Biomathematical modeling for description of metastatic processes and optimization of combined anti-angiogenic + cytotoxic therapies

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Work in collaboration with the group of mathematical modeling in oncology of Marseille

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Clinical problematics

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

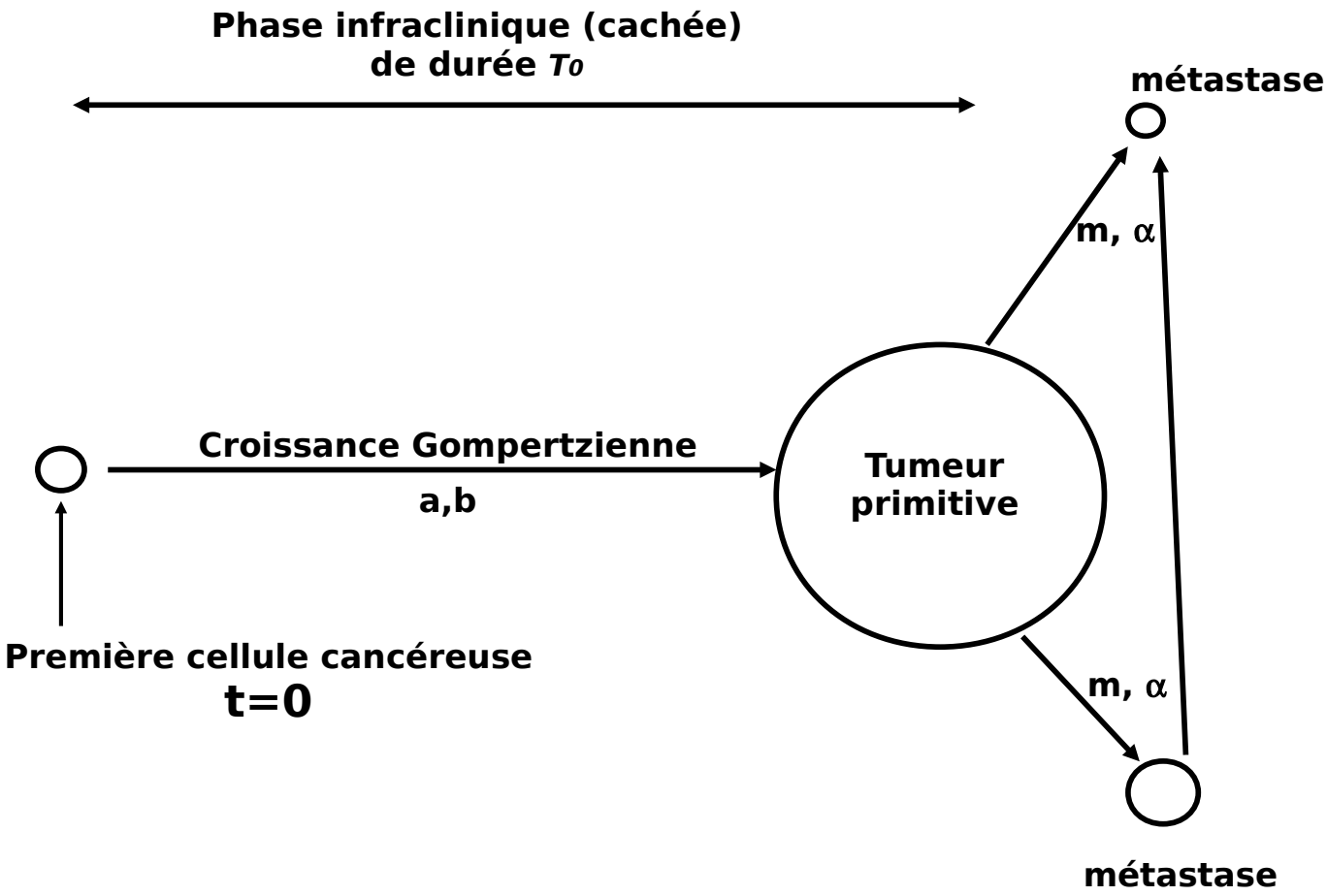
  Weinberg, 2006

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

The tools

- A "simple" modelling (with **few parameters**)
  - of the disease (tumoral and/or metastatic evolution)
    - ⋆ **tumoral growth model (ODE)**
    - ⋆ **renewal model for the metastases (PDE)**

Cancer as a diffuse disease : **continuum** between localized pathology and metastatic cancer.



