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Game Theory for Managing Evolving Systems: Challenges and Opportunities of Including Vector-Valued Strategies and Life-History Traits

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Abstract
Nature exhibits rapid evolution in response to human activities. When using natural resources for their own profit, humans should account for such responses. Stackelberg evolutionary games (SEG) offer a method for modeling interactions between a rational leader (humans) and evolutionary followers (nature). The followers evolve according to the principles of natural selection, and the leader tries to steer these inevitable responses in a desired direction. While the separate elements of this method, Stackelberg and evolutionary game theory, are well established, their joint realization in SEG theory is underdeveloped. Thus far, simple examples and formalisms of SEGs have considered models where the manager and evolving species have a scalar-valued controller and scalar-valued trait, respectively. Here we provide examples from cancer therapy, fisheries management, and pest control to illustrate extensions of SEG theory, where managers are attempting to control a Darwinian system. The models we develop and present highlight extensions of SEG theory to include vector-valued management strategies and vector-valued traits in the evolving species, and traits influencing different life-history stages of the species under management. Throughout we highlight the mathematical challenges that lie ahead.

Keywords Game theory · Stackelberg evolutionary games · Mathematical oncology · Pest management · Fisheries management

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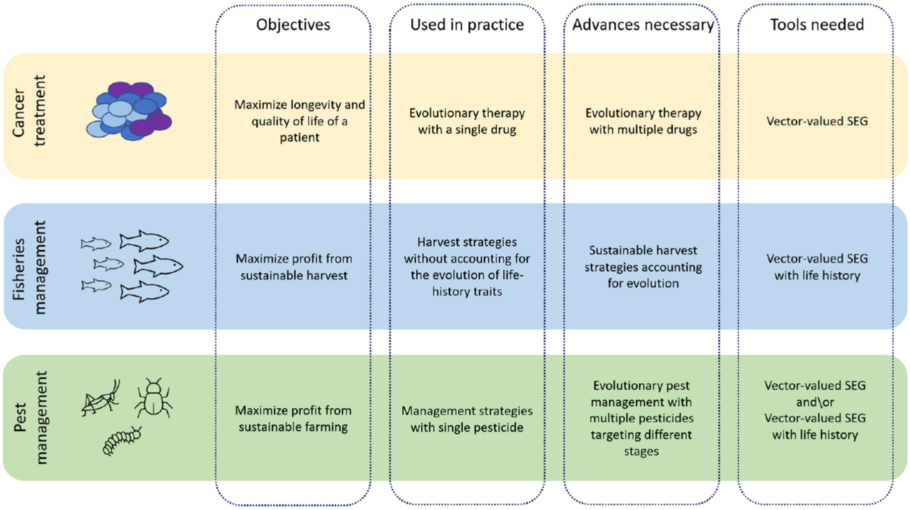
1 Introduction

Rapid evolution in nature driven by human activities has become the norm rather than the exception [61, 101]. Examples are manifold [8, 13, 22, 32, 33, 76, 77, 88, 91, 95, 106, 108, 136]. Three timely examples of rapid evolution that we shall explore include cancer, fisheries and pests (see Fig. 1). The evolution of drug resistance poses the single greatest barrier to curing or prolonging the life of patients with the metastatic disease [51, 137]. If all cancer cells are not killed or removed through surgery, radiation or various adjuvant and neo-adjuvant therapies, the surviving cancer cells evolve resistance in ways that are often much worse for the patient. Commercial fishing, through harvesting intensity or fishing gear such as net size, acts as a strong selective force on life-history traits as has been seen in cod, salmon and diverse other fishes. Frequently, fish will evolve to breed at a smaller size, transition from juvenile to adult at an earlier age, and emphasize reproduction over continued growth [29, 66]. Research on the evolution of pesticide resistance began in the early 1900s and precedes the same for cancer and fisheries [82]. A number of insect pests, including the diamondback moth and the Colorado potato beetle, have evolved resistance to essentially all approved chemical agents [54, 150]. As a consequence, resistance management plans have become a part of integrated pest management (IPM). The goal is to prevent the evolution of resistance by applying pesticides more judiciously or in smaller quantities while maintaining crop damage at acceptable levels [24, 107].

Therefore, the wrong question is: “Will species evolve in response to our rapidly changing world?”. The correct question is: “How much will they evolve and how quickly?” Currently, we are mostly bystanders of these rapid evolutionary events, or we merely react to them. What is needed are conceptual and mathematical tools for anticipating and, if need be, steering



	Objectives	Used in practice	Advances necessary	Tools needed
Cancer treatment	Maximize longevity and quality of life of a patient	Evolutionary therapy with a single drug	Evolutionary therapy with multiple drugs	Vector-valued SEG
Fisheries management	Maximize profit from sustainable harvest	Harvest strategies without accounting for the evolution of life-history traits	Sustainable harvest strategies accounting for evolution	Vector-valued SEG with life history
Pest management	Maximize profit from sustainable farming	Management strategies with single pesticide	Evolutionary pest management with multiple pesticides targeting different stages	Vector-valued SEG and\or Vector-valued SEG with life history

Fig. 1 Managing evolving systems. We consider three examples where managers can act as a rational leader in anticipating and altering the ecological and evolutionary dynamics of evolving systems: cancer treatment, fisheries and pest management. For each, the manager has a principal objective. We briefly describe the current scope of mathematical modelling of the evolutionary components of each system. Although SEG theory is being applied in clinical trials for monotherapies in cancer treatments, the practical application of SEG in pest management and fisheries remain unexplored. For each example, we propose needed advances to SEG and suggest the mathematical tools that could be developed

the evolution of species we deem valuable (aesthetically, economically or socially) or as predators/pests (crop pests, infectious diseases and cancer). Stackelberg evolutionary game theory (SEG) is an emerging branch of game theory that aims to understand, predict and suggest solutions for managing living systems that are both ecologically and evolutionarily dynamic in the face of human activities [130]. The theory applies to systems where human actions act as a selective force on the evolution of other species be they insect pests [15] or commercially valuable fish [119]. With this new selective force, the species can be expected to evolve by natural selection toward a new evolutionary optimum (Evolutionarily Stable Strategy, ESS). The human decision maker(s) can either be just another player that acts based on the current state of the system, or the decision maker can take the lead by anticipating the evolutionary consequences of their actions and act accordingly. As such, the leader's interactions with evolutionary followers can be framed as a special form of a Stackelberg (leader–follower) game.

SEG theory clarifies three ways by which managers may approach a system that involves ecologically and evolutionarily dynamic diseases, pests, harvestable resources, or species of conservation interest. The naive manager takes short-sighted actions that may be expedient, optimal in the short timescale, or that maximize the impact of the intervention. Such an approach is short-sighted in that it does not consider either the ecological or evolutionary consequences of the manager's decision. For instance, in cancer this might involve using maximum tolerable dose of a therapy to maximize the initial shrinkage of a cancerous tumor, or unregulated fishing that permits boats to maximize their catch irrespective of future consequences for the stock of fish. The ecologically enlightened manager is far-sighted in terms of ecological dynamics but does not consider evolutionary dynamics, making it optimal potentially in the short-to-medium timescales. This strategy is typical of maximum sustainable harvest in resource management, or optimal dose–response in the application of antibiotics and pesticides. While appealing in terms of sustaining valuable species, or controlling a pest, it becomes reactive as the manager "chases" emerging circumstances resulting from the species' evolving responses to the interventions by the manager. The evolutionarily enlightened manager is comprehensively far-sighted by anticipating both their ecological and evolutionary consequences. This requires knowledge of how a species might change in numbers and heritable traits, but it allows the manager to steer the species' eco-evolutionary dynamics. In terms of outcome: evolutionarily enlightened $\geq$ ecologically enlightened $\geq$ naive.

Recent works to formalize SEG theory have characterized the distinction between ecologically and evolutionarily enlightened management strategies (which result in Nash and Stackelberg equilibria, respectively), determined under what conditions these two solutions are the same and when the Stackelberg solution is superior to Nash for the manager, analyzed conditions for when the manager's strategy may induce a branching point (increase the species ESS from one strategy to two coexisting strategies), and put forward some conditions for the convergence stability of the population and evolutionary dynamics of the species under management [130]. Thus far, these formalisms apply to managers with a scalar-valued strategy, a single species under management with a scalar-valued trait ESS, and no explicit consideration of life-history states within the species.

