Population-Based Sequential Data Assimilation for Oncology Modeling: Theory and Practical Illustrations

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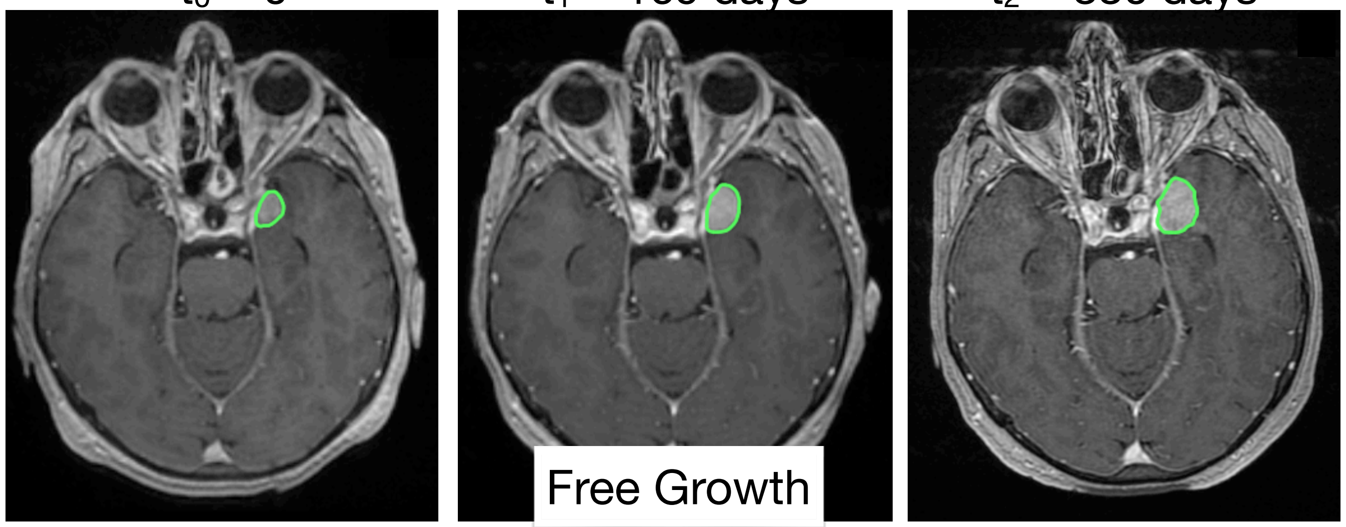
Introduction

A little bit of context

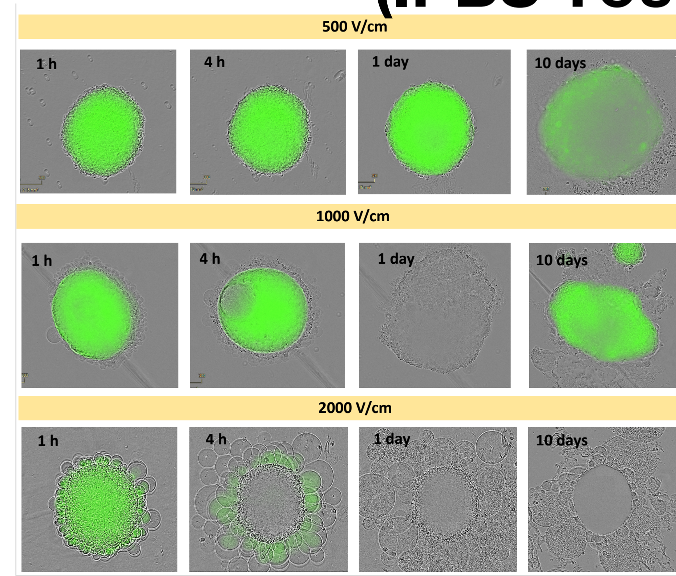
- Available data: medical imaging, clinical data, biological data …

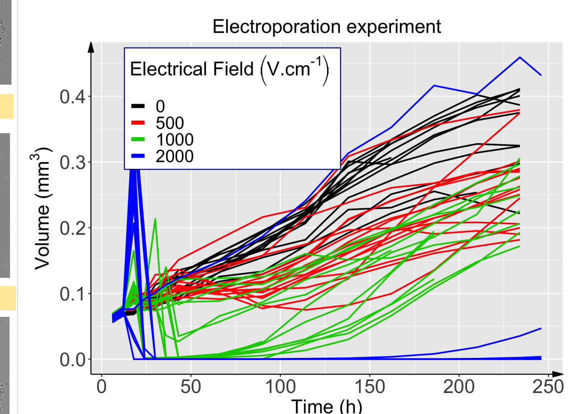
Meningiomas (CHU Bordeaux, MRI T1)

$t_0 = 0$ $t_1 = 169$ days $t_2 = 330$ days



3D spheroids exposed to high intensity pulsed electric fields (IPBS Toulouse)





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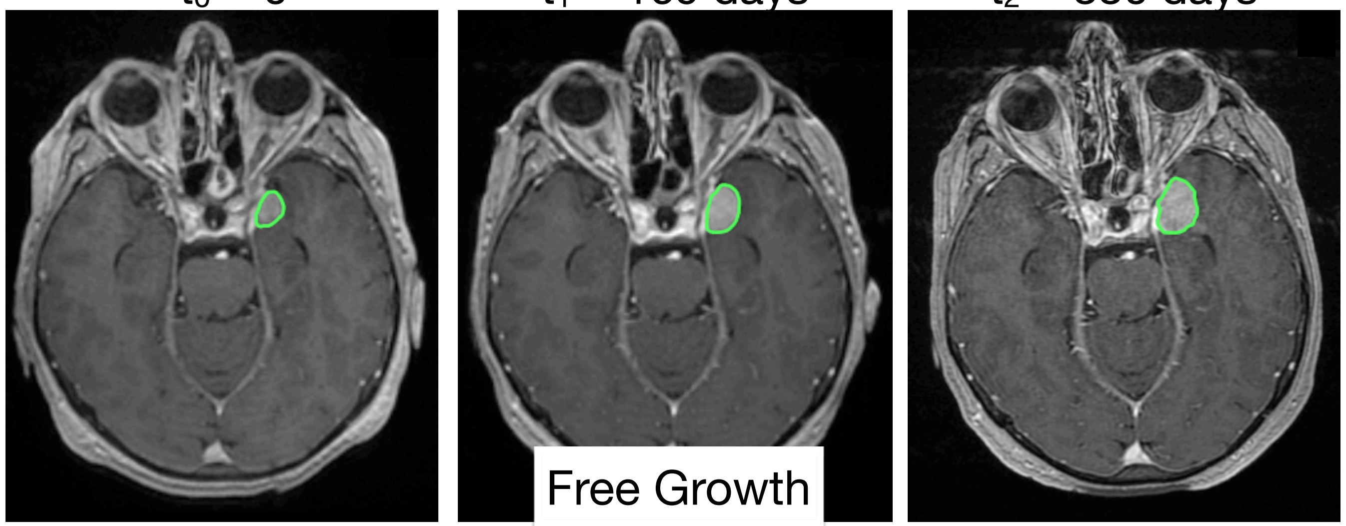

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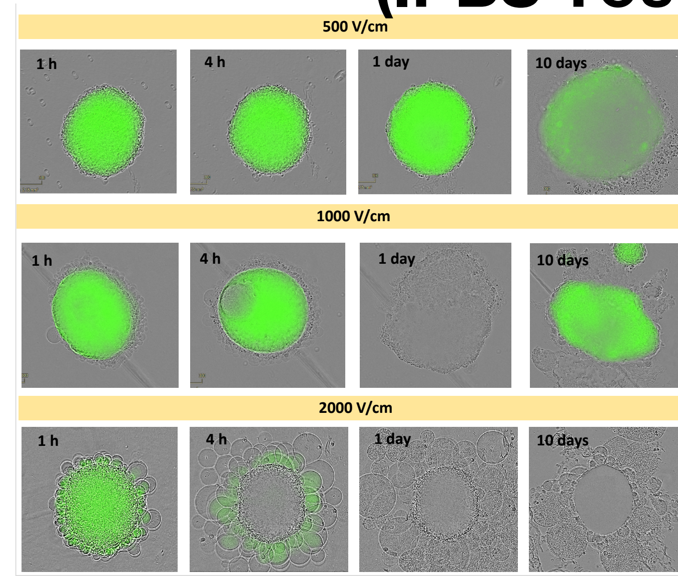
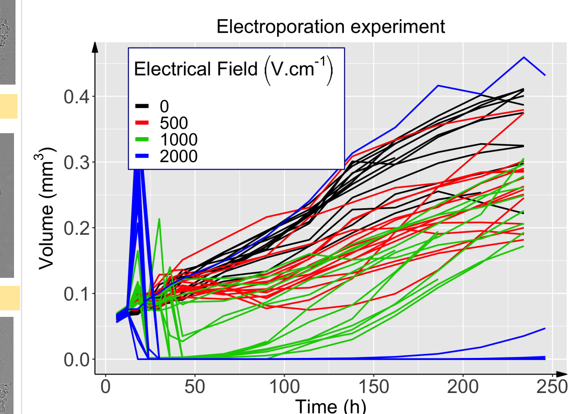




- Link between these series of data?
  - Temporal evolution of some quantities (volume, shape or heterogeneity of the tumor)

- Can we model these processes?
  - Yes: using physical or biological laws …
  - Lead to Ordinary Differential Equations or Partial Differential Equations if spatial aspects

- Objectives:
  - help biologists to understand a phenomenon ;
  - help clinicians to establish a diagnosis or to improve the patient follow-up …

A little bit of context

Model

(ODE or PDE unknown)

State x ; Parameters θ

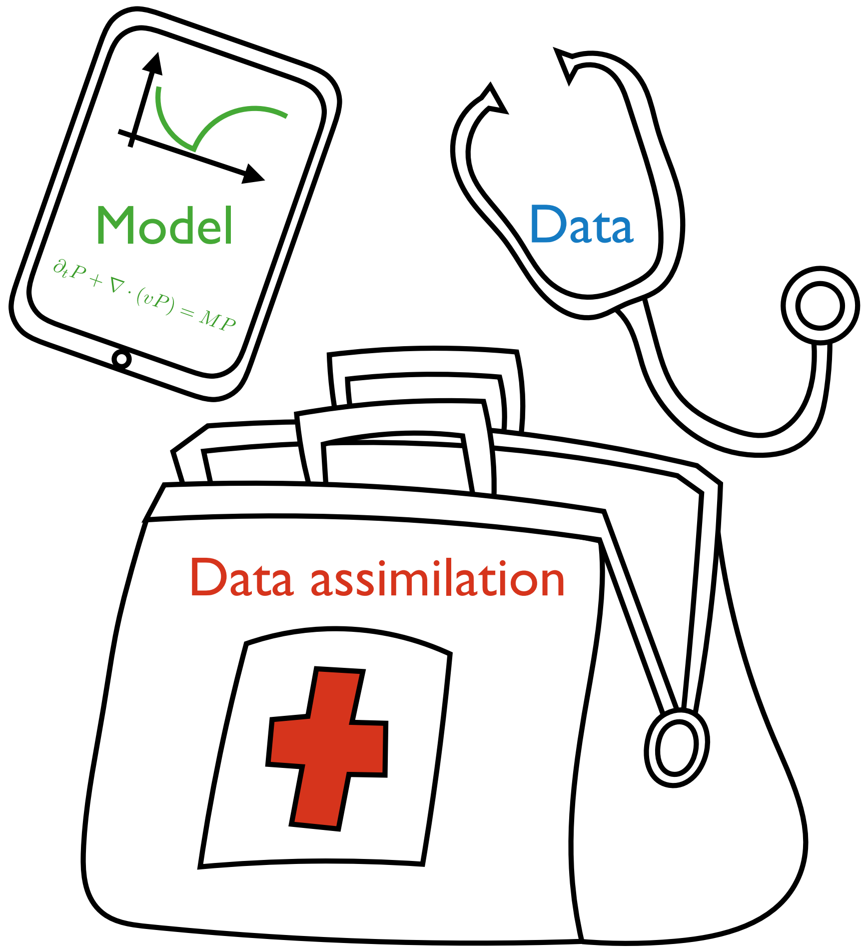
Uncertainties on the **parameters**, on the **initial condition** …

$$\dot{x} = F(x, \theta, t) + B_x v$$

$$\dot{\theta} = 0$$

$$x(0) = x_0 + \xi_x$$

$$\theta(0) = \theta_0 + \xi_\theta$$



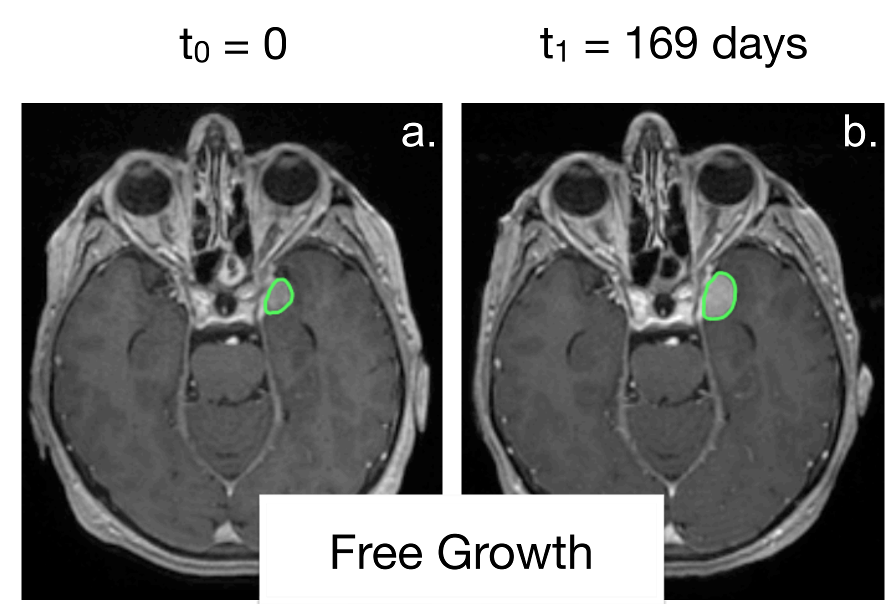
Data

Denoted by y

Partial in time/space

Noisy

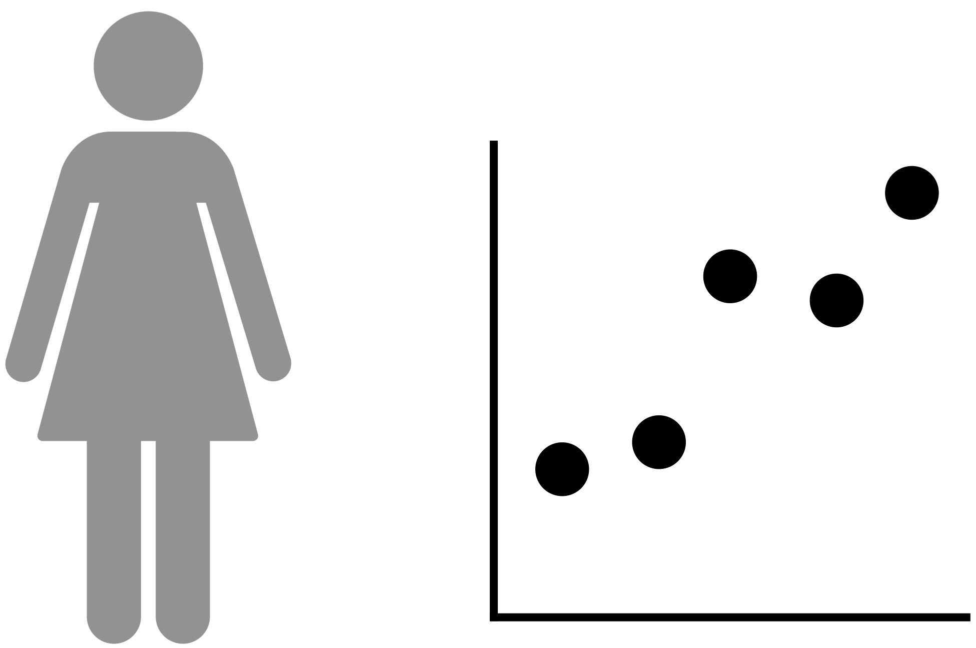
Comparison with the state of the model can be difficult



Difficulties & population-based strategies

- Most estimation strategies are not robust enough in many situations:
  - when measurements are too <u>sparse</u>,
  - or when measurements are <u>noisy</u>,
  - or when strong parameter <u>priors</u>* are not available.

