Optimizing Cancer Treatment Using Game Theory
A Review

Kateřina Staňková, PhD; Joel S. Brown, PhD; William S. Dalton, MD, PhD; Robert A. Gatenby, MD

Herein, we frame cancer treatment as a contest in which the physician enters a predator-prey-like game with the patient’s cancer cells. Therapy options represent the physician’s strategies. Cure occurs if therapy drives the cancer populations extinct. But, for most metastatic cancers, extinction is not achievable because the cancer cells are active “players” in the game. They respond to treatment by evolving effective strategies of therapy resistance. The physician-predator can also “evolve” in the sense that he or she can vary treatments over time.

Contests such as between the physician and cancer cells can be framed mathematically using game theory. Developed by Von Neumann and Morgenstern, Nash, and others, game theory describes the strategies (choices), payoffs (consequences), and dynamical interactions involving both individuals and populations. Although initially focused on conflict and cooperation in economics, Maynard-Smith and Price pioneered its application to evolutionary dynamics. In evolutionary games, the players inherit rather than choose their strategies, and their payoffs are survival and proliferation. Game theoretic approaches have been applied to management of antibiotic resistance and control of agricultural pests, as well as cancer progression and treatment.

The cancer therapy predator-prey game differs from those in nature in ways that limit the physician: he or she does not gain a fitness advantage from killing cancer cells and his or her strategies are constrained by costs, ethics, and treatment toxic effects. However, cancer therapy also contains elements of social/economic games that result in asymmetries that confer critical advantages on the physician, as follows.

First, only the physician is rational and can anticipate future events. In contrast, cancer cells, typical of evolving organisms in nature, can only respond to what is happening or has happened. In particular, cancer cells can never anticipate or adapt to future conditions that differ from current or prior circumstances.

Second, there is a consistent sequence in the game because the physician always makes the first move by applying therapy and only then...
Can cancer cells “play” by responding through the evolution of resistance strategies. Even if the molecular machinery of resistance is present prior to treatment, it is not under selection as a resistance strategy until treatment. Because of this, cancer therapy is a leader-follower game.34 First investigated by von Stackelberg,35 analyses of leader-follower dynamics (or “Stackelberg games”) identify critical advantages to the leader. The physician’s “first move,” along with the ability to anticipate subsequent cancer cell responses, provides a critical opportunity to obtain more favorable outcomes by steering and/or limiting the cancer cell’s resistance strategies.16,17 Furthermore, when therapy is administered episodically or in cycles, the first-move advantage can be used to probe the tumor for available resistance strategies. This “pursuit and evasion” game has been extensively investigated through optimization methods in differential game theory (games with time-varying strategies),16,17 such as the principle of optimality by Bellman.18 Thus, the physician can use information obtained in initial treatment cycles to progressively inform and optimize subsequent cycles.

Methods

Cancer Therapy as a Game

We frame cancer therapy as a game theoretic contest in which the physician assumes a predator-like role by attacking and killing cells within the cancer population. While some cancers may contain a single homogeneous cell population, we assume that most malignant tumors contain multiple subpopulations with varying sensitivities to available therapies. The physician begins the game by applying some treatment. Even as many (perhaps most) cancer cells die, survivors adapt and evolve counter (resistance) strategies. As the game progresses, the physician can then play the game by applying additional treatments, which can be identical to or different from prior treatments. With each new treatment, the tumor cells continue responding and adapting.

Our game theoretic model builds on a well-established mathematical formalism developed over several decades. Figure 1 and Figure 2 provide a brief outline of the quantitative methods and dynamics of the cancer therapy game. However, within the text we frame the discussion entirely in qualitative terms, reserving the formal mathematical analysis for a future publication.

Current treatment protocols for metastatic cancer typically apply a drug or drug combination at maximum tolerated dose (MTD), either continuously or in repeated identical cycles. Response metrics are changes in tumor volume based on imaging Response Evaluation Criteria in Solid Tumors (RECIST) and/or serum biomarkers. The same treatment regimen continues until there are unacceptable toxic effects or unambiguous evidence of tumor progression.

