Modeling of the metastatic evolution and optimization of anti-cancerous therapies

Sébastien Benzekry
under the direction of D. Barbolosi, A. Benabdallah and F. Hubert

LATP, Université de Provence and
Laboratoire de Toxicocinétique et Pharmacocinétique, Université de la Méditerranée
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) are **invisible** with imaging techniques. How to administer adjuvant therapy (after surgery) without seeing anything?

What is the best **scheduling** for: chemotherapy (CT), anti-angiogenics (AA), CT + AA?

The **tool** : a simple modelling (with **few parameters**)

- **tumoral growth model (ODE)**
- **renewal model for the metastases (PDE)**
Outline

1. A model for metastatic evolution
2. An optimal control problem for the metastases
3. Numerical study in a simplified case
ODE model of tumoral growth under angiogenic control

Hahnfeldt et al., Cancer Research 1999

Gompertzian growth

\[ x = \text{Size of the tumor} = \text{Volume/Number of cells} \]

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

Consider \( \theta \) as a variable: the vascular capacity

\[ \frac{d\theta}{dt} = cx - dx^{\frac{2}{3}} \theta \]

Hahnfeldt model and CT/AA combination

\[ \frac{dx}{dt} = ax \ln \left( \frac{\theta}{x} \right) - f \left( u_1(t)(x - x_{\text{min}})^+ \right) \]

\[ \frac{d\theta}{dt} = cx - d\theta x^{\frac{2}{3}} - e \left( u_2(t)(\theta - \theta_{\text{min}})^+ \right) \]

- Log-kill term of the chemotherapy
- AA drugs impact on the tumoral vasculature
Transport equation for the metastases population

\[ \Omega = [1, x_{\text{max}}^2] \]

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

\[ u(t) = (u^1(t), u^2(t)) \]

\[ \overline{G}(t, X; u) = G(X) - B(X)u(t) \]

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

All the tumors follow the ODE model.

**Population of the metastases** structured in size \( x \) and vascular capacity \( \theta \) density \( \rho(t, x, \theta) \in L^1(\Omega) \).

Balance law:

\[ \partial_t \rho + \text{div}(\rho \overline{G}) = 0 \]
Boundary condition. Birth of new metastases

Birth rate of new metastases of parameter $\sigma \in \partial \Omega$ per meta of size $x$ and vascular capacity $\theta$ per unit of time: $b(\sigma, x, \theta)$

We assume

- **Independance** between the vascular capacity of the neo-metastasis and the mother-tumour which emitted it

$$b(\sigma, x, \theta) = N(\sigma)\beta(x, \theta)$$

- That the metastases are born with size 1

$$N(\sigma) = N(1, \theta) = \frac{1}{2\Delta \theta} 1_{\theta \in [\theta_0 - \Delta \theta, \theta_0 + \Delta \theta]}$$

We choose:

$$\beta(x, \theta) = mx^\alpha$$


Two sources of new metastases:

- Primary tumor $X_p(t)$ with $\frac{dX_p}{dt} = \overline{G}(X_p) : N(\sigma)\beta(X_p(t))$

- Metastases themselves: $N(\sigma) \int_{\Omega} \beta(x, \theta) \rho(t, x, \theta) dxd\theta$
Metastatic model

\[
\begin{align*}
\text{(E)} \quad 
\begin{cases}
\partial_t \rho(u) + \text{div}(\overline{G}(u)\rho(u)) = 0 \\
-\overline{G}(t, \sigma; u) \cdot \nu(\sigma) \rho(t, \sigma; u) = N(\sigma) \left\{ \int_\Omega \beta(X) \rho(t, X; u) dX + \beta(X_p(t; u)) \right\} \\
\rho(0) = \rho^0 
\end{cases}
\end{align*}
\]

\[
\overline{G}(t, x, \theta; u) = G(x, \theta) - B(x, \theta)u(t), \quad u(t) = (u^1(t), u^2(t))
\]

**Number of metastases**: \( \int_\Omega \rho(t, x, \theta) dx \, d\theta \). **Metastatic mass**: \( \int_\Omega x \rho(t, x, \theta) dx \, d\theta \)

- Linear transport equation in dimension 2 with nonlocal boundary condition.
- Theoretical and numerical analysis has been performed
  - B., J. Evol. Equ., 2011
  - B., M2AN, 2011
  - Barbolosi, Benabdallah, Hubert, Verga, Math. Biosc., 2008

- Original idea for a structured population equation for the metastases
Anti-angiogenic therapy

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
Combination of cytotoxic and anti-angiogenic therapy

Human parameters. Etoposide (CT)/Bevacizumab (AA) combination. Order of administration?

