Dynamical programming of a chemotherapy preventing resistance for *in vitro* heterogeneous tumours

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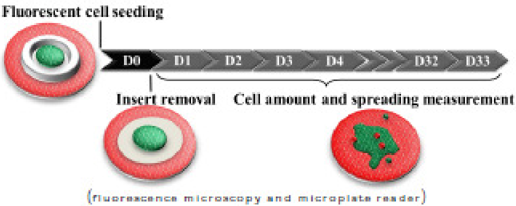
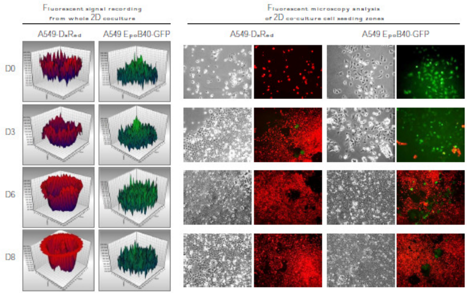
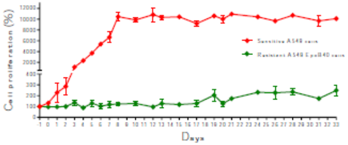
Experiments presentation

Experiments realized at CRO2 by M.Carré and her team

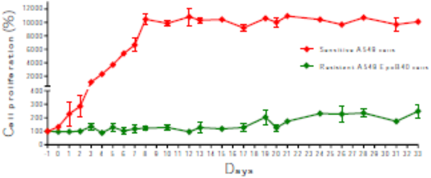






Experiments presentation

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



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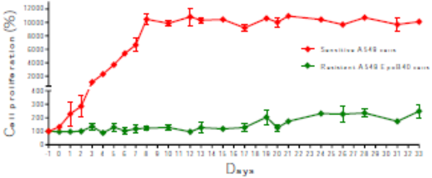

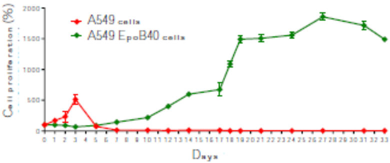

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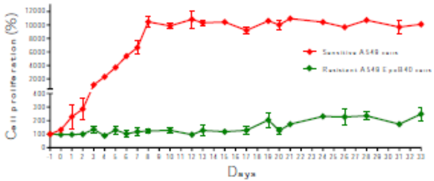
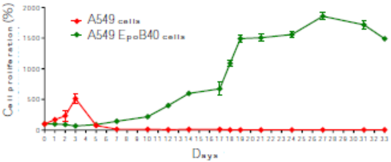
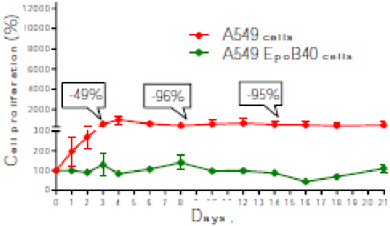






Model

Equations

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

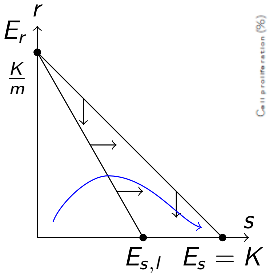
s	number of sensitive cells
r	number of resistant cells
u	treatment concentration
K	Petri well capacity
m	size factor between s and r
α	efficiency of the treatment
β	competition of s on r

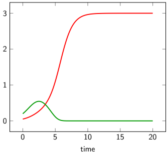
- Represent different drug dosages experiments
- Optimize the treatment to reduce tumoral charge
- First work with optimal control : Optimization of an in vitro chemotherapy to avoid resistant tumours, CC, *JTB* 2017
- New framework: dynamical programming

