Image-based simulation of metastasis to the lung.
and to the liver

Thierry Colin

Institut de Mathématiques de Bordeaux
Institut Polytechnique de Bordeaux- INRIA Bordeaux-Sud-Ouest -CNRS

with F. Cornelis, A. Iollo, J. Jouganous, G. Lefebvre, D. Lombardi, J. Palussière, O. Saut
Coll.: Institut Bergonié, CHU Pellegrin
Introduction: An example

June 7, 2008:

September 22, 2008:

December 10, 2008:

Institut Bergonie 2008.
Introduction: Questions we wish to answer:

For a \textbf{given} pathology, for a \textbf{given} patient:

- When to start a treatment?
- When to stop a treatment?
- When to change a treatment?
Introduction: General strategy:

- Nonlinear PDE model
- Longitudinal, multimodal data
- MRI, CT, PET
- Biological knowledge
- Data assimilation
- Simulation and prediction

Mathematical models in oncology
Patient-specific predictions for clinical use
Nonlinear PDE model
Longitudinal, multimodal data
Data assimilation
Simulation and prediction
Biological knowledge

Thierry Colin DynPred, October 11, 2013
Modeling lung metastasis: Different steps

Some facts about cancer:

- Tumors appear after an alteration of a cell’s genetic material.
- Cancer cells have the ability to produce growth signals and are less responsive to anti-growth signals. They could even escape from death processes.
- Avascular growth is the first stage of a cancer. The tumor obtains adequate nutrients (oxygen,...) from its close environment and existing vasculature.
- Angiogenesis process is the next stage: The tumor builds its own web of blood vessels in order to get the nutrients: a critical step.
- Propagation of metastasis at distant locations.
Modeling lung metastasis: Lung tumor for the anapath

Normal histology

Primitive tumor

Metastasis (Thyroid)

Institut Bergonié
Modeling lung metastasis: Ingredients of a simplified model for metastasis to the lung.

- One proliferating phases $P$ (in which cells divide) with a non constant proliferative rate depending on
- a quantity of oxygen $M$
- A VEGF-like marker secreted by tumor cells, especially hypoxic ones
- a global velocity describing the collective movement.
Modeling lung metastasis: A very simplified model

Population of cells

\[ \partial_t P + \nabla \cdot (vP) = (\gamma_p - \gamma_d)P, \]

Growth and death rates

\[ \gamma_p(M) = \gamma_0 \frac{1 + \tanh(K(M - M_{thr}))}{2}, \]
\[ \gamma_d(M) = \gamma_1 \frac{1 - \tanh(K(M - M_{thr}))}{2}. \]

Velocity

\[ \nabla \cdot v = (\gamma_p - \gamma_d)P, \quad v = -k(P, Q)\nabla \Pi, \quad k = k_1 + (k_2 - k_1)P, \]

VEGF

\[ \partial_t \xi = \alpha \int_{\Omega} (1 - \frac{\gamma_p}{\gamma_0})Pdx - \lambda \xi \]

Oxygen

\[ \partial_t M = -\eta PM + \beta \xi (1 - \frac{\gamma_p}{\gamma_0})P \]
Modeling lung metastasis: The inverse problem

Find values of the parameters: $k_2/k_1$, $M_{thr}$, $K$, $\alpha$, $\lambda$, $\eta$, $\beta$, $\gamma_0$, $\gamma_1$ that minimize

$$\int |P(t_1) - P_{data}(t_1)|^2 + \int |P(t_2) - P_{data}(t_2)|^2$$

$t_1$ and $t_2$ corresponding to the times of the CT-scans 1 and 2. Technics:
1) Construct a reduced order model using a POD decomposition.
2) Solve the inverse problem for the reduced model.
Modeling lung metastasis: progression without treatment-1

Modeling lung metastasis: progression without treatment-2
Modeling lung metastasis: progression without treatment-3

The real tumor

The computed tumor
Modeling lung metastasis: Two nodules of the same tumor-1.

Figure 11: Scan for the third inverse problem, first nodule: a) 06-2008, b) 04-2009, c) 07-2009

Figure 12: Scan for the third inverse problem, second nodule: a) 06-2008, b) 04-2009, c) 07-2009
Modeling lung metastasis: Two nodules of the same tumor-2.

