Estimation of liver conductivities for irreversible electroporation

Gaspard Jankowiak   Thi Ngoc Thuy Phan   Cécile Taing

with

Annabelle Collin   Olivier Gallinato   Sébastien Impériale
Philippe Moireau   Clair Poignard   Olivier Séror

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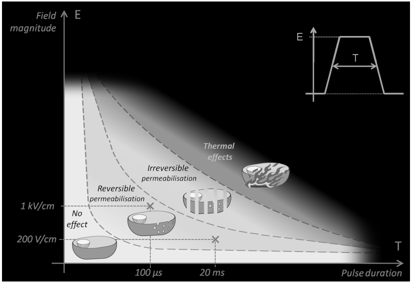
OUTLINE

IRREVERSIBLE ELECTROPORATION (IRE)

- Electric field creates pores opening on the cell membrane
- Leads to imbalances in/out of the cell
- Can be temporary or permanent depending on strength and duration of exposure



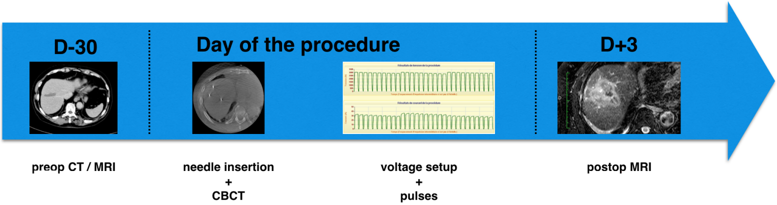
Applications:

- Biology: introduction of DNA (cell modification), of drugs (enhanced chemotherapy)
- Agroindustry: sterilizing and cut french fries
- **Medicine**: ablation of tumors by destruction of tumoral cells (aka NanoKnife)

IRE in the hospital

Issues:

- Electrode location
- Pulse profile/duration
- **WTF are we doing, *i.e.* what area is affected by IRE ??** Without imaging (long, costly, does not allow immediate corrective treatment).



Effects at the cell level (microscopic scale)

- At rest, the cell membrane is made of two layers of lipids (lipid bilayer).
- When a strong electric field is applied, pores open on the membrane (typically $1\mu s$). This **greatly increases the conductivity** of the membrane.
- Later ($10 - 100\mu s$) the lipids will be altered be the electric field, **increasing the conductivity** a bit more

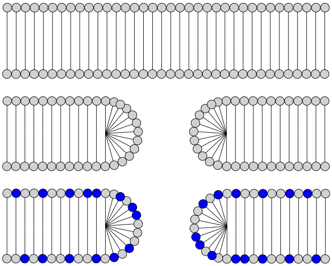
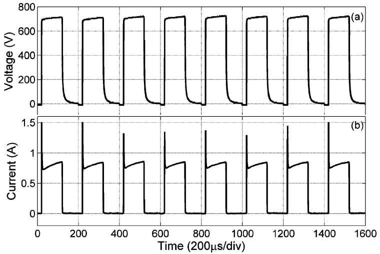


Figure: Side cut of the cell membrane



The (evolution of) electrical properties of the body can be used to define the eletroporated area.

Objectives of our Cemracs project

General goal, for clinicians:

- Using only available measurements (intensities for different applied voltages) to determine the conducting properties of the medium (body), thus deducting the treated area.

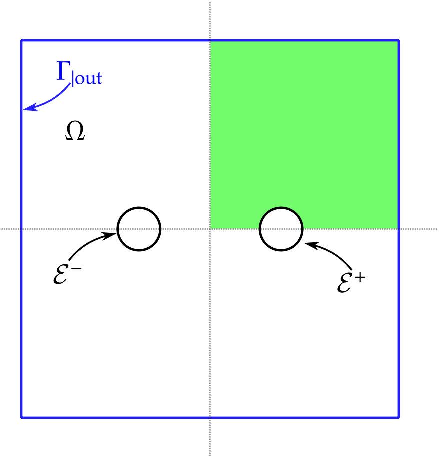
Tools:

- Different models for electroporation, depending on a number of physical properties. Most parameters are not available in the litterature and cannot be directly measured.
- Several automated parameter estimation methods

Our goal this summer:

- Compare the estimation methods
- Provide model parameters to fit real data
- Possibly help validate new models

