Equipe Problèmes Inverses en électrophysiologie CARDiaque (EPICARD)

LIRIMA scientific days

EQUIPE ASSOCIEE Epicard
INRIA Bordeaux Sud-Ouest-LAMSIN

N. Zemzemi & M. Bellassoued

Paris, September 18th 2018

EPICARD members

- From Inria
  - Nejib Zemzemi (CR, co-Head)
  - Yves Coudière (Prof)
  - Jacques Henry (Emeritus)
  - Mostafa Bendahmane (MdC)
  - Amal Karoui (Phd student)
  - Pauline Megerditichan (Eng)
- From Lamsin
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  - Nabil Gmati (Prof)
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  - Moez Kallel (MdC)
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  - Yassine Abidi (Phd student)
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EPICARD collaborators

- From MohamedV Univ
  - Rajae Aboulaich (Prof)
  - Elmahdi Elguarmah (TA)
  - Najib Fikal (PhD)
  - Keltoum Chahour (Phd Students)
- From Inria Sophia-Antipolis
  - Abderrahmane Habbel (MdC)

General context

- Cardiovascular diseases (CVDs) are killing more than 17.1 million people worldwide.
- CVDs are the main cause of mortality in Europe with more than 4.2 million death per year and cost more than 192 Md €.

World Health Organization (WHO)

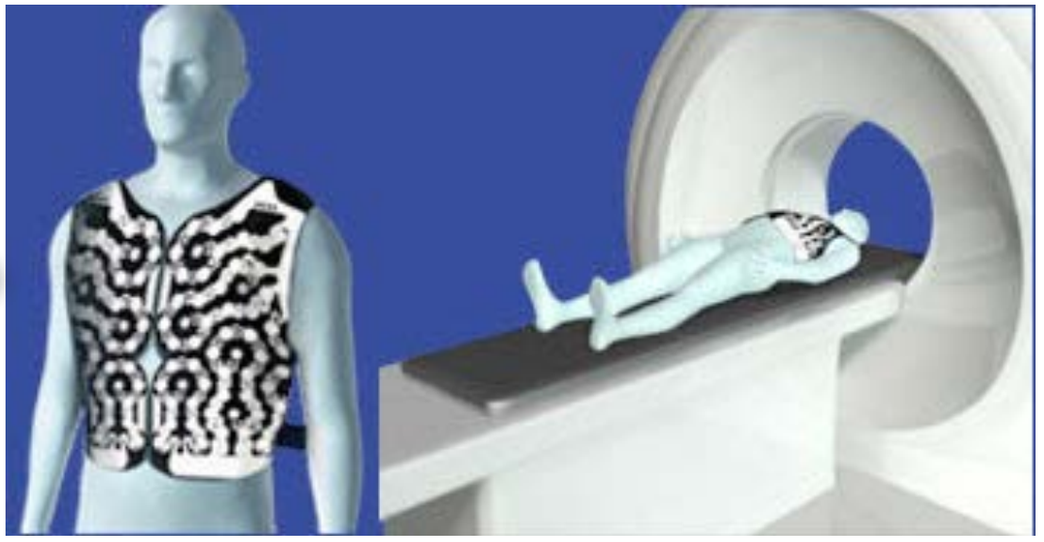
- Numerical simulation is a powerful tool to clarify some misunderstood phenomena.
- Build virtual data base that can help for training new medical tools
- Predict the toxicity of some treatments

Local context in Bordeaux

- IHU-LIRYC investment for the future program (40M€)
- CHU-Bordeaux: Pioneers in cardiac surgery / radio frequency ablation
- **Non invasive cardiac imaging system** is under assessment in the CHU
- Medical doctors (Michel Haissaguere) are convinced by the role of the in silico model in the improvement of the new technology
- In vitro and in vivo experiments are now available in the IHU for validation
- Carmen project is part of LIRYC institute

Electrocardiography system: EcVue

- Electrodes Vest



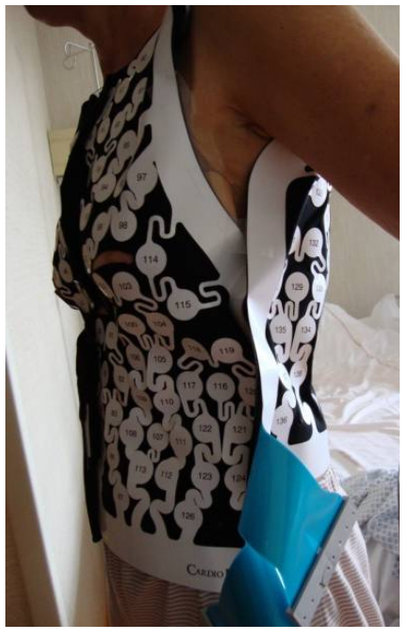
- CT Scan with the vest

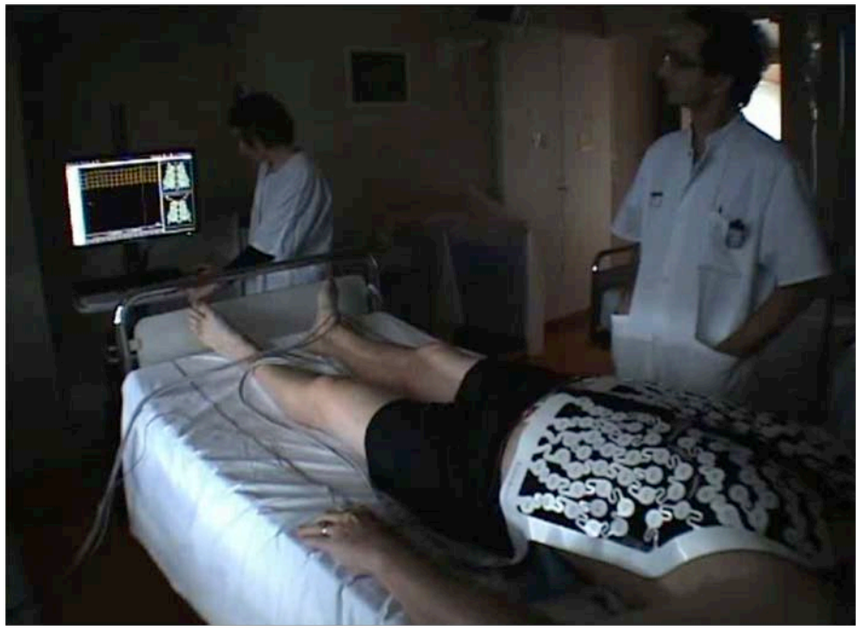
- Measuring signals and mapping the inverse solution

- Medical decision and intervention

Clinical Use

- EcVue System form CardioInsight
  - 252-electrodes Vest
  - Patient examination

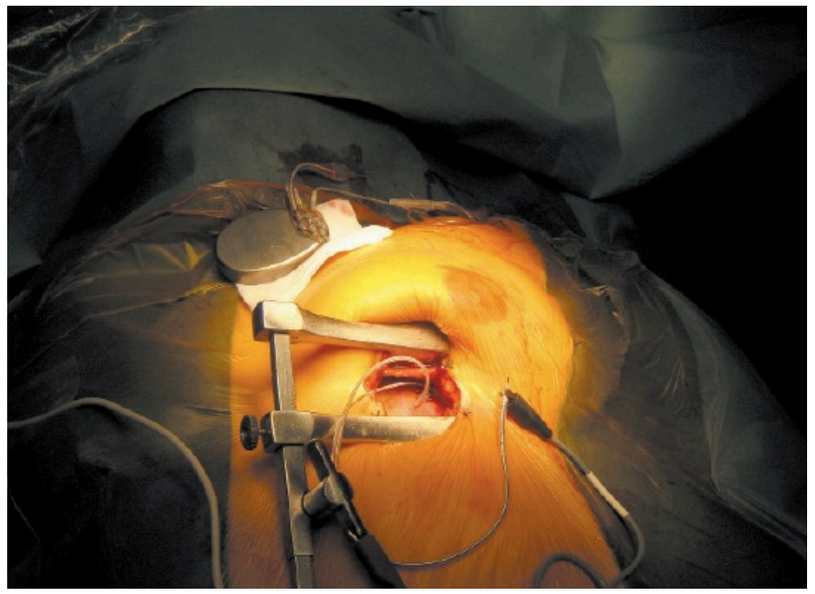




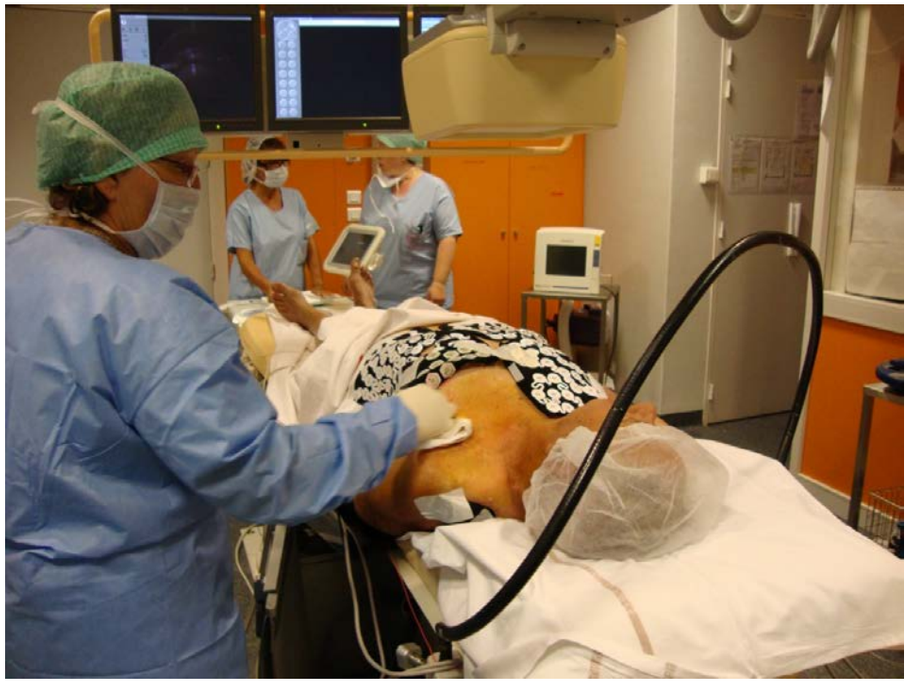
- ECGI has been used for the treatment of:
  - Cardiac resynchronization therapy
  - Atrial fibrillation treatment
  - Focal Arrhythmia (AT, VT, WPW,…)
  - Ventricular Fibrillation

