Modeling of the metastatic evolution and optimization of anti-cancerous therapies

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Clinical problematics

Clinical problematics

- "Metastasis is the main cause of death in cancer disease"

Weinberg, 2006

- Metastatic cancers are **systemic diseases** which have to be thought at the **organism scale**.
- Micrometastases (size $< 10^7$ cells) are **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

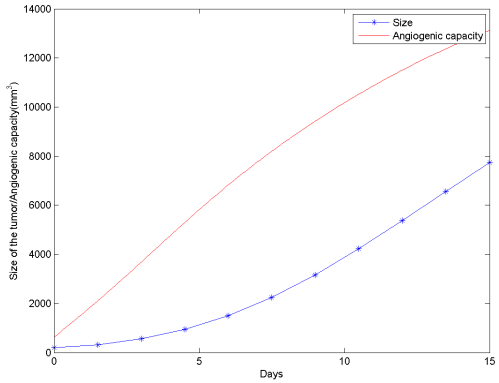
Hahnfeldt et al., Cancer Research 1999

Gompertzian growth
x = Size of the tumor = Volume/Number of cells

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

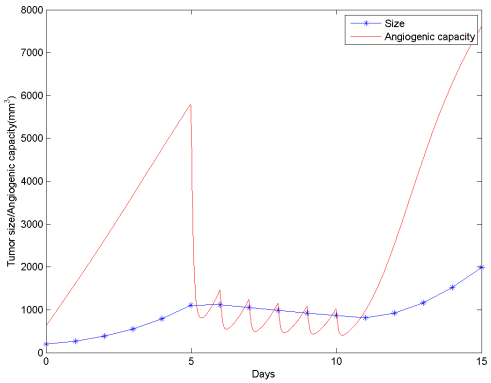
Consider θ as a **variable** : the **vascular capacity**

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



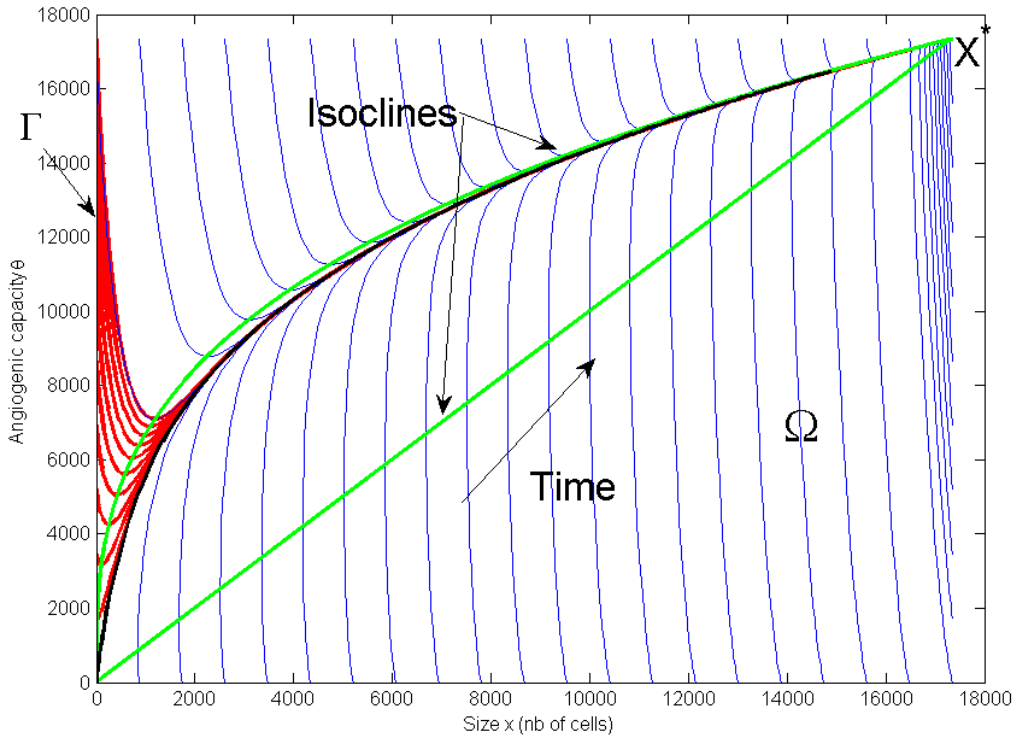
Hahnfeldt model and CT/AA combination

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



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

Transport equation for the metastases population



$$\Omega =]1, x_{max}[^2$$

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

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

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

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

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

Birth rate of new metastases of parameter $\sigma \in \partial\Omega$ per meta of size x and vascular capacity θ per unit of time : $\mathbf{b}(\sigma, x, \theta)$

