Inverse and control problems with applications to cancer detection and therapy

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Dedicated to Prof. L.A. Medeiros on his 90th birthday

Outline

Some words on inverse problems:

- General setting of a direct problem:
  Data $(\mathcal{D}_0 \cup \mathcal{D}_1) \to$ Results $(\mathcal{R}) \to$ Observation (additional information) $(\mathcal{I})$
- A related inverse problem:
  Some data $(\mathcal{D}_0)$ + Information $(\mathcal{I}) \to$ The other data $(\mathcal{D}_1)$

Main questions for the inverse problem:

- Uniqueness: $\mathcal{I} = \mathcal{I}' \Rightarrow \mathcal{D}_1 = \mathcal{D}_1'$?
- Stability: Estimate dist $(\mathcal{D}_1, \mathcal{D}_1')$ in terms of dist $(\mathcal{I}, \mathcal{I}')$
- Reconstruction: Compute (exact or approximately) $\mathcal{D}_1$ from $\mathcal{I}$

FIRST IP: identification of the shape of a domain

(a) Direct problem:

Data: Ω, φ and D

Result: the solution u to

$$\text{(1)} \qquad \begin{cases} -\Delta u = 0, & x \in \Omega \setminus \overline{D} \\ u = 0, & x \in \partial D; \quad u = \varphi, \quad x \in \partial\Omega \end{cases}$$

Information:

$$\text{(2)} \qquad \frac{\partial u}{\partial n} = \alpha, \quad x \in \gamma \subset \partial\Omega$$

(b) Inverse problem:

(Partial) data: Ω and φ

(Additional) information: α (on γ)

Goal: Find D such that the solution to (1) satisfies (2)

[Andrieux-et-al 1993], [Alessandrini-et-al 2000 ...], [Kavian 2002], [Alvarez-et-al 2005], [Doubova-EFC-GlezBurgos-Ortega 2006], [Yan-Ma 2008]

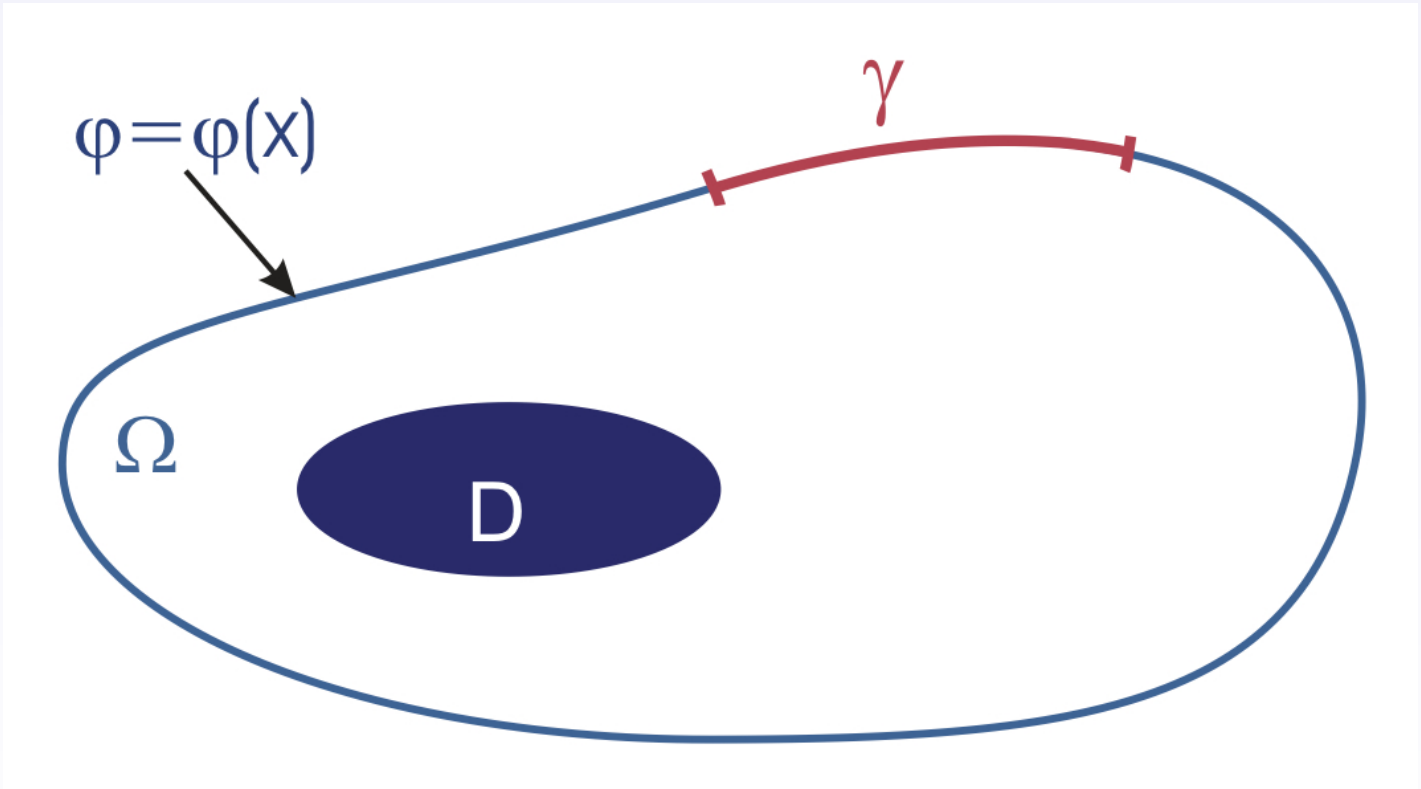


Figure: A geometrical inverse problem: identification of the open set D from Ω, φ and the additional information $\frac{\partial u}{\partial \nu} = \sigma$ on γ

SECOND IP: identification of the conductivity of a dielectric body (Calderón)

(a) Direct problem:

Data: Ω, φ and $a = a(x)$

Result: the solution u to

$$\begin{cases} -\nabla \cdot (a(x)\nabla u) = 0, & x \in \Omega \\ u = \varphi, & x \in \partial\Omega \end{cases} \tag{1}$$

Information:

$$u|_\omega = z \tag{2}$$

(b) Inverse problem:

(Partial) data: Ω and φ

(Additional) information: z (in ω)

Goal: Find a such that the solution to (1) satisfies (2)

Applications to tomography ...

[Calderón 1980], [Sylvester-Uhlman 1987], [Astala-Paavarinta 2003], ...

The sequel

We consider: IPs of these kinds for the Lamé system

$$u_{tt} - \mu\Delta u - (\lambda + \mu)\nabla(\nabla \cdot u) = 0$$
$$+ \dots$$

$u = (u_1, \dots, u_N)$ is the field of displacements
λ, μ are the Lamé coefficients (measure of stiffness)

We assume isotropic homogeneous media and small displacements

Motivation and description

Elastography:

A technique to detect elastic properties of tissue

Aspects:

- Three elements: Acoustic waves generator, Captor, Mathematical solver (MR or ultrasound, identification of tissue stiffness)
- Medical fields of application: breast, liver, prostate and other cancers; arteriosclerosis, fibrosis, deep vein thrombosis, ...
- At present: emerging techniques (a very precise description)

First works: [Ophir-et-al 1991], [Muthupillai-et-al 1995], [Sinkus-et-al 2000], [McKnight-et-al 2002], ...

Many interesting problems in Medicine, Biology, etc. lead to IPs for PDEs of this class: coefficient, source or shape identification

Motivation and description

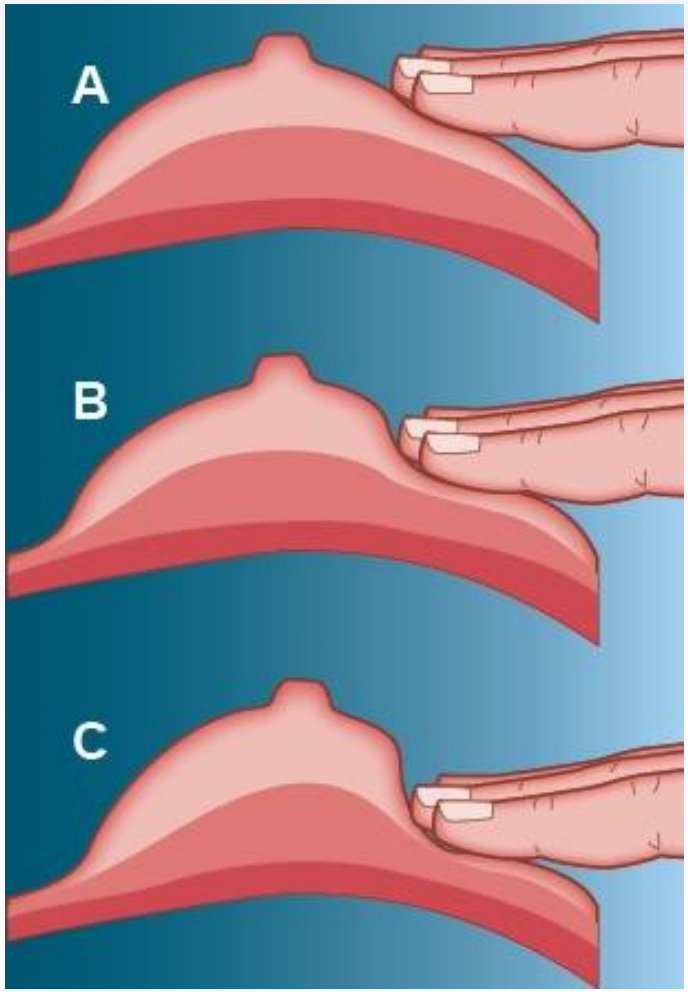


Figure: Classical detection methods in mammography (I): palpation

Motivation and description

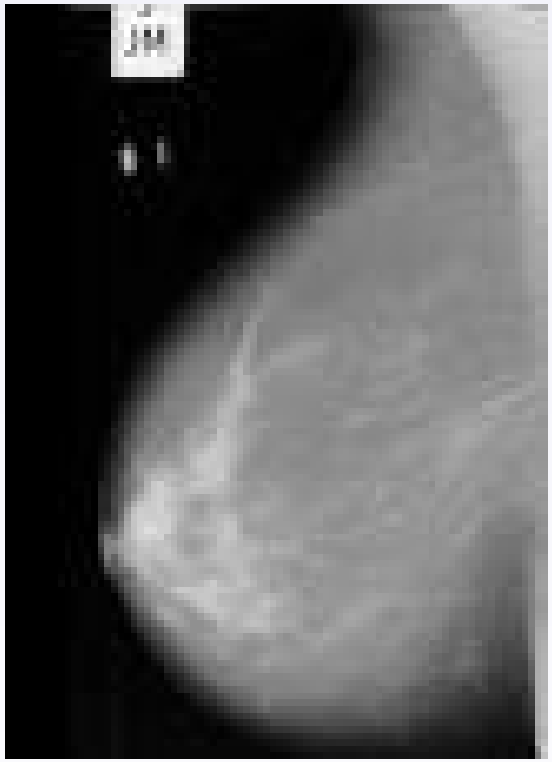


Figure: Classical detection methods in mammography (II): x-rays

Elastography is better suited than palpation and x-rays techniques:

— Tumors can be far from the surface
— or small
— or may have properties indistinguishable through palpation or x-rays

