Modeling and mathematical analysis of metastatic growth under angiogenic control

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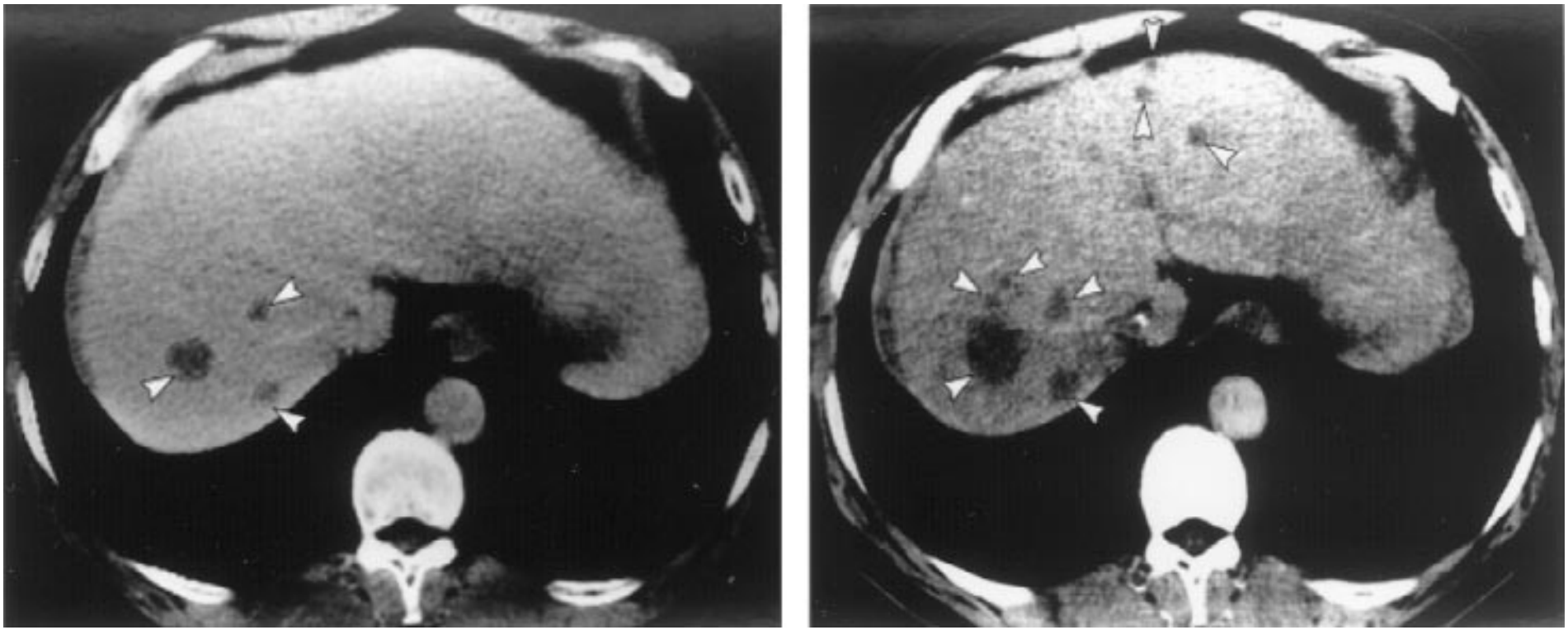
Outline

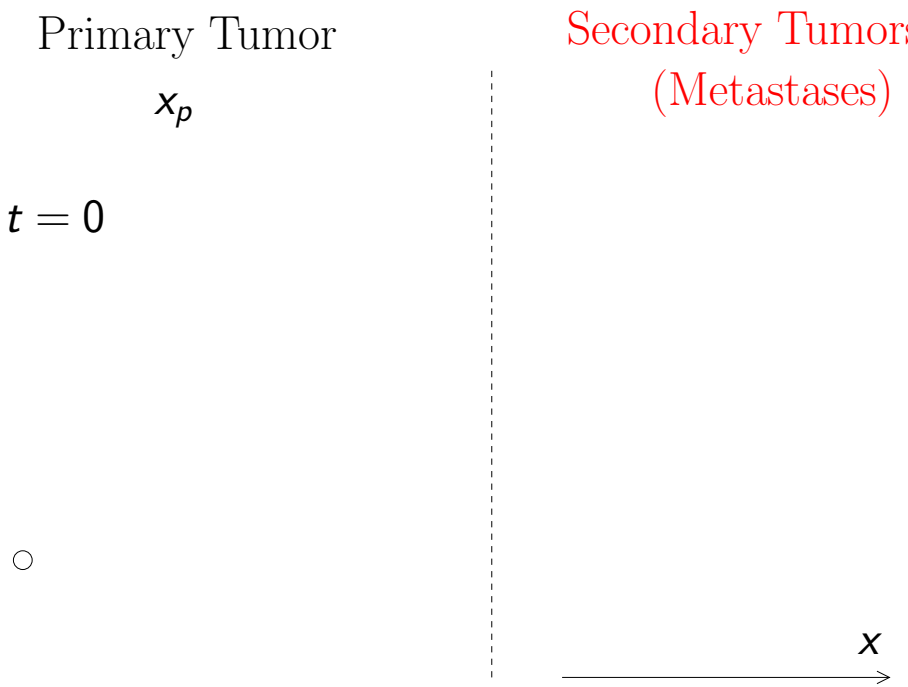
Metastases



Contrast-enhanced X-ray computed tomographies (CT) of the liver with multiple metastatic tumors. Interval : 127 days. Image from **Iwata et al., 2000**

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

Existing model. Iwata et al., 2000. Barbolosi, Benabdallah, Hubert, Verga, 2009.



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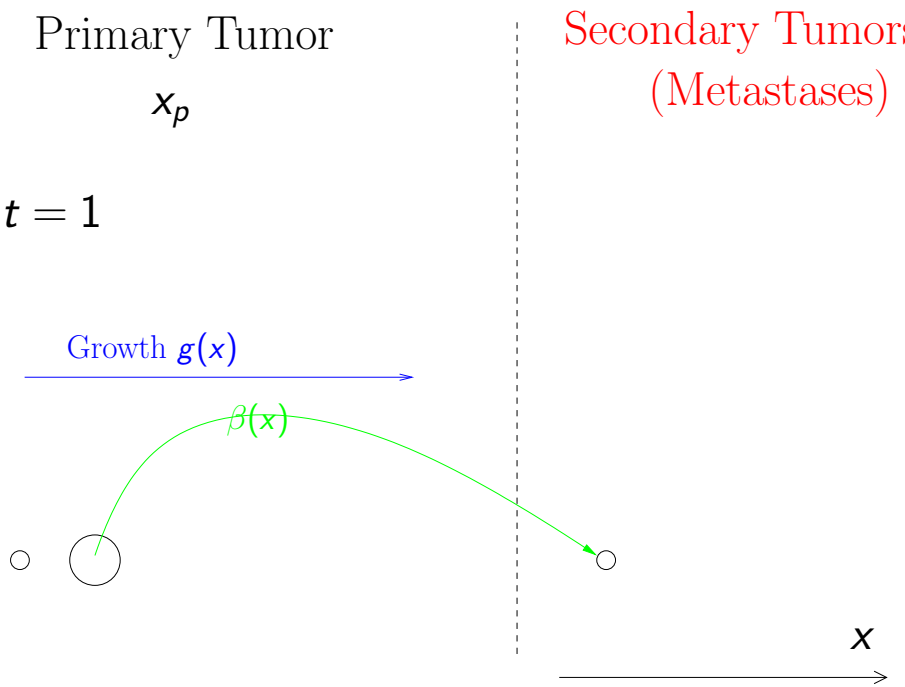

