Mathematical modeling of metastatic development and scheduling optimization of anti-cancerous therapies

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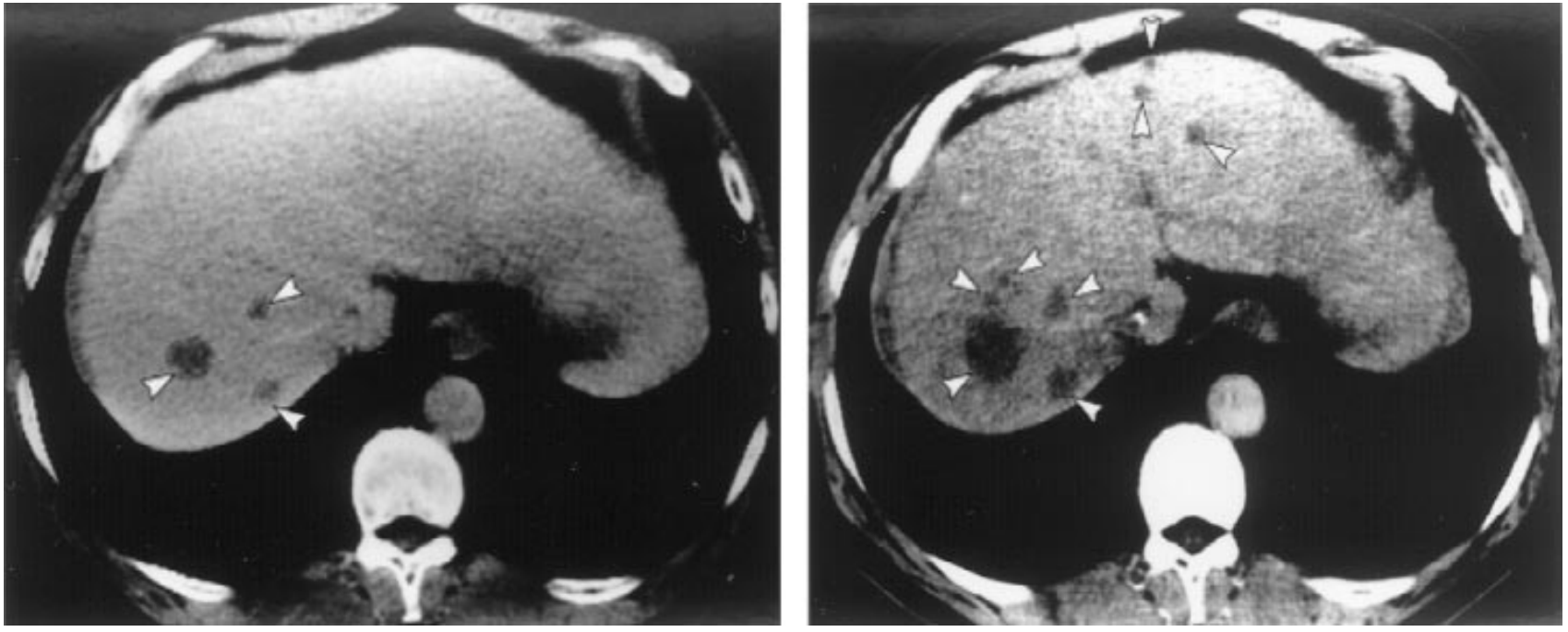
Metronomics workshop

July 18, 2012

Metastases



Iwata et al., 2000

Contrast-enhanced X-ray computed tomographies of the liver with multiple metastatic tumors. Interval : 127 days.

+ some of the metastases are **not visible**.

Clinical problematics

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

Weinberg, 2006

- Micrometastases (size $< 10^7$ cells) invisible with imaging techniques. How to **predict their development** and administer adjuvant therapy (after surgery) without seeing anything?
- What is the best **scheduling** for : chemotherapy (CT), anti-angiogenics (AA), CT + AA?
- Metastatic cancers are **systemic diseases** which have to be thought at the **organism scale**.

Why mathematical models?

- Mathematical **description** of the biological process

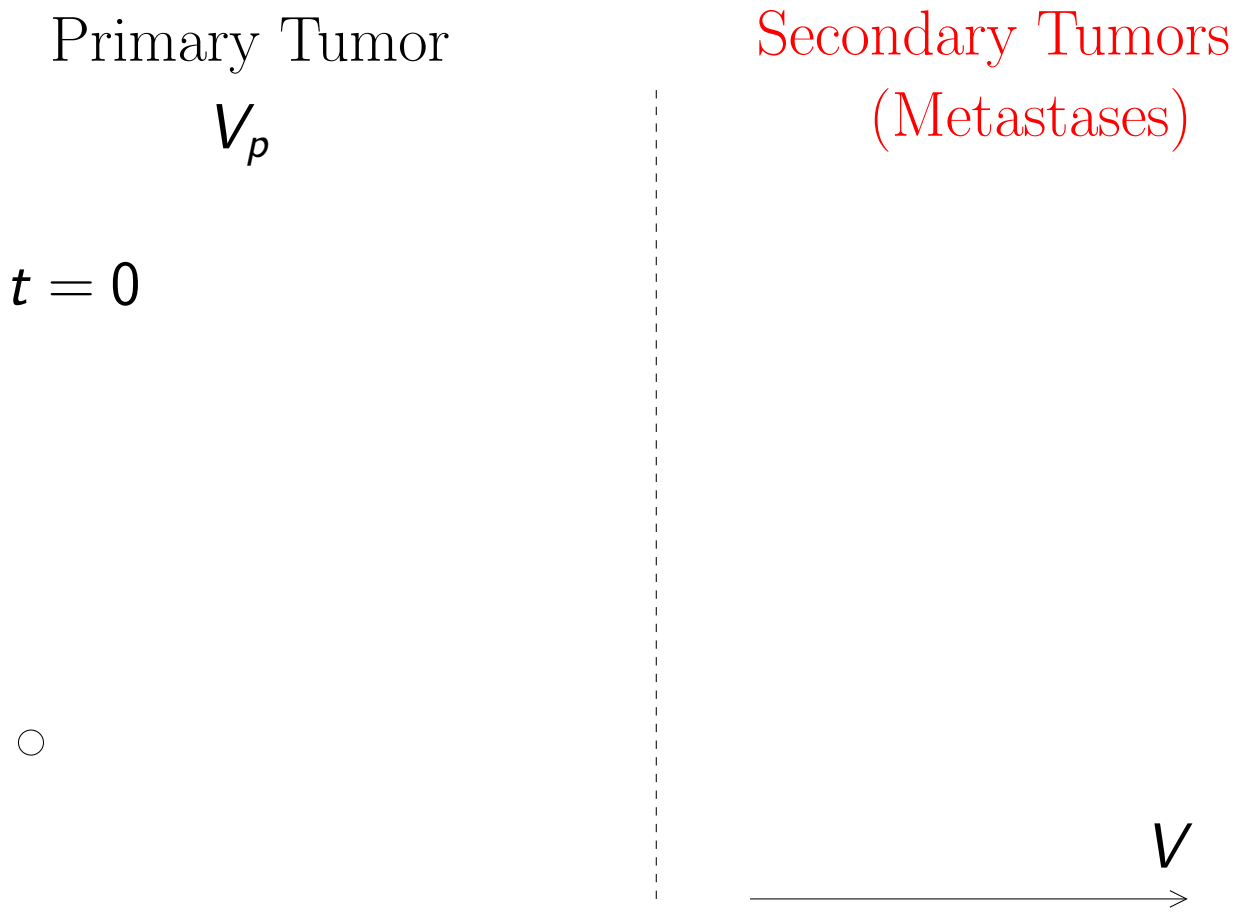
$\Rightarrow$ Medical **prognosis tool**

$\Rightarrow$ Control of this process. **Therapy optimization**

Outline

Cancer at the organism scale

V = size = Volume (mm^3 or number of cells)



Cancer at the organism scale

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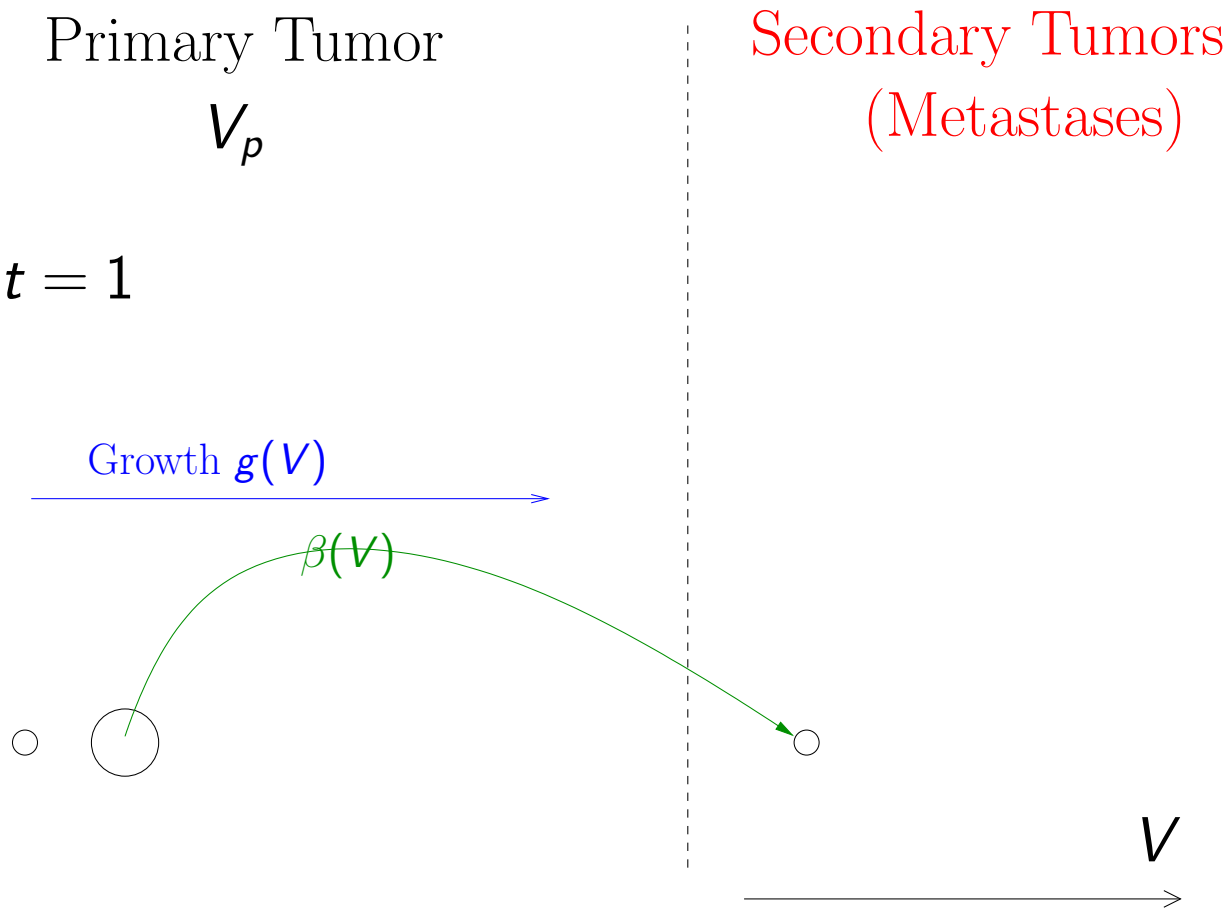