Table 1. Mathematical Formulas for Cancer Therapy Game

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Formula</th>
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<tbody>
<tr>
<td>Cancer cell objective – survive and proliferate following application of therapy</td>
<td>$N = \frac{dN}{dt} = N G(u_C, u_T, N)$</td>
</tr>
<tr>
<td>Dynamics of cancer density $N$</td>
<td>$\dot{N} = \frac{dN}{dt} = N G(u_C, u_T, N)$</td>
</tr>
<tr>
<td>Fitness generating function (to be maximized by cancer)</td>
<td>$J_C(u_C, u_T, N) = G(u_C, u_T, N) = \left(1 - u_C\right)K - N - \frac{u_T}{k + b u_C}$</td>
</tr>
<tr>
<td>Best-response curve of cancer to any treatment $u_C$</td>
<td>$R_C(u_C) = \arg\max_{u_C} G(u_C, u_T, N) = \sqrt{\frac{u_C}{\sqrt{DB}} - \frac{k}{b}}$</td>
</tr>
<tr>
<td>Equilibrium density of cancer cells $N^*$</td>
<td>$N^* = K(1 - u_C) - \frac{uTK}{r(k + bu_C)}$</td>
</tr>
<tr>
<td>Oncologist’s objective – to balance dose toxicity (with maximal dose $D$) with tumor burden (with maximal tumor burden $B$)</td>
<td>$JT = JT(u_C, u_T, N) = \left(\alpha - \alpha\right)D - (D - N) \left(1 - \alpha\right)B - (\alpha - \alpha)N - \frac{\alpha}{\sqrt{\alpha - \alpha}}\partial u_T$</td>
</tr>
<tr>
<td>Quality of life of the patient (to be maximized by the oncologist)</td>
<td>$J_T(u_T, N) = \left{ \begin{array}{ll} \alpha(D - u_C)^2 + (1 - \alpha)(B - N)^2 &amp; \text{if } 0 &lt; N &lt; B \ J_T^{\text{max}} &amp; \text{if } N = 0 \ 0 &amp; \text{if } N \geq B \end{array} \right.$</td>
</tr>
<tr>
<td>Treatment dynamics</td>
<td>Ecologically enlightened treatment (Nash)</td>
</tr>
<tr>
<td>Evolutionarily enlightened treatment (Stackelberg)</td>
<td>$\frac{\partial J_T}{\partial u_T} = -2\alpha(D - u_C) - 2(1 - \alpha)(B - N^<em>) \frac{\partial N^</em>}{\partial u_T} - 2\alpha(D - u_C) - 2(1 - \alpha)(B - N^<em>) \left[ \frac{\partial N^</em>}{\partial u_T} + \frac{\partial N^*}{\partial R_C(u_T)} \frac{\partial R_C(u_T)}{\partial u_T} \right]$</td>
</tr>
<tr>
<td>$\frac{\partial N^*}{\partial u_T}$</td>
<td>$\frac{\partial N^*}{\partial u_T} = -\frac{K}{r(k + bu_C)} + \frac{K}{r(k + bu_C)} - \frac{K}{r(k + bu_C)} \frac{\partial R_C(u_T)}{\partial u_T} + bR_C(u_T) - \frac{K}{r(k + bu_C)} - \frac{bR_C(u_C)}{r(k + bu_C)}$</td>
</tr>
<tr>
<td>$\frac{\partial N^*}{\partial u_T}$</td>
<td>Not applicable</td>
</tr>
<tr>
<td>$\frac{\partial N^*}{\partial u_T}$</td>
<td>$-K + \frac{bR_C(u_C)}{r(k + bu_C)}$</td>
</tr>
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</table>
Implicit in conventional treatment strategies (whether using MTD or metronomic drug scheduling) is that maximum benefit to the patient requires maximum tumor cell killing. In metastatic, incurable clinical settings, this strategy is intuitively appealing. Yet, it may be evolutionarily unwise. As shown in Figures 2, 3, and 4, maximum cell killing is an optimal strategy only if no cancer cells are capable of evolving a successful resistance to the applied therapy. However, if 1 or more cancer subpopulations are resistant a priori or capable of evolving adaptations quickly (ie, before the treatment kills them), this strategy will fail.