We show, using models with direct application to cancer, fisheries, and pest management, how to develop the analytical methods to go beyond scalar-valued strategies. For the cancer model, the physician has two drugs that can be applied to treat the cancer (a vector-valued strategy) and the cancer can evolve resistance to each of these through a vector-valued resistance strategy. A similar model has been numerically analyzed and forms the basis for an ongoing clinical trial on patients with a pediatric osteosarcoma [116]. Absent general results regarding the eco-evolutionary stability properties of these models, the state-of-the-art analysis relies on simulations alone. For the fisheries model, we explicitly consider the dynamics of two life-history stages (adults and juveniles) that grow to a particular size while contributing to fecundity through egg laying. The evolving vector-valued trait determines the length and weight of the fish population. The manger selects from a vector of strategies, namely mesh size and harvest effort that, together, determine the harvest pressure on the fish population. For the pest management model, the farmer can use two pesticides to increase crop production, while pests can develop resistance against both of these chemicals.

In what follows, we highlight open questions as we model these examples. We then use the discussion to suggest future needs for formalizing Stackelberg evolutionary games and to identify even broader classes of games for both the managers and the evolving species.

2 Stackelberg Evolutionary Games: Model

Thus far, SEG were applied to treating metastatic cancers, to sustainable fisheries management and to pesticide-resistance reducing crop management with scalar-valued strategies [15, 25, 26, 53, 116, 119, 128, 130, 140, 148, 149]. While plausible for practical reasons, mathematically an extension to vector-valued strategies constitutes challenges as often one can only obtain numerical solutions. Another reasonable extension of the models considers the evolution of life-history traits [17]. For example, including life-history traits in cancer modeling was demonstrated to be significant for predictions of the system's evolution [2, 18]. Similarly, in sustainable fisheries and pest management applications, practice calls for life-history approaches [58, 71]. In what follows, we first formally define a more general vector-valued SEG model by defining its evolutionary and strategic components. We then extend this model to the variation of SEG that accounts for life-history-trait evolution. We summarize the notation used throughout the manuscript in Table 4.

2.1 Vector-Valued Stackelberg Evolutionary Games

Evolutionary components of the game. Consider a game between a rational leader and n types of evolutionary followers (Fig. 2 left). Let $\mathbf{x} = (x_1, \dots, x_n)$ be a vector that describes population sizes of each type of the follower. Each type in the population can have h traits that evolve. In evolutionary terms, we shall refer to such traits as evolutionary strategies of followers and denote them by an $n \times h$ matrix $U = \big(u_{ij}(t)\big)$. Here, $u_{ij}(t) \in [0, 1]$ is the evolutionary trait j of i-th follower. The leader's actions can be denoted by a vector $\mathbf{m}(t) = (m_1(t), \dots, m_h(t))$. The eco-evolutionary dynamics of the i-th follower can then be determined by the population size $\mathbf{x}$, traits of the followers $U(t)$ and actions of the leader $\mathbf{m}(t)$ and can be written as:

$$\dot{\mathbf{x}} = \mathbf{G}(t)\,\mathbf{x} \tag{1}$$

$$\dot{\mathbf{U}} = \dot{\mathbf{G}} \circ \boldsymbol{\sigma}(t), \tag{2}$$

where $\mathbf{G}(t) = \operatorname{diag}(\mathbf{G}_{ii}(t))$ with $(\mathbf{G}(t))_{ii} = (\mathbf{v}(t), U(t), \mathbf{m}(t), \mathbf{x}(t))\Big|_{\mathbf{v}(t)=\mathbf{u}_i(t)}$, $\mathbf{u}_i(t)$ is the i-th row of $U(t)$, and the matrix of partial derivatives $\dot{G}$ is such that $(\dot{\mathbf{G}})_{ij} = \frac{\partial G_i(\mathbf{v}(t), U(t), \mathbf{m}(t), \mathbf{x}(t))}{\partial v_j(t)}\Big|_{\mathbf{v}(t)=\mathbf{u}_i(t)}$, $\mathbf{v}(t)$ is the vector of traits of the focal types, and $\boldsymbol{\sigma}(t)$ is the matrix of evolutionary speeds of the traits that measure how fast the trait is evolving. Here,

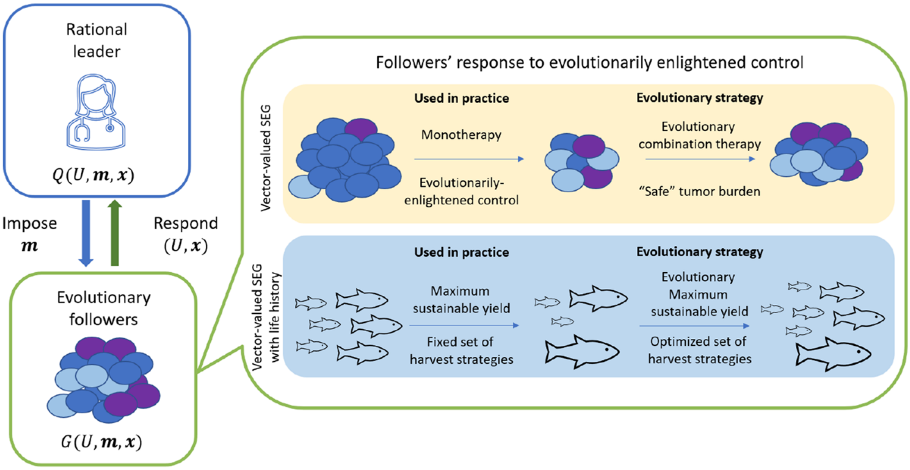


Fig. 2 Vector-valued SEG. The game consists of two parties: the rational leader and the evolutionary followers. Both parties have their own objective functions that they are trying to maximize: Q function for the leader and G function for the followers' fitness. The leader imposes an action $\mathbf{m}$ that directly affects the followers' fitness function. In return, the followers evolve toward their ESS, $\left(U^*(\mathbf{m}), \mathbf{x}^*(\mathbf{m})\right)$

the function $G(\mathbf{v}(t), U(t), \mathbf{m}(t), \mathbf{x}(t))$ is the fitness-generating function-defining fitness (per capita growth rate) of a focal follower [16, 85, 86].

The eco-evolutionary dynamics of the followers can be described in discrete time as

$$\mathbf{x}(t+1) = \mathbf{G}(t)\,\mathbf{x}(t) \tag{3}$$

$$\mathbf{U}(t+1) = \mathbf{U}(t) + \dot{\ln}(\mathbf{G}) \circ \boldsymbol{\sigma}(t), \tag{4}$$

In continuous time, an interior eco-evolutionary equilibrium for a particular $\mathbf{m}$ can be defined as $(U^*(\mathbf{m}),\ \ \mathbf{x}^*(\mathbf{m}))$, such that

$$G(\mathbf{v}, U^*(\mathbf{m}), \mathbf{m}, \mathbf{x}^*(\mathbf{m}))\Big|_{\mathbf{v}(t)=\mathbf{u}_i^*(t)} = 0 \tag{5}$$

$$\frac{\partial G(\mathbf{v}, U^*(\mathbf{m}), \mathbf{m}, \mathbf{x}^*(\mathbf{m}))}{\partial v_j(t)}\Bigg|_{\mathbf{v}(t)=\mathbf{u}_i^*(t)} = 0 \tag{6}$$

If for a particular choice of the leader's actions $\mathbf{m}$ the eco-evolutionary state $(U^*(\mathbf{m}), \mathbf{x}^*(\mathbf{m}))$ of the follower persist in the followers' population and can resist invasion by a rare mutant, we call such a state the *evolutionarily stable state* (ESS). In line with the ESS condition, the ESS of the followers at their ecological equilibrium $\mathbf{x}^*(U(t), \mathbf{m}(t))$, given by $G(\mathbf{v}(t), U(t), \mathbf{m}(t), \mathbf{x}^*(t)) = 0$ will maximize its fitness, that is,

$$\mathbf{u}_i^* = \arg\max_{\mathbf{v}} G(\mathbf{v}, U^*, \mathbf{m}, \mathbf{x}^*) \tag{7}$$

The value (7) is the followers' evolutionary (best) response to the leader's actions $\mathbf{m}$ at ecological equilibrium $\mathbf{x}^*$.

