Designing Evolutionary Treatment for Metastatic Non-Small Cell Lung Cancer

Virginia Ardévol Martínez & Kateřina Staňková

Dynamic Game Theory Team

Department of Data Science & Knowledge Engineering, Maastricht University

Joint work with:

Jakob Nikolas Kather, **Rachel Cavill**, **Monica Salvioli**, **Frank Thuijsman**, **Joel S. Brown**

CATMo 2020

Outline

1. Cancer Treatment as a Stackelberg Evolutionary Game

players	physician (leader)	patients' cancer cells (followers)
strategies	therapy options	effective strategies of therapy resistance
objectives	patients' quality of life	fitness

1. Cancer Treatment as a Stackelberg Evolutionary Game

players	physician (leader)	patients' cancer cells (followers)
strategies	therapy options	effective strategies of therapy resistance
objectives	patients' quality of life	fitness

Two critical asymmetries:

1. Cancer Treatment as a Stackelberg Evolutionary Game

players	physician (leader)	patients' cancer cells (followers)
strategies	therapy options	effective strategies of therapy resistance
objectives	patients' quality of life	fitness

Two critical asymmetries:

1. (rationality) Only the physician is rational and he/she can anticipate future events. In contrast, cancer cells, typical of evolving organisms in nature, can only respond to what is happening or has happened

1. Cancer Treatment as a Stackelberg Evolutionary Game

players	physician (leader)	patients' cancer cells (followers)
strategies	therapy options	effective strategies of therapy resistance
objectives	patients' quality of life	fitness

Two critical asymmetries:

1. (rationality) Only the physician is rational and he/she can anticipate future events. In contrast, cancer cells, typical of evolving organisms in nature, can only respond to what is happening or has happened
2. (timing) 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

1. Cancer Treatment as a Stackelberg Evolutionary Game

players	physician (leader)	patients' cancer cells (followers)
strategies	therapy options	effective strategies of therapy resistance
objectives	patients' quality of life	fitness

Two critical asymmetries:

1. (rationality) Only the physician is rational and he/she can anticipate future events. In contrast, cancer cells, typical of evolving organisms in nature, can only respond to what is happening or has happened
2. (timing) 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

We study how physician can utilize these advantages the best.

1. Cancer Treatment as a Stackelberg Evolutionary Game

players	physician (leader)	patients' cancer cells (followers)
strategies	therapy options	effective strategies of therapy resistance
objectives	patients' quality of life	fitness

Two critical asymmetries:

1. (rationality) Only the physician is rational and he/she can anticipate future events. In contrast, cancer cells, typical of evolving organisms in nature, can only respond to what is happening or has happened
2. (timing) 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

We study how physician can utilize these advantages the best.

Salvioli, PhD thesis 2020; Salvioli et al, PLOS One, in press; Cunningham et al, JTB 2018, PLOS One 2020, Stankova et al, JAMA Onc 2019,...

1. Cancer Treatment As a Stackelberg Evolutionary Game

1. Cancer Treatment As a Stackelberg Evolutionary Game

Physicians as the SEG leaders can achieve a lot if they know a lot.

1. Cancer Treatment As a Stackelberg Evolutionary Game

Physicians as the SEG leaders can achieve a lot if they know a lot.

But: What if we are a leader that

1. Cancer Treatment As a Stackelberg Evolutionary Game

Physicians as the SEG leaders can achieve a lot if they know a lot.

But: What if we are a leader that

- does not know much about resistance mechanisms to the treatment they apply?

1. Cancer Treatment As a Stackelberg Evolutionary Game

Physicians as the SEG leaders can achieve a lot if they know a lot.

But: What if we are a leader that

- does not know much about resistance mechanisms to the treatment they apply?
- does not know much about the effect of treatment on the evolution of resistance in this cancer?

1. Cancer Treatment As a Stackelberg Evolutionary Game

Physicians as the SEG leaders can achieve a lot if they know a lot.

But: What if we are a leader that

- does not know much about resistance mechanisms to the treatment they apply?
- does not know much about the effect of treatment on the evolution of resistance in this cancer?
- has only very limited measurements of treated patients?