In fact, under these game theoretic conditions, maintenance of a constant drug regimen at MTD cedes evolutionary control to the cancer cells. As followers, the cancer cells can begin to adapt only when the treatment is applied. They are at a disadvantage because therapy begins as a Stackelberg game in which the physician is the leader. However, by administering the same drugs and doses within each treatment cycle, the physician subjects cancer cells to a constant and predictable selection force. By adapting to the physician’s current therapeutic regime, the cancer cells are simultaneously adapting to the physician’s future (identical) treatments. Consider cancer treatment as a rock-paper-scissors game in which almost all cells within the cancer play, for example, “paper.” It is clearly advantageous for the treating physician to play “scissors.” Yet, if the physician only plays “scissors,” the cancer cells can evolve to the unbeatable resistance strategy of “rock.”

Thus, continuous application of a single, high dose-density drug regimen provides a shorter-term ecological success (tumor response or remission), but failure to anticipate the longer-term evolutionary arc permits the tumor to evolve resistance unopposed. Consider an eager dog that chases a squirrel by running directly at it. Coyotes, in contrast, have learned that squirrels respond to pursuit by running toward the nearest tree and, therefore, do the same. In the former contest, the squirrel becomes the leader as the dog follows it in a wide arc toward and up the tree. In the latter, the coyote leads and prevents the squirrel from executing its evasive strategy.

Thus, by changing therapy only when the tumor evolves resistance and progresses, the physician has become the follower. He or she simply reacts to evolution of resistance by the leader tumor cells. In this setting, as shown in Figure 2 and Figure 3, the strategy of continuous treatment at MTD until progression is rarely the best available strategy. In fact, it is frequently the poorest strategic approach to the cancer therapy game.

In the context of game theory (the Table provides a glossary of game theory terms), when the physician does not fully use his or her advantages as a rational leader, he or she loses the opportunity to both anticipate and steer. Figure 2 represents a graphical depiction of the cancer therapy game. In the absence of a leader and follower, each player in a time-dependent game such as cancer therapy responds to the actions of the other players. The cancer evolves a best response to the current and ongoing therapy. When the physician observes the shift in cancer strategy—example, radiographic progression—he or she can adjust treatment based on available literature that has demonstrated the best response (ie, second-line treatment) to the current strategies of the cancer cells. Each move and countermove sees both the cancer cells’ strategies and physician’s therapy strategies moving along their respective best-response curves. This can lead to either a perpetual evolutionary arms race (if the cancer cells’ and physician’s best response curves do not intersect) or a Nash solution in which the 2 curves intersect. At the Nash equilibrium, neither player (cancer or physician) gains an advantage by unilaterally altering their strategy. Such outcomes are the norm for evolutionary games in nature (Figure 2).

Game theory models have clear implications for current cancer therapy. If cancer cells can find an adaptive strategy either through existing molecular mechanisms already encoded in the human genome or acquisition of a resistant mutation, survival and progression of a cancer population is an assured outcome. Furthermore, using any conventional cancer treatment approach (whether MTD or metronomic therapy) designed to kill the maximum number of cancer cells while ignoring the underlying evolutionary dynamics, the physician has no available strategy to improve current outcomes.

Exploiting Game Theoretic Advantages in Cancer Therapy
Exploiting the asymmetries in the cancer treatment game will likely require abandoning the current static treatment protocols in favor of...
Dynamic therapy designs that explicitly integrate the evolutionary dynamics of resistance. As demonstrated in Figure 3, a physician can exploit the lead position in the Stackelberg game by anticipating the resistance strategies of the cancer cells. By understanding both the available molecular mechanism(s) of resistance and the Darwinian dynamics that govern the proliferation of resistant phenotypes, treatments can be modified, using mathematical models when necessary, to prolong the time to progression, and perhaps even cure. The key is to have some foreknowledge or estimate of the cancer cell’s best response curve. If I do X, how will the cancer cells respond and adapt over time? Just as the coyote can anticipate the squirrel’s escape options, as leader, the physician can choose to steer the cancer. A Stackelberg solution requires the leader to choose his or her best outcome along the other player’s best response curve. This solution will be at least as good, and generally much better, than the Nash solution.

