

Medical Image Analysis

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Lecture 18.

Review of Medical Image Analysis
and Other Issues

May 01, 2007

Topics
not covered

Topics
covered

Medical Image Analysis Flow

Image Acquisition

Image Acquisition
MRI, fMRI, PET, CT,
EEG, MEG etc.

Importing Image into computer
DIACOM, MINC, ANALYZE, BRIK

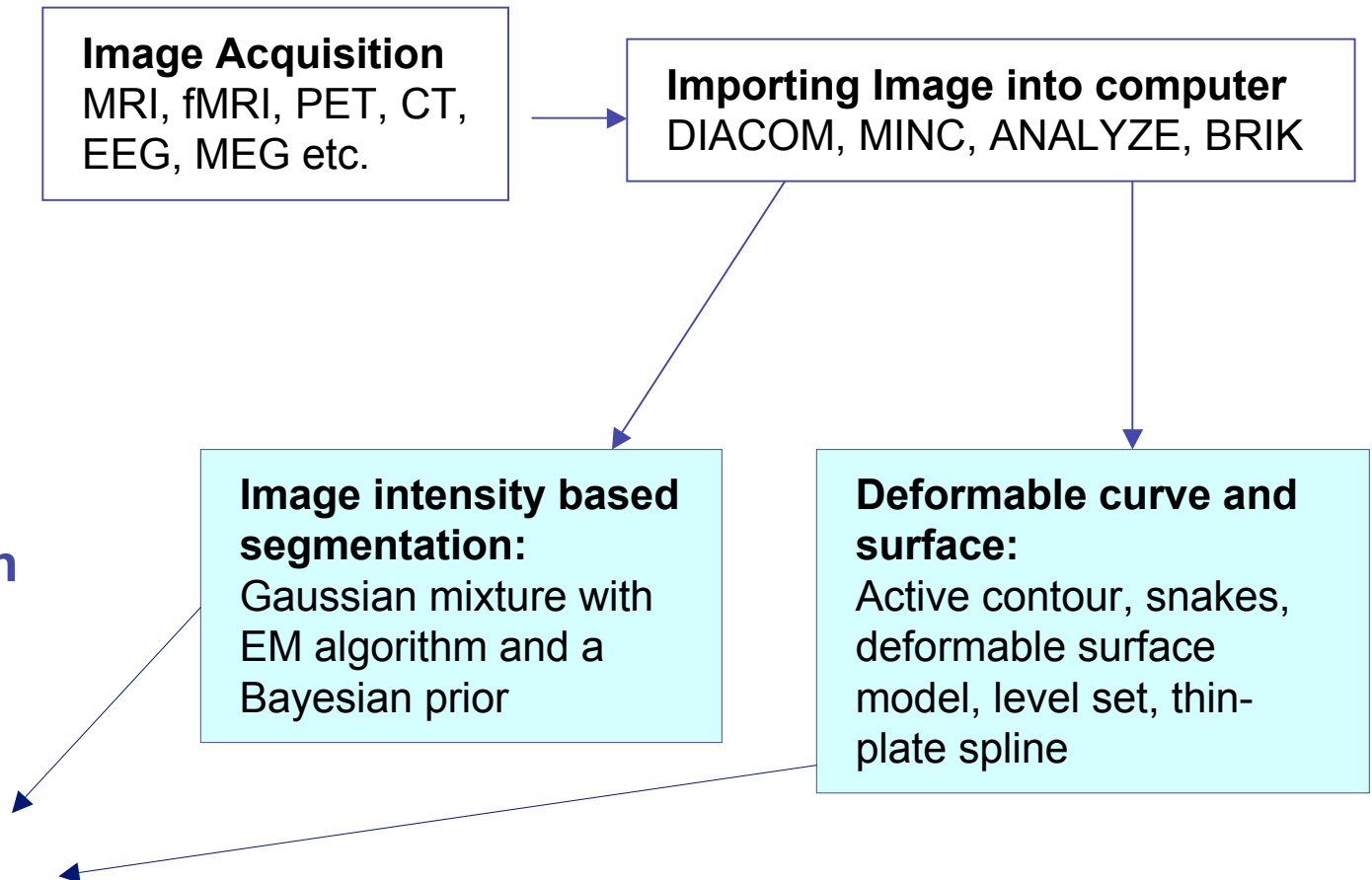
Image Segmentation

Image intensity based segmentation:
Gaussian mixture with
EM algorithm and a
Bayesian prior

Deformable curve and surface:
Active contour, snakes,
deformable surface
model, level set, thin-
plate spline

Image Registration

Numerical methods for PDE



Motivation for using partial differential equation (PDE) based approaches

- PDE models a continuous physical process
- The solution of PDE provides a continuous solution

Applications:

Image segmentation (active contours, level set)

Image registration (elastic or fluid dynamics equation)

Image smoothing (diffusion smoothing)

Cortical thickness estimation (Laplace equation)

Anatomical surface parameterization (conformal mapping)

Image Registration

Similarity measure

$$\rho(\mathbf{x}, \mathbf{y}) = \rho\left(I_1(\mathbf{x}), I_2(\mathbf{y})\right)$$

Variational approach

$$\min_d \left[\int_{\mathbf{x} \in \Omega} \rho\left(\mathbf{x}, \mathbf{x} + d(\mathbf{x})\right) d\mathbf{x} + \lambda \int_{\mathbf{x} \in \Omega} \left\| \frac{\partial d}{\partial \mathbf{x}} \right\| d\mathbf{x} \right]$$



PDE approach

$$\alpha(\mathbf{x}) \cdot \frac{\partial^2 d}{\partial \mathbf{x}^2} + \beta(\mathbf{x}) \cdot \frac{\partial d}{\partial \mathbf{x}} + \gamma(\mathbf{x}) = 0$$

Solving ODE in 1D

Heat diffusion:

$$\frac{\partial f}{\partial t} = \frac{\partial^2 f}{\partial x^2}$$

with initial data $f(x, t) = Y(x)$

Finite difference:

$$f(x, t_{j+1}) = f(x, t_j) + \delta t \widehat{\frac{\partial^2 f}{\partial x^2}}(x, t_j)$$

iteration step size $\delta t = t_{j+1} - t_j$ is fixed



i-th grid position

Finite Difference Method (FDM)

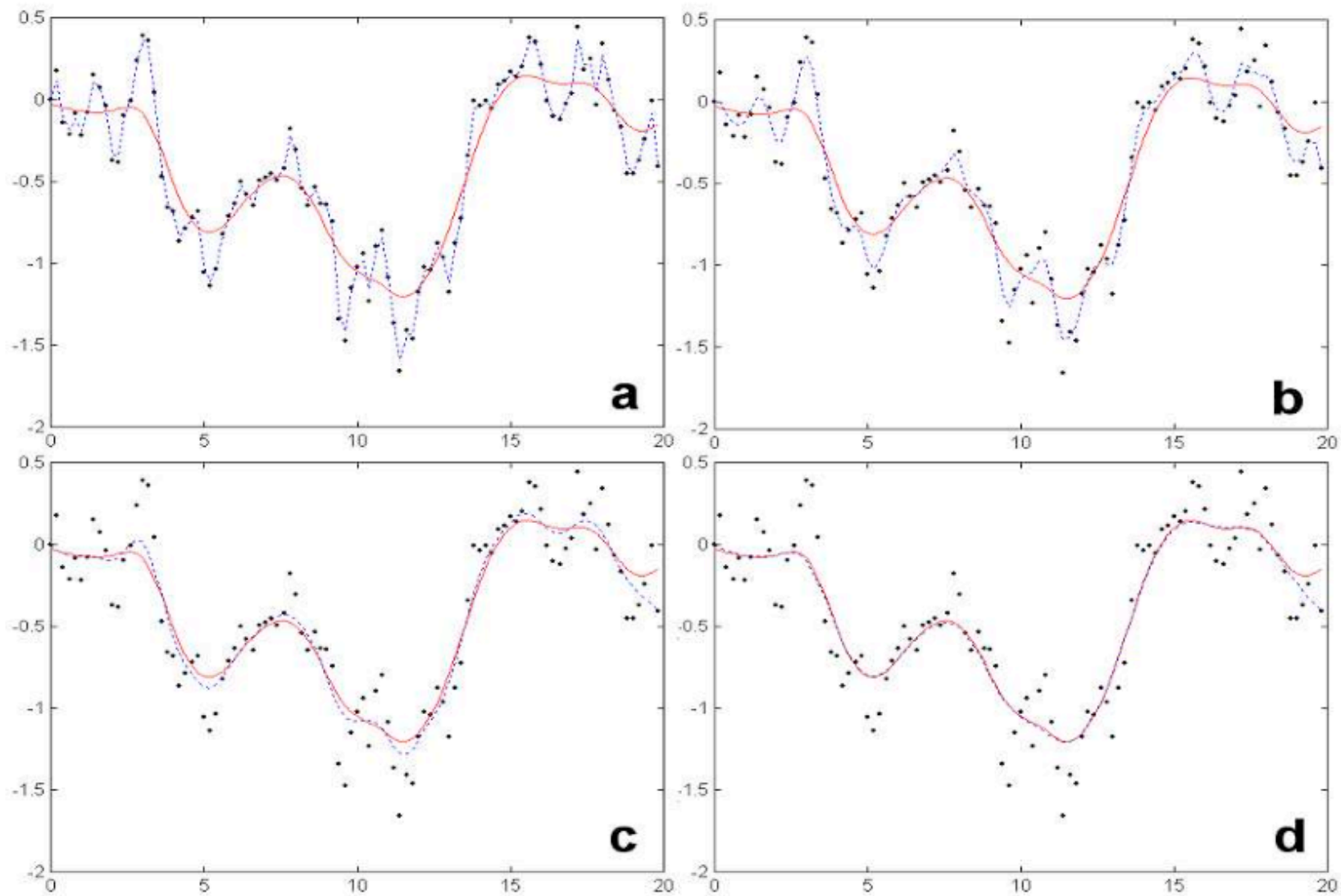
$$\widehat{\frac{\partial f}{\partial x}}(x, t_j) = \frac{f(x + \delta x, t_j) - f(x, t_j)}{\delta x}$$

Apply the 1st FDM one more time:

$$\widehat{\frac{\partial^2 f}{\partial x^2}}(x, t_j) = \frac{\frac{f(x + \delta x, t_j) - f(x, t_j)}{\delta x} - \frac{f(x, t_j) - f(x - \delta x, t_j)}{\delta x}}{\delta x}$$

$$= [f(x - \delta x, t_j) - 2f(x, t_j) + f(x + \delta x, t_j)] / \delta x^2$$

Simulation result



Convergence of FDM

- FDM converges for sufficiently small time step.
- Maximum principle: diffused signal should be between the maximum and the minimum of the previous time step.

Assuming positive data

$$\begin{aligned} f(x_i, t_{j+1}) &= f(x, t_j) + \delta t \frac{\widehat{\partial^2 f}}{\partial x^2}(x, t_j) \\ &\leq \max [f(x_{i-1}, t_j), f(x_i, t_j), f(x_{i+1}, t_j)] \end{aligned}$$

$$\delta t \leq \max \left[\left| \frac{f(x_{i-1}, t_j) - f(x_i, t_j)}{\widehat{\frac{\partial^2 f}{\partial x^2}}} \right|, \left| \frac{f(x_{i+1}, t_j) - f(x_i, t_j)}{\widehat{\frac{\partial^2 f}{\partial x^2}}} \right| \right]$$

Solving PDE in 2D Mesh

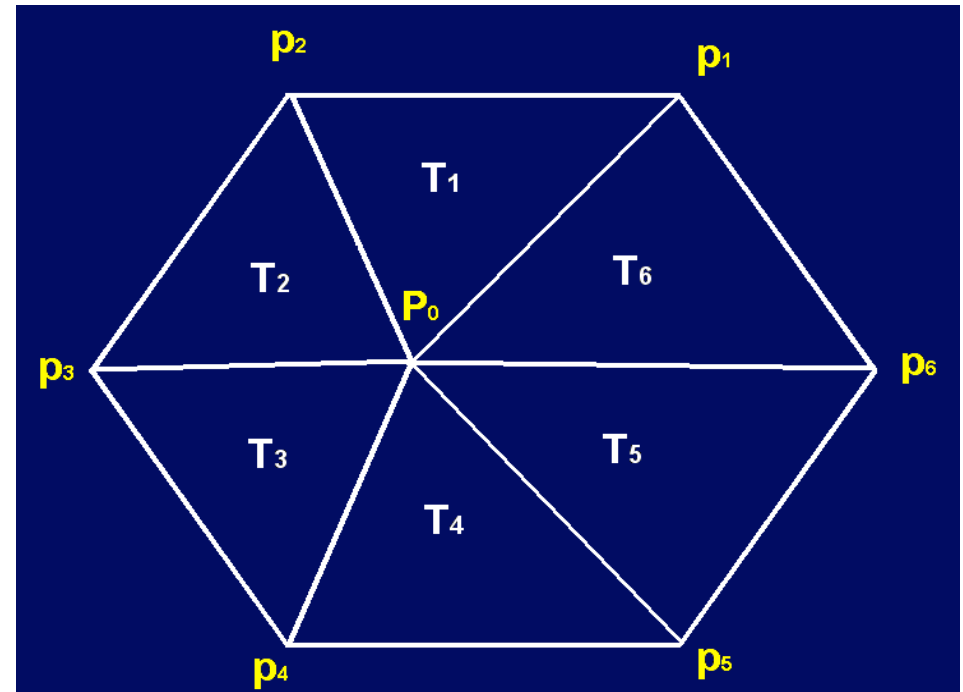
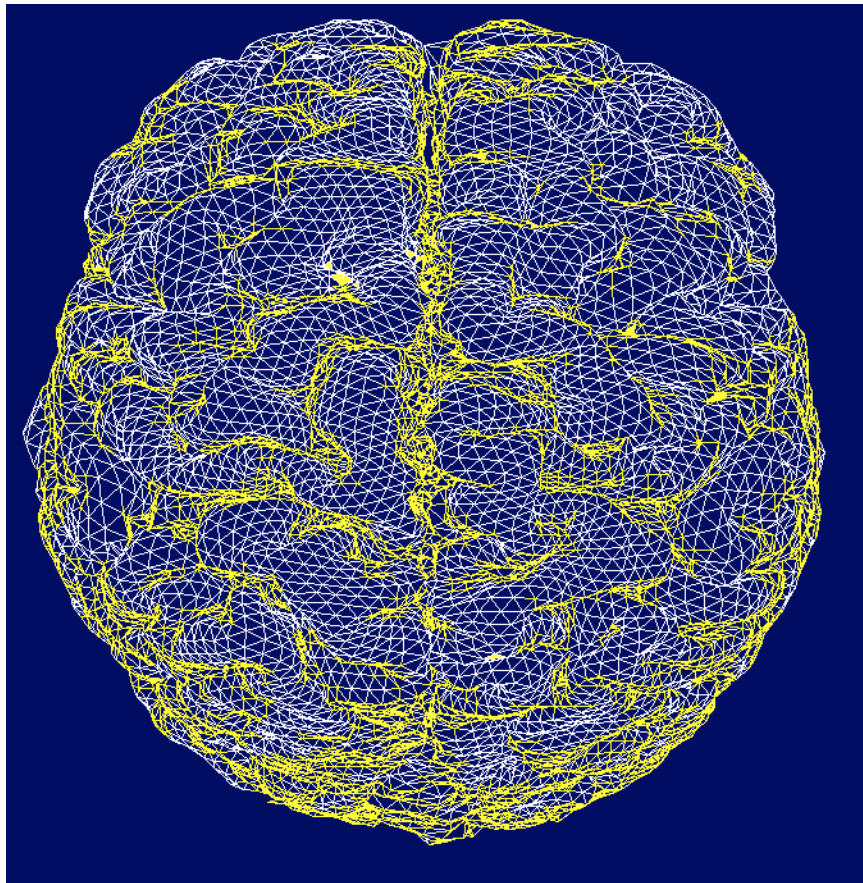
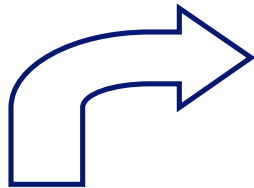
Heat diffusion: $\frac{\partial F}{\partial t} = \Delta F$

with initial condition $F(x, t = 0) = f(x)$

Numerical computation requires the combination of finite element method (FEM) + the finite difference method (FDM).

Basic idea of FEM

FEM is a numerical technique for setting up a PDE on triangle mesh



Solution is approximated as a linear combination of step functions defined on triangle elements.

Finite Element Method (FEM)

$$G, F \in PL\left(\bigcup_{i=1}^N T_i\right) \quad N = 82190$$

space of piecewise
continuous linear functional

For an arbitrary test function G , we have

$$\int_{T_i} G \frac{\partial F}{\partial t} dT = \int_{T_i} G \Delta F dT = - \int_{T_i} \langle \nabla F, \nabla G \rangle dT.$$

Solving this for every triangles, we obtain a system of ODE

$$\frac{d[F]}{dt} = -[A]^{-1}[C][F]$$

 40962 x 40962 sparse matrix

FDM is used to solve ODE via iteration.