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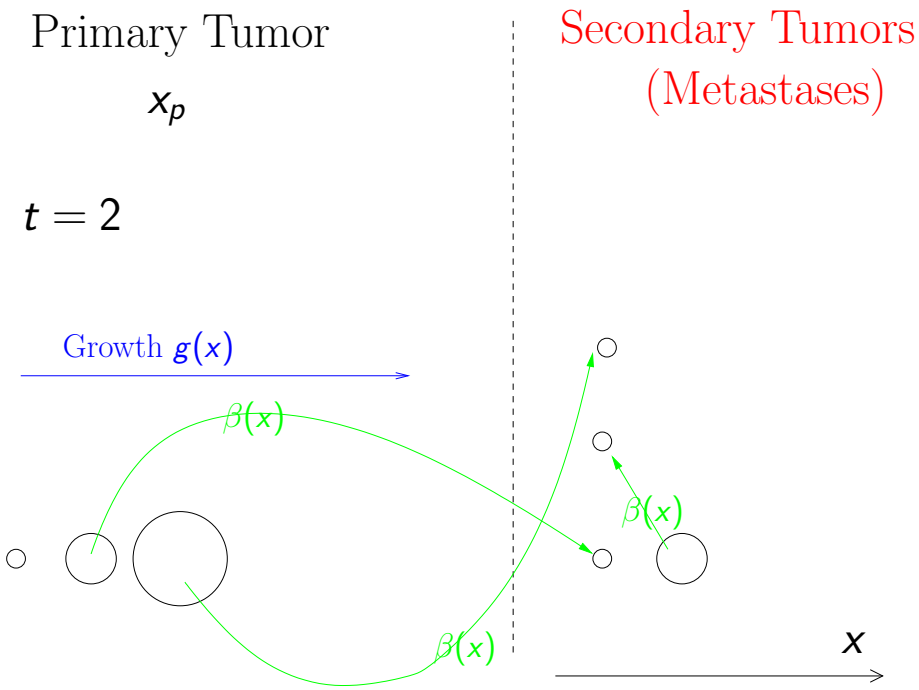

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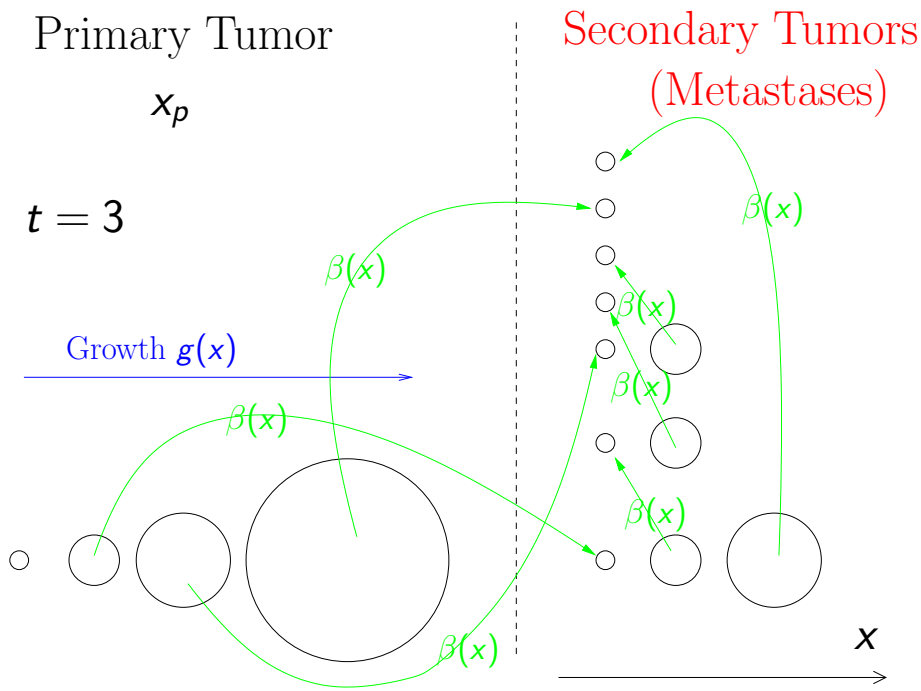
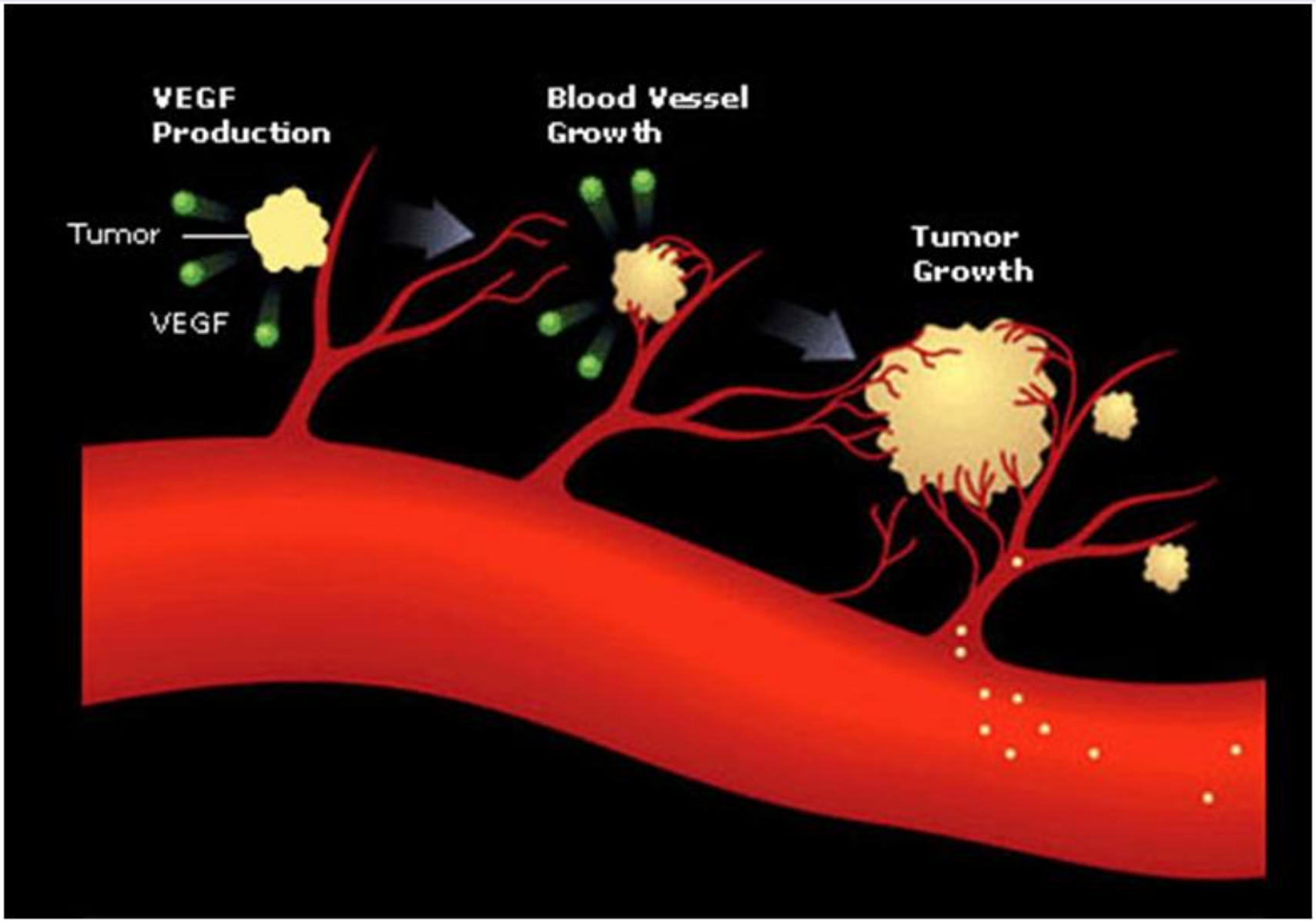


$\rho(t, x) =$ density of metastases of size x at time t.

$$\begin{cases} \partial_t \rho + \partial_x (g\rho) = 0 \\ g(1)\rho(t,1) = \int \beta(x)\rho(t,x)dx + \beta(x_p(t)) \\ \rho(0) = \rho^0 \end{cases}$$

Angiogenesis



Objectives of the model

- Predict the evolution of the number of **metastases**, especially the ones **not visible** with medical imaging (size $\leq 10^8$ cellules), by taking into account the **angiogenic process**.