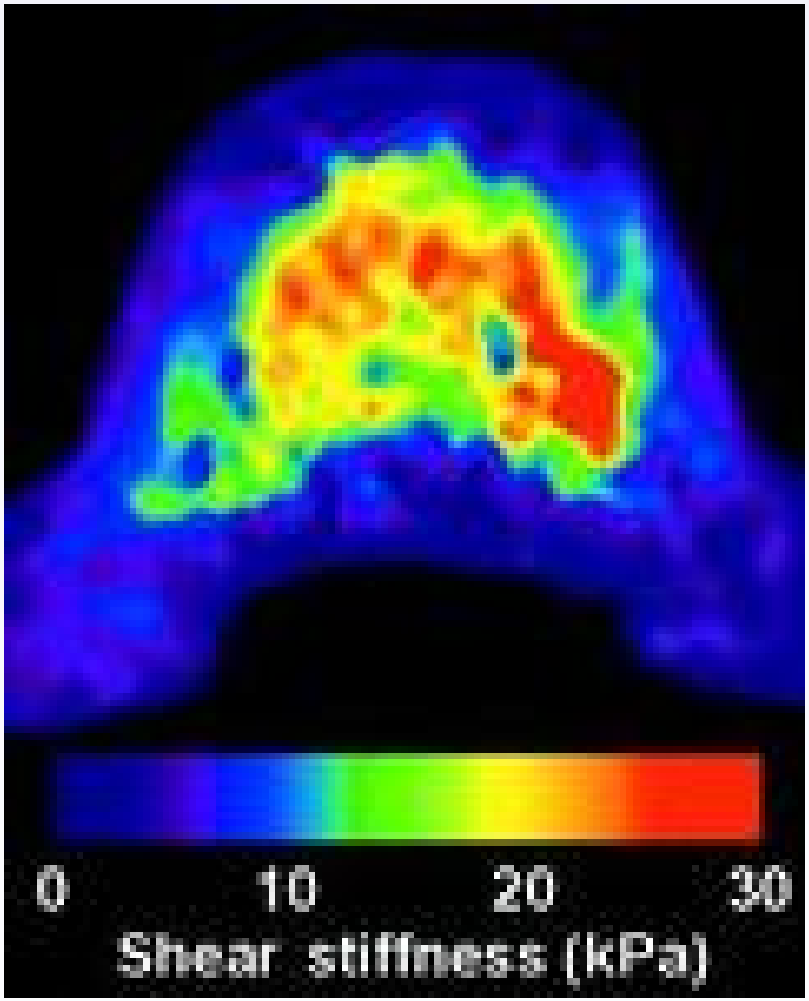


Figure: A breast elastogram. Identification of tissue stiffness

FIRST IP PROBLEM:
a solid tumor (D) inside an elastic tissue region (Ω)

The known data: Ω, T, (u_0, u_1), μ, λ, φ
The system:

$$\begin{cases} u_{tt} - \mu\Delta u - (\lambda+\mu)\nabla(\nabla\cdot u) = 0 & \text{in } \Omega\setminus\overline{D}\times(0,T) \\ u = \varphi & \text{on } \partial\Omega\times(0,T) \\ u = 0 & \text{on } \partial D\times(0,T) \\ u(x,0) = u_0(x), \quad u_t(x,0) = u_1(x) & \text{in } \Omega\setminus\overline{D} \end{cases}$$

The observation: $\sigma(u)\cdot n := \left(\mu(\nabla u + \nabla u^T) + \lambda(\nabla\cdot u)\mathrm{Id.}\right)\cdot n$ on $\gamma\times(0,T)$

The unknown: D

Uniqueness? Reconstruction algorithms and results?

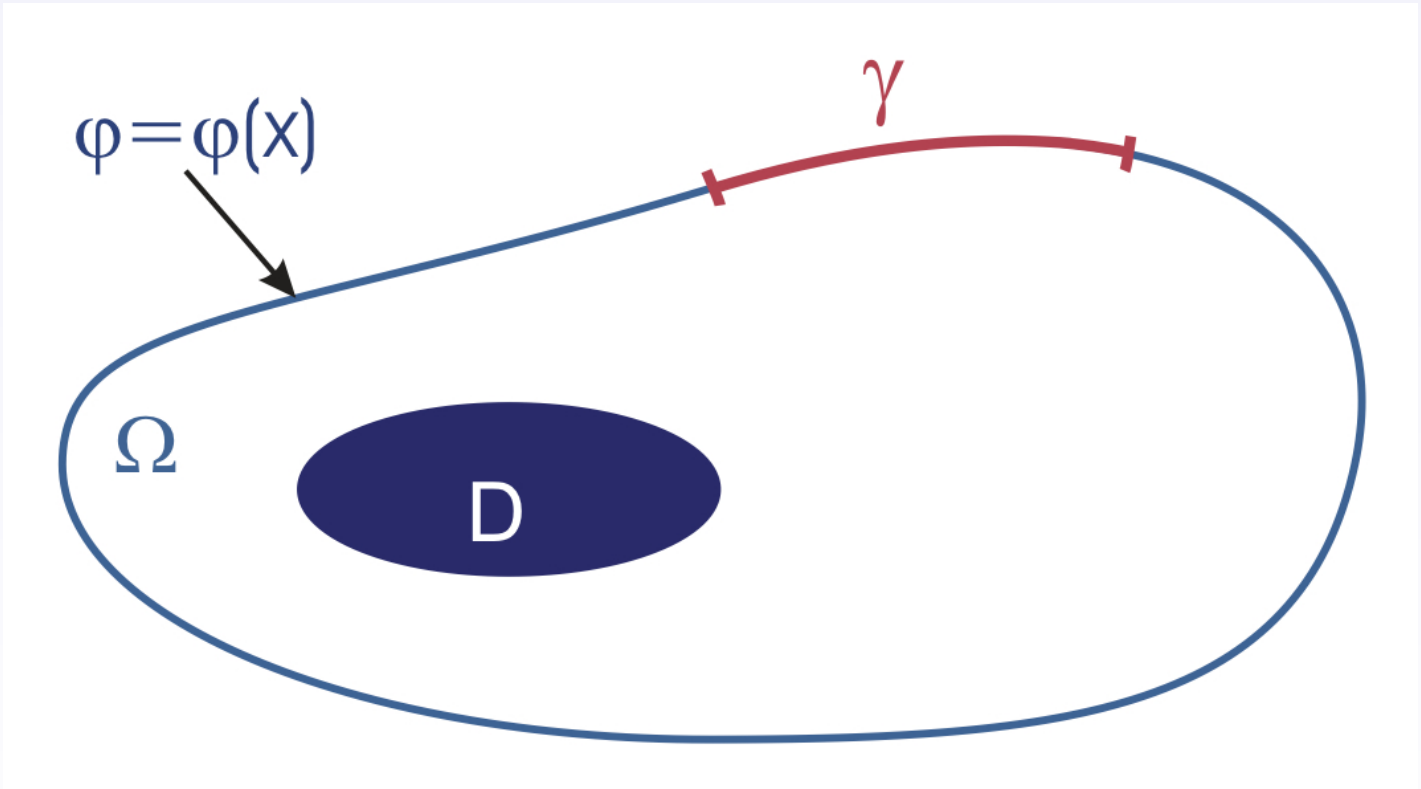


Figure: A geometrical inverse problem: identification of the open set D from Ω, φ and the additional information $\frac{\partial u}{\partial \nu} = \sigma$ on γ

UNIQUENESS

For $i = 0, 1$:

$$\begin{cases} u^i_{tt} - \mu\Delta u^i - (\lambda+\mu)\nabla(\nabla\cdot u^i) = 0 & \text{in } \Omega\setminus\overline{D^i}\times(0,T) \\ u^i = \varphi & \text{on } \partial\Omega\times(0,T) \\ u^i = 0 & \text{on } \partial D^i\times(0,T) \\ u^i(x,0) = u_0(x), \quad u^i_t(x,0) = u_1(x) & \text{in } \Omega\setminus\overline{D^i} \end{cases}$$

Two observations: $\alpha^i = \sigma(u^i)\cdot n$ on $\gamma\times(0,T)$

Theorem [Uniqueness]

Assume $D^0, D^1 \subset\subset \Omega$ non-empty and convex, $T > T_*(\Omega,\gamma)$
Then $\alpha^0 = \alpha^1 \Rightarrow D^0 = D^1$

The key point in the proof: a unique continuation property

(For $\mu = \mu(x)$ and/or $\lambda = \lambda(x)$ other uniqueness results can be applied: Escauriaza, 2005; Nakamura-Wang, 2006; Imanuvilov-Yamamoto, 2012, ...)

RECONSTRUCTION

The usual technique: solve a related extremal problem

The case of a ball

$\widetilde{\alpha} = \widetilde{\alpha}(x,t)$ is given

Find x_0 and r such that $(x_0, r) \in X_b$

$$J(x_0, r) \leq J(x_0', r') \quad \forall (x_0', r') \in X_b, \quad (x_0, r) \in X_b$$

Here:

$$X_b := \{\, (x_0, r) \in \mathbb{R}^4 \ : \ \overline{B}(x_0; r) \subset \Omega, \ r > 0 \,\}$$

$$J(x_0, r) := \frac{1}{2} \iint_{\gamma \times (0,T)} |\alpha[x_0, r] - \widetilde{\alpha}|^2 \, ds \, dt$$

$$\alpha[x_0, r] := \sigma(u) \cdot n \ \text{ on } \gamma \times (0, T)$$

The difficulties: 3D, lack of sensitivity
The algorithm: Augmented Lagrangian + DIRECTNoScal

- Augmented Lagrangian $\rightarrow$ a sequence of extremal problems with only side constraints
- DIRECTNoScal: a variant of the DIRECT algorithm, a dividing rectangle strategy

$$\textbf{Test: } T = 5, \quad \begin{array}{lll} u01 = 10x, & u02 = 10y, & u03 = 10z \\ u11 = 0, & u12 = 0, & u13 = 0 \\ \varphi_1 = 10x, & \varphi_2 = 10y, & \varphi_3 = 10z \end{array}$$

```
x0des = -2,   y0des = -2,   z0des = -2,   rdes = 1
x0ini = 0,    y0ini = 0,    z0des = 0,    rini = 0.6
```

NLopt (AUGLAG + DIRECTNoScal), N° Iter = 1005, FreeFem++:

-2.139917695 -2.469135802 -2.713001067 0.8166666667

```
x0cal   =   -1.981405274
y0cal   =   -2.225232904
z0cal   =   -2.148084171
 rcal   =   0.9504115226
```

