Stackelberg evolutionary games of cancer treatment: Tumor stabilization as an alternative to delaying progression

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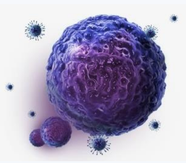
MOFFITT CANCER CENTER

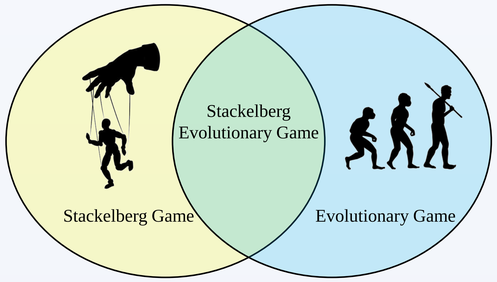
Motivation

- Metastatic cancer, i.e. when cancer has disseminated from its primary site, remains largely incurable [1].
- Standard of care therapy applies the Maximum Tolerable Dose (MTD) of the drug to kill as many cancer cells as fast as possible. However, clinical outcomes and experiments suggest that cancerous cells adapt to this therapy.
- Improving cancer treatment by extending mathematical models that account for treatment resistance using evolutionary dynamics [2].
- Stabilization of the tumor, when cure appears out of reach.

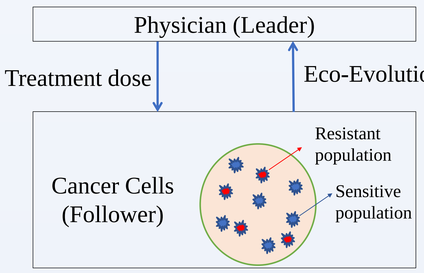


Stackelberg Evolutionary Game

The Stackelberg evolutionary game theory is a leader-follower game where followers play an evolutionary game among each other.



Stackelberg Evolutionary Game of Cancer Treatment



Players	Objectives	Strategies
Physician	Quality of life function (Q)	Treatment dose
Cancer cells	Fitness generating function (G)	Therapy resistance

Evolutionary Game Among Cancer Cells

We consider game-theoretic model of heterogeneous cancer cell populations where treatment-induced resistance is a quantitative evolving trait [3, 4, 5].

Heterogeneous population model:

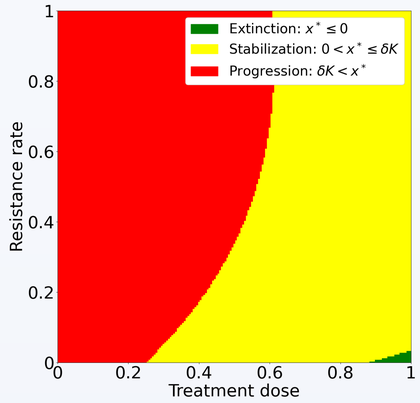
$$\begin{cases} \dot{x}_i = x_i G(v,x,m)|_{v=u_i}, & i \in \{R,S\} \\ \dot{u}_R = \sigma \dfrac{\partial G(v,x,m)}{\partial v}|_{v=u_R} \\ u_S = 0 \end{cases}$$

m: Drug dosage
x_S: Sensitive population
x_R: Resistant population
u_S: Resistance strategy of sensitive cells
u_R: Resistance strategy of resistant cells
v: Resistance strategy (focal individual)
σ: Evolutionary speed

Ecological Equilibrium

The population sizes at the ecological equilibria correspond to:
x_R^* and x_S^* solving equations $0 = x_i G(v,u,x,m)|_{v=u_i}$. We define $x^*(m,u_R) = x_R^*(m,u_R) + x_S^*(m,u_S)$ as the sum of the equilibria reached for each sub-population.

Population Size at the Equilibrium

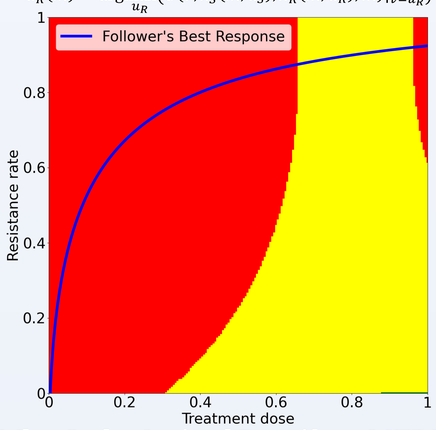


There are three possible regions considering the carrying capacity (K), and progression threshold (δ).

Evolutionary Equilibrium

Since G is concave in u_R, $\frac{\partial G(v,x,m)}{\partial v}|_{v=u_R} = 0$ corresponds to the best response curve of the cancer population.

$$u_R^*(m) = \underset{u_R}{\operatorname{argmax}} \left(G(v, x_S^*(m,u_S), x_R^*(m,u_R), m)|_{v=u_R} \right)$$



What Is the Optimal Dose if not MTD?

The objective of the leader is the quality of life function where toxicity of drug, tumor size, and resistance are penalized.

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

We compare the effect of ecological and evolutionary treatment strategies to that of MTD at cancer eco-evolutionary equilibria.

