Modeling variability in cardiac electrophysiology

GDR Mamovi, Lyon
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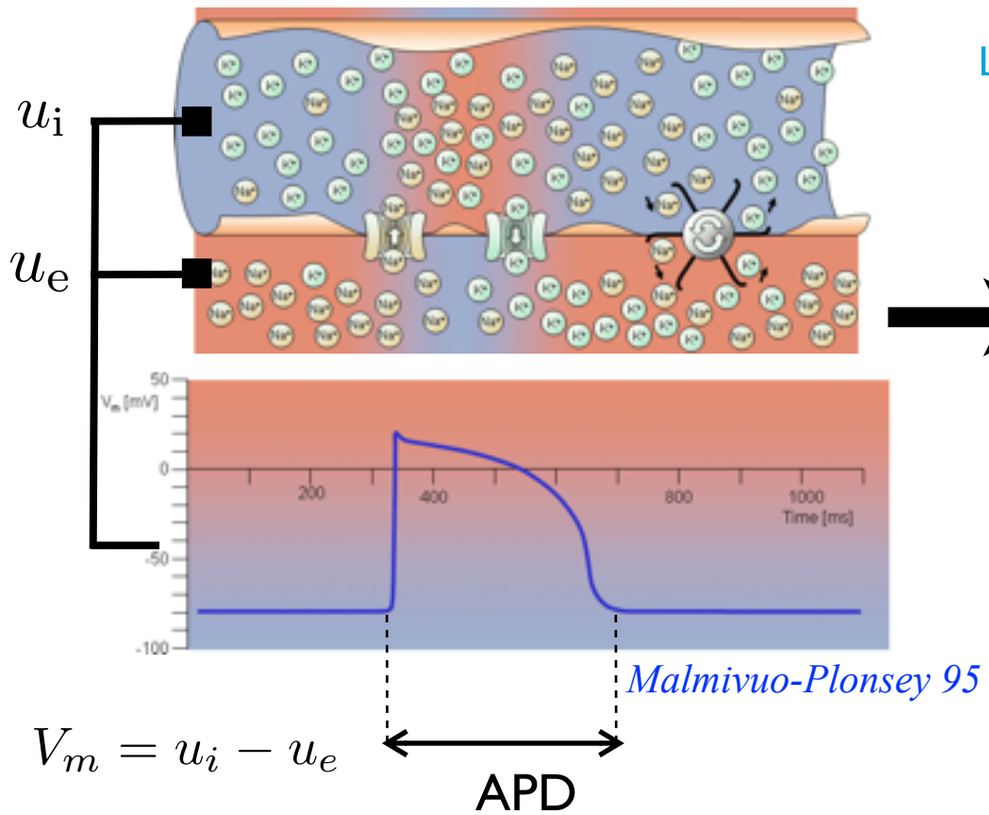
Electrocardiograms

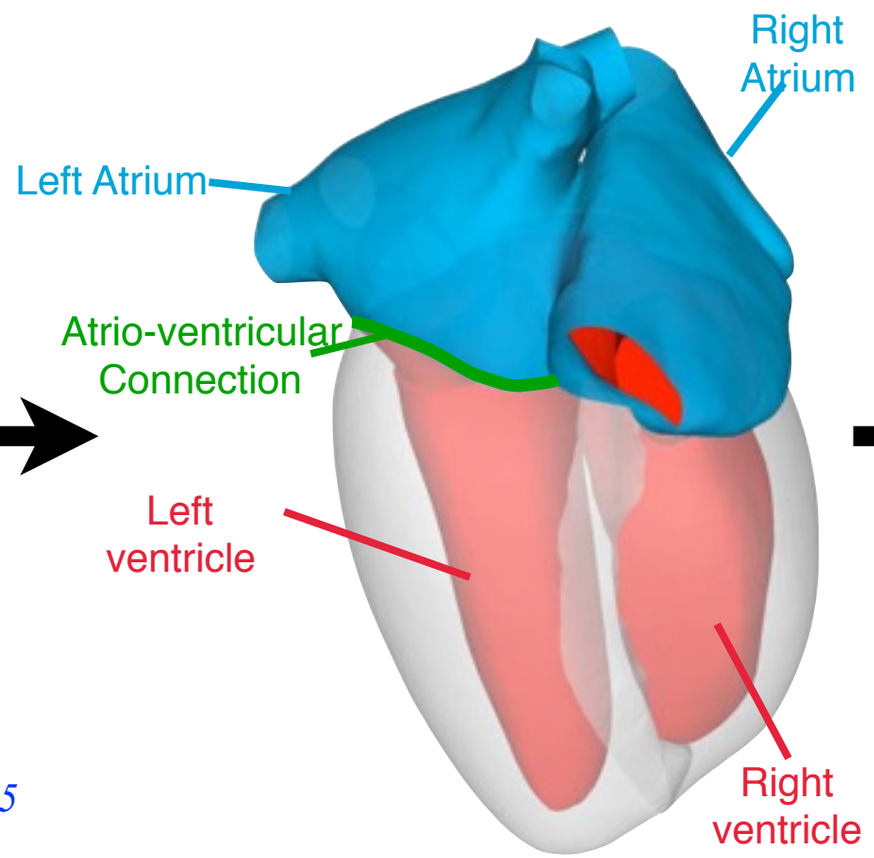
Cell scale:
Hodgkin-Huxley-like models



Malmivuo-Plonsey 95

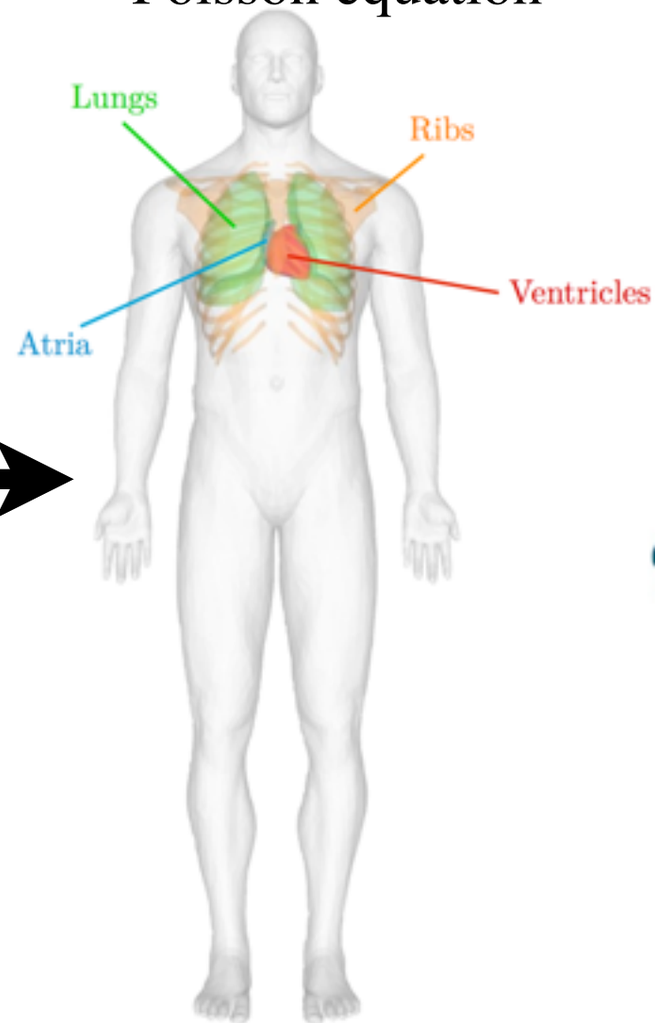
$$\begin{cases} C_{\mathrm{m}} \dfrac{\mathrm{d}V_{\mathrm{m}}}{\mathrm{d}t} + I_{\mathrm{ion}}(V_{\mathrm{m}}, \boldsymbol{g}) = 0 \\ \dfrac{\mathrm{d}\boldsymbol{g}}{\mathrm{d}t} + G(V_{\mathrm{m}}, \boldsymbol{g}) = \boldsymbol{0} \end{cases}$$

Myocardium:
bidomain models



$$\begin{cases} A_{\mathrm{m}} \left(C_{\mathrm{m}} \dfrac{\partial V_{\mathrm{m}}}{\partial t} + I_{\mathrm{ion}}(V_{\mathrm{m}}, \boldsymbol{g}) \right) - \mathrm{div}(\boldsymbol{\sigma}_{\mathrm{i}} \boldsymbol{\nabla} u_{\mathrm{i}}) = A_{\mathrm{m}} I_{\mathrm{app}}, \\ \mathrm{div}(\boldsymbol{\sigma}_{\mathrm{e}} \boldsymbol{\nabla} u_{\mathrm{e}}) + \mathrm{div}(\boldsymbol{\sigma}_{\mathrm{i}} \boldsymbol{\nabla} u_{\mathrm{i}}) = 0 \\ \dfrac{\partial \boldsymbol{g}}{\partial t} + G(V_{\mathrm{m}}, \boldsymbol{g}) = 0, \end{cases}$$

Torso:
Poisson equation

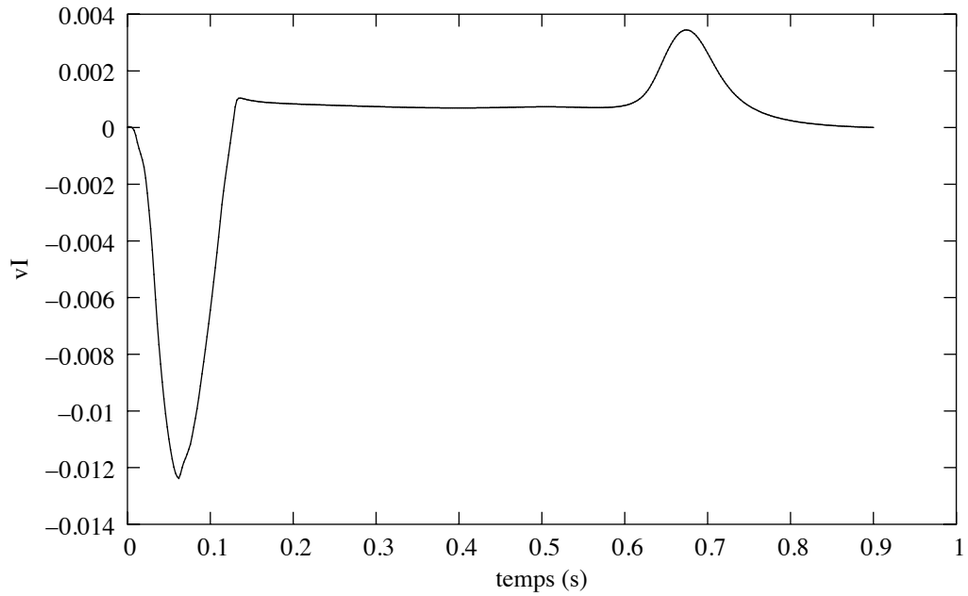


$$\begin{cases} \mathrm{div}(\boldsymbol{\sigma}_{\mathrm{T}} \boldsymbol{\nabla} u_{\mathrm{T}}) = 0 \\ \quad + \textit{transmission condition} \\ \quad \textit{on the epicardium} \end{cases}$$

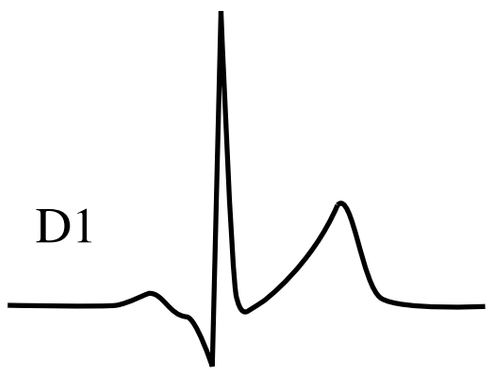
e.g.: Pullan et al. 05, Sundes et al. 06,...

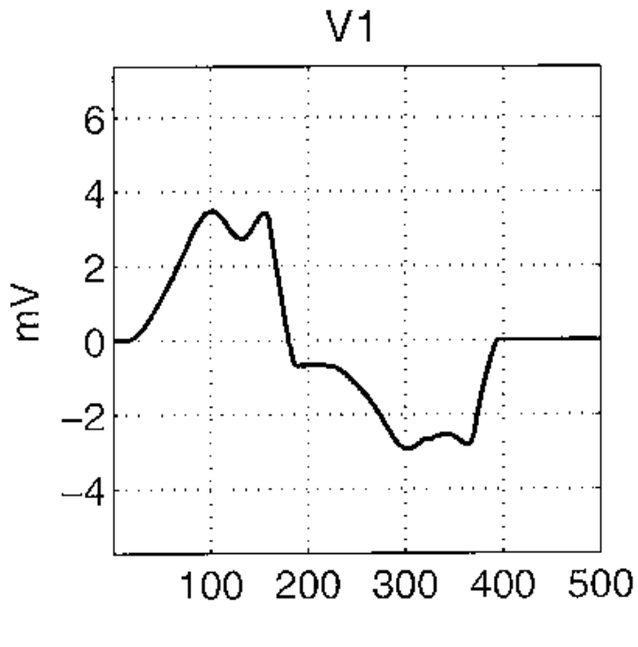
Boulakia, Cazeau, Fernández, JFG, Zemzemi, *Annals Biomed Engng 2010*

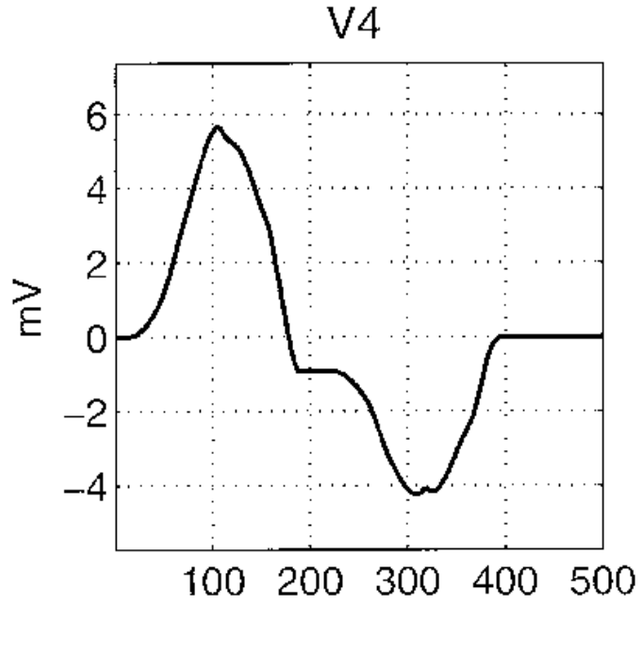
First results…



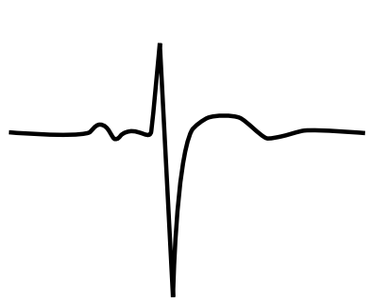
In 2007...



