Modeling and mathematical analysis 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 Analysis

3 Numerical simulations
   - Limit 2D-1D
   - Simulations
1 Modeling
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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.

- **Primary Tumor**: $x_p$
- **Secondary Tumors** (Metastases): $x$

At $t = 0$: $x_p$

\[
\begin{align*}
\text{Primary Tumor} & \quad x_p \\
\text{Growth } g(x) & \quad \beta(x) \\
\text{Secondary Tumors} & \quad (\text{Metastases})
\end{align*}
\]
Existing model.  


\[ \text{Primary Tumor} \quad x_p \]

\[ t = 2 \]

\[ \text{Secondary Tumors} \quad (\text{Metastases}) \]

$$\rho(t,x) = \text{density of metastases of size } x \text{ at time } t.$$
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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ODE model of tumoral growth under angiogenic control

Folkman et al., Cancer Research 1999

**Gompertzian** growth

\[ x = \text{Size of the tumor} \]

\[
\frac{dx}{dt} = ax \ln \left( \frac{\theta}{x} \right)
\]
ODE model of tumoral growth under angiogenic control

Folkman et al., Cancer Research 1999

Gompertzian growth

\[ x = \text{Size of the tumor} \]

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

Consider \( \theta \) as a variable:

the angiogenic capacity

\[ \frac{d\theta}{dt} = \left( \text{Stimulation by the tumor} \right) - \left( \text{Inhibition} \right) \]

\[ = cx - dx^2 \theta \]
Anti-angiogenic drug.

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

\[ \frac{d\theta}{dt} = cx - d\theta^2 - e\gamma(t)\theta \]
Phase plan of the system

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

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

\[ \frac{dX}{dt} = G(X) \]

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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Numerical simulations

1. Limit 2D-1D
2. Simulations
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 $\theta$:

$$\rho(t, x, \theta) \in L^1(\Omega).$$

Balance law:

$$\partial_t \rho + \text{div}(\rho G) = 0$$
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 $\theta$:

$$\rho(t, x, \theta) \in L^1(\Omega).$$

Balance law:

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

Birth rate of new metastases of parameter $\sigma$ per meta of size $x$ and angiogenic capacity $\theta$ per unit of time:

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

We choose:

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

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: $N(\sigma)\int_\Omega \beta(x, \theta)\rho(t, x, \theta)dx\,d\theta$
PDE model for the metastasis density

\[
\begin{aligned}
\partial_t \rho + \text{div}(G \rho) &= 0 & \text{on } ]0, \infty[ \times \Omega \\
-G \cdot \nabla \rho(t, \sigma) &= N(\sigma) \int_{\Omega} \beta \rho(t, x, \theta) dx d\theta + f(t, \sigma) & \text{on } \partial \Omega \\
\rho(0) &= \rho^0 & \text{on } \Omega
\end{aligned}
\]
Equation

\[
\begin{aligned}
\partial_t \rho + \text{div}(G \rho) &= 0 \\
-G \cdot \nabla \rho(t, \sigma) &= N(\sigma) \int_\Omega \beta \rho(t, x, \theta) dx d\theta + f(t, \sigma) \\
\rho(0) &= \rho^0
\end{aligned}
\]

on $]0, \infty[ \times \Omega$

on $\partial \Omega$

on $\Omega$

- Linear transport equation in **dimension 2**, with **vanishing velocity field**.
PDE model for the metastasis density

\[
\begin{align*}
\partial_t \rho + \text{div}(G \rho) &= 0 \quad \text{on } ]0, \infty[ \times \Omega \\
-G \cdot \nu \rho(t, \sigma) &= N(\sigma) \int \beta \rho(t, x, \theta) dx d\theta + f(t, \sigma) \quad \text{on } \partial \Omega \\
\rho(0) &= \rho^0 \quad \text{on } \Omega
\end{align*}
\]

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

- **Nonlocal boundary condition**
Equation

\[
\begin{aligned}
\frac{\partial}{\partial t} \rho + \text{div}(G \rho) &= 0 \\
-G \cdot \vec{v}(t, \sigma) &= N(\sigma) \int_\Omega \beta \rho(t, x, \theta) dx d\theta + f(t, \sigma) \\
\rho(0) &= \rho^0
\end{aligned}
\]