1. Cancer Treatment As a Stackelberg Evolutionary Game

Physicians as the SEG leaders can achieve a lot if they know a lot.

But: What if we are a leader that

- does not know much about resistance mechanisms to the treatment they apply?
- does not know much about the effect of treatment on the evolution of resistance in this cancer?
- has only very limited measurements of treated patients?

Is there still a potential to predict what's going on to happen to patients on this treatment and/or learn what could have been done differently for those patients where the treatment failed?

1. Cancer Treatment As a Stackelberg Evolutionary Game

Physicians as the SEG leaders can achieve a lot if they know a lot.

But: What if we are a leader that

- does not know much about resistance mechanisms to the treatment they apply?
- does not know much about the effect of treatment on the evolution of resistance in this cancer?
- has only very limited measurements of treated patients?

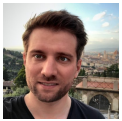
Is there still a potential to predict what's going on to happen to patients on this treatment and/or learn what could have been done differently for those patients where the treatment failed?

What is the minimal knowledge necessary?

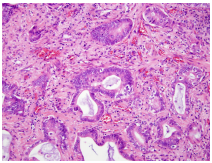
2. SEG Application to Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC)

2. SEG Application to Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC)

Data on NSCLC treated with Immune Checkpoint Inhibitian:



- Stage 4, anti-PD1 drug Atezolizumab (MPDL3280A)
- Tumor diameter over time, typically few time points
- In our dataset typically 2 or 3 metastases per patient



2. SEG Application to Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC)

Data on NSCLC treated with Immune Checkpoint Inhibitian:

Stage 4, anti-PD1 drug Atezolizumab (MPDL3280A)

Tumor diameter over time, typically few time points

In our dataset typically 2 or 3 metastases per patient

2. SEG Application to Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC)

Data on NSCLC treated with Immune Checkpoint Inhibitian:

Stage 4, anti-PD1 drug Atezolizumab (MPDL3280A)

Tumor diameter over time, typically few time points

In our dataset typically 2 or 3 metastases per patient

Our questions:

Based on the initial tumor volume proxy and its trend, can we predict how its volume will change in the future?

Would adaptive immunotherapy work in cases where tumor keeps growing when treated in the standard way?

2. SEG Application to Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC)

Data on NSCLC treated with Immune Checkpoint Inhibitian:

Stage 4, anti-PD1 drug Atezolizumab (MPDL3280A)

Tumor diameter over time, typically few time points

In our dataset typically 2 or 3 metastases per patient

Our questions:

Based on the initial tumor volume proxy and its trend, can we predict how its volume will change in the future?

Would adaptive immunotherapy work in cases where tumor keeps growing when treated in the standard way?

Our modelling approach to answer question 2:

Fitting the data into minimalistic G-function model

Optimizing the treatment for cases with tumor growing

2. SEG Application to Treatment of Metastatic NSCLC

Example of data :

All patients treated with the same immune checkpoint inhibition

Treatment starts between the rst and second data points

Are these different trends a result of treatment-induced resistance and other patient- and tumor-speci c factors?

2. SEG Application to Treatment of Metastatic NSCLC

NSCLC model details (Vincent and Brown (2005)):

$$\underline{x} \quad x\,G\hat{}m;u;x\bullet$$

$$\underline{u} \quad \frac{@G\hat{}m;u;x\bullet}{@u}$$

$$G\hat{}m;u;x\bullet \quad r\hat{}u\bullet\,\langle\,1 \quad \frac{x}{K}\bullet \quad \frac{m}{k \quad b\,u} \quad d$$

symbol & range	meaning
$m > \tilde{} 0;1\bullet$	treatment (on or off)
$u > 0;1$	rate of treatment-induced resistance
$K\ A\ 0$	carrying capacity
$x > 0;K$	cancer cell population
$G\hat{}m;u;x\bullet$	tness-generating function
$r_{max}\ A\ 0$	maximal growth rate
$d\ A\ 0$	natural death rate
$C\ 0$	evolutionary speed
$k\ A\ 0$	innate resistance
$b\ A\ 0$	effect of u