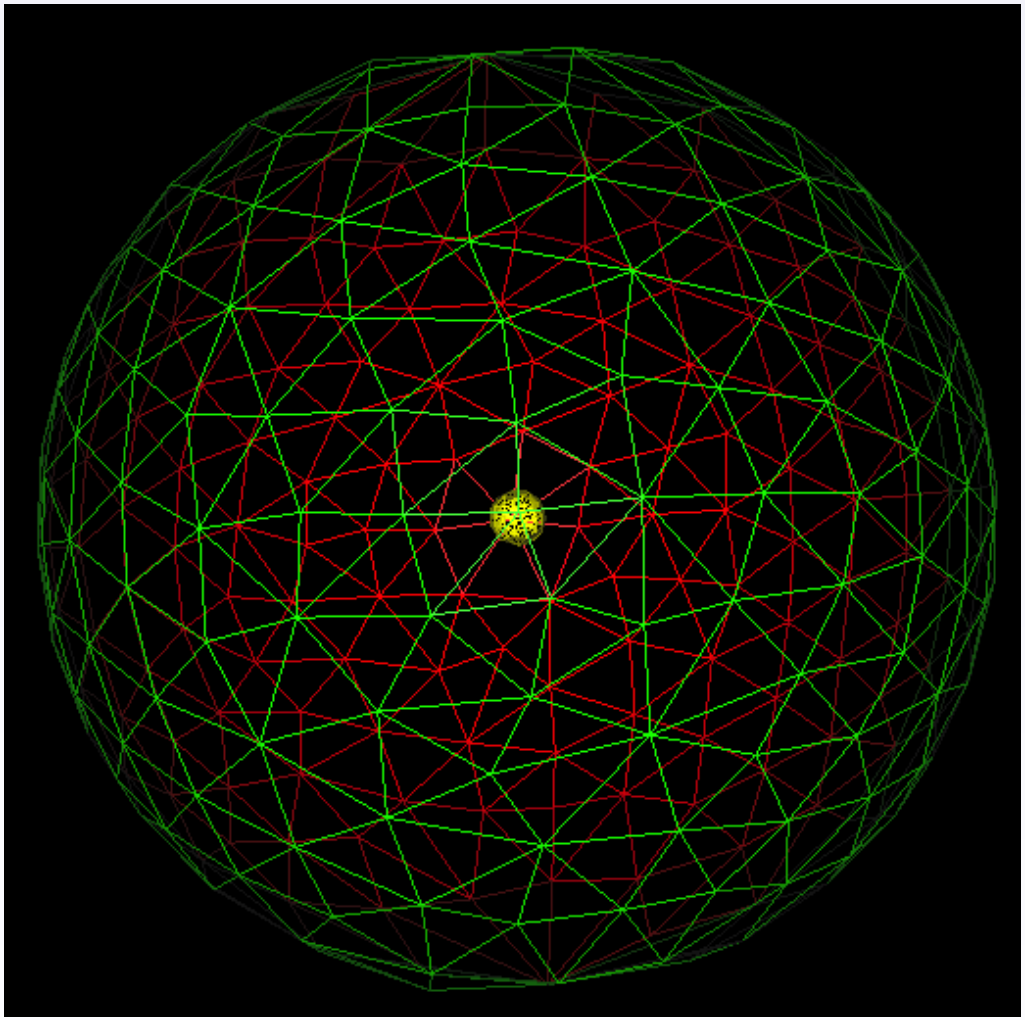


Figure: Initial mesh. Points: 829, tetrahedra: 4023, faces: 8406, edges: 5210, boundary faces: 720, boundary edges: 1080

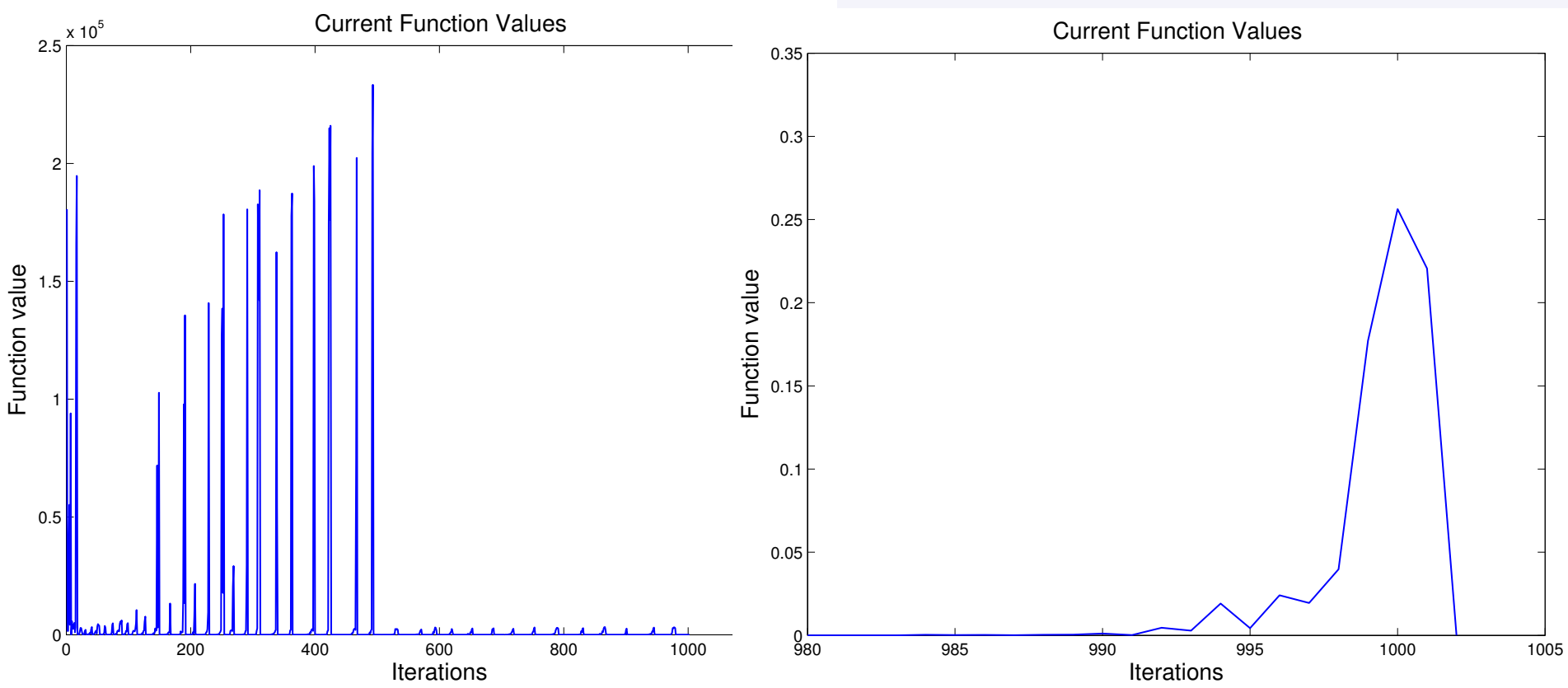


Figure: Cost evolution versus number of iterates (left) and detail (right).

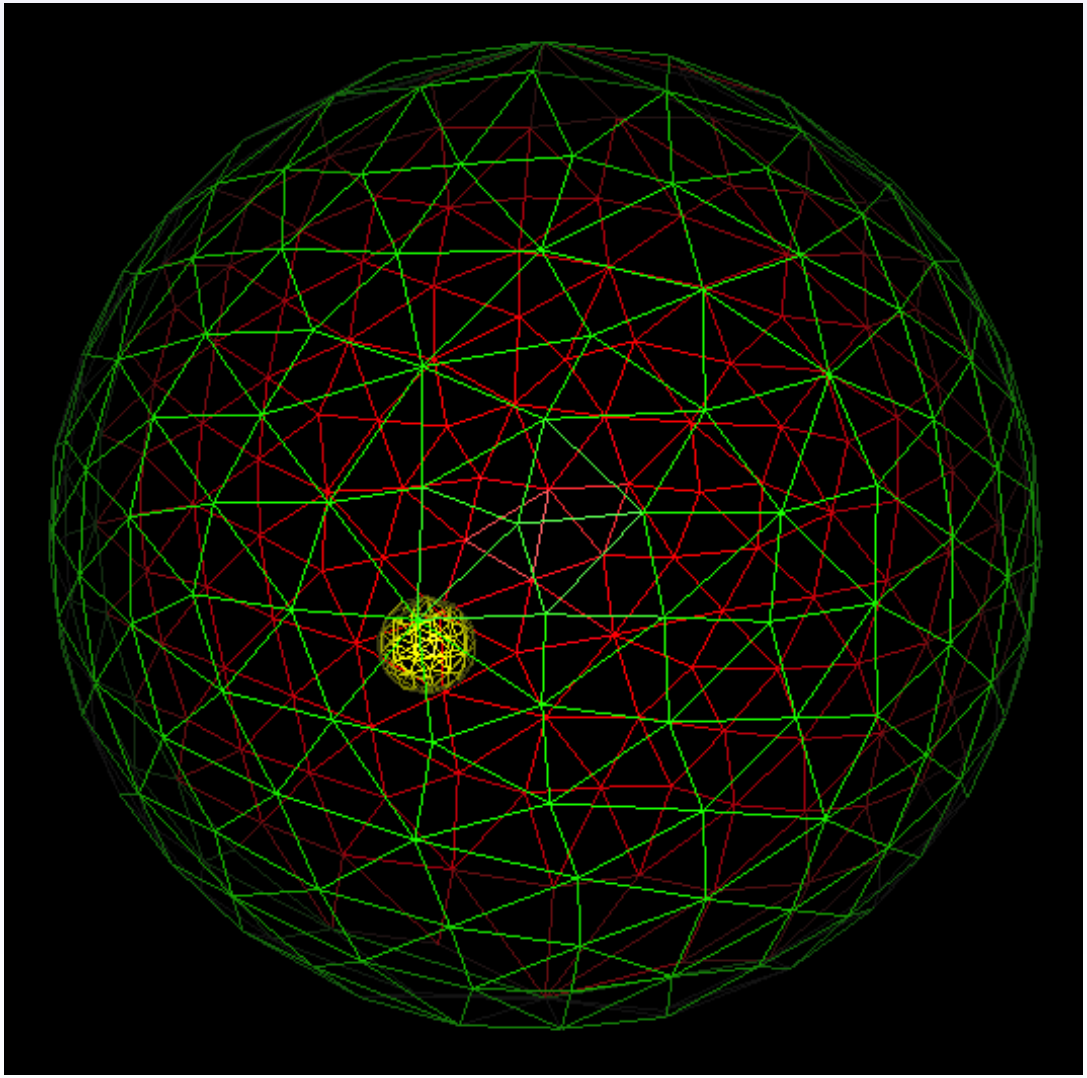


Figure: Desired and computed configuration

SECOND IP PROBLEM:
the tumor is elastic (very different μ and λ)

The known data: Ω, T, (u_0, u_1), φ
The system:

$$\begin{cases} u_{tt} - \nabla \cdot \left(\mu(\nabla u + \nabla u^T) + \lambda(\nabla \cdot u)\mathrm{Id.}\right) = f(x,t) & \text{in } \Omega \times (0,T) \\ u = \varphi & \text{on } \partial\Omega \times (0,T) \\ u(x,0) = u_0(x), \quad u_t(x,0) = u_1(x) & \text{in } \Omega \end{cases}$$

The observation: $\sigma(u) \cdot n := \left(\mu(\nabla u + \nabla u^T) + \lambda(\nabla \cdot u)\mathrm{Id.}\right) \cdot n$ on $\gamma \times (0,T)$

The unknowns: $\mu = \mu(x)$ and $\lambda = \lambda(x)$

More difficult – Reconstruction algorithms and results?

RECONSTRUCTION

Assume $f, f_t \in L^2(Q)^N$, $u_0 = 0$, $u_1 \in H_0^1(\Omega)^N$, $\Upsilon \in L^2(\Sigma)^N$

Introduce a related (direct) extremal problem ($R > 0$ is given):

$$\begin{cases} \text{Minimize } I(\mu, \lambda) \\ \text{Subject to } (\mu, \lambda) \in \mathbb{K}(R) \end{cases}$$

$$I(\mu, \lambda) := \frac{1}{2} \int_0^T \|\sigma(u) \cdot n\big|_\gamma - \Upsilon\|^2 \, dt$$

$$\mathbb{K}(R) = \{ (\mu, \lambda) \in \mathbb{BV}(\Omega), \ \ \alpha \leq \mu, \lambda \leq \beta, \ \ TV(\mu), TV(\lambda) \leq R \}$$

Theorem

For all $R > 0$ there exists at least one solution (μ_R, λ_R).