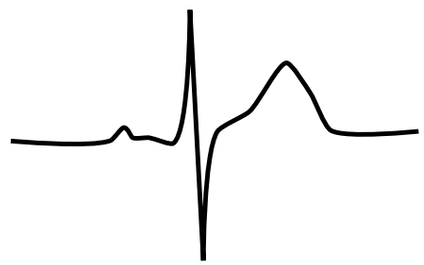




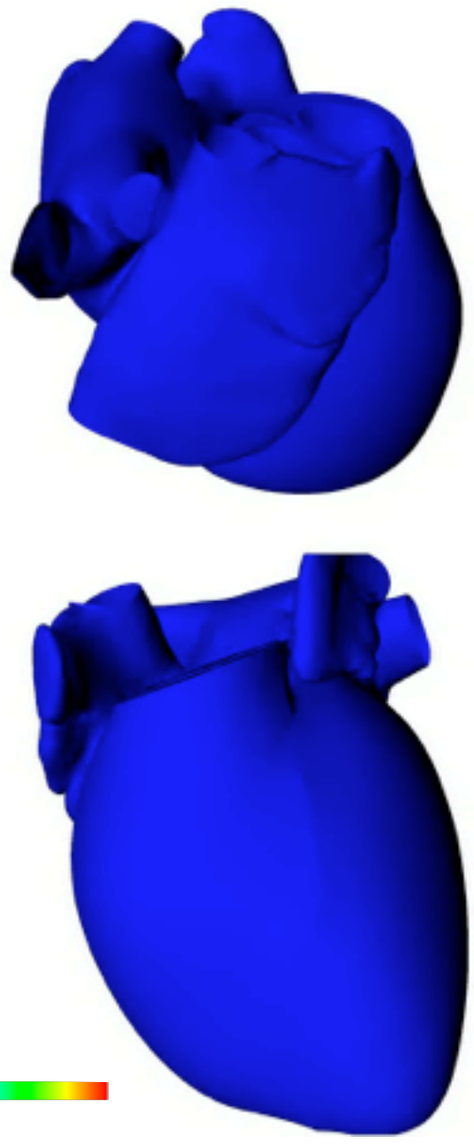
(Sundnes et al., Springer 2006)



V1



V4



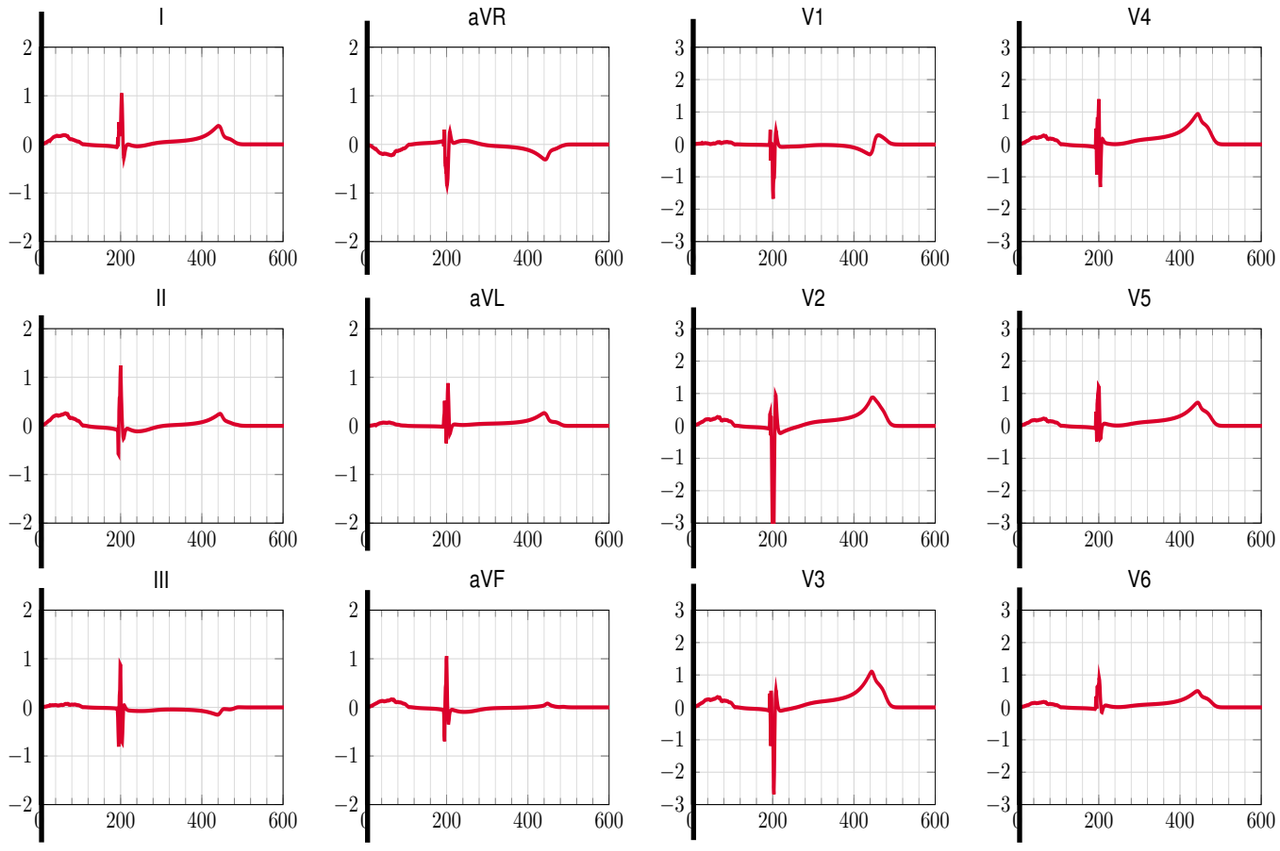
Body
Potential u_T (mV)

-1.0 0.0

Transmembrane
Potential V_m (mV)

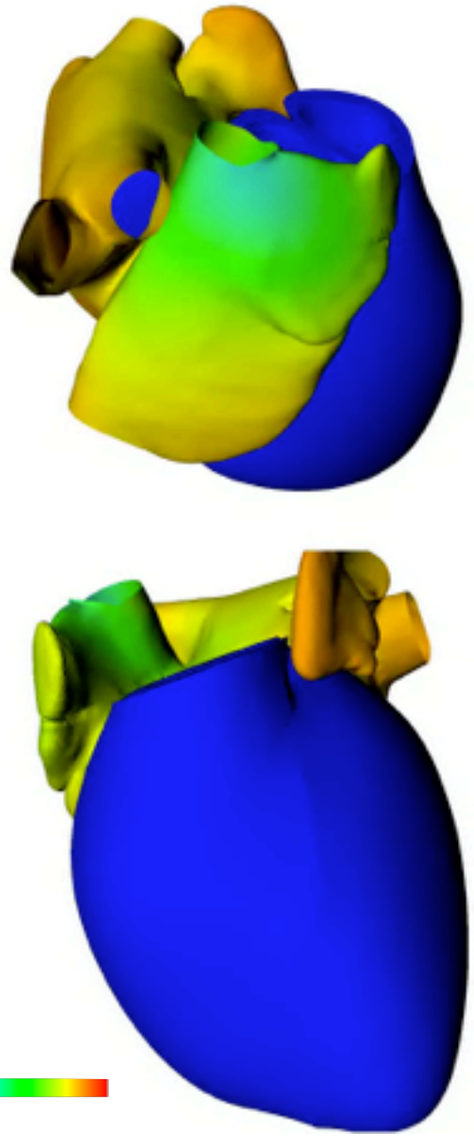
-80.0 20.0

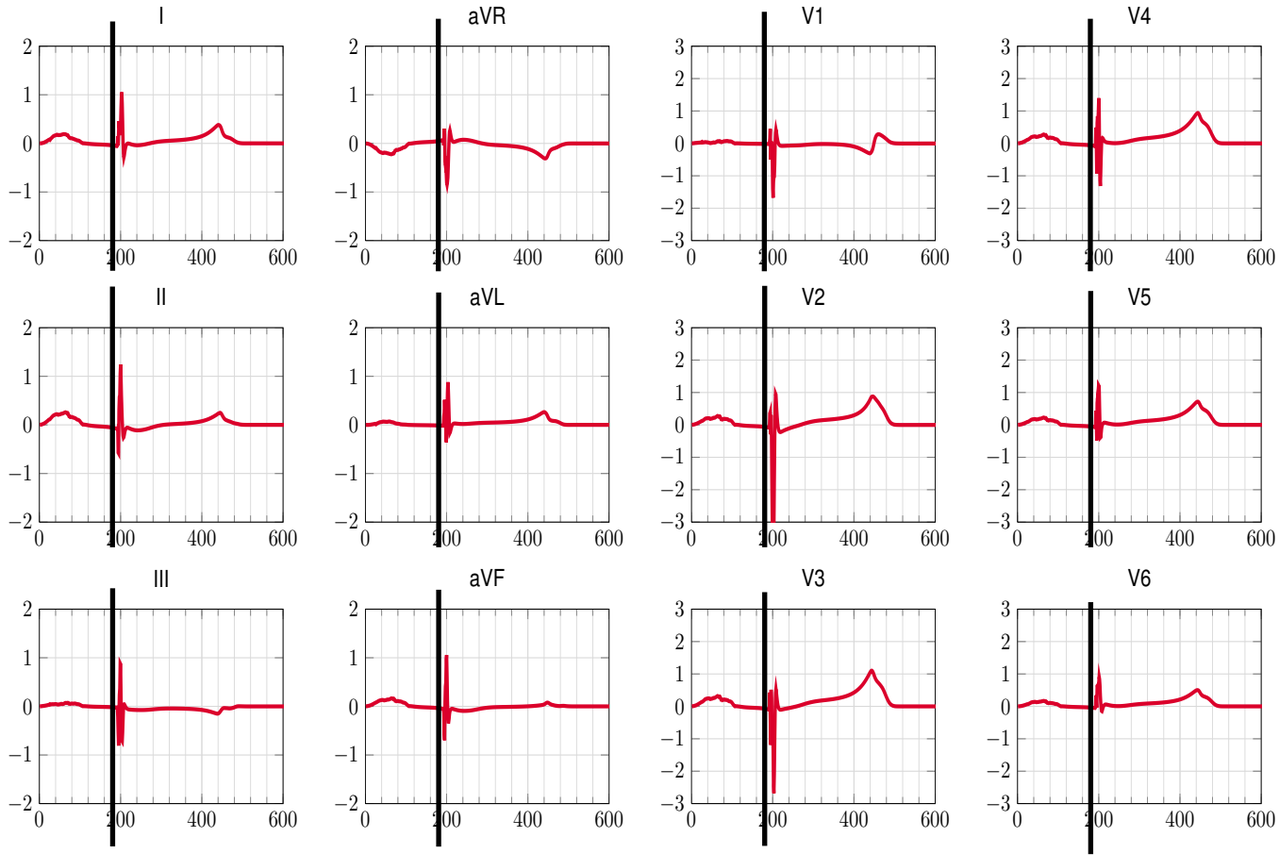
Standard 12-lead ECG



Schenone, Collin, JFG, *Int. J. Num. Meth. Biomed. Engng.*, 2016

Standard 12-lead ECG





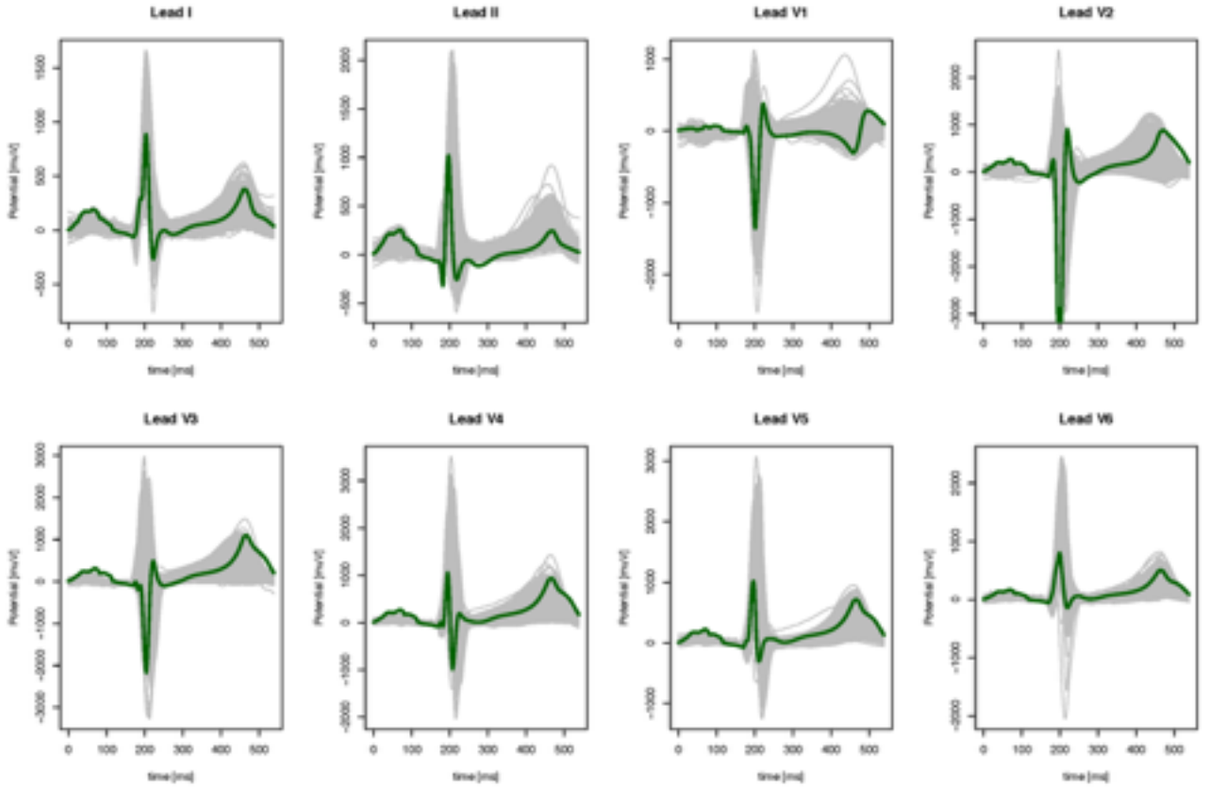
Body
Potential u_T (mV)

