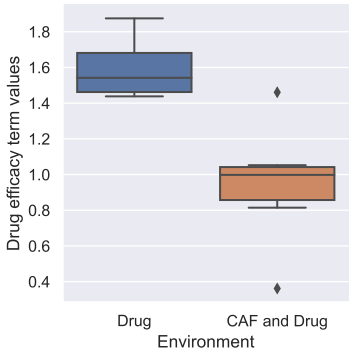

Figure 5.5: Drug efficacy (λ) in environments where drug is present. The boxplots of the drug efficacy parameter for sensitive populations illustrate the fit outcomes in different wells of monotypic culture. The presence of CAFs decreases the effect of the administered drug.

effect of sensitive cells on resistant ones through the competition coefficient α_{RS}. However, in the presence of CAFs and drug, the influence of sensitive cells on resistant cells via the competition coefficient α_{RS} decreases compared to the case where only the drug is administered. Furthermore, the competition coefficients can take values exceeding 1 when the drug is present. In the DMSO environment, the median of α_{SR} is slightly higher than α_{RS}, which means that the influence of resistant cells on sensitive ones is slightly larger than the other way around. The presence of CAFs slightly decreases the median α_{SR} and slightly increases the median of α_{RS}. This causes the median of α_{RS} to become larger than the median of α_{SR}, indicating that CAFs caused the effect of sensitive cells on resistant ones to be higher. However, when the drug is also added to the environment, CAFs have a different effect and decrease the effect of sensitive cells on resistant ones.

We used the one-way ANOVA test on α_{SR} for each pair of environments, which is, in total, six tests. The α_{SR} values only change significantly when we either add the drug to an environment that has CAFs, or when we add both the CAFs and the drug to the DMSO environment. We repeated the six ANOVA tests for each pair of environments for α_{RS}, and we observed that all environment pairs except the presence of both drug and CAFs, compared to when only the drug is present, led to significant changes. We also performed a one-way ANOVA for α_{SR} and α_{RS} in each environment and observed that the effect of sensitive cells on resistant ones, compared to the other way around, is significant in the environment where only the drug is present.

5.3.4. ENVIRONMENTAL INFLUENCE ON COMPETITION OUTCOMES BETWEEN CELL TYPES

Considering the median of competition coefficients derived from the co-culture experiment, we examine the outcomes of the competition between sensitive and resistant cell types in different environments by analyzing the Jacobian of the model (Equation 5.7) and the trajectories (Figure 5.7). In the CAF environment, the model predicts coexis-

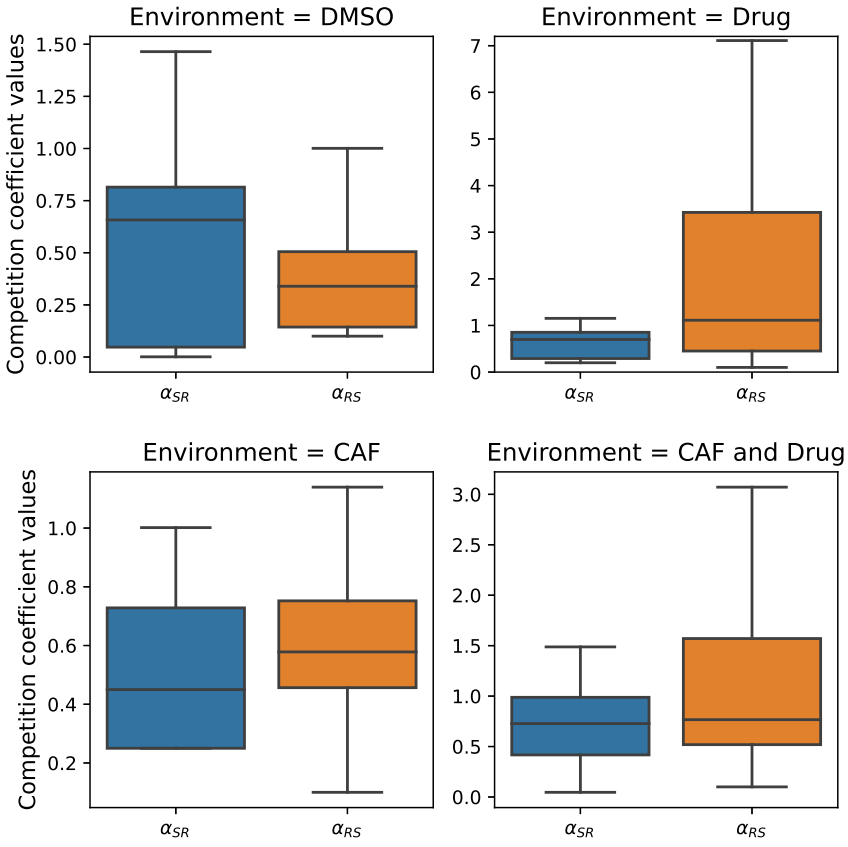

Figure 5.6: Competition coefficients (α_{SR} and α_{RS}) derived for ratio-dependent drug effects and a logistic model where all parameters but competition coefficients were fixed. The presence of the drug leads to a large increase in the competition coefficient α_{RS}. Note that the y-axis scale is different in the presence of the drug, and α_{RS} has values larger than 1.

tence of the two cell types. In the DMSO environment, the stable equilibrium occurs when the number of sensitive cells is much lower than that of resistant cells. In environments with the drug present, the resistant cells outcompete the sensitive ones.

The ρ_1, ρ_2, K_1, and K_2 parameters are considered to be the same in all four environments. Therefore, the different equilibrium properties in CAF compared to those at DMSO is the result of the increase in α_{RS} and decrease in α_{SR}. The distribution of α_{SR} is not significantly different in DMSO and CAF (p-value is 0.1). However, the median has a large difference, which strongly influences the equilibrium outcome. The presence of the drug decreases the number of sensitive cells and, through that, changes the equilibrium outcome. For more details on how the change in parameters λ and α_{SR} affects the possibility of mixed equilibria, see Appendix C.3.

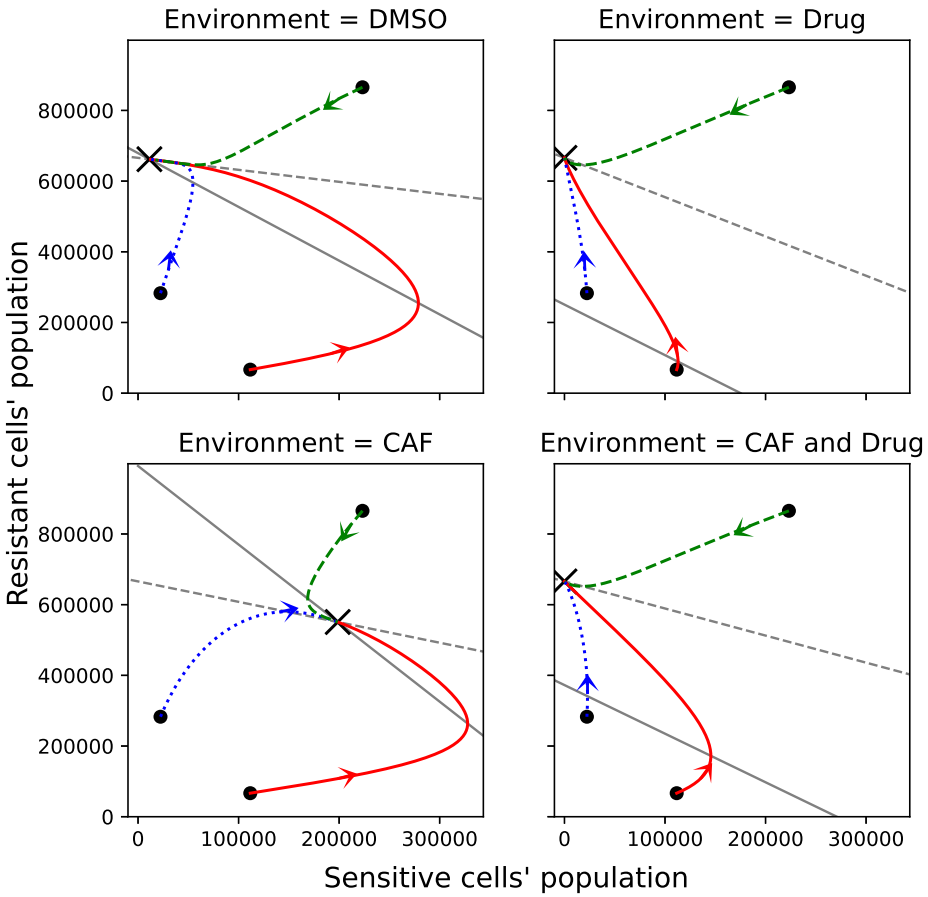

Figure 5.7: Part of phase plane of the model presented in Equation 5.7 using the median of the parameters derived from fitting the co-culture data in all environments. The × shows the stable equilibrium in each environment. The equilibrium in the CAF environment shows coexistence of resistant and sensitive cells. The equilibrium in DMSO shows the dominance of resistant cells. The equilibrium in environments where the drug is present shows that sensitive cells become extinct. The trajectories of the model, starting from three randomly chosen initial points, are illustrated in solid red, dashed green, and dotted blue lines. The solid grey line shows ($\frac{\dot{S}}{S} = 0$) and the dashed grey line shows ($\frac{\dot{R}}{R} = 0$), find more detail in C.3.

