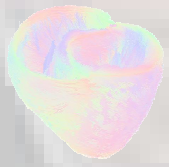
*Les défis scientifiques du 21ème siècle*

*Informatique et imagerie médicale*

# Le patient numérique personnalisé

***12 mai 2009***

**Académie des Sciences**



Nicholas Ayache

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

INRIA

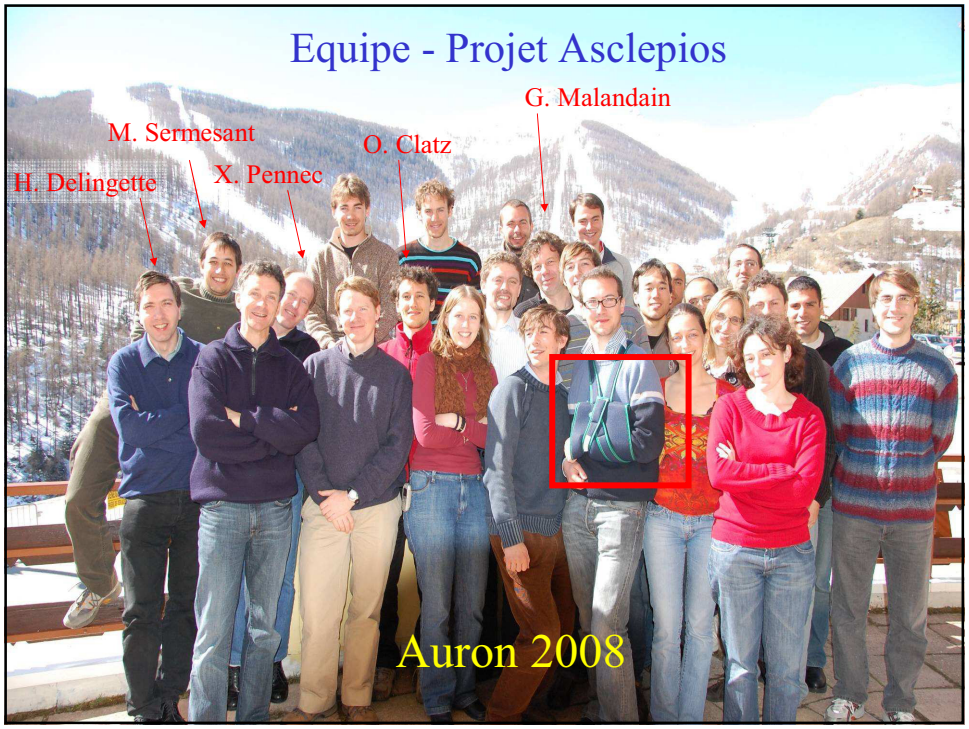
## Gilles Kahn

1946-2006
Président de l'INRIA 2004-2006
Directeur Scientifique: 1994-2004

# Remerciements

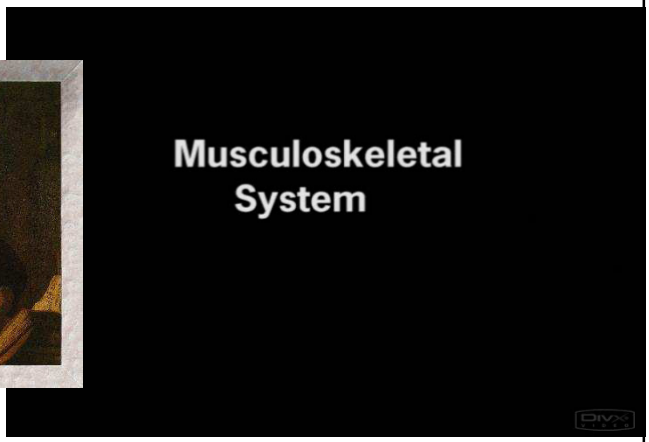
- Equipe-projet Asclépios de l'INRIA
- Partenaires académiques, cliniques, industriels





# 1632...

La Leçon d'Anatomie du Dr. Tulp
*Rembrandt*




Dinesh Pai, Rutgers

# … 1895…

1901 : Willem Roentgen
Premier prix Nobel de Physique



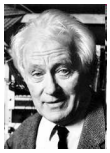
Physique
Chimie
Médecine

# Prix Nobel

1901, Rayons X — 1903, Radioactivité naturelle — 1935, radioactivité artificielle — 1952, RMN

Wilhelm Röntgen Henri Becquerel Marie Curie Pierre Curie Irène Joliot Frédéric Joliot Felix Bloch Edward Purcell

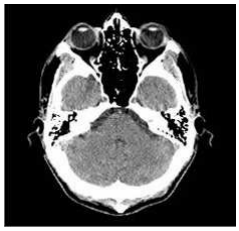
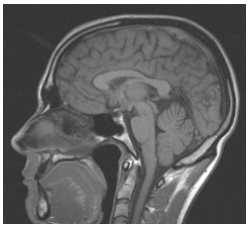
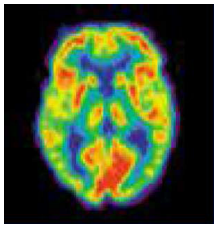
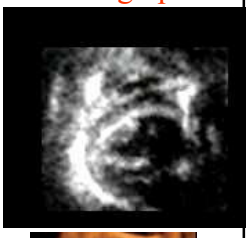
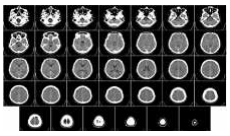
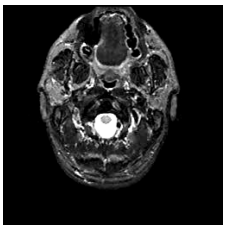
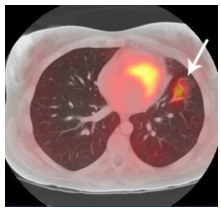
1979, TDM (Scanner X) — 1991, RMN — 1992, Chambre à fils — 2003, IRM