<u>Observations</u>



<u>Estimation</u>

Parameters

$\theta \in \mathbb{R}^{N_\theta}$

Hypothesis (example)

$\theta \sim \boxed{\mathcal{N}(\theta_0, \Sigma_\theta)}^*$

Difficulties & population-based strategies

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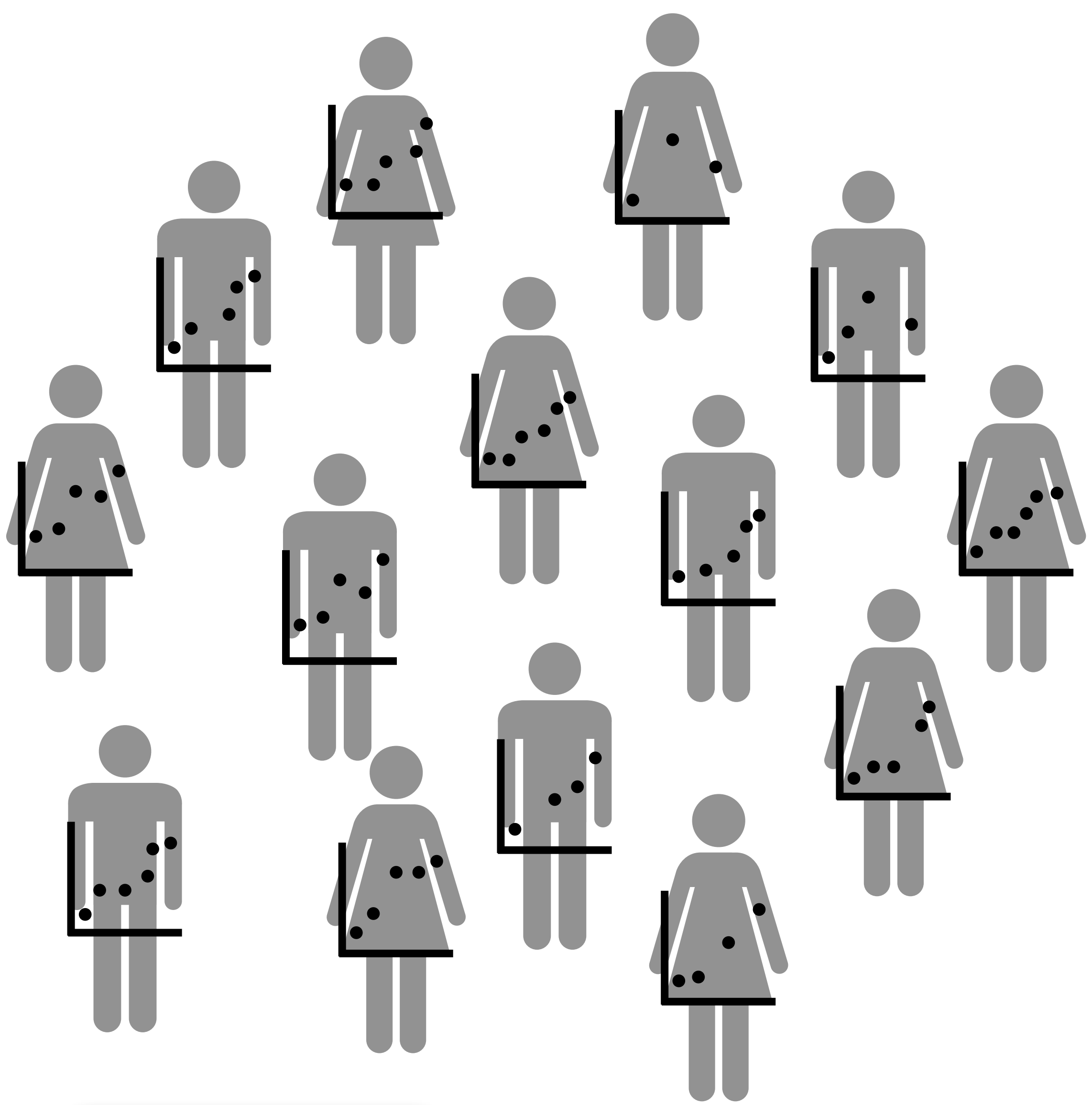


Estimation

Parameters of each patient
or each biological experiment i

$$\theta^i \in \mathbb{R}^{N_\theta}$$

Hypothesis (mixed-effect models)

$$\theta^i = \theta_f + \theta_m^i$$
$$\theta_m^i \sim \mathcal{N}(0, \Sigma_\theta)$$

Estimation performed by pooling all
subject measurements together
and estimating a global distribution of
uncertainties in the population.

M. Lavielle. Mixed effects models for the population approach: models, tasks, methods and tools. CRC press, 2014.

A quite simple example

Joint work with

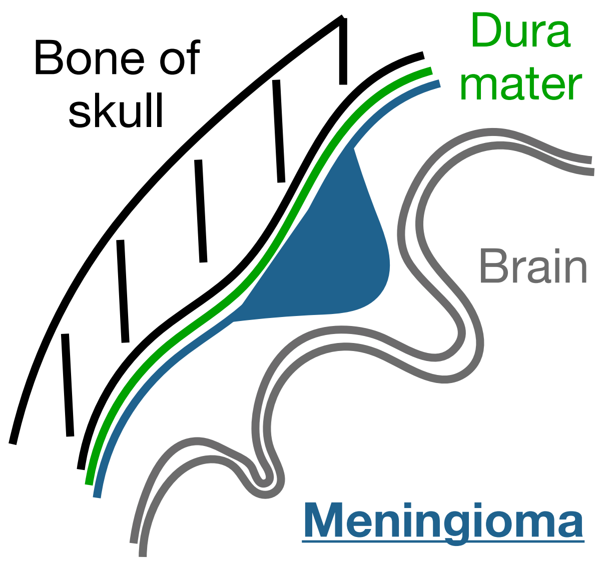
Virginie Montalibet and Olivier Saut

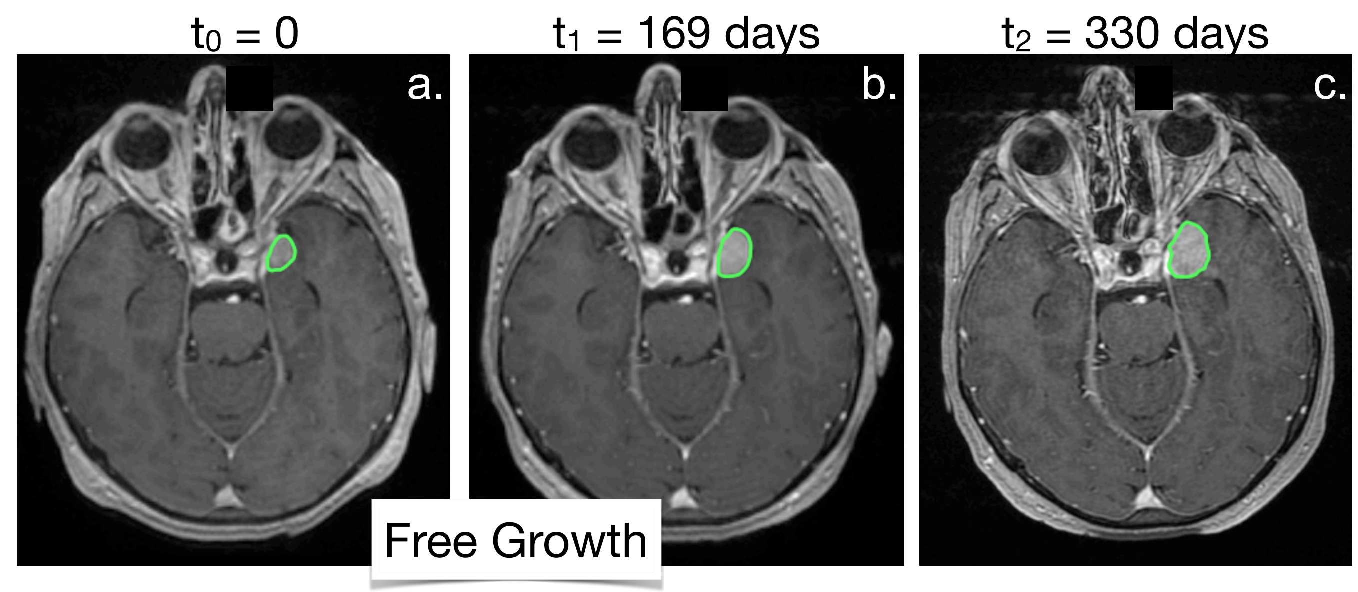
[clinicians]

Julien Engelhardt and Hugues Loiseau (neurosurgeons)

Meningioma - objective

- Meningiomas: intracranial tumors with slow growth & surgical ablation as main treatment
- Cohort of 315 patients with 333 meningiomas
- **Objective:** Help decision by predicting the tumor progression





Pat.	Age	G	Pos.
1	52	F	ER
2	48	M	BLPS
3	50	F	BRPM
4	53	F	BMPS
5	33	F	BLPI
6	44	F	IMAM
7	34	F	BLAS
8	70	F	ELI
9	77	F	BLPI
10	50	F	IRAS
11	52	M	BRAS
12	60	F	BRAS ...

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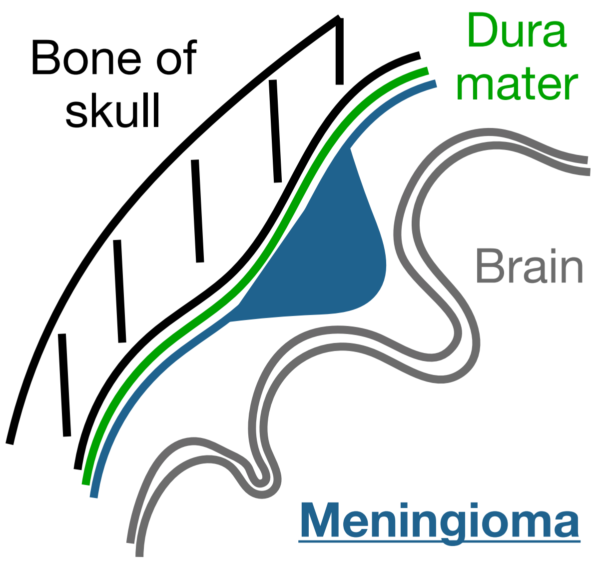

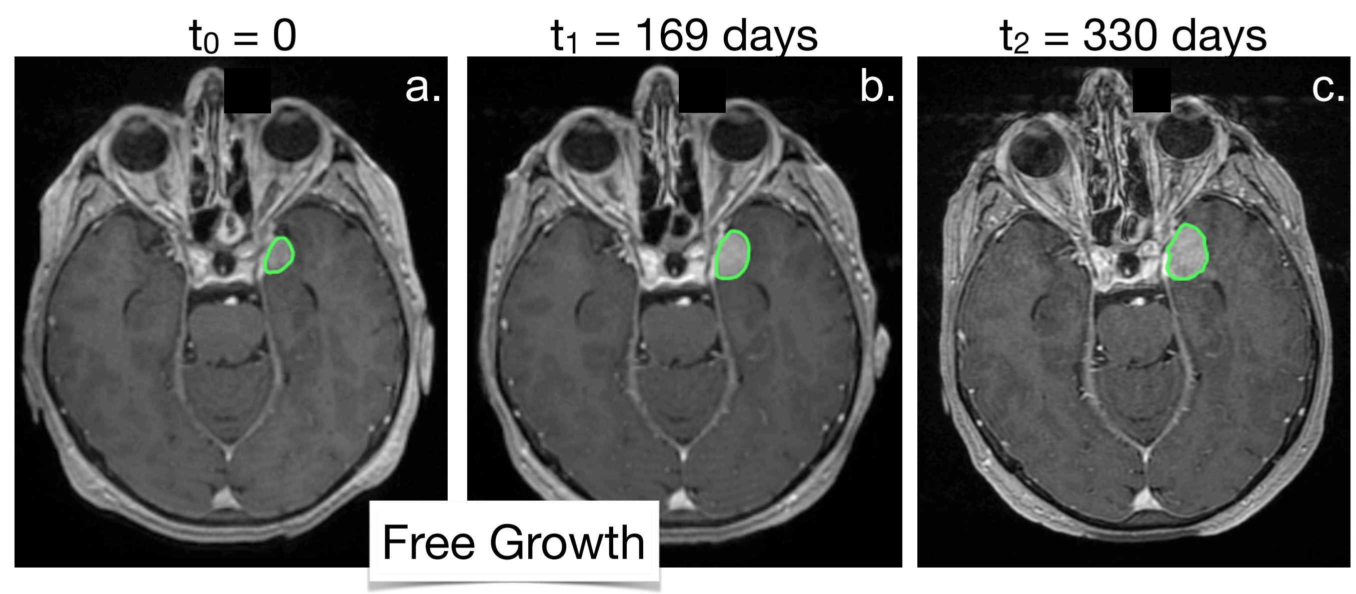

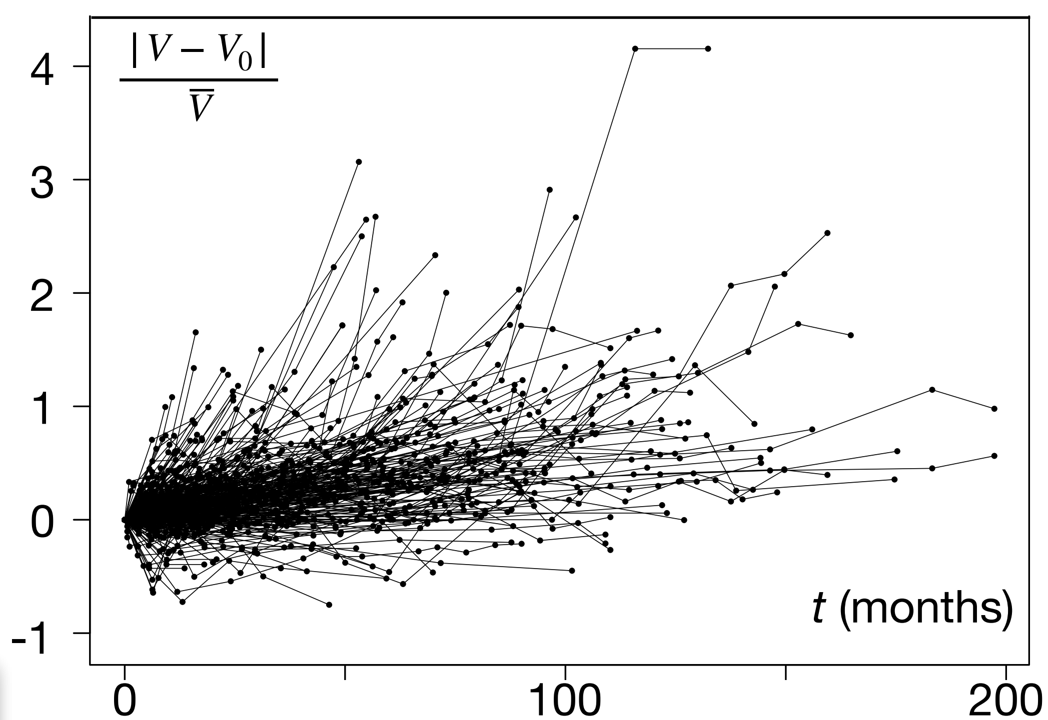

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Meningioma - 0D model & description

