

A model of metastatic growth under angiogenic control.

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Outline

1 Modeling

- Introduction
- ODE model of tumoral growth under angiogenic control (Folkman, 1999)
- PDE model for the metastasis density

2 Theoretical results

- Existence, uniqueness, regularity and asymptotic behavior.
- Numerical scheme
- Limit 2D-1D

3 Simulations

1 Modeling

● Introduction

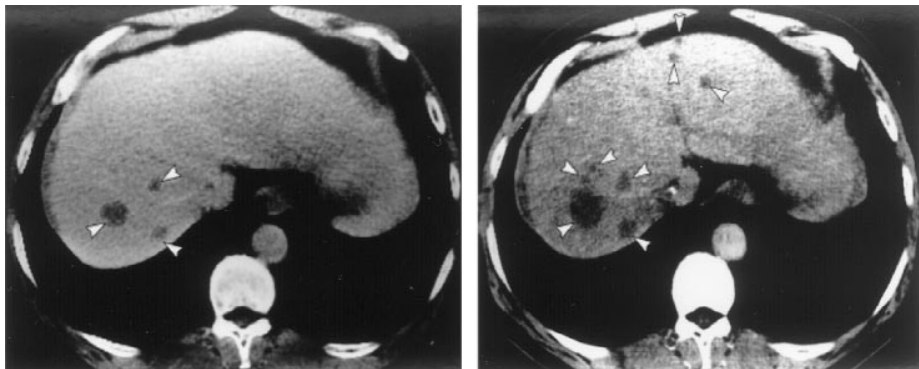
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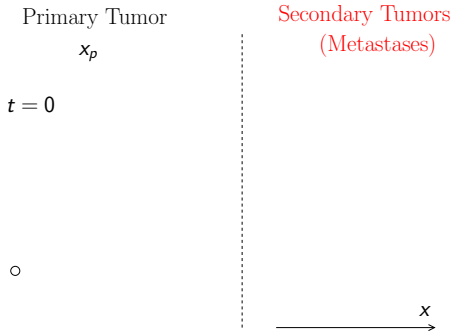
Metastases



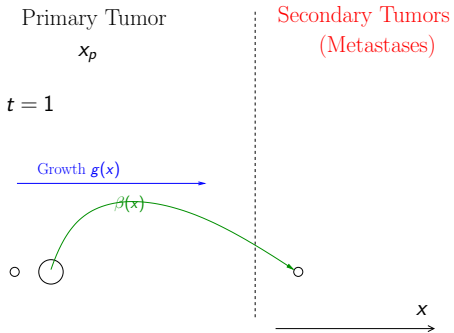
Contrast-enhanced X-ray computed tomographies (CT) of the liver with multiple metastatic tumors. Interval : 127 days. Image from [Iwata et al., 2000](#)

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

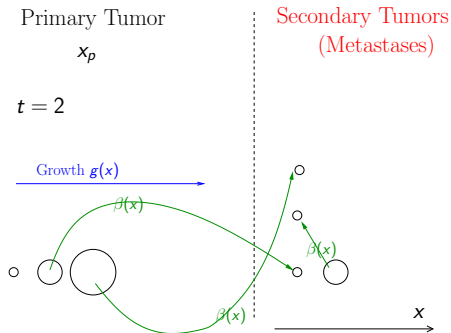
Existing model. Iwata et al., 2000. Barbolosi, Benabdallah, Hubert, Verga, 2009.