0.0 10.0

Transmembrane
Potential V_m (mV)

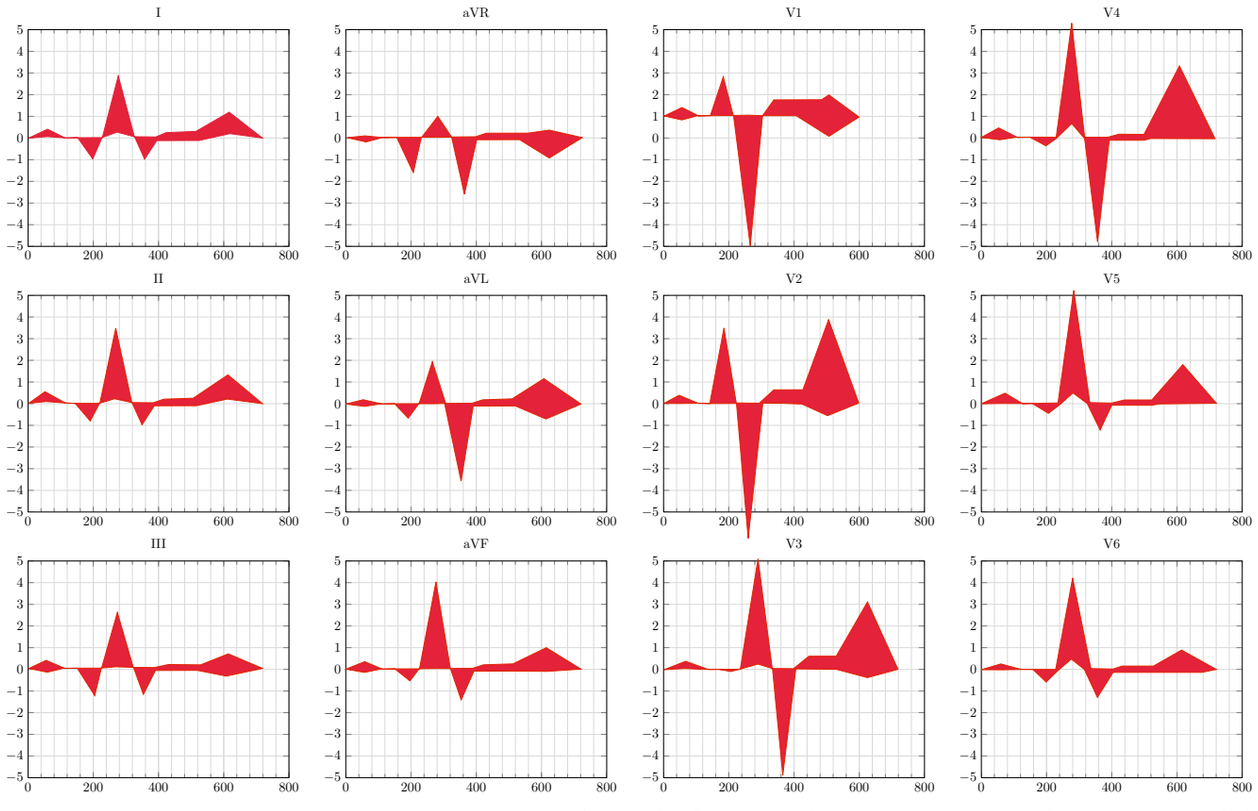
-80.0 20.0

Schenone, Collin, JFG, *Int. J. Num. Meth. Biomed. Engng.*, 2016

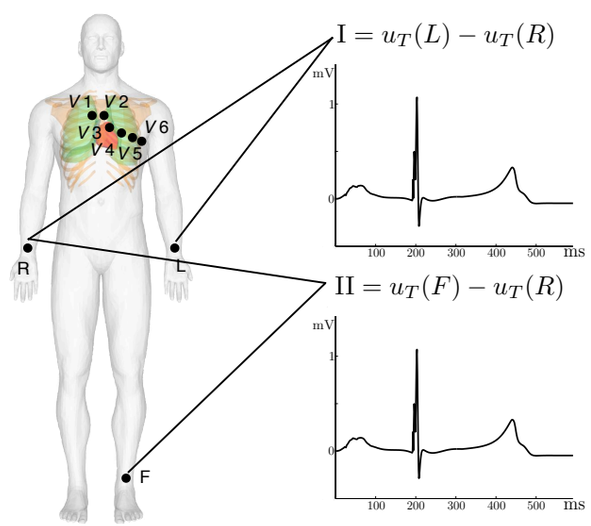


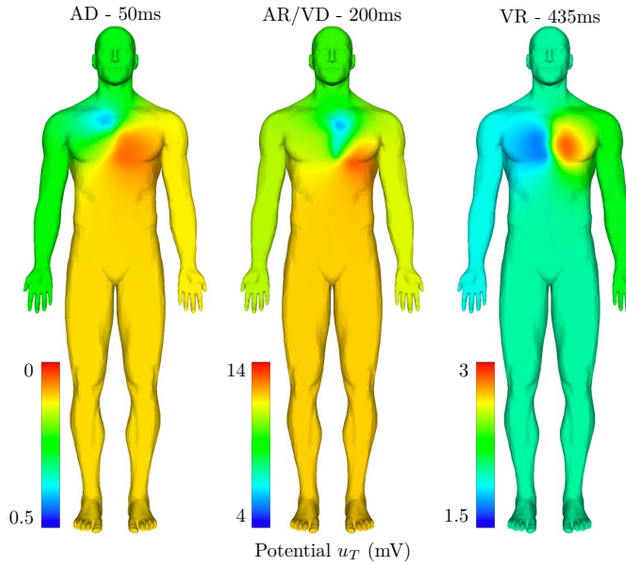
ECG Simulation

N.Tarabelloni, A.M.Paganoni & F.Ieva (Politecnico di Milano)



"normal ECGs" (from Joseph Wartak)





	P wave	PR interval	Q wave	QR interval	S wave	QRS interval	QT interval
Typical ECG	< 0.12	0.12 to 0.21	< 0.04	< 0.03 V1-V2 < 0.05 V5-V6	< 0.04	< 0.10	0.35 to 0.45
Healthy Simul.	0.08	0.19	0.015	0.015 V1-V2 0.02 V5-V6	0.01	0.04	0.29

Wave/Interval	Description	Simulated ECG
P wave	≤ 0.25mV	✓ 0.2mV
	positive I, II, V3 to V6	✓
	negative aVR	✓
Q wave	limb leads $\leq 25\%$ of R	✓
	precordial leads $\leq 15\%$ of R	✓
	always negative	✓ except for aVL
R wave	limb leads ≤ 2mV	✓
	precordial leads ≤ 3mV	✓
	always positive, negative in aVR	✓
	R wave progression, see Figure 12	✓
S wave	always negative	✓
	small I, II, V5, V6	✓
	important V1 to V3	✓
ST interval	-0.05mV to 0.1mV	✓
	isoelectric	✓
	displacement of 0.02mV in V1, V3	✓
T wave	positive I, II, V3 to V6	✓
	negative aVR (follow the QRS)	✓

Variability modeling

Our goal:

- Given measurements in a population of individuals
- Infer a probability density function (pdf) for some parameters

Standard approaches:

- Solve an inverse problem for each individual separately
- Population approach:
  - consider all the individuals together
  - look for average population parameters, standard deviation, …

E Kuhn, M Lavielle, "Maximum likelihood estimation in nonlinear mixed effects models", Comp Stat Data Analysis, 2005.

E Grenier, V Louvet, P Vigneaux, "Parameter estimation in non-linear mixed effects models with SAEM alrogithm: extension from ODE to PDE", M2AN, 2013.

Variability modeling

Our wishes:

- Non-intrusive: black box algorithm
- Non-parametric: no assumption on the distribution
- Moderate number of model evaluations

Our approach:

- Match the *moments* of the "*observables*" and of the measurements

Variability modeling: moments matching

- Hausdorff moment problem:
  - find a distribution given its moments

$$m_j = \int_\Theta \theta^j \rho(\theta)\, d\theta$$

  - in general, an ill-posed problem

- Regularization: **Maximum Entropy Principle** (Jaynes, 1957)
  - Maximises the Shanon entropy:

$$S(\rho) = -\int_\Theta \rho(\theta) \log(\rho(\theta))\, d\theta$$

Under the constraints defined by the available information

Examples

- Information:
  - X a random variable with values in $[a, b]$

  Maximum Entropy Principle $\Longrightarrow$ ρ is a uniform pdf on $[a, b]$

- Information:
  - X a random variable with values in $\mathbb{R}_+^*$
  - $\mathbb{E}(X) < +\infty$ given
  - $\mathbb{E}(\log(X)) < +\infty$ given.

  Maximum Entropy Principle $\Longrightarrow$ ρ is a Gamma pdf

- Information:
  - X a random variable with values in $\mathbb{R}$
  - $\mathbb{E}(X) < +\infty$ given
  - $\mathbb{E}(X^2) < +\infty$ given

  Maximum Entropy Principle $\Longrightarrow$ ρ is a Gaussian pdf

Variability modeling: moments matching

- Moment of the parameters are not available
- But empirical moments of measurable quantities can be computed:

$$\hat{\mu}_m(\mathbf{x}_j) = \frac{1}{N}\sum_{i=1}^{N} y_i(\mathbf{x}_j)^m, \qquad m = 1, \ldots, n_{mom}$$

measurements at $\mathbf{x}_j$, $j = 1 \ldots N_{\mathbf{x}}$

$\mathbf{x} = (x, t) \in \mathcal{D}$ (space-time physical domain)

- Assume that p parameters explain the variability: $\boldsymbol{\theta} = (\theta_1, \ldots, \theta_p)$
- Simulated moments:

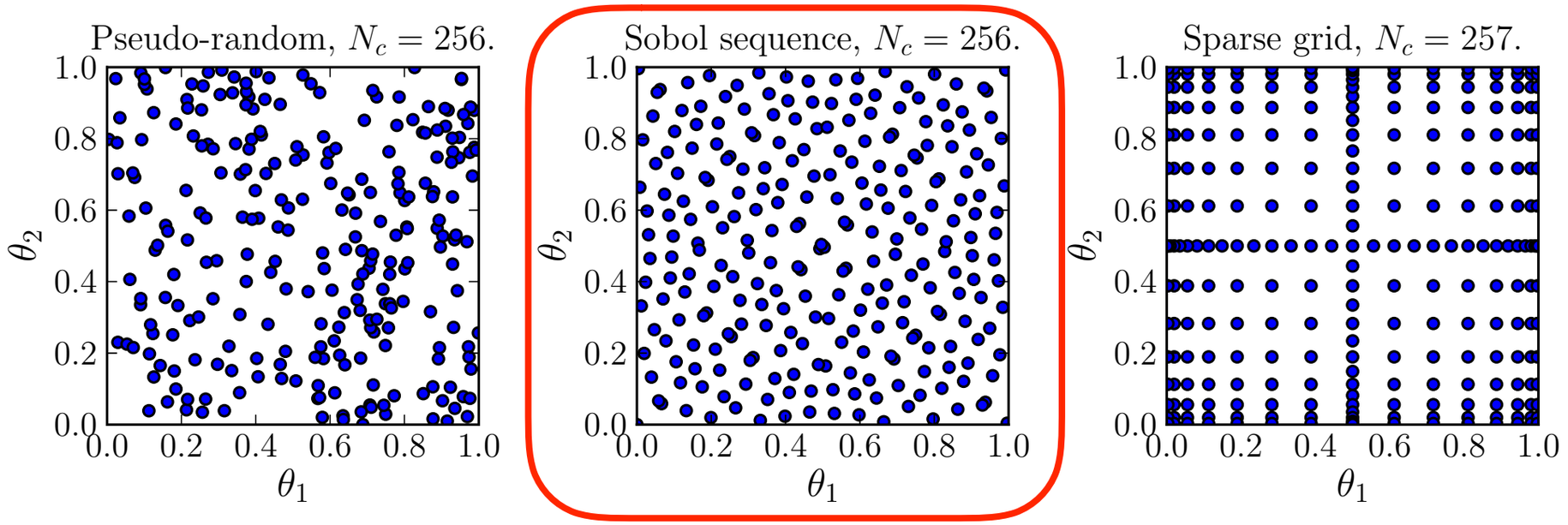
$$\mu_m^{\rho}(\mathbf{x}_j) = \int_{\Theta} \rho(\boldsymbol{\theta}) g(\mathbf{x}_j, \boldsymbol{\theta})^m \mathrm{d}\boldsymbol{\theta}$$

unknown pdf

model outputs
("observables")