Modelling elements



- Electrostatic type phenomenon
- Starting point: classical electrostatic equation:

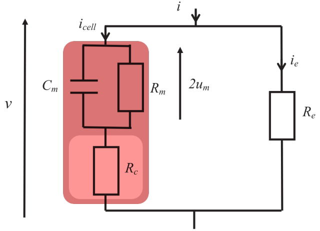
$$\begin{cases} \nabla \cdot (\sigma(x)\nabla V(x)) = 0 & x \in \Omega \\ \nabla V \cdot \mathbf{n} = 0 & x \in \Gamma_{out} \\ V = g^{\pm} & x \in \mathcal{E}^{\pm} \end{cases}$$

- V: electric *potential* (∇V electric *field*)
- σ: conductivity
- $I^{\pm} = \int_{\mathcal{E}^{\pm}} \sigma \nabla V \cdot \mathbf{n} \, \mathrm{d}s$: intensity

The biphase model, Voyer and al. 2018

Half phenomenological - half physiological

- Model the tissue like an electric circuit
- Three conducting regions: the intra-/extracellular media, and the cell membrane.



$$i = i_e + i_{cell}$$

$$i_{cell} = 2\left(u_m R_m^{-1} + C_m \frac{d}{dt} u_m\right)$$

$$= (v - 2u_m) R_c^{-1}$$

$$i_e = v R_e^{-1}$$

$$\frac{d}{dt} i_e = 0 \Rightarrow \left(R_c^{-1} + R_m^{-1}\right) i_{cell} + C_m \frac{d}{dt} i_{cell} = \frac{R_e}{R_c R_m} i_e$$

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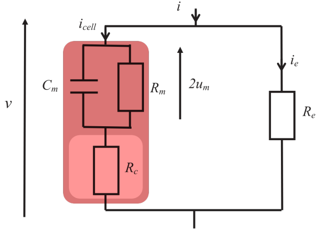

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Static biphase model

$$\nabla \cdot (\sigma_e \nabla \phi_e + \mathbf{J}_c) = 0,$$
$$(\sigma_c + \sigma_m(|\mathbf{E}_m|))\mathbf{J}_c = \sigma_c \sigma_m(|\mathbf{E}_m|) \nabla \phi_e,$$
$$\mathbf{n} \cdot \nabla \phi_e|_{\Gamma_{\text{out}}} = 0, \quad \phi_e|_{\mathcal{E}^\pm} = g^\pm,$$

where $\mathbf{E}_m = -\nabla \phi_e + \sigma_c^{-1} \mathbf{J}_c$ is the *trans-membrane* electric field.

From the biphase model to the standard model

Monodomain limit and standard model

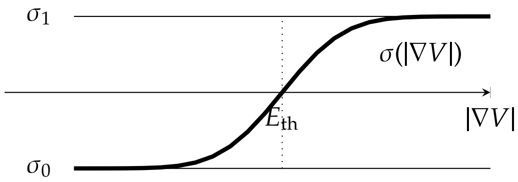
This can be rewritten in terms of $\mathbf{E}_m$ only:

$$\nabla \cdot \left(\left(\sigma_e + \frac{\sigma_c \sigma_m(|\mathbf{E}_m|)}{\sigma_c + \sigma_m(|\mathbf{E}_m|)} \right) \nabla \phi_e \right) = 0.$$

It is a generalized form of the electrostatic equation:

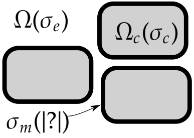
Standard model

$$-\nabla \cdot (\sigma(\|\nabla V\|) \nabla V) = 0, \quad \text{in } \Omega,$$
$$\mathbf{n} \cdot \nabla V|_{\Gamma_{\text{out}}} = 0, \quad V|_{\mathcal{E}^{\pm}} = g^{\pm},$$



Bidomain model

A physiological model



The microscopic model:

$$\begin{cases} \sigma_e \Delta u_e = 0 & x \in \Omega \setminus \Omega_c \\ \sigma_c \Delta u_c = 0 & x \in \Omega_c \\ \sigma_e \nabla u_e \cdot \mathbf{n} = \sigma_c \nabla u_c \cdot \mathbf{n} & x \in \Gamma_e \\ (\sigma_m[?])\,(u_e - u_c) = \sigma_c \nabla u_c \cdot \mathbf{n} & x \in \Gamma_e \end{cases}$$