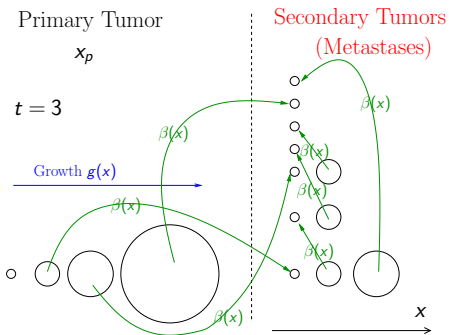
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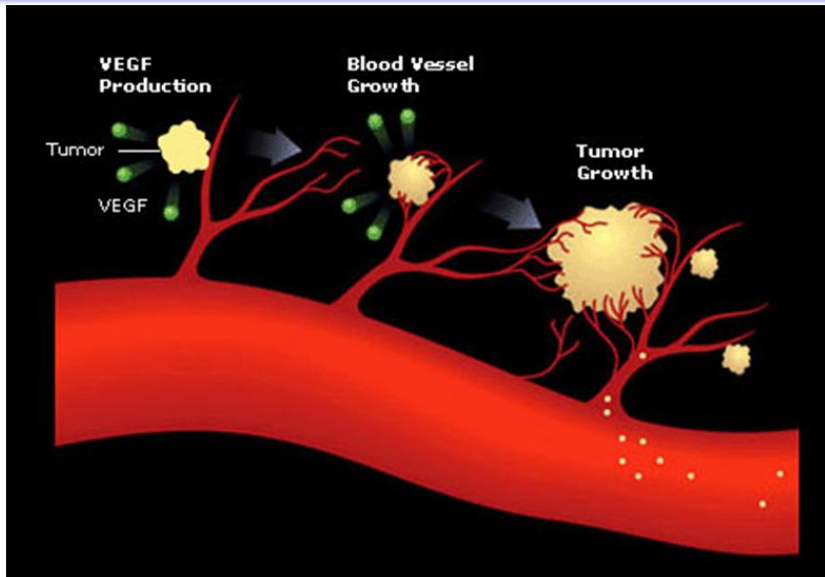
Existing model. Iwata et al., 2000. Barbolosi, Benabdallah, Hubert, Verga, 2009.



$\rho(t, x)$ = 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 $\leq 10^8$ cells), 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**.

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ODE model of tumoral growth under angiogenic control (Folkman, 1999)

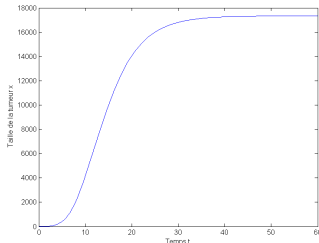
ODE model of tumoral growth under angiogenic control

Folkman et al., *Cancer Research* 1999

Gompertzian growth

x = Size of the tumor

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



ODE model of tumoral growth under angiogenic control (Folkman, 1999)

ODE model of tumoral growth under angiogenic control

Folkman et al., Cancer Research 1999

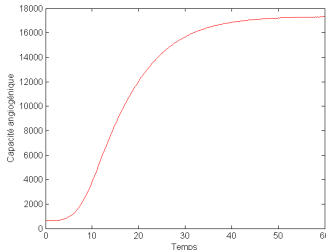
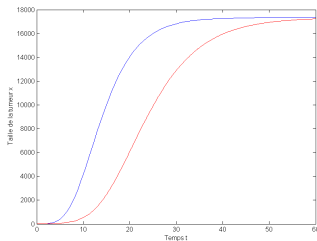
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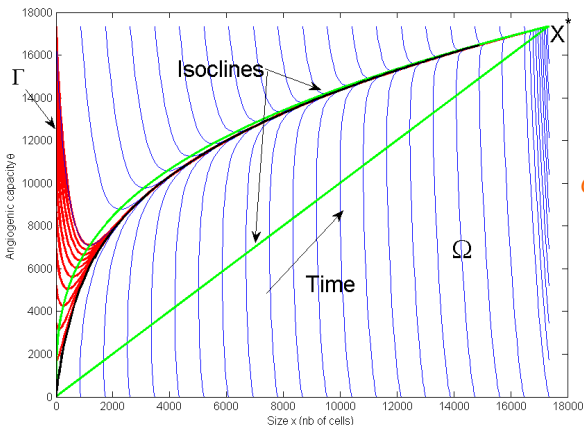
$$\frac{dx}{dt} = ax \ln\left(\frac{\theta}{x}\right)$$

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

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



Phase plan of the system



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

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

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

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 **d'Onofrio Gandolfi, 2004**.