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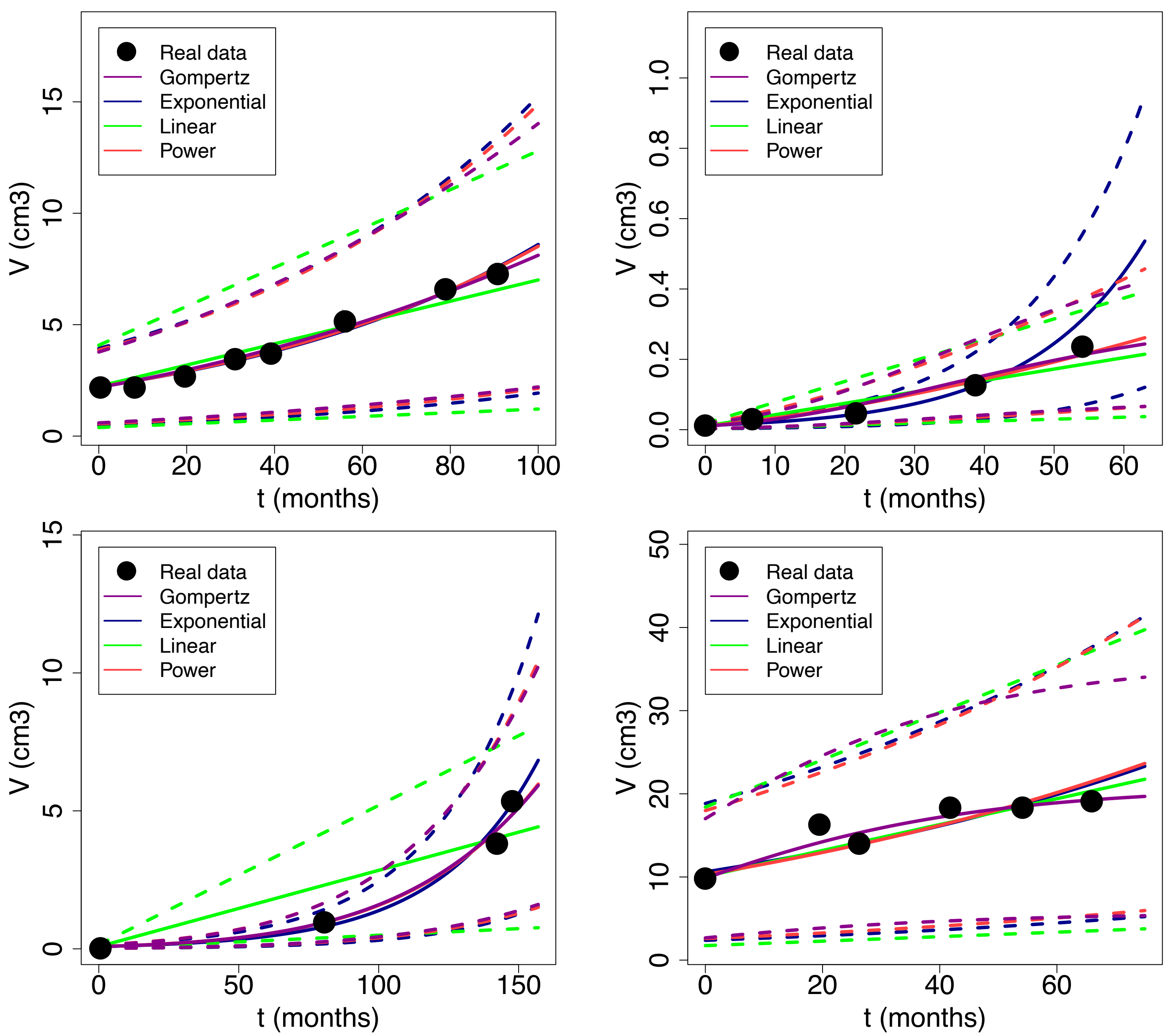

4 models:

Linear model $V(t) = V_0 + at$

Exponential model $V(t) = V_0 e^{at}$

$\boxed{\text{Gompertz model } V(t) = V_0 e^{\frac{a}{b}(1-e^{-bt})}}$

Power model $V(t) = (V_0^{1-b} + a(1-b)t)^{\frac{1}{1-b}}$

Mixed-effects approach (ex. for Gompertz):

$$V_0^j = V_{0,MRI}^j(1 + e_0^j),$$

$$\log(\{a^j, b^j\}) = \log(\{a^{pop}, b^{pop}\}) + \{\zeta_a^j, \zeta_b^j\},$$

with $e_0^j \sim \mathcal{N}(0, \sigma_{V_0}^2)$, $\zeta_a^j \sim \mathcal{N}(0, \sigma_a^2)$, $\zeta_b^j \sim \mathcal{N}(0, \sigma_b^2)$

J. Engelhardt, V. Montalibet, H. Loiseau, O. Saut, and A. Collin. Evaluation of four tumour growth models to describe the natural history of meningiomas. EBioMedicine, 2023.

Meningioma - 0D model & prediction

Meningioma 1	Meningioma 2		Meningioma N_m
(t_0, V_0)	(t_0, V_0)		(t_0, V_0)
(t_1, V_1)	(t_1, V_1)	$\dots$	(t_1, V_1)
$\vdots$	$\vdots$		$\vdots$
(t_{N_1}, V_{N_1})	(t_{N_2}, V_{N_2})		$(t_{N_{N_m}}, V_{N_{N_m}})$

Spatial mechanistic modeling for prediction of the growth of asymptomatic meningiomas. A. Collin, C. Copol, V. Pianet, T. Colin, J. Engelhardt, G. Kantor, H. Loiseau, O. Saut, B. Taton. Computer Methods and Programs in Biomedicine, 2021.

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(t_1, V_1)	(t_1, V_1)		(t_1, V_1)
$\vdots$	$\vdots$		$\vdots$
(t_{N_1}, V_{N_1})	$\cancel{(t_{N_2}, V_{N_2})}$		$(t_{N_{N_m}}, V_{N_{N_m}})$

Prediction based on a leave-one out approach: Delete the last data of one meningioma, learn the parameters using the mixed-effect approach and predict the last volume of the considered meningioma at the last time …

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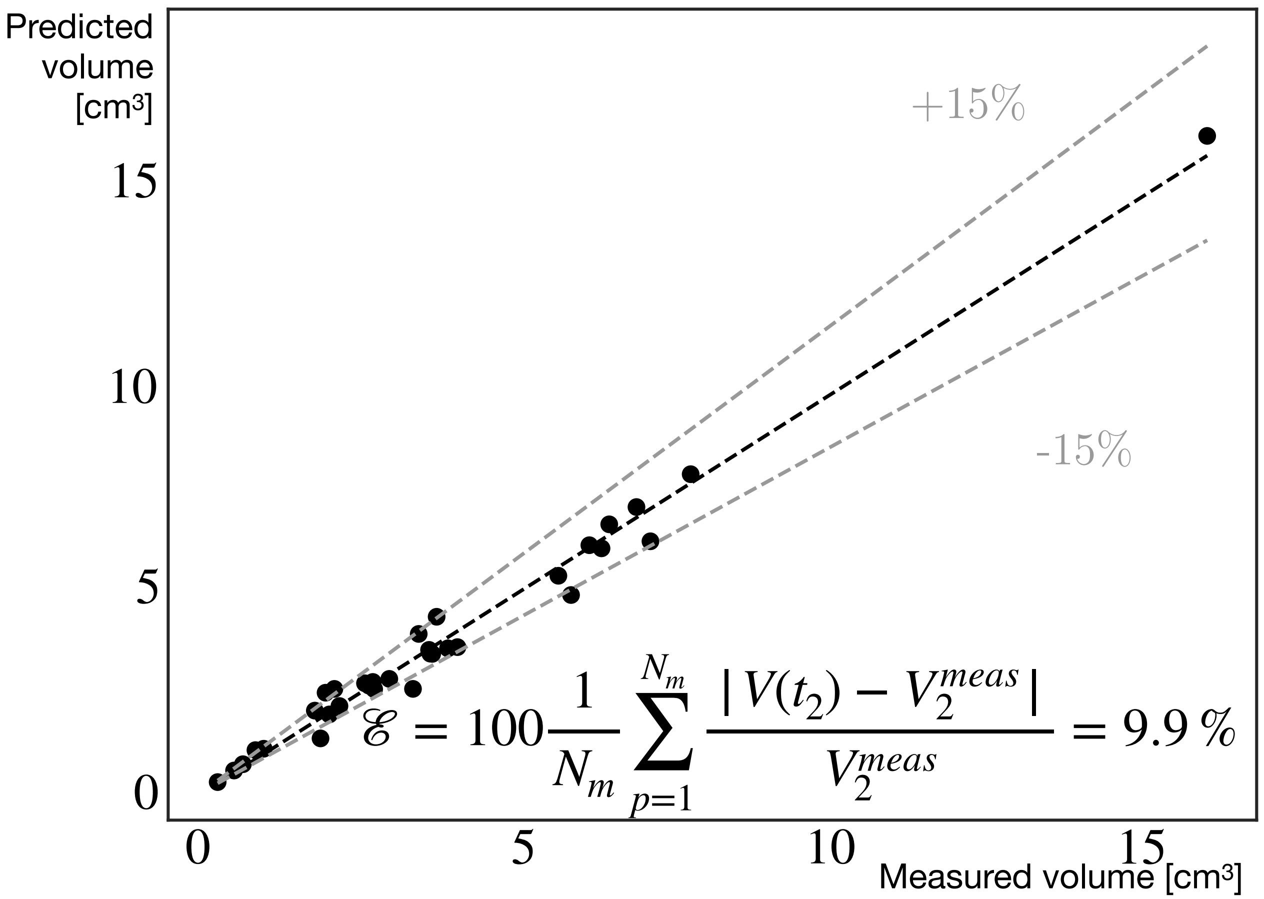

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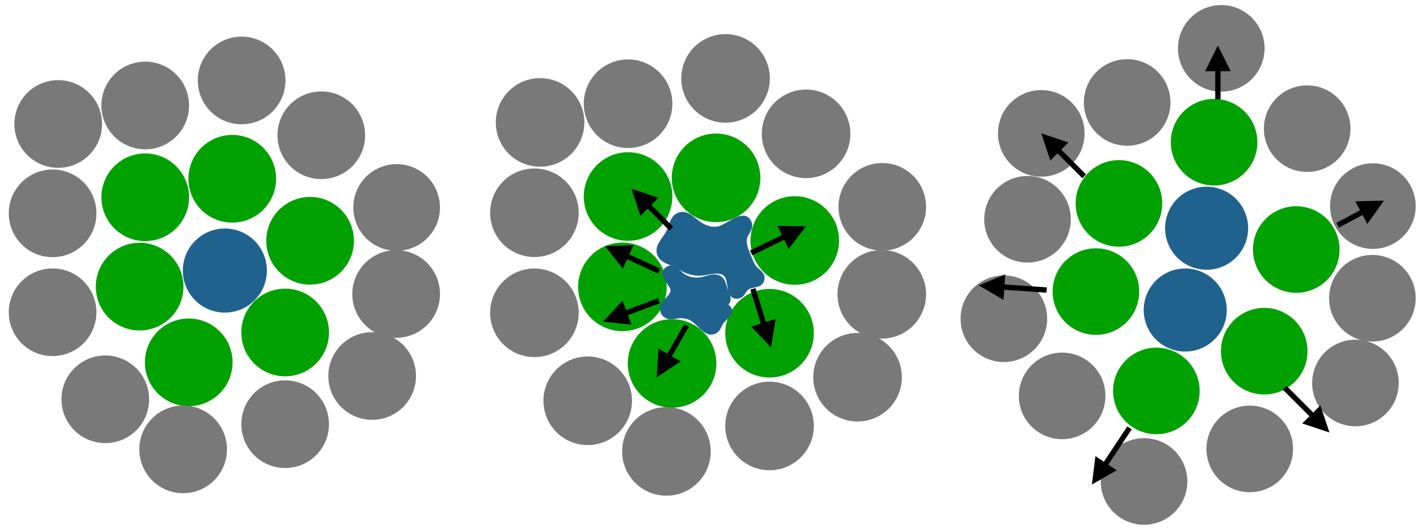
Meningioma - 3D model & prediction

- Link with a 3D PDE model: tumor cell densities T & healthy cell density S



$$
\begin{aligned}
\partial_t T + \nabla \cdot (\vec{v}\, T) &= a e^{-bt}\, T, && \mathscr{B},\\
S + T &= 1, && \mathscr{B},\\
\nabla \cdot \vec{v} &= \tau^G(t)\, T, && \mathscr{B},\\
\vec{v} &= -\nabla \pi, && \mathscr{B},
\end{aligned}
$$

Proposition -

- Existence & Uniqueness under assumptions
- Physical property: $0 \leq T \leq 1$ under assumptions

Proof relies on the model hyperbolic properties, combined with Gagliardo-Nirenberg estimates in Sobolev spaces.

Joint state-parameter estimation for tumor growth model. **A. Collin**, T. Kritter, C. Poignard and O. Saut. SIAM JAM, 2021.

Proposition - The volume V of the lesion at time t verifies: $V(t) := \displaystyle\int_{\mathscr{B}} T(t,x)\,dx = V_0 e^{\frac{a}{b}(1-e^{-bt})}$.

Proof relies on Reynolds and Green theorems.