2. SEG Application to Treatment of Metastatic NSCLC

NSCLC model details (Vincent and Brown (2005)):

$$\frac{dx}{dt} = x\,G(m,u,x)$$

$$\frac{du}{dt} = \frac{\partial G(m,u,x)}{\partial u}$$

$$G(m,u,x) = r(u)\left(1 - \frac{x}{K}\right) - \frac{m}{k + b\,u} - d$$

symbol & range	meaning
$m \in \{0,1\}$	treatment (on or off)
$u \in [0,1]$	rate of treatment-induced resistance
$K > 0$	carrying capacity
$x \in [0,K]$	cancer cell population
$G(m,u,x)$	fitness-generating function
$r_{max} > 0$	maximal growth rate
$d > 0$	natural death rate
$\alpha \geq 0$	evolutionary speed
$k > 0$	innate resistance
$b > 0$	effect of u

Three different forms of $r(u)$ considered:

- Quadratic cost of resistance: $r(u) = r_{max}(1 - u^2)$
- Linear cost of resistance: $r(u) = r_{max}(1 - u)$
- No cost of resistance : $r(u) = r_{max}$

2. SEG Application to Treatment of Metastatic NSCLC

Fitting the model (also for predictions) :

The population of cancer cells is estimated from the diameter.

Distinguishing 6 groups of tumors: 3 according to initial volume and 2 according to initial trend.

Fix K , b and per group, estimate r_{max}, k and u^0• per patient, d xed to 0 :01.

	Small	Medium	Large
Increasing	K 0:1 b 100 0:01	K 2 b 150 0:01	K 2 b 0:9 0:05
Decreasing	K 1000 b 5 0:05	K 0:5 b 2 0:01	K 1000 b 10 0:01

$$\frac{x}{u} \quad \frac{x\,G\hat{}m;u;x\bullet}{\frac{@G\hat{}m;u;x\bullet}{@u}}$$

$$G\hat{}m;u;x\bullet \quad r\hat{}u\bullet\langle 1 \quad \frac{x}{K}\bullet \quad \frac{m}{k \quad b\,u} \quad d$$

2. SEG Application to Treatment of Metastatic NSCLC

Fitting the model (also for predictions) :

The population of cancer cells is estimated from the diameter.

Distinguishing 6 groups of tumors: 3 according to initial volume and 2 according to initial trend.

Fix K , b and per group, estimate r_{max}, k and uˆ0• per patient, d xed to 0 :01.

	Small	Medium	Large
Increasing	K 0:1 b 100 0:01	K 2 b 150 0:01	K 2 b 0:9 0:05
Decreasing	K 1000 b 5 0:05	K 0:5 b 2 0:01	K 1000 b 10 0:01

$$\frac{x}{u}\quad \frac{x\,G\hat{}m;u;x\bullet}{\frac{@G\hat{}m;u;x\bullet}{@u}}$$

$$G\hat{}m;u;x\bullet \quad r\hat{}u\bullet\langle 1 \quad \frac{x}{K}\bullet \quad \frac{m}{k \quad b\,u} \quad d$$

Jakob Nikolas Kather: "There is no cost of resistance or carrying capacity in cancers I am dealing with"

2. SEG Application to Treatment of Metastatic NSCLC

Fitting the model :

2. SEG Application to Treatment of Metastatic NSCLC

Comparison with linear and exponential models :

Mean of the R2-scores: 0:59, 0:72, 0:80 for linear, exponential and evolutionary models, respectively.

Linear, exponential and evolutionary model with quadratic cost of resistance

2. SEG Application to Treatment of Metastatic NSCLC

Evolution of treatment-induced resistance only plays an important role in tumors that exhibit a rapid change of trend.

Evolutionary model with quadratic cost of resistance with and without evolution of resistance

2. SEG Application to Treatment of Metastatic NSCLC

Evolution of treatment-induced resistance only plays an important role in tumors that exhibit a rapid change of trend.