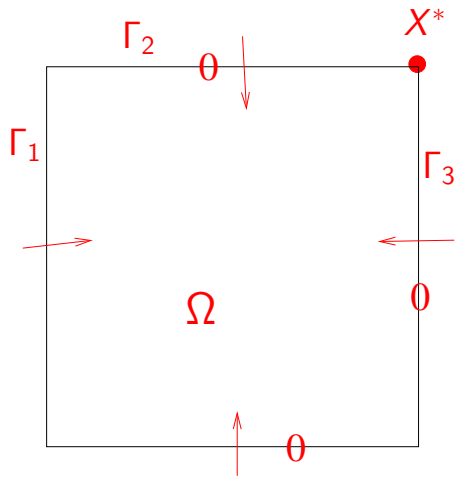
We assume

- **Independance** between the vascular capacity of the neo-metastasis and the mother-tumour which emitted it

$$\mathbf{b}(\sigma, x, \theta) = N(\sigma)\beta(x, \theta)$$

- That the metastases are born with size 1

$$N(\sigma) = N(1, \theta) = \frac{1}{2\Delta\theta}\mathbf{1}_{\theta\in[\theta_0-\Delta\theta,\theta_0+\Delta\theta]}$$



We choose :

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

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

Two sources of new metastases :

- Primary 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

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

$$\overline{G}(t,x,\theta;u) = G(x,\theta) - B(x,\theta)u(t), \quad u(t) = (u^1(t), u^2(t))$$

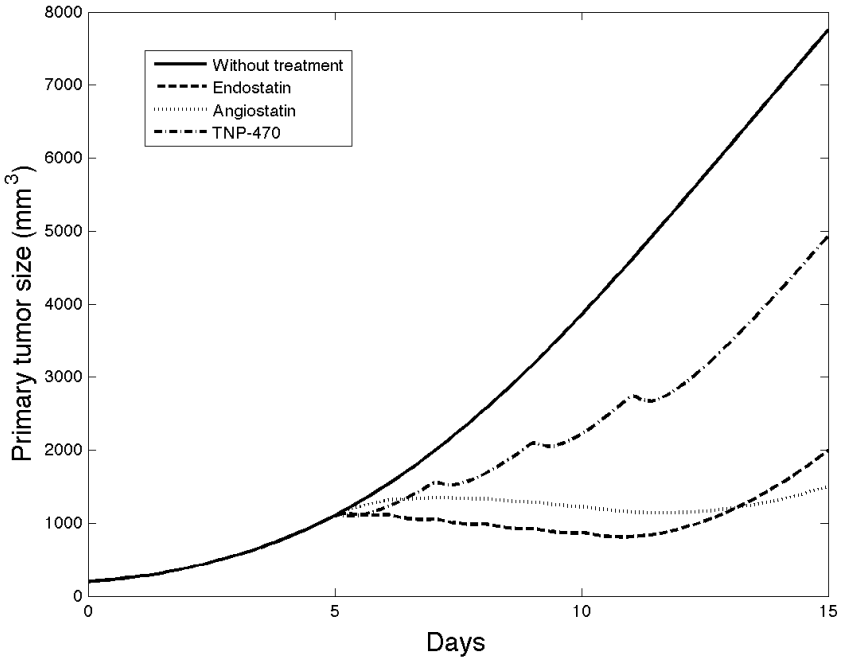
Number of metastases : $\int_\Omega \rho(t,x,\theta)dx\,d\theta$. **Metastatic mass :** $\int_\Omega x\rho(t,x,\theta)dx\,d\theta$

