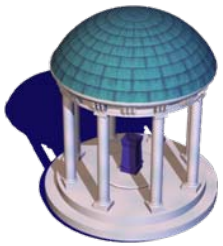
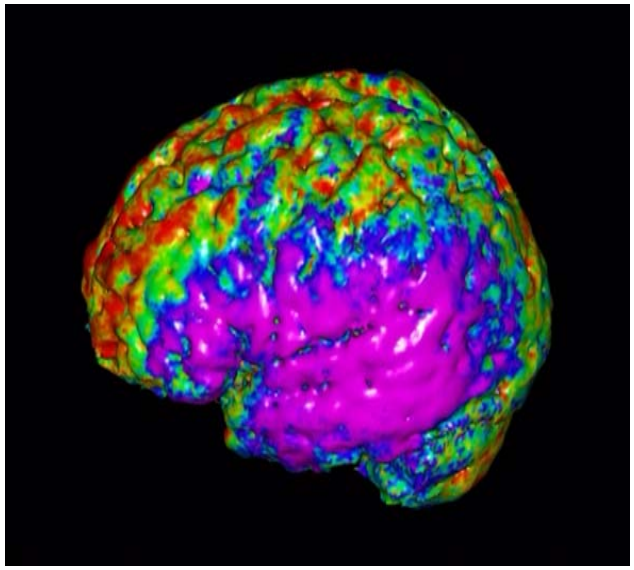


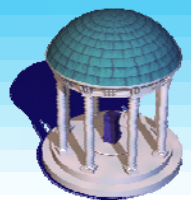
SAMSI Summer 2013 Program on Neuroimaging Data Analysis
Lecture 1: Introduction

Hongtu Zhu, Ph.D.

Department of Biostatistics and Biomedical Research Imaging Center

University of North Carolina at Chapel Hill





Part 1. SAMSI Summer Program
Neuroimaging Data Analysis

Overview

The term "**Neuroimaging Data Analysis**" (NDA) is aimed at encompassing a broad array of imaging, mathematical, and statistical methods for the analysis of neuroimaging data. This NDA program is motivated by the great need in the analysis of **high-dimensional, correlated, and complex neuroimaging data and clinical and genetic data** obtained from various cross-sectional and clustered neuroimaging studies.

The NDA program seeks to bring together a diverse group of researchers from **statistics, mathematics, computer science, biomedical engineering, psychiatry, psychology, neuroscience, radiology,** and beyond, to explore the common structure that underlies NDA methodologies, with a view toward motivating and synthesizing new approaches.

NDA

Program Leaders

Jane-Ling Wang, Robert Kass, Haipeng Shen, Hongtu Zhu

Directorate

Ezra Miller

Advisory board committee members for SI:

John Aston, F. DuBois Bowman, Brian Caffo, David Isaacson, Robert E. Kass, Nicole Lazar, Jeffery Morris, Hernando C. Ombao, Kui Ren, Haipeng Shen, Gunther Uhlmann, Jane-Ling Wang, Chunming Zhang, Hongtu Zhu, UNC-CH

NDA

President Obama officially announced $100 million in funding for arguably the most ambitious neuroscience initiative ever proposed.

The Brain Research through
Advancing Innovative Neurotechnologies or BRAIN,
aims to reconstruct the activity of every single neuron as they fire simultaneously in different brain circuits, or perhaps even whole brains.

Research foci

- Image reconstruction
- Image segmentation
- Image registration
- Shape analysis
- Statistical group analysis
- Connectivity analysis
- Multimodal analysis
- Imaging genetics
- NDA applications

Schedule of activities

The first four days, from **Tuesday 4 June to Friday 7 June**, will be spent on training courses concerning structural and functional neuroimaging data analysis, taught by

Hongtu Zhu, UNC (Biostatistics)
Marc Niethammer, UNC (Computer Science)
Dinggang Shen, UNC (Radiology)
Martin Styner, UNC (Computer Science and Psychiatry)

F. DuBois Bowman, Emory (Biostatistics)
Martin Lindquist, Johns Hopkins (Biostatistics)
John Aston, Warwick (Statistics)
Hernando C. Ombao, UC Irvine (Statistics)

ASA Statistics in Imaging (SI)

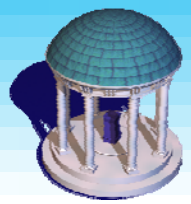
Acting Officers:

- 2010-11: Chair: Daniel Rowe, Program Chair: Ranjan Maitra
- 2011-12: Chair: Hongtu Zhu, Program Chair: Martin Lindquist.
- 2012-13: Chair: Timothy Johnson, Program Chair: Martin Lindquist.
- 2013-14: Chair: Ciprian Crainiceanu, Program Chair: Haipeng Shen.

Secretary: Brian Caffo, Treasurer: DuBois Bowman, Rep to COS: Kary Myers,

- NeuroStat Google Group

http://groups.google.com/group/neurostat/



Part 2. Imaging Science

Imaging Science
From Wikipedia, the free encyclopedia

Imaging Science
is a multidisciplinary field concerned with the generation, collection, duplication, analysis, modification, and visualization of images.

As an evolving field, it includes research and researchers from

Physics, Mathematics, Statistics, Electrical Engineering, Computer Vision, Computer Science and Perceptual Psychology.

Three key components of imaging science

- **Image acquisition:** studies the physical mechanisms and mathematical models and algorithms by which imaging devices generate image observations.

- **Image interpretation/application:** is to see, monitor, and Interpret the targeted world/patterns being imaged.

- **Image processing:** is any linear or nonlinear operator that operates on the images and produces targeted patterns.

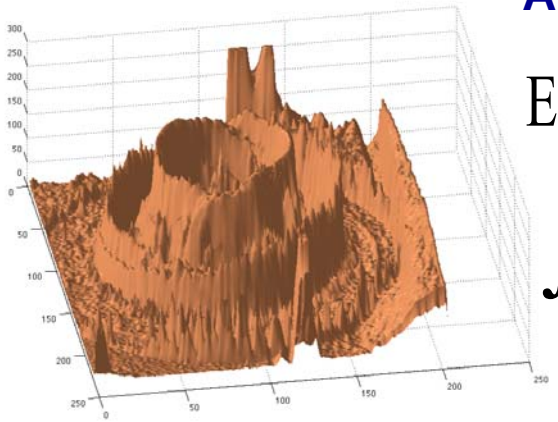
What is image?

(i) In computer science an image is an exact replica of the contents of a storage device (a hard disk drive or CD-ROM for example) stored on a second storage device.
(ii) is an optically formed duplicate or other reproduction of an object formed by a lens or mirror.

Mathematics. Image is the point or set of points in the range corresponding to a designated point in the domain of a given function.

As $\tilde{x} \in \Omega \subseteq R^k \quad f(\tilde{x}) \in M \subseteq R^m \quad f : \Omega \rightarrow M \subseteq R^m$

Ω is a compact set.



Additional Conditions:

Each component of $f(\tilde{x})$ is nonnegative.

$\int_{\Omega} \| f(\tilde{x}) \|^k \, d\tilde{x} < \infty$ for any $k > 0$

Digitized Images $f : \Omega_0 \rightarrow \{0,1,\cdots,M_0\}$

- **Sampling (grid points):** $\Omega_0 \in \Omega$

  An ordered array or a triangular array or etc;
  A set of small cells of the same shape and size (pixels, voxels).
  Sometime, it involves interpolation.

  Sampling Rate ensure that all the relevant information contained in the image is largely retained by sampling.

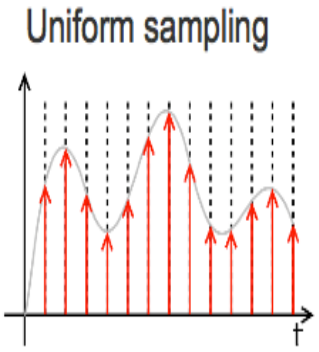
- **Quantization: is a process of assigning the function value at each sampling point to one of the finite set of integers.**

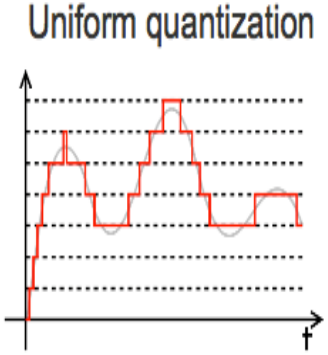
$$0,1,2,\cdots,2^m \text{ for } m = 5 \sim 12, \text{that is } M_0 = 2^{\text{m}}$$

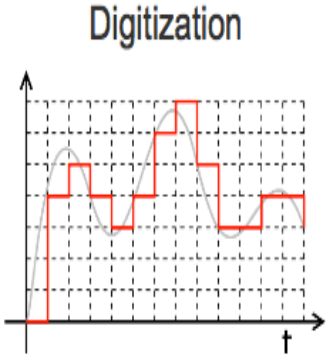
Sampling Arrangements

- Uniform sampling Square grid, Rectangular grid, Hexagonal grid
- Non-uniform sampling Closer where it is necessary, eye.
- Image size 128*128, 256*256, 512*512,
- The sampling is normally determined
- by the sensor arrangement

Digitization



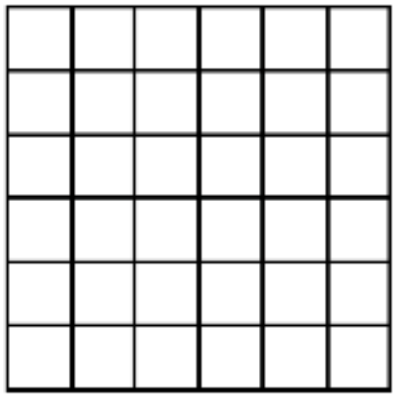




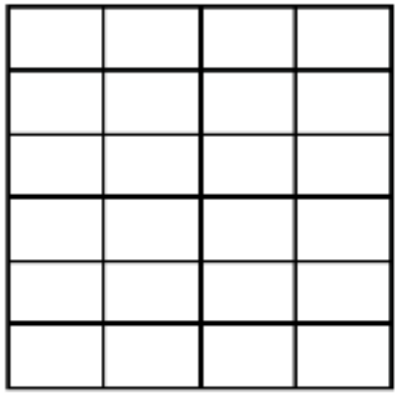
- Sampling rate – spatial resolution
- Quantization - grey level resolution

Images from Wikimedia Commons

Representation and Connectivity (2D)

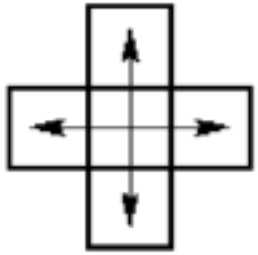


Square

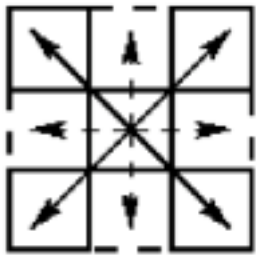


Rectangular

Hexagonal



4 connectedness



8 connectedness

6 connectedness

General Digital Image

$$f(x,y,z,t,s):\Omega \rightarrow \{0,1,\cdots,M_0\}$$

- Spatial parameters

$$(x,y,z)$$

- Time parameters

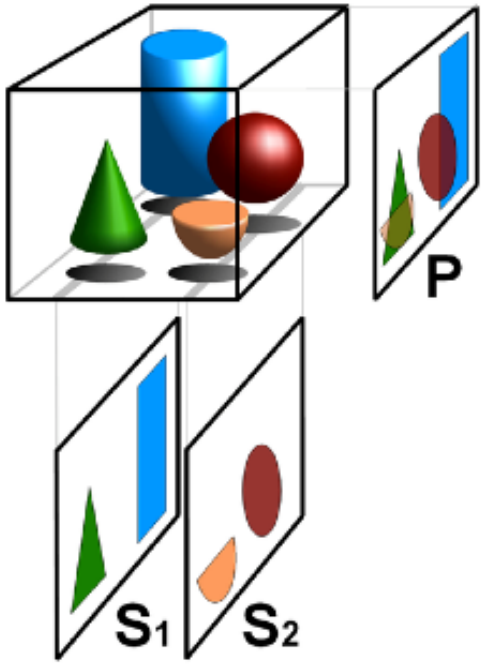
$$t$$

- Spectral parameters

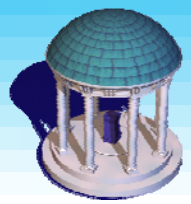
$$s$$

- A limited range of values

$$M_0$$



- Spatial resolution
- Temporal resolution
- Spectral resolution
  Range of wave-length
  Number of color
- Gray scale resolution



Part 3. Imaging Modalities

Imaging Devices

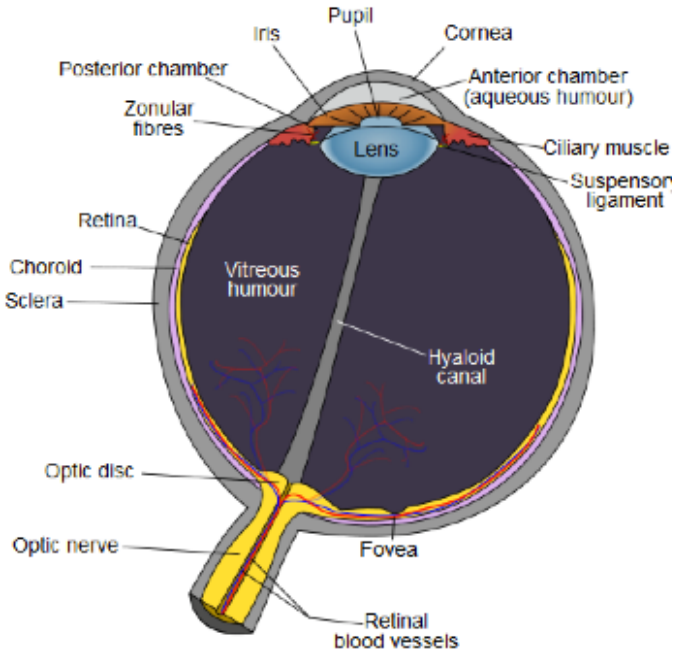
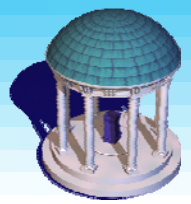


Figure 5.13 PET scanner. A movable table shifts the patient through the circular hole in the gantry. The external design is similar to that of a CT scanner and to some extent to that of an MRI scanner. (Courtesy of the Department of Nuclear Medicine.)