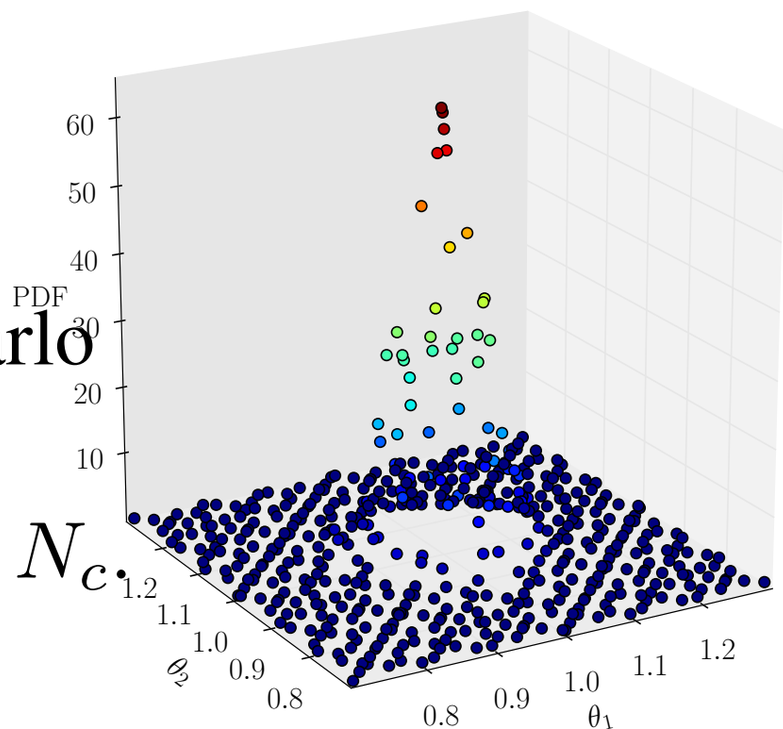
Observable Moments Matching

- Sampling: $\boldsymbol{\theta}_i \in \Theta,\ i = 1, \ldots, N_c$



$\longrightarrow$ Sobol sequence in the parameter space.

- The model is evaluated on each $\boldsymbol{\theta}_i$ *(off-line)*
- Integrals over Θ approximated by quasi-Monte-Carlo
- We look for an approximation of $\rho(\theta_i),\ i = 1, \ldots, N_c$.



Observable Moments Matching

- Maximize the entropy $S(\rho) = -\int_\Theta \rho \log(\rho)$ under the constraints

$$c_\rho(\mathbf{x}_j, m) = \mu_m^\rho(\mathbf{x}_j, m) - \hat{\mu}_m(\mathbf{x}_j, m) = 0, \text{ for } N_k \text{ points } \mathbf{x}_j \in \mathcal{D}$$

- Saddle-point problem: $\inf_\rho \sup_{\lambda, \lambda_0, \nu \geq 0} \mathcal{L}(\rho, \lambda, \lambda_0, \nu)$

$$\mathcal{L}(\rho, \lambda, \nu) = \underbrace{\int_\Theta \rho \log(\rho)}_{-S(\rho)} - \sum_{j=1}^{N_\mathbf{k}} \sum_{m=1}^{n_{mom}} \lambda(\mathbf{x}_j, m) \underbrace{c_\rho(\mathbf{x}_j, m)}_{\text{mom. cons.}} - \lambda_0 \underbrace{\left(\int_\Theta \rho - 1 \right)}_{\text{normalization}} - \underbrace{\cancel{\int_\Theta \rho\nu}}_{\cancel{\text{positivity}}}.$$

- "Inf" step done analytically. Positivity constraint automatically verified
- "Sup" step done numerically using quasi-Newton method
- Dense linear system of size $(N_k n_{mom}) \times (N_k n_{mom})$

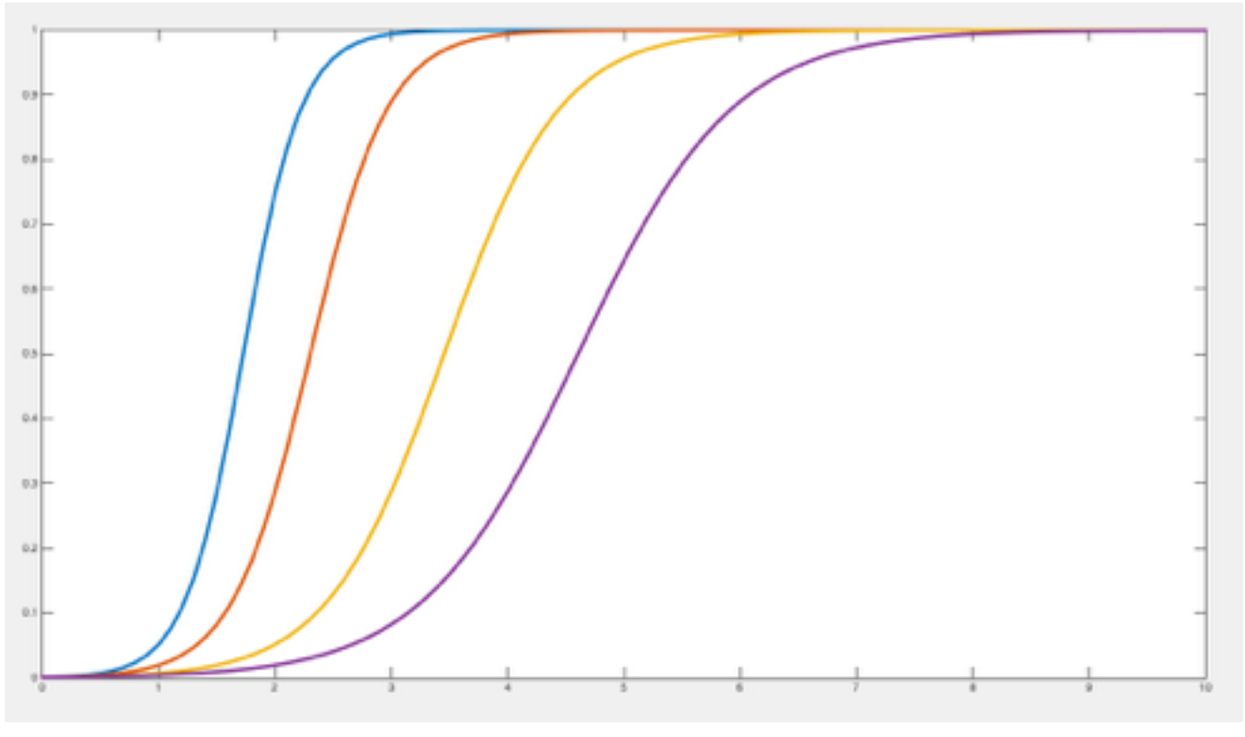
Selection of physical points: sensitivity

Issue

- Too many points in the physical space
- Many points are redundant: big and ill-conditioned problem

Illustrative example

- Logistic equation $\dfrac{du}{dt} = k\,u(1-u)$ for different values of k



Selection of physical points: sensitivity

Strategy

- Quantify how the parameters affect the variability at a given $\mathbf{x}_j$.
- Sensitivity Gramm matrix, using the model outputs:

$$\mathbf{C}(\mathbf{x}_j) = \int_{\Theta} \left[\nabla_{\boldsymbol{\theta}} g(\mathbf{x}_j, \boldsymbol{\theta})\right] \left[\nabla_{\boldsymbol{\theta}} g(\mathbf{x}_j, \boldsymbol{\theta})\right]^T \rho(\boldsymbol{\theta}) d\boldsymbol{\theta}$$

estimated *off-line*

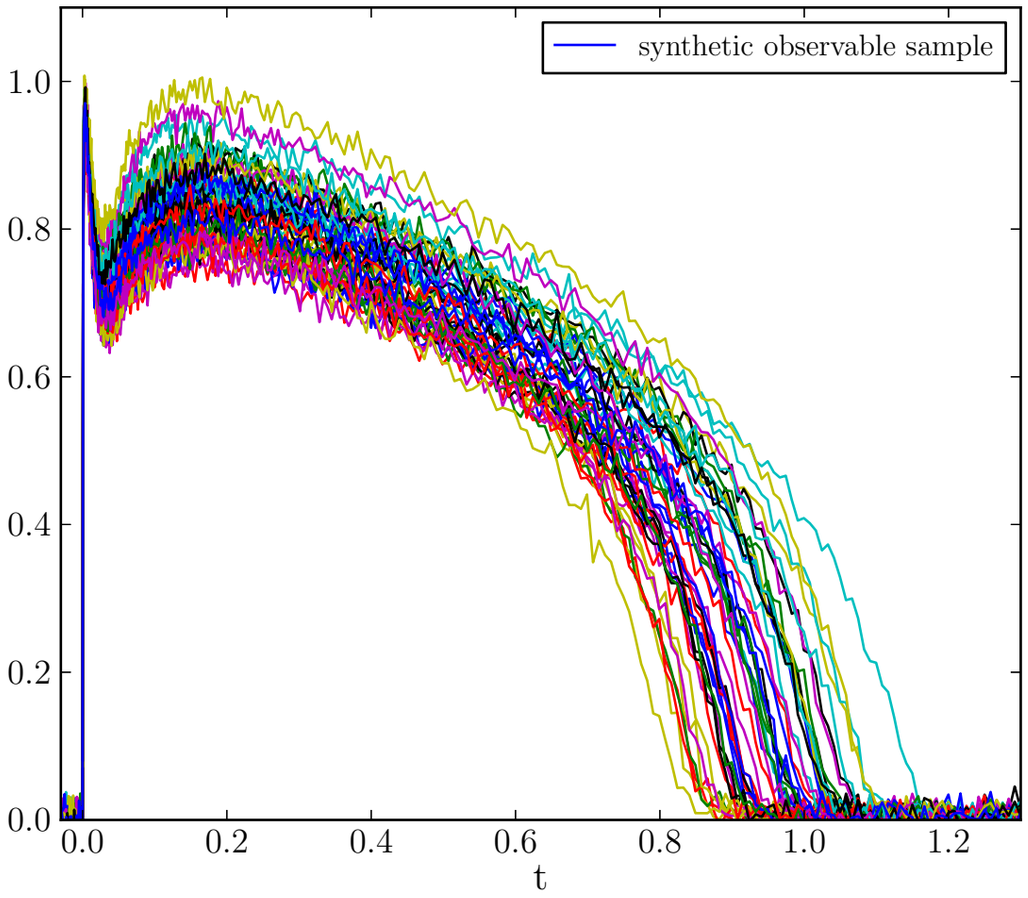
start with a guess
then iterate

- Eigenvalue decomposition of $\mathbf{C}(\mathbf{x}_j)$: $\lambda_{j,k}, \mathbf{e}_{j,k}$
- $\mathbf{e}_{j,1}$ = direction in Θ of maximum variation on average
- $\lambda_{j,1}$: mean-squared derivative of the observable along the direction $\mathbf{e}_{j,1}$

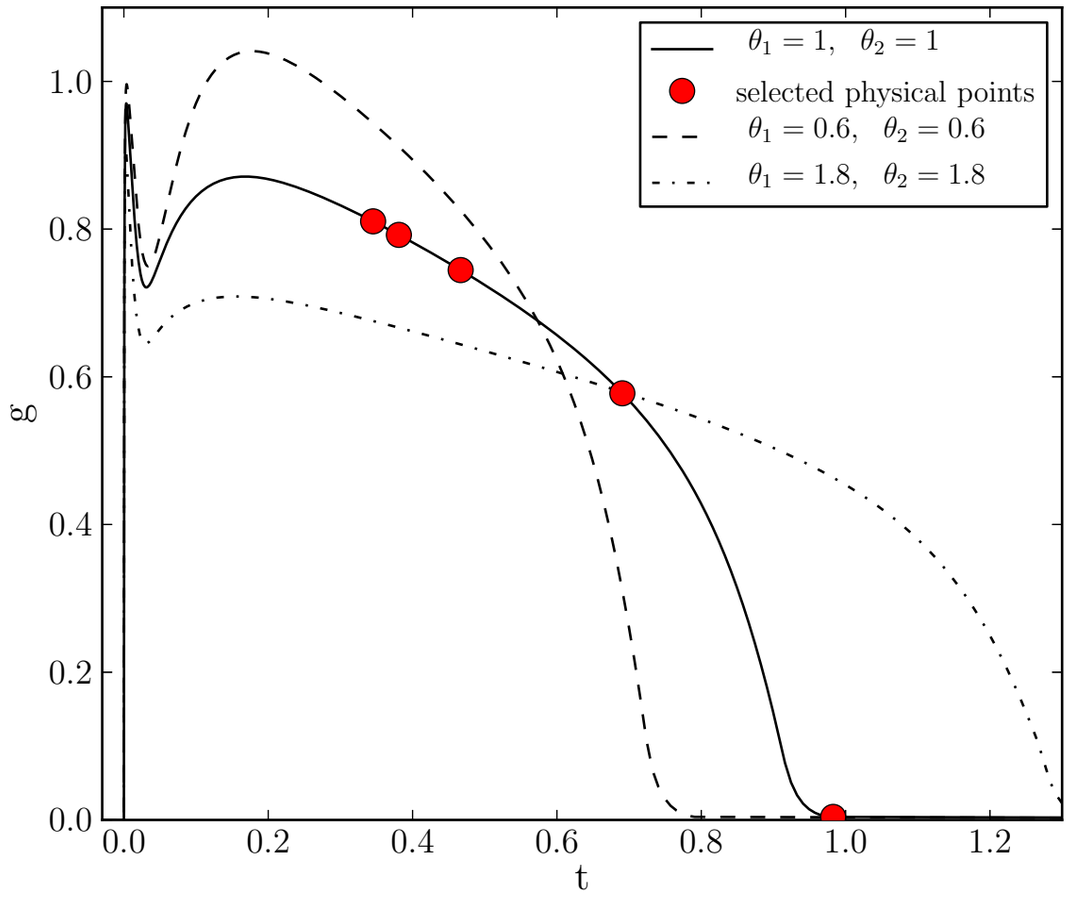
Selection of physical points: clustering