5.4. DISCUSSION

Evolutionary game theoretic models can capture cancer eco-evolutionary dynamics and assist in optimizing its treatment (Aguadé-Gorgorió et al., 2024; Wölfl et al., 2022; Zhang et al., 2022). In this paper, we analyzed data from experiments between two cancer cell lines from Kaznatcheev et al. (2019), also analyzed in Soboleva et al. (2025). We found

that the best fit to the data resulted from the two-population Lotka-Volterra competition model with distinct inter-population competition coefficients and with ratio-dependent drug efficacy.

Kaznatcheev et al. and Soboleva et al. fitted this data using replicator dynamics and a two-population Gompertz model with Norton-Simon death rate, respectively (Kaznatcheev et al., 2019; Soboleva et al., 2025). They both concluded that these models adequately capture the dynamics of the cancer cells studied. Both studies also reported that Alectinib inhibits the growth of sensitive cells. They also concluded that Alectinib does not affect the growth of resistant cells in monoculture. We confirm these results with our best-fitting model as well.

In the heterotypic culture, Kaznatcheev et al. concluded that cancer-associated fibroblasts (CAFs) enhanced the growth of sensitive cells (Kaznatcheev et al., 2019). We observed that CAFs both decreased resistant cells' ability to outcompete the sensitive ones and increased the ability of the sensitive cells to outcompete the resistant ones, as seen through median values of the corresponding competition coefficients. While this outcome failed the significance test by a small margin (p-value of 0.1), we believe that if these observations are confirmed in future studies, they can help in designing novel therapies aimed at reducing cancer cells' competitiveness, for example, by targeting the CAFs concentrations (Biffi & Tuveson, 2021; Kim et al., 2025; Monteran & Erez, 2019). Immunotherapy may be the best type of treatment for this purpose (Liu et al., 2019; Song et al., 2025).

Kaznatcheev et al. observed that resistant cells tend to have higher growth rates than sensitive cells even without the treatment targeting the sensitive cells (Kaznatcheev et al., 2019). Soboleva et al. (2025) did not confirm this conclusion. Through our analysis, we found that resistant cells have a larger carrying capacity compared to sensitive ones, rather than having larger intrinsic growth rates. This nuance could not be observed with the simpler models of Kaznatcheev et al. and Soboleva et al. As the first evolutionary therapies in prostate cancer targeted the carrying capacity of cancer cells rather than their growth rate (Zhang et al., 2017), this suggests opportunities for treating non-small cell lung cancer as well.

Kaznatcheev et al. concluded that in the environment where only CAFs are present, the sensitive and resistant cells can coexist while in all other environments, the resistant cancer cell population will outcompete the sensitive population (Kaznatcheev et al., 2019). We also conclude that coexistence of the twopopulations is possible when only CAFs are present in the environment. In contrast, in environments where the drug is present, it leads to a fully resistant, stable equilibrium point. However, our model also predicts the coexistence of sensitive and resistant cells in DMSO, albeit with low abundances of sensitive cells. Kaznatcheev et al. concluded that resistant cells will outcompete sensitive cells under DMSO. Furthermore, the drug efficacy parameter λ is smaller in the presence of both CAFs and the drug compared to the environment where only the drug is present. We also confirm the positive effect of cancer-associated fibroblasts on the sensitive cells relative to the resistant cells.

Our model considers two types of cancer cells, one resistant to the Alectinib drug and one sensitive to it, that are well-mixed in the environment. However, that might not be the case, depending on how the experiments are carried out. If the two populations are

not well-mixed, spatially explicit models may be more suitable to model their dynamics (Miti et al., 2024). We could use agent-based, partial-differential equation, or other types of spatial models to address this issue (Coggan & Page, 2022; Schneider et al., 2024; You et al., 2017). Furthermore, we do not consider the resistance level of resistant cells as an evolving trait (Pressley et al., 2021; Satouri et al., 2025; Stein et al., 2023). This aspect could be an interesting aspect for future research, as the resistant cells may evolve in the course of the experiments if they last sufficiently long.

We estimated how the presence of CAFs and the Alectinib drug affect the model parameters and, through that, the outcome of competition between sensitive and resistant cells. We presented how the presence of CAFs results in the coexistence of sensitive and resistant cells. Reaching the studied equilibria may be possible through dose adjustment in response to the anticipated tumor burden in (Cunningham et al., 2020; Salvioli, Garjani, et al., 2024; Satouri et al., 2025; Stein et al., 2023).

Experiments are usually not performed to analyze both steady state behavior of the studied system and the transient dynamics leading towards this behavior. Even if that is the case, the number of replicates is often limited due to practical constraints. Here, we utilized our prior knowledge of the cells' behavior and estimated model parameters for analyzing the steady-state behavior of cancer cells under different conditions.

The model we have found to be the most appropriate for capturing the dynamics of NSCLC within these experiments could form the basis for model-informed treatment. Of interest is treatment optimization within this model, to explore and compare treatment strategies to improve patients' quality of life and survival.

6

CONCLUSIONS AND FUTURE PERSPECTIVES

In this concluding chapter, we summarize our results and address the research questions listed in the Introduction chapter. Furthermore, we highlight promising paths for future research.

6.1. CONCLUSIONS

In this thesis, we investigated Stackelberg Evolutionary Game (SEG) theory as a framework for managing evolving systems. We explored various applications of such games, with the main focus on cancer treatment. We demonstrated that the Stackelberg strategy, aligned in cancer treatment with a lower treatment dose, consistently leads to better or equal outcomes for the leader, defined as patient's quality of life in the cancer treatment game. Our findings highlight the potential of game-theoretic approaches to optimize cancer treatment strategies and improve patient's quality of life. Additionally, we fitted non-small cell lung cancer (NSCLC) data derived from an *in-vitro* experiment to various models, providing insights into the dynamics of drug-sensitive and drug-resistant cancer cell populations. We next address each of the research questions concerning our results in more detail:

1. **How can we use Stackelberg evolutionary games for managing evolving systems, and what are the applications?**

   The Stackelberg evolutionary game framework introduces a rational leader who strategically influences the evolutionary followers to achieve the leader's desired outcome. Evolutionary followers inherit their traits (in the game theory context, "strategies") to increase their fitness in the environment according to principles of natural selection. The leader uses their strategy for maximizing their objective function, which is also influenced by the evolutionary followers. Nash and Stackelberg strategies are two potential strategies that the leader can employ, depending on the information regarding followers' response to their actions, which

they take into account. Our study formalized the Stackelberg evolutionary game and presented mathematical definitions for the Nash and Stackelberg solutions. We formulated the leader's optimal strategy in both the transient dynamics and the steady state of the Stackelberg evolutionary games. However, we mainly focused on the steady state and explored the two situations where the ecological dynamics reach equilibria and where both the ecological and evolutionary dynamics reach equilibria. Furthermore, we demonstrated that at steady state, the Stackelberg strategy leads to better or equal outcomes than the Nash strategy, and typically, both lead to better outcomes than the naive strategy. Stackelberg evolutionary games offer a framework for managing evolutionary systems, such as fisheries management, pest control, and cancer treatment. Our findings are presented in more detail in Chapter 3.

2. **What treatment approach should a physician select if cancer can be stabilized?**

   Since complete tumor eradication is unachievable in many metastatic cancers, tumor containment and managing cancer as a chronic condition can be beneficial. The Stackelberg evolutionary game framework provides a structured approach to managing cancer, which is a complex, evolving system. We presented an evolutionary game theoretic model for cancer involving two cancer cell population types, those sensitive to the drug and those drug-resistant, where the resistant population's resistance evolves according to the fitness gradient. The physician, acting as the leader of the Stackelberg game, influences the evolutionary game through the drug dose. We formulated an objective function for the physician capturing patient's quality of life, considering the population of cancer cells at the equilibrium, their resistance level, and the drug toxicity. The maximum tolerable dose is the most commonly applied treatment. However, depending on the physician's knowledge of the evolutionary game between cancer cells, the optimal treatment strategy is either the Nash or Stackelberg strategy. Both Nash and Stackelberg strategies keep the tumor population at a viable level for the patient, typically using less drug than the maximum tolerable dose. Our findings showed that the Stackelberg strategy leads to significant improvements in treatment outcomes, such as reduced treatment-induced resistance, lower drug dosage, and higher patient quality of life, compared to the standard maximum tolerable dose, with Nash strategy leading to outcomes between the Stackelberg strategy and those corresponding to the maximum tolerable dose. A more detailed discussion of these findings is provided in Chapter 4.