Homogenization limit $\Downarrow$ Manon Deville's thesis

Static bidomain model

$$\begin{cases} \nabla \cdot (\sigma_e \nabla u_e + \sigma_c \nabla u_c) = 0 & x \in \Omega \\ \alpha\,(\sigma_m[?])\,(u_e - u_c) - \nabla \cdot (\sigma_c \nabla u_c) = 0 & x \in \Omega \end{cases}$$

?	Good	Bad
$u_e - u_c$	rigorous derivation	**no electroporation at the center***
∇u_e	**matches experiments**	purely phenomenological

Boundary conditions:

$$u_e|_{\mathcal{E}^\pm} = g^\pm\,, \quad \mathbf{n} \cdot \nabla u_e|_{\Gamma_{\text{out}}} = 0\,, \quad \mathbf{n} \cdot \nabla (u_e - u_c)|_{\Gamma_{\text{out}} \cup \mathcal{E}^\pm} = 0\,.$$

Dynamical models

In the previous derivation from the electric circuit equilavence, we can keep $\partial_t \mathbf{J}_c \neq 0$ and get

Dynamic biphase model

$$\begin{cases} \nabla \cdot (\sigma_e \nabla \phi_e + \mathbf{J}_c) = 0, \\ \epsilon_0 \epsilon_m \partial_t \mathbf{J}_c + (\sigma_c + \sigma_m(t, |\mathbf{E}_m|))\, \mathbf{J}_c = \sigma_c \sigma_m(t, |\mathbf{E}_m|) \nabla \phi_e, \\ \mathbf{n} \cdot \nabla \phi_e|_{\Gamma_{\text{out}}} = 0, \quad \phi_e|_{\mathcal{E}^\pm} = g^\pm, \end{cases}$$

Still reasoning with a membrane capacity, we also derive

Dynamic bidomain model

$$\begin{cases} \nabla \cdot (\sigma_e \nabla u_e + \sigma_c \nabla u_c) = 0 \\ C_m \partial_t (u_e - u_c) + \alpha\,(\sigma_m(t, \nabla u_e))\,(u_e - u_c) - \sigma_c \Delta u_c = 0 \\ u_e|_{\mathcal{E}^\pm} = g^\pm\,, \quad \mathbf{n} \cdot \nabla u_e|_{\Gamma_{\text{out}}} = 0\,, \\ \mathbf{n} \cdot \nabla (u_e - u_c)|_{\Gamma_{\text{out}} \cup \mathcal{E}^\pm} = 0\,. \end{cases}$$

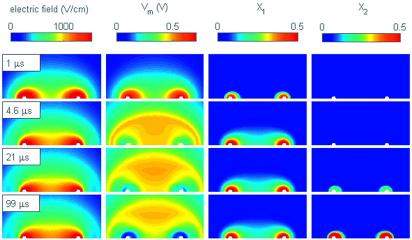
Dynamical models

Membrane conductivity dynamics

The conductivity can be considered time-dependent:

$$\sigma_m(t,\mathbf{E}) = \sigma_0^m + \sigma_1^m X_1(t,\mathbf{E}) + \sigma_e^m X_2(t,\mathbf{E}).$$

Phenomenon	Symbol	Evolution	Dynamics
Poration	X_1	$\dot{X}_1 = \left(\frac{\beta_1(\mathbf{E})-X_1}{\tau_1}\right)_+$	fast ($\tau_1 \simeq 1\mu s$)
Permeabilisation	X_2	$\dot{X}_2 = \left(\frac{\beta_2(X_1)-X_2}{\tau_2}\right)_+$	slow ($\tau_2 \simeq 100\mu s$)



Model parameters and available data

Parameters:

Model	Class	Parameters	Symbols
standard	static	4	$\mathrm{E_{th}}, k_{ep}, \sigma_0, \sigma_1$
bidomain	static	4	$\mathrm{E_{th}}, k_{ep}, \sigma_0, \sigma_1, \sigma_e, \sigma_c$
bidomain	dynamic	12	$\sigma_e, \sigma_c, C_m, \sigma_{0,1,2}, \tau_{1,2}, k_{1,2}, Th_{1,2}$
biphase	static	6	$\mathrm{E_{th}}, k_{ep}, \sigma_0, \sigma_1, \sigma_e, \sigma_c$
biphase	dynamic	12	$\sigma_e, \sigma_c, \epsilon_m, \sigma_{0,1,2}, \tau_{1,2}, k_{1,2}, Th_{1,2}$