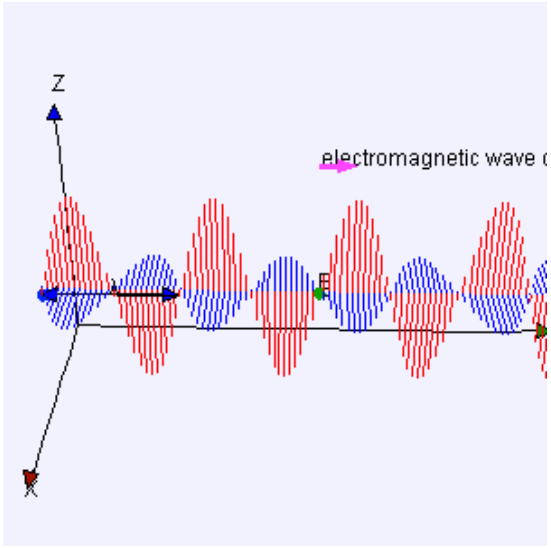


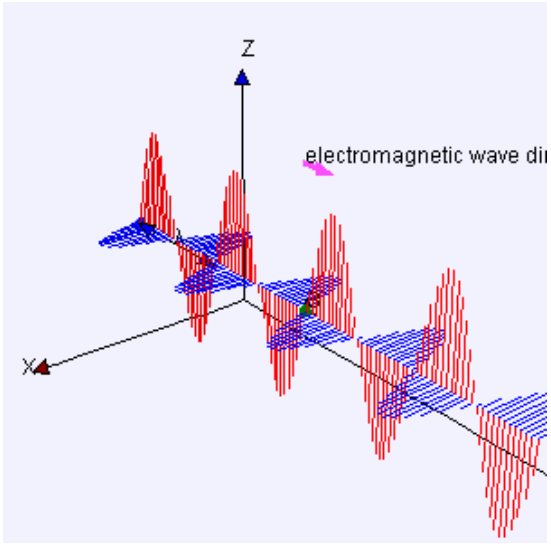
Targets

- Electromagnetic waves (most technologies)
- Sound (ultrasound)
- Particles (electron microscopy)
- Mechanical contact forces (scanning probe microscopy)

Electromagnetic Waves

Electromagnetic radiation (**EM radiation** or **EMR**) is a form of energy emitted and absorbed by charged particles, which exhibits wave-like behavior as it travels through space. EMR has both electric and magnetic field components, which stand in a fixed ratio of intensity to each other, and which oscillate in phase perpendicular to each other and perpendicular to the direction of energy and wave propagation.





Electromagnetic Waves

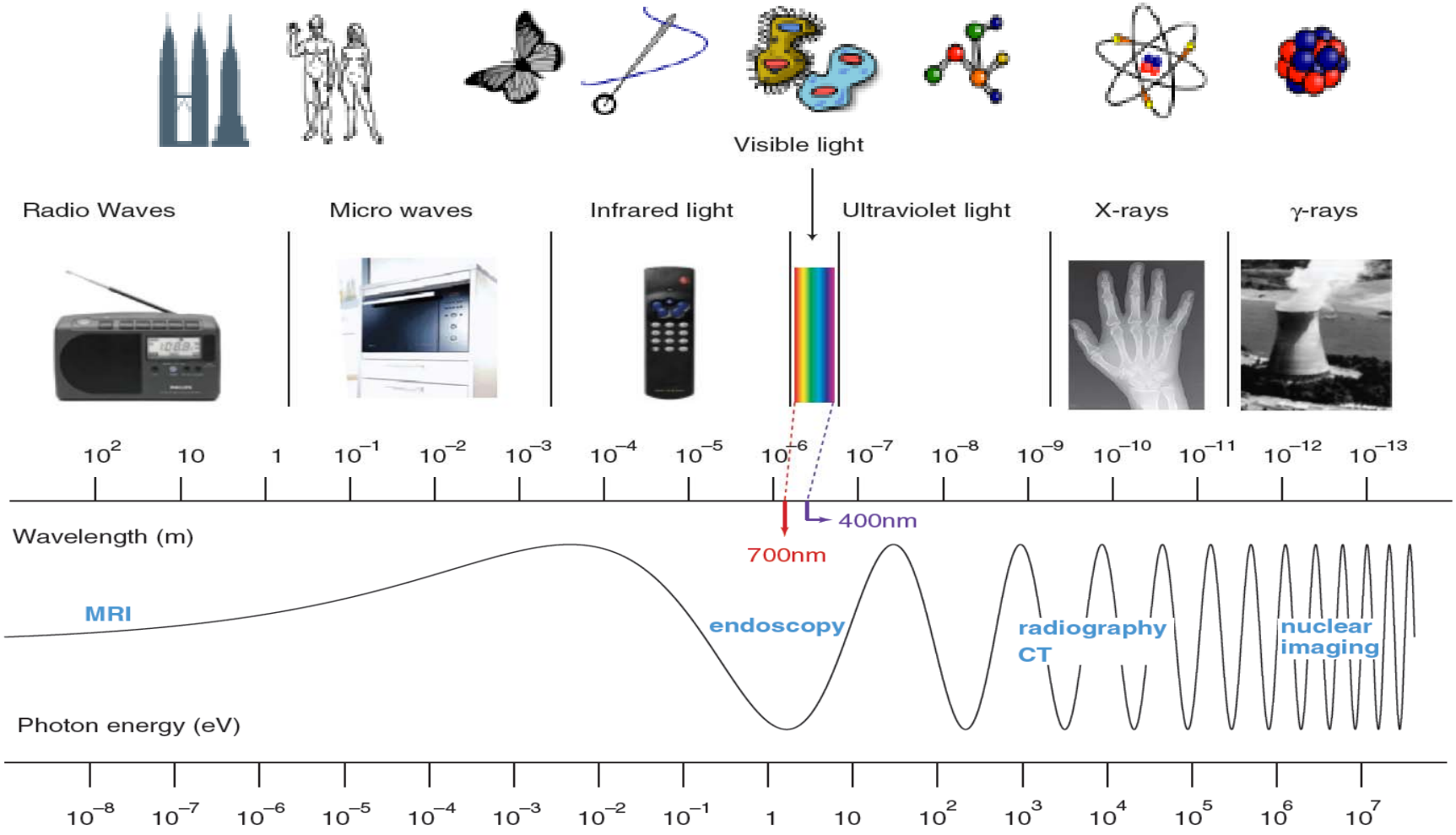


Figure 2.1 The electromagnetic spectrum.

nm (nanometer, E-9m)

Electromagnetic Imaging

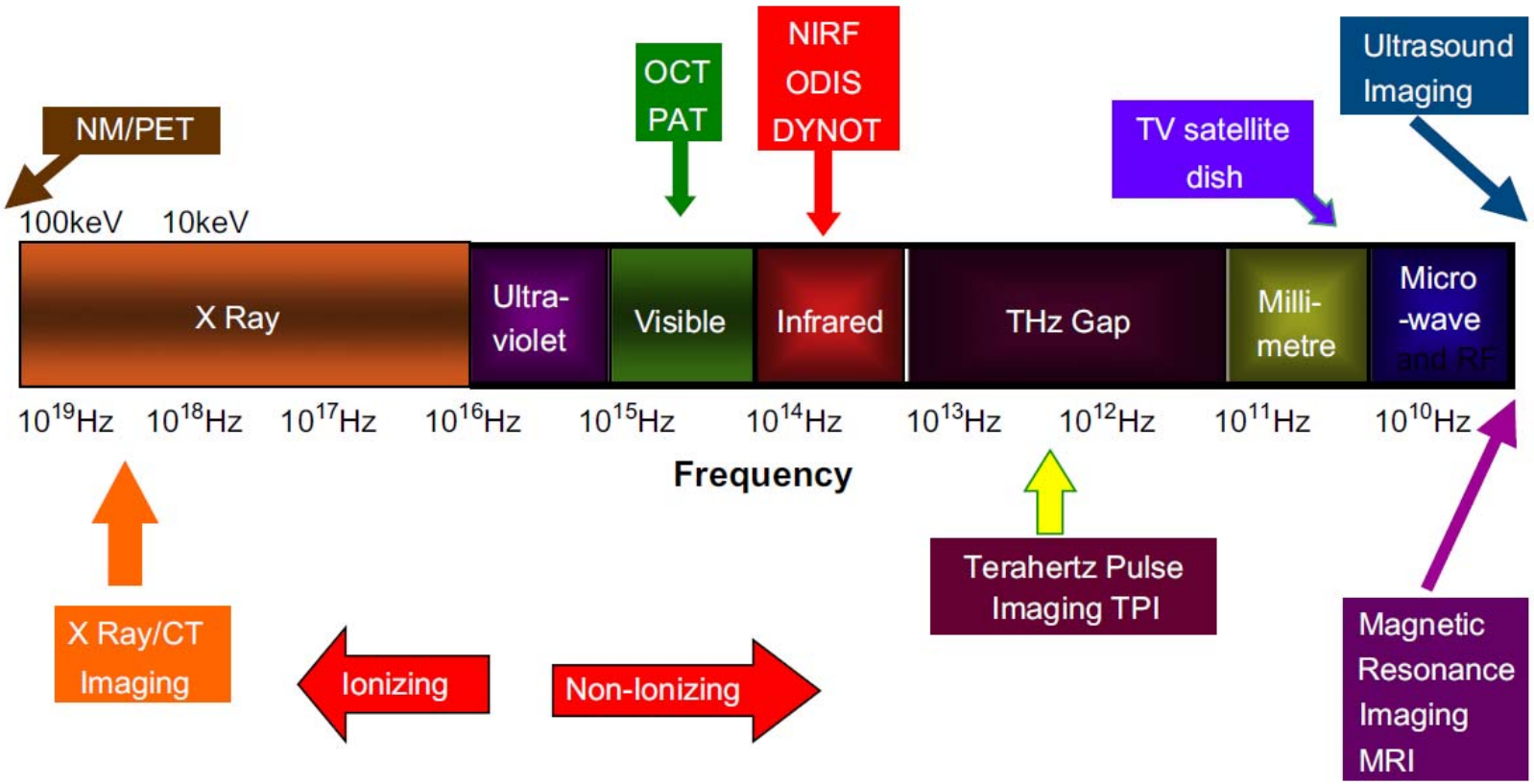
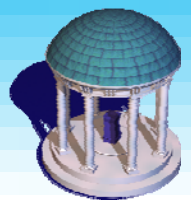


Figure 4 – Frequency spectrum of electromagnetic radiation imaging technologies.