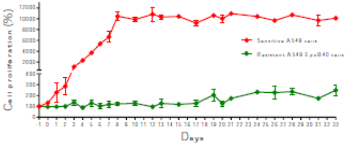
Trajectories study

No treatment

$u = 0$







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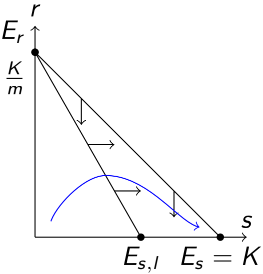
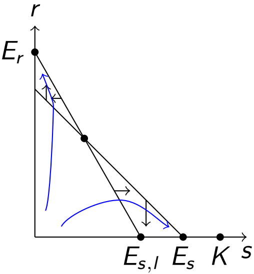
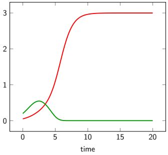
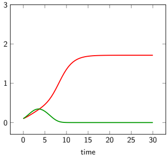


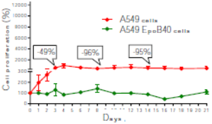
Weak treatment

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









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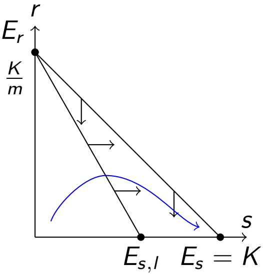

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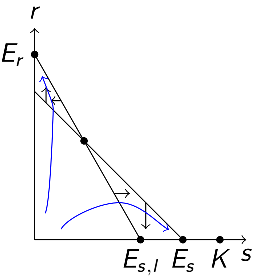

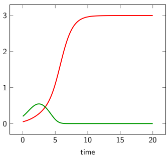

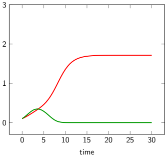

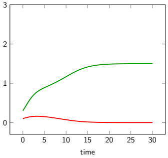

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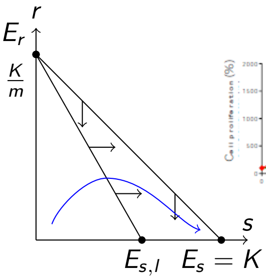
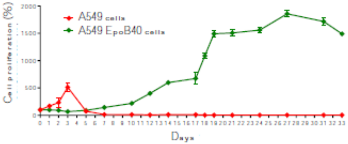
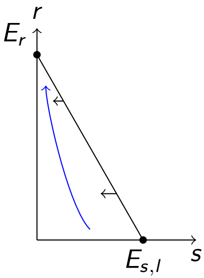
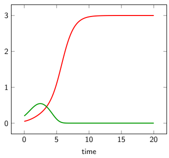


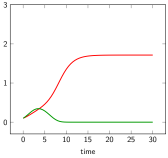


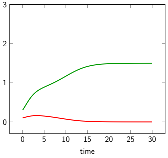
Strong treatment

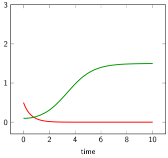
$u > \frac{\rho}{\alpha}$











Trajectories study

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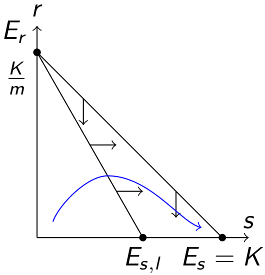

Weak treatment

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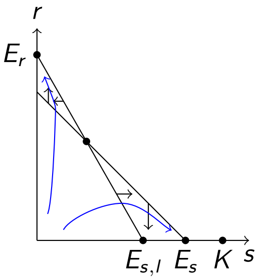

Strong treatment

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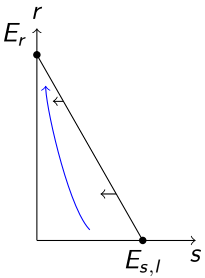
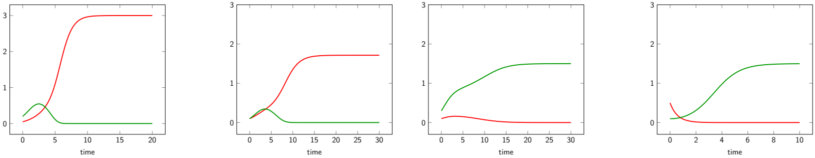




