PERSONALIZING PHYSIOLOGICAL MODELS WITH MEDICAL DATA

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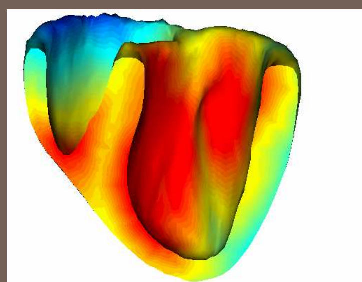
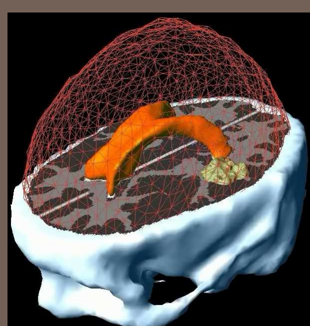
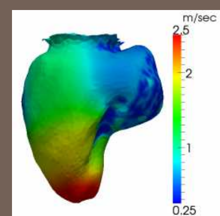
Physiological Modelling

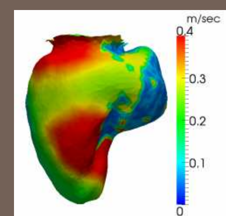
Models

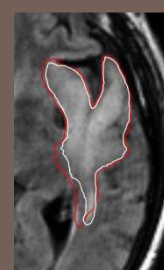




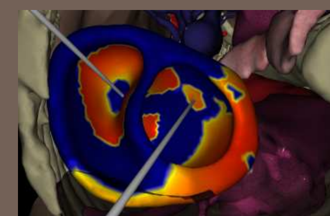
Personalization

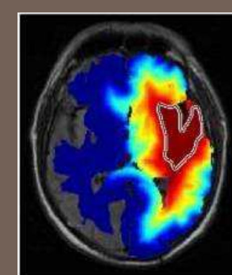




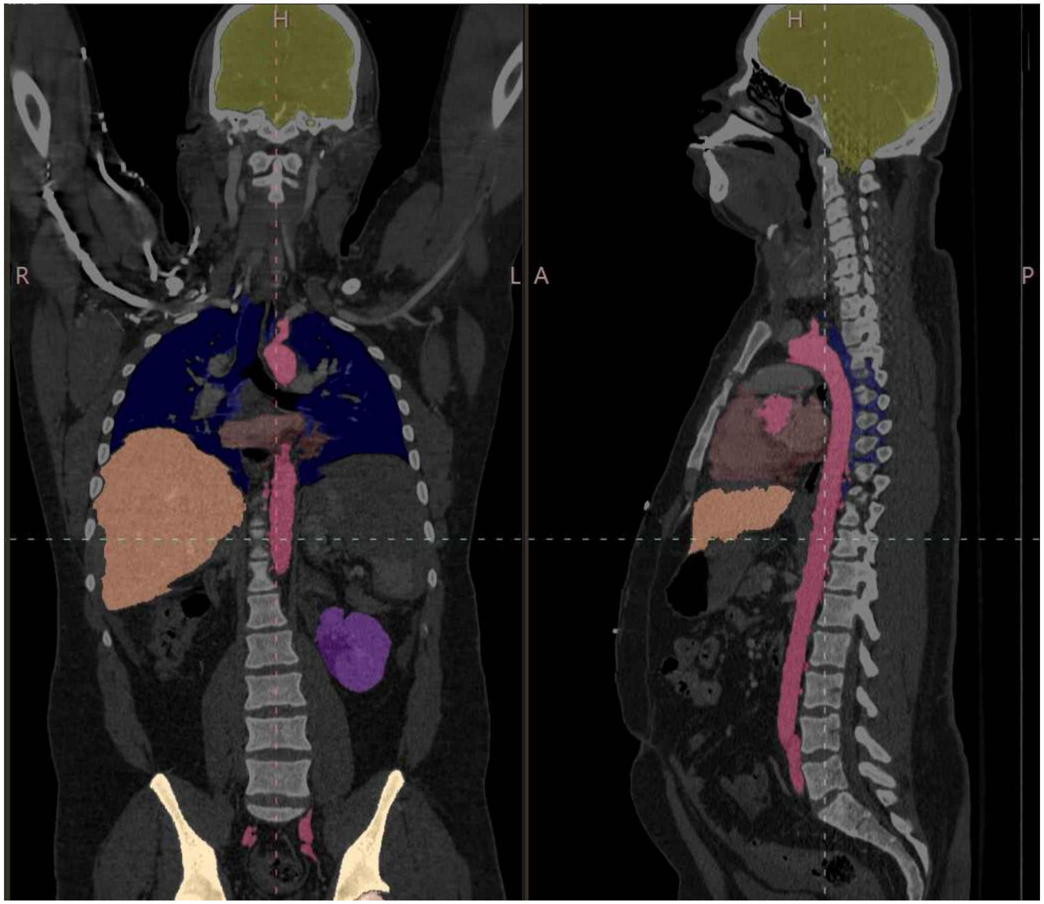


Simulations for Treatment





Anatomical Modelling

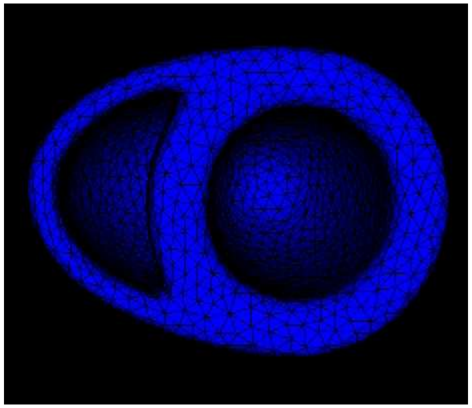


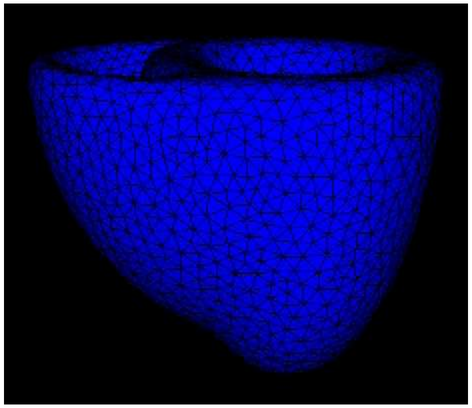
Geometrical Understanding

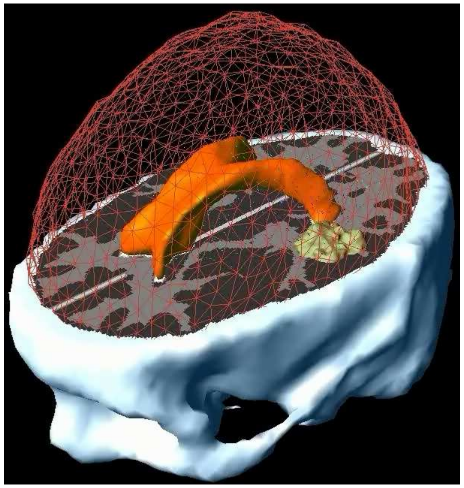
Parameterizations
-Surfaces
-Volumes
-Fibre bundles

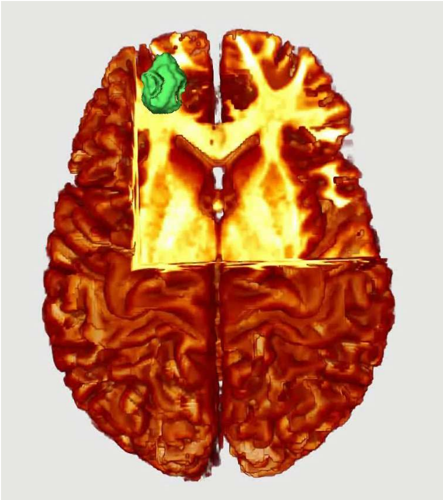
Personalization
-Segmentation
-Registration
-Tractography

Physiological Modelling









Functional Understanding

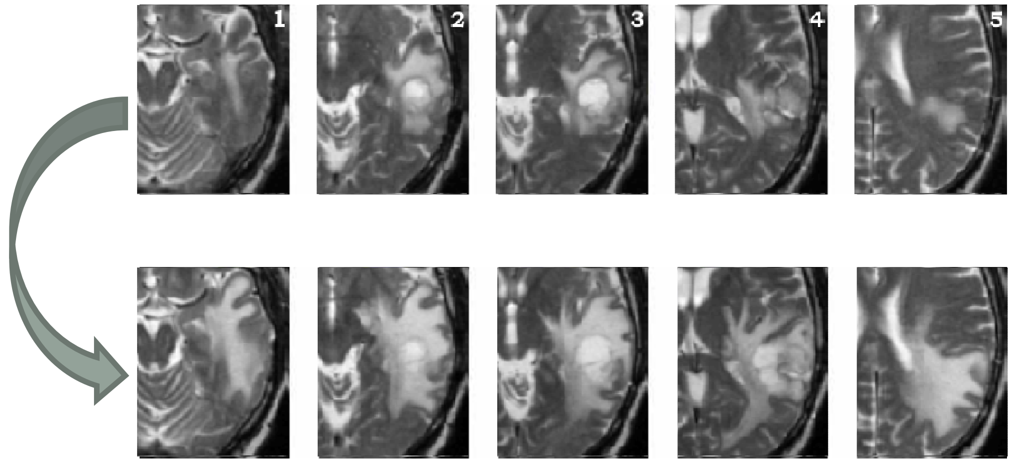
Parameterizations
-Mathematical Models
-Computational Models
-Simulations

Personalization
-Model Fitting
-Parameter Estimation

Parameterization - Personalization

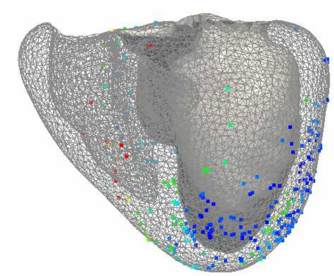
Behaviour of Tumour Cells

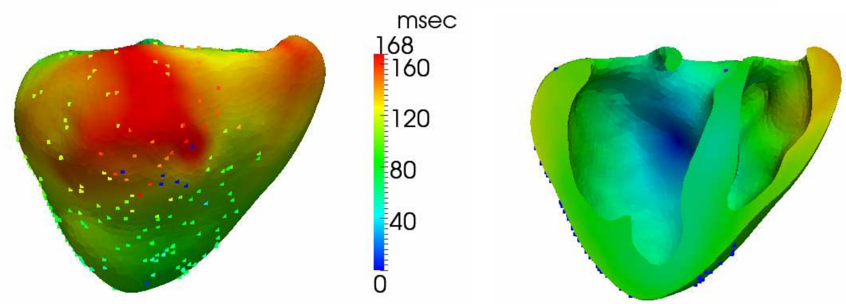
$$\frac{\partial u}{\partial t} = \nabla \cdot (\mathbf{D}\nabla u) + \rho u(1-u), \quad (\boldsymbol{\eta} \cdot \mathbf{D}\nabla)u|_{\partial\Omega} = 0$$



Electrical Conduction

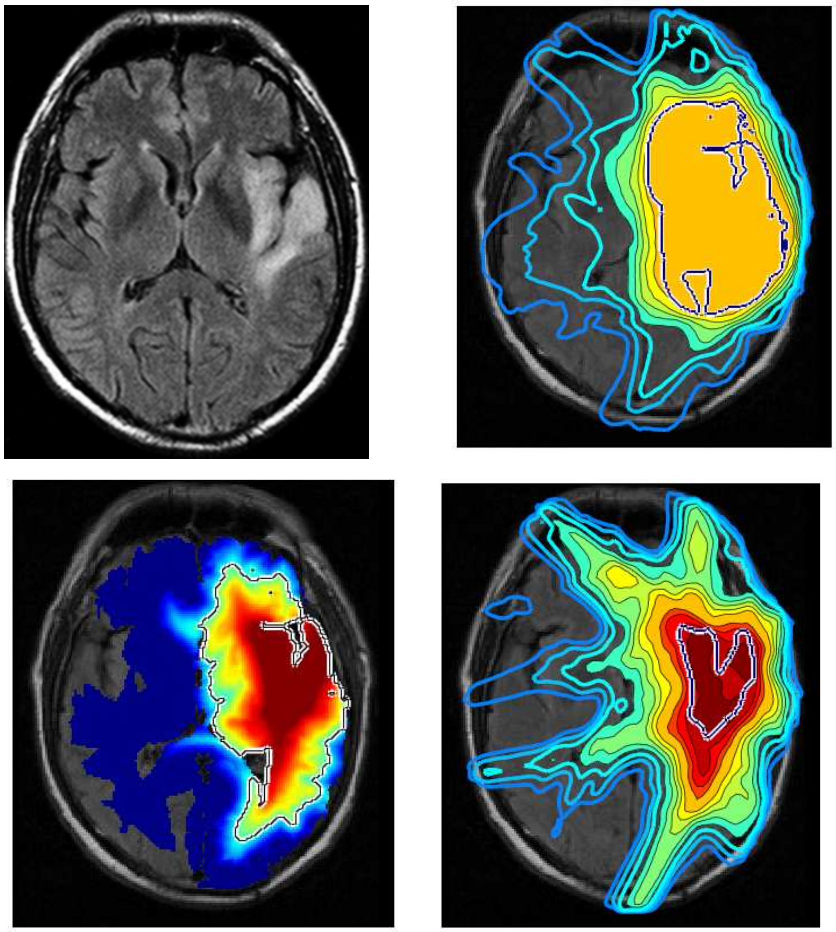
$$c_0 D(x)\left(\sqrt{\nabla T(x)^t \boldsymbol{M}(x)\nabla \mathrm{T}}\right) - \nabla \cdot \left(D(x)\boldsymbol{M}(x)\nabla \mathrm{T}(\mathrm{x})\right) = \tau, x \in \Omega/\Omega_E$$



