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

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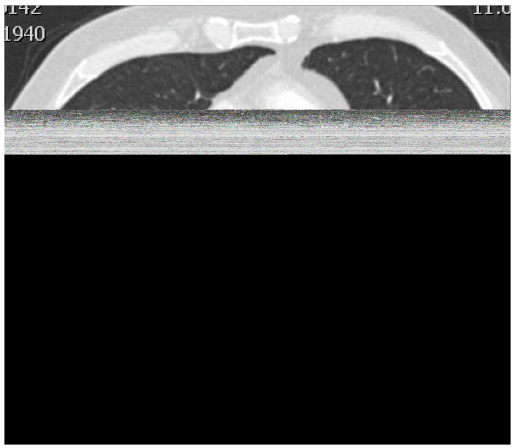
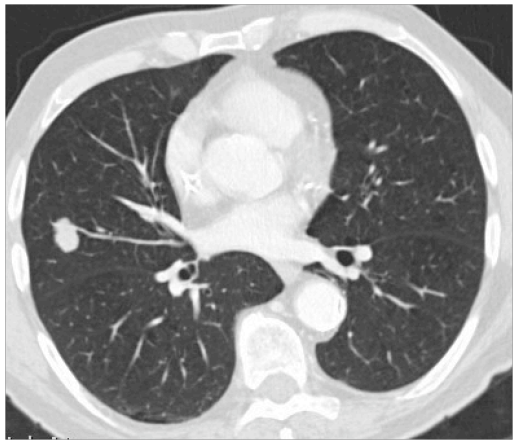
Coll.: Institut Bergonié, CHU Pellegrin

Introduction: An example

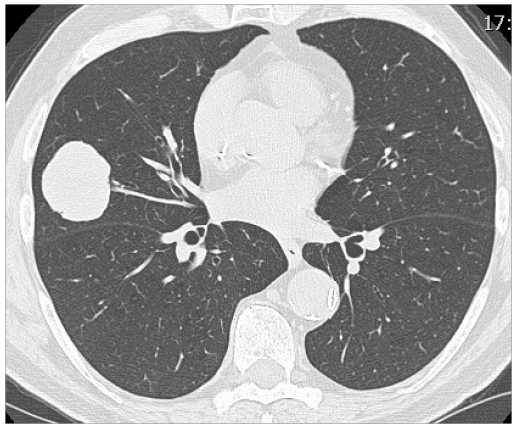
June 7, 2008:



September 22, 2008:



December 10, 2008:



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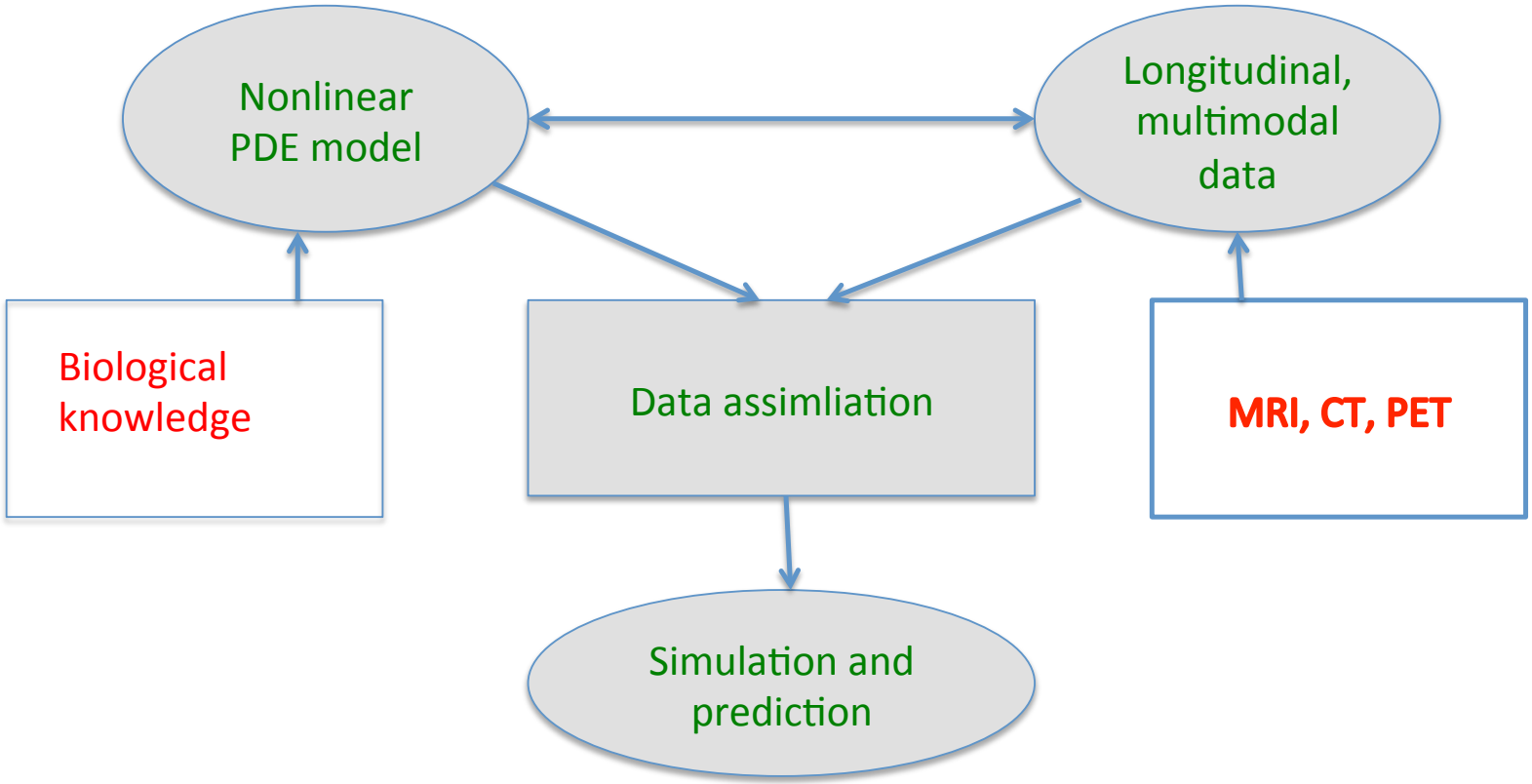
Introduction: Questions we wish to answer:

For a given pathology, for a given patient:

- When to start a treatment?
- When to stop a treatment?
- When to change a treatment?

Introduction: General strategy:



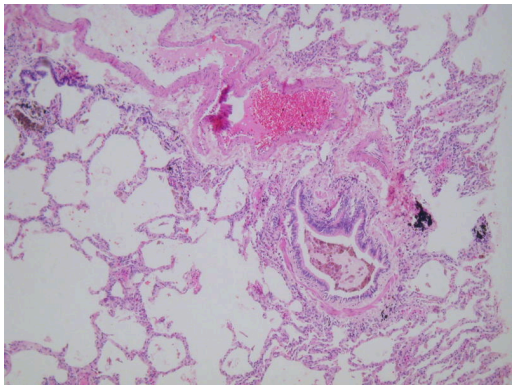
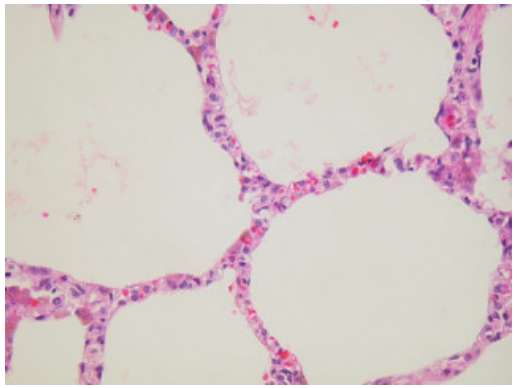
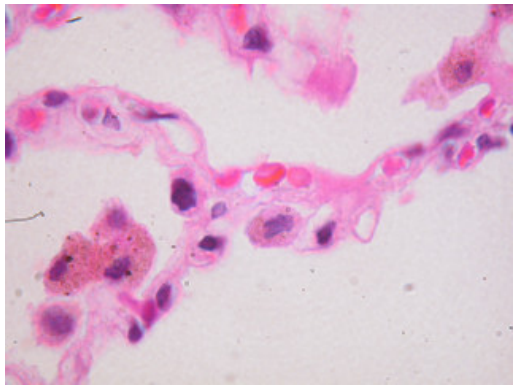
Modeling lung metastasis: Different steps

Some facts about cancer:

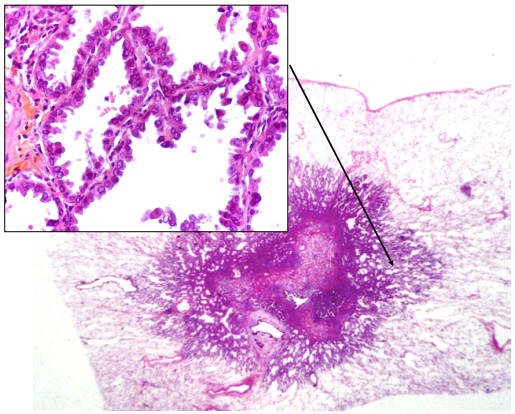
- Tumors appear after an alteration of a cell's genetic material.
- Cancer cells have the ability to produce growth signals and are less responsive to anti-growth signals. They could even escape from death processes.
- Avascular growth is the first stage of a cancer. The tumor obtains adequate nutrients (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

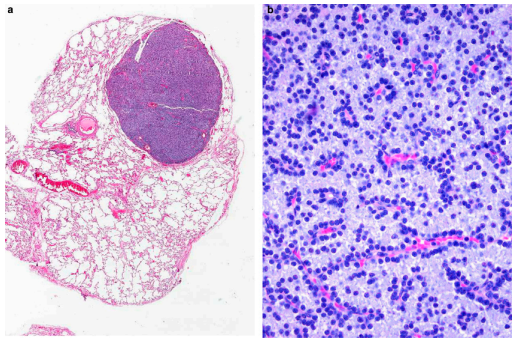
Normal histology

Primitive tumor



Metastasis (Thyroid)



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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

$$\nabla \cdot v = (\gamma_p - \gamma_d)P, \;\; v = -k(P, Q)\nabla\Pi, \;\; k = k_1 + (k_2 - k_1)P,$$

VEGF

$$\partial_t \xi = \alpha \int_\Omega (1 - \frac{\gamma_p}{\gamma_0})P dx - \lambda\xi$$

Oxygen

$$\partial_t M = -\eta P M + \beta\xi(1 - \frac{\gamma_p}{\gamma_0})P$$

Modeling lung metastasis: The inverse problem

Find values of the parameters: k_2/k_1, M_{thr}, K, α, λ, η, β, γ_0, γ_1 that minimize

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

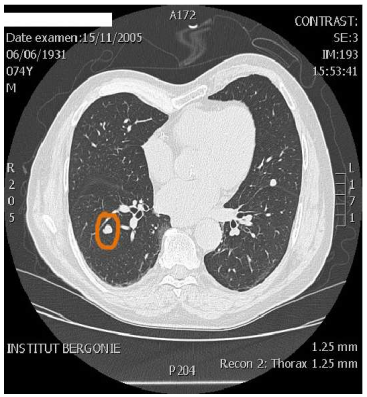
t_1 and t_2 corresponding to the times of the CT-scans 1 and 2.

