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

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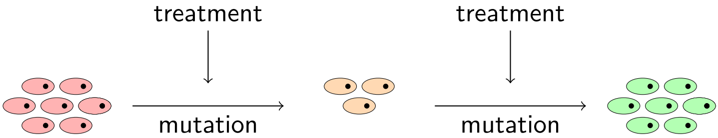
CRO2 Centre de Recherche en Oncologie biologique et Oncopharmacologie

Introduction

How do tumours become resistant to chemotherapies?



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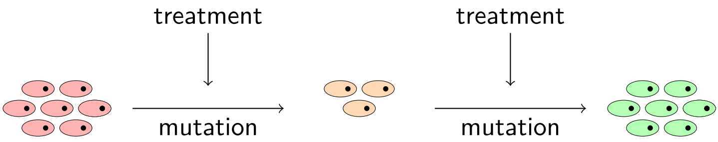
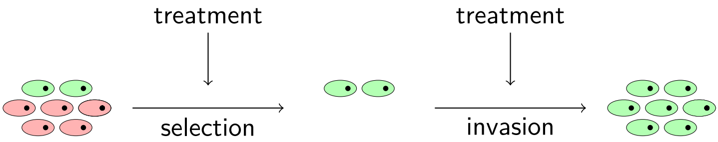


Tumour initially heterogeneous



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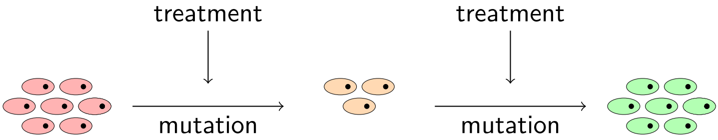

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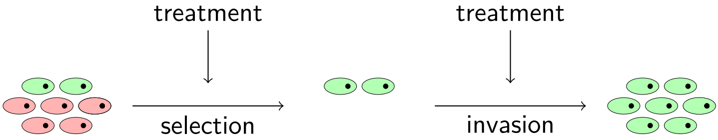
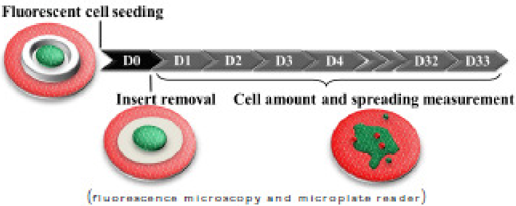


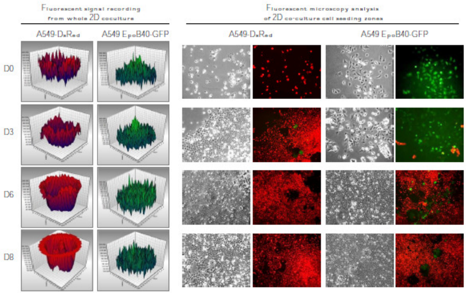
Question

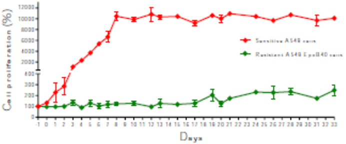
How can we reduce the tumoral charge while maintaining its heterogeneity?

Experiments presentation

Experiments realized at CRO2 by M.Carré and her team

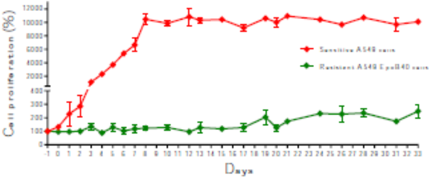






Experiments presentation

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



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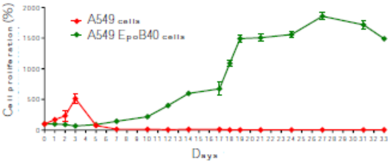

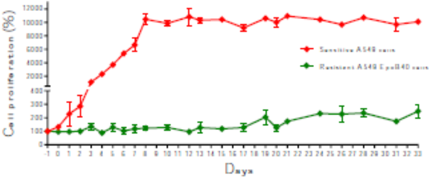

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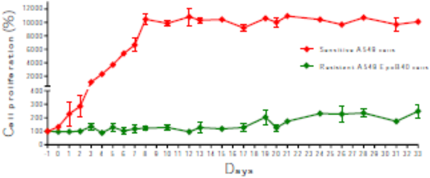
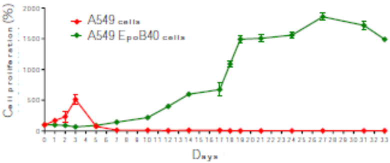
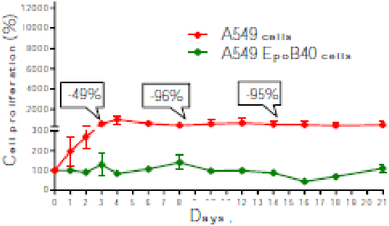




