Optimal schedules for therapies in metastatic cancers

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Clinical problematics

Clinical problematics

- In the case of breast cancer, 10% of cancers in stage T1N0M0 give rise to metastasis.

  Elias (2006), Spielmann & al (2006)

- Micrometastases (size $< 10^8$ cells $\simeq$ 100 mg) invisible with imaging techniques. How to administer adjuvant therapy (after surgery) without seeing anything?
- What is the best **scheduling** for : chemotherapy (CT), anti-angiogenics (AA), CT + AA?

The tool : a "simple" modelling (with **few parameters**)

- **tumoral growth model (ODE)**
- **renewal model for the metastases (PDE)**

Outline

ODE model of tumoral growth under angiogenic control

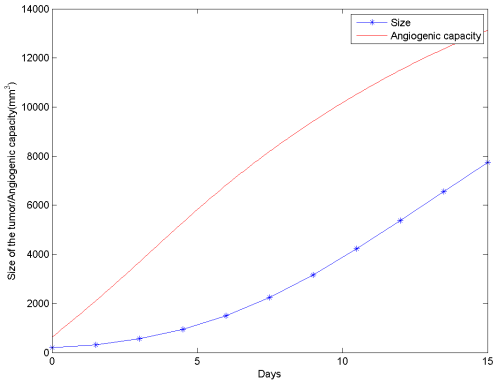
Hahnfeldt et al., Cancer Research 1999

Gompertzian growth
$x =$ Size of the tumor

$$\frac{dx}{dt} = ax \ln\left(\frac{\theta}{x}\right)$$

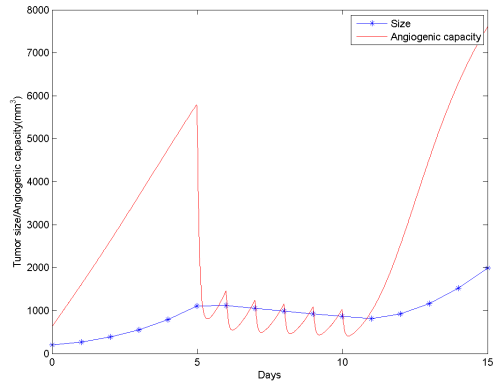
Consider θ as a **variable** : the **vascular capacity**

$$\frac{d\theta}{dt} = \underbrace{cx}_{\text{Stimulation by the tumor}} - \underbrace{dx^{\frac{2}{3}}\theta}_{\text{Inhibition}}$$



Hahnfeldt model and CT/AA combination

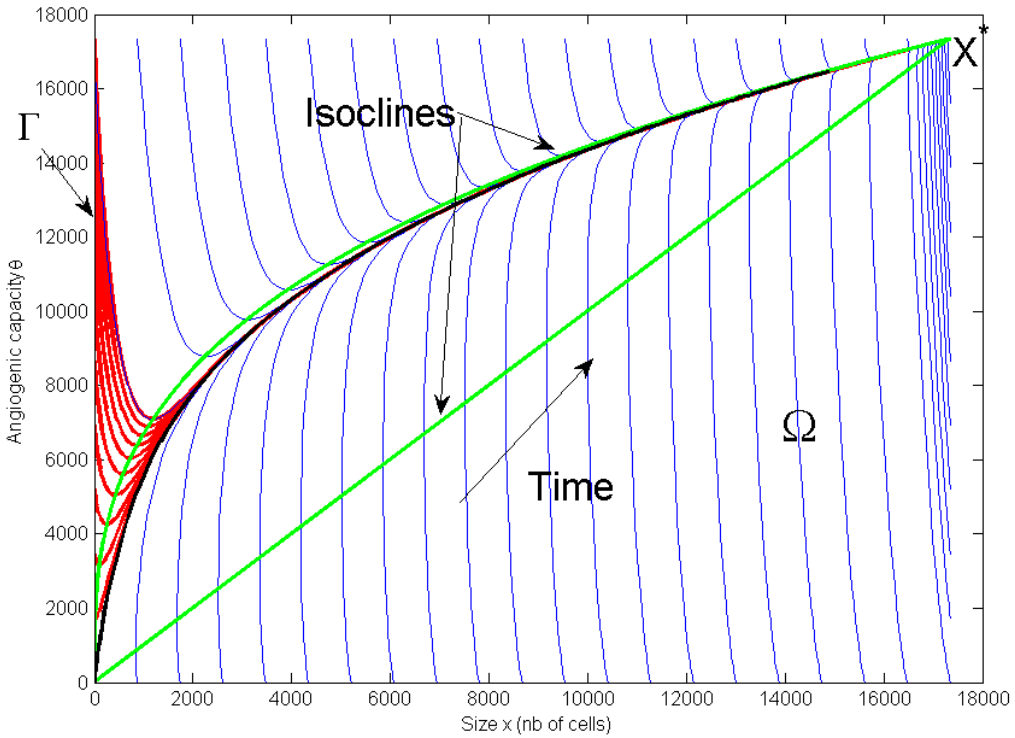
$$\begin{aligned}\frac{dx}{dt} &= ax \ln\left(\frac{\theta}{x}\right) - f\, u^1(t)(x - x_{min})^+ \\ \frac{d\theta}{dt} &= cx - d\theta x^{\frac{2}{3}} - e\, u^2(t)(\theta - \theta_{min})^+\end{aligned}$$