Data:

- 3 different electrode sizes
- 5 different voltages (200V to 1000V)
- 19 samples, from $0.07\mu s$ to $97\mu s$

The problem of parameter estimation (static case)

Consider

- $\theta \in (\Theta, \|\cdot\|_{P_\diamond^{-1}})$, a fixed vector of parameter values
- $y \in \mathcal{Y}$ the solution to the *forward* problem ($\mathcal{A}$: model operator):

$$y = \{\mathrm{y} : \mathcal{A}(\mathrm{y}, \theta) = 0\} =: \mathcal{L}(\theta)$$

- $(\mathcal{Z}, \|\cdot\|_R)$ the space of observations or measurements we have access to.

We can map $\mathcal{Y}$ to $\mathcal{Z}$, *i.e* make a measurement on our solution:

$$z = \mathcal{C}(y)$$

Our goal is to "invert" the operator $\Psi = \mathcal{C} \circ \mathcal{L}$. This could be done by minimizing the following functional:

$$\mathcal{J}(\theta) = \frac{1}{2}\|\theta - \theta_\diamond\|^2_{P_\diamond^{-1}} + \frac{1}{2}\|z^* - \Psi(\theta)\|^2_R.$$

$\theta_\diamond$ a priori estimate, $P_\diamond$: uncertainty on the parameters, R: measurement noise

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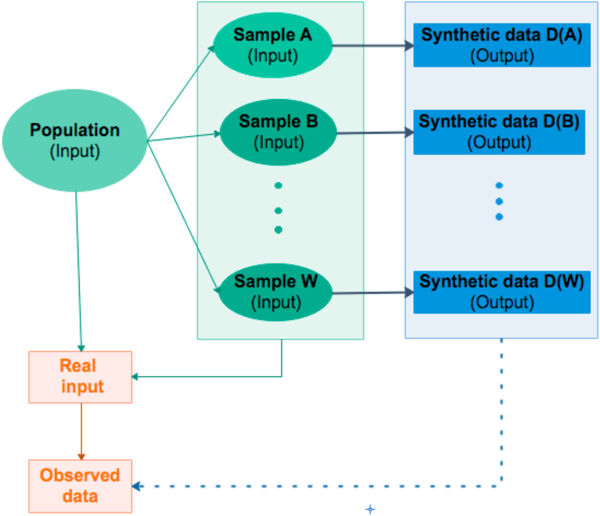
Estimation methods

Method	**Good**	**Bad**
Gradient descent	Can be fast	Needs Jacobian local minima, tuning
Monte-Carlo / Metropolis	easy	slow
Fitering methods	easy	not cheap, tuning

Monte Carlo method

- Introduction
  - Computing experiment: Computational physics, computational chemistry, computational biology,...
  - What is Monte Carlo method?
  Lets you see all the possible outputs of your inputs.

- How does Monte Carlo method work?



Applying the Monte Carlo method to the standard static model

- Step 1: Generate randomly a set of parameters $\{\theta_i\}_i$ $(i = 1, ..., N)$ of the form uniform distribution from a priori value of θ_0.
  Where: $\theta_i = (Eth(i),\ kep(i),\ \sigma_0(i),\ \sigma_1(i)) \quad (i = 1, ..., N)$
- Step 2: Compute the corresponding outputs (set of model intensities $\{\Psi(\theta_i)\}_i$ $(i = 1, ..., N)$ with 3 different electrode diameters $d \in \{0.3,\ 0.7,\ 1.1\}$ and 2 different voltages $V \in \{600,\ 800\}$.
- Step 3: Use the Least-Squares Error Minimization to find the best matching set of parameters.

