Mathematical modelling of tumor growth.

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with F. Billy, J.-P. Boissel, D. Bresch, E. Grenier, A. Iollo, D. Lombardi, J. Palussière, B. Ribba, O. Saut

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Introduction

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.

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Complex problem with many scales involved

- Genetic level: cells response to environmental factors depends on the set of mutations they have undergone.
- Cellular level: the evolution of a cell also depends on its close neighbourgh (*e.g.* cell-cell adhesion), nutrients.
- Macroscopic level: tumoral invasion, basal membrane...
- Organism level: metastasis,...

In this talk, we will describe a multi-scale model at molecular, cellular and macroscopic scales.

Goals

- Be able to predict the evolution of a tumor starting from medical imaging.
- Check in silico the efficacy of some treatments or of coupling of treatments.
- Decide for a particular case, which is the best strategy.

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Lung cancer

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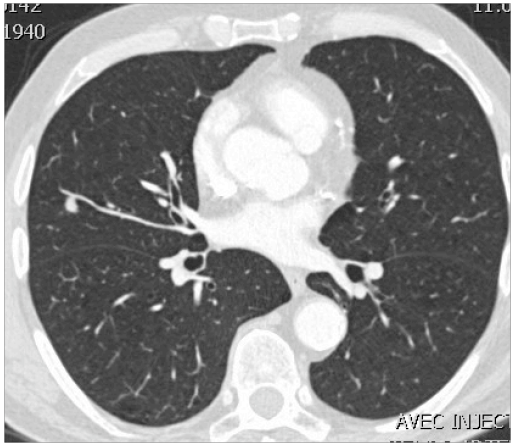

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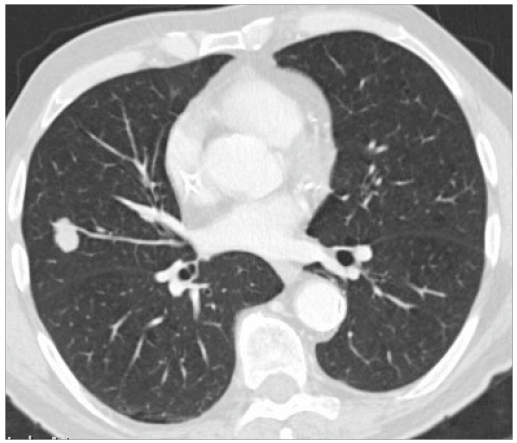

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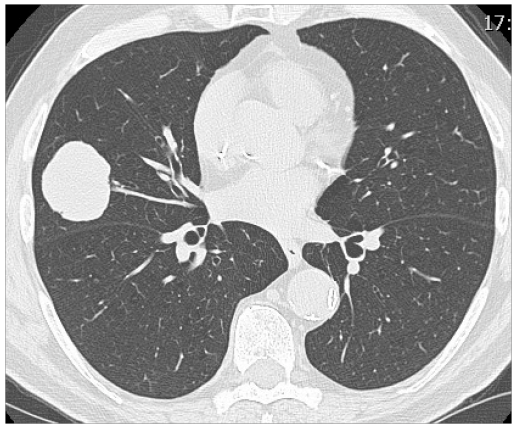

Institut Bergonié 2008.

In a ideal case, we need to model

- Genetic regulations and molecular pathways.
- Different populations of cells and their evolution.
- The diffusion of nutrients and the angiogenesis.
- The mechanics of the tissues and the interaction between the tumor and the healthy tissues
- The drug delivery.
- Obtaining parameters from medical imaging (MRI, scans, pet-scans)

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Existing models

Models exist at different scales:

- Microscopic models: discrete models
  - *Cellular automata:*
    - Easy description of small scale effects (genetic and cellular scales).
    - Movement?, Computationally expensive.
- Macroscopic models: continuous models (average over a large number of cells).
  - *Boundary models:* one describes only the evolution of the tumoral boundary (Friedman, Lowengrub...)
    - Mathematical study, computationaly efficient. Good for spheroids
    - Microscopic environment? Realistic shape?
  - *Fluid models:* cells are described in a multi-fluid approach.
    - Computationaly efficient, CFD.
    - Rendering of smaller scales, fluidic approximation.

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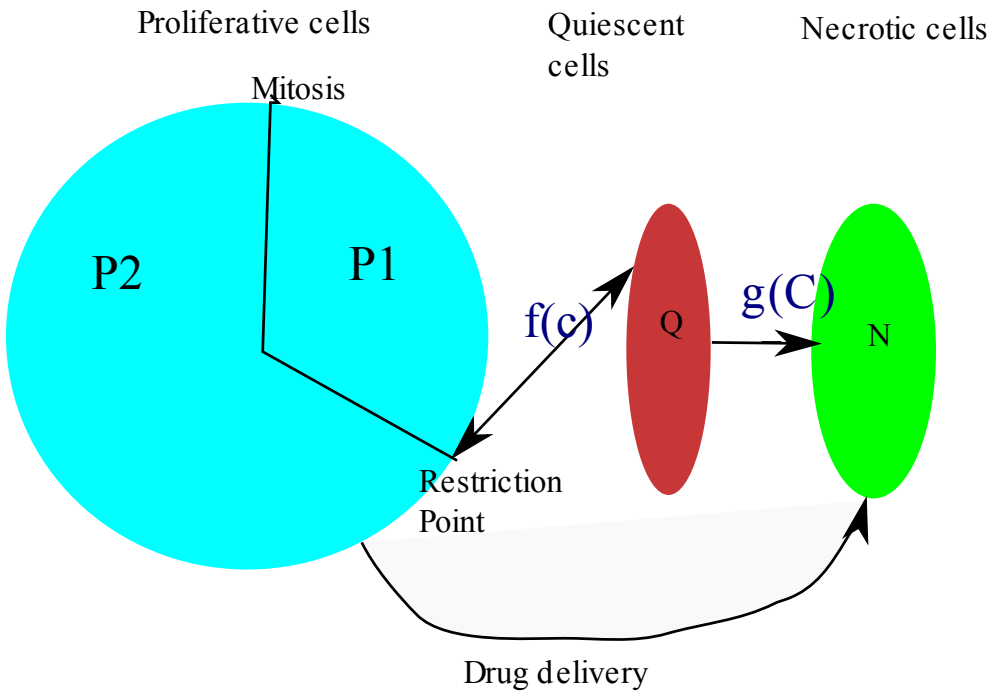
Outline