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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 :

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

Equation for the metastases

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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 :

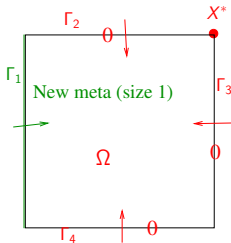
$$B(\sigma, x, \theta) = N(\sigma)\beta(x, \theta), \quad \sigma \in \partial\Omega$$

We choose :

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

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 : $N(\sigma) \int_{\Omega} \beta(x, \theta) \rho(t, x, \theta) dx d\theta$



Equation

$$\begin{cases} \partial_t \rho + \operatorname{div}(G\rho) = 0 & \Omega \\ -G \cdot \vec{\nu} \rho(t, \sigma) = N(\sigma) \int_{\Omega} \beta \rho(t, x, \theta) dx d\theta + f(t, \sigma) & \partial\Omega \\ \rho(0) = \rho^0 & \Omega \end{cases}$$

Equation

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

Equation

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

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Existence, uniqueness and regularity

Benzekry, 2009

$$W_{\text{div}}(\Omega) := \{V \in L^1(\Omega) \mid \text{div}(GV) \in L^1(\Omega)\}$$

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

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 $f(0) = 0$,

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

Asymptotic behavior

Benzekry, 2009

Theorem

Let $(\lambda_0, V, \Psi) \in \mathbb{R}^+ \times D(A) \times D(A^*)$ solving $AV = \lambda_0 V$, $A^*\Psi = \lambda_0$ (+ normalization conditions). Then,

$$\int_{\Omega} |\rho(t, x, \theta) - m(t)V(x, \theta)| \Psi(x, \theta) dx d\theta \xrightarrow[t \rightarrow +\infty]{} 0$$

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

- We also have :

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

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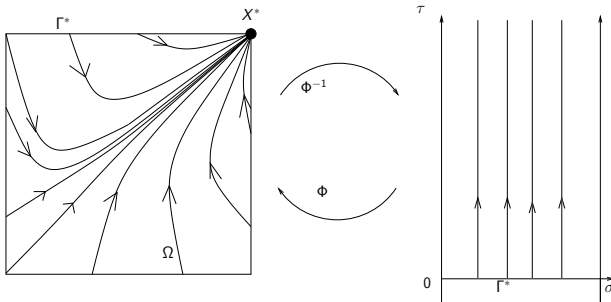
- Existence, uniqueness, regularity and asymptotic behavior.
- **Numerical scheme**
- Limit 2D-1D

3 Simulations

Straightening up the characteristics.

- Classical upwind scheme is **not stable**.
- Scheme based on **integration along the characteristics**.
- Change of variables :

$$\begin{array}{l} \partial_\tau \Phi = G(\Phi) \\ \Phi(0) = \sigma \end{array} \quad \left| \quad \begin{array}{l} \Phi :]0, \infty[\times \Gamma^* \rightarrow \Omega \\ (\tau, \sigma) \mapsto \Phi_\tau(\sigma) \end{array} \right.$$



Scheme

Benzekry, 2010

At the continuous level :

$$J(\tau, \sigma) := \text{Jac}(\Phi) = -G \cdot \vec{\nu}(\sigma) e^{\int_0^\tau \text{div}(G(\Phi_s(\sigma))) ds}$$

$$\begin{aligned} \bar{\rho}(t, \tau, \sigma) := \rho(t, \Phi_\tau(\sigma)) &\Rightarrow \partial_t(\bar{\rho}J) + \partial_\tau(\bar{\rho}J) = 0 \\ &\Rightarrow (\bar{\rho}J)(t + s, \tau + s, \sigma) = (\bar{\rho}J)(t, \tau, \sigma) \end{aligned}$$