- 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.**

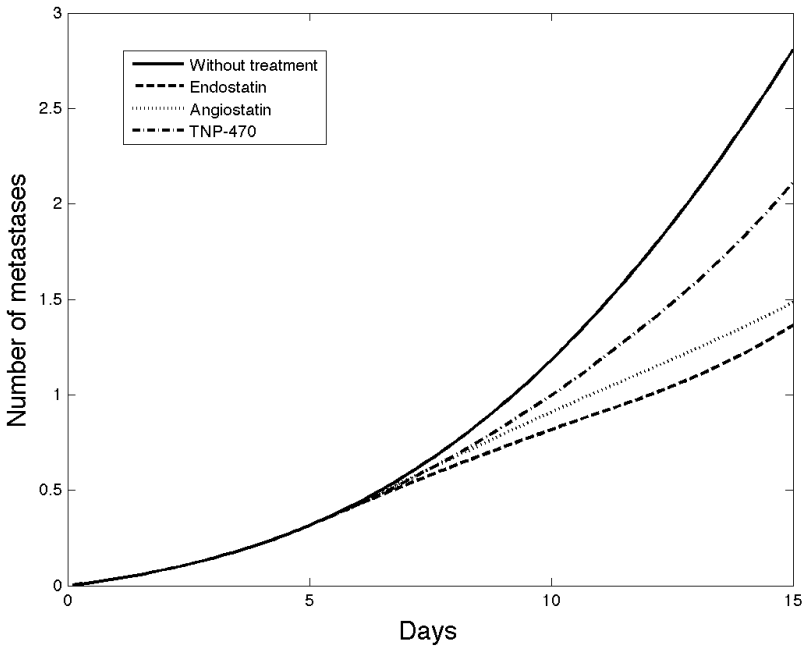
Anti-angiogenic therapy

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

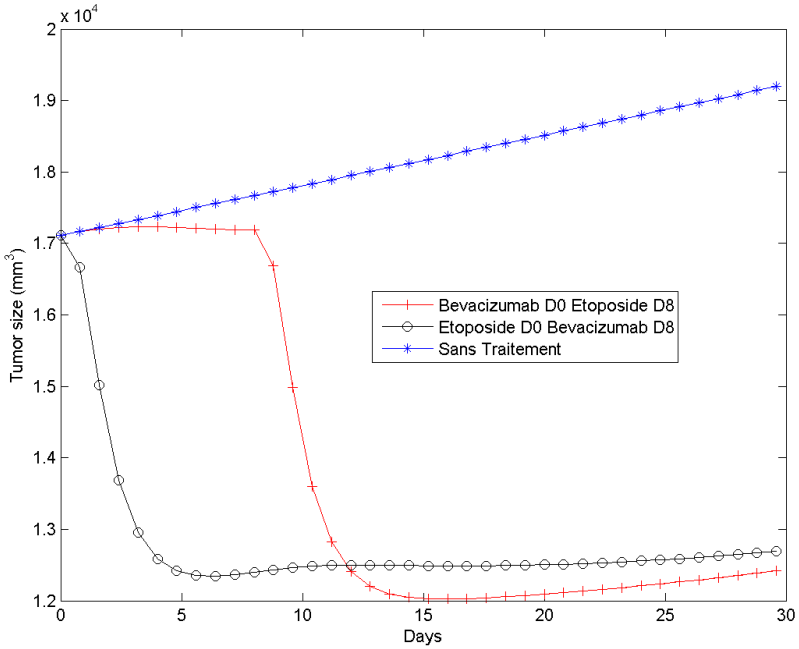


Metastatic evolution

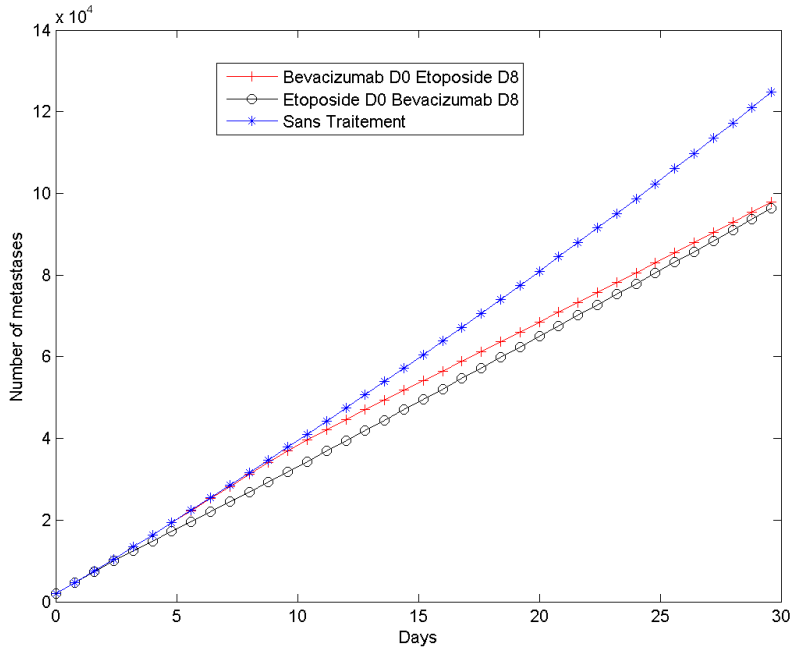
Combination of cytotoxic and anti-angiogenic therapy

Human parameters. Etoposide (CT)/Bevacizumab (AA) combination. Order of administration?

Bevacizumab D0 Etoposide D8 VS Etoposide D0 Bevacizumab D8



Tumoral growth



Total number of metastases

In these two first examples, the best protocol/drug is

not the same for the primary tumor

and for the number of metastases.