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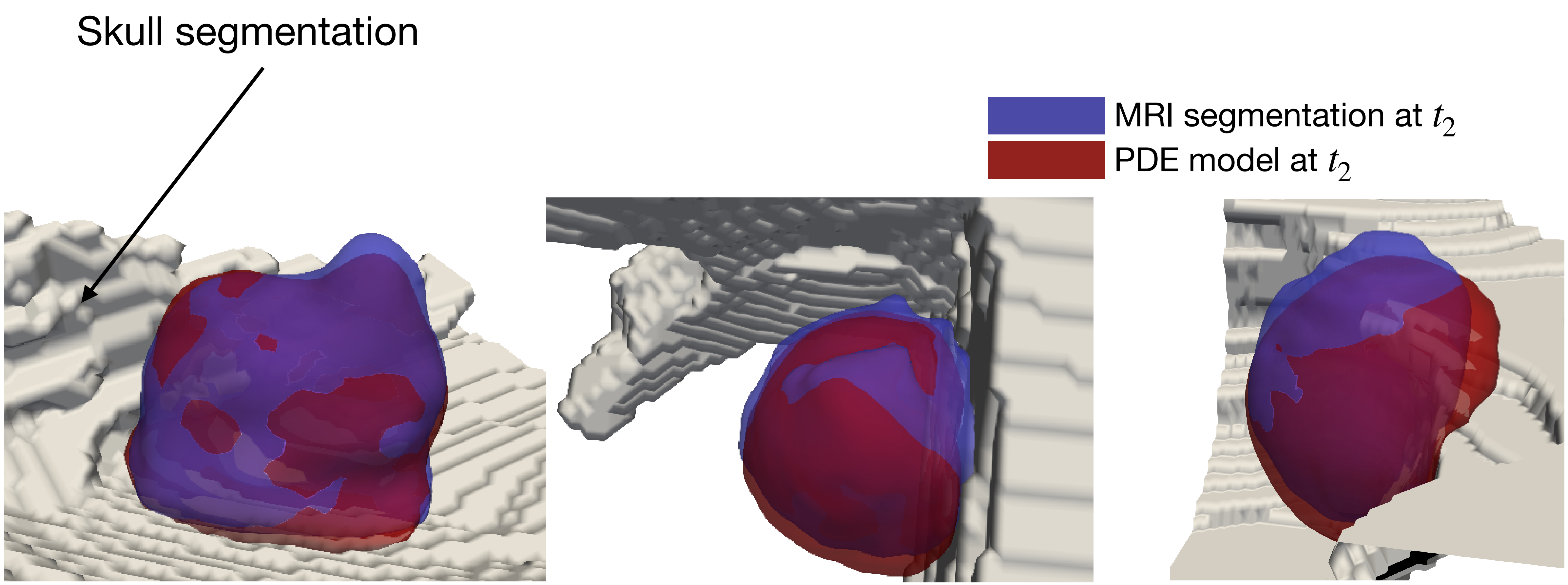
Meningioma - 3D model & prediction

- 0D and 3D models share the same parameters
- 3D simulations can then be done once the parameters estimated with the 0D model (with the prediction approach)

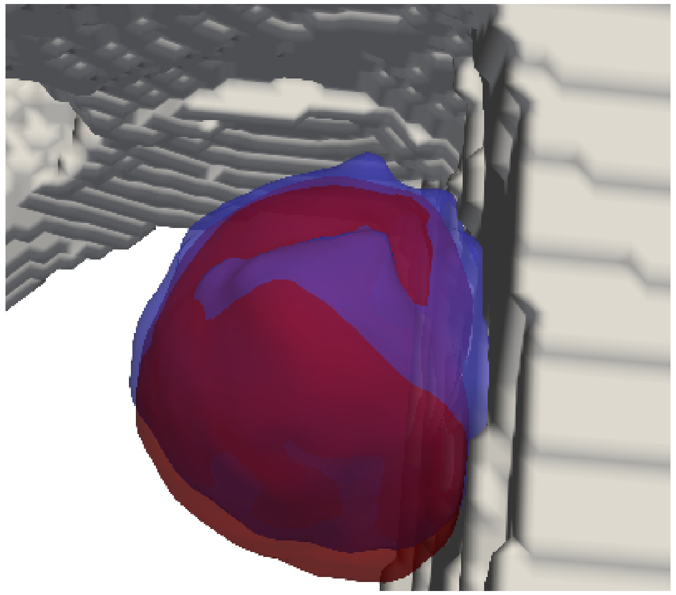


Three illustrative meningiomas

Spatial mechanistic modeling for prediction of the growth of asymptomatic meningiomas. **A. Collin**, C. Copol, V. Pianet, T. Colin, J. Engelhardt, G. Kantor, H. Loiseau, O. Saut, B. Taton. Computer Methods and Programs in Biomedicine, 2021.

Intermediate conclusion and main limitation

- Intermediate conclusion : An illustrative example of how mixed-effects models can be used to successfully estimate parameters and answer clinical questions



- Main limitation : it remains a challenge to increase the size of the dynamics – for example, when using **PDE systems** – with acceptable complexity costs of the algorithm

- Objective: design a population-based estimator for PDE systems based on sequential strategies.

Population-based estimator compatible for PDE systems

Joint work with

Mélanie Prague and Philippe Moireau

Maximum likelihood estimation (variational approach)

- Consider the augmented state (coupled the system state x and the parameters θ)
- Minimize the criterion with respect to the uncertainties under the constraint of the model dynamics

$$(\hat{\xi}, \hat{\nu}) = \text{argmax}(\log \mathscr{L}_T((\zeta, \nu); y(t_1), \ldots, y(t_{N_T})))$$

ξ Uncertainties (parameters / initial conditions)

ν Model error

y Observations

- Corresponds to least-square minimisation when Gaussian laws are considered

$$\min_{\xi,\nu} \left\{ \mathscr{J}_T(\xi,\nu) = \underbrace{\frac{1}{2}\left\langle \xi, P_\diamond^{-1}\,\xi \right\rangle}_{\text{uncertainties priors}} + \overbrace{\frac{1}{2}\int_0^T \left\langle \nu(t), Q(t)^{-1}\nu(t) \right\rangle dt}^{\text{model error}} + \overbrace{\frac{1}{2}\sum_{k=0}^{N_{T,obs}} \left\langle y_k - H\big(z(t_k)\big), (W_k)^{-1}(y_k - H\big(z(t_k)\big) \right\rangle}^{\text{comparison between y and z}} \right\}$$

with $\dot{z} = F(t,z) + B\nu(t)$

$z(0) = z_0 + \xi$

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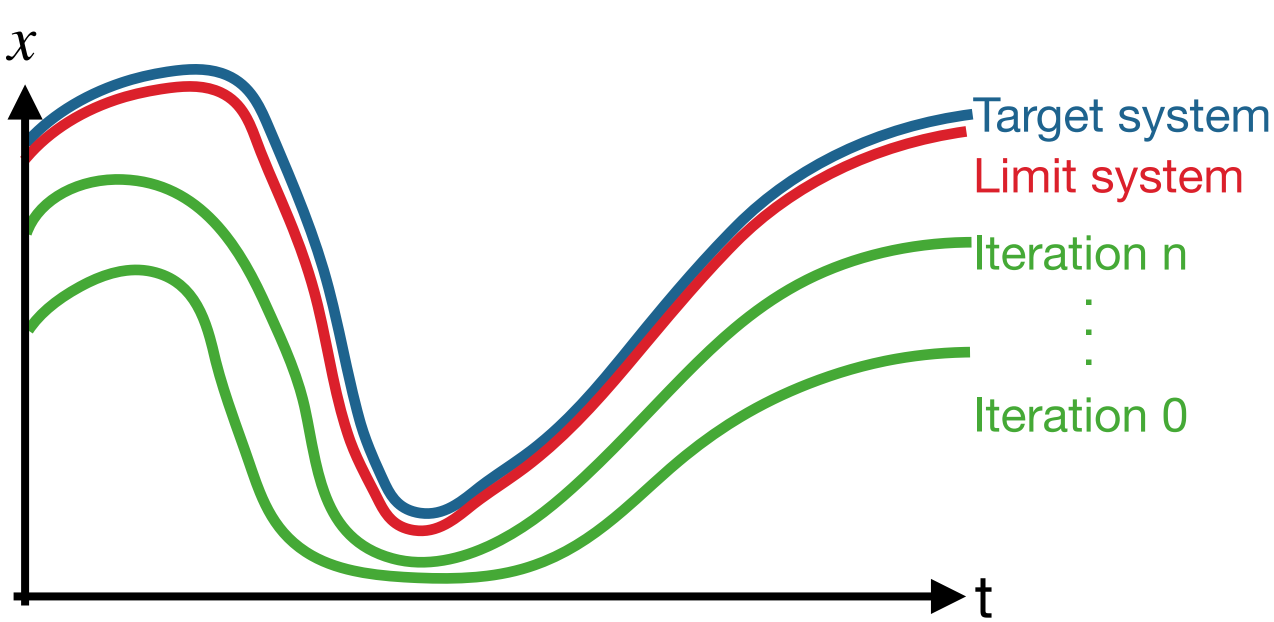
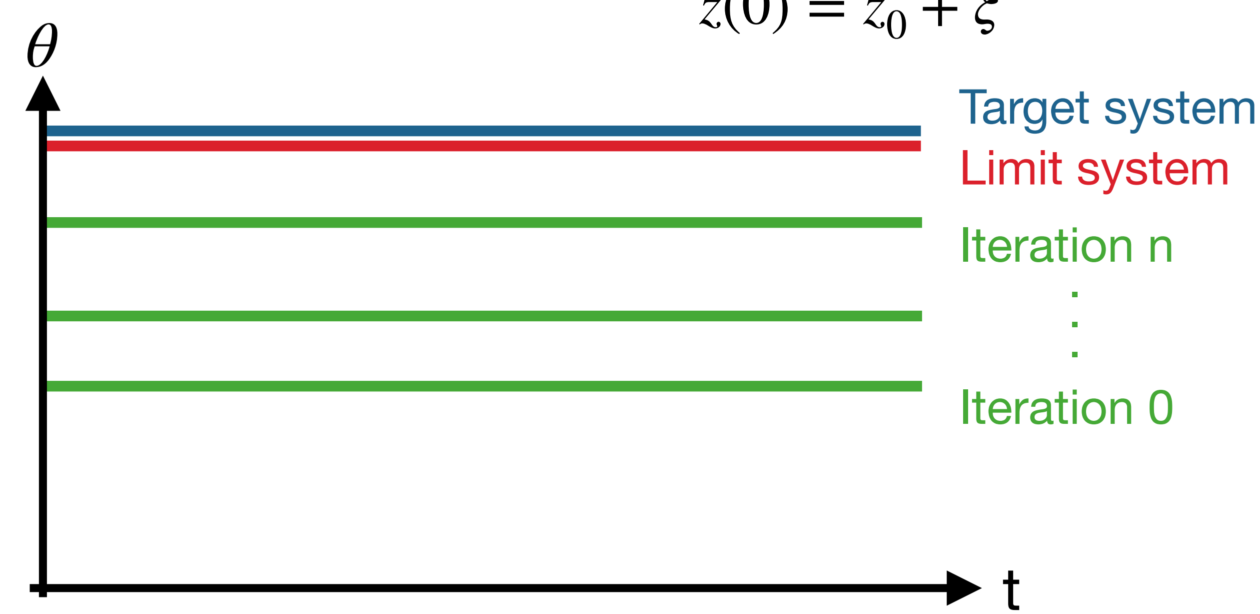




Iterative procedures: Gradient descent method, Newton–Raphson method, Quasi-Newton methods (Fisher's scoring …), Expectation–maximization (EM) algorithm, Nelder-Mead algorithm, Monte Carlo Markov chain methods etc.

Sequential approach

- Correct the dynamics by a feedback based on the discrepancy combining the data and the model state

Target model

$$\dot{z} = F(t, z) + B\nu(t)$$
$$z(0) = z_0 + \xi$$

state

$$z = \begin{pmatrix} x \\ \theta \end{pmatrix}$$

parameters

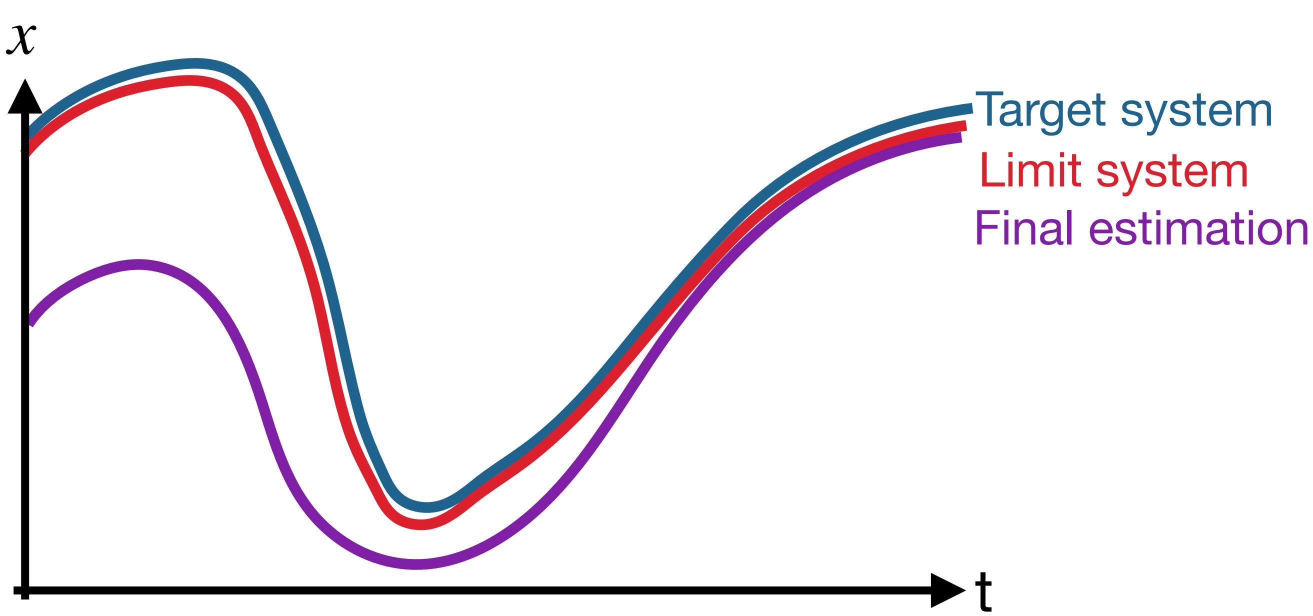
$$\boxed{\begin{array}{l} \|x - \hat{x}\| \to_{t\to\infty} 0 \\ \|\theta - \hat{\theta}\| \to_{t\to\infty} 0 \end{array}}$$

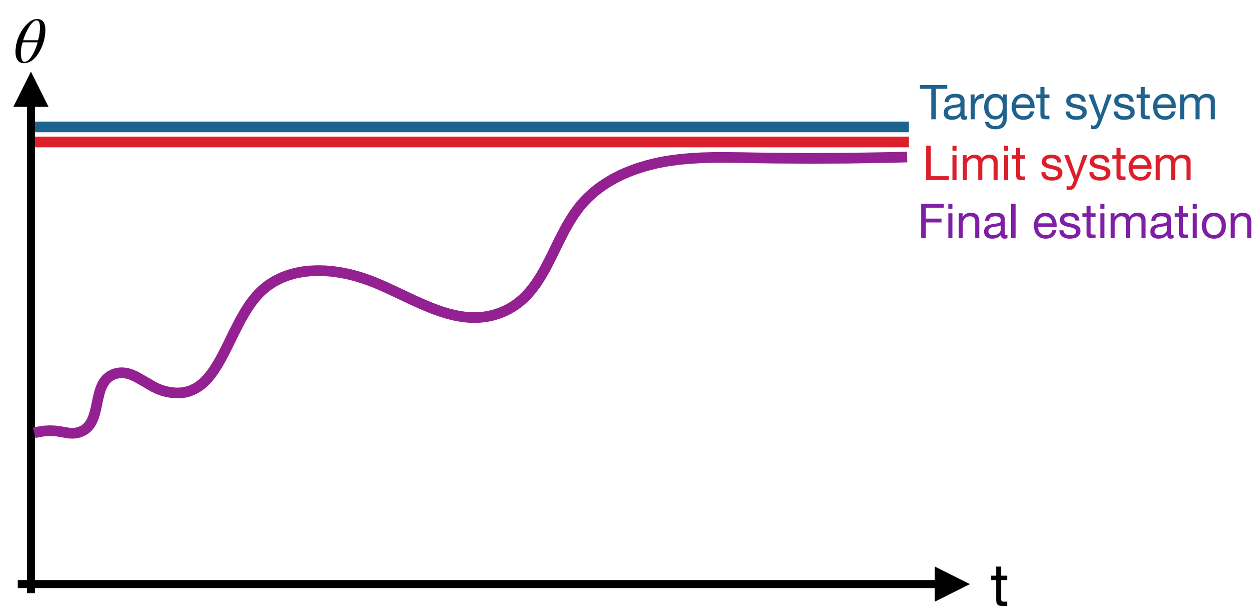
Observer model

$$\dot{\hat{z}} = F(t, \hat{z}) \;\; (+B\nu(t)) \; + G(y - H(\hat{z}))$$
$$\hat{z}(0) = z_0$$

Discrepancy D

Gain operator G





Parameters have a dynamics too !
Allow also to estimate initial conditions and model error.