Idea the proof:

- A minimizing sequence (μ_n, λ_n) converges weakly-$*$ in $\mathbb{BV}(\Omega)$, strongly in $L^p(\Omega)$ for all $p < +\infty$
- The associated $(u_n, u_{n,t}, u_{n,tt})$ converge weakly-$*$
- $\nabla u_n \in$ compact set in $L^2(Q)$ (much more in fact!) – A delicate point Implied by Meyers' estimates together with interpolation results, [Tartar]

A NUMERICAL EXPERIMENT, FIXED λ

The domain and the mesh

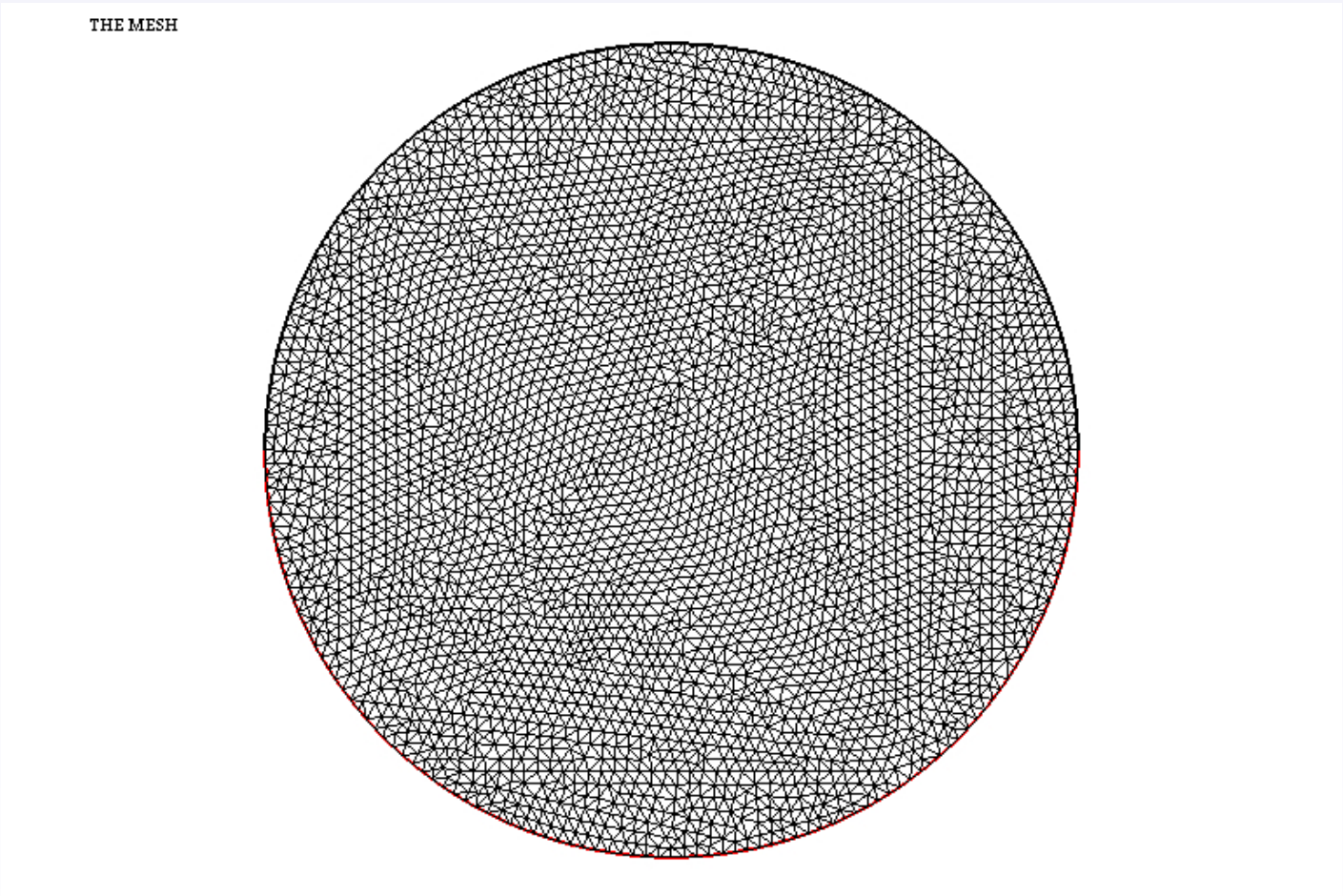


Figure: Number of nodes: 3629 – Number of triangles: 7056

TEST 1

Starting: $\mu = 5$ Target: $\mu = 10$ in D, $\mu = 1$ outside

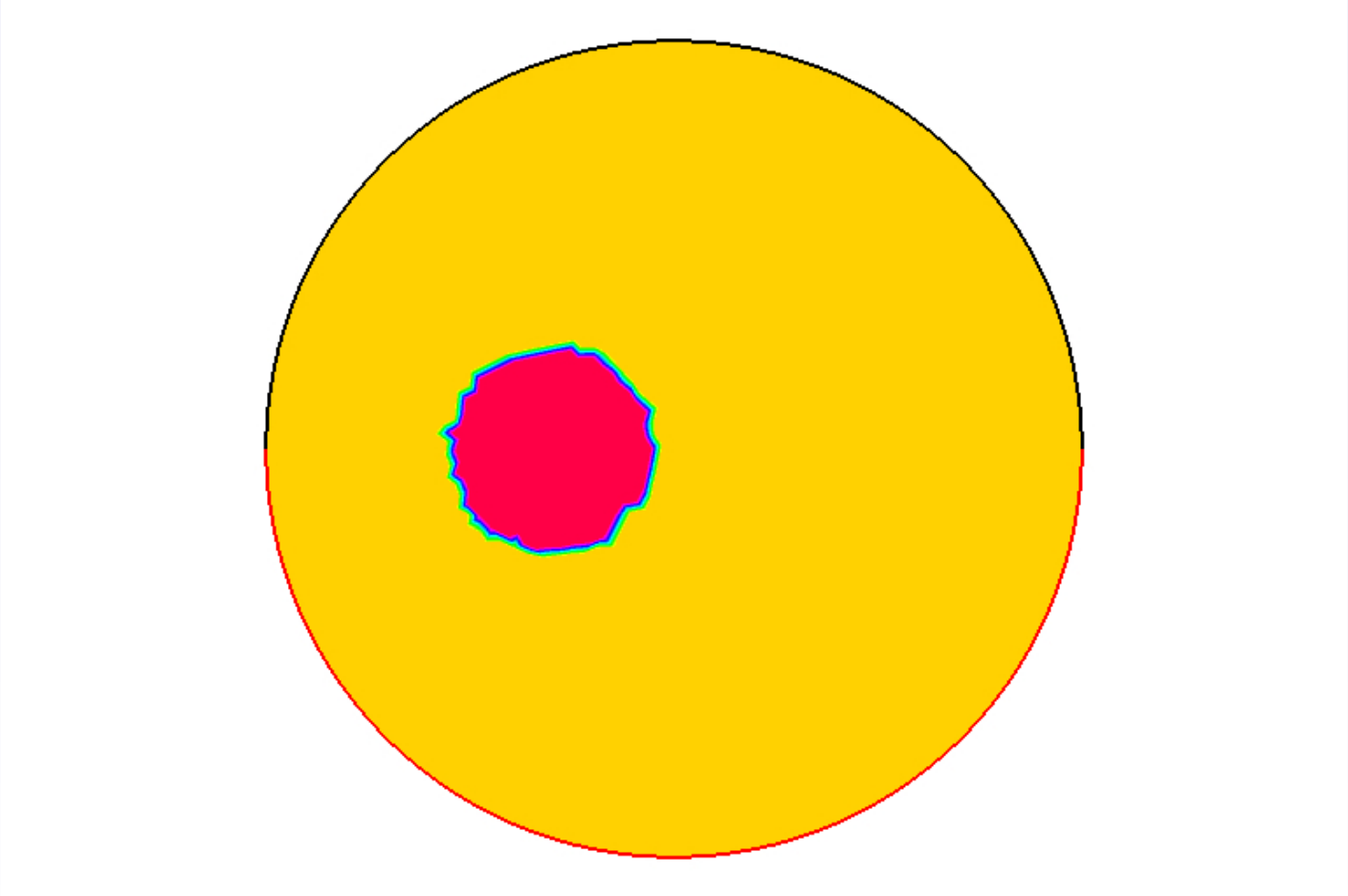


Figure: The target μ

The algorithm: Augmented Lagrangian + L-BFGS
(limited memory quasi-Newton, Broyden, Fletcher, Goldfarb and Shanno)
Final cost $\sim 9.6 \times 10^{-8}$, 158 comp. of the cost, 78 comp. of the gradient.