Allan Cormack Godfrey Hounsfield Richard Ernst Georges Charpak Paul Lauterbur Peter Mansfield

# XX$^{ème}$ Siècle

Scanner X | IRM | TEP | Echographie

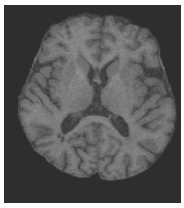
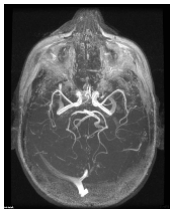
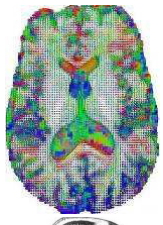
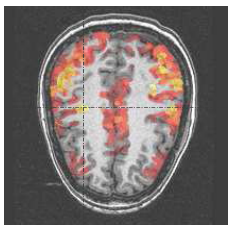
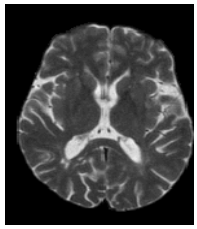
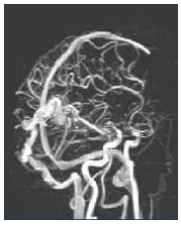
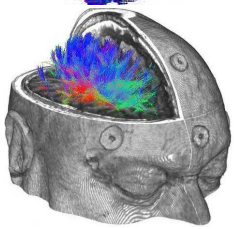
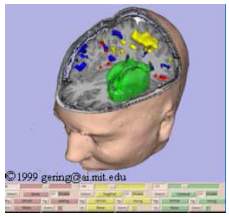








Source :T. Peters



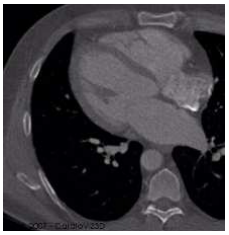
# Images multiparamétriques

IRM T1, T2 | Angio IRM | IRMd | IRMf

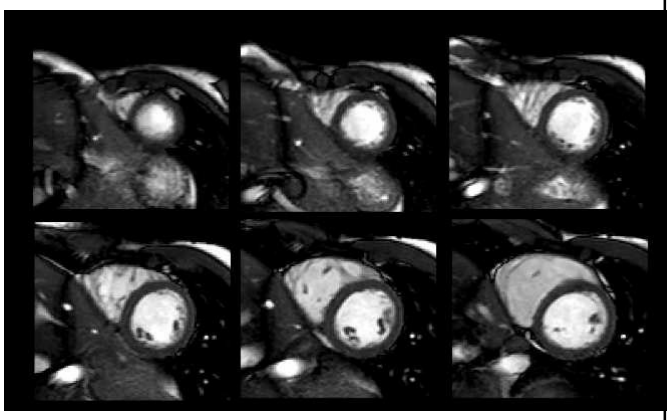









# Images dynamiques (4-D)

Scanner X



IRM

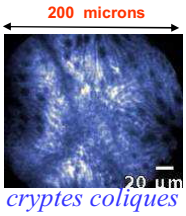




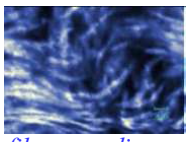
# Nouvelles Images

- Imagerie Spectroscopique (IRMs)
- MEG, EEG
- Elastographie (IRM, US, etc.)
- Imagerie microscopique confocale *in vivo*
- Tomographie Optique Cohérente (OCT)
- Imagerie Terahertz
- etc.

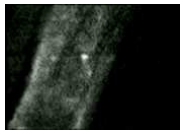
Biospace, Mauna Kea Technologies, Supersonic Imagine...




*cryptes coliques*



*fibres cardiaques*



*microvaisseaux*

Source : Mauna Kea Technologies

# L'imagerie médicale aujourd'hui

- Nombreuses modalités d'imagerie *in vivo*
- Informations anatomiques et fonctionnelles
- Images multidimensionnelles, multiparamétriques
- Grandes bases de données
- Thérapies guidées par l'image
- La quantité d'information ne peut plus être exploitée de façon optimale sans l'aide de l'informatique

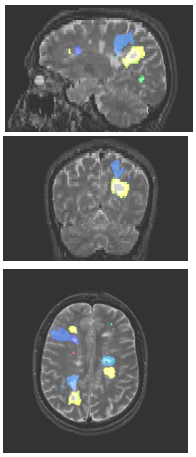


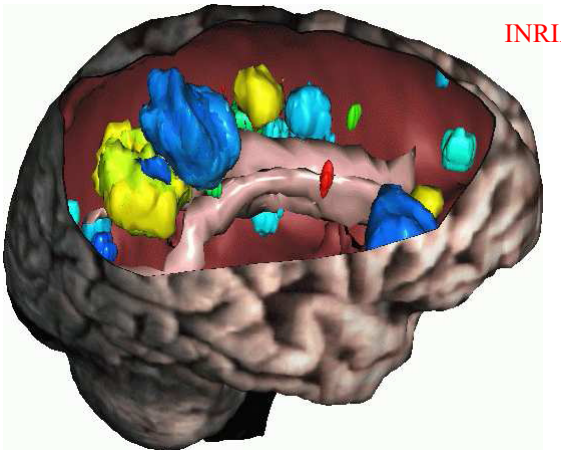
# Analyse et simulation informatique (1980 – aujourd'hui)

- Aide au diagnostic
  - mesures quantitatives objectives
  - fusion d'images multimodales
- Aide à la thérapie
  - Planification, simulation *(avant)*
  - Contrôle *(pendant),* suivi *(après)*

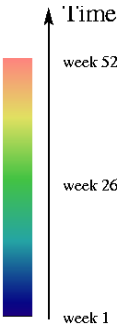
J. Duncan & N. Ayache, *Medical Image Analysis, Progress over two decades and the challenges ahead*, IEEE – Pami, 2000.

