Modelling tumoral heterogeneity for chemotherapy optimisation: optimal control, theoretical and numerical analysis

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How do tumours become resistant to chemotherapies?

Tumour initially heterogeneous

Question

How can we reduce the tumoral charge while maintaining its heterogeneity?
Introduction

How do tumours become resistant to chemotherapies?

Tumour initially heterogeneous

- Treatment
  - Mutation

- Selection
  - Invasion
Introduction

How do tumours become resistant to chemotherapies?

Tumour initially heterogeneous

Question
How can we reduce the tumoral charge while maintaining its heterogeneity?
| 1. | In vitro experiments |
| 2. | Trajectories study |
| 3. | Optimal control |
|   | - Control problem |
|   | - Numerical results |
| 4. | Dynamic programming |
|   | - Viability and Reachability problems |
|   | - Numerical results |
1. **In vitro experiments**

2. **Trajectories study**

3. **Optimal control**
   - Control problem
   - Numerical results

4. **Dynamic programming**
   - Viability and Reachability problems
   - Numerical results
Experiments presentation

Experiments realized at CRO2 by M.Carré and her team
Experiments presentation

- Lung cancer cells A549
- Resistant clone A549 Epo50
- Drug: Epothilen B
Experiments presentation

- Lung cancer cells A549
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Experiments presentation

- Lung cancer cells A549
- Resistant clone A549 Epo50
- Drug: Epothilen B
In vitro experiments
Trajectories study
Optimal control
Dynamic programming
Conclusion

Model

Equations

\[
\begin{align*}
\frac{ds}{dt} &= \rho s (1 - \frac{s + mr}{K}) - \alpha C(t)s \\
\frac{dr}{dt} &= \rho r (1 - \frac{s + mr}{K}) - \beta sr
\end{align*}
\]

<table>
<thead>
<tr>
<th>$s$</th>
<th>number of sensitive cells</th>
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<tbody>
<tr>
<td>$r$</td>
<td>number of resistant cells</td>
</tr>
<tr>
<td>$C$</td>
<td>treatment concentration</td>
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<tr>
<td>$K$</td>
<td>Petri well capacity</td>
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<tr>
<td>$m$</td>
<td>size factor between $s$ and $r$</td>
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- Represent different drug dosages experiments
- Design protocols that reduce the tumoral charge
- Optimize the treatment
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Trajectories study

No treatment

\[ C = 0 \]

\[ \frac{K}{m} \]

\[ E_r \]

\[ r \]

\[ E_s, l \]

\[ E_s = K \]
Trajectories study

No treatment

\[ C = 0 \]

\[ s = K \]

Weak treatment

\[ C < \frac{\rho \ K \beta}{\alpha \ K \beta + \rho} \]

\[ s = K \]
In vitro experiments

Trajectories study

Optimal control

Dynamic programming

Conclusion

Trajectories study

No treatment

\[ C = 0 \]

Weak treatment

\[ C < \frac{\rho}{\alpha} \frac{K\beta}{K\beta + \rho} \]

\[ E_r \]

\[ E_s = K \]

\[ E_{s,l} \]

\[ K \]

\[ m \]

\[ s \]

\[ r \]

\[ \rho \]

\[ \alpha \]

\[ \beta \]

\[ \rho \]

\[ \alpha \]

\[ K \beta + \rho \]

\[ E_{s,l} \]

\[ E_s \]

\[ K \]

\[ s \]

\[ time \]

\[ 0 \]

\[ 5 \]

\[ 10 \]

\[ 15 \]

\[ 20 \]

\[ 0 \]

\[ 1 \]

\[ 2 \]

\[ 3 \]

\[ 0 \]

\[ 5 \]

\[ 10 \]

\[ 15 \]

\[ 20 \]

\[ 25 \]

\[ 30 \]

\[ 0 \]

\[ 1 \]

\[ 2 \]

\[ 3 \]

\[ 0 \]

\[ 5 \]

\[ 10 \]

\[ 15 \]

\[ 20 \]

\[ 25 \]

\[ 30 \]
Trajectories study

No treatment
\[ C = 0 \]

\[ E_r \]
\[ r \]
\[ K \]
\[ m \]

\[ E_s, l \]
\[ E_s = K \]

