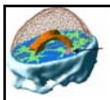
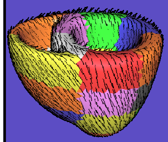
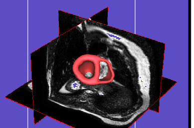


Modélisation cardiaque et croissance de tumeurs

Hervé DELINGETTE

Herve.Delingette@inria.fr

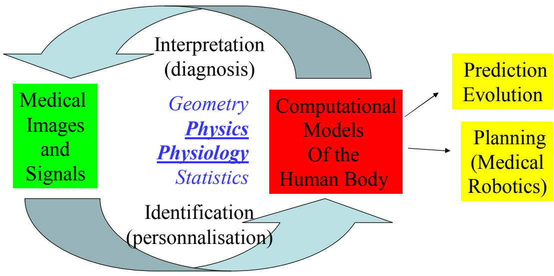




40 ans

INRIA

Computational Models of the Human Body



40 ans

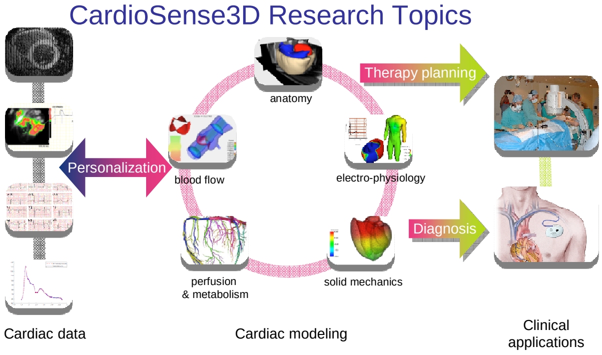
INRIA

PART I
Cardiac Modeling
(CardioSense3D project)

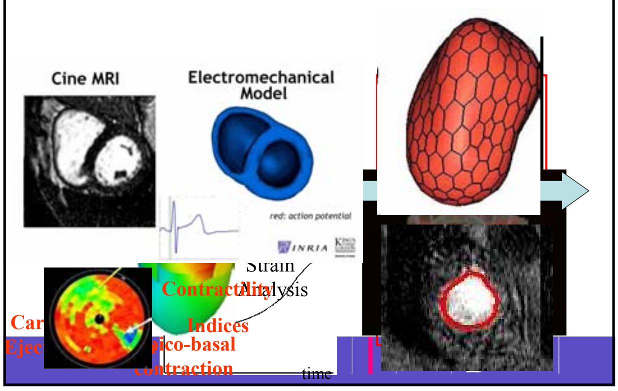
INRIA

JM Peyrat, M. Sermesant, H. Delingette, N. Ayache
Asclepios Team, INRIA
P. Moireau, D. Chapelle, Macs Team, INRIA
M. Sorine, Sisyphe Team, INRIA
M. Fernandez, JF. Gerbeau, Reo Team, INRIA

CardioSense3D Research Topics



Next Generation of Cardiac Models



CardioSense3D : Academic / Clinical / Industrial Partnership

Physiology/Control
- **Sisyphe/Sosso**, INRIA

Numerical Analysis
- **Macs**, INRIA
- **Reo**, INRIA
- Geometrica, INRIA
- Gamma, INRIA
- Univ. de Nantes
- Pzlen Univ. (Czech Rep.)
- LIRMM (Montpellier)

Industrial Partners
- Philips Research France
- ELA Medical
- Siemens

Imaging/Simulation
- **Asclepios**, INRIA
- UCL / King's College (London)
- Creatis, CNRS

Clinical Sites
- Guy's Hospital (London)
- NIH (Washington)
- HEGP, U678 (Paris)
- Hopital Henri Mondor (Créteil)
- Sunnybrook Health Sciences Center
- InParys, Clinique George Bizet
- Hopital Bicêtre + Paris XI U. +INSERM (Paris)

Objectives

Build a patient specific heart simulator

Estimate the parameters of this model from observations of the cardiac function,

Propose models having a low number of parameters

Develop clinical applications (Cardiac Resynchronisation Therapy, radiofrequency ablation,..)

.

40 ans INRIA

Positioning of CardioSense3D

•Integrate/Couple 4 physiological phenomena :

Electrophysiology, *Contraction/Relaxation Mechanics*, *Arterial Circulation*, *Perfusion/Metabolism*

•To propose models having a low number of parameters in order to estimate them from clinical data.