Are such strategies achievable in clinical settings? A few recent trials have demonstrated successful integration of evolutionary principles into treatment protocols. For example, bipolar androgen therapy24-26 anticipates androgen receptor overexpression as an adaptive resistance mechanism in metastatic castration-resistant prostate cancer. To exploit this adaptive strategy, bipolar androgen therapy administers androgen to induce a tumor response and to restore normal androgen expression, rendering them once again vulnerable to androgen deprivation therapy (ADT). A study by Antonia et al27 demonstrated that when small cell lung cancers evolved resistance to immunotherapy, their response to subsequent cytotoxicity greatly increased. A study11 treating patients with metastatic castration-resistant prostate cancer with abiraterone explicitly applied a game theoretic mathematical to delay onset of resistance.

Treatment With Imperfect Knowledge of Tumor Cells’ Strategies—Applications of Differential Game Theory

In a perfect-information Stackelberg game, the physician would be continuously aware of the evolutionary and ecological states of the tumor. However, imperfect knowledge is the norm in clinical practice, and this knowledge is often acquired over time as the patient progresses through treatment. The challenge is to design treatments that can adapt to the evolving resistance landscape, much like the coyote that can anticipate the squirrel’s escape options. A Stackelberg solution in this context requires the leader to choose a strategy that is optimal given the expected responses of the follower. This solution will be at least as good, and generally much better, than the Nash solution.

Dynamic therapy designs that explicitly integrate the evolutionary dynamics of resistance. As demonstrated in Figure 3, a physician can exploit the lead position in the Stackelberg game by anticipating the resistance strategies of the cancer cells. By understanding both the available molecular mechanism(s) of resistance and the Darwinian dynamics that govern the proliferation of resistant phenotypes, treatments can be modified, using mathematical models when necessary, to prolong the time to progression, and perhaps even cure. The key is to have some foreknowledge or estimate of the cancer cell’s best response curve. If I do X, how will the cancer cells respond and adapt over time? Just as the coyote can anticipate the squirrel’s escape options, as leader, the physician can choose to steer the cancer. A Stackelberg solution requires the leader to choose his or her best outcome along the other player’s best response curve. This solution will be at least as good, and generally much better, than the Nash solution.

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tumor. However, in reality physicians must oftentimes treat cancers with drugs for which the molecular mechanisms and eco-evolutionary dynamics governing resistance are poorly understood or entirely unknown. Furthermore, while the game dynamics occur continuously, tumor responses are measured through tests obtained at intervals of weeks or months. During the time between tests, treatments typically remain fixed except in cases of toxic effects. In the terminology of differential games, clinical cancer treatment is an unusual contest that can be “open loop” and “closed loop” at different timepoints. That is, during each cycle of therapy, the game, from the physician’s view, is an open-loop game because he or she cannot directly observe the strategies of the cancer cells and, therefore, cannot adjust his or her treatment strategy. However, at some time points, the game could become closed loop if the associated tests reveal the strategies of the cancer cells during the prior cycle.

The recursive dynamics during cycles of therapy, particularly in tumors in which several effective treatment strategies are available, provide a potential opportunity to probe the tumor to determine and measure key resistant and sensitive populations (Figure 4). The therapy probes would then give way to a more definitive therapy based on knowledge of (1) the strategies available to the cancer populations, (2) an estimate of their current relative sizes, (3) observed past and estimated future changes in cancer populations, and (4) past and present evolutionary dynamics.

From the late 1950s, dynamic programming and calculus of variations were developed to control systems (initially rockets) in which actions can and should vary with time (eg, the Bellman principle of optimality, the Pontryagin maximum principle). By the 1970s, dynamic programming expanded into differential game theory. Here, 2 players have time-dependent strategies. Each tries to maximize accrued payoffs or some payoff defined over a fixed time (eg, pursuit evasion games found in nature, dogs and squirrels, or in modern weapons systems). These complex, seemingly intractable problems are solved by breaking them into a sequence of small, nested subproblems. Optimal strategies are uncovered by recursively combining the solutions to each subproblem.

Figure 4 represents a highly simplified example of how an oncologist “leader” can use the Bellman principle to probe the tumor with short bursts of different therapies to uncover the available cancer cells’ strategies and the relative subpopulation sizes. This “revealed information” can optimize outcomes in subsequent rounds of the game. An interesting alternative approach is physical perturbation of the tumor (eg, by focused ultrasound), which causes cancer cells to release macromolecular biomarkers. A preclinical study showed how these serum markers accurately reflect the intratumoral population distribution.