Kalman-based filters

- Kalman & Bucy (61) showed that the minimizer of the following least-square minimisation

$$\min_{\xi,\nu} \left\{ \mathcal{J}_T(\xi,\nu) = \frac{1}{2}\left\langle \xi, P_\diamond^{-1}\,\xi \right\rangle + \frac{1}{2}\int_0^T \left\langle \nu(t), Q(t)^{-1}\nu(t) \right\rangle dt + \frac{1}{2}\sum_{k=0}^{N_{T,obs}} \left\langle y_k - h\big(z(t_k)\big), (W_k)^{-1}(y_k - h\big(z(t_k)\big) \right\rangle \right\} \boxed{\begin{array}{l} \dot z = F(t,z) + B\nu(t) \\ z(0) = z_0 + \xi \end{array}}$$

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when model and observer operators are linear verifies (time discrete version!)

Target Model

$$z_{k+1} = F_{k+1|k}\, z_k$$

Discrete transition operator

$\Leftrightarrow$

Observer Model

$$\hat z_{k+1} = F_{k+1|k}\, \hat z_k + K_k(y_k - H_k \hat z_k)$$

$$\hat P_{k+1} = F_{k+1|k} \hat P_k F_{k+1|k}^T - K_k H_k \hat P_k$$

with $K_k = P_k H_k^T (H_k P_k H_k^T + W)^{-1}$

z state and parameters
H observation operator
y observations
Covariance matrices:
W observation error
P estimation error

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with $K_k = P_k H_k^T (H_k P_k H_k^T + W)^{-1}$

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- If it is not linear?
  - Extended Kalman Filter (EKF): tangent operators.
  - Unscented Kalman Filter (UKF): finite difference approximations based on sampling points which propagate the mean and covariance of a random variable,
  - General nonlinear context: The Mortensen Filter*.

*A Discrete-time Optimal Filtering Approach for Non-linear Systems as a Stable Discretization of the Mortensen Observer. P. Moireau. ESAIM: Control, Optimisation and Calculus of Variations, 2018.

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$\Longleftrightarrow$

Observer Model

$$\hat{z}_{k+1} = F_{k+1|k}\,\hat{z}_k + K_k(y_k - H_k\hat{z}_k)$$

$$\hat{P}_{k+1} = F_{k+1|k}\hat{P}_k F_{k+1|k}^T - K_k H_k \hat{P}_k$$

with $K_k = P_k H_k^T (H_k P_k H_k^T + W)^{-1}$

z state and parameters
H observation operator
y observations
Covariance matrices:
W observation error
P estimation error

- If it is not linear?
  - Extended Kalman Filter (EKF): tangent operators.
  - Unscented Kalman Filter (UKF): finite difference approximations based on sampling points which propagate the mean and covariance of a random variable,
  - General nonlinear context: The Mortensen Filter*.

- Reduced order strategy
  - Prohibitive computational times due to the covariance matrix P (full matrix of size $N_z \times N_z$)
  - SVD decomposition: $P = LU^{-1}L^T$, U invertible matrix of small size and L extension operator.

*A Discrete-time Optimal Filtering Approach for Non-linear Systems as a Stable Discretization of the Mortensen Observer. P. Moireau. ESAIM: Control, Optimisation and Calculus of Variations, 2018.

Luenberger observer

- Introduce a correction such that the error between the observed trajectory and the observer system tends to zero.
- **Objective**: simplest possible to avoid prohibitive additional computational times.

Target model

$$\dot{z} = F(t, z)$$
$$z(0) = z_0 + \xi$$

state

$$z = \begin{pmatrix} x \\ \theta \end{pmatrix}$$

parameters

Observer model

$$\dot{\hat{z}} = F(t, \hat{z}) + G(y - H(\hat{z}))$$
$$\hat{z}(0) = z_0$$

Error model

$$\dot{\tilde{z}} = F(t, z) - F(t, \hat{z}) - G(H(\hat{z}) - H(z))$$
$$\tilde{z}(0) = \xi$$

$$\boxed{\|\tilde{z}\| \to_{t \to \infty} 0}$$

Linear case

$$\dot{\tilde{z}} = (F - GH)\tilde{z}$$
$$\tilde{z}(0) = \xi$$

- Has to be adapted to each model: need theoretical proof.
- Very efficient in terms of computational times.
- Most of the Luenberger filter are defined only for estimating the state.

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Joint state and parameter observer

Target model

$$\dot{x} = F(t, x, \theta)$$
$$\dot{\theta} = 0$$
$$x(0) = x_0 + \xi_x$$
$$\theta(0) = \theta_0 + \xi_\theta$$

Observer model

$$\dot{\hat{x}} = F(t, \hat{x}, \hat{\theta}) + G_x(y - H(\hat{x}))$$ Luenberger observer (large dimension)

$$\dot{\hat{\theta}} = G_\theta(y - H(\hat{x}))$$ Kalman observer (small dimension)

$$\hat{x}(0) = x_0$$
$$\hat{\theta}(0) = \theta_0$$

P. Moireau, D. Chapelle, Reduced-Order Unscented Kalman Filtering with Application to Parameter Identification in Large-Dimensional Systems. COCV 2011.

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Joint state and parameter observer

Target model

$$\dot{x} = F(t, x, \theta)$$
$$\dot{\theta} = 0$$
$$x(0) = x_0 + \xi_x$$
$$\theta(0) = \theta_0 + \xi_\theta$$

Observer model

$$\dot{\hat{x}} = F(t, \hat{x}, \hat{\theta}) + G_x(y - H(\hat{x}))$$

Luenberger observer (large dimension)

$$\dot{\hat{\theta}} = G_\theta(y - H(\hat{x}))$$

Kalman observer (small dimension)

$$\hat{x}(0) = x_0$$
$$\hat{\theta}(0) = \theta_0$$

P. Moireau, D. Chapelle, Reduced-Order Unscented Kalman Filtering with Application to Parameter Identification in Large-Dimensional Systems. COCV 2011.

Luenberger state observer coupled with a Reduced-order Unscented Kalman Filter

Time t^n

Generate p particles around the mean value using the covariance reduced to parametric space

Prediction

Apply the stabilized model to this particle to compute one time step

Innovation

Compute the discrepancy w.r.t the observations for each particle

Correction

Gather the errors the parameter sensitivity hence the feedback correction

Population Kalman observer

- Objective: develop a population Kalman observer inspired from mixed effect approach.
- A population of N_{pop} subjects indexed by i: $\xi^i = \xi^{pop} + \tilde{\xi}^i$

If $\xi^{pop} = \dfrac{1}{N_{pop}} \sum_{i=1}^{N_{pop}} \xi^i$, one can prove that the **COUPLED** problem can be rewritten as:

Concatenation of variables & operators

$$\min_{\xi} \mathcal{J}(\xi) = \left[\frac{1}{2} \left[\xi, (P_0^{pop})^{-1} \xi \right] + \frac{1}{2} \sum_{k=0}^{N_{T,obs}} \left[y_k - h(z(t_k)), (W_k)^{-1} (y_k - h(z(t_k)) \right] \right]$$

where P_0^{pop} is an invertible matrix of dimension $(N_{pop} \times N_z)^2$ defined by

$$P_0^{pop} = \left(\underbrace{\frac{1}{N_{pop}^2} \vec{1}_{N_{pop}} \vec{1}_{N_{pop}}^T \otimes P_f^{-1}}_{\text{Fixed covariance}} + \underbrace{[I_{N_{pop}} - \frac{1}{N_{pop}} \vec{1}_{N_{pop}} \vec{1}_{N_{pop}}^T] \otimes P_m^{-1}}_{\text{Mixed covariance}} \right)^{-1}, \qquad \xi = \begin{pmatrix} \xi^1 \\ \vdots \\ \xi^{N_{pop}} \end{pmatrix}$$

with $\vec{1}_{N_{pop}} = (1 \ \cdots \ 1)^T \in \mathbb{R}^{N_{pop}}$.

- The key of our uncertainty modeling is that P_0^{pop} **couples** the population members.

- Through SVD on P_0^{pop}: possibility to reduce to the parametric space.

A. Collin, M. Prague, and P. Moireau. Estimation for dynamical systems using a population-based Kalman filter–Applications in computational biology. MathematicS In Action, 2022.

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Illustration of the approach

Joint work with

Clair Poignard

[biologists]

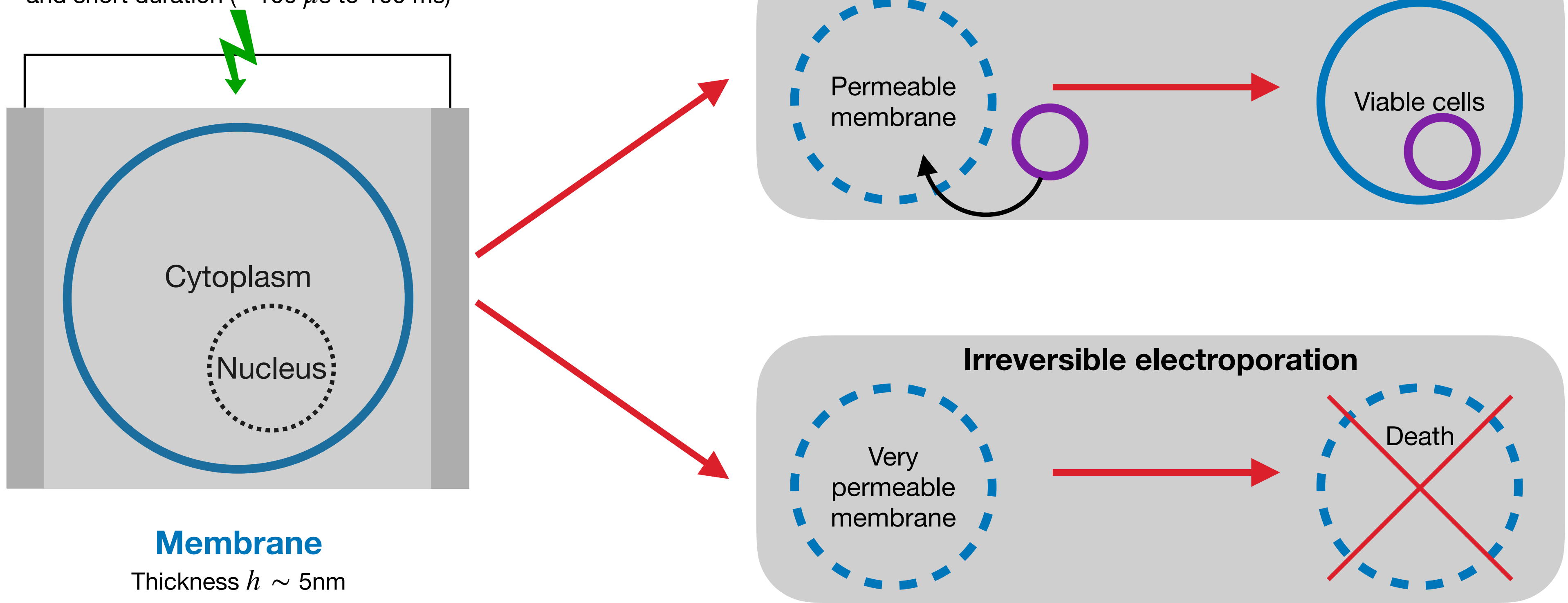
Jelena Kolosnjaj, Muriel Golzio, Marie-Pierre Rols

Concept of electroporation

Cell

Radius ~ 5 to 10 μm
Intra-cellular conductivity σ_c ~ 0.5 to 1 S.m^{-1}
Intra-cellular conductivity σ_e ~ 1 to 1.5 S.m^{-1}

High voltage pulses (100 < |E| < 3000 V.cm^{-1})
and short duration (~ 100 μs to 100 ms)



Membrane

Thickness $h \sim$ 5nm
Permitivity $\varepsilon \sim 4.5\varepsilon_0$
Capacitance C_m
Conductance S_m

Applications (in oncology):
- In vitro gene transfection
- Electrochemotherapy

Applications:
- Tumoral ablation
- Cardiac ablation

<u>Some open questions</u>:
- Accurate understanding of cell death (and especially pore formation)
- Determine the treated zone
- **Better understanding of the effects of reversible electroporation to develop efficient electrochemotherapy**

