Mathematical models of tumoral growth

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Introduction

We are interested in modeling cancer growth.

- 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.

Main collaborators:

INRIA EPI MC2: T. Colin, A. Iollo, JB Lagaert, D. Lombardi, Y. Mammeri, C. Poignard.

INRIA NumMed: D. Bresch, E. Grenier, B. Ribba.

Institut Bergonié: J. Palussière.

INSERM U577: M.C. Durieu, F. Guillemot.

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Problem 1: deriving *adequate* models

We would like to derive mathematical models adequate to describe tumoral growth:

- Models should behave according to our knowledge of biology.
- They should be easily/efficiently discretized.
- Ultimately, we want quantitative results to make predictions.

We choose to consider continuous models based on PDEs because:

- they are not so computationally expensive (when compared to discrete models).
- they can render a lot of biological phenomena and in particular the mechanical effects (interaction between cells is a weak part of discrete models like models based on cellular automata).

Basis of continuous models based on PDEs

Each species (nutrient, cellular types...) **is described by its density depending on time and space variables** *e.g.* N(t,**x**).

In order to describe the evolution of the system, one has to write an evolution equation on N.

Classically, we write down that the total mass is conserved in every elementary volume, yielding the so-called *mass-balance equation*.

We write the conservation of matter between two times arbitrary close.

Evolution equations on densities

One gets $$\partial_t N + \nabla \cdot \mathbf{J} = \text{birth} - \text{death},$$

where **J** is the total flux of cells *i.e.* the density of cells entering/exiting this elementary volume.

Two different problems to model:

- **Description of cellular movement** occurring through the flux term **J**. *In this talk*, we will assume that the flux has the form $\mathbf{J} = N\mathbf{v}$, where **v** is the velocity corresponding to the movement due to cellular division.
- **Description of cellular division** and cellular death appearing as source terms.

These problems may be coupled: cellular incompressibility prescribes $\nabla \cdot \mathbf{v}$

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Accounting for the cell-cycle

Classically, cancer growth is given by a linear, exponential or logistic term. For instance:

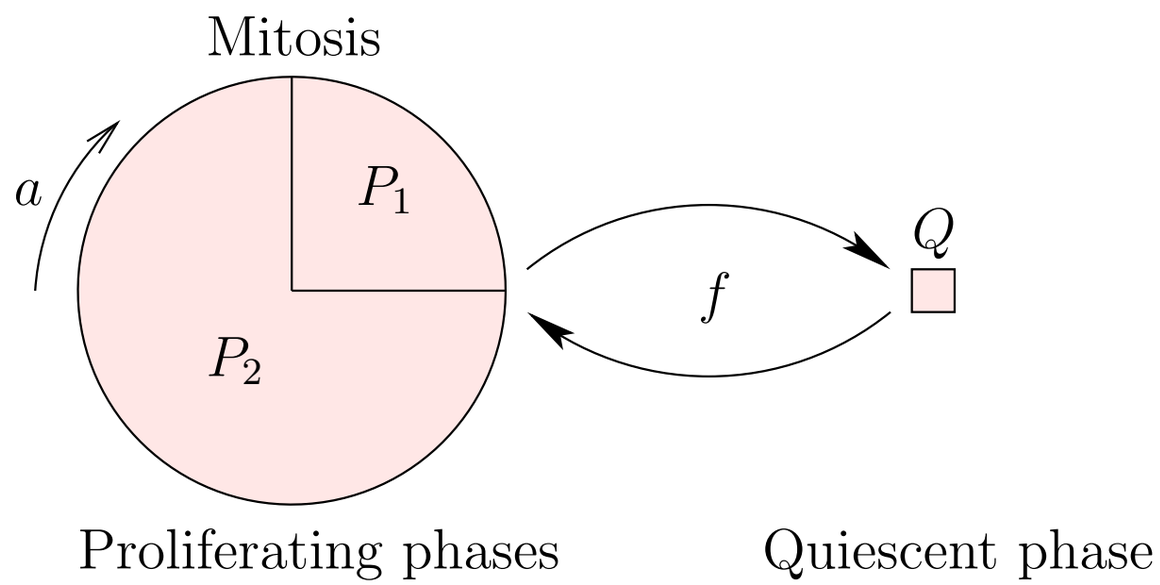
$$\partial_t N + \mathrm{Mov.} = \alpha(\mathrm{Env})N(1-N),$$

Where $\mathrm{N(t,x)}$ is the number of cancer cells per unit volume. However, it is far from being satisfying as:

- **Cellular division (*mitosis*) is not an instantaneous process.** The set of steps a cell should undergo before its division is called the *cell cycle*.
- **If the environment is not favorable, the division process can be interrupted.** The cell enters a quiescent state and may die. Upon the restoration of favorable conditions, cells can resume their division.