Equations (5) and (6) provide necessary but not sufficient conditions for an ESS leading to a fitness maximum described by Eq. (7). In fact, the eco-evolutionary dynamics can result in a convergent stable minimum of the adaptive landscape [14] termed evolutionarily stable minima by Abrams et al. [1]. Thus, it is possible that the manager's action would result in such an outcome in SEG. It has been suggested that convergent stable minima are branching points that may lead to the speciation of the strategy into two or more coexisting strategies [35, 118]. For the examples that follow, the models produce best response curves of the evolving species that satisfy equation (7).

Strategic component of the game. In most applications, the leader who is trying to manage the system is concerned with an existence, uniqueness, and stability of the interior equilibrium for the leader's $\mathbf{m}$. The leader's actions are often directed toward keeping $(U(\mathbf{m}), \mathbf{x}(\mathbf{m}))$ within a set of strategies leading to trajectories whose $\sum_i x_i(t)$ is always below a particular threshold δ, defining a safety set $\mathcal{S} = \{(U(\mathbf{m}), \mathbf{x}(\mathbf{m})) : \mathbf{x}(\mathbf{m}) \leq \delta\}$. That is, the leader's decisions are strategic as they have to account for the responses of the evolutionary followers.

In line with the previous research [130], we assume that either the ecological or evolutionary dynamics have reached its equilibrium due to separation of timescales. Then, the leader faces an optimization problem in which they are maximizing an objective function $Q(U(t), \mathbf{m}(t), \mathbf{x}(t))$.

Case 1: Naive leader: In the simplest scenario, the leader does not directly consider the effects of their actions on the ecological or evolutionary dynamics of the followers. The manager chooses a strategy and then suffers the consequences of the species (followers) evolving to their new ESS. Generally a naïve strategy means choosing the most aggressive strategy: $\mathbf{m} = \mathbf{m}_{\max}$.

Case 2: Ecologically enlightened leader: In this case, the leader anticipates the ecological consequences of their strategy, but not the evolutionary consequences. Thus, this manager maximizes their objective by including $\mathbf{x}^*(\mathbf{m})$ into their objective function. In this way the manager evaluate Q in terms of both the direct effect of $\mathbf{m}$ on Q but also the effect of $\mathbf{m}$ on Q via $\mathbf{x}^*$. This translates into:

$$\mathbf{m}^* = \arg\max_{\mathbf{m}} \; Q(U, \mathbf{m}, \mathbf{x}^*), \tag{8}$$

where $\mathbf{x}^* = \mathbf{x}^*(U, \mathbf{m})$. Then, the strategy of the ecologically enlightened leader will result in a Nash equilibrium as the manager reacts to the ESS of the followers. The resulting solution occurs at the intersection of the manager's and the evolving species' best response curves: $\mathbf{m}^*(\mathbf{u})$ and $\mathbf{u}^*(\mathbf{m})$, respectively.

Case 3: Evolutionarily enlightened leader: In this case, the leader anticipates the new ESS that will result from their strategy. In this way, the manager includes $U^*(\mathbf{m})$, and $\mathbf{x}^*$ into their objective function. Thus, the manger takes into account the direct effect of $\mathbf{m}$ on Q, and the indirect effects of $\mathbf{m}$ via $U^*(\mathbf{m})$ and $\mathbf{x}^*$. This translates into:

$$\mathbf{m}^S = \arg\max_{\mathbf{m}} \; Q(U^*(\mathbf{m}), \mathbf{m}, \mathbf{x}^*), \tag{9}$$

where $\mathbf{x}^* = \mathbf{x}^*(U^*(\mathbf{m}), \mathbf{m})$. Knowing that the follower will evolve to its best response curve, $u^*(\mathbf{m})$, the strategy of an evolutionarily enlightened manger represents the point on the follower's best response curve that maximizes Q.

Independent of the leader's strategy, followers always respond with their corresponding ESS. It was shown that at equilibrium, these cases can be ordered according to the desired features of the resulting evolutionary response [130]:

$$Q_{\mathbf{m}_{\max}} \leq Q_{\mathbf{m}^*} \leq Q_{\mathbf{m}^S} \tag{10}$$

There exist conditions when ecologically and evolutionarily enlightened leaders act the same, leading to $Q_{\mathbf{m}^*} = Q_{\mathbf{m}^S}$. Such a situation can arise when (i) the leader's actions do not affect the evolution of the trait, (ii) the leader's objective is independent of the follower's evolutionary trait, and (iii) when there is no frequency-dependent selection between the followers [130].

Relation (10) implies that the profit of the evolutionarily enlightened leader at equilibrium, quantified by $Q_{\mathbf{m}^S}$, is at least as high as the profit of an ecologically enlightened leader, quantified by $Q_{\mathbf{m}^*}$. Thus, a strategy/control chosen by an evolutionarily enlightened leader is superior to the ecologically enlightened leader [130]. This is in agreement with the *axiom* that more information about causal relations is beneficial in controlling a system. For example, the anticipation of evolving resistance of cancer cells in response to cancer treatment allows a treatment adjustment prior to cancer cells reaching resistance, hence prolonging the cancer patient's lifespan. Similarly, harvest strategies that account for its effect on the mean of the evolving body size of fish populations, therefore following Case 3, can only enhance a fisher's profit. Clearly, such applications of Relation (10) depend on the assumption that the deterministic model adequately captures the evolution of the species, the traits, and the leader's actions. While Relation (10) holds for any given deterministic model, relative differences between the models are likely parameter-dependent, which could be investigated using bifurcation theory [81, 130, 134]. Given the uncertainty in predicting evolution [144], the sensitivity of actions $\mathbf{m}_{\max}$, $\mathbf{m}^*$, and $\mathbf{m}^S$ and their corresponding outcomes $Q_{\mathbf{m}_{\max}}$, $Q_{\mathbf{m}^*}$, and $Q_{\mathbf{m}^S}$ should further be assessed by comparing them to alternative model formulations, including stochastic systems, to test model robustness.

2.2 Life-History Models as Stackelberg Evolutionary Games

When moving from a vector-valued SEG to a vector-valued SEG with life history, the main difference lies in the formulation of the dynamics of the evolutionary component, where matrix population (MP) models are often used. MP models describe population dynamics in structured populations, such as in age, locations, or classes [17]. The fitness of the entire population is then determined by how many individuals are in each class and the average fitness of each of those classes. When considering an age-structured population, we can capture the size of the entire population, as well as the size of each age group. To do so, we use the equations

$$\dot{\mathbf{x}} = P\mathbf{x} \tag{11}$$

or, in discrete time,

$$\mathbf{x}(t+1) = P\mathbf{x}(t), \tag{12}$$

where an $l \times l$ projection matrix P describes transition probabilities between classes. This matrix is often derived from life cycles of a specific population (see [17] for more details). Here, the behavior of the population dynamics is described by the spectral radius of P, $r(P)$. Formally, the matrix P depends on the life-history traits that are subject to evolutionary pressure and the controls applied by the leader. These traits can be represented, among others, by average body size of individuals in each class or, for example, their reproduction rates [46]. The evolution of these traits can be captured as: [27, 28]

$$\dot{\mathbf{u}} = \boldsymbol{\sigma}(t)\frac{\partial}{\partial u}\ln r(P), \tag{13}$$

or, in discrete time, as

$$\mathbf{u}(t+1) = \mathbf{u}(t) + \boldsymbol{\sigma}(t)\frac{\partial}{\partial u}\ln r(P). \tag{14}$$

Keeping in mind all considerations discussed in this section, one can imagine many biological and ecological situations where SEG can inform management decisions and help to steer the system toward the desired state. In what follows, we will outline three examples where SEG has been applied and argue that more work is necessary for the SEG method to live up to its full potential.