Strong treatment
\[ C > \frac{\rho}{\alpha} \]

\[ E_r \]
\[ r \]
\[ E_s, l \]
In vitro experiments

Trajectories study

Optimal control

Dynamic programming

Conclusion

**Trajectories study**

No treatment

\[ C = 0 \]

\[ E_s = K \]

Weak treatment

\[ C < \frac{\rho}{\alpha} \frac{K\beta}{K\beta+\rho} \]

Strong treatment

\[ C > \frac{\rho}{\alpha} \]
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Optimal control problem

Optimization problem

Given \(s(0), r(0)\) and \(T\), minimize the cost

\[
s(T)^2 + r(T)^2 + \int_0^T (As^2(t) + Br^2(t)) \, dt
\]

ever measurable functions \(C : [0, T] \rightarrow [0, C_{\text{max}}]\).

Pontryagin Minimum Principle

Necessary condition for \(C^*\) to be optimal: it must minimize among \(C : [0, T] \rightarrow [0, C_{\text{max}}]\) the Hamiltonian:

\[
H(s^*, r^*, p_1^*, p_2^*, C) = As^{*2} + Br^{*2} + \left\langle \left( \begin{array}{c} p_1^* \\ p_2^* \end{array} \right), \left( \begin{array}{c} \rho s^* (1 - \frac{s^* + mr^*}{K}) - \alpha Cs^* \\ \rho r^* (1 - \frac{s^* + mr^*}{K}) - \beta s^* r^* \end{array} \right) \right\rangle
\]

where \((s^*, r^*)\) is the optimal trajectory and

\[
\begin{align*}
\frac{dp_1^*}{dt} &= -\frac{\partial H}{\partial s}(s^*, r^*, p_1^*, p_2^*, C^*) \\
\frac{dp_2^*}{dt} &= -\frac{\partial H}{\partial r}(s^*, r^*, p_1^*, p_2^*, C^*) \\
\end{align*}
\]

\[
\begin{align*}
p_1^*(T) &= 2s^*(T) \\
p_2^*(T) &= 2r^*(T)
\end{align*}
\]
Optimal control problem

Characterization of the optimal treatment

\[ H(s^*, r^*, p_1^*, p_2^*, C) = As^*^2 + Br^*^2 + \left\langle \left( \begin{array}{c} p_1^* \\ p_2^* \end{array} \right), \left( \begin{array}{c} \rho s^* (1 - \frac{s^* + mr^*}{K}) \\ \rho r^* (1 - \frac{s^* + mr^*}{K}) - \beta s^* r^* \end{array} \right) \right\rangle \]

\[ -p_1^* \alpha s^* C \]

The optimal treatment \( C^* \) satisfies:

- If \( p_1^*(t) > 0 \) then \( C^*(t) = C_{\text{max}} \)
- If \( p_1^*(t) < 0 \) then \( C^*(t) = 0 \)
- If \( p_1^* \equiv 0 \) on an interval,
  \[ C^* = \frac{1}{\alpha s^*} \left( \frac{B}{A} r^*^2 \left( \frac{\rho}{K} + \beta \right) + s^* \rho (1 - \frac{s^* + 2mr^*}{K}) \right). \]

Singular arcs may correspond to metronomic treatments: giving smaller doses of drug on a longer period of time.