- Take into account the effect of cytotoxic and **cytostatic** drugs in order to **optimize the temporal administration protocols**.

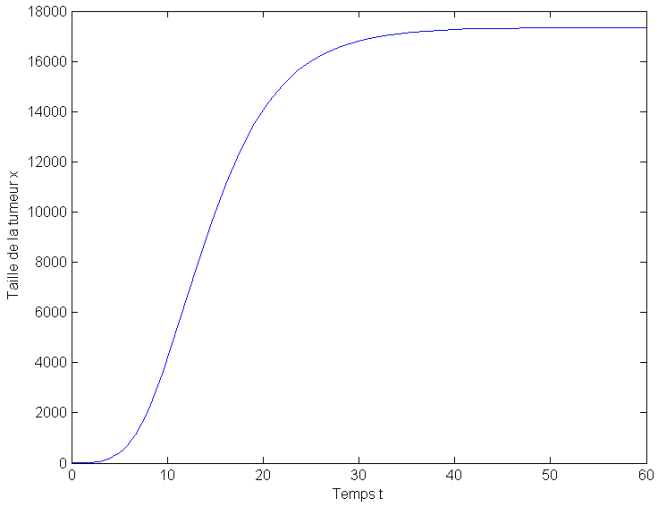
- The model is based on the conjugation of two existing models : **Folkman et al., Cancer research 1999** and **Iwata et al., Journal of theoretical biology 2000**.

ODE model of tumoral growth under angiogenic control

Folkman et al., Cancer Research 1999

Gompertzian growth
$x =$ Size of the tumor

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



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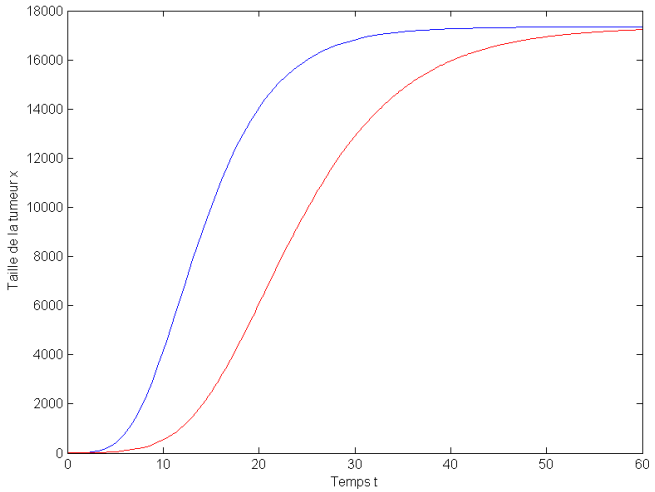
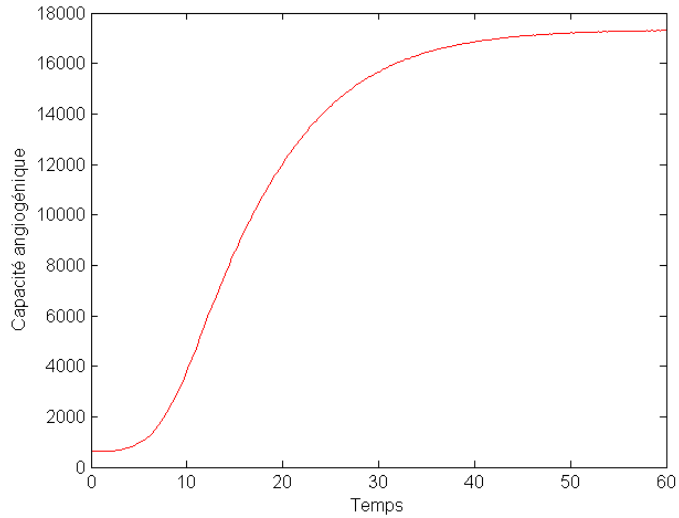


Consider θ as a **variable** :
the angiogenic capacity

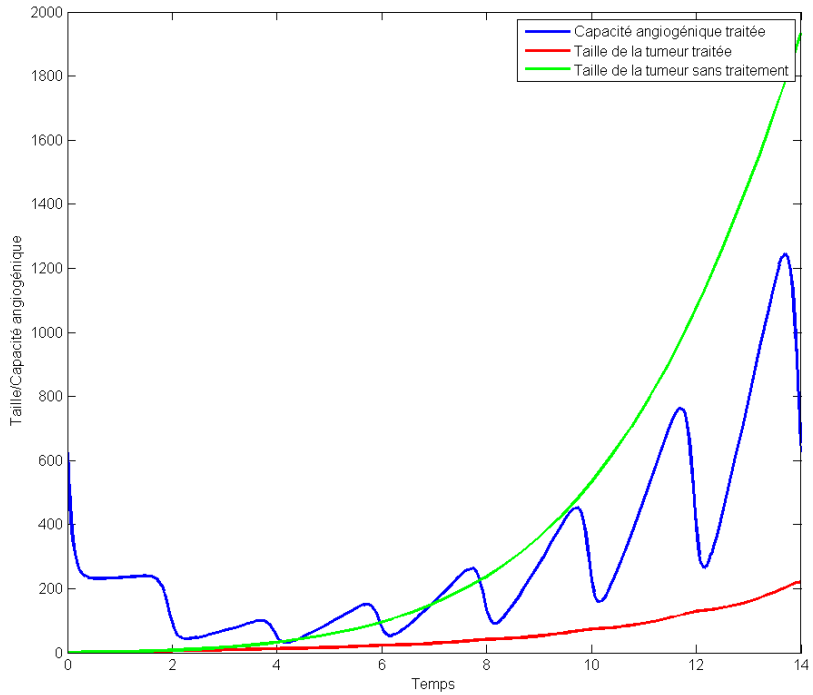
$$\frac{d\theta}{dt} = \underbrace{cx}_{\text{Stimulation by the tumor}} - \underbrace{dx^{\frac{2}{3}}\theta}_{\text{Inhibition}}$$