Electromagnetic Imaging

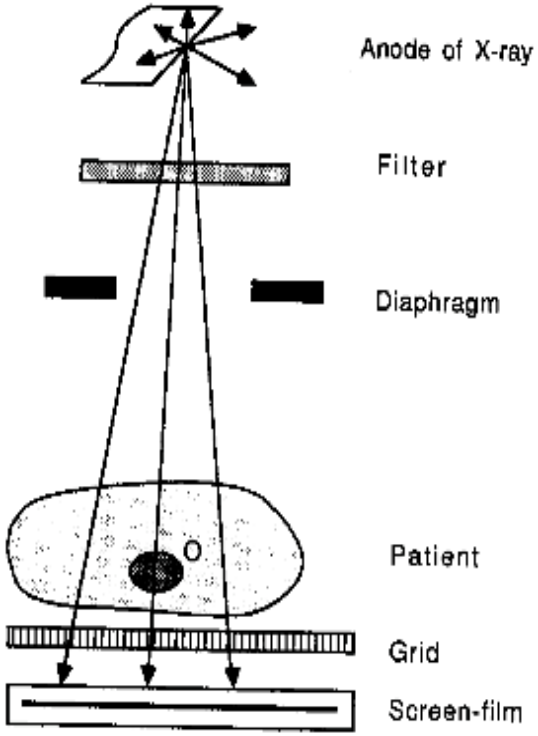
- Radio range: radio astronomy, MRI
- Microwave range: RADAR
- Visible range: Standard camera, light microscopy
- X-ray range: CT, micro-CT
- Gamma range: Gamma camera

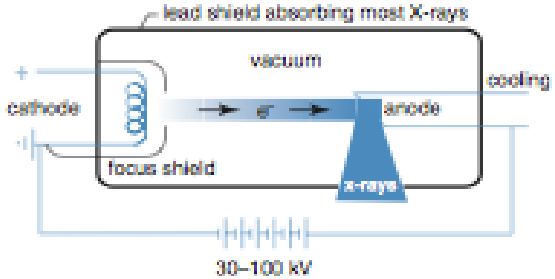
Medical imaging
From Wikipedia, the free encyclopedia

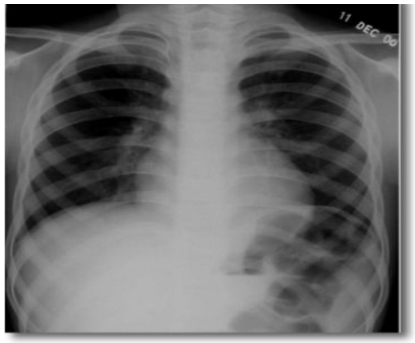
- Medical imaging is the technique and process used to create images of the human body (or parts and function thereof) for clinical purposes (medical procedures seeking to reveal, diagnose or examine disease) or medical science (including the study of normal anatomy and physiology).
- 2010, 5 billion medical imaging studies were done worldwide.

X-rays are ionizing waves consisting of photons traveling at the speed of light with energy E=hf

- X-rays produced by a tube.
- Filtered to removed undesired energy.
- Restriction to illuminate organ of interest
- Grid removes scattered radiation.
- Recording of image on electronic plate (or film).







Computed Tomography (3D X-rays) is an imaging method employing tomography created by computer. Digital geometry processing is used to generate a 3D image of the inside of an object from a large series of 2D X-ray images taken around a single axis of rotation.

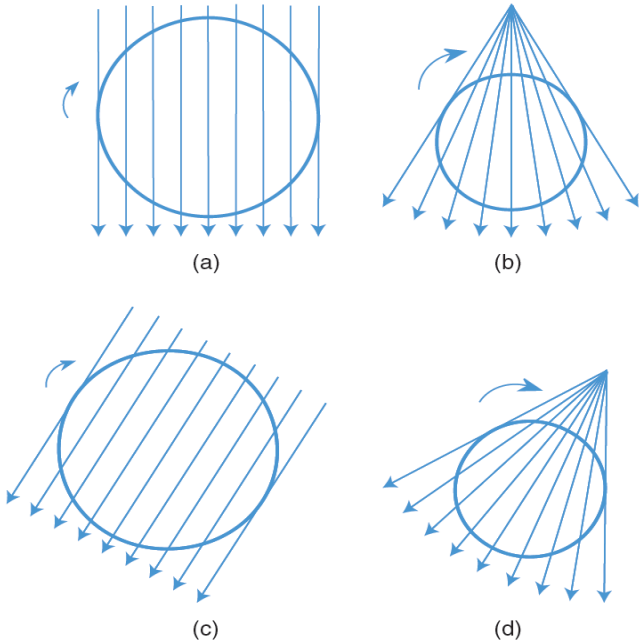
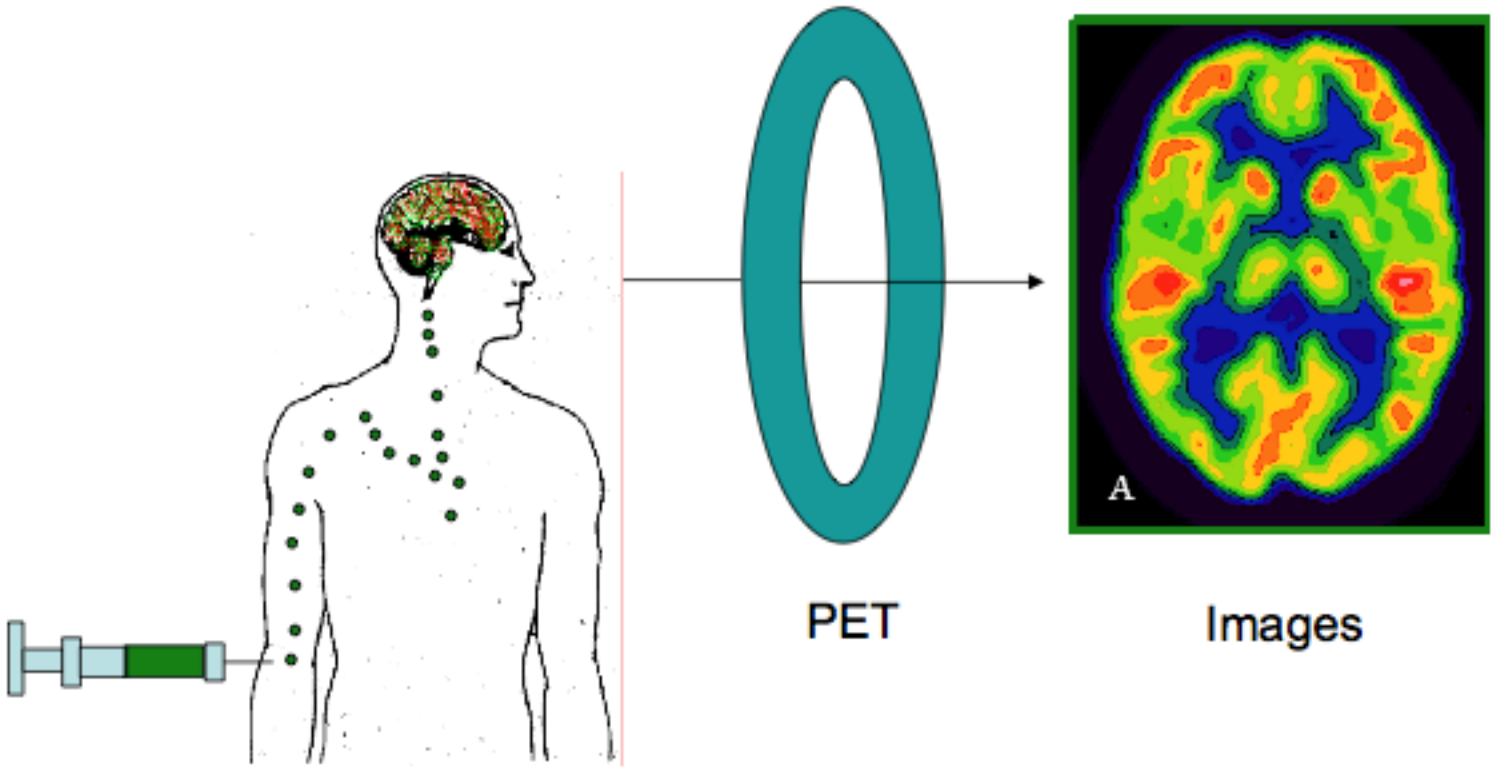


Figure 3.2 Basic scanning procedure in CT. A set of lines is scanned covering the entire field of view: **(a)** parallel-beam geometry and **(b)** fan-beam geometry. This process is repeated for a large number of angles (**c** and **d**).

Figure 3.1 **(a)** Schematic representation, and **(b)** photograph of a CT scanner. (Courtesy of GE Healthcare.)

SPECT and PET



SPECT=Single-Photon Emission Computed Tomography

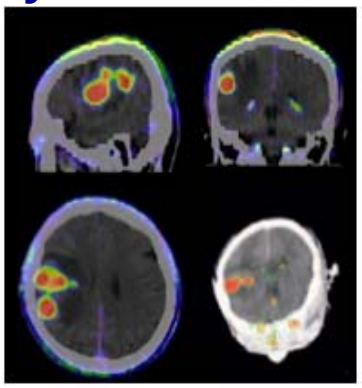
is a nuclear medicine tomographic imaging technique using gamma rays for measuring the blood flow to the brain.

Radio-labeled chemical (ECD or HMPAO) is quickly injected at time of seizure onset to detect the region of increased blood flow, which is associated with seizure activity.

By comparing the ictal scan (imaged during seizure) and the interictal scan (imaged without seizure), the regions of activation in the brain are detected to locate the seizure origin.

http://www.youtube.com/watch?v=l6V6VLxQlkY

PET=Positron Emission Tomography is a functional imaging technique to extensively study the relationship between energy consumption and neuronal activity. It uses positron-emitting radioactive tracers that are attached to molecules that enter biological pathways of interest.



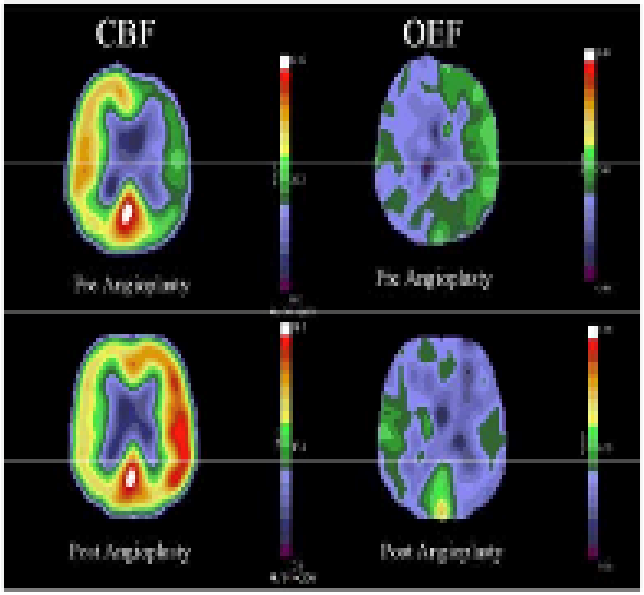
FDG: Fluorodeoxyglucose (similar to Glucose).

Brain uses glucose as major source of energy.
Normal brain picks up FDG in a large amount.

In epilepsy, the brain cell (neuron) does not function right or the neurons are lost due to a variety of reasons.

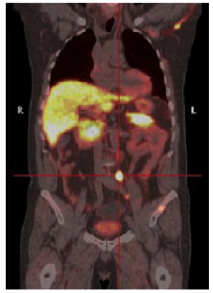
FDG-PET scan detects the regions of brain where the Glucose uptake is low (hypo-metabolism), which is often associated with the site of seizure origin.

PET measures

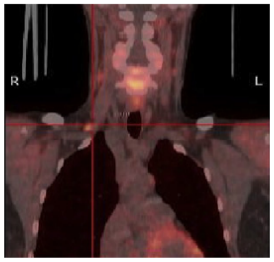


Reduced Cerebral Blood Flow (CBF) and elevated compensatory Oxygen Extraction (OEF) before and after carotid artery angioplasty (stroke risk)

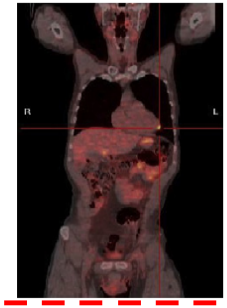
PET tracers



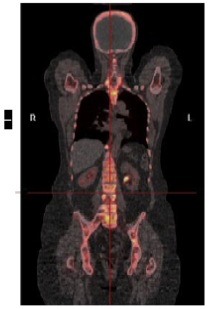
Prostate cancer
^{11}C Acetate



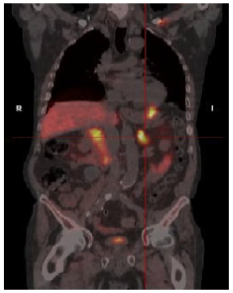
Parathyroid cancer
^{11}C-Methionine



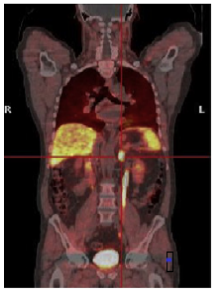
Neuroendocrine tumours
^{11}C-5-Hydroxytryptophan



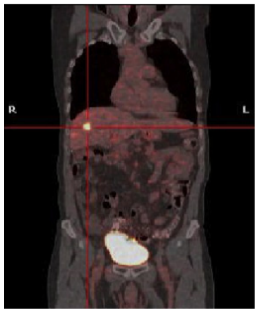
Bone metastases
^{18}F-Fluoride



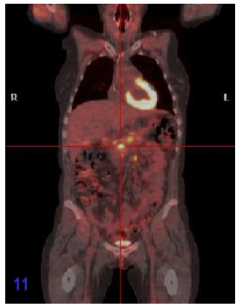
Adrenocortical tumours
^{11}C-Metomidate



Pheochromocytomas
^{11}C-Hydroxyephedrine



Neuroendocrine tumours
^{68}Ga DOTA-GOC



Malignant tumours
^{18}F-Fluorodeoxyglucose

Figure 13 – Examples of PET tracers in oncology where endogenous substances are framed (courtesy of Imanet Uppsala).