# Cartographie spatio-temporelle (sclérose en plaques)





INRIA-Harvard



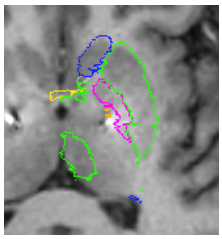

D. Rey, G. Subsol, H. Delingette, N.Ayache. : *Automatic Detection and Segmentation of Evolving Processes in 3D Medical Images: Application to Multiple Sclerosis.* Medical Image Analysis, 6(2):163-179, June 2002.

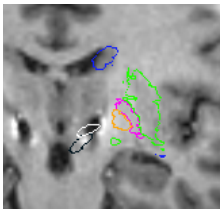


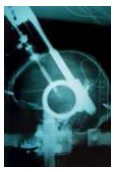
# Neurochirurgie guidée par l'image

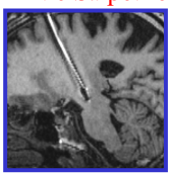
- Electrostimulation de patients Parkinsoniens

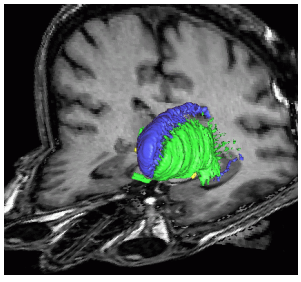
INRIA
Pitié Salpêtrière

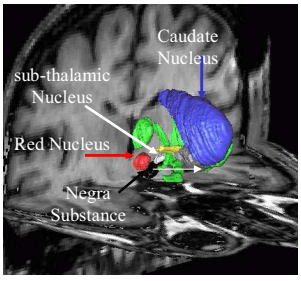






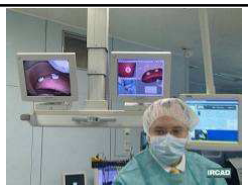


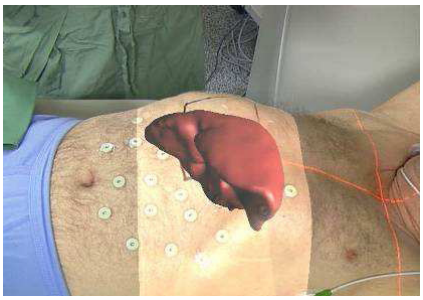


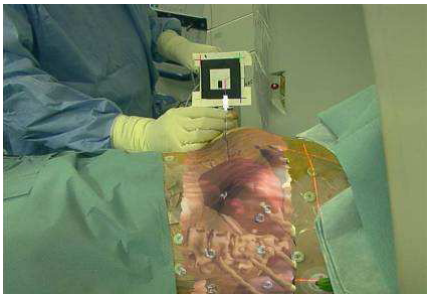



J Yelnik, E Bardinet, D Dormont, G Malandain, S Ourselin, D Tande, C Karachi, N Ayache., P Cornu, Y Agid. *A 3-D, histological and deformable atlas of the human basal ganglia. I. Atlas construction based on immunohistochemical and MRI data.* Neuroimage, 2007

# Réalité Augmentée







Ablation radio-fréquence de tumeurs hépatiques

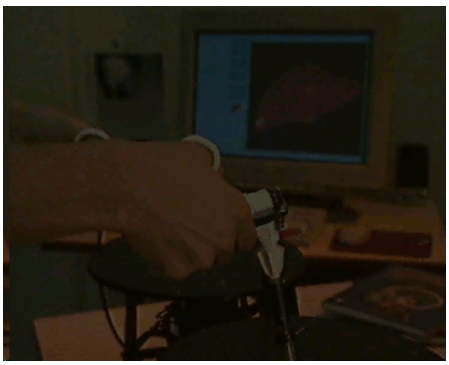
INRIA - IRCAD

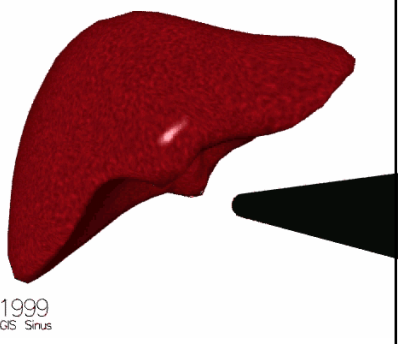
S. Nicolau, A. Garcia, X. Pennec, L. Soler, and N. Ayache.. Augmented reality guided radiofrequency tumor ablation. Computer Animation and Virtual World 16(1) 2005.