Least-Squares Error

- The residual measures the difference between a observed data and the corresponding model estimate: $z - \Psi(\theta_i)$
- Since the residuals can be positive or negative, we can not assess a sum of residuals as a good measure of overall error in the fit.
- A better way is to take the sum of squared residuals, $\mathcal{J}(\theta_i)$, which is only zero if every residual is zero.

$$\mathcal{J}(\theta_i) = \sum_{d,\,V} (z - \Psi(\theta_i))^2\,, \quad (i = 1, \ldots, N)$$

- Estimated parameter is taken as $\theta^* = \operatorname{argmin}_i(\mathcal{J}(\theta_i))$

Filtering methods
Kalman filter

Assuming a fully linear system

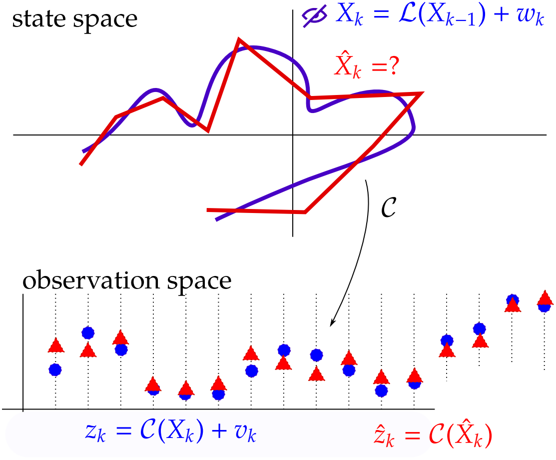
Estimated state: $\hat{X}_{k|\cdot}$
Estimated uncertainty:
$P_{k|\cdot} = \text{cov}(X_k - \hat{X}_{k|k})$

Prediction

- $\hat{X}_{k|k-1} = \mathcal{L}\hat{X}_{k-1|k-1}$
- $P_{k|k-1} = \mathcal{L}P_{k-1|k-1}\mathcal{L}^T + Q$

Update

- $\hat{y}_{k|k-1} = z_k - \mathcal{C}\hat{X}_{k|k-1}$
- $S_k = R + \mathcal{C}P_{k|k-1}\mathcal{C}^T$
- $K = P_{k|k-1}\mathcal{C}^T S^{-1}$
- $\hat{x}_{k|k} = \hat{X}_{k|k-1} + K\hat{y}_k$
- $P_{k|k} = (I - K\mathcal{C})P_{k|k-1}(I - K\mathcal{C})^T + KRK^T$



Filtering methods
Kalman filter

What about parameter estimation?
One can simply consider the joint parameter-state space as the new state space, with $\theta_{k|k-1} = \theta_{k-1|k-1}$.

This works if:

1. The state space is small, otherwise $P_{k|k}$ is too big to work with
2. The model $\mathcal{L}$ is linear
3. The model $\mathcal{L}$ depend linearly in the parameters
4. The observation operator $\mathcal{C}$ is linear

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Solutions:

2. & 3. Nonlinear extensions: Extended KF (EKF) and Unscented KF (UKF)

1. Reduced-order Unscented KF (RoUKF)

Numerical results

Software

Tools/libraries:

- python
- numpy (general scientific computing)
- fenics (FEM)
- filterpy (Kalman related utilities)

Software written:

- Solvers for the static problems: standard and bidomain (Gaspard)
- Solvers for the dynamic problems: work in progress
- Monte Carlo estimator (Thuy and al.)
- General Kalman filter library: static, dynamic and with state estimator (Cécile and Gaspard)
- Glue code for Kalman estimation for the static case (Cécile)