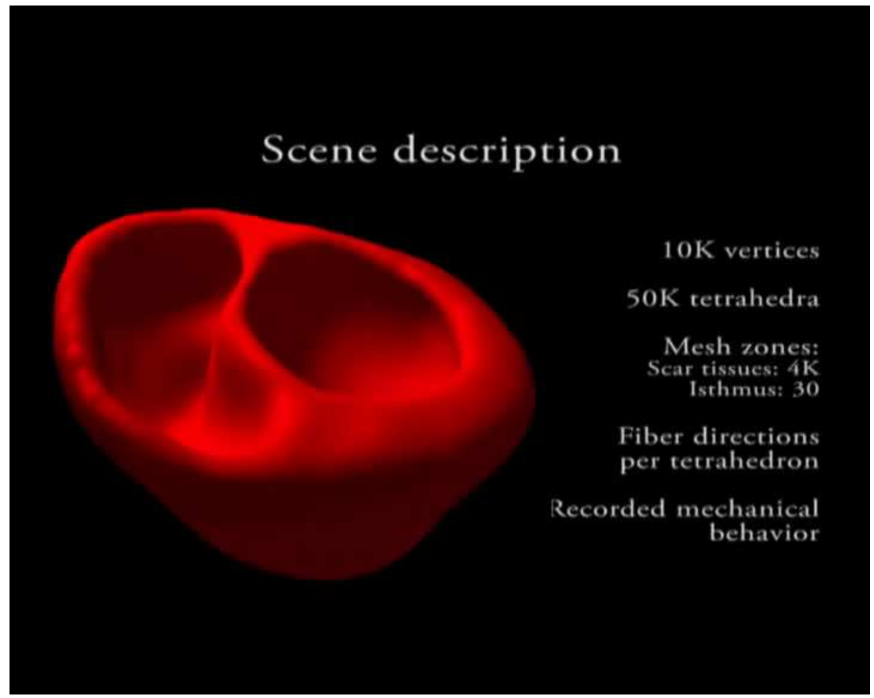


Personalization:
Patient Specific Parameters
Patient Specific Geometry

Modelling for Patient-Specific Treatment



Irradiation Margins taking into account growth dynamics

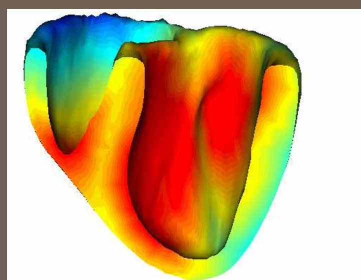


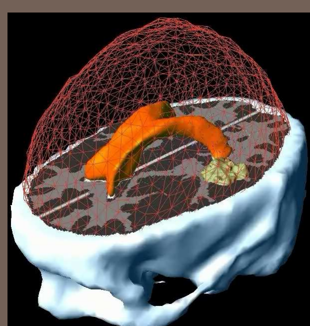
Simulating invasive procedures

Unkelbach et al. AAIP 2011
Pernod et al. Comp. Graph. 2011

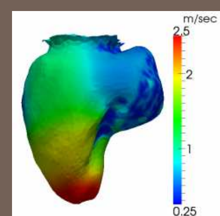
Physiological Modelling

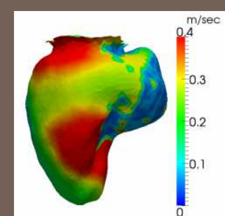
Models

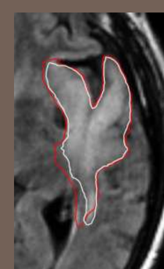




Personalization







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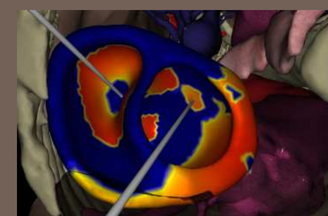
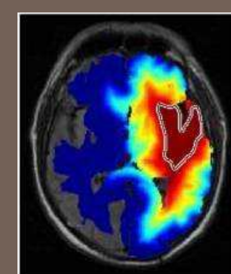


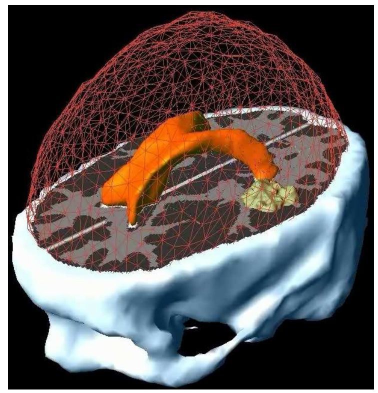


Outline

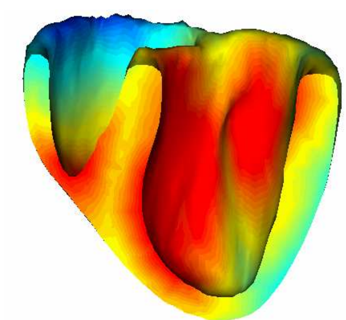
Personalization

Mathematical Model

Clinical Data



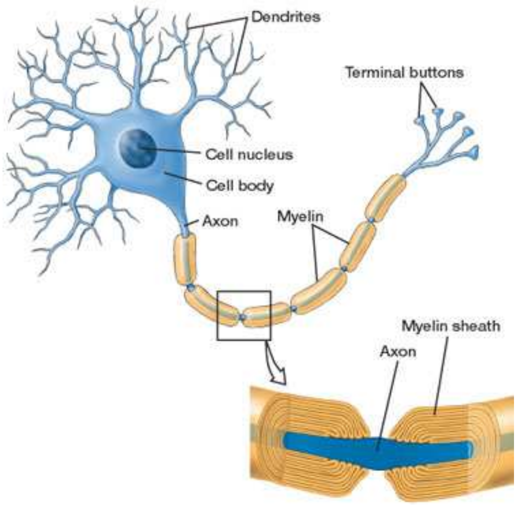
Growth of Glioma
-Spatio-temporal model,
-Longitudinal images,
-Deterministic method



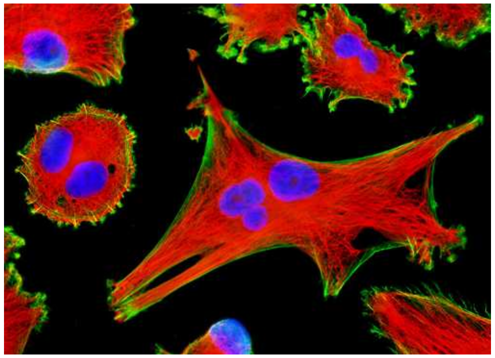
Cardiac Electrophysiology
-Spatial Model,
-Cardiac Mappings,
-Stochastic method

Glioma

- Neoplasms of glial cells
- Commonly in cerebral hemisphere
- Large variation in characteristics
- Proliferation
- Invasion through infiltration



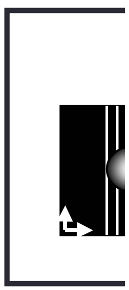
Pshychology: An Introduction, C. G. Morris, A.A. Maisto, 2001



Human Brain Glioma Cells
[www.microscopyu.com]

Growth Model: Reaction-Diffusion

$$\frac{\partial u}{\partial t} = \nabla \cdot (\mathbf{D}\nabla u) + \rho u(1-u), \quad (\boldsymbol{\eta} \cdot \mathbf{D}\nabla)u\big|_{\partial\Omega} = 0$$



$\mathbf{D} = \{ c$

Anis

u : tumor cell density

t : time

$\mathbf{D}$: diffusion tensor

ρ : proliferation rate

$\partial\Omega$: boundary of the brain

$\boldsymbol{\eta}$: normal to the boundary

Clatz [IEEE TMI 2005]

Jbabdi [MRM 2005]

Hogea [MICCAI 2006, 2007]

Murray [Mathematical Biology 2002]

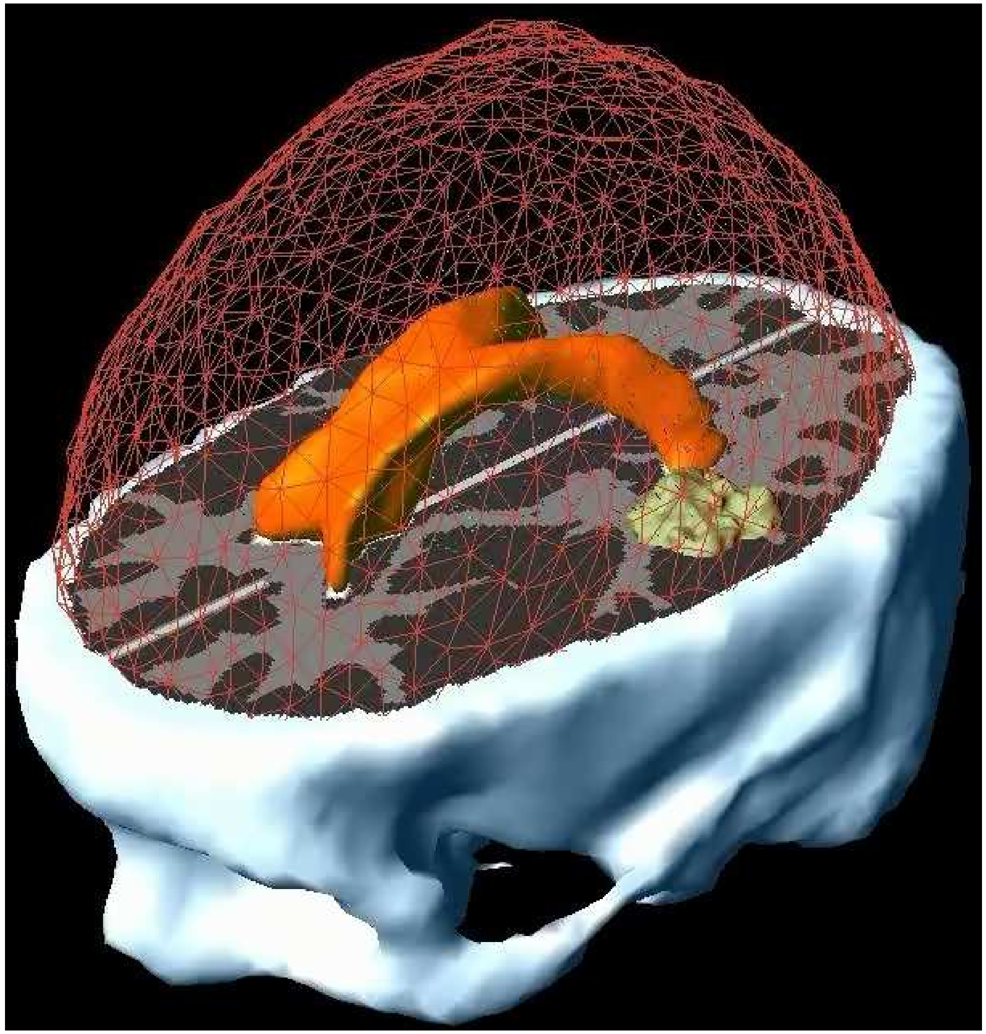
Prastawa-Gerig [MICCAI 2005, MedIA 2008]

Stein [J Biophys. 2007]

Swanson [Br. J. Cancer 2002, 2008]