Technics:

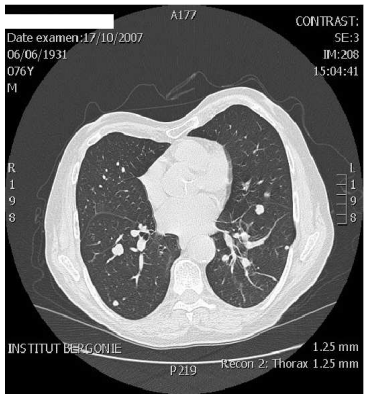
1) Construct a reduced order model using a POD decomposition.
2) Solve the inverse problem for the reduced model.

Modeling lung metastasis: progression without treatment-1

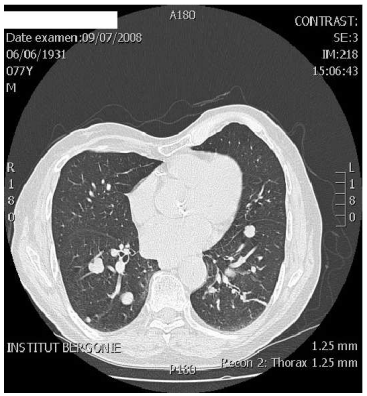
a) 11/2005, b) 10/2007, c) 07/2008, d) 04/2009.



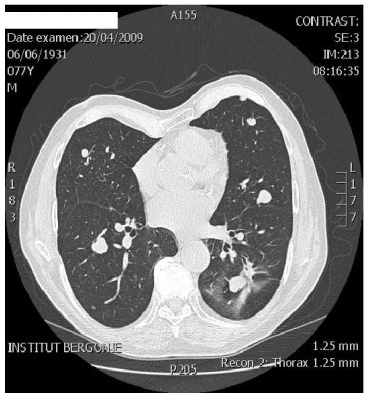
(a)



(b)

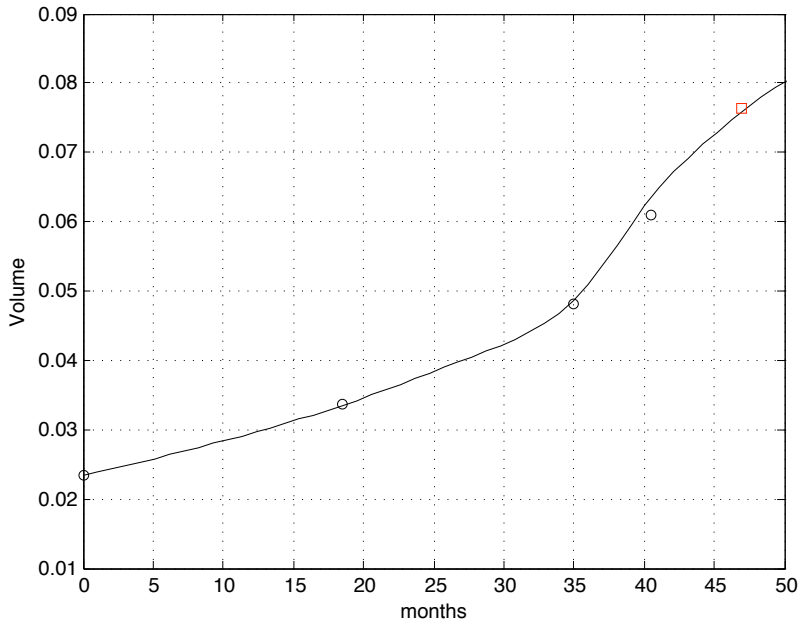


(c)



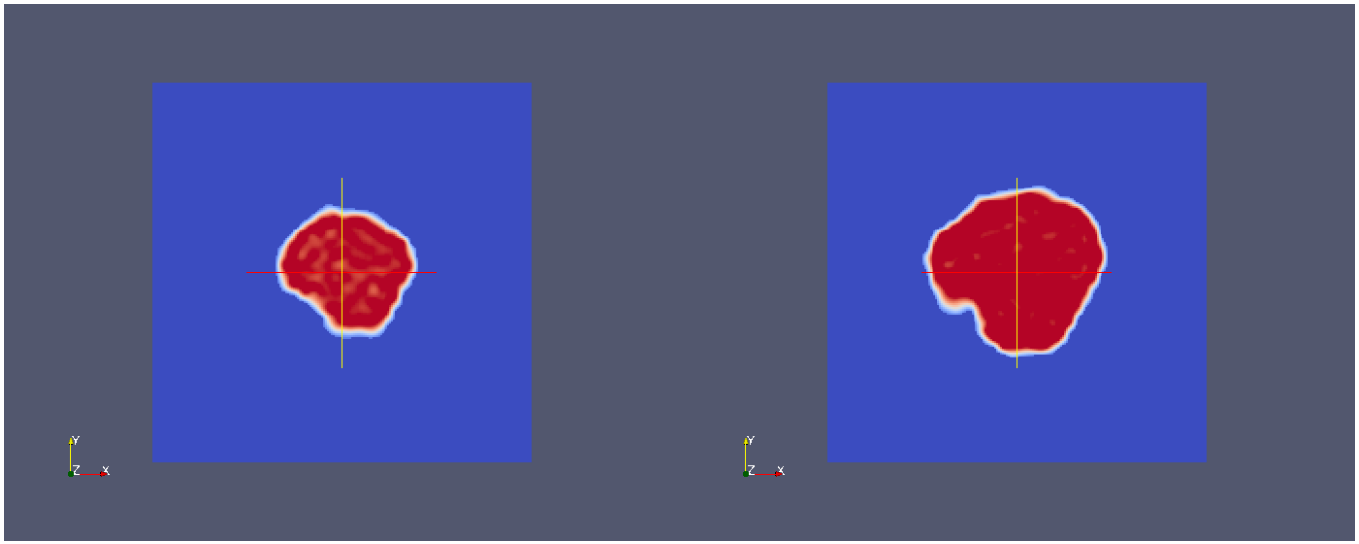
(d)

Modeling lung metastasis: progression without treatment-2

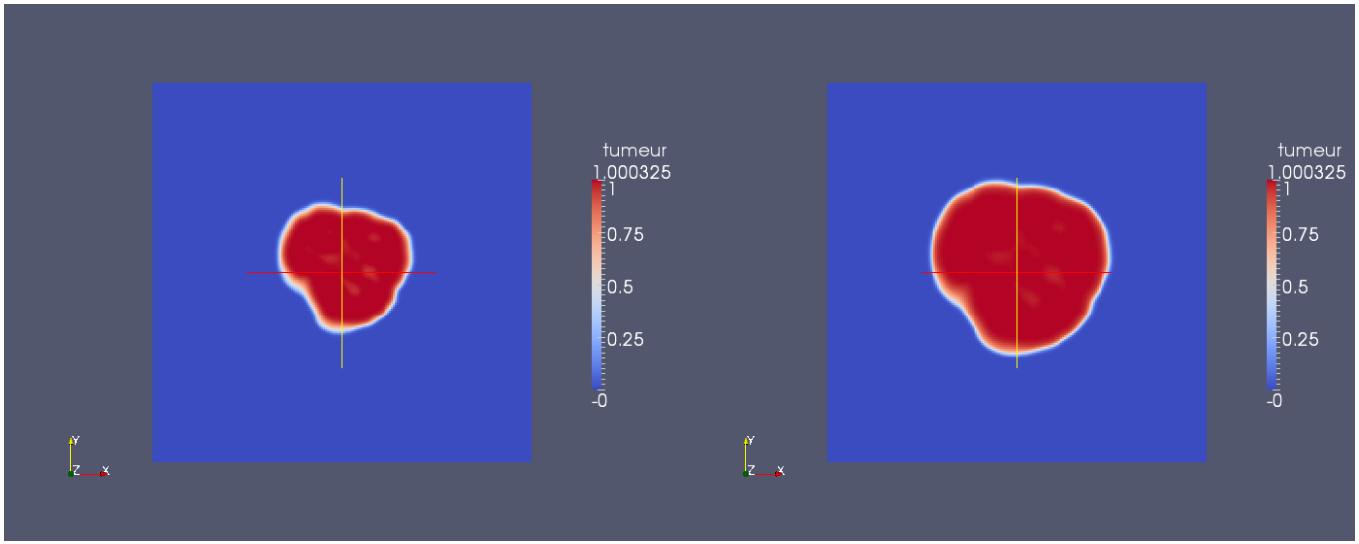


Modeling lung metastasis: progression without treatment-3

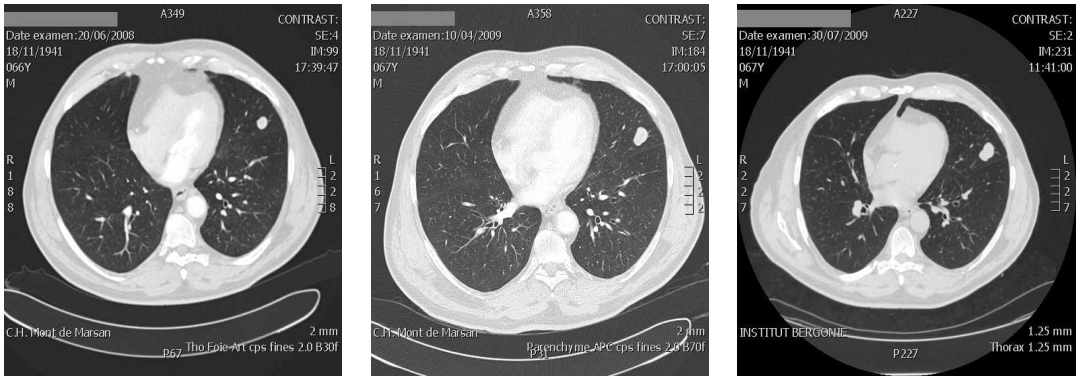
The real tumor



The computed tumor

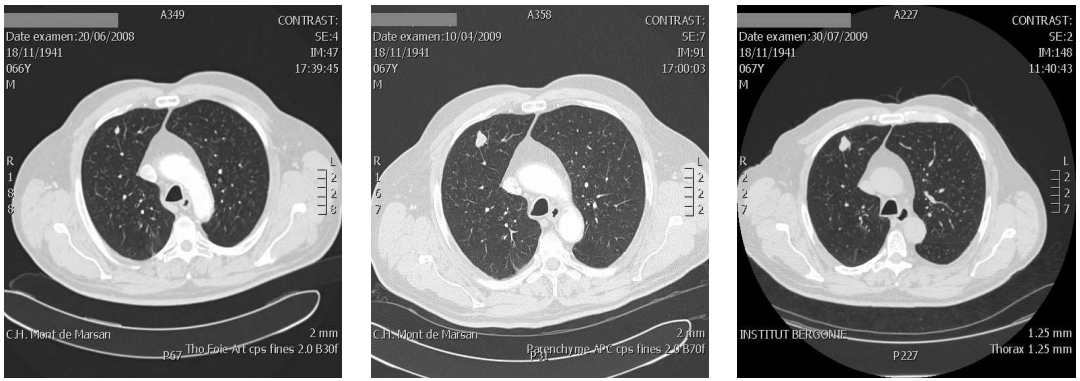


Modeling lung metastasis: Two nodules of the same tumor-1.