Qualitative results
Standard model

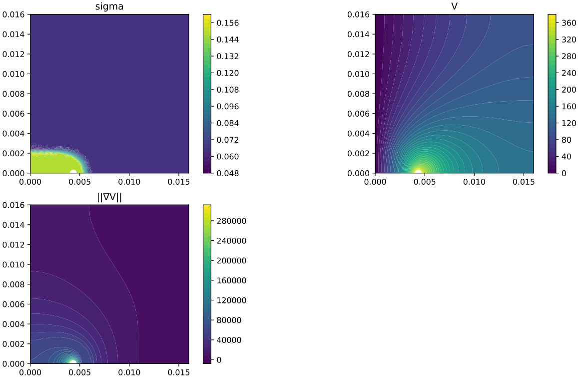


Figure: Standard static model typical solution

Qualitative results
Bidomain model

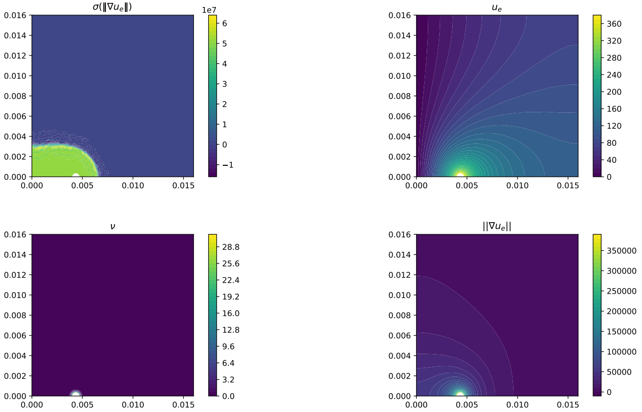
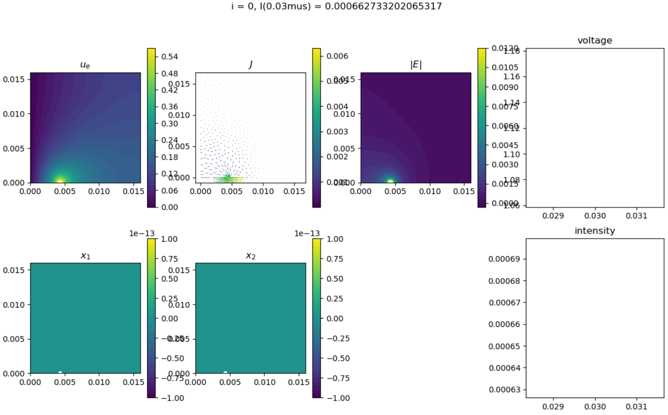


Figure: Bidomain static model typical solution

Qualitative results
Dynamic biphase model



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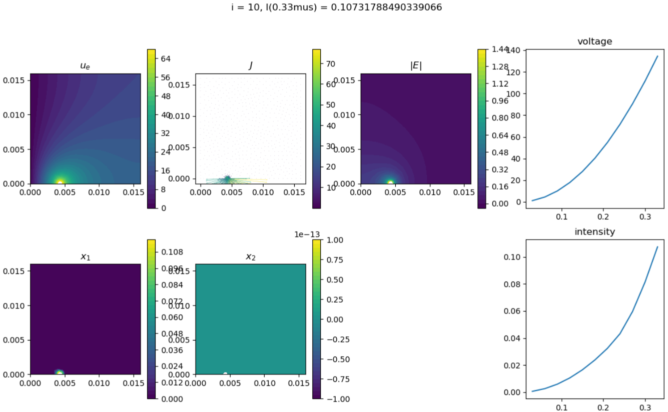

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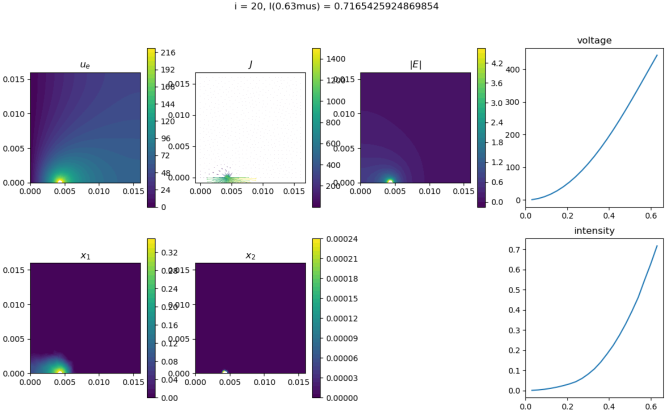

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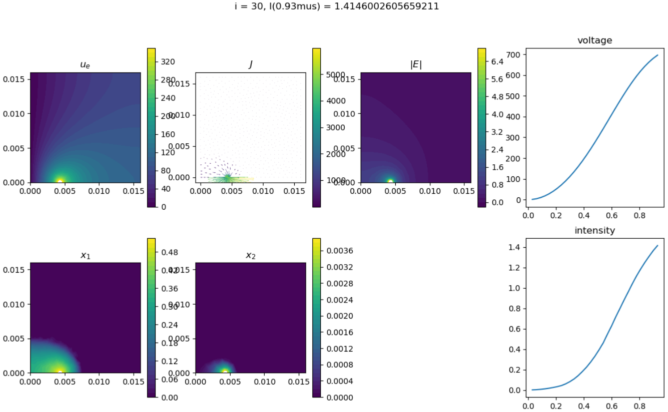