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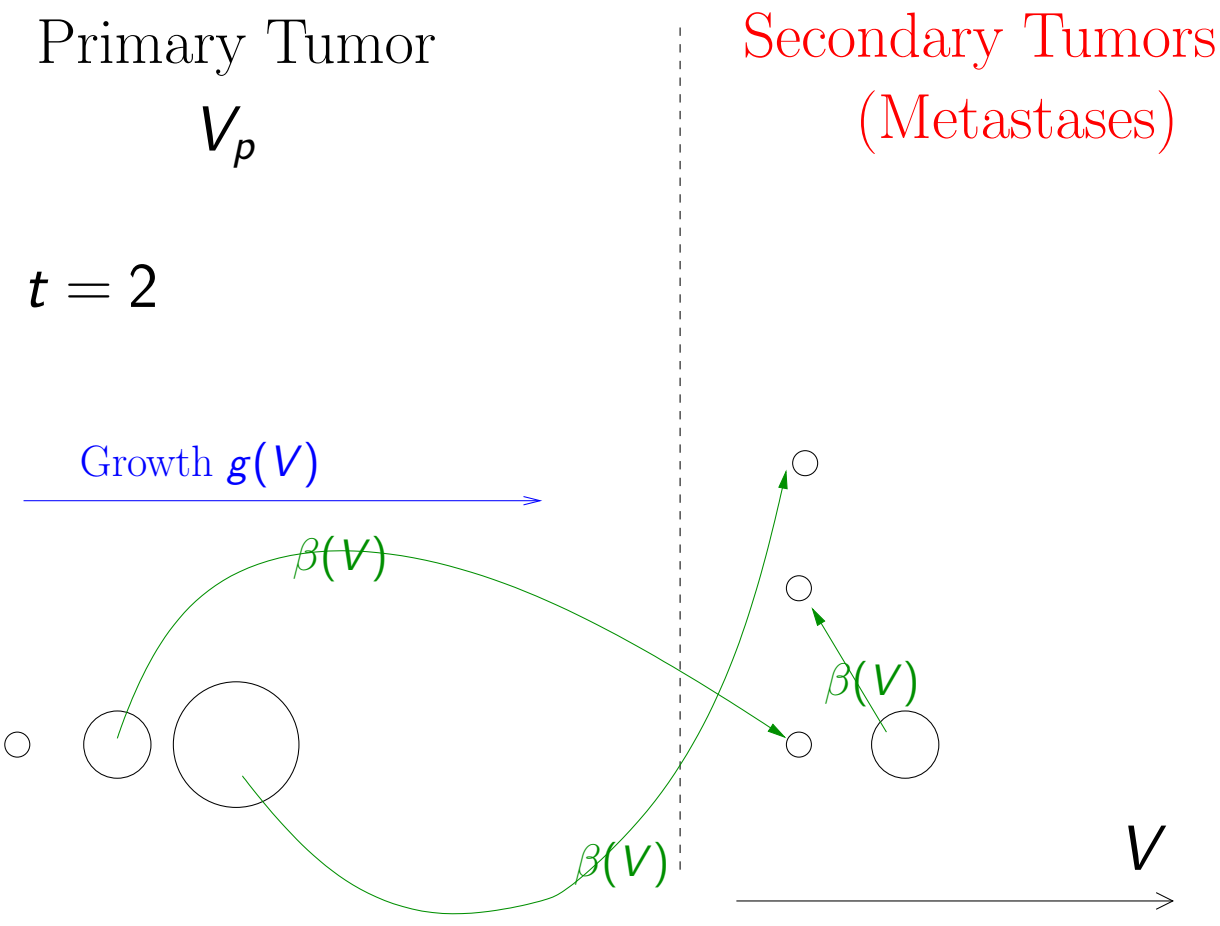

A mathematical model with size structure

Iwata & al., 2000

- **Population** of metastases structured in **size** V described by a **density** $\rho(t, V)$. Number of mets between V_1 and $V_2 = \int_{V_1}^{V_2} \rho(t, V) dV$

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$\Rightarrow$ Conservation of the number when tumors grow

$$\partial_t \rho(t, V) + \partial_V (g(V)\rho(t, V)) = 0$$

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- Spreading of new metastases with emission rate $\beta(V) = mV^{\alpha}$ $\alpha =$ fractal dimension of the vasculature, $m =$ metastatic agressiveness

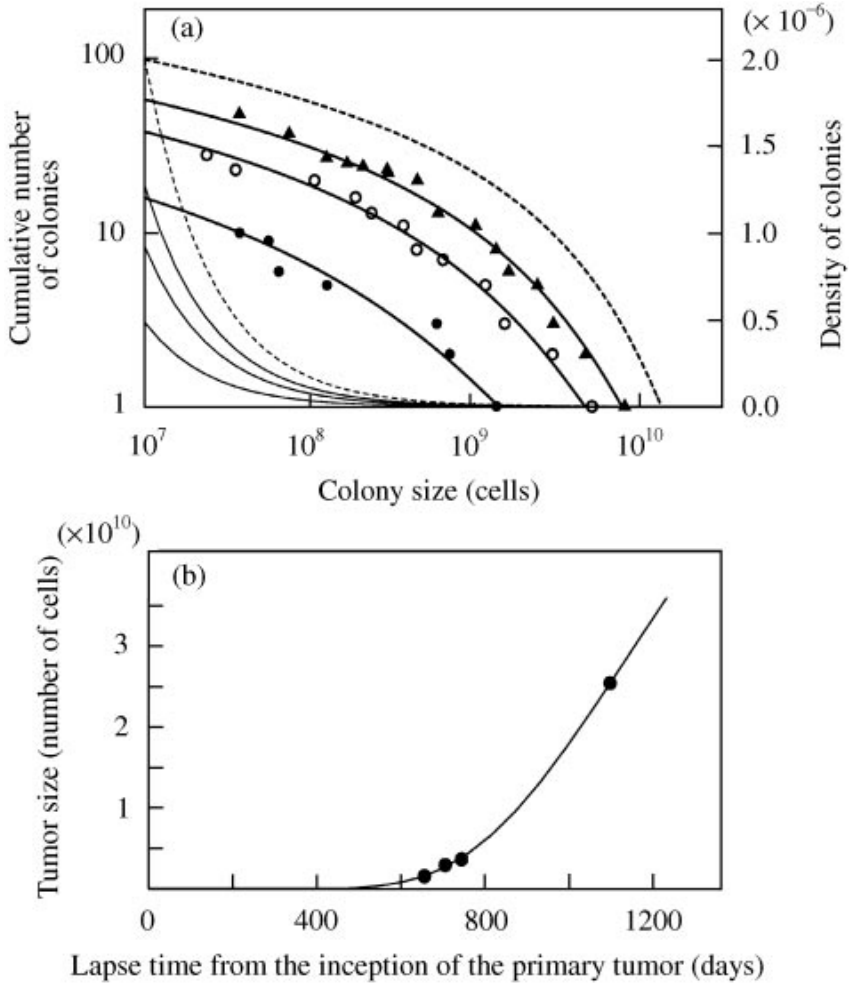
$\Rightarrow$ Entering flux of new metastases

$$g(V_0)\rho(t, V_0) = \int_1^b \beta(V)\rho(t, V)\, dV + \beta(V_p(t))$$

- Primary tumor growth $V_p' = g(V_p)$

Fit to a patient data

Iwata & al., 2000



Study of Koscielny & al., 1984

- 2648 patients treated for breast cancer at the IGR
- Proportion of patients which develop at least one visible metastasis in terms of the initial tumor size.

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One patient = One set of parameters (a, K, m, α)

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%

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But for clinical use of the model we need to estimate the parameters values without data on the metastases!!

Chemotherapy = reduction of the growth speed

$$g(V) = aV \ln\left(\frac{K}{V}\right) - C(t)V$$

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Toward taking into account inter-individual variability

- Simulation of 10 **virtual patients** with breast cancer
- Chemotherapy : 6 cycles of 21 days **Viens & al., 2001**
- Number of visible metastases ($> 10^8$ cel.) 5 years after the end of the treatment.

Patient	m	# metastases	Patient	m	# metastases
$n°1$	1.7×10^{-8}	0	$n°6$	7.0×10^{-8}	0
$n°2$	1.9×10^{-8}	0	$n°7$	1.3×10^{-7}	1
$n°3$	2.7×10^{-8}	0	$n°8$	2.7×10^{-7}	2
$n°4$	5.0×10^{-8}	0	$n°9$	4.0×10^{-7}	3
$n°5$	6.1×10^{-8}	0	$n°10$	6.1×10^{-7}	4

What about **angiogenesis** and

anti-angiogenic treatments?