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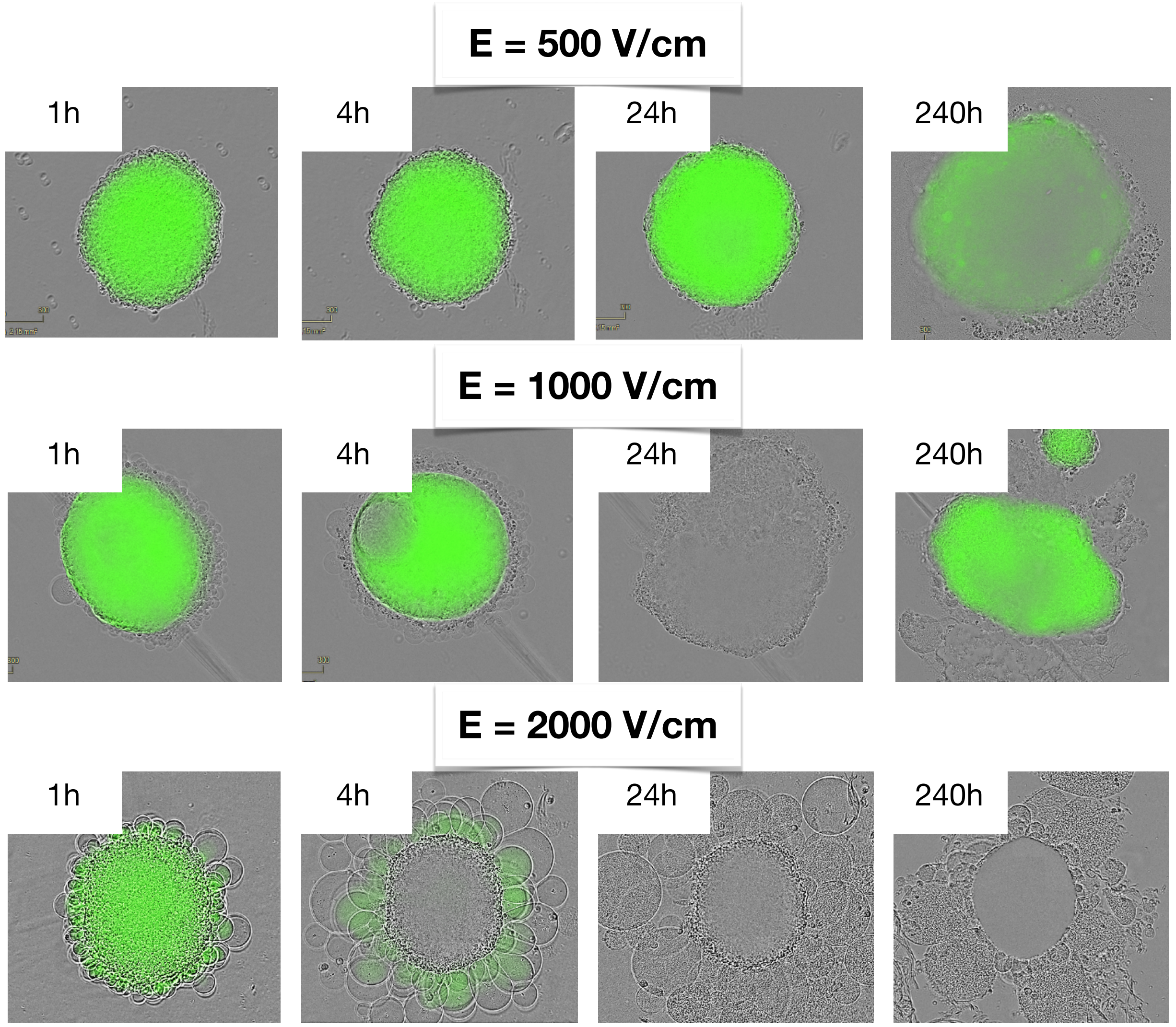
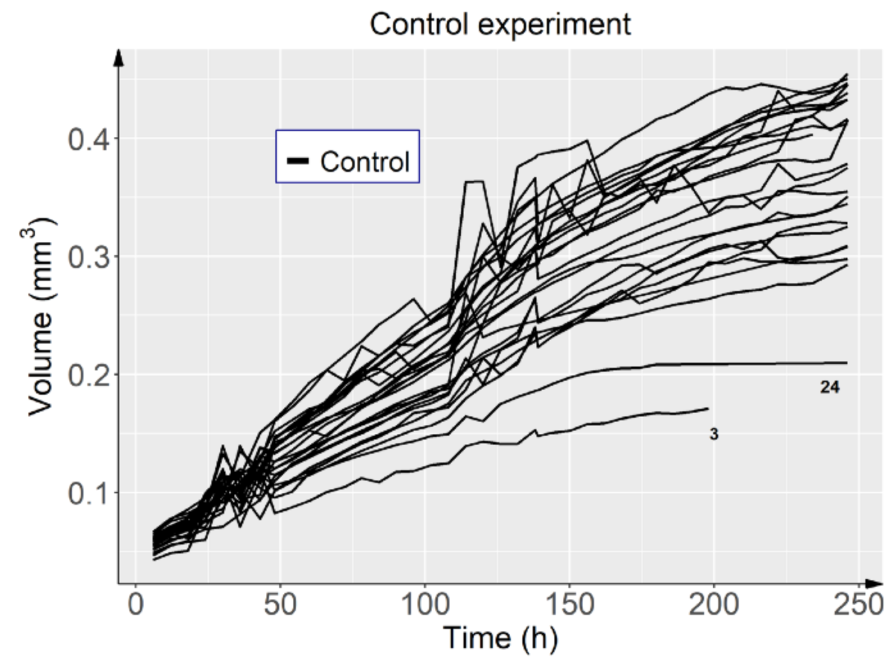
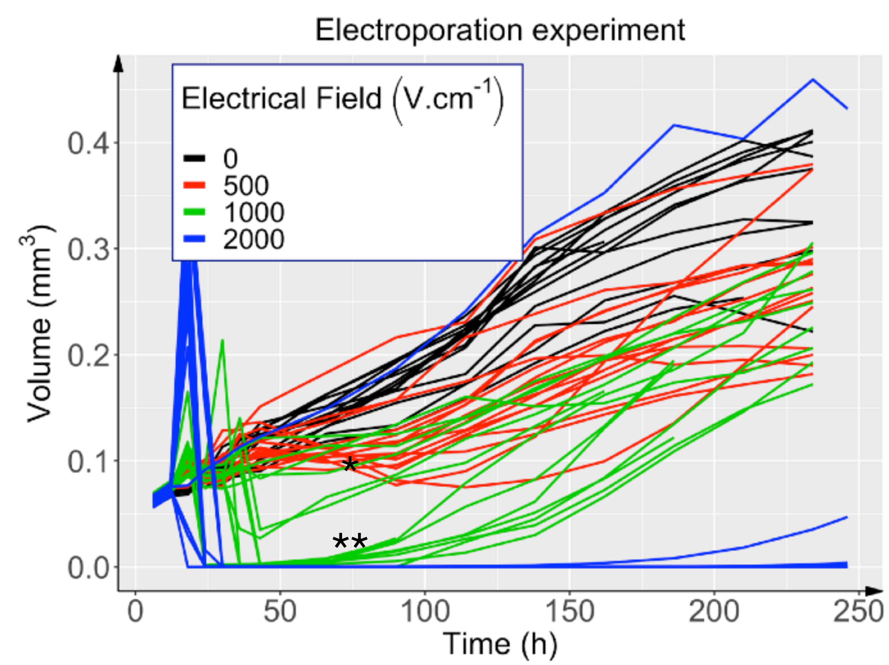
Data presentation & Problematic

- Evolution of 83 **3D spheroids** (cell strain: HCT 116) over 250 h exposed to high intensity pulsed electric fields (IPBS, Toulouse).
- Measurements are made using optical instruments.







EF = 1000 V.cm^{-1}: 2 types of behavior appear (* and **)

- Objective: quantify the effects of electroporation considering the pulses intensity

Electroporation - General Equations

- PDE System

Proliferative cells

$$\partial_t P + \nabla \cdot (\vec{v}P) = \tau^G(P+Q) - \tau^{PtoQ}P,\ \Omega(t)$$

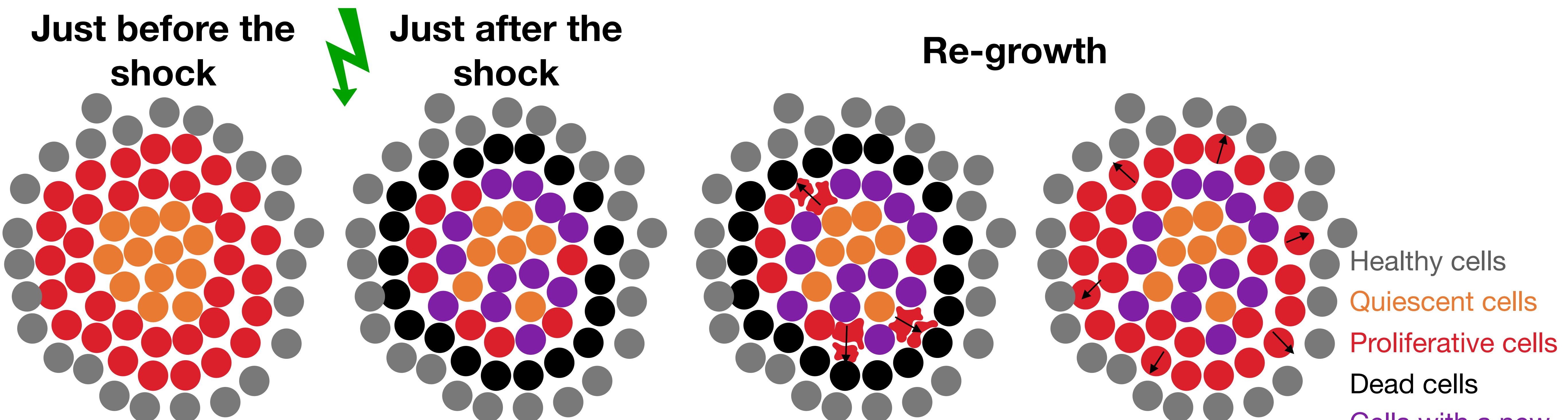
Quiescent cells

$$\partial_t Q + \nabla \cdot (\vec{v}Q) = \tau^{PtoQ}P,\ \Omega(t)$$

Cells with a modified metabolism

$$\partial_t F + \nabla \cdot (\vec{v}F) = 0,\ \Omega(t)$$

- Impacts of the electrical shock:
  - (1) a part of proliferative and quiescent cells is destroyed *i.e.* $R(t_{as}) = (1-p)R(t_{bs})$,
  - (2) the metabolism of a part of the cells is modified *i.e.* $F(t_{as}, x) = \lambda(P(t_{as}, x) + Q(t_{as}, x))$, for $x \in \Omega(t_{as})$,
  - (3) the value of a appearing in the growth rate $\tau^G(t) = ae^{-bt}$ increases. We denote by m the multiplicative value: $a_{new} = ma$.



$P + Q + F = 1,\ \Omega(t)$
(saturation hypothesis)

Electroporation - Radial Equations

- 1D PDE System

$$\partial_t P = -\tau^G(r^{-2}I - rI(t,1))\partial_r P + \tau^G(1-F)(1-P) - \tau_{PtoQ}P, \qquad [0,t_{last}]\times[0,1]$$

$$\partial_t F = -\tau^G(r^{-2}I - rI(t,1))\partial_r F - \tau^G(1-F)F, \qquad [0,t_{last}]\times[0,1]$$

$$I = \int_0^r (1-F)\underline{r}^2 d\underline{r} \qquad [0,t_{last}]\times[0,1]$$

$$R' = R\tau^G I(t,1), \qquad [0,t_{last}]$$

$$Q = 1-(P+F), \qquad [0,t_{last}]\times[0,1]$$

- High quiescent proportion of cells in the spheroid center:

$$\tau^{PtoQ} = \tau_b - \frac{\tau_b - \tau_e}{1 + e^{\frac{(R(t)(1-r)-d)}{s}}}$$

- Observation: $y = R$
- **Objective**: estimate: a, b, p, m, λ (τ_b, τ_e, d, s not identifiable & fixed using the literature)
- **Strategy**: Joint Luenberger observer (**state**) & reduced Kalman-based filter (**parameters**)

A. Collin, H. Bruhier, J. Kolosnjaj, M. Golzio, M.-P. Rols, and C. Poignard. Spatial mechanistic modeling for prediction of 3D multicellular spheroids behavior upon exposure to high intensity pulsed electric fields. AIMS Bioengineering, 9(2):102–122, 2022.

Electroporation - State observer

- Luenberger observer system

$$\partial_t \hat{P} = -\tau^G (r^{-2}\hat{I} - r\hat{I}(t,1))\partial_r \hat{P} + \tau^G (1-\hat{F})(1-\hat{P}) - \hat{\tau}_{PtoQ}\hat{P}, \qquad [0,t_{last}] \times [0,1]$$

$$\partial_t \hat{F} = -\tau^G (r^{-2}\hat{I} - r\hat{I}(t,1))\partial_r \hat{F} - \tau^G (1-\hat{F})\hat{F}, \qquad [0,t_{last}] \times [0,1]$$

$$\hat{I} = \int_0^r (1-\hat{F})\underline{r}^2 d\underline{r} \qquad [0,t_{last}] \times [0,1]$$

$$\hat{R}' = \hat{R}\tau^G \hat{I}(t,1) - \boxed{\gamma(\hat{R}-R)}, \qquad [0,t_{last}]$$

$$\hat{Q} = 1 - (\hat{P} + \hat{F}), \qquad [0,t_{last}] \times [0,1]$$

High quiescent proportion of cells in the spheroid center

$$\hat{\tau}^{PtoQ} = \tau_b - \frac{\tau_b - \tau_e}{1 + e^{\frac{(\hat{R}(t)(1-r)-d)}{s}}}$$

τ_b, τ_e, d, s fixed with the literature

- Uncertainties reduced to the initial conditions

$$R(0) = R_0 + \boxed{\xi_R}, \quad \hat{R}(0) = R_0$$

$$P(0,r) = P_0 + \boxed{\xi_P}, \quad Q(0,r) = 1 - P(0,r), \quad F(0,r) = 0 \quad \hat{P}(0) = P_0, \quad \hat{Q}(0,r) = 1 - \hat{P}(0,r), \quad \hat{F}(0) = 0, \quad r \in [0,1]$$

Proposition - [*in a well-posed context*]

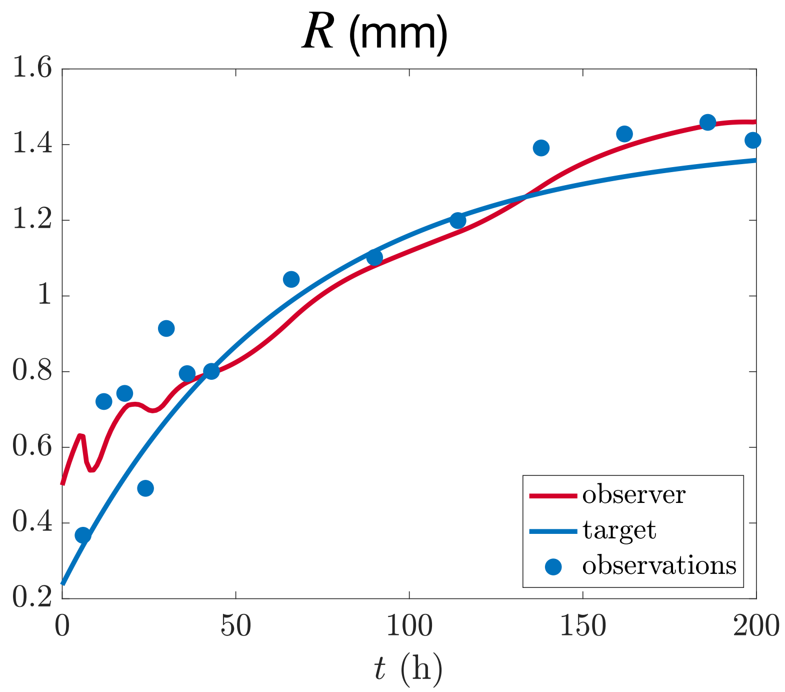
If $\gamma > \dfrac{ma}{3}$, the radius $t \mapsto (\hat{R} - R)(t)$ converges exponentially to 0 when t goes to $+\infty$.

If $\gamma > \dfrac{ma}{3} + \tau_e$, the norm $t \mapsto \|(\hat{P} - P)(t,\cdot)\|^2_{L^2(]0,1[)}$ converges exponentially to 0 when t goes to $+\infty$.