Bevacizumab D0 Etoposide D8 VS Etoposide D0 Bevacizumab D8

![Tumoral growth](image1)

![Total number of metastases](image2)
In these two first examples, the best protocol/drug is not the same for the primary tumor and for the number of metastases.
A model for metastatic evolution

An optimal control problem for the metastases

Numerical study in a simplified case
Formulation of an optimal control problem

On the primary tumor growth: \( \dot{X}_p(t; u) = G(X_p(t; u)) - B(X_p(t; u))u(t) \)

- Already studied

- Two possible criteria to be minimized for the primary tumor size

\[
J_T(u) = x_p(T; u) \quad \text{and} \quad J_m(u) = \min_{t \in [0, T]} x_p(t; u)
\]

- Toxicity constraints

\[
\mathcal{U}_{ad} = \left\{ u \in (L^\infty(0, T))^2; \left( \begin{array}{c} 0 \\ 0 \end{array} \right) \leq u(t) \leq \left( \begin{array}{c} v_{\text{max}} \\ u_{\text{max}} \end{array} \right) \forall t \text{ and } \int_0^T u(t) dt \leq \left( \begin{array}{c} C_{\text{max}} \\ A_{\text{max}} \end{array} \right) \right\}
\]
Formulation of an optimal control problem

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On the metastases

\[ J(u) = \int_{\Omega} \rho(T, x, \theta; u) dx d\theta \quad \text{and} \quad J_M(u) = \int_{\Omega} x \rho(T, x, \theta; u) dx d\theta \]

- **Total number of metastases**
- **Metastatic mass**
Is there a **difference** in the optimal minimizer $u^*$ between the metastatic and primary tumor criteria?
Existence of an optimal solution

**Theorem**

Under some regularity assumptions there exists \((u^*, u^*_M) \in \mathcal{U}_{ad}\) such that

\[
J(u^*) \leq J(u), \quad \forall u \in \mathcal{U}_{ad}, \quad J_M(u^*_M) \leq J_M(u), \quad \forall u \in \mathcal{U}_{ad}
\]

The proof is based on the following proposition

**Proposition**

Under some regularity assumptions if \(\rho(u)\) is the solution of \((E)\), then \(\rho \in W^{1,\infty}(Q)\) and there exists a continuous function \(C\) which can be explicited in terms of \(\|\beta\|_{W^{1,\infty}(\Omega)}, \|N\|_{W^{1,\infty}(\partial \Omega)}, \|G\|_{L^\infty(\Omega)}\) and \(\|B\|_{L^\infty(\Omega)}\) such that, for all \(u \in \mathcal{U}_{ad}\)

\[
\|\rho(u)\|_{W^{1,\infty}(Q)} \leq C(\|u\|_{L^\infty(Q)})
\]
Optimality system for $J$

In the case of $J(u) = \int_\Omega \rho(T,X;u)\,dX$ and without the source term in the boundary condition

**Proposition**

Let $u^*$ be a solution of the optimal control problem. We have the following **optimality system**:

\[
\begin{cases}
\partial_t \rho^* + \text{div}(\rho^* \overline{G}(u^*)) = 0 \\
-G \cdot \nu(t,\sigma;u^*)\rho^*(t,\sigma;u^*) = N(\sigma) \{ \int_\Omega \beta(X) \rho^*(t,X;u^*)\,dX + \beta(X_p(t;u^*)) \} \\
\rho^*(0,X;u^*) = \rho^0
\end{cases}
\]

\[
\begin{cases}
-\partial_t p^*(t,X;u^*) - \overline{G}(X;u^*) \nabla p^*(t,X;u^*) - \beta(X) \int_{\partial \Omega} N(\sigma) p^*(t,\sigma)\,d\sigma = 0 \\
p^*(T) = -1.
\end{cases}
\]

\[
\int_0^T \int_\Omega p^* \text{div}(\rho^* B(X) \cdot (\nu - u^*)) \,dX \,dt \leq 0, \quad \forall \nu \in \mathcal{U}_{ad}.
\]
A model for metastatic evolution

An optimal control problem for the metastases

Numerical study in a simplified case
Optima comparison in a two-dimensional case

Administer total given amounts of agents \((C_{\text{max}}, A_{\text{max}})\) from time 0 to times \((t_v, t_u)\) at constant rates \(V = \frac{C_{\text{max}}}{t_v}\) and \(U = \frac{A_{\text{max}}}{t_u}\).