Mathematical models

- Primary tumor growth (ODEs)
  - Gompertz. Model used in the phase I trial **You et al., ASCO 2007**
    only cancer cells $\Rightarrow$ **CT**
  - Hahnfeldt - Folkman **Hahnfeldt et al., Cancer Research 1999**
    cancer cells + blood vessels $\Rightarrow$ **CT + AA**
  - New model **Benzekry et al., 2011**
    cancer cells + stable/unstable vessels $\Rightarrow$ **CT+AA interactions**
- Metastatic population (PDEs) **Iwata et al., 2000, Barbolosi et al., 2008, Benzekry, 2011**
  - Evolution characterized by **two parameters** :
    metastatic aggressiveness **m**
    fractal dimension of the vasculature α
  - Metastatic module can be plugged on any tumoral model

Creation of a **Metastatic Index**

Confrontation with a study of Koscielny, Tubiana & al.

Verga PhD thesis

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

One patient = One set of parameters

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%

Adjuvant chemotherapy **Barbolosi, Benabdallah, Hubert, Verga (2010)**

Take into account inter-individual variability

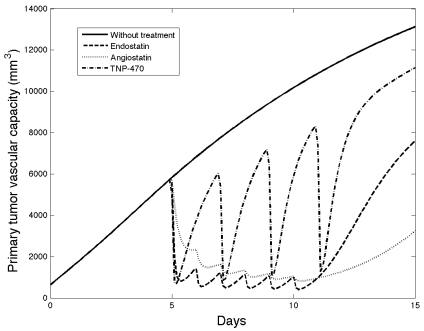
- We simulate 10 **virtual patients** with breast cancer classified T1N0M0.
- Protocol from **Viens & al., Am. J. Clin. Onc. 2001** : 6 cycles of 21 days (75mg of DTX then 100mg d'EPI) VS optimized protocol
- Number of visible metastases ($> 10^8$ cel.) 5 years after the end of the treatment.
- Adapt the number of cycles to each patient

m	Viens Protocol			Optimized protocol		
	6 cycles 126 jours	9 cycles 189 jours	12 cycles 252 jours	9 cycles 126 jours	13 cycles 182 jours	18 cycles 252 jours
1.3×10^{-7}	**1**	0	$\star$	0	$\star$	$\star$
2.7×10^{-7}	**2**	1	0	2	0	$\star$
4.0×10^{-7}	**3**	2	1	3	1	0
6.1×10^{-7}	**5**	4	3	4	3	1

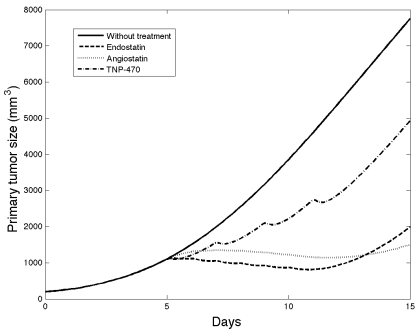
Anti-angiogenic monotherapy

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

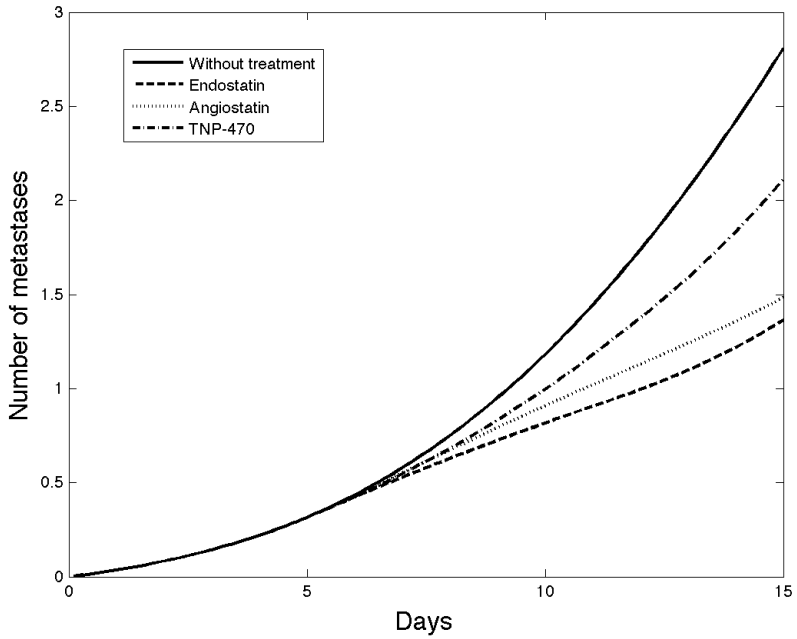
Endostatine 20 mg/kg/day, Angiostatine 20 mg/kg/day,
TNP-470 30 mg/kg/q.o.d