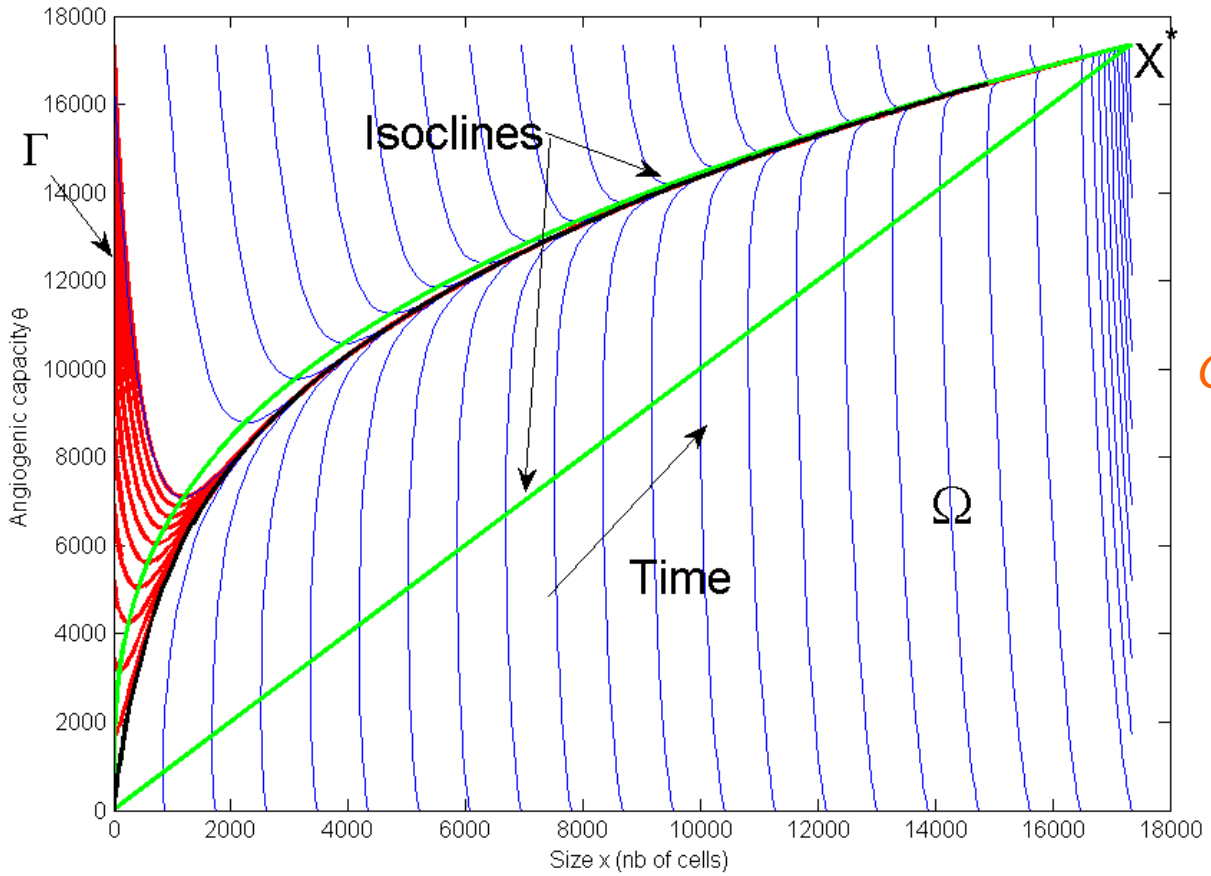
Anti-angiogenic drug.

Interest of this model = take into account for the effect of a **anti-angiogenic drug (mice data).**

$$\frac{d\theta}{dt} = cx - dx^{\frac{2}{3}}\theta - e\gamma(t)\theta$$



Phase plan of the system



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

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

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

Convergence to an equilibrium point $X^* = \left(\left(\frac{c}{d}\right)^{\frac{3}{2}}, \left(\frac{c}{d}\right)^{\frac{3}{2}}\right)$. Studied in **Gandolfi and d'Onofrio et al., 2004**.

Conservation equation for the metastases

Primitive tumor and metastases follow the previous ODE model.
Population of the metastases structured in **size x and angiogenic capacity θ** :
$\rho(t, x, \theta) \in L^1(\Omega)$. Balance law :

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

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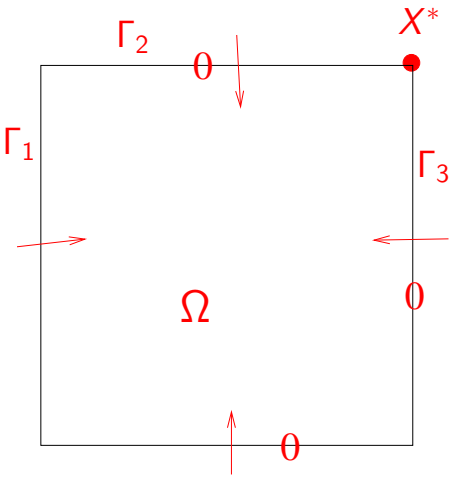
Birth rate of new metastases of parameter σ per meta of size x and angiogenic capacity θ per unit of time :

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



We choose :

$$N(\sigma) = \frac{1}{2\Delta\sigma}\mathbf{1}_{\sigma\in[\sigma_0-\Delta\sigma,\sigma_0+\Delta\sigma]}, \ \beta(x,\theta) = mx^\alpha$$

Two sources of new metastases :

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

Equation

$$\begin{cases} \partial_t \rho + \mathrm{div}(G\rho) = 0 & \text{on }]0,\infty[\times\Omega \\ -G\cdot\vec{\nu}\,\rho(t,\sigma) = N(\sigma)\int_\Omega \beta\rho(t,x,\theta)dxd\theta + f(t,\sigma) & \text{on } \partial\Omega \\ \rho(0) = \rho^0 & \text{on } \Omega \end{cases}$$

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- Linear transport equation in **dimension 2**, with **vanishing velocity field**.

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- Linear transport equation in **dimension 2**, with vanishing velocity field.
- **Nonlocal boundary condition** $+$

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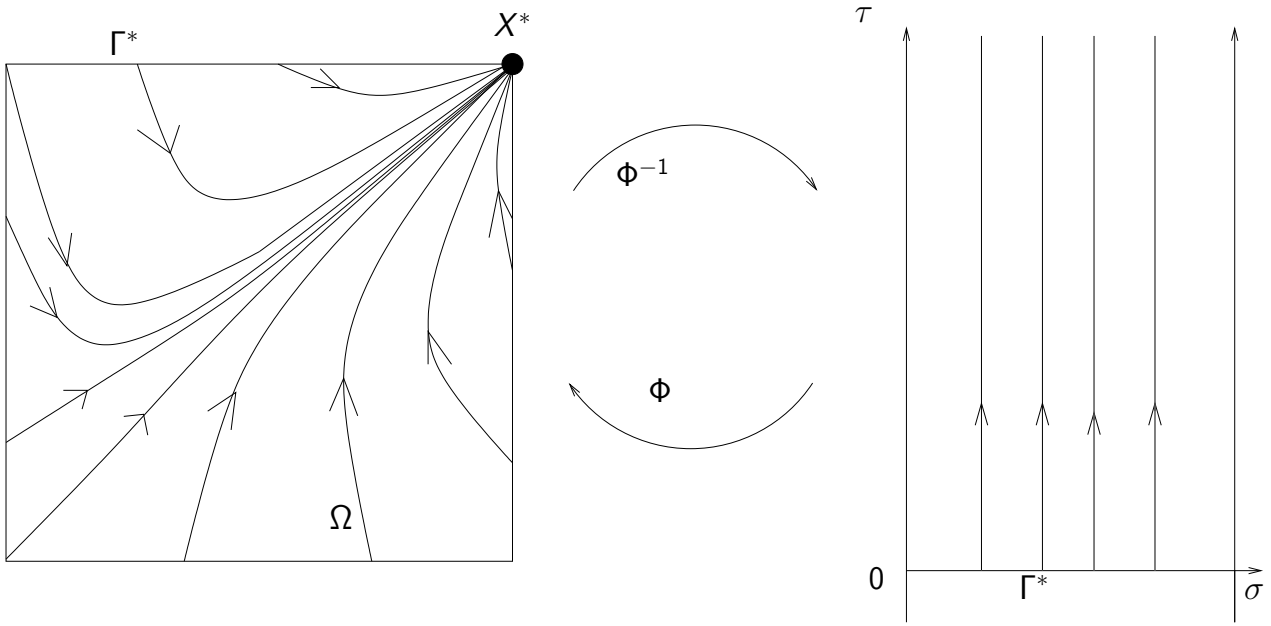
- Linear transport equation in **dimension 2**, with vanishing velocity field.
- Nonlocal boundary condition + **Source term**

Straightening up the characteristics

$$W_{\mathrm{div}}(\Omega) := \left\{ V \in L^1(\Omega) \,|\, \mathrm{div}(GV) \in L^1(\Omega) \right\}$$

- Change of variables :

$$\begin{array}{l} \partial_\tau \Phi = G(\Phi) \\ \Phi(0) = \sigma \end{array} \quad \left| \quad \Phi : \begin{array}{ccc}]0,\infty[\times\partial\Omega^* & \to & \Omega \\ (\tau,\sigma) & \mapsto & \Phi_\tau(\sigma) \end{array} \right. \quad \left| \quad "\partial_\tau V(\Phi_\tau(\sigma)) = G \cdot \nabla V"$$



Φ is a **locally bilipschitz homeomorphism**.

