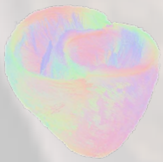
From Biomedical Images To Virtual Personalized Physiological Patients

Let's Imagine the Future

for Jean-Pierre Banâtre

Rennes

9 November 2012



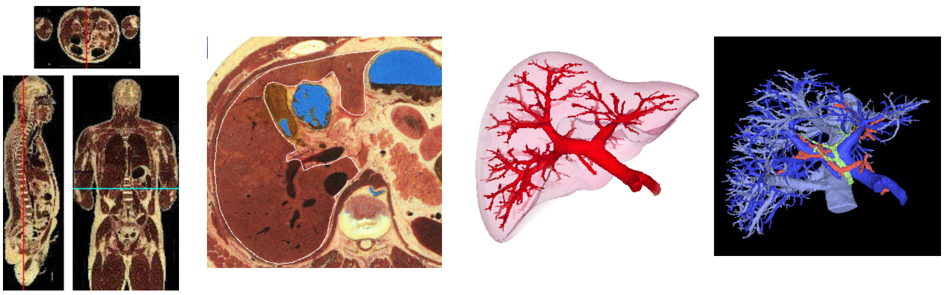
Nicholas Ayache

http://www-sop.inria.fr/Asclepios/

Inria

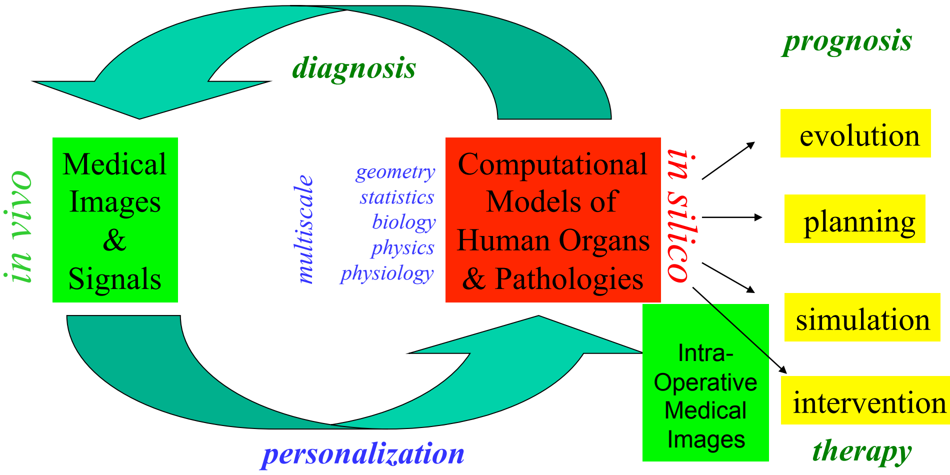
INVENTORS FOR THE DIGITAL WORLD

The Visible Human Project-NLM 1996-2002



- Anatomy only
- 1 subject
- No function
- No variability

Oct 2004 -2012 : Virtual Personalized Physiological Patient



•Computational Models for the Human Body, Elsevier, July 2004. Ayache, N, Ciarlet P., Lions JL(Editors)
•Towards Virtual Physiological Human (VPH), European White Paper , Nov. 2005. Ayache, N, Frangi A, Hunter P, Hose R, Magnin I, Viceconti M. et al., The Virtual Physiological Human, Interface Focus, Royal Society 2011, Coveney P, Diaz V, Hunter PJ, Kohl P, Viceconti M

April 2012-17

erc MedYMA
Advanced Grant 291080

- Push forward Statistical & Biophysical Models
- *Analysis* and *Simulation* of **Me**dical **Dy**namic **Ima**ges
- To improve *diagnosis*, *prognosis*, *therapy*

Clinical Applications

- Computational Oncology
  - **Brain tumors** (gliomas), Liver, etc…
- Computational Neurology
  - **Alzheimer's Disease,** Multiple Sclerosis,…
- Computational Cardiology
  - **Heart Failure, Arrhythmia,**…

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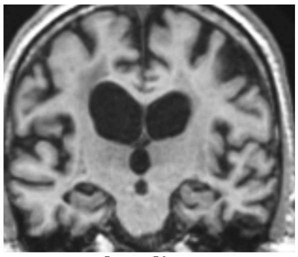
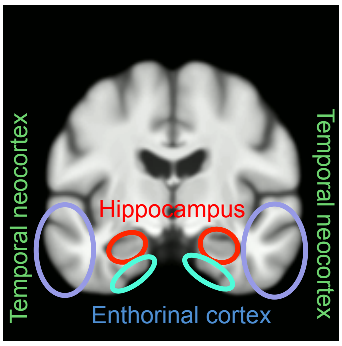
Alzheimer's Disease

- Most common form of dementia
- 18 Million people worldwide
- Prevalence in advanced countries
  - 65-70: 2%
  - 70-80: 4%
  - 80 -   : 20%
- If onset was delayed by 5 years, number of cases worldwide would be halved

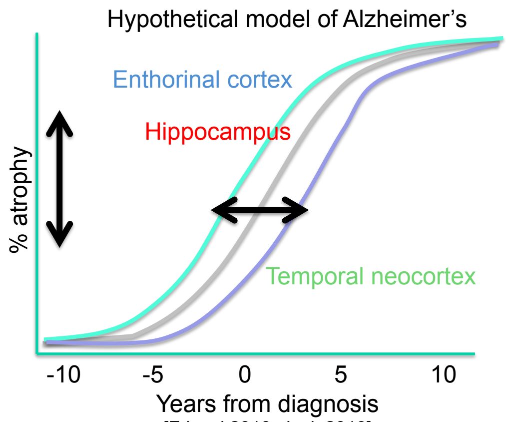


baseline

Longitudinal atrophy in Alzheimer's disease



[Lorenzi 2011]



[Frisoni 2010, Jack 2010]

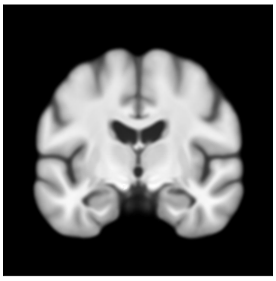
Discovery
Where, when?