A first model with size structure

Angiogenesis
- Modeling
- Simulations

Scheduling optimization
- Formulation of an optimal control problem
- Concentrating VS diluting the dose

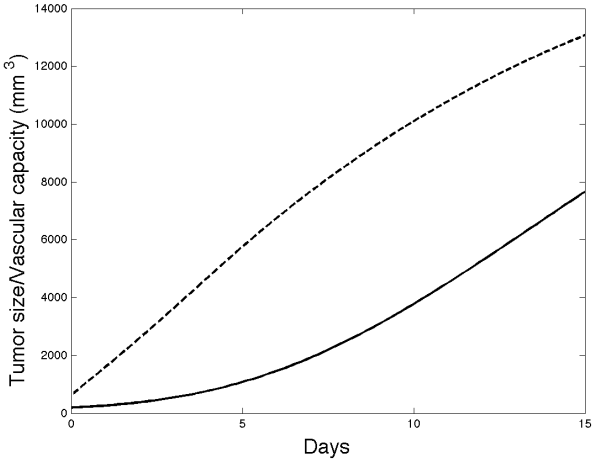
A model for low dose anti-angiogenic chemotherapy

Tumoral growth under angiogenic control Hahnfeldt et al., 1999

$$\frac{dV}{dt} = aV \ln\left(\frac{K}{V}\right)$$

Consider K as a **variable** representing the **vasculature**

$$\frac{dK}{dt} = \underbrace{cV}_{\text{Stimulation by the tumor}} - \underbrace{dV^{\frac{2}{3}}K}_{\text{Inhibition}}$$



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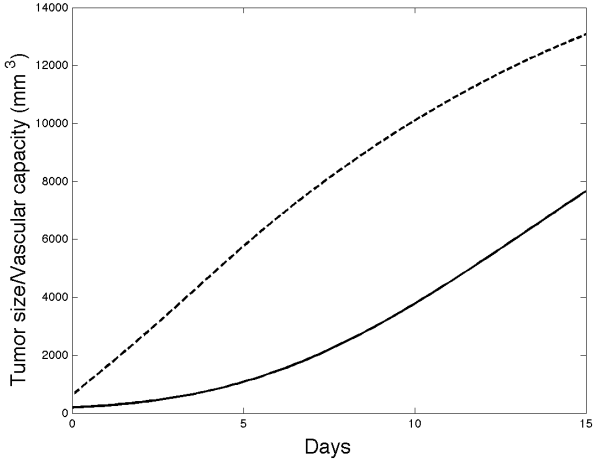
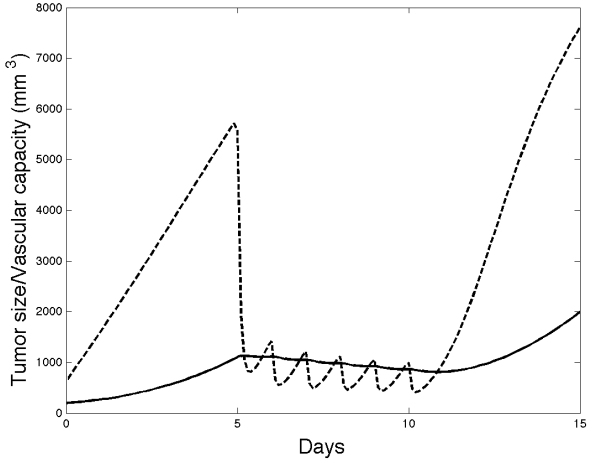


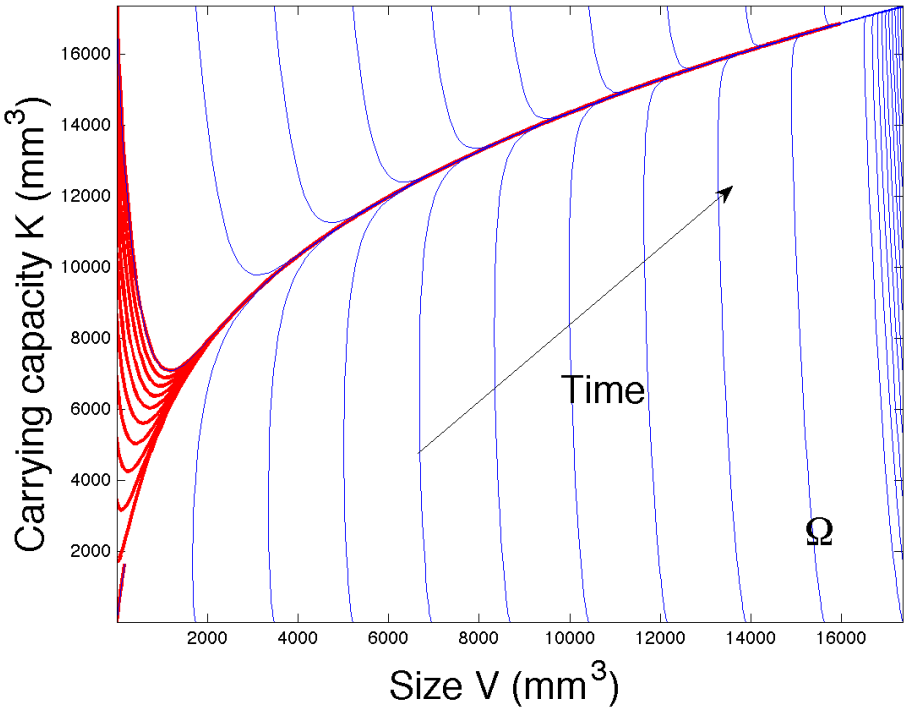
Treatment

$$\frac{dV}{dt} = aV \ln\left(\frac{K}{V}\right) - \underbrace{f\,C(t)V}_{\text{cytotoxic}}$$

$$\frac{d\theta}{dt} = cV - dV^{\frac{2}{3}}K - \underbrace{e\,A(t)K}_{anti-angiogenic}$$



Transport equation for the metastases population



$$\Omega =]V_0, b[^2, \quad b = \left(\frac{c}{d}\right)^{\frac{3}{2}}$$

$$G = \begin{pmatrix} aV \ln\left(\frac{K}{V}\right) \\ cV - dV^{\frac{2}{3}}K \end{pmatrix}$$

$$\overline{G} = G - Bu(t)$$

$$u(t) = (C(t), A(t))$$

$$\rho(t, V, K)$$

Conservation law

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

Boundary condition. Birth of new metastases

Birth rate of new metastases of parameter $\sigma \in \partial\Omega$ per meta of size V and carrying capacity K per unit of time : $\mathbf{b}(\sigma, V, K)$

We assume that the metastases are born with size 1 cell (V_0) and same carrying capacity K_0

$$b(\sigma, V, K) = \delta_{\sigma=(V_0,K_0)}\beta(V, K)$$

We take :

$$\beta(V, K) = mV^{\alpha}$$

Metastatic model with angiogenesis

B., 2011

$$\begin{cases} \partial_t \rho + \mathrm{div}(\overline{G}\rho) = 0 \\ -\overline{G}(t,\sigma)\cdot\nu(\sigma)\rho(t,\sigma) = \delta_{\sigma=(V_0,K_0)}\left\{\int_\Omega \beta(V)\rho(t,V,K)dVdK + \beta(V_p(t))\right\} \\ \rho(0) = \rho^0 \end{cases}$$

Number of mets $= \int_\Omega \rho(t,V,K)dVdK$

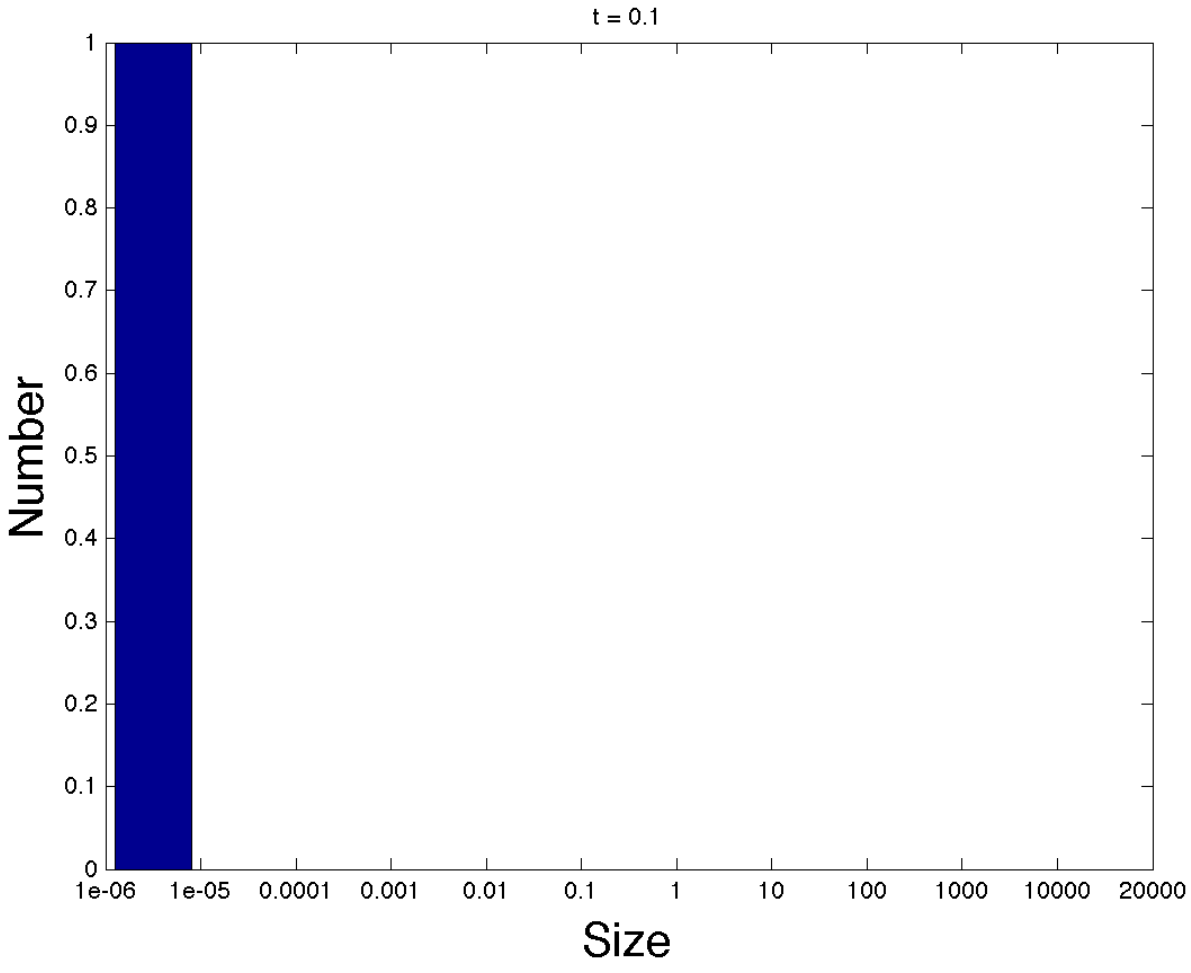
Metastatic mass $= \int_\Omega V\rho(t,V,K)dVdK$

