Control of a heterogenous population of cancerous cells

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June 11, 2015

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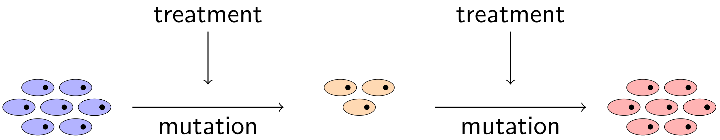
Introduction

Progressive resistance to a treatment



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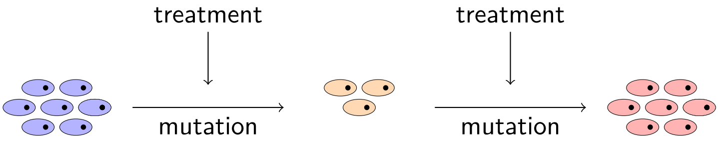
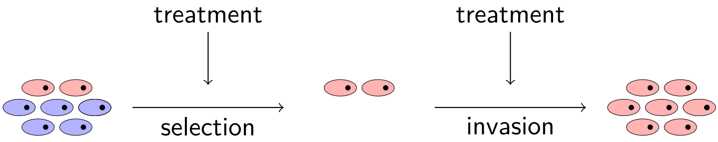


Heterogeneous initial tumour



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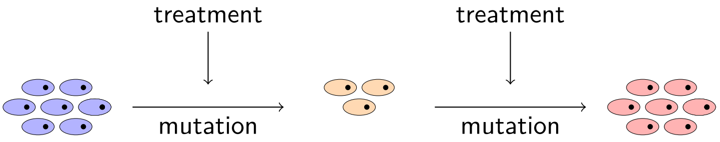
Progressive resistance to a treatment



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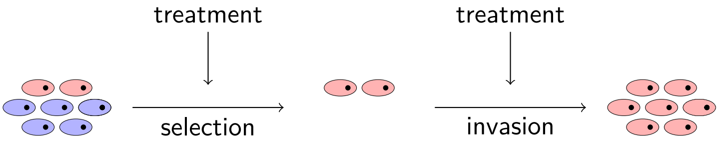


Question

How to maintain heterogeneity while reducing the tumour volume ?

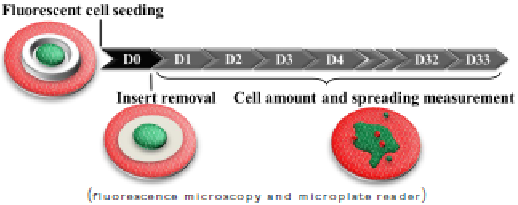
1. Manon Carré's experiment

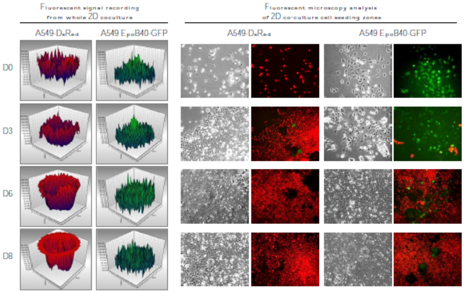
2. Under a constant treatment
   - System of equations
   - Study of trajectories
   - Stabilization

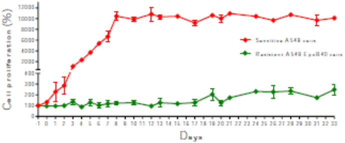
3. Optimization of the treatment
   - First approach
   - A more complex problem
   - Numerical results

4. Conclusion

Presentation of the experiment

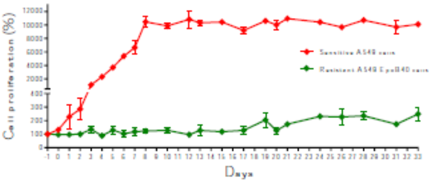






Presentation of the experiment

- Sensitive lung cancer cells A549
- Resistant cells A549 Epo40
- Drug : Epothilone B



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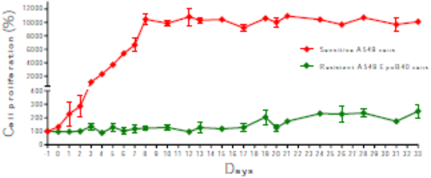