(a) (b) (c)

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



(a) (b) (c)

Modeling lung metastasis: Two nodules of the same tumor-2.

The result

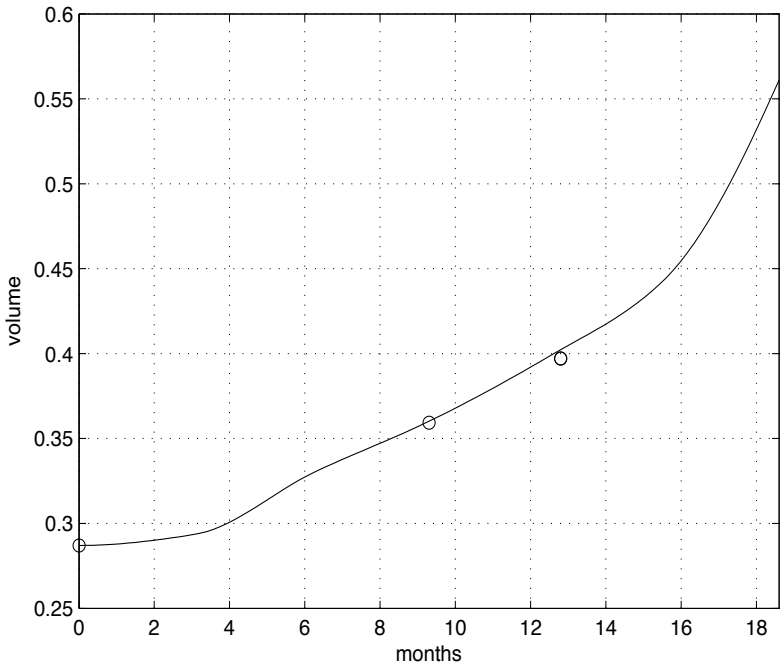


Figure 14: Volume curve as function of time

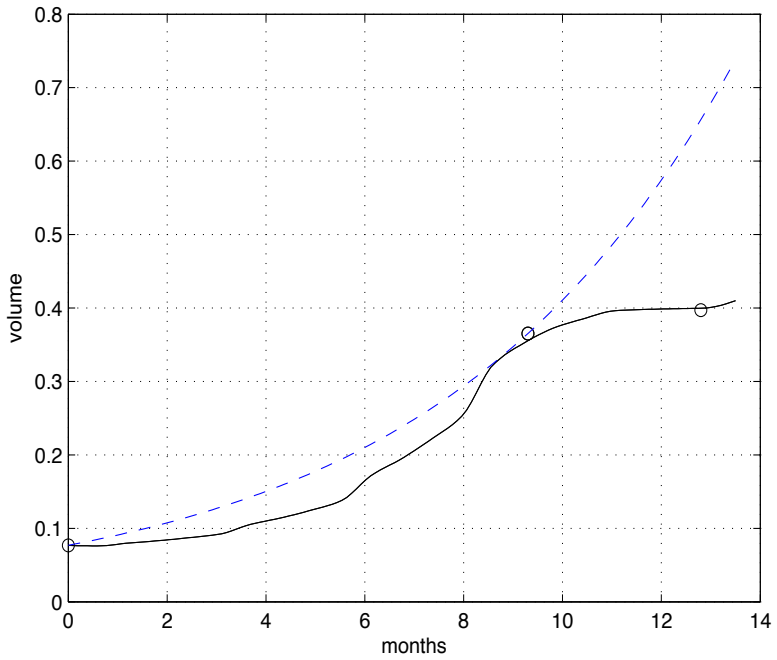
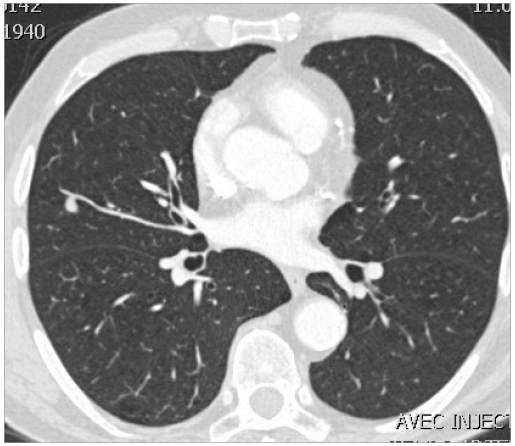


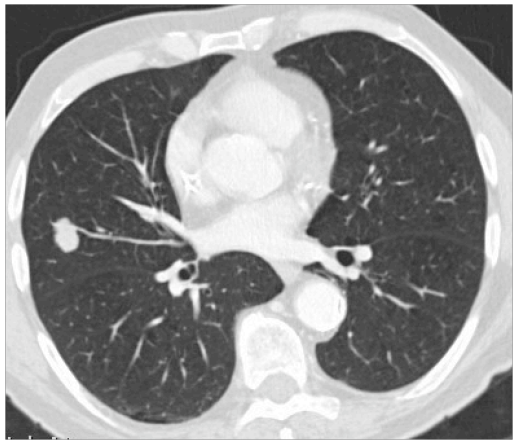
Figure 16: Volume curve as function of time

Modeling lung metastasis: Lung metastasis and chemo-1

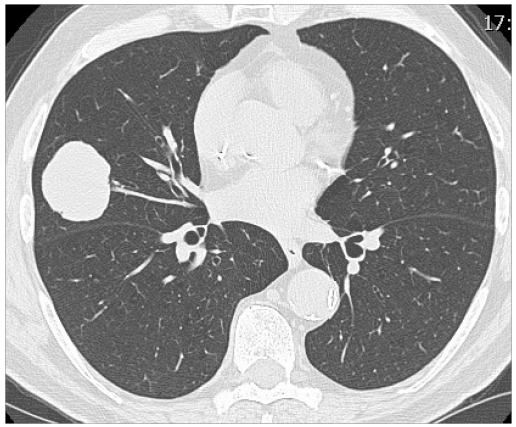
June 7, 2008:



September 22, 2008:



December 10, 2008:



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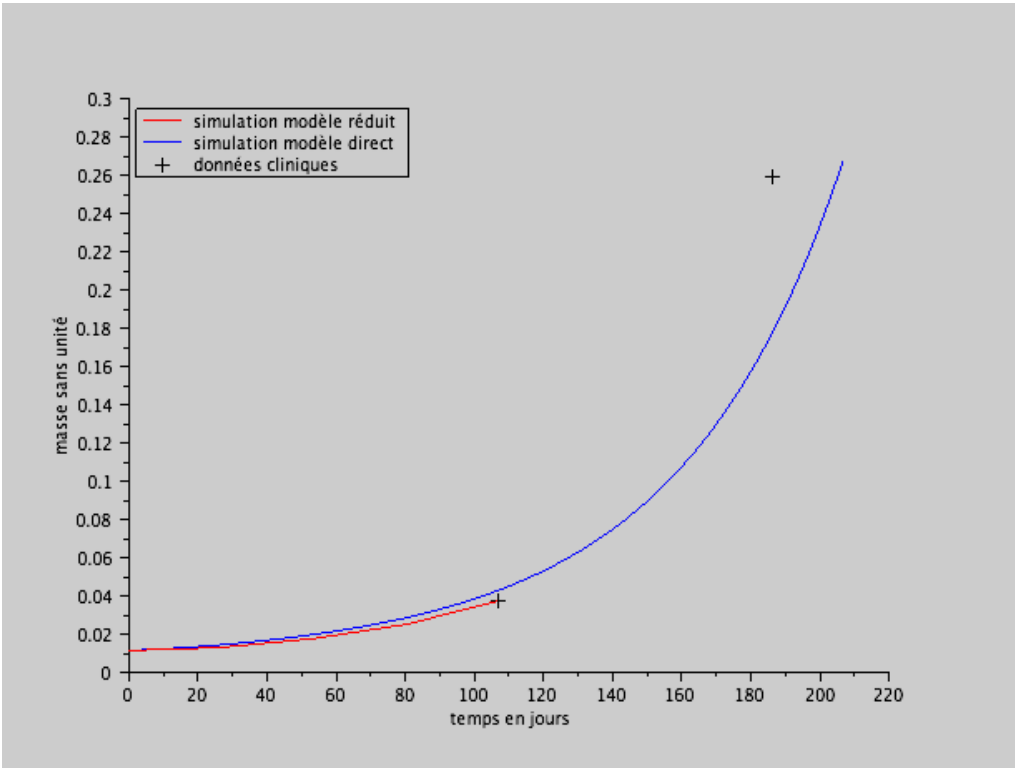
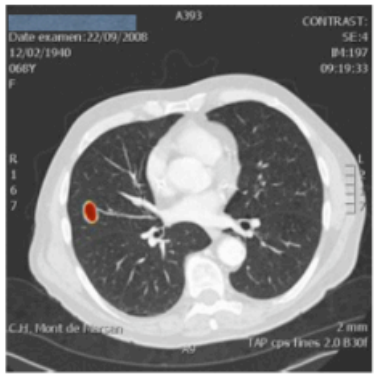
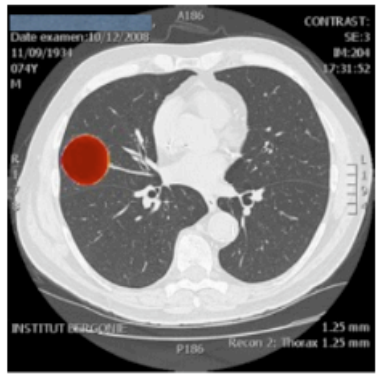
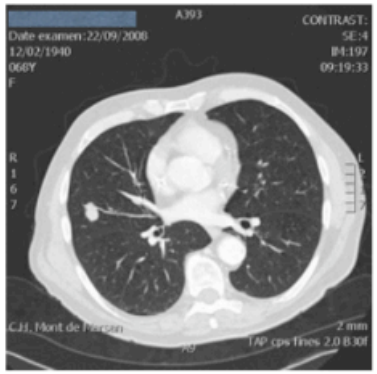
Modeling lung metastasis: Lung metastasis and chemo-2