- Log-kill term of the chemotherapy
- AA drugs impact on the tumoral vasculature

Studied in **d'Onofrio, Gandolfi, 2004**

Transport equation for the metastases population



$$\Omega = \left]1, \left(\frac{c}{d}\right)^{\frac{3}{2}}\right[^2$$

$$G(X) = G(x,\theta) = \begin{pmatrix} ax \ln\left(\frac{\theta}{x}\right) \\ cx - d\theta x^{\frac{2}{3}} \end{pmatrix}$$

$$u(t) = (u^1(t), u^2(t))$$

$$\overline{G}(t, X; u) = G(X) - B(X)u(t)$$

$$\frac{dX}{dt} = G(X)$$

All the tumors follow the ODE model.

Population of the metastases structured in size x and vascular capacity θ
density $\rho(t,x,\theta) \in L^1(\Omega)$.

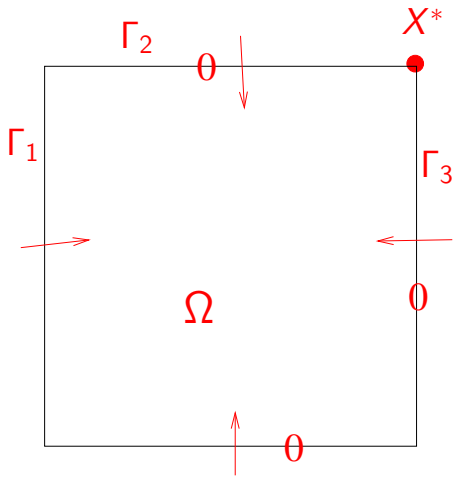
Balance law :

$$\partial_t \rho + \mathrm{div}(\rho \overline{G}) = 0$$

Boundary condition. Birth of new metastases

We assume

- That the metastases are born with size 1
- **Independance** between the vascular capacity of the neo-metastasis and the mother-tumour which emitted it



Birth rate of new metastases of parameter σ per meta of size x and angiogenic capacity θ per unit of time :

$$B(\sigma, x, \theta) = N(\sigma)\beta(x, \theta), \quad \sigma \in \partial\Omega$$

We choose :

$$N(\sigma) = \frac{1}{2\Delta\sigma}\mathbf{1}_{\sigma\in[\sigma_0-\Delta\sigma,\sigma_0+\Delta\sigma]}$$

$$\beta(x, \theta) = mx^{\alpha}$$

Iwata et al., J. Theor. Biol., 2000

Two sources of new metastases :

- Primitive tumor $X_p(t)$ with $\frac{dX_p}{dt} = \overline{G}(X_p)$: $N(\sigma)\beta(X_p(t))$
- Metastases themselves : $N(\sigma)\int_\Omega \beta(x, \theta)\rho(t, x, \theta)dxd\theta$

Metastatic model

$$(E)\quad \begin{cases} \partial_t \rho(u) + \mathrm{div}(\overline{G}(u)\rho(u)) = 0 &]0,\infty[\times\Omega \\ -\overline{G}(t,\sigma;u)\cdot\nu(\sigma)\rho(t,\sigma;u) = N(\sigma)\left\{\int_\Omega \beta(X)\rho(t,X;u)dX + \beta(X_p(t;u))\right\} & \partial\Omega \\ \rho(0) = \rho^0 & \Omega \end{cases}$$

$$\overline{G}(t,X;u) = G(X) - B(X)u(t), \quad u(t) = \left(u^1(t), u^2(t)\right)$$

Number of metastases : $\int_\Omega \rho(t,X)dX$. **Metastatic mass :** $\int_\Omega x\rho(t,X)dX$

- Linear transport equation in dimension 2 with nonlocal boundary condition.
- Theoretical and numerical analysis has been performed — **B., J. Evol. Equ., 2011**; **B., M2AN, 2011**; **Barbolosi, Benabdallah, Hubert, Verga, Math. Biosc., 2008**
- Original idea for a structured population equation for the metastases — **Iwata et al., J. Theor. Biol.**

