PERSONALIZED ONCOLOGY WITH ARTIFICIAL INTELLIGENCE: THE CASE OF TEMOZOLOMIDE
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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:

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Tumor mass (g)</th>
<th>Patients with severe toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTD</td>
<td>70.97</td>
<td>15/96</td>
</tr>
<tr>
<td>OPP</td>
<td>12.68</td>
<td>1/192</td>
</tr>
</tbody>
</table>

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

\[
\begin{align*}
\dot{y}_1 &= -d_1 y_1 + c_1 \\
\dot{y}_2 &= -d_2 y_2 + c_2 + (y_3 - y_2)K_H \quad (y_3 - y_2)H_c \\
\dot{y}_3 &= -d_3 y_3 - y_3K_H + (y_2 - y_3)H_c \\
\dot{y}_4 &= -d_4 y_4 - 4 y_4 \\
\end{align*}
\]

App. 2: Monte-Carlo Tree Search

[Diagram of Monte-Carlo Tree Search]