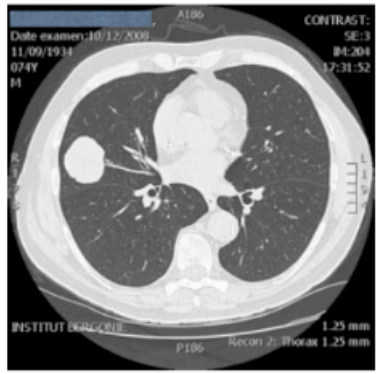
The result



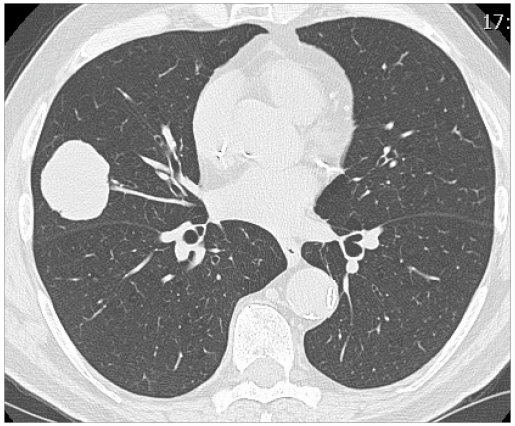


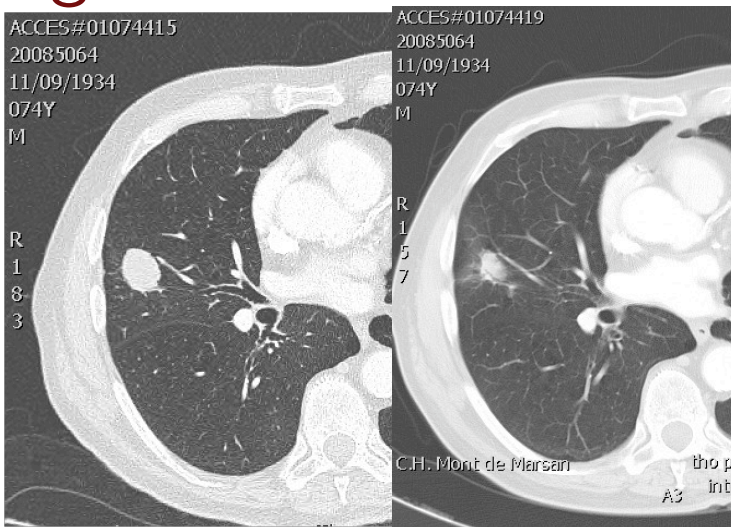


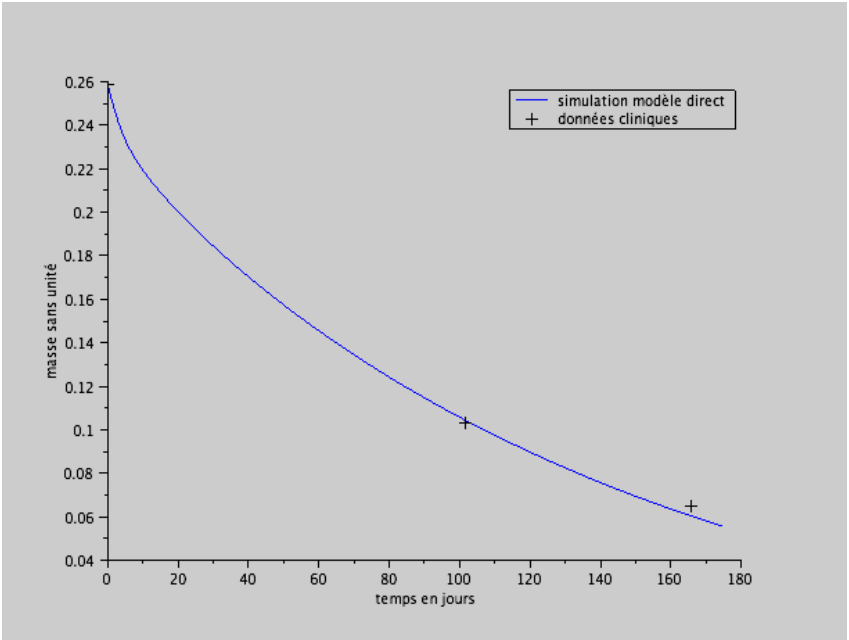




Modeling lung metastasis: Lung metastasis and chemo-3

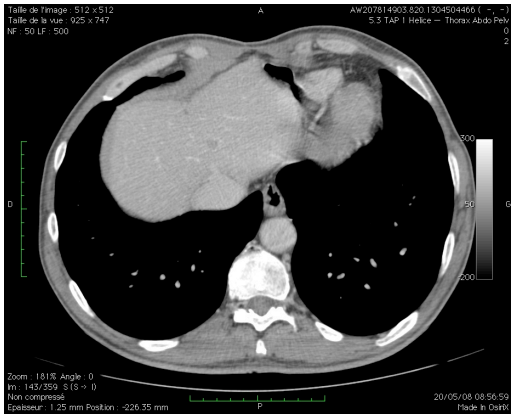






Liver metastasis-1

May, 20, 2008:



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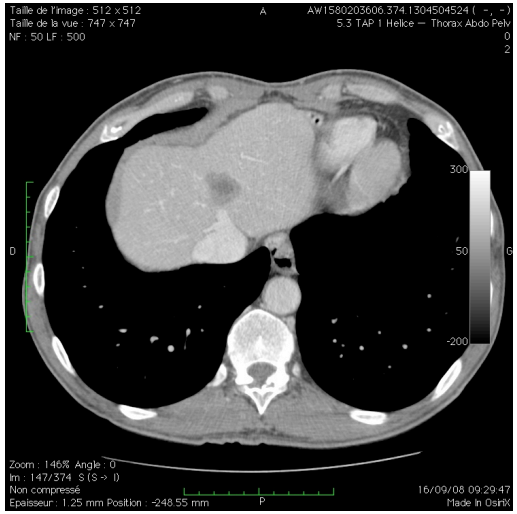
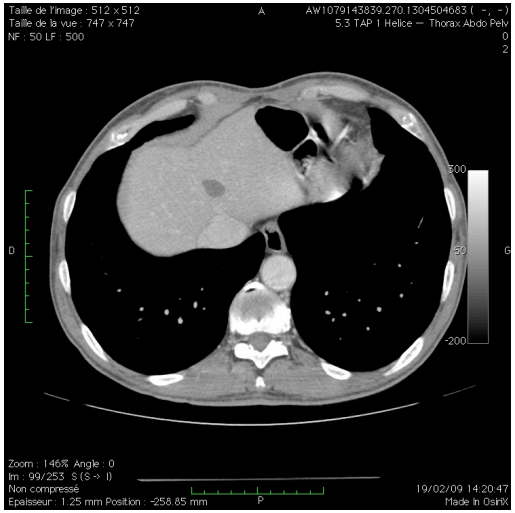
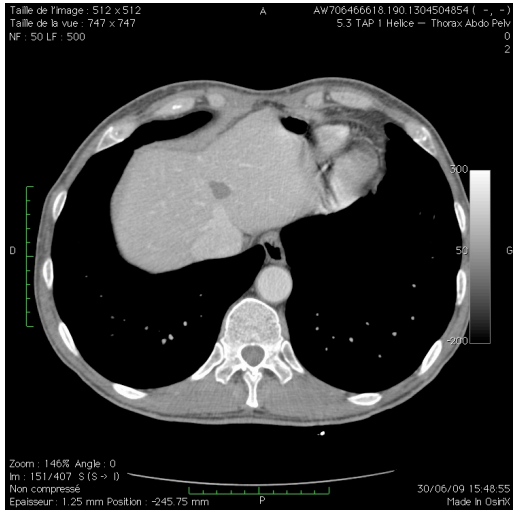


February 19, 2009:



June 30, 2009:



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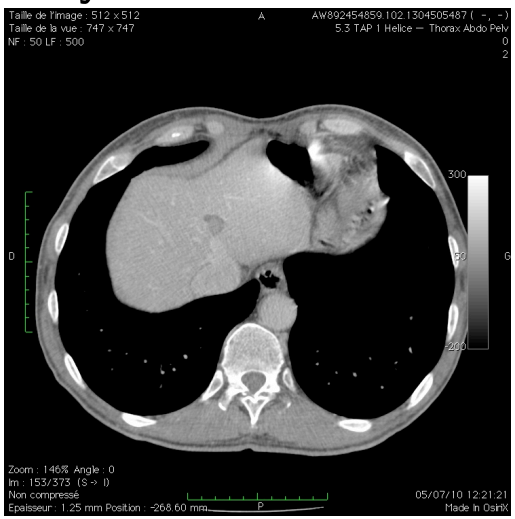
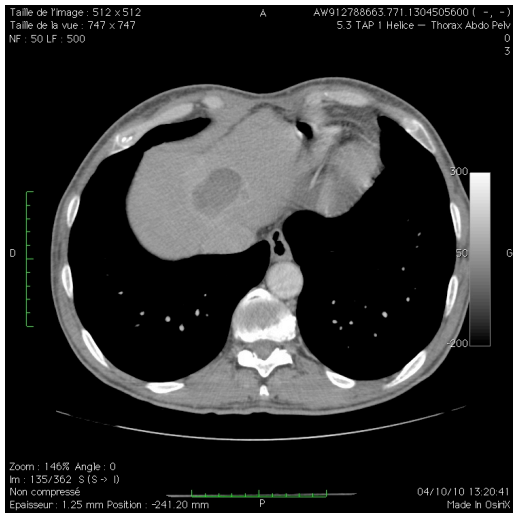
Liver metastasis-2

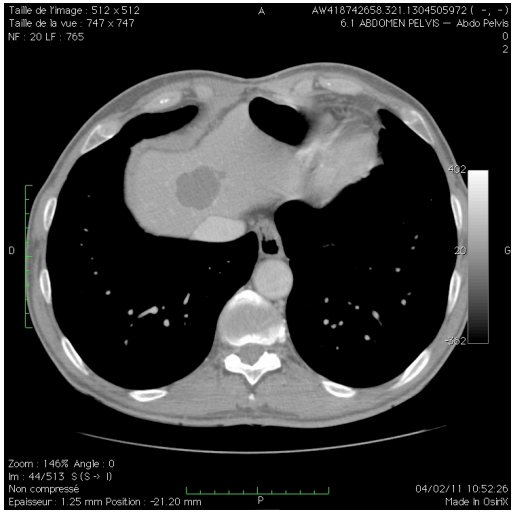
July 5, 2010:



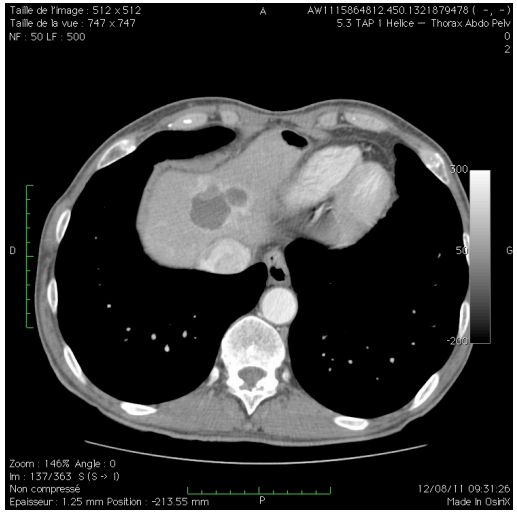
October 4, 2010:



February 4, 2011:



August 12, 2011:



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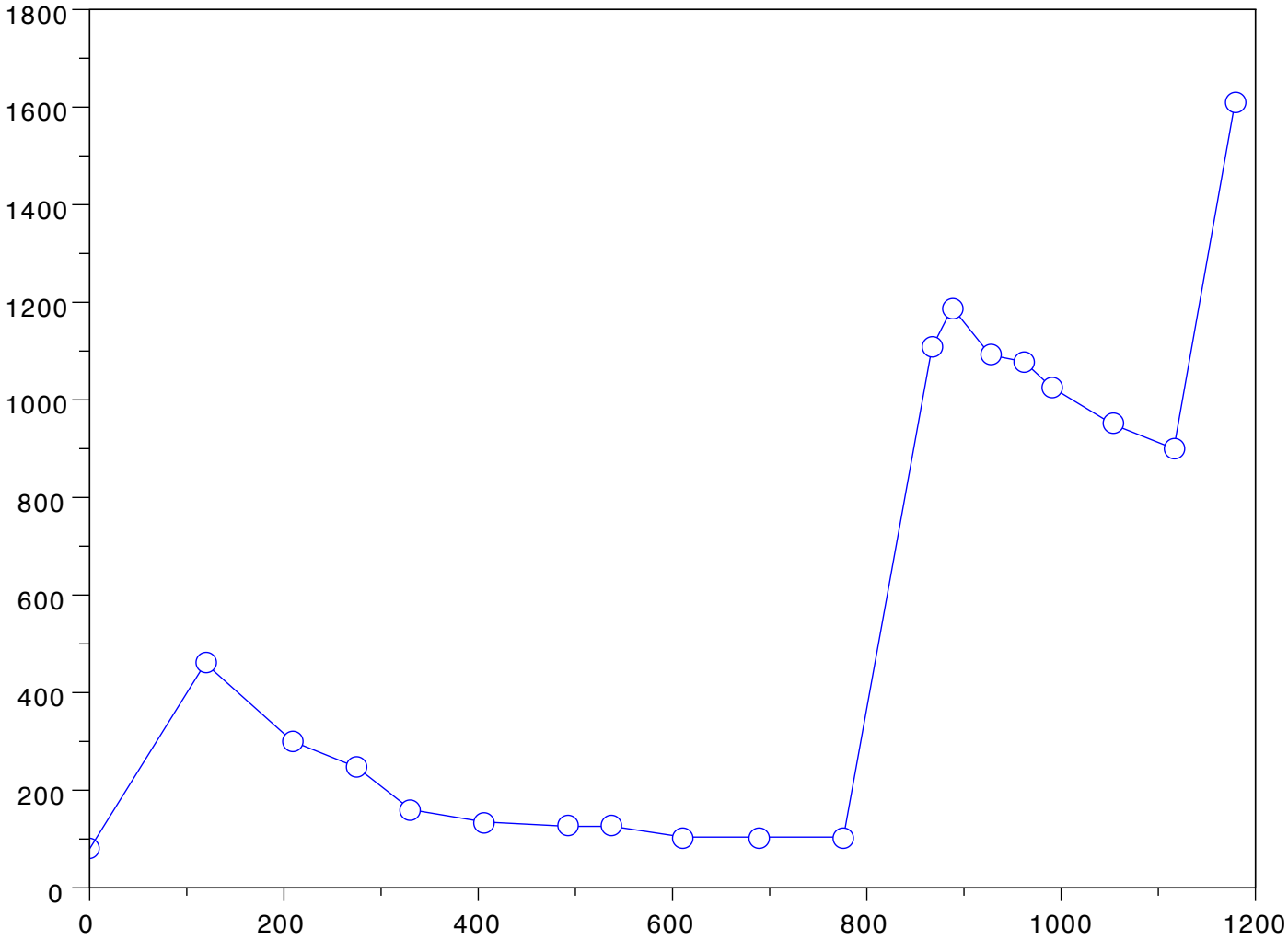
RECIST Criteria

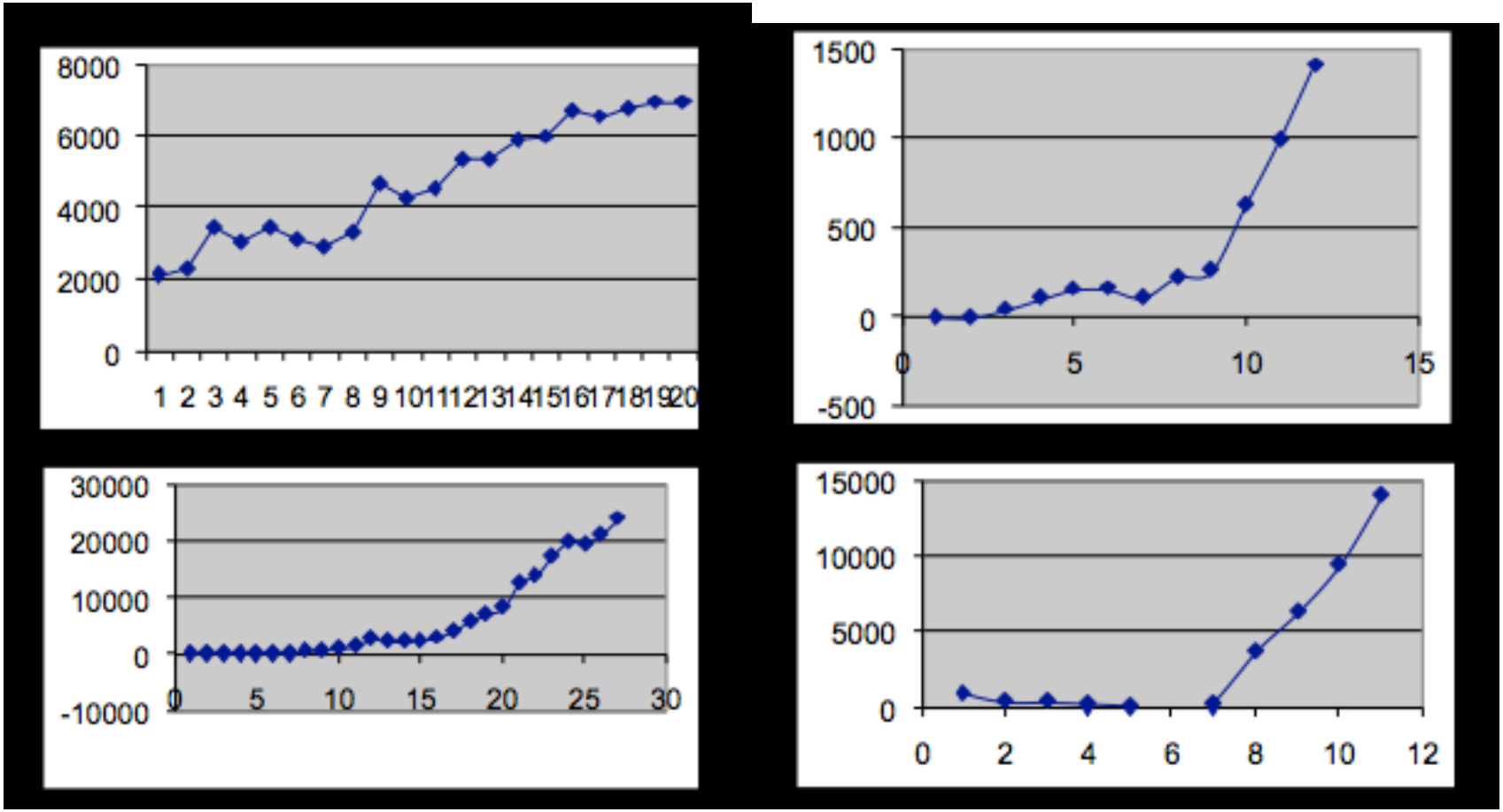


Hypotheses on the tumor for liver metastasis of a GIST

Observation Most cases of metastasis to the liver of GIST (Gastro-Intestinal Stromal Tumor) behaves similary:

- 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 other profiles



Two genetetic 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:

$$\partial_t P_1 + \nabla \cdot (vP_1) = \gamma_{PP} P_1 - \gamma_{PD} P_1 - (\delta f(t) + \nu(1 - g(t))MP_1,$$

$$\partial_t P_2 + \nabla \cdot (vP_2) = \gamma_{PP} P_2 - \gamma_{PD} P_2 - (\nu(1 - g(t))MP_2,$$

$$\partial_t P_3 + \nabla \cdot (vP_3) = \gamma_{PP} P_3 - \gamma_{PD} P_3,$$

Healthy cells:

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

- $\delta f(t)M$ antiproliferative drugs.
- γ_{PP} proliferation $= \frac{\gamma_0}{2} \{1 + \tanh[R(M - M_{hyp})]\}$.
- γ_{PD} apoptosis due to hypoxia $\frac{\gamma_1}{2} \{1 - \tanh[R(M - M_{hyp})]\}$.

Healthy tissue, blood flux and necrosis

Necrotic tissues:

$$\partial_t N + \nabla \cdot (vN) = \gamma_{PD}(P_1 + P_2) + \gamma_{Sd} S$$

$$+\delta f(t) M P_1 + \nu(1 - g(t)) M(P_1 + P_2) - \mu(1 + M)N,$$

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:

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

- 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:

$$P_1 + P_2 + P_3 + S + N = 1$$

$$\nabla \cdot v = \gamma_{PP}(P_1 + P_2 + P_3) - \mu(1 + M)N$$

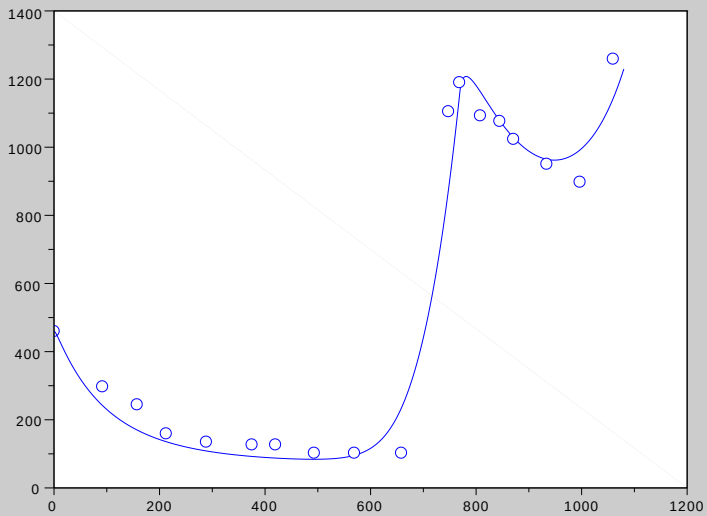
Darcy's law for the tissue:

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

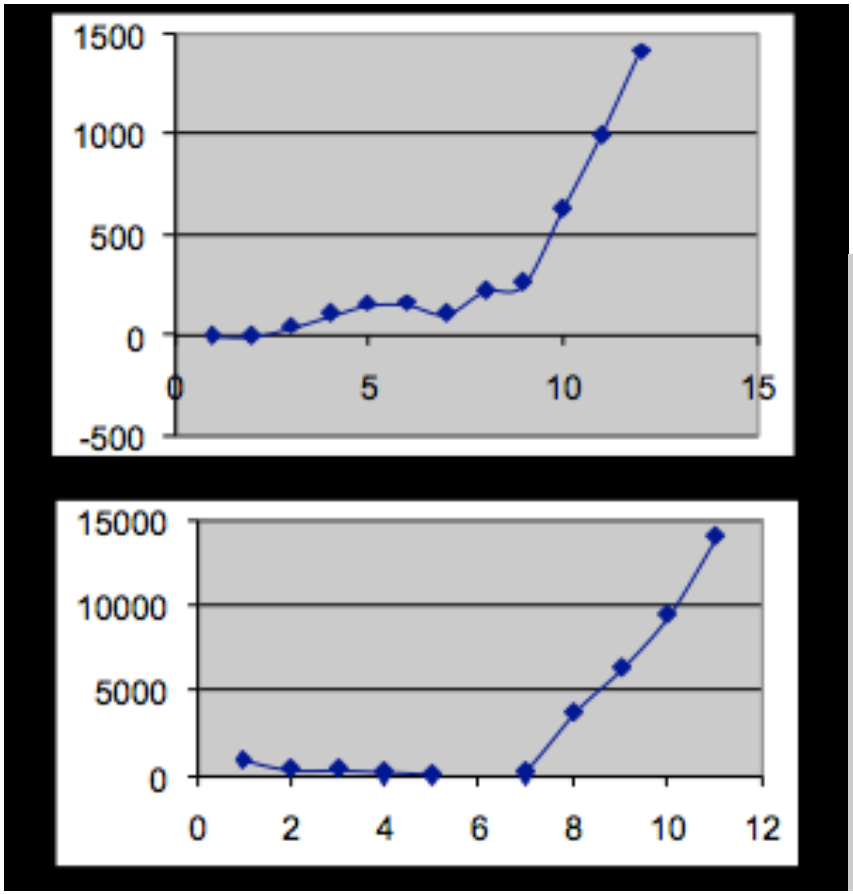
- Green Tumoral growth
- Blue Elimination of necrosis