Part I

Description of the model

How to describe cellular division: the cell cycle

For the sake of simplicity, we consider that tumoral cells can be found in four phases. Their position in the cell cycle is described by the variable a :



Cancer cells

Evolution of the cancer cells

The three phases evolve through the following equations

$$
\begin{aligned}
\partial_t P_1 + \partial_a P_1 + \nabla \cdot (\mathbf{v}\, P_1) &= 0, \\
\partial_t P_2 + \partial_a P_2 + \nabla \cdot (\mathbf{v}\, P_2) &= 0, \\
\partial_t Q + \nabla \cdot (\mathbf{v}\, Q) &= g(1-f) P_1(a = a_{\max,P_1}) \\
&\quad - \left[\frac{d}{dt} f\right]^+ Q(t^-) + \left[\frac{d}{dt} g\right]^- Q(t^-), \\
\partial_t N + \nabla \cdot (\mathbf{v}\, N) &= (1-g) P_1(a = a_{\max,P_1}) \\
&\quad - \left[\frac{d}{dt} g\right]^- Q(t^-),
\end{aligned}
$$

The transition between phases of the cell cycle is also described by boundary conditions (on the variable a).

Boundary conditions

The boundary conditions on a:

$$\begin{cases} P_1(a=0) = 2\,P_2(a=a_{\max,P_2}), \\ \\ P_2(a=0) = f\,P_1(a=a_{\max,P_1}) + \left[\frac{d}{dt}f\right]^+ Q(t^-). \end{cases}$$

Expansion

Evolution of healthy cells

Let us denote by M the density of sane tissue. It satisfies

$$\partial_t M + \nabla \cdot (\mathbf{v} M) = 0.$$

We assume that the following saturation assumption holds

$$M + \int_a (P_1 + P_2) + Q = 1.$$

Summing the evolution equations on M, P_1, P_2, Q and N we obtain an additional equation on $\mathbf{v}$.

Divergence of the velocity

$$\nabla \cdot \mathbf{v} = P_2(a_{\max,P_2}).$$

Computation of the velocity

In order to describe the dynamic of the motion of the tumor, one has to calculate the velocity $\mathbf{v}$. Classically, the velocity and pressure are obtained through a Darcy's law.

Darcy's law

$$\begin{cases} -\nabla(k\nabla P) &= P_2(a_{\max,P_2}), \\ \mathbf{v} &= -k\nabla P, \end{cases}$$

where k is the porosity.

Oxygen

- The oxygen concentration is denoted by $C(t, \mathbf{x})$.
- Oxygen is consumed by tumoral cells and undergoes a diffusion process.
- We also assume that in a part of the domain, this concentration C is fixed (blood vessels...).

Evolution of the oxygen concentration

$$\begin{cases} -\nabla \cdot (D \nabla C) = -\alpha_1 (P_1 + P_2) - \alpha_2 (Q + M) - \alpha_3 C \text{ on } \Omega \setminus O, \\ C = C_0 \text{ on } \partial\Omega, \\ C = C_{\max} \text{ on } O. \end{cases}$$

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Angiogenesis

- The hypoxic tumor cells secrete VEGF.
- VEGF attract unstable endothelial cells by a chemotaxis motion and binds to endothelial cells.
- After maturation, unstable endothelial cells become stable and form new blood vessels.
- Endostatin is released by living tumor cells (proliferative and quiescent) and binds to the endothelial cells.
- Angiopoietin1 they bind to unstable endothelial cells. They are necessary for the maturation of the blood vessels.
- Angiopoietin2 is produced by tumor cells and unstable endothelial cells. They bind to unstable endothelial cells. They block the maturation of the blood vessel.

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Unstable endothelial cells

$$\frac{\partial n}{\partial t} = \nabla\cdot(D_e\nabla n)+\alpha n\left(1-\frac{n+n_s}{N_{max}}\right)-\nabla\cdot\left(\chi\frac{n+n_s}{N_{max}}\nabla[VEGF]\right)-\frac{\partial n_s}{\partial t}.$$

variation = diffusion + proliferation + chemotaxis + maturation.

- $D_e = C_e(1-\lambda(P+Q+N))$: less diffusion in the tumor.
- $E_{VEGF,prolif} = \frac{1}{1+\frac{K_V}{[VEGF]}\left(1+\frac{[endos]}{K_e}\right)}$.
- $\chi = \frac{\chi_{max}}{1+\frac{K_V}{[VEGF]}\left(1+\frac{[endos]}{K_e}\right)}$.

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Stable endothelial cells

$$\frac{\partial n_s}{\partial t} = \mu H(E_{Ang1} - E_{Ang1,min}) H(n + n_s - N_{min}) n,$$

- μ is the maturation rate
- $E_{Ang1} = \frac{E_{max}}{1+\frac{K_{ang1}}{[Ang1]}\left(1+\frac{[Ang2]}{K_{ang2}}\right)}$ the maximal effect of angiopoietin-1.
- H the Heaviside function.

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VEGF

$$0 = \nabla \cdot (D_V \nabla [VEGF]) + \alpha_V Q - \beta_V n - \delta_v [VEGF].$$

variation = diffusion + production − binding + natural decay.

- Binding rate $\beta_V = \frac{\beta_{max,V}}{1+\frac{K_V}{[VEGF]}\left(1+\frac{[endos]}{K_e}\right)}$

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Angiopoietin-2

$$0 = \nabla \cdot (D_A \nabla [Ang2]) + \alpha_{A1}(P + Q) + \alpha_{A2} n - \beta_A n - \delta_A [Ang2].$$

variation = diffusion + production − binding + natural decay.