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

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

Is there a **difference** in the optimal minimizer u^*

between the metastatic and primary tumor criteria?

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** *:*

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

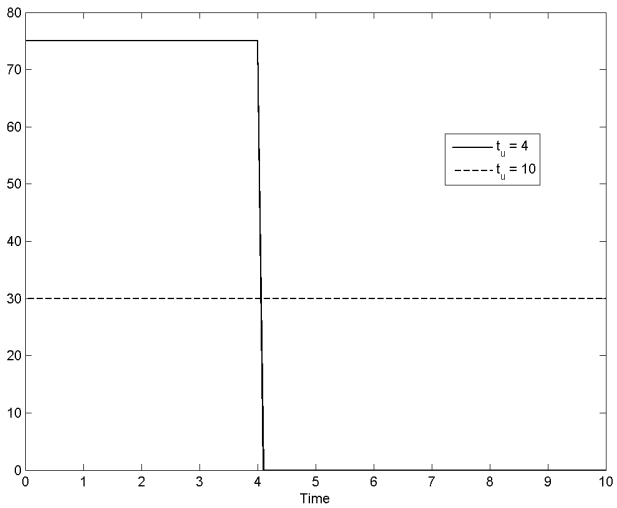
$$\begin{cases} -\partial_t p^*(t, X; u^*) - \overline{G}(X; u^*) \nabla p^*(t, X; u^*) - \beta(X) \int_{\partial\Omega} N(\sigma) p^*(t, \sigma) d\sigma = 0 \\ p^*(T) = -1. \end{cases}$$

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

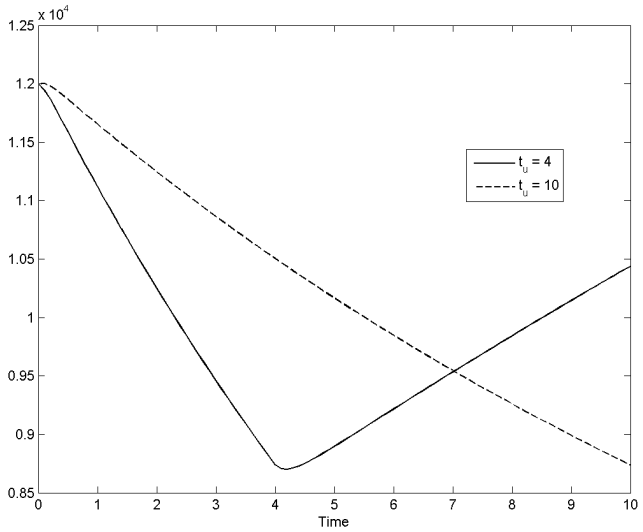
Optima comparison in a two-dimensional case