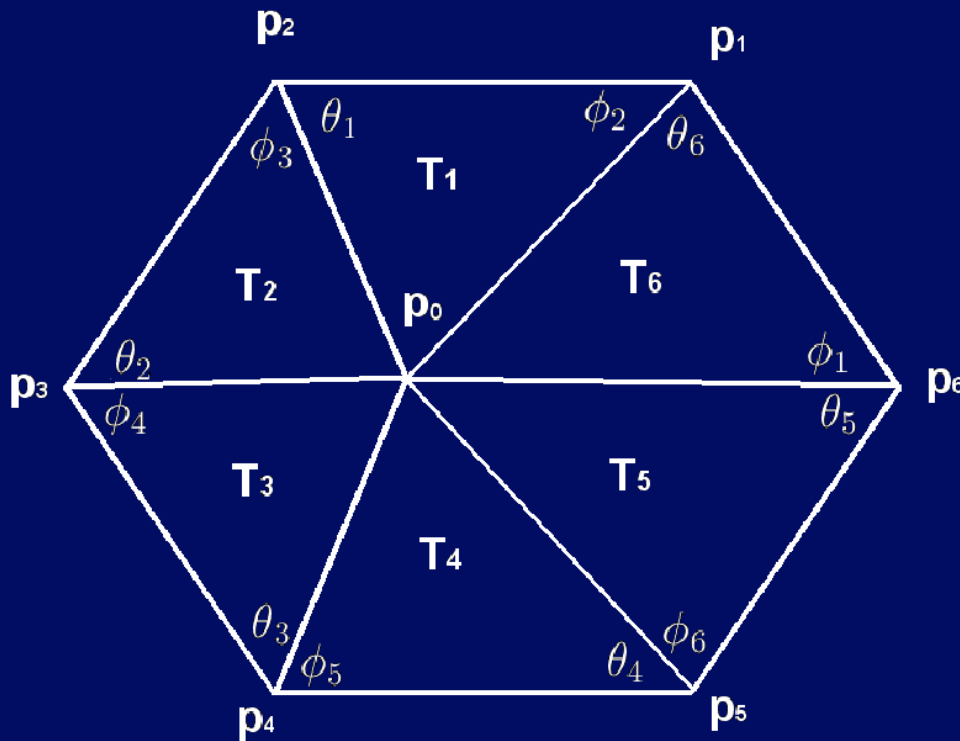
Laplace-Beltrami Operator (Graph Laplacian)

The Laplacian on graph can be estimated via computer algebra package (Maple, Mathematica).

Matrix inversion via Maple

$$\widehat{\Delta} F(p) = \sum_{i=1}^m w_i (F(p_i) - F(p))$$

$$w_i = \frac{\cot \theta_i + \cot \phi_i}{\sum_{i=1}^m |T_i|}$$



Finite Difference Scheme


$$\frac{\partial F}{\partial t} = \Delta F$$

$$\frac{F(x, t_{n+1}) - F(x, t_n)}{t_{n+1} - t_n} = \widehat{\Delta} F(x, t_n)$$

Stability condition (maximal principle):

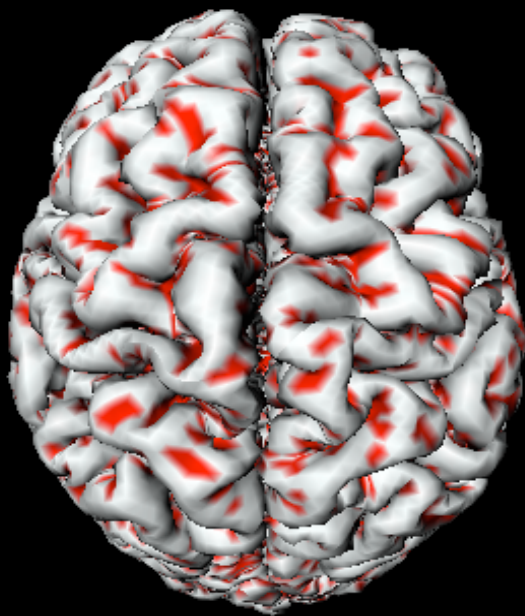
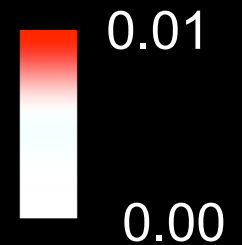
$$\min_i F(p_i, t_n) \leq F(p, t_{n+1}) \leq \max_i F(p_i, t_n)$$

Convergence condition for time step:

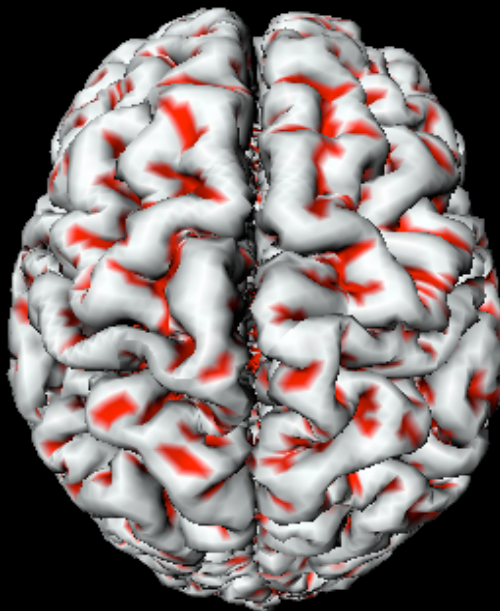
$$t_{n+1} - t_n \leq \min \left(\left| \frac{\max_i F(p_i, t_n) - F(p, t_n)}{\widehat{\Delta} F(p, t_n)} \right|, \left| \frac{\min_i F(p_i, t_n) - F(p, t_n)}{\widehat{\Delta} F(p, t_n)} \right| \right)$$

2D mesh simulation result

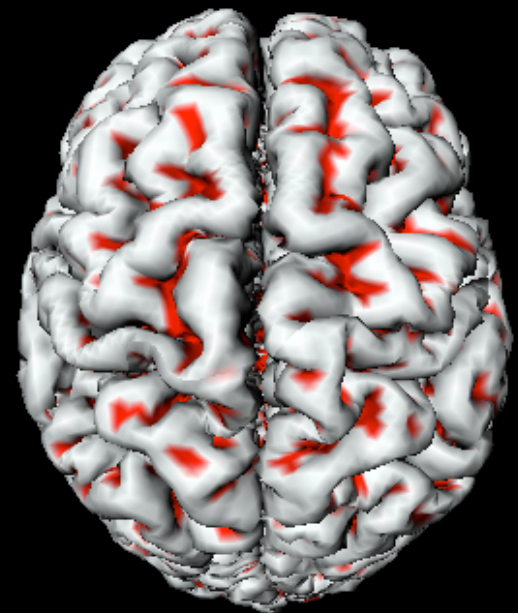
5mm FWHM filter size



Noisy data



20 iterations



100 iterations

Medical Image Analysis Flow

**Image
Segmentation**



**Image
Registration**

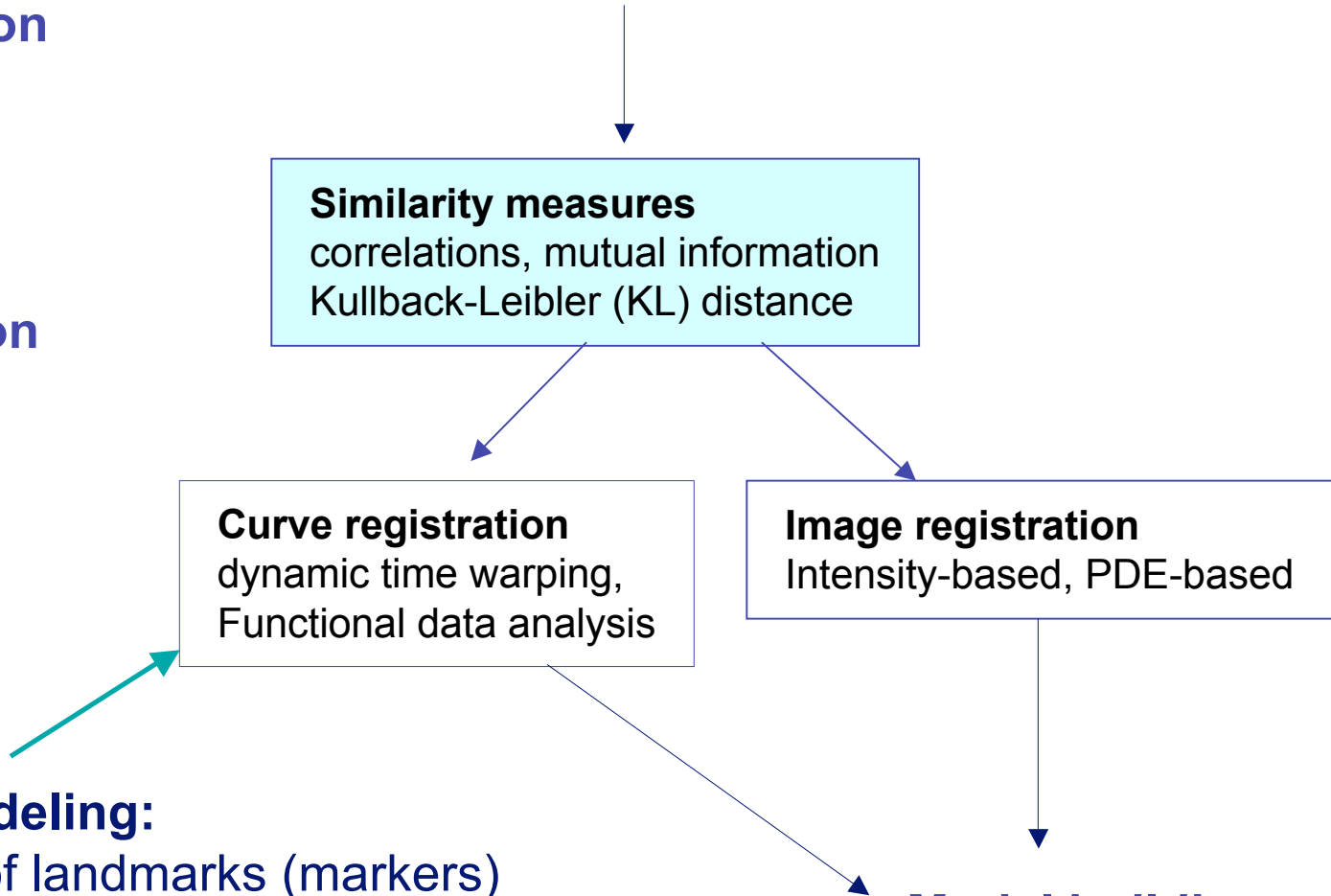
Similarity measures
correlations, mutual information
Kullback-Leibler (KL) distance

Curve registration
dynamic time warping,
Functional data analysis

Image registration
Intensity-based, PDE-based

Curve modeling:
modeling of landmarks (markers)
along anatomical boundary

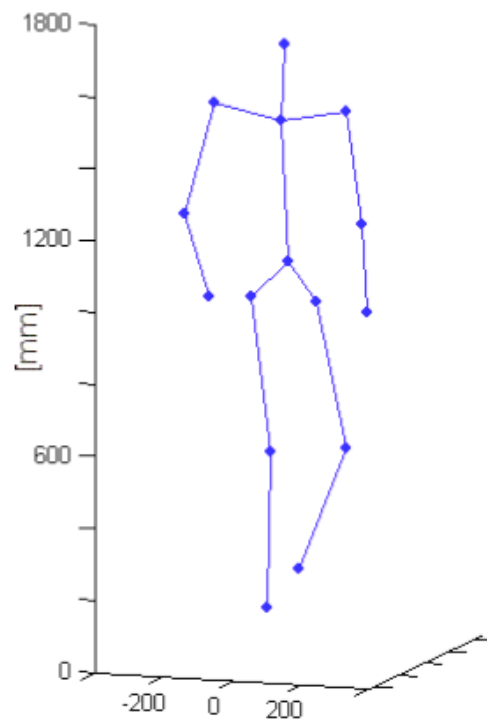
Model building



Decomposing biological motion: A framework for analysis and synthesis of human gait patterns

Nikolaus F. Troje

Ruhr-Universität, Bochum, Germany

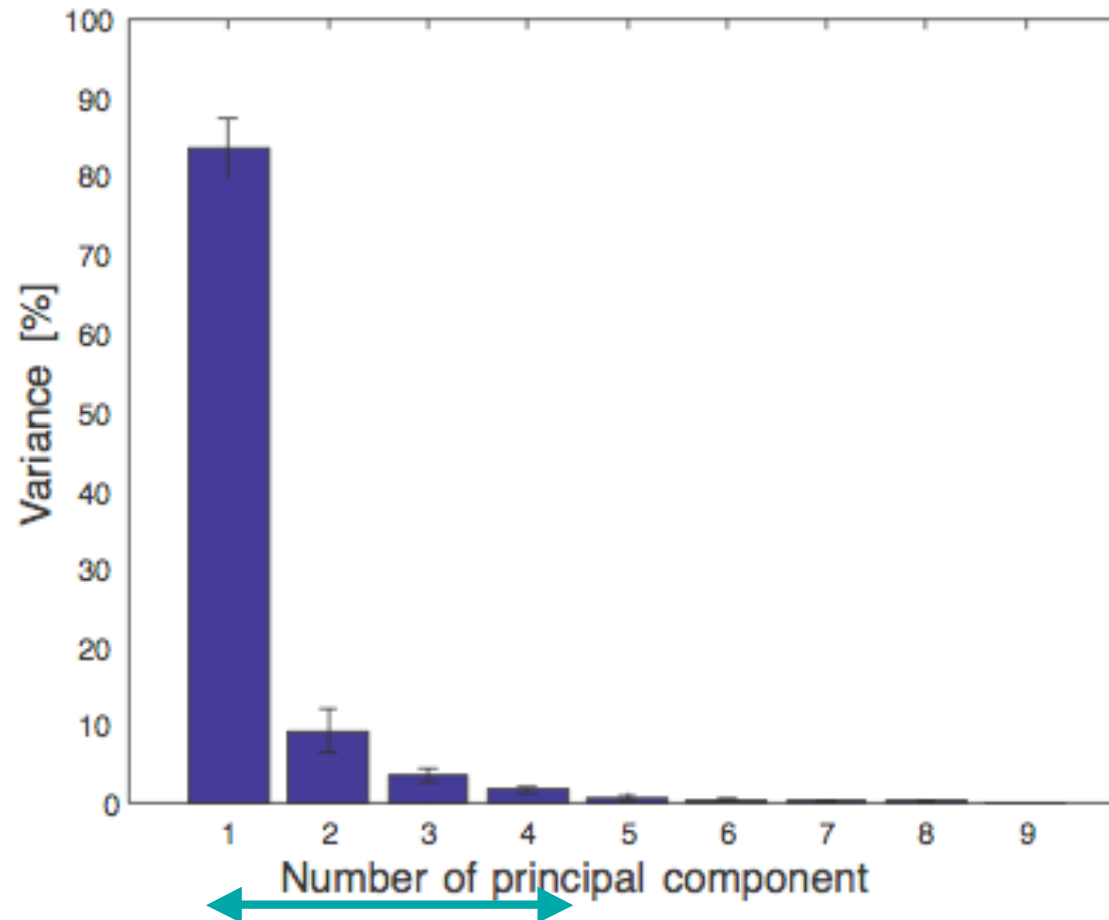


15 markers are located at the major joints of the human body and their movements are recorded continuously for 40 subjects (1400 measurements over time while walking)

Data: 3 coordinates x 15 makers = 45 dim. vector **p**.

Principal components analysis (PCA)

1400 posture vectors will give a set of PC for each subject. The bars denote the s.d. of PC over 40 subjects.