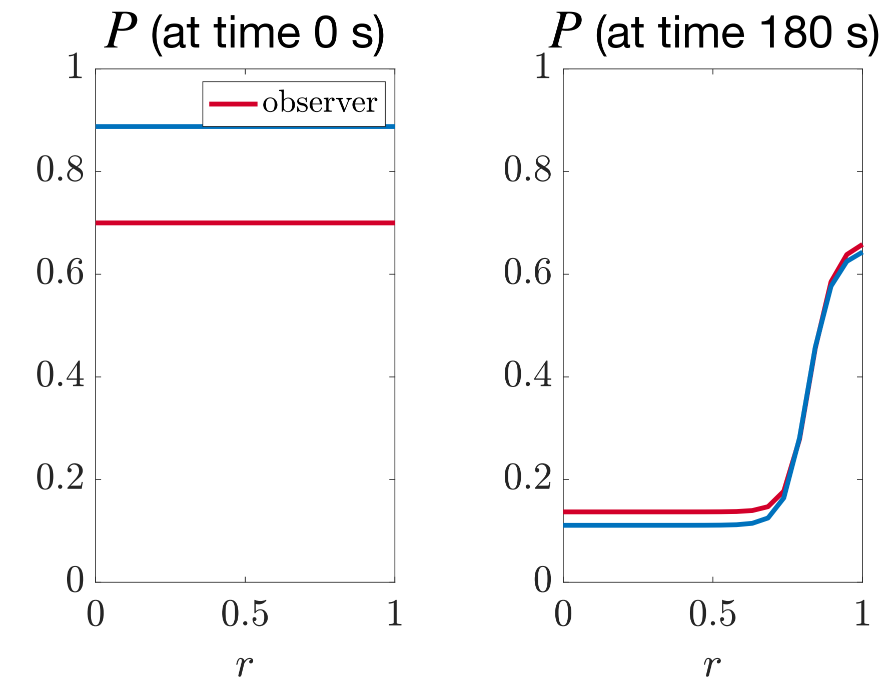
A. Collin. Population-based estimation for PDE systems – Applications in spheroids electroporation. Control, Optimisation and Calculus of Variations, 2023.

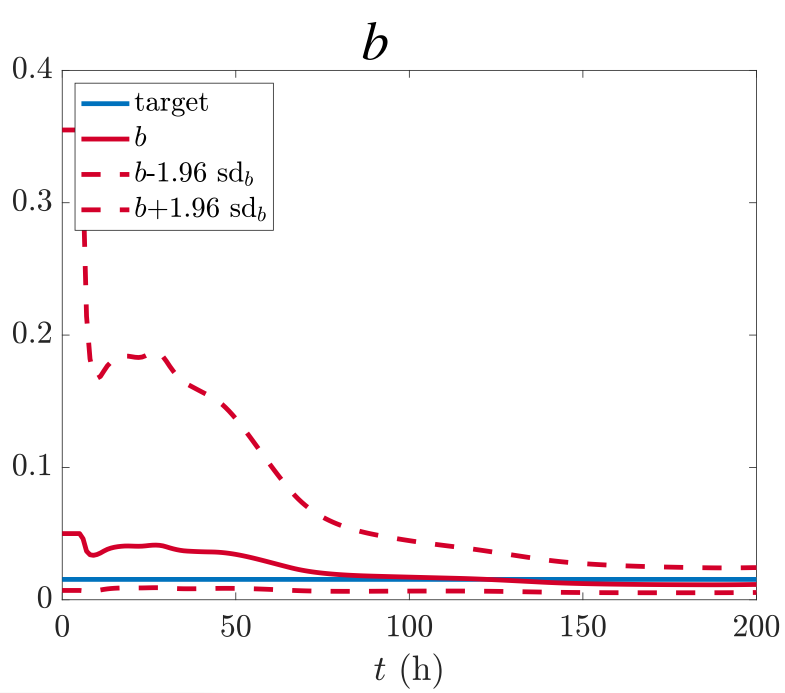
Electroporation - Joint state and parameter observer

- Synthetic case (only **free growth**: 2 parameters b and $k = a/b$)
- Scenario: weak priors & false initial conditions with state observer

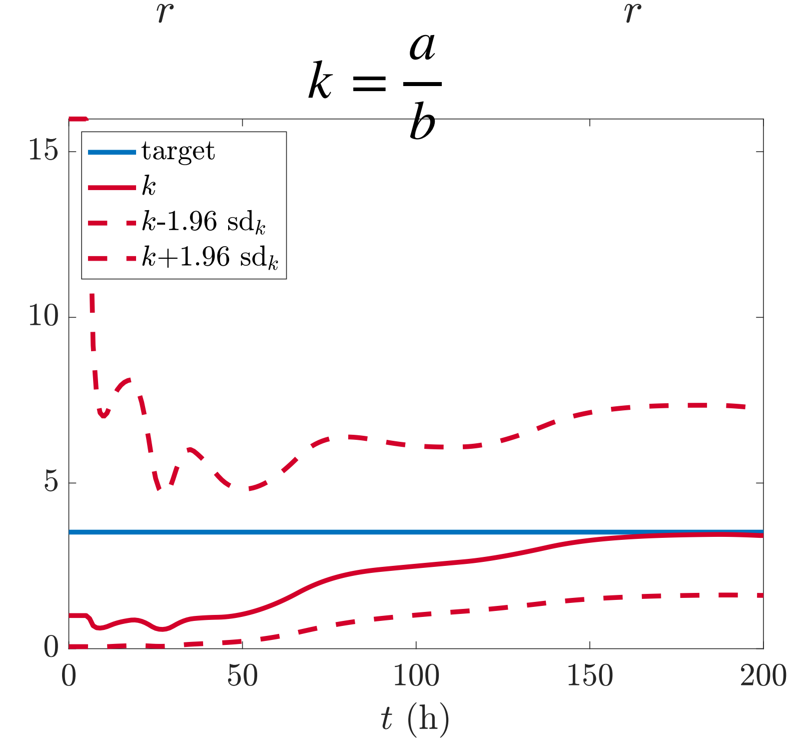


State





Parameters



Electroporation - Joint state and parameter observer

- Synthetic case (only **free growth**: 2 parameters b and $k = a/b$)
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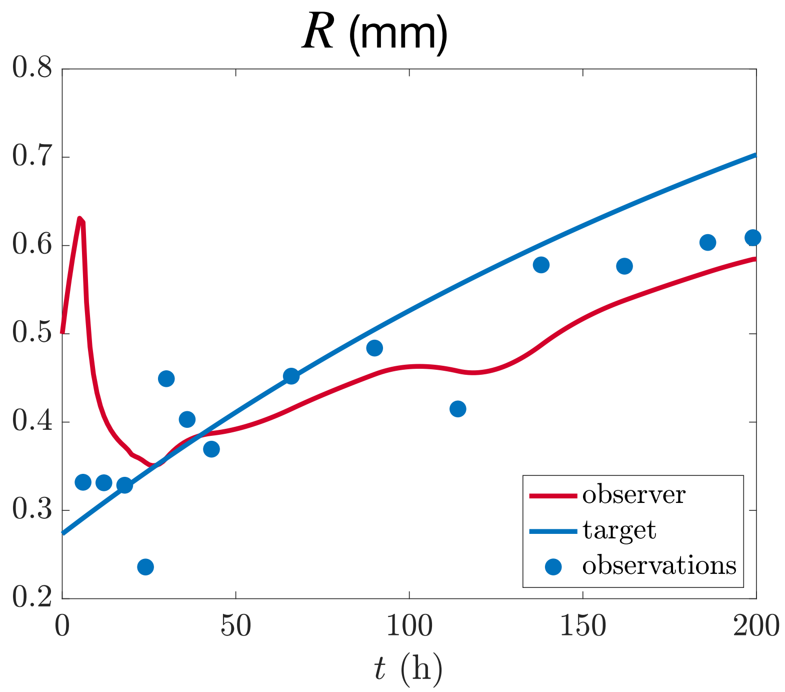
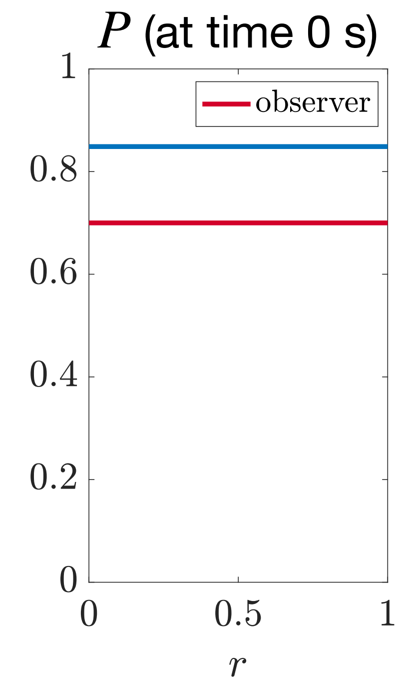
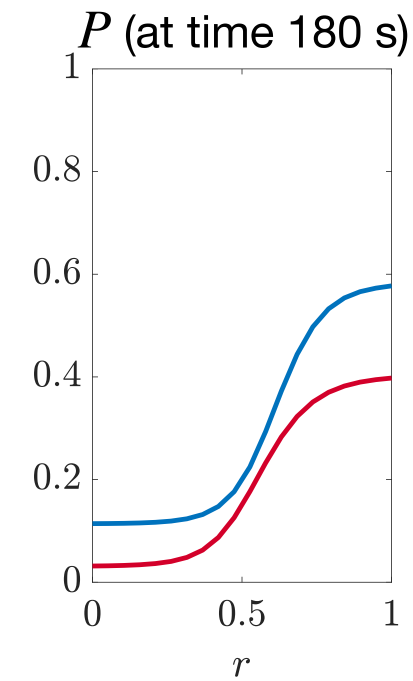
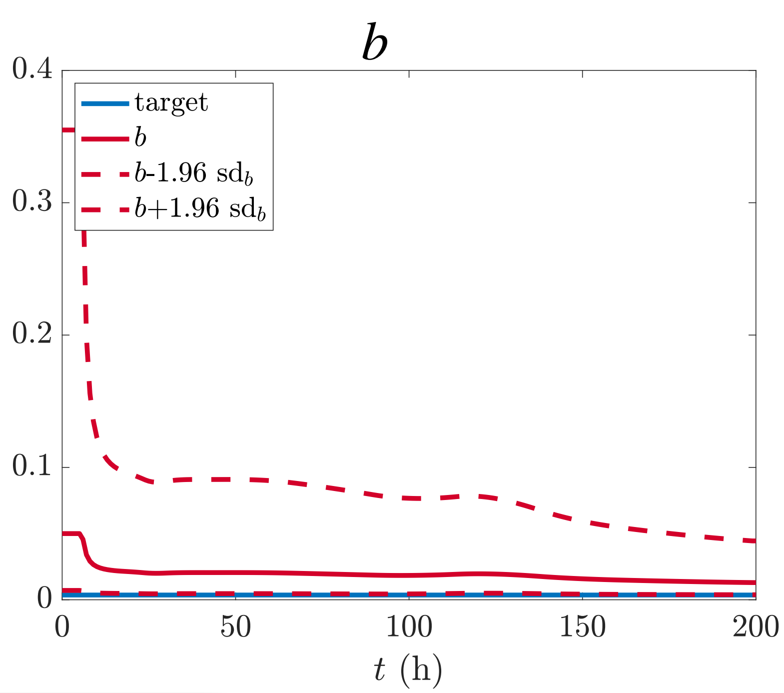