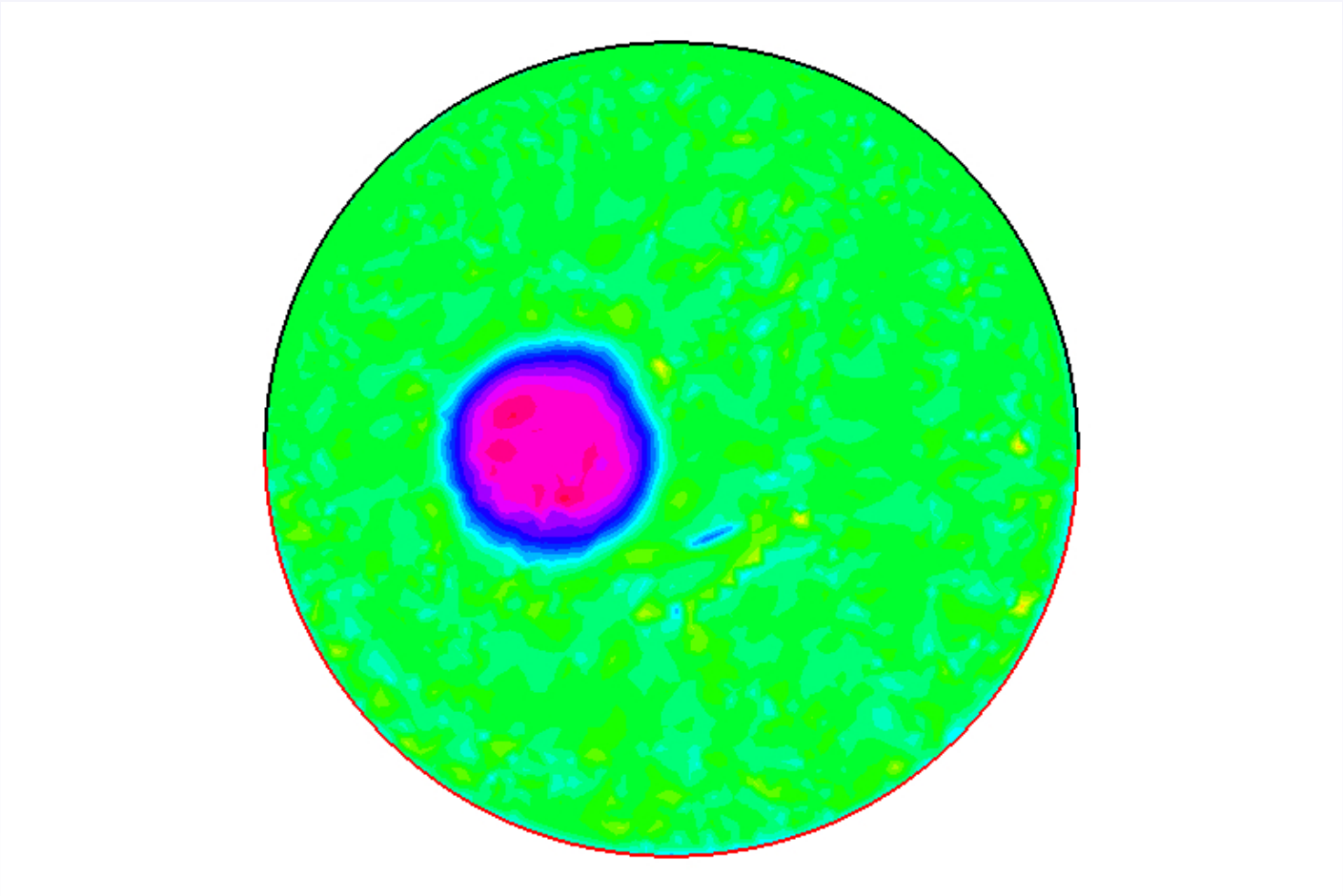


Figure: The computed μ

TEST 2

Starting: $\mu = 5$ Target: $\mu = 10$ in $D_1 \cup D_2$, $\mu = 1$ outside

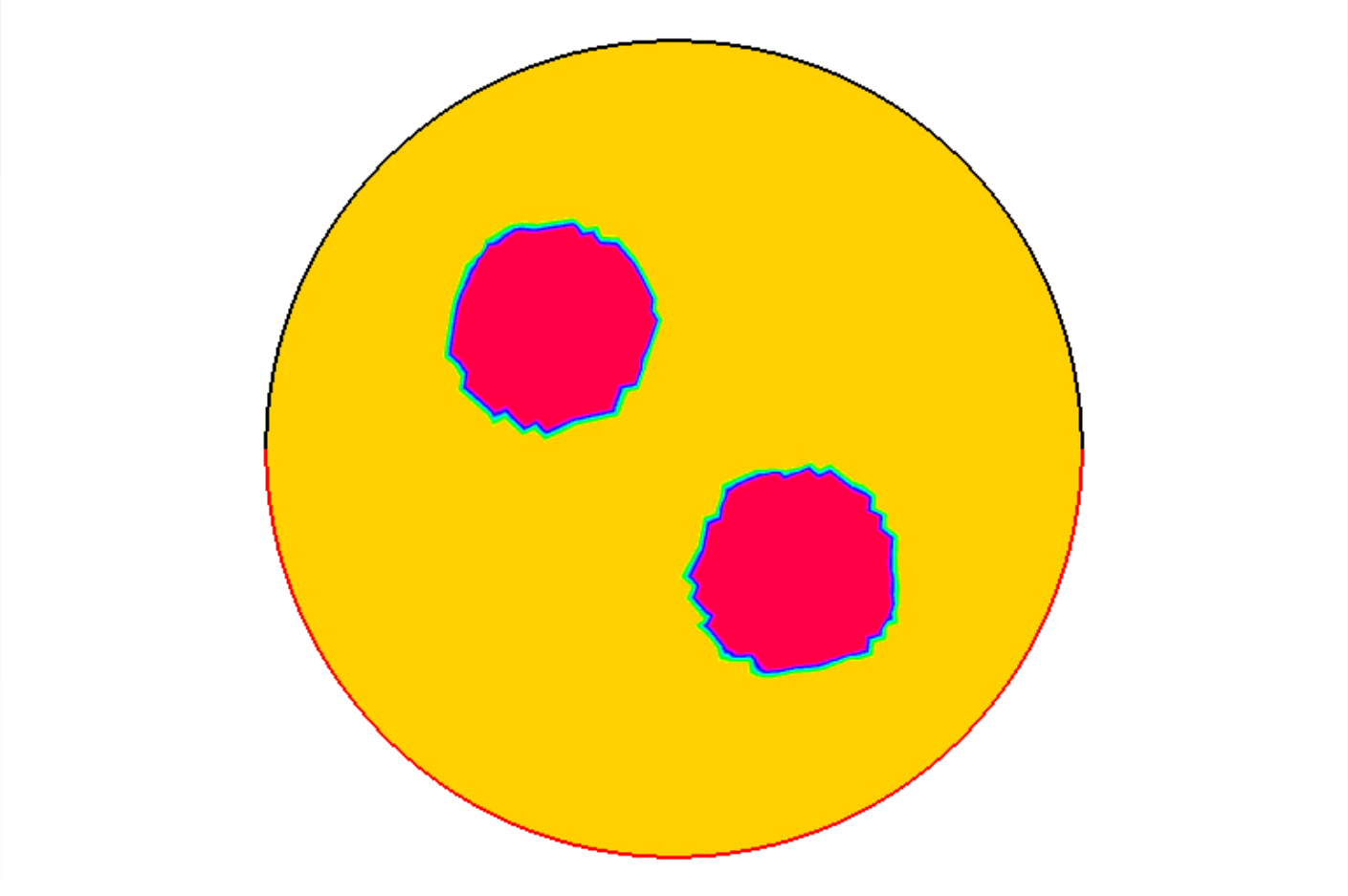


Figure: The target μ

The algorithm: Augmented Lagrangian + L-BFGS
Final cost $\sim 9.6 \times 10^{-8}$, 180 comp. of the cost, 80 comp. of the gradient.

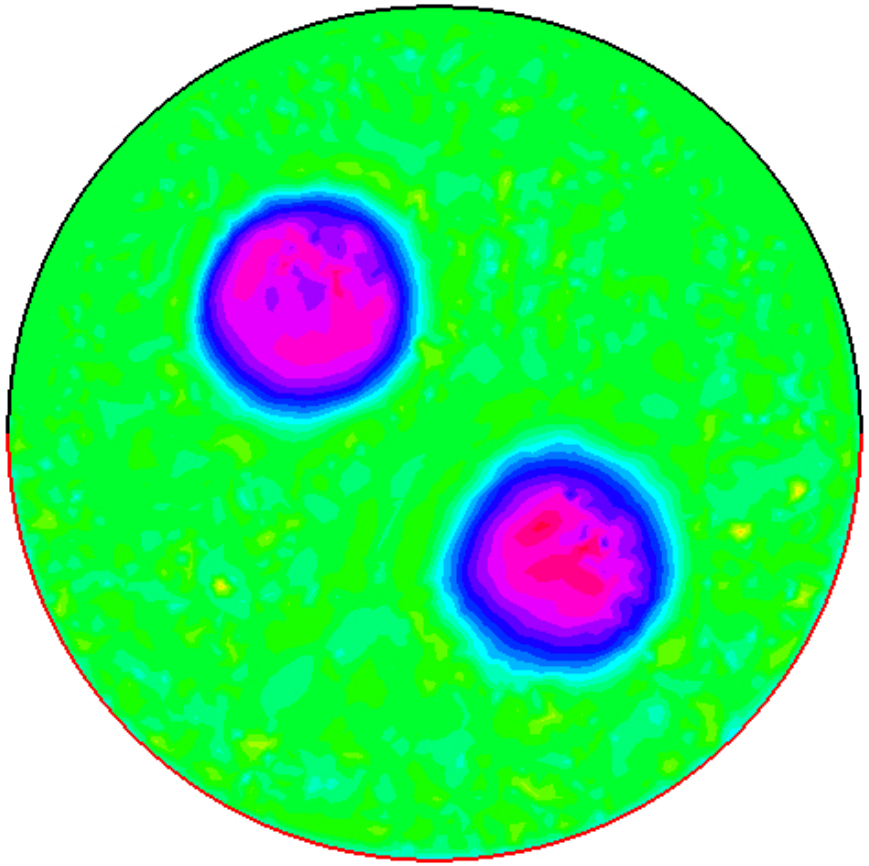
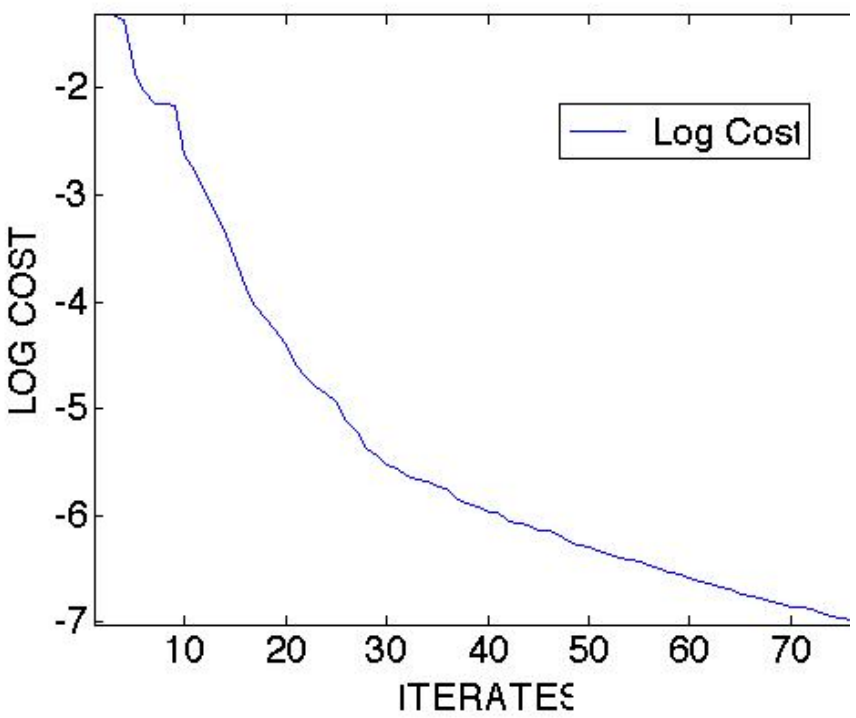


Figure: The computed μ



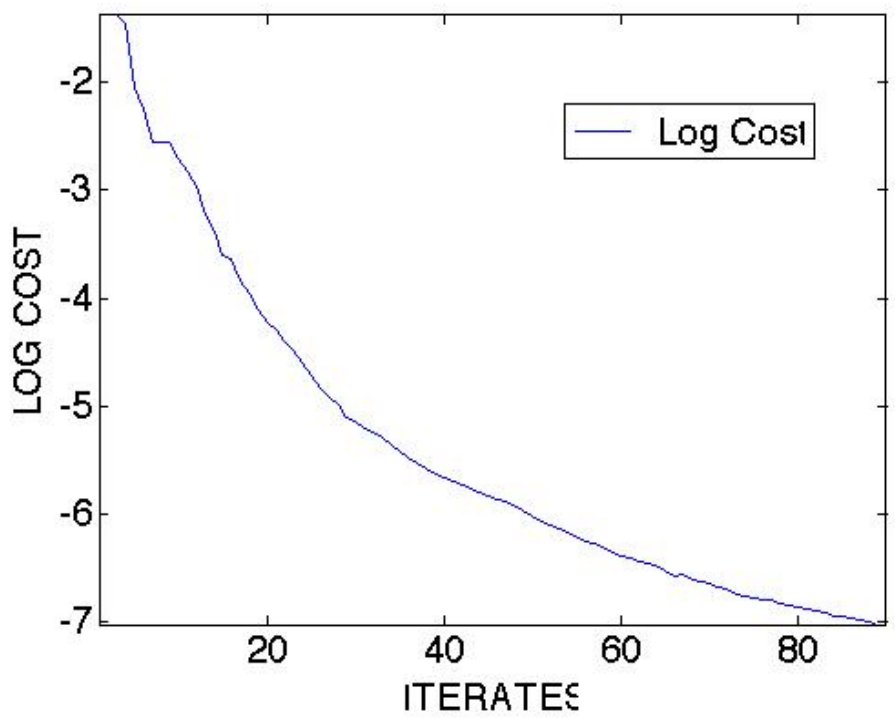


Figure: log of the cost versus number of iterates. Case 1 (left) and Case 2 (right).

