Optimal schedules for therapies in metastatic cancers

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Clinical problematics

- In the case of breast cancer, 10% of cancers in stage T1N0M0 give rise to metastasis. 

- Micrometastases (size $< 10^8$ cells $\simeq 100$ mg) 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
   - Formulation of an optimal control problem
   - Theoretical study

3 Numerical study in a simplified case
   - First examples
   - Optima comparison in a two-dimensional case
ODE model of tumoral growth under angiogenic control

Hahnfeldt 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 **vascular capacity**

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

Stimulation by the tumor

Inhibition

Hahnfeldt model and CT/AA combination

\[ \frac{dx}{dt} = ax \ln \left( \frac{\theta}{x} \right) - f u^1(t)(x - x_{\text{min}})^+ \]

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

- Log-kill term of the chemotherapy
- AA drugs impact on the tumoral vasculature

Studied in d’Onofrio, Gandolfi, 2004
A model for metastatic evolution
An optimal control problem for the metastases
Numerical study in a simplified case

Transport equation for the metastases population

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

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

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

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

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

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

We assume

- That the metastases are born with size 1
- **Independance** between the vascular capacity of the neo-metastasis and the mother-tumour which emitted it

**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:

$$N(\sigma) = \frac{1}{2\Delta\sigma}1_{\sigma \in [\sigma_0 - \Delta\sigma, \sigma_0 + \Delta\sigma]}$$

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


**Two sources of new metastases:**

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

\[
\begin{aligned}
\frac{\partial \rho(u)}{\partial t} + \text{div}(\overline{G(u)}\rho(u)) &= 0 \\
-\overline{G}(t,\sigma;u) \cdot \nu(\sigma)\rho(t,\sigma;u) &= N(\sigma) \left\{ \int_{\Omega} \beta(X)\rho(t,X;u)dX + \beta(X_0(t,u)) \right\} \\
\rho(0) &= \rho^0
\end{aligned}
\]

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

Number of metastases: \( \int_{\Omega} \rho(t,X)dX \). Metastatic mass: \( \int_{\Omega} x\rho(t,X)dX \)

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

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On the metastases

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

\( \text{Total number of metastases} \quad \text{Metastatic mass} \)
Formulation of an optimal control problem

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

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On the metastases

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J(u) = \int_\Omega \rho(T, X; u)dX \quad \text{and} \quad J_M(u) = \int_\Omega x\rho(T, X; u)dX
\]

Total number of metastases

Metastatic mass

Is there a difference in the optimal minimizer \( u^* \) for \( J_T, J_m, J, J_M \)?
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 \(u \in \mathcal{U}_{ad}\)

\[
\|\rho(u)\|_{W^{1,\infty}(Q)} \leq C(\|u\|_{L^{\infty}(Q)})
\]
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**:

\[
\begin{align*}
\partial_t \rho^* + \text{div}(\rho^* \overline{G}(u^*)) &= 0 \\
- G \cdot \nu(t, \sigma; u^*) \rho^*(t, \sigma; u^*) &= N(\sigma) \left\{ \int_{\Omega} \beta(X) \rho^*(t, X; u^*) dX + \beta(X_p(t; u^*)) \right\} \\
\rho^*(0, X; u^*) &= \rho^0 \\
-\partial_t p^*(t, X; u^*) - \overline{G}(X; u^*) \nabla p^*(t, X; u^*) - \beta(X) \int_{\partial \Omega} N(\sigma) p^*(t, \sigma) d\sigma &= 0 \\
p^*(T) &= -1.
\end{align*}
\]

\[
\int_0^T \int_{\Omega} p^* \text{div}(\rho^* B(X) \cdot (v - u^*)) \, dX \, dt \leq 0, \quad \forall v \in \mathcal{U}_{ad}.
\]
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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
First examples

Combination of cytotoxic and anti-angiogenic therapy

Human parameters. Etoposide/Bevacizumab combination. Order of administration?

- Bevacizumab D0 Etoposide D8 VS Etoposide D0 Bevacizumab D8

The best protocol is **not the same** for the primary tumor and for the number of metastases.
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. Ledzewicz et al., Math. Medic. and Biol., 2010

Examples of administration of the AA drug

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

\[
\mathcal{U}_{ad} \approx \left[ \frac{C_{\text{max}}}{v_{\text{max}}}, T \right] \times \left[ \frac{A_{\text{max}}}{u_{\text{max}}}, T \right] = [1, 10] \times [4, 10]
\]

Primary tumor evolution

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Optimal schedules in metastatic cancers

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Optima comparison in a two-dimensional case

Monotherapy cases

Criteria $J_T$, $J_m$ and $J$ give **different optimal values**.
- Metastatic mass $J_M$ gives the same optimal value as $J_T$.
- Difference between CT and AA: shape of $J_M$.

AA alone. $C_{\text{max}} = 0$

CT alone. $A_{\text{max}} = 0$. 
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

$t_v = 1$

Effect of CT on AA

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

$t_v = 10$

$t_u = 4$

Effect of AA on CT

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

$t_u = 10$
Conclusion

- Simple model for metastatic evolution
- 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 theoretical study of the theoretical optimality system
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