Modeling of the cell cycle

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



- Two proliferating phases $\mathrm{P}_1(t, a, \mathbf{x})$ and $\mathrm{P}_2(t, a, \mathbf{x})$ (in which cells divide).
- One quiescent phase $\mathrm{Q}(\mathrm{t},\mathrm{x})$ (in which cells rest) not age-structured.

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Modeling the cell cycle (3)

The progression of the three phases in the cell cycle can be translated into the following equations

$$
\begin{aligned}
\partial_t P_1 + \partial_a P_1 + \mathrm{Mov.} &= 0, \\
\partial_t P_2 + \partial_a P_2 + \mathrm{Mov.} &= 0, \\
\partial_t Q + \mathrm{Mov.} &= (1-f) P_1(a = a_{\max,P_1}) \\
&\quad - \left[\tfrac{d}{dt} f\right]^+ Q(t^-).
\end{aligned}
$$

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

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How to compute the velocity of movement?

Incompressibility of the cells gives $\nabla \cdot \mathbf{v}$.

But we need more in order to compute **v**.

Several approaches can be used:

- Potential flow models: The velocity has the form: $\mathrm{v}=-\mathrm{K}\nabla P$ using the condition on the divergence, it can be computed.
- Stokes models: The velocity satisfies a (Navier-)Stokes equation, where **F** represents the action of an elastic membrane surrounding the tumor for instance.

$$\begin{cases} -\nabla \cdot (\nu D(\mathbf{v})) + \nabla p = \mathbf{F}, \\ \nabla \cdot \mathbf{v} = \sum_{\text{species}} (\text{birth} - \text{death}) \end{cases}$$

- Mechanical models.

Viscoelastic modeling of the movement

We consider the various species as components of a viscoelastic material.

$$\nabla \cdot \sigma - \nabla p = -\nu \Delta \mathbf{v}$$

The constitutive law for the stress is

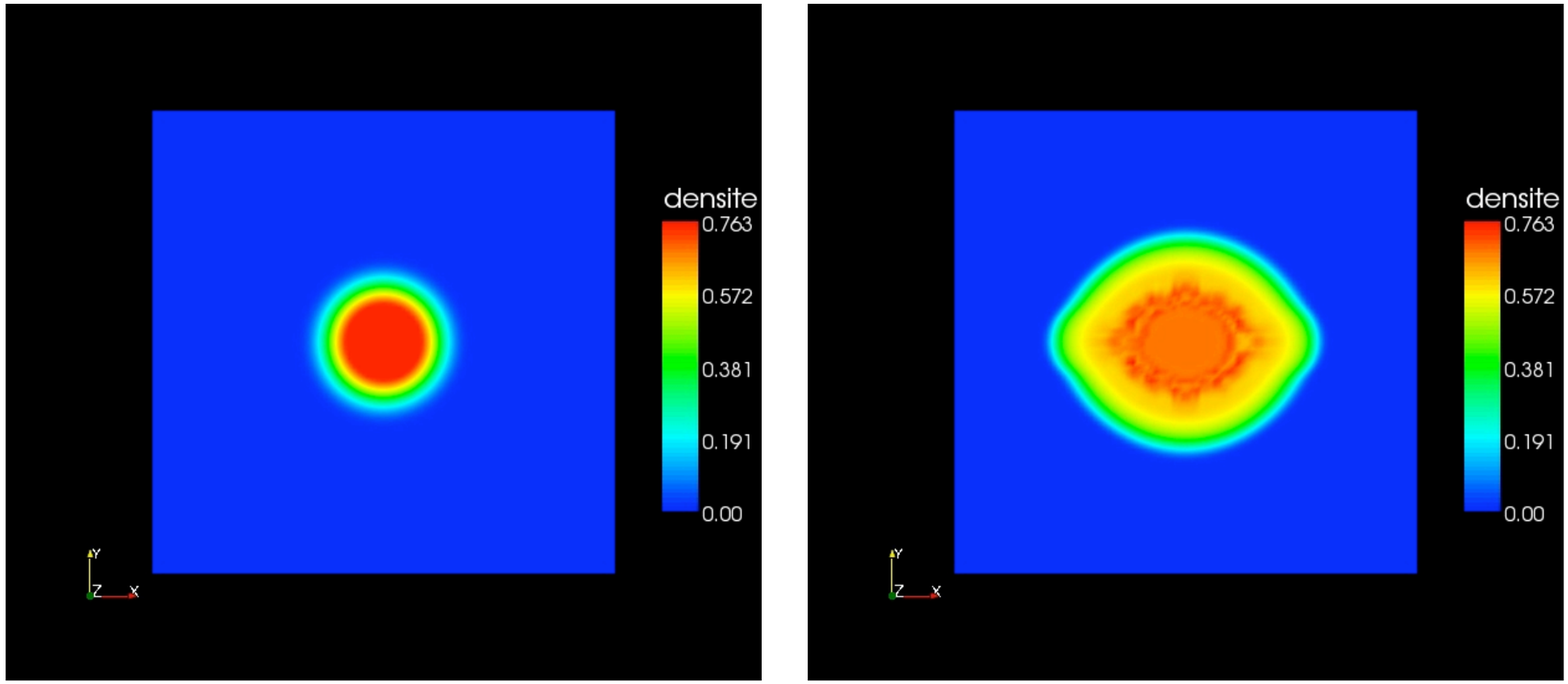
$$\partial_t \sigma + \mathbf{v} \cdot \nabla \sigma - \nabla \mathbf{v}^t \sigma - \sigma \nabla \mathbf{v} + \frac{\sigma}{\tau} = \frac{\beta(\tau)}{\tau} D(\mathbf{v})$$