Preliminary result

- The jacobian

$$J_\Phi(\tau,\sigma) = G\cdot\vec{\nu}(\sigma)e^{\int_0^\tau \operatorname{div}(G(\Phi_s(\sigma)))ds}$$

Benzekry, 2009

- From the singularity of G, $J_\Phi^{-1} \notin L^\infty$.

Proposition

The spaces $W_{\mathrm{div}}(\Omega)$ *and* $W^{1,1}((0,+\infty);\ L^1(\partial\Omega))$ *are conjugated via* Φ *:*

$$V \in W_{\mathrm{div}}(\Omega) \Leftrightarrow (V\circ\Phi)|J_\Phi| \in W^{1,1}((0,+\infty)\,;\,L^1(\Gamma)).$$

For $V \in W_{\mathrm{div}}(\Omega)$ *we have*

$$\partial_\tau(V\circ\Phi|J_\Phi|) = (\operatorname{div}(GV)\circ\Phi)|J_\Phi|.$$

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$\Rightarrow$ **Trace**

$$V_{|\partial\Omega}(\sigma) := V\circ\Phi(0,\sigma) \in L^1(\partial\Omega; G\cdot\nu d\sigma)$$

Existence, uniqueness and regularity

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$$D(A) = \left\{ V \in W_{\text{div}};\ -G \cdot \vec{\nu}\, V_{|\Gamma}(\sigma) = N(\sigma) \int_\Omega \beta V \right\}$$

Theorem

- *For* $\rho^0 \in L^1(\Omega)$ *and* $f \in L^1(]0,\infty[\times\Gamma)$, *there is a* **unique weak solution** *and*

$$\rho \in \mathcal{C}([0,\infty[; L^1(\Omega)).$$

- *For* $\rho^0 \in D(A)$ *and* $f \in \mathcal{C}^1([0,\infty[; L^1(\Gamma))$, *with* $f(0) = 0$,

$$\rho \in \mathcal{C}^1([0,\infty[; L^1(\Omega)) \cap \mathcal{C}([0,\infty[; W_{\text{div}}(\Omega))$$

Spectral problem

Find

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$$\begin{cases} (\lambda, V, \Psi) \in \mathbb{R}_+^* \times D(A) \times D(A^*) \\ AV = \lambda V, \quad A^*\Psi = \lambda \Psi \\ \int_\Omega V\Psi dx d\theta = 1, \quad \int_{\partial\Omega} \Psi N = 1, \ \Psi \geq 0 \end{cases}$$

Proposition

Under the assumption $\int_0^\infty \int_{\partial\Omega} \beta(\Phi_\tau(\sigma))N(\sigma)d\tau d\sigma > 1$, *there is a* **unique solution** (λ_0, V, Ψ). *The principal eigenvalue* λ_0 *solves*

$$\int_0^{+\infty} \int_{\partial\Omega} \beta(\Phi_\tau(\sigma))N(\sigma)e^{-\lambda_0\tau} d\tau d\sigma = 1$$

The eigenvectors are given by
$V(\Phi_\tau(\sigma)) = C_{\lambda_0} N(\sigma)e^{-\lambda_0\tau}|J_\Phi|^{-1}, \Psi(\Phi_\tau(\sigma)) = e^{\lambda_0\tau} \int_\tau^\infty \beta(\Phi_s(\sigma))e^{-\lambda_0 s} ds$

Asymptotic behavior

Benzekry, 2009

Theorem

Assume that there exists $\mu > 0$ *such that* $\beta - \mu\Psi \geq 0$. *Then*

$$||\rho(t)e^{-\lambda_0 t} - m(t)V||_{L^1_\Psi} \leq e^{-\mu t}\{||\rho^0 - m_0 V||_{L^1_\Psi} + 2\int_0^t e^{-(\lambda_0-\mu)s}\int_{\partial\Omega}|f|(s,\sigma)\Psi(\sigma)ds\},$$

$$||f||_{L^1_\Psi} = \int_\Omega |f|\Psi$$

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- Convergence with **exponential rate**

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$$m(t) = e^{-\lambda_0 t}\int_\Omega \rho(t)\Psi = \int_\Omega \rho^0\Psi + \int_0^t e^{-\lambda_0 s}\int_{\partial\Omega} f(s,\sigma)\Psi(\sigma)d\sigma ds.$$

- Convergence with exponential rate
- Takes into account the **source term**

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Benzekry, 2009

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- Convergence with exponential rate
- Takes into account the **source term**
- In the applications $\beta(x,\theta) = mx^\alpha \Rightarrow$ **assumption is OK, and** $\Psi \geq m > 0$.
  We also have :

$$\frac{e^{\lambda_0 t} - 1}{b^\alpha} \leq \int_\Omega \rho(t,x,\theta)dxd\theta \leq b^\alpha e^{\lambda_0 t}$$

Discretization of the problem.

- Classical upwind scheme is **not stable**.
- Scheme based on **integration along the characteristics**.
- Problem : high computational cost (2D). How to improve it?

Discretization of the problem.

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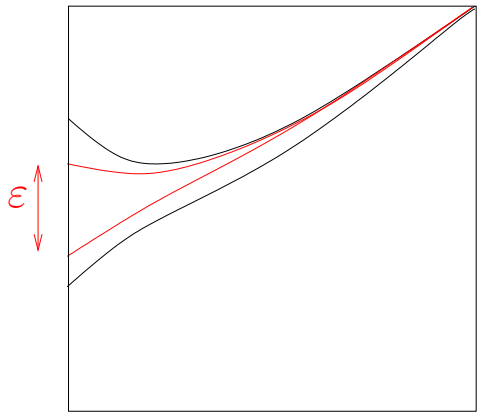
- Scheme based on **integration along the characteristics**.
- Problem : high computational cost (2D). How to improve it?

Idea : assume that new metastases are born with a vasculature very close to a value σ_0.

$$N(\sigma) = N^\varepsilon(\sigma) = \frac{1}{2\varepsilon} = \mathbf{1}_{\sigma\in[\sigma_0-\varepsilon,\,\sigma_0+\varepsilon]} \xrightarrow[\varepsilon\to 0]{} \delta_{\sigma=\sigma_0}$$

$$\begin{cases} \partial_t \rho^\varepsilon + \mathrm{div}(\rho^\varepsilon G) = 0 \\ -G\cdot\nu(\sigma)\rho^\varepsilon(t,\sigma) = N^\varepsilon(\sigma)\left\{\int_\Omega \beta\rho^\varepsilon(t) + f(t)\right\} \\ \rho^\varepsilon(0) = 0 \end{cases}$$



Theorem (Benzekry, 2010)

We have

$$\rho^{\varepsilon}(t) \rightharpoonup d\rho(t) \in \mathcal{C}([0,T];(\mathcal{C}_b)'),$$

with convergence in $\mathcal{C}([0,T];*-(\mathcal{C}_b)')$ *for all* $T>0$. *The expression of* $d\rho(t)$ *is given by :* $\forall \psi \in \mathcal{C}_b(\Omega)$

$$< d\rho(t), \psi >= \int_0^{\infty} \psi(\Phi_\tau(\sigma_0)) n(t,\tau) d\tau$$