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

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

- Change of variables:

\[
\begin{align*}
\partial_\tau \Phi &= G(\Phi) \\
\Phi(0) &= \sigma \\
\Phi : \Omega &\rightarrow \Omega \\
(\tau, \sigma) &\mapsto \Phi_\tau(\sigma) \\
\end{align*}
\]

\[
\partial_\tau V(\Phi_\tau(\sigma)) = G \cdot \nabla V
\]

\[ \Phi \text{ is a \textbf{locally bilipschitz homeomorphism}.} \]
Preliminary result

- The jacobian
  \[ J_{\Phi}(\tau, \sigma) = G \cdot \overrightarrow{v}(\sigma)e^{\int_0^\tau \text{div}(G(\Phi_s(\sigma)))ds} \]

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

**Proposition**

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

\[ V \in W_{\text{div}}(\Omega) \iff (V \circ \Phi)|J_{\Phi}| \in W^{1,1}((0, +\infty); L^1(\Gamma)). \]

For \( V \in W_{\text{div}}(\Omega) \) we have

\[ \partial_{\tau}(V \circ \Phi|J_{\Phi}|) = (\text{div}(GV) \circ \Phi)|J_{\Phi}|. \]
The jacobian

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

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

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\[ V \in W_{\text{div}}(\Omega) \iff (V \circ \Phi)|_{J_\Phi} \in W^{1,1}((0, +\infty); L^1(\Gamma)). \]

For \( V \in W_{\text{div}}(\Omega) \) we have

\[ \partial_\tau(V \circ \Phi|_{J_\Phi}) = (\text{div}(GV) \circ \Phi)|_{J_\Phi}. \]

⇒ **Trace**

\[ V|_{\partial\Omega}(\sigma) := V \circ \Phi(0, \sigma) \in L^1(\partial\Omega; G \cdot \nu d\sigma) \]
Existence, uniqueness and regularity

\[ D(A) = \left\{ V \in W_{\text{div}}; -G \cdot \nabla V_{|\Gamma}(\sigma) = N(\sigma) \int_{\Omega} \beta V \right\} \]

**Theorem**

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

- For \( \rho^0 \in D(A) \) and \( f \in C^1([0, \infty]; L^1(\Gamma)) \), with \( f(0) = 0 \),
  \[ \rho \in C^1([0, \infty]; L^1(\Omega)) \cap C([0, \infty]; W_{\text{div}}(\Omega)) \]
Spectral problem

Find

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

**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* \((\lambda_0, V, \psi)\). *The principal eigenvalue* \(\lambda_0\) *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*

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

**Theorem**

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

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

\[
\| f \|_{L^1_\Psi} = \int_\Omega |f|\Psi
\]
Asymptotic behavior

**Theorem**

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

$$\| \rho(t)e^{-\lambda_0 t} - m(t)V \|_{L^1_\Psi} \leq e^{-\mu t}\{\| \rho^0 - m_0 V \|_{L^1_\Psi}$$

$$+ 2 \int_0^t e^{-(\lambda_0 - \mu)s} \int_{\partial\Omega} |f(s, \sigma)|\Psi(\sigma)ds\},$$

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

- Convergence with **exponential rate**
Asymptotic behavior

**Theorem**

Assume that there exists \( \mu > 0 \) such that \( \beta - \mu \psi \geq 0 \). Then

\[
||\rho(t)e^{-\lambda_0 t} - m(t)\nabla||_{L^1_\psi} \leq e^{-\mu t} \{ ||\rho^0 - m_0 \nabla||_{L^1_\psi} \\
+ 2 \int_0^t e^{-(\lambda_0 - \mu)s} \int_{\partial\Omega} |f|(s, \sigma)\psi(\sigma)d\sigma ds \},
\]

\[
||f||_{L^1_\psi} = \int_{\Omega} |f|\psi
\]

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

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

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

$$||\rho(t)e^{-\lambda_0 t} - m(t)V||_{L^1_\Psi} \leq e^{-\mu t} \{||\rho^0 - m_0 V||_{L^1_\Psi}$$

$$+ 2 \int_0^t e^{-(\lambda_0 - \mu) s} \int_{\partial \Omega} |f(s, \sigma)\Psi(\sigma)| ds\},$$

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

- Classical upwind scheme is not stable.
- 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 $\sigma_0$.