Clinical Use (CRT)

- Use of ECGI for CRT guidance



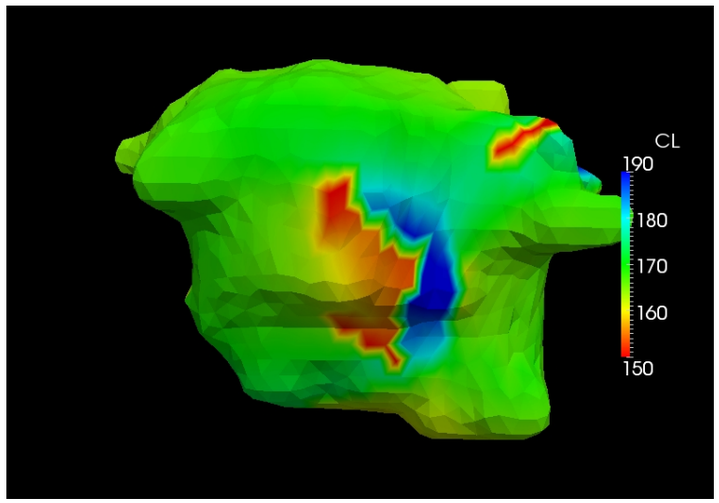
- Real time observation of the conduction patterns before during and following insertion of the device



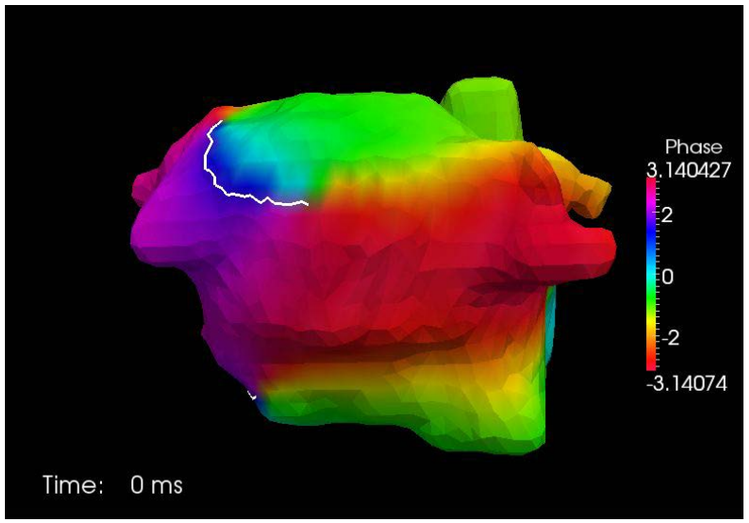
Clinical Use (AF ablation)

- Use of ECGI for atrial fibrillation treatment

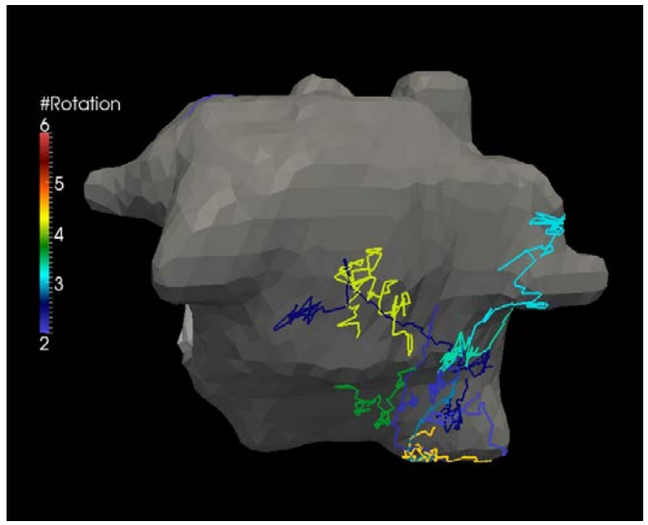
  - Temporal cycle length

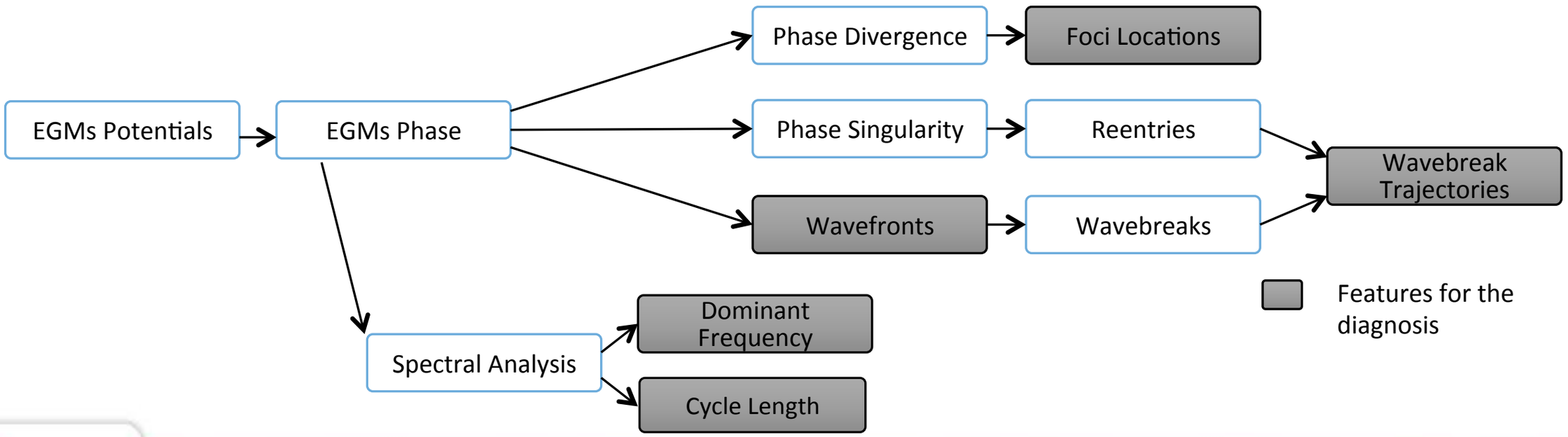


  - Phase mapping



  - Foci location





Goals of the ECGI procedure

Medical goals

- Detect the pathway of the electrical wave on the heart surface
- Localize in space the origin of arrhythmia
- Help medical doctor for a better diagnosis of the heart condition
- Better understanding of the mechanism of some pathologies
- Guide the medical doctors during interventions (RFA)

Mathematical and numerical goals

- Mathematical formulation of the medical issues
- Treat fundamental questions
- Design and participate in building technical solutions

EPICARD Production 2015-2017

- Journal Papers
  - 1 *Mathematical biosciences*
  - 2 *Inverse problem* papers
  - 2 *Mathematical modeling of natural Phenomena*
- International conferences + proceedings
  - 1 papers *FIMH 2015*
  - 1 papers *International Symposium on Biomedical Imaging 2016*
  - *Computing in cardiology* 1 to 2 papers each year
- International conferences without proceedings
  - *Picof 2016: 5 abstracts*
  - *Colloque international du laboratoire Euro-maghrébin de mathématiques et leurs interactions*

EPICARD Production 2015-2017

- African Conferences
  - TamTam 2015, 3 talks.
  - CARI 2016: 2 papers
  - *TamTam 2017: 6 talks*

Local presentations

- LIRYC scientific days: 2 to 3 posters each year. IHU-LIRYC
- Seminars at the IMB.
- Seminars at Inria-Bordeaux.
- Seminars at LAMSIN.
- Journées de Bio-mathématique et Calcul Numérique, 2 to 3 talks each year.

EPICARD Production 2015-2017

- Five major publications

[1] Y Abidi, M Bellassoued, M Moncef, N Zemzemi. On the identication of multiple space dependent ionic parameters in cardiac electrophysiology modelling. ***Journal of Inverse Problems (2018)***.

[2] S. Aouadi, W. Mbarki and N. Zemzemi. Stability analysis of decoupled timestepping schemes for the specialized conduction system/myocardium coupled problem in cardiology. ***Mathematical Modelling of Natural Phenomena***. (2017).

[3] J. Lassoued, M. Mahjoub, N. Zemzemi, Stability results for the parameter identication inverse problem in cardiac electrophysiology, ***Inverse Problems*** 32, 2016, p. 1-31, [doi:10.1088/0266-5611/32/11/115002], [hal:hal-01399373].

[4] R. Aboulaich, N. Fikal, E. M. EL Guarmah, N. Zemzemi(2016). Stochastic Finite Element Method for torso conductivity uncertainties quantication in electrocardiography inverse problem. ***Mathematical Modelling of Natural Phenomena***, 11(2), 1-19.