Vascular capacity

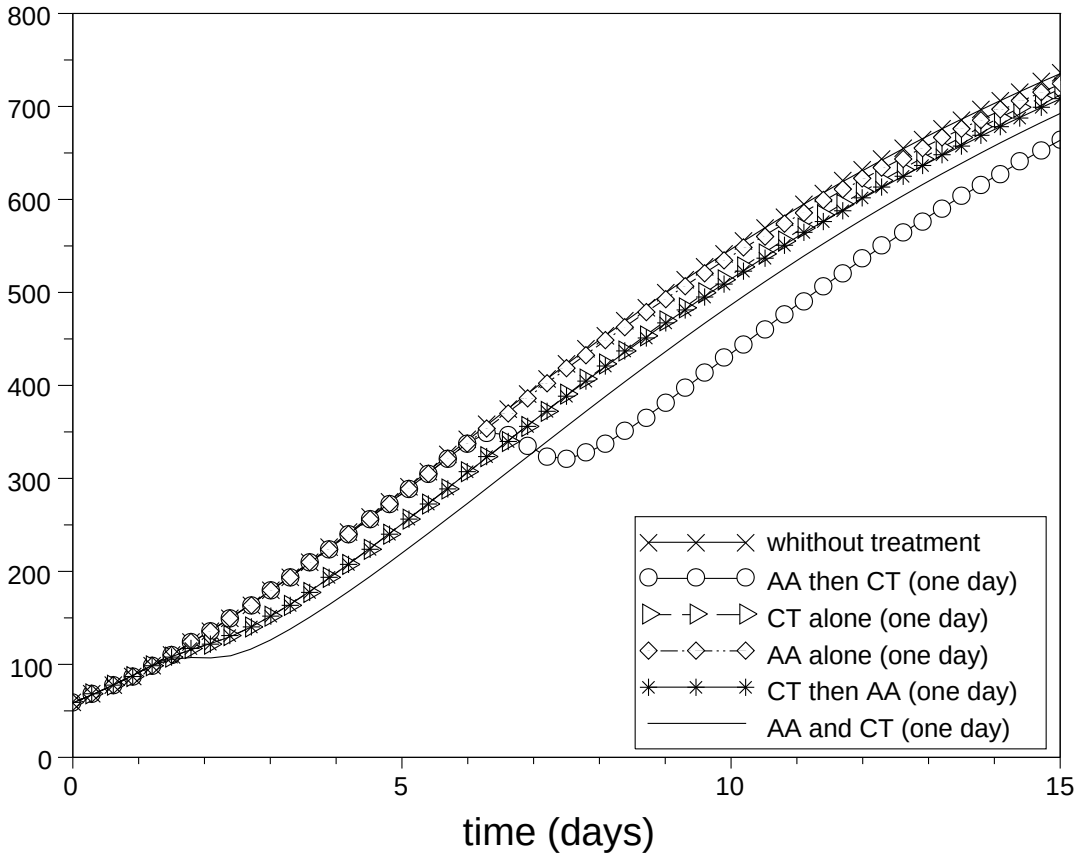


Tumoral growth



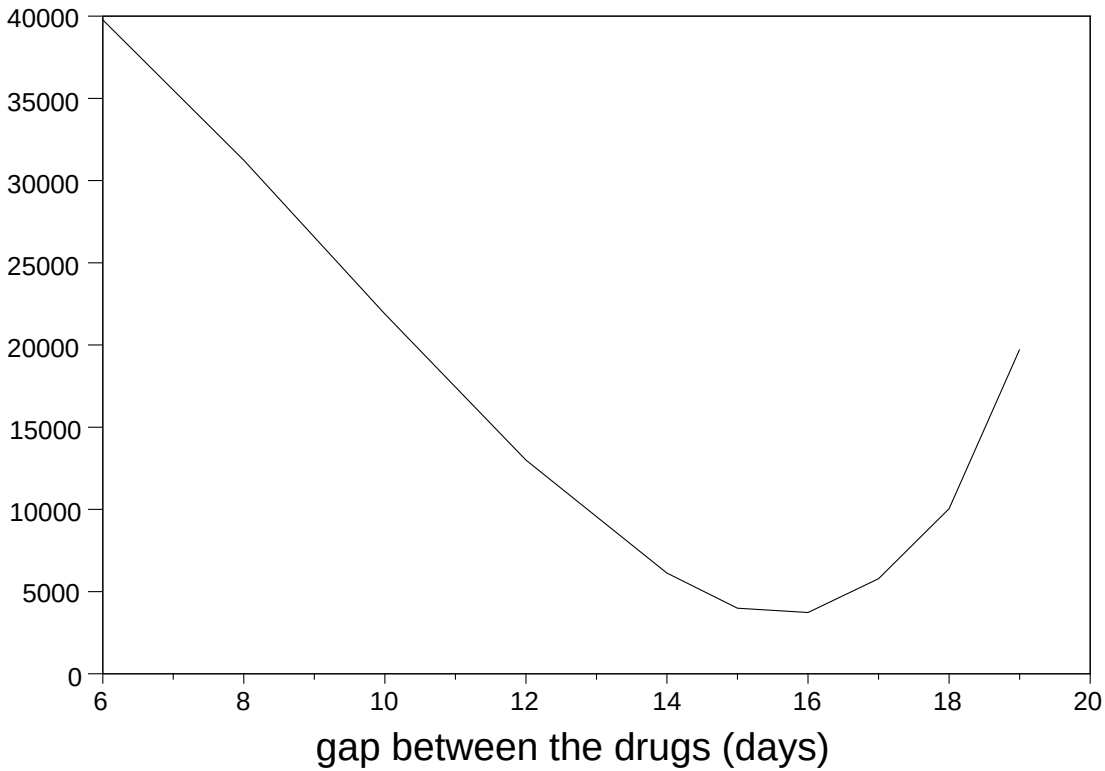
Metastatic evolution

CT/AA combination. Order of administration?



Tumor size

CT/AA combination. Optimization of the time gap between the drugs.



Final tumor size VS time gap between AA and CT

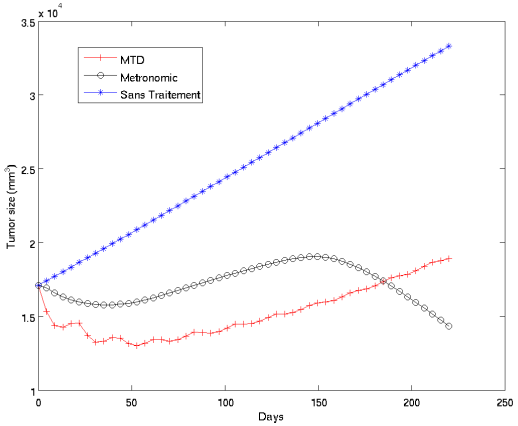
Metronomic CT

Barbolosi, Benzekry, André (2009,...)