Discussion

The therapeutic contest between physicians and cancer cells contains 2 important asymmetries. First, only the physician can plan
Synergies in cancer treatment can be optimized using game theory. These include:

1. **Define the Goal of Treatment**
   The goal of treatment can be curative or palliative. Palliative treatment aims to improve quality of life and control symptoms, while curative intent is to cure the disease. Initially, the treatment is designed to maximize the probability of cancer cell extinction. However, as the tumor progresses, the leader physician becomes the follower. In contrast, after action reports focus on evaluating cohort outcomes using well-defined metrics of tumor responses (ecological dynamics) and can identify molecular properties that will confer resistance. Then, as feasible, the treatment strategy can be adjusted to maximize the time to progression. Here, evolutionary dynamics are harnessed to suppress the growth of resistant phenotypes. Because the physician cannot, by definition, control resistant cells, the therapeutic strategy must focus on adaptive approaches that retain treatment-sensitive cells to suppress the growth of resistant cells.

2. **Table. Glossary of Game Theory Terms**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Game</td>
<td>Any situation in which a player's payoff depends on the player's own strategy and the strategies of the other players</td>
</tr>
<tr>
<td>Players</td>
<td>Participants in the game</td>
</tr>
<tr>
<td>Strategies (or actions)</td>
<td>Choices that players make</td>
</tr>
<tr>
<td>Payoffs</td>
<td>Benefits that accrue to the player that depend on his or her strategy and the strategies of the other players</td>
</tr>
<tr>
<td>Best reply</td>
<td>The payoff-maximizing strategy for player $i$ given that player $j$ uses strategy $u_j$</td>
</tr>
<tr>
<td>Nash equilibrium</td>
<td>An equilibrium state in which no player can increase his or her payoff by unilaterally deviating from his or her current strategy; in a Nash equilibrium the strategy of each player is a best reply to strategies of other players</td>
</tr>
<tr>
<td>Stackelberg equilibrium (or solution) with player $i$ as the leader and the other players as followers</td>
<td>An equilibrium state in which player $i$ obtains the highest possible payoff for himself or herself when the other players use their best reply strategy to the strategy of the leader (player $i$); the leader’s payoff is always at least as good as and mostly much better than his or her payoff at the Nash equilibrium</td>
</tr>
</tbody>
</table>

3. **Perform “After Action Reports”**
   Outcomes of military and emergency activities are often analyzed through after action reports. They encourage self-evaluation—what did I do right and what did I do wrong? Current clinical research in oncology focuses on evaluation of cohorts within some well-defined treatment protocol. In contrast, after action reports focus on evaluating the outcomes of every patient, even those not enrolled in a formal protocol, by asking, Was the stated goal of treatment (ie, cure or control) achieved? If not, what are plausible explanations for failure and could outcomes have been improved by altering the treatment goal or the RMP?

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Conclusions

Cancer therapy is a Stackelberg game. Game theoretic analyses of cancer therapy suggest that “precision medicine” in oncology can be broadened from its current focus on molecular targets that maximize the probability of immediate response. Additionally, precision medicine should incorporate the cancer therapy game to anticipate and steer patient-specific and treatment-specific evolutionary dynamics that govern the emergence and success of resistant populations. Even with initially well-targeted therapies, resistance leads to failure, progression, and patient death. Taking control of the Stackelberg game will require (1) the application of dynamic and sophisticated therapies and (2) the investigation of response metrics that move beyond the current focus on changes in tumor size (ie, the tumor ecology) and include measurements of the sensitive and resistant subpopulations (evolutionary state and dynamics). Emerging technologies that investigate circulating DNA and tumor cells\(^2\)\(^-\)\(^4\) will probably become key. New image analytic tools (eg, radiomics\(^5\)\(^-\)\(^6\) and habitat imaging\(^6\)) may generate biomarkers for treatment-sensitive and treatment-resistant intratumoral population through clinical computed tomography and magnetic resonance imaging studies. Finally, even with imperfect understanding of the resistance mechanisms and the size of resistant subpopulations, judicious applications of initial therapy can reveal the eco-evolutionary dynamics. As the cancer cells’ strategies and future responses become unmasked, the physician can adjust subsequent treatment cycles accordingly.

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