[5] C. Corrado, J. Lassoued, M. Mahjoub, N. Zemzemi(2015), Stability analysis of the POD reduced order method for solving the bidomain model in cardiac electrophysiology. ***Mathematical Biosciences***,, [doi:10.1016/j.mbs.2015.12.005].

EPICARD Production 2015-2017

- PHD thesis:
  - Jamila Lassoued. Quelques approches mathématiques en électrophysiologie cardiaque: Problèmes inverses et méthodes d'ordre réduit. Ph.D thesis defended on 20/07/2016
  - Najib Fikal: Quantification d'incertitudes en électrocardiographie par la méthode éléments finis stochastique. Ph.D thesis defended on July 22nd 2017.
  - Wajih M'Barki. Modélisation et analyse d'un problème d'interaction en biomathématiques : couplage en électrophysiologie cardiaque. Ph.D thesis defended on July 28th, 2017.
- Master thesis
  - Ronald-Reagan Moussitou. Problème inverse en électrocardiographie Théorie de la factorisation. Thesis defended on 13/09/2016.
  - Karoui Amal. Méthodes numériques pour la resolution du problème inverse en électrocardiographie. PFE defended on 11/09/2017.

EPICARD Production 2015-2017

- Events Organizations
  - R. Aboulaich organized workshop-biomath in Rabat, on November 11th-12th 2015.
  - *N. Zemzemi organized a mini-symposium intitled “Imaging and inverse modeling” in PICOF. June 1st-3rd 2016, Autrans, France.*
  - *N. Gmati Co-organized CIMPA research school 2016: Mathématiques pour la biologie. From 04/10 to 10/10. Tunis, Tunisia.*
  - *N. Gmati organized CARI 2016. From 11/10 to 14/10. Tunis Tunisia*
  - *Carmen Team members participate each year in the organization of the LIRYC scientific days*
- Scientific diffusion
  - *M. Mahjoub and N. Zemzemi gave courses in CIMPA schools 2016*
  - *Master + Doctoral courses on the topic at FST each year.*

EPICARD Production 2018

- Journal Papers
  - One paper has been accepted in Inverse Problems.
  - In 2018: we are organizing a **special issue** in the ***MMNP*** Journal named: «Mathematical modeling in cardiac electrophysiology »: Five papers from EPICARD members has been submitted, four are already accepted.
  - One paper has been submitted to ***Frontiers in Physiology***
- International conferences + proceedings
  - *Computing in cardiology 2018, Maastricht, Netherland*
- International conferences without proceedings
  - *Picof 2018: 3 abstracts presentations, Beyrouth Libanon*
  - *9th International Conference "Inverse Problems: Modeling and Simulation" (2018): Malte, Italy*

EPICARD Production

Running Ph.Ds:

- Rabeb Chamekh. Nash game theory applied to the inverse problem in electrocardiography Ph.D defense expected in 2019.
- Yassine Abidi: Parameters identification problems in cardiac electrophysiology modeling. Ph.D defense expected in 2019.
- Amal Karoui: Nouvelles approaches en imagerie électrocardiographique. Started on October 2017. The defence is expected in 2020.

Visits financial contributions

- Scientific Visits
  - Each year 2 to 3 Ph.D. students from Tunisia and Morocco visit Inria 1 month to 4 months period
  - ***In 2018**: Phd students Y. Abidi, R. Chamekh and K. Chakour have been visiting Inria.*
  - *Each year 4 to 5 senior members visits either in Tunis or in Bordeaux. One or two weeks visits.*
- Financial contributions
  - *Inria 10,000€/year*
  - *LAMSIN: Internship for Ph.D. students + travel fees ~5,000 to 6,000€/year*
  - *Université Mohammed V: travel fees 1,000 to 1,5000€/year*
  - ***In 2018**: LAMSIN and MESRS, supported 4 months visit for Phd students Y. Abidi, R. Chamekh*

Major results

Contributions to the stationary formulation of the ECGI problem

- **Optimal control formulation of the ECGI problem**
- Invariant embedding method in 3D
- Incomplete data on the accessible boundary
- **Effect of neglecting conductivity heterogeneities**
- **Quantification of the uncertainty of the ECGI solution with respect to conductivities uncertainty and noise on the data**
- Torso conductivities optimization in the forward problem. **Combing ECGI-inverse solution and conductivities optimization**

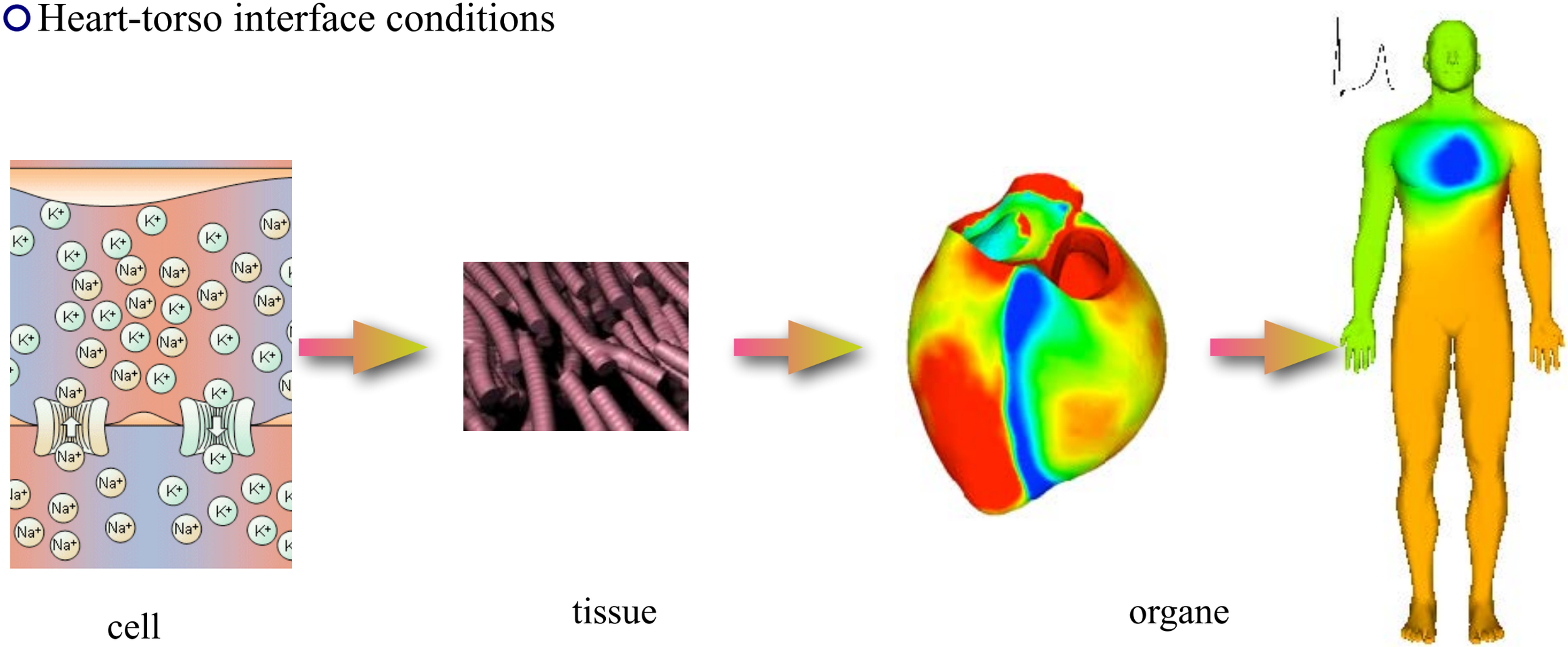
Contributions to the non-stationary inverse problem in ECGI

- **Theoretical results on parameters identification problems**
- **Numerical methods for parameters estimation in cardiac electrophysiology**
- **Reduced order modeling in cardiac electrophysiology**

Modelling in cardiac electrophysiology

ECG modeling: from cell to body surface

- Main ingredients:
  - Model for the electrical activity of the heart
  - Torso model
  - Heart-torso interface conditions