Formulation of an optimal control problem

On the primary tumor growth : $\dot{X}_p(t;u) = G(X_p(t;u)) - B(X_p(t;u))u(t)$

- Already studied

  A. d'Onofrio, U. Ledzewicz, H. Maurer and H. Schättler, Math. Biosc., 2009

  A. Ergun, K. Camphausen, L. M. Wein, Bull. Math. Biol., 2003 (radiotherapy)

- Two possible criteria to be minimized for the primary tumor size

$$J_T(u) = x_p(T;u) \quad \textbf{and} \quad J_m(u) = \min_{t\in[0\,T]} x_p(t;u)$$

- Toxicity constraints

$$\mathcal{U}_{ad} = \left\{ u \in (L^\infty(0,T))^2;\ \begin{pmatrix} 0 \\ 0 \end{pmatrix} \leq u(t) \leq \begin{pmatrix} v_{max} \\ u_{max} \end{pmatrix} \ \forall t \ \textbf{and} \ \int_0^T u(t)dt \leq \begin{pmatrix} C_{max} \\ A_{max} \end{pmatrix} \right\}$$

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On the metastases

$$J(u) = \underbrace{\int_\Omega \rho(T,X;u)dX}_{\textbf{Total number of metastases}} \quad \textbf{and } J_M(u) = \underbrace{\int_\Omega x\rho(T,X;u)dX}_{\textbf{Metastatic mass}}$$

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Is there a difference in the optimal minimizer u^* for $J_T,\ J_m,\ J,\ J_M$?

Existence of an optimal solution

Theorem

Under some regularity assumptions **there exists** $(u^*, u_M^*) \in \mathcal{U}_{ad}$ *such that*

$$J(u^*) \leq J(u), \quad \forall u \in \mathcal{U}_{ad}, \quad J_M(u_M^*) \leq J_M(u), \quad \forall u \in \mathcal{U}_{ad}$$

The proof is based on the following proposition

Proposition

Under some regularity assumptions if $\rho(u)$ *is the solution of* (E), *then* $\rho \in W^{1,\infty}(Q)$ *and there exists a continuous function* C *which can be explicited in terms of* $||\beta||_{W^{1,\infty}(\Omega)}$, $||N||_{W^{1,\infty}(\partial\Omega)}$, $||G||_{L^\infty(\Omega)}$ *and* $||B||_{L^\infty(\Omega)}$ *such that, for all* $u \in \mathcal{U}_{ad}$

$$||\rho(u)||_{W^{1,\infty}(Q)} \leq C(||u||_{L^\infty(Q)})$$

Optimality system for J

In the case of $J(u) = \int_\Omega \rho(T, X; u)dX$ and without the source term in the boundary condition

Proposition

Let u^* be a solution of the optimal control problem. We have the following **optimality system** *:*

$$\begin{cases} \partial_t \rho^* + \mathrm{div}(\rho^* \overline{G}(u^*)) = 0 \\ -G \cdot \nu(t, \sigma; u^*)\rho^*(t, \sigma; u^*) = N(\sigma)\left\{\int_\Omega \beta(X)\rho^*(t, X; u^*)dX + \beta(X_p(t; u^*)\right\} \\ \rho^*(0, X; u^*) = \rho^0 \end{cases}$$

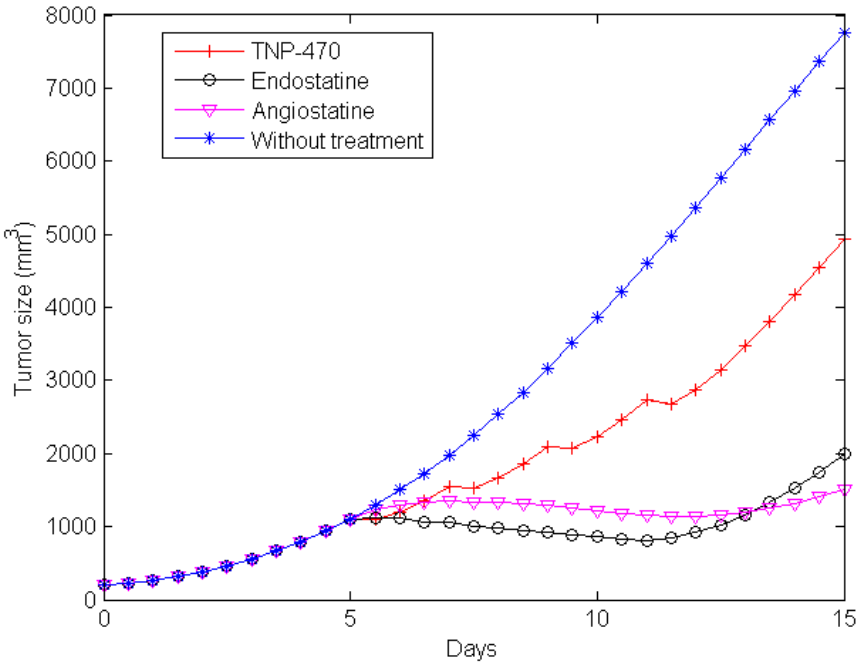
$$\begin{cases} -\partial_t p^*(t, X; u^*) - \overline{G}(X; u^*)\nabla p^*(t, X; u^*) - \beta(X)\int_{\partial\Omega} N(\sigma)p^*(t, \sigma)d\sigma = 0 \\ p^*(T) = -1. \end{cases}$$