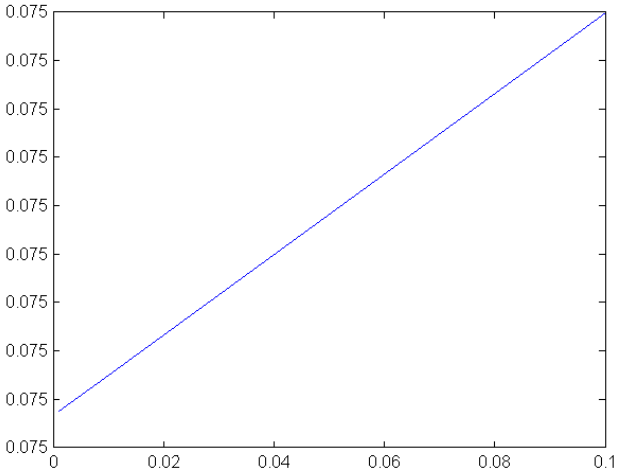
with n solving the 1D problem

$$(E1D) \qquad \left\{ \begin{array}{l} \partial_t n + \partial_\tau n = 0 \\ n(t,0) = \int_0^{\infty} \beta(\Phi_\tau(\sigma_0)) n(t,\tau) + f(t), \quad n(0,\tau) = 0 \end{array} \right. .$$

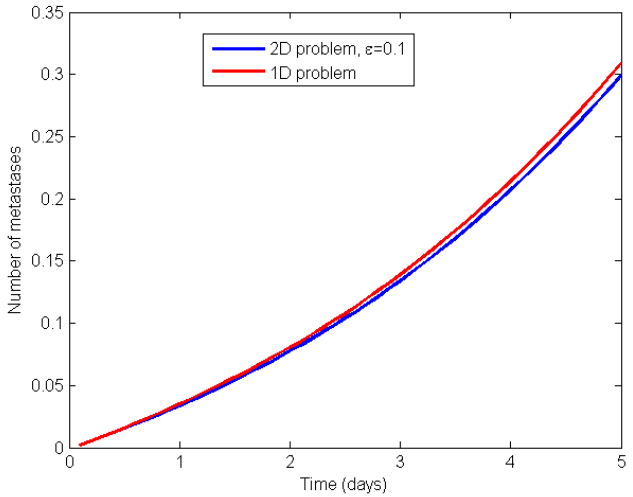
The measure $d\rho(t)$ *solves the following problem :*

$$\left\{ \begin{array}{c} \partial_t d\rho + \mathrm{div}(d\rho G) = 0 \\ -G \cdot \nu(\sigma) d\rho(t,\sigma) = \delta_{\sigma=\sigma_0} \left\{ \int_\Omega \beta d\rho(t) + f(t) \right\}, \quad d\rho(0) = 0 \end{array} \right. .$$

Numerical illustration



Relative difference between the 1D problem and the 2D one VS ε.



Comparison between the 2D problem with $\varepsilon = 0.1$ and the 1D problem.

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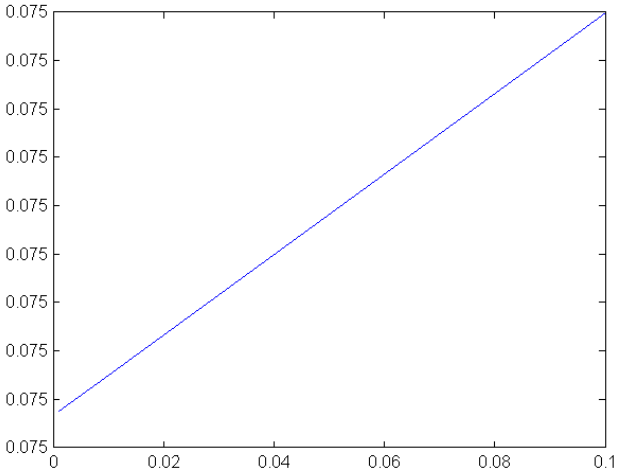
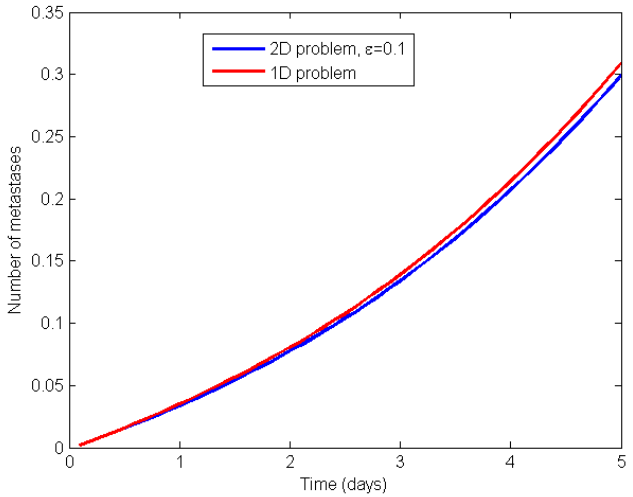


Relative difference between the 1D problem and the 2D one VS ε.



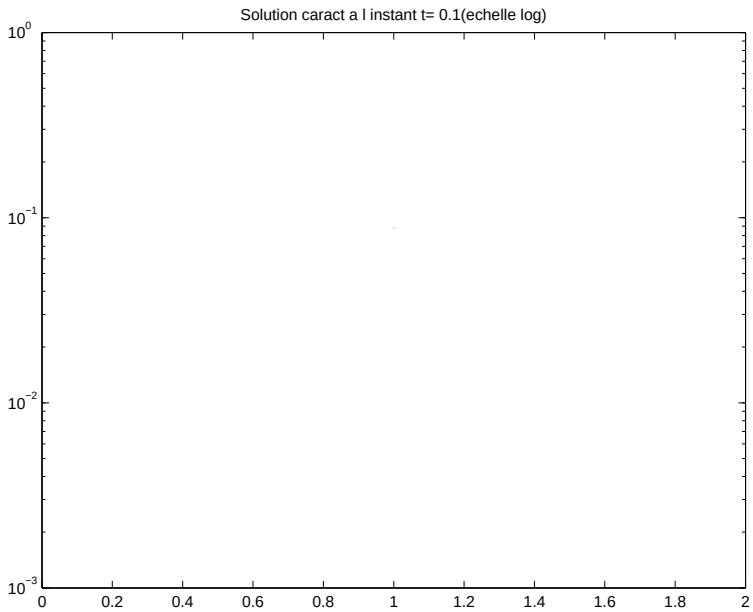
Comparison between the 2D problem with $\varepsilon = 0.1$ and the 1D problem.

$\Rightarrow$ Improvement of the computational time :

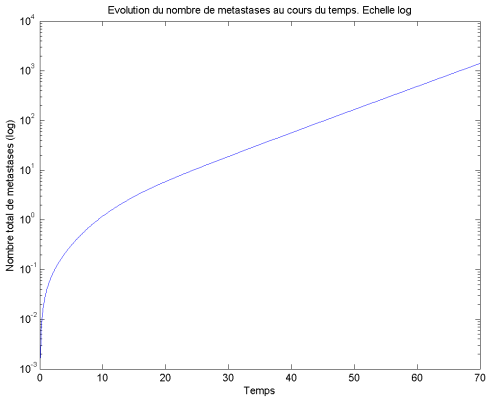
	2D	1D
$T = 5,\ dt = 0.1$	5.8	4.7
$T = 5,\ dt = 0.01$	333	35
$T = 20,\ dt = 0.01$	5331	519

Computation times in seconds on a personal computer.