Tracqui [Cell Proliferation 1995]

condition



Clatz et al. TMI 2005

Manual Adjustments

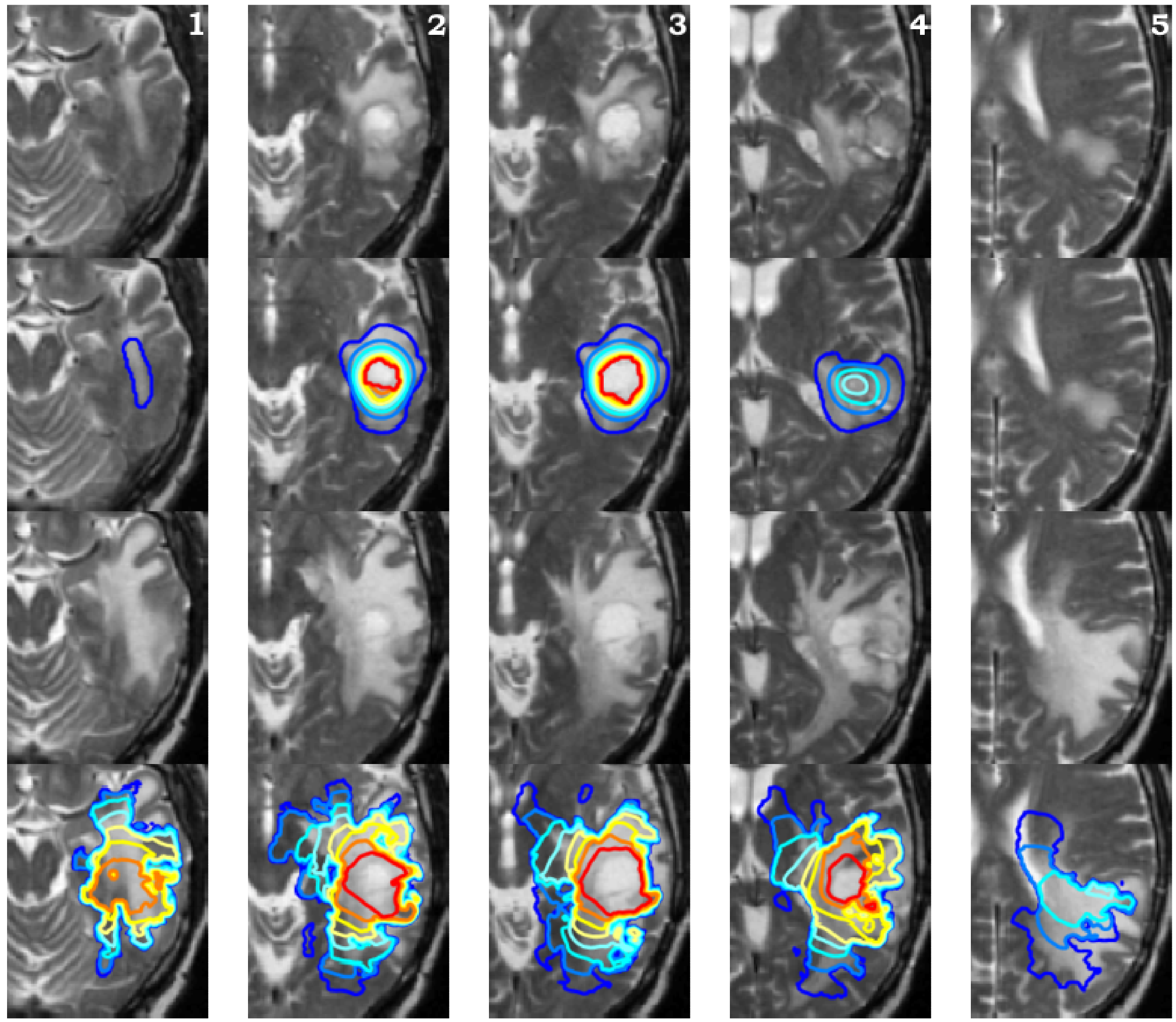
Different Slices

March 2002

March 2002 + initial contour

September 2002

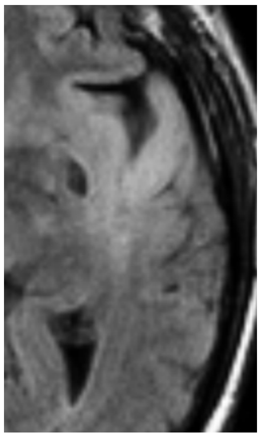
September 2002 + simulation contours



Clatz et al. TMI 2005

Data: Longitudinal Studies

Time 1



120 days

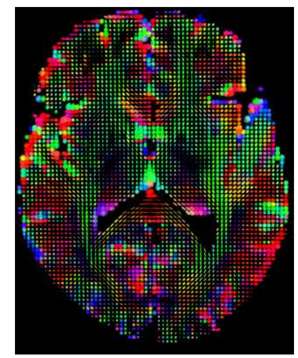
Time 3

270 days

Time 5

Evolution of a grade II glioma

Patient DTI



Time 1

21 days

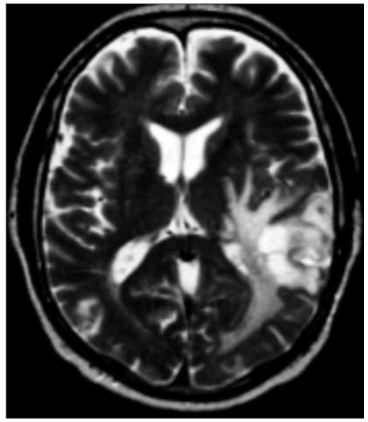
Time 2

46 days

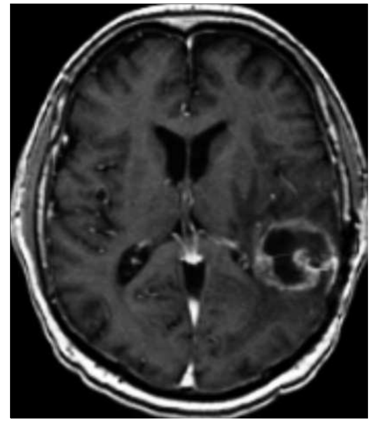
Time 3

Evolution of a grade IV glioma

Limited Observations

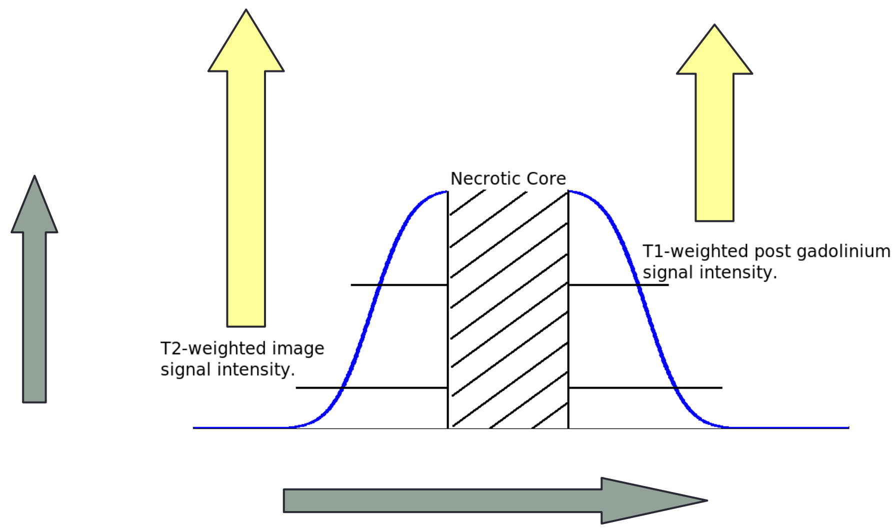


T2w



T1w post-gad

Tumor cell density

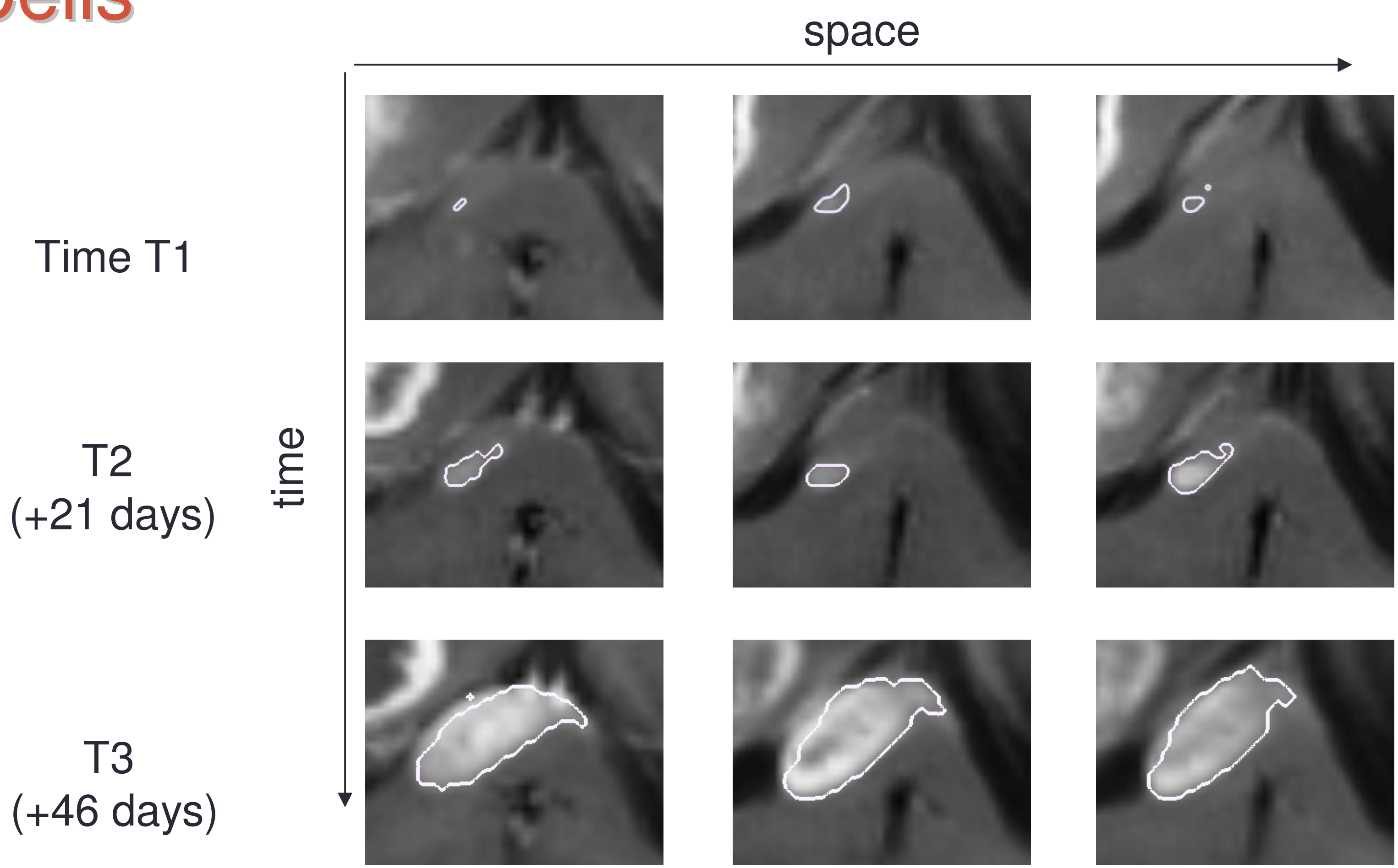


space

Hypothetical tumor cell distribution

Unknown Thresholds

Evolution of the Delineation **not** the Tumour Cells

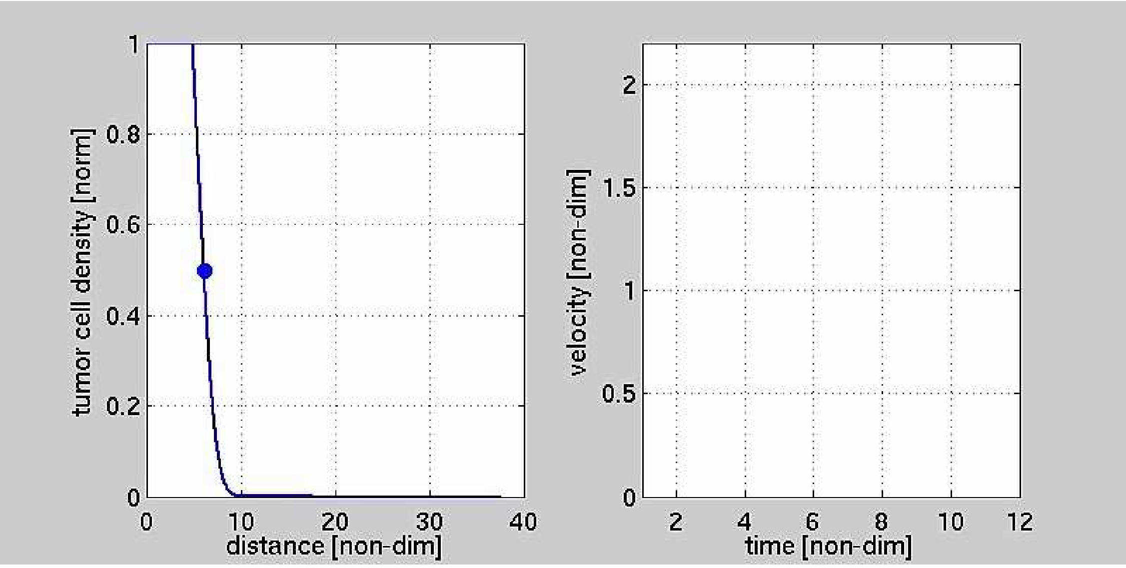


Model Reduction for Parameter Estimation

Evolution of Tumour Cell Densities

$$\frac{\partial u}{\partial t} = \nabla \cdot (\mathbf{D}\nabla u) + \rho u(1-u)$$