- Points with similar dominant directions are considered as redundant
- Agglomerative hierarchical **clustering algorithm**
- The $N_{\mathbf{x}}$ points of the full physical set are divided into N_k clusters
- Points with maximum trace of $\mathbf{C}(\mathbf{x}_j)$ are chosen as cluster representative
- Subset $\mathcal{S}$ where the moments are matched: the N_k representatives

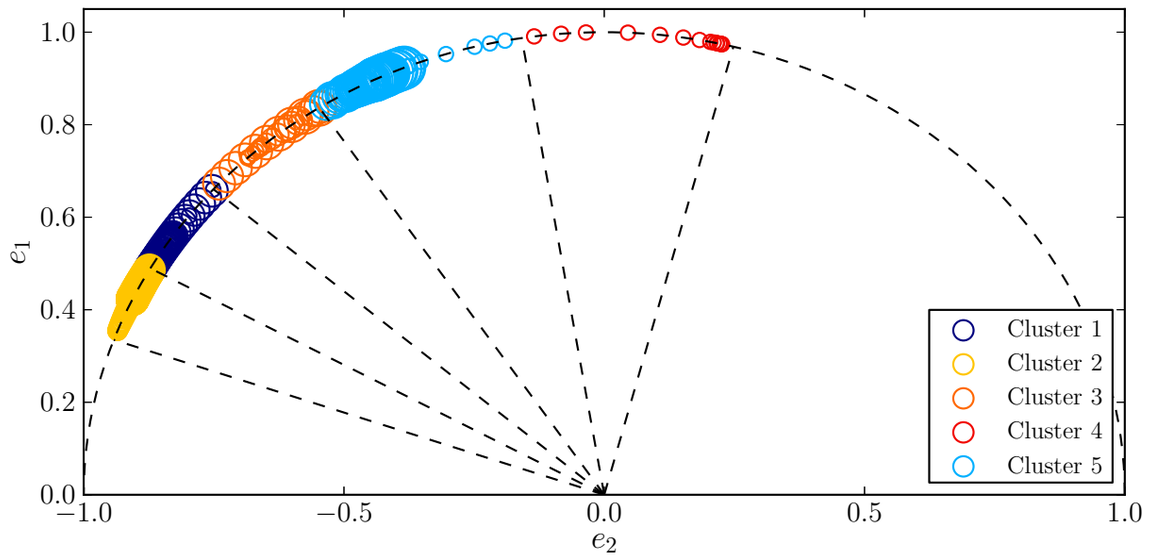
Example with an ODE



Cardiac cell Action Potential



- Two parameters θ_1, θ_2
- $N_c = 1024$ Sobol points in $[0.6, 1.8]^2$
- $N_{\mathbf{x}} = 334$ time instants, $N_k = 5$ clusters



First eigenvectors of the Sensitivity Gram Matrices at each time instants

Algorithm

- Initial guess: $\rho^{(0,0)}$ uniform density over Θ
- $j = 1$
- While $\|R(\rho^{(j-1,0)})\| \geq$ tol
  - Clustered Sensitivities with $\rho^{(j-1,0)}$
    $\Longrightarrow$ nested subsets $\mathcal{S}^k$ of k physical points
  - $n = 1$
  - While $\|R(\rho^{(j-1,n-1)})\| \geq$ tol
    - Observable Moments Matching on S^n
      $\Longrightarrow \rho^{(j-1,n)}$
    - $n \leftarrow n + 1$
  - $\rho^{(j,0)} \leftarrow \rho^{(j-1,n)}$
  - $j \leftarrow j + 1$
- $n_{iter} = j$

Remarks:

- Residual on all the N_x physical points:

$$R(\rho) = \sum_{j=1}^{N_x} \sum_{m=1}^{n_{mom}} c_\rho(\mathbf{x}_j, m)^2$$

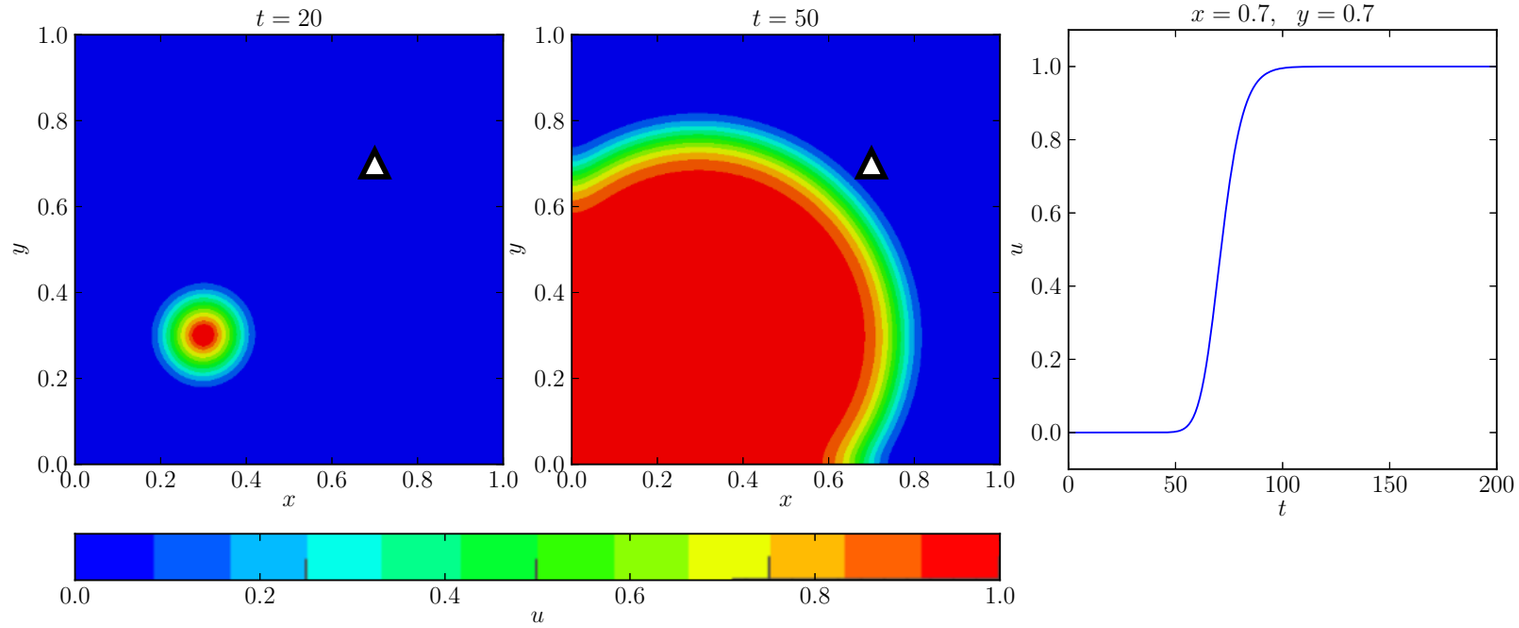
with

$$c_\rho(\mathbf{x}_j, m) = \mu_m^\rho(\mathbf{x}_j, m) - \hat{\mu}_m(\mathbf{x}_j, m)$$

- In practice $n_{iter} \approx 3$

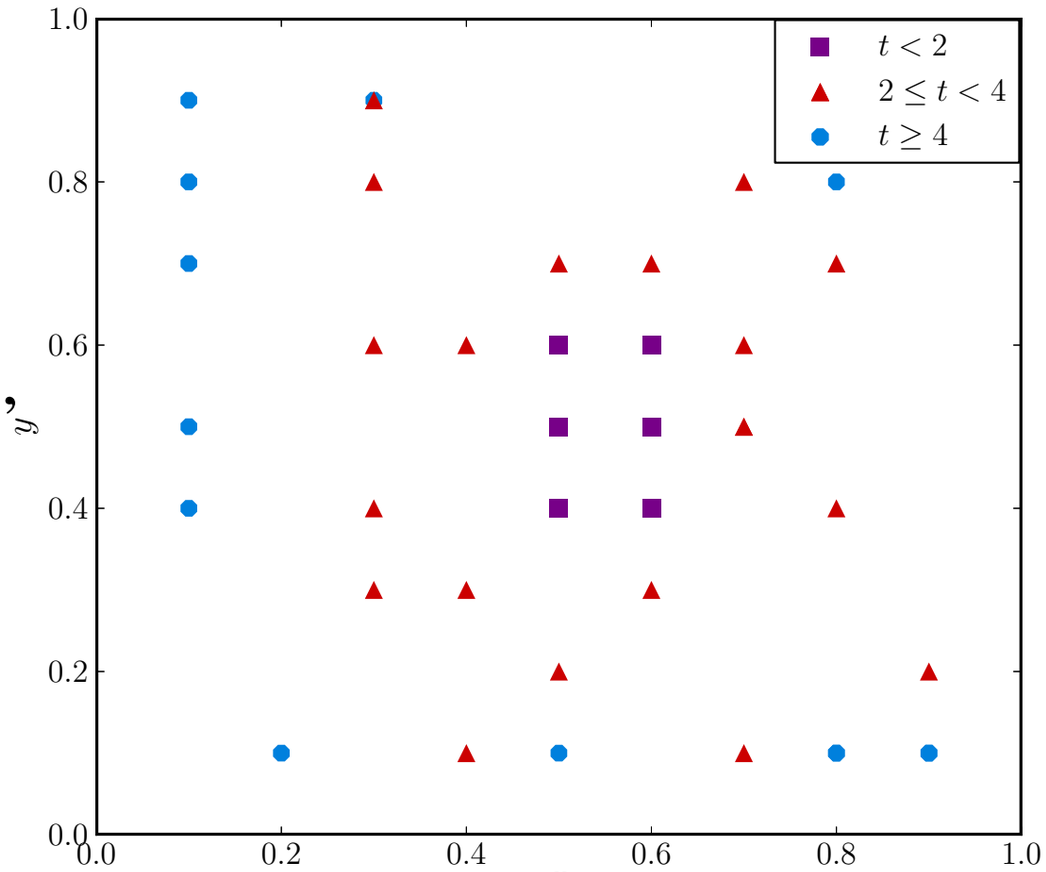
Example 1: Fisher-Kolmogorov

- Nonlinear parabolic equation: $$\frac{\partial u}{\partial t} - \underbrace{\alpha \Delta u}_{\text{diffusion}} = \underbrace{Ru(1-u)}_{\text{reaction}} + \underbrace{f(\mathbf{x}, t)}_{\text{stimulation}}$$

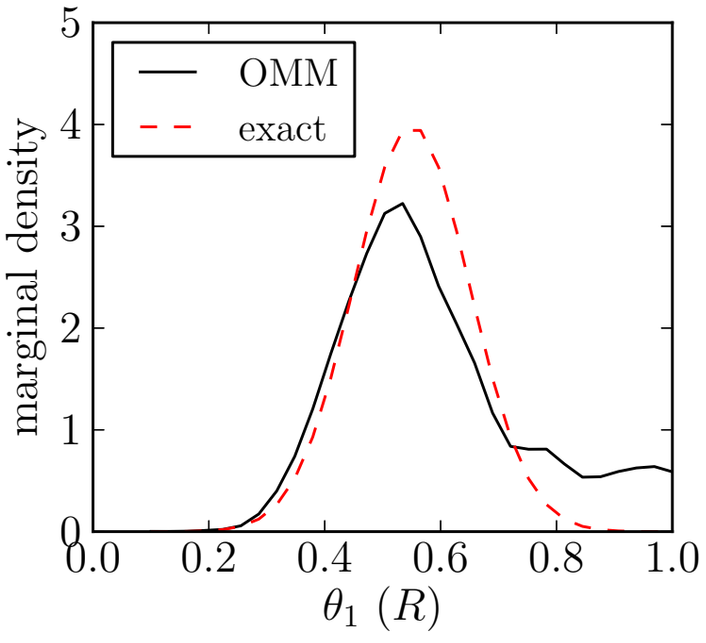


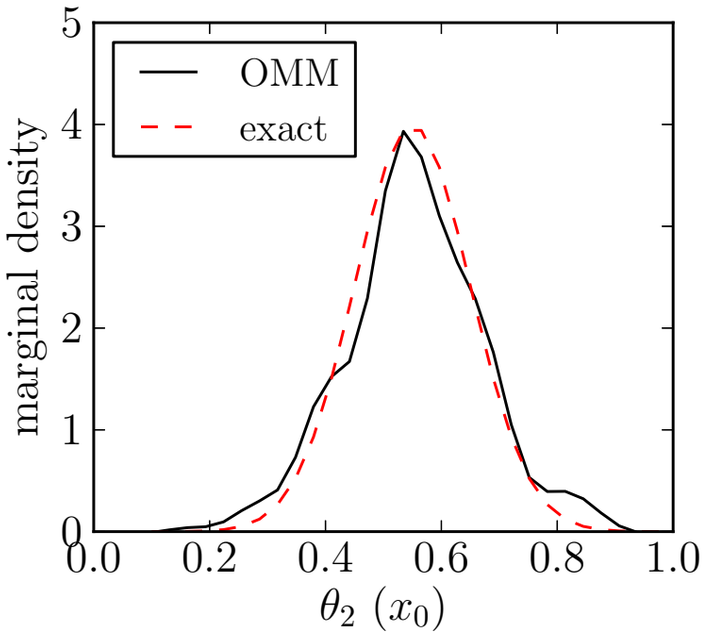
- 3 parameters responsible for variability:
  x_0, y_0 (stimulation position) and R (reaction)
- Measurements: N_x = 81 points in space $\times$ 200 time instants
- Synthetic data: 10^3 parameters sampled from a normal distribution
  $\boldsymbol{\mu} = [0.55, 0.55, 0.50]$, $\boldsymbol{\Sigma} = \sigma^2 \times \mathbf{I}_3$, with $\sigma = 0.1$
- Model evaluated for each sample + noise addition + different mesh