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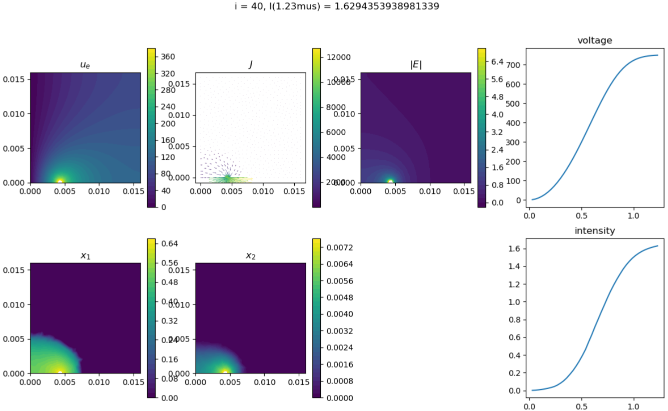

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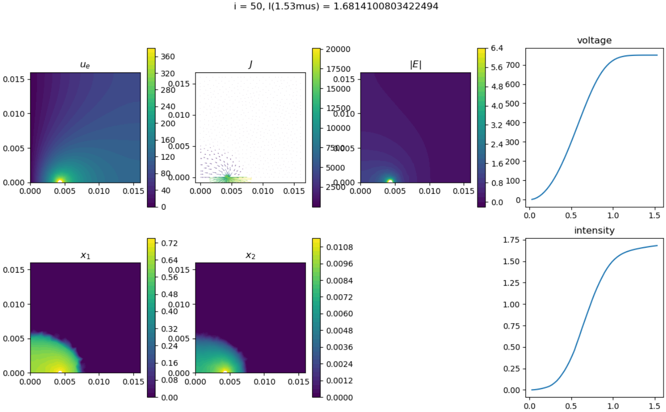

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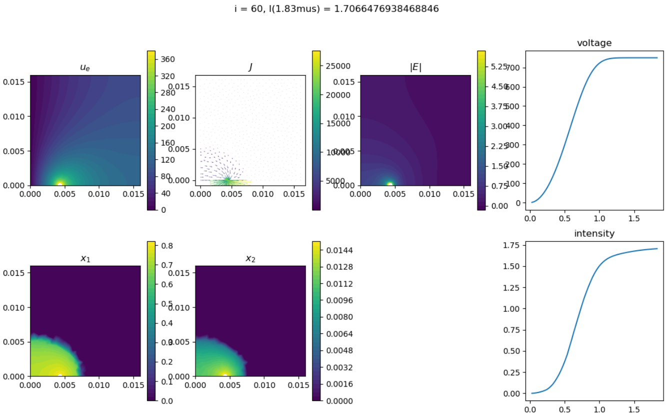
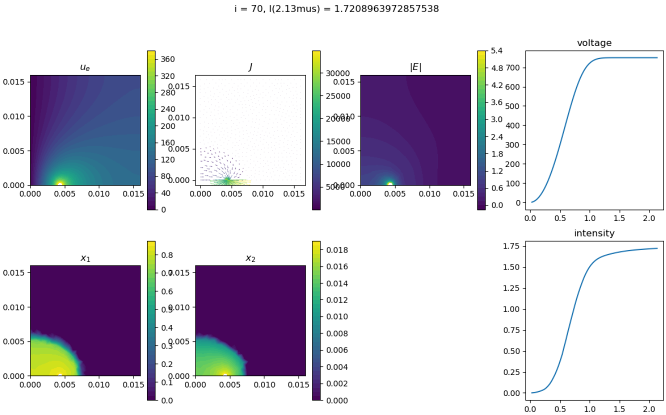


QUALITATIVE RESULTS
DYNAMIC BIPHASE MODEL



Numerical results
Monte Carlo

Paramater	E_{th}	k_{ep}	σ_0	σ_1
Init. value	5.75×10^4	5×10^{-3}	6.5×10^{-2}	1.483×10^{-1}
Variance	25	2×10^{-3}	2.5×10^{-2}	0.9×10^{-1}