\[U_{\text{ad}} = \{u^1(t) = \frac{C_{\text{max}}}{t_v} \mathbf{1}_{[0,t_v]}(t), \ u^2(t) = \frac{A_{\text{max}}}{t_u} \mathbf{1}_{[0,t_u]}(t), \ \left(\frac{C_{\text{max}}}{v_{\text{max}}}, \frac{A_{\text{max}}}{u_{\text{max}}}\right) \leq (t_v, t_u)\}.\]

\[U_{\text{ad}} \simeq \left[ \frac{C_{\text{max}}}{v_{\text{max}}}, T \right] \times \left[ \frac{A_{\text{max}}}{u_{\text{max}}}, T \right] = [1, 10] \times [4, 10]\]
Monotherapy cases

AA alone. $C_{max} = 0$

CT alone. $A_{max} = 0$. 
Monotherapy cases

- Number of metastases and primary tumor criteria yield different optimal values: strong dose/short time, small dose/large time, nontrivial minimum value

- Metastatic mass gives the same result as final tumor size

- Same qualitative but different quantitative results between CT and AA
CT-AA combination

<table>
<thead>
<tr>
<th>Criterion</th>
<th>$J_T$</th>
<th>$J_m$</th>
<th>$J$</th>
<th>$J_M$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$(t_v^<em>, t_u^</em>)$</td>
<td>(9.5, 9.5)</td>
<td>(1, 4)</td>
<td>(1, 5.5)</td>
<td>(10, 9)</td>
</tr>
</tbody>
</table>

- We can regroup $J$ and $J_m$ under the **strong dose/short time** strategy and $J_T$ and $J_M$ under the **low dose/large time** one.
Influence of the presence of a drug on the behavior of the other

Effect of $\text{CT}$ on $\text{AA}$

$J_T$, $J$ and $J_M$ are almost identical but $J_m$ has the reverse behavior

Effect of $\text{AA}$ on $\text{CT}$

Drastrical changes for $J_T$ and $J_M$. $J$ is stable
Conclusion

- Simple model for metastatic evolution, taking into account for the effects of CT and AA therapies
- Difference of the optimal solution between the primary tumor and the metastases.
- Necessity to define precisely the objective(s) to be minimized.

**How to cleverly combine** tumoral and metastatic reduction?

Use the **metastatic mass** $J_M = \int_\Omega x \rho(t, x, \theta) dx d\theta$?

**Linear combination** between a tumoral criterion and the number of metastases?

**Perspectives**

- Numerical method for the infinite-dimensional optimal control problem on the metastases (PDE)
- Further study of the theoretical optimality system
Thank you for your attention!
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
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Y. Dermenjian
F. Hubert
M. Gonzales Burgos

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


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


Confrontation with a study of Koscielny, Tubiana & al.

- 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.

<table>
<thead>
<tr>
<th>Primary tumor size</th>
<th>% computed by our model</th>
<th>% observed by Koscielny</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 2.5 cm</td>
<td>25.5%</td>
<td>27%</td>
</tr>
<tr>
<td>2.5 - 3.5 cm</td>
<td>44.25%</td>
<td>42%</td>
</tr>
<tr>
<td>3.5 - 4.5 cm</td>
<td>60.5%</td>
<td>56.7%</td>
</tr>
<tr>
<td>4.5 - 5.5 cm</td>
<td>68.6%</td>
<td>66.5%</td>
</tr>
<tr>
<td>5.5 - 6.5 cm</td>
<td>75.5%</td>
<td>72.8%</td>
</tr>
<tr>
<td>6.5 - 7.5 cm</td>
<td>78.25%</td>
<td>83.8%</td>
</tr>
<tr>
<td>7.5 - 8.5 cm</td>
<td>83.25%</td>
<td>81.3%</td>
</tr>
<tr>
<td>&gt;8.5 cm</td>
<td>89.25%</td>
<td>92%</td>
</tr>
</tbody>
</table>

Breast cancer: Relationship between the size of the primary tumor and the probability of metastatic dissemination

Koscielny, Tubiana & al. (1984)

The difficulties of use of the model

- Estimate the parameters.
  - Work in progress: Use ana-pathological informations on the primary tumor and homology derived tools to obtain good covariables for the estimation of $m$.

- Model validation on mice in progress (ANR MEMOREX_PK).
CT-AA combination

Graphs of $t_v \mapsto \arg\min_{t_u} J_x(t_u, t_v)$
- For $J_m$: **synchronization effect**
- $J$, $J_M$ and $J_T$ are stable

Graphs of $t_u \mapsto \arg\min_{t_v} J_x(t_u, t_v)$
- For $J_T$: change in the optimal value $t_v^*$.
- $J$, $J_M$ and $J_m$ are stable