CONTROL PROBLEMS

What is usual: act to get good (or the best) results for

$$\begin{cases} E(U) = F \\ + \dots \end{cases}$$

What is easier? Solving? Controlling?

Two classical approaches:

- Optimal control
- Controllability

OPTIMAL CONTROL

A general optimal control problem

$$\begin{array}{l} \text{Minimize } \ J(v) \\ \text{Subject to } \ v \in \mathcal{V}_{ad}, \ \ y \in \mathcal{Y}_{ad}, \ (v, y) \ \text{ satisfies} \\ \qquad\qquad E(y) = F(v) \quad + \ \ldots \end{array} \tag{S}$$

Main questions: $\exists$, uniqueness/multiplicity, characterization, computation, ...

We could also consider similar bi-objective optimal control:

$$\begin{cases} \text{"Minimize"} \ \ J_1(v), J_2(v) \\ \text{Subject to } \ v \in \mathcal{V}_{ad}, \ldots \end{cases}$$

A lot of contributions: [Pontryaguin, J.-L. Lions, Kunisch, Troltzsch, ...]

CONTROLLABILITY

A null controllability problem

Find (v, y)
Such that $v \in \mathcal{V}_{ad}$, (v, y) satisfies (ES), $y(T) = 0$

with $y : [0, T] \mapsto H$,

$$E(y) \equiv y_t + A(y) = F(v) \quad + \ \ldots \qquad (ES)$$

Again many interesting questions: $\exists$, uniqueness/multiplicity, characterization, computation, ...

A very rich subject for PDEs, see [Russell, J.-L. Lions, Coron, Zuazua, ...]

A general tumor growth model

$$\begin{cases} y_t + Ay = B(y, v) \\ + \dots \end{cases}$$

$y = (y_1, \dots, y_n)$ is (for instance) a n-tuple of cell densities
$v = (v_1, \dots, v_m)$ is the therapy strategy (a radiation, a drug, a surgery, ...)

Very usually: $B(\cdot\,, \cdot)$ is bilinear!

We may ask v either

- To maximize a benefit (optimal control)
- Or lead y to a desired state (controllability)

AN OPTIMAL CONTROL PROBLEM

A) *Pre-therapy:*

$$\begin{cases} C_{0,t} &= D\Delta C_0 + \rho\,(1 - C_0)\,C_0, & \text{in } Q_0 := \Omega \times (0, t_1), \\ C_0(x,0) &= c_0(x), & x \in \Omega, \\ \dfrac{\partial C_0}{\partial \nu} &= 0, & \text{on } \Sigma_0 := \partial\Omega \times (0, t_1). \end{cases} \tag{1}$$

B) *j-th therapy* for $j = 1, 2, \ldots, n-1$:

$$\begin{cases} C_{j,t} &= D\Delta C_j + \rho\,(1 - C_j)\,C_j, & \text{in } Q_j := \Omega \times (t_j, t_{j+1}), \\ C_j(x, t_j) &= S(d_j(x))C_{j-1}(x, t_j), & x \in \Omega, \ldots \end{cases} \tag{2}$$

Here: $S(d_j) := e^{-\alpha_t d_j - \beta_t d_j^2}$

C) *Post-therapy:*

$$\begin{cases} C_{n,t} &= D\Delta C_n + \rho\,(1 - C_n)\,C_n, & \text{in } Q_n := \Omega \times (t_n, +\infty), \\ C_n(x, t_n) &= S(d_n(x))C_{n-1}(x, t_n), & x \in \Omega, \ldots \end{cases} \tag{3}$$

The state: $(C_0, C_1, \ldots C_n)$ (normalized cell densities, $0 \le C_j \le 1$)
The control: $(t_1, \ldots, t_n; d_1, \ldots, d_n)$

AN OPTIMAL CONTROL PROBLEM

Maximize

$$T_*(t_1,\dots,t_n;d_1,\dots,d_n) := \inf\{\, T\in\mathbb{R}_+ : \int_\Omega C(x,T^+)\,dx > M_*\,\}$$

Subject to $(t_1,\dots,t_n;d_1,\dots,d_n)\in\mathcal{U}_{ad}$

$$\begin{aligned}\mathcal{U}_{ad} \quad := \quad & \{\,(t_1,\dots,t_n;d_1,\dots,d_n)\in\mathbb{R}^n\times L^2(\Omega)^n :\\ & 0\le t_1\le\ldots\le t_n\le\tilde{T},\ \ 0\le d_j\le d_*\ \text{ a.e.},\\ & \alpha_t\sum_{j=1}^n d_j+\beta_t\sum_{j=1}^n |d_j|^2\le E_*\ \text{ a.e.}\,\},\end{aligned}$$

Difficulties:

- Bilinear action of the control, acting on initial data at each t_j (instantaneous, Dirac)
- Possibly nonregular functional

Illustration of the process:

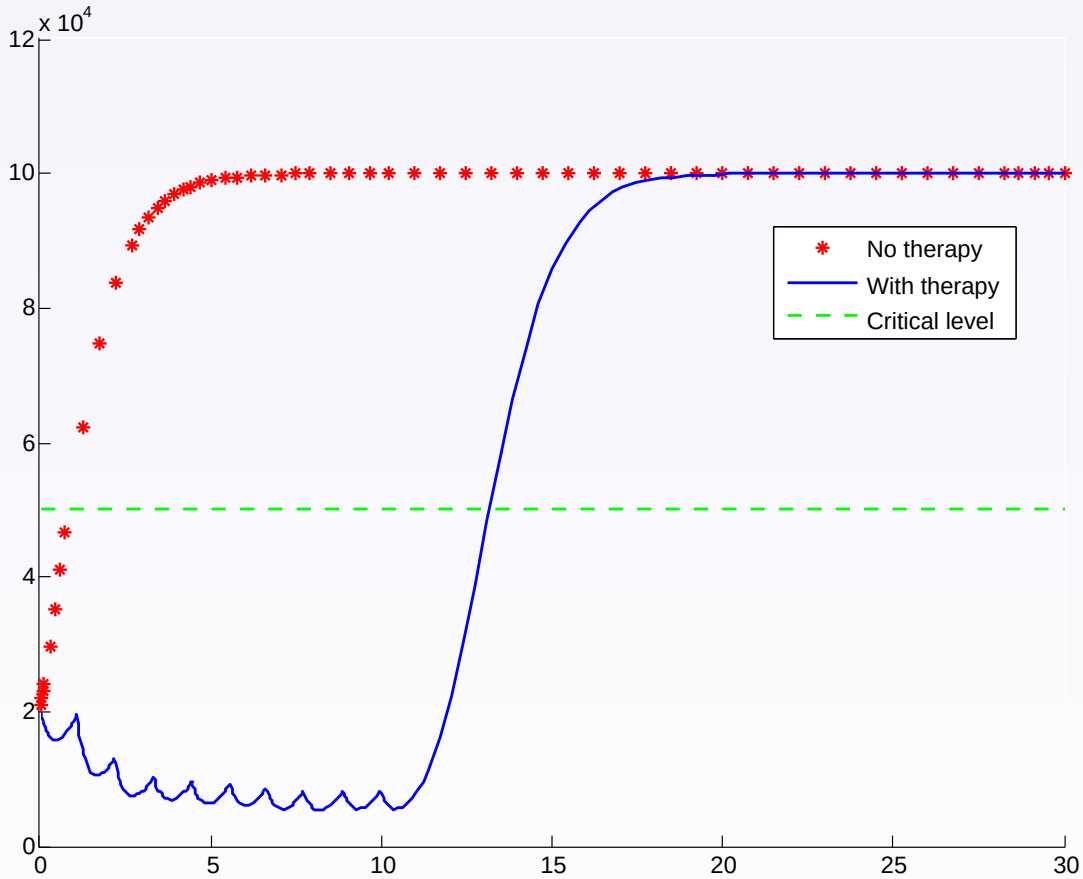


Figure: What we expect to get . . .

Maximize

$$T_*(t_1,\dots,t_n;d_1,\dots,d_n) := \inf\{\, T\in\mathbb{R}_+ : \int_\Omega C(x,T^+)\,dx > M_*\,\}$$

Subject to $(t_1,\dots,t_n;d_1,\dots,d_n)\in\mathcal{U}_{ad}$

An existence result:

Theorem [existence of optimal control]

Assume: $0 < M_* < |\Omega|$. Then: there exists at least one optimal control.

Idea of the proof:

- $\forall (t_1,\dots,t_n;d_1,\dots,d_n)\in\mathcal{U}_{ad}:\ \ \{\, T : \int_\Omega C(x,T^+)\,dx > M_*\,\}\neq\emptyset$ and $T_*(t_1,\dots,t_n;d_1,\dots,d_n)$ makes sense
- $\mathcal{U}_{ad}$ is bounded, closed and convex
- $(t_1,\dots,t_n;d_1,\dots,d_n)\mapsto T_*(t_1,\dots,t_n;d_1,\dots,d_n)$ is u.s.c.

Hence, ...

A numerical experiment in a simplified but realistic situation:
Fixed times t_j, free and constant d_j; $n = 40$

Monday	*Tuesday*	*Wednesday*	*Thursday*	*Friday*	*Sat*	*Sun*
.	.	X	X	X	.	.
X	X	X	X	X	.	.
X	X	X	X	X	.	.
X	X	X	X	X	.	.
X	X	X	X	X	.	.
X	X	X	X	X	.	.
X	X	X	X	X	.	.
X	X	X	X	X	.	.
X	X	.	.	.	.	.

Table: Treatment with 40 doses in 8 weeks.

A numerical experiment in a simplified but realistic situation:

Cycle	4 weeks	5 weeks	6 weeks	7 weeks	8 weeks
C-dose	179.085	195.752	209.945	226.501	243.050
SQP	179.086*	195.752*	209.945*	226.502*	243.050*
AS	179.010	195.750	209.945	226.499	243.048
IP	178.983	195.666	209.866	226.418	243.047

Table: Comparisons of the computed survival times for various cycle durations. “C-dose" means all $d_j = d_{\text{st.}}$; “SQP" means *sequential quadratic programming* algorithm; “AS" means *active-set* algorithm; “IP" means *interior point* algorithm.