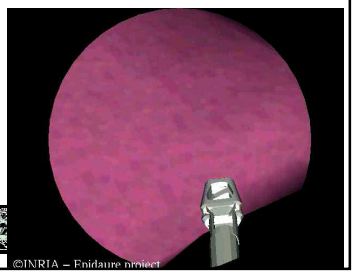
# Réalité Virtuelle

INRIA - IRCAD

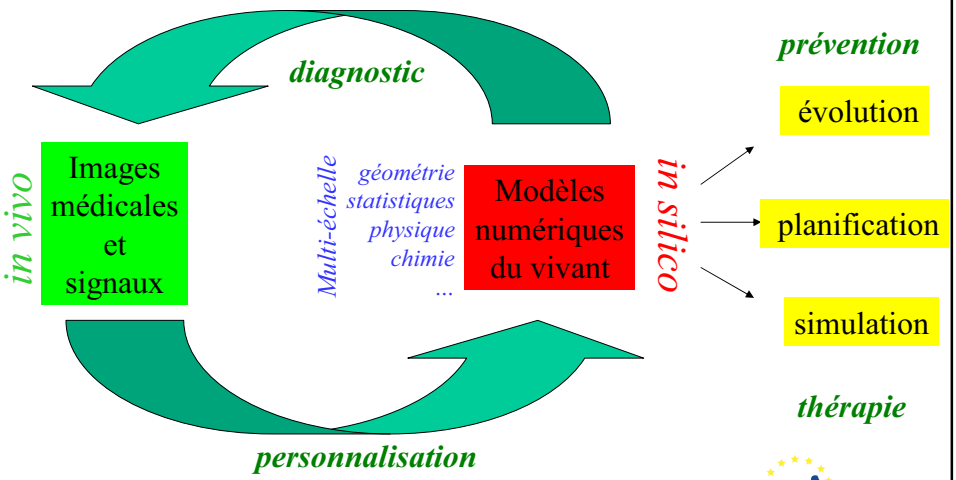




H. Delingette, X. Pennec, L. Soler, J. Marescaux, and N. Ayache.. *Computational Models for Image Guided, Robot-Assisted and Simulated Medical Interventions.* Proceedings of the IEEE, 2006.



# Le patient numérique personnalisé




- *Computational Models for the Human Body*, N. Ayache., Ph Ciarlet, J.L. Lions (Editors), 2004
- *Virtual Physiological Human* (VPH) European Program (2008-2012)

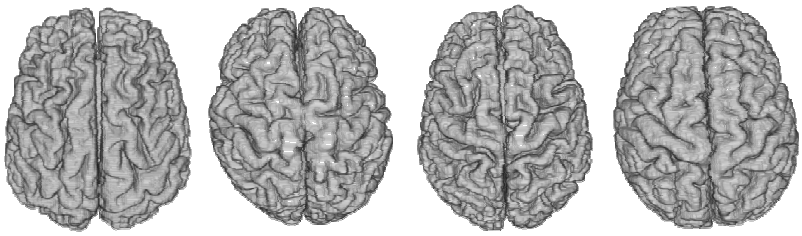


# Trois exemples

- Variabilité du cortex
- Croissance tumorale
- Fonction cardiaque

*rôle transverse des modèles informatiques : modalités, organes, pathologies, disciplines médicales*

## Variabilité structurelle du cortex

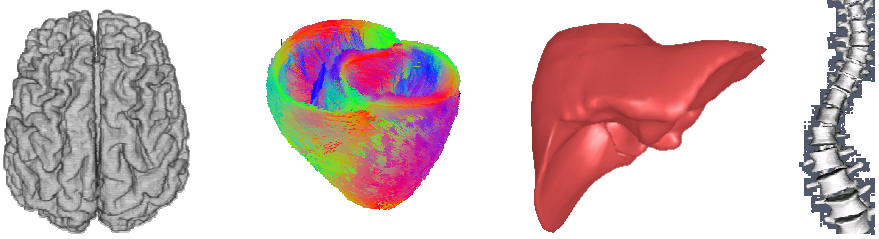


- Structure moyenne?
- Mesurer variabilité autour de cette moyenne?
- Détecter variations anormales?



## Anatomie Algorithmique

### *Computational Anatomy*



- Modélisation et analyse de la variabilité de l'anatomie humaine


- P. Thompson, M. Miller, *Computational Anatomy, an emerging discipline*, NeuroImage special issue (2004)
- X. Pennec and S. Joshi, *Mathematical Foundations of Computational Anatomy*, MICCAI'06 workshop.
- F. Bookstein, C. Davatzikos, I. Dryden, O. Faugeras, T. Fletcher, P.Golland, G. Gerig, H. Tagare, S. Joshi, M. Styner, C. Twinning, B. Vemuri, etc.

## Statistiques sur des variétés anatomiques

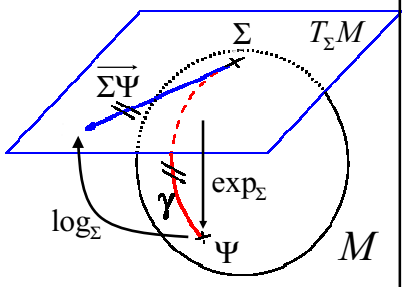
- Méthode
  - Extraire des primitives géométriques
    - Repères, tenseurs, courbes, surfaces, volumes
  - Mise en correspondance (transformations)
  - Estimer des distributions de probabilité
- Problème difficile
  - Bruit, combinatoire
  - Statistiques sur des variétés qui ne sont pas des espaces vectoriels

M. Miller, *NeuroImage* 2005



## Définition d'un cadre riemannien

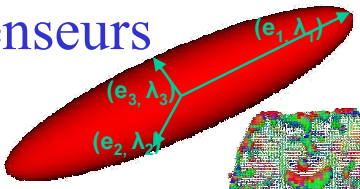
- Outils mathématiques
  - Cartes Logarithmiques et Exponentielles
  - Métrique riemanienne
  - Géodésiques
  - Moyenne de Fréchet
  - Matrice de covariance
  - Distance de Mahalanobis
  - etc.