•Develop clinical applications (CRT, RF Ablation) based on personalized models

40 ans INRIA

Overview

Introduction

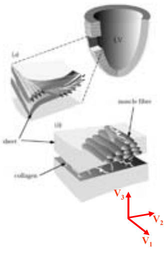
Work in progress

- Geometric Modeling
- Electrophysiology Modeling
- Mechanical Modeling
- Clinical Evaluation

Conclusion

40 ans INRIA

Cardiac Microstructure [LeGrice,1995]



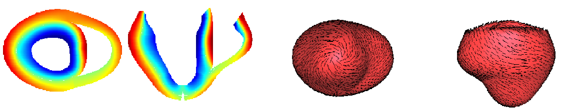
- Myocardial fibers
- Laminar sheets

- Play an important role in cardiac modeling (Electrophysiology, Mechanics)

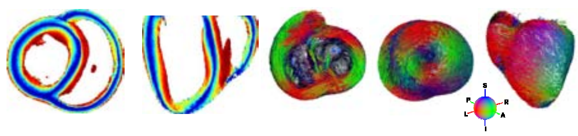
- Correlation with DT MRI eigenvectors [Scollan,1998] [Helm,2005]
  - primary as fiber orientation
  - secondary as orthogonal to fibres in the sheet plane
  - tertiary as normal to sheet plane

Modelling the Cardiac Anatomy

Dissection *(P. Hunter group, Auckland University, New Zealand)*



Diffusion Tensor MR *(NIH, JHU. Mean tensors: J-M Peyrat)*

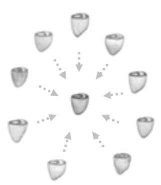


Fibre tracking visualisation with *MedINRIA* developed by Pierre Fillard and Nicolas Toussaint, INRIA, Asclepios. *AHA segments*

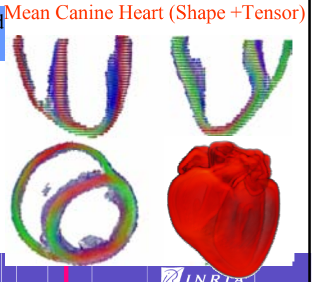
Statistical Atlas of cardiac DTI

Based on 9 canine hearts (E. McVeigh, NIH, JHU)

Diffusion tensor MRI Registered in a common anatomical frame

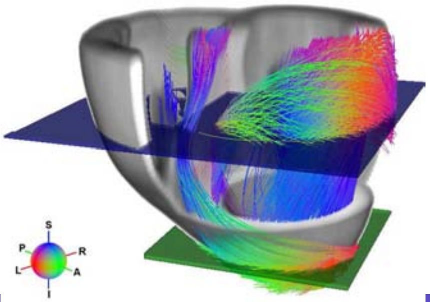


Mean Canine Heart (Shape +Tensor)



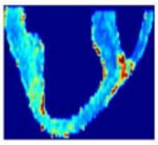
J.M. Peyrat, M. Sermesant, X. Pennec, H. Delingette, C. Xu, E. McVeigh, N. Ayache, MICCAI, Oct 2006

Fiber Tracking on the Average Cardiac DTI



http://www.inria.fr/asclepios/software/MedINRIA

Variability of Cardiac Structures



Covariance Computed in the Log-Euclidean Metrics

J.M. Peyrat, M. Sermesant, X. Pennec, H. Delingette, C. Xu, E. McVeigh, N. Ayache, MICCAI, Oct 2006

Primary eigenvector

Secondary eigenvector

Tertiary eigenvector

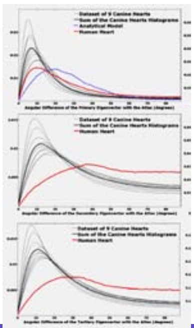


Fig. 6. [Left Column] Normalized histogram eigenvectors variations around their mean. [R primary, secondary and tertiary eigenvectors

	Angular Difference	Mahalanobis
Distance		
Primary		
Secondary		
Tertiary		

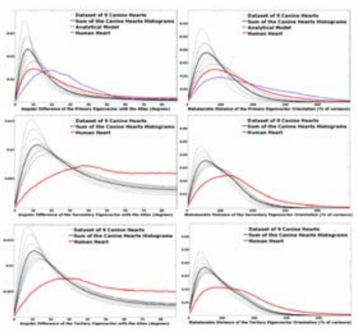


Fig. 6. [Left Column] Normalized histograms of the primary, secondary and tertiary eigenvectors variations around their mean. [Right Column] Mahalanobis distance of the primary, secondary and tertiary eigenvectors variations around their mean.

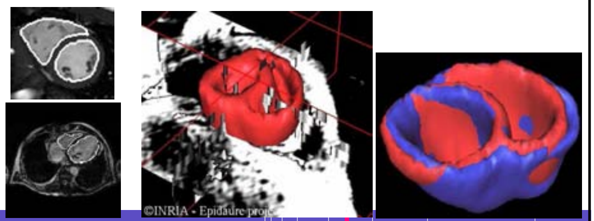
Patient-specific Model

From medical images to specific anatomy:

blood pool segmentation *(fuzzy classification, semi-automatic)*

affine registration with model *(automatic)*

biomechanical deformable model *(semi-automatic)*



Sermesant M, Rhode K, Sanchez-Ortiz G, Camara O, Andriantsimiavona R, Hegde S, Rueckert D, Lambiase P, Bucknall C, Rosenthal E, Delingette H, Hill D, Ayache N, Razavi R. Simulation of cardiac pathologies using an electromechanical biventricular model and XMR interventional imaging. *Medical Image Analysis*, 9(5): 467-80 M, 2005.