3. **Which evolutionary game represents the interactions between drug-sensitive and drug-resistant cancer cells across different microenvironments?**

   The logistic, Gompertz, and Von Bertalanffy growth models are commonly employed in the development of evolutionary game models. Additionally, various drug efficacy models, including Norton-Simon, linear, and ratio-dependent models, are utilized to represent the effects of drug administration. We examined the representation abilities of evolutionary game models using data from an *in-vitro* experiment on non-small cell lung cancer (NSCLC). The experiment is conducted

in four microenvironments accounting for the presence and absence of the Alectinib drug and the presence and absence of cancer-associated fibroblasts (CAFs). Our findings indicated that the evolutionary game model with logistic growth and ratio-dependent drug efficacy represents the data most accurately. Using this model, we concluded that both the presence of CAFs and the Alectinib drug significantly influence the interactions between cancer cell populations. In the presence of CAFs, both sensitive and resistant cells can coexist, while the Alectinib drug enables the resistant cells to outcompete the sensitive ones. By fitting NSCLC data to our models, we gained valuable insights into the dynamics of drug-sensitive and drug-resistant cancer cell populations. The analysis showed that growth rates and carrying capacities of the two types of cells do not significantly change with the presence or absence of CAFs. However, cell interactions in co-cultures vary across different environments, due to changes in competition coefficients and drug efficacy parameters. These insights can inform the development of more effective treatment strategies that target interactions within the tumor microenvironment. Chapter 5 explores these findings in greater depth.

In conclusion, our study highlights the potential of SEG theory to advance cancer treatment strategies and lays the foundation for future research on managing dynamic biological systems. Furthermore, we concluded which evolutionary game model is representative of NSCLC *in-vitro* data. Combining this game-theoretic approach with empirical data can enhance outcomes in various fields, such as fisheries management, pest control, and drug resistance.

6.2. FUTURE PERSPECTIVES

Our research lays the groundwork for exploring further questions in future work.

1. **An extended evolutionary game theoretic model that considers more types of cancer cells with multiple strategies**

   Our model in Chapter 4 considers two population types: sensitive to the drug and resistant to the drug. The sensitive cells have a resistance trait that is permanently fixed at zero, and the resistant cells have a resistance trait that varies over time. However, different types of cancer have different numbers of cancer cell types and can have different survival strategies. The cancer cell types can differ due to their different drug responses. However, the variations might also be due to traits other than resistance to the drug, such as the amount or type of nutrition the cancer cells consume and the byproducts of their energy production.

2. **Exploring the transient behavior of the cancer population models**

   In the Stackelberg evolutionary game framework, the objective function of the leader (physician) is the quality of life of the patient. In Chapter 4, we have considered the weighted population of cells at equilibria of cancer population and resistance dynamics, the weighted resistance level, and the weighted amount of drug accounting for drug toxicity as influential variables in the quality of life function. Furthermore, we have found Nash and Stackelberg strategies that optimize the equilibrium population size and resistance level, depending on the information regarding cancer cells' equilibria utilized by the physician. We have illustrated that the equilibria we found have a large region of attraction. However, further research into analyzing whether there are cases we might go through infeasible regions where the patient cannot tolerate the disease is necessary. Another complication is the time it takes the dynamics to reach the desired equilibria, which might not be practical. Furthermore, including transient behavior in the quality of life function can address constraints like accumulated drug levels, which can be another step toward personalized treatments for people with different drug tolerances. Without accounting for cancer transient dynamics, we might find solutions that reach a desired steady state through undesired transient trajectories, such as reaching an undesirably high tumor burden.

3. **Improving the representability of evolutionary game models using experiments designed for system identification**

   In Chapter 5, we used an *in-vitro* dataset of sensitive and resistant cell populations to find the most representative evolutionary game model. Even though we had repeated measurements on population growth, we did not have enough observations for each initial population since the experiment duration was fixed for all repetitions. Having the full transient and steady-state transitions of cell growth in all repetitions would lead to more accurate parameter estimation. In close collaborations between experimentalists and modelers, decisions about experiment length, measurement frequency, and repetition conditions are made mutually to

better support model development. More of this kind of research, where experiments are designed with system identification in mind, will improve the quality and reliability of evolutionary game models in the future.

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A

APPENDIX OF CHAPTER 3

A.1. INTERPRETATION OF THE NASH EQUILIBRIUM

The Nash equilibrium (m^N, u^N) is defined as the intersection between the best response curve of the leader (i.e., the set of all points $\{u, m^*(u)\}$) and the best response curve of the follower (i.e., the set of all points $\{m, u^*(m)\}$). For simplicity, here we consider only the case with unique best responses. This means that for every value u, there is a unique best response $m^*(u)$ of the leader, and for every value of m, there is a unique best response $u^*(m)$ of the follower . The best responses are defined by equations (4.1) and (4.2) in the main text. The Nash equilibrium may be reached in one of the following ways

- If the leader has perfect knowledge about the evolutionary dynamics, they can play m^N directly. The evolving system responds with $u^N = u^*(m^N)$, and we obtain the Nash equilibrium (m^N, u^N).

- Alternatively, we can converge to the Nash equilibrium iteratively. Say we start with the initial trait value u_0. The leader replies with their best response to u_0, i.e. $m_1 = m^*(u_0)$. The evolutionary followers reply by $u^*(m_1)$. This iterative process continues until the Nash equilibrium is reached, as illustrated in Figure A.1.

The Stackelberg strategy of the leader typically leads to a better outcome for the leader than the Nash strategy because the Stackelberg leader knows (through anticipation or a trial and error process, where the leader tries different options for their strategy and observes the best response of the followers) what the best response curve of the followers is. Therefore, the leader can select such a strategy, so that the pair of that strategy and followers' best response brings the leader the best possible outcome (the best outcome on the followers' ESS curve). If there is no better strategy for the leader than the Nash strategy, then their Nash and Stackelberg strategies coincide.

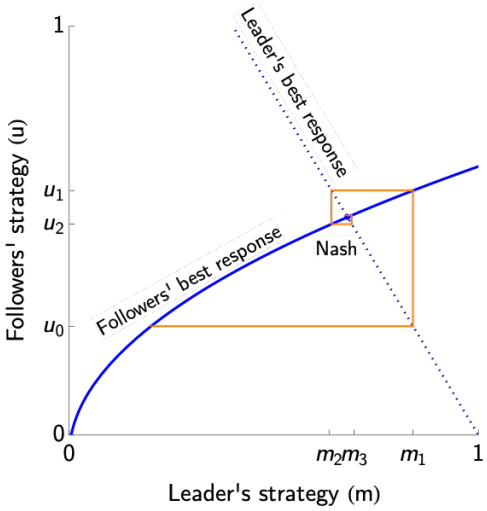

Figure A.1: Iterative interpretation of the Nash equilibrium (in orange). The Nash equilibrium lies at the intersection of the best response of the leader (blue dotted line) and best response, or ESS curve, of the followers (blue solid line). Let us assume that the leader observes the followers playing u_0. Then the leader responds by playing their best response, $m_1 = m^*(u_0)$. The followers adjust their strategy accordingly, i.e. by playing $u_1 = u^*(m_1)$, and so does the leader by playing $m_2 = m^*(u_1)$. The iterative procedure continues until the Nash equilibrium is reached. At this point, the procedure stops, as no player can improve their outcome by changing their strategy unilaterally.

A.2. DETAILED CALCULATIONS FOR THE FISHERIES APPLICATION

In the following, we first calculate the eco-evolutionary equilibrium of the evolutionary followers defined by equation (5.1) in the main text. Afterwards, we compute the Nash and Stackelberg equilibria given the objective in equation (5.2) of the main text.

A.2.1. COMPUTATIONS FOR THE EVOLUTIONARILY STABLE STRATEGY (ESS)

The interior fish's ecological equilibrium occurs when $G(u,u,x,m) = 0$, corresponding to

$$x^* = \frac{K_{\max} e^{-\frac{u^2}{\sigma_H^2} - \frac{u^2}{\sigma_K^2}} \left(r e^{\frac{u^2}{\sigma_H^2}} - m \right)}{r}. \tag{A.1}$$

At the ESS, we must have $\frac{\partial G}{\partial v} = 0$ when evaluated at $v = u$ and $x = x^*(u)$. This yields three options:

$$u_0^*(m) = 0 \quad \text{and} \quad u_\pm^*(m) = \pm \sigma_H \sqrt{\ln\left(\frac{m\sigma_H^2 + m\sigma_K^2}{r\sigma_H^2} \right)}. \tag{A.2}$$

While in the main text $u^*(m)$ denotes the implicitly unique followers' ESS, here $u_0^*(m)$ and $u_\pm^*(m)$ denote potential ESS, and we discuss below which ones are really ESS and

under what conditions. We recognize the structure of a pitchfork bifurcation with bifurcation point at $m = m_c$ given by

$$m_c = r/\theta \quad \text{with} \quad \theta = 1 + \frac{\sigma_K^2}{\sigma_H^2}. \tag{A.3}$$

When the harvesting level is below m_c, the fish's ESS is $u^* = 0$. When the harvesting level is above m_c, the fish's ESS has two coexisting stable strategies u_+^* and u_-^* that diverge as m increases. The bifurcation curve corresponding to (A.2) is illustrated in Figure 3 of the main text. For $m > m_c$, $u^* = 0$ becomes a fitness minimum of the fish, as shown through the dashed line in Figure 3 of the main text.