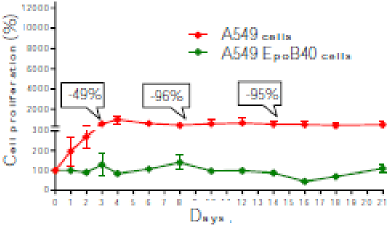


Model

Equations

$$\begin{cases} \frac{ds}{dt} = \rho s(1 - \frac{s+mr}{K}) - \alpha C(t)s \\ \frac{dr}{dt} = \rho r(1 - \frac{s+mr}{K}) - \beta sr \end{cases}$$

s	number of sensitive cells
r	number of resistant cells
C	treatment concentration
K	Petri well capacity
m	size factor between s and r

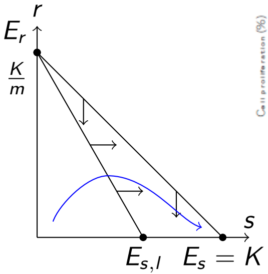


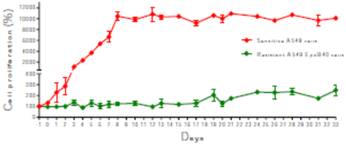
- Represent different drug dosages experiments
- Design protocols that reduce the tumoral charge
- Optimize the treatment

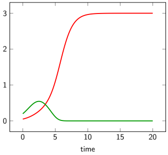
Trajectories study

No treatment

$C = 0$







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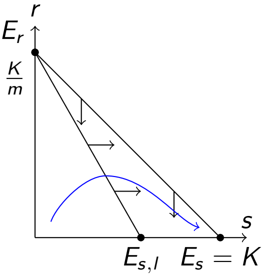
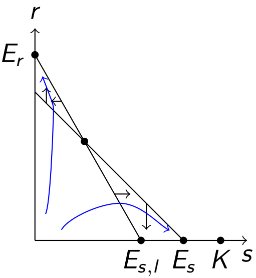
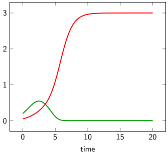
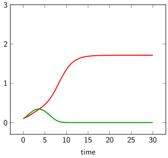


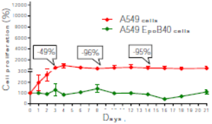
Weak treatment

$C < \frac{\rho}{\alpha} \frac{K\beta}{K\beta+\rho}$









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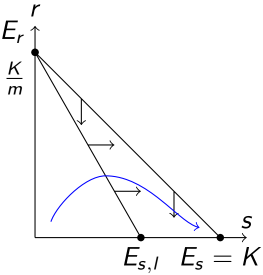

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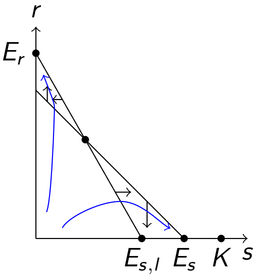

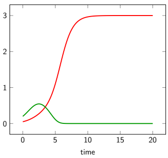

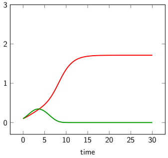

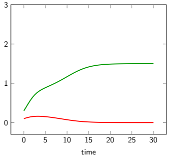

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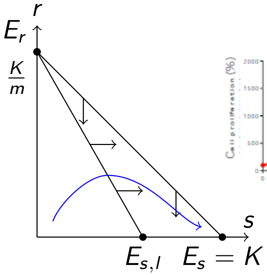
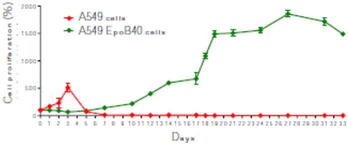
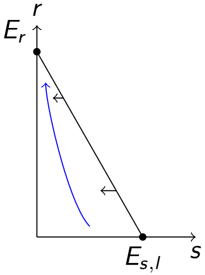
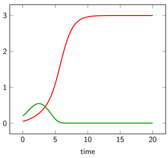


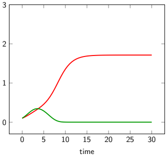


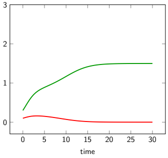
Strong treatment

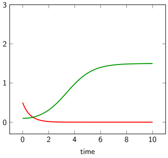
$C > \frac{\rho}{\alpha}$











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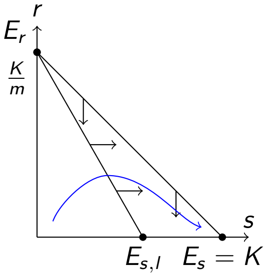