PET and SPECT

PET and SPECT scan is different from CT, MRI or Ultrasound, which detect structure changes and anatomy, can provide physiological and molecular information of brain.

PET and SPECT are clinically indicated for pre-surgical localization of seizure origin. They are covered by most insurance providers.

They provide valuable seizure localization information in addition to MRI scan, EEG and clinical assessment to the surgeons.

Ultrasound imaging involves exposing part of the body to high-frequency sound waves to produce pictures of the inside of the body.

- Because ultrasound images are captured in real-time, they can show the structure and movement of the body's internal organs, as well as blood flowing through blood vessels.

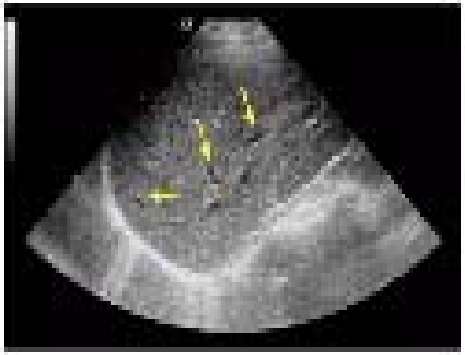
- When a sound wave strikes an object, it bounces back, or echoes. By measuring these echo waves it is possible to determine how far away the object is and its size, shape, and consistency (whether the object is solid, filled with fluid, or both).

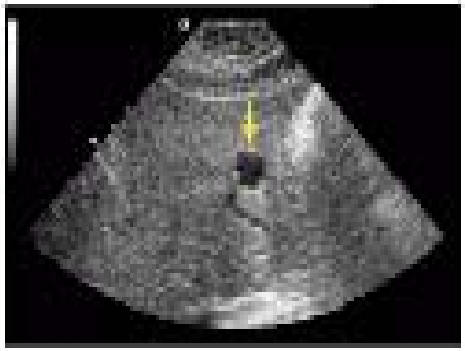
- In medicine, ultrasound is used to detect changes in appearance of organs, tissues, and vessels or detect abnormal masses, such as tumors.

Fetus at 14 weeks Fetus at 29 weeks

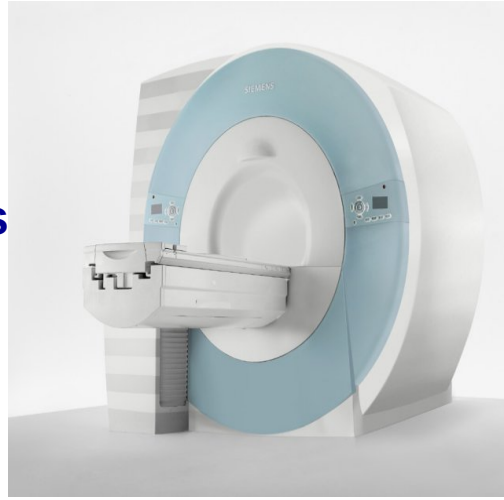
Figure 6.34 Example of a commercial echocardiographic scanner. (Courtesy of the Department of Cardiology.)

2D transducer: general appearance





Magnetic Resonance Imaging (MRI) is to visualize detailed internal structures. The good contrast is provides between the different soft tissues of the body make it useful in brain, muscles, heart, and cancer.
No ionizing radiation.

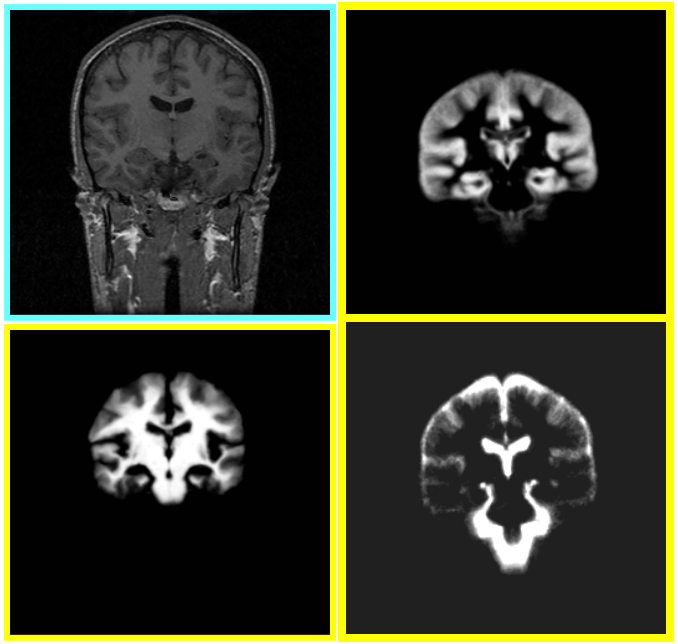


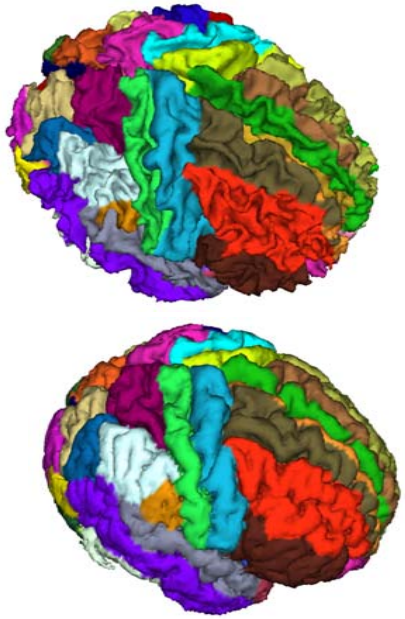
It uses a powerful magnetic field to align the magnetization of some atoms in the body, then uses radio frequency fields to systematically alter the alignment of this magnetization. This causes the nuclei to produce a rotating magnetic field detectable by the scanner.

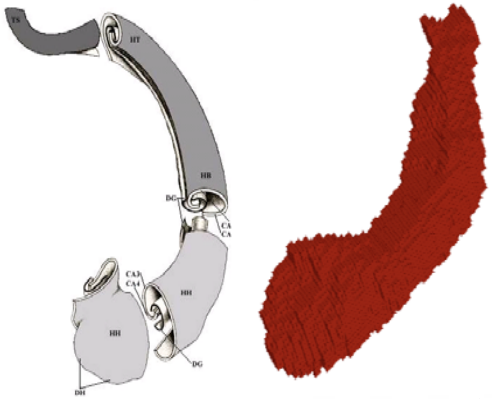
Paul Lauterbur and Peter Mansfield were awarded the 2003 Nobel Prize in Physiology or Medicine for their "discoveries concerning magnetic resonance imaging".

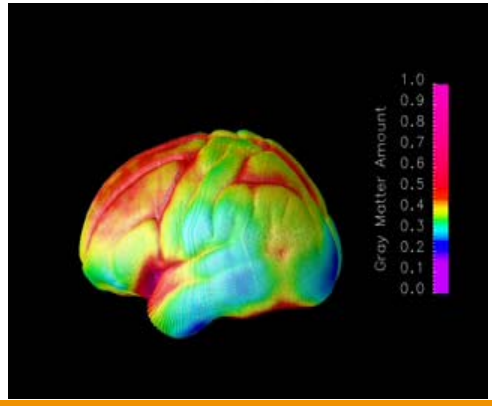
http://www.youtube.com/watch?v=6_2D3Lh1v74&feature=related

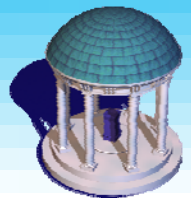
Magnetic Resonance Imaging (MRI)



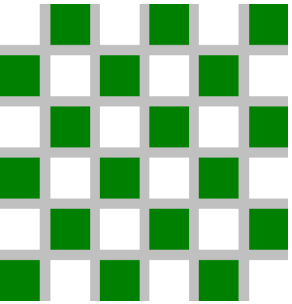


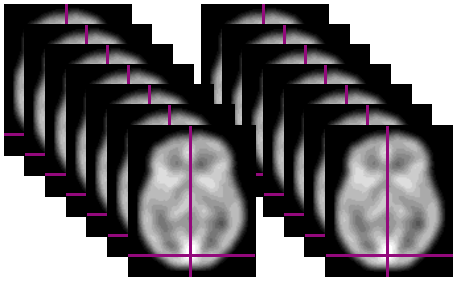




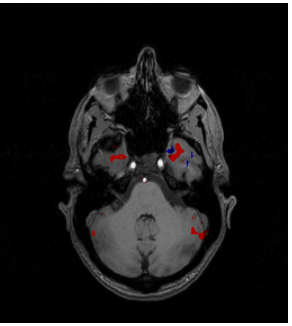


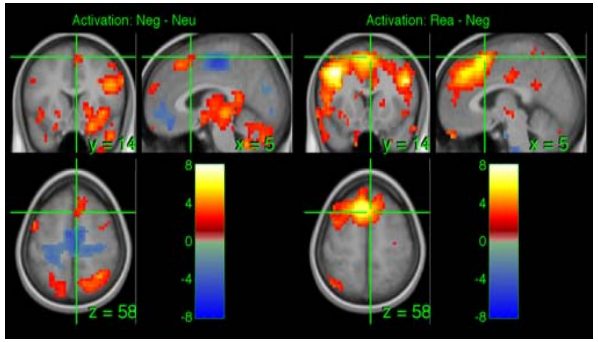
Functional MRI measures the hemodynamic response (change in blood flow) related to neural activity in the brain or spinal cord of humans or other animals. Since the early 1990s, fMRI has come to dominate the brain mapping field due to low invasiveness, absence of radiation exposure, and relatively wide availability.