- Binding rate $\beta_A = \dfrac{\beta_{max,A}}{1 + \frac{K_{A2}}{[Ang2]}\left(1 + \frac{[Ang1]}{K_{A1}}\right)}$

Position of blood vessels: $O = \{\mathbf{x} \in \Omega,\ n_s(t, \mathbf{x}) \neq 0\}$.

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Position of blood vessels: $O = \{\mathbf{x} \in \Omega,\ n_s(t, \mathbf{x}) \neq 0\}$.

Part II

Applications

Anti-angiogenic drugs

One uses an intratumoral administration of an adenovirus encoding the endostatin gene.
Overproduction due to treatment.

$$0 = \nabla \cdot (D_V \nabla[endos]) + \alpha_e (P + Q) - \beta_e n - \delta_e [endos]$$

$$+ C_{endos} \alpha_e (P + Q) \mathbf{1}_{[t_1, t_2]}.$$

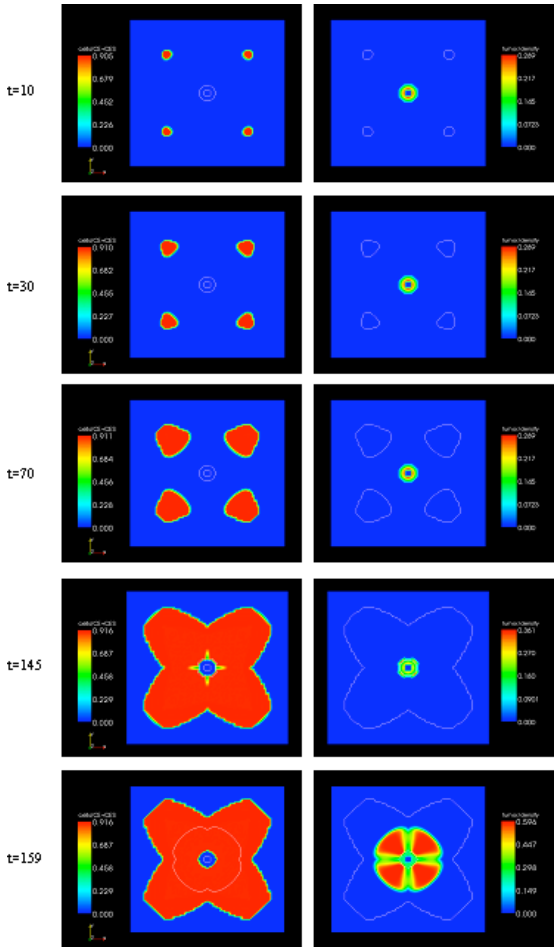


Figure 7: From top to down: spatio-temporal evolution of endothelial cells (unstable + stable) and tumor cells densities. Left panel, pictures show the spatio-temporal evolution of endothelial cells (density) proliferating and migrating from the pre-existing vessels towards tumor cells. The contour fine line delimitates the area of the tumor. Right panel, pictures show the spatio-temporal evolution of tumor cells density. Fine contour line delimitates the distribution of endothelial cells.

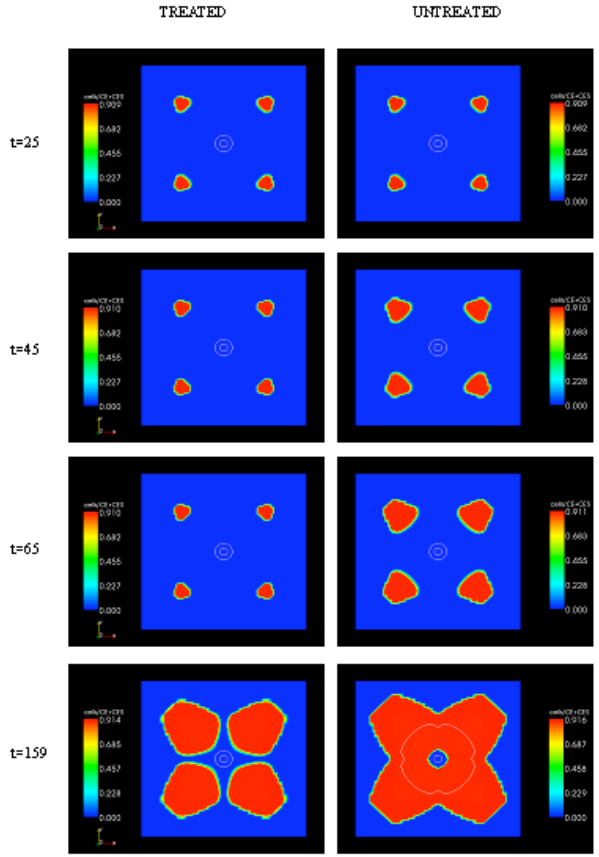


Figure 8: From top to down: spatio-temporal evolution of endothelial cells density with (left panel) and without (right panel) endostatin overproduction (from t=30 to t=60). The contour fine line delimitate the tumor.