So far, we computed the first derivative $\frac{\partial G(v,u,x,m)}{\partial v}\Big|_{v=u}$ to obtain an expression for the points satisfying the first order necessary conditions to be an evolutionarily stable strategy (ESS) $u^*(m)$. Now, we calculate the second derivative of $G(v,u,x,m)$ after v to distinguish between minima and maxima of the fitness-generating function. The second derivative reads as

$$\frac{\partial^2 G(v,u,x,m)}{\partial v^2}\Big|_{v=u} = -\frac{2rxe^{\frac{u^2}{\sigma_K^2}}}{K_{\max}\sigma_K^2} - \frac{4ru^2xe^{\frac{u^2}{\sigma_K^2}}}{K_{\max}\sigma_K^4} + \frac{2me^{-\frac{u^2}{\sigma_H^2}}}{\sigma_H^2} - \frac{4mu^2e^{-\frac{u^2}{\sigma_H^2}}}{\sigma_H^4}. \tag{A.4}$$

We evaluate this expression for $u = u_i^*(m)$ and $x = x^*(u_i^*(m), m)$ with $i = 0, +, -$. We start with $u_0^*(m) = 0$. In this case, (A.4) simplifies to

$$\frac{2m}{\sigma_H^2} - \frac{2(r-m)}{\sigma_K^2}. \tag{A.5}$$

This expression is positive for $m > m_c$ and negative for $m < m_c$. Thus, $u_0^*(m)$ locally maximizes G for $m < m_c$ and locally minimizes $G(v,u,x,m)$ for $m > m_c$.

Next, we consider $u_+^*(m)$ and $u_-^*(m)$. The second derivative (A.4) in both cases simplifies to

$$-\frac{4r\ln\left(\frac{m(\sigma_H^2+\sigma_K^2)}{r\sigma_H^2}\right)}{\sigma_K^2}, \tag{A.6}$$

which is negative for $m > m_c$, meaning that $u_\pm^*$ locally maximizes $G(v,u,x,m)$. While $u_\pm^*$ locally maximizes $G(v,u,x,m)$, due to the symmetry of the model, a population in which all individuals play $u_+(m)$ could be neutrally invaded by individuals playing strategy $u_-(m)$, and vice versa. Therefore, $u_\pm^*(m)$ are not an ESS, but, for $m > m_c$, the set of states where any individual in the population plays either u_+ or u_- may be shown to be an evolutionarily stable *set*.

A.2.2. COMPUTATIONS FOR THE NASH STRATEGY

We can find the best response curve of the manager by solving $\frac{\partial Q(m,u,x^*(m,u))}{\partial m} = 0$ resulting in

$$m^*(u) = \frac{r e^{\frac{u^2}{\sigma_H^2}} \left(K_{\max} - c\, e^{\frac{u^2}{\sigma_H^2} + \frac{u^2}{\sigma_K^2}} \right)}{2K_{\max}} \tag{A.7}$$

In order to see whether $m^*(u)$ maximizes or minimizes the objective $Q(m,u,x^*(m,u))$, we need to test concavity. As the second derivative of Q

$$\frac{\partial^2 Q(m,u,x^*(m,u))}{\partial m^2} = -\frac{2K_{\max}}{r}. \tag{A.8}$$

is negative, the objective $Q(m,u,x^*(m,u))$ is concave in m and thus $m^*(u)$ maximizes $Q(m,u,x^*(m,u))$.

Since $m^*(u)$ maximizes $Q(m,u,x^*(m,u))$ and $u^*(m)$ is an ESS maximizing $G(v,u,x,m)$ as discussed above, each intersection of the two curves $m = m^*(0)$ and $u = u^*(m)$ defines a Nash equilibrium. We separate two cases. If $m^*(0) < m_c$, then the best response of the leader $m^*(u)$ intersects with ESS u_0^*, but not with $u_\pm^*$. This condition is equivalent to

$$\frac{r(K_{\max} - c)}{2K_{\max}} < \frac{r}{\theta}. \tag{A.9}$$

For $m^*(0) > m_c$, the best response $m^*(u)$ intersects with $u_\pm^*$, but not with u_0^*.

We calculate the intersection under condition $m < m_c$. The ESS is $u^*(m) = 0$, and the Nash strategy of the leader reads

$$m_0^N = m^*(u=0) = \frac{r(K_{\max} - c)}{2\,K_{\max}}. \tag{A.10}$$

The corresponding trait value is $u_0^N = 0$. If $m^*(0) > m_c$, that is, if the best response of the leader to $u = 0$ would trigger a bifurcation, then the best-response curve of the leader intersects with $u_\pm^*$ and we have

$$m_\pm^N = m_c \left(\frac{K_{\max}}{c} \frac{\sigma_K^2 - \sigma_H^2}{\sigma_K^2 + \sigma_H^2} \right)^{\frac{\sigma_K^2}{\sigma_K^2 + \sigma_H^2}}. \tag{A.11}$$

The corresponding trait values are

$$u_\pm^N = \pm \sqrt{\frac{\sigma_K^2 \sigma_H^2}{\sigma_K^2 + \sigma_H^2} \ln \left(\frac{K_{\max}}{c} \frac{\sigma_K^2 - \sigma_H^2}{\sigma_K^2 + \sigma_H^2} \right)}. \tag{A.12}$$

The condition $m^*(0) > m_c$ implies that $\frac{\sigma_K^2 - \sigma_H^2}{\sigma_K^2 + \sigma_H^2} \frac{K_{\max}}{c} > 1$, so that $m_\pm^N$ and $u_\pm^N$ in (A.12) are well defined. The population may be monomorphic (all individuals with trait u_+^N or all individuals with trait u_-^N), or polymorphic (some individuals with trait u_+^N, others with trait u_-^N).

A.2.3. COMPUTATIONS FOR THE STACKELBERG STRATEGY

The Stackelberg strategy is found by maximizing $Q(m, u^*(m), x^*(m, u^*(m)))$. Again, we consider the two different domains $m \leq m_c$ and $m \geq m_c$. If $m^*(0) \leq m_c$, the Stackelberg strategy is $m_0^S = m^*(0) = \frac{r(K_{\max}-c)}{2K_{\max}}$. It then coincides with the Nash strategy. This is consistent with Theorem 4.1, since for $m < m_c$, $\frac{\mathrm{d}u^*(m)}{\mathrm{d}m} = 0$. If $m^*(0) > m_c$, the Stackelberg strategy is equal to the bifurcation value: $m_\pm^S = m_c$, just avoiding the potential speciation. Most importantly, for $m > m_c$, the quantity $Q(m, u^*(m), x^*(m, u^*(m)))$ is lower than for $m = m_c$.

To show this, let $Q_S(m) \overset{\text{def}}{=} Q(m, u^*(m), x^*(m, u^*(m)))$. The Stackelberg strategy is the value m_S of m that maximizes Q_S on $[0, +\infty)$. We claim the following:

Claim 1: On $[0, m_c]$, Q_S is maximal at $m = m^*(0) = \frac{r}{2}\left(1 - \frac{c}{K_{\max}}\right)$ if $m^*(0) \leq m_c$, and at $m = m_c$ otherwise.

Claim 2: On $(m_c, +\infty)$, $Q_S(m) < Q_S(m_c) \leq \max_{0 \leq m \leq m_c} Q_S(m)$.

Claims 1 and 2 imply that the maximum of Q_S is attained at $m_S = m^*(0)$ if $m^*(0) \leq m_c$, and at $m_S = m_c$ otherwise. In any case, $m_S \leq m_c$, thus $u^*(m_S) = 0$, and the Stackelberg strategy creates neither a bifurcation nor a potential speciation. It remains to prove Claims 1 and 2.

Proof of Claim 1: for $m \leq m_c$, $u^*(m) = 0$ and $H(u^*(m), m) = H(0, m) = m$. Thus, $Q_S(m) = m(x^*(m, 0) - c)$. Moreover, the stable ecological equilibrium is such that $x^*(m, 0) = K_{\max}\left(1 - \frac{m}{r}\right)$. Therefore,

$$Q_S(m) = K_{\max} m \left(1 - \frac{m}{r} - \frac{c}{K_{\max}}\right).$$

This expression is increasing for $m \leq m^*(0) = \frac{r}{2}\left(1 - \frac{c}{K_{\max}}\right)$ and decreasing for $m \geq m^*(0)$. Thus, its maximum on $[0, m_c]$ is attained at $m = m^*(0)$ if $m^*(0) \leq m_c$ and at $m = m_c$ otherwise.

□

Proof of Claim 2: for $m > m_c$, $u^*(m) \neq 0$, and the ecological and evolutionary equilibrium conditions lead to:

$$\frac{x(m, u^*(m))}{K(u^*(m))} = 1 - \frac{H(u^*(m), m)}{r} \quad \text{and} \quad \frac{x(m, u^*(m))}{K(u^*(m))} = \frac{H(u^*(m), m)}{r} \frac{\sigma_K^2}{\sigma_H^2}$$

Together these conditions imply that for all $m > m_c$, $H(u^*(m), m) = \frac{r}{\theta} = m_c$. Using the ecological equilibrium condition to express x as a function of H and then injecting the equality $H = m_c$ leads to (writing u for $u^*(m)$)

$$\begin{aligned} Q_S(m) &= m_c\left(1 - \frac{m_c}{r}\right) K_{\max} e^{\frac{-u^2}{\sigma_K^2}} - c m_c e^{\frac{u^2}{\sigma_H^2}} \\ &< m_c\left(1 - \frac{m_c}{r}\right) K_{\max} - c m_c = Q_S(m_c) \leq \max_{0 \leq m \leq m_c} Q_S(m). \end{aligned}$$

□

Note that we did not use the standard first-order optimality condition $\frac{\mathrm{d}Q_S(m)}{\mathrm{d}m} = 0$ to find the maximizer of Q_S, as when $m_S = m_c$, Q_S is not differentiable at m_S and therefore, this condition is not valid in such a case. This is because Q_S is given by two different expressions for $m \leq m_c$ and $m \geq m_c$.