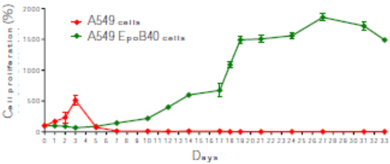

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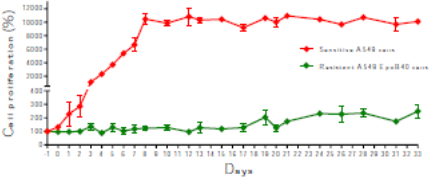
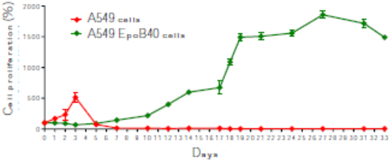
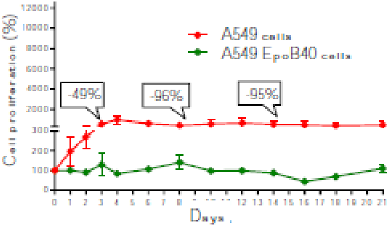


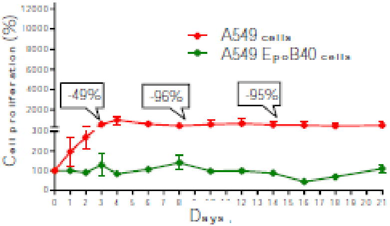




Modelling

Equations

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



- Represent the system for different treatments
- Propose minimization strategies
- Optimize the treatment

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System of equations

Equations

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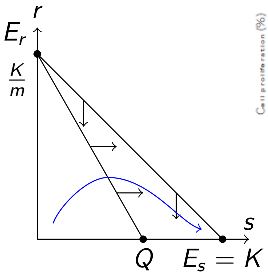
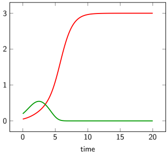
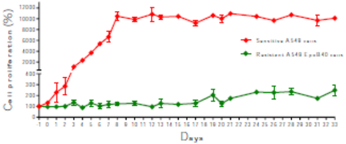
Study of trajectories

No treatment

$C = 0$







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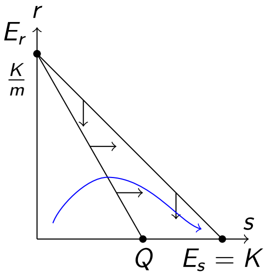
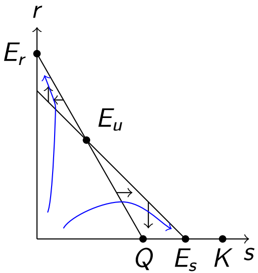
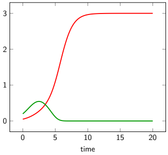
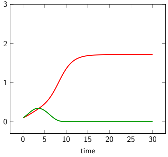


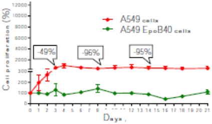
Weak treatment

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









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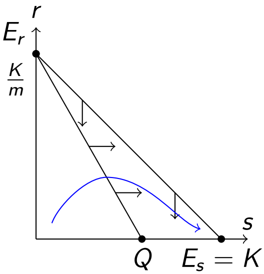

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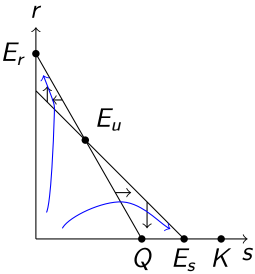

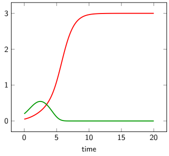

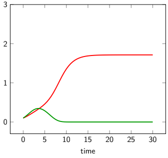

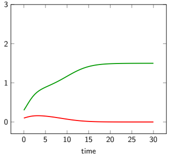

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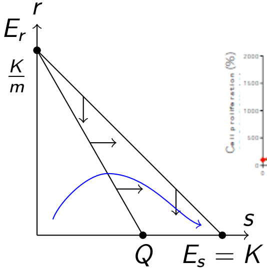
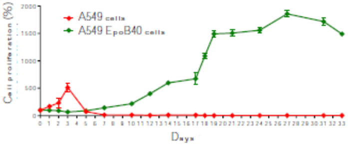
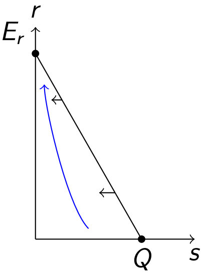
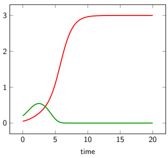