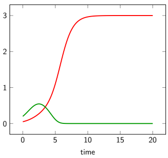

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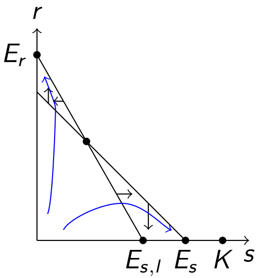

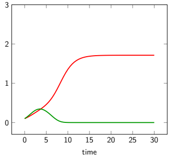

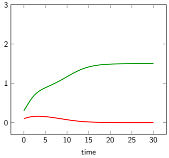

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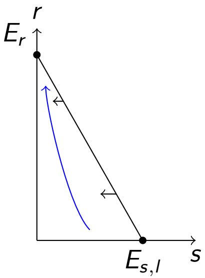
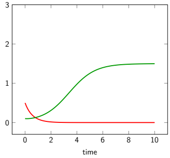




1. In vitro experiments

2. Trajectories study

3. Optimal control
   - Control problem
   - Numerical results

4. Dynamic programming
   - Viability and Reachability problems
   - Numerical results

Optimal control problem

Optimization problem

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

$$s(T)^2 + r(T)^2 + \int_0^T (As^2(t) + Br^2(t))dt$$

over measurable functions $C : [0, T] \to [0, C_{\max}]$.

Pontryagin Minimum Principle

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

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

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

$$\begin{cases} \frac{dp_1^*}{dt} = -\frac{\partial H}{\partial s}(s^*, r^*, p_1^*, p_2^*, C^*) \\ \frac{dp_2^*}{dt} = -\frac{\partial H}{\partial r}(s^*, r^*, p_1^*, p_2^*, C^*) \end{cases} \qquad \begin{cases} p_1^*(T) = 2s^*(T) \\ p_2^*(T) = 2r^*(T) \end{cases}$$

Optimal control problem

Characterization of the optimal treatment

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

The optimal treatment C^* satisfies:

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

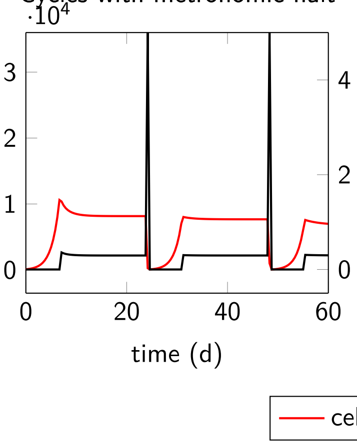
Singular arcs may correspond to metronomic treatments: giving smaller doses of drug on a longer period of time.

Could this problem generate singular arcs?

Numerical results

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

Cycles with metronomic halt



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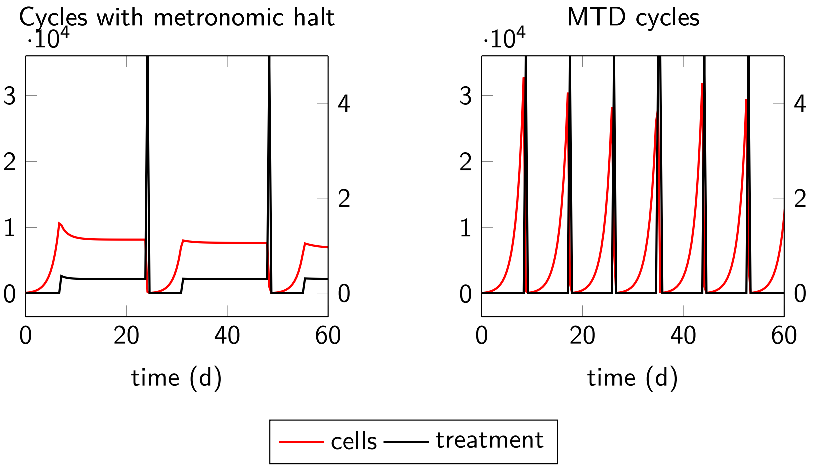

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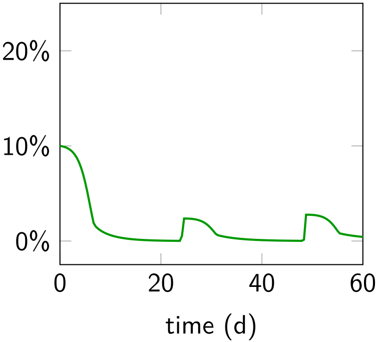
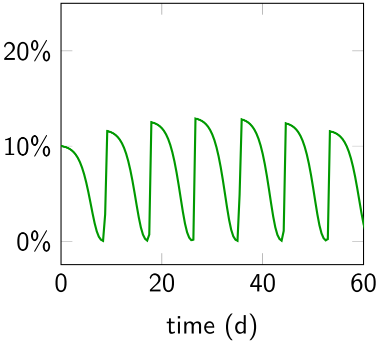