A.3. INTRODUCTION TO STACKELBERG EQUILIBRIA

In this supplement, we briefly introduce readers unfamiliar with the concept of Stackelberg equilibria to a difference between the Nash and Stackelberg equilibria in the simplest types of noncooperative games, namely bimatrix and continuous-kernel/infinite one-shot/static games (i.e. games where the decision spaces of players are infinite but each player plays only once). For dynamic games, we refer readers to the classic book on dynamic noncooperative game theory (Başar & Olsder, 1999). This supplement is in fact largely based on chapters 3 and 4 of this book and on the last author's unpublished lecture notes for MSc course "Dynamic game theory".

As in classical game theory, in this exposition we will assume that all players are rational.

A.3.1. MOTIVATION

The Nash equilibrium is an appropriate outcome of games where the roles of players are symmetric, i.e., where no single player dominates the decision process. However, in many real-world decision problems one of the players has an ability to impose her strategy on the other player(s). For such situations, we need to introduce a hierarchical equilibrium concept, known as Stackelberg equilibrium (Başar & Olsder, 1999; Simaan & Cruz, 1973; von Stackelberg, 1934).

Let us now consider such a situation. Following the original work of H. von Stackelberg (1934) (Başar & Olsder, 1999; Simaan & Cruz, 1973; von Stackelberg, 1934), we will refer to the player in this more powerful position as the *leader*, and the other player(s), who react to the leader's decision, as the *follower(s)*. There are also situations with multi-level hierarchy in decision making, but for the sake of clarity and simplicity of the presentation, unless stated differently, we confine ourselves to hierarchical decision processes with two players: one leader and one follower. Extension of the theory summarized here to a situation with one leader and more followers is straightforward.

A.3.2. STACKELBERG EQUILIBRIA IN BI-MATRIX GAMES

Let us first consider the bimatrix game (A, B) defined by matrices

$$A = \begin{pmatrix} 3^{S_1} & 1 & 3/2^{S_2} \\ 2 & 2^N & 0 \\ 4 & 1 & 1 \end{pmatrix}, \quad B = \begin{pmatrix} 4^{S_1} & 2 & 15/4^{S_2} \\ 1 & 3^N & 2 \\ 3 & 2 & 7/2 \end{pmatrix}, \tag{A.13}$$

or, equivalently, defined as

$$\begin{pmatrix} 3,4^{S_1} & 1,2 & 3/2,15/4^{S_2} \\ 2,1 & 2,3^{N} & 0,2 \\ 4,3 & 1,2 & 1,7/2 \end{pmatrix},$$

where both the row player $P1$ and column player $P2$ want to maximize their outcomes. We will therefore refer to their outcomes as to their profits.

This bimatrix game has a unique Nash equilibrium solution in pure strategies (P1 playing the middle row and P2 playing the middle column), with the corresponding profit pair being $(2,3)$. Let us now assume that the roles of the players are not symmetric and P1 can impose her strategy on P2. Then, before P1 announces her strategy, she should take into account possible reactions of P2 (the follower), and, in view of this, she has to decide what strategy is the most profitable for her. Let us go over the reasoning that P1 has to go through. If P1 chooses "top row" (T), then P2 has a unique best response "left column" (L), yielding a profit 3 to P1. If P1 chooses "middle row" (M), then P2 has a unique best response "middle column" (M), yielding a profit 2 to P1. If P1 chooses "bottom row" (B), then P2 chooses "right column" (R), yielding profit 1 to P1. Since the highest of the profits is the first one, T is the most logical choice for the leader in this hierarchical decision problem. We therefore say that T is the Stackelberg strategy for the leader (P1) in this game and the pair (T,L) is the Stackelberg equilibrium with P1 as the leader. The profit pair $(3,4)$ is the Stackelberg profit pair of the game with P1 as the leader. Note that this profit is actually better for both players than their Nash profit - this is however not always the case. If, for example, the players switch their roles and P2 is the leader while P1 is the follower, then the unique Stackelberg equilibrium is (T,R), with the Stackelberg profit pair $(3/2,15/4)$. This outcome is clearly not preferred by P1 (the follower), when compared to their Nash profit. For P2 (the leader), the Stackelberg profit is again better than their Nash profit.

We can extend the concept of the Stackelberg equilibrium in bimatrix games to all two-player (single-act or multi-act) finite games without chance moves. Let Γ^1 and Γ^2 denote the pure-strategy decision spaces for P1 and P2, respectively, and $J^i(\gamma^1,\gamma^2)$ denote the profit obtained by Pi corresponding to a strategy pair (γ^1,γ^2) where $\gamma_1 \in \Gamma^1$, $\gamma_2 \in \Gamma_2$.

Definition A.3.1 *(Best response) In a two-person finite game, the set $R^2(\gamma^1) \subset \Gamma^2$ defined for each $\gamma^1 \in \Gamma^1$ by*

$$R^2(\gamma^1) = \{\psi \in \Gamma^2 : J^2(\gamma^1,\psi) \geq J^2(\gamma^1,\gamma^2), \quad \forall \gamma^2 \in \Gamma^2\} \tag{A.14}$$

is the set of best responses of P2 to the strategy $\gamma^1 \in \Gamma^1$ of P1.

If *the follower's best response to every strategy of the leader is unique*, calculation of the Stackelberg equilibrium in a two-player finite game in normal form is similarly straightforward as in the bimatrix game defined by (A.13). In such a situation, we can define Stackelberg equilibrium through the following definition.

Definition A.3.2 *(Stackelberg equilibrium) In a two-person finite game with P1 as the leader, where the follower's best response $R^2(\gamma^1)$ to every strategy $\gamma^1 \in \Gamma^1$ of the leader is*

unique, a strategy $\gamma_S^1 \in \Gamma^1$ *is called a Stackelberg strategy for the leader, if*

$$J^1(\gamma_S^1, R^2(\gamma_S^1)) = \max_{\gamma^1 \in \Gamma^1} J^1(\gamma^1, R^2(\gamma^1)) \stackrel{\text{def}}{=} J_S^1 \tag{A.15}$$

The pair $(\gamma_S^1, R^2(\gamma_S^1))$ *is then the Stackelberg equilibrium with P1 as the leader, and* $\left(J^1(\gamma_S^1, R^2(\gamma_S^1)), J^2(\gamma_S^1, R^2(\gamma_S^1))\right)$ *is the corresponding Stackelberg profit pair.*

Theorem A.3.3 *Every two-person finite game admits a Stackelberg strategy for the leader.*

Proof 2 *This proof can be deduced from the fact that the leader optimizes her objective, which is defined everywhere on a finite set. For details, see proof of Theorem 3.3 in (Başar & Olsder, 1999).*

Proposition A.3.4 *(Nash versus Stackelberg profits) For a given two-person finite game, let* J_S^1 *and* J_N^1 *be the Stackelberg and Nash profits for the leader P1, respectively. If* $R^2(\gamma^1)$ *is a singleton for each* $\gamma^1 \in \Gamma^1$*, then* $J_S^1 \geq J_N^1$*.*

Proof 3 *This result follows from the fact that the leader can select any strategy* γ^1 *(and the follower responds by* $R^2(\gamma^1)$*), including their Nash strategy.*

A.3.3. INFINITE (CONTINUOUS-KERNEL) GAMES

Here we focus on static games where the number of alternatives available to each player is infinite (known also as infinite or continuous-kernel games) and players' profit functions are continuous. In particular, we shall consider the class of games for which a pure strategy of each player can be represented as an element of a finite-dimensional space, and hence take $U^i \subset \mathbb{R}^{m_i}$, where m_i is an integer denoting the dimension of the decision vector of Pi.

BEST RESPONSE CURVES AND NASH EQUILIBRIA

Pure-strategy Nash equilibrium in infinite static games can be obtained as the intersection point of the best response curves of the players.

We now make this notion precise for N-person games.