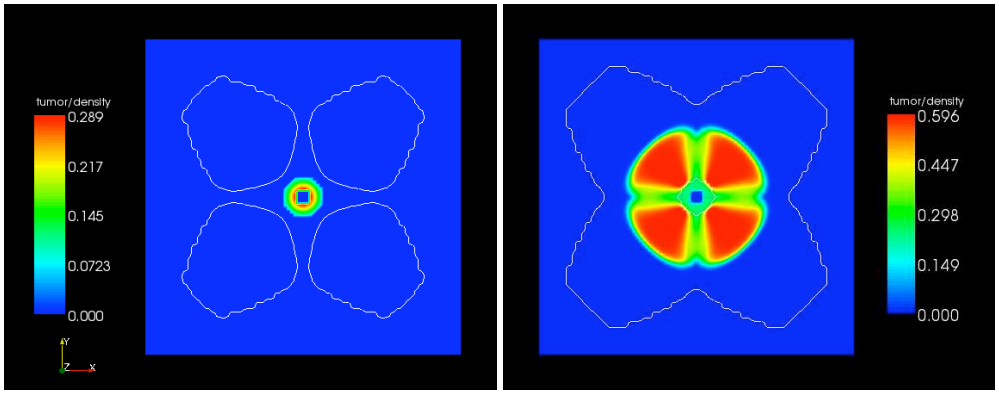
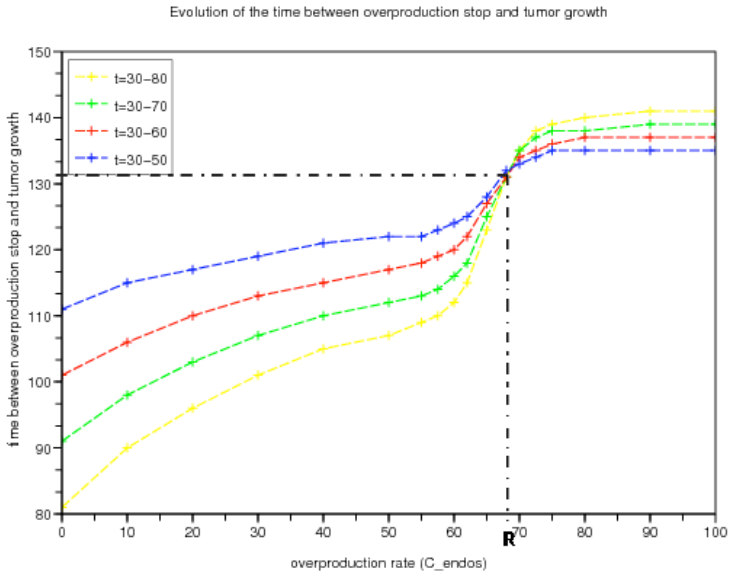


Figure 9: Tumor density at time=159 (end of simulation) with (left panel) and without (right panel) endostatin overproduction. The fine line shows the contour of endothelial cells.



Simulation of a growth of a lung tumor

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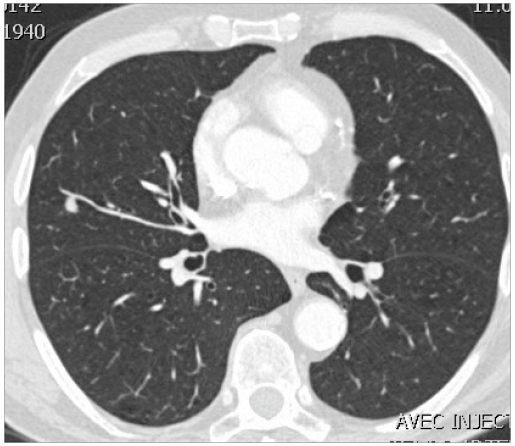

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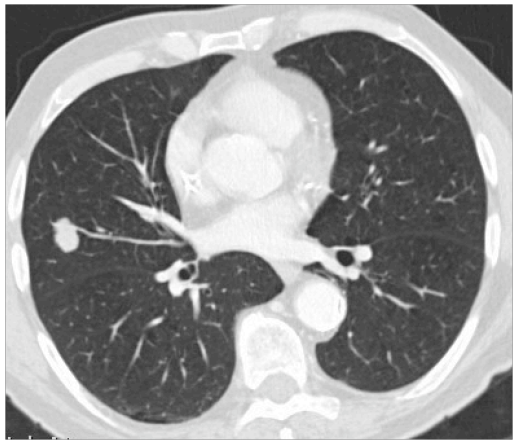

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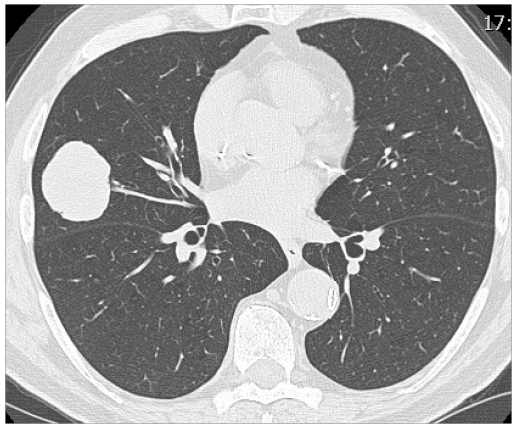

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Simulation of a growth of a lung tumor

A very simplified model

Population of cells

$$\partial_t P + \nabla \cdot (vP) = (2\gamma - 1)P,$$

$$\partial_t Q + \nabla \cdot (vQ) = (1 - \gamma)P,$$

Velocity

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

Oxygen

$$\nabla \cdot (D(P, Q)\nabla C) = \alpha PC + \lambda C, \mathrm{D} = D_{max} - K(P + Q),$$

Growth rate

$$\gamma = \frac{1 + \tanh(R(C - C_{hyp}))}{2}$$

Simulation of a growth of a lung tumor

The inverse problem

Since we have acces only to $Y = P + Q$, write the equation satisfied by $Y = P + Q$:

$$\partial_t Y + \nabla \cdot (vY) = \gamma P$$

.

The other equations becomes:

$$\nabla \cdot v = \gamma P$$

$$k(Y)\nabla \times v = \nabla k(Y) \times v$$

$$\nabla \cdot (D(Y)\nabla C) = \alpha PC + \lambda C, \mathrm{D} = D_{max} - KY.$$

Simulation of a growth of a lung tumor

The inverse problem

- Unkowns: Parameters: k_2/k_1, D_{max}, K, α, λ, C_{hyp}.
  Fields that are not observable: v, P, C.
- Normally, only two-three scans are available: the problem is greatly under-determined.
- Infinitely many solutions are possible and fit the images in an optimal sens.

Simulation of a growth of a lung tumor

The POD decomposition

$$P = a_i^{(P)} \phi_i^{(P)}, \ i = 1 \dots N_P$$
$$C = a_i^{(C)} \phi_i^{(C)}, \ i = 1 \dots N_C$$
$$v = a_i^{(v)} \phi_i^{(v)}, \ i = 1 \dots N_v$$
$$\gamma P = a_i^{(\gamma P)} \phi_i^{(\gamma P)}, \ i = 1 \dots N_{\gamma P}$$

Eigenfunctions are extracted from a database of simulations by means of a Proper Orthogonal Decomposition (POD).