Quantification (clinical trials, diagnosis)
How much?

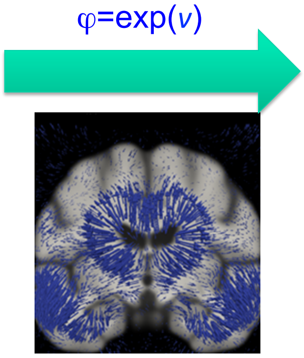
M Lorenzi, N Ayache, X Pennec. Regional flux analysis of longitudinal atrophy in Alzheimer's disease. MICCAI 2012

Non-linear registration for longitudinal analysis

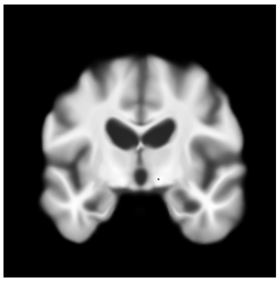
Baseline MRI

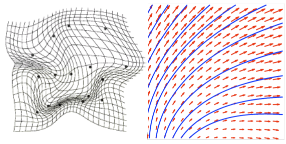


Apparent
Deformation
$\varphi = \exp(v)$



Follow-up MRI





Deformation φ : exponential of a stationary velocity field

T Vercauteren, X Pennec, A Perchant, and N Ayache, *Diffeomorphic Demons: Efficient Non-parametric Image Registration*. NeuroImage, 2009

Generative Model of Brain Atrophy for AD

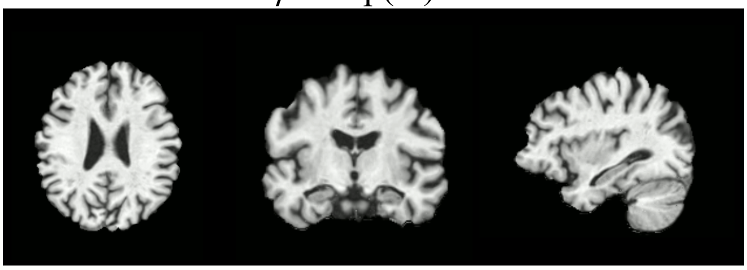
Average evolution from 70 AD patients (ADNI data)

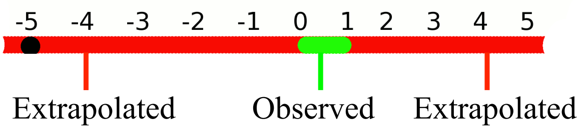
Measure SVF: 1 year **Extrapolation: -+ 7 years**

$$\bar{\varphi} = \exp(t\bar{v})$$

M Lorenzi

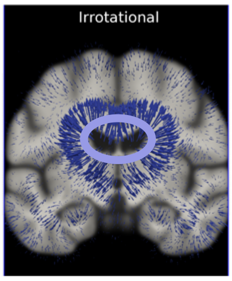
X Pennec





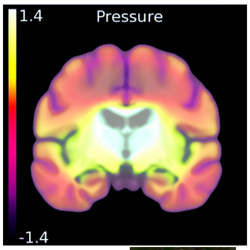
[Lorenzi, Ayache, Pennec IPMI 2011]

Analysis of Stationary Velocity Field



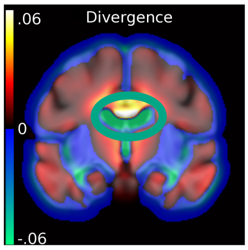
Discovery

“Virtual” Pressure p
Defines **sources and sinks**
of the atrophy process



Quantification

Divergence $\nabla \cdot \nabla p$
Defines **flux** across
expanding/contracting regions

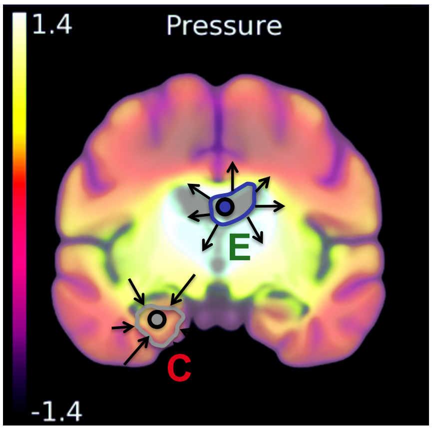


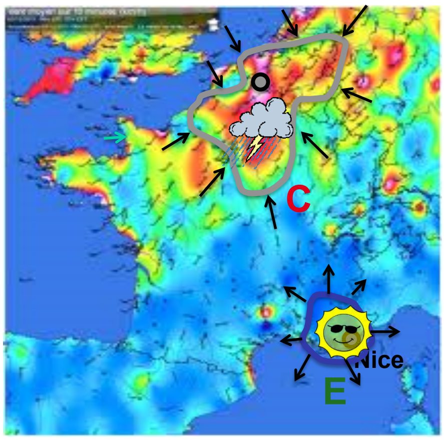
Divergence Theorem

$$\oint_{\partial V} \underline{\nabla p \cdot n \, dS} = \int_V \underline{\nabla \cdot \nabla p \, dV}$$

__M Lorenzi__, N Ayache, __X Pennec__. Regional flux analysis of longitudinal atrophy in Alzheimer's disease. MICCAI 2012