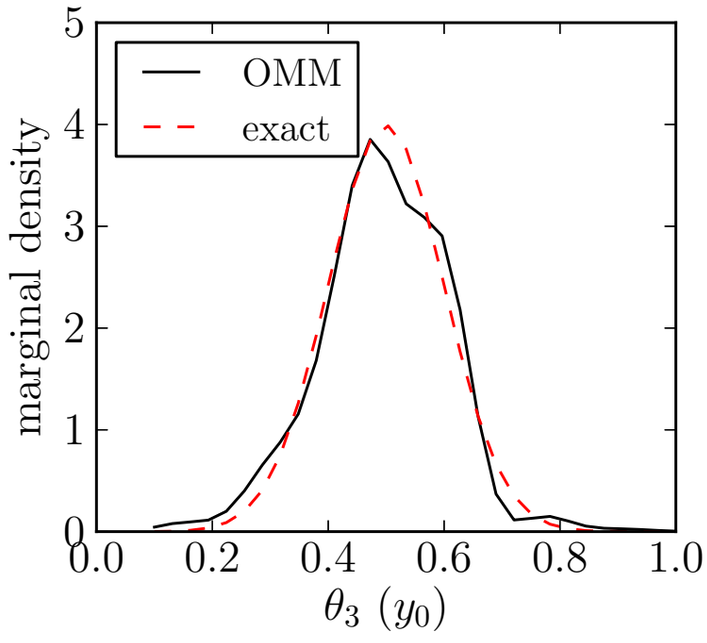
- $N_c = 2048$ Sobol points over $\Theta = [0.1, 1.0]^3$,
- $n_{mom} = 3$
- $N_k = 48$ selected space-time points
- $n_{iter} = 3$ iterations



Selected points







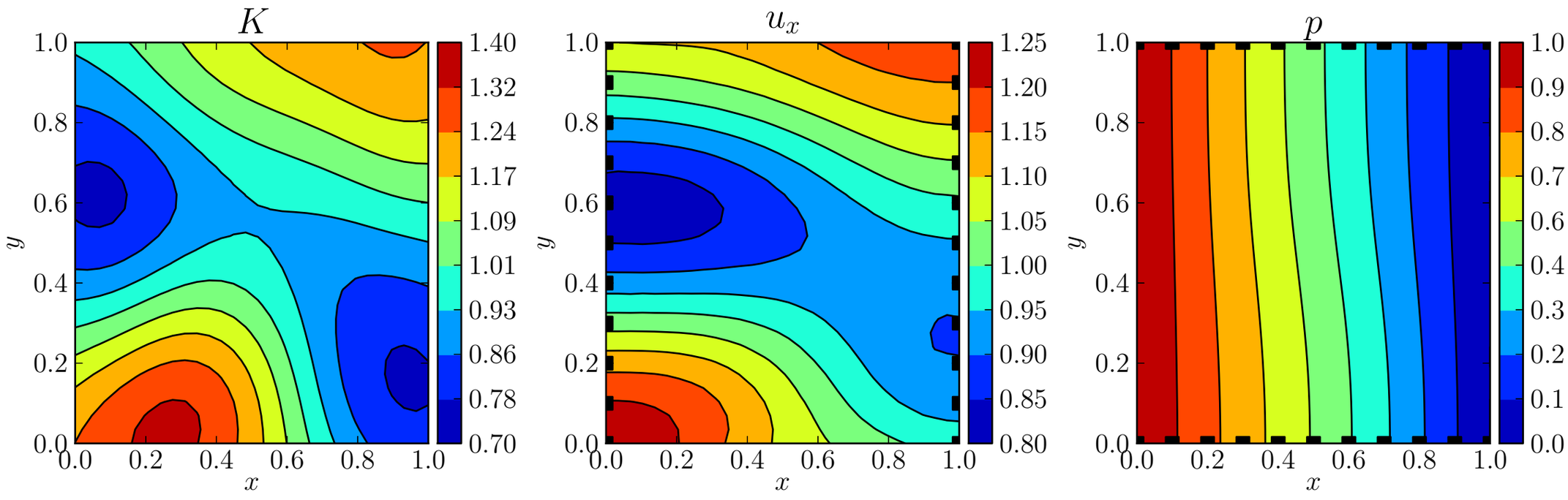
Example 2: Darcy equation

- Darcy equation:

$$\begin{cases} \mathbf{u} + K\boldsymbol{\nabla} p &= 0 \\ \operatorname{div} \mathbf{u} &= 0, \end{cases}$$

- Measurements: p and u_x on domain boundaries
- Variability: 5 coefficients θ_k defining the permeability

$$K(x,y) = 1 + \sum_{k=1}^{5} \theta_k \Psi_k(x,y)$$



- Synthetic data:

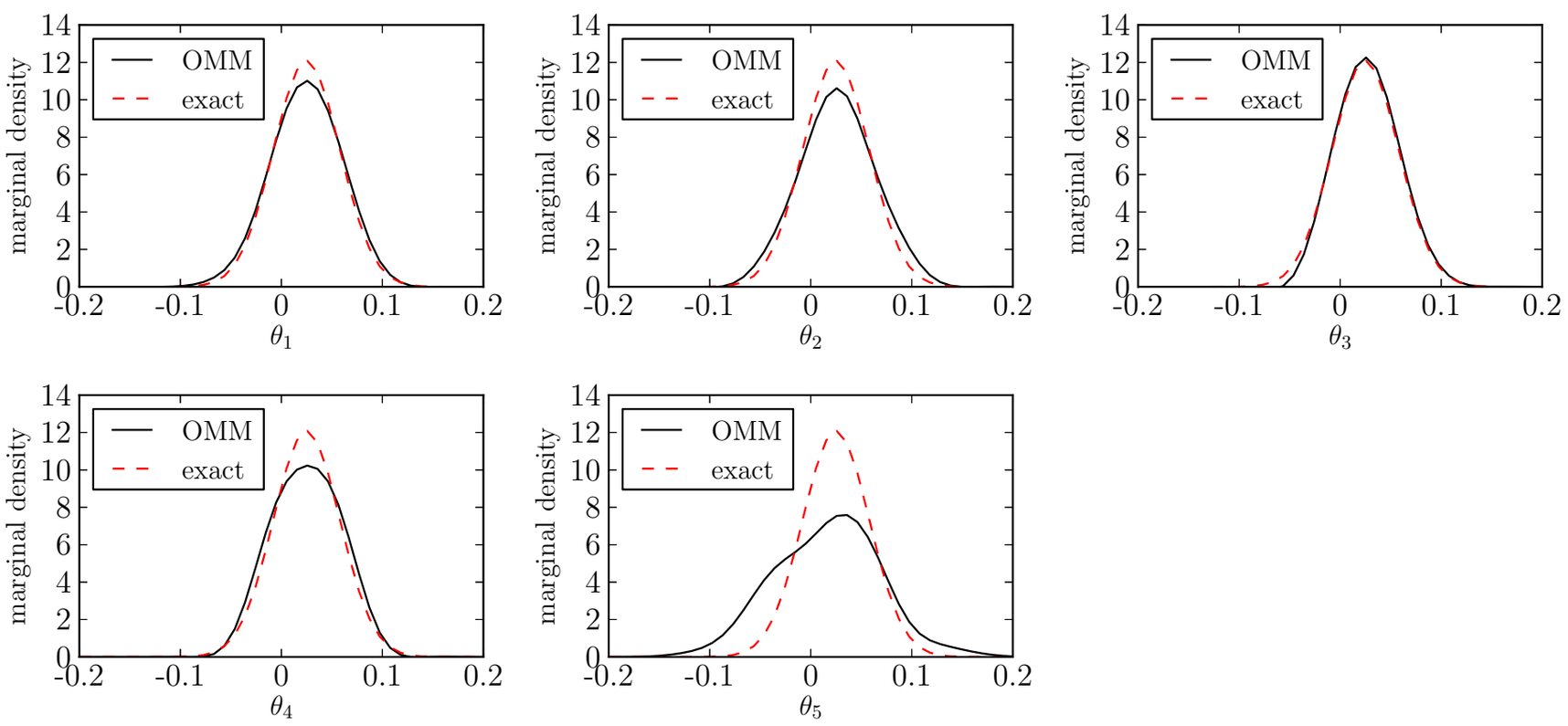
  Evaluation of the model for $N = 10^4$ samples of $\boldsymbol{\theta} = (\theta_1, \ldots, \theta_5)$.
  drawn from an uncorrelated multivariate normal distribution
  $\boldsymbol{\mu} = 2.5\ 10^{-2} \times [1, 1, 1, 1, 1]$, $\boldsymbol{\Sigma} = \sigma^2 \times \mathbf{I}_5$, $\sigma = 3.3\ 10^{-2}$.

- Moment matching algorithm:

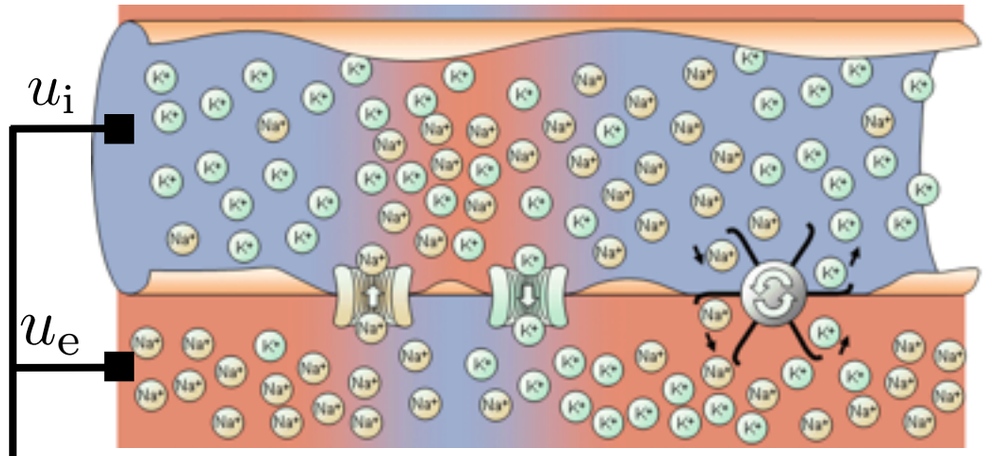
  $N_c = 16384$ Sobol points over $\Theta = [-0.2, 0.2]^5$

  $n_{mom} = 3$

25 points selected by the Clustered Sensitivities algorithm (out of 400 sensors)