Viability and Reachability problems

Viability Problem

Let $Q > 0$ be a size threshold. An initial tumour (s_0, r_0) is *viable* if for any variation $\alpha : [0, +\infty) \to [\alpha_{\min}, \alpha_{\max}]$ there exists a treatment $u_\alpha : [0, +\infty) \to [0, u_{\max}]$ such that:

$$\forall t > 0,\ s^{\alpha, u_\alpha}(t) + m r^{\alpha, u_\alpha}(t) \leq Q$$

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

Reachability Problem

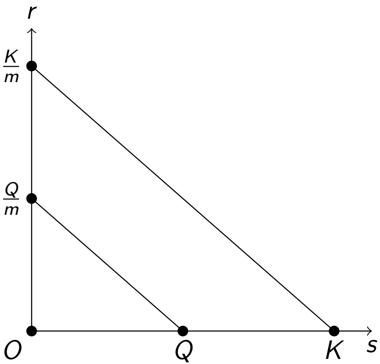
Let (s_0, r_0) be an initial tumour, does there exist for any variation $\alpha : [0, T] \to [\alpha_{\min}, \alpha_{\max}]$ a treatment $u_\alpha : [0, T] \to [0, u_{\max}]$ such that

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

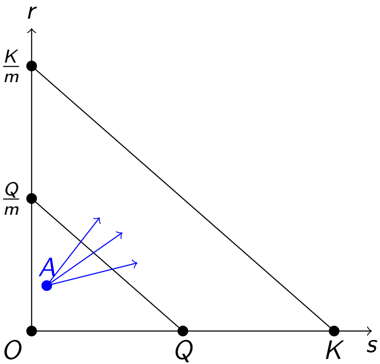
and if so, minimize the time of entry t_{in}:

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

Viability and Reachability problems



Viability and Reachability problems



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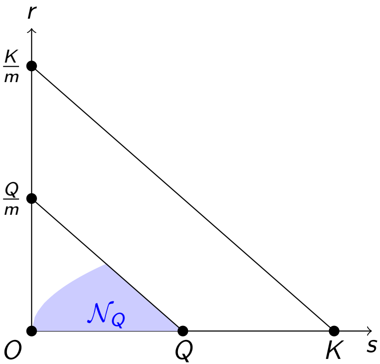

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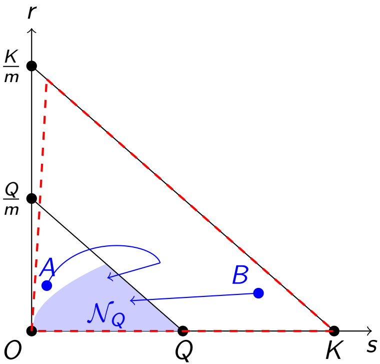

Solving the Viability problem

Definition: value function

We define the following value function $V_Q(s_0, r_0)$:

$$\min_{u:\mathbb{R}^+\to[0,u_{\max}]} \max_{\alpha:\mathbb{R}^+\to[\alpha_{\min},\alpha_{\max}]} \int_0^{+\infty} e^{-\lambda t} \max(s^{\alpha,u}(t) + mr^{\alpha,u}(t) - Q, 0)dt$$

A.Altarovici, O.Bokanowski, H.Zidani, A general Hamilton-Jacobi framework for non-linear state-constrained control problems. *ESAIM: Control, Optimisation and Calculus of Variations* 2013.

Solving the Viability problem

Definition: value function

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Property

V_Q satisfies the following:

$$(s,r) \in \mathcal{N}_Q \iff V_Q(s,r) = 0$$

Theorem

V_Q is a viscosity solution of

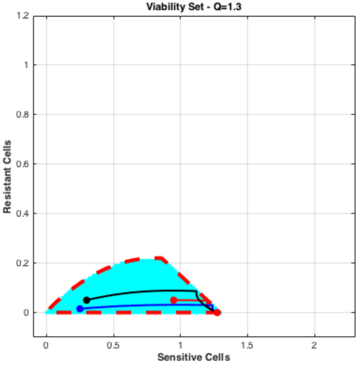
$$\lambda V_Q + H((s,r);\nabla V_Q) = \max(s + mr - Q, 0)$$