Size of param set	Estimated param	Min of squared residuals
30	$Eth = 5.750 \times 10^4$ $k_{\text{ep}} = 1.848 \times 10^{-2}$ $\sigma_0 = 8.412 \times 10^{-2}$ $\sigma_1 = 4.256 \times 10^{-1}$	0.357
100	$Eth = 5.750 \times 10^4$ $k_{\text{ep}} = 8.528 \times 10^{-3}$ $\sigma_0 = 6.871 \times 10^{-2}$ $\sigma_1 = 4.444 \times 10^{-1}$	0.345
500	$Eth = 5.750 \times 10^4$ $k_{\text{ep}} = 1.442 \times 10^{-2}$ $\sigma_0 = 4.674 \times 10^{-3}$ $\sigma_1 = 4.165 \times 10^{-1}$	0.312

Numerical results

Kalman filtering on synthetic data:

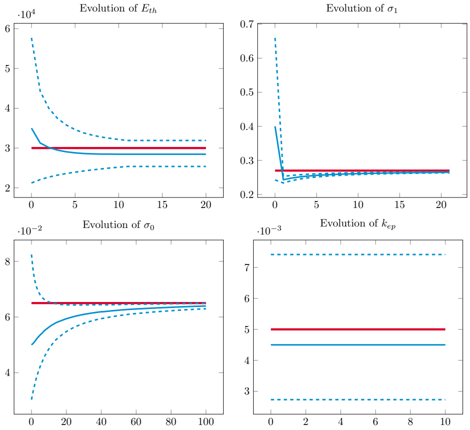


Figure: Independent estimation of the 4 parameters

Numerical results

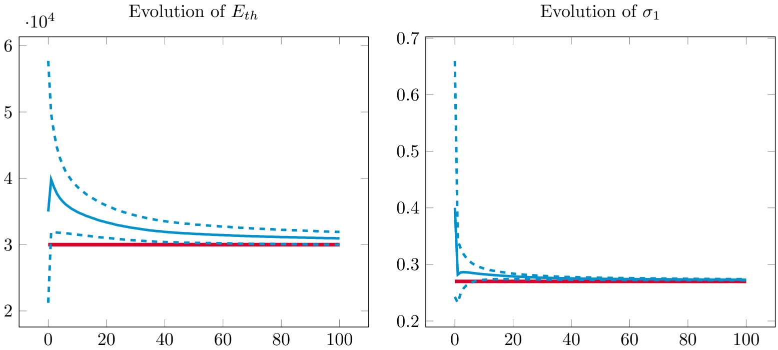


Figure: Simultaneous estimation of E_{th} and σ_1

Numerical results

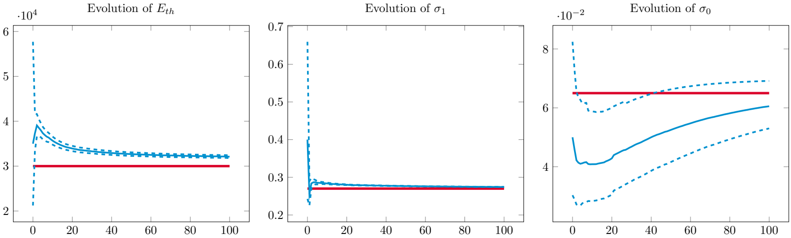


Figure: Simultaneous estimation of E_{th}, σ_0 and σ_1

WORK TO BE DONE, FUTURE WORK AND OPEN QUESTIONS

Work done

- Implementation of the (nonlinear) direct solvers with a common interface
- Implementation of several parameter estimation methods
- Qualitative comparison with clinical data

Work to be done

- Quantitative comparison with clinical data (in progress)
- Parameter estimation in the dynamical case (soon)
- Fix the direct bidomain and dynamic model solvers (very soon)

Future work and open questions

- Theory
  - Well-posedness of the inverse problems
  - Write a good state estimator for the dynamical problems
- Modelling
  - Physiological evolution equation for $\sigma_m(t)$
  - Correct derivation of the $\sigma_m(|\nabla u_e|)$

Thank you for your attention!