Evolution of Tumour Delineation



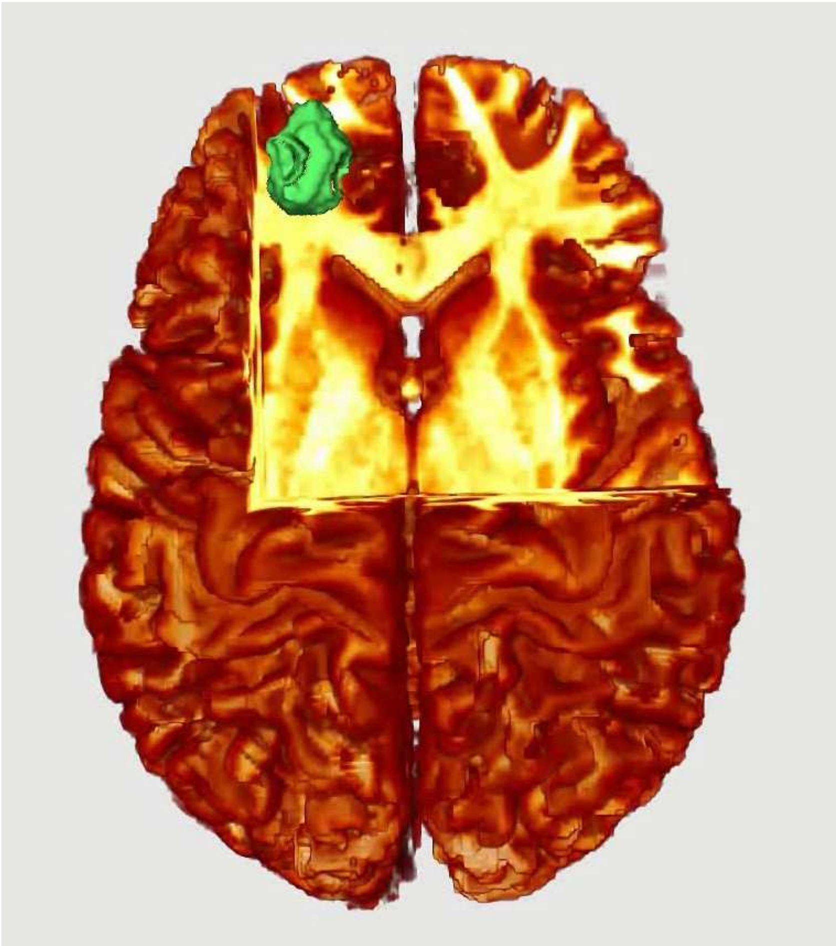
Travelling wave solutions of reaction-diffusion equations

$$u(\mathbf{x},t) = u(\mathbf{x}\cdot\mathbf{n} - vt)$$

Travelling time formulation for tumor evolution

$$\left\{\frac{4\rho T - 3}{2T\sqrt{\rho}} - 0.3\sqrt{\rho}\left(1 - e^{-|\kappa_{eff}|/(0.3\sqrt{\rho})}\right)\right\}\sqrt{\nabla T' \mathbf{D} \nabla T} = 1, \ \kappa_{eff} = \nabla \cdot \frac{\mathbf{D}\nabla T}{\sqrt{\nabla T' \mathbf{D} \nabla T}}$$

Konukoglu et al. TMI 2010



Growth of the delineation with RD dynamics

Parameter Estimation

$$\mathbf{D} = \begin{cases} \alpha d_w \mathbf{D}_{\mathbf{water}}, & \text{white matter} \\ d_g \mathbf{I}_3, & \text{gray matter} \end{cases}, \rho$$

Minimization Cost

$$C = \sum_{i=1,..,N-1} dist\left(\Gamma_i, \hat{\Gamma}_i\right)^2$$

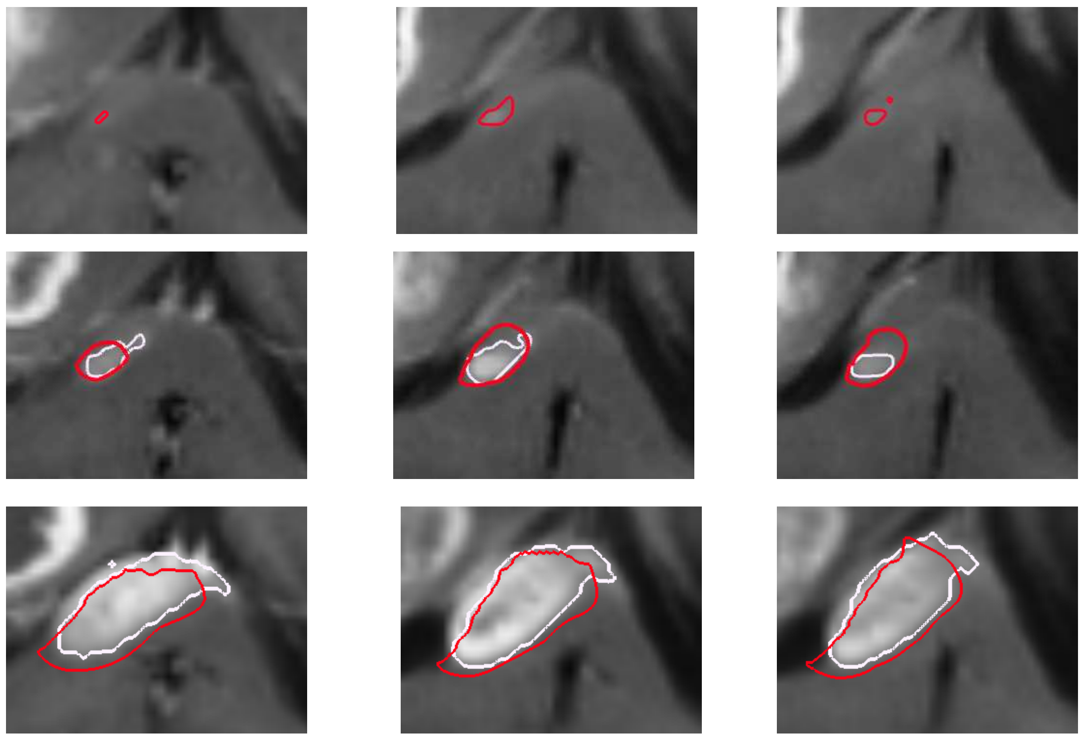
space

Time T1

T2
(+21 days)

T3
(T2 + 46 days)

time



Powell, Mathematical Programming, vol. 92, no. 3, 2002

Personalization leading to Prediction: Grade IV

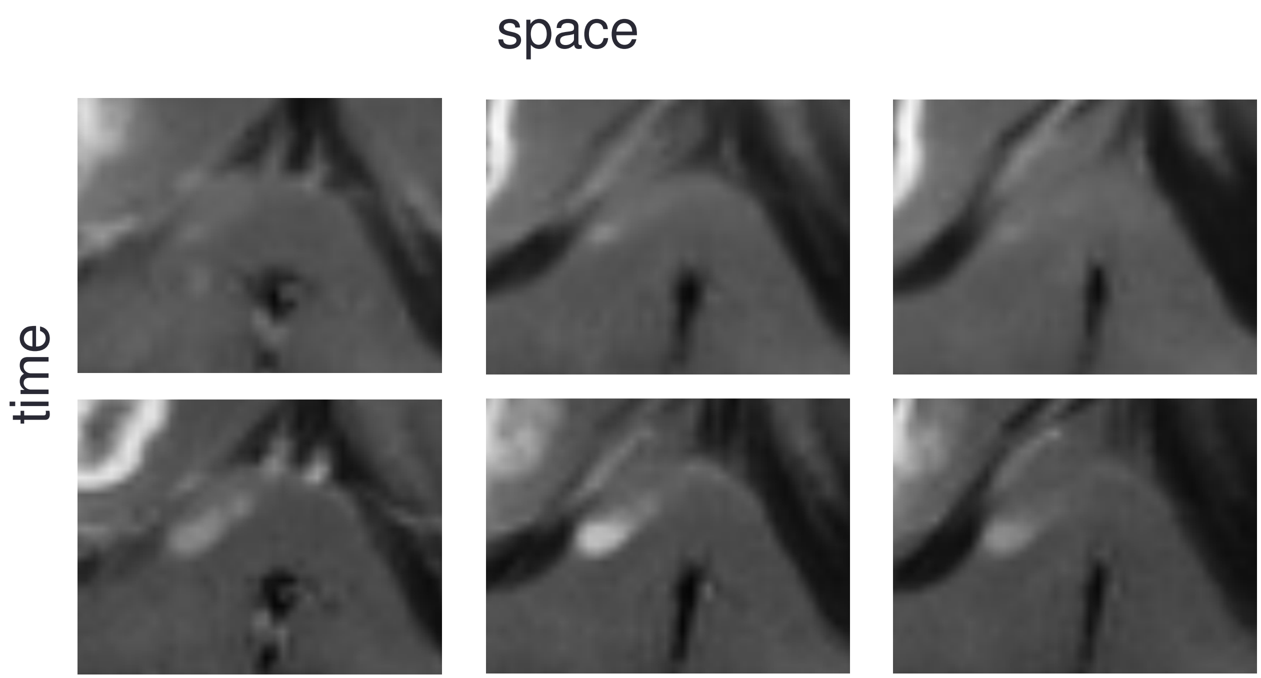
Estimated from Time 1 & Time 2 :

ρ	d_w	d_g
0.05 / day	0.66 mm^2/day	0.0013 mm^2/ day

High grade glioma
(glioblastoma multiforme)

*MRI T1 Gd, 0.5*0.5*6.5mm*
3 time points

MR DTI : 2.5mm (time 2)



Konukoglu et al. TMI 2010

Personalization leading to Prediction: Grade II-III

Estimated from Time 1 to Time 4 :

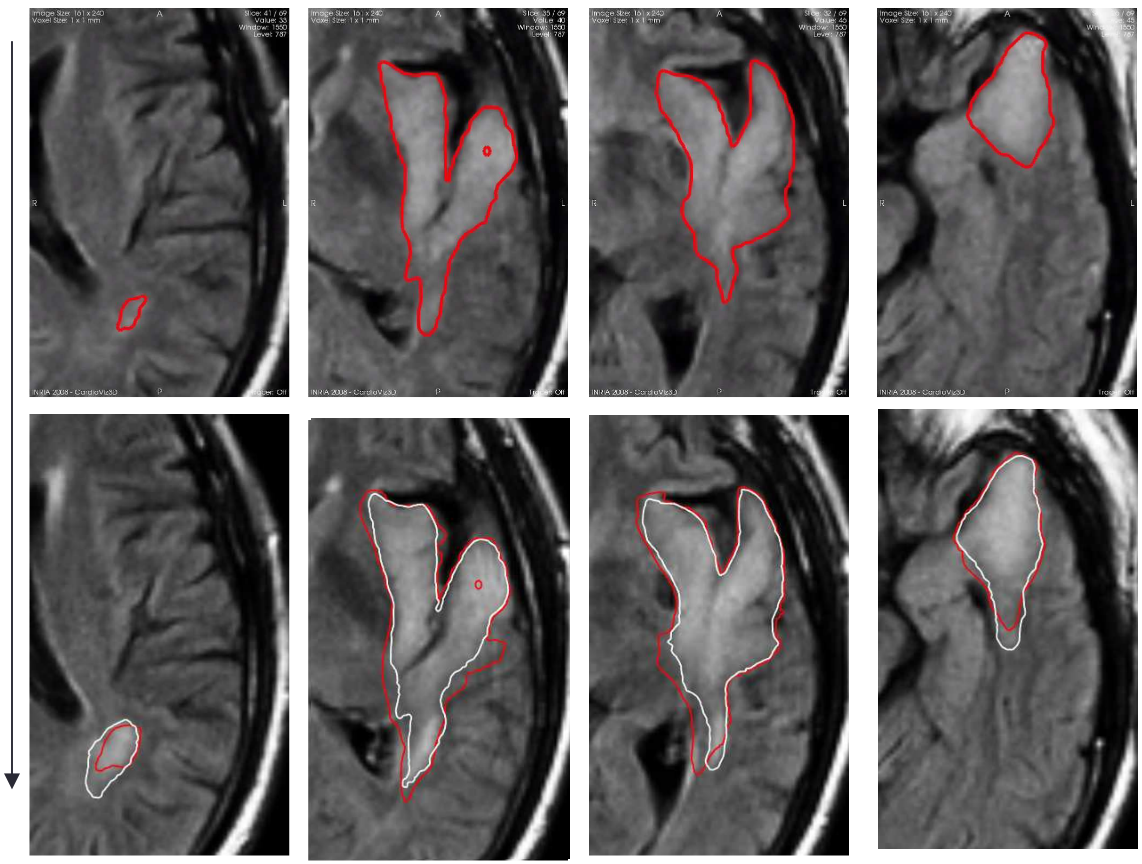
ρ	d_w	d_g
0.008 / day	0.20 mm^2/day	0.0007 mm^2/ day

space

time

Time 4

Time 5
(T4+180)



Low grade glioma
(grade 2 Astrocytoma)

*MRI T2 Flair 0.5*0.5*6.5mm*
5 time points

MR DTI : 2.5mm (time 1)