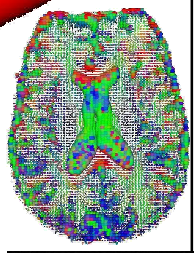

- Algorithmes efficaces de calcul

- X. Pennec & N Ayache. *Uniform distribution, distance and expectation problems for geometric features processing*, Journal of Mathematical Imaging and Vision, Vol.9, pp. 49–67, 1998.
- X. Pennec : *Intrinsic Statistics on Riemannian Manifolds: Basic Tools for Geometric Measurements, JMIV'06.*
- [Lenglet JMIV'06] [Moakher SIAM'05] [Batchelor MRM'05] [Fletcher CVMIA'04]

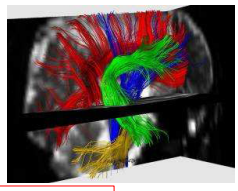
# Calcul sur les tenseurs




- Diffusion des molécules d'eau



- Lissage, suivi (tractographie)

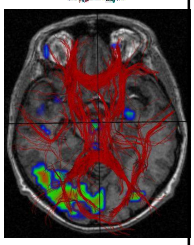


  - Métrique affine-invariante

$$dist(\Sigma,\Psi)^2 = \left\langle \overrightarrow{\Sigma\Psi} \mid \overrightarrow{\Sigma\Psi} \right\rangle_\Sigma = \left\| \log(\Sigma^{-1/2}.\Psi.\Sigma^{-1/2}) \right\|_{L_2}^2$$

  - Métrique log-euclidienne

$$dist(\Sigma,\Psi)^2 = \left\| \log(\Sigma) - \log(\Psi) \right\|^2$$

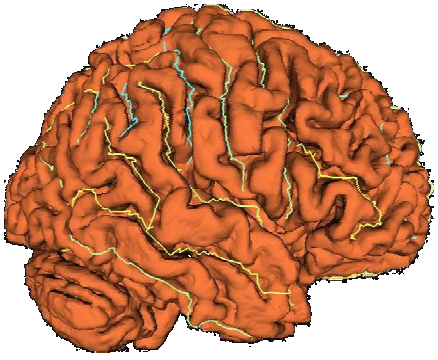


- X Pennec, P.Fillard, N.Ayache: *A Riemannian Framework for Tensor Computing*, Int. J. of Computer Vision, 2006.
- V. Arsigny, X Pennec, P.Fillard, N.Ayache: *Fast and Simple Calculus on Tensors in the Log-Euclidean Framework*, SIAM'06
- Skovgaard, Fletcher-Joshi, Lenglet-Deriche, Batchelor, Alexander, Basser, Westin et al., Descoteaux, etc.



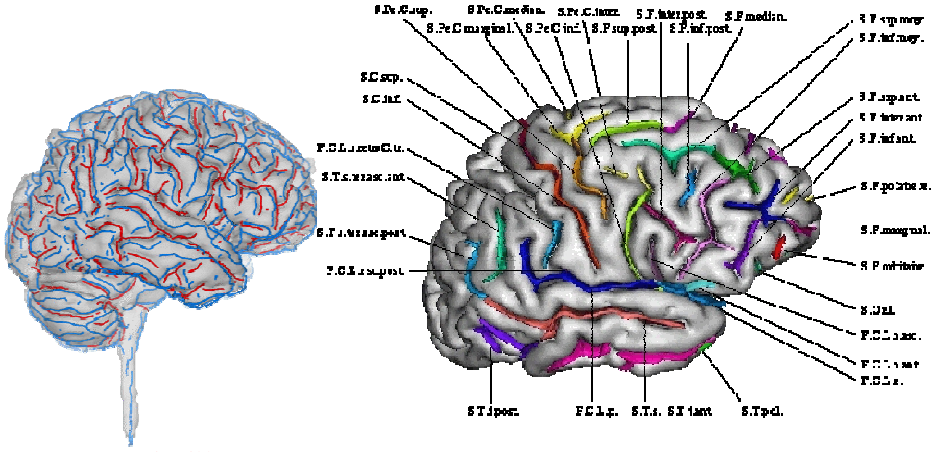
# Utilisation des lignes sulcales

- 72 lignes sulcales
- 700 sujets et patients



•Collaboration avec LONI (UCLA) : P. Thompson et al.