The first four components explain 98% of the overall variability

Modeling on posture vector $\mathbf{p}$

$$\mathbf{p} = \mathbf{p}_0 + \sum_i c_i \mathbf{p}_i$$

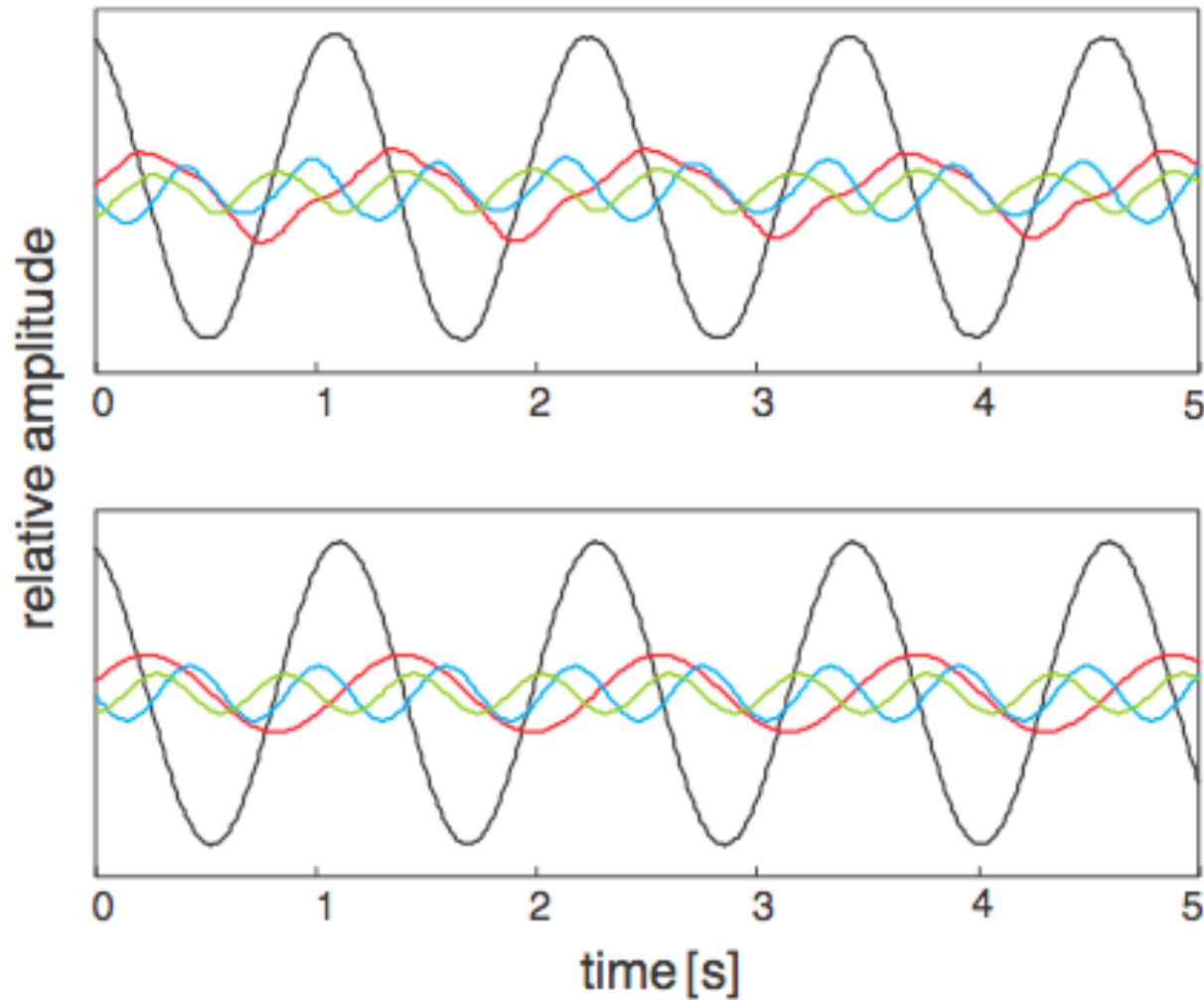


average posture



weighted linear
combination of the
first four PCA

PC change over time of a single subject



Four principal components over time

Model fit using sine functions
R-square values:
0.99, 0.95, 0.94,
0.90

Model for posture (single subject)

$$\begin{aligned}\mathbf{p}(t) = & \mathbf{p}_0 + \mathbf{p}_1 \sin(\omega t) + \mathbf{p}_2 \sin(\omega t + \varphi_2) \\ & + \mathbf{p}_3 \sin(2\omega t + \varphi_3) + \mathbf{p}_4 \sin(2\omega t + \varphi_4)\end{aligned}$$

j -th subject

$$\begin{aligned}\mathbf{p}_j(t) = & \mathbf{p}_{j,0} + \mathbf{p}_{j,1} \sin(\omega_j t) + \mathbf{p}_{j,2} \sin(\omega_j t + \varphi_{j,2}) \\ & + \mathbf{p}_{j,3} \sin(2\omega_j t + \varphi_{j,3}) + \mathbf{p}_{j,4} \sin(2\omega_j t + \varphi_{j,4})\end{aligned}$$

Subpixel Curvature Estimation of the Corpus Callosum via Splines and its Application to Autism

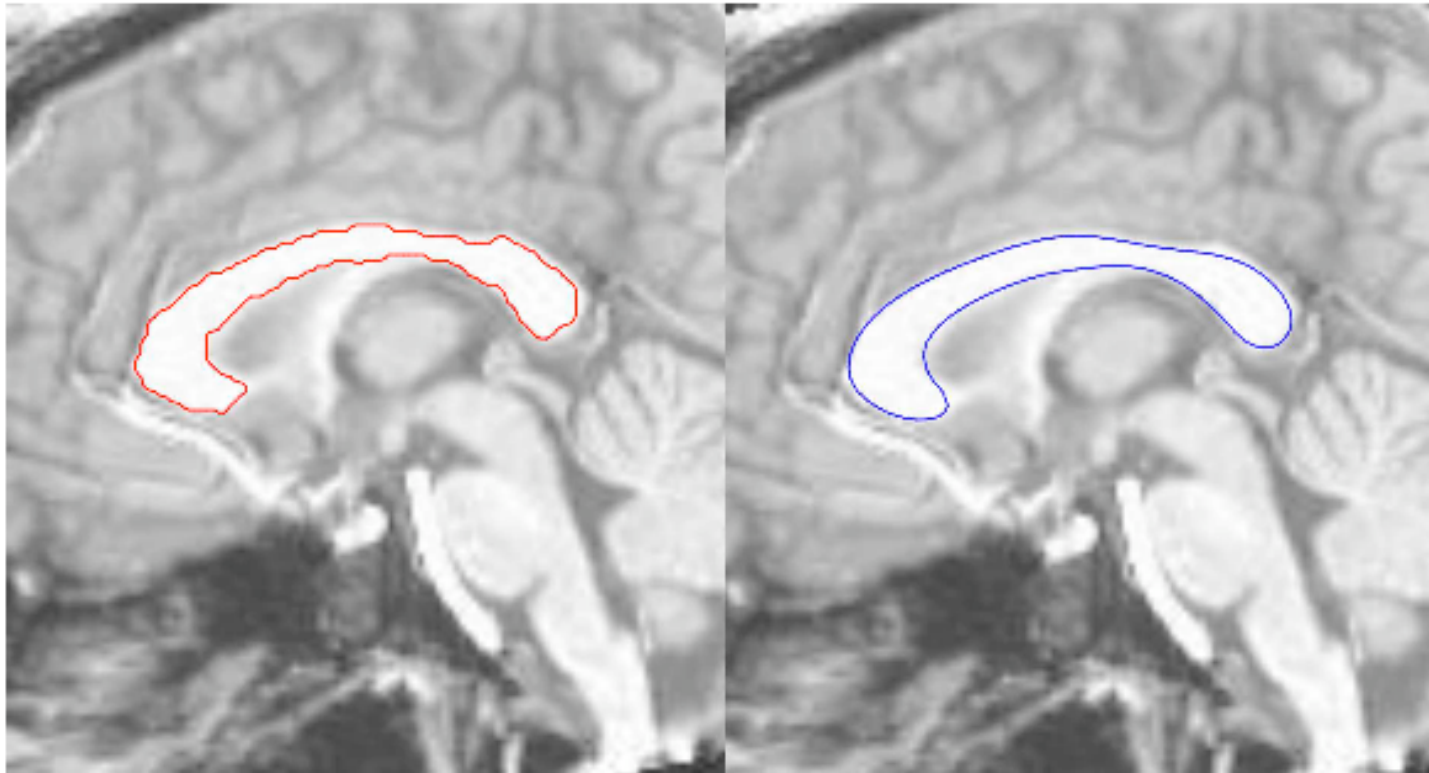
Thomas J. Hoffmann¹, Moo K. Chung^{1,2,3}, Kim D. Dalton³, Andrew L. Alexander^{3,4,5}, Grace Wahba^{1,2}, Richard J. Davidson^{3,4,6}

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University of Wisconsin, Madison, WI 53706

June 16, 2004

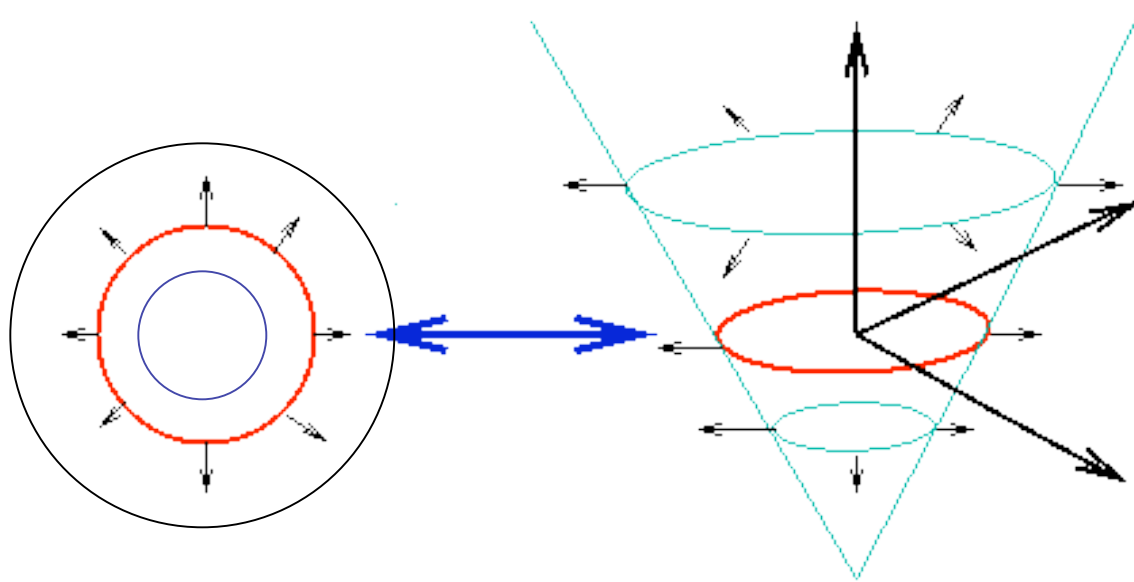


Level set segmentation

Spline smoothing

Level set segmentation

- The anatomical boundary is modeled as the zero level set of a function $\phi(x,y,t)$.



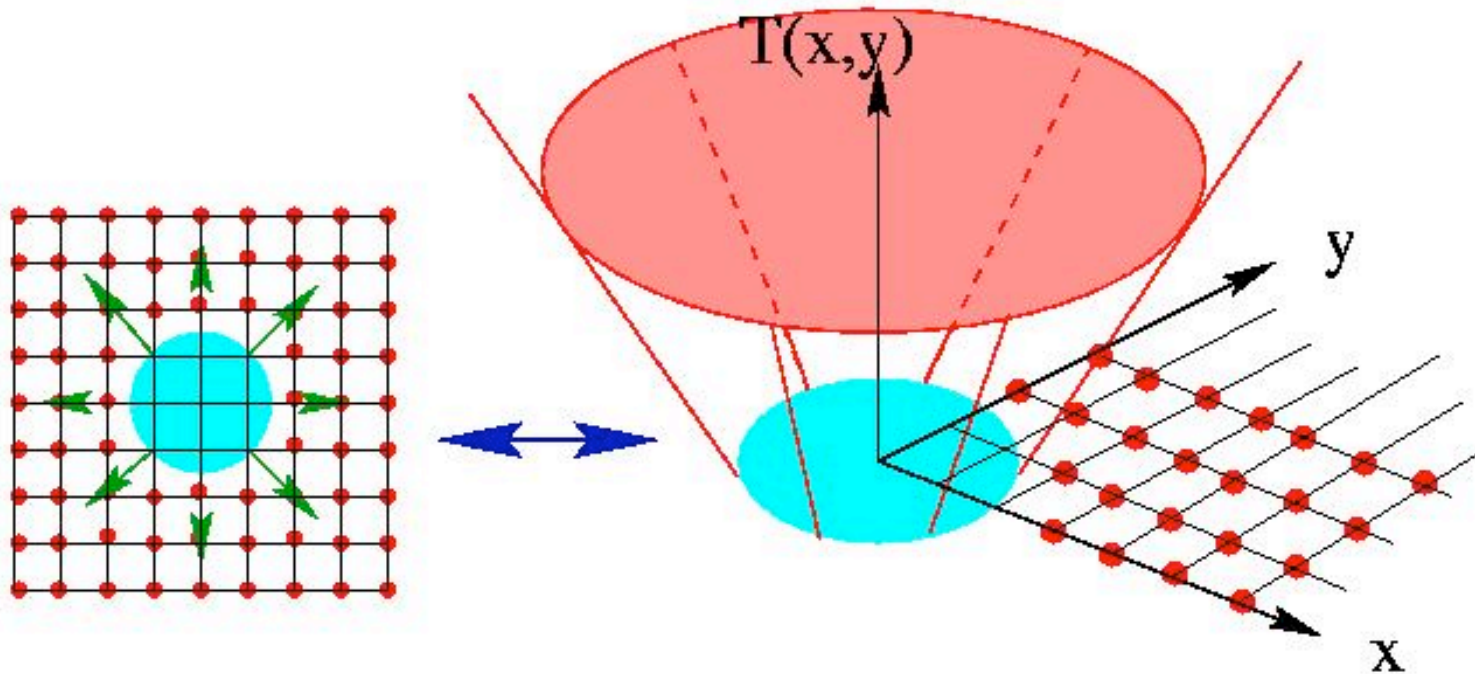
Red= $\phi(x,y,0)$ = anatomical boundary

$$\frac{\partial \phi}{\partial t} + F|\nabla \phi| = 0$$

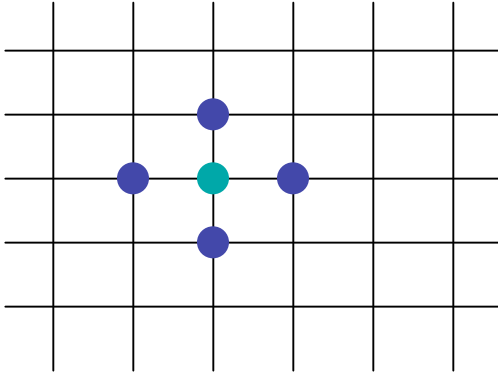
boundary
propagation
velocity

Fast marching cube

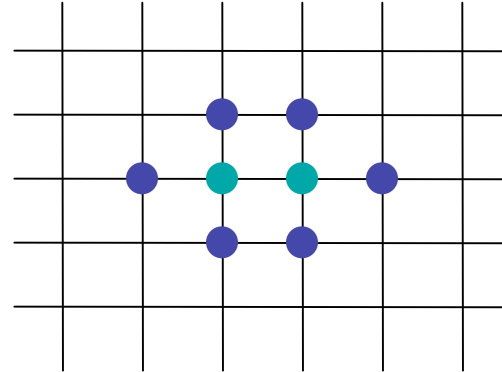
Fast marching cube method is used to incrementally propagate the boundary (level set).



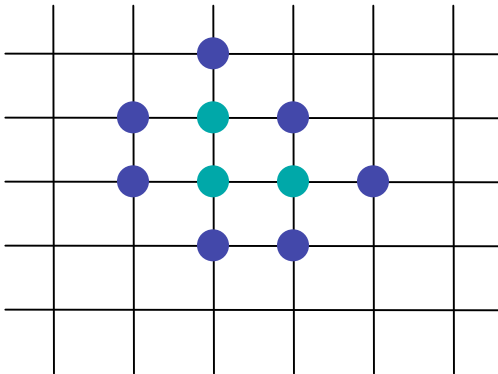
Fast Marching Cube



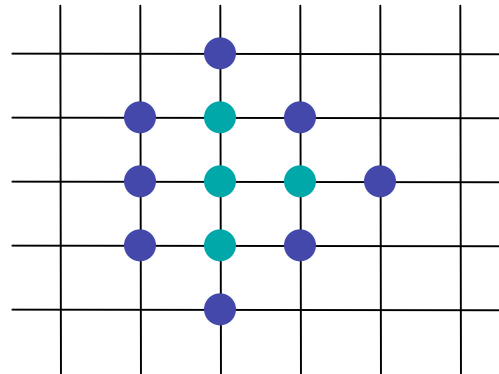
(i)



(ii)