Konukoglu et al. TMI 2010

A small step back to digest

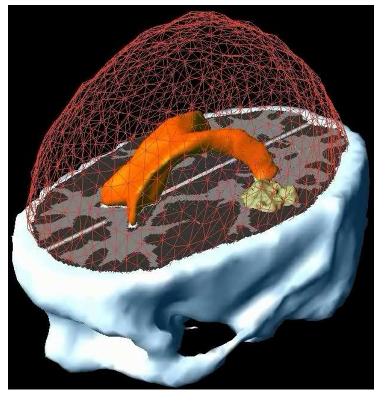
- Patient-specific parameters for growth quantification
- Personalized model - predictions on the growth patterns
- Model reduction
  - Regularization – Constraint Optimization [Relan et al. IEEE TBE 2011, Delingette IEEE TBE 2011]
  - Restrict the search space
  - Enlarge the model via incorporating observation model [Hogea et al. HJ Theo. Biol. 2011]
- Loss of information vs. uncertainty on the inverse problem
  - Influence of uncertain data on the parameters
  - Influence of uncertain parameters on the simulations
  - Probabilistic treatment [Konukoglu et al. PBMB 2011, Menze et al. IPMI 2011]

Outline

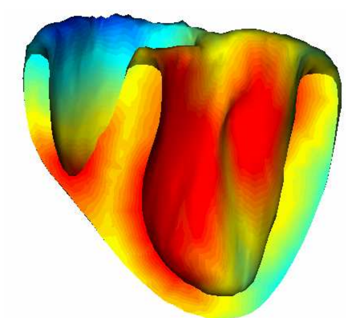
Parameter Estimation

Mathematical Model

Clinical Data



Growth of Glioma
-Spatio-temporal model,
-Longitudinal images,
-Deterministic method



Cardiac Electrophysiology
-Spatial Model,
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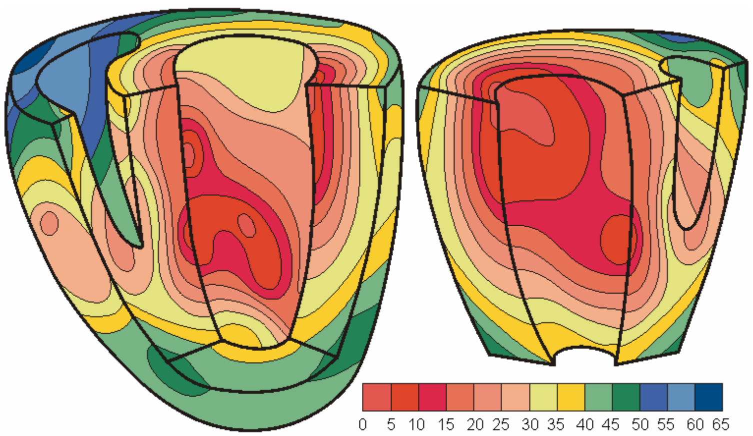
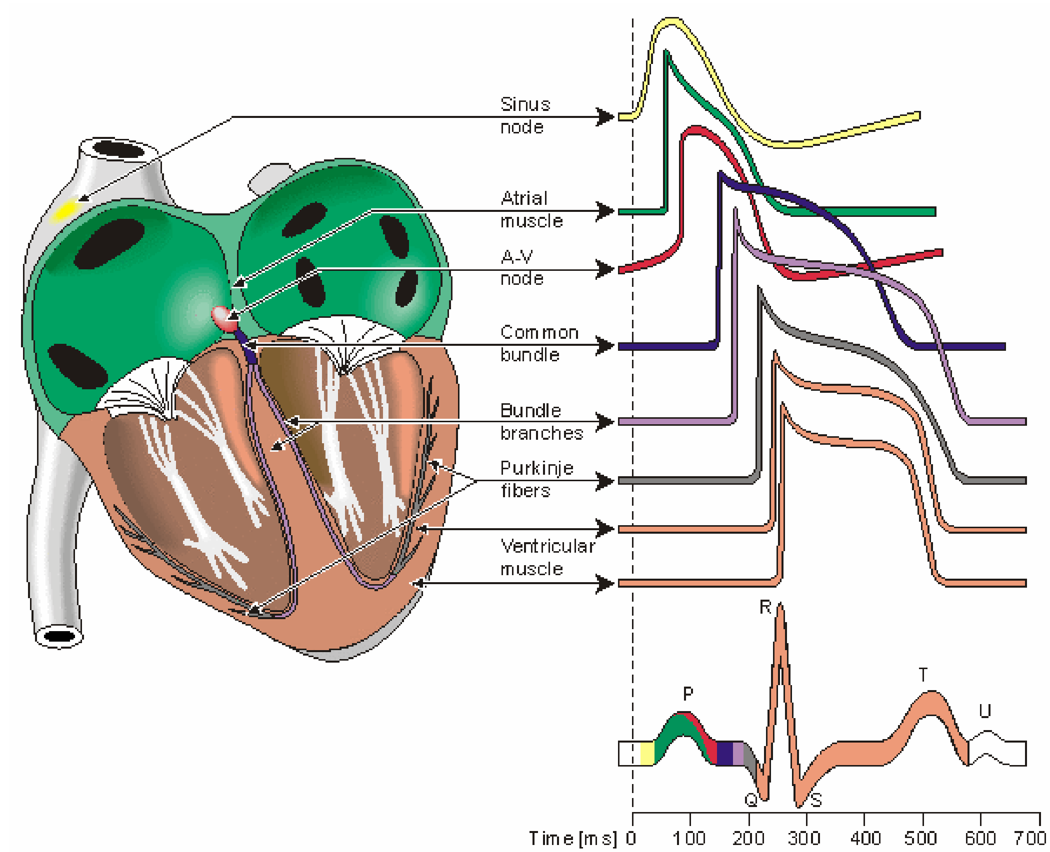
Cardiac Electrophysiology

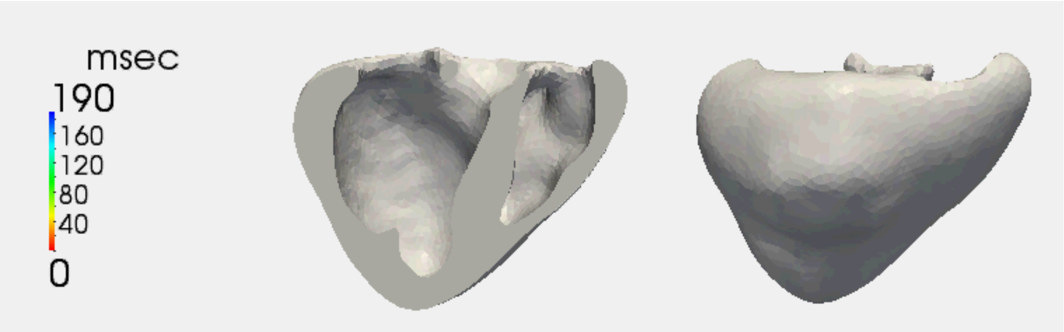




Images taken from Durrer *et al.,* 1970 and Malmivuo and Plonsey, 1995

Model: Eikonal-Diffusion

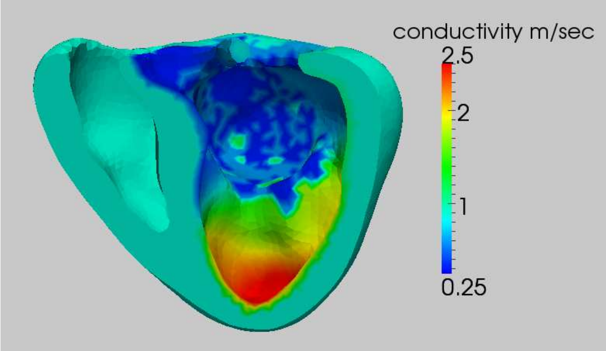
- Model of depolarization times
- Fast Simulations
- Purkinje network is approximated
- Fibres from an atlas

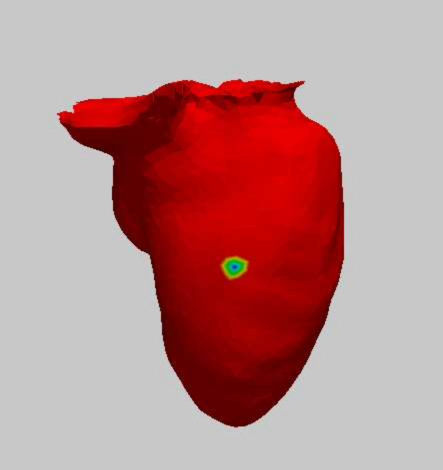


$$c_0 D(x)\left(\sqrt{\nabla T(x)^t \boldsymbol{M}(x)\nabla \mathrm{T}}\right) - \nabla \cdot \left(D(x)\boldsymbol{M}(x)\nabla \mathrm{T}(\mathrm{x})\right) = \tau, x \in \Omega/\Omega_E$$

$$T(x) = 0, x \in \Omega_E$$

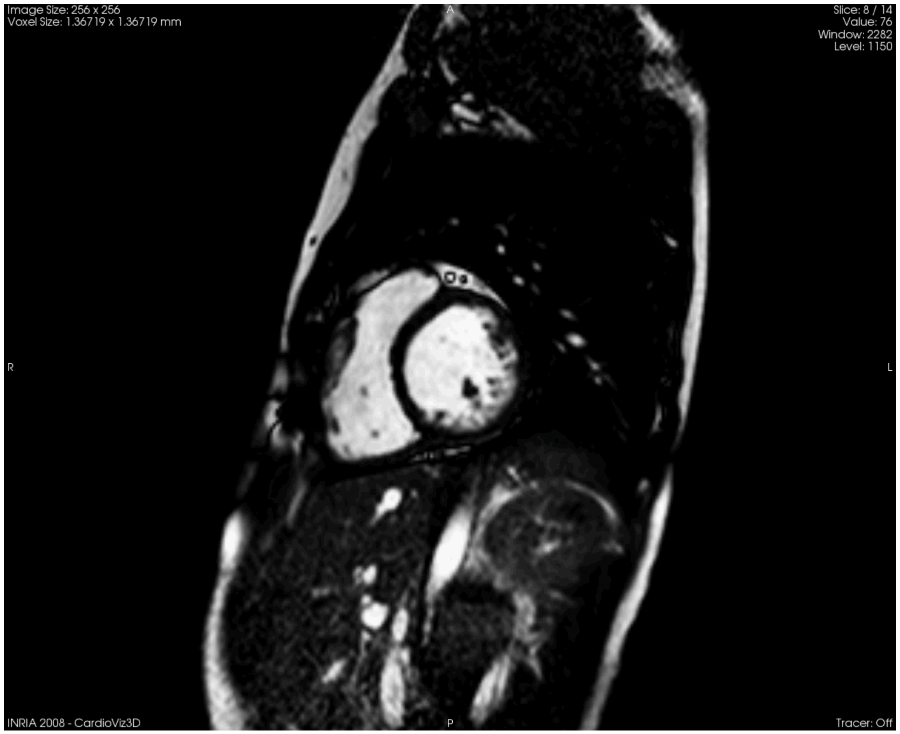
T: depolarization times in the cardiac tissue
c_0: dimensionless constant
τ: cell membrane time constant
D(x): conductivity
M(x): local fibre orientation
Ω_E: onset location

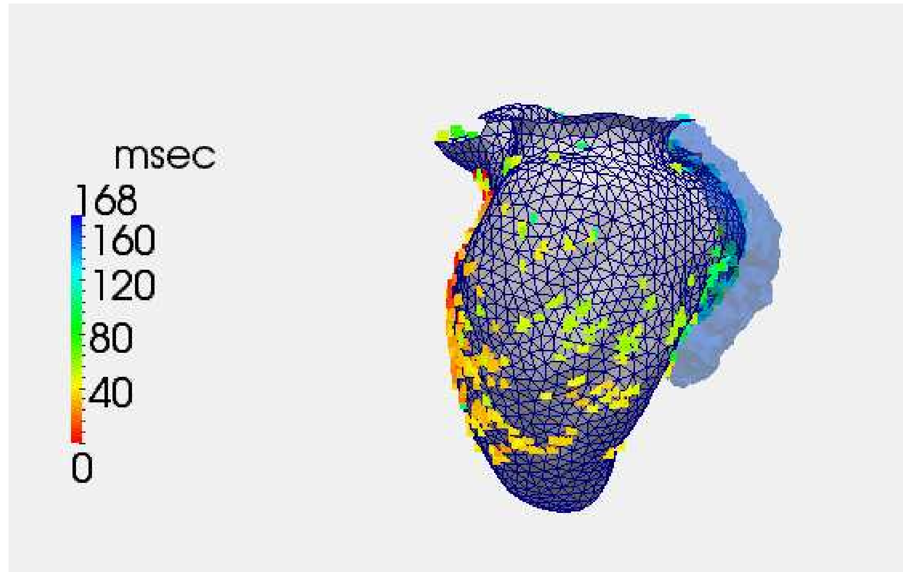




Sermesant et al. MedIA 2003, Sermesant et al. FIMH 2003, Konukoglu et al. IPMI 2007, Chipchapatnam et al. TMI 2007
Relan et al. IEEE TBE 2011