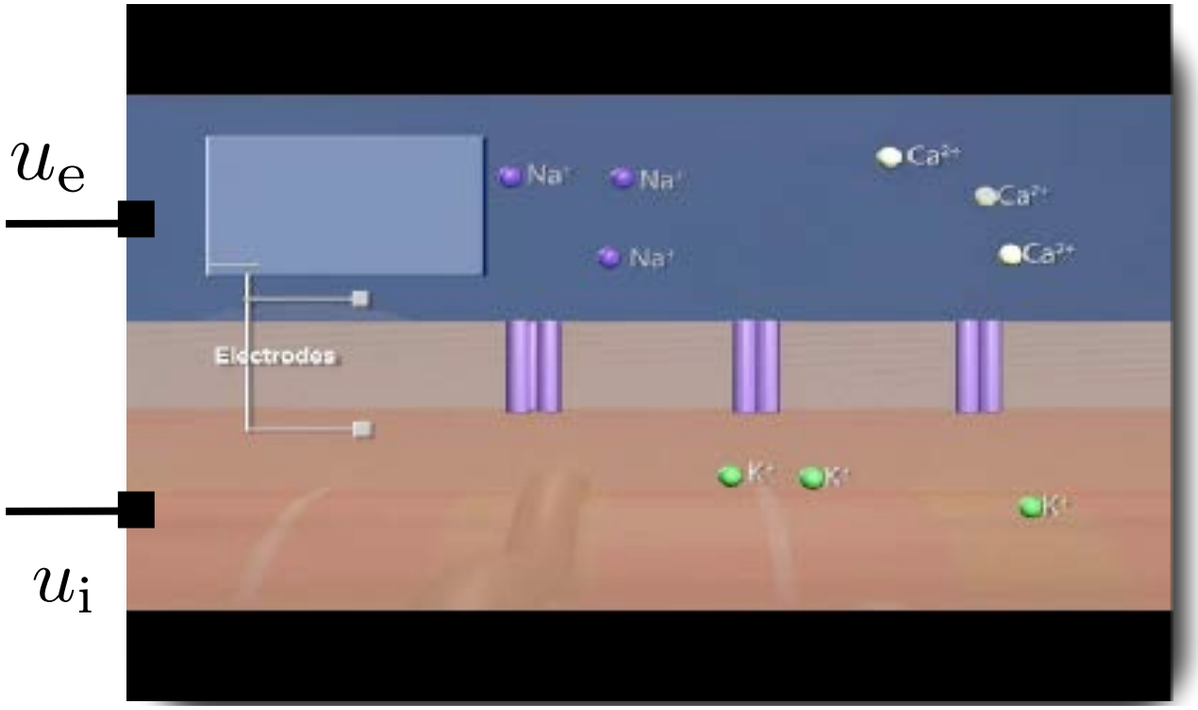


cell

tissue

organe

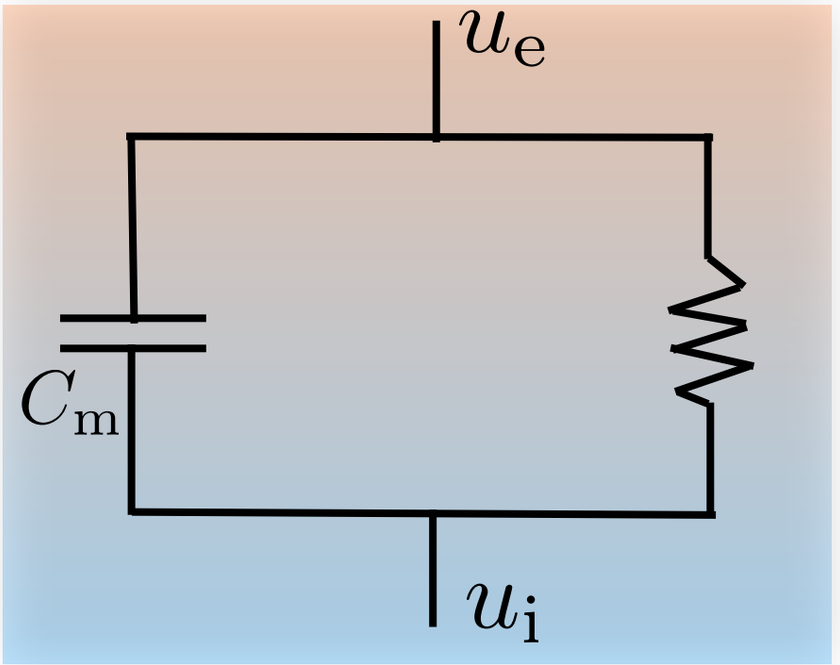
Modeling: cell scale



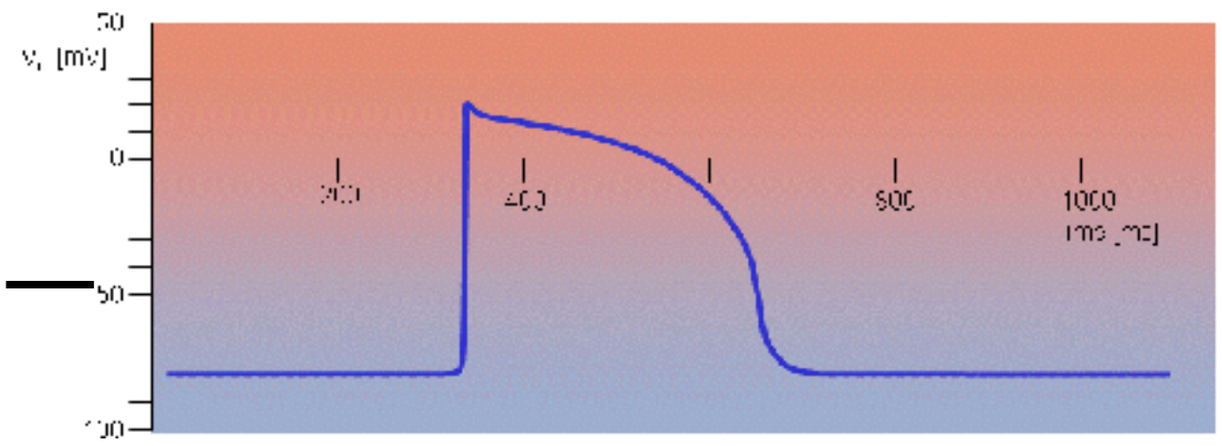
extra-cellular medium

membrane

intra-cellular medium



electric analog



transmembrane potential: $V_\mathrm{m} = u_\mathrm{i} - u_\mathrm{e}$

intra-cellular potential: u_i

extra-cellular potential: u_e

Ionic model (ODE):

$$\begin{cases} C_\mathrm{m} \dfrac{\mathrm{d}V_\mathrm{m}}{\mathrm{d}t} + i_\mathrm{ion}(V_\mathrm{m}, w) = I_\mathrm{app} \\ \dfrac{\mathrm{d}w}{\mathrm{d}t} + G(V_\mathrm{m}, w) = 0 \end{cases}$$

(Hodkin-Huxley 52, Noble 62, Beeler-Reuter 77, Luo-Rudy91,...,Grandi2010)

Multiple space dependent parameter Identification inverse problem

- Monodomain model: dynamic model

$$\begin{cases} \partial_t v - \mathrm{div}(\sigma \nabla v) = I_{app} + I_{ion}(\bar{\varrho}, v, \mathbf{w}, \mathbf{z}) & \text{in } Q \equiv \Omega \times (0,T), \\ \partial_t \mathbf{w} = \boldsymbol{F}(v, \mathbf{w}) & \text{in } Q, \\ \partial_t \mathbf{z} = \boldsymbol{G}(\bar{\varrho}, v, \mathbf{w}, \mathbf{z}) & \text{in } Q, \\ \sigma \nabla v \cdot \nu = 0 & \text{on } \Sigma \equiv \partial\Omega \times (0,T). \end{cases}$$

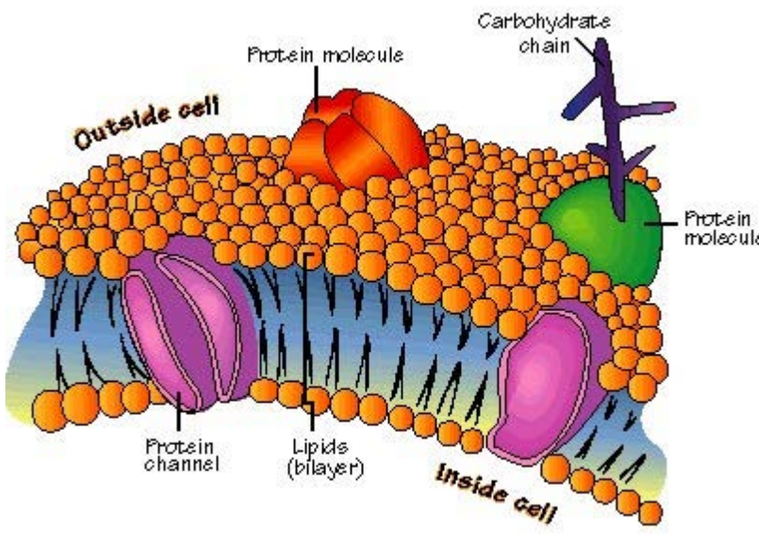
where, the ionic model is a generalization of the H.H physiologically detailed ionic

$$I_{ion}(\bar{\varrho}, v, \mathbf{w}, \mathbf{z}) = \sum_{i=1}^{N} \bar{\varrho}_i y_i(v) \prod_{j=1}^{k} w_j^{p_{j,i}} (v - E_i(\mathbf{z})),$$

$$E_i(\mathbf{z}) = \overline{\gamma}_i \log\left(\frac{z_e}{z_i}\right), \quad \mathbf{z} = (z_1, \ldots, z_m),$$

$$\partial_t w_j = F_j(v, w_j) := \alpha_j(v)(1 - w_j) - \beta_j(v) w_j, \quad j = 1, \ldots, k,$$

$$\partial_t z_i = G_i(\bar{\varrho}, v, \mathbf{w}, \mathbf{z}) := -J_i(\bar{\varrho}, v, \mathbf{w}, \log z_i) + H_i(\bar{\varrho}, v, \mathbf{w}, \mathbf{z}), \quad i = 1, \ldots, m,$$



- Solution existence for bidomain model *(M. Veneroni 2009)*

Multiple space dependent parameter Identification inverse problem

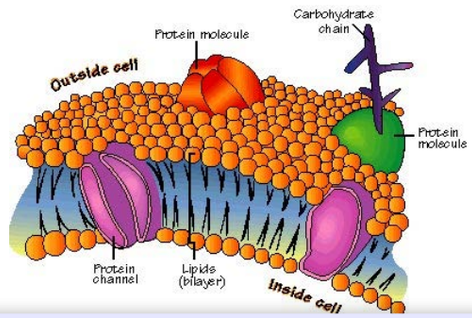
- Why Conductance parameter?
  - Scaling factors of the different ionic currents, built on sigle cell experiments
  - Related to heart conditions (pathological conditions, gene mutation for instance)
  - different physiological biomarkers are related to the conductances: Propagation velocity, repolarization times, …
- Hypothesis on the ionic model
  - Regularities on the RHS of the ionic model and on the stimuli function. (Also needed for existence)
  - **Needed Observation: As many as the number of parameters to estimate.**

$$\Lambda(\widetilde{v}_\ell(x), \widetilde{\mathbf{w}}_\ell(x), \widetilde{\mathbf{z}}_\ell(x)) = \begin{pmatrix} S_{1,1}(x) & S_{2,1}(x) & \dots & S_{N,1}(x) \\ S_{1,2}(x) & S_{2,2}(x) & \dots & S_{N,2}(x) \\ \vdots & \vdots & \ddots & \vdots \\ S_{1,N}(x) & S_{2,N}(x) & \dots & S_{N,N}(x) \end{pmatrix},$$

$$S_{i,\ell}(x) = y_i(\widetilde{v}_\ell(x))\,(\widetilde{v}_\ell(x) - E_i(\widetilde{\mathbf{z}}_\ell(x)))\prod_{\cdot}^{k}{}_{\cdot}(\widetilde{w}_\ell)_j^{p_{j,i}}(x)\,,\ 1 \leqslant \ell, i \leqslant N\,.$$