$$\int_0^T \int_\Omega p^* \mathrm{div}(\rho^* B(X) \cdot (v - u^*))\, dX\, dt \leq 0, \quad \forall v \in \mathcal{U}_{ad}.$$

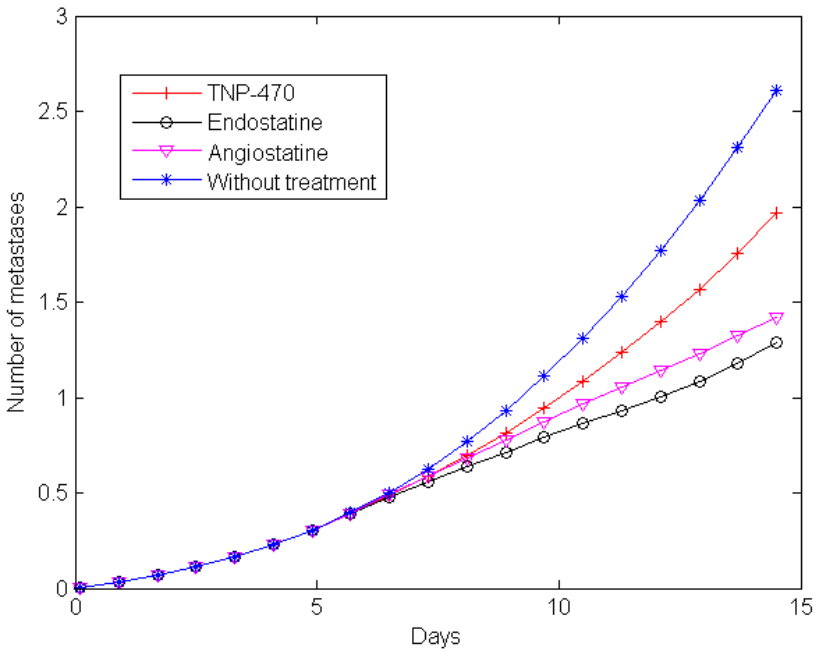
Anti-angiogenic therapy

Testing the drugs from **Hahnfeldt et al., Cancer Res. 99** (mice data) :

- Endostatine 20 mg/kg/day
- Angiostatine 20 mg/kg/day
- TNP-470 30 mg/kg/q.o.d



Primary tumor growth

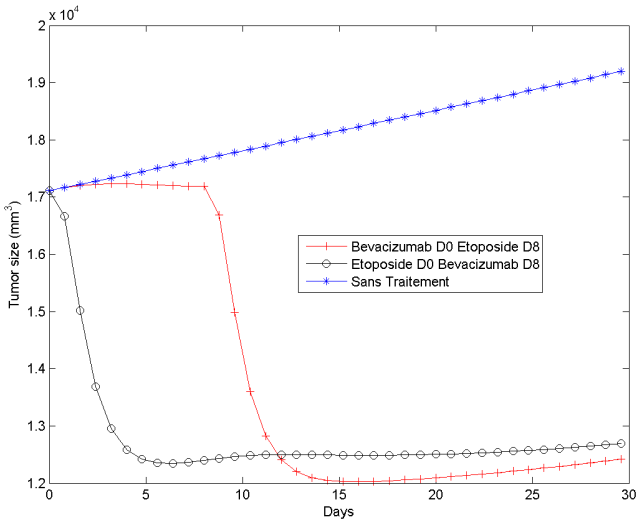


Metastatic evolution

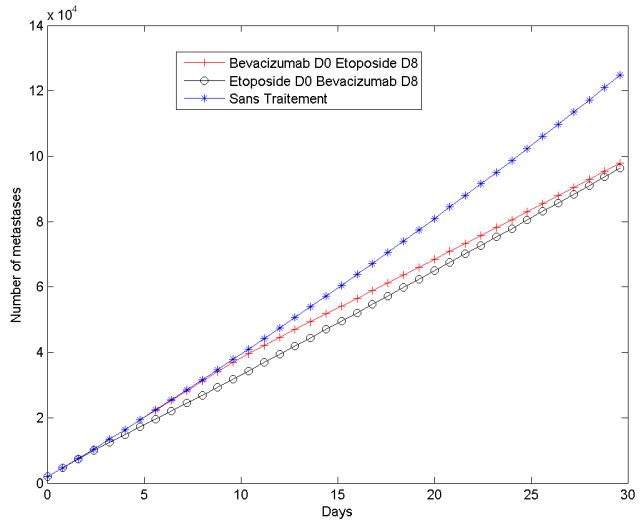
Combination of cytotoxic and anti-angiogenic therapy