3 SEG in Cancer Treatment

While most cancers can be treated successfully at early stages, the mortality rates from metastatic cancer are very high [65]. The reason for such differences are the approaches to cancer treatments at late stages: physicians often try to eradicate the disease by applying the Maximum Tolerable Dose (MTD) [43, 50], leading to either cure of the cancer or tumor progression due to either development of unacceptable toxicity or resistance against the therapy [5, 9, 49, 78, 127, 133, 140]. SEG led to the development of evolutionary (or adaptive) cancer therapy [25, 26, 53, 116, 128, 140, 148, 149]. While most of these studies focused on a mono-therapy, there is a need for combination therapies, as for example non-small cell lung cancer [31, 67, 110, 128, 129, 135]. Such need arises from the increased speed of treatment-induced resistance against mono-therapy [110, 141, 143]. We formulate a general model in “Appendix B”. In Table 1, we consider an example with two possible formulations for the population dynamics and discuss the results.

The choice of the quality of life function will change both the Nash and Stackelberg equilibria, as well as determining whether they differ a lot, a little or not at all. The choice will also influence the data required to find these solutions, and the complexity of the corresponding optimization problem. The quality of life function $Q(\mathbf{m}, \mathbf{u}, \mathbf{x}^*(\mathbf{m}, \mathbf{u}))$ that we used in our example of evolutionary therapy may provide a good representation when cure is not possible but a chronic disease state is. However, it applies only if the cancer’s eco-evolutionary trajectories do not stray into regions of progression or even death when approaching their ESS for the given treatment strategy. It remains to be shown whether, and under which conditions, the cancer eco-evolutionary trajectories remain in the safety region, where evolutionary trajectories stay in the safe region, and whether treatment strategies exist that could prevent them from leaving this set. One would then try to find the strategies that maximize the patient’s quality of life, for example as defined by (16) in “Appendix B”, only among dynamic treatment strategies that safely arrive at the cancer’s ESS. When it is impossible to keep cancer eco-evolutionary dynamics in the safety region, the goal may be to delay disease progression or maximize overall survival time.

Additionally, every patient likely has a different perception of quality of life. We assumed that the entire population of patients is homogeneous, or that we know explicitly a patient’s quality of life function. Patients may have a different $Q^{\max}$ and weights on the 3 remaining components of Eq. (16). Depending on these weights, there might not exist an interior Nash or Stackelberg equilibrium. Hence, sensitivity analyses across all key parameters become crucial for finding strategies that are effective for a wide range of parameter values. This advancement will also allow us to anticipate when eco-evolutionary responses are sensitive to small perception errors and determine potentially safe or unsafe trajectories for the physician’s actions. When no safe trajectory exists, the leader may want to play a safer ecologically enlightened strategy leading to the Nash solution.

In addition, different cancer types and stages may require different components for Q and their weights. The patient and their health team can decide on the best meaning of quality of life and tailor Q to the patient’s needs and wishes. Hence, ideally, the formulation of Q should offer flexibility and permit an individualized approach. Multi-criteria decision making, such

Table 1 Comparison of two alternative approaches to modeling dynamics of cancer evolution

For a two-drug therapy, let 0-type denote the cell that does not develop resistance against either drug 1 or 2, 1-type and 2-type be the cell resistant against drug 1 and 2, respectively. Then, we obtain the following fitness functions:

$$G_0 = r_{\max}\left(1 - \frac{\alpha_{00}x_0+\alpha_{01}x_1+\alpha_{02}x_2}{K}\right) - d - \frac{m_1}{k_1} - \frac{m_2}{k_2}$$

$$G_1 = r_{\max}e^{-g_1u_1}\left(1 - \frac{\alpha_{10}x_0+\alpha_{11}x_1+\alpha_{12}x_2}{K}\right) - d - \frac{m_1}{b_1u_1+k_1} - \frac{m_2}{k_2}$$

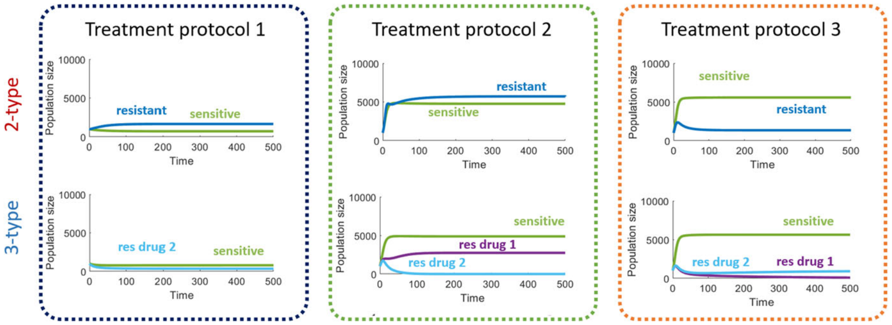
$$G_2 = r_{\max}e^{-g_2u_2}\left(1 - \frac{\alpha_{20}x_0+\alpha_{21}x_1+\alpha_{22}x_2}{K}\right) - d - \frac{m_1}{k_1} - \frac{m_2}{b_2u_2+k_2}$$

We can alternatively consider only two populations (sensitive and resistant) in line with [109]. Here, the resistant population develops resistance to both drugs simultaneously, while the sensitive cell population does not. Hence, the fitness functions are now given by:

$$G_S = r_{\max}\left(1 - \frac{\alpha_{SS}x_S+\alpha_{SR}x_R}{K}\right) - d - \frac{m_1}{k_1} - \frac{m_2}{k_2}$$

$$G_R = r_{\max}e^{-g_1u_1-g_2u_2}\left(1 - \frac{\alpha_{RS}x_S+\alpha_{RR}x_R}{K}\right) - d - \frac{m_1}{b_1u_1+k_1} - \frac{m_2}{b_2u_2+k_2}$$

Such formulation sacrifices the possibility that different drugs need completely different (potentially conflicting) resistant strategies and that these cells might have different impacts on each other. For example, this excludes a competition like Rock-Paper-Scissors. In addition, behavior of the population dynamics varies, which affects the strategies the manager can execute. Let us consider an example when MTD of both drugs does not lead to cure (left panel in the figure). Note that mono-therapy also does not cure the cancer even though the effect of the drugs is symmetric (middle panel). Moreover already with mono-therapy, predictions of the two models differ significantly. However, we can mitigate this effect for given parameter values by applying the Stackelberg equilibrium treatment strategy, for which both dynamical systems exhibit qualitatively similar behavior allowing for safe tumor burden (right panel in the figure). This example demonstrates that vector-valued SEG can help maintain tumor burden in a safe zone while decreasing the toxicity effect of the therapy, in this case, by keeping $m_1 + m_2 = 1$, and does it better than mono-therapy.



$m_1^{MTD} = 1, m_2^{MTD} = 1$ $m_1^{MTD} = 1, m_2 = 0$ $m_1^S = 0.4, m_2^S = 0.5$

as the best–worst method [117], can help to identify essential elements of the patient's quality of life function.

Achieving a Stackelberg solution requires quite precise information on the cancer's eco-evolutionary dynamics in response to possible treatment options. It may be difficult to estimate evolutionary dynamics from standard of care data, which typically comprises imaging and blood biomarkers [37]. Liquid biopsies may help us with estimating resistant clones early enough, but become less helpful if resistance is epigenetic or results from phenotypic plasticity [70, 80, 83, 147]. Moreover, the frequency of measurements may be limited especially for imaging and biopsies. Besides interpolating and extrapolating dynamics from a limited number of measurements, there may be error or time lags associated with each measurement adding to uncertainty in the model's predictions. In the future with a better alignment of measurements and modeling, real-time model predictive control methods have the potential to guide clinical trials, where the model and the corresponding optimal treatment schedules can be updated with each new measure of the patient's state [4, 89, 92]. This methodology could also incorporate adjustments to the patient's quality of life function, which may change during the course of treatment.

4 SEG in Fisheries Management

Many questions arise regarding the best way to model harvested population's eco-evolutionary dynamics. While the dynamics of some species can be modeled using (one-stage) surplus models [10], which is a common tool for data-poor species [34, 75, 142], multi-stage models are typically preferred, especially for long-lived species [62, 111]. Age-structured population models belong to the repertoire of traditional stock assessments [62, 64, 112, 114] and are commonly implemented whenever age-dependent data is available. For example, the stock assessment for the Australian Barramundi (Lates calcarifer) population was based on an age-structured model with 25 age-classes [132] and the stock assessment of Rusty Jobfish (Alphareus rutilans) considered 30 age-classes and, for some regions, further distinguished between their 2 sexes [93]. Independent of the model choice, crucial model parameters for the species' sustainability are the reproduction and survival rates. Commonly, these are estimated from the data and assumed to remain constant over time. However, observations suggest that these model parameters are trait-dependent and may change in response to external factors, such as harvest pressure [40, 60, 145].