- Column ℓ corresponds to the ℓ-th stimulus (frequency, position, duration, magnitude,…)
- Rows i corresponds to the derivative of the ionic current to the i-th parameter

Multiple space dependent parameter Identification inverse problem



- Stability result

Theorem 3.1. *Let $t_0 \in (0,T)$, ω be a subdomain of Ω and let $\bar{\varrho}^{(2)} \in \mathcal{A}$ be arbitrary fixed. We assume that $I_{app}^{\ell} \in L^p(0,T;L^2(\Omega)) \cap H^1(0,T;L^2(\Omega))$, $p > 4$, $1 \leqslant \ell \leqslant N$, satisfy*

$$\det(\Lambda(v_\ell^{(2)}(x,t_0), \mathbf{w}_\ell^{(2)}(x,t_0), \mathbf{z}_\ell^{(2)})(x,t_0)) \neq 0, \quad \forall x \in \Omega. \tag{3.57}$$

Here $(v_\ell^{(2)}, \mathbf{w}_\ell^{(2)}, \mathbf{z}_\ell^{(2)}))$ is the solution of (2.8) with $\bar{\varrho} = \bar{\varrho}^{(2)}$ and $I_{app} = I_{app}^{\ell}$. Furthermore, we assume that

$$\|v_\ell^2\|_{W^{1,\infty}(Q)} + \|\mathbf{w}_\ell^2\|_{C^1(Q)} + \|\mathbf{z}_\ell^2\|_{C^1(Q)} \leqslant M, \tag{3.58}$$

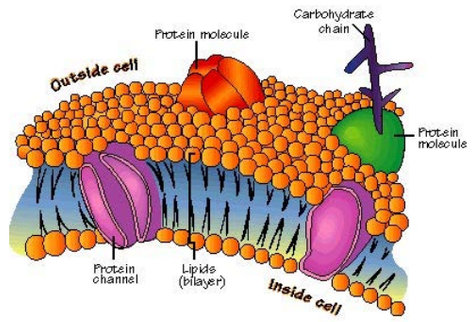
for some positive M. Then there exists a constant $C > 0$, depending only on T, Ω, ω, M_0 such that we have:

$$\begin{aligned}\|\bar{\varrho}^{(1)} - \bar{\varrho}^{(2)}\|_{(L^2(\Omega))^N} \leqslant C\Big(\sum_{\ell=1}^{N} \|(v_\ell^{(1)} - v_\ell^{(2)})\|_{H^1(0,T;H^1(\omega_0))} \\ + \|(v_\ell^{(1)} - v_\ell^{(2)})(\cdot,t_0)\|_{L^2(\Omega)} + \|(\mathbf{w}_\ell^{(1)} - \mathbf{w}_\ell^{(2)})(\cdot,t_0)\|_{L^2(\Omega)} + \|(\mathbf{z}_\ell^{(1)} - \mathbf{z}_\ell^{2})(\cdot,t_0)\|_{L^2(\Omega)}\Big),\end{aligned} \tag{3.59}$$

- Uniqueness is a consequence of the stability theorem
- Proof based on Carleman Estimates
- On going work: Numerical estimation of conductance parameters

(Abidi-Bellassoued-Mahjoub-NZ-2017)

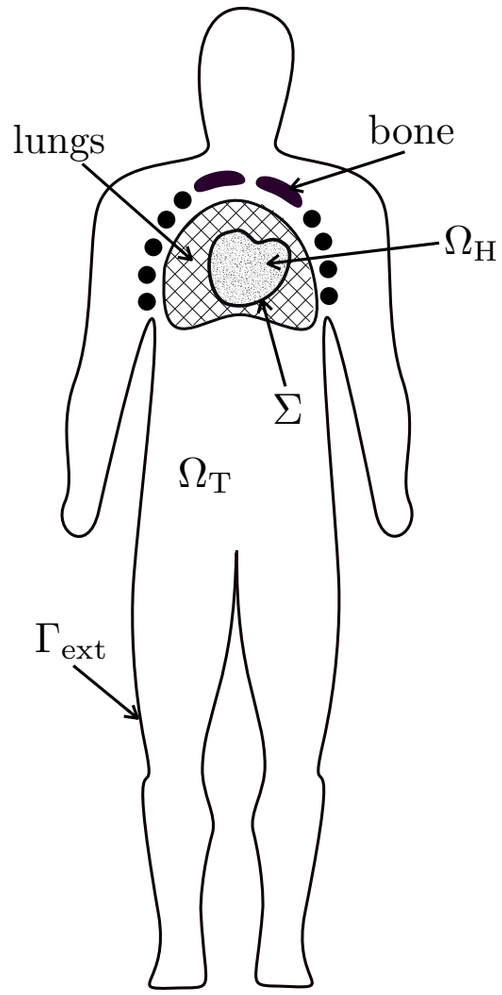
Multiple space dependent parameter Identification inverse problem



- **Challenge for the next two years**
  - Estimate ionic parameter using accessible electrical measurements on a patient torso.

- Heart model (bidomain):

$$\begin{cases} \dfrac{\partial w}{\partial t} + G(V_{\mathrm{m}}, w) = 0, & \text{in} \quad \Omega_{\mathrm{H}} \\ \chi_{\mathrm{m}} \dfrac{\partial V_{\mathrm{m}}}{\partial t} + I_{\mathrm{ion}}(V_{\mathrm{m}}, w) - \operatorname{div}\left(\boldsymbol{\sigma}_{\mathrm{i}} \boldsymbol{\nabla}(V_{\mathrm{m}} + u_{\mathrm{e}})\right) = I_{\mathrm{app}}, & \text{in} \quad \Omega_{\mathrm{H}} \\ \boldsymbol{\sigma}_{\mathrm{i}} \boldsymbol{\nabla}(V_{\mathrm{m}} + u_{\mathrm{e}}) \cdot \boldsymbol{n} = 0, & \text{on} \quad \Sigma \\ - \operatorname{div}\left(\boldsymbol{\sigma}_{\mathrm{i}} \boldsymbol{\nabla}(V_{\mathrm{m}} + u_{\mathrm{e}})\right) - \operatorname{div}(\boldsymbol{\sigma}_{\mathrm{e}} \boldsymbol{\nabla} u_{\mathrm{e}}) = 0, & \text{in} \quad \Omega_{\mathrm{H}} \end{cases}$$



- Torso model:

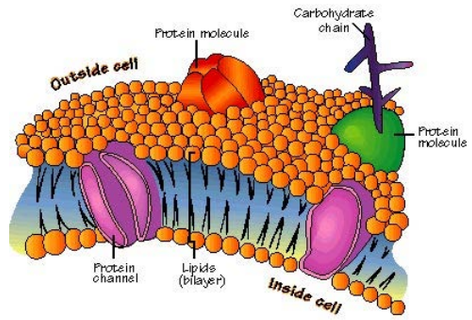
$$\begin{cases} -\operatorname{div}(\boldsymbol{\sigma}_{\mathrm{T}} \boldsymbol{\nabla} u_{\mathrm{T}}) = 0, & \text{in} \quad \Omega_{\mathrm{T}} \\ \boldsymbol{\sigma}_{\mathrm{T}} \boldsymbol{\nabla} u_{\mathrm{T}} \cdot \boldsymbol{n}_{\mathrm{T}} = 0, & \text{on} \quad \Gamma_{\mathrm{ext}} \end{cases}$$

- Heart-torso interface conditions:

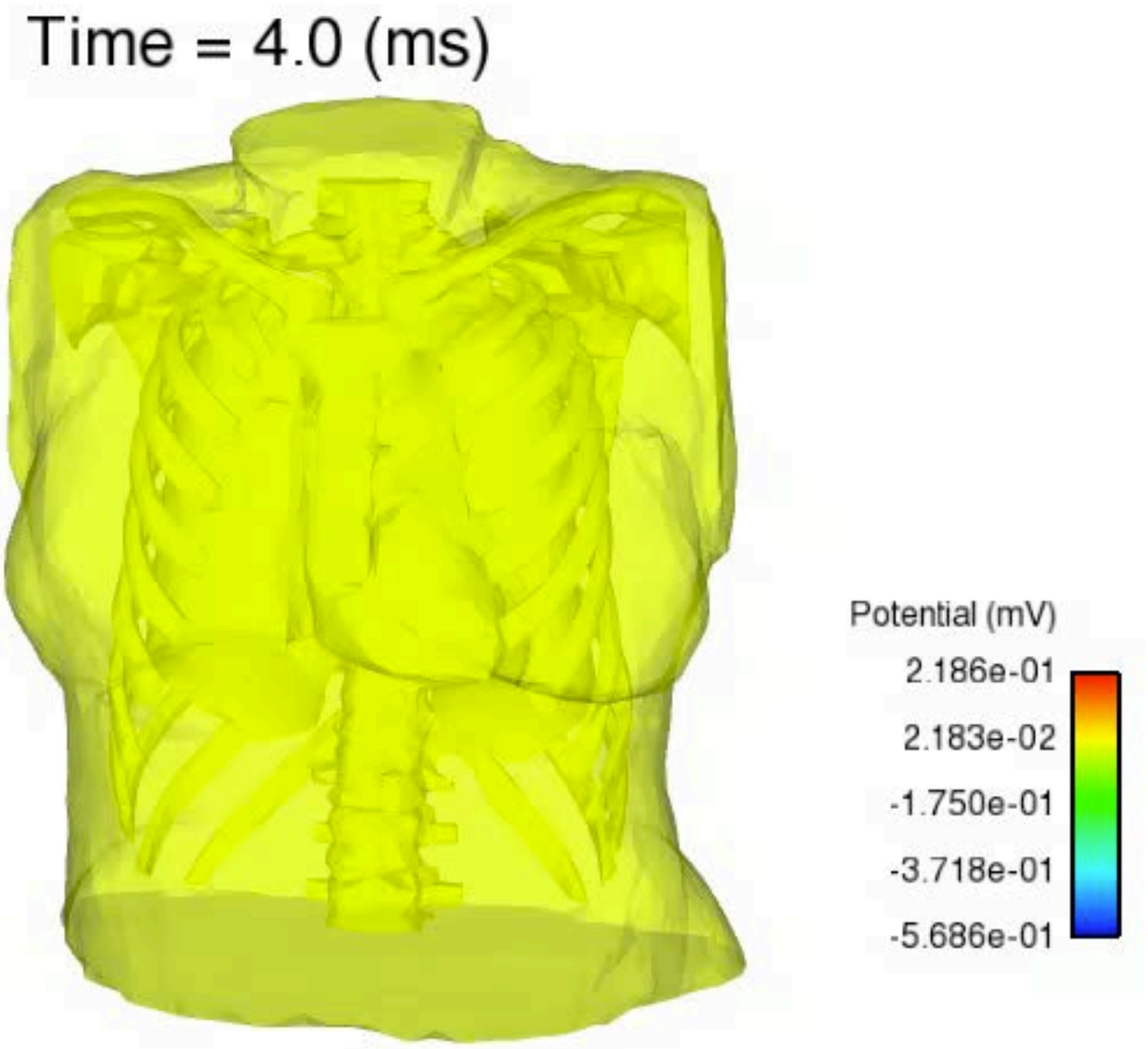
$$\begin{cases} u_{\mathrm{T}} = u_{\mathrm{e}}, & \text{on} \quad \Sigma \\ \boldsymbol{\sigma}_{\mathrm{i}} \boldsymbol{\nabla}(V_{\mathrm{m}} + u_{\mathrm{e}}) \cdot \boldsymbol{n} + \boldsymbol{\sigma}_{\mathrm{e}} \boldsymbol{\nabla} u_{\mathrm{e}} \cdot \boldsymbol{n} = -\boldsymbol{\sigma}_{\mathrm{T}} \boldsymbol{\nabla} u_{\mathrm{T}} \cdot \boldsymbol{n}_{\mathrm{T}} & \text{on} \quad \Sigma \end{cases}$$

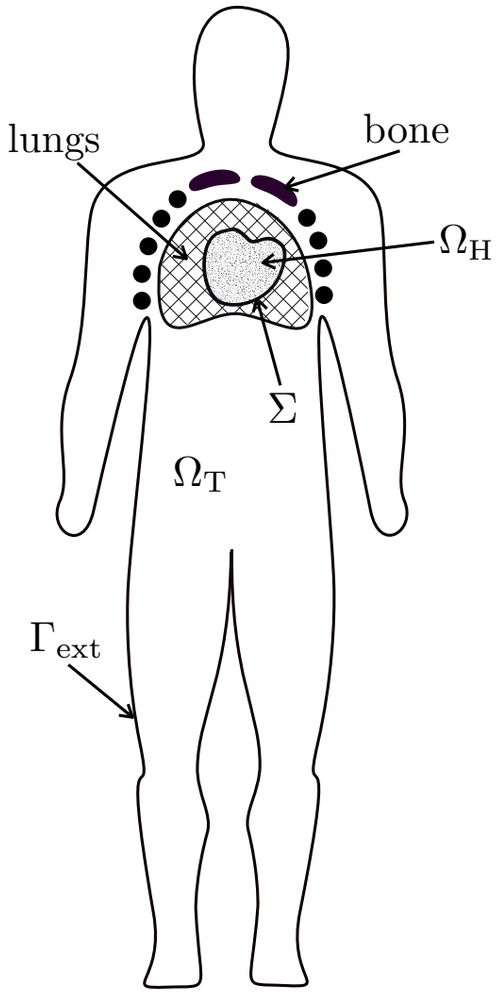
- Analysis of the parameter identification problem on the heart is in ongoing study

Multiple space dependent parameter Identification inverse problem



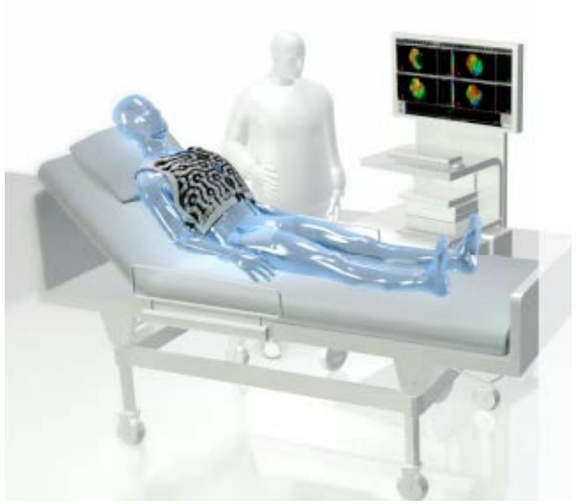
- Challenge for the next two years





ECGI inverse problem

CT-scan (X-ray)



Estimation of the cardiac potential

BSP measurements

Motivation and Goals

Goals

Reconstruct the electrical potential on the heart surface from measurements on the body surface ECGs

Challenging questions:

- Detect and localize some complex electrical pathway in the heart
- Assess the effect of torso heterogeneity on the inverse solution
- Analyze the errors of the inverse solution based on synthetical data

ECGI inverse problem

- Solve in terms of Least square

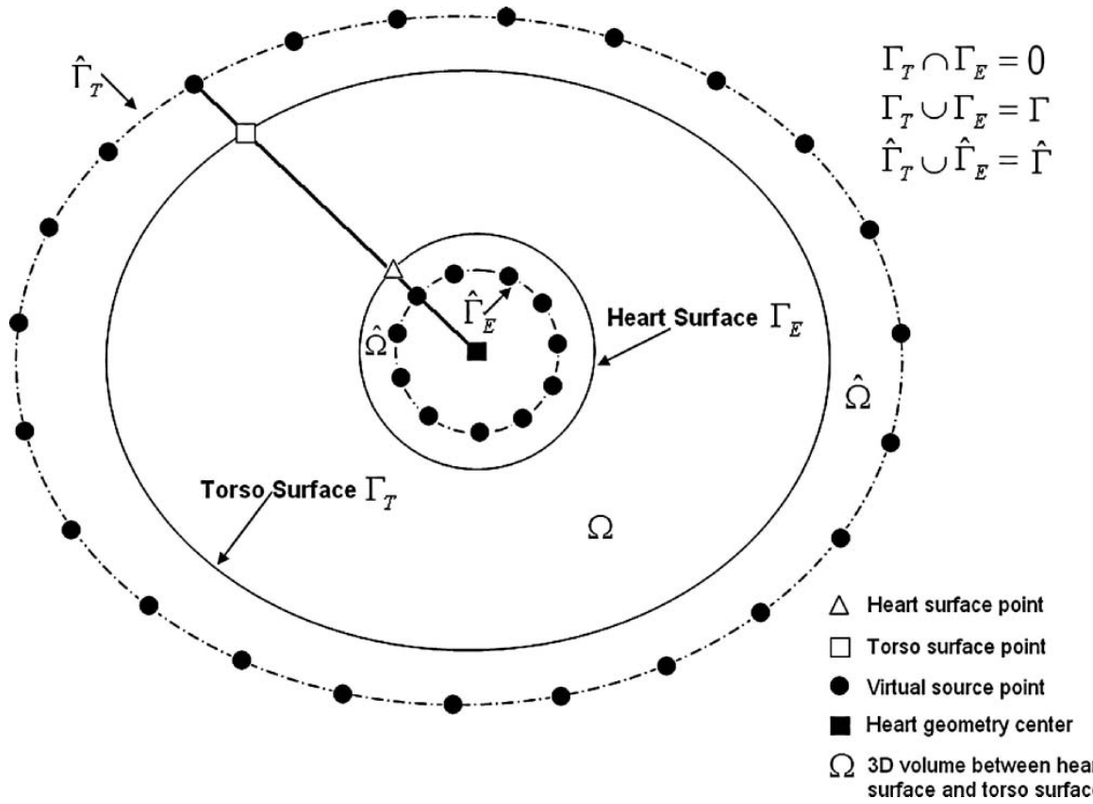
$$\hat{A}\vec{a} = \vec{b}$$

where

$$\hat{A} = \begin{pmatrix} 1 & f(\|x_1 - y_1\|) & \cdots & f(\|x_1 - y_M\|) \\ \vdots & \vdots & \cdots & \vdots \\ 1 & f(\|x_N - y_1\|) & \vdots & f(\|x_N - y_M\|) \\ 0 & \frac{\partial f(\|x_1 - y_1\|)}{\partial n} & \cdots & \frac{\partial f(\|x_1 - y_M\|)}{\partial n} \\ \vdots & \vdots & \cdots & \vdots \\ 0 & \frac{\partial f(\|x_N - y_1\|)}{\partial n} & \cdots & \frac{\partial f(\|x_N - y_M\|)}{\partial n} \end{pmatrix} \quad \vec{a} = \begin{pmatrix} a_0 \\ a_1 \\ \vdots \\ a_M \end{pmatrix}$$