Pressure Extrema





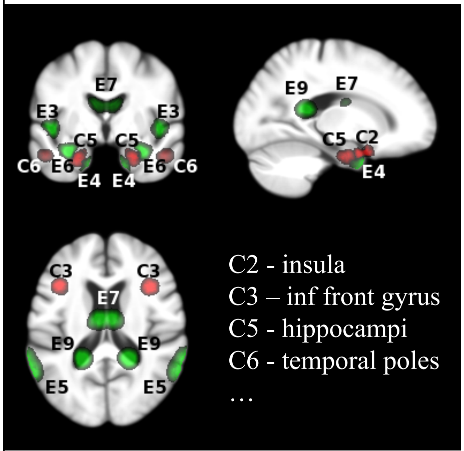
Step1. local maxima (sources) and minima (sinks) of pressure field

Step2. **E**xpansion and **C**ontraction: areas of maximal outwards/inwards flux

M Lorenzi, N Ayache, X Pennec. Regional flux analysis of longitudinal atrophy in Alzheimer's disease. MICCAI 2012

Discovery

Group Analysis



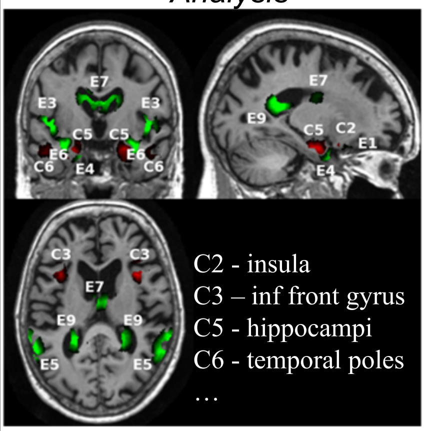
ADNI dataset
(http://adni.loni.ucla.edu/)

- *20 Alzheimer's patients*
- *1 year follow-up*
- *two time points*

M Lorenzi, N Ayache, X Pennec. Regional flux analysis of longitudinal atrophy in Alzheimer's disease. MICCAI 2012

Quantification

Subject Specific Analysis



Probabilistic masks in the subject space

MICCAI 2012 grand Challenge
Effect size on Atrophy Measure

Group	six months	one year	two years
INRIA - Regional Flux	1.02	1.33	1.47

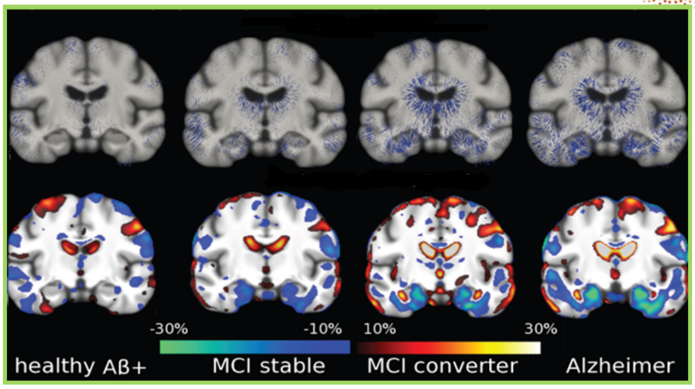
Ranked 1st & 2nd on Hippocampus

Major competitors:

- Freesurfer (Harvard, USA)
- Montreal Neurological Institute, Canada
- Mayo Clinic, USA
- University College of London, UK
- University of Pennsylvania, USA

M Lorenzi, G B. Frisoni, N Ayache, and X Pennec. Probabilistic Flux Analysis of Cerebral Longitudinal Atrophy. MICCAI workshop NIBAD 2012

Future Challenges

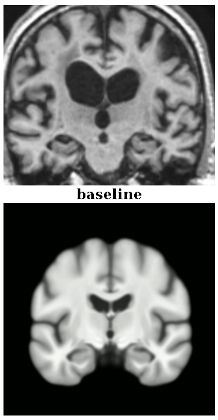


- Biomarkers for early detection of abnormal atrophy patterns and efficient follow-up of treatment

M Lorenzi, N Ayache, X Pennec G B. Frisoni, for ADNI. Disentangling the normal aging from the pathological Alzheimer's disease progression on structural MR images. 5th Clinical Trials in Alzheimer's Disease (CTAD'12), Monte Carlo, October 2012.

Future Challenges

- Generative Biophysical Models of Atrophy
  - Based on Discovered atrophy regions
  - From geometry & Statistics to biological and physical laws
- Synthetic but Realistic Databases of multimodal images with ground truth
  - for training and benchmarking



M Lorenzi, N Ayache, X Pennec G B. Frisoni, for ADNI. Disentangling the normal aging from the pathological Alzheimer's disease progression on structural MR images. 5th Clinical Trials in Alzheimer's Disease (CTAD'12), Monte Carlo, October 2012.

3 Clinical Applications

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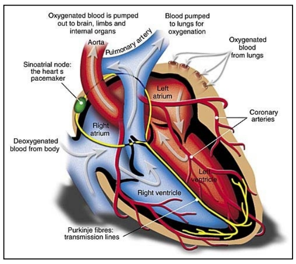
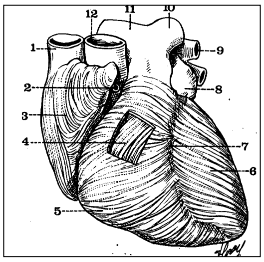
Cardiovascular Diseases

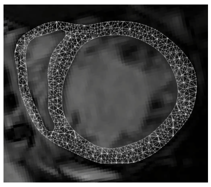




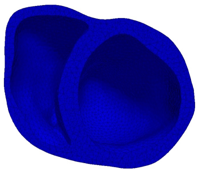
First cause of death in the world
30% of deaths, 17.3 millions in 2008 (WHO)