An example of a crucial age-dependent model parameter is reproduction. This is because juveniles (sexually immature individuals), in contrast to (sexually mature) adults, do not contribute to the per-capita growth of the population. Although stage-dependent models allow the modeling of realistic properties, age-dependent parameters are (generally) assumed to be constant over time. More advanced models, such as NOAA's advocated *Stock Synthesis* Tool [84], allow time-dependent model parameters to account for environmental changes. The consideration of trait-dependent model parameters that evolve over time to increase an individual's fitness is, as we argue, a worthwhile addition to the model complexity, leading to more insight into harvested species' struggle for survival. In fact, the interplay between harvest and evolution of traits has been recognized and analyzed in previous works [38, 39, 41, 42, 56, 97]. This small selection of papers highlights the different mathematical modeling techniques commonly used to formulate evolutionary population models. Typically, these eco-evolutionary models of harvested populations do not include evolving harvest strategies. For example, suppose that a species evolves to remain at small body sizes in reaction to harvest pressure with a fixed mesh size. Then, an informed fisherman (leader) may invest in a net with smaller mesh size. Incorporating not only the evolution of traits but also strategies in the mathematical models that are used to formulate harvest strategies will aid the prediction of a species' chance for survival.

The harvested population's evolving trait(s) are an essential component of the SEG and in "Appendix C" we formulate a general SEG model for fisheries. Should the model consider traits such as size, fecundity and survivorship separately for each age or stage? In Table 2, we demonstrate that even for two seemingly identical models, the choice of evolving traits may significantly impact the manager's optimal combination of strategies. Hence, it should be systematically studied how traits affect resulting equilibria of the model, and if there exist life-history trade-offs that need to be accounted for. Additionally, since the leader can choose the mesh size, considerations of the evolving traits might influence the dimensionality of the leader's strategy. If different ages and stages can be harvested separately, perhaps because of timing or habitat, then the manager's mesh size can vary across seasons and/or space.

To formulate sustainable harvest strategies, it is important to note that there are generally more than one party involved in the fishing process. For example, a governmental body may set the quotas on volumes and legal limits on sizes of harvested fish, to guarantee the sustainability of the species. The commercial fishing industry, reporting on their catch, aims to maximize their profit. Thus, these two parties have potentially conflicting objectives. Moreover, multiple fishers might be involved, creating competition, which can manifest itself in the variety of technological advances, for example, with radar systems to detect fish schools. Such competition should be considered by the governmental body responsible for the fisheries management, which should be expressed in the functional form of Q. Such a model would be somewhat hierarchical in that there may be a rational leader (governing bodies) influencing the game among rational followers (fishers) whose collective decision influences the eco-evolutionary dynamics of the harvested species.

Lastly, the example shown here assumed maximizing profit as the difference between the gain from the fishing and the cost of harvesting [21, 45]. However, fisheries managers

Table 2 Example of a two-stage evolutionary fisheries model

As an example of a two-stage model with vector-valued strategies, consider (17) with sexually immature juveniles x_1 and sexually mature adults x_2, based on [28],

$$x_1(t+1) = f(u)\varphi(x_1(t), x_2(t))x_2(t)$$

$$x_2(t+1) = (1 - h(u, \mathbf{m}))s(u)\sigma(x_1(t), x_2(t))x_1(t)$$

where u is the average body size, $f(u) = \frac{b}{1+u}$ represents the fertility, $s(u) = \frac{u}{1+u}$ is the natural survival, and the harvest rate $h(u, \mathbf{m}) = m_1 e^{-\frac{(u-m_2)^2}{\sigma_m^2}}$ with effort m_1 and mesh size m_2. Furthermore, $\varphi = \frac{1}{1+c_{21}x_1+c_{22}x_2}$ and $\sigma = \frac{1}{1+c_{11}x_1+c_{12}x_2}$. Then, u follows (14) with $r(P) = \sqrt{R_0}$, where $R_0 = f(u)(1 - h(u, \mathbf{m}))s(u)\varphi(x_1, x_2)\sigma(x_1, x_2)$ is the net reproductive number.

Such a vector-valued model allows the analysis of the optimal combination of fisher's strategies m_1 and m_2 that maximize their profit at the ESS (x_1^*, x_2^*, u^*). We visualize the leader's profit function at the ESS for different leader's strategy combinations (first row, left panel). In this one-trait model, the profit is optimized for effort levels around $m_1 \approx 0.5$ and mesh size $m_2 \approx 0.4$, although for near-by values, the profit remains approximately the same. Additionally, we plot the adult to juvenile density ratios, which may be relevant from a fishery sustainability perspective (first row, right panel). We observe that in general, higher profit margins correspond to more imbalance. However, there exists an overlap, indicating a control that benefits the species sustainability as well as the fisher.

We further consider an extension of this model, incorporating two different traits as body length u_1 and body weight u_2:

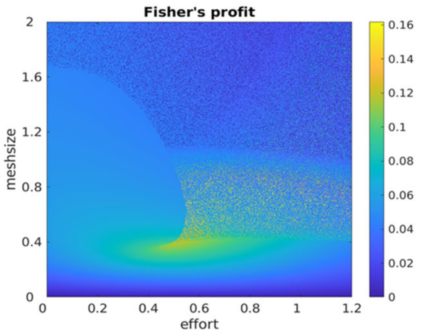
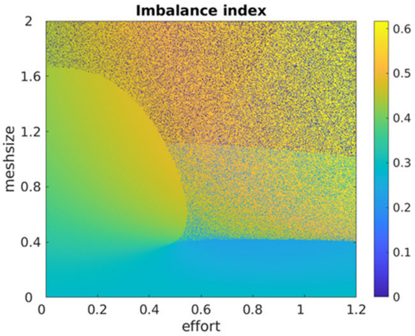
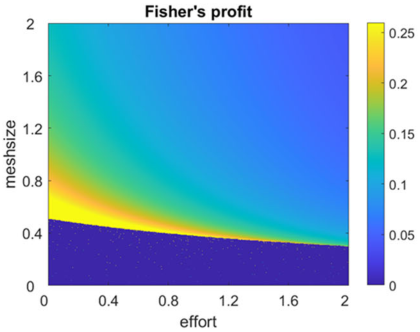
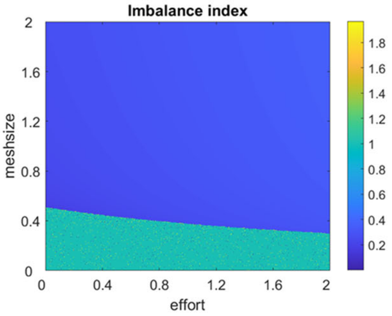
$$x_1(t+1) = f(u_1)\varphi(x_1(t), x_2(t))x_2(t)$$

$$x_2(t+1) = (1 - h(\mathbf{u}, \mathbf{m}))s(u_2)\sigma(x_1(t), x_2(t))x_1(t),$$

where $h(\mathbf{u}, \mathbf{m}) = m_1 e^{-\frac{(u_1-m_2)^2}{\sigma_m^2}} \left(1 - \delta e^{-\frac{u_2^2}{\sigma_2^2}}\right)$.

In the figure below we plot Q and an imbalance index, based on the ratio of adults to juveniles. We observe that the optimal Stackelberg strategy is achieved by choosing low to medium values of fishing mesh. Now, the imbalance index is high for any values of positive profit. These computations reveal that choice of traits can significantly impact policy-making.

Table 2 continued

One Trait		
Two Traits		

should also be concerned about the sustainability of the fishery and the prevention of the fishery's collapse [47, 121]. The manager's or societal objectives may include maintaining the population structure sufficiently close to the pre-harvest population. Subsequently, a form of imbalance index could also enter the objective function of the leader.