- Renewal equation in **dimension 2** for the trait $X = (V,K)$
- Theoretical and numerical **analysis** has been performed : well-posedness, regularity, asymptotic behavior, error estimate

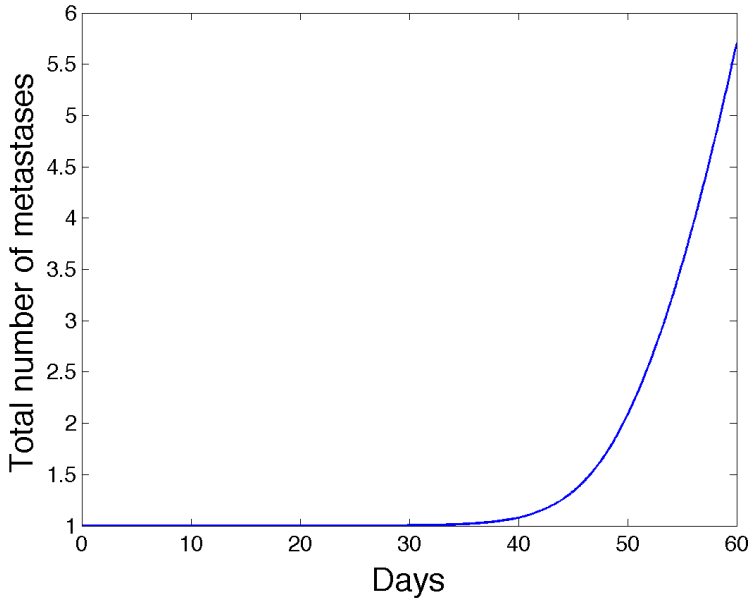
B., JEE, 2011

B., M2AN, 2012

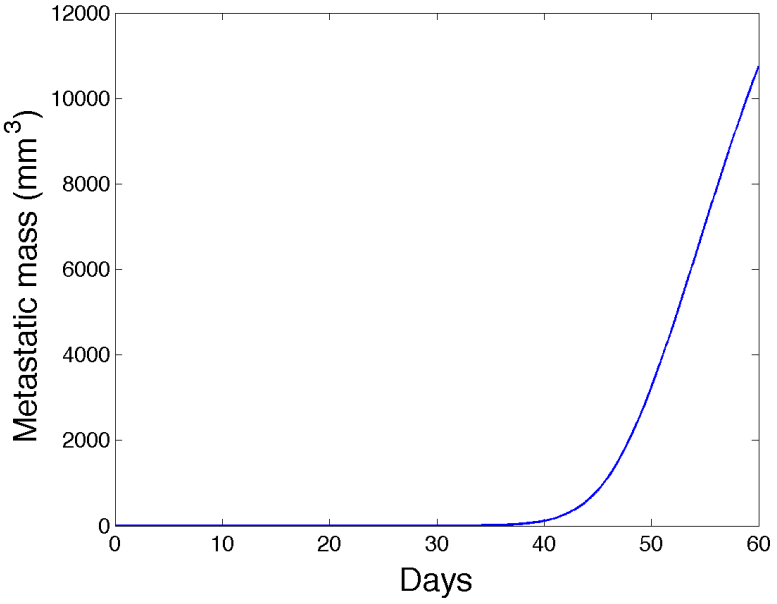
Simulation of cancer history



Simulation of cancer history. Growth curves

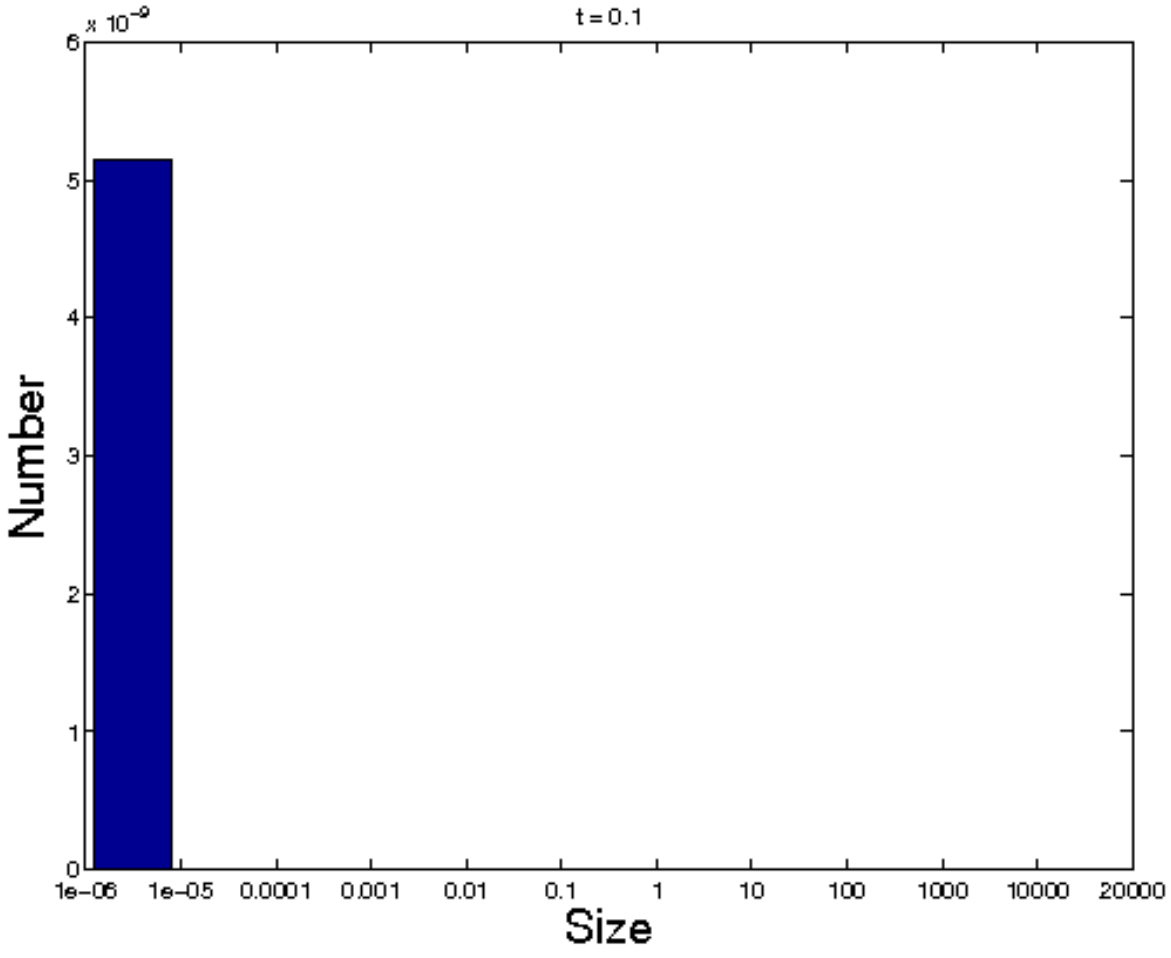


Number of metastases

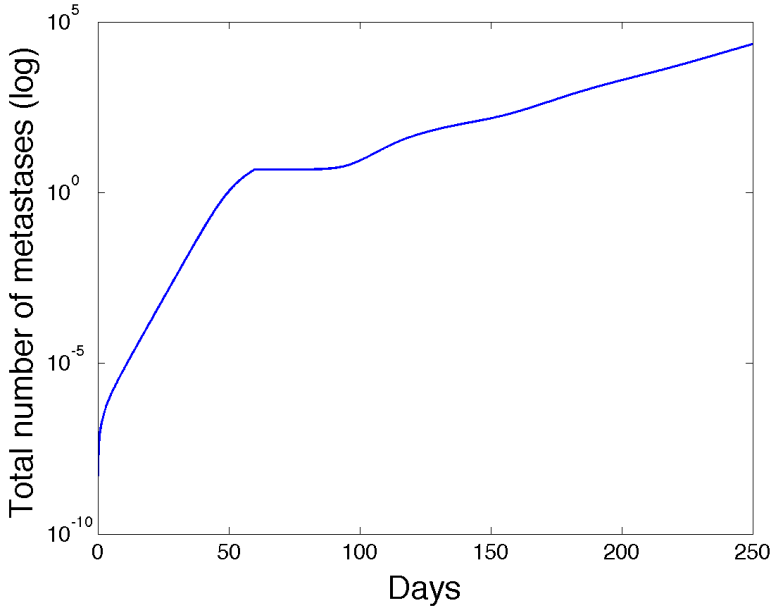


Metastatic mass

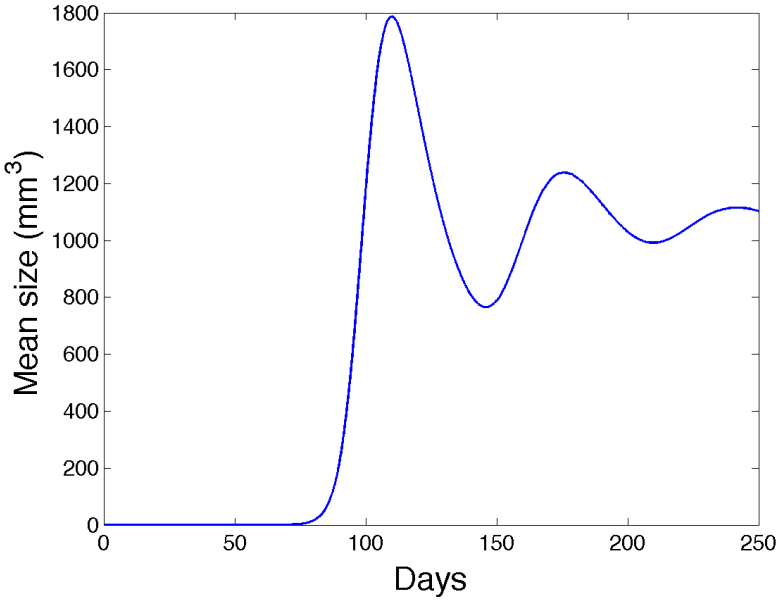
Surgery and development of the metastatic population