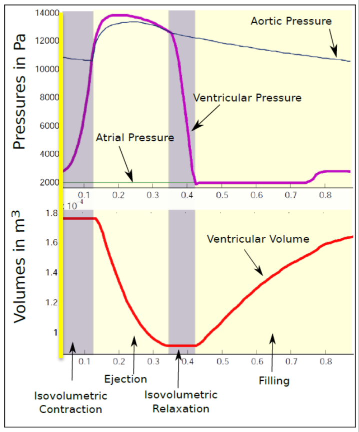
Computational Cardiac Model

- to Integrate
  - imaging & electrical & hemodynamic & biological measures

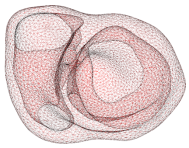


- to Quantify & Simulate cardiac function

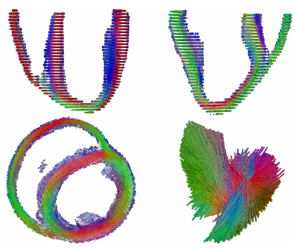


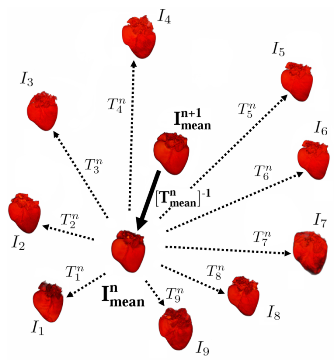


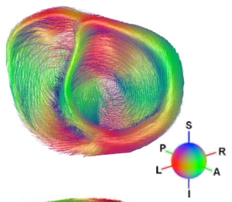
1. Anatomy & Structure

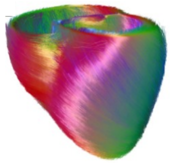


- Cardiac Atlas (NIH & Creatis)









DTI Images

Statistical Analysis

Average structure

H Lombaert, JM Peyrat, P Croisille, S Rapacchi, L Fanton, P Clarysse, H Delingette, N Ayache. Statistical Analysis of the Human Cardiac Fiber Architecture from DT-MRI. FIMH 2011

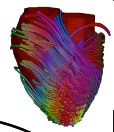
2. Electrophysiology: Mitchell-Schaeffer Model

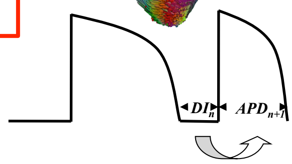
Simplified from Fenton- Karma

Phenomenological model of Sodium (Na^+), Calcium (Ca^{2+}) & Potassium (K^+) currents.

$$\begin{cases} \partial_t u &= \mathrm{div}(d_{MS}\mathbf{M}\nabla u) + \underbrace{\frac{zu^2(1-u)}{\tau_{\mathrm{in}}}}_{\text{Inward currents } (Na^+, Ca^{2+})} - \underbrace{\frac{u}{\tau_{\mathrm{out}}}}_{\text{Outward currents } (K^+)} + J_{\mathrm{stim}}(t) \\ \partial_t z &= \begin{cases} \dfrac{(1-z)}{\tau_{\mathrm{open}}} & if \quad u < u_{\mathrm{gate}} \\ \dfrac{-z}{\tau_{\mathrm{close}}} & if \quad u > u_{\mathrm{gate}} \end{cases} \end{cases}$$

*Matrix **M** : cardiac fibers*



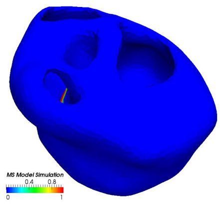


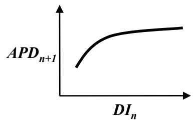
Variables :

u	cardiac **action potential**
z	Na^+ & Ca^{2+} gate potential

Parameters :

d_{MS}	Diffusion coefficient
τ_{in}	Na^+ & Ca^{2+} currents time-constant
τ_{out}	K^+ current –
τ_{open}	Na^+ & Ca^{2+} gate opening –
τ_{close}	Na^+ & Ca^{2+} gate closing –

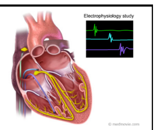




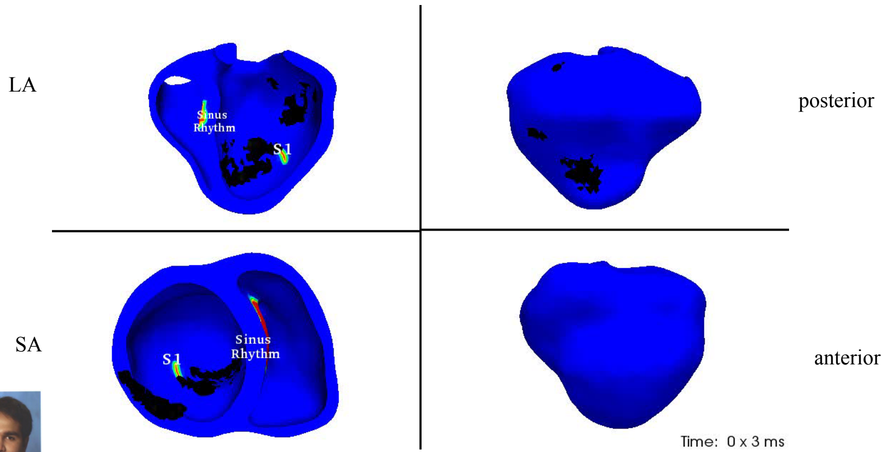
- *Decoupling of **c** and **APD***
- ***APD** as a function of diastolic interval **DI** (Restitution curve)*

[MS03] C. Mitchell and D. Schaeffer, "A two-current model for the dynamics of cardiac membrane," Bulletin of mathematical biology, vol. 65, no. 5, pp. 767–793, 2003.