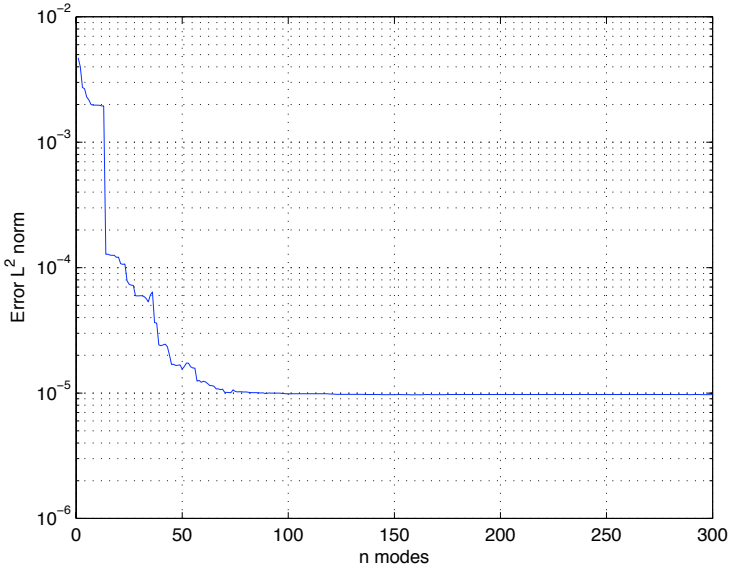
$$\phi_i = \frac{\sum_j b_j^i P_j}{\lambda_i^{1/2}}$$

where λ and b are the eigenvalues and the eigenvectors of the autocorrelation matrix:

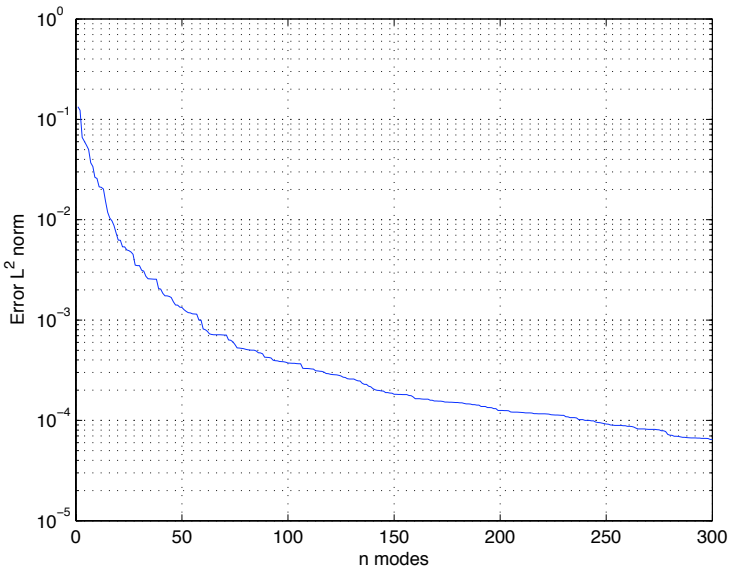
$$A_{ij}^P = < P_k(t_h), P_m(t_n) >, \ h, n = 1, ..., N; \ k, m = 1, ..., M.$$

Simulation of a growth of a lung tumor

The base is orthonormal.



Representation of C



Representation of P

Simulation of a growth of a lung tumor

The POD expansion are substituted into the equations written for the observable Y:

$$\partial_t Y + a_i^v \nabla \cdot (Y \phi_i^v) = a_j^{\gamma P} \phi_j^{\gamma P}$$

$$a_i^v \nabla \cdot \phi_i^v = a_j^{\gamma P} \phi_j^{\gamma P}$$

$$k(Y) a_i^v \nabla \times \phi_i^v = \nabla k(Y) \times a_i^v \phi_i^v$$

$$a_i^C \nabla \cdot k(Y) \nabla \phi_i^C) = \alpha a_i^C a_i^P \phi_i^C \phi_i^P + \lambda a_I^C \phi_i^C$$

$$2 a_i^{\gamma P} \phi_i^{\gamma P} = 1 + \tanh(R(a_i^C \phi_i^C - C_{hyp}))$$

Unkowns: Parameters: k_2/k_1, D_{max}, K, α, λ, C_{hyp}.
Expansion coefficients: a_i^v, a_i^P, a_i^C, $a_i^{\gamma P}$.

Simulation of a growth of a lung tumor

- Solution of the non-linear system written at the time t, when Y is observed: minimization of the residual.
- Residual is minimized using a Newton solver
- Condition on the variable P are imposed via a penalization technique.
- Reaction-Diffusion equation for the oxygen is critical since the variable is not observed, but entirely regularized.

Simulation of a growth of a lung tumor

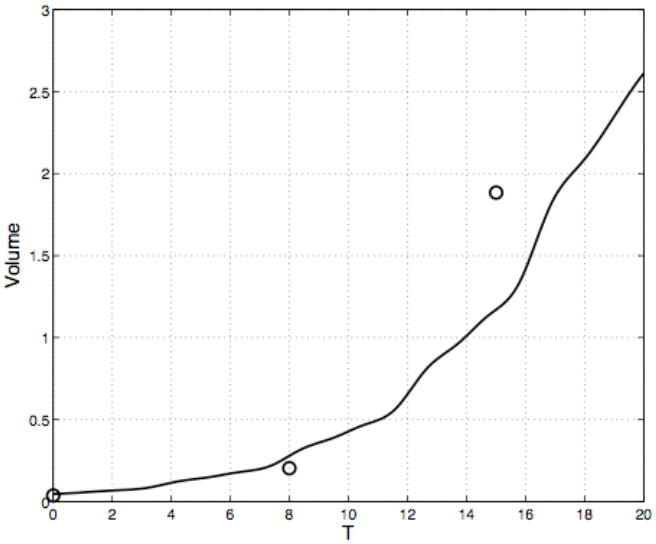
- In the equation for the observable the time derivative dY/dt is unknown.
- To solve the problem the time derivative is approximated by interpolation.
- Several type of interpolation have been tested:
  i) Linear: $Y = tA + (1-t)B$.
  ii) Exponential: $\partial_t Y = Aexp(\zeta t) + Bexp(-\zeta t)$.
  iii) Logistic: $Y = AG(\omega, \sigma) + BG(-\omega, -\sigma)$ where $G(\omega, \sigma) = \frac{\omega \exp(\omega t)}{\omega - \sigma \exp(\omega t)}$.