# Extraction automatique

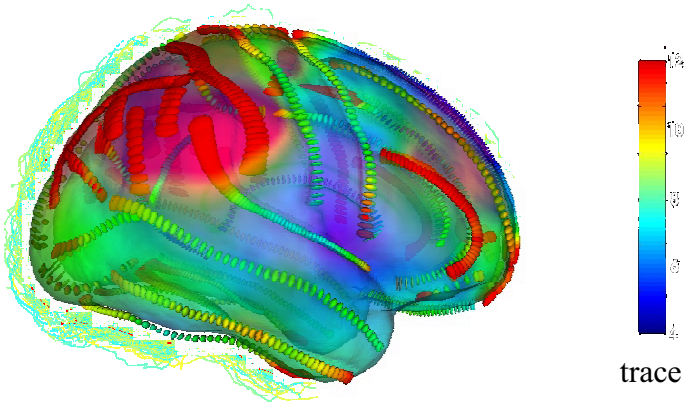


Pennec-Ayache.-Thirion-2000

JF. Mangin, D. Rivière, 2003,
SHFJ-CEA, Neurospin



# Variabilité des lignes sulcales



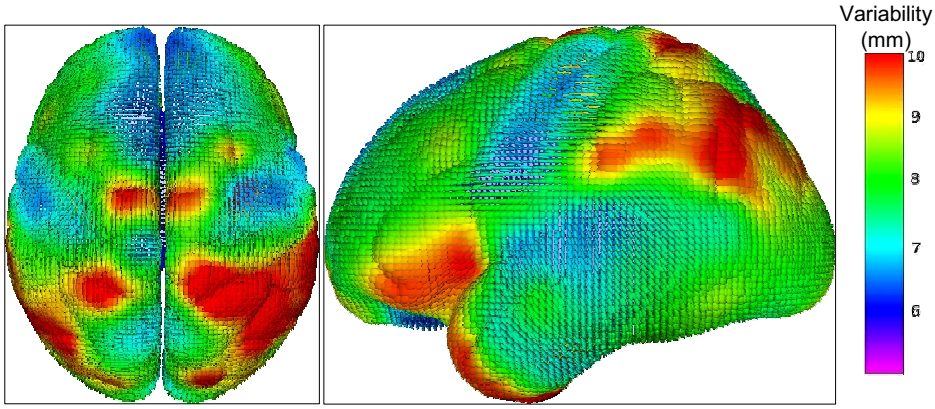
100 sujets

Normalisation affine

trace

Fillard, Arsigny, Pennec,Thompson, Ayache., IPMI 2005

# Extrapolation by Diffusion




Minimization d'une fonctionnelle sur les tenseurs *(métrique log-euclidienne)*

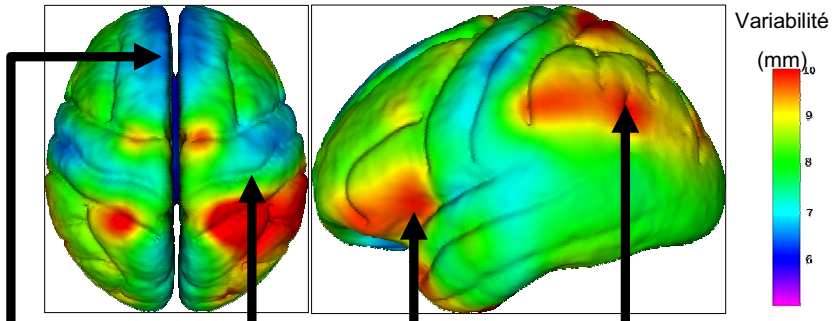
$$C(\Sigma) = \frac{1}{2}\int_{\Omega}\sum_{i=1}^{n} G_{\sigma}(x - x_i)\, dist(\Sigma(x), \Sigma_i)^2\, dx + \frac{\lambda}{2}\int_{\Omega}\|\nabla\Sigma\|^2$$

V. Arsigny, X Pennec, P.Fillard, N.Ayache.: *Fast and Simple Calculus on Tensors in Log-Euclidean Framework,* SIAM'06



# Variabilité corticale

trace



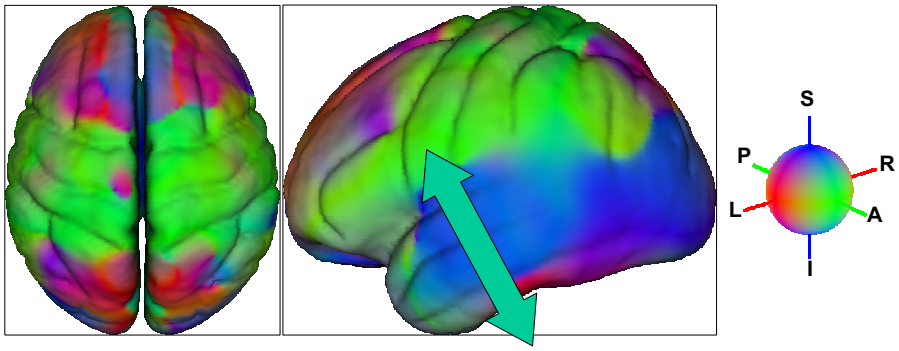

faible variabilité:
- Sillon central
- Gyrus supérieur frontal

haute variabilité
- Cortex pariétal
- Aire de Broca

P. Fillard, V. Arsigny, X. Pennec, P. Thompson, N. Ayache. *Extrapolation of Sparse Tensor Fields: application to the Modeling of Brain Variability.* In Neuroimage 2007

# Variabilité Corticale : directions privilégiées

Vecteur propre principal



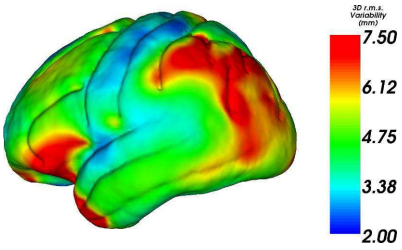

P. Fillard, V. Arsigny, X. Pennec, P. Thompson, N. Ayache. *Extrapolation of Sparse Tensor Fields: application to the Modeling of Brain Variability.* In Neuroimage 2007



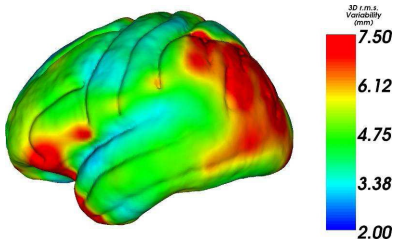
# Perspectives médicales

- Géométrie et statistiques
  - Analyses de groupes (Contrôles, Patients)
  - Mieux guider la superposition d'un atlas
  - Mieux reconstruire à partir de données incomplètes