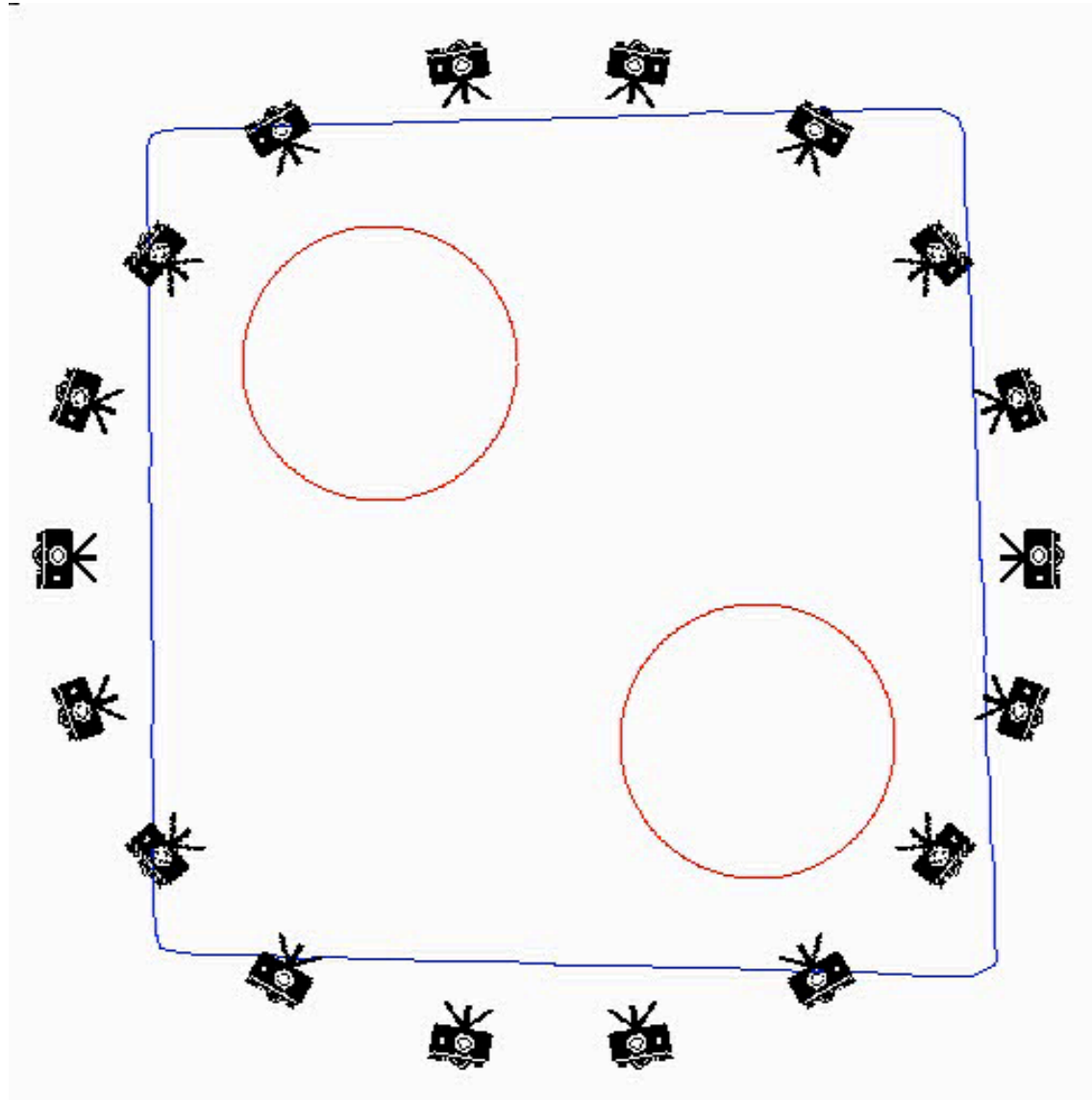


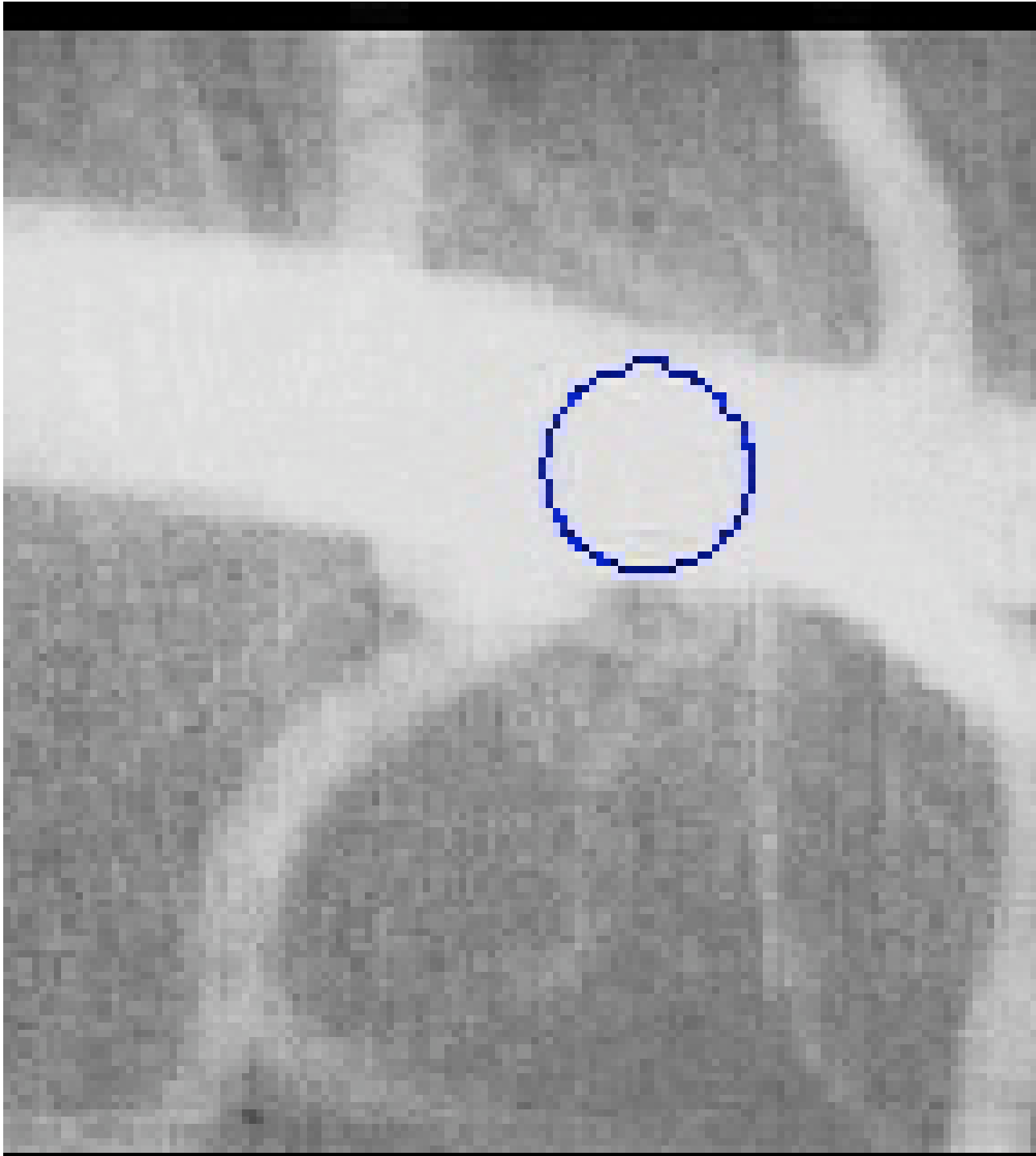
(iii)



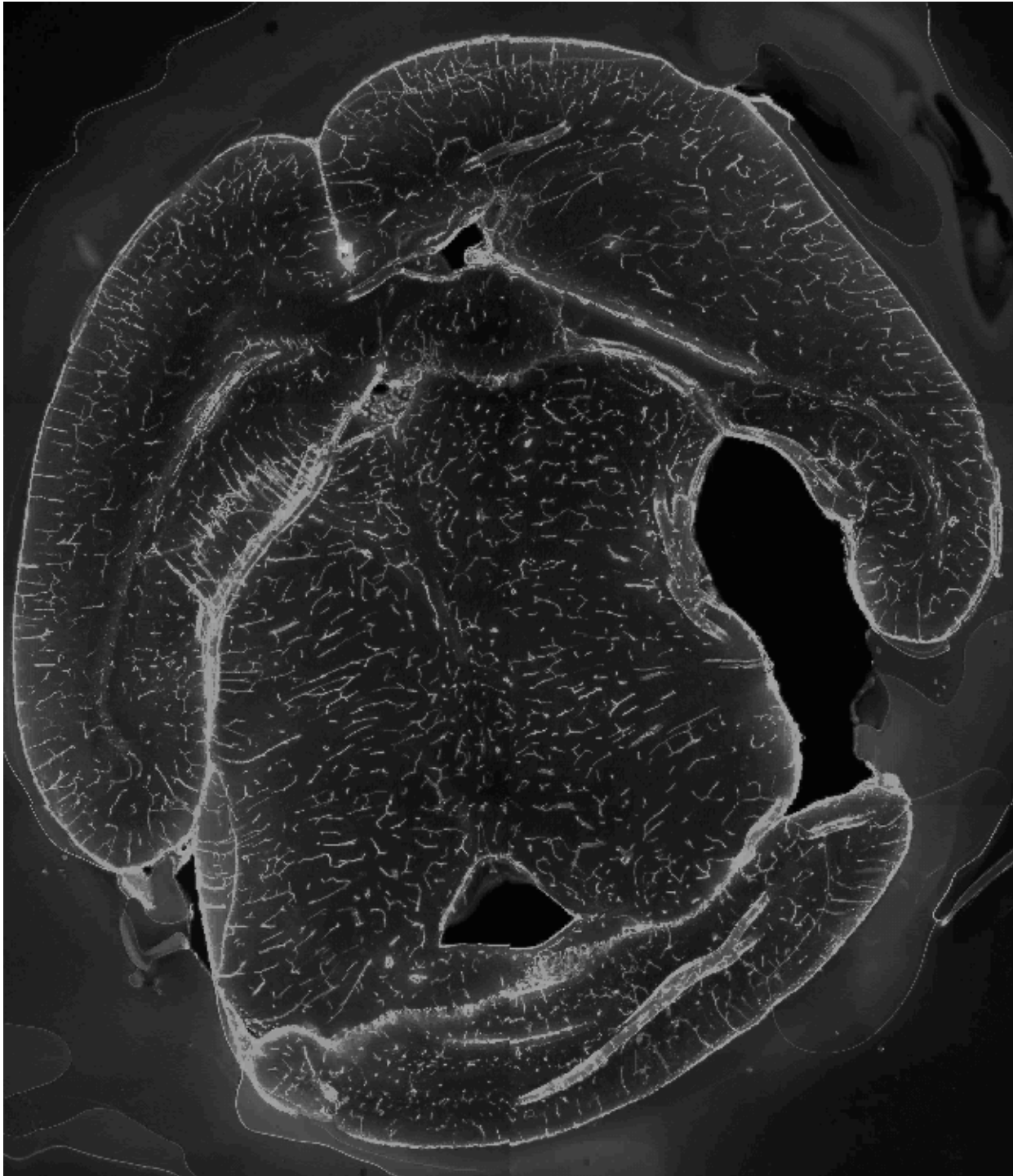
(iv)

Level set simulation



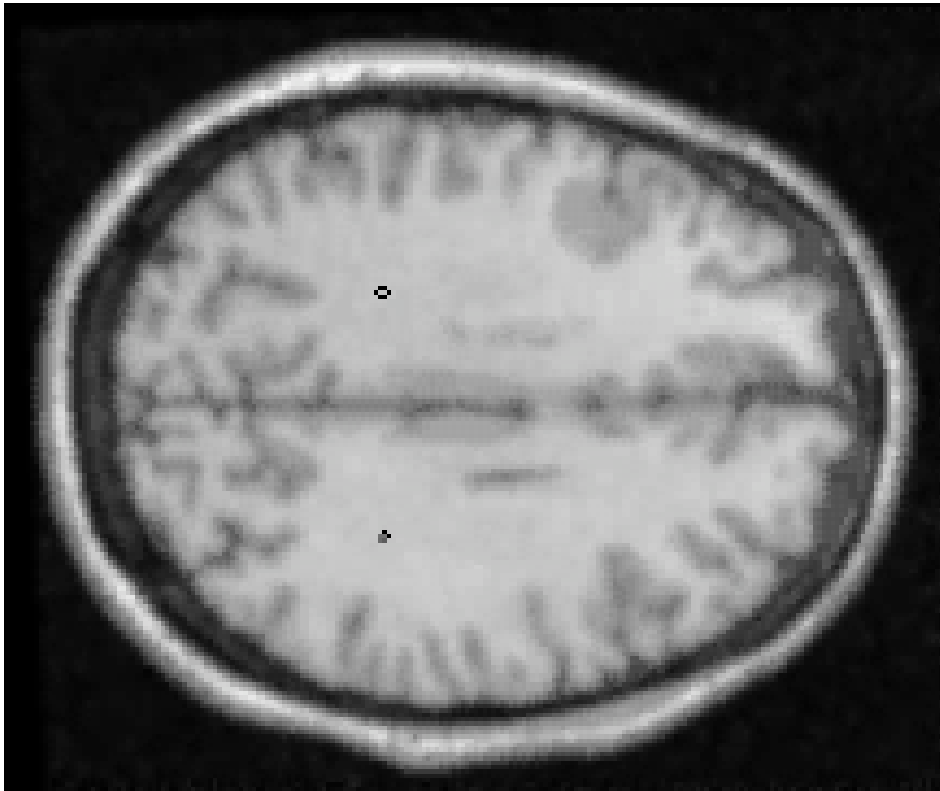


Artery
segmentation

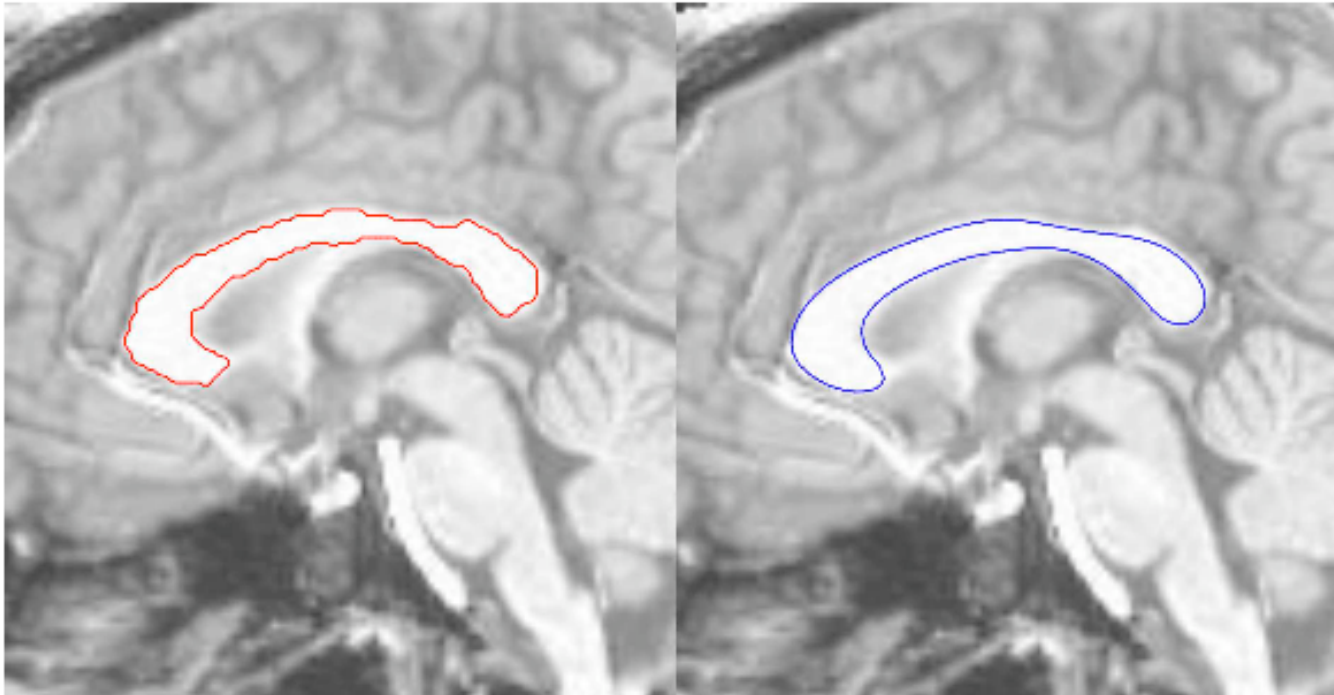


Microscopic
image
segmentation

White matter segmentation



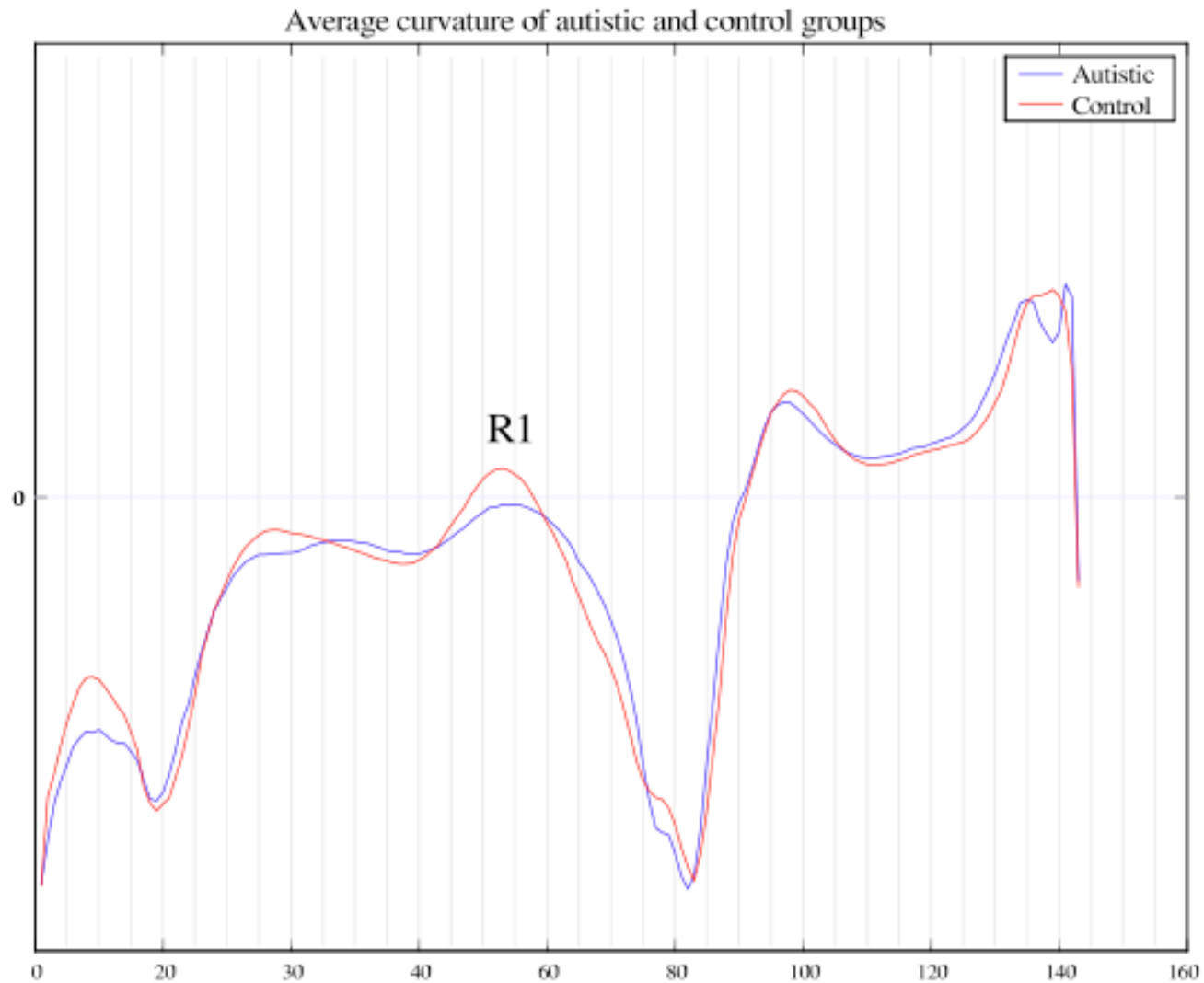
Level set segmentation produces noisy boundary



$$\min_g \frac{1}{n} \sum_{j=1}^n [Y_j - g(t_j)]^2 + \lambda \int [g'''(t)]^2 dt$$