Metastatic population. Growth curves



Number of metastases

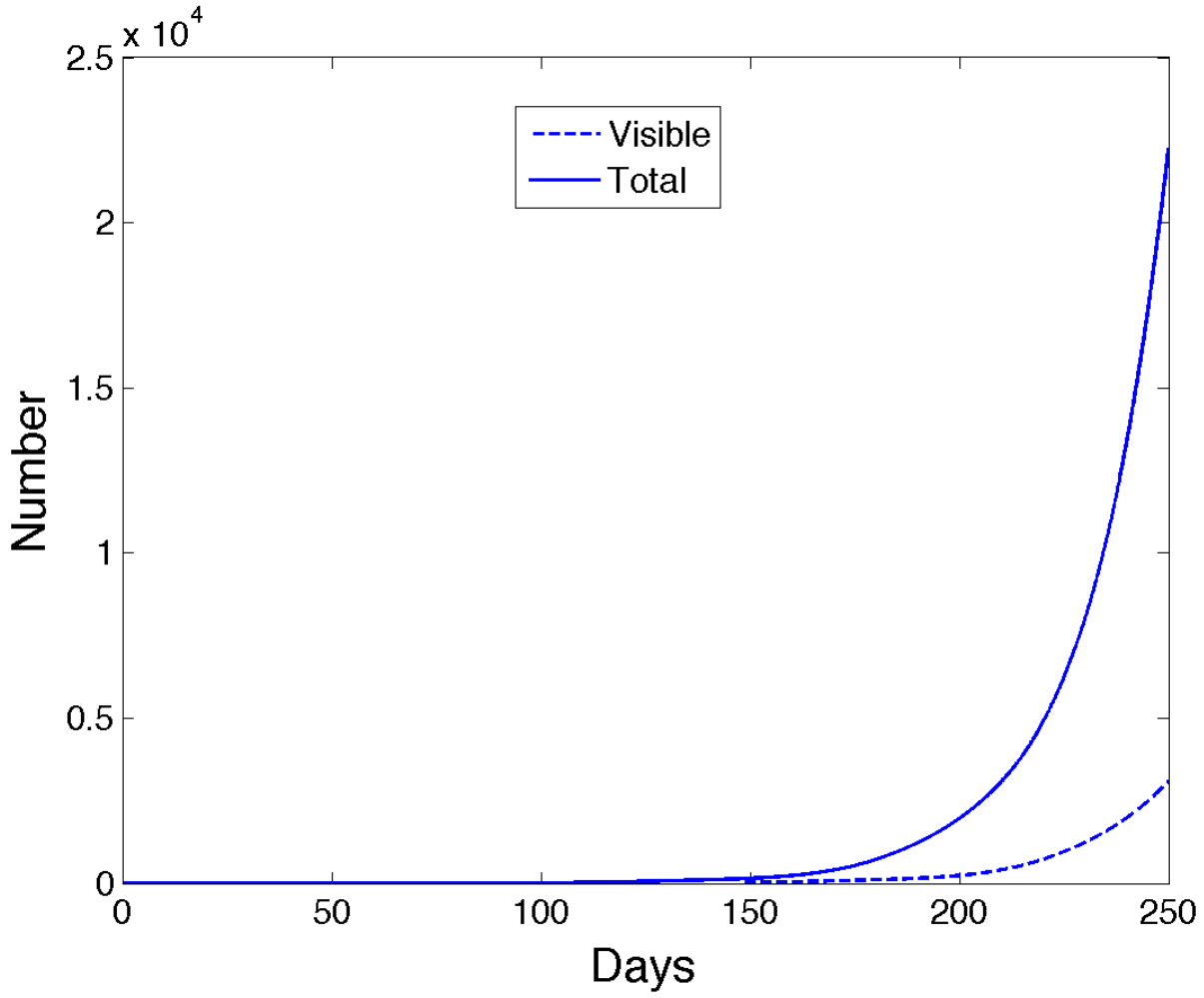


Mean size

$$\rho(t, V, K) \sim_{\Psi} Ce^{\lambda_0 t}\Phi(V, K)$$

$$\overline{V}(t) = \frac{\text{Mass}}{\text{Number}}$$

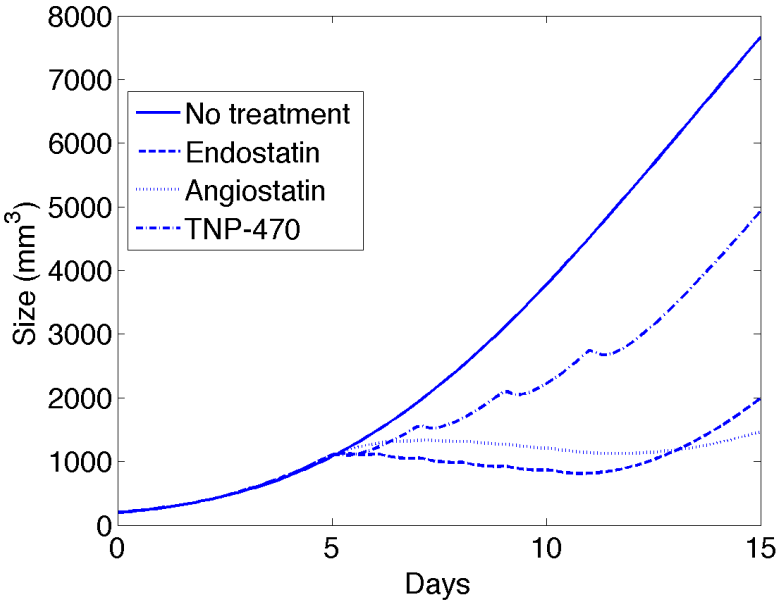
Visible metastases VS Total



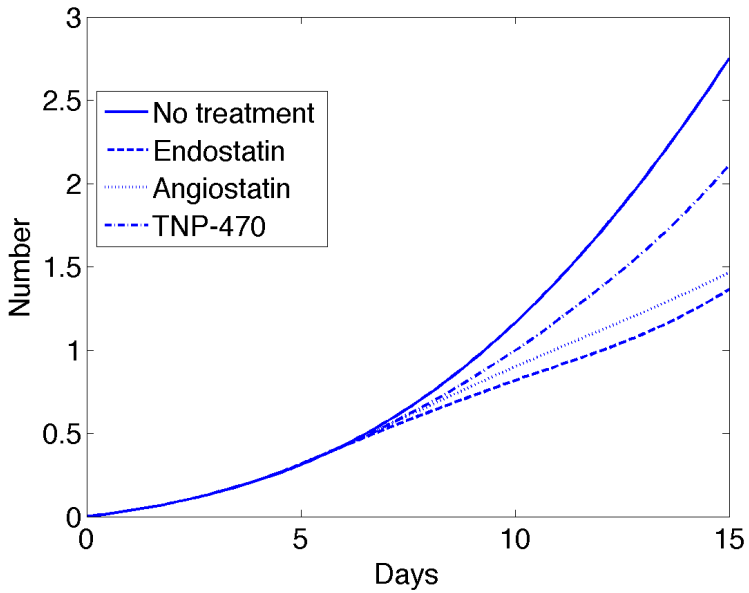
Anti-angiogenic monotherapy

Testing the drugs from Hahnfeldt et al., 99 (mice data)

Endostatin 20 mg/kg/day, Angiostatin 20 mg/kg/day, TNP-470 30 mg/kg/q.o.d



Primary tumor

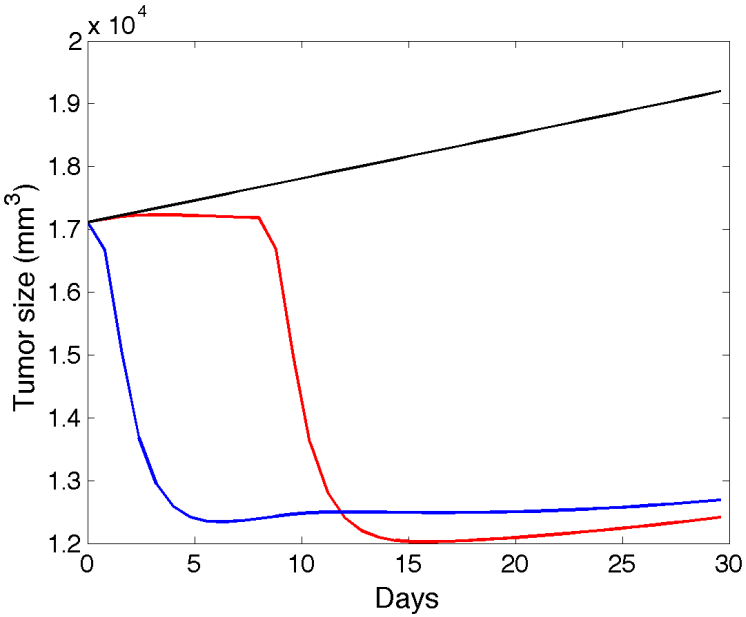


Metastases

CT/AA combination. Order of administration?

Etoposide (CT)/Bevacizumab (AA) combination

Bevacizumab D0 Etoposide D8 VS Etoposide D0 Bevacizumab D8



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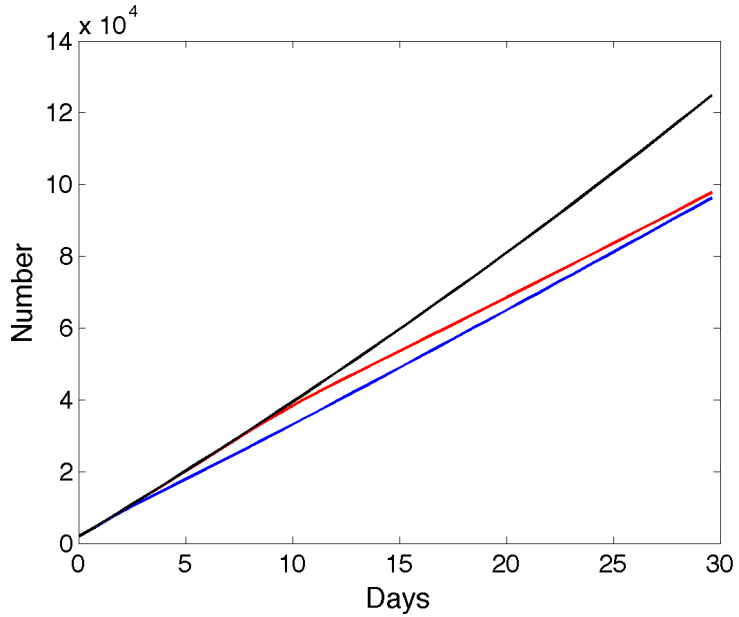


Metastases

In these two first examples, the best protocol/drug is **not the same** for the primary tumor and for the number of metastases.