# Analyse de groupe

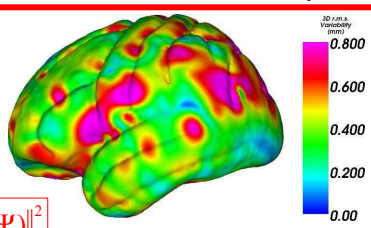



40 contrôles




43 Syndromes de Williams

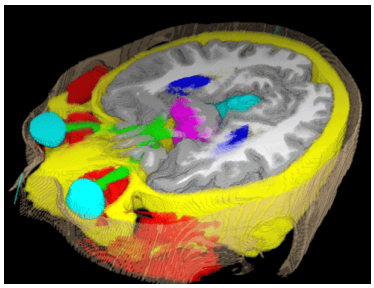
Différence

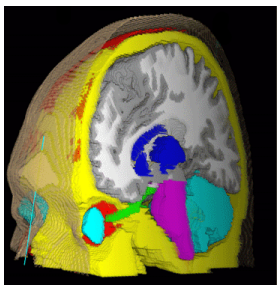



$$dist(\Sigma,\Psi)^2 = \left\|\log(\Sigma) - \log(\Psi)\right\|^2$$

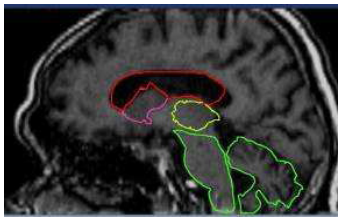


# Ajustement d'atlas en radiothérapie



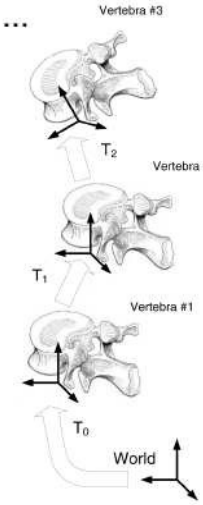


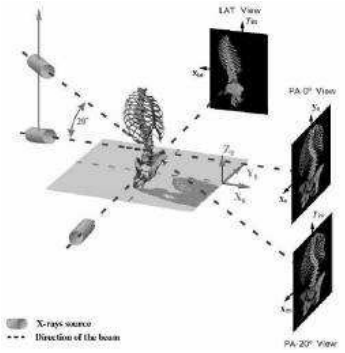
*Inria-CAL-Dosisoft*



O Commowick, R Stefanescu, P Fillard, V Arsigny, N Ayache., X Pennec, G Malandain. *Incorporating Statistical Measures of Anatomical Variability in Atlas-to-Subject Registration for Conformal Brain Radiotherapy*. MICCAI 2005.

# Colonne vertébrale



*INRIA-Hôpital Ste Justine, Montreal*

Boisvert, Cheriet, Pennec, Labelle, Ayache.: *Principal Deformation Modes of Articulated Models for the Analysis of 3-D Spine Deformations*, Letters on Computer Vision and Image Analysis, Dec 2008.



# Géométrie et Statistiques
# Quelques Défis

- Variabilité évolution anatomique (4-D)
  - Croissance (morphogénèse), vieillissement, …
- Atlas « intelligent »
  - toutes les images… les plus proches d'une image donnée

# Trois exemples

- Variabilité du cortex — *Géométrie, Statistiques*
- Croissance tumorale — *Géométrie, Physique, Physiopathologie*
- Fonction cardiaque



# Croissance de tumeurs cérébrales

- Caractériser l'évolution
- Prédire la progression
- Délimiter l'extension invisible

gliome

IRM T2

*Mars*

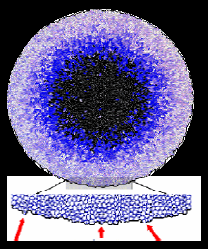
*Septembre*

- Personnaliser diagnostic et thérapie

# Croissance Tumorale

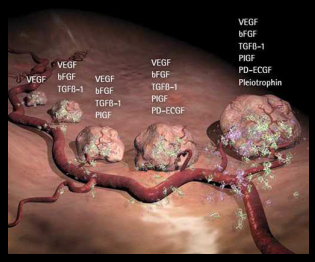
- extrêmement complexe
- gènes ↔ protéines ↔ enzymes ↔ cellules ↔ tissus ↔ organes
- 3 grandes phases

Croissance avasculaire



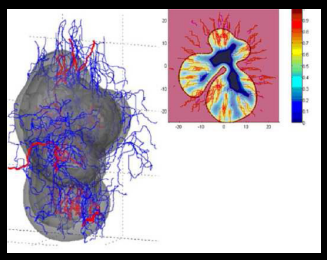
Drasdo et al., Phys. Biol., vol 2, pg. 133-147, 2005

Angiogénèse




www.researchvegf.com

Croissance vasculaire



Sanga et al., NeuroImage, vol 37, pg. S120-S134, 2007.