Overview

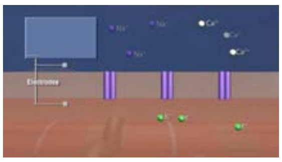
Introduction

Work in progress

- Geometric Modeling
- ⇒ Electrophysiology Modeling
- Mechanical Modeling
- Clinical Evaluation

Conclusion

Modelling Cardiac Electrophysiology



Three main approaches:

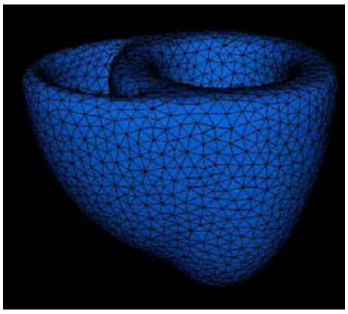
1. Biophysical ionic models
   Hodgkin-Huxley, Luo-Rudy, Noble
2. Phenomenological models
   Mitchell;Schaeffer, FitzHugh-Nagumo, Aliev-Panfilov
3. Eikonal Equation
   Keener, Colli-Franzone

Aliev-Panfilov *reaction-diffusion* equations

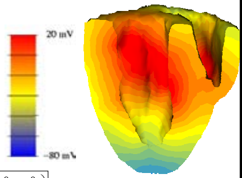
$$\begin{cases} \partial_t u = \mathrm{div}\,(D\,\nabla u) + ku(1-u)(u-a) - uz \\ \partial_t z = -\varepsilon(ku(u-a-1)+z) \end{cases}$$

u transmembrane potential
D diffusion tensor including fibre orientations
z repolarisation variable

ElectroPhysiology Simulation



$$\begin{cases} \dfrac{\partial u}{\partial t} = div(D\nabla u) + f(u) - z \\ \dfrac{\partial z}{\partial t} = b(u - cz) \end{cases}$$



Color : Action Potential u

$$D = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 0.6 & 0 \\ 0 & 0 & 0.6 \end{pmatrix}$$

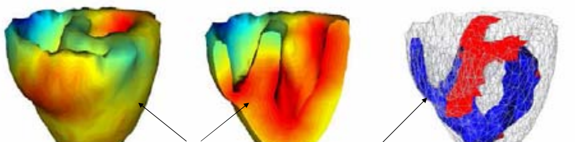
Electrophysiology Modeling

Developing fast EP models for real-time simulation (training or therapy guidance)

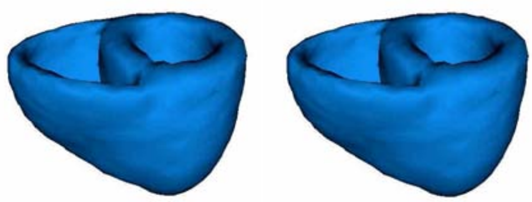
$$c\,\|\nabla T\| - k\,\|\nabla T\|\, div\left(\frac{\nabla T}{\|\nabla T\|}\right) = 1$$

(Keener, Colli-Franzone)

1 second of computation for 1 cardiac cycle !!



Pathology Simulation *(preliminary results)*

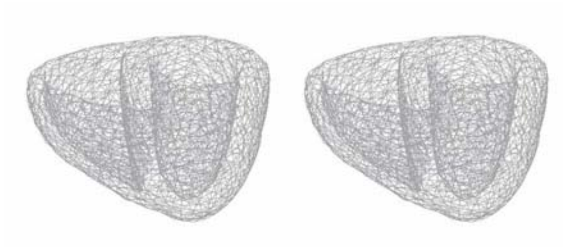


Normal heart
Ectopic Pacing

Pseudo-potential
Blue: excitable
Red: depolarised
Yellow: refractory

Infarcted Area
10 times less conductive
→Ventricular tachycardia
→Ventricular fibrillation?

Pathology Simulation *(preliminary results)*

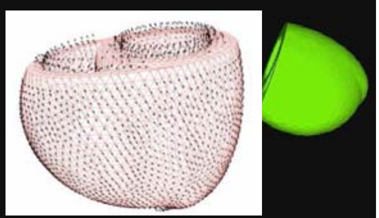


Normal heart
Ectopic Pacing

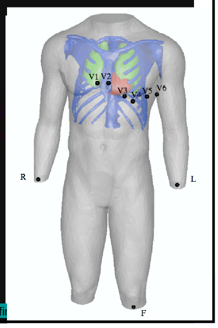
Depolarisation Front
Blue: depolarised side
Red: excitable side
*Black: **Repolarisation Front***

Infarcted Area
10 times less conductive
→Ventricular tachycardia
→Ventricular fibrillation?