Spline is used to obtain smooth boundary

Curvature estimation



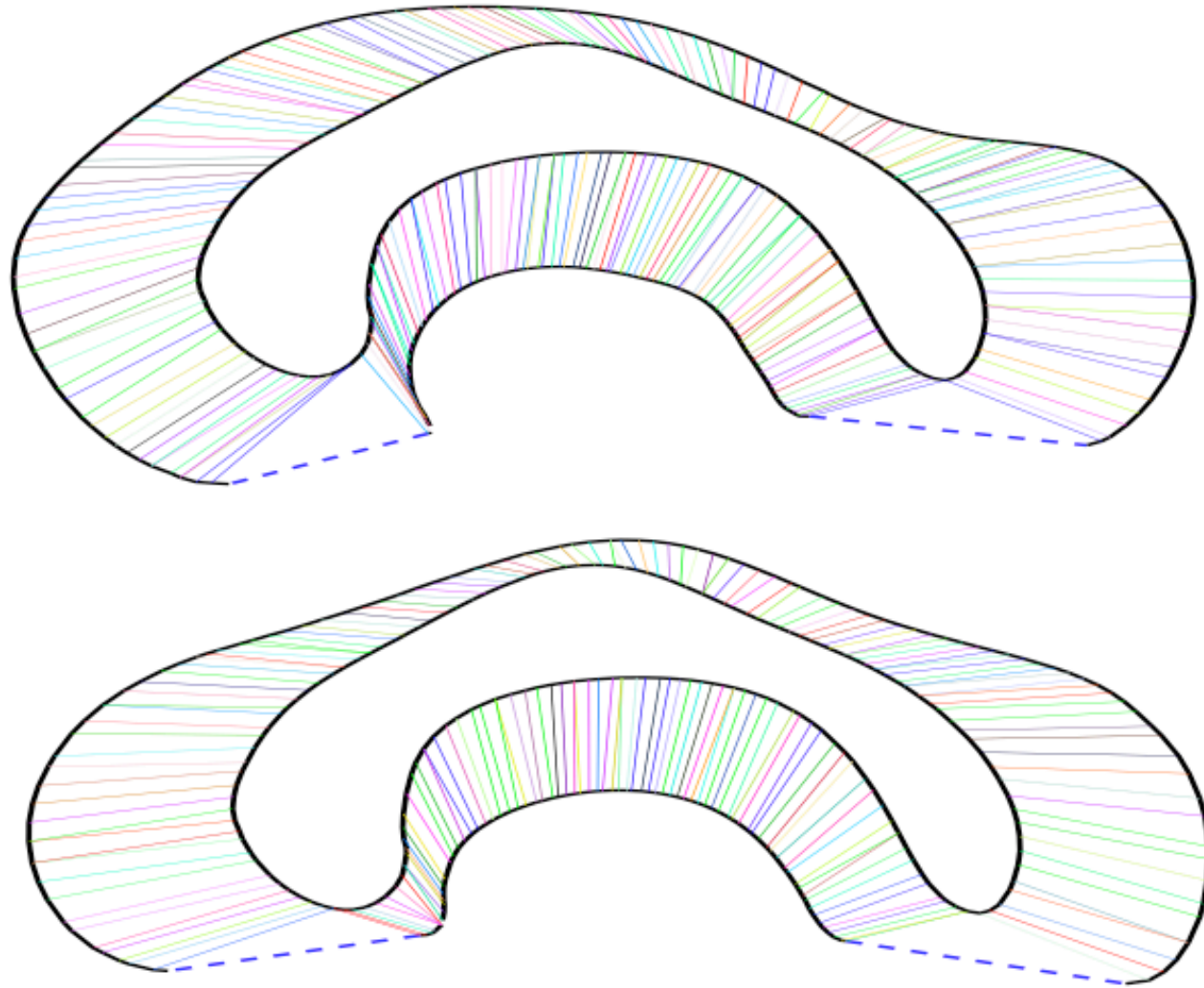
Curve registration via curvature matching

Find smooth deformation field d by minimizing

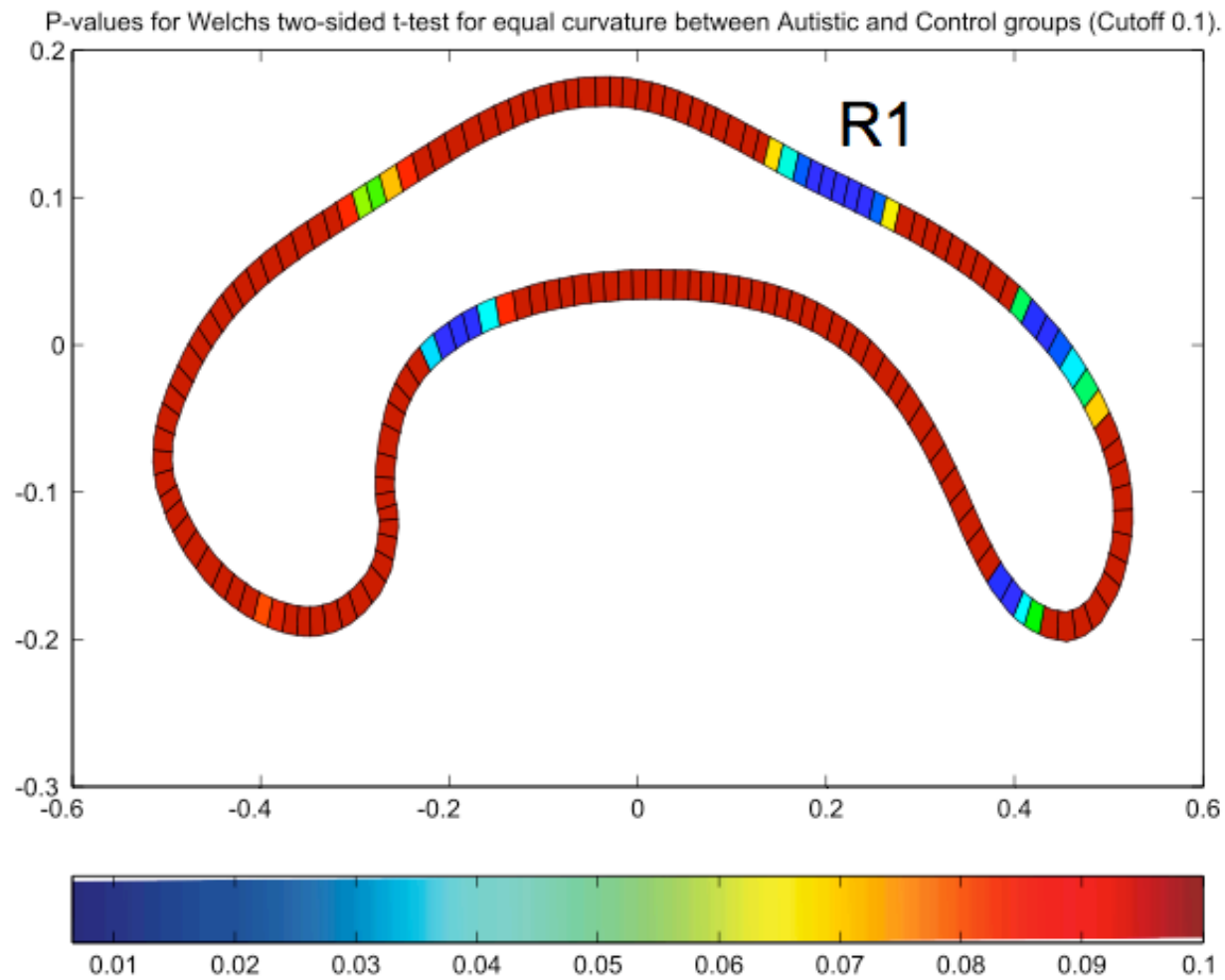
$$\frac{1}{n} \sum_{j=1}^n \|X(t_j) - X(d(t_j))\| + \lambda \int |\kappa_1(t) - \kappa_2(d(t))| dt$$

positional difference curvature difference

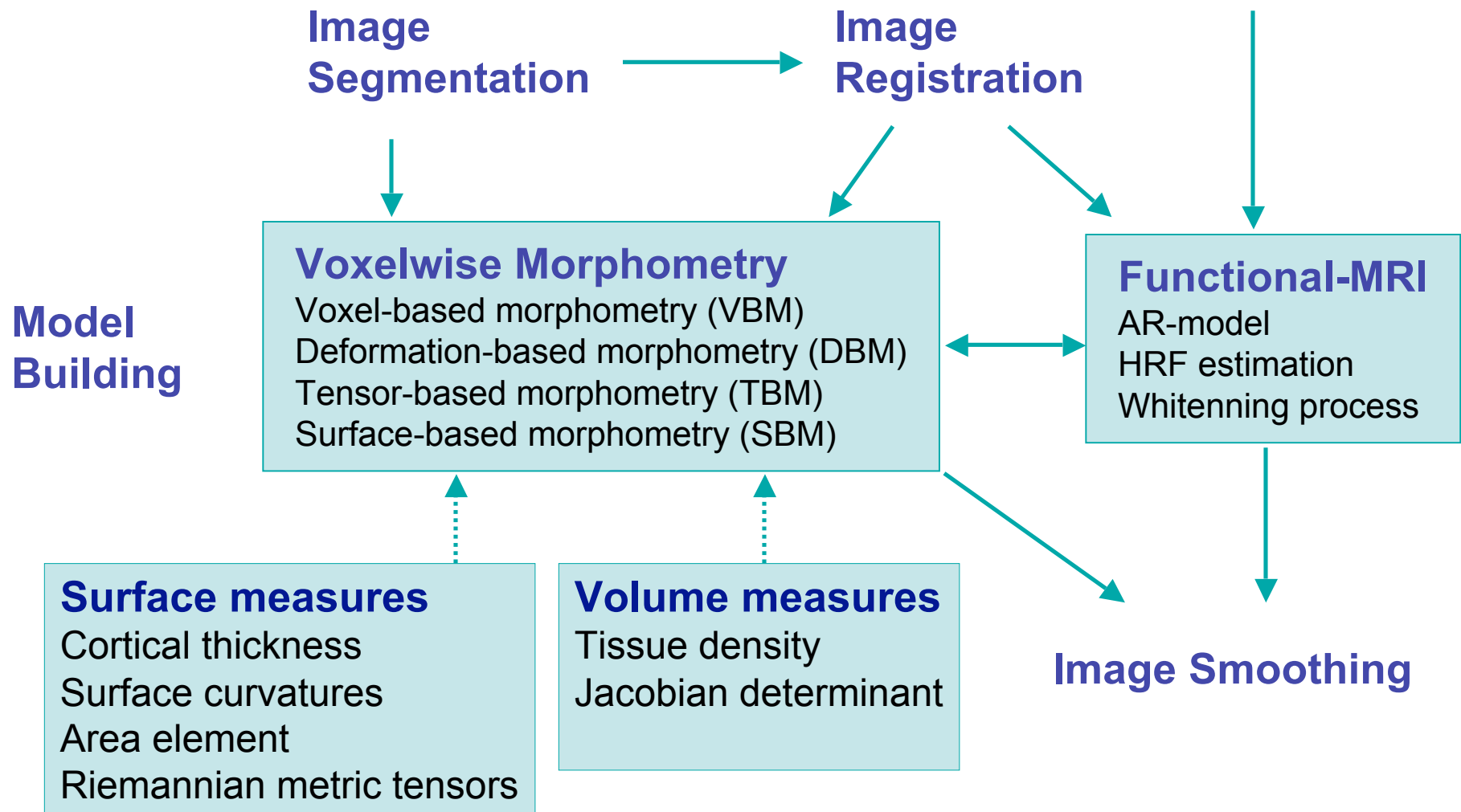
Visualization of displacement vector



P-value map (uncorrected) of group difference



Medical Image Analysis Flow



- Morphometry

- Ashburner, J., Friston, K.J. 2000. Voxel-based morphometry-the method, *NeuroImage*. 11:805-821. [Introduces VBM](#)
- Good, C.D., Johnsrude, I.S., Ashburner, J., Henson, R.N.A., Friston, K.J., and Frackowiak, R.S.J. 2001. A Voxel-Based Morphometric Study of Ageing in 465 Normal Adult Human Brains, *NeuroImage*. 14:21-36. [Introduces optimized-VBM](#)
- Bookstein, F.L. 2001. Voxel-based morphometry should not be used with imperfectly registered images. *NeuroImage* 14:1454-1462. [Main issues of VBM](#)
- Ashburner, J., Friston, K.J. 2001. Why Voxel-based morphometry should be used. *NeuroImage*. 14:1238-1243. [Main issues of VBM](#)
- Davatzikos, C. 2004. Why voxel-based morphometric analysis should be used with great caution when characterizing group differences. *NeuroImage* 23:17-20. [Main issues of VBM](#)
- Chung, M.K., Worsley, K.J. , Paus, T., Cherif, C., Giedd, J.N., Rapoport, J.L, Evans, A.C. 2001. A Unified Statistical Approach to Deformation-Based Morphometry, *NeuroImage* 14:595-606. [Compares DBM vs. TBM](#)
- Crum, W.R., Griffin, L.D., Hill, D.L.G., Hawkes, D.J. 2003. Zen and the art of medical image registration: correspondence, homology, and quality. *NeuroImage* 20:1425-1437. [Distributional assumption of TBM](#)

- Anatomical boundary segmentation/parameterization

Xu, C. and Prince, L. 1998. Snakes, shapes and gradient vector flow, *IEEE Trans. on Image Proc*, 7:359-369. [Active contour](#)

Sethian., J.A., 1996. Level Set Methods and Fast Marching Methods. Cambridge Univ. Press, Cambridge, UK. [Level set algorithm](#)

MacDonald, J.D., Kabani, N., Avis, D., and Evans, A.C. 2000. Automated 3-D Extraction of Inner and Outer Surfaces of Cerebral Cortex from MRI. *NeuroImage* 12:340–356. [Deformable surface model](#)

Angenent, S., Haker., S. 1999. A. Tannenbaum, and Ron Kikinis, “On the Laplace-Beltrami Operator and Brain Surface Flattening”, *IEEE Trans. Medical Imaging*. 18:700-711. [Conformal mapping](#)

Li Shen, James Ford, Fillia Makedon, and Andrew Saykin. A Surface-based Approach for Classification of 3D Neuroanatomic Structures. *Intelligent Data Analysis, An International Journal*, Volume 8(6), pp. 519-542, 2004 [SPHARM](#)

Chung, M.K., Dalton KM, Shen L, Evans AC, Davidson RJ. 2007. Weighted Fourier Series representation and its application to quantifying the amount of gray matter. *IEEE Transactions on Medical Imaging (Special Issue on Computational Neuroanatomy)*. 26:566-581, 2007 [SPHARM](#)

- Cortical thickness analysis

Fischl, B. and Dale, A.M. 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images, PNAS 97:11050-11055 [FreeSurfer](#)

Chung, M.K., Worsley, K.J., Robbins, S., Paus, P., Taylor, J., Giedd, J.N., Rapoport, J.L., Evans, A.C. 2003. Deformation-Based Surface Morphometry with an Application to Gray Matter Deformation, *NeuroImage*. 18:198-213. [Compares cortical thickness vs. TBM along surface](#)

Chung, M.K., Robbins, S., Dalton, K.M., Alexander, A.L., Davidson, R.J., Evans, A.C. 2005. Cortical thickness analysis in autism via heat kernel smoothing. *NeuroImage* 25:1256-1265. [How to smooth cortical thickness](#)

Miller, M.I., Massie, A.B., Ratnanather, J.T., Botteron, K.N., Csernansky, J.G. 2000. Bayesian construction of geometrically based cortical thickness metrics. *NeuroImage* 12:676-687. [Bayesian framework](#)

Lerch, J.P., Pruessner, J.C., Zijdenbos, A., Hampel, H., Teipel, S.J., Evans, A.C. 2005. Focal decline of cortical thickness in Alzheimer's disease identified by computational neuroanatomy. *Cerebral Cortex* 15:995-1001. [Application to AD](#)

Cortical thickness vs. gray matter density

- Validation is difficult since cortical thickness is obtained from 2D surface mesh while gray matter density is obtained from 3D whole brain image.
- **Solution:** convert 2D cortical mesh data to 3D volume data using distance map

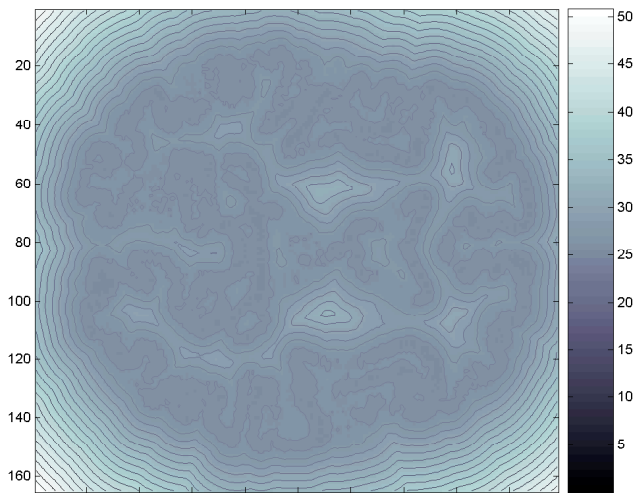
Distance map

- At each voxel position x ,

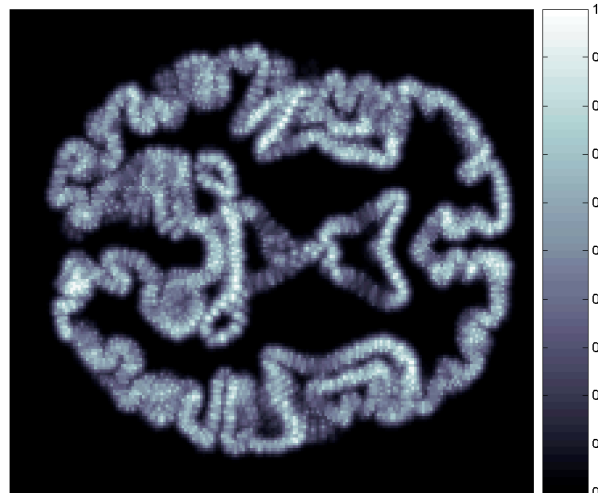
$$dist(x) = \min_{y \in surface} \|x - y\|$$

- Optimization is performed using the nearest neighbor search algorithm on an optimized k-D tree (MATLAB)
- Given inner and outer surfaces, we can compute the average distance map.