A numerical experiment in a simplified but realistic situation:

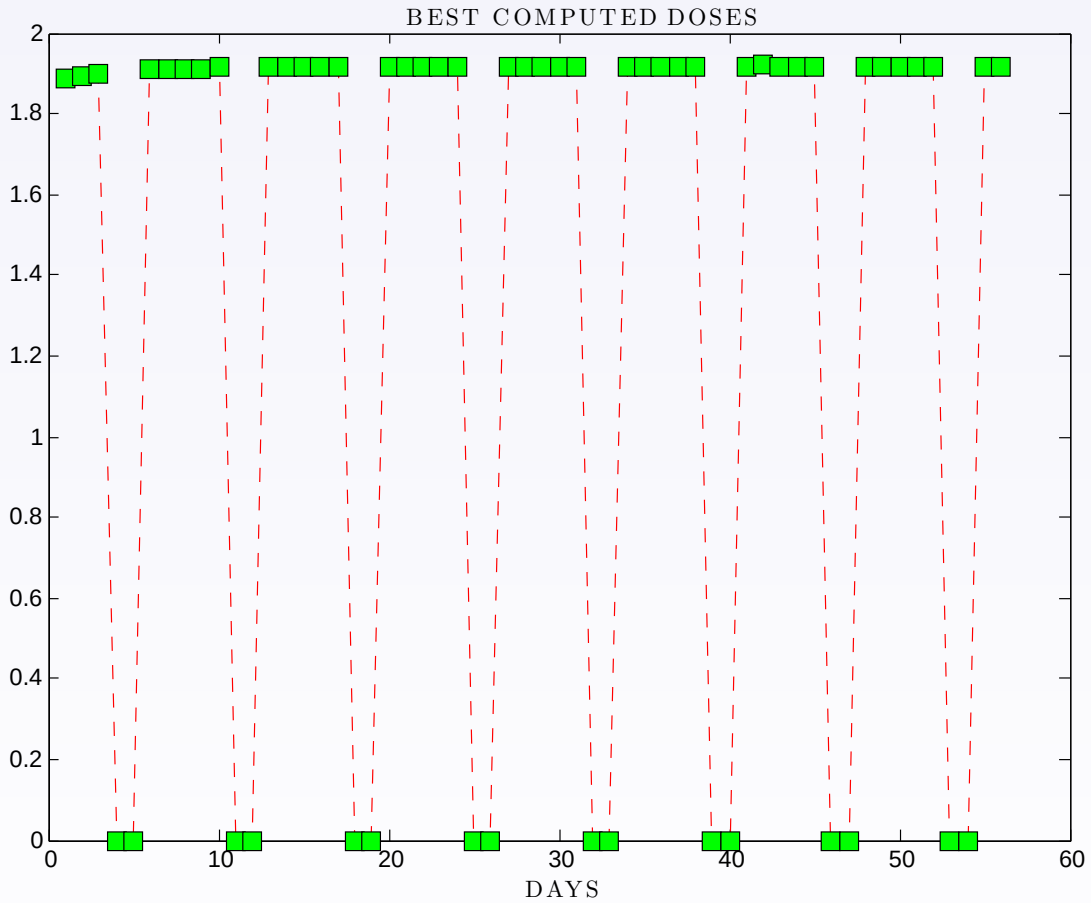


Figure: The best 40 doses found with the SQP algorithm (quasi-constant distribution).

A numerical experiment in a simplified but realistic situation:

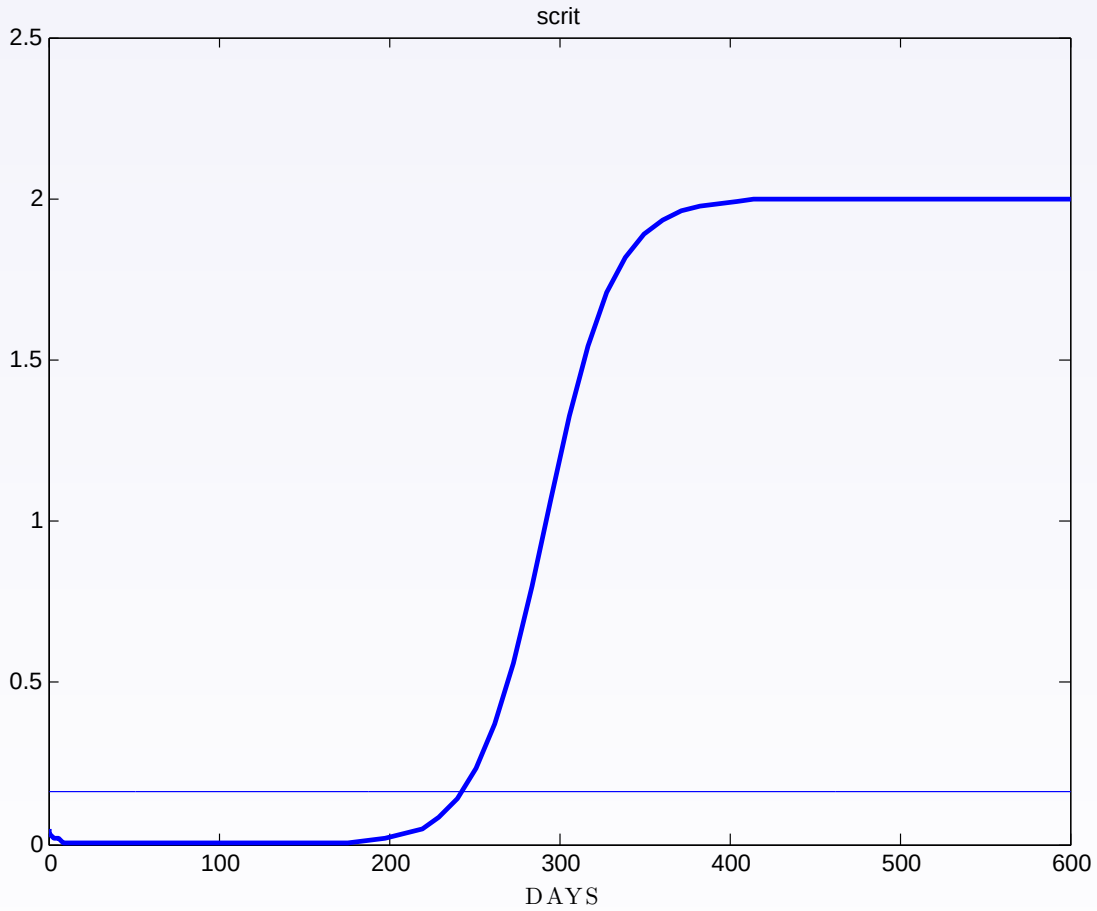


Figure: Evolution in time of the tumor size – 40 doses.

A numerical experiment in a simplified but realistic situation:

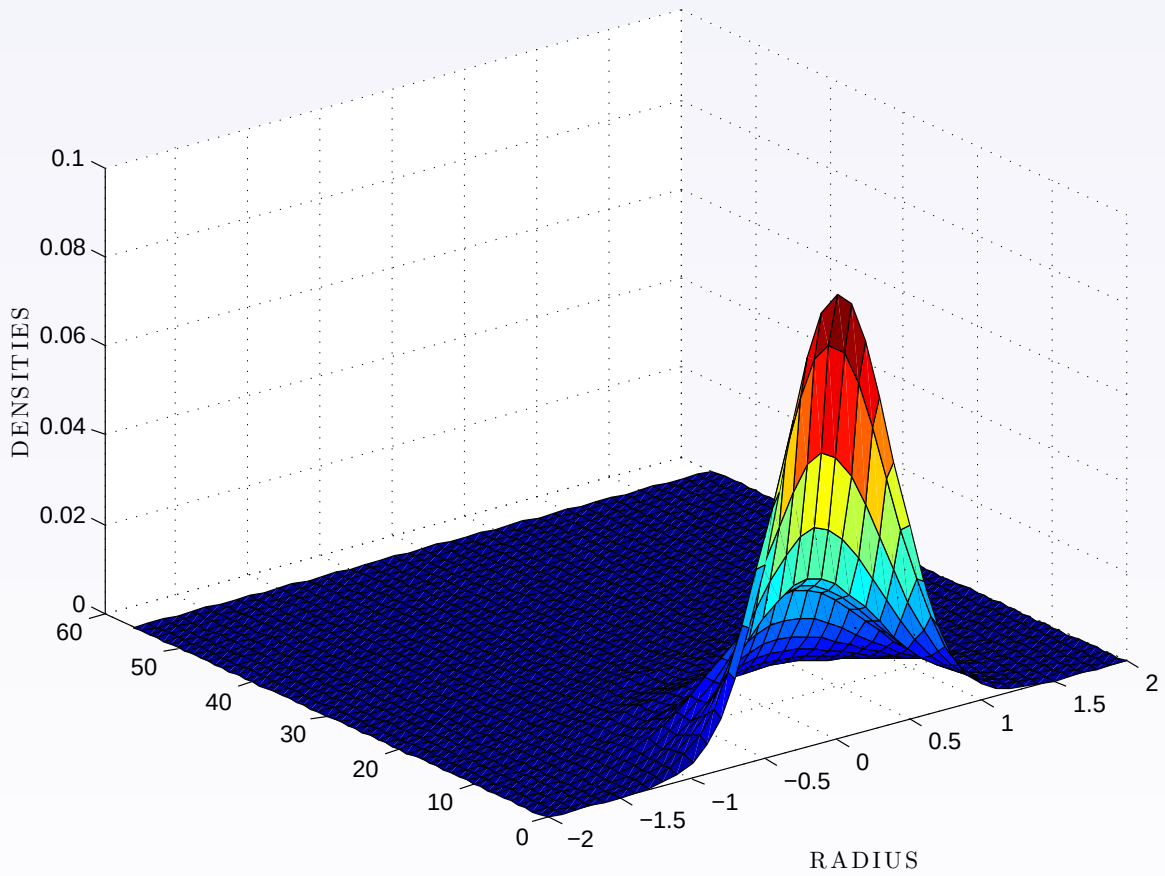


Figure: The evolution in time of the density of tumor cells (3D views) – 40 doses; pre-therapy and therapy.

A numerical experiment in a simplified but realistic situation:

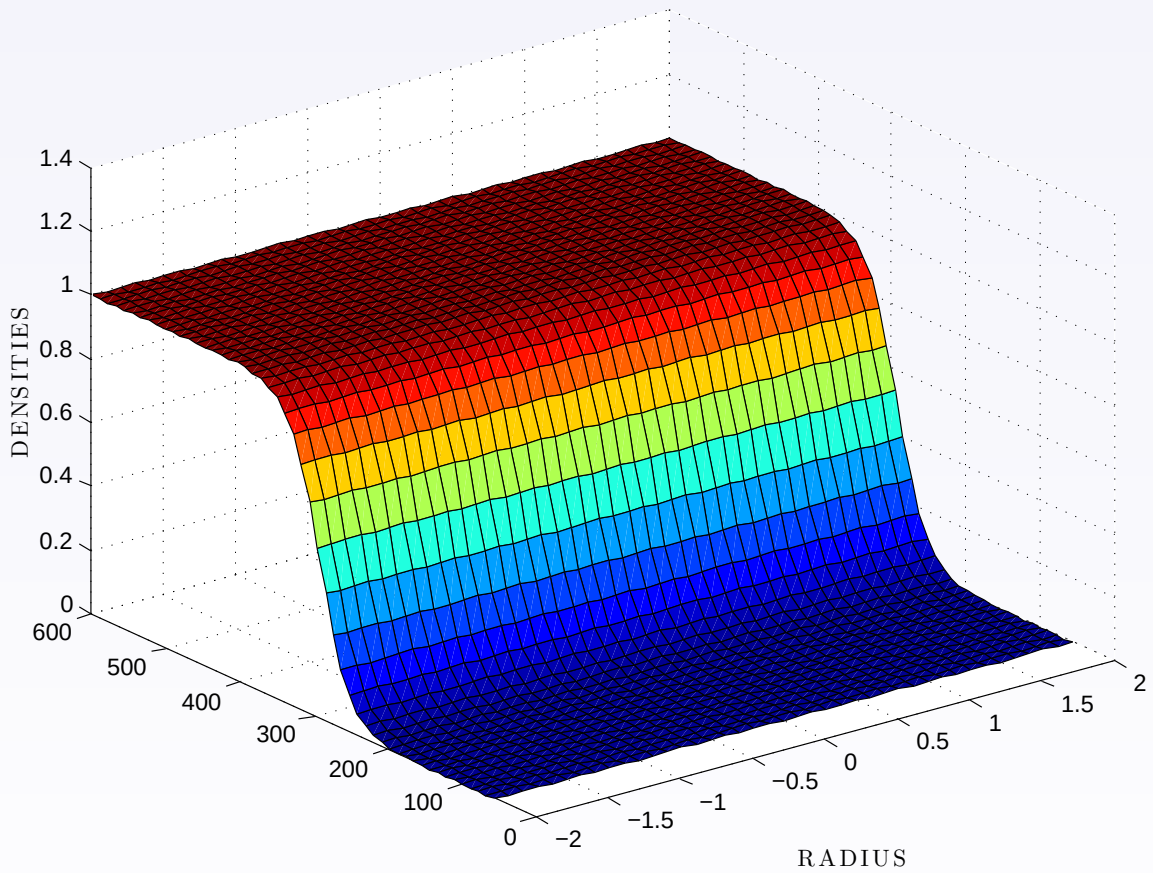


Figure: The evolution in time of the density of tumor cells (3D views) – 40 doses; post-therapy.