[redacted]



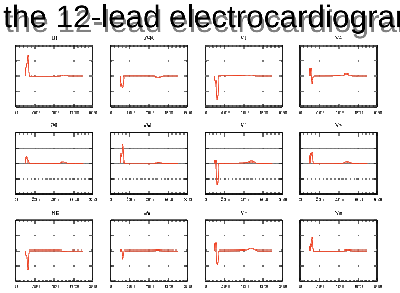
finite element mesh: 61 512 tetrahedra



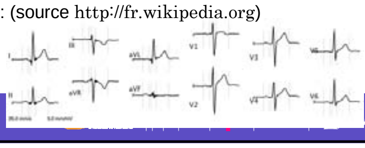
M. Boulakia, MA Fernandez, JF Gerbeau, N. Zemzemi, "Towards the numerical simulation of electrocardiograms", FIMH'07, June 2007

Simulating the 12-lead electrocardiogram

- Simulated ECG:



- Normal ECG: (source http://fr.wikipedia.org)



Overview

- Introduction
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  - Geometric Modeling
  - Electrical Modeling
  - Mechanical Modeling
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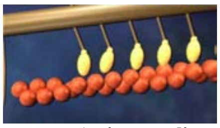
Electromechanical Coupling



Bestel-Clément-Sorine coupling equations inspired from Huxley Filament model

Active non-linear visco-elastic anisotropic and incompressible Material

$$
\begin{aligned}
&\rho \ddot{P} - \mathrm{div}(K_p \mathcal{E}_p + C_p \dot{\mathcal{E}}_p + \sigma_c + C_c \dot{\mathcal{E}}_c + K_c \xi_0) = 0 \\
&\partial_t K_c = K_0 |u|_+ - (|\dot{\mathcal{E}}_c| + |u|) K_c \\
&\partial_t \sigma_c = \sigma_0 |u|_+ - (|\dot{\mathcal{E}}_c| + |u|) \sigma_c + K_c \dot{\mathcal{E}}_c \\
&\sigma_c + C_c \dot{\mathcal{E}}_c + K_c \xi_0 = K_s (\mathcal{E}_p - \mathcal{E}_c)
\end{aligned}
$$

Compact Model (5 variables) adapted to the macroscopic modeling of the cardiac function and clinical applications

Cardiac Contraction

4 Cardiac Phases:
- Filling
- Isovolumetric Contraction
- Ejection
- Isovolumetric Relaxation

2 Volumetric Conditions:
- Pressure Field in the endocardium
- Isovolumetric Constraint of myocardium

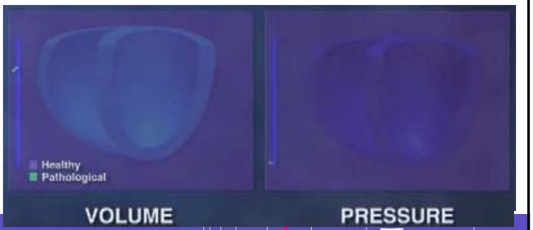
Slowed 6 times

Pathology Simulation

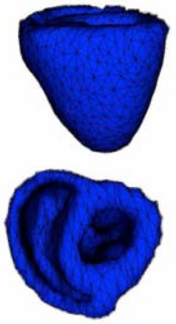
Simulation of a Left Bundle Branch Block

Slowed

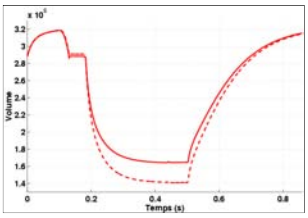
9 times



Infarct Simulation



Simulation Of Infarcted zone



volume

Ejection Fraction:
56 % → 48 %

Overview

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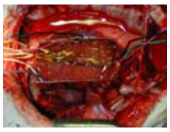
Clinical Evaluation : A Scalable Approach

Motion/Anatomical Data	Electrophysiological Data	Comments
Tagged + anatomical + DTI MR	Socket of Electrodes	Very invasive Registered data E. McVeigh NIH

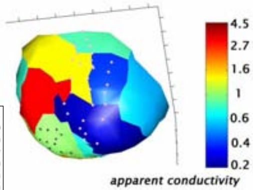


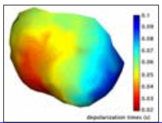
In Vivo Measures (Canine Heart)

National Institute of Health, Laboratory of Cardiac Energetics

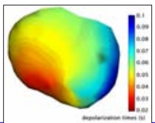
Elliot McVeigh, Owen Faris, Hiroshi Ashikaga

- Artificial electrical pacing
- Electrical: epicardial electrodes socket (128 positions* 500 t)
- Motion: MR Images (102 positions * 32 t)





Measured depolarisation times



Simulated depolarisation times

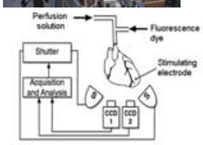
A large part of the infarcted area is included in the zones of low conductivity

Data acquisition, processing and fusion

Joint work with Sunnybrook Health Sciences Center, Toronto, Canada

Getting model and measures

1. Optical recording of electrical waves based on voltage-sensitive fluorescence dye



[Pop, M., Sermesant, M., Chung, D., Liu, G., McVeigh, E., Crystal, E., Wright, G.: **An experimental framework to validate 3D models of cardiac electrophysiology via optical imaging and MRI**. In: FIMH'07 and submitted to Medical Image Analysis (in revision)]