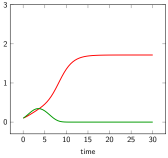


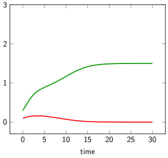
Strong treatment

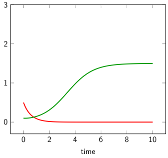
$C > \frac{\rho}{\alpha}$











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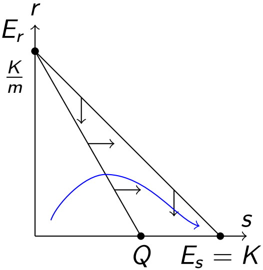

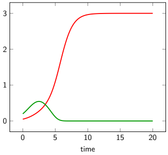

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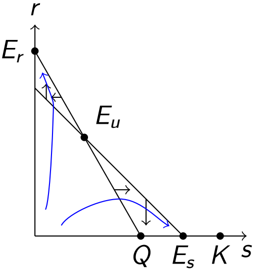

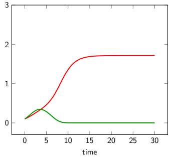

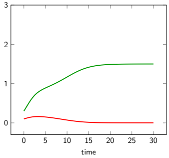

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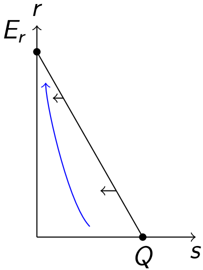
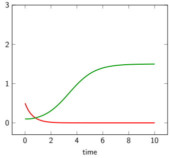
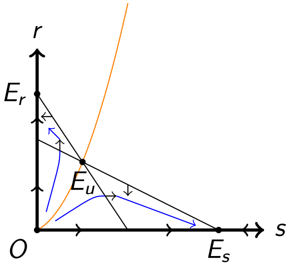




An algorithm for stabilization



$E_s = (K\frac{\rho-\alpha C}{\rho}, 0)$ is stable until

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

and there

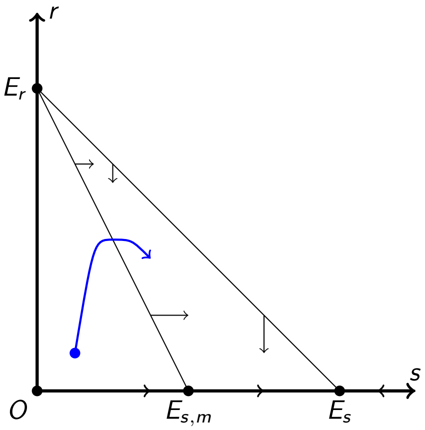
$$E_{s,m} = \left(\frac{\rho K}{\rho+\beta K}, 0\right)$$

Stabilization problem

Given an initial data $(s(0), r(0))$ bring the system as close as possible to

$$(s_m, r_m) = \left(\frac{\rho K}{\rho+\beta K}, 0\right)$$

An algorithm for stabilization



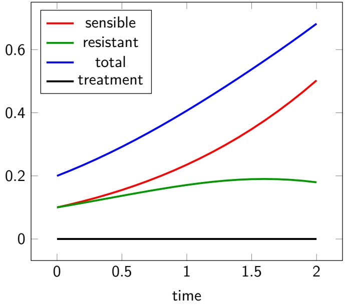
Initialization

Impose

$$C = 0$$

until

$$\rho m r + (\rho + K\beta)s \geq \rho K$$



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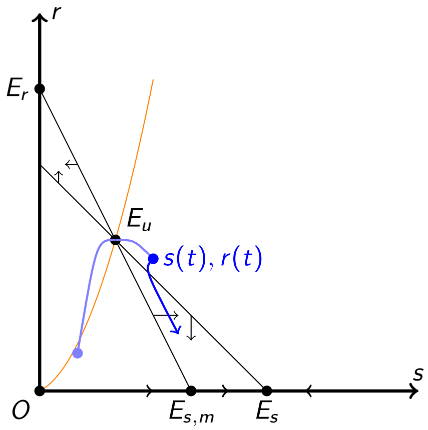