Predict Ventricular Tachycardia



- VT-stim Protocol simulated near scars at high frequencies (S1 - 400ms, 150bpm)



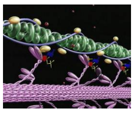
J. Relan, P. Chinchapatnam, M. Sermesant, K. Rhode, M. Ginks, H. Delingette, C. A. Rinaldi, R. Razavi, N. Ayache., *"Coupled personalisation of cardiac electrophysiology models for prediction of ischemic ventricular tachycardia," Royal Society Journal on Interface Focus*, (3):396-407, 2011.

3. Mechanical Model

M .Sorine

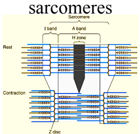
Inspired by Hill-Maxwell rheological model

ATP



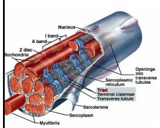
nano

sarcomeres



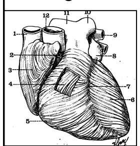
micro

fibers



méso

organ

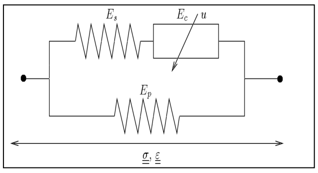


macro

active non-linear viscoelastic anisotropic incompressible material.

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

K_c stiffness
u action potential
ε_c strain
σ_c stress



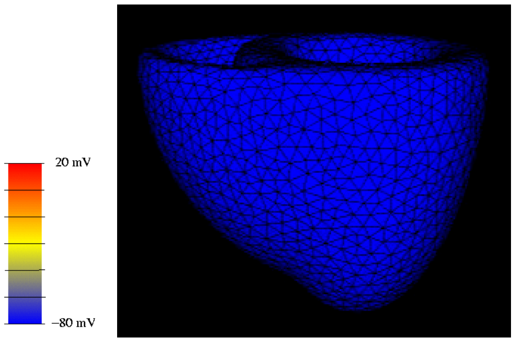
E_s and E_p: elastic material laws,
E_c contractile electrically-activated element.

J. Bestel, F. Clément, and M. Sorine. *A Biomechanical Model of Muscle Contraction* MICCAI 2001.

D. Chapelle, P. Le Tallec, P. Moireau, M. Sorine An energy-preserving muscle tissue model: formulation and compatible discretizations, International Journal of Multiscale Computational Engineering, 2010

N. Ayache
Rennes 9 Nov. 2012

Electro-Mechanical Simulation

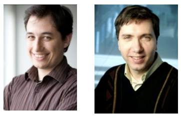


- Action potential u controls contractile element:

  $u > 0$: Contraction
  $u \leq 0$: Relaxation

- u also modifies stiffness k of the material.

action potential u

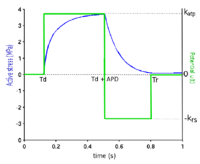


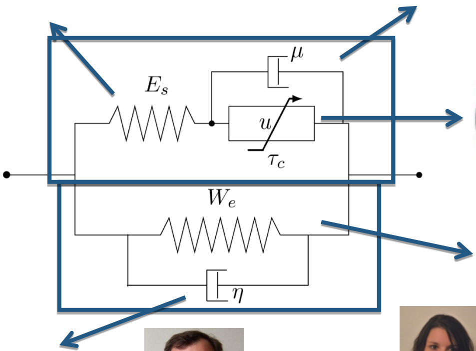
M. Sermesant, H. Delingette, N. Ayache. An Electromechanical Model of the Heart for Image Analysis and Simulation. *IEEE Transactions on Medical Imaging*. 2006 May;25(5):612-25.

Parameters of Bestel-Clement-Sorine model

Stéphanie Marchesseau

→10 global parameters to estimate





Active part

Passive part

Energy Dissipation

Contractile Sarcomere
$(\sigma_0, k_{rs}, k_{atp})$

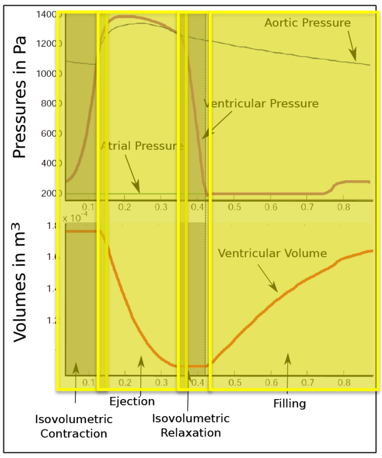
Elasticity of the extracellular matrix
(K, c_1, c_2)

Marchesseau, MICCAI 2012

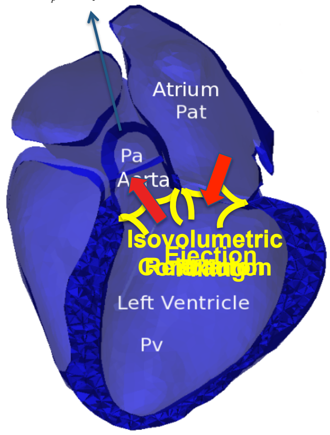
[Bestel .et al, 2001] [Chapelle et al, 2012]

Parameters of Windkessel Model

→4 additional global parameters to estimate



4-element Windkessel
(R_p, C, Z_c, L)



Marchesseau, MICCAI 2012

Methods for Mechanical Personalization

- Variational

H. Delingette

  - Adjunct method to compute functional gradient

H. Delingette, F. Billet, K. C. L. Wong, M. Sermesant, K. Rhode, M. Ginks, C. A. Rinaldi, R. Razavi, and N. Ayache. Personalization of Cardiac Motion and Contractility from Images using Variational Data Assimilation. IEEE Trans. in Biomedical Engineering Letters, 2011.