Time evolution of the density



Asymptotic behavior



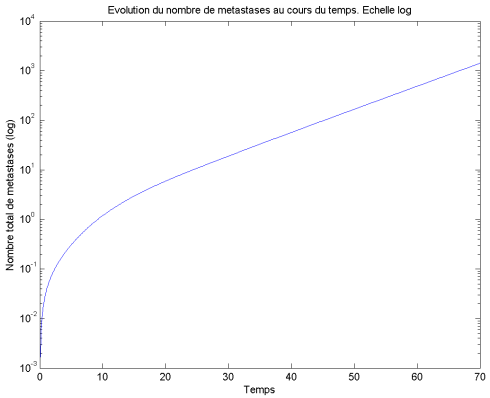
Number of metastases (log scale).

$$\lambda_0 = 0.10682$$

Spectral equation :

$$\int_0^\infty \int_{\partial\Omega} \beta(\Phi_\tau(\sigma)) e^{-\lambda_0 \tau} = 0.9909$$

Asymptotic behavior



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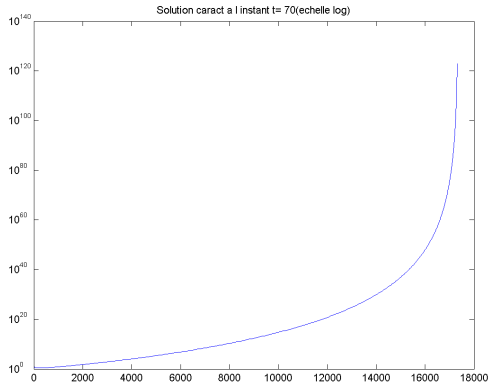
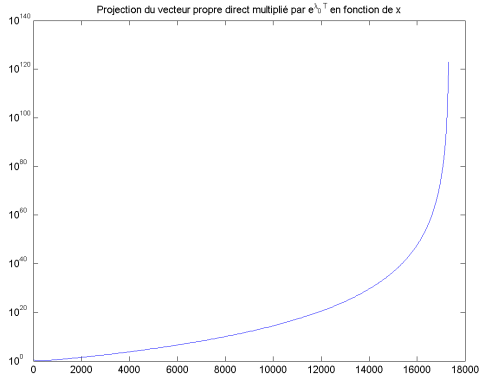
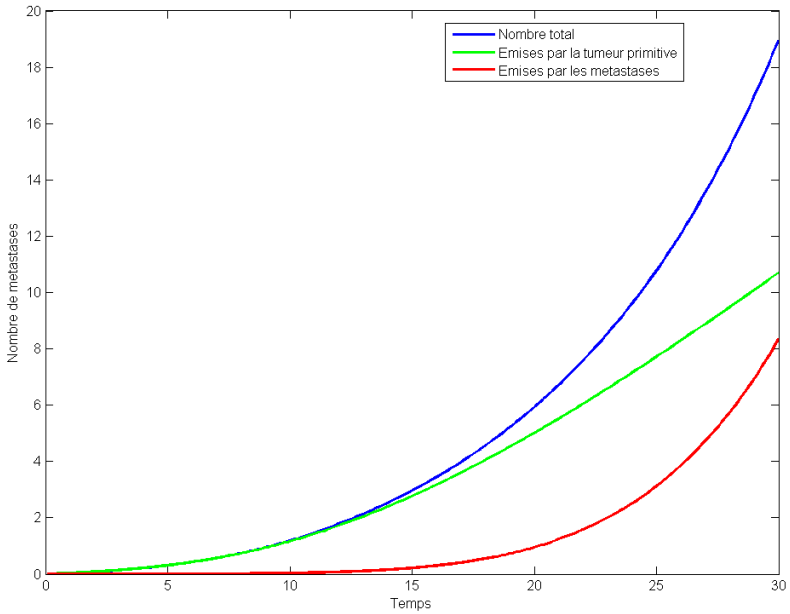


Asymptotic distribution of the density (projection in x).

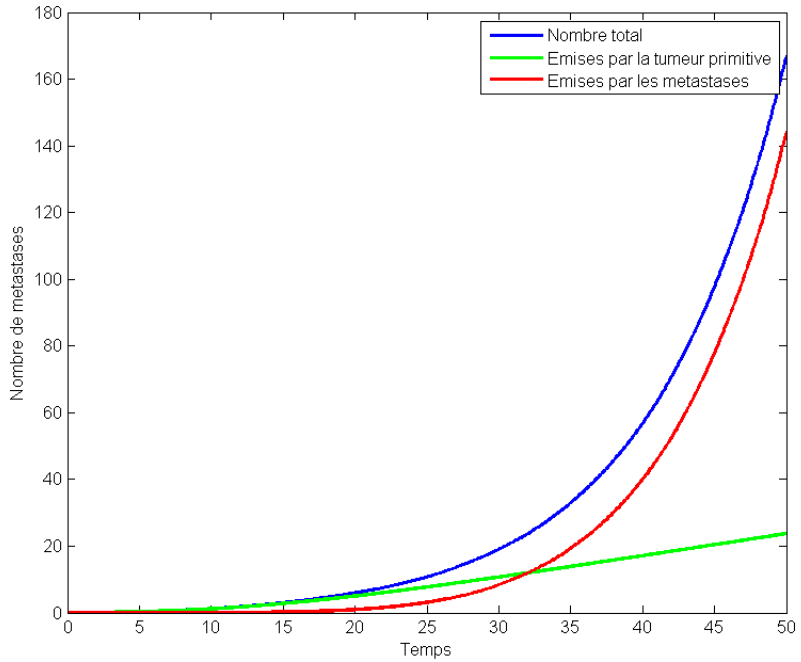


Direct eigenvector times $e^{\lambda_0 T}$ (projection in x).

Without treatment. Primary tumor VS Metastases.