Data acquisition, processing and fusion

Joint work with Sunnybrook Health Sciences Center, Toronto, Canada

Getting model and measures

1. Optical recording of electrical waves based on voltage-sensitive fluorescence dye

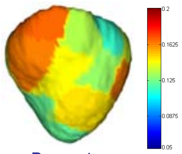
raw signal

[Pop, M., Sermesant, M., Chung, D., Liu, G., McVeigh, E., Crystal, E., Wright, G.: **An experimental framework to validate 3D models of cardiac electrophysiology via optical imaging and MRI**. In: FIMH'07 and submitted to Medical Image Analysis (in revision)]

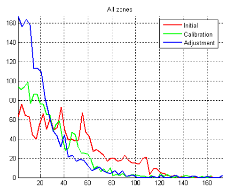
Results on APD

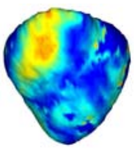
Mean global error on action potential duration :

- Initial → 44.6 *ms*
- Calibration → 28.1 *ms*
- Adjustment → 21.5 *ms*

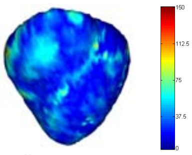


Parameter *a*





Initial error

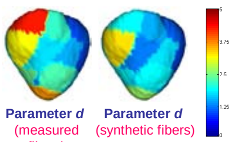


Adjustment error

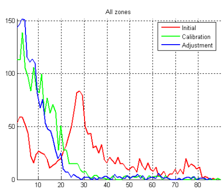
Results on depolarization time

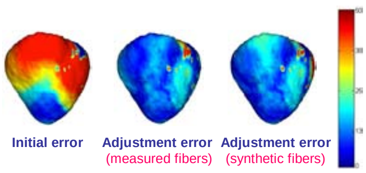
Mean global error on depolarization times :

- Initial → 30.6 *ms* / 37.9 *ms*
- Calibration → 12.0 *ms* / 10.9 *ms*
- Adjustment → 10.0 *ms* / 10.7 *ms*



Parameter *d* (measured fibers) **Parameter *d*** (synthetic fibers)

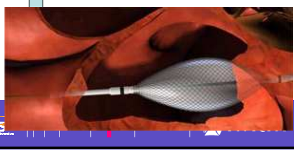




Initial error **Adjustment error** (measured fibers) **Adjustment error** (synthetic fibers)

Clinical Evaluation

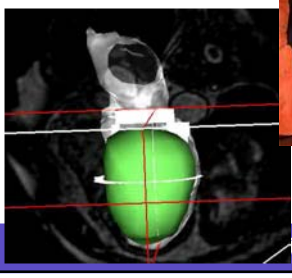
Motion/Anatomical Data	Electrophysiological Data	Comments
Tagged + anatomical + DTI MR	Socket of Electrodes	Very invasive Registered data NIH
Tagged + anatomical MR	ESI 3D endocardial mapping	Less invasive Non-Registered data Guy's Hospital, KCL



In Vivo Clinical Measures

King's College, division of Imaging Sciences
The Guy's, King's and St Thomas' School of Medicine

- Electrical : Basket of electrodes inserted through catheters
- Motion : tagged MRI + Angiography

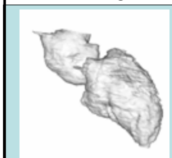


Sermesant-Hill et al
Miccai'04

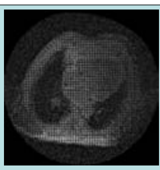
INRIA

Clinical Case (Guy's Hospital)

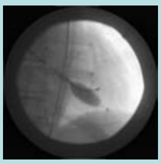
- Patient aged 68 post-infarctus



MR Anatomical Image



Tagged MR Image

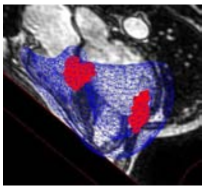


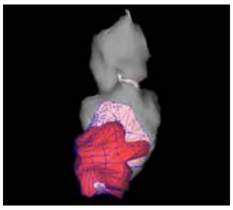
X-Ray Image with ESI system

Data fusion

40 ans INRIA 39

Left Bundle Branch Block Simulation

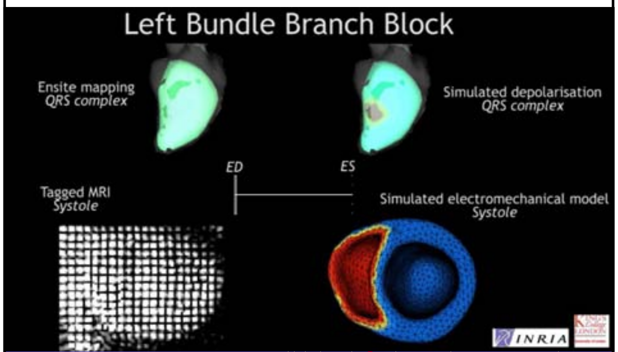




1. Adjustment of a generic model
2. Inclusion of infarted zones

3. Registration of Electrophysiological Mapping on the Anatomical Surface

Model initialised with ESI



A Scalable Approach

Motion/Anatomical Data	Electrophysiological Data	Comments
Tagged + anatomical + DTI MR	Socket of Electrodes	Very invasive Registered data NIH
Tagged + anatomical MR	ESI 3D endocardial mapping	Less invasive Non-Registered data Guy's Hospital
Cine MR or 3D echo	ECG or VCG or ECGI	Non invasive Partial data HEGP InParys