Summary

- We have established a mathematical model for the development of **metastases**
- Takes into account: proliferation, **angiogenesis**, metastatic spreading
- **Therapies**: surgery, chemotherapy, anti-angiogenic therapy
- Best therapy can **differ between primary tumor and metastases**

A first model with size structure

Angiogenesis
- Modeling
- Simulations

Scheduling optimization
- Formulation of an optimal control problem
- Concentrating VS diluting the dose

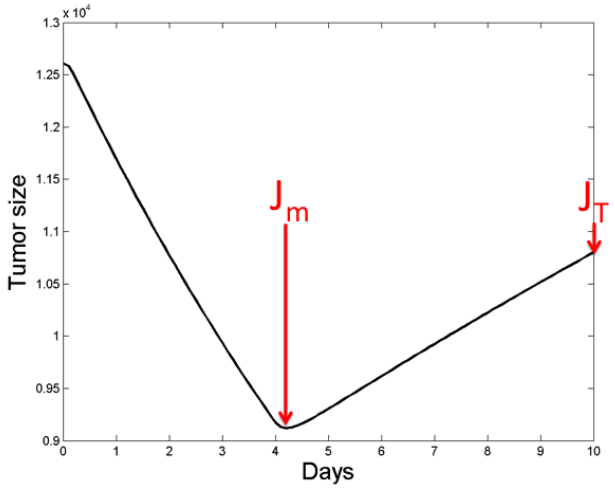
A model for low dose anti-angiogenic chemotherapy

On the primary tumor

$$X_p := (V_p, K_p), \quad \dot{X}_p(t;u) = G(X_p) - B(X_p)u(t)$$

Two possible criteria to be minimized for the primary tumor size

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



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Toxicity constraints

$$\mathcal{U}_{ad} = \left\{ \begin{pmatrix} 0 \\ 0 \end{pmatrix} \leq u(t) \leq \begin{pmatrix} c_{max} \\ a_{max} \end{pmatrix} \ \forall t \ \textbf{and} \ \int_0^T u(t)dt \leq \begin{pmatrix} C_{max} \\ A_{max} \end{pmatrix} \right\}$$

Optimal control problem : find $u^* \in \mathcal{U}_{ad}$ such that $J_m(u^*) \leq J_m(u)$ for all $u \in \mathcal{U}_{ad}$, studied in

U. Ledzewicz and H. Schättler, SIAM J. on Control and Optimization, 2007

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

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

On the metastases

- Two new criteria

$$J(u) = \underbrace{\int_\Omega \rho(T, V, K; u) dV dK}_{\textbf{Total number of metastases}}$$

$$J_M(u) = \underbrace{\int_\Omega V\rho(T, V, K; u) dV dK}_{\textbf{Metastatic mass}}$$

- Optimal control problem

Find $(u^*, u_M^*) \in \mathcal{U}_{ad}$ such that

$$J(u^*) = \min_{u\in\mathcal{U}_{ad}} J(u) \textbf{ and } J_M(u_M^*) = \min_{u\in\mathcal{U}_{ad}} J_M(u)$$

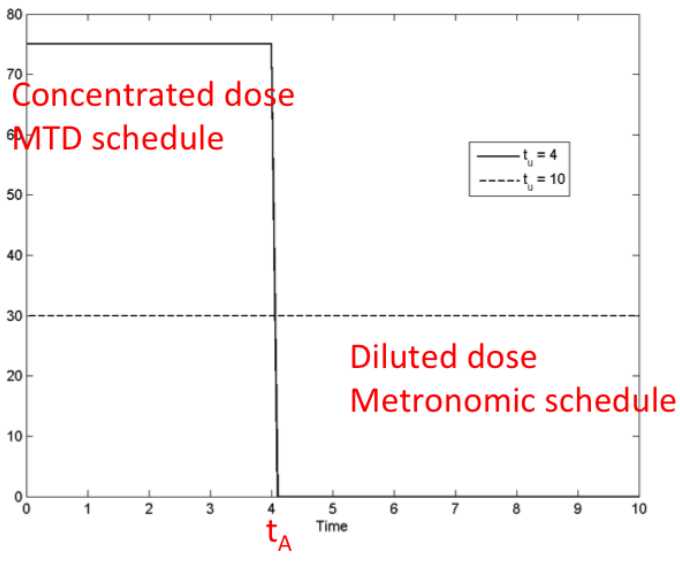
Is there a **difference** in the optimal minimizer **between the metastatic and primary tumor** criteria?

Concentrating VS diluting the dose

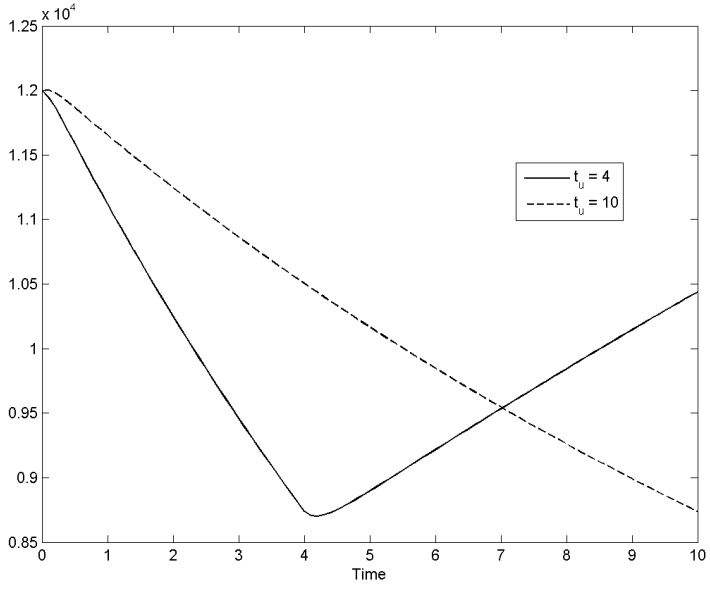
Simpler situation: constant administration then 0 **Ledzewicz & al., 10**

Same total AUC $= (C_{max}, A_{max})$

Variable = durations = (t_C, t_A)