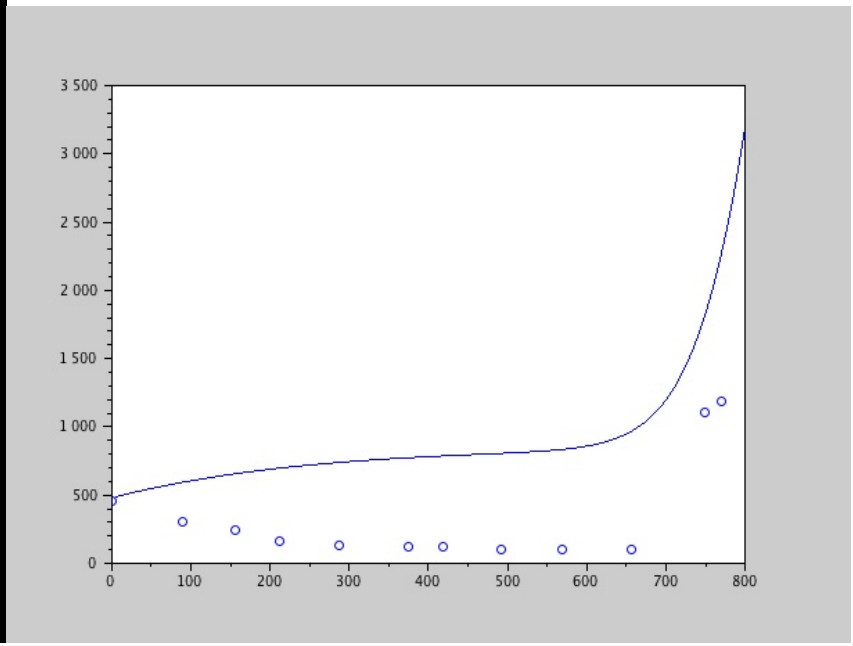
Comparison-1

Total number of tumor cells: Quantitative agreement.



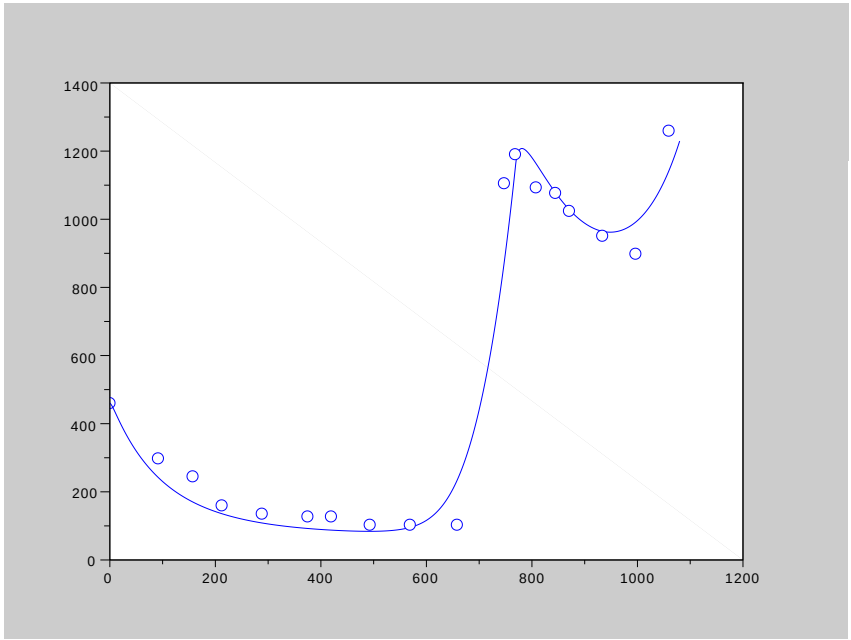
Comparison-2

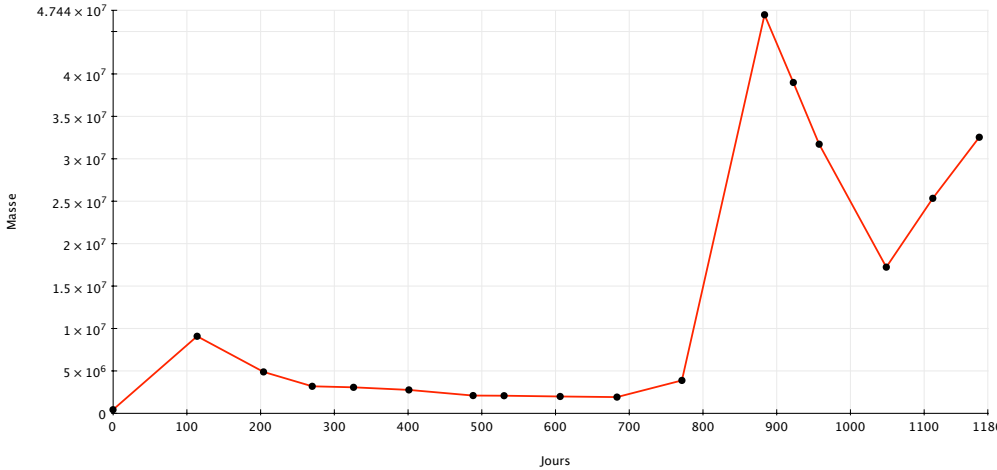


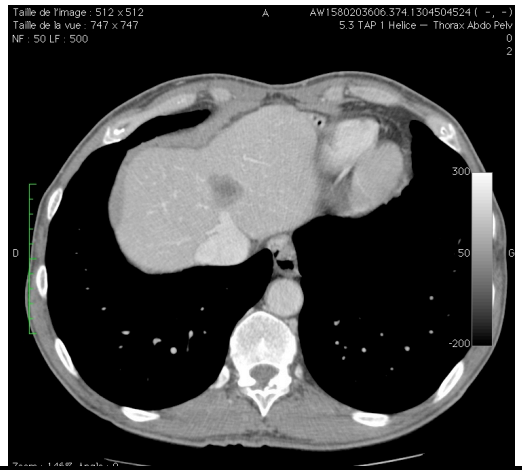


Comparison-3

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

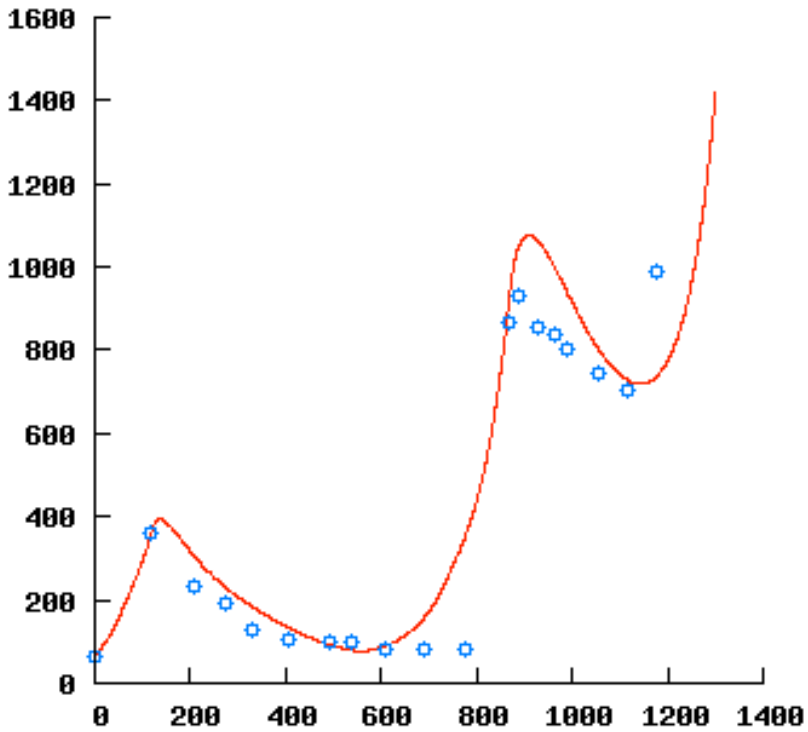


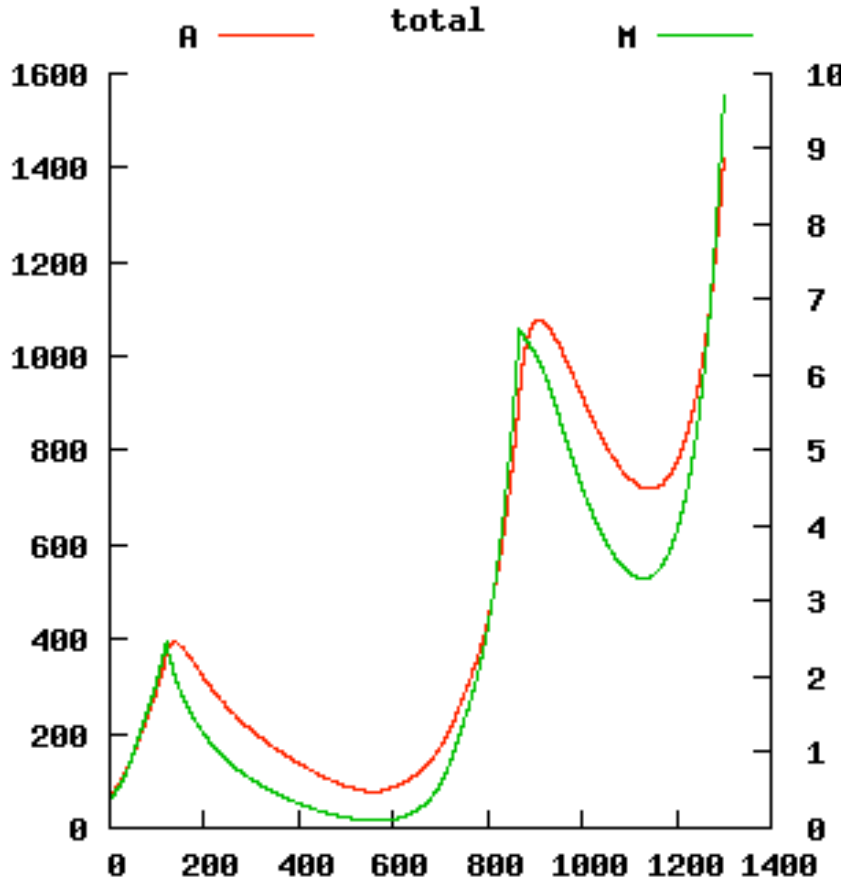




Comparison-4

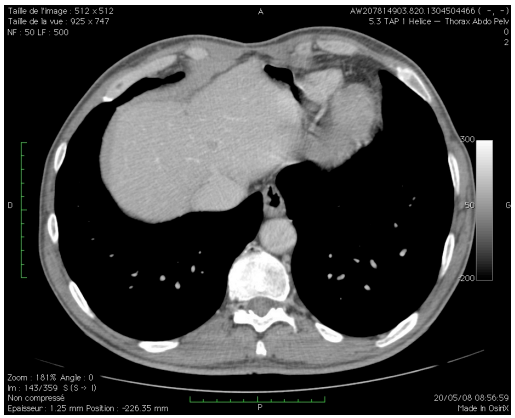
Use of the density in the scan: Necessity of Functional Imaging and spatial computations.