Perspectives

Automatically adjust model parameters from observations (preliminary results on EP and EM)

Validation the EM model by comparing cardiac motion from tagged MRI + ECG

Optimization of pacemaker leads for CRT

Use of non-invasive Data (3D US + ECGI)

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D. Hill

Univ. Nantes
Y. Coudière

Site : www.inria.fr/CardioSense3D

PART II
Patient Specific Tumor Growth Modeling

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Asclepios Team, INRIA

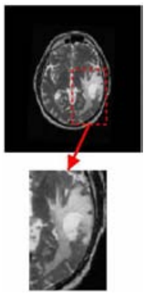
Pierre-Yves Bondiau
C. Antoine Lacassagne, Nice

Problem position

Understanding both the diffusion process of gliomas and its mechanical influence

Using the model to

- Characterize the tumor growth from MR Images
- Identify invaded area that are not visible in the MRI
- Predict future evolution of the tumor



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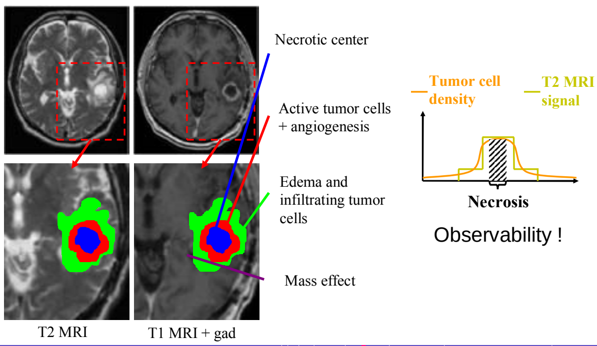
Tumor biology



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Overview

Introduction

Glioblastoma growth simulation

Patient Specific Simulation

Radiotherapy margin computation

Perspectives

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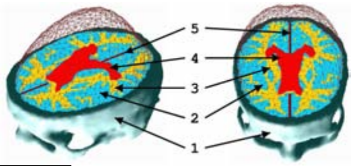
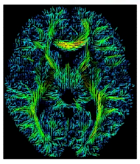
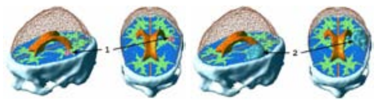
Geometric model



1. Skull.
2. Gray matter
3. White Matter
4. Ventricles
5. Falx cerebri



DTI (patient - atlas)



Initial position of the tumor

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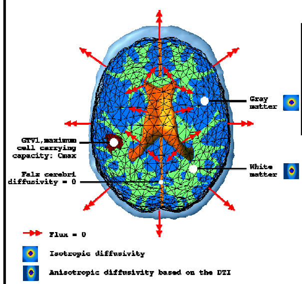
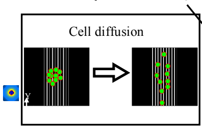
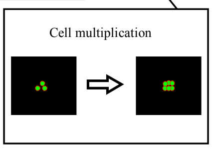
Diffusion model

Reaction diffusion equation $\frac{\partial c}{\partial t} = \nabla \cdot (D\nabla c) + \rho c(1-c), \ (D\nabla c)\cdot n_B = 0$







40 ans | INRIA

Mechanical model

- Linear elasticity for the brain :

$\sigma = \lambda tr(\varepsilon) + 2\mu\varepsilon \quad \varepsilon = \frac{1}{2}\left(\nabla u + \nabla u^T\right)$

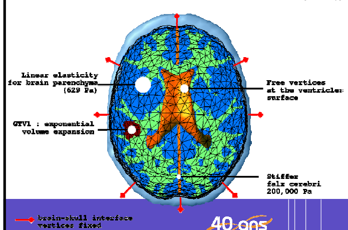
σ = Stress
ε = Stress

λ, μ = Lamé Coefficient
u = Displacement

- Influence of tumor cells on the mechanics

$\mathrm{div}(\sigma - \alpha c\, I_3) + Fe = 0$

α = Coupling factor
Fe = External forces



Summary:

- *Linear relationship force | displacement*
- *Tumor acts as a local pressure*

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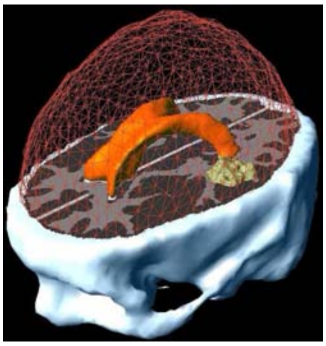
Tumor Growth simulation