- Optimal Filtering

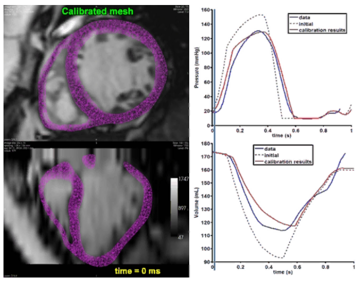
D. Chapelle

  - Unscented Kalman Filter to jointly estimate state variables and model parameters (recursive)

A. Imperiale, R. Chabiniok, P. Moireau, and D. Chapelle, Constitutive Parameter Estimation Methodology Using Tagged-MRI Data, FIMH 2011

Diagnostic Value?

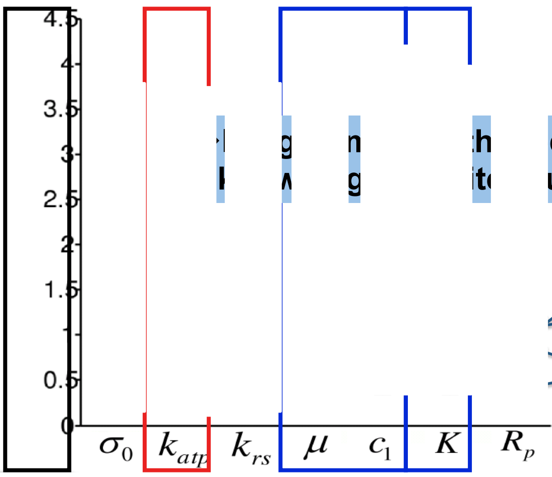
- First Specificity Study
  - 7 Physiological Parameters
  - 6 Healthy Controls
  - 2 HF Patients
    - **1 Dilated Cardio-Myopathy (DCM)**
    - **1 post-Myocardial Infarction (post-MI)**



S. Marchesseau, H. Delingette, M. Sermesant, K. Rhode, S.G. Duckett, C.A. Rinaldi, R. Razavi, & N. Ayache. Cardiac Mechanical Parameter Calibration based on the Unscented Transform. In MICCAI 2012

Preliminary Specificity Study

DCM HF ▲ **Post-MI HF** ● Healthy



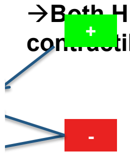
→DCM HF has higher stiffness (c_1 and K)

→DCM HF has smaller ph resistance (Rp)

dical ure

t-MI HF has smaller tion rate (Krs)

→Both HF have smaller contractility (Sigma)



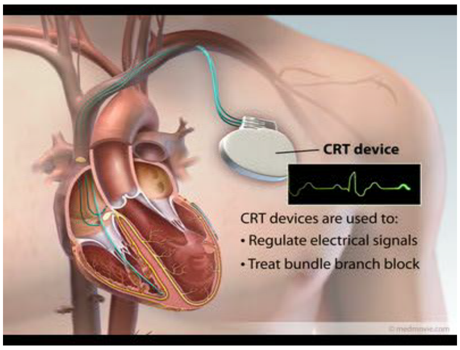
Box plot for healthy controls

Pathological cases

S. Marchesseau, H. Delingette, M. Sermesant, K. Rhode, S.G. Duckett, C.A. Rinaldi, R. Razavi, & N. Ayache. Cardiac Mechanical Parameter Calibration based on the Unscented Transform. In MICCAI 2012

Predictive Value?

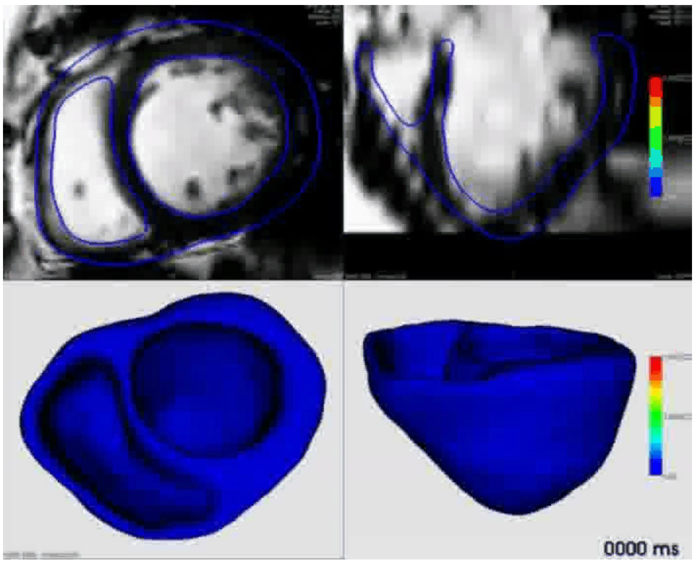
- Predict the effect of a Cardiac Resynchronization Therapy (CRT)

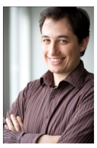


Personalized Asynchronous Heart

Woman
60 years
LBBB

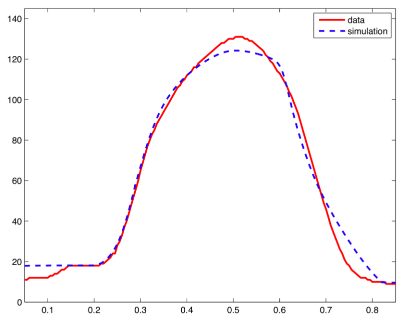
asynchrony



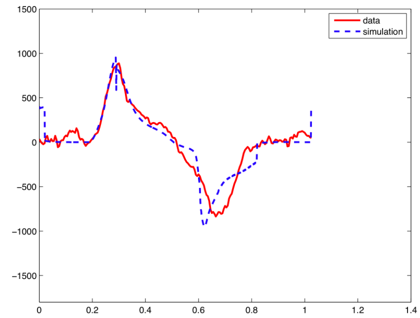


M. Sermesant, F. Billet, R Chabiniok, T Mansi, P Chinchapatnam, P Moireau, JM Peyrat, K Rhode, M Ginks, P Lambiase, S Arridge, H Delingette, M Sorine, A Rinaldi, D Chapelle, R Razavi, N Ayache, *Personalised Electromechanical Model of the Heart for the Prediction of the Acute Effects of Cardiac Resynchronisation Therapy,* Medical Image Analysis 2012

Pressure and dP/dt Curves



Measured (solid red) and *simulated* (dashed blue) **pressure** curves in sinus rhythm.