Human parameters. Etoposide/Bevacizumab combination. Order of administration?

- Bevacizumab D0 Etoposide D8 VS Etoposide D0 Bevacizumab D8



Tumoral growth



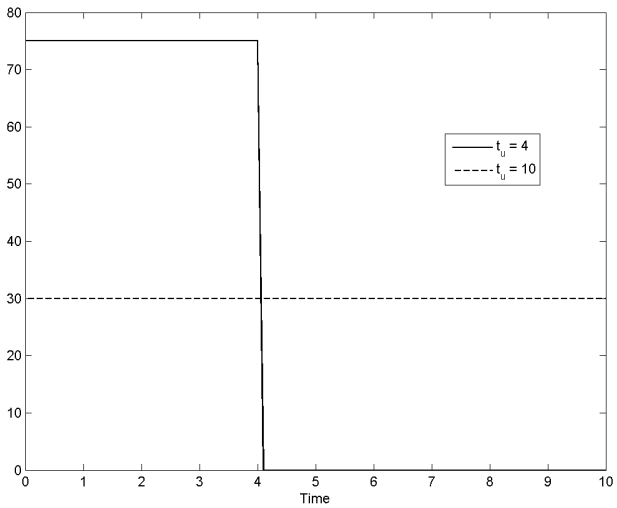
Total number of metastases

The best protocol is **not the same** for the primary tumor and for the number of metastases.

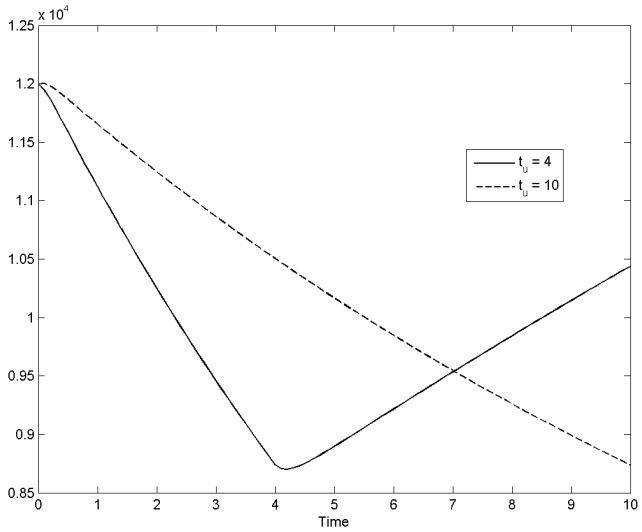
Optima comparison in a two-dimensional case

Administer total given amounts of agents (C_{max}, A_{max}) from time 0 to times (t_v, t_u) at constant rates $V = \frac{C_{max}}{t_v}$ and $U = \frac{A_{max}}{t_u}$.