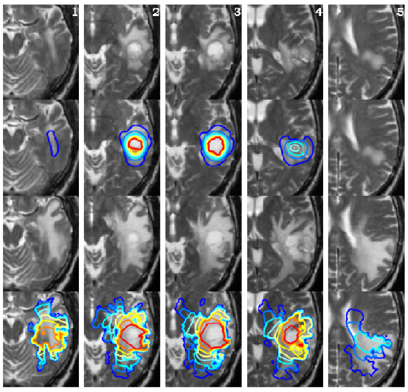
Results

March 2002

March 2002 +
initial contour

September 2002

September 2002 +
simulation contours



Analyzing Diffusion Model

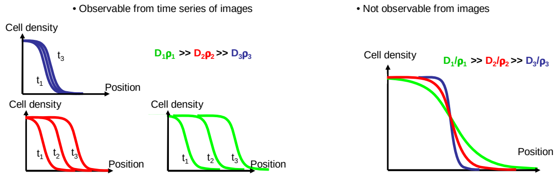
$$\frac{\partial c}{\partial t} = \nabla.(D\nabla c) + \rho c(1-c)$$

$v \propto D\rho$

- Growth speed
- Parameter Estimation
- Quantification
- Observable from time series of images

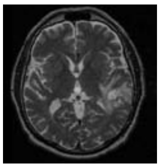
D/ρ

- Tumor profile
- Infiltration extent
- Extrapolation
- Not observable from images



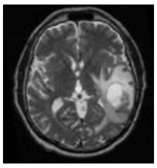
Overview

Model Based Growth Quantification



6 months

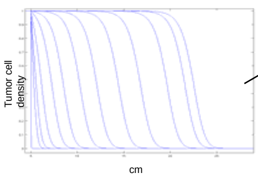
v_w, v_g

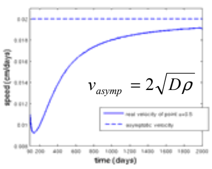


- What is the speed in the white and in the grey matter?
- Speed of progression as a tool for characterization/quantification.
- Tumor fronts (CTV extent) :
  - Tumor infiltrated edema extent for high grade tumors
  - Bulk tumor extent for low grade tumor

Front Motion Approximation

- Using the asymptotic approximation in the 1D case:



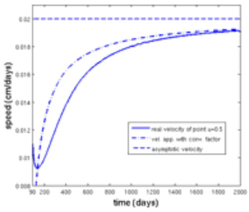


- Assuming visible tumor front is an iso-density surface.
- Generalizing into 3D gives the traveling time formulation for the motion of the tumor front:

$$\sqrt{\nabla T' D \nabla T} = \frac{1}{2\sqrt{\rho}}$$

Front Approximation 2nd Order

- A second order approximation includes:
  - Transient motion towards the asymptotic speed.
  - Effect of the curvature on the 3D tumor front.



$$v(t) = 2\sqrt{(n'Dn)\rho} - \underbrace{\frac{3}{2t}\sqrt{\frac{n'Dn}{\rho}}}_{\text{convergence}} - \underbrace{(n'Dn)\kappa}_{\text{curvature}}$$

$$\sqrt{\nabla T' D \nabla T} = \frac{2T\sqrt{\rho}|\nabla T|}{4T\rho|\nabla T| - 3|\nabla T| - 2T\sqrt{(\nabla T' D \nabla T)\rho\kappa}}$$

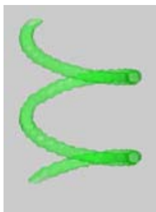
Recursive Fast Marching

Anisotropic Eikonal equation

Recursively correcting errors due to anisotropy.


Normal Fast Marching

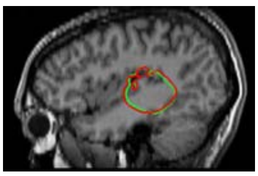

Recursive Fast Marching

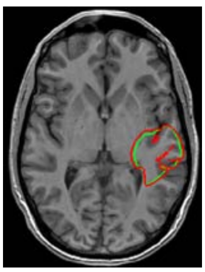


Fast and efficient even for very high anisotropies.

Works on general meshes.

Comparing Approximation with the Model



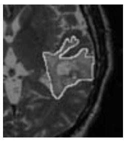


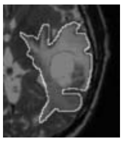
Green: Tumor iso-density surface computed with the reaction-diffusion model.

Red: Same iso-density computed with the asymptotic approximation.

Speed of Progression

- Speed in wm and speed in gm between two images.
- Inputs are tumor delineations.
- Optimizing the D and the ρ such that mathematical formulation explains the observed delineations.