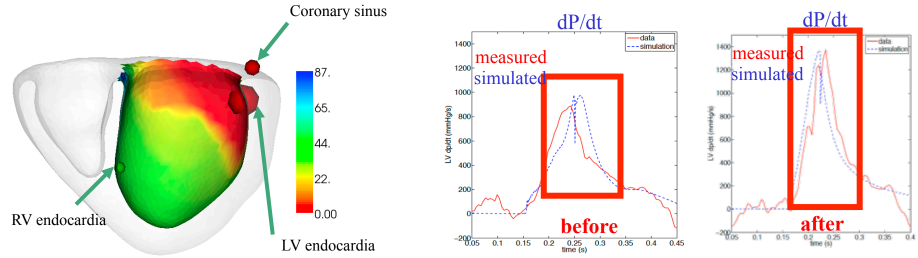


Measured (solid red) and *simulated* (dashed blue) **dP/dt** curves in sinus rhythm.

Personalised electromechanical model reproduces pressure characteristics

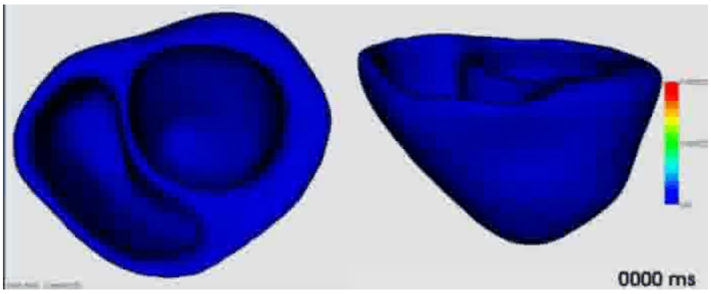
M. Sermesant, F. Billet, R Chabiniok, T Mansi, P Chinchapatnam, P Moireau, JM Peyrat, K Rhode, M Ginks, P Lambiase, S Arridge, H Delingette, M Sorine, A Rinaldi, D Chapelle, R Razavi, N Ayache, *Personalised Electromechanical Model of the Heart for the Prediction of the Acute Effects of Cardiac Resynchronisation Therapy,* Medical Image Analysis 2012

Virtual Pacemaker



Simulated CRT

resynchronization



M. Sermesant, F. Billet, R Chabiniok, T Mansi, P Chinchapatnam, P Moireau, JM Peyrat, K Rhode, M Ginks, P Lambiase, S Arridge, H Delingette, M Sorine, A Rinaldi, D Chapelle, R Razavi, N Ayache, *Personalised Electromechanical Model of the Heart for the Prediction of the Acute Effects of Cardiac Resynchronisation Therapy,* Medical Image Analysis 2012

Validated dP/dT for 2 patients for various positions of the leads

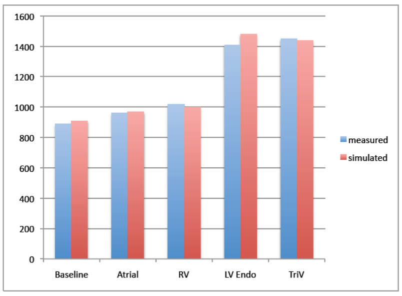


Figure 16: Patient 1: Measured (blue) and simulated (red) $(dP/dt)_{max}$ for different pacing conditions. Parameters were estimated on baseline and then kept constant.

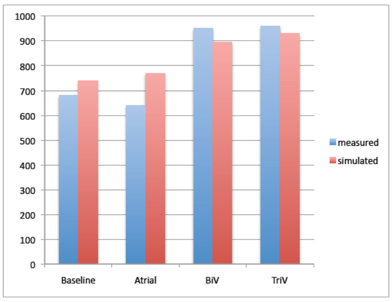


Figure 17: Patient 2: Measured (blue) and simulated (red) $(dP/dt)_{max}$ for different pacing conditions. Parameters were estimated on baseline and then kept constants.

M. Sermesant, F. Billet, R Chabiniok, T Mansi, P Chinchapatnam, P Moireau, JM Peyrat, K Rhode, M Ginks, P Lambiase, S Arridge, H Delingette, M Sorine, A Rinaldi, D Chapelle, R Razavi, N Ayache, *Personalised Electromechanical Model of the Heart for the Prediction of the Acute Effects of Cardiac Resynchronisation Therapy,* Medical Image Analysis 2012

What Else?

Image Simulation

- Vary parameters of Biophysical Model to generate databases of realistic images with ground truth

erc MedYMA

  - To benchmark Image Processing Algorithms
  - To Train Machine Learning Algorithms

