PERSONALIZED ONCOLOGY WITH ARTIFICIAL INTELLIGENCE: THE CASE OF TEMOZOLOMIDE

Nicolas Houy (CNRS, GATE, Écully, France), François Le Grand (emlyon business school, Écully, France)

Introduction

Our article builds on the concept of "personalized" medicine: administering the right drug to the right patient with the right schedule. This idea is generally understood with a static meaning and the techniques used to design optimal protocols mostly involve a unique dimension.

Here, we allow our optimization program to deal with a huge dimensionality and we let it learn from past actions. We use a heuristic that is well-known in Artificial Intelligence: the Monte-Carlo Tree Search.

We run an *in-silico* clinical trial, where we compare our optimal protocols to the standard protocol (Maximum Tolerated Dose, MTD). Results are twofold:

- efficacy is greatly improved: the tumor size at day 336 is divided by more than 6;
- toxicity is not deteriorated: a smaller number of patients experience a severe toxicity.

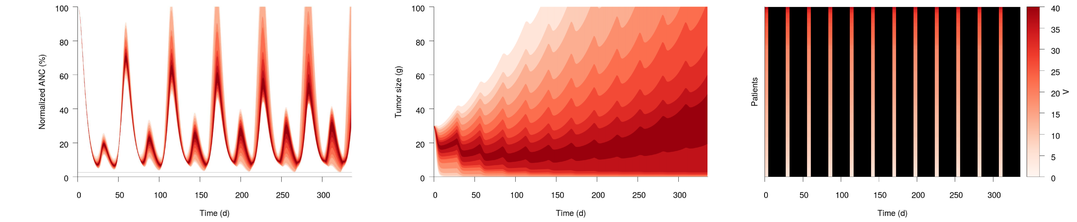
Method

We use a model of population Pharmacokinetics/Pharmacodynamics for temozolomide to simulate an *in silico* clinical trial. For determining optimal personalized protocols in a population of heterogeneous patients, we define:

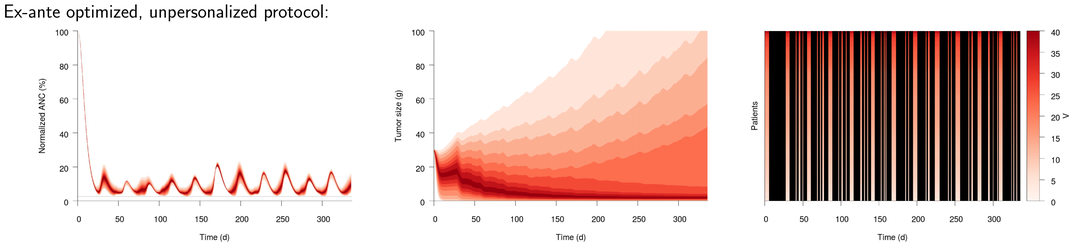
- a heuristic, which is a variation on Monte-Carlo Tree Search:
  - highly flexible,
  - requires a significant amount of work for "fine tuning";
- an objective: minimize tumor size at day 336 (12 MTD cycles);
- a constraint: lower bound on ANC nadir;
- some information for Bayesian update:
  - static: body surface area,
  - dynamics: reaction to the treatment.

Results

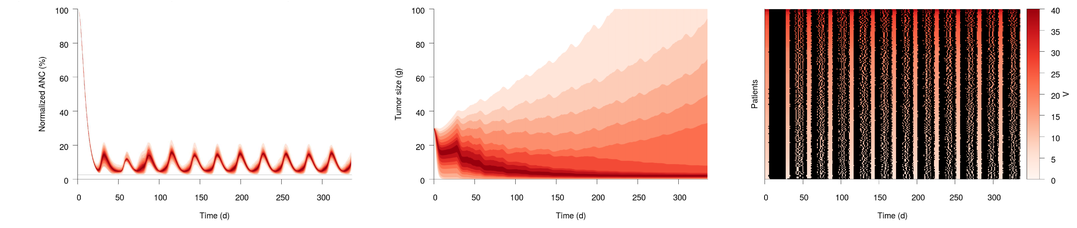
MTD (standard protocol):



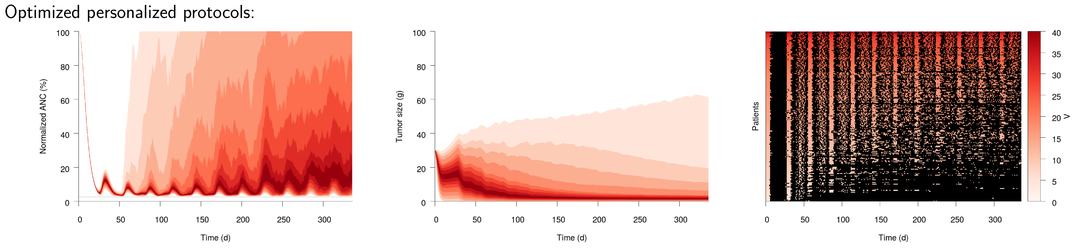
Ex-ante optimized, unpersonalized protocol:



Optimized with static personalization protocols:



Optimized personalized protocols:



Conclusion

Take-away results:

Protocol	Tumor mass (g)	Patients with severe toxicity
MTD	79.86 $[0.001-292.9]$	$10/192$
OPP	12.68 $[0.00001-61.46]$	$3/192$

What we are looking for:

- we have a convincing Proof of Concept on retrospective data;
- our concept has been applied to other problems: immunotherapy, drug combination, EPO;
- we are looking for partners to go beyond the Proof of Concept.

App. 1: Model for temozolomide

$$\begin{cases} \dot{y_1} = -k_a.y_1 + u(t) \\ \dot{y_2} = -k_e.y_2 + \frac{k_a}{V} y_1 \end{cases}$$

$$\begin{cases} \dot{y_3} = -a_1 \exp(-b_1.y_3)y_3 + (y_2 - c_1)H(y_2 - c_1) \\ \dot{y_4} = -a_2 \exp(-b_2.y_4)y_4 + (y_2 - c_2)H(y_2 - c_2) \\ \dot{y_5} = \lambda y_6 \log\left(\frac{K}{y_5}\right) y_5 - \exp(-r.y_7)u_1.y_3 \\ \dot{y_6} = 1 - (1 + u_2.y_4)y_6 \\ \dot{y_7} = (y_2 - c_1)H(y_2 - c_1) \end{cases}$$

$$\begin{cases} \dot{y_8} = [H(K_D - y_2).\left(r_{max} - (r_{max} - r_{min}).\left(\frac{y_{11}}{y_{11}+K_m}\right)\right) - k_1\Big] y_8 \\ \dot{y_9} = k_1.y_8 - k_2.y_9 \\ \dot{y_{10}} = k_2.y_9 - k_3.y_{10} \\ \dot{y_{11}} = k_3.y_{10} - k_{el}.y_{11} \end{cases}$$

App. 2: Monte-Carlo Tree Search