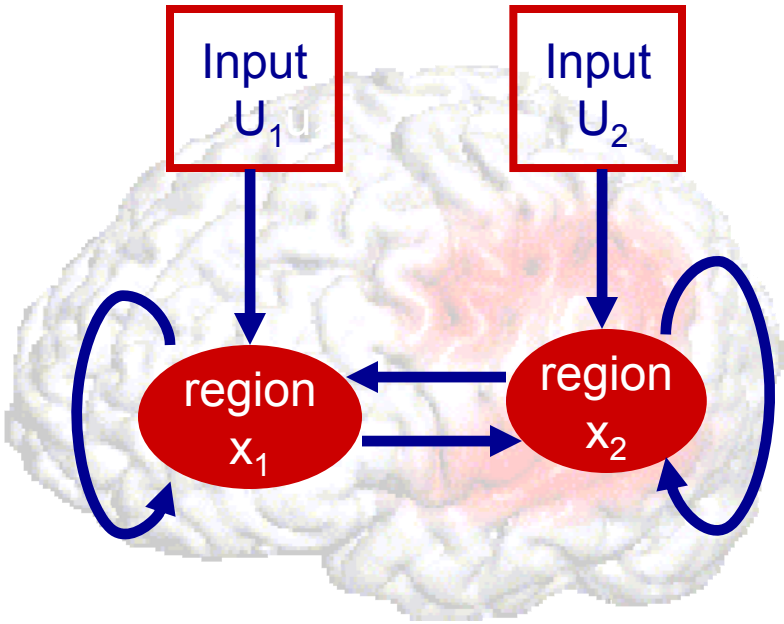




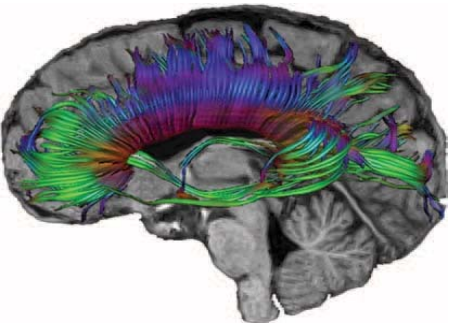
group 1 *group 2*

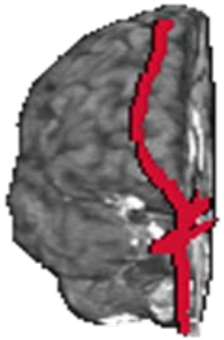


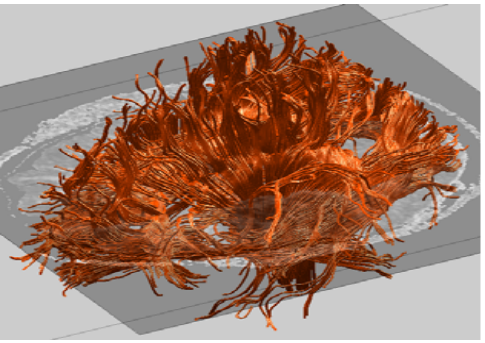


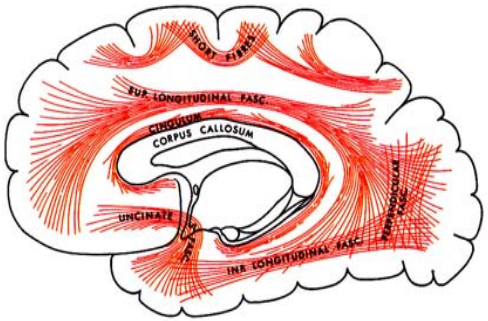


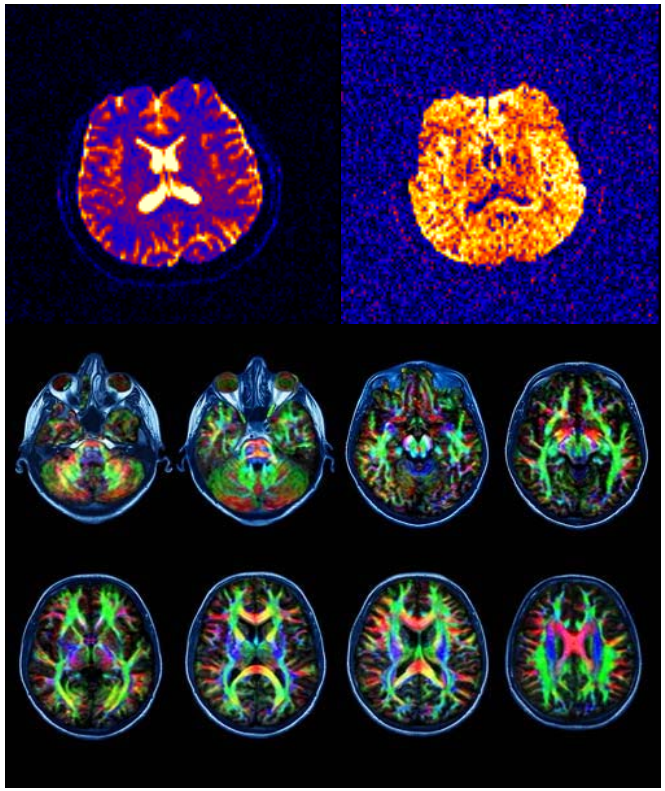
Diffusion MRI can provide information about damage to parts of the nervous system and about white matter connections among brain regions.











http://www.youtube.com/watch?v=XwUn64d5Ddk&feature=related

Molecular Imaging originated from the field of radiopharmacology to better understand the molecular pathways inside organisms.

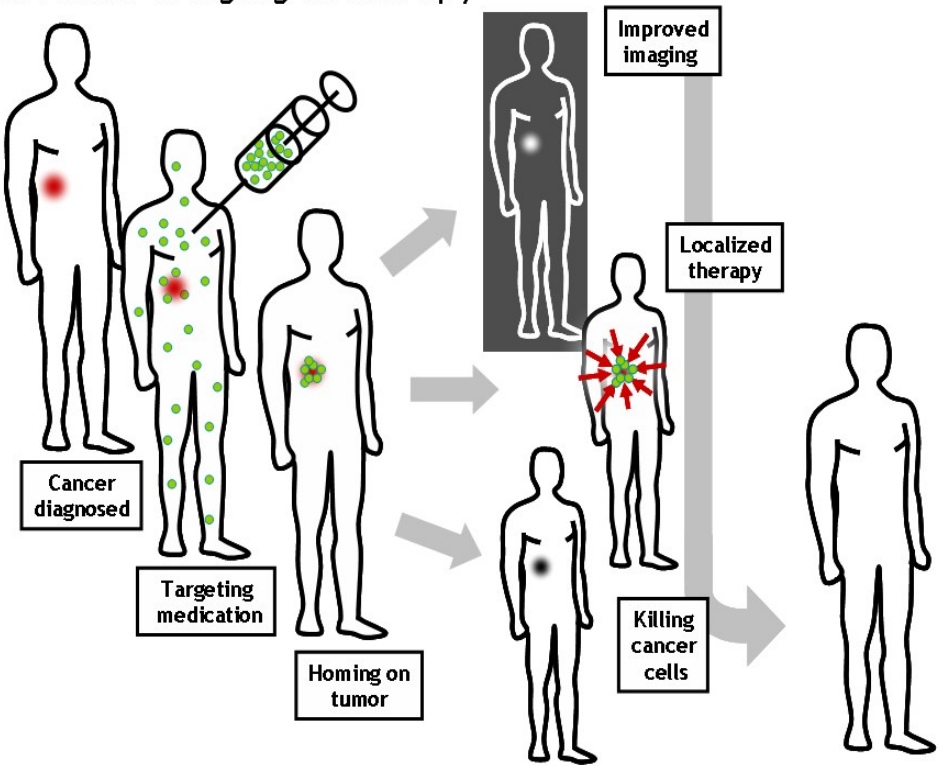
- Molecular imaging uses biomarkers to help image particular targets or pathways. Probes interact chemically with their surroundings and in turn alter the image according to molecular changes occurring with the area of interest.

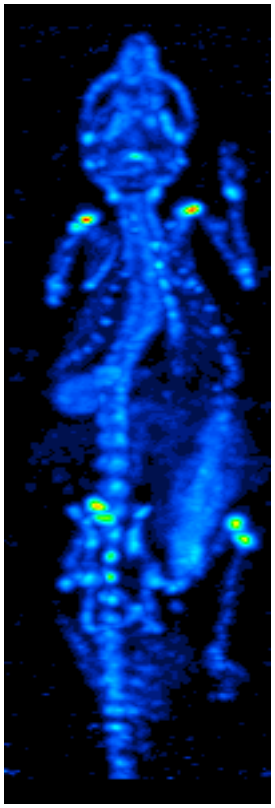
- This process is markedly different from previous methods of imaging which primarily imaged differences in qualities such as density or water content.

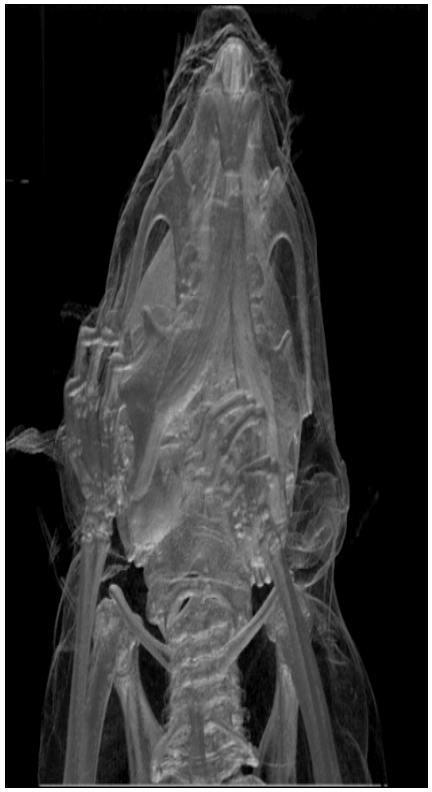
- This ability to image fine molecular changes opens up an incredible number of exciting possibilities for medical application, including early detection and treatment of disease and basic pharmaceutical development.

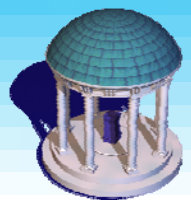
- Molecular imaging allows for quantitative tests, imparting a greater degree of objectivity to the study of these areas.

Molecular imaging & therapy

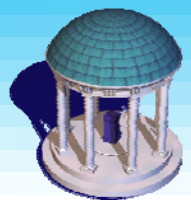








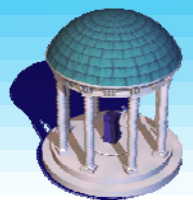
Part 4. Challenges and Strategies



- Society
- Conferences
- Methodology
- Publications
- Data Sets
- Software
- Training
- References
- Grants

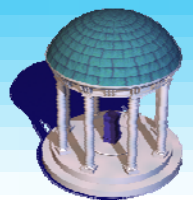
SI and Giants

flickr.com
blog.transparency.org



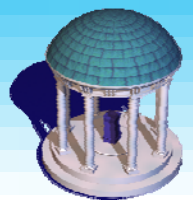
Giants

Society for Industrial and Applied Mathematics
IEEE Computer Society
IEEE Signal Processing Society
Organization for Human Brain Mapping
International Society for Magnetic Resonance in Medicine
Medical Image Computing and Computer Assisted Intervention



Conferences

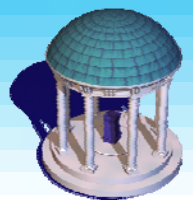
SIAM Conference on Imaging Science (IS)
Human Brain Mapping (HBM)
IEEE Conference on Computer Vision and Pattern Recognition (CVPR)
Medical Image Computing and Computer Assisted Intervention (MICCAI)
Information Processing in Medical Imaging (IPMI)
International Symposium on Biomedical Imaging (ISBI)
Neural Information Processing Systems Foundation (NIPS)



Methodology

The **reconstruction, enhancement, segmentation, analysis, registration, compression, representation, and tracking** of two and three dimensional images are vital to many areas of science, medicine, and engineering.

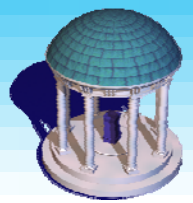
Sophisticated mathematical, statistical, and computational methods include **transform and orthogonal series methods, nonlinear optimization, numerical linear algebra, integral equations, partial differential equations, Bayesian and other statistical inverse estimation methods, operator theory, differential geometry, information theory, interpolation and approximation, inverse problems, computer graphics and vision, stochastic processes,** and others.



Publications

SIAM Journal on Imaging Sciences
IEEE Pattern Analysis and Machine Intelligence
NeuroImage
IEEE Transactions on Medical Image
IEEE Transactions on Signal Processing
IEEE Transactions on Image Processing
IEEE Transactions on Signal Processing Magazine
Medical Imaging Analysis
Human Brain Mapping

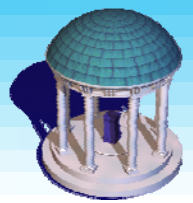
Annals of Applied Statistics
Biometrics
Biostatistics
Journal of American Statistical Association ACS



Data Sets

Public Data Sets:

- **1000 Functional Connectomes Project**
- **Alzheimer's Disease Neuroimaging Initiative (ADNI)**
- **NIH MRI Study of Normal Brain Development**
- **National Database for Autism Research**
- **Human Connectome Project**

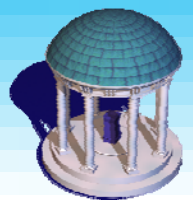


Software

http://www.nitrc.org/

NITRC = The Source for Neuroimaging Tools and Resources

- Statistical Parametric Mapping (SPM)
- FMRIB Software Library (FSL)
- Analysis of Functional NeuroImages (Afni)
- 3D Slicer
- FreeSurfer
- ……



Training

- Courses on Imaging Statistics and Statistical Computing
- Courses on pattern recognition and machine learning.
- Introductory Training Courses in ENAR and JSM
- Advanced Imaging Statistical Courses in HBM and MICCAI
- Applying Imaging Related Training Grants.
- Collaborating with Statisticians from other universities
- Attracting good students and scholars

Grants

National Science Foundation

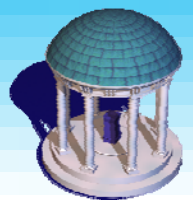
National Institute of Mental Health

National Institute of Biomedical Imaging

National Cancer Institute

- **BMRD Study Section**
- **BDMA Study Section**

…



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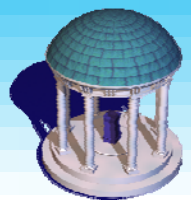
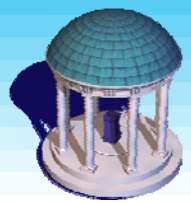
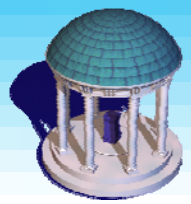


Part 5. Research Opportunities



- Imaging Sequence
- Imaging Reconstruction
- Imaging Signal Model
- Imaging Registration
- Imaging Segmentation
- Shape Analysis
- Population Statistics
- Network Analysis
- Imaging Genetics



Imaging Sequence
Evaluation and Optimization

Statistical Methods in Diagnostic Medicine

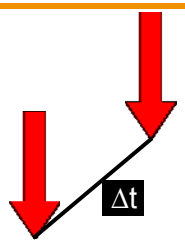
Experimental Design

Evaluation

- 3 Types of Excitation

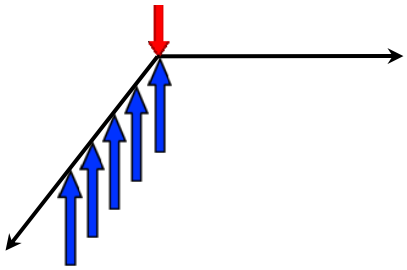
Single F/1.5
(SP1.5)

Single F/3
(SP3)

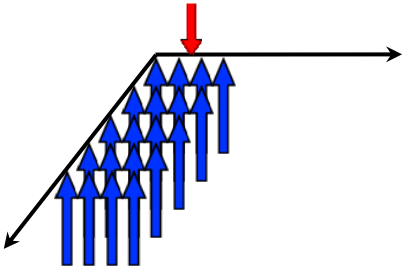


Double F/1.5
(DP)