One takes $\tau = (1 - L) + \frac{1-L}{1-S}$ and $\beta(\tau) = \beta_0 + \tau \beta_\infty$

where L is the density of interstitial liquid and S the density of sane tissue considered as elastic.

An example on the influence of stress

The initial tumor is a spheroid, the oxygen distribution is isotropic. The mechanical stress is lowered in the horizontal direction.



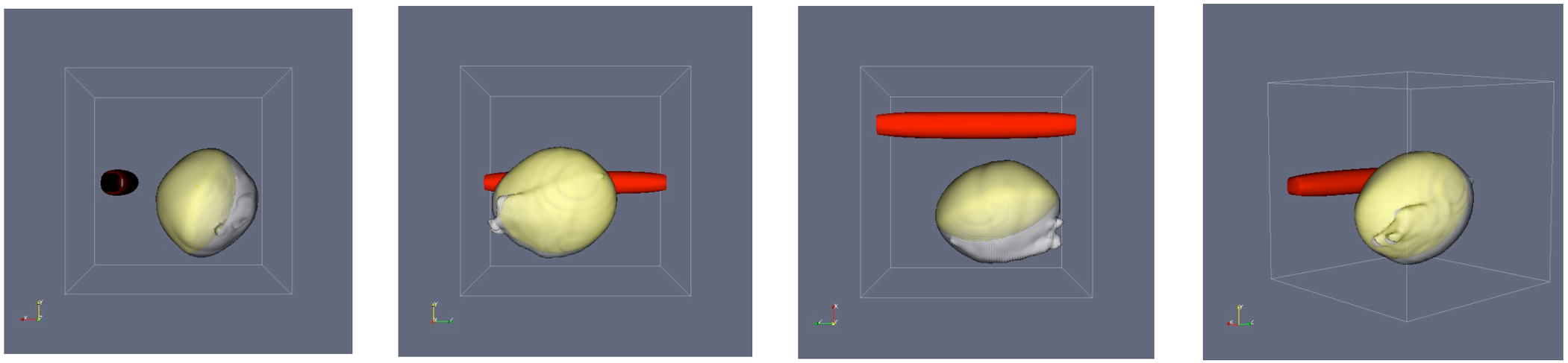
This is in agreement with experimental results from Harvard U.

Problem 1': specific models

Each cancer is different. One has to derive a model specific for each type considered.

- We are trying to model the growth of gliomas (brain tumors).

- Initially, tumors are not vascularized but as they grow, the process of vascularization (*angiogenesis)* has a great influence → We also have to develop models for angiogenesis.



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Problem 2: Parameters? Validation?

We need to determine the various parameters involved in our models.

- Some of these parameters are *obtainable* from experimental data (*e.g.* diffusion coefficients) → we need experiments (*in vitro*, *in vivo,* non treated tumors...).

- Others parameters can not be easily determined.
  - We use an optimization algorithm to fit parameters with temporal series of medical data. This technique (gradient-based optimization) is very expensive from a computational point of view → we need flops.

