Modeling and mathematical analysis of metastatic growth under angiogenic control

Sébastien Benzekry

LATP, University of Provence.
Pharmacokinetic Laboratory UMR MD3.
Marseille

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Outline

1. Modeling
   - Cancer
   - EDO model of tumoral growth under angiogenic control (Folkman, 1999)
   - PDE model for the metastasis density
2. Analysis
   - A preliminary result
   - Existence, uniqueness and regularity
   - Qualitative behavior
3. Numerical simulations

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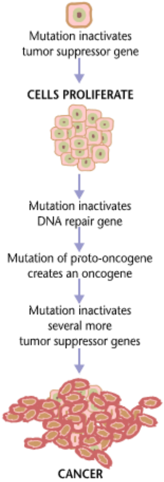
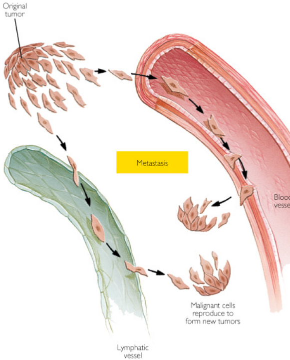
Cancer

Definition

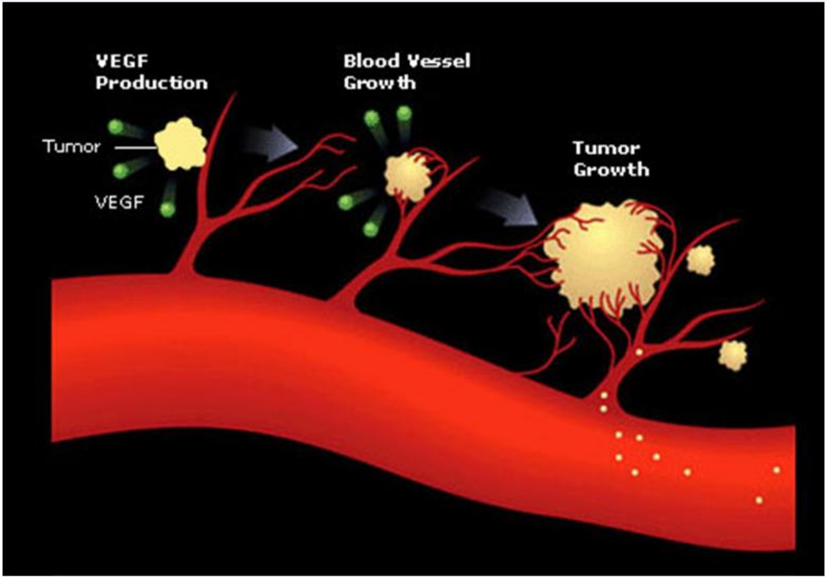
The cancer is a disease characterized by a group of cells, the **primitive tumor**, *showing abnormal* **cellular proliferation**. *All the cells derive from a same cell which underwent various genetic mutations. During the evolution of the disease, some groups of cells can detach and spread to form* **metastases**.

- First cause of mortality in France
- Relatively badly treated : 52% of 5 years survival all cancers taken together





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**.

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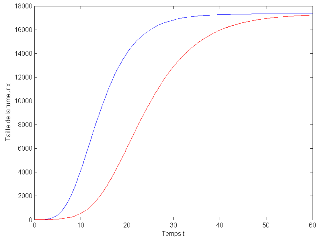
EDO model of tumoral growth under angiogenic control

Folkman et al., Cancer Research 1999

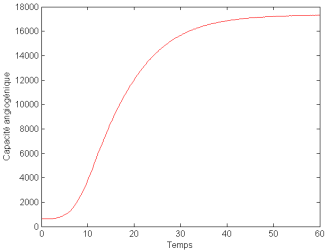
Gompertzian growth
x = Size of the tumor

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

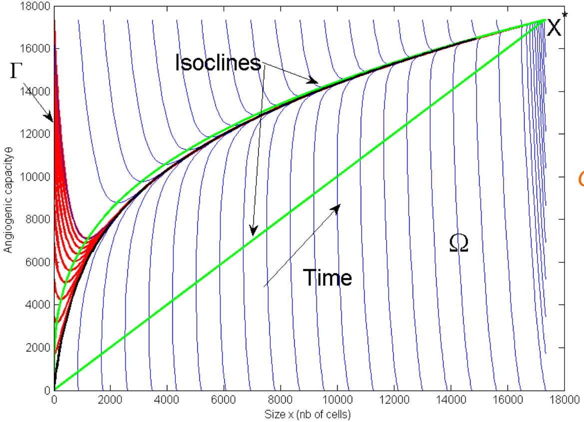


Consider θ as a **variable** :
the angiogenic capacity

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



Phase plan of the system



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

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

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

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**.