A numerical experiment in a simplified but realistic situation:

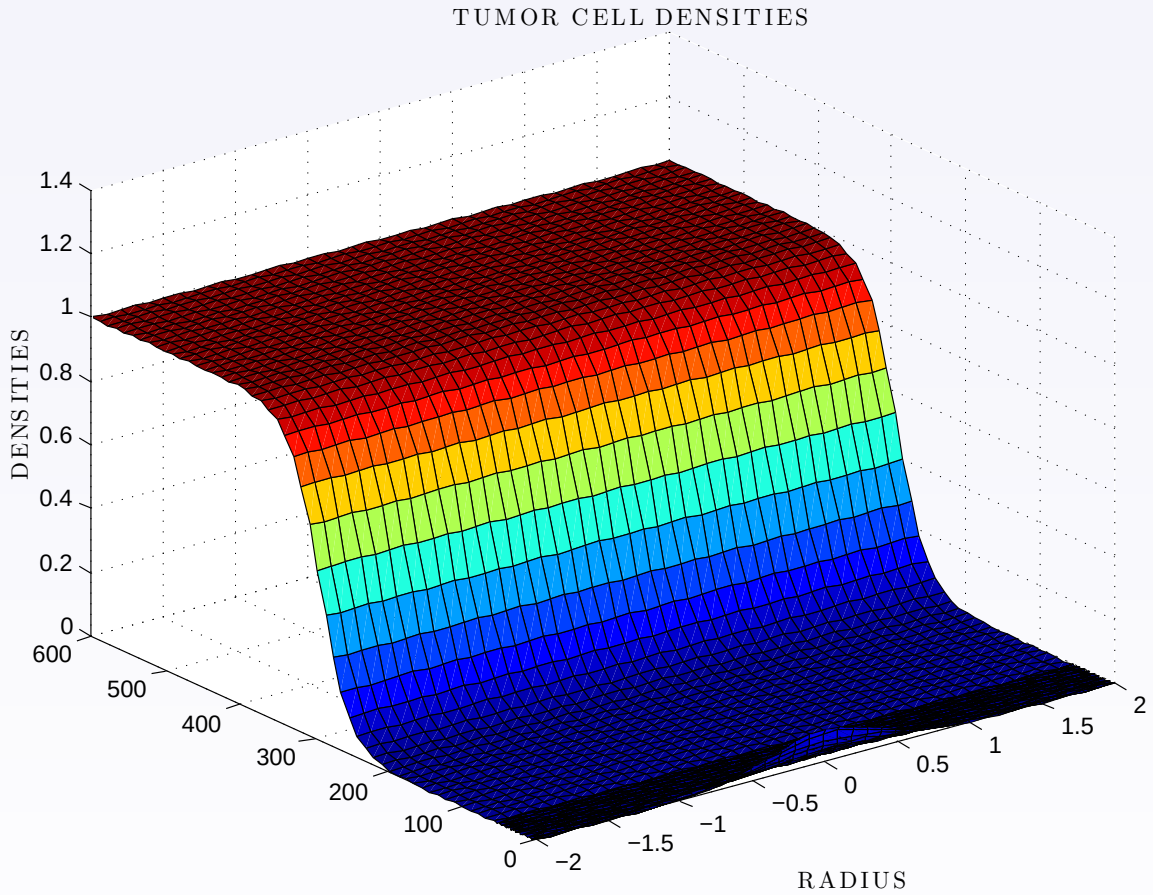


Figure: The evolution in time of the density of tumor cells (3D views) – 40 doses; global evolution.

AN EXACT CONTROLLABILITY PROBLEM

An idealized model:

$$\begin{cases} c_t - \Delta c = (v 1_\omega) c, & (x,t) \in Q \\ c(x,0) = c_0(x), & x \in \Omega, \dots \end{cases}$$

c: the cancer cell population v: the radiotherapy action

The exact controllability problem: Find v such that $c(x,T) \equiv \overline{c}(x,T)$

($\overline{c}$ is a fixed solution, another cell population)

Reformulation as a null controllability problem: $c = \overline{c} + y$, $c_0 = \overline{c}(\cdot\,,0) + y_0$

$$\begin{cases} y_t - \Delta y = (v 1_\omega)(\overline{c} + y), & (x,t) \in Q \\ y(x,0) = y_0(x), & x \in \Omega, \dots \end{cases}$$

The goal is now: Find v such that $y(x,T) \equiv 0$

For interesting applications:

$$\overline{c}(\cdot\,,0), c_0 \geq 0, \quad \overline{c}(\cdot\,,0), c_0 \not\equiv 0, \quad y_0 = c_0 - \overline{c}(\cdot\,,0) \geq 0 \ \text{(large)}$$

What we pretend:

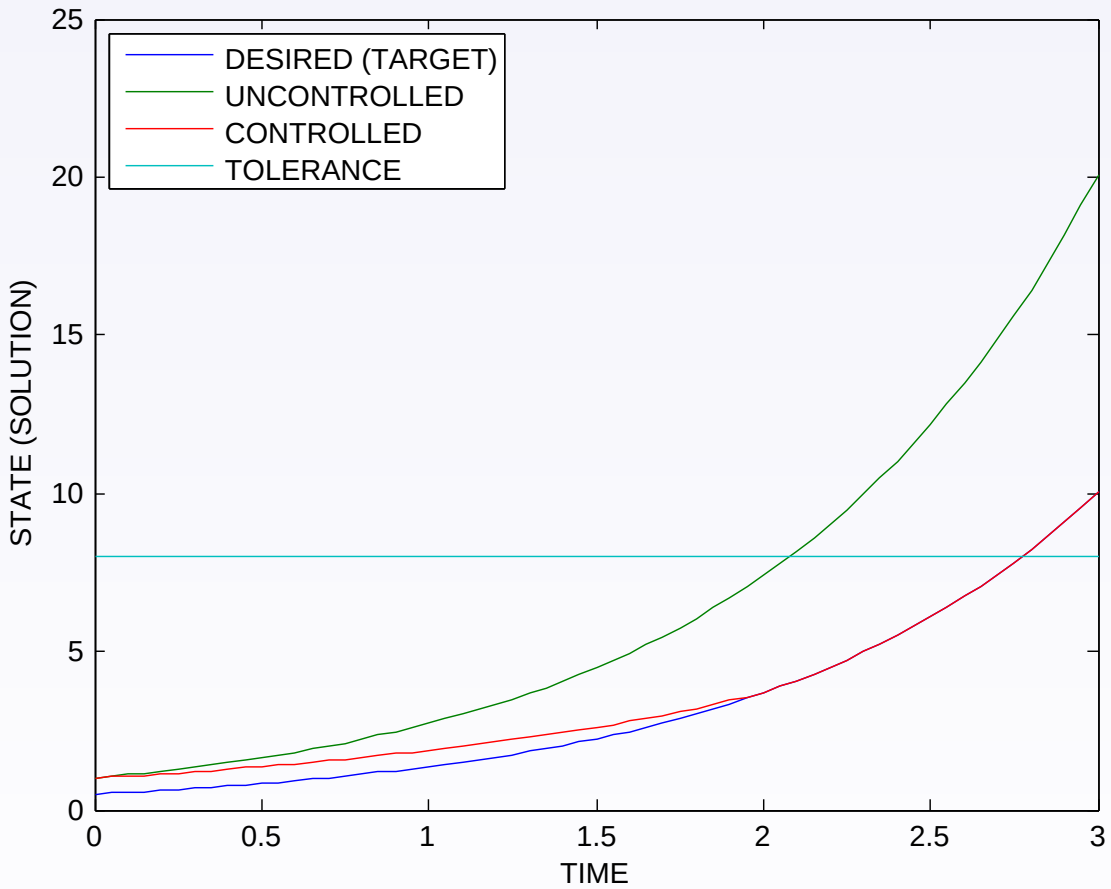


Figure: The desired, the uncontrolled and the controlled trajectories.

$$\begin{cases} y_t - \Delta y = (v 1_\omega)(\overline{c} + y), & (x,t) \in Q \\ y(x,0) = y_0(x), & x \in \Omega, \dots \end{cases}$$

Goal: Find v such that $y(x,T) \equiv 0$
Note: we can assume that $\overline{c} \geq 2\delta > 0$ in $\omega \times (0,T)$
A local result:

Theorem [Local controllability; Khapalov, 1990's]

$\exists \varepsilon > 0$ such that $y_0 \geq 0, \|y_0\|_{L^2} \leq \varepsilon \Rightarrow$ OK

For the proof, solve the NC problem for

$$\begin{cases} y_t - \Delta y = u 1_\omega, & (x,t) \in Q \\ y(x,0) = y_0(x), & x \in \Omega, \dots \end{cases}$$

Then take $v := u/(\overline{c} + y)$ in $\omega \times (0,T)$
y_0 small $\Rightarrow$ u small $\Rightarrow$ $y \geq -\delta$ in $\omega \times (0,T) \Rightarrow \overline{c} + y \geq \delta$ in $\omega \times (0,T)$

$$\begin{cases} y_t - \Delta y = (v 1_\omega)(\overline{c} + y), & (x,t) \in Q \\ y(x,0) = y_0(x), & x \in \Omega, \dots \end{cases}$$

Goal: Find v such that $y(x,T) \equiv 0$

An open problem: NC for large y_0?
It would suffice: global approximate controllability, i.e.
For small $\varepsilon > 0$, find v_ε such that $\|y(\cdot\,,T)\|_{L^2} \leq \varepsilon$
Unknown

A related question:

$$\begin{cases} y_t - \Delta y = u 1_\omega, & (x,t) \in Q \\ y(x,0) = y_0(x), & x \in \Omega, \dots \end{cases}$$

For small $\varepsilon > 0$, $\delta > 0$, find $u_{\varepsilon,\delta}$ such that

$$\|y(\cdot\,,T)\|_{L^2} \leq \varepsilon, \quad y \geq -\delta \ \text{ in } \ \omega \times (0,T)$$

Also unknown – Note: false for $\delta = 0$!

More results

IN PROGRESS:

- Calderón-like IPs for 3D Lamé systems, with F. Mestre
- Radiotherapy optimal strategies for more complex systems, with L. Prouvée
- Optimal chemotherapy techniques for spherical tumors, with M. Cavalcanti and A.L. Ferreira

Additional results and comments

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FERNÁNDEZ-CARA, E., PROUVÉE, L.
Optimal control of a two-equation model of radiotherapy,
in preparation.

THANK YOU VERY MUCH . . .

AND CONGRATULATIONS TO PROF. LUIS ADAUTO !!! . . .