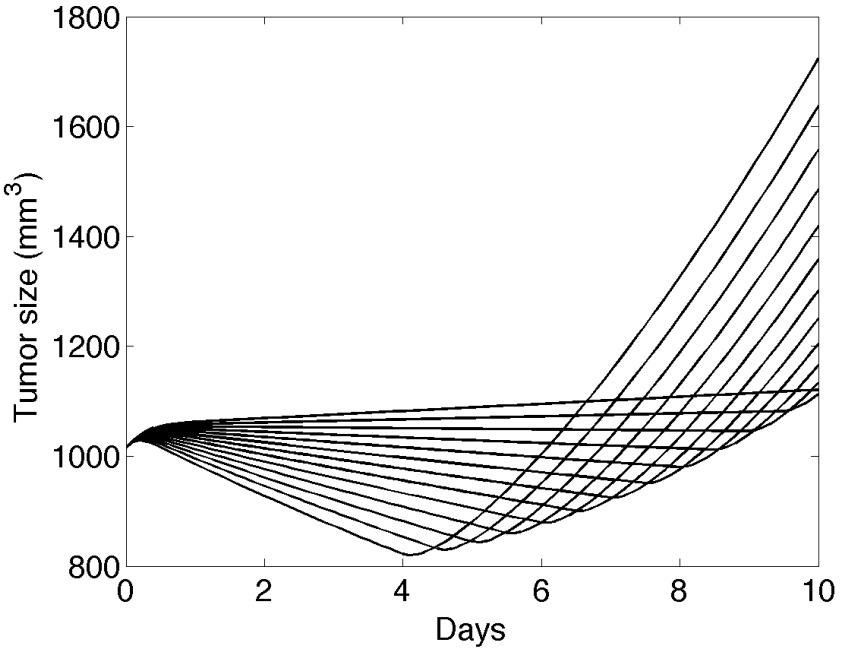


Drug administration

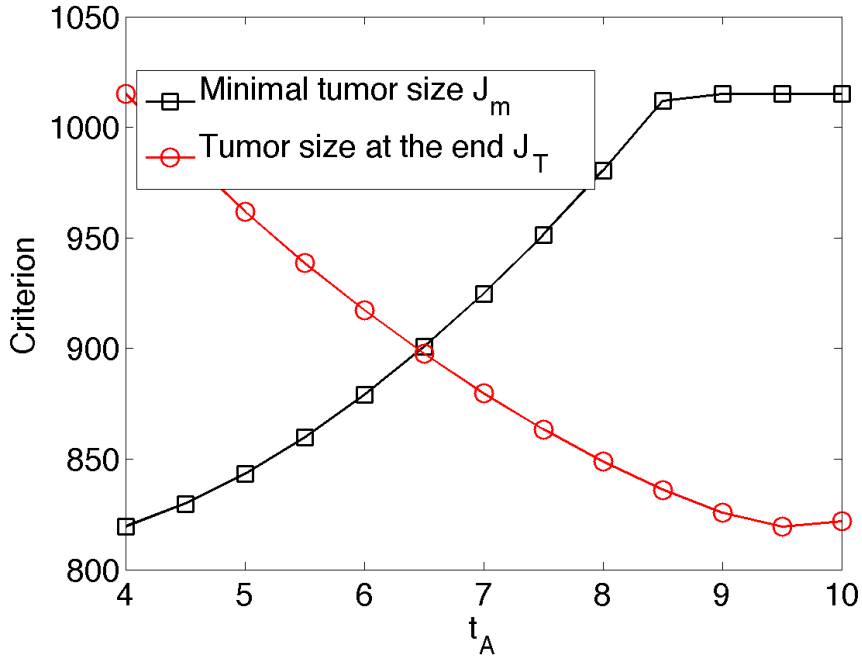


Primary tumor

AA monotherapy. Primary tumor



Growth time curves

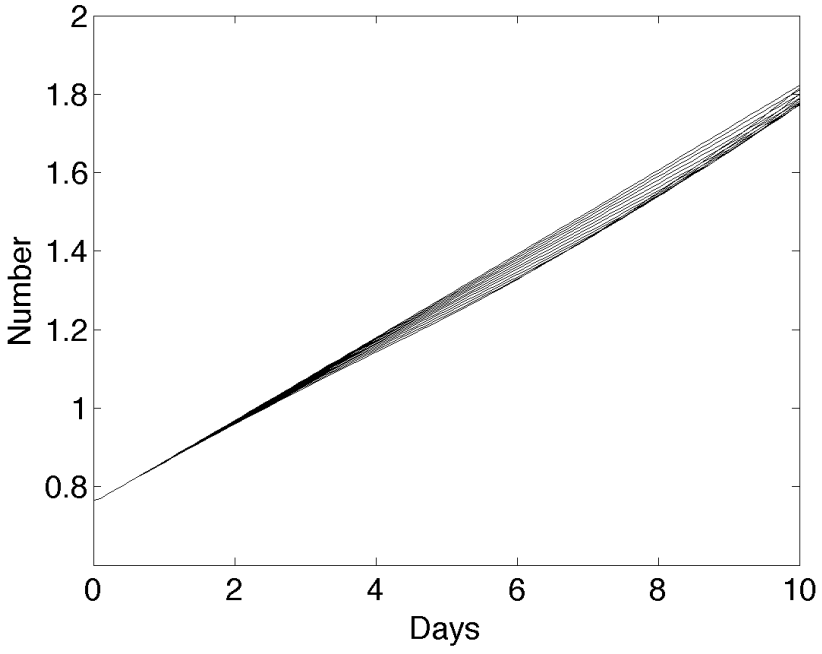


Criteria

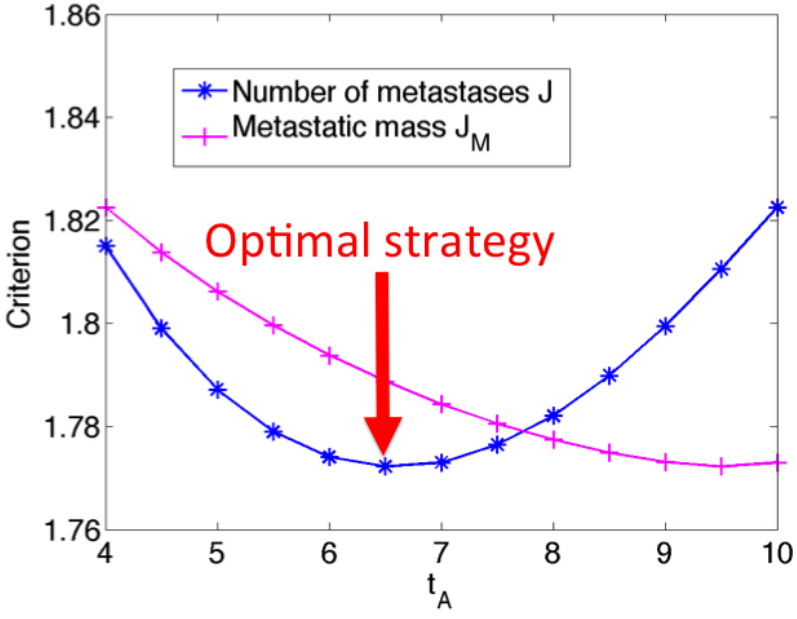
- Better **short term** tumoral reduction J_m with **MTD**
- Better **long term** tumoral reduction J_T with **metronomic**

(for these values of parameters and initial conditions)

AA monotherapy. Metastases



Time curves



Criteria

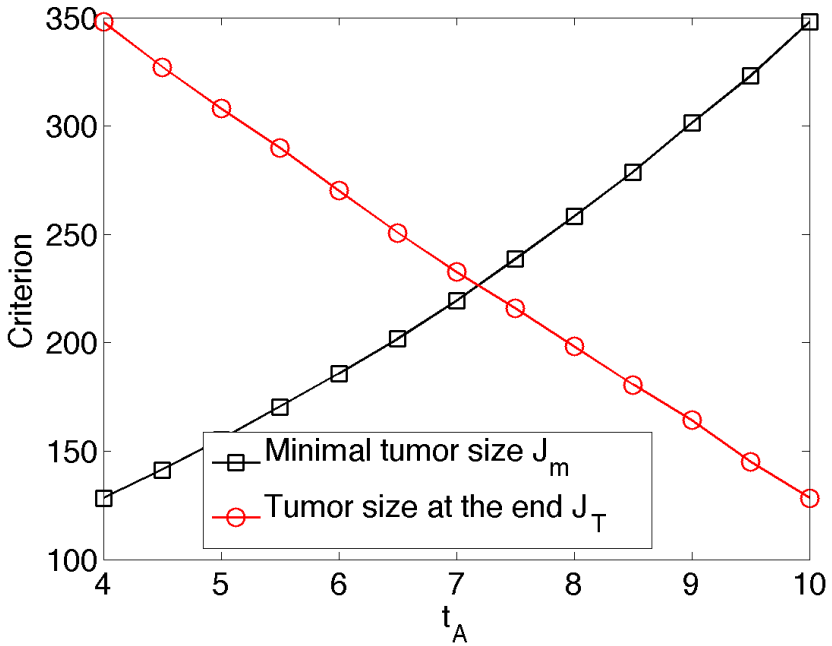
- **Nontrivial optimal scheduling** for the number of mets
- Metastatic mass J_M is qualitatively the same as tumor size J_T

Quantification of the effect of scheduling optimization

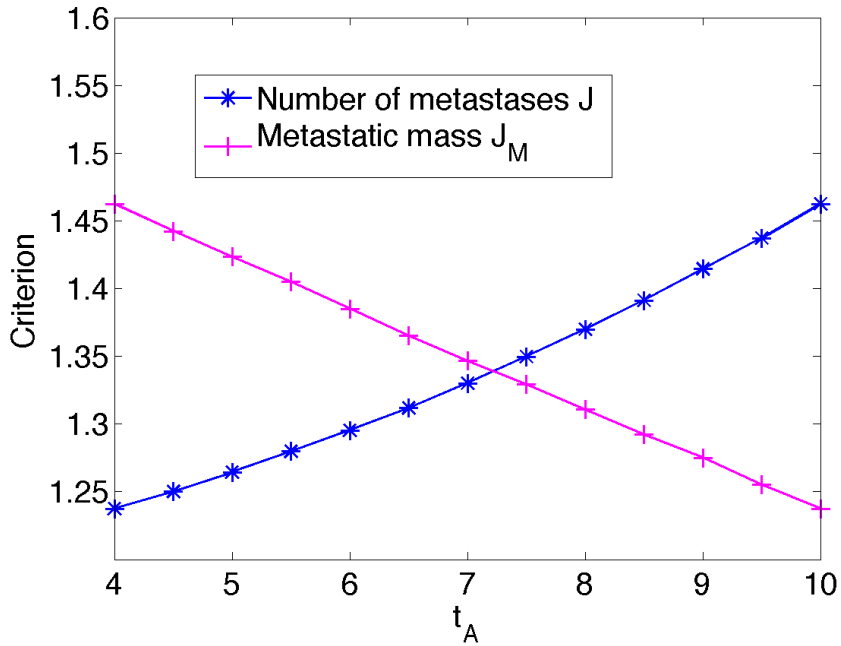
Criterion	Min size J_m	End size J_T	Nb mets J	**Mass $\mathbf{J}_M$**
Min /Max reduction (%)	-19/0	+10/+70	+132/+138	**+33/+154**

- The scheduling has a strong impact on the tumoral criteria and on the **metastatic mass**
- Impact on the number of metastases is much smaller

CT monotherapy



Primary tumor



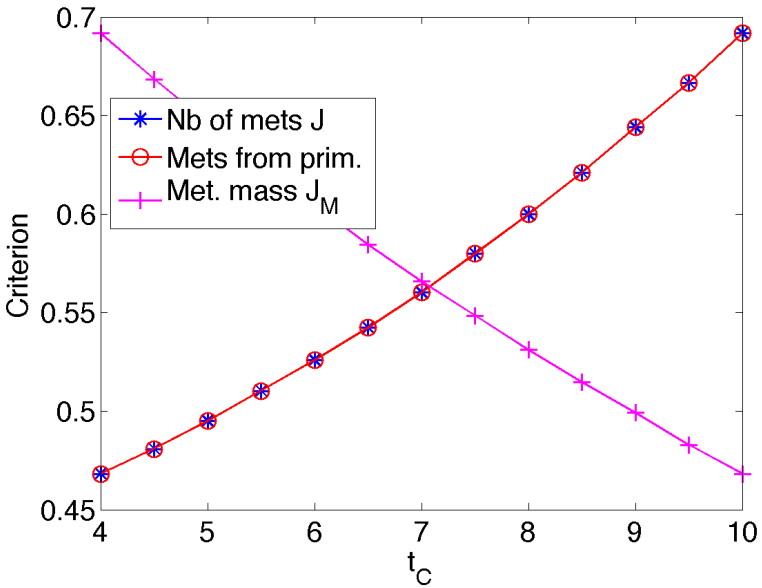
Metastases

- Optimal strategy for the number of metastases **differs from AA monotherapy**. Now **MTD**

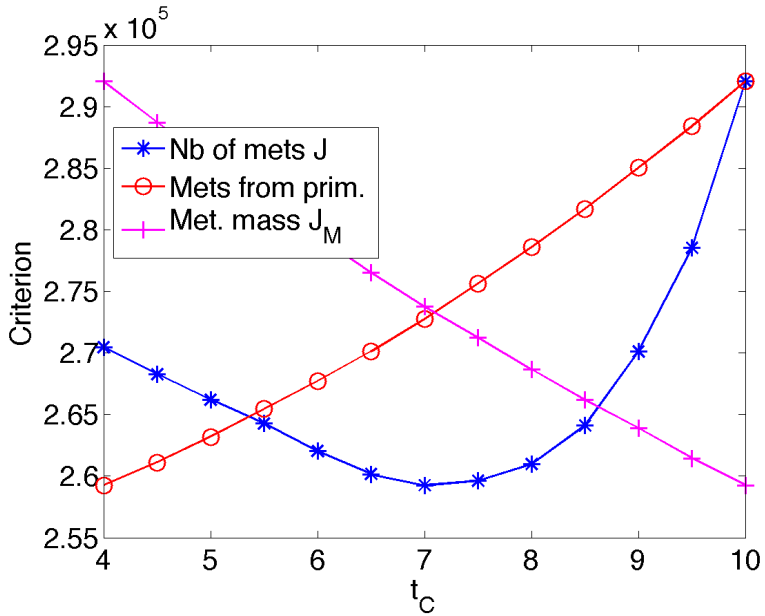
- Same behavior for the other criteria

CT monotherapy. Influence of metastatic agressiveness m

For small value of m, the metastases are mostly spread by the primary tumor $= m \int_0^T V_p^\alpha(s)ds$