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Conservation equation for the metastases

Primitive tumor and metastases follow the model **Folkman**.
Population of the metastases structured in size x and angiogenic capacity θ :
density $\rho \in L^1(\Omega)$. Conservation of the number of metastases $\Rightarrow \rho$ is transported by G

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

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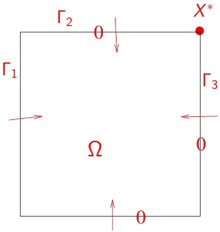
Birth rate of new metastases of parameter σ per meta of size x and angiogenic capacity θ per unit of time :

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



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

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

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

Equation

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- **Nonlocal boundary condition** +

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- Linear transport equation in **dimension 2**, with vanishing velocity field.
- Nonlocal boundary condition + Source term
- Existing 1D model structured only in size : **Iwata et al., 2000. Benabdallah, Barbolosi, Hubert and Verga 2009**.

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State of the art. Structured populations dynamics.

$$\begin{cases} \partial_t \rho + \mathrm{div}(F(t,X,\rho)) = -\mu(t,X,\rho) & \Omega \\ -G\cdot\nu\rho(t,\sigma) = \mathcal{B}(t,\sigma,\rho) & \sigma\in\partial\Omega \ s.t. \ G\cdot\nu(\sigma)<0 \\ \rho(0,X) = \rho^0(X) & \Omega \end{cases}.$$

- Introduction of such equations : **Sharpe-Lotka, 1911** et **McKendrick, 1926**.
- In a lot of cases, age structure ⇒ **dimension 1** :

$$X = a \in \mathbb{R}, \; F(t,a,\rho) = \rho$$

- Principally three approaches :

Integral equations.	Semigroups.	General relative entropy.
Ianelli, 1994	**Diekmann-Metz, 1986**	**Perthame, 2007**

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- Principally three approaches :

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- Here, **dimension 2 and source term**

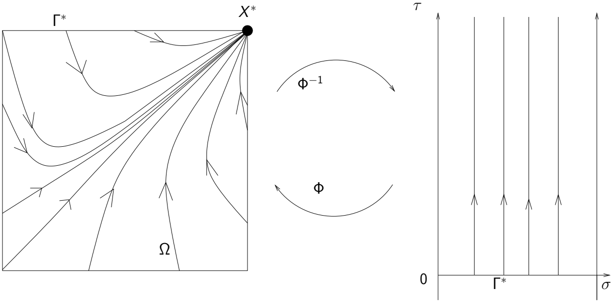
$$F(t,X,\rho) = G\rho, \quad \mu = 0, \quad \mathcal{B}(t,\sigma,\rho) = N(\sigma)\int_\Omega \beta\rho(t)dxd\theta + f(t,\sigma)$$

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 :

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



Φ is a **locally bilipschitz homeomorphism**.

Preliminary result

- The jacobian **Benzekry, 2009**

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

- 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*

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

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

$\Rightarrow$ **Trace**

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

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

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

Existence, uniqueness and regularity

Benzekry, 2009

Theorem

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

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

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

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

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

Proof :

$$\rho = \underbrace{e^{tA}\rho^0}_{\text{semigroup}} + \underbrace{\mathcal{T}f}_{\text{fixed point}}$$

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Classical theory. Age structure **Perthame**

For the equation

$$\begin{cases} \partial_t \rho + \partial_a \rho = 0 \\ \rho(t, a=0) = \int \beta(\cdot)\rho(t,\cdot) \\ \rho(0,\cdot) = \rho^0 \end{cases}$$

Classical theory. Age structure Perthame

For the equation

$$\begin{cases} \partial_t \rho + \partial_a \rho = 0 \\ \rho(t, a=0) = \int \beta(\cdot)\rho(t,\cdot) \\ \rho(0,\cdot) = \rho^0 \end{cases}$$

- The **growth** of the system is governed by the **principal eigenvalue** λ_0, the **Malthus parameter**.
- The **direct eigenvector** V gives the asymptotic age distribution.

$$\rho(t,\cdot) \underset{+\infty}{\sim} e^{\lambda_0 t} m_0 V$$

- The convergence is controlled by the **adjoint eigenvector** Ψ.

$$\int \left| e^{-\lambda_0 t}\rho(t,a) - m_0 V(a) \right| \Psi(a) da \to 0,$$

where $m_0 = \int \rho^0(a) da$.