- Leader knows ecological equilibrium point of the followers

Nash solution → Ecological treatment → m^N

- Leader knows the ecological equilibrium point and the best response curve of the followers

Stackelberg solution → Evolutionary treatment → m^S

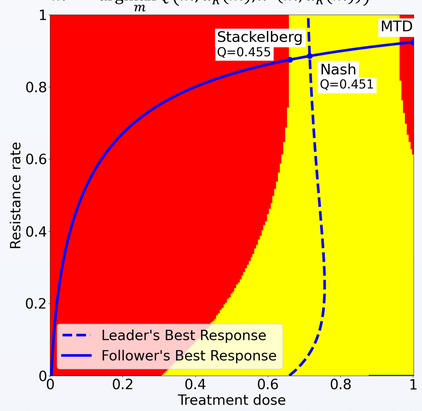
Best Response Curve of the Leader

Q is concave in u_R and the best response curve of the leader is as follows.

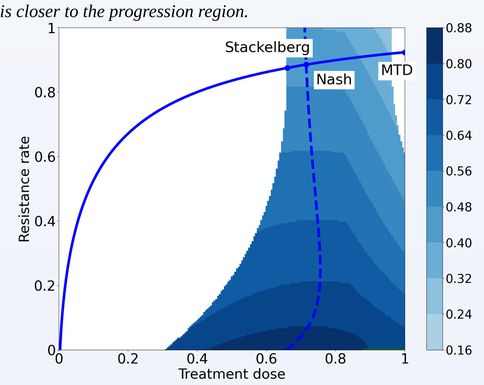
$$m^*(u_R) = \underset{m}{\operatorname{argmax}}\, Q\left(m, u_R, x^*(m,u_R)\right)$$

- Nash: Intersection of the leader and followers best responses.
- Stackelberg:

$$m^S = \underset{m}{\operatorname{argmax}}\, Q\left(m, u_R^*(m), x^*(m, u_R^*(m))\right)$$



MTD is inside the progression region while Nash and Stackelberg are in stabilization region. Stackelberg results in higher quality of life than the Nash but it is closer to the progression region.



Quality of life in $(m, u_R) \in [0,1] \times [0,1]$. Stackelberg results in higher quality of life than the Nash.

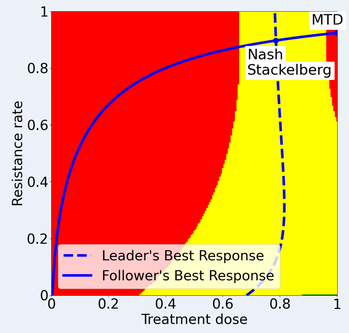
When do Nash and Stackelberg Coincide?

If leader's Nash and Stackelberg strategies are characterized by first-order optimality conditions, then they coincide in the following cases [4]:

a) If $\frac{du_R^*(m)}{dm} = 0$.

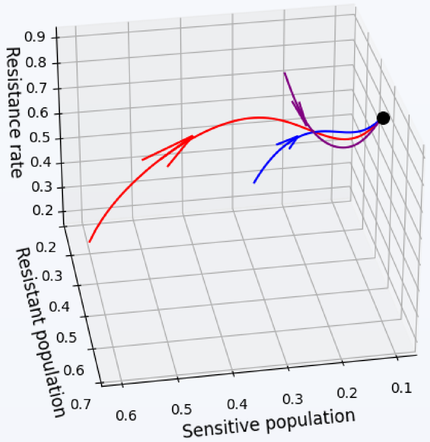
b) If $\frac{\partial Q(m,u_R,x)}{\partial u_R} = 0$ and, moreover, $\frac{\partial Q(m,u_R,x)}{\partial x} = 0$ or $\frac{\partial x^*(m,u_R)}{\partial u_R} = 0$.

With $Q = Q_{max} - c_1 \left(\frac{x^*(m,u_R)}{K} \right)^2 - c_3 m^2$ the above mentioned condition holds.



Stability and Reachability of the Solutions

Using the Jacobian matrix of dynamics and analyzing the phase plane, we deduced that the Nash and Stackelberg equilibrium points are stable.



The reachability of the Nash strategy from three distinct starting points is illustrated.

Conclusions

- We demonstrate that stabilization of tumors is possible when the maximum tolerable dose fails.
- We show that at the eco-evolutionary equilibrium, Stackelberg strategies lead to the best results in terms of patient's quality of life, equivalent or followed by Nash strategies, with MTD leading to the progression.
- We demonstrate under what conditions Nash and Stackelberg solutions coincide.

Future Work

- Extend the model to include multiple resistant cell types and/or multiple resistance traits.
- Rather than aiming for a constant dose based on equilibrium behavior, we can use dynamic game theory to find optimal decisions under variable behavior.
- We will consider mutations between distinct cell types.
- We will determine the representability of the model by fitting *in-vitro* and *in-vivo* data.

References

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[5] M. Salvioli, H. Garjani, M. Satouri, M. Broom, Y. Viossat, J. S. Brown, J. Dubbeldam, and K. Staňková, Stackelberg evolutionary games of cancer treatment: Tumor stabilization as an alternative to delaying progression, under submission.

Acknowledgments

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