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

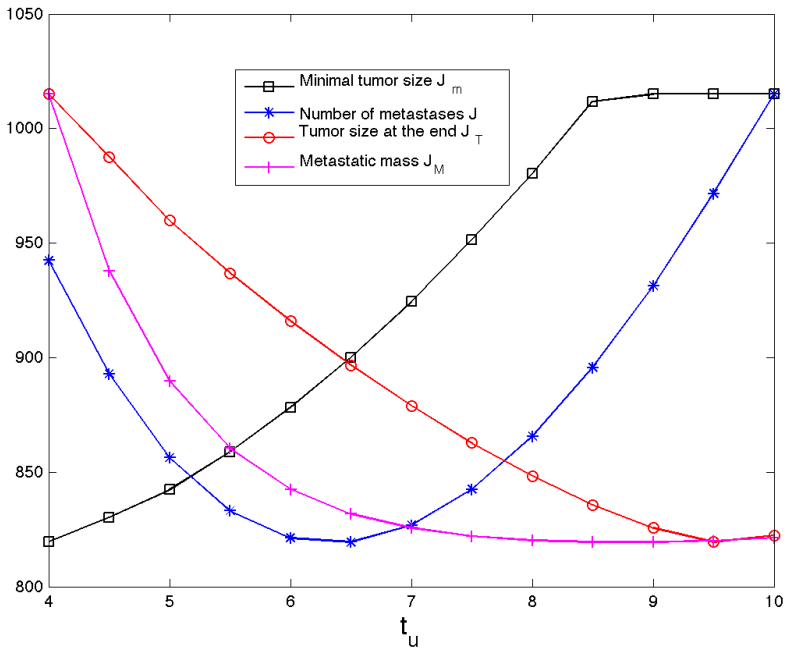


Primary tumor evolution

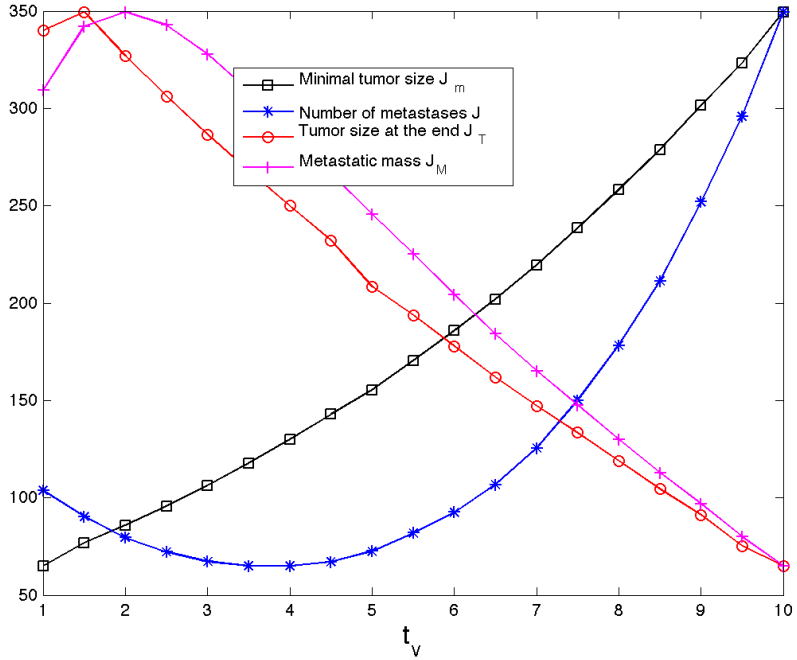
$$\mathcal{U}_{ad} = \{u^1(t) = \frac{C_{max}}{t_v}\mathbf{1}_{[0,t_v]}(t),\ u^2(t) = \frac{A_{max}}{t_u}\mathbf{1}_{[0,t_u]}(t),\ \left(\frac{C_{max}}{v_{max}}, \frac{A_{max}}{u_{max}}\right) \leq (t_v, t_u)\}.$$