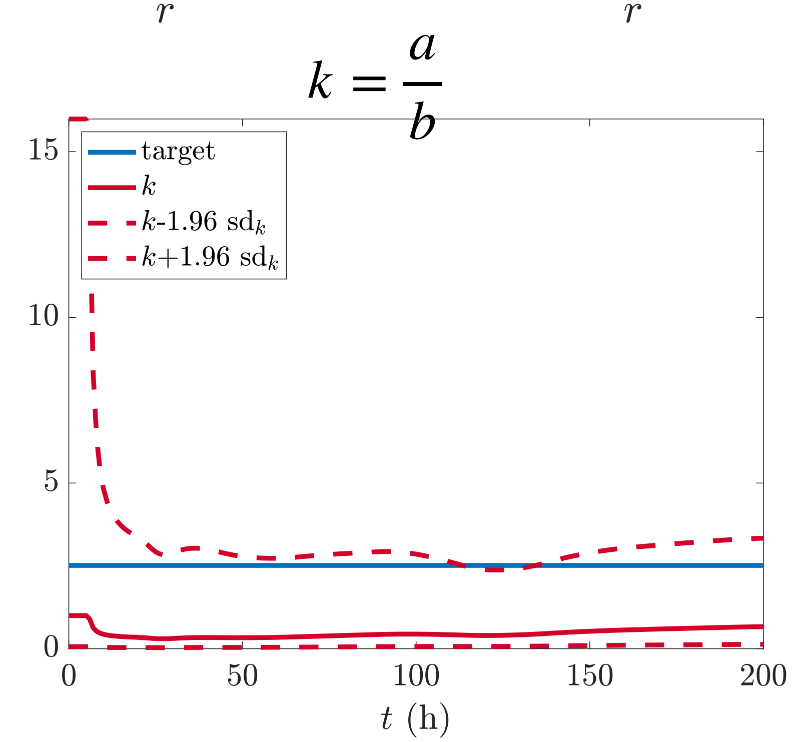




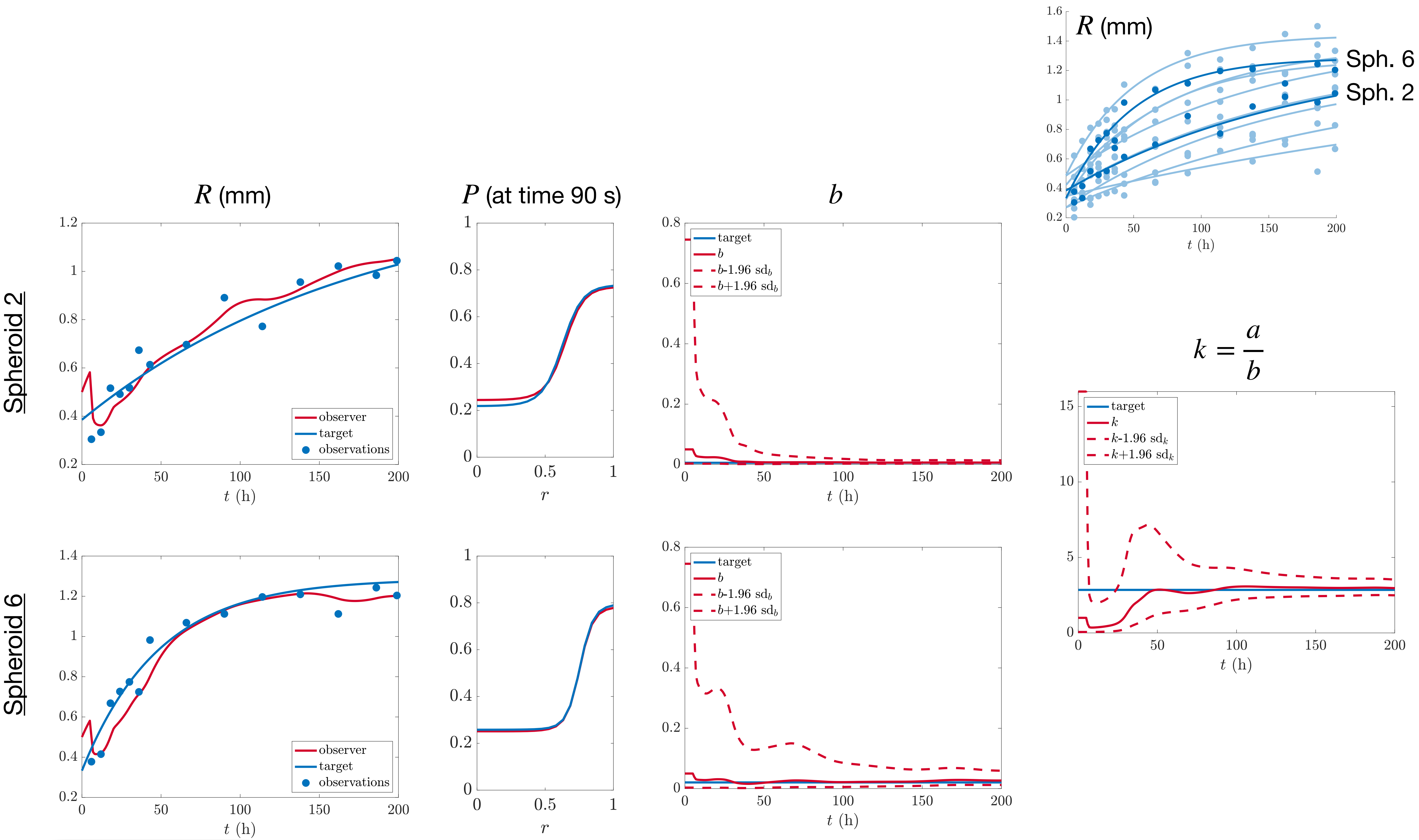
State



Parameters



Validation on synthetic data: cohort of 10 spheroids



Observation Error $\sigma_R = 0.08$

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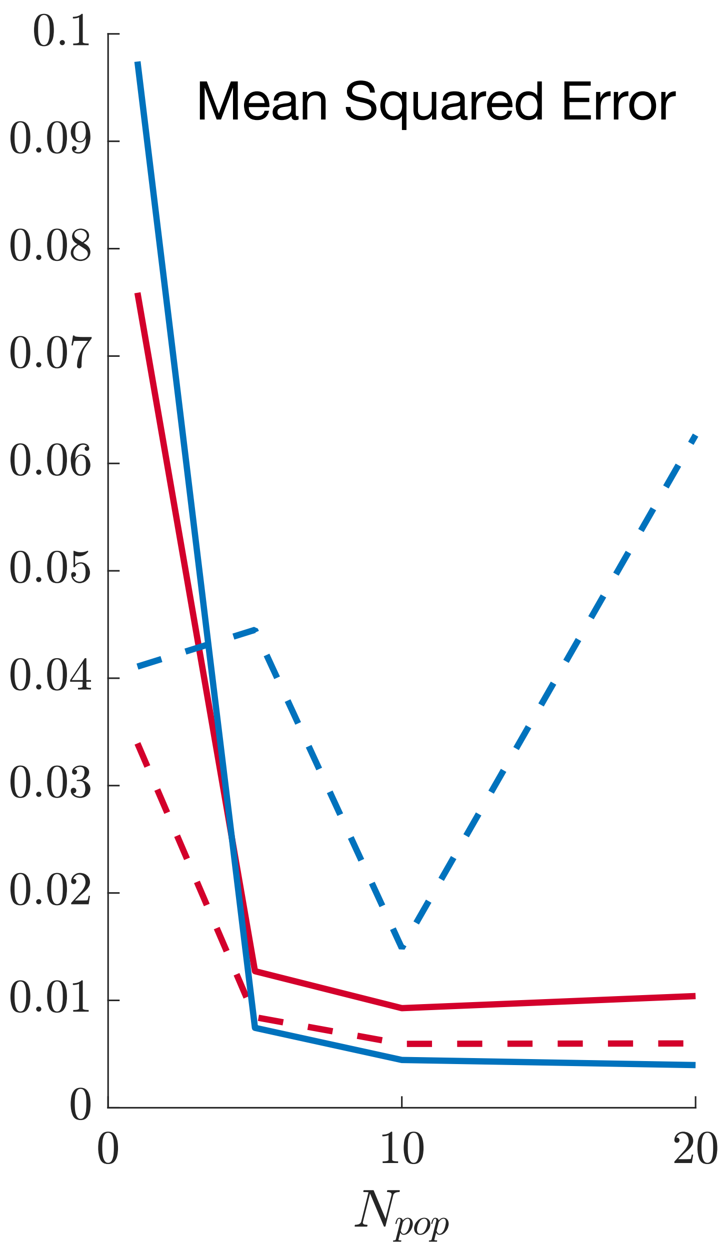
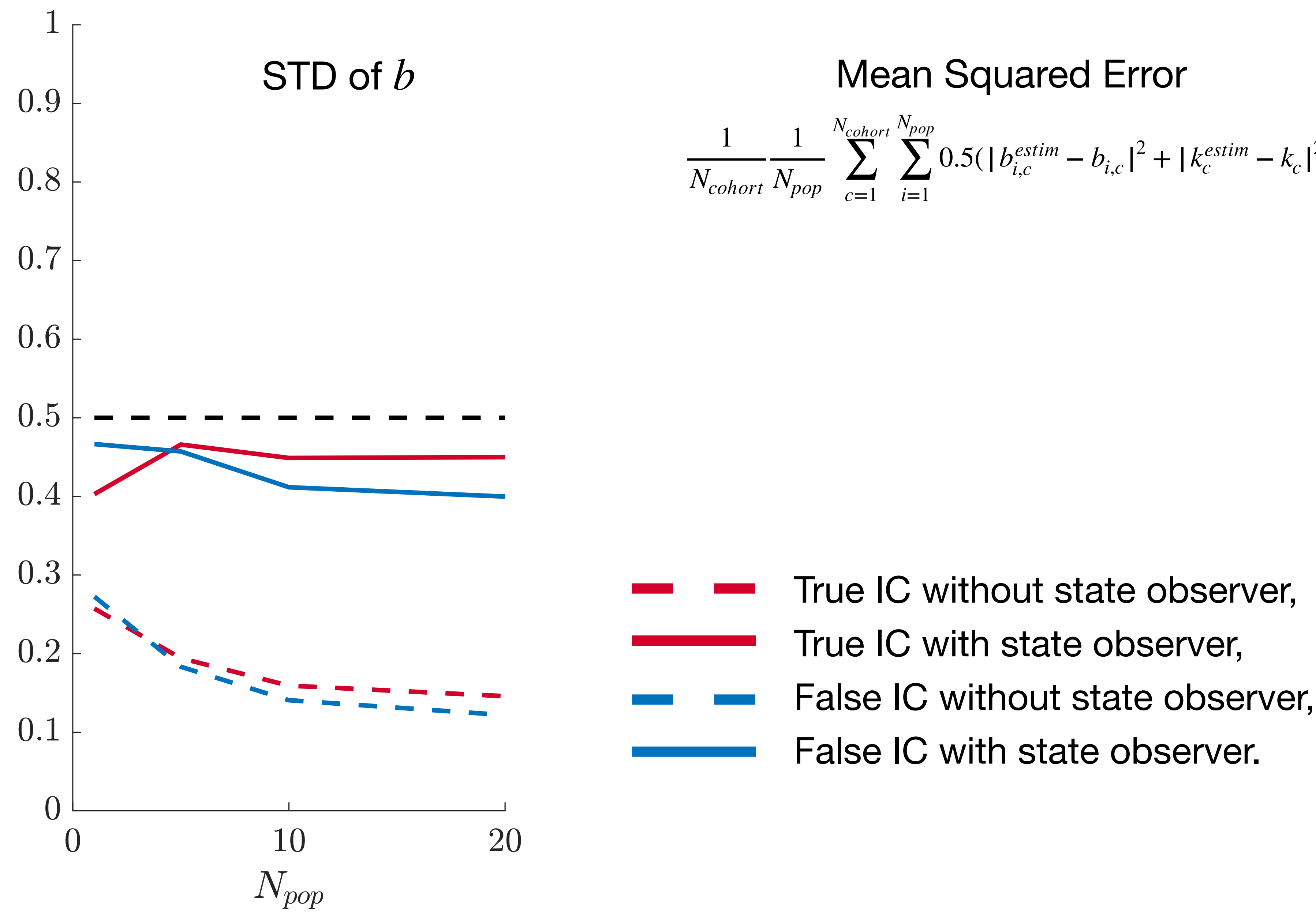
Validation on synthetic data

Observation Error $\sigma_R = 0.08$





Mean Squared Error

$$\frac{1}{N_{cohort}}\frac{1}{N_{pop}}\sum_{c=1}^{N_{cohort}}\sum_{i=1}^{N_{pop}} 0.5(|b_{i,c}^{estim}-b_{i,c}|^2+|k_c^{estim}-k_c|^2)$$

A. Collin. Population-based estimation for PDE systems – Applications in spheroids electroporation. COCV (minor revisions), 2023.

Comparing with existing strategy

- Computational times (min) on synthetic data

Algos	Space step	$N_S = 1$	$N_S = 5$	$N_S = 10$	$N_S = 40$
L+PKF*	0.05	0.03	0.3	1	12
L+PKF*	0.01			3.5	
L+PKF*	0.001			60	
NImefitsa (SAEM)	0.05		80		

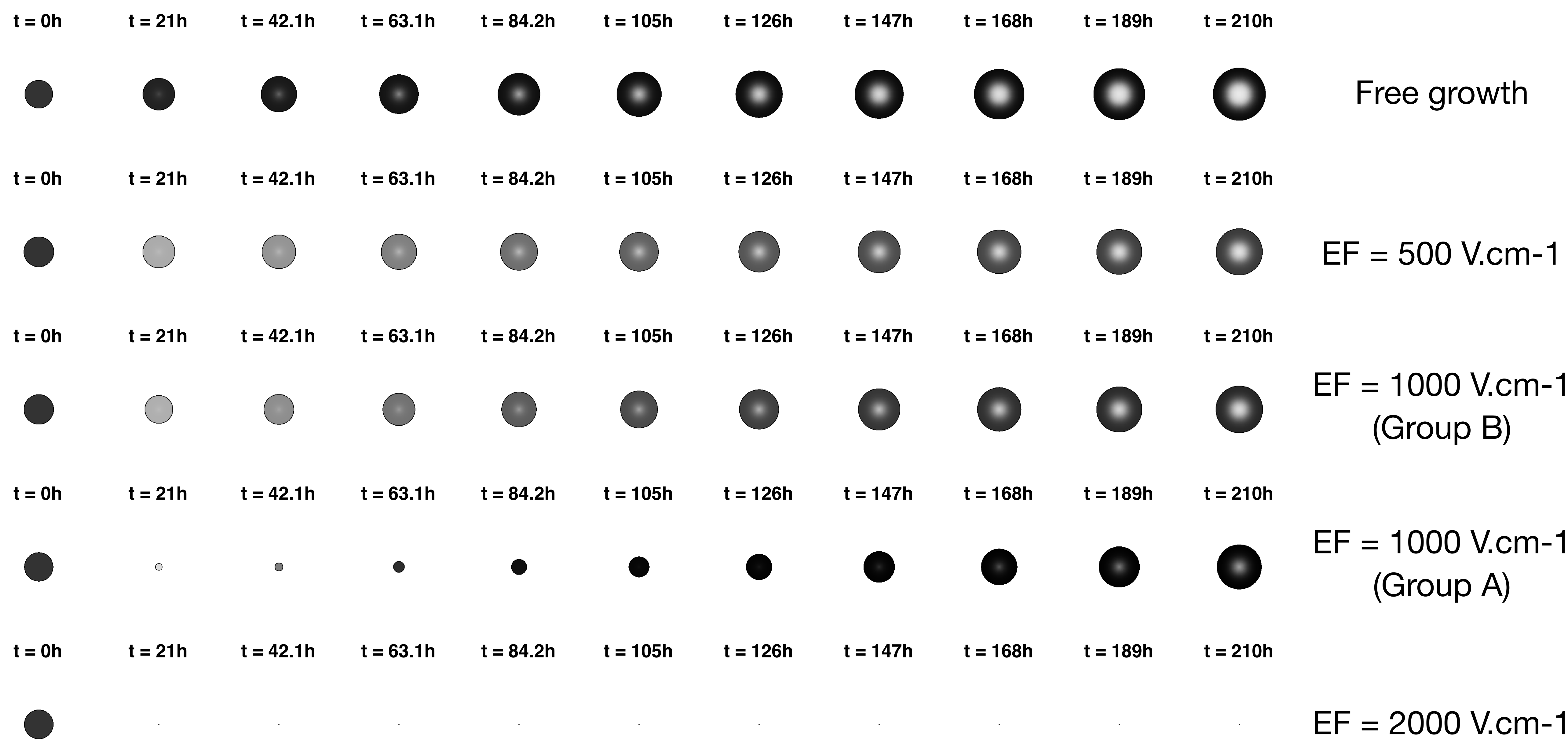
* Luenberger & Population Kalman Filters

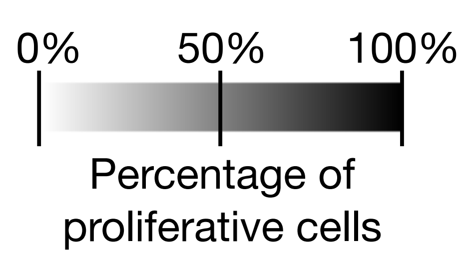
- Parameters estimation on real data

EF	Algos	$p \nearrow$	$\lambda \nearrow$	$m \nearrow$
500 V.cm-1	L+PKF*	0.10 (m) - 0.0028 (s)	0.37 (m) - 0.035 (s)	1.14 (m) - 0.18 (s)
($N_S = 12$)	NImefitsa (SAEM)	0.11 (m) - 0.014 (s)	0.22 (m) - 0.092 (s)	1.11 (m) - 0.024 (s)
1000 V.cm-1 (B)	L+PKF*	0.14 (m) - 0.012 (s)	0.36 (m) - 0.045 (s)	1.21 (m) - 0.16 (s)
($N_S = 5$)	NImefitsa (SAEM)	0.18 (m) - 0.086 (s)	0.37 (m) - 0.012 (s)	1.40 (m) - 0.16 (s)
1000 V.cm-1 (A)	L+PKF*	0.89 (m) - 0.015 (s)	0.69 (m) - 0.04 (s)	5.3 (m) - 0.77 (s)
($N_S = 6$)	NImefitsa (SAEM)	0.83 (m) - 0.010 (s)	0.77 (m) - 0.10 (s)	5.19 (m) - 1.02 (s)
2000 V.cm-1	L+PKF*	0.999 (m) - 2×10^{-6} (s)	0.92 (m) - 0.0015 (s)	×
($N_S = 14$)	NImefitsa (SAEM)	0.998 (m) - 9×10^{-5} (s)	0.97 (m) - 0.065 (s)	×

p percentage of destroyed cells
λ percentage of cells whose metabolism is altered
m growth rate increase in tumor resumption

Electroporation - Results





Collin, A et al. Spatial mechanistic modeling for prediction of 3D multicellular spheroids behavior upon exposure to high intensity pulsed electric fields. Bioengineering 2022.

Final conclusion

- Strategy to combine the principle of data assimilation through joint state and parameter estimation with the population configuration classically considered in the formulation of nonlinear mixed-effects models.

- Two important methodological strategies: (1) a population-based Kalman filter and (2) a joint state-parameter estimation.

- Validation of a 1D PDE model for tumor spheroid electroporation with synthetic and real data.

- Using the state observer in conjunction with the Kalman observer for the parameters leads to better results when weak priors are considered and especially when the initial conditions are false.