N. Ayache
Rennes 9 Nov. 2012

From Biomedical Images to Virtual Personalized Physiological Patients

Inria informatics mathematics

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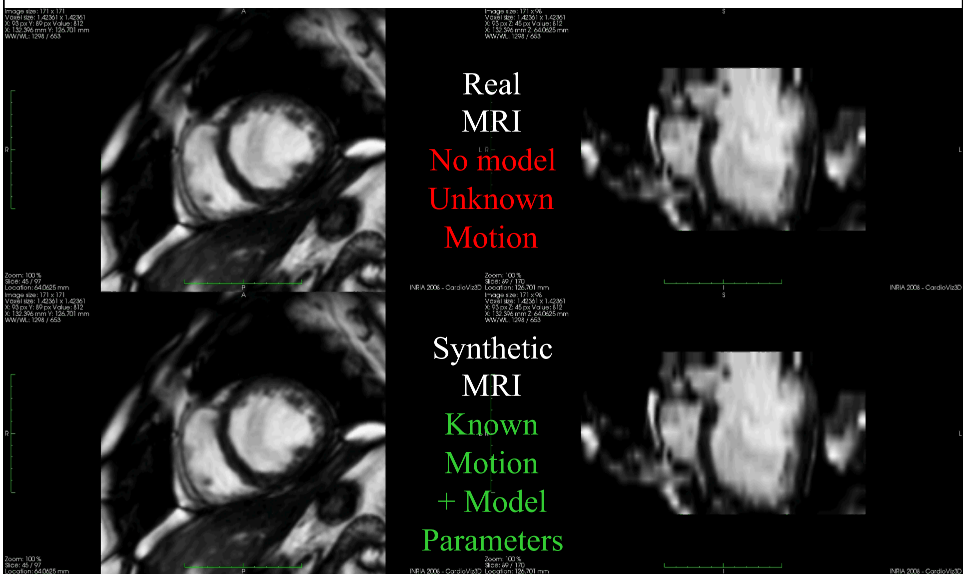
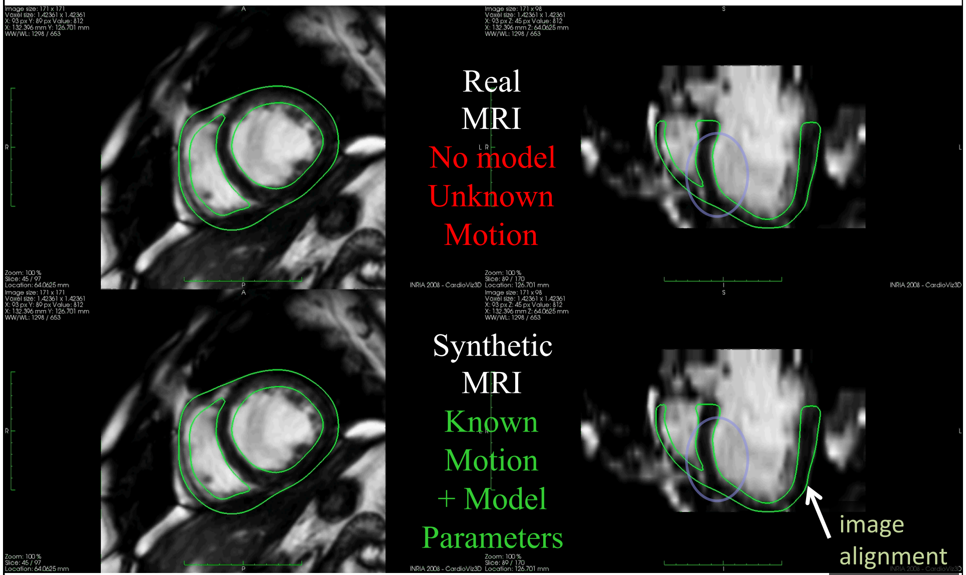
Real vs. Synthetic MRI

erc MedYMA



A Prakosa, M Sermesant, H Delingette, S Marchesseau, E Saloux, P Allain, N Villain, and N Ayache. Generation of Synthetic but Visually Realistic Time Series of Cardiac Images Combining a Biophysical Model and Clinical Images. IEEE Transactions on Medical Imaging, 2012. In press.

Real vs. Synthetic MRI

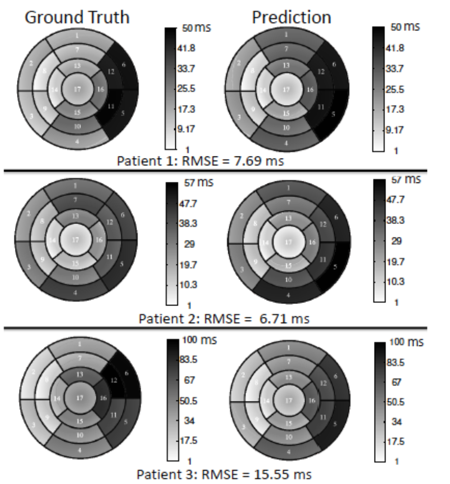


A Prakosa, M Sermesant, H Delingette, S Marchesseau, E Saloux, P Allain, N Villain, and N Ayache. Generation of Synthetic but Visually Realistic Time Series of Cardiac Images Combining a Biophysical Model and Clinical Images. IEEE Transactions on Medical Imaging, 2012. In press.

Machine Learning for EP

- Preliminary promising results for EP:
  - Depolarisation Times (DT) learned from strain measurements on simulated images

A Prakosa, M Sermesant, H Delingette, S. Marechesseau, N Ayache. *Cardiac Electro-physiological Activity Pattern Learning from Synthetic Images; Submitted 2012*. Earlier version in MICCAI 2011

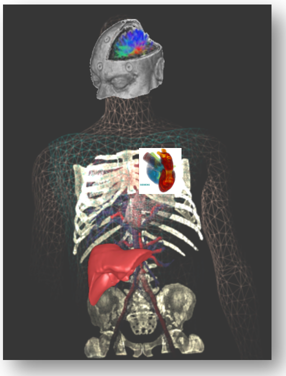


ïig. 4. **Depolarization Time Estimation from Clinical 3D MR Sequences.** ïirst evaluation of the learning process in the prediction of the LV surface lepolarization time on a patient (left) is compared to the ground truth value. ïimilar pattern in the same range is observed on both of them.

40

Virtual Physiological Patient
& Computational Biomedical Imaging

Opens new frontiers towards



- A paradigm shift from
  - reactive standardized medicine
- Towards
  - preventive predictive personalized

Medicine of 21st century.

Thank You!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On Medical Image
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and Computer
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Interventions