Spectral problem

Find **Benzekry, 2009**

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

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

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

Qualitative properties

Benzekry, 2009

Proposition

For weak solutions and all $t \geq 0$

(i)

$$\int_\Omega |\rho(t)|\Psi \leq e^{\lambda_0 t}\left\{\int_\Omega |\rho^0|\Psi + \int_0^t \int_{\partial\Omega} \Psi(\sigma) e^{-\lambda_0 s}|f|(s,\sigma)d\sigma ds\right\}$$

(ii) (Evolution of the mean-value in L^1_Ψ)

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

(iii) (Comparison principle) If $f \geq 0$

$$\rho_1^0 \leq \rho_2^0 \quad \Rightarrow \quad \rho_1(t) \leq \rho_2(t)$$

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

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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** $\Psi \geq m > 0$.

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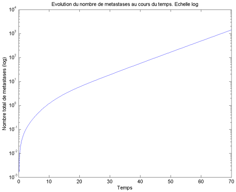


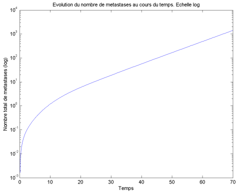
Number of metastases (log scale).

$$\lambda_0 = 0.10682$$

Spectral equation :

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

Asymptotic behavior



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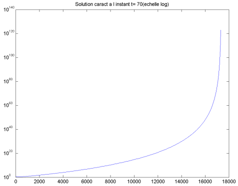
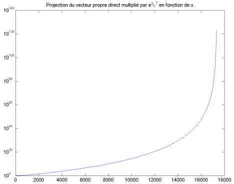
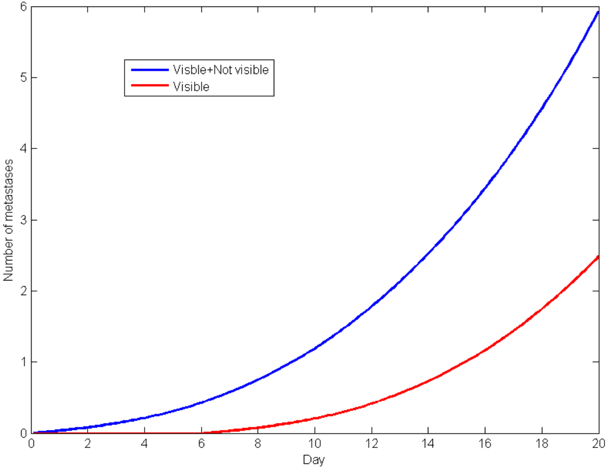


Asymptotic distribution of the density (projection in x).



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

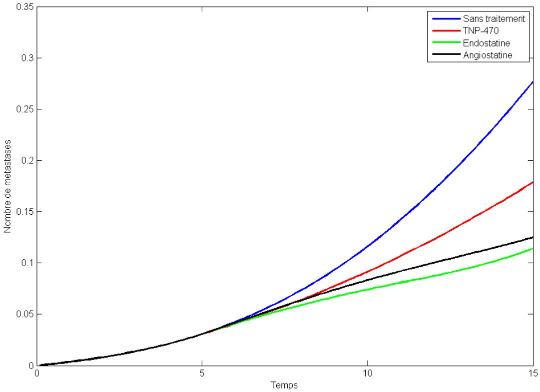
Without treatment. Visible VS not visible.



With anti-angiogenic treatment

Testing various drugs :

$$\frac{d\theta}{dt} = cx - d\theta x^{\frac{2}{3}} - e\theta \sum_{i=1}^{N} De^{-\mathrm{clr}(t-t_i)} \mathbf{1}_{t \geq t_i}$$



Conclusion and perspectives

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Future :

- **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!