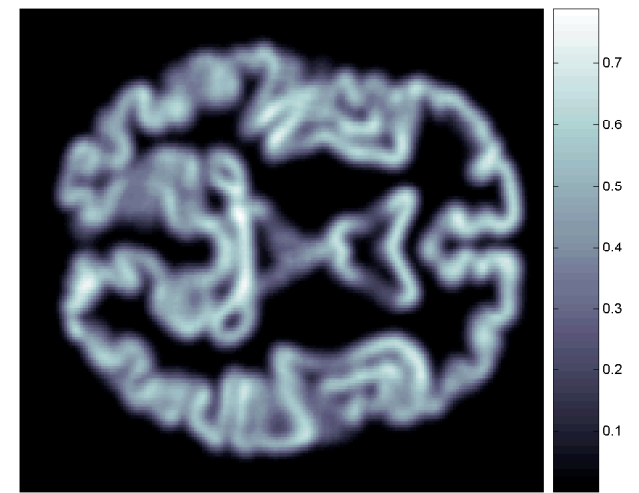
From surface mesh, we obtain distance map



Contour plot of
average
distance map

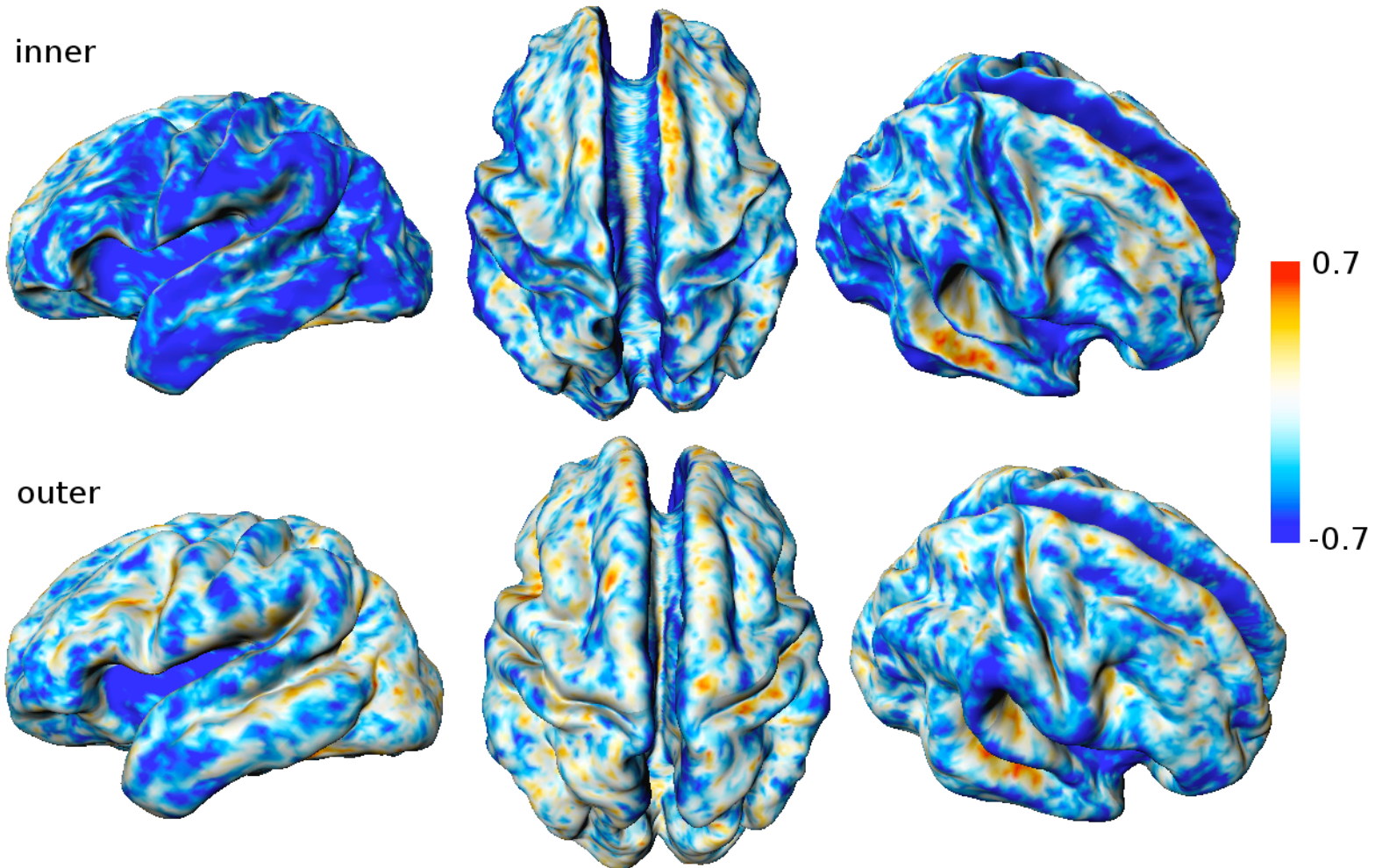


Density map
as a function of
distance map



Kernel smoothing

Counter-intuitive result showing negative correlation between cortical thickness and gray matter density



Thickness and density do not correlate well near tissue boundary

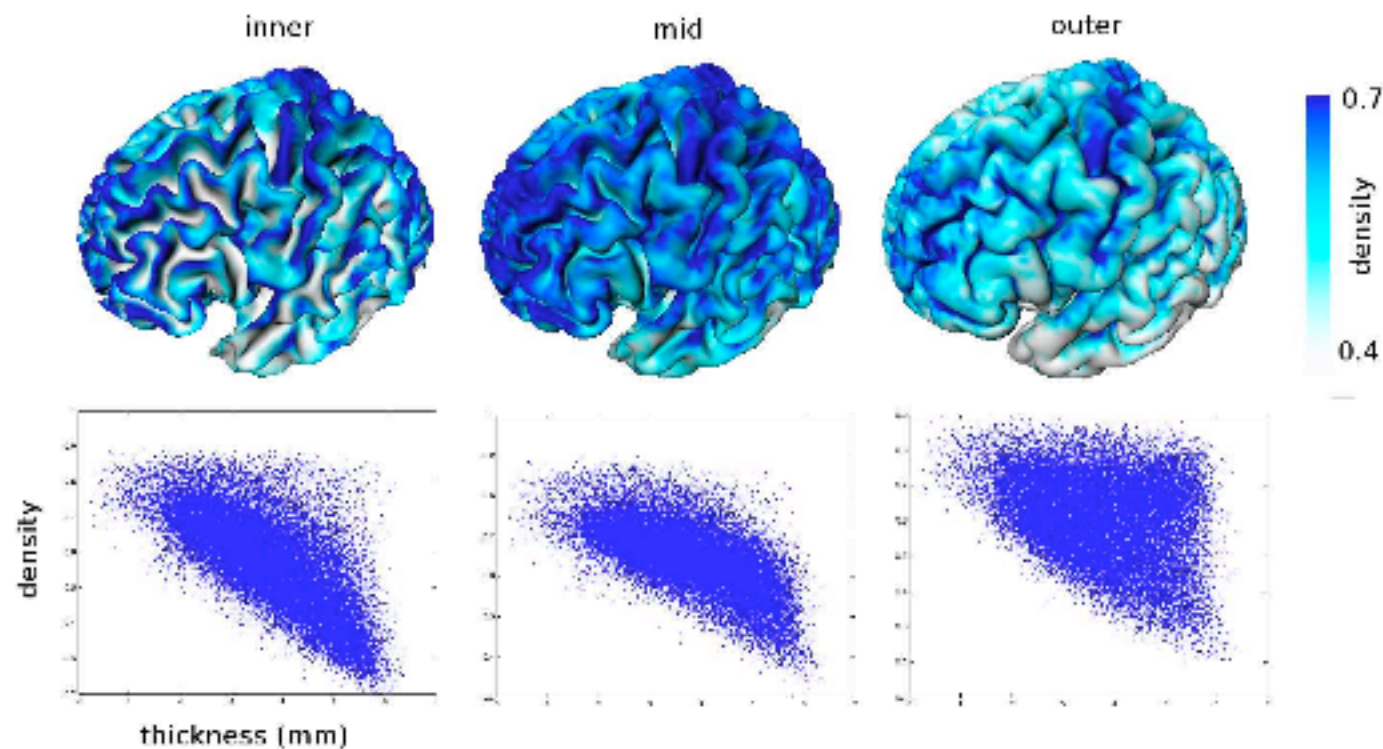
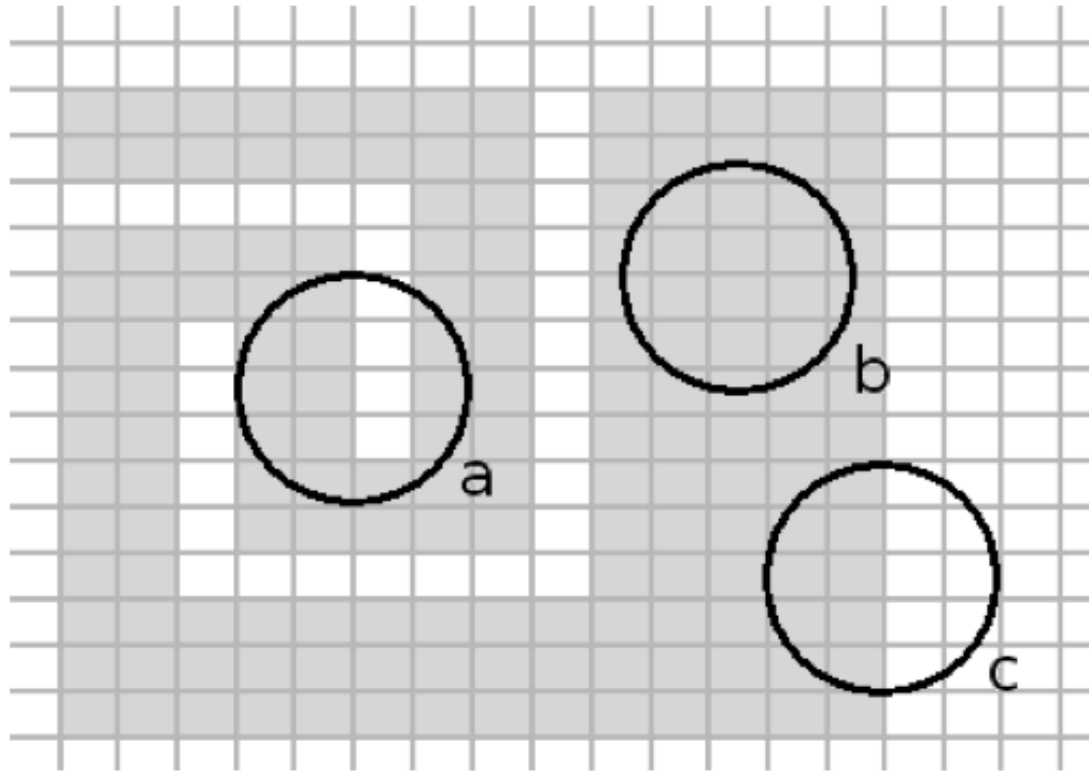


Fig. 11. Top: gray matter density projected onto inner, mid and outer surfaces. On the inner surface, the deep sulcal regions show the low density while the gyral ridges show high density. On the outer surface, this is opposite. The deep sulcal regions show high density while the gyral ridges show lower density. The middle surface shows high density. Bottom: Scatter plot of gray matter density over thickness. They show negative correlations.



Gray matter density does not necessarily measure the amount of gray matter.

Cortical thickness is only 1D measure defined on 2D surface. It will not completely quantify the amount of gray matter (3D measure).

Fig. 13. Simple 2D schematic showing the negative correlation between thickness and gray matter density. Gray colored pixels are gray matter. The black circle is the contour of heat kernel. There are more gray matter pixels in region (a) than region (c) although the thickness in region (c) is thicker than that of region (a). The gray matter density in the middle of the gray matter (b) is 1 for almost all subject indicating very small between-subject and between-group variability. Because of the small between-group variability, VBM does not usually detect signal in the middle of the gray matter. Most of significant signal detected in VBM is near the tissue boundary where the between-group variability is high.

- Surface-based morphometry

Joshi, S.C., Miller, M.I., Grenander, U. 1997. On the geometry and shape of brain sub-manifolds, *Int. J. Pattern Recog. Art. Intell.* 11:1317-1343. [Curvature estimation of anatomical boundary](#)

Miller M., Banerjee A., Christensen G., Joshi S., Khaneja N., Grenander U., Matejic L. 1997. Statistical methods in computational anatomy. *Stat Methods Med Res.* 6:267-99. [Random field modeling of deformation field](#)

Chung, M.K., Worsley, K.J., Robbins, S., Paus, P., Taylor, J., Giedd, J.N., Rapoport, J.L., Evans, A.C. 2003. Deformation-Based Surface Morphometry with an Application to Gray Matter Deformation, *NeuroImage.* 18:198-213. [Surface area](#)

Thompson, P. M., MacDonald, D., Mega, M. S., Holmes, C. J., Evans, A. C., and Toga, A. W. 1997. Detection and mapping of abnormal brain structure with a probabilistic atlas of cortical surfaces. *J. Comput. Assist. Tomogr.* 21: 567–581. [Tensor mapping for surface](#)

Thompson, P.M., Hayashi K.M., de Zubicaray G., Janke A.L., Rose S.E., Semple J., Herman D., Hong M.S., Dittmer S.S., Doddrell D.M., Toga A.W. 2003. Dynamics of gray matter loss in Alzheimer's disease. *J Neurosci.* 23:994-1005. [Tensor mapping](#)

Focal Decline of Cortical Thickness in Alzheimer's Disease Identified by Computational Neuroanatomy

Jason P. Lerch¹, Jens C. Pruessner^{1,2}, Alex Zijdenbos¹, Harald Hampel², Stefan J. Teipel² and Alan C. Evans¹

¹McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada, and
²Alzheimer Memorial Center, Dementia Research Section and Memory Clinic, Department of Psychiatry, Ludwig-Maximilian University, Munich, Germany

36 subjects (17 controls, 19 AD)
Mini Mental State Examination (MMSE) score
Age
T1 weighted MRI (three scans per subject)

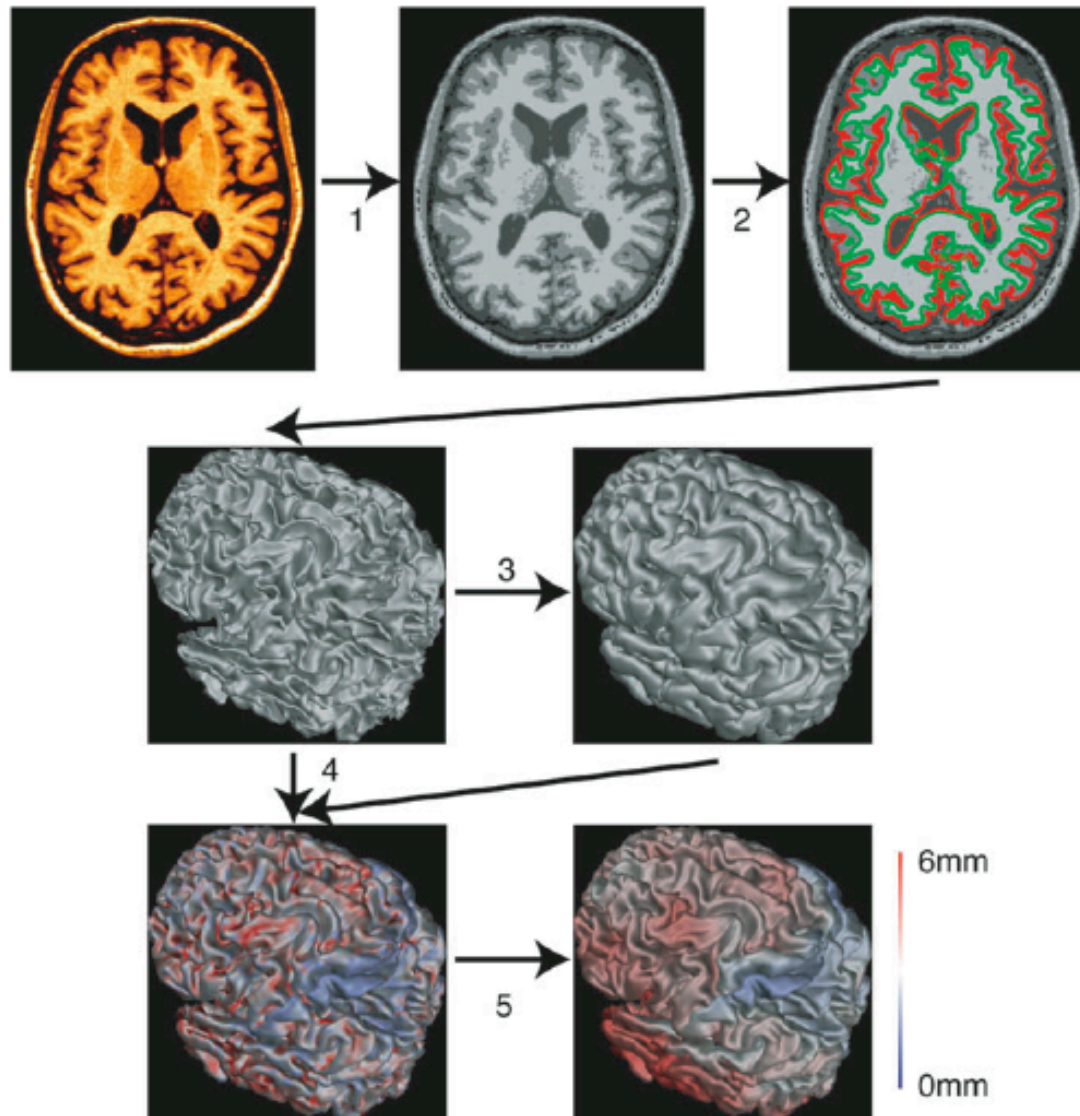
$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + e$$

Group variable
0 control, 1 AD

Scan variable
1,2,3

Age

MMSE



Cortical thickness
Analysis pipeline

20mm FWHM
diffusion smoothing
(Chung et al., 2003)
was used

Figure 1. An overview of the steps involved in cortical thickness analysis. First, the images are non-uniformity corrected and registered into stereotaxic space. They are then classified (1) and fit with a white matter surface (2). The gray surface is found by expanding out from the white (3). Cortical thickness is measured at every vertex (4), and blurred using a 20 mm surface-based kernel (5).