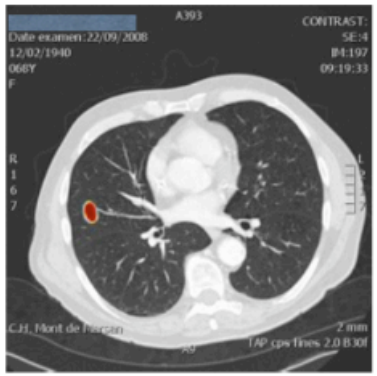
Simulation of a growth of a lung tumor

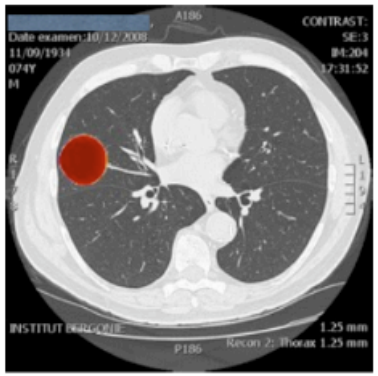
The result

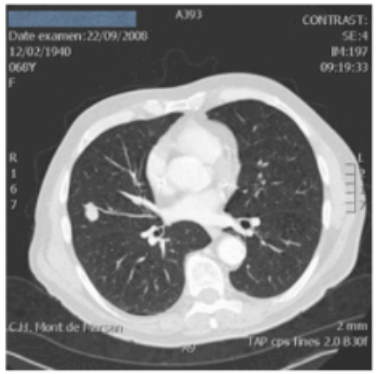
Volume history:

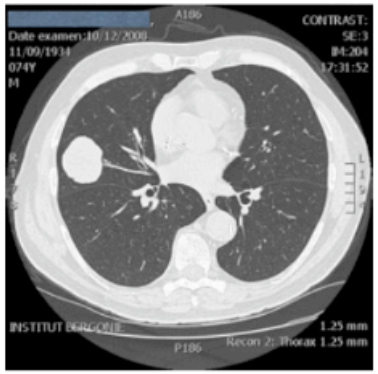
- Simulation (continuous line);
- scan (circle)