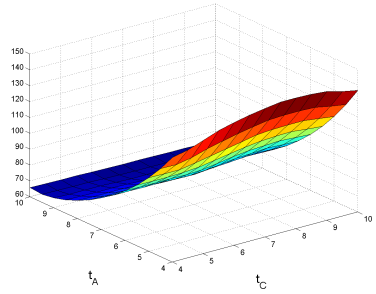
m=0.001



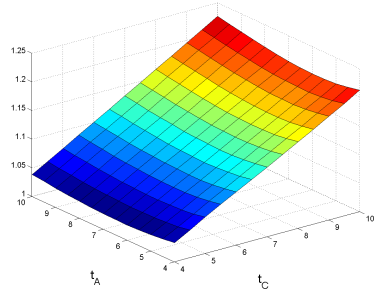
m=100

- **Change in the optimal strategy** for the number of mets
- Whatever the metastatic agressiveness of the cancer, **same optimal strategy** for the mass, i.e. **metronomic**

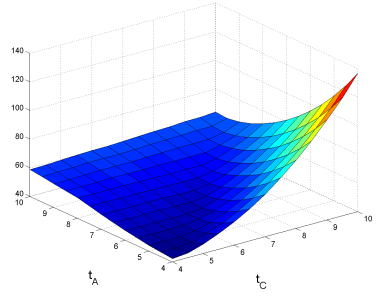
CT-AA combination



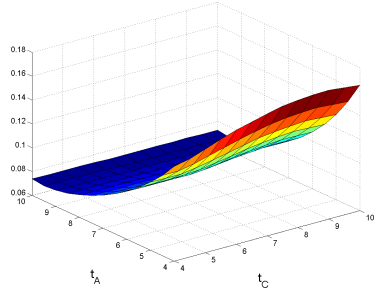
Tumor size J_T



Number of metastases J



Minimal tumor size J_m



Metastatic mass J_M

Criterion	J_T	J_m	J	J_M
(t_C^*, t_A^*)	(9.5, 9.5)	(4, 4)	(4, 6.5)	(9.5, 9.5)

Summary

- **Scheduling is important**

- Number of metastases and primary tumor criteria yield **different optimal strategies** : strong dose/short time (Maximum Tolerate Dose), small dose/large time (metronomic), nontrivial minimum value

- Metastatic mass gives the same optimal strategy as final tumor size : it prefers a situation with **more but smaller metastases** (rather than less but bigger). This happends independently of the value of the spreading rate m.

A first model with size structure

Angiogenesis
- Modeling
- Simulations

Scheduling optimization
- Formulation of an optimal control problem
- Concentrating VS diluting the dose

A model for low dose anti-angiogenic chemotherapy

So far

So far the presented models did not take into account for three important features:

- Resistance
- Pharmacokinetics/Pharmacodynamics
- (Toxicity)

The paradigm of metronomic schedules

- Administer the chemotherapy with **low doses but more frequent**
- Limit the toxicities
- **Anti-angiogenic effect** of these therapies, with **less resistances**
- In fine, make the disease become chronic

- Tumoral growth

$$\begin{aligned}\dot{V} &= aV \ln\left(\frac{K}{V}\right) - fC_1(t)V \\ \dot{K} &= cV - dV^{\frac{2}{3}}K - gC_2(t)K\end{aligned}$$

- PK and interface model for the effective concentrations Meille& al., 2008

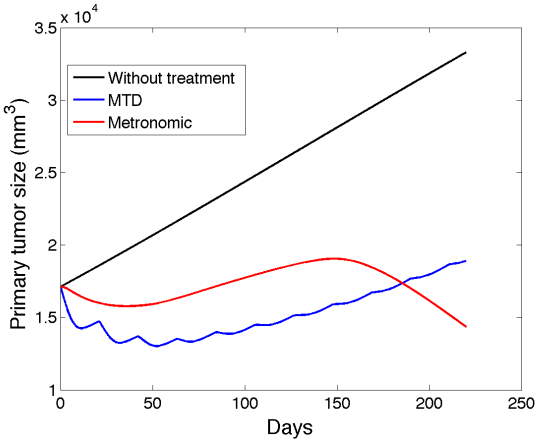
$$\begin{aligned}\dot{c}_1(t) &= -k_e c_1(t) + k_{12}(c_1(t) - c_2(t)) - k_{13}(c_1(t) - c_3(t)) + \frac{I(t)}{V} \\ \dot{c}_2(t) &= k_{21}(c_1(t) - c_2(t)) \\ \dot{c}_3(t) &= k_{31}(c_1(t) - c_3(t)) \\ \dot{C}(t) &= -\alpha_I e^{-\beta_I C(t)} C(t) + c_1(t)\end{aligned}$$

- **Resistances** only for the action on cancerous cells :

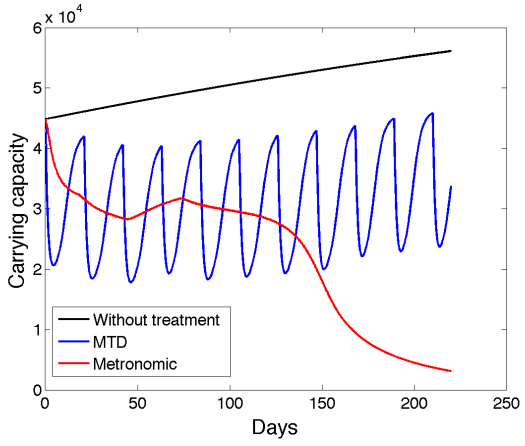
$$C_1(t) = C(t)e^{-R\int_0^t C(s)ds}, \quad C_2(t) = C(t)$$

Example of metronomic administration for breast cancer

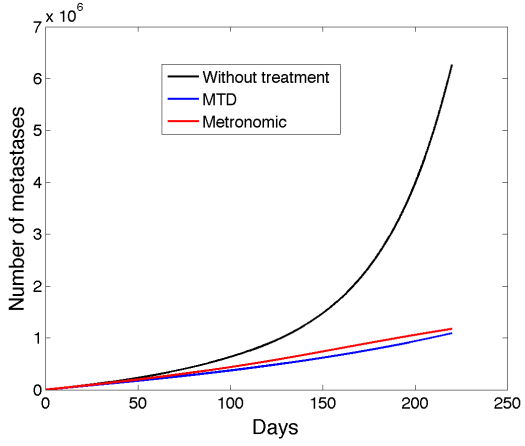
- MTD : DTX 100 mg at day 0. 21 days cycle
- **Metronomic for DTX : 10 mg per day, every day**



Tumoral growth



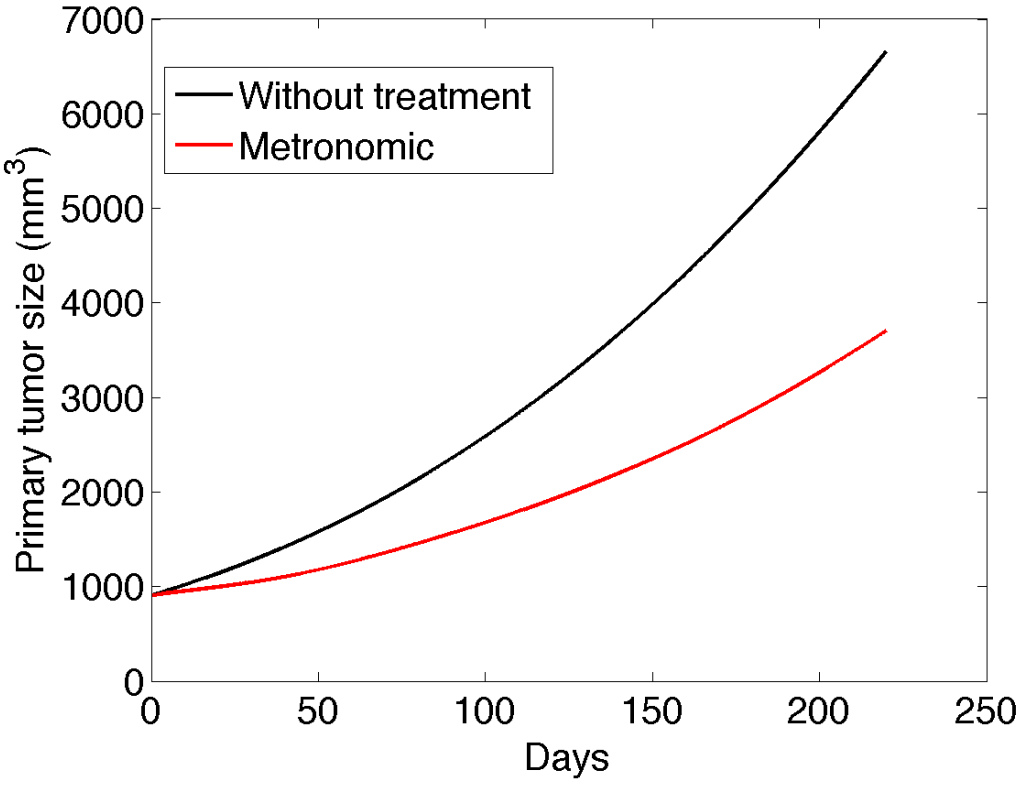
Carrying capacity



Metastases

Long term advantage of metronomic therapy.

Dosis 8mg



If the dosis of the drug is too low (< 8 mg), the treatment does not suppress tumor growth

Conclusion

- **Systemic model** for metastatic growth taking into account all the fundamental aspects of a cancer disease : proliferation, angiogenesis, metastasis
- Could be used to predict the **development of the (micro and visible) metastases**, in the clinic. But we have to find a way to estimate the metastatic parameters m and α with only primary tumor data.
- Simulation of CT and AA **therapies** (and surgery)
- Theoretical study of the impact of **scheduling**
- Treatment of metastases $\neq$ treatment of primary tumor
- A mathematical model able to describe **long term efficacy of metronomic scheduling**.

Thank You for listening!

This work was done in collaboration with

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