Data: Catheter Mappings and dynamic MRI





Geometry from MRI:
-Healthy muscle
-Scar regions
-Complex geometry

Depolarization times from Catheter
-Points on the boundary
-Sparse Data
-Noisy Data

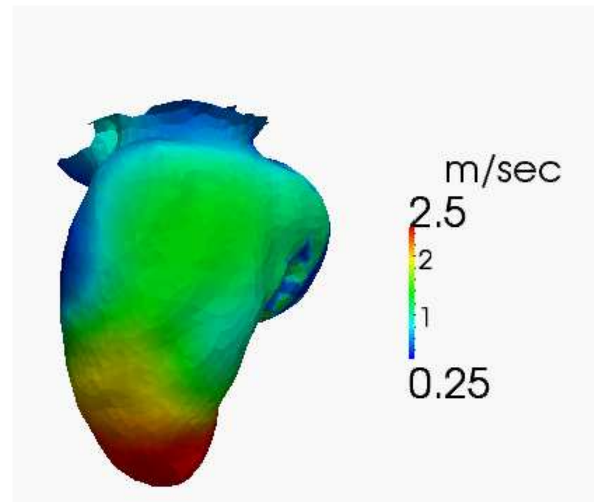
Courtesy of Michel Haïssaguerre and Bordeaux University Hospital

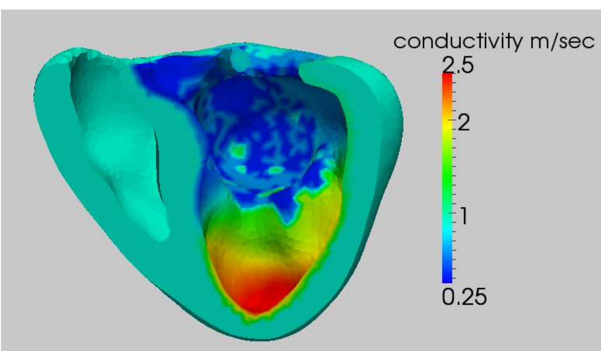
Parameters: Functional Conductivity

Conductivity:
-Spatially varying conductivity in the endocardium surface
-Global conductivity for the healthy muscle
-Conductivity for the scar and the peri-scar region

Anatomically defined regions

RBF Approximation



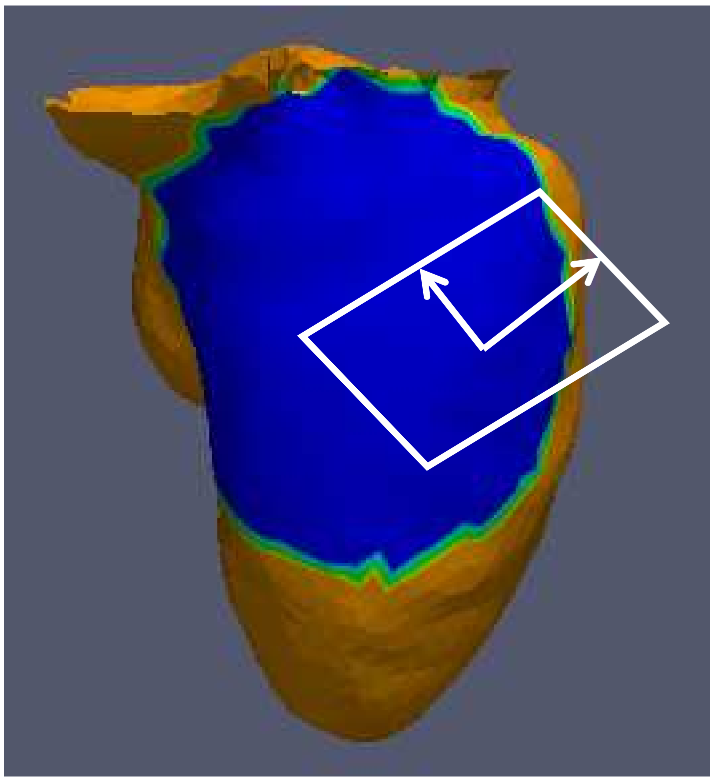


$$D(x) = \begin{cases} D_0 \; if \; x \in \Omega_{myo} \\ 1/Z(x) \sum_{m=1}^{M} D_m \exp\left(-\frac{||x - x_m||^2}{\sigma^2}\right) if \; x \in \Omega_{endo} \end{cases}$$

$$Z(x) = \sum_{m=1}^{M} \exp(-||x - x_m||^2/\sigma^2)$$

$\boldsymbol{D} = [D_0, D_1, \dots, D_M]$: estimation of the ***D*** vector, M+1: dimension of the inverse problem

Parameters: Onset Location



- Onset location on the septum
- Simplification for the Purkinje network along with the fast conductivity
- 2D parameterization of the surface patch

$$\Omega_E = (x_E, y_E)$$

Probabilistic Formulation

- Parameter as a random variables
- PDE as conditional dependencies

Joint Distribution of observations and parameters

$\tilde{T} = \{\tilde{T}_1, \tilde{T}_2, \ldots, \tilde{T}_N\}$: Observations

$$p(\tilde{T}, T, D(x), \Omega_E) = \underbrace{p(\tilde{T}|T)}_{\text{Observation Model}}\underbrace{p(T|D(x), \Omega_E)}_{\text{Physiological Model}}\underbrace{p(D(x))p(\Omega_E)}_{\text{Parameter priors}}$$

Assuming independence of observations

$$p(\tilde{T}, T, \boldsymbol{D}, \boldsymbol{\Omega}_E) = \prod_{i}^{N}\{p(\tilde{T}(x_i)|T(x_i))p(T(x_i)|\boldsymbol{D}, \Omega_E)\}p(\boldsymbol{D})p(\Omega_E)$$

Posterior Distribution

Using the uniqueness of the forward problem

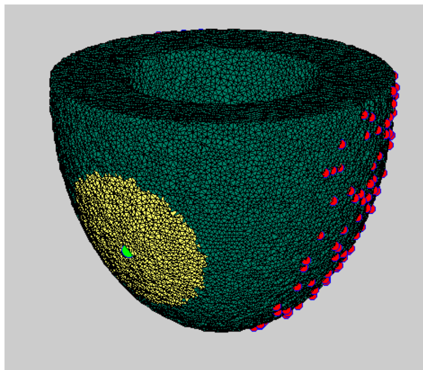
$p(T(x)|\boldsymbol{D}, \Omega_E) = \delta(T(x|\boldsymbol{D}, \Omega_E))$: solution of the forward problem

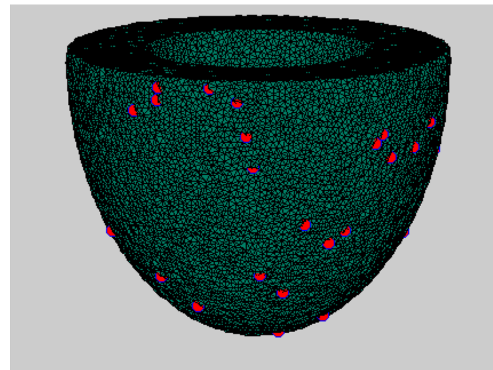
$$p\left(\boldsymbol{D}, \Omega_E \middle| \widetilde{T}\right) = \frac{\prod_{i=1}^{N} p\left(\widetilde{T}(x_i) \middle| T(x_i|\boldsymbol{D}, \Omega_E)\right) p(\boldsymbol{D}) p(\Omega_E)}{\int_{\Sigma(\boldsymbol{D})} \prod_{i=1}^{N} p\left(\widetilde{T}(x_i) \middle| T(x_i|\boldsymbol{D}, \Omega_E)\right) p(\boldsymbol{D})\, p(\Omega_E) d\boldsymbol{D} d\Omega_E}$$

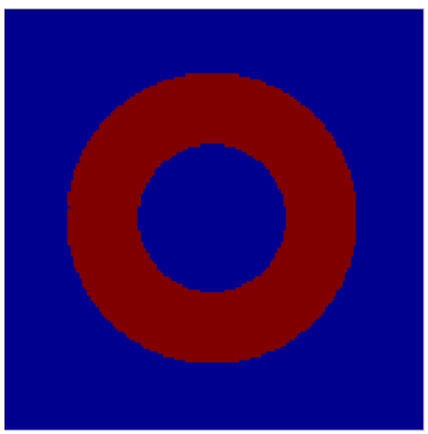
Konukoglu et al. PBMB 2011

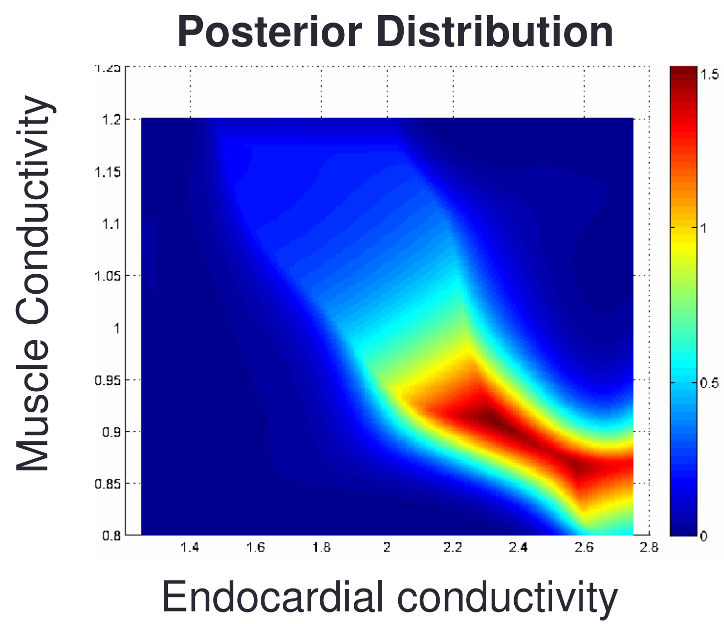
Inferred Posterior Distribution: Toy Example

$$c_0 D(x) \left(\sqrt{\nabla T(x)^t \boldsymbol{M}(x) \nabla \mathrm{T}} \right) - \nabla \cdot \left(D(x) \boldsymbol{M}(x) \nabla \mathrm{T}(\mathrm{x}) \right) = \tau, x \in \Omega / \Omega_E$$









Posterior Distribution

Using the uniqueness of the forward problem

$p(T(x)|\boldsymbol{D},\Omega_E) = \delta(T(x|\boldsymbol{D},\Omega_E))$: solution of the forward problem

$$p\left(\boldsymbol{D},\Omega_E\middle|\widetilde{T}\right) = \frac{\prod_{i=1}^{N} p\left(\widetilde{T}(x_i)\middle|T(x_i|\boldsymbol{D},\Omega_E)\right) p(\boldsymbol{D})p(\Omega_E)}{\int_{\Sigma(\boldsymbol{D})} \prod_{i=1}^{N} p\left(\widetilde{T}(x_i)\middle|T(x_i|\boldsymbol{D},\Omega_E)\right) p(\boldsymbol{D})\, p(\Omega_E) d\boldsymbol{D} d\Omega_E}$$

- Analytical solution only if the model is analytically solvable
- Sampling based methods: MCMC
- Collocation based methods: Sparse grid reconstructions
- Computational bottleneck – # of sample simulations for high dimensional parameters
- 20 dimensional problem ~ 10^5 simulations ~ 20 seconds / simulation ~ 23 days…

Spectral Representations for Random Variables

Polynomial Chaos Expansion for random variables

$$\boldsymbol{D} \triangleq \boldsymbol{D}(\boldsymbol{\xi}) = \sum_{i=0}^{\infty} \boldsymbol{d}_i \Phi_i(\boldsymbol{\xi}) \approx \sum_{i=0}^{P} \boldsymbol{d}_i \Phi_i(\boldsymbol{\xi})$$

$\boldsymbol{d}_i$: spectral basis for $\boldsymbol{D}$

$\boldsymbol{\Phi}_i$: orthogonal polynomial basis in the probability space

$$< \Phi_i, \Phi_j >= \int_{\Sigma(\boldsymbol{\xi})} \Phi_i(\boldsymbol{\xi}) \Phi_j(\boldsymbol{\xi}) p(\boldsymbol{\xi}) d\boldsymbol{\xi} = \delta_{ij}$$

$$\boldsymbol{d_i} = \int_{\boldsymbol{\Sigma}(\xi)} \boldsymbol{D}(\boldsymbol{\xi}) \Phi_i(\boldsymbol{\xi}) p(\boldsymbol{\xi}) d\boldsymbol{\xi}$$

Gaussian – Hermite
Uniform – Legendre
…

[Ghanem 2006, Xiu 2009]

Spectral Representation of the PDE

Randomness in model solution can be represented using the same spectral basis

$$T(x) \triangleq T(x,\xi) = \sum_{i=0}^{\infty} T_i(x)\Phi_i(\xi) \approx \sum_{i=0}^{P} T_i(x)\Phi_i(\xi)$$

T_i: spectral basis functions for *T(x)*

Let $\widetilde{\boldsymbol{D}}, \widetilde{\boldsymbol{\Omega}_{\boldsymbol{E}}}$ be a specific instance of the parameters

Then there is a unique $\tilde{\xi} \rightarrow \boldsymbol{D}(\tilde{\xi}), \Omega_E(\tilde{\xi}) = \widetilde{\boldsymbol{D}}, \widetilde{\boldsymbol{\Omega}_{\boldsymbol{E}}}$ due to orthogonality and

$$T\left(x \middle| \widetilde{D}, \widetilde{\Omega_E}\right) = T\left(x, \tilde{\xi}\right) \approx \sum_{i=0}^{P} T_i(x)\Phi_i(\tilde{\xi})$$

Linear superposition instead of solving the PDE numerically

[Ghanem 2006, Xiu and Karniadakis 2002, Xiu 2009,…]

Expansions for ED parameters

Uninformative prior for the vector $\boldsymbol{D} = [D_0, D_1, \dots, D_M]$

$D_m \sim U(D_m^a, D_m^b)$: independent uniform distributions

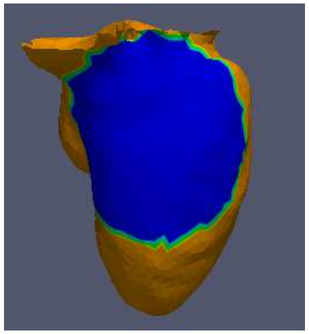
Then we can set $\boldsymbol{\xi} = [\xi_0, \xi_1, \dots, \xi_M]$ with

$\xi_m \sim U(-1,1) \forall m \in [0,1, \dots, M]$

Spectral basis: $D_m = D_m(\xi) = \frac{D_m^b - D_m^a}{2} \xi_m + \frac{D_m^b + D_m^a}{2}$

And $\{\Phi_i(\boldsymbol{\xi})\}$ becomes multivariate Legendre polynomial basis.