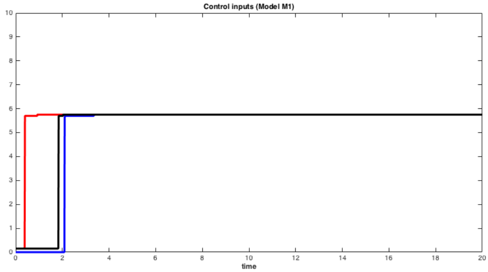
where $H(x;p) = \max_{u\in[0,u_{\max}]} \min_{\alpha\in[\alpha_{\min},\alpha_{\max}]}\langle -f(x,\alpha,u)\cdot p\rangle$

Simulations with Roc-HJ

The trajectories found numerically are ultimately optimal:

$$V_Q(s_0, r_0) \geq \lim_{h \to 0} \int_0^{+\infty} e^{-\lambda t} \max(s^h(t) + mr^h(t) - Q, 0) dt$$





O.Bokanowski, N.Forcadel, H.Zidani, Reachability and minimal times for state constrained nonlinear problems, *SIAM Journal on Cont. and Opt.* 2010.

Reachability Problem

Definition: value function

$$W_Q(s_0, r_0; t) = \min_{u:[0,t]\to[0,u_{\max}]} \max_{\alpha:[0,t]\to[\alpha_{\min},\alpha_{\max}]} dist^s(s^{\alpha,u}(t), r^{\alpha,u}(t); \mathcal{N}_Q)$$

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

Property

For any α, W_Q satisfies the following:

$$\forall h > 0,\ W_Q(s_0, r_0; t + h) \geq \min_{u:[0,t]\to[0,u_{\max}]} W_Q(s^{\alpha,u}(h), r^{\alpha,u}(h); t)$$

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

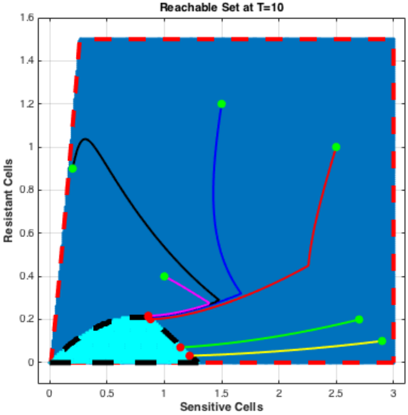
Theorem

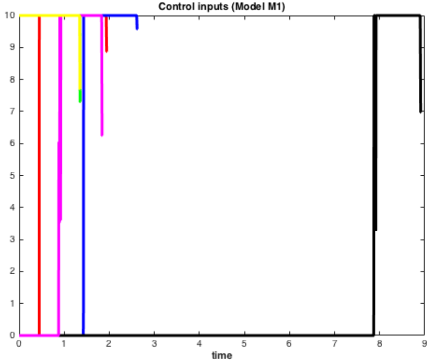
W_Q is a viscosity solution of

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

Simulations with Roc-HJ

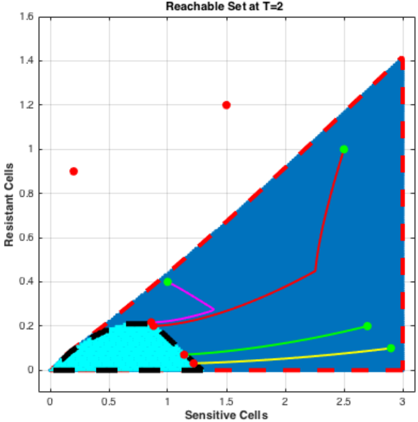
Reachability problem, $T = 10$

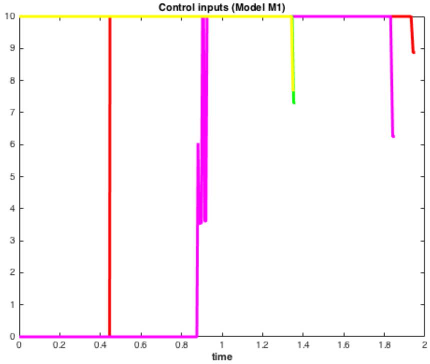




Simulations with Roc-HJ

Reachability problem, $T = 2$





Conclusions and Perspectives

Conclusions:

- Importance of metronomic treatments
- Framework for future work

Meanwhile, on the biological side:

- Experiments were done with optimal control solution
- Ongoing 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 multiple objectives
- Take into account partial information

Thank you for your attention