U. Ledzewicz et al., Math. Medic. and Biol., 2010



Examples of administration of the AA drug

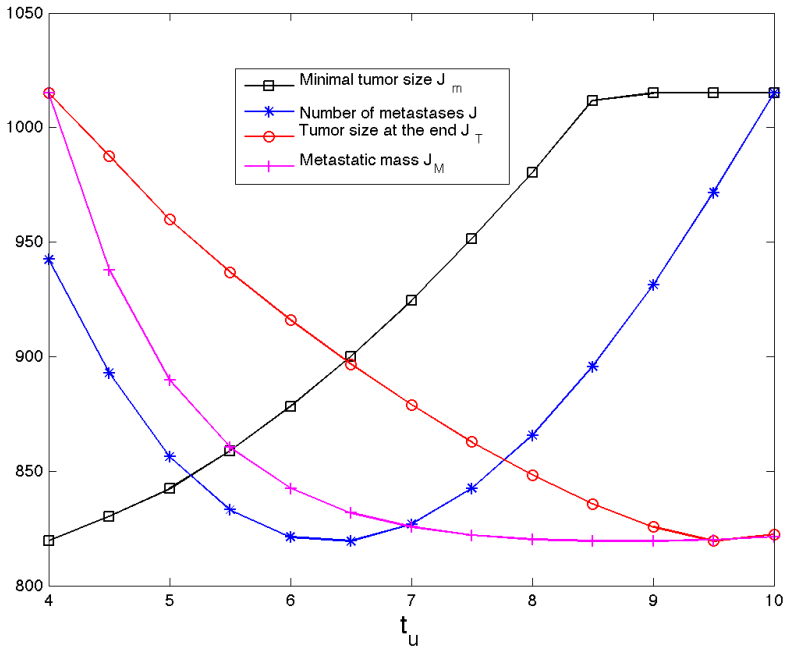


Primary tumor evolution

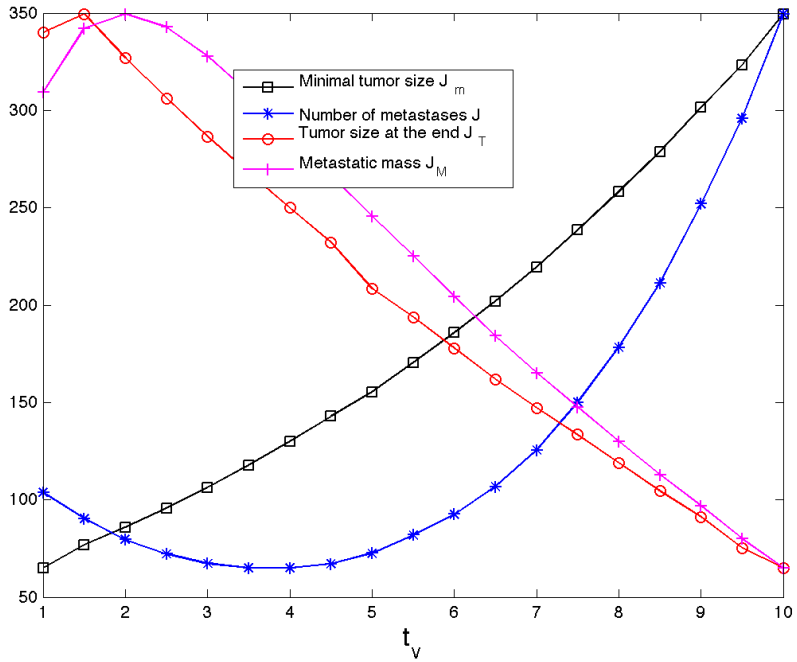
$$\mathcal{U}_{ad} = \{u^1(t) = \frac{C_{max}}{t_v}\mathbf{1}_{[0,t_v]}(t),\ u^2(t) = \frac{A_{max}}{t_u}\mathbf{1}_{[0,t_u]}(t),\ \left(\frac{C_{max}}{v_{max}}, \frac{A_{max}}{u_{max}}\right) \leq (t_v, t_u)\}.$$

$$\mathcal{U}_{ad} \simeq \left[\frac{C_{max}}{v_{max}}, T\right] \times \left[\frac{A_{max}}{u_{max}}, T\right] = [1, 10] \times [4, 10]$$

Monotherapy cases



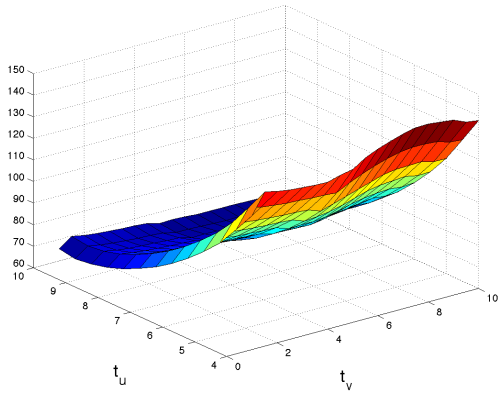
AA alone. $C_{max} = 0$



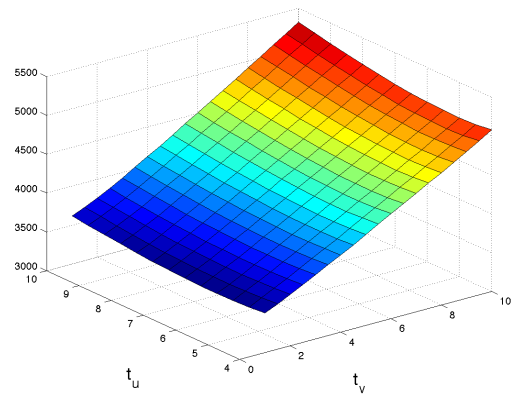
CT alone. $A_{max} = 0$.

- Criteria J_T, J_m and J give **different optimal values**.
- Metastatic mass J_M gives the same optimal value as J_T.
- Difference between CT and AA : shape of J_M.