Same construction for the onset location



Expansion for the Depolarization Times

$$T(x|D,\Omega_E) = T(x,\xi) \approx \sum_{i=0}^{P} T_i(x)\Phi_i(\xi)$$

Computation of the basis for $\{T_i(x)\}$ which also satisfies

$$T_i(x) = \int_{\Sigma(\xi)} T(x,\xi)\Phi_i(\xi)p(\xi)d\xi$$

Computational Bottleneck

- Galerkin projections into the PDE [Marzouk 2007, 2009]
  - Nonlinearities become a problem
  - Computationally expensive for high dimensional problems, i.e. high *M*
- Numerical integration / Stochastic Collocation [Marzouk 2009]
  - Curse of dimensionality
  - Computationally expensive for high dimensional problems, O(10^5) samples for a problem of 15 dimensions. [Ma 2009]
- Solution: Sparse reconstructions…

Sparse link between parameters and solutions

- For a given point only a small number of parameters influence the result of the ED model.
- We expect a sparse representation in the spectral domain:
  - Only a small number of basis functions $T_i(x) > 0 \; i \in [0, \dots, P]$
  - They can be recovered by a small number of random projections

$$\hat{\boldsymbol{\xi}} = \{\boldsymbol{\xi}_{\boldsymbol{n}}\}_{n=0}^{K} \text{ with K} \ll \text{P}$$

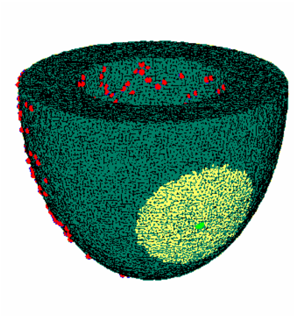
  - And they can be computed by the following problem

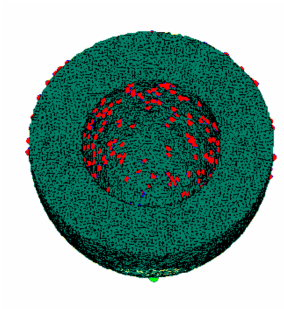
$$\arg\min_{\boldsymbol{T}(x)} \left|\left|\boldsymbol{T}(x)\right|\right|_1 \; subject\ to \; \left|\left|T\left(x, \hat{\boldsymbol{\xi}}\right) - \boldsymbol{\Phi}\left(\hat{\boldsymbol{\xi}}\right)\boldsymbol{T}(\boldsymbol{x})\right|\right|_2 < \delta, \forall x \in \Omega$$

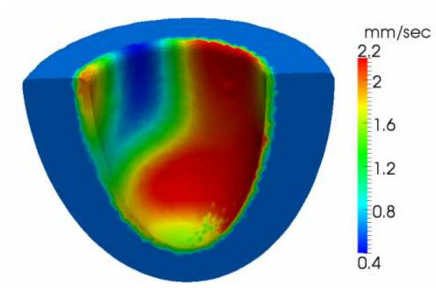
$$\boldsymbol{T}(x) = [T_0(x), \dots, T_P(x)]^t \qquad \left[\boldsymbol{\Phi}\left(\hat{\boldsymbol{\xi}}\right)\right]_{\mathbf{ij}} = \Phi_j(\boldsymbol{\xi}_{\boldsymbol{i}})$$

[Doostan 2009] studied 1D linear diffusion equation

Sparse Reconstruction for the ED Model

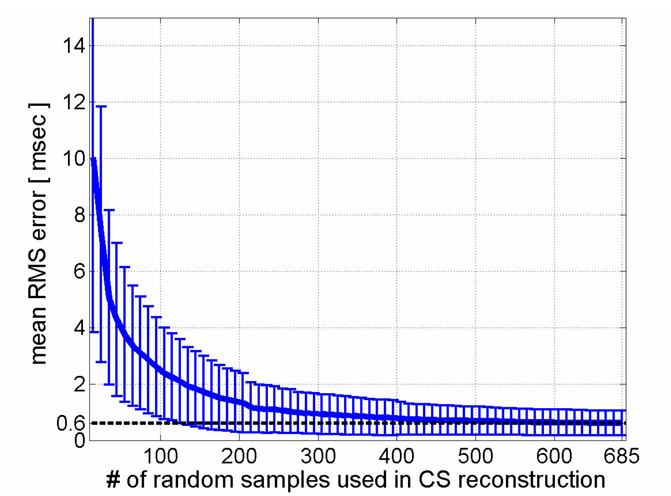

a

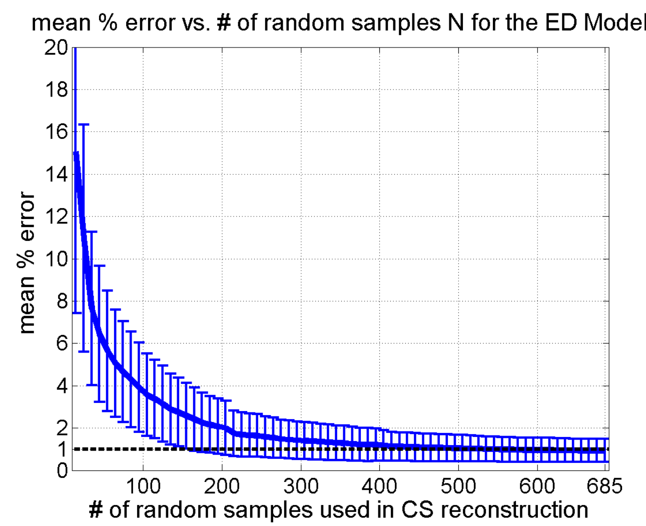

b



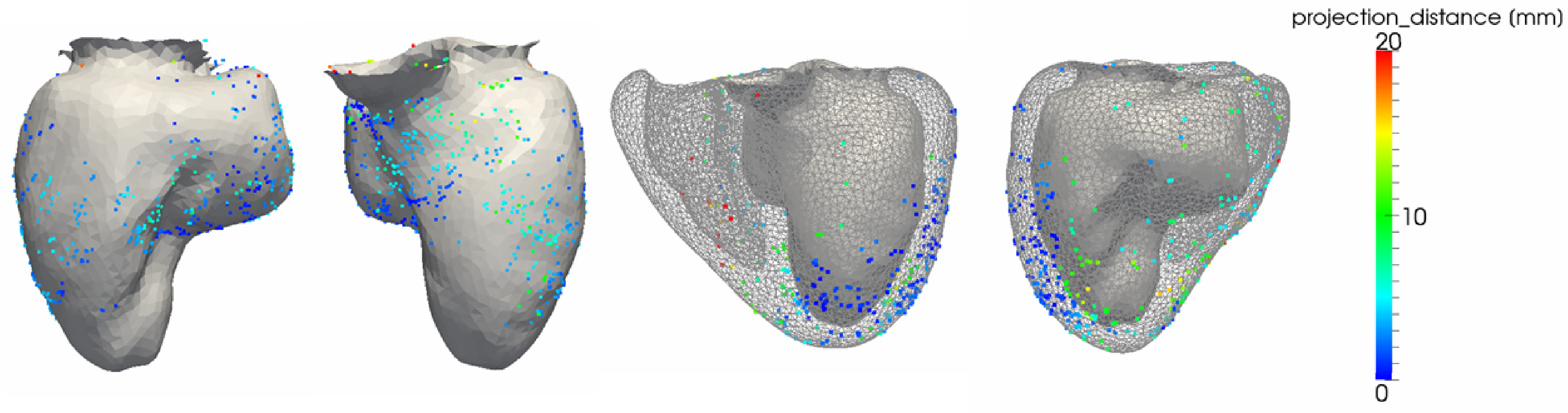
c

- 18 parameters for conductivity
- 2 parameters for onset location
- Cartesian grid in 3D
- Size: 15x15x10 cm^3,
- Resolution: $1mm^3$





Patient Data: Observation Model

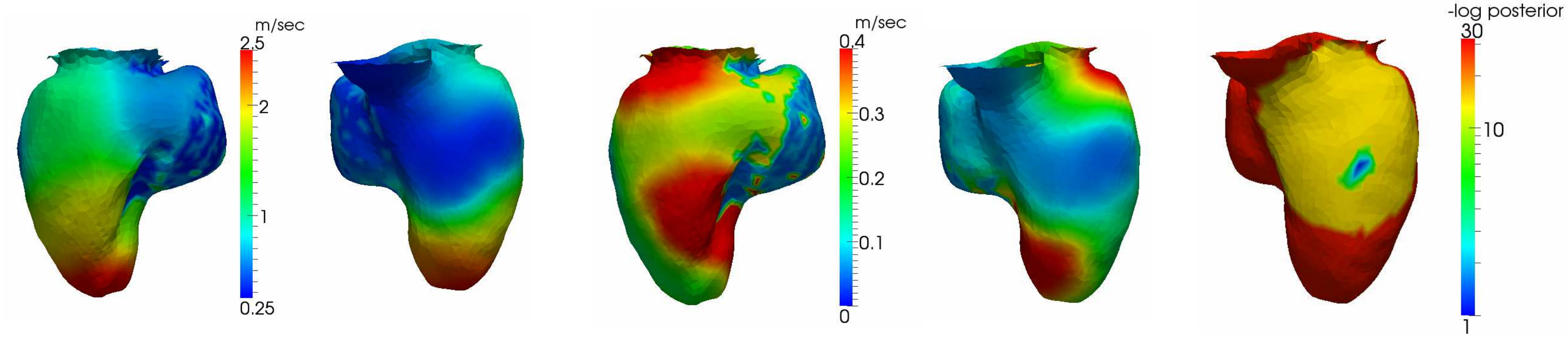


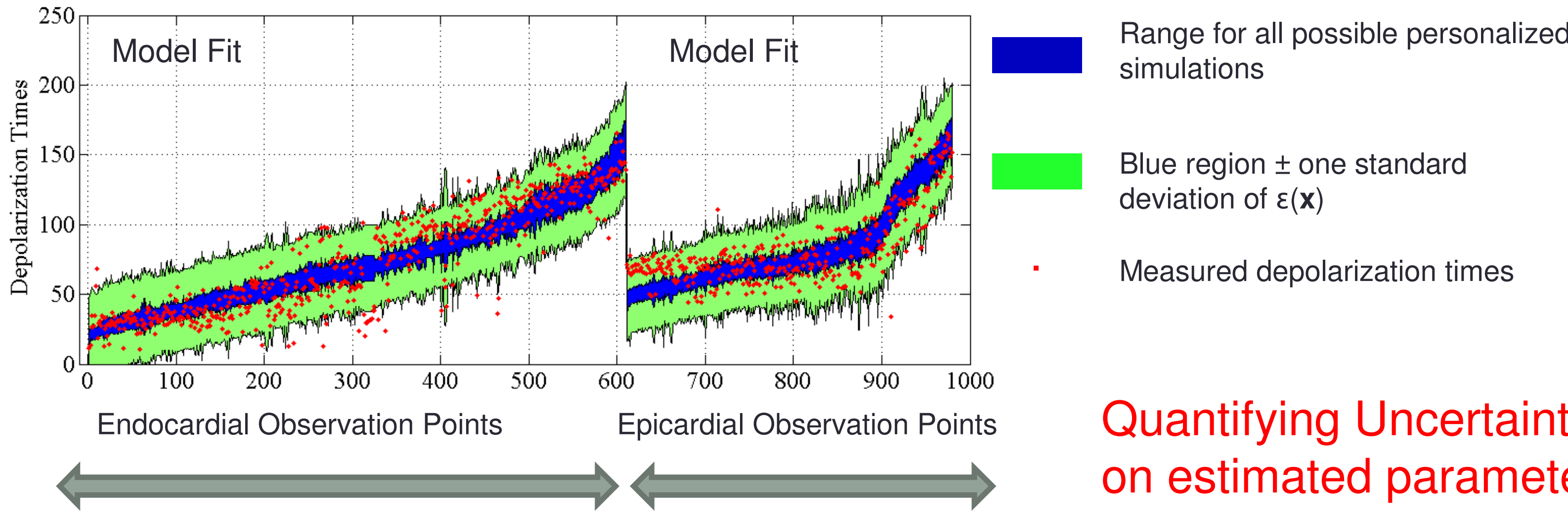
Sources of Uncertainty:
-Acquisition via catheter: motion artefacts
-Projection of observation points onto the patient mesh
-Depolarization times are estimated from potential measurements