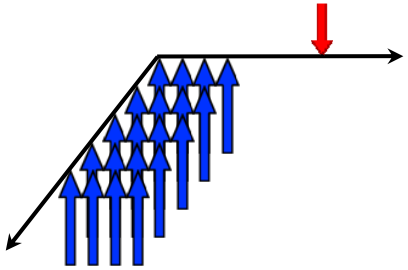
- 3 Types of Tracking



Single A-line RX
(SRx)



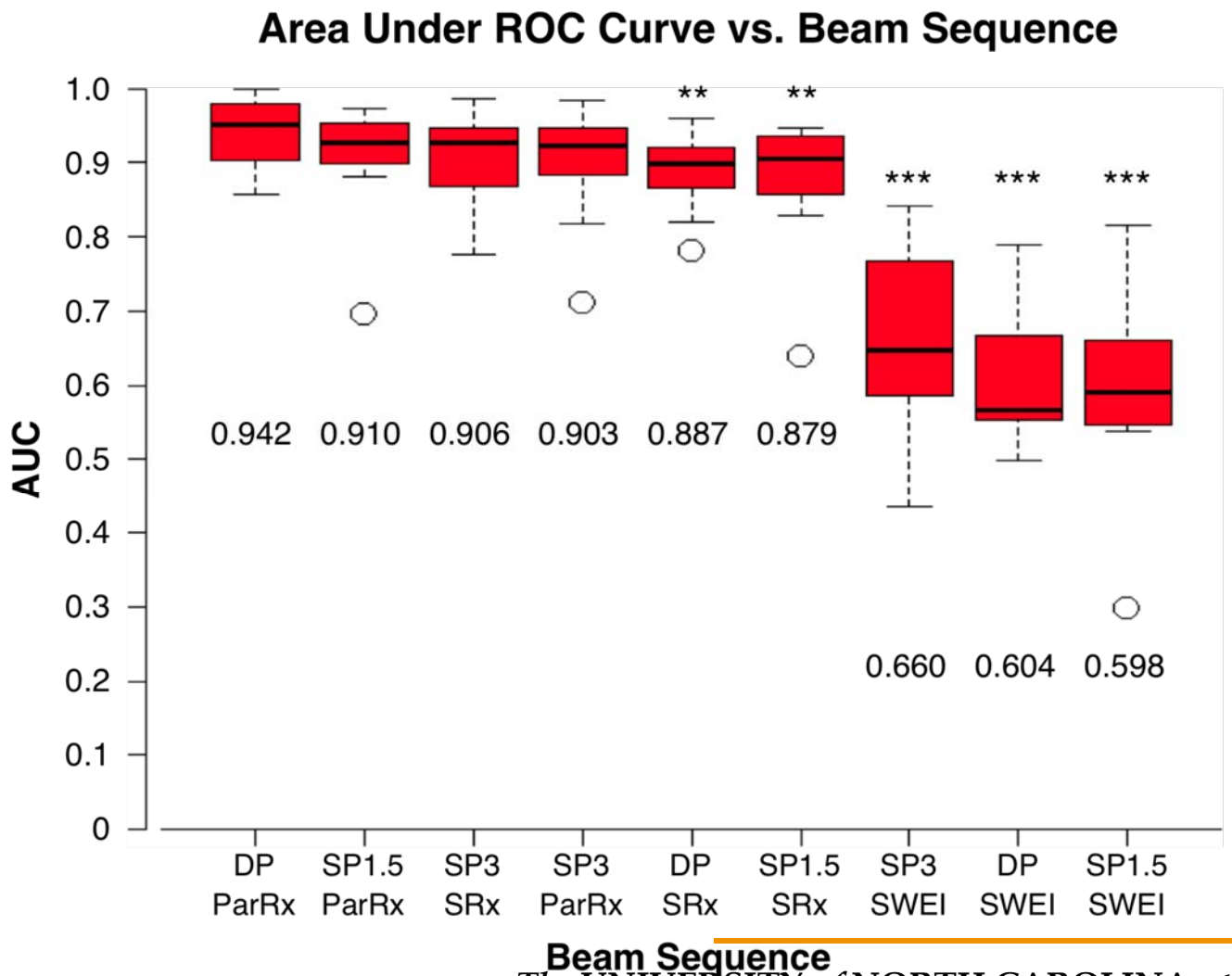
4:1 Parallel RX
(ParRx)



SWEI

- Combine for 9 Total Sequences

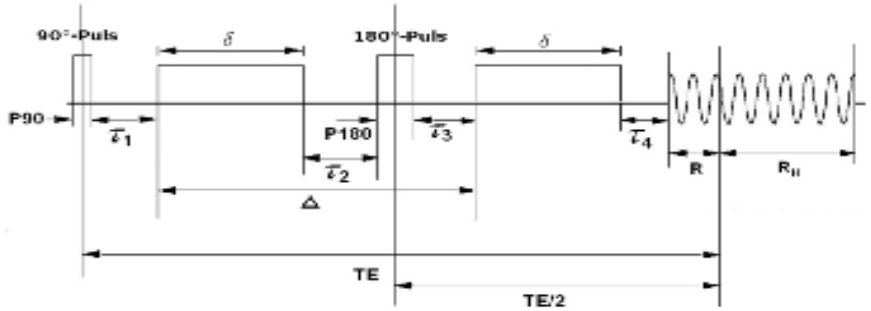
ROC



** p<0.02
*** p<0.005

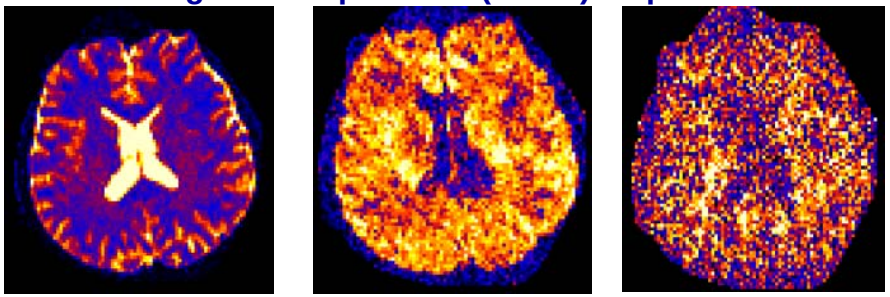
Optimization

Acquisition Scheme (Imaging Parameters)

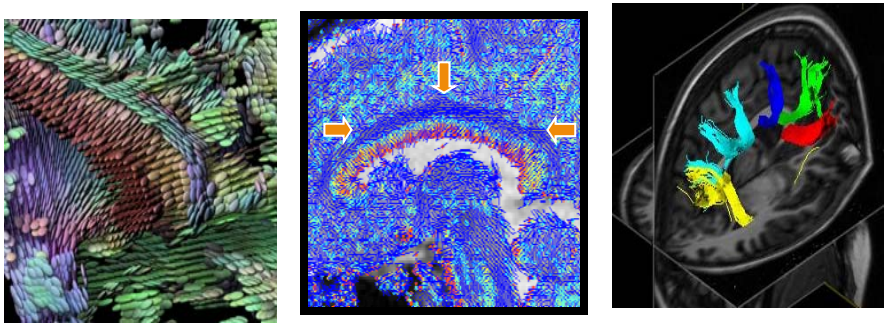


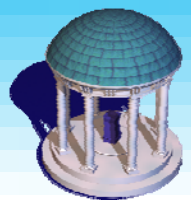
Puled-gradient spin-echo (PGSE) sequence

Noisy Images



Images Reconstruction





STATISTICAL MODEL

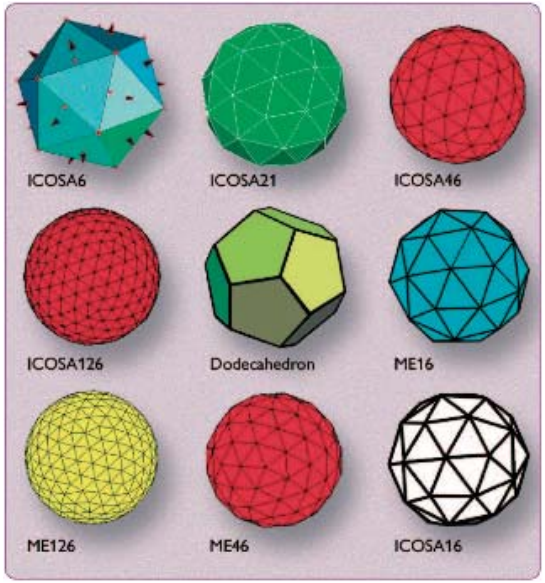
Gradient Orientations & b factors

Design Criterion

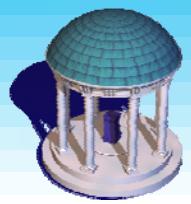
Global Optimization

$$S \approx S_0 e^{-bg^T Dg} = f(x,\theta)$$

$$p(S,b,g \mid S_0, D)$$

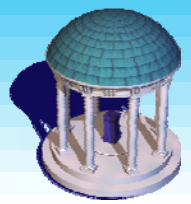


Gradient directions (Hasan & Narayana, 2005, MedicaMundi)



Imaging Reconstruction

- Variable Selection Problem
- Matrix Decomposition
- Optimization



MRI Measurement Model

$$Y_i = s(t_i) + \varepsilon_i = \int f(\vec{r}) e^{-i2\pi < \vec{k}(t), \vec{r} >} d\vec{r} + \varepsilon_i = F(\vec{k}(t)) + \varepsilon_i,$$

$\vec{r}$: spatial coordinates;

$\vec{k}(t)$: k - space trajectory of the MR pulse sequence;

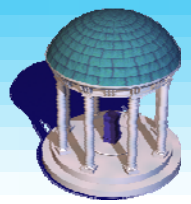
$f(\vec{r})$: transverse magnetization;

$F(\vec{k}(t))$: Fourier transform of $f(\vec{r})$;

$e^{-i2\pi < \vec{k}(t), \vec{r} >}$: spatial information $\Rightarrow$ Nobel Prize

Goal : Reconstruct $f(\vec{r})$ based on $Y_1, \cdots, Y_n$

Under-determined problem



- **Discrete-discrete Formulation**

$$Y = A\tilde{f} + \varepsilon, \text{ where } A = (a_{ij}) \text{ is an } n \times N \text{ matrix and } \tilde{f} = (f_1, \cdots, f_N)^{\mathrm{T}}.$$

Goal is to estimate $\tilde{f} = (f_1, \cdots, f_N)^{\mathrm{T}}$

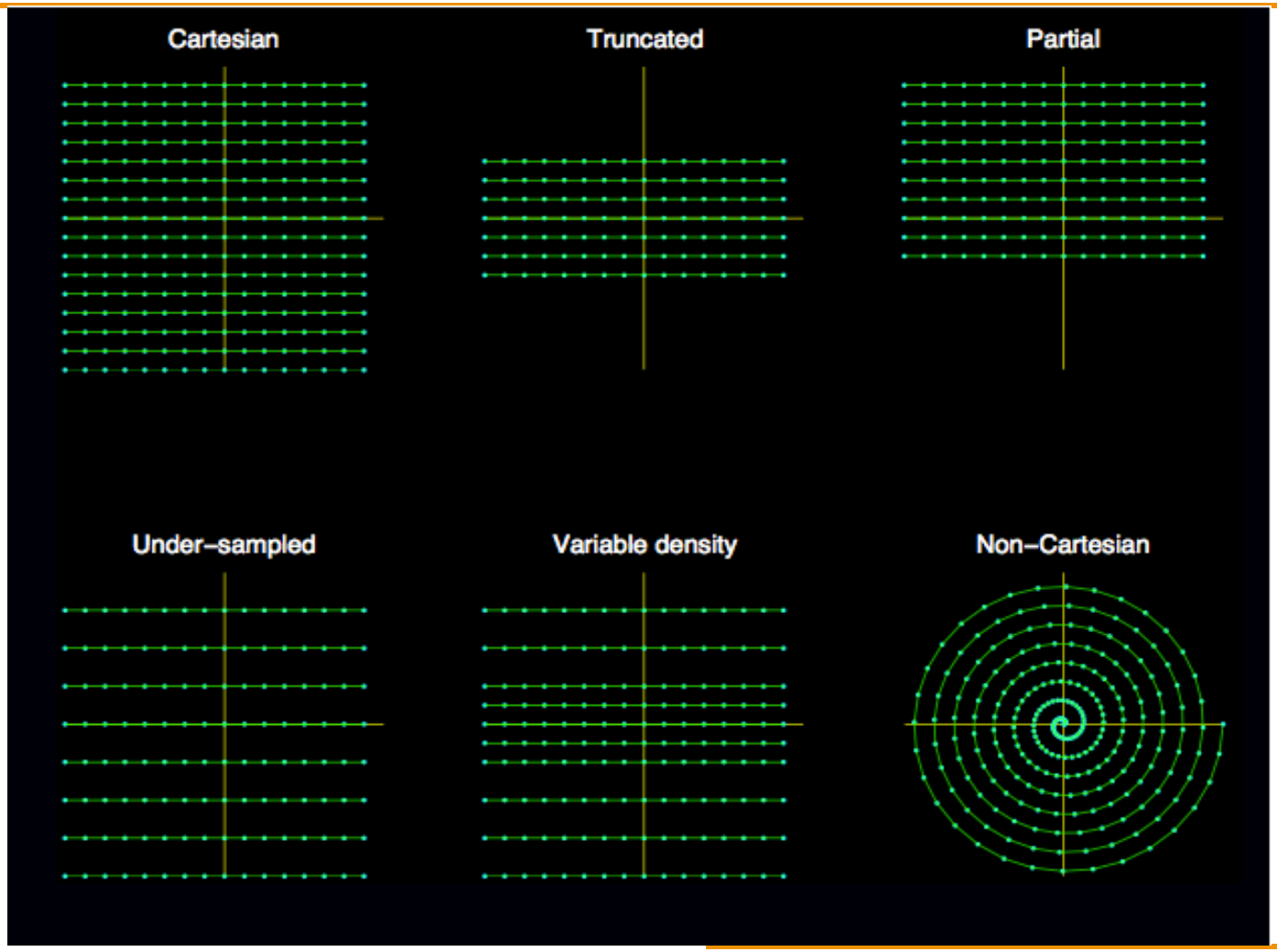
Estimate object by minimizing a cost function:

$$\hat{f} = \arg\min \| Y - A\tilde{f} \|^2$$

- Negative log-likelihood of Gaussian distribution
- Equivalent to maximum-likelihood (ML) estimation