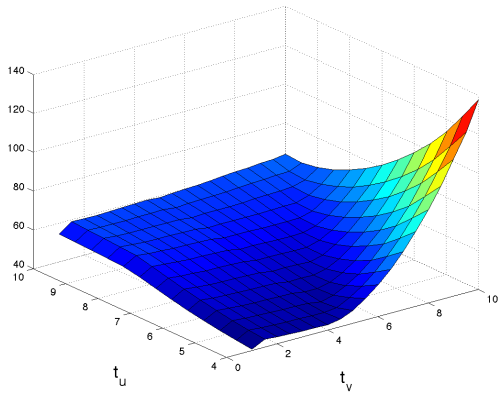
CT-AA combination



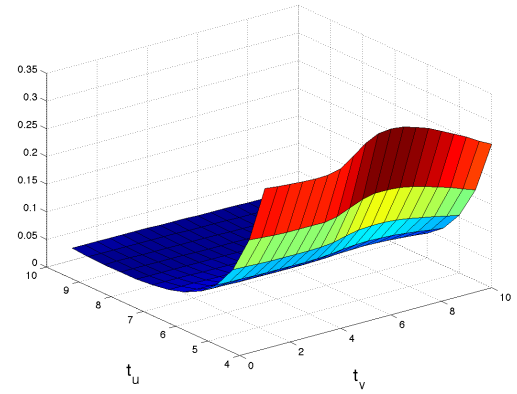
Tumor size J_T



Number of metastases J



Minimal tumor size J_m



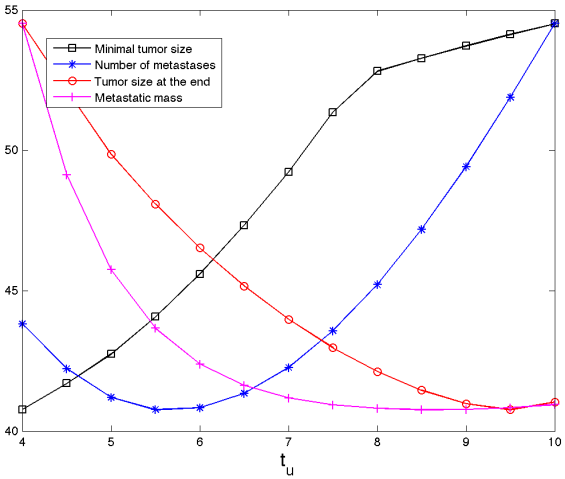
Metastatic mass J_M

Criterion	J_T	J_m	J	J_M
(t_v^*, t_u^*)	(9.5, 9.5)	(1, 4)	(1, 5.5)	(10, 9)

- We can regroup J and J_m under the strong dose/short time strategy and J_T and J_M under the low dose/large time one.