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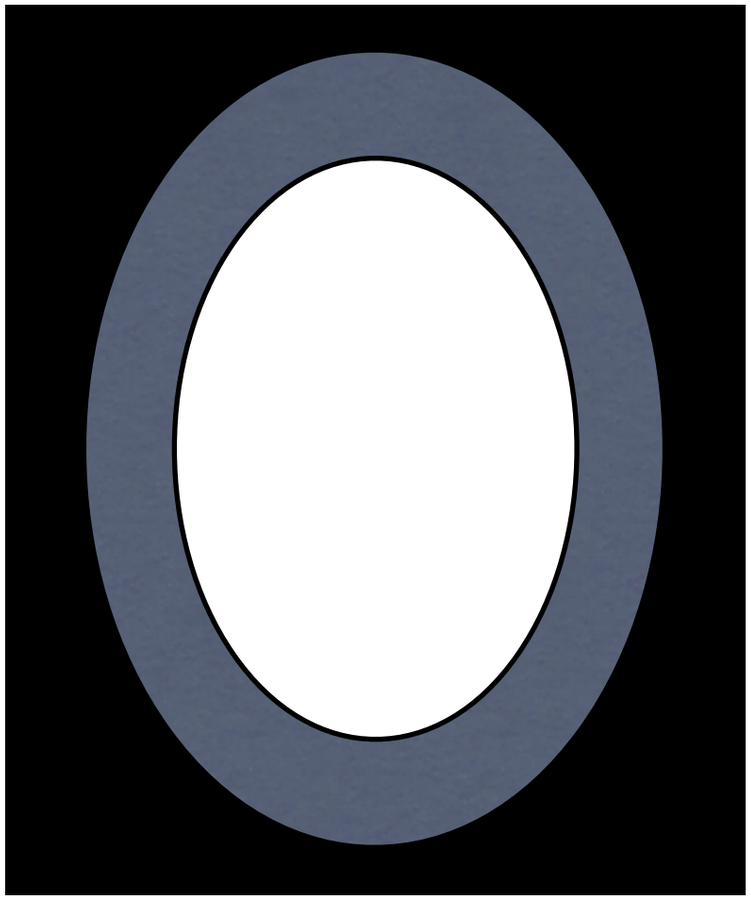
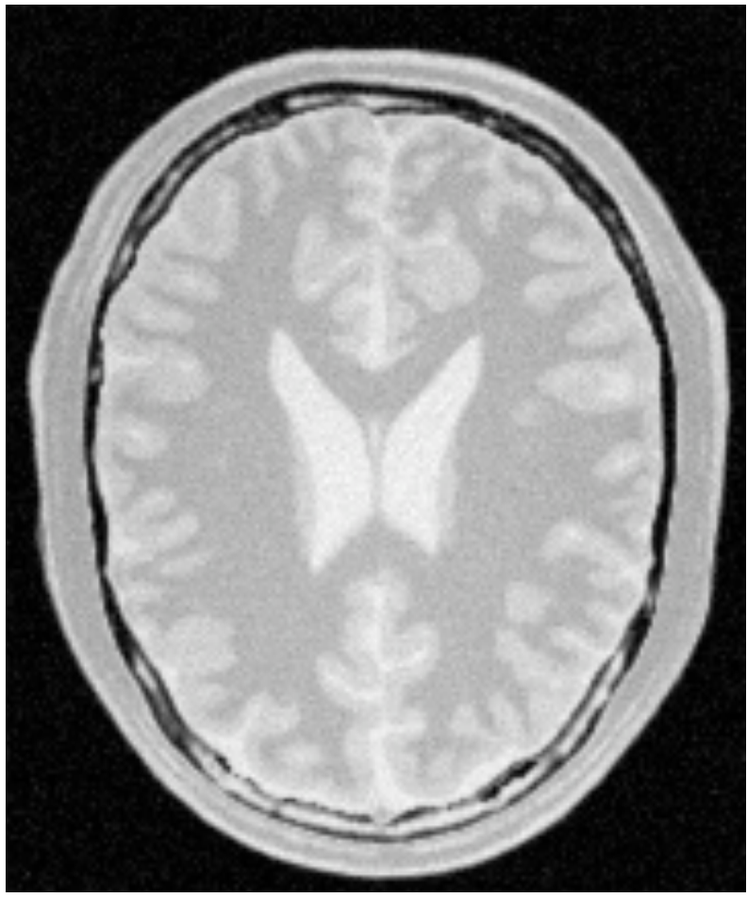
Problem 3: Dealing with real data

- We want to use our models with realistic setups.



Mathematical Brain



Brain from MRI

We have to deal with complex geometries.

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Problem 3: Dealing with real data

We need:

- to use the information provided by medical images (*e.g.* DICOM files from MRI...)
  - **Segmentation** (*e.g.* to determine gray and white matters from MRI). We are using Insight Toolkit (http://www.itk.org) but it is not completely satisfying.
- to have high order schemes in space (boundaries between domains of interest may be sharp, discontinuous parameters). We use:
  - **Penalization method:** easy to implement but only of order 1 in space.
  - **Ghost Fluid method (+AMR):** order 2 in space, but not easy to write for complex equations (Stokes, viscoelastic models).

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Problem 4: Fast computations

We need very fast computations to use our models in 3D, in real time or for the optimization process.

Two approaches are followed:

- Reduced order modeling (POD methods).
- Parallelization of algorithms, domain decomposition.

Conclusion

Modeling tumoral growth raises several problems:

1. Precise models are needed.
2. They have to be fully parametrized and validated.
3. We have to use realistic setups/data.
4. We need to reduce computation times.

We could use some help :)

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