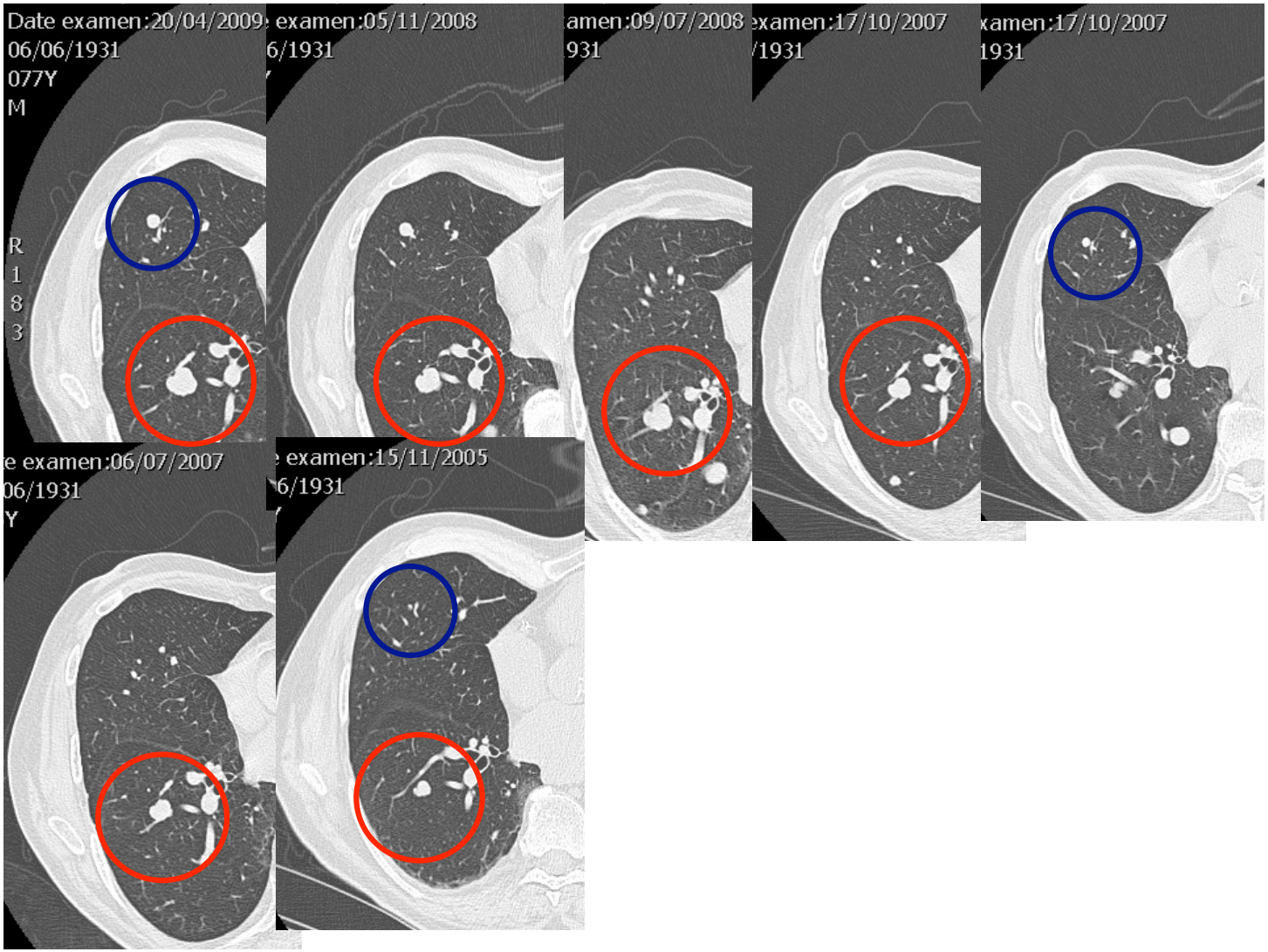






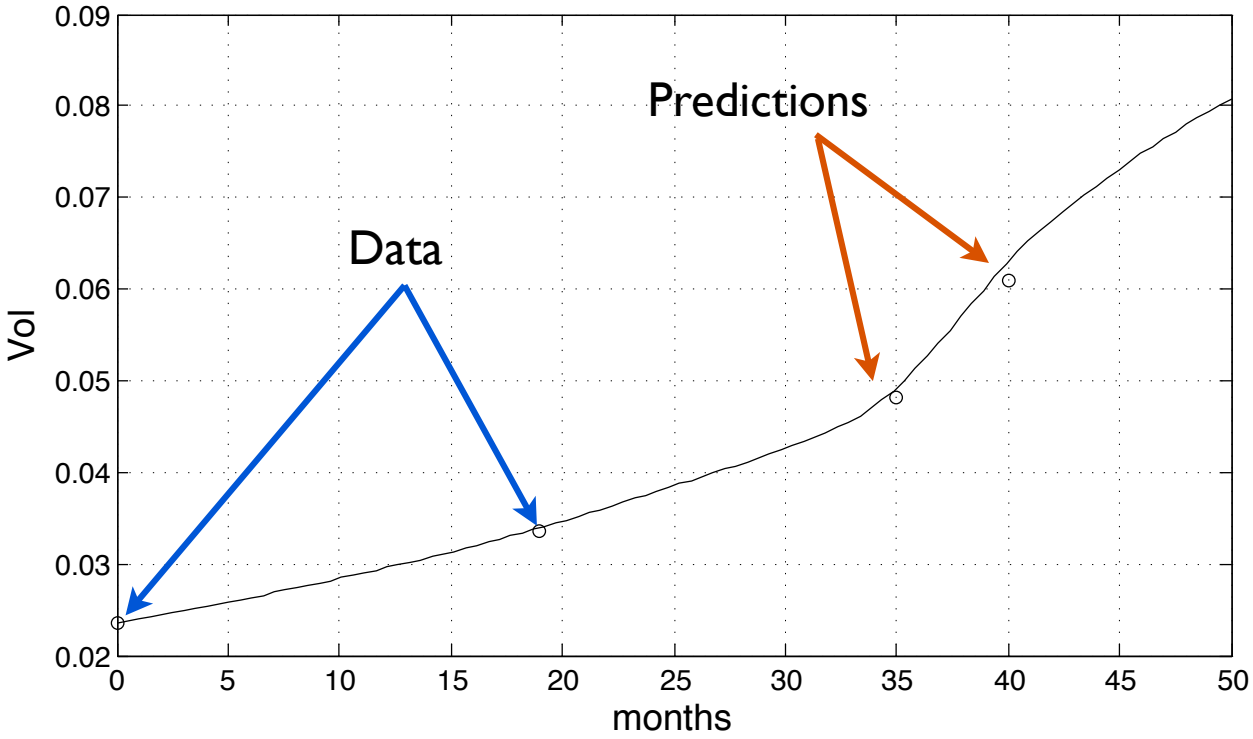
Simulation of a growth of a lung tumor

The next one



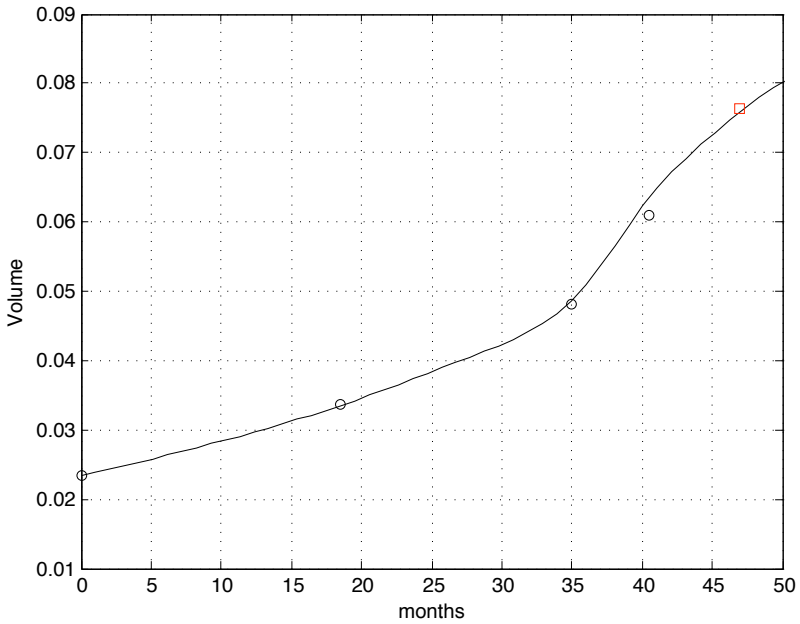
Simulation of a growth of a lung tumor

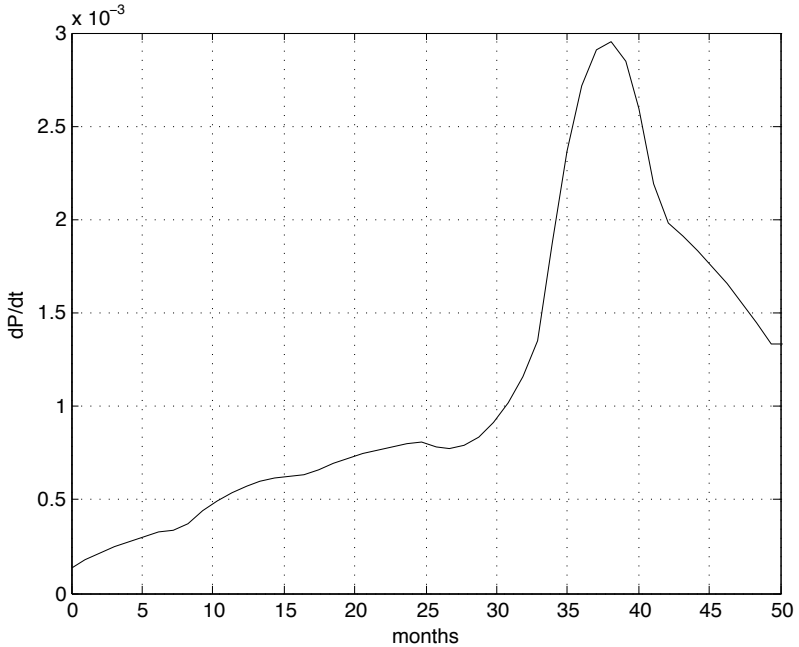
The result



Simulation of a growth of a lung tumor

The result

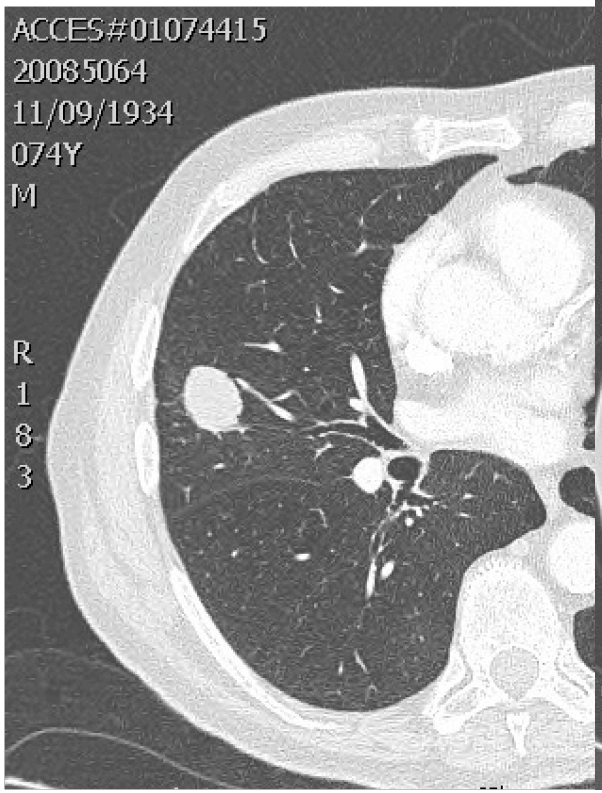