$$\widetilde{T}_i = T_i + \epsilon(x)$$

$$\epsilon(x) = N(0{,}400 + \rho_{proj}^2)$$

Personalization

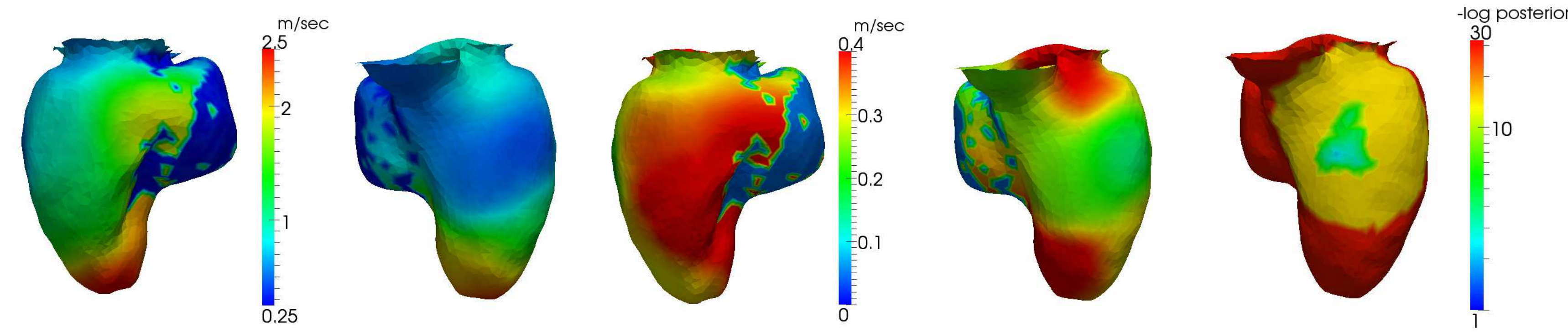


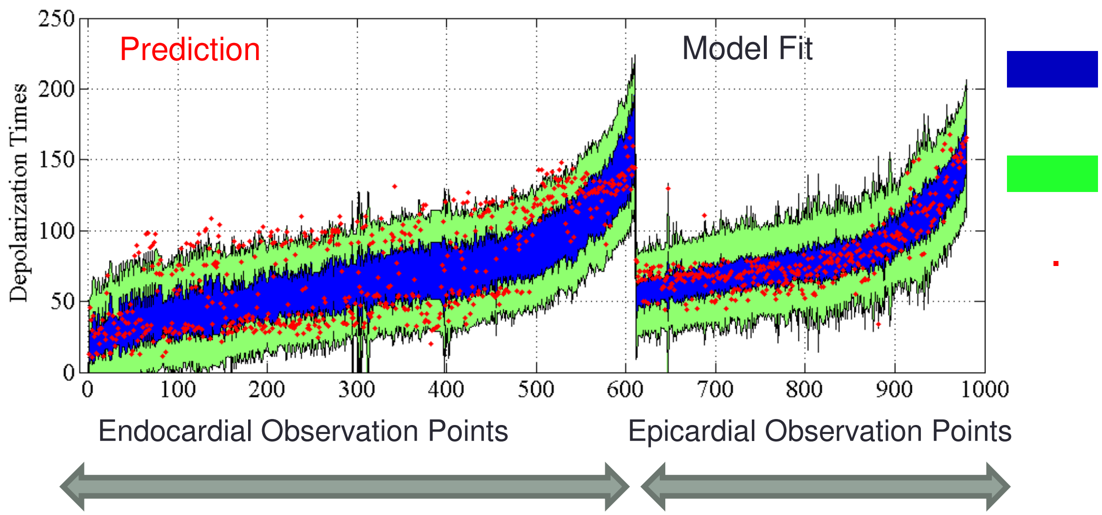


Quantifying Uncertainty on estimated parameters

Konukoglu et al. PBMB 2011

Personalization and Endocardial Prediction





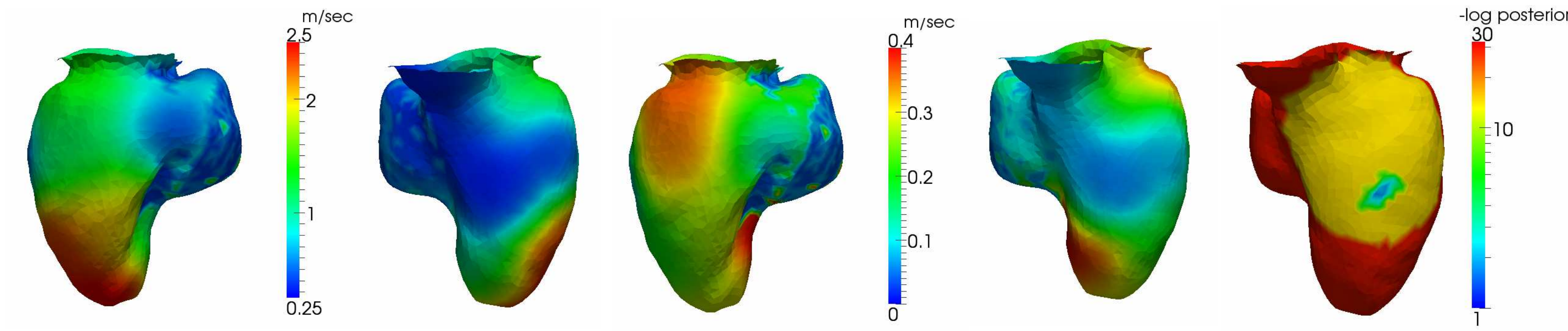
Range for all possible personalized simulations

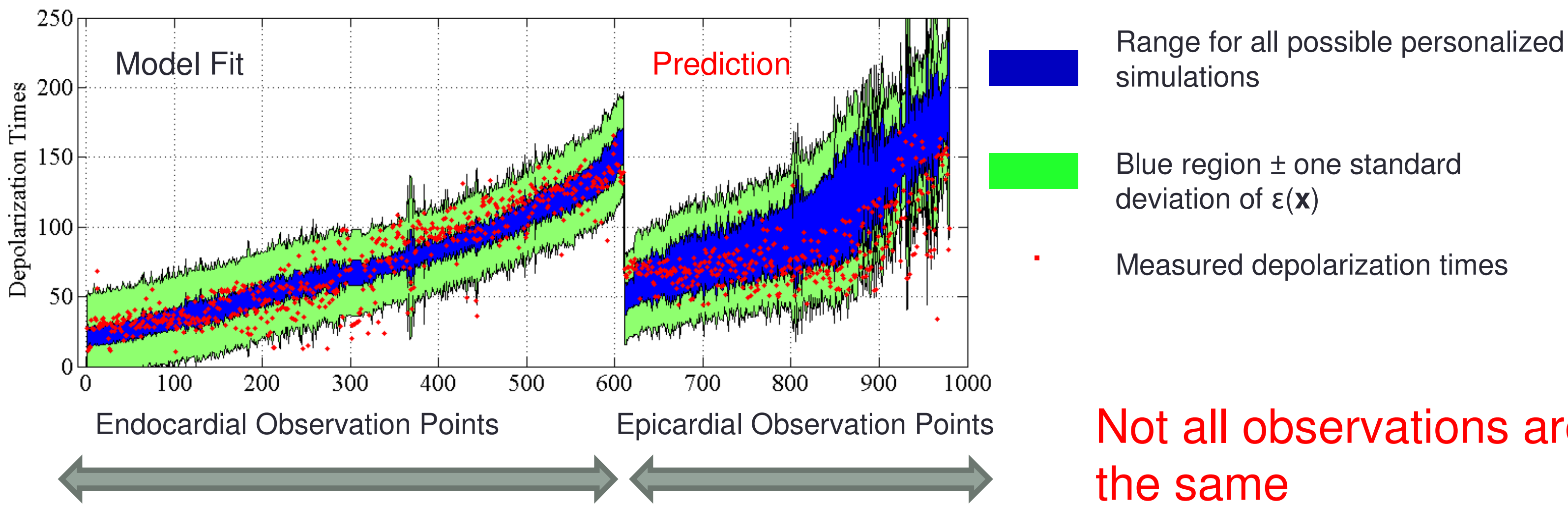
Blue region ± one standard deviation of ε(**x**)

Measured depolarization times

Quantifying Uncertainty on the model predictions

Personalization and Epicardial Prediction





Not all observations are the same

Challenges

- Detailed yet tractable models
- Fusion of information from more sources
- Novel methods for taking into account high dimensional uncertainty
- Multi-scale models
  - Integrating more information: micro arrays, pathology results, history
  - Integrating different scales of computation
  - Numerical challenges
- Inference of micro-scale information from macro-scale data.

Thanks

Microsoft Research Cambridge

Inner eye

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INRIA
centre de recherche SOPHIA ANTIPOLIS - MÉDITERRANÉE

ASCLEPIOS

- Nicholas Ayache
- Maxime Sermesant
- Olivier Clatz
- Xavier Pennec
- Bjoern H. Menze
- Hervé Delingette
- Eric Pernod
- Michel Haïssaguerre

- Andrew Blake
- Antonio Criminisi
- Kilian M. Pohl
- Ben Glocker
- Emmanuel Mandonnet
- Pierre-Yves Bondiau
- Erin Stretton
- Phani Chipchapatnam

- Health-e-Child European project
- Compu-Tumor initiative
- Microsoft-Amalga product team

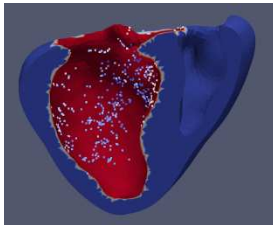
Thanks

- Health-e-Child European project
- Compu-Tumor initiative
- Microsoft-Amalga product team

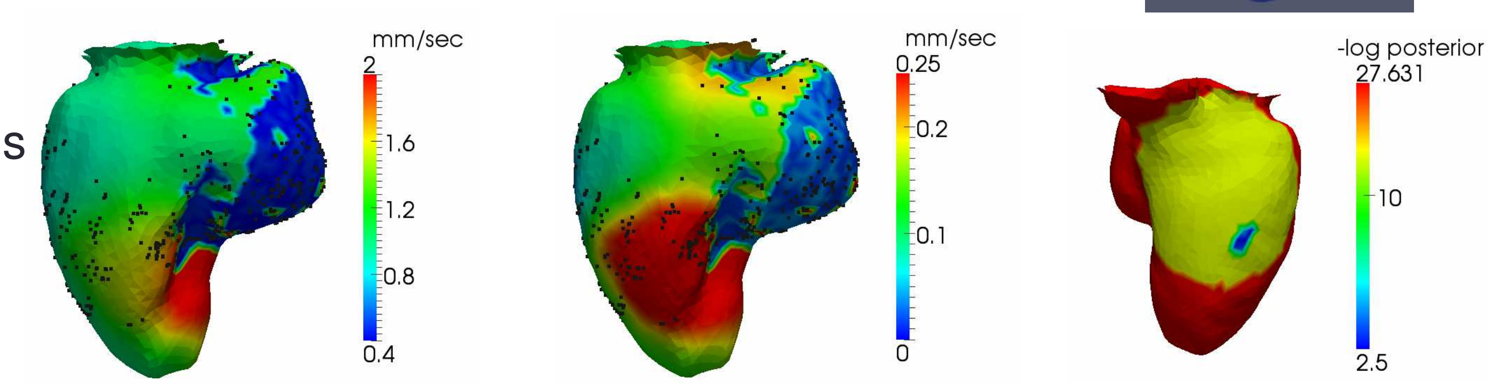
Personalization under Uncertainty [PBMB under revision]

$$c_0 D(x)\left(\sqrt{\nabla T(x)^t \boldsymbol{M}(x)\nabla \mathrm{T}}\right) - \nabla \cdot \left(D(x)\boldsymbol{M}(x)\nabla \mathrm{T}(\mathrm{x})\right) = \tau, x \in \Omega/\Omega_E$$

- Functional Conductivity
- Onset Location
- Efficient Inference using Spectral Methods



Homogeneous Uncertainty



Uncertainty based on Projection Distances