Definition A.3.5 *In an* N*-person nonzero-sum game, let the maximum of the profit function of P1,* $J^1\left(u^1, \ldots, u^N\right)$*, with respect to* $u^1 \in U^1$ *be attained for each* $u^{-1} \in U^{-1}$*, where* $u^{-1} \stackrel{\text{def}}{=} \{u^2, \ldots, u^N\}$ *and* $U^{-1} \stackrel{\text{def}}{=} U^2 \times \ldots \times U^N$*. Then, the set* $R^1(u^{-1}) \subset U^1$ *defined by*

$$R^1(u^{-1}) = \left\{\xi \in U^1 : J^1(\xi, u^{-1}) \geq J^1(u^1, u^{-1}), \quad \forall u^1 \in U^1\right\}$$

is called the best response set of P1. If $R^1(u^{-1})$ *is a singleton for every* $u^{-1} \in U^{-1}$*, then it is called the best response curve of P1. The best response sets and curves of Pi,* $i = 2, \ldots, N$ *are defined similarly.*

To illustrate the role of best response curves in the derivation of Nash equilibria, we have sketched Figure A.2, where we refer to the leader and follower as L and F, respectively. Here we can see the level curves of the two profit functions J^L and J^F for a specific two-person game with $U^L = U^F = \mathbb{R}$. For fixed u^L, say $u^L = \bar{u}^L$, the best the follower F can do is

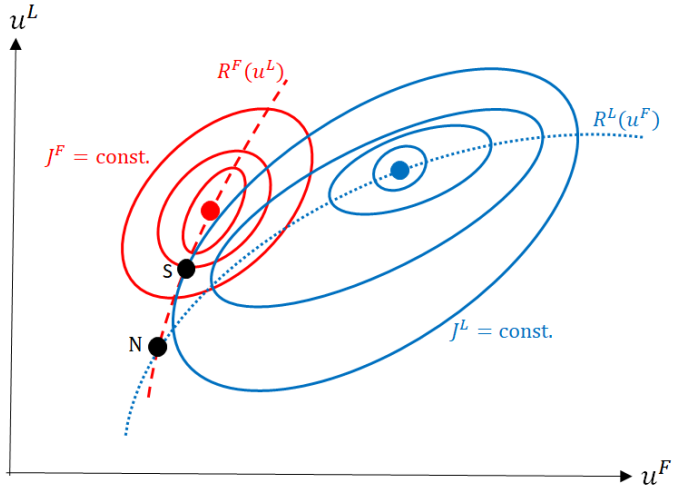

Figure A.2: Level curves of leader's and follower's profits in blue and red and their best response curves denoted by dotted blue and dashed red curves, respectively. The leader's and follower's team optima, denoted by a blue and a red dot, respectively, are the best profits that they could get, obtained if both players would optimize that player's objective. The Nash equilibrium (N) lies at the intersection of the best response curves, while the Stackelberg equilibrium (S) lies where a level curve of the leader's objective is tangent to the follower's best response curve.

to maximize J^F along the line $u^L = \bar{u}^L$. Assuming that this maximization problem admits a unique solution, the said optimal response of P2 is determined as the point where the line $u^L = \bar{u}^L$ is tangent to the level curve J^F = constant. For each different $\bar{u}^L$, a possibly different unique optimal response can thus be found for follower F, and the collection of all these points forms the best response curve of the follower, indicated by a red dashed curve in the figure. The reaction curve of the leader is constructed similarly: It is the collection of all points (u^L, u^F) where horizontal lines are tangent to the level curves of J^L, indicated by a dotted blue curve in the figure. By definition, the Nash solution must lie on both best response curves, and, therefore, if these curves have only one point of intersection, as in the figure, a unique Nash solution exists. We can generalize this outcome in the following theorem.

Theorem A.3.6 (Existence of Nash equilibria) *For each $i \in N$, let U^i be a closed, bounded, and convex subset of a finite-dimensional Euclidian space, and the profit functional $J^i : U^1 \times \ldots \times U^N \to \mathbb{R}$ be jointly continuous in all its arguments and strictly concave in u^i for every $u^j \in U^j$, $j \in N$, $j \neq i$. Then, the associated N-person nonzero-sum game admits a Nash equilibrium in pure strategies.*

Proof 4 *See proof of Theorem 4.3 in (Başar & Olsder, 1999).*

In the N-person nonzero-sum game where $u^i \in U^i$ denote the action (decision) variable of Pi, her action set U^i is a continuum and is assumed to be a subset of appropriate metric space, and the profit function J^i of Pi be defined as a continuous function on

the product space $U^1 \times U^2$, we can also give following general definition of a Stackelberg equilibrium solution.

Definition A.3.7 *In a two-person game, with P1 as the leader and where the best reply set $R^2(u^1)$ is a singleton for each $u^1 \in U^1$ and where both players maximize their profits, a strategy $u_S^1 \in U^1$ is called a Stackelberg strategy for the leader if*

$$J^1(u_S^1, l_2(u_S^1)) \geq J^1(u^1, R_2(u^1)) \tag{A.16}$$

for all $u^1 \in U^1$.

If a Stackelberg equilibrium exists for the leader, then the left-hand side of the inequality (A.16) is known as the leader's Stackelberg profit and is denoted by J_S^1. A more general definition for J_S^1 is, in fact,

$$J_S^1 = \sup_{u^1 \in U^1} J^1(u^1, R_2(u^1)), \tag{A.17}$$

which also covers the case when a Stackelberg equilibrium does not exist (e.g., due to decision spaces being open intervals). It follows from this definition that the Stackelberg profit of the leader is a well-defined quantity, and that there will always exist a sequence of strategies for the leader which will ensure her a profit arbitrarily close to J_S^1.

This also implies that even in the case of continuous-kernel games, if the best response of the follower to any action of the leader is a singleton and profit functions of the leader and follower are continuous, $J_S^1 \geq J_N^1$, i.e. leader's Stackelberg profit can only improve their Nash profit. In fact, this is true for dynamic games, given some standard assumptions on the player's decision spaces and their profits.

B

APPENDIX OF CHAPTER 4

B.1. BASINS OF ATTRACTION OF ECO-EVOLUTIONARY EQUILIBRIA

The determination of the local stability of the eco-evolutionary equilibria involves the analysis of the Jacobian matrix at these equilibria. We confirm the local stability of the equilibria for treatment dosage m within 0.6 to 0.8 numerically, through analysis of the eigenvalues of the corresponding Jacobian matrix. We employ numerical modeling to demonstrate the domain of attraction for the Stackelberg and Nash equilibria (Figure 4.5). Similarly, we can investigate the basins of attraction for other derived equilibria, such as those in Figure 4.4. The sensitive and resistant populations (x_S and x_R) are normalized (assuming $K = 1$), to make the visualizations more informative. We consider initial values $x_S(0)$, $x_R(0)$, $u_R(0)$ as points in the grid $\ell \times \ell \times \ell$ where $\ell = \{0.1, 0.2, 0.3, \ldots, 1\}$, and $x_S(0) + x_R(0) < 1$. The model converges to the eco-evolutionary equilibrium for all initial conditions within this grid. As an example, we illustrate this convergence to the equilibria from 3 different initial values. In Figure B.1, we illustrate how cancer eco-evolutionary dynamics starting in the stabilization region remain in the same region when reaching the Nash equilibrium. As we have not proven this for all possible parametrizations, there may be parametrizations with which the evolutionary dynamics leave the stabilization region before reaching equilibrium.

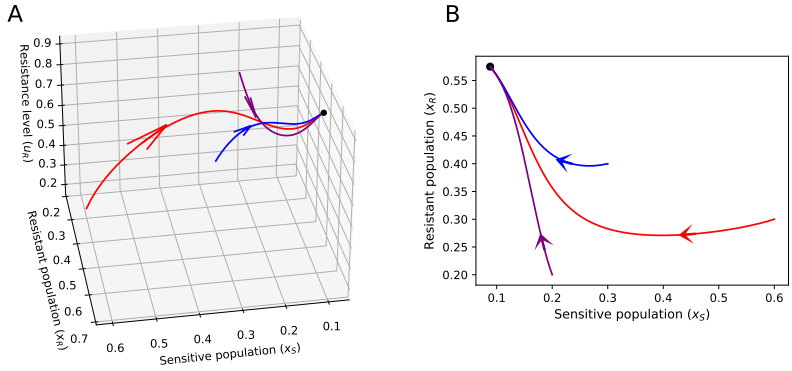

Figure B.1: Eco-evolutionary dynamics of cancer while applying the Nash strategy dose ($m_N = 0.723$), starting from 3 different initial conditions, with $(x_S(0), x_R(0), u_R(0))$ equal to $(0.5, 0.1, 0.2)$, $(0.3, 0.4, 0.5)$, and $(0.2, 0.2, 0.7)$, respectively. The eco-evolutionary dynamics starting from these three initial conditions are denoted in red, blue, and purple, respectively. We see how the eco-evolutionary dynamics starting at these initial conditions evolve in time and converge to the Nash equilibrium. **A)** The eco-evolutionary dynamics. **B)** The ecological dynamics. Parametrization: $\delta = 0.7$, $r_{\max} = 0.45$, $g = 0.8$, $K = 10000$, $d = 0.01$, $k = 2$, $b = 10$, $\alpha_{SS} = \alpha_{RR} = 1$, $\alpha_{SR} = 0.15$, $\alpha_{RS} = 0.9$, $\sigma = 1$.