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

Monotherapy cases



AA alone. $C_{max} = 0$

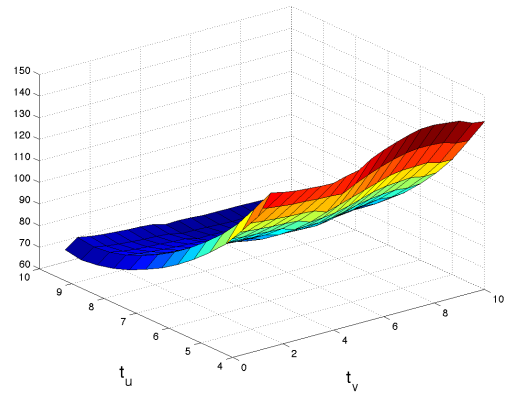


CT alone. $A_{max} = 0$.

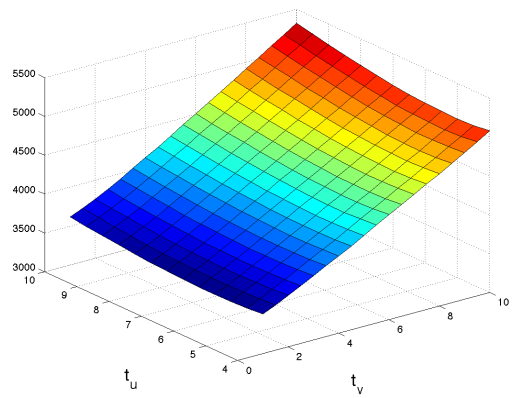
Monotherapy cases

- Number of metastases and primary tumor criteria yield **different optimal values** : strong dose/short time , small dose/large time , nontrivial minimum value
- Metastatic mass gives the same result as final tumor size
- **Same qualitative** but **different quantitative** results between CT and AA