# Quelques modèles mathématiques et algorithmiques

- Ashraf-Davatzikos [Media 2006],
- Athale-Deisboeck [JTB 2006],
- Byrne [Math Med Bio 2003, MMMAS 2006],
- Breward [Bull. Math. Biol. 2004],
- Chaplain [NeuroOncology 2003],
- Drasdo [Phys. Biol. 2005],
- Frieboes-Cristini [NeuroImage 2007],
- Jbadbi-Benali [MRM 2005], Miga et al [2008]
- Murray [Mathematical Biology 2002],
- Prastawa-Gerig [MICCAI 2005]
- Stamatakos [Brit. J. Rad. 2006],
- Swanson [British Journal of Cancer 2002, 2008],
- Tracqui [Cell Proliferation 1995],
- etc…

# Choisir le bon niveau d'analyse

- Modèles macroscopiques
  - Phase croissance vasculaire
  - Compatible avec l'échelle d'observation (images)
- Nombre de paramètres limités
  - Pour la personnalisation



# Un modèle numérique de croissance (Clatz 2005)

- Combine
  - Géométrie
  - Statistiques (Atlas)
  - Biomécanique
  - Physiopathologie

Mars

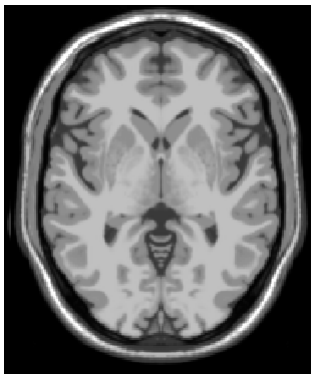
Septembre

Coll. CAL-CHU (Nice) & SPL BWH (Harvard)

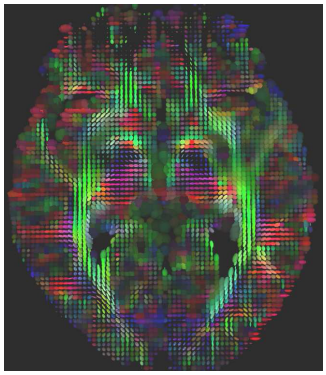
Travaux antérieurs : Swanson, Jbaadbi, Murray, Prastawa, Tracqui et al.

O. Clatz, M. Sermesant, P.-Y. Bondiau, H. Delingette, S. Warfield, G. Malandain, N. Ayache: Realistic Simulation of the 3D Growth of Brain Tumors in MR Images Including Diffusion and Mass Effect. *IEEE Transactions on Medical Imaging*. 24(10):1334-1346, Oct. 2005.

# 1. Modèle Géométrique



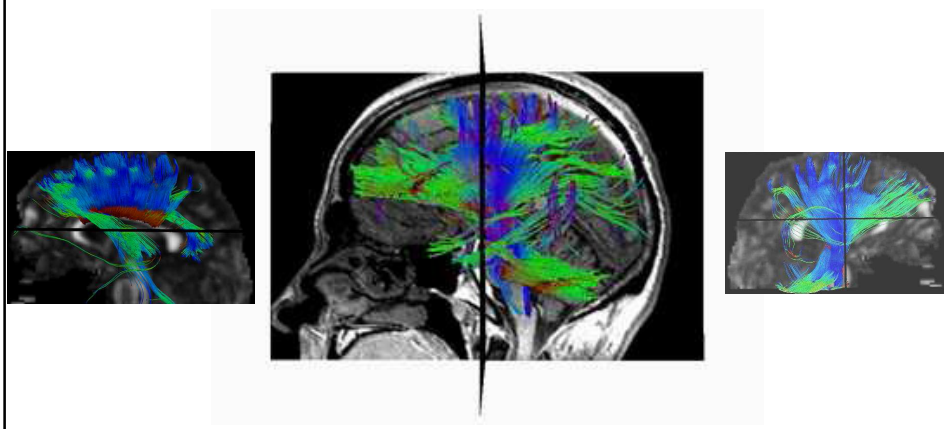
IRM T1 Segmentée
(Brainweb)
MG, MB, LCR, Crâne, etc.



DTI
Principaux faisceaux
de fibres de MB



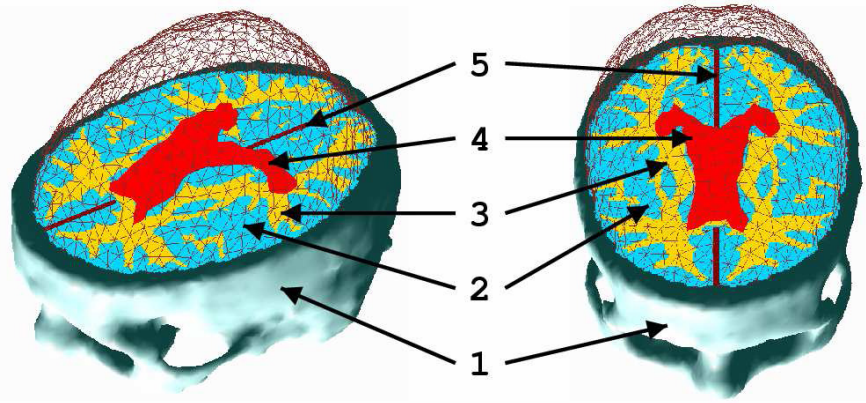
# Faisceaux de fibres reconstruits



Pierre Fillard

# 2. Modèle biomécanique

## élastique linéaire hétérogène anisotrope




1 Crâne. 2 Matière grise 3 Matière blanche.
4 Ventricules. 5 Faux



# 3. Modèle Physiopathologique

Fisher Kolmogorov

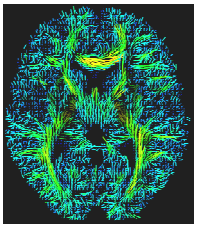
$$\frac{\partial c}{\partial t} = \nabla.(D\nabla c) + \rho c(1-c)$$

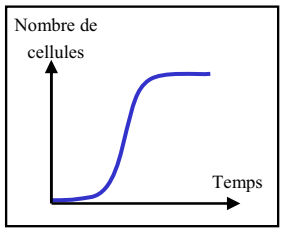
+CL

c densité tumorale

Migration cellulaire anisotrope

Multiplication cellulaire






Couplage biomécanique

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

Effet de masse associé

Collaboration Centre Antoine Lacassagne et Harvard