Clearly, the SEGs can be applied to broader scenarios beyond the model presented here. In fact, there may be other evolutionary traits, such as shape, habitat selection (e.g. both spawning and feeding, spawning season, schooling propensity). All or at least some of these traits may evolve to decrease fishing mortality that depends on the fishing gear, methods, strategies and regulations. The considered profit function may also be more complex as the profit could depend on the harvested sizes and their reproductive states. For example, fish roe of some species are considered a seafood delicacy and recreational fishers may only target specifically large individuals. Although our example only considered two strategies, mesh size and harvest intensity, other strategies, such as fishing location, applied technology, and length of fishing season, could be also considered. These strategies do, however, have to satisfy legal limitations, such as restrictions on legal limit sizes. For example, the minimum legal limit size for Amberjack (Seriola dumerili) is 36 inches Fork Length in some US states [125]. All of these mentioned extensions are accessible through SEG, but will require often more complex models with vector-valued strategies for both the managers and the phenotypic traits of the harvested population.

5 SEG in Pest Management

Pest management poses major challenges for agriculture and crop management. Insect pests and others have demonstrated rapid evolution of resistance to new pesticides compromising their efficacy and crop yields [104]. Additionally, chemical pesticides raise concerns for health and negative environmental effects necessitating strict regulatory constraints on management strategies. In practice, some farmers become inventive and use biological control agents. For example, in some organic farms, Trichogramma wasps are applied to fields for the control of moths and caterpillars [73]. While such sustainable strategies might not always be feasible or may even be damaging in the long term (one example is Cane toads introduced in 1935 into Australia to control the gray-backed cane beetle and French beetle [122, 123]), most frequently farmers use chemicals or combined measures to control harmful insect populations [15].

In “Appendix D”, we formulate a general model for pest management and in Table 3, we provide one possible formulation of this game and analyze the equilibria. When dealing with two pesticides and two resistant traits, it is possible to encounter multiple best responses of followers and leaders. Hence, other optimality considerations might influence the leader’s choice of pesticide usage.

First of all, the leader as an environmental policymaker may consider the impact of pesticides on the environment and public health [79, 115]. These constraints in turn may enter the objective function Q, but could also be considered as part of the evolutionary response of the followers. That is, when multiple eco-evolutionary equilibria are possible (see Table 3), the exact choice of action might be dictated by other constraints. However, a bigger question is whether these constraints should enter the decision-making process initially (and hence influence the optimal actions) or should be used as a means for selecting among equally good equilibria. The stability properties of equilibria with respect to different forms of Q and G require analysis.

Additionally, the policymaker might be concerned with the pesticide drifting onto non-farmland. In some ecosystems and landscapes, this might be more relevant than others [94]. For instance, the pesticide may drift onto pasture land where it may be ingested by livestock, or incidentally reduce herbivorous insects present on the pasture. Or, the pesticide may drift onto nature preserves where any reduction of insects might negatively impact birds or other animals of conservation interest. Hence, apart from vector-valued controls and life-history traits, the leader may need to consider the spatially explicit landscapes with different land uses [44]. Spatial control problems are typically solved numerically, due to their complexity [20, 36]. Effective numerical schemes will likely be needed for the application of spatio-temporal control in pest management.

IPM refers to enforcing guidelines to control the pests’ evolution of resistance to pesticides [126]. These guidelines, developed decades ago, do not aim at eliminating pests but at keeping pest populations under control, so that economic damage to the crops is limited while maintaining the pesticide’s efficacy into the future. Most IPM practices are simple rules of thumb that help maintain high crop yields [87, 124] while advocating against the over-application of pesticides. IPM has been widely adopted worldwide. Anticipating and steering evolutionary responses of pests to the pesticides may lead to better results, and formulating the problem as SEGs may identify more sophisticated and successful pesticide-use strategies. Future research could take real-world scenarios and formulate these into SEGs.

Sustainable and organic farming requires the use of less toxic pesticides. This often means less effective pesticides that must be used in combination with other pesticides and control measures. In addition, the different life-history stages of a pest species may have different effects on the crop [57]. For instance, the caterpillar stage of the tobacco horned worm can be a voracious herbivore of the tobacco plants, even as the adult moth serves as a pollinator [131]. Hence, more sophisticated vector-valued controls with stage-structured models are required for the optimal management of pesticide-resistance strategy [58]. However, it comes with similar challenges as we discussed for fisheries management: how many traits should be accounted for at each life-history stage?, what are the essential trade-offs?, how many decision makers are involved? and what other social, health and market pressures might influence pesticide use? While similar to the fisheries management questions, pest management has an opposite objective. Instead of preserving the population, the main goal is to minimize the negative impact of pests on crop production by reducing their population size. Hence, in terms of the objective function, pest management is more similar to cancer treatment. It may be that a common denominator for all three examples is the general superiority of the Stackelberg solution over the Nash solution over unrestrained actions (maximum tolerable dose in cancer, unsustainably high fishing rates, and unregulated use of chemical pesticides), and the scaling

Table 3 Multiplicity of followers' best responses in a vector-valued SEG

Let us consider first a simple scenario without life-history trait evolution. Vector-valued formulation of a pest management problem that accounts for evolution of resistance against pesticide can have the form extended from [15]. The fitness-generating function can have the form similar to the cancer example defined as

$$G(x, \mathbf{u}, \mathbf{m}) = r\frac{(1-u_1)(1-u_2)K-x}{K} - \frac{m_1}{k_1+b_1v_1} - \frac{m_2}{k_2+b_2v_2}, \tag{15}$$

and the population dynamics can be defined as

$$\dot{x} = xG(x, u, E). \tag{16}$$

Here, the ecological equilibrium is given by

$$x^* = (1-u_1)(1-u_2)K - \frac{Km_1}{(k_1+b_1v_1)r} - \frac{Km_2}{(k_2+b_2v_2)r}. \tag{17}$$

The traits $(u_1,\ u_2)$ are then evolving to maximize the fitness function, given the control applied by the farmer $(m_1,\ m_2)$ as

$$u_1^* = \arg\max_{u_1} G(x, \mathbf{u}, \mathbf{m}) = \sqrt{\frac{m_1b_1-rk_1u_2}{b_1^2r}} - \frac{k_1}{b_1} \tag{18}$$

$$u_2^* = \arg\max_{u_2} G(x, \mathbf{u}, \mathbf{m}) = \sqrt{\frac{m_2b_2-rk_2u_1}{b_2^2r}} - \frac{k_2}{b_2}. \tag{19}$$

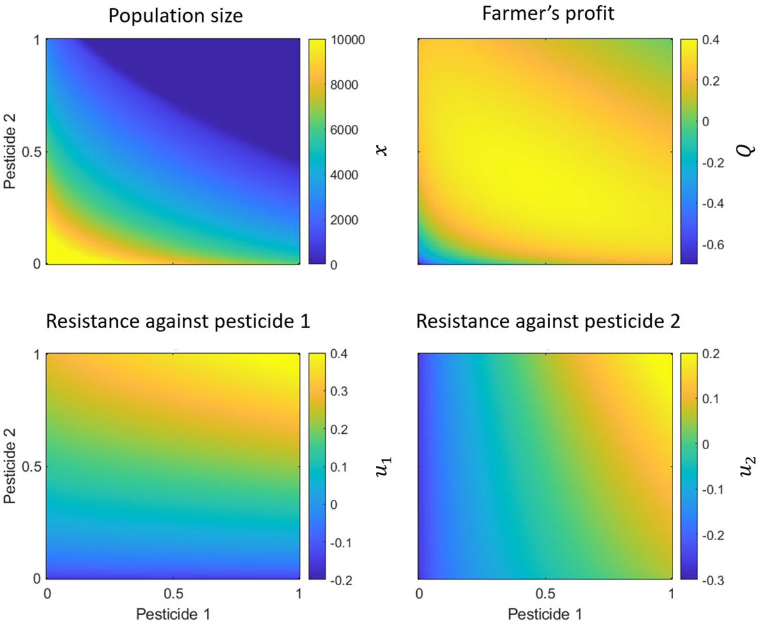
Let us assume that the profit of the farmer is defined by

$$Q(\mathbf{x}, \mathbf{u}, \mathbf{m}) = Y(1 - a * (x/K)^2) - c_1m_1 - c_2m_2, \tag{20}$$

where Y is the harvesting rate, a is the effect of the pests on the crop production, c_1 and c_2 are the costs of pesticides 1 and 2, respectively. Note that $(u_1^*,\ u_2^*)$ are functions of each other. One can numerically solve this system of equations; however, exact solutions are not feasible, due to the complexity of the functional form.