The result

Figure 14: Volume curve as function of time

Figure 16: Volume curve as function of time
Modeling lung metastasis: Lung metastasis and chemo-1

June 7, 2008:

September 22, 2008:

December 10, 2008:

Institut Bergonié 2008.
Modeling lung metastasis: Lung metastasis and chemo-2

The result

![Graph and images related to the modeling of lung metastasis.](image-url)
Modeling lung metastasis: Lung metastasis and chemo-3
Liver metastasis-1

May, 20, 2008:

February 19, 2009:

June 30, 2009:

September 16, 2008:

Liver metastasis-2

July 5, 2010:

October 4, 2010:

February 4, 2011:

August 12, 2011:

Institut Bergonié 2010-2011.
RECISt Criteria
Observation Most cases of metastasis to the liver of GIST (Gastro-Intestinal Stromal Tumor) behaves similarly:

- Phase 1: good answer to Glivec.
- Phase 2: Resistance to Glivec but good answer to Sutent
- Phase 3: Resistance to Sutent and uncontrolled growth.
Two genetic mutations that leads to resistance to Glivec.
Hypotheses on the treatment

- Glivec *acts like a chemotherapy*: it gives back apoptosis in the cell cycle.
- Sutent *acts like an anti-angiogenic drug*, with some cytotoxic effects.
The equations

Proliferative cells:

\[
\begin{align*}
\partial_t P_1 + \nabla \cdot (vP_1) &= \gamma_{PP} P_1 - \gamma_{PD} P_1 - (\delta f(t) + \nu(1 - g(t)))MP_1, \\
\partial_t P_2 + \nabla \cdot (vP_2) &= \gamma_{PP} P_2 - \gamma_{PD} P_2 - (\nu(1 - g(t)))MP_2, \\
\partial_t P_3 + \nabla \cdot (vP_3) &= \gamma_{PP} P_3 - \gamma_{PD} P_3,
\end{align*}
\]

Healthy cells:

\[
\partial_t S + \nabla \cdot (vS) = -\gamma_{Sd} S,
\]

- \( \delta f(t) \) M antiproliferative drugs.
- \( \gamma_{PP} \) proliferation = \( \frac{\gamma_0}{2} \{1 + \tanh [R(M - M_{hyp})]\} \).
- \( \gamma_{PD} \) apoptosis due to hypoxia \( \frac{\gamma_1}{2} \{1 - \tanh [R(M - M_{hyp})]\} \).
Healthy tissue, blood flux and necrosis

Necrotic tissues:

\[ \partial_t N + \nabla \cdot (vN) = \gamma_{PD}(P_1 + P_2) + \gamma_{Sd} S + \delta f(t) MP_1 + \nu (1 - g(t)) M(P_1 + P_2) - \mu (1 + M) N, \]

VEGF-like factor:

\[ \partial_t \xi = \alpha \left\{ g(t) \int_{\Omega} \left( 1 - \frac{\gamma_{PP}}{\gamma_0} \right)(P_1 + P_2) + \int_{\Omega} \left( 1 - \frac{\gamma_{PP}}{\gamma_0} \right) P_3 \right\} - \lambda \xi \]

Oxygen:

\[ \partial_t M - \xi \frac{\nabla S}{||\nabla S||} \nabla M = c_0 S(1 - \frac{M}{2M_s}) - \eta PM + \psi \Delta M \]

- Angiogenesis induced by hypoxia.
- in green angiogenesis term sensible to Sutent.
- in red angiogenesis term not sensible to Sutent.
- \( g(t) \) effect of sutent
The velocity

Using:

\[ P_1 + P_2 + P_3 + S + N = 1 \]

\[ \nabla \cdot \mathbf{v} = \gamma P (P_1 + P_2 + P_3) - \mu (1 + M) N \]

Darcy’s law for the tissue:

\[ \mathbf{v} = -k \nabla \Pi, \text{ and } k = k_0 + k_1 (P_1 + P_2 + P_3) \text{ with } 0 < k_0 < k_1 \]

- Green Tumoral growth
- Blue Elimination of necrosis
Comparison-1

Total number of tumor cells: Quantitative agreement.
Comparison-2
Comparison-3

Use of the density in the scan: Necessity of Functional Imaging and spacial computations.
Comparison-4

Use of the density in the scan: Necessity of Functional Imaging and spatial computations.
Comparison-5

May, 20, 2008:

September 16, 2008:
Comparison-6

February 19, 2009:

June 30, 2009:

Comparison-7

**July 5, 2010:**

**October 4, 2010:**
Comparison-8

February 4, 2011:

August 12, 2011:

Institut Bergonié 2010-2011.
Conclusion

For the lung:

▶ Evaluation of the procedure on a large (20) set of cases
▶ Extension to primary tumor (early response to avastin, coll. Bergonié) with perfusion MRI.
▶ Extension to primary tumor evaluated with Pet (coll. Bergonié)

For the liver:

▶ Can we solve the inverse problem in order to predict the escape time? Probably: no!
▶ Use of functional imaging? Perfusion MRI?
▶ Work on the texture of the image (collaboration with GE).
Conclusion-2: Meningiomas

Géométrie

OS
Dure-Mère
Pte-Mère
Cerveau
Arachnoïde

OS
Dure-Mère
Pte-Mère
Cerveau
Tumeur
Arachnoïde
Conclusion-2: Meningioma: the data

CHU Bordeaux 2012.
Conclusion-2: Meningioma: the results
Conclusion-2: Meningioma-mixt effects