$$\vec{b} = \begin{pmatrix} u_T(x_1) \\ \vdots \\ u_T(x_N) \\ 0 \\ \vdots \\ 0 \end{pmatrix}$$

and $f(r) = \frac{1}{4\pi r}$



Wang and Rudy, *Annals of Biomedical Enginnering*, 2006

- Once weighs are computed, potential at any point in space is obtained

$$u_T(x_k) = a_0 + \sum_{j=1}^{M} a_j f(\|x_k - y_j\|)$$

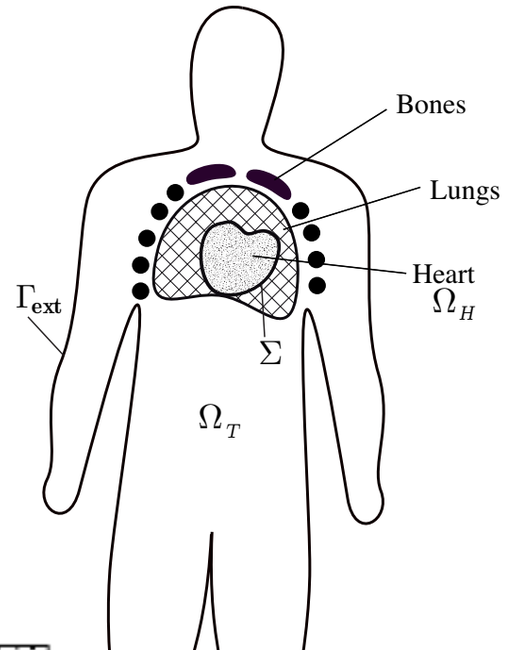
- Meshless method. Fast construction
- But neglects heterogeneities and anisotropy in the torso

ECGI inverse problem

- For a given ECG data measured by the of vest electrodes

$$\phi_e(t_i) = \min_{v \in \mathbb{R}^n} J(v, t_i), \text{ where}$$
$$J(v, t_i) = \| Mv - ECG(t_i) \|_{l^p}^p + \lambda \| L(v) \|_{l^q}^q$$

M is the transfer matrix and L is a penalization operator (Id, Grad,...,)



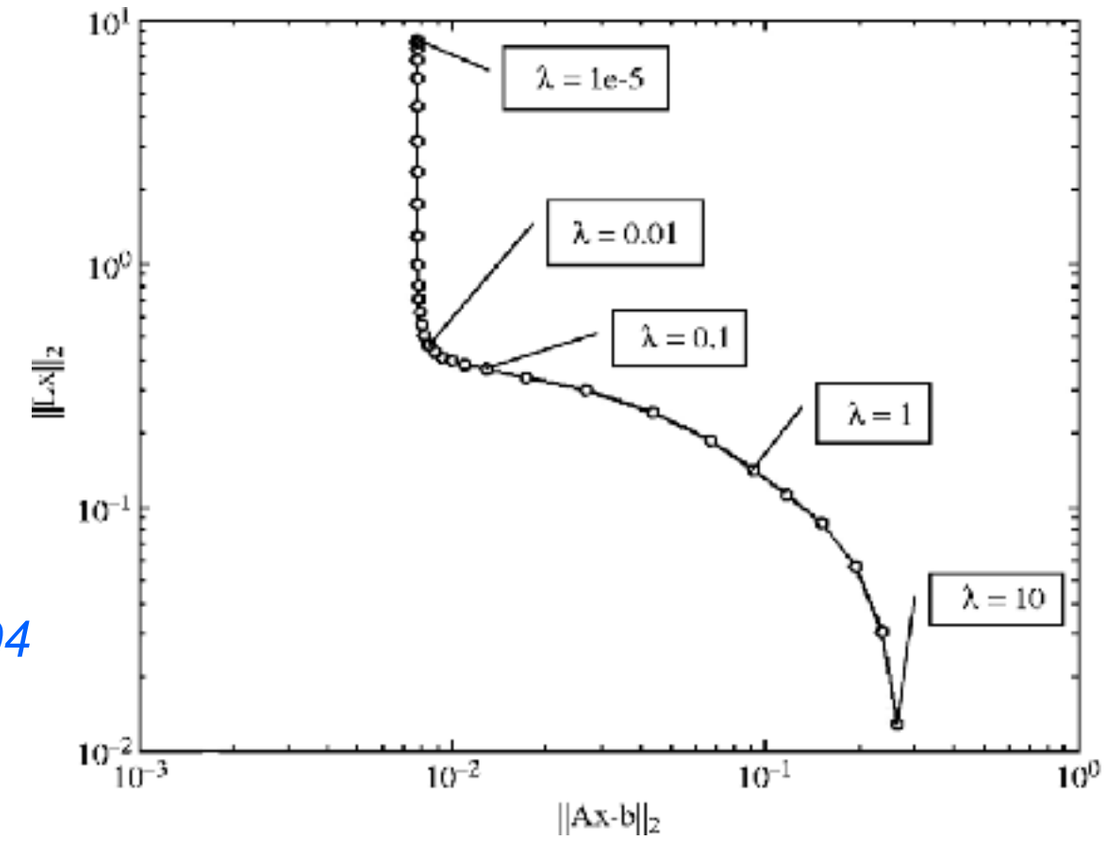
- Choice of regularization parameter

→ L-curve analysis

  - CRESO (*Colli-Franzone et al 85*)
  - Zero-Crossing (*Lian et al 98*)
  - Trancated SVD (*Cheng et al 2001*)

- Iterative Methods

  - GMRes: *Brooks et al 94*
  - Conjugate Gradient: *Carulatha 2004*



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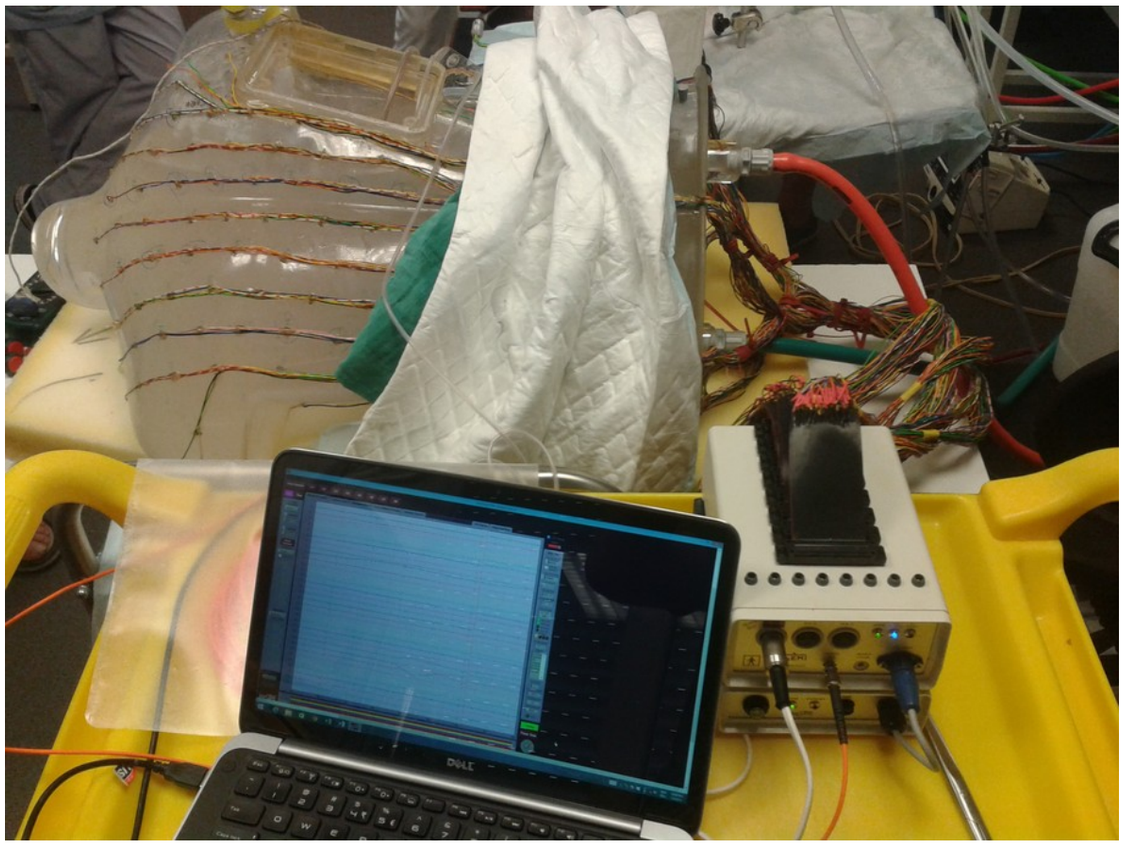
On going work

- We compare 15 different algorithm by varying:
  - The method used to compute ***M: MFS, FEM methods***
  - The operator L: Identity for zero order, gradient for first order
  - The algorithm used for the choice of the regularization parameter: CRESO, ZERO crossing, GCV, R-GCV, U-curve. All are based on the SVD of the matrices M and L