Statistical parametric maps

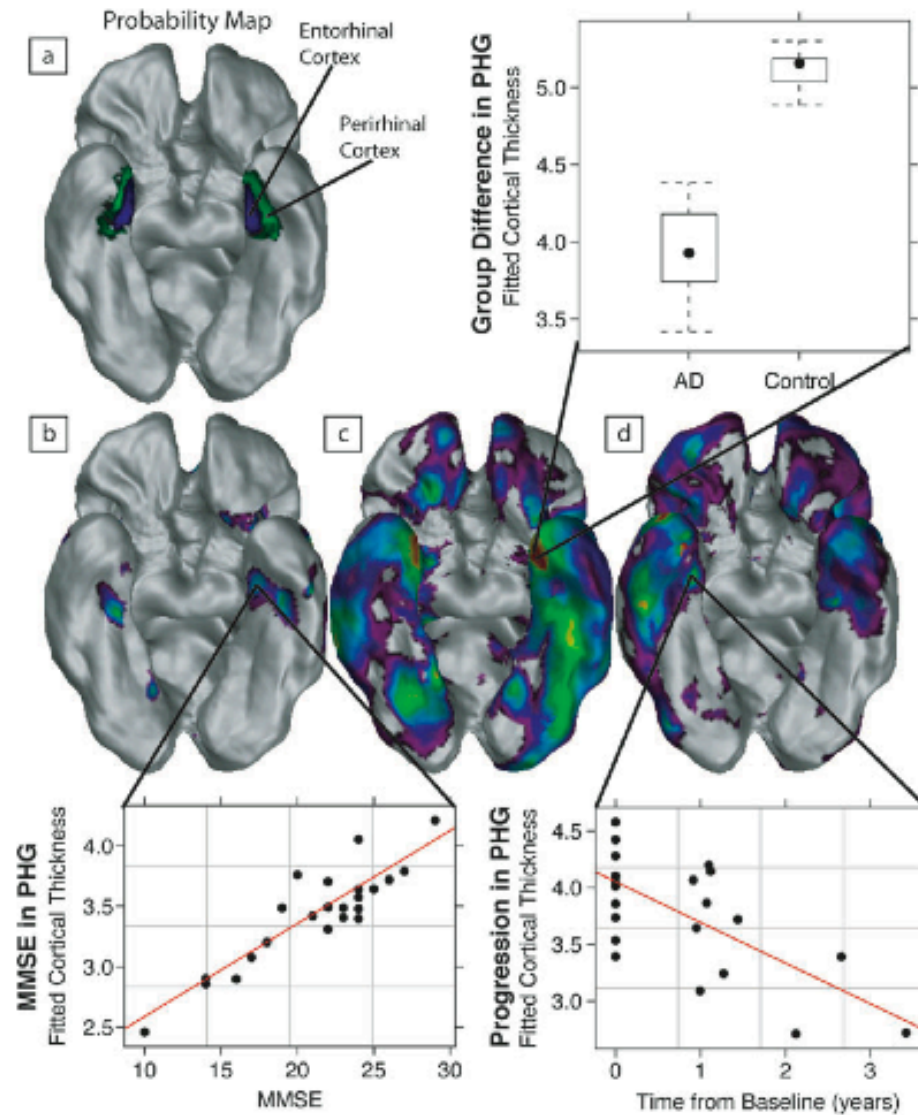


Figure 5. Regional analysis using the cortical thickness methodology in AD versus normal controls displaying differences in the entorhinal cortex. The four cortical views show: (a) the probability maps of the entorhinal and perirhinal cortices in this population; (b) the t -statistics of the MMSE regression; (c) the group analysis; and (d) the time difference from baseline. The color scales are the same as in Figures 2–4, 6 and 7 respectively. The graphs illustrate the effects at the vertex indicated by the black lines. Atrophy of the PHG is clearly implicated in each of the three analyses shown.

- Surface data smoothing

Kiebel, S., Friston, K.J. 2002. Anatomically informed basis functions in multisubject studies. *Human Brain Mapping*. 16:36-46. [Anisotropic kernel smoothing on fMRI](#)

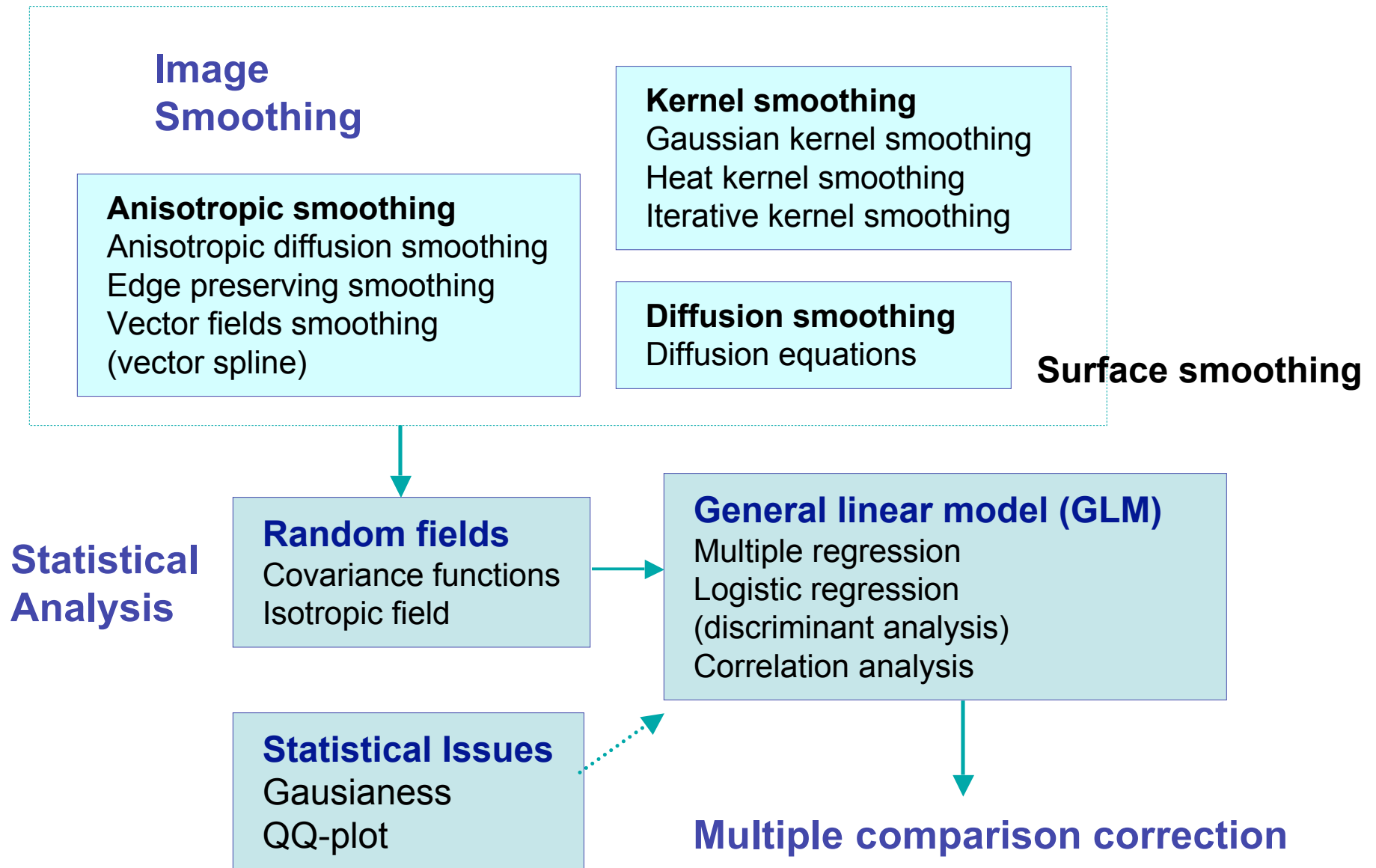
Andrade, A., Kherif, F., Mangin, J., Worsley, K.J., Paradis, A., Simon, O., Dehaene, S., Le Bihan, D., Poline, J-B. 2001. Detection of fMRI Activation using Cortical Surface Mapping, *Human Brain Mapping*, 12, 79-93. [Diffusion smoothing on fMRI](#)

Chung, M.K., Worsley, K.J., Robbins, S., Paus, P., Taylor, J., Giedd, J.N., Rapoport, J.L., Evans, A.C. 2003a. Deformation-Based Surface Morphometry with an Application to Gray Matter Deformation, *NeuroImage*. 18:198-213. [Diffusion smoothing on MRI](#)

Chung, M.K., Robbins, S., Dalton, K.M., Alexander, A.L., Davidson, R.J., Evans, A.C. 2005. Cortical thickness analysis in autism via heat kernel smoothing. *NeuroImage* 25:1256-1265. [Heat kernel smoothing on MRI](#)

Lerch, J. P., Evans, A.C. 2005. Cortical thickness analysis examined through power analysis and a population simulation. *NeuroImage* 24:163-173. [Validation of diffusion smoothing](#)

Medical Image Analysis Flow



Surface smoothing

- Motivation: segmented anatomical surfaces are noisy.

A Signal Processing Approach To Fair Surface Design

Gabriel Taubin¹

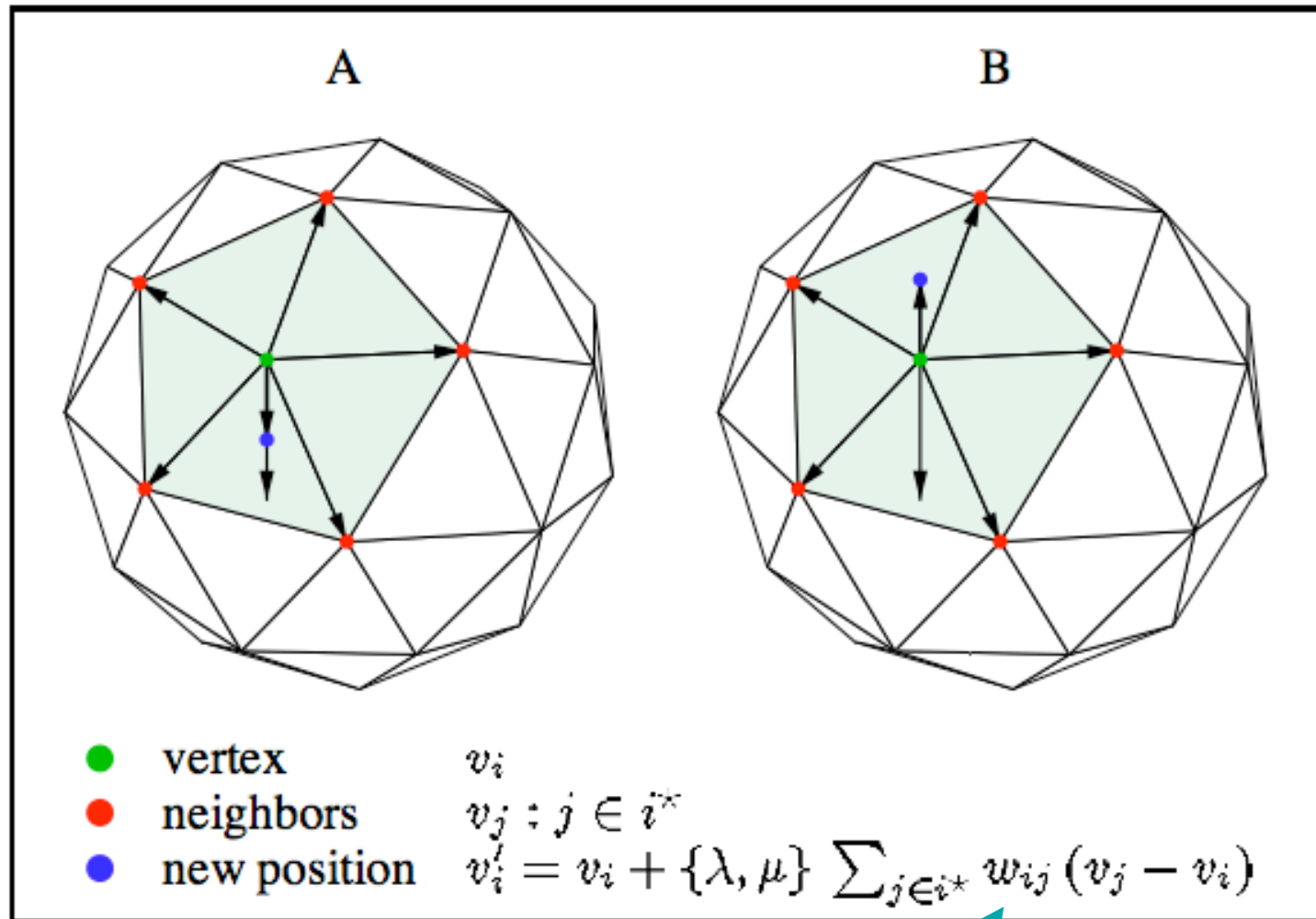
IBM T.J.Watson Research Center

- History: closed curve fairing via *Fourier descriptors*, which is first introduced in

C.T. Zahn and R.Z. Roskies. Fourier descriptors for plane closed curves. *IEEE Transactions on Computers*, 21(3):269–281, March 1972.

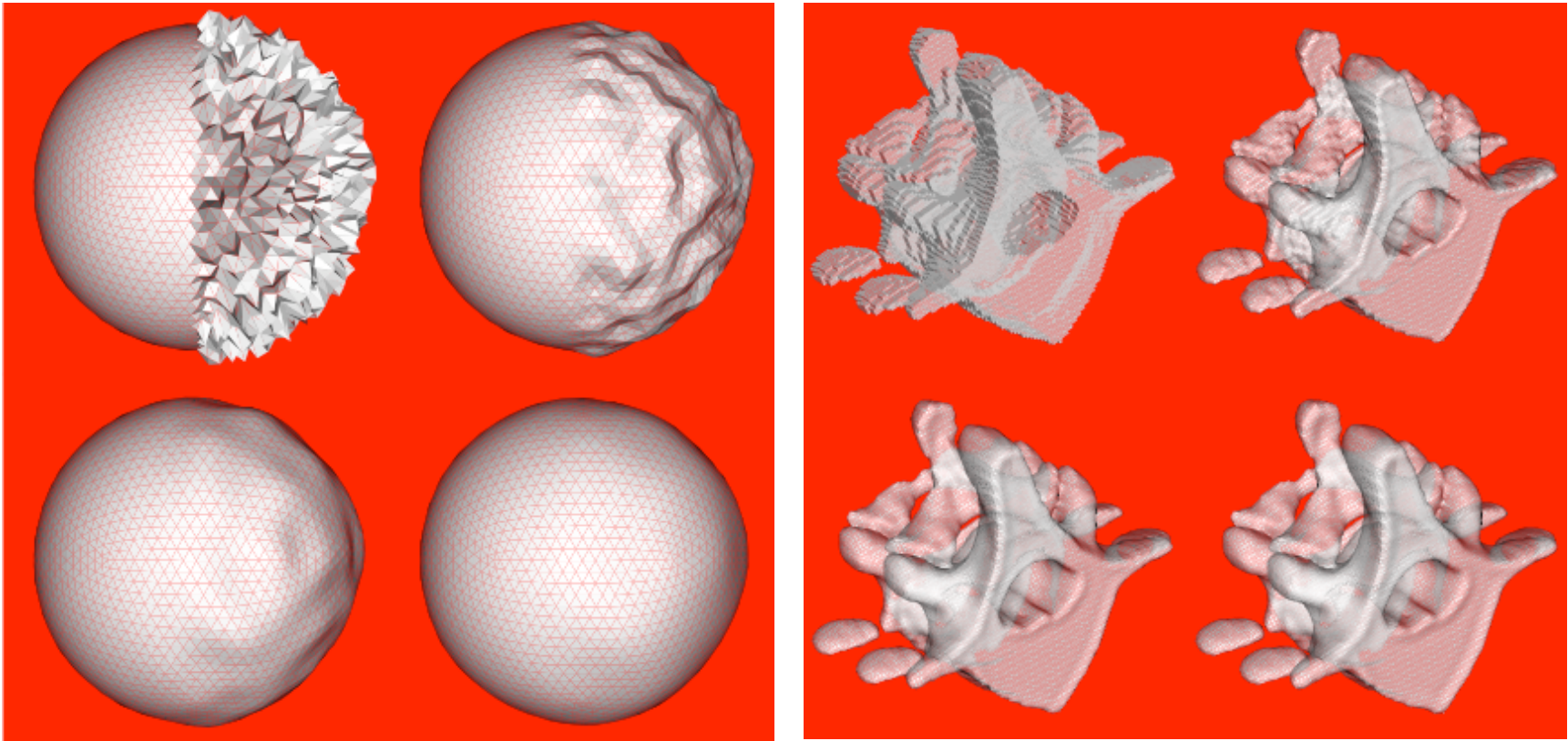
- Taubin's surface fairing approach extend this idea: surface signal is decomposed into the linear combination of eigenfunction of surface Laplacian.