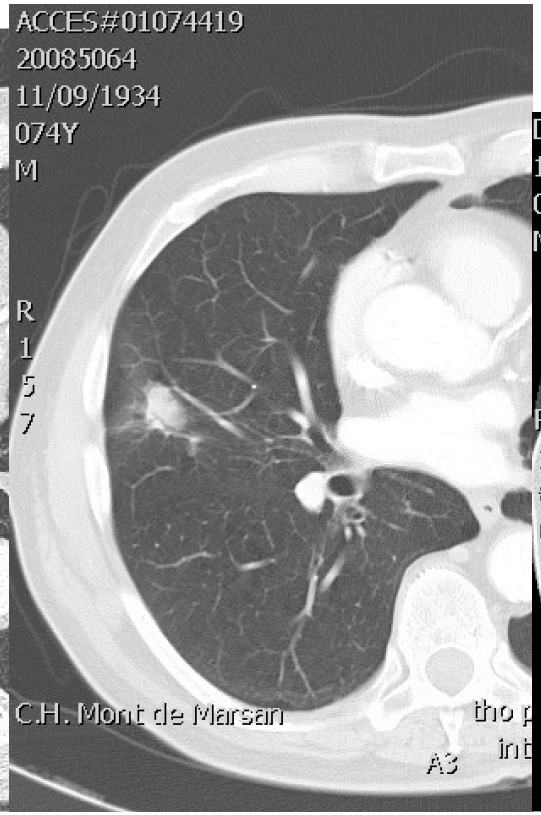
Conclusion

- We need to develop specific model for specific tumor, e.g. Gliomas for Brain cancer.
- We need to add the effect of combined treatment (chemiotherapy+ antiangiogenic..)
- A huge effort to obtain a software usefull for Medical Doctors

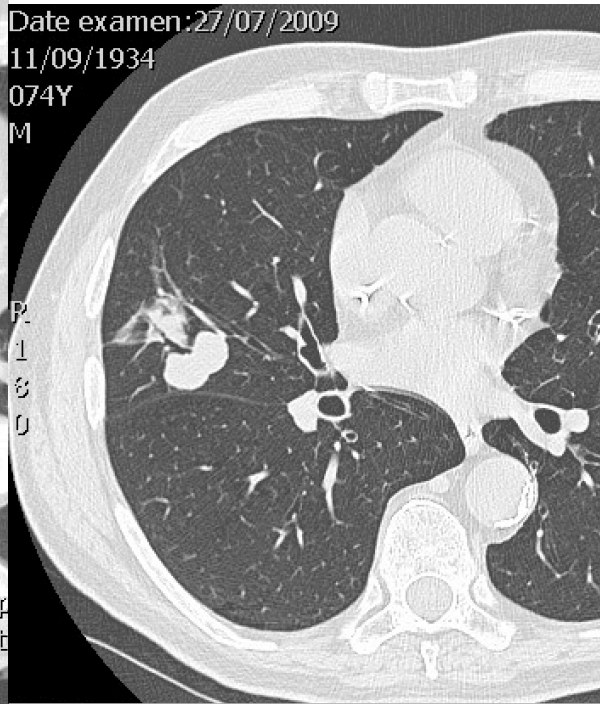
Next test case



During chemotherapy.



Juste after.



2 months later.