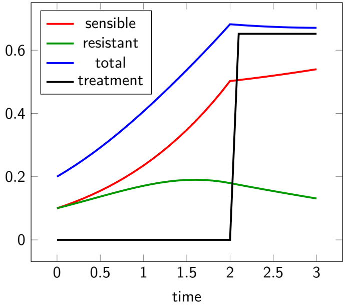
Repeat

Impose

$$C < \frac{1}{\alpha}\frac{\beta\rho}{\rho + \beta K}(K - r(t)m)$$

so that

$$r_u > r(t)$$



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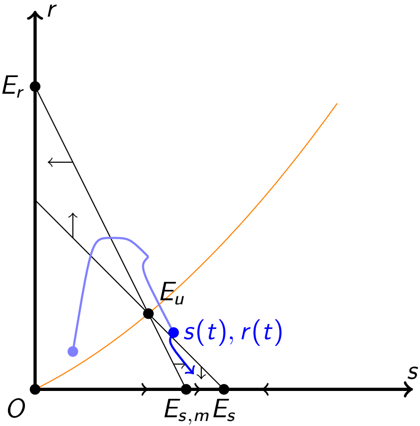

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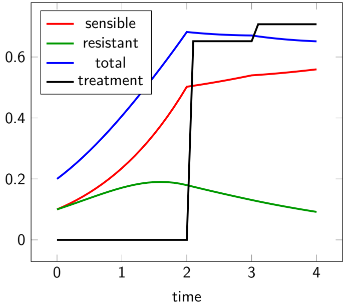

An algorithm for stabilization

Results on Scilab

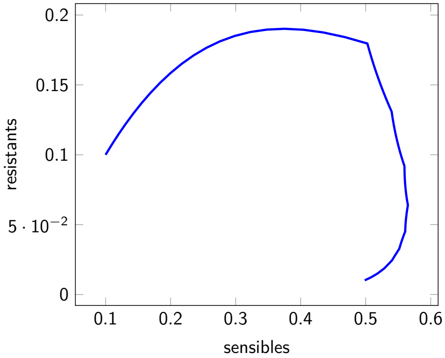

FIGURE : Phase plane

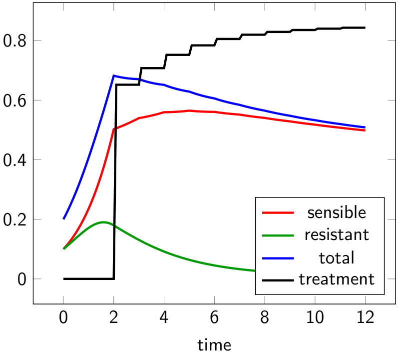

FIGURE : Time evolution

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General optimization

Optimization problem

Given $s(0)$, $r(0)$ and T, under the condition $C(t) \leq C_{\max}$, minimize

$$s(T) + r(T)$$

$\rightarrow$ use of Optimal Control Theory

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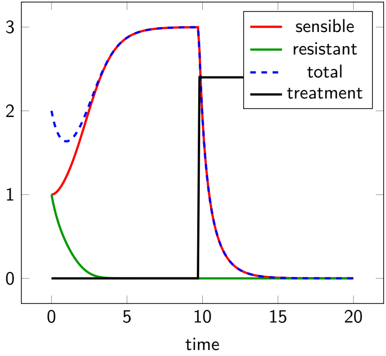

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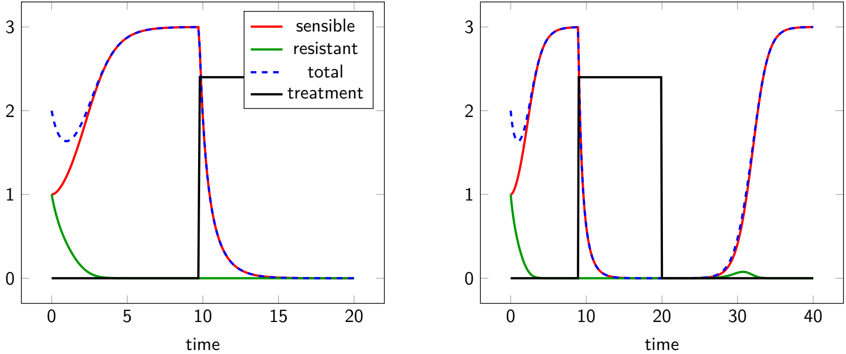

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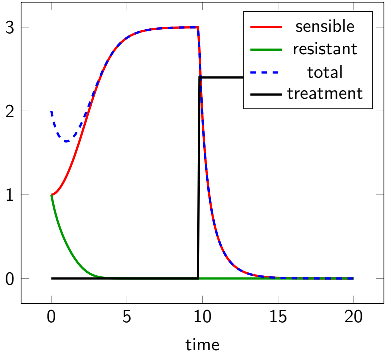