Scheme

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$$J_h(i, j) \simeq J(\tau_i, \sigma_j), \quad \rho_h^k(i, j) \simeq \bar{\rho}(t_k, \tau_i, \sigma_j)$$

$$\left\{ \begin{array}{l} \rho^0(i, j) = 0, \quad \forall i, j \\ \rho_h^{k+1}(i+1, j) = \rho_h^k(i, j) \frac{J_h(i, j)}{J_h(i+1, j)}, \quad \forall j, 1 \leq i \leq k \\ \rho_h^{k+1}(1, j) = \frac{N(\sigma_j)}{-G(t, \sigma_j) \cdot \vec{\nu}(\sigma_j)} \{ \mathcal{T}_{q_2}(k+1, \beta_h^{k+1} \rho_h^{k+1}) + \beta_h^{k+1}(k+1, j_0) \}, \quad \forall j \end{array} \right.$$

with

$$\mathcal{T}_{q_2}(k, \beta^k, \rho^k) := \sum_{i, j} \beta(\Phi_{\tau_i}(\sigma_j)) \rho^k(i, j) J_h(i, j) \simeq \int_{\Omega} \beta(x, \theta) \rho(t_k, x, \theta) dx d\theta$$

Error estimate

Benzekry, 2010

Piecewise constant functions on $V(i, j) := \{\Phi_\tau(\sigma); \tau_i \leq \tau \leq \tau_{i+1}, \sigma_j \leq \sigma \leq \sigma_{j+1}\}$

$$\rho_\tau^k(X) = \rho_h^k(i, j), \mathbb{P}\rho(t_k, \cdot) = \rho(t_k, \Phi_{\tau_i}(\sigma_j)) \text{ if } X \in V(i, j).$$

$$\|\varepsilon^k\|_1 := \|\rho_\tau^k - \mathbb{P}\rho(t_k)\|_{L^1}$$

- Numerical resolution of the ODE system of order α_c
- Quadrature method for the 1D integral in J of order α_1

Theorem

We assume that $\alpha_c, \alpha_1 \geq 2$, $\rho \in \mathcal{C}^1(\Omega_{t_k})$ and $\beta \in \mathcal{C}^1(\Omega)$. Then there exists a constant C such that for δt and $\delta\sigma$ small enough

$$\|\varepsilon^k\|_1 \leq C(\delta t + \delta\sigma)$$

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Limit 2D-1D

- Problem : high computational cost (2D). **How to improve it?**

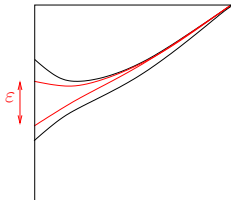
Limit 2D-1D

- 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 .

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

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



Theorem (Benzekry, 2010)

We have

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

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

$$\langle d\rho(t), \psi \rangle = \int_0^\infty \psi(\Phi_\tau(\sigma_0)) n(t, \tau) d\tau$$

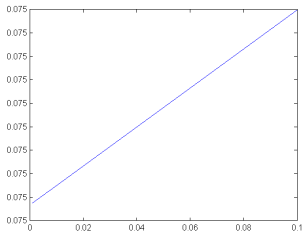
with n solving the 1D problem

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

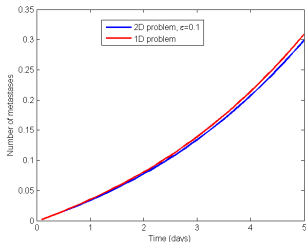
The measure $d\rho(t)$ solves the following problem :

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

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.

⇒ 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.

1 Modeling

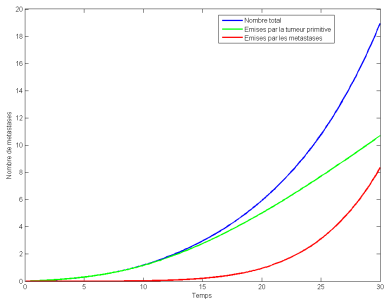
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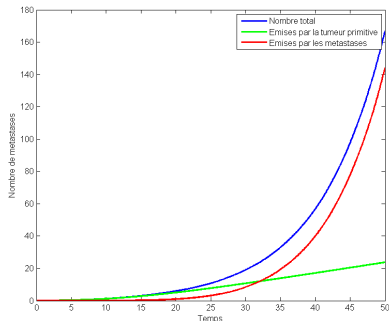
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Without treatment. Primary tumor VS Metastases.