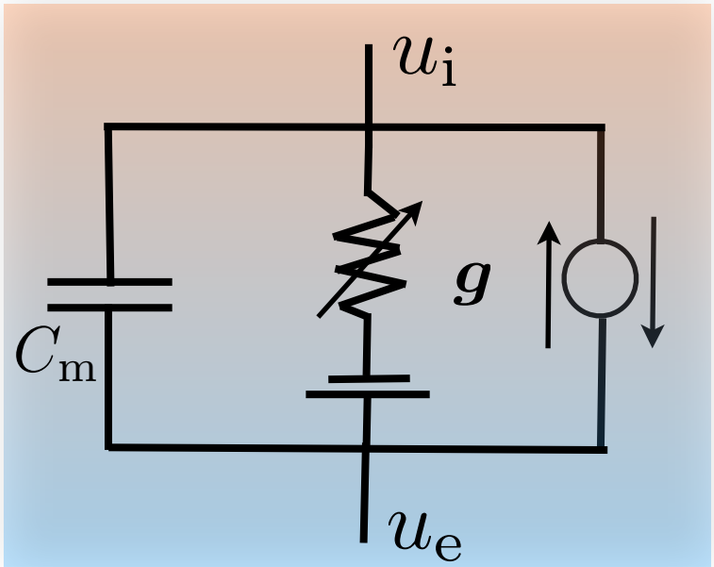
Cardiac cell model



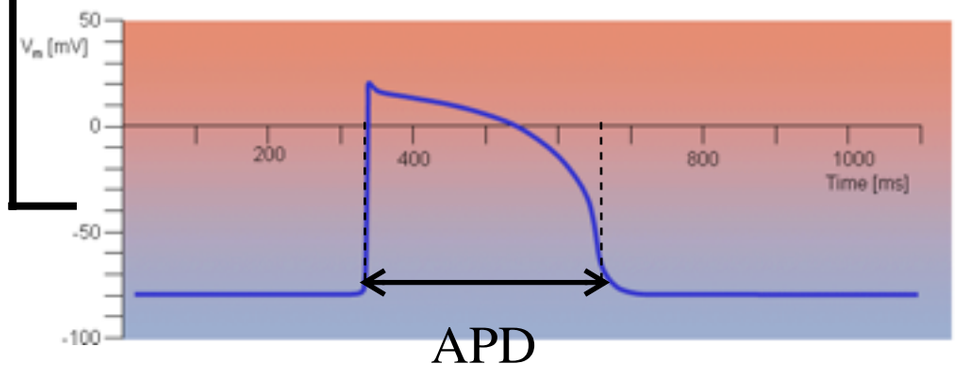
intracellular medium

membrane

extracellular medium



circuit analogy

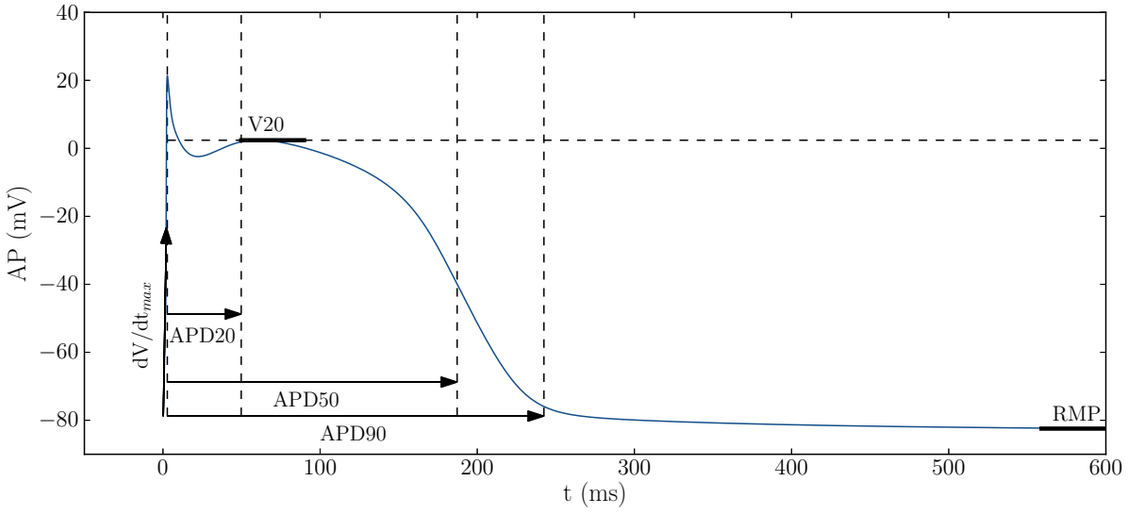


Extra-cellular potential: u_i

Extra-cellular potential: u_e

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

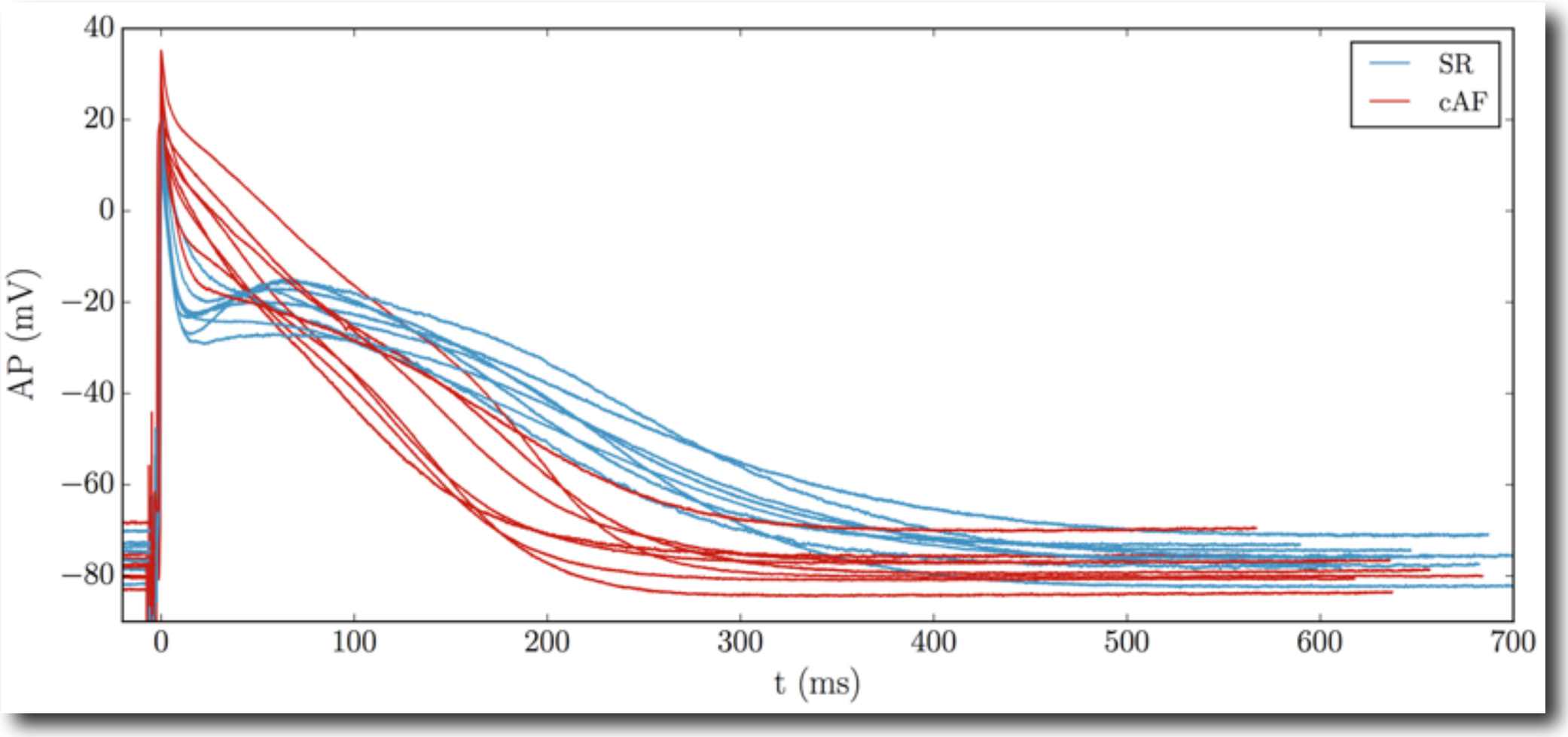
Biomarkers :



$$\begin{cases} C_\mathrm{m}\dfrac{\mathrm{d}V_\mathrm{m}}{\mathrm{d}t} + I_\mathrm{ion}(V_\mathrm{m}, \boldsymbol{g}) = 0 \\ \dfrac{\mathrm{d}\boldsymbol{g}}{\mathrm{d}t} + G(V_\mathrm{m}, \boldsymbol{g}) = \mathbf{0} \end{cases}$$

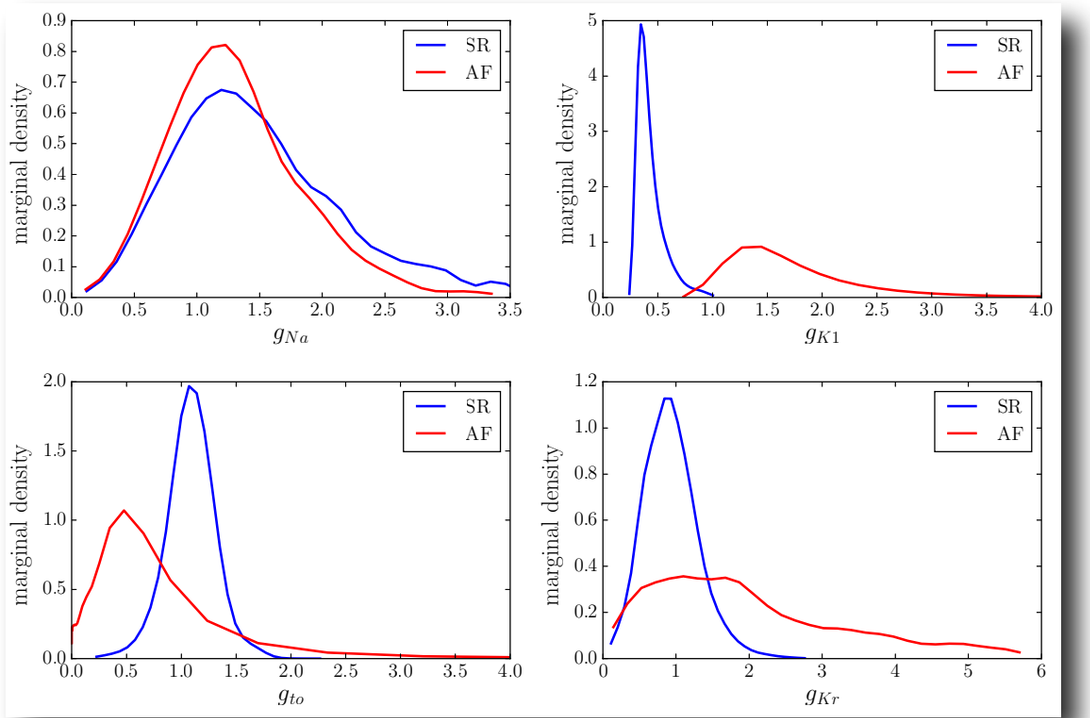
(Hodgkin-Huxley 52, Cronin 81, Pullan et al. 05, Sundes et al. 06,...)

Example 3: atrial fibrillation

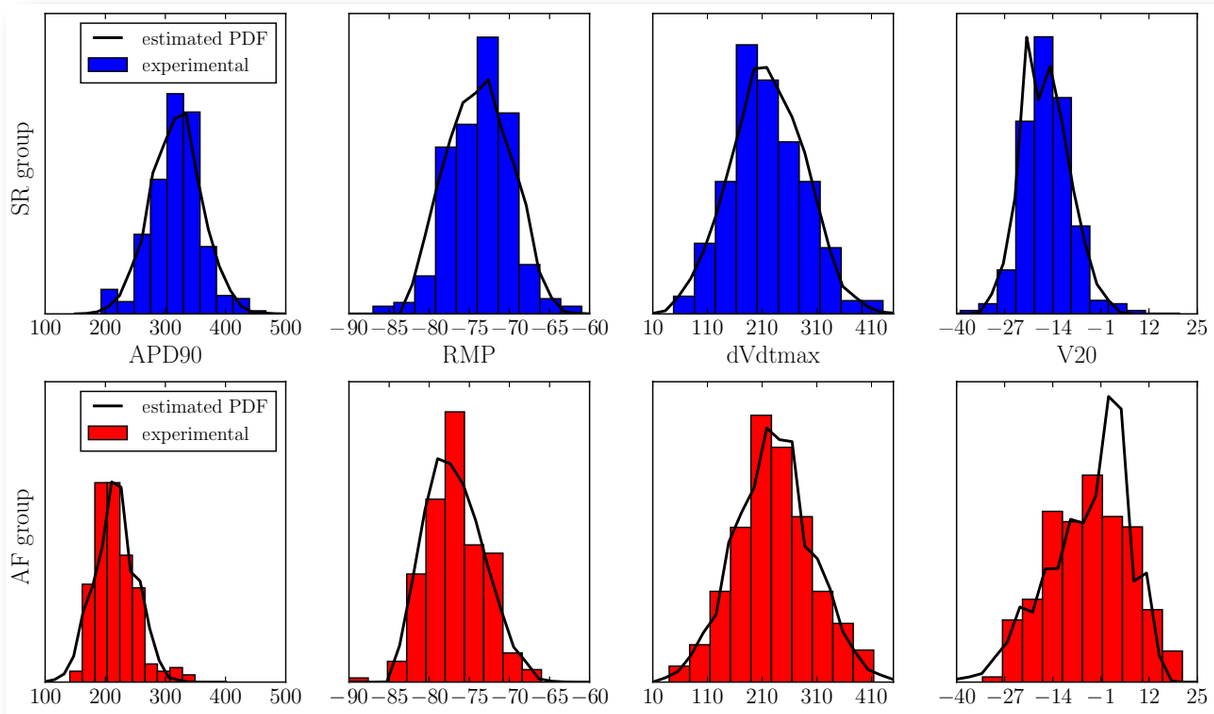


- Measurements from 2 populations: healthy (SR), atrial fibrillation (AF)
- Observable: set of AP features (4 biomarkers) for 469 subjects
- Strong inter-subject variability

Sanchez *et al.*, "Inter-Subject Variability in Human Atrial Action Potential in Sinus Rhythm versus Chronic Atrial Fibrillation", Plos One (2014).