MTD cycles



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 $C : [0, +\infty) \to [0, C_{\max}]$ such that:

$$\forall t > 0,\ s(t) + mr(t) \leq Q$$

Determine the viability set $\mathcal{N}_Q$

Reachability Problem

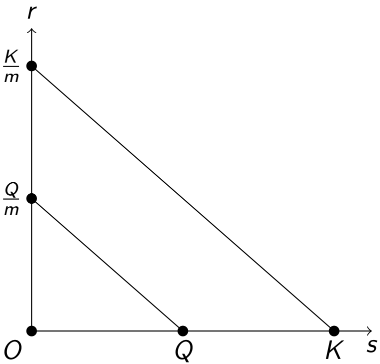
Let (s_0, r_0) be an initial tumour, does there exist a treatment $C : [0, T] \to [0, C_{\max}]$ such that

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

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

$$\forall t > t_{in},\ (s(t), r(t)) \in \mathcal{N}_Q$$

Viability and Reachability problems



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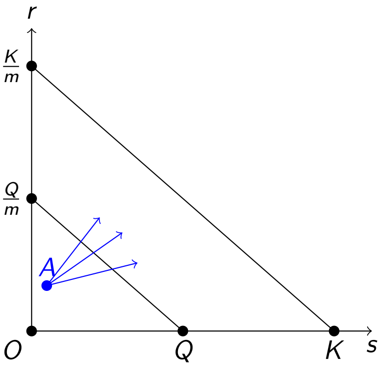

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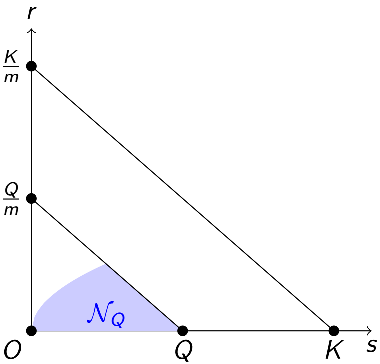

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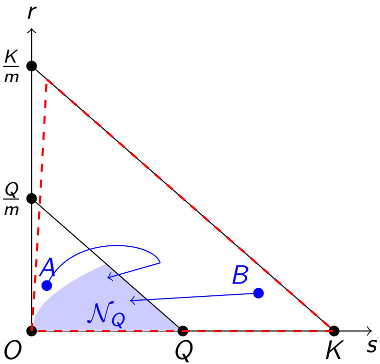
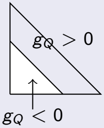


Hamilton-Jacobi-Bellman framework

Definition: value function

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

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 $H(x; p) = \max_{c \in [0, C_{\max}]} \langle -f(x, c) \cdot p \rangle$

Hamilton-Jacobi-Bellman framework

Definition: value function

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

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

Property

W_Q satisfies the following:

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

$\longrightarrow$ follow trajectories minimizing W_Q to minimize time of entry

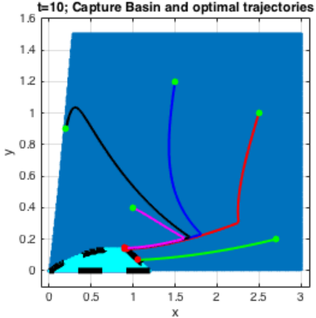
Theorem

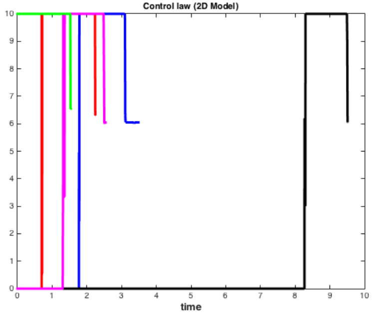
W_Q is a viscosity solution of

$$\partial_t W(s, r; t) + H((s, r); \nabla W(s, r; t)) = 0$$

Numerical results

Simulations realized with Roc-HJ

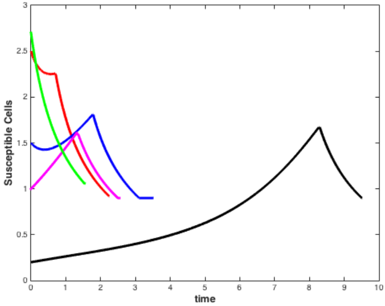


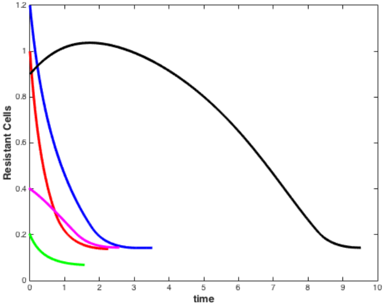


Work in progress: article with Hasnaa Zidani, *Dynamic programming of chemotherapy for heterogeneous tumours*

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