Issues:

- computing minimizer rapidly
- stopping iteration (?)
- image quality


Cartesian
Truncated
Partial
Under–sampled
Variable density
Non–Cartesian

$$Y = A\tilde{f} + \varepsilon, \text{ where } A = (a_{ij}) \text{ is an } n \times N \text{ matrix and } \tilde{f} = (f_1, \cdots, f_M)^{\mathrm{T}}.$$

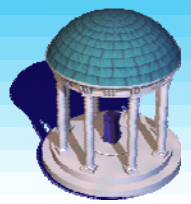
$$\tilde{f} = (f_1, \cdots, f_N)^{\mathrm{T}}$$

Estimate object by minimizing a cost function:

$$\hat{f} = \arg\min \| Y - A\tilde{f} \|^2 + \alpha R(\tilde{f}),$$

$R(\tilde{f})$ is to control noise by penalizing roughness,

$$e.g., R(\tilde{f}) = \int \| \nabla f \|^2 \, d\vec{r}$$



Quadratic Penalization

1D example: squared differences between neighboring pixel values:

$$\mathrm{R}(\tilde{f}) = \sum_{j=2}^{N} 0.5(f_j - f_{j-1})^2 = 0.5 \, \| Cf \|^2$$

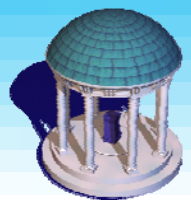
where

$$C = \begin{bmatrix} -1 & 1 & 0 & 0 & \dots & 0 \\ 0 & -1 & 1 & 0 & \dots & 0 \\ & & & \ddots & \ddots & \\ 0 & \dots & 0 & 0 & -1 & 1 \end{bmatrix}$$

For 2D and higher-order differences, modify differencing matrix C.

Leads to closed-form solution (a formula of limited practical use):

$$\begin{aligned} \hat{f} &= \arg\min_{f} \|y - Af\|^2 + \alpha \|Cf\|^2 \\ &= [A'A + \alpha C'C]^{-1} A'y. \end{aligned}$$



Imaging-signal Model

Parametric Models

Nonparametric Models

Data

$$\{(S_i(v), b_i, g_i) : i = 1, \ldots, n; v \in V\}$$

Rician Regression or Log-linear Model

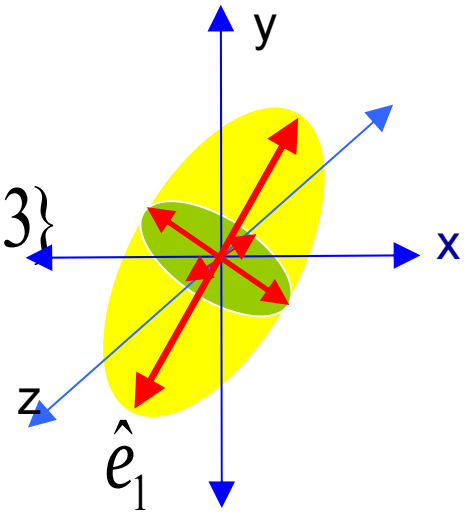
$$S_i(v) = S_0(v)\exp(-b_i g_i^T D(v) g_i) + \text{noise}$$

Estimated Diffusion Tensor

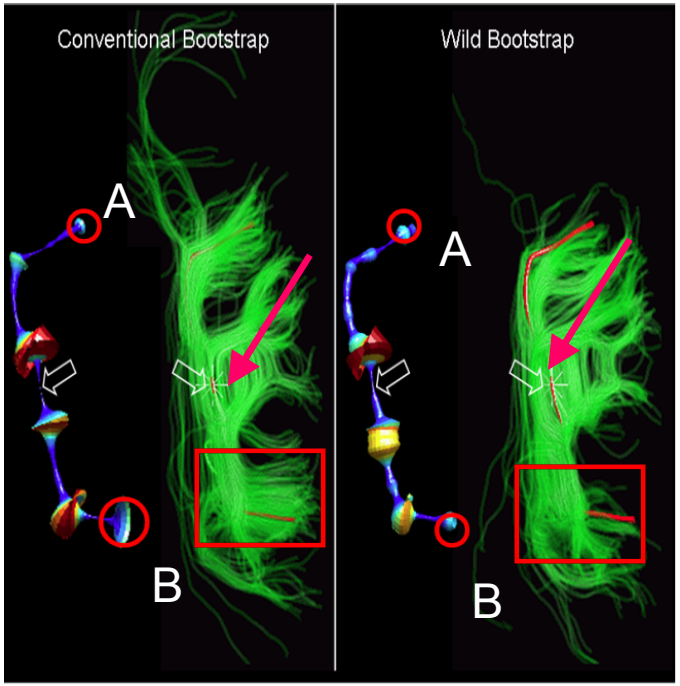
$$\hat{D}(v)$$

Estimated Eigenvalues or Eigenvectors

$$\{(\hat{\lambda}_k, \hat{e}_k) : k = 1,2,3\}$$

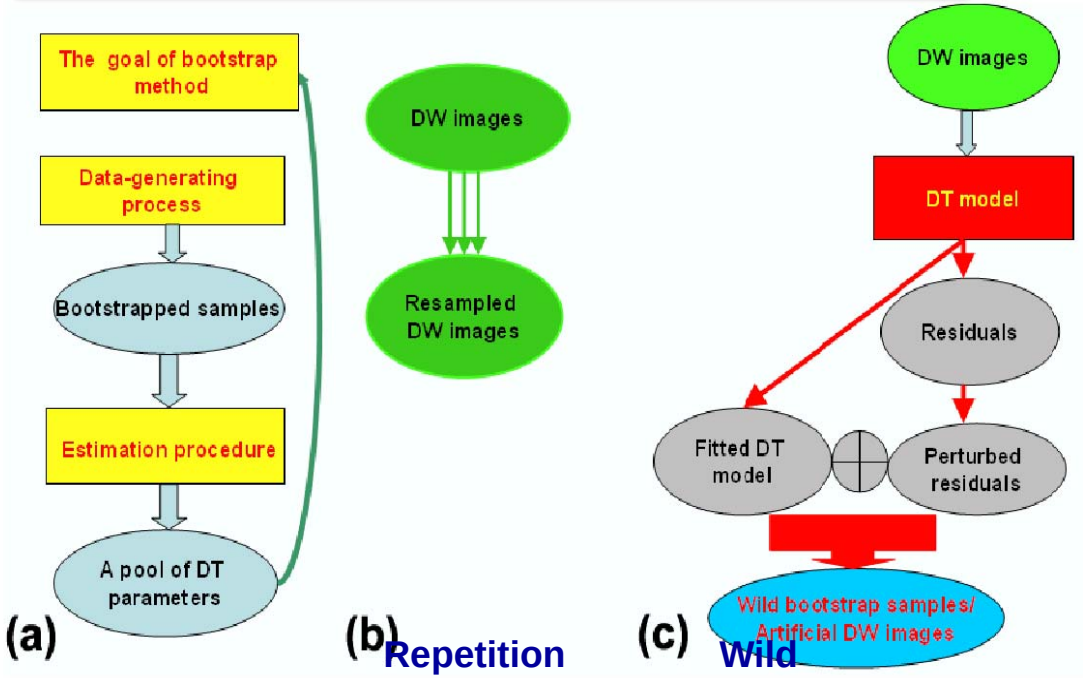


Quantifying Uncertainty by using bootstrap methods



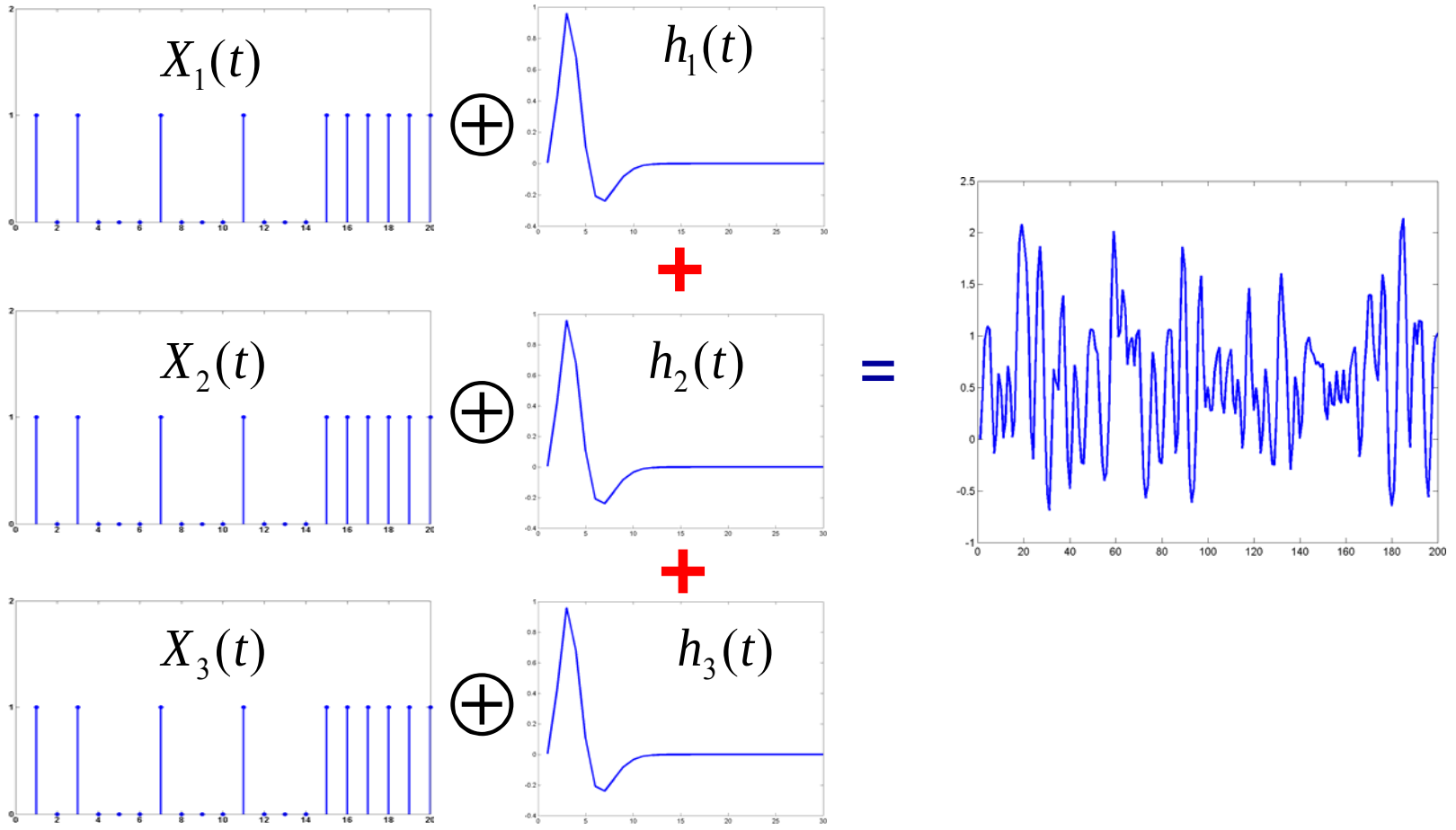
Repetition Wild

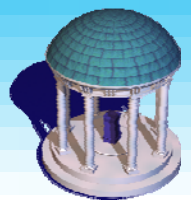
Bootstrap



Repetition Wild

BOLD: Multiple Sequences of Events





Bold Model with Multiple Events

$$Y(d,t) = \mathbf{h}(d,\cdot) \otimes \mathbf{X}(t) = \int \mathbf{h}(d,t-u) \cdot \mathbf{X}'(u)du + \epsilon(d,t)$$