\[
\begin{align*}
    N(\sigma) &= N^\varepsilon(\sigma) = \frac{1}{2\varepsilon} = 1_{\sigma \in [\sigma_0-\varepsilon, \sigma_0+\varepsilon]} \\
    \delta\sigma &= \sigma_0 \\
    \partial_t \rho^\varepsilon + \text{div}(\rho^\varepsilon G) &= 0 \\
    -G \cdot \nu(\sigma)\rho^\varepsilon(t, \sigma) &= N^\varepsilon(\sigma) \left\{ \int_\Omega \beta \rho^\varepsilon(t) + f(t) \right\} \\
    \rho^\varepsilon(0) &= 0
\end{align*}
\]
Theorem (Benzekry, 2010)

We have

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

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

\[ \forall \psi \in C_b(\Omega) \]

\[ < d\rho(t), \psi > = \int_0^\infty \psi(\Phi_\tau(\sigma_0))n(t, \tau) d\tau \]

with \( n \) solving the 1D problem

\[
\begin{align*}
\partial_t n + \partial_\tau n &= 0 \\
n(t, 0) &= \int_0^\infty \beta(\Phi_\tau(\sigma_0))n(t, \tau) + f(t), \quad n(0, \tau) = 0.
\end{align*}
\]

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

\[
\begin{align*}
\partial_t d\rho + \text{div}(d\rho G) &= 0 \\
- G \cdot \nu(\sigma)d\rho(t, \sigma) &= \delta_{\sigma=\sigma_0} \left\{ \int_\Omega \beta d\rho(t) + f(t) \right\}, \quad d\rho(0) = 0.
\end{align*}
\]
Numerical illustration

Relative difference between the 1D problem and the 2D one VS $\varepsilon$.

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

Improvement of the computational time:

\[
\begin{array}{ccc}
T & dt & T & dt \\
5 & 0.1 & 5.8 & 0.133 & 35 \\
20 & 0.1 & 5.9 & 0.351 & 519
\end{array}
\]

Computation times in seconds on a personal computer.

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Numerical illustration

Relative difference between the 1D problem and the 2D one VS $\varepsilon$.

$\Rightarrow$ Improvement of the computational time:

<table>
<thead>
<tr>
<th>$T$</th>
<th>$dt$</th>
<th>2D</th>
<th>1D</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T = 5$, $dt = 0.1$</td>
<td>5.8</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>$T = 5$, $dt = 0.01$</td>
<td>333</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>$T = 20$, $dt = 0.01$</td>
<td>5331</td>
<td>519</td>
<td></td>
</tr>
</tbody>
</table>

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

Computation times in seconds on a personal computer.
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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

Number of metastases (log scale).

Asymptotic distribution of the density (projection in $x$).

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

$\lambda_0 = 0.10682$

Spectral equation:

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

\[ G_2(t, x, \theta) = cx - d\theta x^3 - e\gamma(t) \]

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.
Conclusion and perspectives

- Construction of a **simple model** (5 parameters) for the metastatic process.

- Theoretical study of the equation.

- Efficient numerical scheme.

**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 $\rho \in C([0, \infty[; L^1(\Omega))$ such that: for all $T > 0$ and all $\psi \in C_c^1([0, T] \times \overline{\Omega}^*)$

$$\int_0^T \int_{\Omega} \rho [\partial_t \psi + G \cdot \nabla \psi] + \int_{\Omega} \rho^0(\cdot) \psi(0, \cdot) - \int_{\Omega} \rho(T, \cdot) \psi(T, \cdot)$$

$$- \int_0^T \int_{\partial \Omega} N(\sigma) \int_{\Omega} \beta(x, \theta) \rho(t, x, \theta) dx d\theta \psi(t, \sigma) d\sigma dt = 0$$
Weak solutions

Definition

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 $\rho \in C([0, \infty[; L^1(\Omega))$ such that: for all $T > 0$ and all $\psi \in C^1_c([0, T[ \times \overline{\Omega}^*)$

$$\int_0^T \int_\Omega \rho [\partial_t \psi + G \cdot \nabla \psi] + \int_\Omega \rho^0(\cdot) \psi(0, \cdot) - \int_\Omega \rho(T, \cdot) \psi(T, \cdot)$$

$$- \int_0^T \int_{\partial \Omega} N(\sigma) \int_\Omega \beta(x, \theta) \rho(t, x, \theta) dx d\theta \psi(t, \sigma) d\sigma dt = 0$$

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

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

- Assumptions on the data

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