Influence of the presence of a drug on the behavior of the other

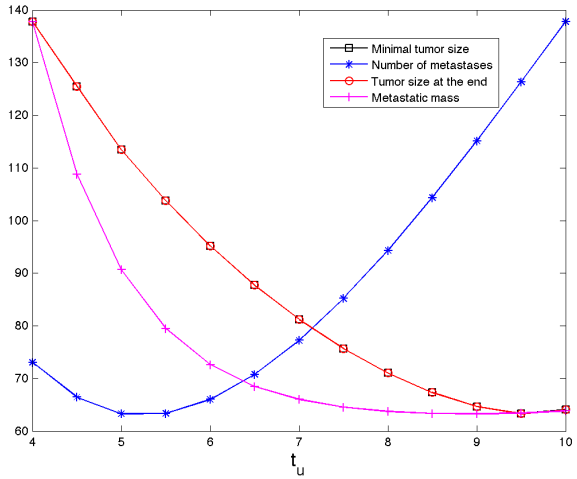
$t_v = 1$



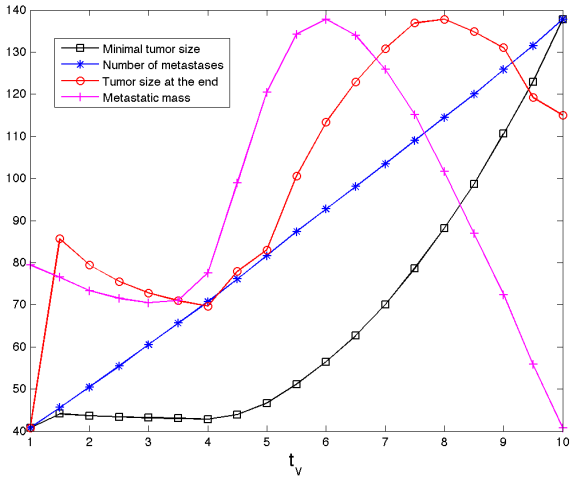
Effect of **CT on AA**

J_T, J and J_M are almost identical but J_m has the **reverse** behavior

$t_v = 10$



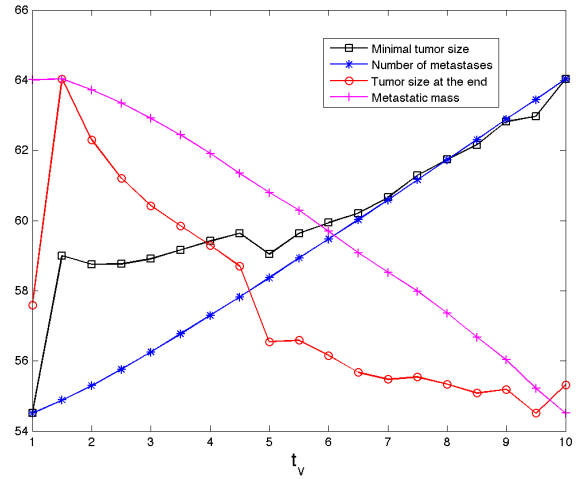
$t_u = 4$



Effect of **AA on CT**

Drastical changes for J_T and J_M. J is stable

$t_u = 10$



Conclusion

- Simple model for metastatic evolution
- Difference of the optimal solution between the primary tumor and the metastases.
- Necessity to define precisely the objective(s) to be minimized.

How to **cleverly combine** tumoral and metastatic reduction?

Use the **metastatic mass** $J_M = \int_\Omega x\rho(t,x,\theta)dxd\theta$?

Linear combination between a tumoral criterion and the number of metastases?

Perspectives

- Numerical method for the infinite-dimensional optimal control problem on the metastases (PDE)
- Further theoretical study of the theoretical optimality system

CT-AA combination

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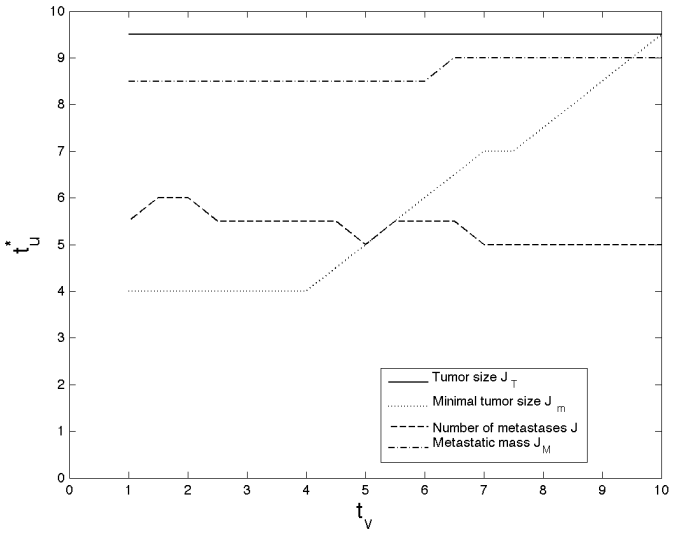
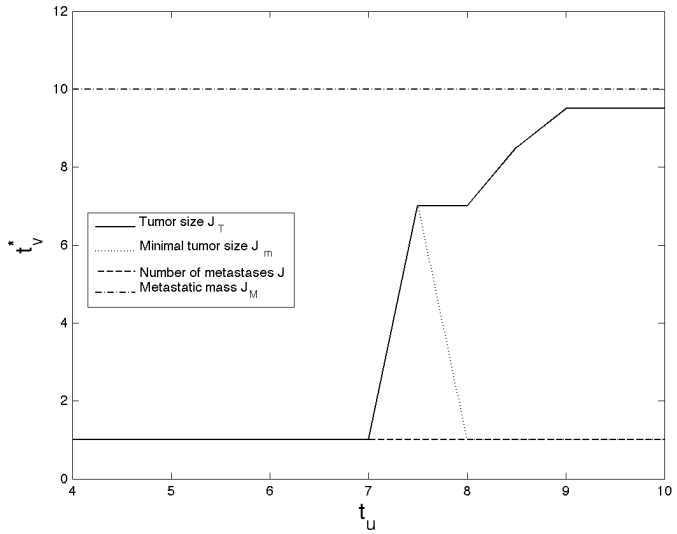


Graphs of $t_v \mapsto \underset{t_u}{\operatorname{argmin}}\, J_x(t_u, t_v)$

- For J_m : **synchronization effect**
- J, J_M and J_T are stable



Graphs of $t_u \mapsto \underset{t_v}{\operatorname{argmin}}\, J_x(t_u, t_v)$

- For J_T : change in the optimal value t_v^*.
- J, J_M and J_m are stable