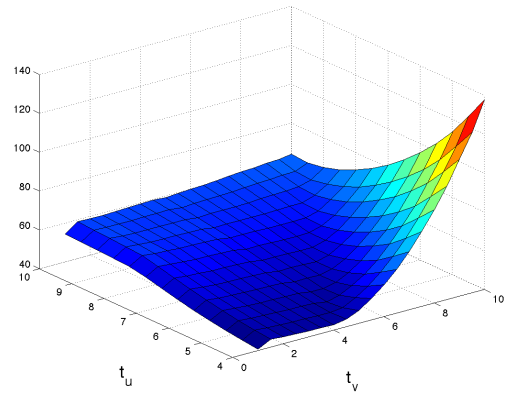
CT-AA combination



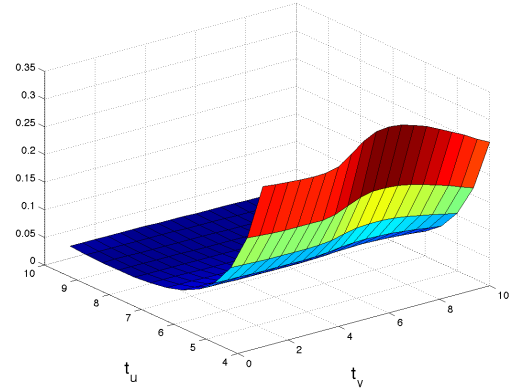
Tumor size J_T



Number of metastases J



Minimal tumor size J_m



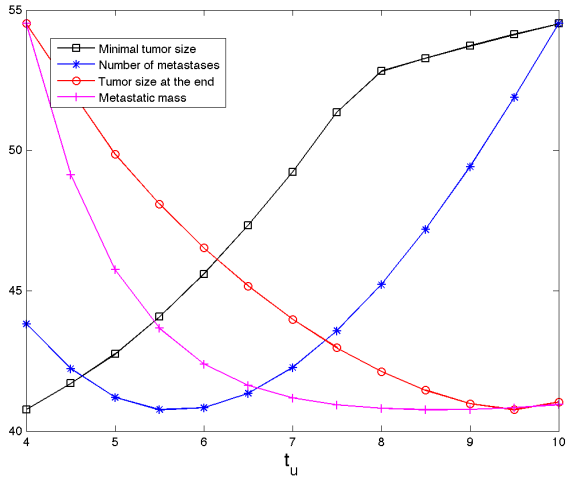
Metastatic mass J_M

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

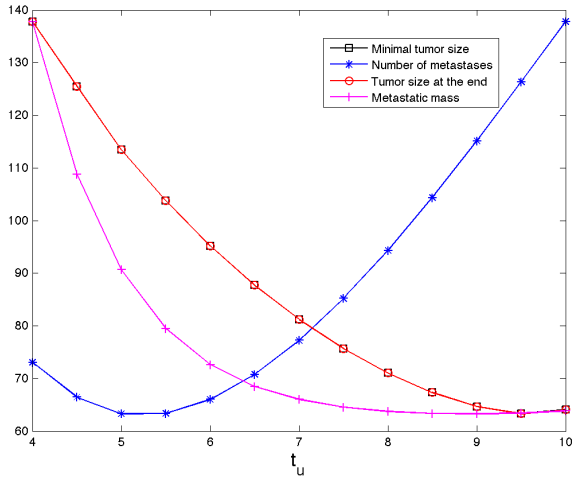
$t_v = 1$



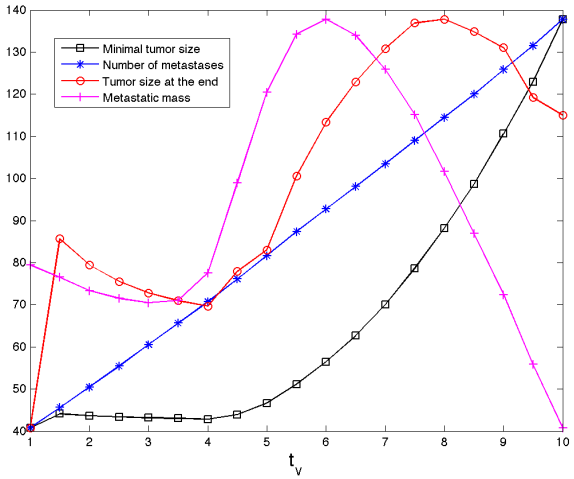
Effect of **CT on AA**

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

$t_v = 10$



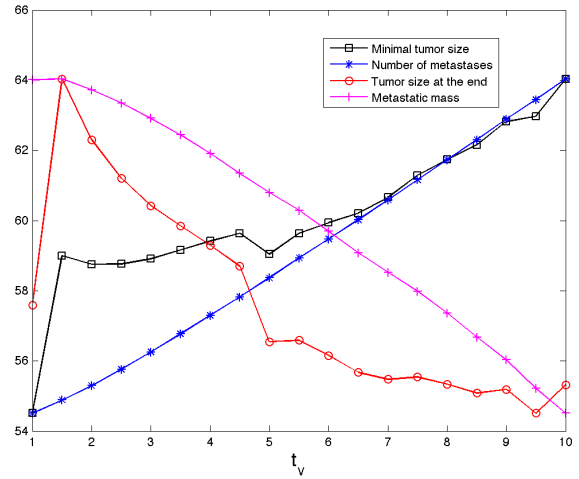
$t_u = 4$



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, taking into account for the effects of CT and AA therapies
- 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 study of the theoretical optimality system

Thank you for your attention!

Thematic school - Present challenges of mathematics in oncology and biology of cancer: Modeling and mathematical analysis

Aix-Marseille université CIRM CNRS ANR

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Organizing committee :

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- **Contacts:** mcc@latp.univ-mrs.fr

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Barbolosi, D. and Benabdallah, A. and Benzekry, S. and Ciccolini, J. and Faivre, C. and Hubert, F. and Verga, F. and You, B. *A mathematical model for growing metastases on oncologist's service*, to appear.

Confrontation with a study of Koscielny, Tubiana & al.

F. Verga PhD thesis

Confrontation with a study of Koscielny & al.

- 2648 patients treated for breast cancer at the IGR between 1954 and 1972.
- Proportion of patients which develop at least one visible metastase in terms of the initial tumor size.