B.2. MAXIMIZING QUALITY OF LIFE FUNCTION

[1] The $x^*(m, u_R)$, defined in equation 4.10, is not a smooth function, which causes unsmoothness in the quality of life function:

$$Q(m, u_R, x^*(m, u_R)) = \begin{cases} Q^{\max} - c_1\left(\frac{x^*(m,u_R)}{K}\right)^2 - c_2 u_R^2 - c_3 m^2 & (m, u_R) \in \mathscr{Y}_\delta \\ \text{undefined} & \text{elsewhere.} \end{cases} \tag{B.1}$$

In Figure 4.3, for the m and u_R values between $[0, 1]$, the total population at the equilibrium consists of three regions: one where both cells coexist, one where only resistant cells exist, and one where there are no cancer cells. The quality of life function is defined in the yellow region ($(m, u_R) \in \mathscr{Y}_\delta$) illustrated in Figure 4.1, so the boundary that needs further investigation to address the unsmoothness occurs where sensitive cells' population reaches zero defined as curve m_1:

$$m_1 \stackrel{\text{def}}{=} \frac{r_{\max} - d - \alpha_{SR} r_{\max} + \alpha_{SR}\, d\, e^{g u_R}}{\frac{1}{k} - \frac{\alpha_{SR} e^{g u_R}}{k + b u_R}} \tag{B.2}$$

The quality of life corresponding to the region with only resistant cells present (dashed area in Figure B.2) is concave with respect to m. The m_2 curve maximizes the quality of life function as long as the m_2 curve lies in the dashed region.

$$m_2 \stackrel{\text{def}}{=} \frac{2c_1\, e^{g u_R}\, r_{max}\,(k + b u_R) - 2c_1\, d\, e^{2 g u_R}(k + b u_R)}{2c_3\, r_{max}^2 (k + b u_R)^2 + 2c_1\, e^{2 g u_R}} \tag{B.3}$$

[1] This appendix is not part of the original paper and is included for clarity.

The quality of life corresponding to the case where both cells coexist is concave with respect to m.
The m_3 curve maximizes this quality of life function as long as m_3 lies in the grey region illustrated in Figure B.2.

$$m_3 \stackrel{\text{def}}{=} \frac{c_1\left(\frac{(1-\alpha_{SR})e^{gu_R}}{k+bu_R}+\frac{1-\alpha_{RS}}{k}\right)\left(r_{\max}(2-\alpha_{RS}-\alpha_{SR})-(1-\alpha_{RS})d-(1-\alpha_{SR})de^{gu_R}\right)}{c_1\left(\frac{(1-\alpha_{SR})\,e^{gu_R}}{(k+b\,u_R)}+\frac{1-\alpha_{RS}}{k}\right)^2+c_3\,r_{\max}^2(1-\alpha_{SR}\alpha_{RS})^2} \tag{B.4}$$

m_1 curve is the maximizer of the quality of life in the region where only resistant cells are present (the dashed region in Figure B.2) since m_2 which is calculated by setting the derivative of quality of life function to zero falls on the left-hand side of m_1. We numerically compare the quality of life values for m_3 and m_1 curves and see that m_3 maximizes the objective function. The curves are illustrated in Figure B.2.

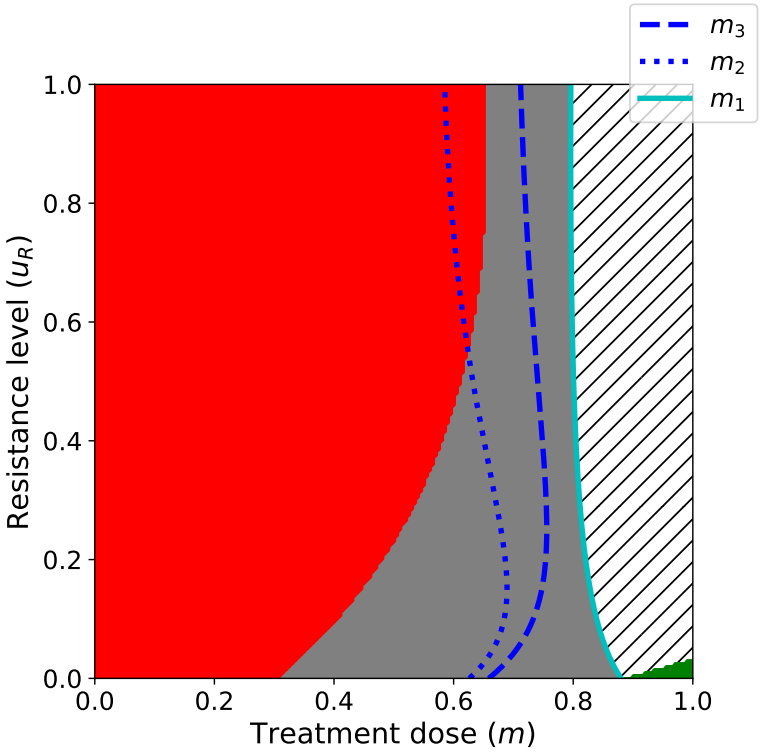

Figure B.2: Potential maximizing curves. The quality of life function is not defined in green and red regions that account for extinction and progression, respectively. The cyan curve represents $x_S^*(m, u_R) = 0$ where the quality of life function becomes unsmooth, the dashed blue curve maximizes the quality of life function defined in the grey area, and the dotted blue line represents the curve that sets the derivative of the quality of life function defined in the dashed area to zero (which falls outside of the defined region). The dashed blue line maximizes the quality of life function. Parametrization: $\delta = 0.7$, $r_{\max} = 0.45$, $g = 0.8$, $K = 10000$, $d = 0.01$, $k = 2$, $b = 10$, $\alpha_{SS} = \alpha_{RR} = 1$, $\alpha_{SR} = 0.15$, $\alpha_{RS} = 0.9$, $Q^{\max} = 1$; $c_1 = 0.5$, $c_2 = 0.25$, $c_3 = 0.25$.

C

APPENDIX OF CHAPTER 5

C.1. GENERAL FORM OF TWO-POPULATION MODELS WITH GOMPERTZ AND VON BERTALANFFY GROWTH

The general form of two-population models with Gompertz and von Bertalanffy growth and Norton-Simon drug effect is presented in Tables C.1, C.2.

Gompertz 1	$\dot{S}(t) = \rho \ln(\frac{K}{S(t)+R(t)})(1-\lambda C(t))S(t)$ $\dot{R}(t) = \rho \ln(\frac{K}{S(t)+R(t)})R(t).$
Gompertz 2	$\dot{S}(t) = \rho_1 \ln(\frac{K}{S(t)+R(t)})(1-\lambda C(t))S(t)$ $\dot{R}(t) = \rho_2 \ln(\frac{K}{S(t)+R(t)})R(t).$
Gompertz 3	$\dot{S}(t) = \rho \ln(\frac{K}{S(t)+\alpha_{SR}R(t)})(1-\lambda C(t))S(t)$ $\dot{R}(t) = \rho \ln(\frac{K}{S(t)+R(t)})R(t).$
Gompertz 4	$\dot{S}(t) = \rho \ln(\frac{K}{S(t)+R(t)})(1-\lambda C(t))S(t)$ $\dot{R}(t) = \rho \ln(\frac{K}{\alpha_{RS}S(t)+R(t)})R(t).$
Gompertz 5	$\dot{S}(t) = \rho \ln(\frac{K}{S(t)+\alpha_{SR}R(t)})(1-\lambda C(t))S(t)$ $\dot{R}(t) = \rho \ln(\frac{K}{\alpha_{RS}S(t)+R(t)})R(t).$

Table C.1: Models inspired by Gompertz growth. Sensitive and resistant population growth follows the ODE model presented at each block. The unknown parameters in the Gompertz 1 model are ρ, K, and λ. Unknown parameters in Gompertz 2 are ρ_1, ρ_2, K, and λ. Unknown parameters in Gompertz 3 are ρ, K, α_{SR}, and λ. Unknown parameters in Gompertz 4 are ρ, K, α_{RS}, and λ. Unknown parameters in Gompertz 5 are ρ, K, α_{SR}, α_{RS}, and λ.

Von Bertalanffy 1	$\dot{S}(t) = \rho(1 - \frac{\sqrt[3]{S+R}}{K})(1-\lambda C(t))S^{\frac{2}{3}}(t)$ $\dot{R}(t) = \rho(1 - \frac{\sqrt[3]{S+R}}{K})R^{\frac{2}{3}}(t).$
Von Bertalanffy 2	$\dot{S}(t) = \rho_1(1 - \frac{\sqrt[3]{S+R}}{K})(1-\lambda C(t))S^{\frac{2}{3}}(t)$ $\dot{R}(t) = \rho_2(1 - \frac{\sqrt[3]{S+R}}{K})R^{\frac{2}{3}}(t).$
Von Bertalanffy 3	$\dot{S}(t) = \rho(1 - \frac{\sqrt[3]{S+\alpha_{SR}R}}{K})(1-\lambda C(t))S^{\frac{2}{3}}(t)$ $\dot{R}(t) = \rho(1 - \frac{\sqrt[3]{S+R}}{K})R^{\frac{2}{3}}(t).$
Von Bertalanffy 4	$\dot{S}(t) = \rho(1 - \frac{\sqrt[3]{S+R}}{K})(1-\lambda C(t))S^{\frac{2}{3}}(t)$ $\dot{R}(t) = \rho(1 - \frac{\sqrt[3]{\alpha_{RS}S+R}}{K})R^{\frac{2}{3}}(t).$
Von Bertalanffy 5	$\dot{S}(t) = \rho(1 - \frac{\sqrt[3]{S+\alpha_{SR}R}}{K})(1-\lambda C(t))S^{\frac{2}{3}}(t)$ $\dot{R}(t) = \rho(1 - \frac{\sqrt[3]{\alpha_{RS}S+R}}{K})R^{\frac{2}{3}}(t).$

Table C.2: Models inspired by von Bertalanffy growth. Sensitive and resistant population growth follows the ODE model presented at each block. The unknown parameters in the Von Bertalanffy 1 model are ρ, K, and λ. Unknown parameters in Von Bertalanffy 2 are ρ_1, ρ_2, K, and λ. Unknown parameters in Von Bertalanffy 3 are ρ, K, α_{SR}, and λ. Unknown parameters in Von Bertalanffy 4 are ρ, K, α_{RS}, and λ. Unknown parameters in Von Bertalanffy 5 are ρ, K, α_{SR}, α_{RS}, and λ.