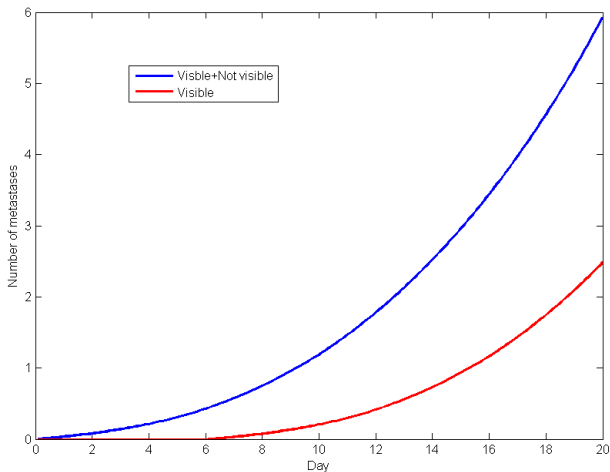


Number of metastases until time $T = 30$ days.



Number of metastases until time $T = 50$ days

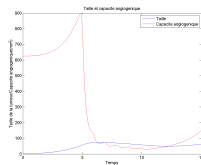
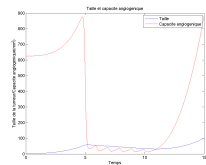
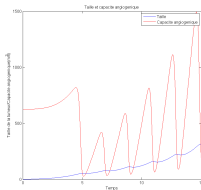
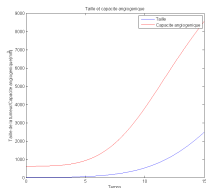
Without treatment. Visible VS not visible.



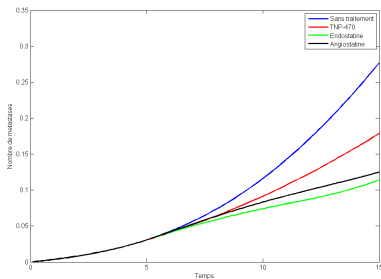
With anti-angiogenic treatment

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

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 $\psi \in \mathcal{C}_c^1([0, T[\times \overline{\Omega}^*)$

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

Weak solutions

Definition

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

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

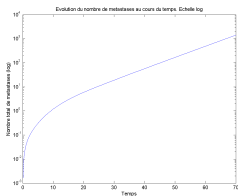
$$D(A) = \left\{ V \in W_{\operatorname{div}}; -G \cdot \vec{\nu} V|_{\partial\Omega}(\sigma) = N(\sigma) \int_{\Omega} \beta V \right\}$$

- Assumptions on the data

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

Time evolution of the density

Numerical illustration of the asymptotic behavior



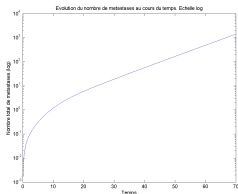
Number of metastases (log scale).

$$\lambda_0 = 0.10682$$

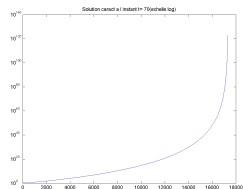
Spectral equation :

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

Numerical illustration of the asymptotic behavior



Number of metastases (log scale).

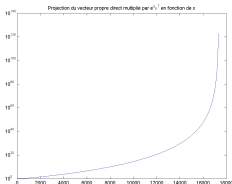


Asymptotic distribution of the density
(projection in x).

$$\lambda_0 = 0.10682$$

Spectral equation :

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



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

Spectral problem

Find

Benzekry, 2009

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

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

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