Evolutionary model with quadratic cost of resistance with and without evolution of resistance

2. SEG Application to Treatment of Metastatic NSCLC

Comparison of the different forms of $r\hat{}u\bullet$:

Quadratic and linear cost of resistance

No cost of resistance

2. SEG Application to Treatment of Metastatic NSCLC

Optimization

$$m^{\ddagger} \in \arg\min_{m(t) \in [0,1]} x(T)$$

$$\underline{x}(t) = x(t) \in G(m(t), u(t), x(t))$$

$$\underline{u}(t) = \frac{\partial G(m(t), u(t), x(t))}{\partial u(t)}$$

$$G(m(t), u(t), x(t)) = r(u(t)) \left(1 - \frac{x(t)}{K}\right) \frac{m(t)}{k + b\,u(t)}, \quad t \in [0, T]$$

2. SEG Application to Treatment of Metastatic NSCLC

Optimization

$$
\begin{aligned}
m^{\ddagger}(\cdot) &= \arg\min_{m(t)\in[0,1]} x(T) \\
\underline{x}(t) &= x(t) - G(m(t), u(t), x(t)) \\
\underline{u}(t) &= \frac{\partial G(m(t), u(t), x(t))}{\partial u(t)} \\
G(m(t), u(t), x(t)) &= r\,u(t)\left(1 - \frac{x(t)}{K}\right)\left(\frac{m(t)}{k + m(t)} - u(t)\right), \quad t \in [0, T]
\end{aligned}
$$

Preliminary results:

- With linear and/or quadratic cost of resistance, the best is to always treat or not treat at all
- With no cost of resistance, sometimes it is the best to switch between no and standard treatment. We do not understand yet when precisely.
- With the objective $\min x(T)$, we can never stop the growth, we can only slow it down

2. SEG Application to Treatment of Metastatic NSCLC

Optimization - preliminary results :

3. Conclusions & Future Research

3. Conclusions & Future Research

Hypothesis: With objective of nal tumor minimization, adaptive therapy could help the patients with NSCLC only if it there is no cost of resistance

3. Conclusions & Future Research

Hypothesis: With objective of nal tumor minimization, adaptive therapy could help the patients with NSCLC only if it there is no cost of resistance

This may not hold with other treatment objectives, we will explore this next

3. Conclusions & Future Research

Hypothesis: With objective of nal tumor minimization, adaptive therapy could help the patients with NSCLC only if it there is no cost of resistance

This may not hold with other treatment objectives, we will explore this next

For tumors that change diameter rapidly, evolution of treatment-induced resistance plays a role

3. Conclusions & Future Research

- Hypothesis: With objective of final tumor minimization, adaptive therapy could help the patients with NSCLC only if it there is no cost of resistance
- This may not hold with other treatment objectives, we will explore this next
- For tumors that change diameter rapidly, evolution of treatment-induced resistance plays a role
- For small tumors the error in estimating tumor volume may cause issues with the best fit; it may be that our conclusion would change with better tumor proxy

3. Conclusions & Future Research

- Hypothesis: With objective of final tumor minimization, adaptive therapy could help the patients with NSCLC only if it there is no cost of resistance
- This may not hold with other treatment objectives, we will explore this next
- For tumors that change diameter rapidly, evolution of treatment-induced resistance plays a role
- For small tumors the error in estimating tumor volume may cause issues with the best fit; it may be that our conclusion would change with better tumor proxy
- Our model has better predictive capabilities than linear/exponential models used until now

4. Discussion Points/Questions for You

- Does resistance to immune checkpoint inhibition in NSCLC carry a cost?
- If yes, is there any way how to estimate it from other measurements (For other projects/cancers, we are exploring whether genomics and histopathology can help us to answer such questions, but here we know too little)?
- What other information can be useful here?
- Would a model with immune cells as active players be a better choice here?

Thank you !

02/12/2020

Marie Skłodowska-Curie Actions

fully funded

Evolutionary Game Theory & Population Dynamics: From Theory to Applications

15 Early Stage Researcher positions as part of the H2020 MSCA ETN project EvoGamesPlus

Intended starting date: July - September 2021

15 different EU hosts + 15 different partners where secondments take place (incl. Moffitt, Cancer Research UK, but also with Yannick at Université Paris Dauphine!)

Check the details on www.evogamesplus.eu and/or @EvoGamesPlus!

Maastricht University NWO

UNIKLINIK RWTH AACHEN MOFFITT CANCER CENTER