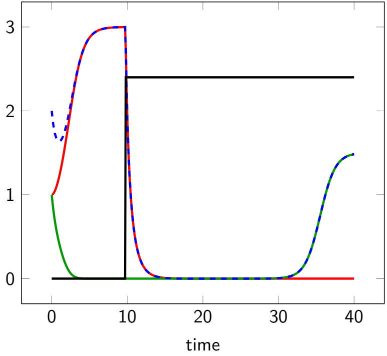

A new problem

Optimization problem

Given $s(0)$, $r(0)$ and T, under the condition $C(t) \leq C_{\max}$, minimize

$$s(T) + r(T) + \frac{A}{T}\int_0^T (s^2(t) + r^2(t))dt$$

Characterization of optimal treatment

Using Pontryagin Maximum Principle, an optimal treatment is at every time t :

$$C(t) = \begin{cases} 0 \\ C_{\max} \\ 0 < C(s,r) < C_{\max} \end{cases}$$

- Metronomic treatment can refer to a singular arc of C
- Could this problem generate singular arcs ?

Numerical results

Objective

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

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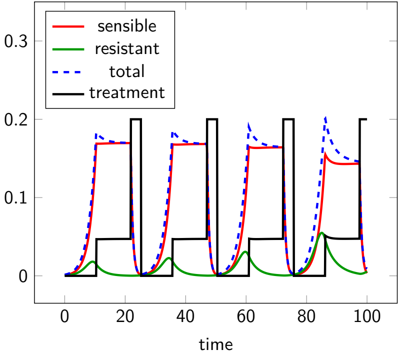
Cycle with a metronomic halt



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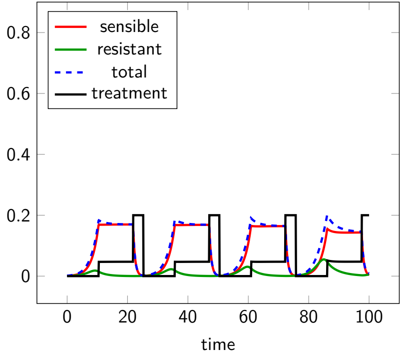
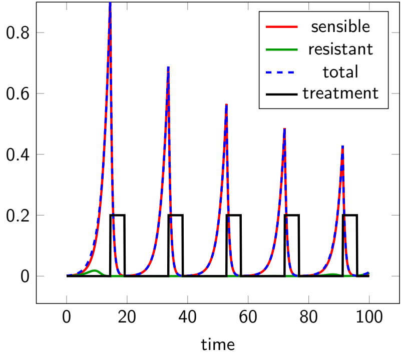


MTD cycle



Conclusion

Direct results and applications

1. An extensive study of constant treatments
2. Proposition of a "stabilization" strategy
3. MTD versus Metronomics

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Ongoing studies : the biological side

1. Explain the action of sensible cells on the resistant
2. Calibrate the model and validate it
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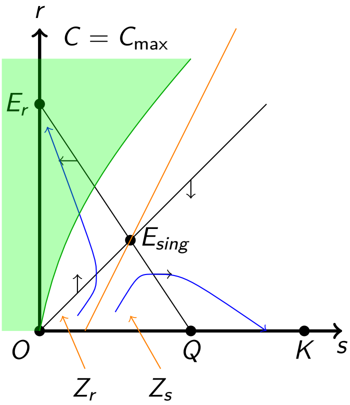
Ongoing studies : the maths side

1. Take into account toxicity
2. Spatial propagation
3. Works on numerical optimization

Conclusion

Thank you for your attention

On a singular arc



The system on a singular arc becomes

$$C(s,r) = \frac{1}{\alpha s}\left(r^2\left(\frac{\rho}{K}+\beta\right) + s\rho\left(1-\frac{s+2mr}{K}\right)\right)$$

with $0 \leq C \leq C_{\max}$

$$\begin{cases} \frac{ds}{dt} & = r\left(s\frac{\rho m}{K} - r\left(\frac{\rho}{K}+\beta\right)\right) \\ \frac{dr}{dt} & = \rho r\left(1-\frac{s+mr}{K}\right) - \beta s r \end{cases}$$

Final comportement

$$(s(t), r(t)) \to \begin{cases} E_r \text{ if } (s_0, r_0) \in Z_r \\ (s^*, 0) \text{ if } (s_0, r_0) \in Z_s \end{cases}$$

with $s_Q \leq s^* \leq K$