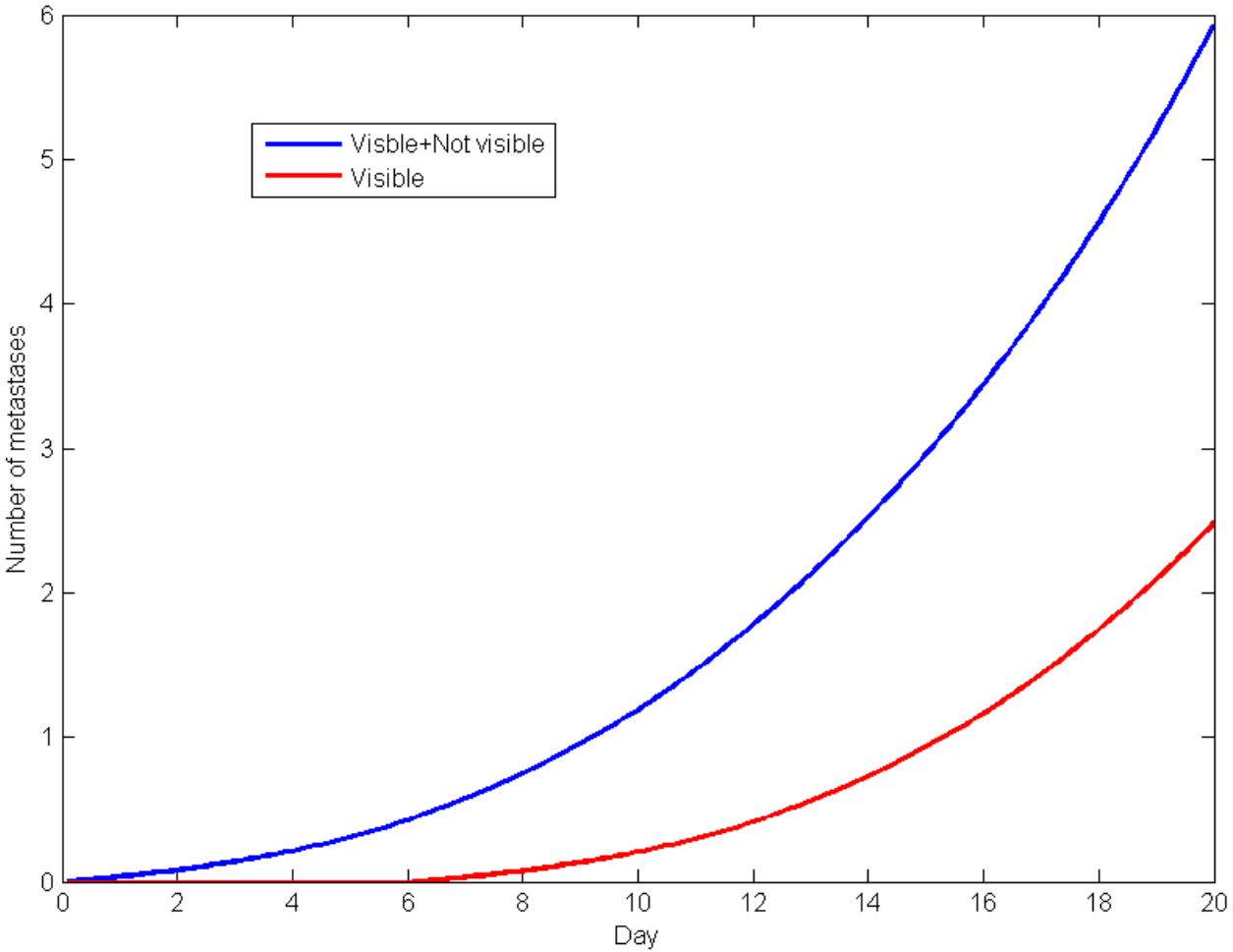


Number of metastases until time $T = 30$ days.



Number of metastases until time $T = 50$ days

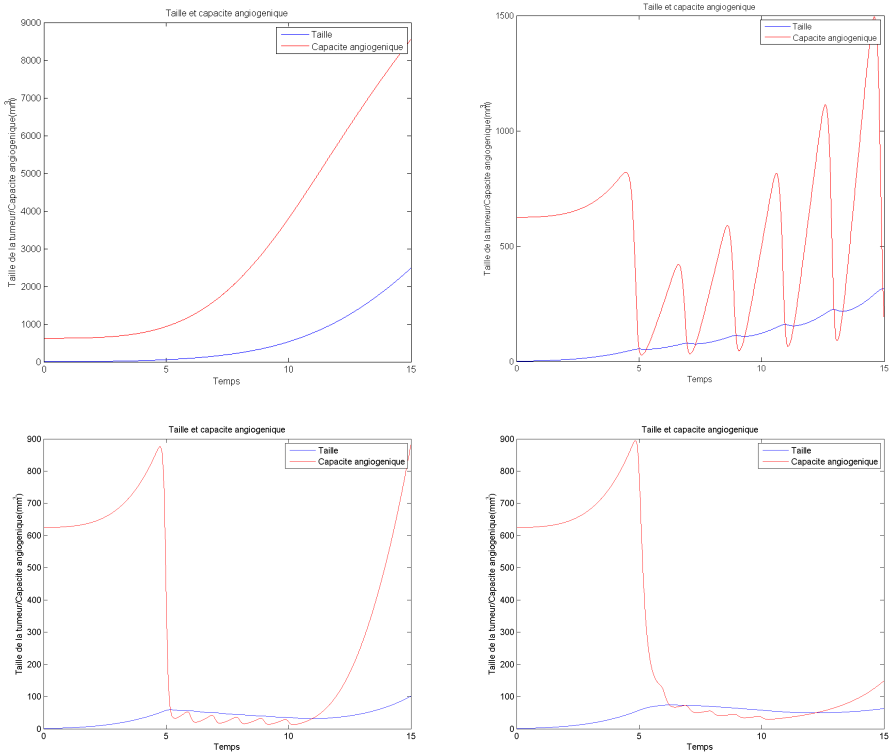
Without treatment. Visible VS not visible.



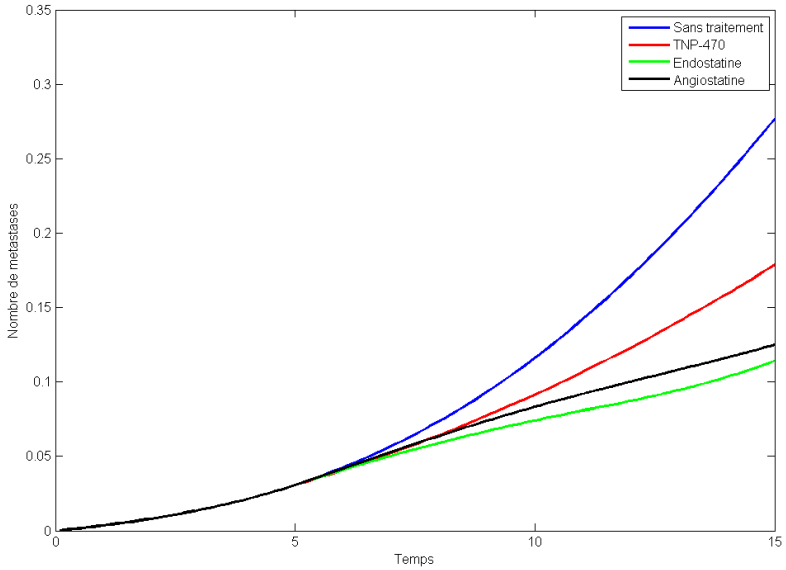
With anti-angiogenic treatment

$$G_2(t,x,\theta) = cx - d\theta x^{\frac{2}{3}} - e\gamma(t)$$

Testing various drugs :



Primary tumor growth



Metastatic evolution

Conclusion and perspectives

- Construction of a **simple model** (5 parameters) for the metastatic process.
- Theoretical study of the equation.
- Efficient numerical scheme.

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Perspectives :

- **Validation** of the model by comparison with mice experiments.
- Use the model to test *in silico* various **administration protocols** for the drugs. Combination of cytotoxic/anti-angiogenic drugs. Integrate more complex PK's, interface model and toxicities control.
- Address and solve the **inverse problem**. Parameters identification.

Thank you for your attention!

Weak solutions

Definition

For $\rho^0 \in L^1(\Omega)$ and $f \in L^1(]0,\infty[\times\partial\Omega)$, a **weak solution** *of the equation is a function $\rho \in \mathcal{C}([0,\infty[; L^1(\Omega))$ such that : for all $T > 0$ and all $\psi \in \mathcal{C}^1_c([0,T[\times\overline{\Omega}^*)$*

$$\int_0^T \int_\Omega \rho[\partial_t\psi + G\cdot\nabla\psi] + \int_\Omega \rho^0(\cdot)\psi(0,\cdot) - \int_\Omega \rho(T,\cdot)\psi(T,\cdot)$$
$$- \int_0^T \int_{\partial\Omega} N(\sigma) \int_\Omega \beta(x,\theta)\rho(t,x,\theta)dxd\theta\psi(t,\sigma)d\sigma dt = 0$$

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- For regular solutions define the **domain** of the operator $A : V \mapsto -\mathrm{div}(GV)$:

$$D(A) = \left\{ V \in W_{\mathrm{div}};\ -G\cdot\vec{\nu}\, V_{|\partial\Omega}(\sigma) = N(\sigma)\int_\Omega \beta V \right\}$$

- Assumptions on the data

$$\beta \in L^\infty,\ \beta \geq 0\ pp,\ N \in Lip_c(\partial\Omega^*),\ N \geq 0,\ \int_{\partial\Omega} N = 1$$