We consider a numerical example where two pesticides have different effects on the evolution and have different costs for the farmer. As it can be seen, best results in terms of the profit are achieved along the diagonal $m_1 + m_2 = 1$. In this region, the farmer can achieve the highest profit while containing the population size of pests reasonably low. Moreover, while there exists a unique maximum, the differences between profits of several options of (m_1, m_2) are ϵ-small. However, optimal resistance rates along the diagonal vary. Hence, there might exist multiple combinations of (m_1, m_2) leading to the profit ϵ-close to the optimal profit $Q_{\mathbf{m}^S}$ and population size x^*, but different resistance rates, which implies multiplicity of equilibria to the same action of the leader, making it difficult to anticipate the exact action of the follower and assuring desired properties of the resulting equilibria.

Table 3 continued



back of the intervention (dose rate, fishing rate and pesticide usage) to minimize the evolution of the evolving cancer, fish, or pest.

6 Discussion

Game theory and evolutionary game theory, in particular, have proven useful for modeling systems with complex interactions among diverse individuals and agents [138, 139]. Many studies have been devoted to working out mechanisms on both sides: on the side of the management (optimality and rationality of behavior but also its limitations [68, 113]), and on the side of the system itself (complex ecological and evolutionary dynamics [30, 63, 105]). It is now well-understood and appreciated that biological systems can exhibit rapid evolution in response to human actions [100, 101]. Yet, in practice, evolutionary responses to managerial actions are often overlooked during decision making. Reasons for this are the complexity of possible solutions even in the absence of evolutionary considerations and the traditional assumption that evolution in nature occurs too slowly to be relevant [55, 69, 146].

Despite these challenges, Stackelberg evolutionary games attend to the desire of incorporating the interdependence of evolutionary changes and external management strategies and, therefore, provide a more realistic mathematical modeling framework. Management models should include predicting both ecological and evolutionary changes [98, 144]. Stackelberg evolutionary games have been successfully applied to the treatment of metastatic cancers [128, 143] and fisheries management [119, 130]. However, despite the promising results, the current state of the theory has limitations. Thus far, mathematical formalism and solution concepts only exist for a scalar-valued trait and a single-action interaction between the evolving system and the manager. Utilizing a mono-trait and single-action approach limits applicability. For example, in aggressive cancers, patients rarely receive mono-therapies. Instead, two or more drugs are given in combination [120]. Hence, there is a need for SEG theory applicable to vector-valued traits and vector-valued leader's actions. Such an extension comes with significant complications.

Choosing the leader's objective function. Defining an appropriate objective function for the leader poses challenges and will depend on the application. In cancer therapy, such a function defines the patient's quality of life, typically including the cancer population size (tumor burden), the leader's strategy regarding the treatment dose (as it impacts drug toxicity), and the followers' evolutionary response (resistance to the selected treatments). When discussing application of SEG in fisheries management, we argue that evolutionary sustainability should enter the leader's objective function. For pest management, we used a function that is independent of the followers' response to the pesticides. Depending on the exact application, the reasoning for the functional form of Q may differ, and this in turn will determine the resulting Stackelberg strategy and corresponding equilibria. It was shown that the Stackelberg outcome may either outperform or coincide with Nash, depending on the functional form of Q [130]. Therefore, when expanding this framework to vector-valued traits and vector-valued life-history traits, it is critical to determine how the functional form of Q affects the existence and properties of the evolving system's equilibria.

Modeling eco-evolutionary dynamics. Even with a one-dimensional SEG, the eco-evolutionary dynamics of the followers can exhibit bifurcations, where for one action of a leader there might exist multiple responses of the followers [130]. Bifurcations may be more difficult to track and analyze in the multivariate case. If such a bifurcation occurs, it is unclear what strategy the leader should choose. In classical Stackelberg games with rational leaders and followers, the answer would be to apply a mixed strategy or assume that the rationality of the follower would make them choose the worse outcome for the leader [7]. However, the evolutionary followers do not anticipate but rather react to the leader's actions, according to the principles of Darwinian evolution. Hence, choosing a mixed strategy or assuming that followers are choosing the option most harmful for the leader does not apply. In such a situation, the Nash strategy, to which the leader will converge by adjusting their choices based on the evolutionary response of the system, may be less risky. However, that means giving up the Stackelberg solution that will likely lead to a better outcome. Additionally, we show with our example in Table 1 that the Stackelberg strategy might reduce ambiguity as different eco-evolutionary dynamics often respond to the Stackelberg strategy in a qualitatively similar manner.

The goal of the manager may include steering the followers' eco-evolutionary dynamics toward the desired state more effectively and/or preventing the eco-evolutionary dynamics from traversing to undesirable (unsafe) states. These considerations may result in higher sensitivity of the eco-evolutionary dynamics to small changes in the leader's actions (including bifurcations), and hence, less controllable systems. Mathematically, incorporating transient dynamics in the game will likely allow for comparison to open-loop, closed-loop, and feedback strategies of the leader [7], differing in their assumptions of what the leader knows when deciding on their strategy.

Equilibrium behavior. Here, we assumed that followers' response to the leader's actions $\mathbf{m}$ goes to an eco-evolutionary equilibrium $(U^*(\mathbf{m}), \mathbf{x}^*(U^*(\mathbf{m}), \mathbf{m}))$. However, the system may take time to reach this equilibrium or may not reach it in a meaningful time at all. The system might also have multiple equilibria and the leader's actions might change stability properties of those equilibria, forcing the system to switch. Some traits may take several generations to evolve to a noticeable level, while others may exhibit rapid evolution. Hence, the leader's actions, optimal when the eco-evolutionary equilibrium is assumed, might be suboptimal during the transient phase of the followers' eco-evolutionary dynamics. Some applications of SEG may require safety margins on the followers' ecological and/or evolutionary dynamics (safe tumor burden for cancer patients, sustainable populations for fisheries, and safe levels of pesticides use). Analyzing followers' transient dynamics will help determine whether/when $\mathbf{x}^*(t)$ will exceed a safety threshold. If exceeding the safety threshold is inevitable, we may aim at either maximizing the time to exceeding this threshold (cancer and pests) or maximizing the time before reaching extinction (fisheries).

In addition, many other mathematically challenging questions arise when analyzing SEGs, to name a few: (i) Can the Folk Theorem [23] be extended to this broader class of bioeconomic games, in hope that over time the system dynamics converge to either Nash or Stackelberg equilibria? (ii) What is the role of various forms of frequency-dependence among the evolving species in determining the effects of the manager on the species' ESSs and the attainability of the ESSs? (iii) What is the effect of a time scale separation between the species' dynamics of population sizes, strategy values, and possibly stage distributions in matrix models? (iv) What if there is more than one ESS for the followers, i.e., what if a particular manager's strategy leads to more than one best response curve for the evolving species? (v) How do the stability concepts from evolutionary game theory (ESS, convergence stability, Neighborhood invader strategy—NIS, mutual invasibility) apply in the presence of a leader?

Errors and information. Given the level of complexity of analyzing even a simple SEG, another question arises: As leaders, when do we need to obtain the optimal outcome or when a particular ("simple enough" or "stable enough") structure of the obtained strategy is more important? Perhaps, we could instead focus on the outcomes that are "good enough", with a rule of thumb that has some set of desirable properties. As with the example in Table 3, there might exist a set of the leader's strategies that yield ϵ-different profits. In such a situation, the leader might focus on the stability of the eco-evolutionary equilibria corresponding to these different strategies, or their other properties. But before we even start with answering these questions, we have to determine what constitutes "good enough" outcomes. These questions need to be answered systematically.

In the analyses of this paper and previous works [119, 130], it was assumed that the leader has perfect information on the followers' eco-evolutionary response. That is rarely the case. Future research must focus on the sensitivity of the SEGs with respect to small errors in the perceived ecological and/or evolutionary responses, and on what frequency and type of data is needed to accurately predict the followers' behavior and subsequent outcomes. In these cases, we may utilize results known in classical Stackelberg game theory with incomplete information (e.g. [100]) and adapt them to SEG.