Could this problem generate singular arcs?
Objective: Minimizing the cost for regular cycling treatments
No drug → Metronomic treatment → Maximum Tolerated Dose

Cycles with metronomic halt

-10^4

0

1

2

3

4

0

20

40

60

time (d)

red: cells  black: treatment
Numerical results

Objective: Minimizing the cost for regular cycling treatments
No drug → Metronomic treatment → Maximum Tolerated Dose

**Cycles with metronomic halt**

**MTD cycles**

- Time (d)
- Cells
- Treatment
Numerical results

Objective: Minimizing the cost for regular cycling treatments
No drug $\rightarrow$ Metronomic treatment $\rightarrow$ Maximum Tolerated Dose

Published in *Journal of Theoretical Biology*, 2017
*Optimization of an in vitro chemotherapy to avoid resistant tumours*
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Viability and Reachability problems

Viability Problem
Let \( Q > 0 \) be a size threshold. An initial tumour \((s_0, r_0)\) is *viable* if there exists a treatment \( C : [0, +\infty) \rightarrow [0, C_{\text{max}}] \) such that:

\[
\forall t > 0, \quad s(t) + mr(t) \leq Q
\]

Determine the viability set \( \mathcal{N}_Q \)

Reachability Problem
Let \((s_0, r_0)\) be an initial tumour, does there exist a treatment \( C : [0, T] \rightarrow [0, C_{\text{max}}] \) such that

\[
(s(T), r(T)) \in \mathcal{N}_Q
\]

and if so, minimize the time of entry \( t_{in} \):

\[
\forall t > t_{in}, \quad (s(t), r(t)) \in \mathcal{N}_Q
\]
Viability and Reachability problems
Viability and Reachability problems
Viability and Reachability problems
Viability and Reachability problems
Hamilton-Jacobi-Bellman framework

**Definition: value function**

\[ V_Q(s_0, r_0) = \min_{C: \mathbb{R}^+ \rightarrow [0, C_{\text{max}}]} \max_{t \geq 0} e^{-\lambda t} g_Q(s^C(t), r^C(t)) \]

where \( g_Q(s, r) < 0 \iff s > 0, r > 0 \) and \( s + mr < Q \)

**Property**

\( V_Q \) satisfies the following:

\[ (s, r) \in \mathcal{N}_Q \iff V_Q(s, r) \leq 0 \]

**Theorem**

\( V_Q \) is a viscosity solution of

\[ \min(\lambda V_Q + H((s, r); \nabla V_Q), V_Q - g_Q) = 0 \]

where \( H(x; p) = \max_{c \in [0, C_{\text{max}}]} \langle -f(x, c) \cdot p \rangle \)
Hamilton-Jacobi-Bellman framework

Definition: value function

\[ W_Q(s_0, r_0; t) = \min_{C:[0,t] \to [0,C_{\text{max}}]} \text{dist}^s(s^C(t), r^C(t); \mathcal{N}_Q) \]

where \( \text{dist}^s(s, r; \mathcal{N}_Q) \) is the signed distance to \( \mathcal{N}_Q \).

Property

\( W_Q \) satisfies the following:

\[ \forall h > 0, \ W_Q(s_0, r_0; t + h) = \min_{C:[0,t] \to [0,C_{\text{max}}]} W_Q(s^C(h), r^C(h); t) \]

\( \rightarrow \) follow trajectories minimizing \( W_Q \) to minimize time of entry

Theorem

\( W_Q \) is a viscosity solution of

\[ \partial_t W(s, r; t) + H((s, r); \nabla W(s, r; t)) = 0 \]
Numerical results

Simulations realized with Roc-HJ

Work in progress: article with Hasnaa Zidani, *Dynamic programming of chemotherapy for heterogeneous tumours*
Numerical results

Simulations realized with Roc-HJ

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Conclusions and Perspectives

Conclusions:

- Importance of metronomic treatments
- Experiments were done with optimal control solution
- Framework for future work

Meanwhile, on the biological side:

- Reason for resistant cells repression
- Experiments on heterogeneous tumours encapsulated in sane tissue
- Experiments on heterogeneous tumours in mice

Perspectives:

- Adapt model to experiments
- New models, taking into account sane cells, immune system...
- Pareto fronts to take into account several objectives
- Take into account partial information
- Study mechanisms of resistance appearance
Thank you for your attention