C.2. AIC GOODNESS OF FIT MEASURE

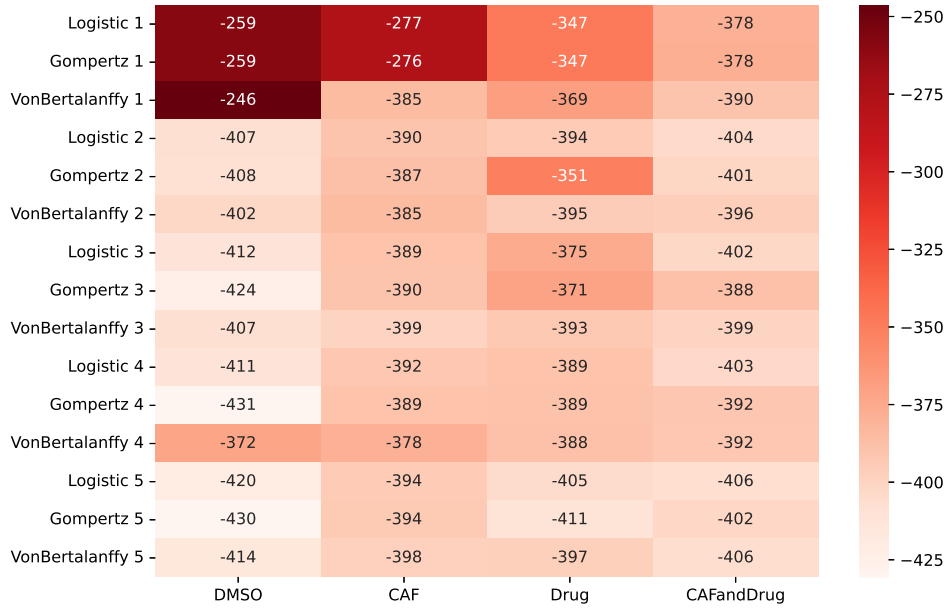

Figure C.1: AIC result of the two-population model fits. Heatmap of the fit results for the proposed fifteen models in Tables 5.1, C.1, C.2. Models with more than three parameters fit the data well.

C.3. ANCOVA TEST ON RELATIVE GROWTH

To determine the growth dynamics, we analyze the relation between the population's relative growth ($\frac{1}{x}\frac{dx}{dt}$) with respect to the population (x). By determining the nonlinearity order of the relation, we can differentiate between logistic, Gompertz, and von Bertalanffy growth dynamics. The analysis is done for sensitive and resistant cells within monotypic cultures in DMSO and CAF environments. We employ the ANCOVA test to identify the factors that significantly influence the relative growth of the cell population. The specific variables examined include the number of the well, the cell population, their cross-correlation, the intercept, and the second-order term of the population. The selected factors hold significant biological and experimental relevance to growth dynamics: the number of wells and cell population serve as primary experimental variables, cross-correlation addresses potential interactions, the intercept reflects baseline effects, and the second-order term allows the examination of nonlinear relationships in growth behavior. First, we analyze the relative growth explainability with cell population as the continuous variable, well number as the categorical variable, and their correlation ($\frac{1}{x}\frac{dx}{dt} = C(Well) + C(Well)\cdot x + x$). We observe that the population's and intercept's effects are statistically significant in DMSO and CAF environments since the p-values of the population variable and intercept for sensitive and resistant cells are less than 0.001. In the next step, we analyzed the significance of the second order of the population variable. For the model with the first order of population, the second order of population, and intercept on the right-hand side ($\frac{1}{x}\frac{dx}{dt} = C(Well) + x + x^2$), the second-order term was not statistically significant for sensitive and resistant populations. We conclude that the Logistic model is more suitable here than Gompertz and von Bertalanffy since the relative growth is linearly related to the population.

C.4. NULLCLINE OF THE POPULATION MODEL

$\dot{S} = 0$ result in two lines $S = 0$ and $\frac{\dot{S}}{S} = 0$ and $\dot{R} = 0$ result in two lines $R = 0$ and $\frac{\dot{R}}{R} = 0$. The intersection of $S = 0$ and $\frac{\dot{R}}{R} = 0$ results in equilibrium point P_1 at $(S, R) = (0, K_2)$. The intersection of $R = 0$ and $\frac{\dot{S}}{S} = 0$ results in equilibrium point P_2 at $(S, R) = (\frac{K_1}{1-\lambda\rho_1}, 0)$. The intersection of $\frac{\dot{S}}{S} = 0$ and $\frac{\dot{R}}{R} = 0$ results in a mixed equilibrium point, P_3, which might not exist for some parameter values. The value of P_4: $(S, R) = (\frac{K_2}{\alpha_{RS}}, 0)$ and P_5: $(S, R) = (0, \frac{K_1}{\alpha_{SR}}(1 - \frac{\lambda}{\rho_1}))$ could be higher and lower than P_2 and P_1, respectively, depending on parameter values. This determines whether the mixed equilibrium point exists or not. As illustrated in Fig C.2, depending on α_{SR}, α_{RS}, and λ values, there can be cases where the mixed equilibrium located at P_3 does not exist. For our parameter values, P_4 is always larger than P_2. However, in the presence of the drug, λ and α_{SR} become larger. Due to this change, P_5 becomes smaller than P_1, which leads to disappearance of the mixed equilibrium points and extinction of sensitive cells. Furthermore, adding only CAFs to the DMSO environment leads to a decrease in α_{SR}, which causes P_5 to be larger than P_1, leading to a mixed equilibrium point with a large population of sensitive cells.

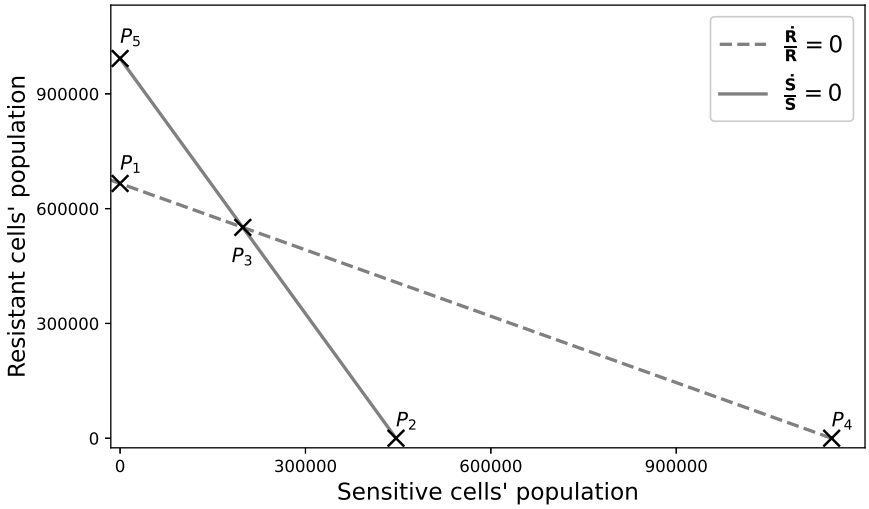

Figure C.2: Intersection of nullclines of Eq 5.7. Setting the derivative of sensitive population to zero, $\dot{S} = 0$, results in two lines $S = 0$ and $\frac{\dot{S}}{S} = 0$. Setting the derivative of resistant population to zero, $\dot{R} = 0$, results in two lines $R = 0$ and $\frac{\dot{R}}{R} = 0$. P_1 point shows $(S, R) = (0, K_2)$; P_2: $(S, R) = (\frac{K_1}{1-\lambda\rho_1}, 0)$; P_3 shows the mixed equilibrium which might not exist for some parameter values; P_4: $(S, R) = (\frac{K_2}{\alpha_{RS}}, 0)$; P_5: $(S, R) = (0, \frac{K_1}{\alpha_{SR}}(1 - \frac{\lambda}{\rho_1}))$.

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LIST OF PUBLICATIONS

1. **Identifying representative evolutionary game models of cancer cell growth: insights from an in-vitro experiment on non-small cell lung cancer**

   Under review

2. **Stackelberg evolutionary games of cancer treatment: What treatment strategy to choose if cancer can be stabilized?**

   Dynamic Games and Applications *2024*

3. **Stackelberg evolutionary game theory: how to manage evolving systems**

   Philosophical Transactions of Royal Society B *2023*