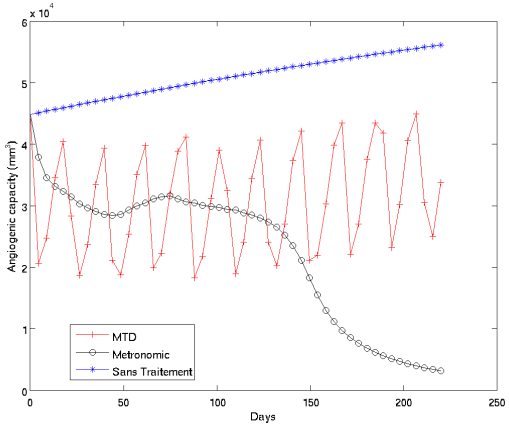
Example of metronomic administration for breast cancer, adapted from

Baruchel & al., Eur. J. Cancer 2005

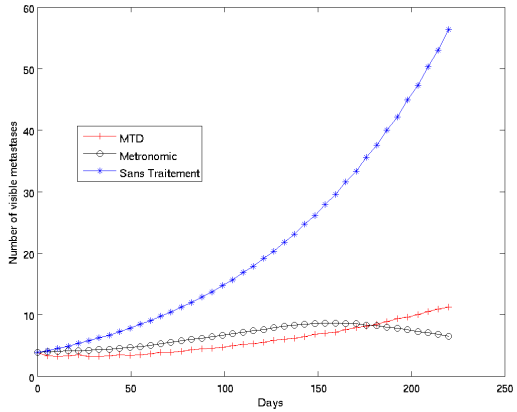
- Maximal Tolerate Dose (MTD) : DTX 100 mg at day 0.
- Metronomic for DTX : 10 mg per day, every day.



Tumoral growth



Vascular capacity



Visible metastases

- Long term advantage of metronomic therapy.
- If the dosis of the drug is too low (< 8 mg), the treatment is ineffective.

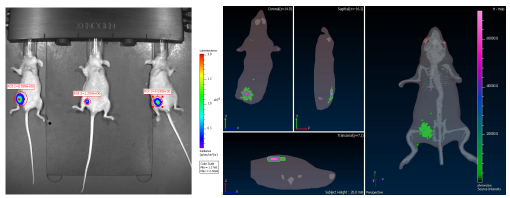
Conclusion. Perspectives

Conclusion

- The **metastatic index** derived from our model could be used to refine existing classifications.
- The best drug/schedule can be different for primary tumor and metastases.
- Our mathematical model for CT/AA combination suggests the existence of an **optimal time gap** between AA and CT.

Perspectives

- The theoretical, *in silico* results have to be **validated** by confrontation with data.
- We are currently performing mice experiments (ANR MEMOREX-PK project)



J. Ciccolini

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

CIRM, Marseille France
March 19-23 , 2012

Organizing committee **:**

A. Benabdallah
S. Benzekry
G. Chapuisat
Y. Dermenjian
F. Hubert
M. Gonzales Burgos

Mini course :

D. Bennequin
H. M.Byrne
J. Ciccolini
A. D'Onofrio
B. Perthame
O. Saut
J. P. Zubelli

Scientific commitee **:**

N. André
D. Barbolosi
N. Bellomo
J. Clairambault
T. Colin
C. Falcoz

- **Special session on medical challenges**
- **All the infos on:** http://www.latp.univ-mrs.fr/mcc
- **Contacts:** mcc@latp.univ-mrs.fr

The Marseille group

Mathematics

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- C. Faivre (UMR MD3)
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- A. Iliadis (UMR MD3)
- H. Marouani (UMR MD3)
- C. Woloch (UMR MD3)

Clinic

- N. André (Oncologie pédiatrique, Timone)
- C. Mercier (Pôle oncologie, Timone)
- J. C. Gentet (Oncologie pédiatrique)

Want to know more?


Barbolosi, D., Verga, F., Benabdallah, A., Hubert, F., Mercier, C., Ciccolini, J. and Faivre, C. *Modélisation du risque d'évolution métastatique chez les patients supposés avoir une maladie localisée*, Oncologie, 2011.


Benzekry, S., Hubert, F., Benabdallah, A., Faivre, C., Ciccolini, J., Andre, N. and Barbolosi, D.*Modelling the impact of anticancer agents on metastatic spreading.*, submitted.


Benzekry, S., Chapuisat, G., Ciccolini, J., Erlinger, A. and Hubert, F.*A new model of coupling cytotoxic and anti-angiogenic drugs in the treatment of cancer*, in preparation.


Benzekry, S. *Mathematical and numerical analysis of the anti-angiogenic therapy in metastatic cancers.* to appear in M2AN, 2011.

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