Taubin's surface fairing

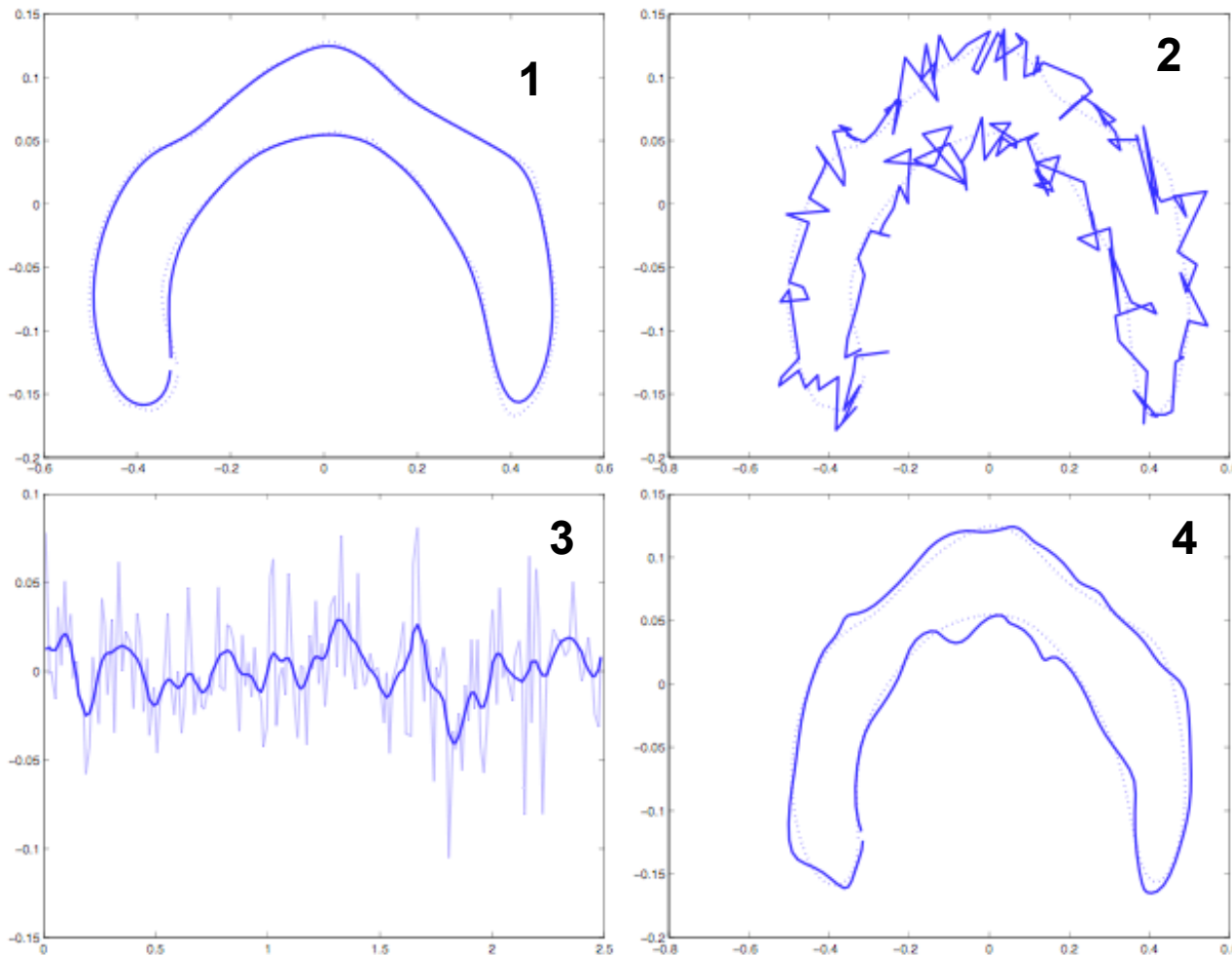


Weights are determined from the discrete surface Laplacian

Smoothing is applied iteratively

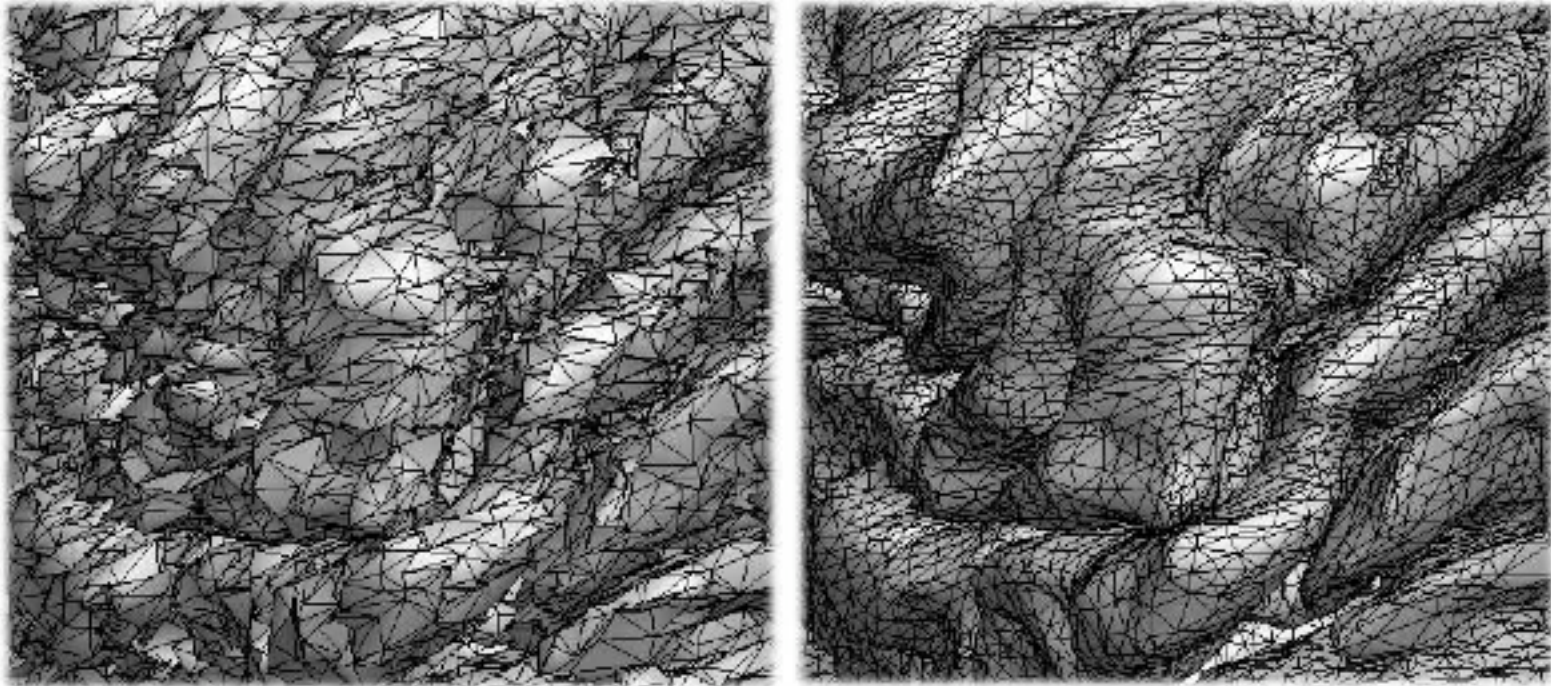


Smoothing closed curve

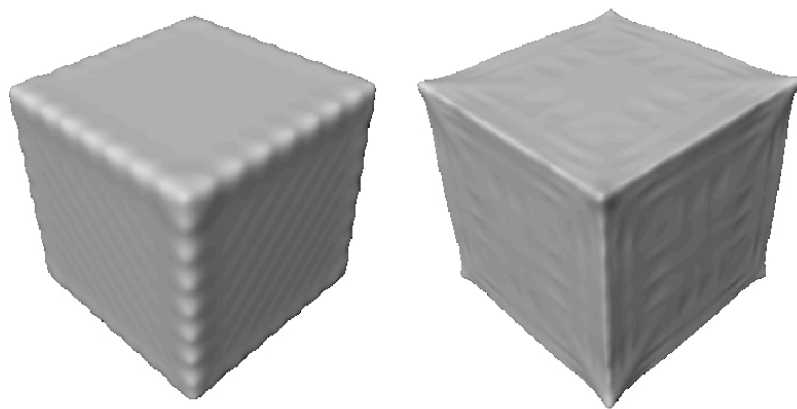


1. Iterated kernel smoothing of corpus callosum boundary
2. Gaussian white noise is added to curve 2.
3. X-coordinate function and its iterated kernel smoothing
4. Simulated curve obtained from smoothing curve 2.

Smoothing cortical boundary

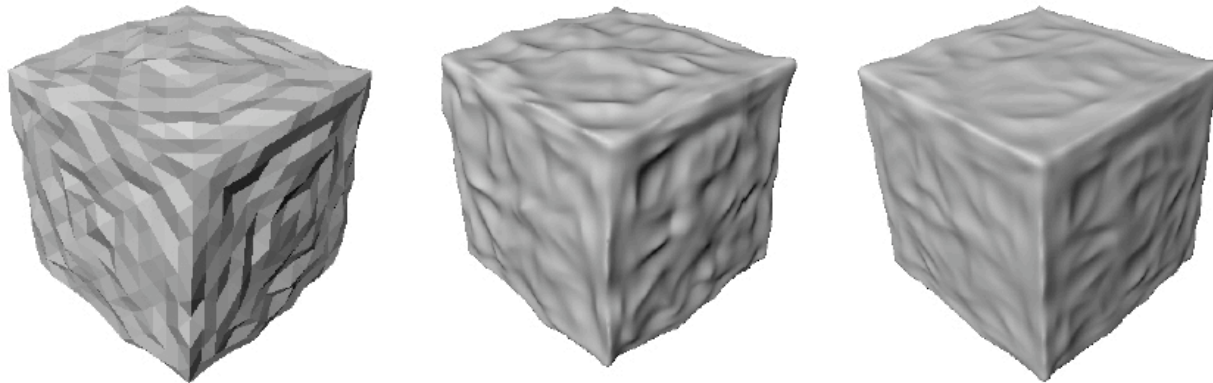


Anisotropic surface smoothing



- Extension of edge preserving smoothing in 2D image

- This requires anisotropic boundary information

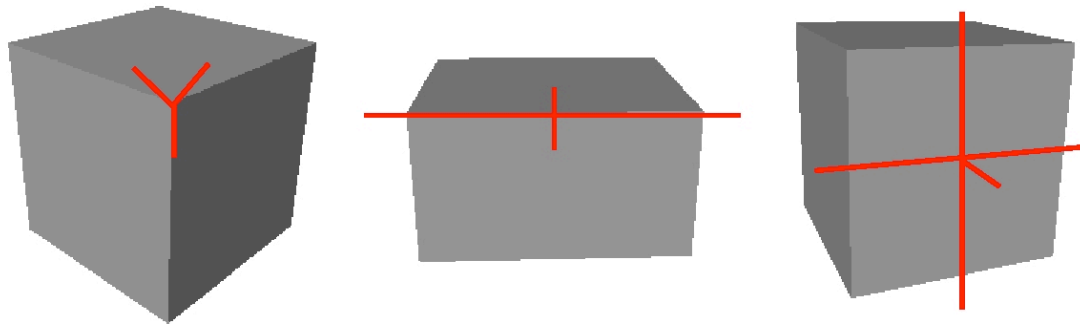


Anisotropic Boundary Information

Direction of Anisotropy

$$C(\mathbf{p}) = \sum_{i=1}^n (\mathbf{v}_i - \mathbf{c})(\mathbf{v}_i - \mathbf{c})^T$$

where $\mathbf{v}_i$ is the location of the surface point on the neighborhood
and $\mathbf{c}$ is the centroid of the neighborhood.



Corner: all eigenvalues are nearly equal

Edge: one dominating eigenvalue

Planar: two eigenvalues nearly equal and larger than the third

- **Surface Smoothing/fairing**

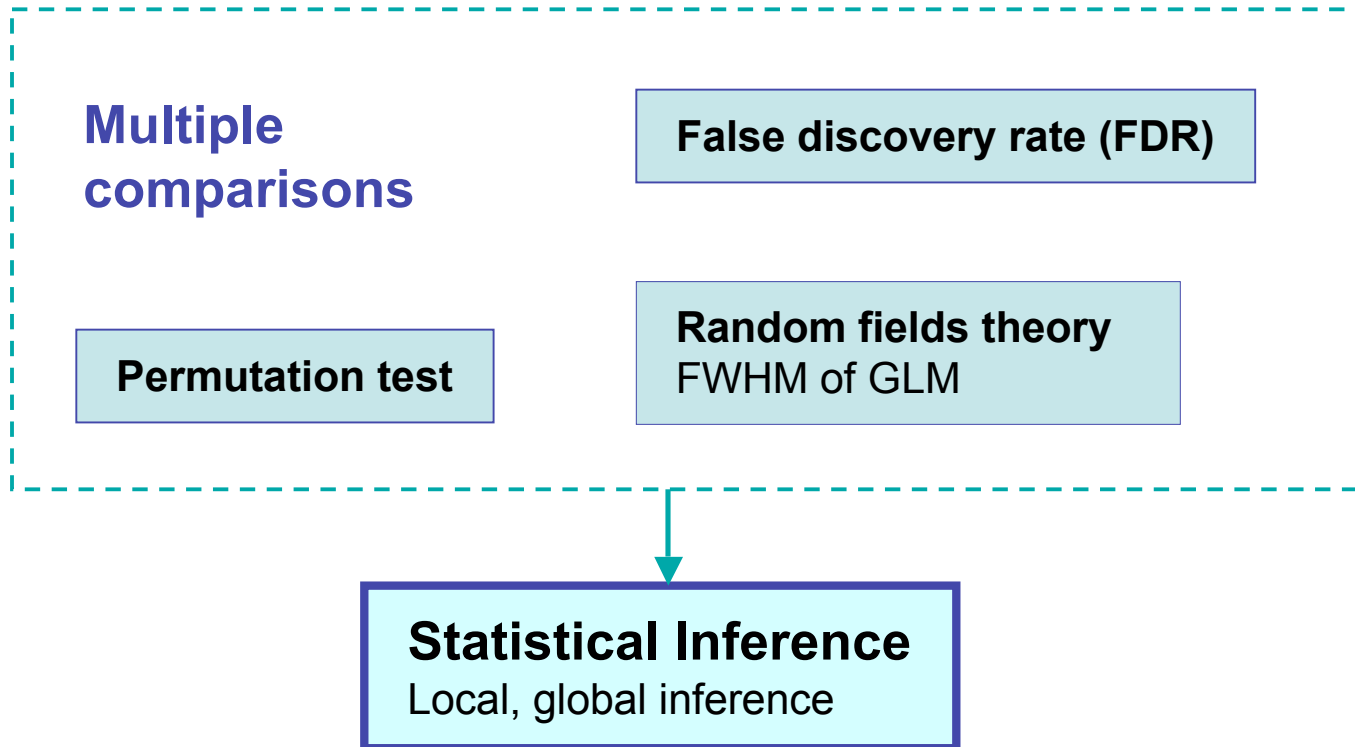
Chen, F. and D. Suter, "Multiple Order Laplacian Spline – Including Splines with Tension", *MECSE 1996-5, Dept. of Electrical and Computer Systems Engineering Technical Report, Monash University, July 1996*

Turk, G. and J.F. O'Brien, "Shape Transformation Using Variational Implicit Functions", *SIGGRAPH Proceedings, Aug. 1999, pp. 335–342*

Lee, M. and G. Medioni, "Inferring Segmented Surface Description from Stereo Data", *Computer Vision and Pattern Recognition Proceedings, 1998, pp. 346–352*

H.Q. Dinh, G. Turk, and G. Slabaugh, "Reconstructing Surfaces by Volumetric Regularization Using Radial Basis Functions", *IEEE Transactions on Pattern Analysis and Machine Intelligence, October 2002*

Medical Image Analysis Flow



Validation and Simulation

- In statistical literature, simulation is widely used as a way to demonstrate the correctness of proposed methodologies.
- In imaging literature, simulation is somewhat limited due to the difficulty of simulating realistic images.

- Multiple comparison corrections

Worsley, K.J., Marrett, S., Neelin, P., Vandal, A.C., Friston, K.J., Evans, A.C. 1996. A unified statistical approach for determining significant signals in images of cerebral activation, *Human Brain Mapping*, 4:58-73. [Random field theory](#)

Nichols, T., Hayasaka, S. 2003. Controlling the familywise error rate in functional neuroimaging: a comparative review. *Stat Methods Med Res.* 12:419-46. [Comparative analysis](#)

Nichols, T.E. and Holmes, A.P. 2002. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Human Brain Mapping.* 15:1–25. [Permutation test](#)