Potential applications. Thus far, SEGs have been successfully applied to cancer treatment and fisheries management, and a model was proposed for pest management. However, many more applications exist where this method may lead to potentially better outcomes such as conservation ecology. Sustainability and conservation policies post an optimization problem under strict budget and time constraints. Challenges lie in the complexity of ecological and conservation modeling and data analysis [11, 52, 72], as well as in the choice of the leader's objective function [96]. Beyond the analytical complexity, there are also strategic considerations influencing the decision making as conservation decisions are often made in collaboration with multiple stakeholders and require coordinated actions [12, 99, 102]. Yet, despite all the efforts, not all initiatives are successful and new techniques are necessary to find the most effective approach to conservation [48, 59, 103]. Apart from exploring completely new techniques for conservation, many studies argue that conservation decisions should take into account the evolutionary pressures faced by the ecosystems due to rapidly changing environmental conditions [19, 90]. It was argued that ecological and medicine modeling should have more exchange of knowledge, as both are concerned with questions of coexistence and extinctions of entire populations [3]. SEGs can offer a method that combines all elements needed to find the best conservation strategies, including constrained optimization with evolutionary responses. Moreover, SEGs can be extended to scenarios with multiple leaders arranged as a prespecified hierarchy. For instance, several policy makers may need to coordinate actions with stakeholders when making environmental decisions [12, 99]. Such a framework has the potential to be applied to many other pressing issues where evolving systems need to be managed efficiently and sustainably.

Author Contributions All authors contributed equally.

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Availability of data and materials All codes for figures in this manuscript, including the information on parameter values, are available at https://github.com/kleshnina/SEGopinion.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical Approval Not applicable.

Appendix A: Table of Notation

See Table 4.

Table 4 Table of notation used throughout the manuscript

Symbol	Description
$\mathbf{x}$	Population size of followers
$\mathbf{x}^*$	Population size of followers at equilibrium
U	Matrix of evolutionary traits of followers
U^*	Matrix of evolutionary traits of followers at equilibrium
$\boldsymbol{\sigma}(t)$	Matrix of evolutionary speeds of the traits
$\sigma_j(t)$	Evolutionary speed of trait j
$\mathbf{v}$	Focal individual's trait
$\mathbf{m}$	Control applied by the leader
$\mathbf{m}_{\max}$	Maximally possible value of controls
$\mathbf{m}^*$	Control applied by the leader at Nash equilibrium
$\mathbf{m}^S$	Control applied by the leader at Stackelberg equilibrium
$G(U, \mathbf{m}, \mathbf{x})$	Followers' fitness-generating function
P	Projection matrix
$r(P)$	Spectral radius of P
$Q(U, \mathbf{m}, \mathbf{x})$	Leader's objective function

Appendix B: Vector-Valued SEG for Cancer Treatment

A model that accounts for vector-valued traits and multiple controls can be set as follows. Consider a cancer population that may consist of n distinct types. For example, these types could be cells resistant to a particular drug or, on the contrary, sensitive to this drug. Let $\mathbf{x} = (x_1, \ldots, x_n)$ be a vector that describes population sizes of each cell type. Each type of cancer cells can have a trait that is subject to evolution. In evolutionary terms, we shall refer to such traits as evolutionary strategies of cancer cells and denote them by $\mathbf{u} = (u_1, \ldots, u_h)$. Then, accordingly, the patient can be administered h types of drugs in quantities $\mathbf{m} = (m_1, \ldots, m_h)$. We can model the cancer cell population dynamics x_i and the traits u_i continuously using (1) and (2), respectively, with the fitness function

$$G(v, \mathbf{u}, \mathbf{x}, \mathbf{m}) = r(v)\left(1 - \frac{\sum_{j=1}^{n} \alpha_{ij} x_j}{K}\right) - d - \sum_{j=1}^{h} \frac{m_j}{k_j + b_j u_j}\Big|_{v=u_i}, \tag{15}$$

where $r(v) = r_{\max} e^{-g_j v}$ is the growth rate, g_j is the cost of resistance strategy v, α_{ij} are the interaction coefficients between types i and j, K is the carrying capacity, d is the natural death rate, k_i are the innate resistance that may be present before drug exposure, and b_i are the benefit of the evolved resistance trait in reducing therapy efficacy.

The leader (physician) faces the optimization problem in which, apart from trying to reduce the tumor size, they are concerned with the patient's quality of life. A possible objective function representing patient's quality of life may be defined by:

$$Q(\mathbf{m}, \mathbf{u}, \mathbf{x}^*(\mathbf{m}, \mathbf{u})) = Q^{\max} - c_1 \left(\frac{\sum_i x_i^*}{K}\right)^2 - c_2 \sum_i \omega_i m_i^2 - c_3 \sum_i \sum_j \rho_{ij} u_{ij}^2, \tag{16}$$

for $(\mathbf{u}(\mathbf{m}), \mathbf{x}^*(\mathbf{m})) \in \mathcal{S}$, where $Q^{\max}$ is the quality of life of a healthy patient, $\sum_i \omega_i = 1$ is the drug toxicity, $\sum_i \sum_j \rho_{ij} = 1$ is the effect of resistance rates, and c_i's are the weights that determine the impact of tumor burden, drug toxicity, and treatment-induced resistance rate, respectively. Apart from tumor burden and drug toxicity, u_{ij}'s are also expected to reduce patient's quality of life as it was suggested that in some cancers drug resistance can cause physical discomfort directly [6, 74].

Appendix C: Life-History SEG for Fisheries

We consider the discrete N-stage-structured population model, where x_i represents the population of the i-th stage class and is modeled by (3) as

$$\begin{aligned} x_1(t+1) &= G_1(v, \mathbf{u}, \mathbf{x}(t), \mathbf{m}) \\ x_i(t+1) &= (1 - h_i(v, \mathbf{u}, \mathbf{m})) s_i(v, \mathbf{u}) G_i(v, \mathbf{u}, \mathbf{x}(t), \mathbf{m}), \quad 2 \le i \le N, \end{aligned} \tag{17}$$

where G_1 includes the stock recruitment function, $s_i \in [0, 1]$ is the natural survival, $h_i \in [0, 1]$ is the harvest rate of stage-class i, and G_i represents the change in stage-class i from time t to time $t + 1$. In the case of stage-classes, the evolution of traits follows (14).

The leader's profit function at any time t can be described by

$$Q(\mathbf{u}, \mathbf{x}, \mathbf{m}) = \sum_{i=1}^{N} p_i h_i(v, \mathbf{u}, \mathbf{m}) s_i(v, \mathbf{u}) G_i(\mathbf{u}, \mathbf{x}(t), \mathbf{m}) - \sum_{i=1}^{k} c_i m_i,$$

where c_i are the costs for a harvest strategy m_i ($i = 1, \ldots, k$) and p_i, for $i = 1, \ldots, N$, is the price of individual fish in the different stage-classes, potentially dependent on their respective trait.

Appendix D: Vector-Valued SEG for Pest Management

We formulate a bioeconomic vector-valued SEG between farmers and pests without accounting for life-history trait evolution (based on [15]). The fitness-generating function of pests as a function of a vector-valued control applied by the farmer can have the form:

$$G(\mathbf{x}, \mathbf{u}, \mathbf{m}) = F(\mathbf{x}, \mathbf{u}) - \mu(\mathbf{u}, \mathbf{m}), \tag{18}$$

where $F(\mathbf{x}, \mathbf{u})$ is the population growth rate in the absence of pesticides and $\mu(\mathbf{u}, \mathbf{m})$ is the pesticide-induced mortality rate. The farmers' profit function depends on the volume of crop production minus the cost of controlling the pests population (other costs can be subtracted from the value of the crop without changing the Nash or Stackelberg solutions of this SEG), specifically,

$$Q(\mathbf{x}, \mathbf{u}, \mathbf{m}) = Y(\mathbf{x}, \mathbf{u}) - \mathbf{cm}, \tag{19}$$

where $Y(\mathbf{x}, \mathbf{u})$ is the crop production and $\mathbf{cm}$ is the cost of pesticide application.

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