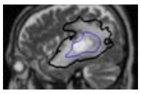


Γ_1 Γ_2

$$C(v_w, v_g) = \frac{1}{2}\left[dist\left(\Gamma_2, \overline{\Gamma_2}\right), dist\left(\overline{\Gamma_2}, \Gamma_2\right)\right]$$

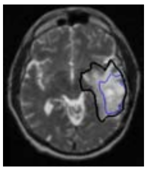
$$\overline{\Gamma_2} = \left\{ x \middle| T(x) = t_2 - t_1, \sqrt{\nabla T' D \nabla T} = \frac{1}{2\sqrt{\rho}}, T(\Gamma_1) = 0 \right\}$$

Speed of Progression



$v_w = 0.43 \frac{mm}{day}$

$v_g = 0.041 \frac{mm}{day}$



Blue: Manual delineation of the tumor at the 1st time acquisition.

Black: Tumor front computed by the model for the 2nd time acquisition with the optimum parameters.

- Gives us simple numerical values characterizing the tumor:
  - Statistics on populations
  - Staging of the tumor
  - Therapy efficacy
- Gives us the patient specific parameters for the general model.

Overview

Introduction

Glioblastoma growth simulation

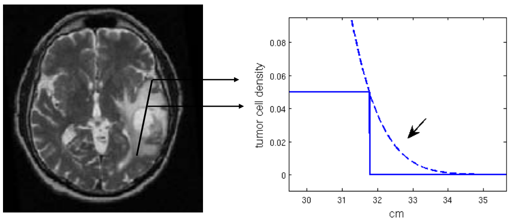
Patient Specific Simulation

→ Radiotherapy margin computation

Perspectives

Extrapolating Tumor Invasion

- CT and MR have limited resolution for tumor cells.
- We do not see the whole tumor infiltration.
- Use of growth dynamics to understand the extents of the tumor.

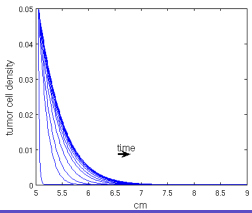


Tail Distribution

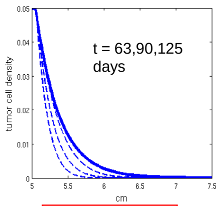
$$\frac{\partial c}{\partial t} = \nabla.(D\nabla c) + \rho c(1-c)$$

Traveling wave solution in the infinite cylinder with constant D:

$$c(\vec{x},t) = u(\vec{x}\cdot\vec{n} - vt) = c(\xi)$$



$$u(\xi) = u_0 \exp\left(-\sqrt{\frac{\rho}{\vec{n}\cdot(D\vec{n})}}\,\xi\right)$$



$$\frac{\sqrt{\nabla u\cdot(D\nabla u)}}{\sqrt{\rho u}} = 1$$

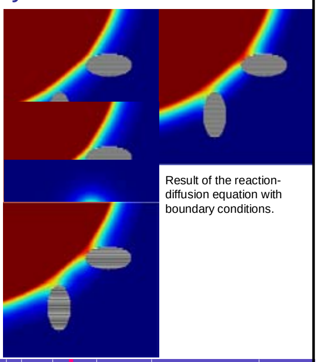
Effect of the Boundary Condition

No flux boundary condition affects the tumor cell density.

Therefore it affects the tails of the tumor profile.

This can be taken into account in the tail distribution formulation by method of reflection.

Reflecting the tumor cells off the boundaries.

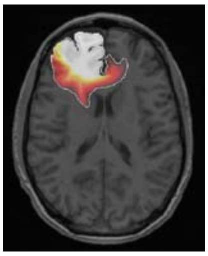


Result of the reaction-diffusion equation with boundary conditions.

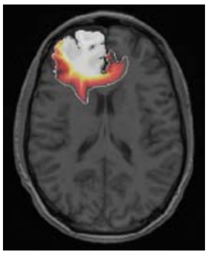
Comparison with the Model

White: Visible part of the tumor

Yellow – Red: Tails of the tumor from 10% to 1% of the tumor cell capacity.

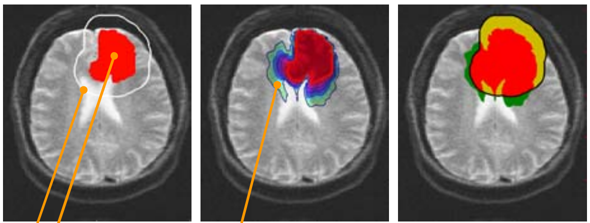


Tails of the tumor computed by the reaction-diffusion model



Tails approximated by the extrapolation method

Invasion Extent vs. Irradiation Margin



Visible tumor

Radiotherapy margin (2cm)

Simulated probability of finding tumor cells

Invaded area targetted by radiotherapy

Area targetted by radiotherapy BUT NOT invaded

Area invaded BUT NOT targetted by radiotherapy

Perspectives

Validation of the model through
- Predicting growth for untreated cases.
- Recurrence after surgery/therapy.

Provide a confidence interval
- In the extent of the tumor
- In the tumor cell probability

Modeling the therapy response
- Response to drug.
- Response to irradiation.

Including more modalities and improving the model.
- Spectroscopy
- PET,…

Thank you.