ECGI inverse problem: Evaluation

Evaluation data

- Explanted heart experiment at the LIRYC institute
  - Ex-vivo pig hearts are introduced in the torso tank
  - Different stimulation protocols
  - Introducing different types of arrhythmia: VF, AF,…



ECGI inverse problem: Evaluation

Evaluation results

- stimulation site localizations

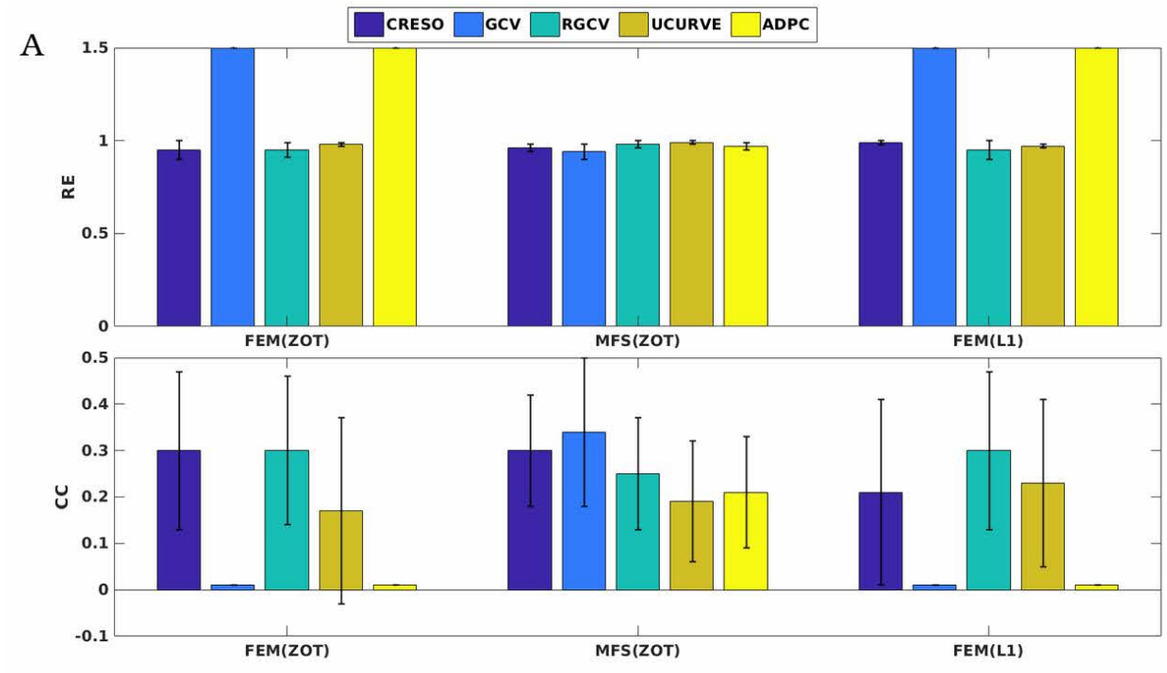
		CRESO	GCV	RGCV	UCurve	ADPC
RV	MFS-ZOT	2.8 ± 1.2	2.4 ± 1.1	1.9 ± 0.9	2.4 ± 0.8	2.5 ± 0.8
	FEM-ZOT	2.7 ± 0.8	N.A	2.7 ± 0.9	2.0 ± 0.1	N.A
	FEM-L1	1.9 ± 0.5	N.A	1.8 ± 0.3	1.8 ± 0.4	N. A
LV	MFS-ZOT	1.7 ± 0.7	2.1 ± 0.3	2.0 ± 1.1	1.3 ± 0.6	2.1 ± 0.2
	FEM-ZOT	2.1 ± 0.4	N.A	2.8 ± 1.0	3.0 ± 0.2	N.A
	FEM-L1	1.3 ± 0.5	N.A	1.2 ± 0.6	1.3 ± 0.6	N.A
BiV	MFS-ZOT	$2.5/N.A$	$2.3/1.5$	$0/N.A$	$2.3/N.A$	$2.7/2.0$
	FEM-ZOT	$1.8/N.A$	N.A	$1.8/2.1$	2.5/N.A	N.A
	FEM-L1	2.5/N.A	N.A	$1.3/1.4$	1.4/N.A	N.A

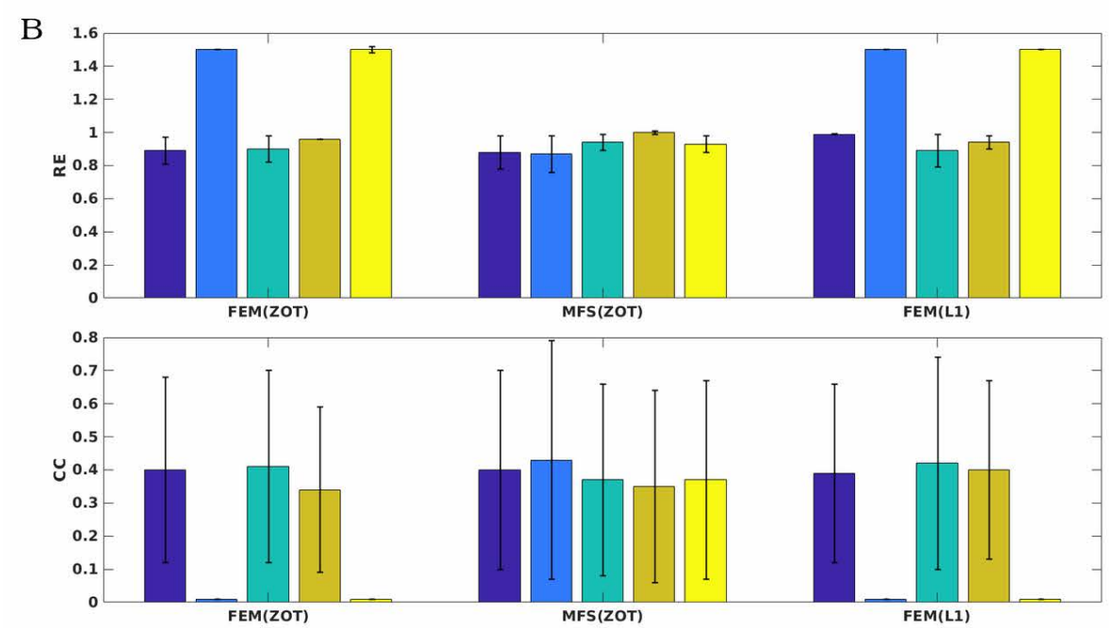
Table 1. mean errors and standard deviations of localization of pacing sites for the 2 paced rhythms RV,LV using the 3 numerical methods MFS-ZOT, FEM-ZOT and FEM-L1 combined with the regularization parameter choice methods. For BiV, values are the geodesic distances (LV/RV). N.A means that one could not extract the pacing site from the reconstructed signals.

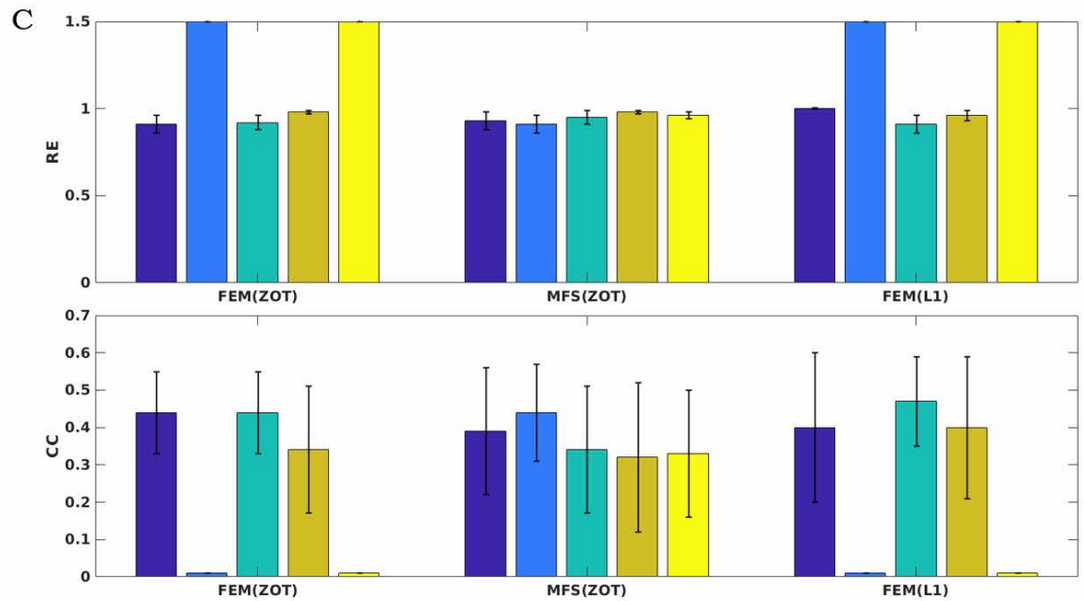
ECGI inverse problem: Evaluation

Evaluation results

- Relative Errors and Correlation coefficients







- Relative Errors are too high
- It is not the case with simulated data
- Two possible causes:
  - ★ Too much noisy data
  - ★ Limitation of the transfer function

ECGI inverse problem: Evaluation

- **Challenge for the next two years**
  - Understand the origin of the high error in the reconstructed signals
  - Use a personalized heterogeneous torso
  - Laplace equation model in the torso domain may be revised
  - Test more other methods once the forward problem of the ECGI is validated
  - Design with the experimentalists different protocols to evaluate the forward problem
  - Use the dynamic model to construct a time coherent electrical map
    - Volume sources would be considered
    - Many macroscopic and microscopic parameters have to be estimated
    - Link with the parameter identification problem: analysis and numerics.
  - Once validated: test methods on clinical data