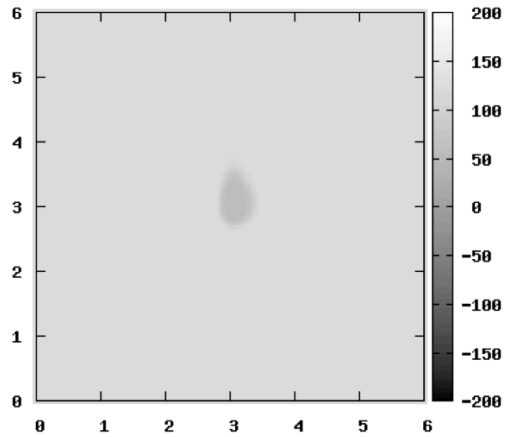




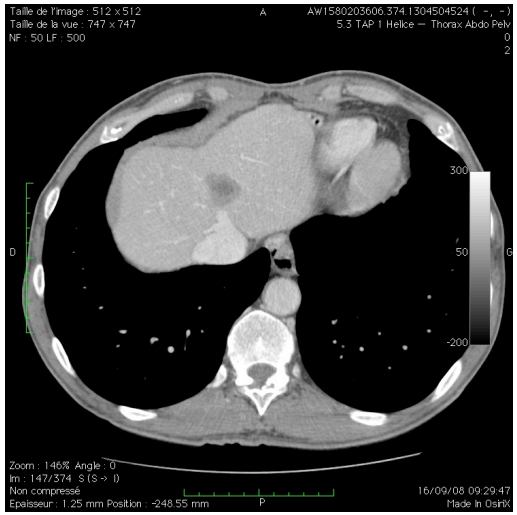
Comparison-5

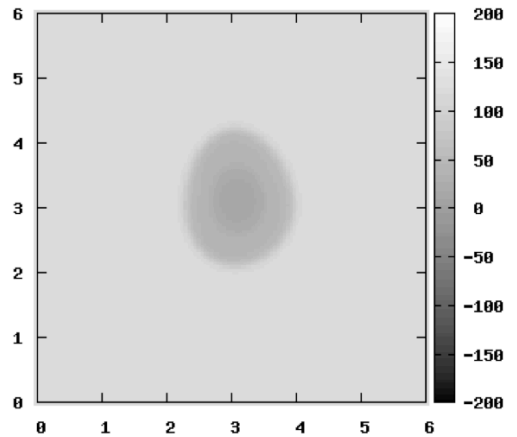
May, 20, 2008:





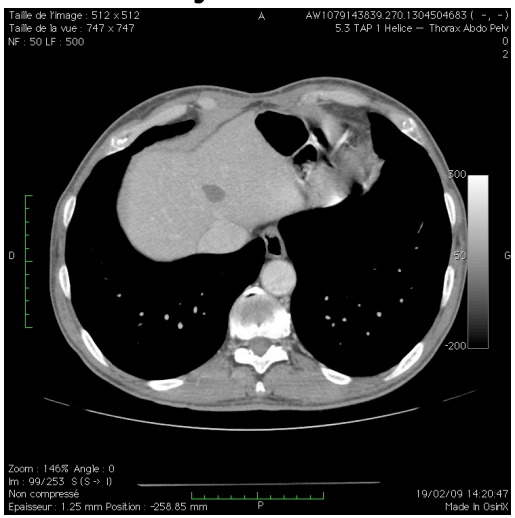
September 16, 2008:

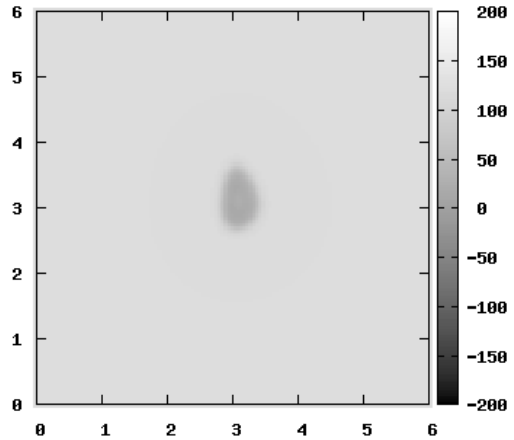




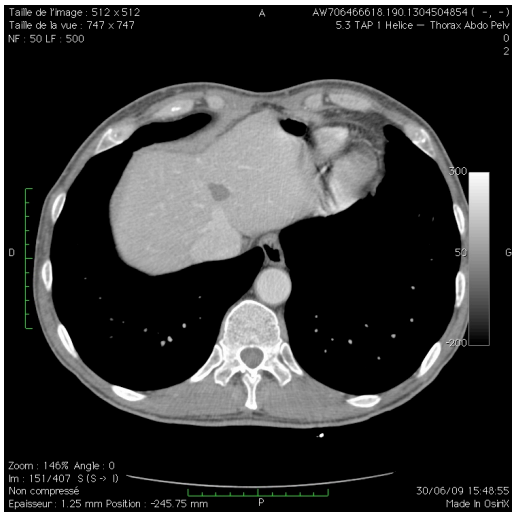
Comparison-6

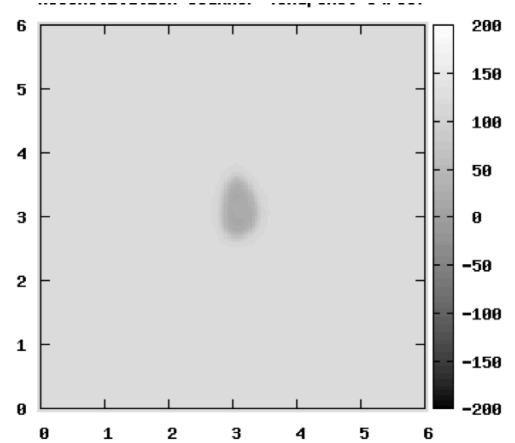
February 19, 2009:





June 30, 2009:

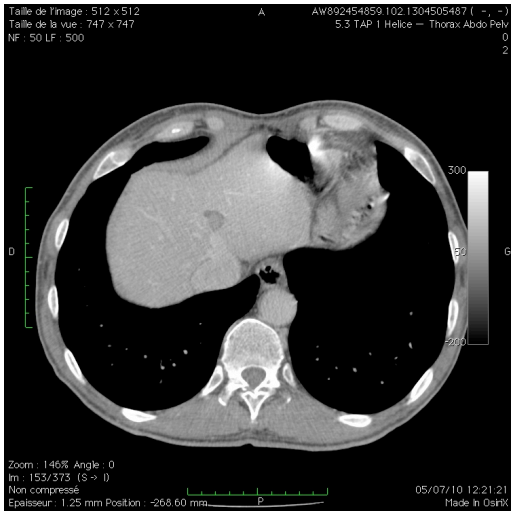


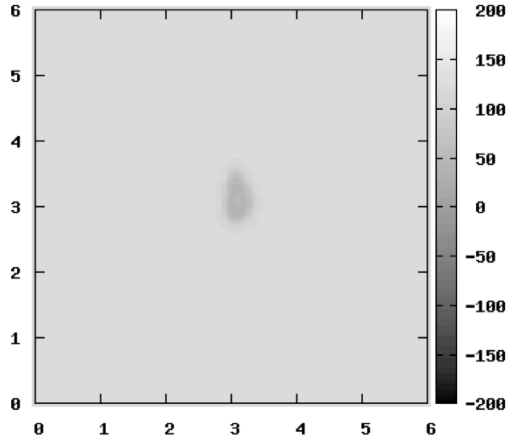


Institut Bergonié 2008-2009.

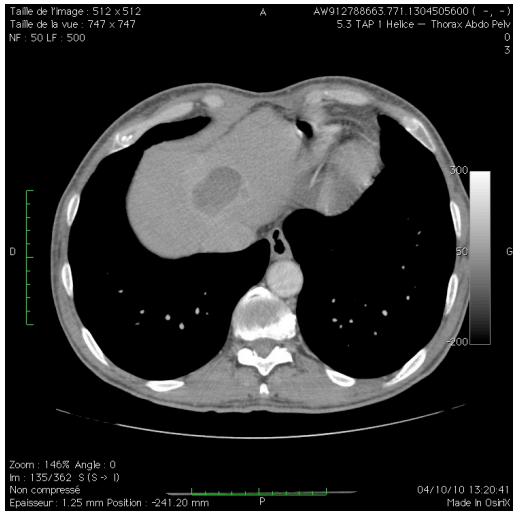
Comparison-7

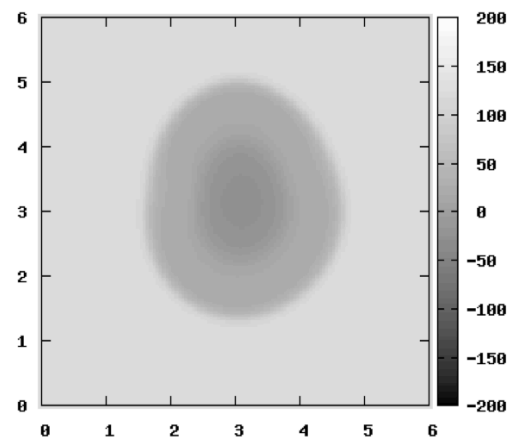
July 5, 2010:





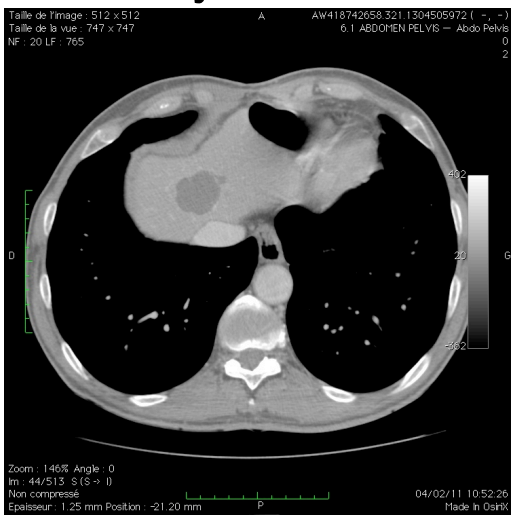
October 4, 2010:

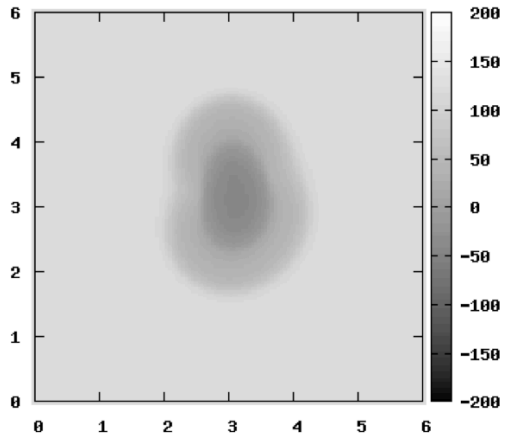




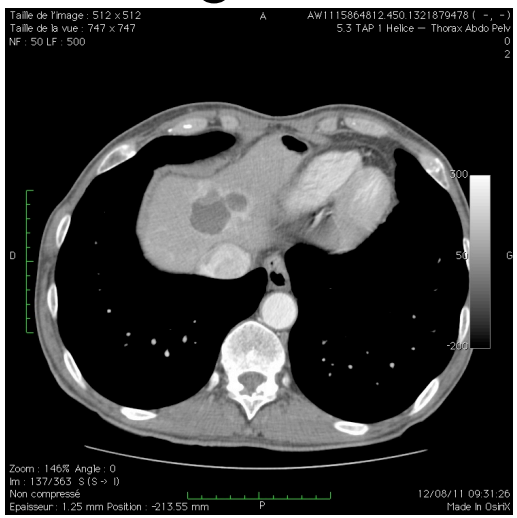
Comparison-8

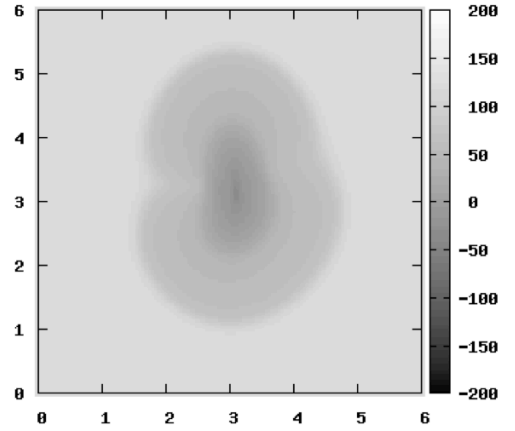
February 4, 2011:





August 12, 2011:





Institut Bergonié 2010-2011.

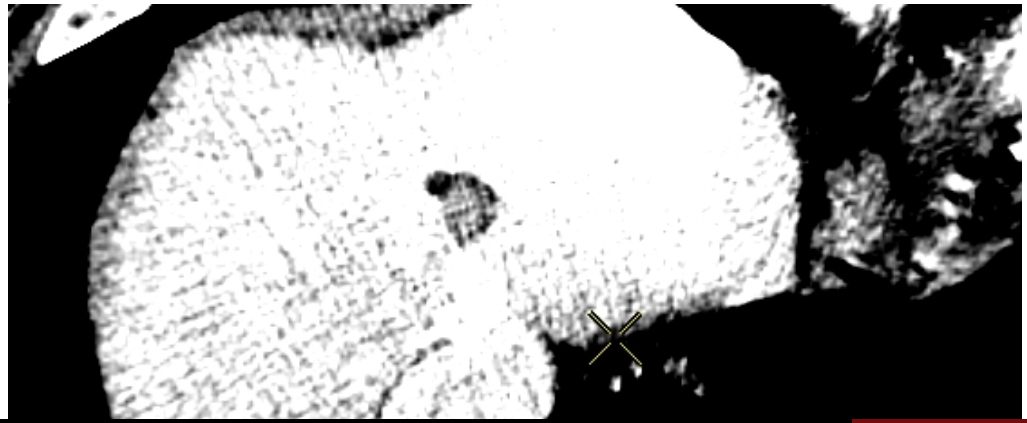
Conclusion

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)

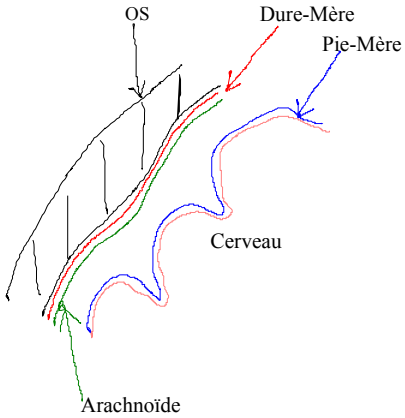
For the liver:

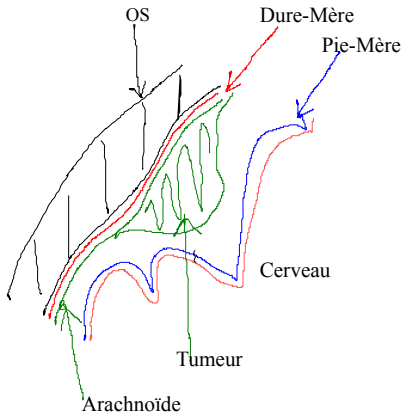
- Can we solve the inverse problem in order to predict the escape time? Probably: no!
- Use of functional imaging? Perfusion MRI?
- Work on the texture of the image (collaboration with GE).



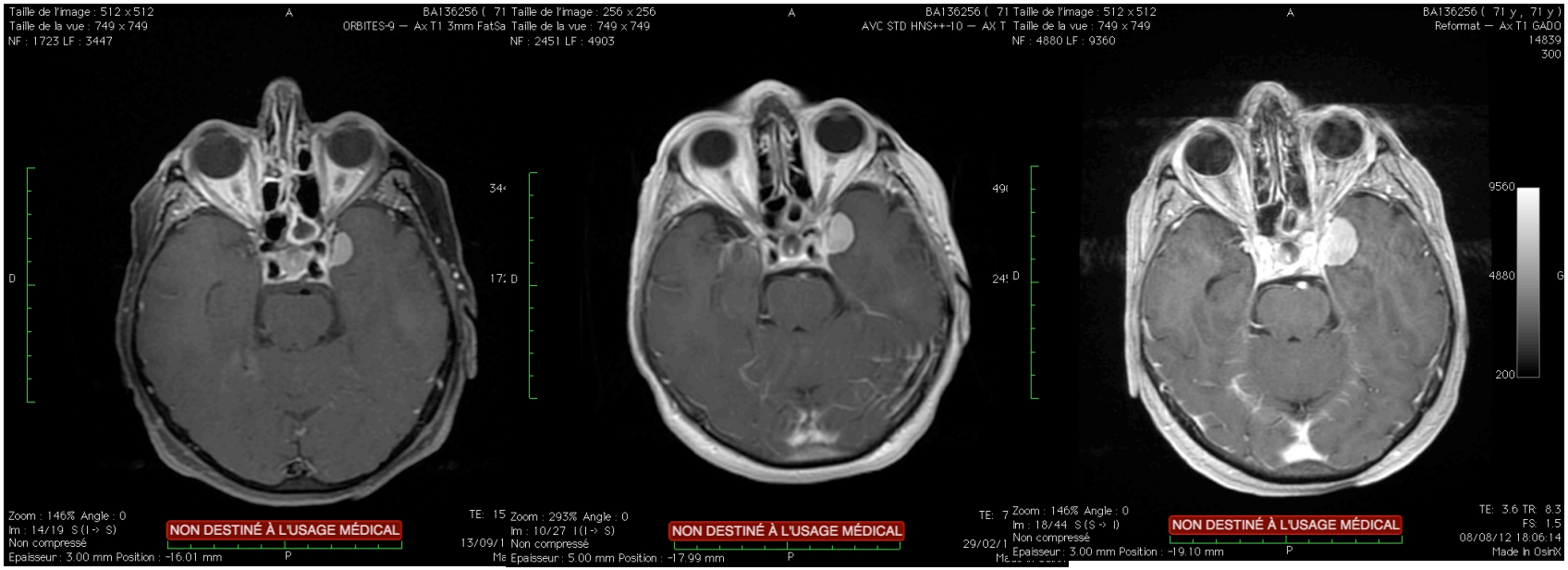
Conclusion-2: Meningiomas

Géométrie



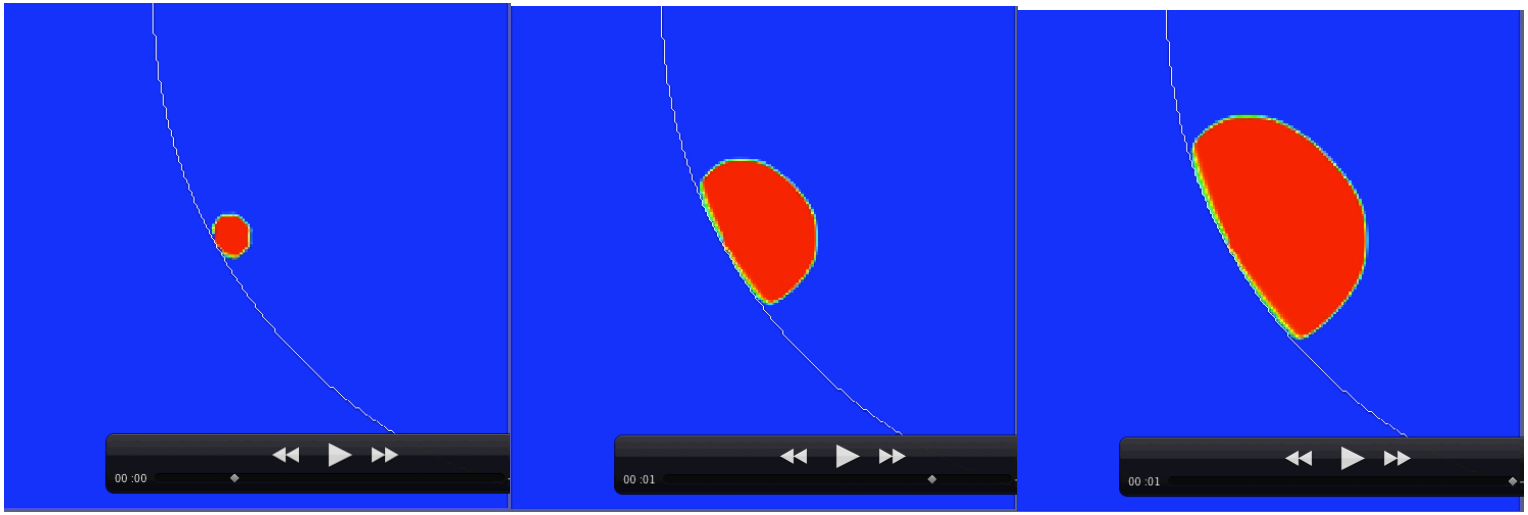


Conclusion-2: Meningioma: the data



CHU Bordeaux 2012.

Conclusion-2: Meningioma: the results



Conclusion-2: Meningioma-mixt effects

Pool of 30 patients with meningiomas with radiotherapy. Thesis of T. Haaser (CHU Bordeaux).