Primary tumor size	% computed by our model	% observed by Koscielny
1 - 2.5 cm	25.5%	27%
2.5 - 3.5 cm	44.25%	42%
3.5 - 4.5 cm	60.5%	56.7%
4.5 - 5.5 cm	68.6%	66.5%
5.5 - 6.5 cm	75.5%	72.8%
6.5 - 7.5 cm	78.25%	83.8%
7.5 - 8.5 cm	83.25%	81.3%
>8.5 cm	89.25%	92%

Br. J. Cancer (1984), **49**, 709–715

Breast cancer: Relationship between the size of the primary tumour and the probability of metastatic dissemination

S. Koscielny[1], M. Tubiana[2], M.G. Lê[2], A.J. Valleron[1], H. Mouriesse[2], G. Contesso[2] & D. Sarrazin[2]

[1]*Unité de Recherches Biomathématiques et Biostatistiques Inserm U 263 and Université Paris 7-2, Place Jussieu 75251 Paris Cedex 05.* [2]*Institut Gustave Roussy, (Department of radiation therapy, pathology and medical statistics), Rue Camille Desmoulins 94800 Villejuif, France.*

Koscielny, Tubiana & al. (1984)

The difficulties of use of the model

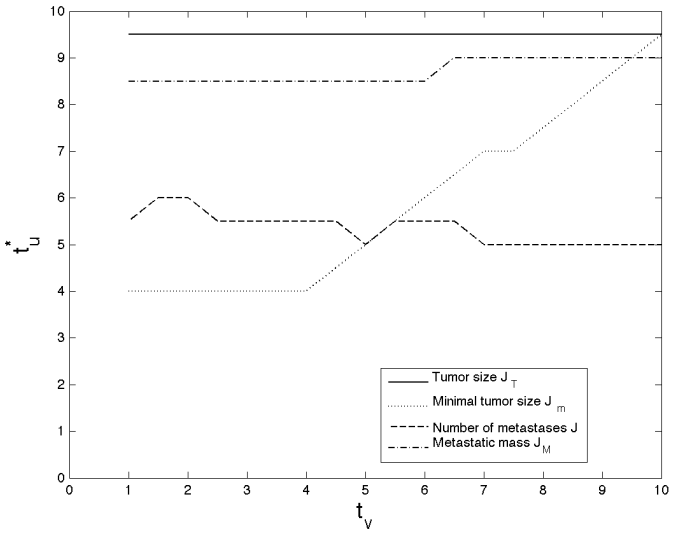
- Estimate the parameters.

  Work in progress : Use ana-pathological informations on the primary tumor and homology derived tools to obtain good covariables for the estimation of m.

  B., Bennequin, Cailloux

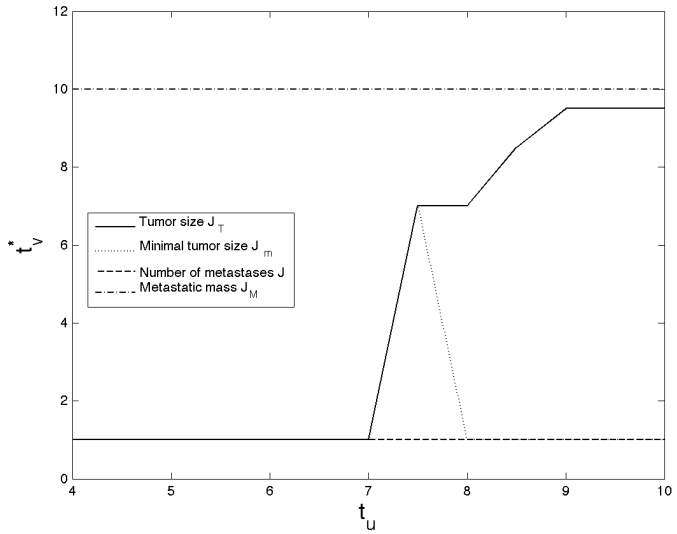
- Model validation on mice in progress (ANR MEMOREX_PK).

CT-AA combination



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