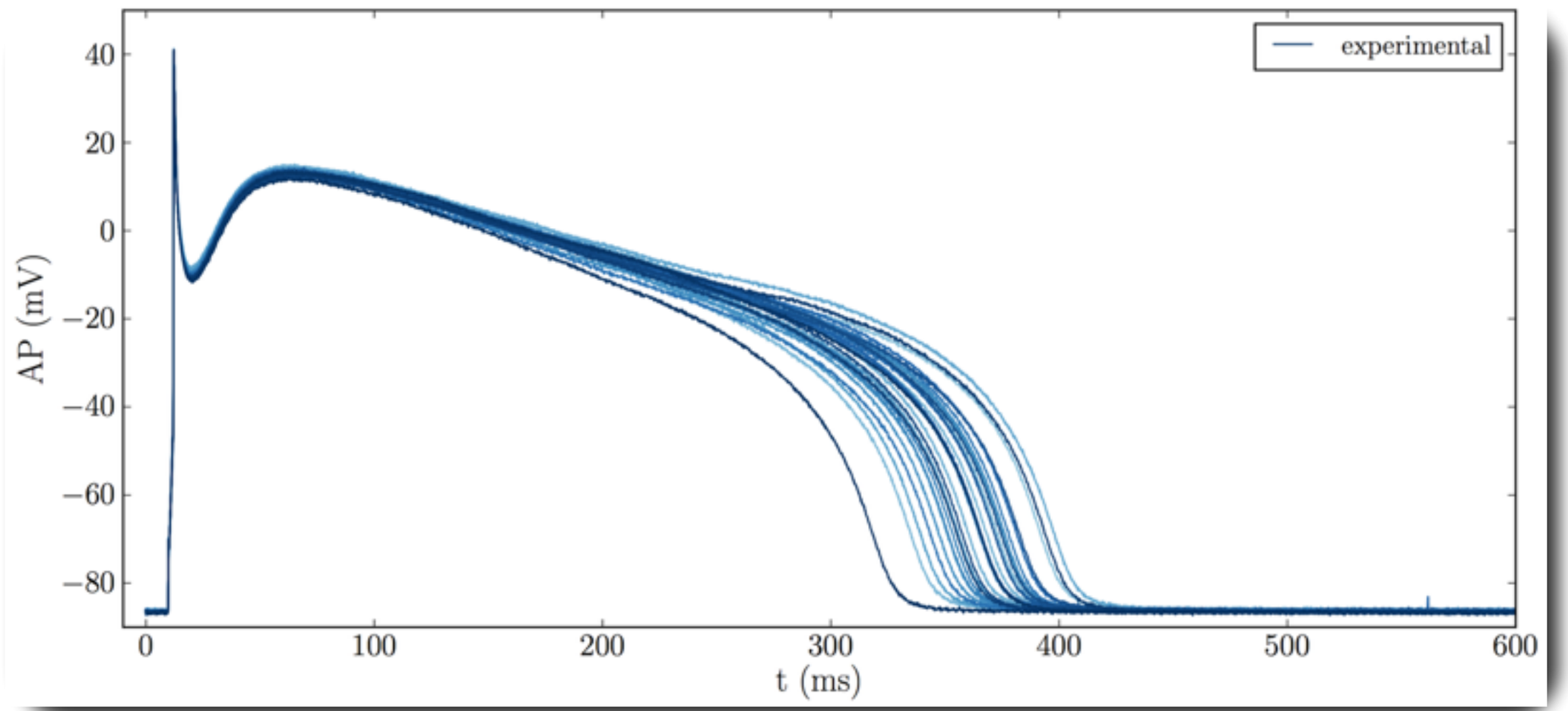
Distribution of 4 parameters
(healthy and pathological)



Distribution of the biomarkers
(estimated and experimental)

- Model: Courtemanche-Ramirez
- # samples: $N_c = 16384$; # moments: $n_{mom} = 2$; # clusters: $N_k = 6$

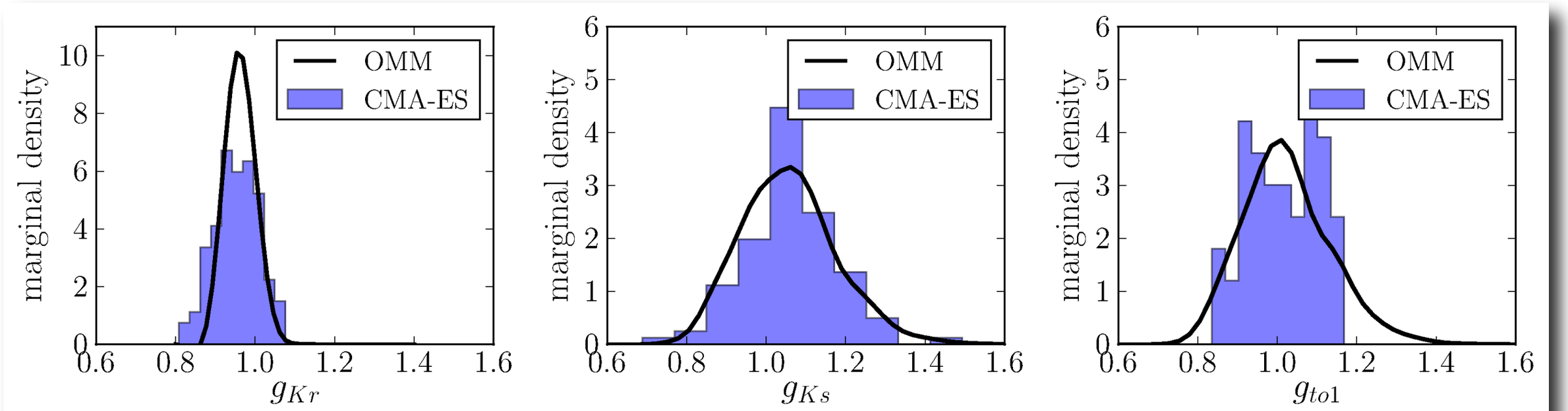
Example 4: Canine Action Potential



Samples of canine ventricular AP experimental recordings

- Measurements (100 APs) from canine heart cells
- Observable: set of AP features (biomarkers)
- Beat-to-beat variability

Johnstone *et al.*, "Uncertainty and variability in models of the cardiac action potential: Can we build trustworthy models?", *J. of Molecular and Cellular Cardiology* (2015).



Marginal distributions of 3 parameters estimated from experimental data.

- Model: Davies
- Hypothesis: only 3 parameters responsible for the variability
- Validation with individual parameter identification (evolutionary algo: CMA-ES)
- # samples: $N_c = 8192$; # moments: $n_{mom} = 2$; # clusters: $N_k = 3$

Conclusions & Perspectives

Summary

- Approximate parameters distribution from observed variability in a population
- Non-parametric and black-box approach
- Tested with synthetic & experimental data

Perspectives

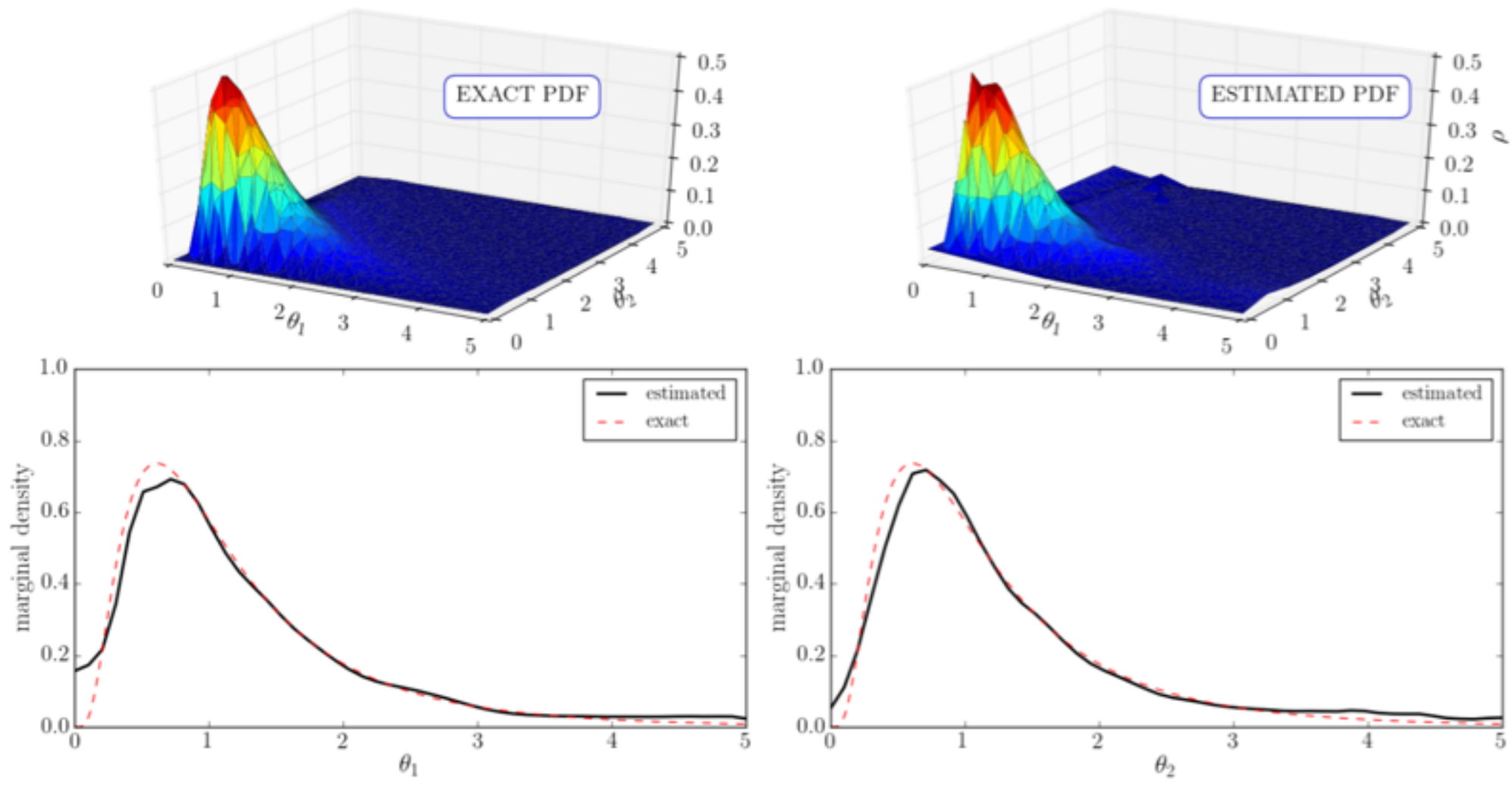
- How to determine which parameters are responsible for variability?
- What to do with the remaining parameters?
- How to choose relevant biomarkers? **[Eliott Tixier's talk]**
- Use the obtained distribution as a *prior* for more sophisticated inverse problem algorithms

J-F. Gerbeau, D. Lombardi, E. Tixier, "A moment-matching method to study the variability of phenomena described by partial differential equations", available on HAL: https://hal.archives-ouvertes.fr/hal-01391254/

E. Tixier, D. Lombardi, B. Rodriguez, J-F. Gerbeau, "Modeling Variability in Cardiac Electrophysiology: A Moment Matching Approach", Journal of the Royal Society Interface (2017).

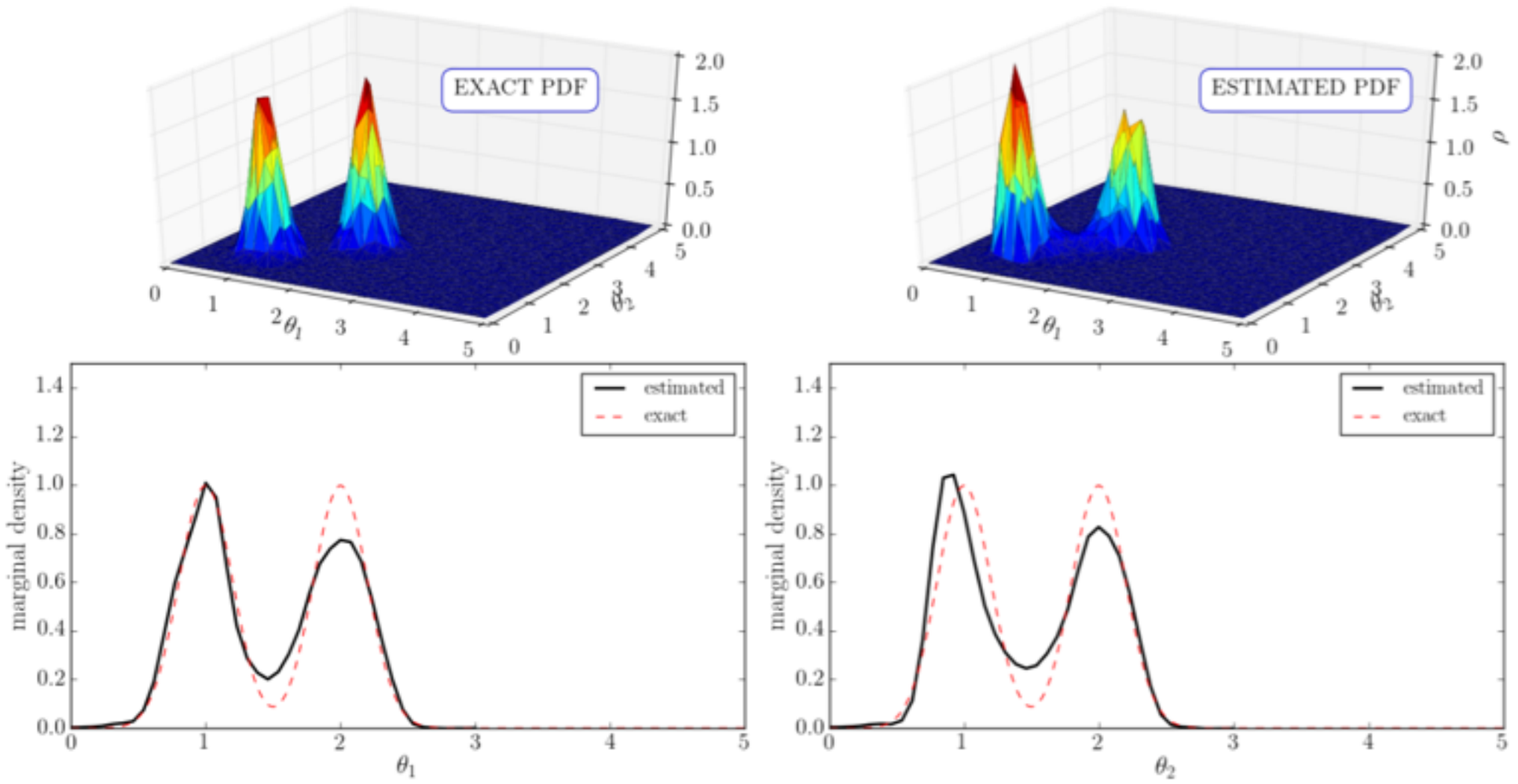
- You can test it: **https://github.com/eltix/omm_jrsi.git**

- Bi-variate **log-normal** distribution
- Strongly skewed
- Numerical settings: $N_c = 2048$, $n_{mom} = 4$ and $N_{\mathbf{x}} = 10$



Observable moment matching applied to synthetic data. Log-normal distribution

- Gaussian mixture **bimodal** distribution
- θ_1 and θ_2 are strongly correlated
- Numerical settings: $N_c = 2048$, $n_{mom} = 4$, $N_{\mathbf{x}} = 16$



Observable moment matching applied to synthetic data. Bimodal distribution