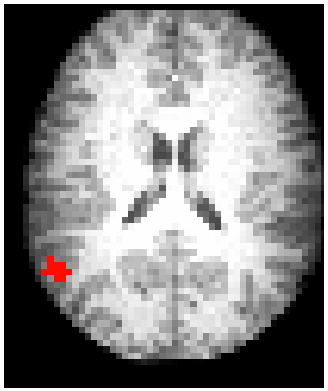
$$= \int h_1(d,t-u) \cdot X_1(u)du + \cdots + \int h_m(d,t-u) \cdot X_m(u)du + \epsilon(d,t)$$

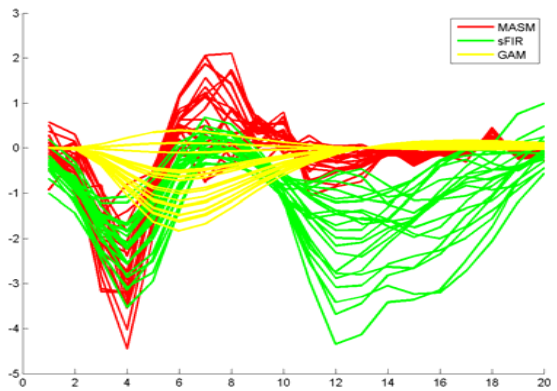
$$\mathbf{X}(t) = (X_1(t), \cdots, X_m(t)), \quad \mathbf{h}(d,t) = (h_1(d,t), \cdots, h_m(d,t))$$

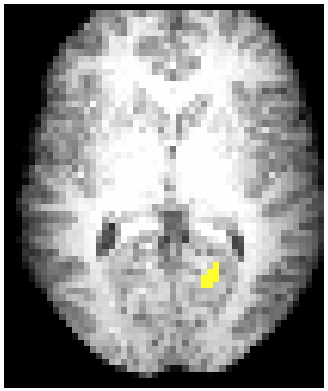
Time-domain Models:

Convolution Model:

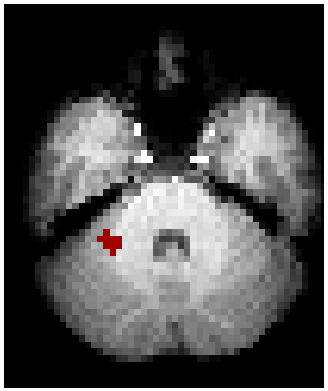
$$\phi_Y(d,f) = \mathbf{H}(d,f) \cdot \phi'_{\mathbf{X}}(f) + \phi_\epsilon(d,f) \quad f \in \Re$$

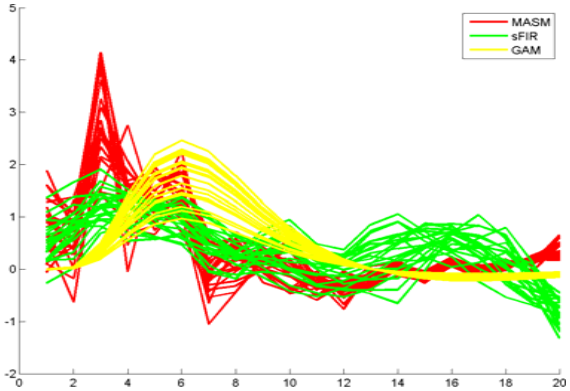


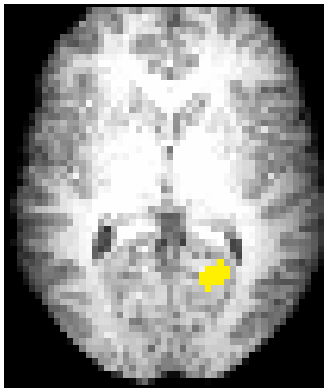

MASM
sFIR
GAM

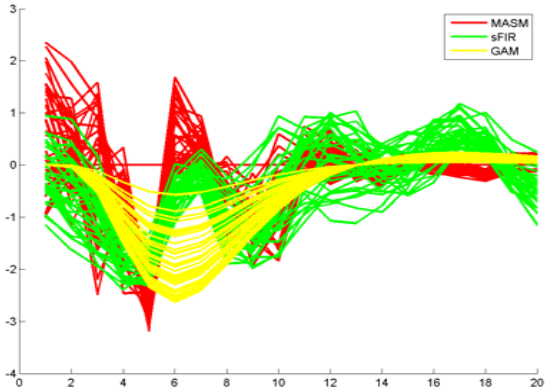


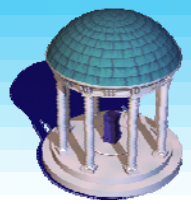
MASM
sFIR
GAM




MASM
sFIR
GAM

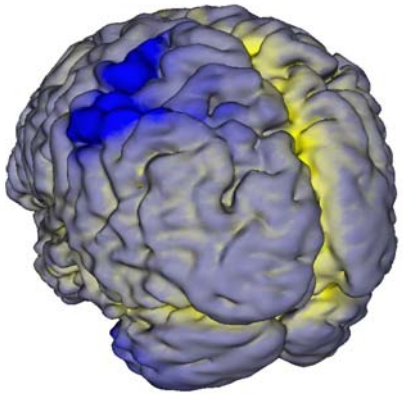


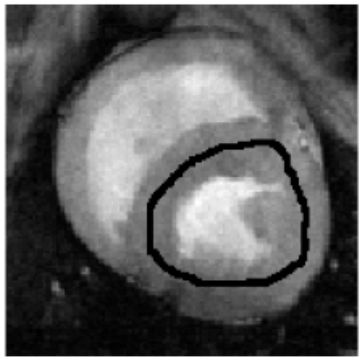

MASM
sFIR
GAM

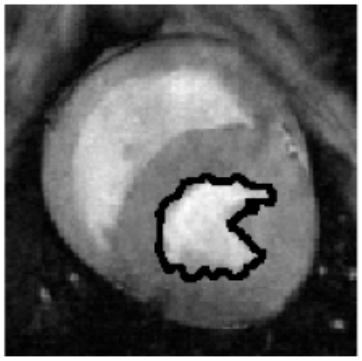


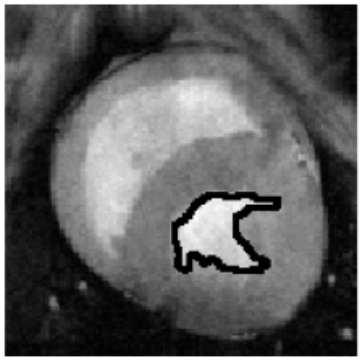
Imaging Segmentation

Cluster Analysis
Markov Random Field
Partial Differential Equation
Bayesian Methods

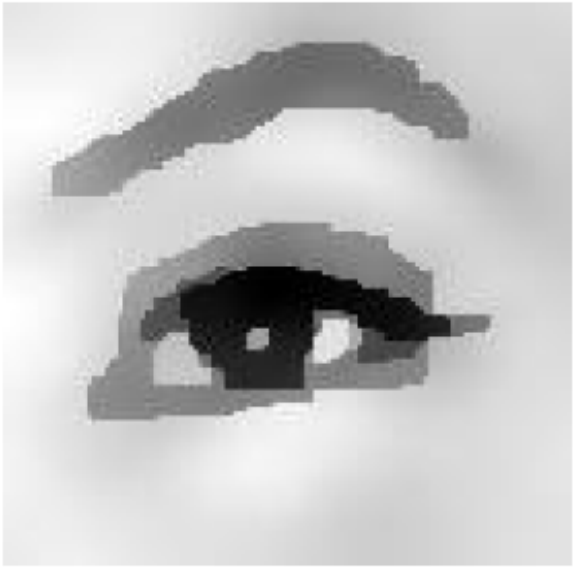


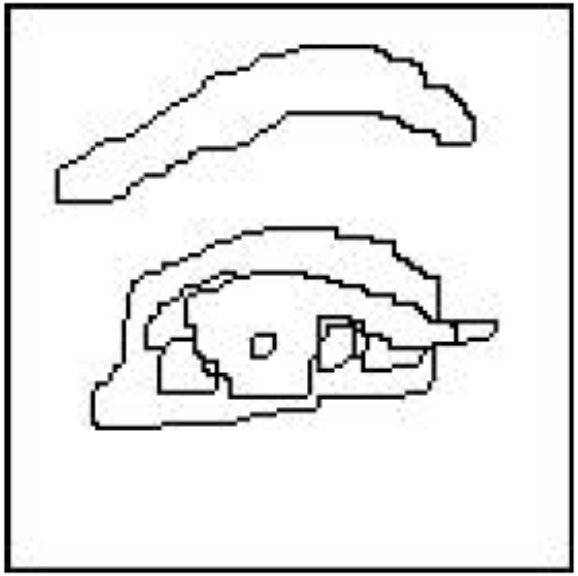






[Image: Mumford]



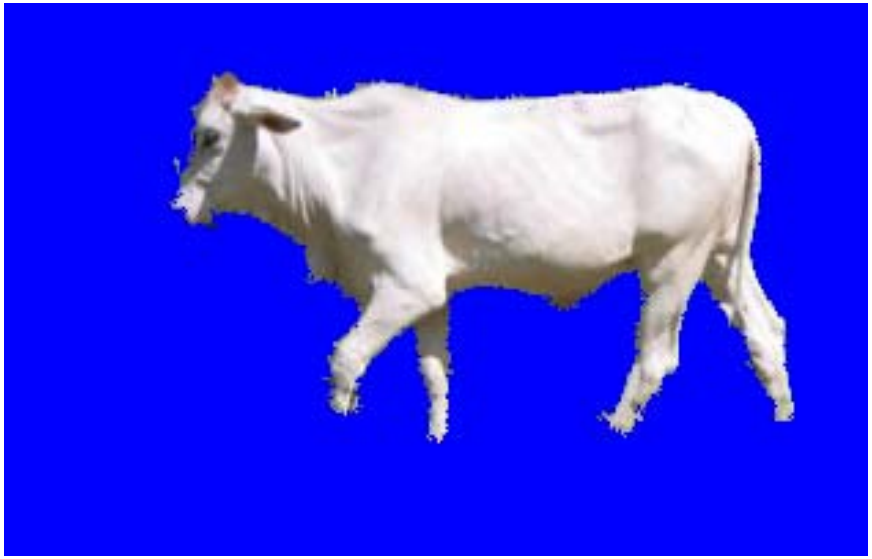


The Mumford Shah model is a method that yields a segmentation and at the same time a (piece-wise smooth) image reconstruction.

$$E(f,C) = \alpha \underbrace{\int_{\Omega} (f-I)^2 \, dx}_{=\text{image match}} + \beta \underbrace{\int_{\Omega \setminus C} \|\nabla f\|^2 \, dx}_{=\text{smooth reconstruction}} + \gamma \underbrace{\int_0^L ds}_{=\text{length prior}}$$

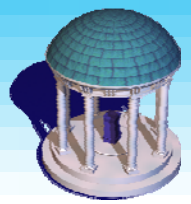
Alternative approach through graph construction (vs. PDE)

Example: Binary Segmentation

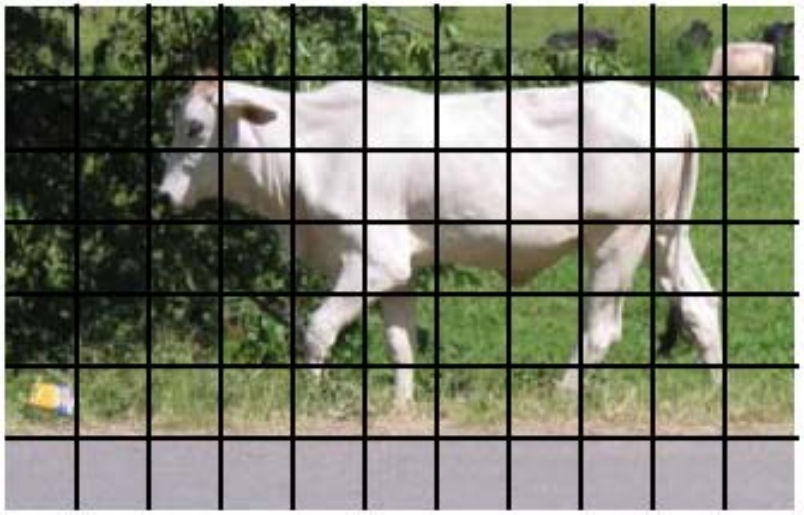


Need to partition the picture into foreground and background.

Images from ECCV Tutorial, Kumar/Kohli



Segmentation by Graph-Cut



Optimization Problem: Minimize

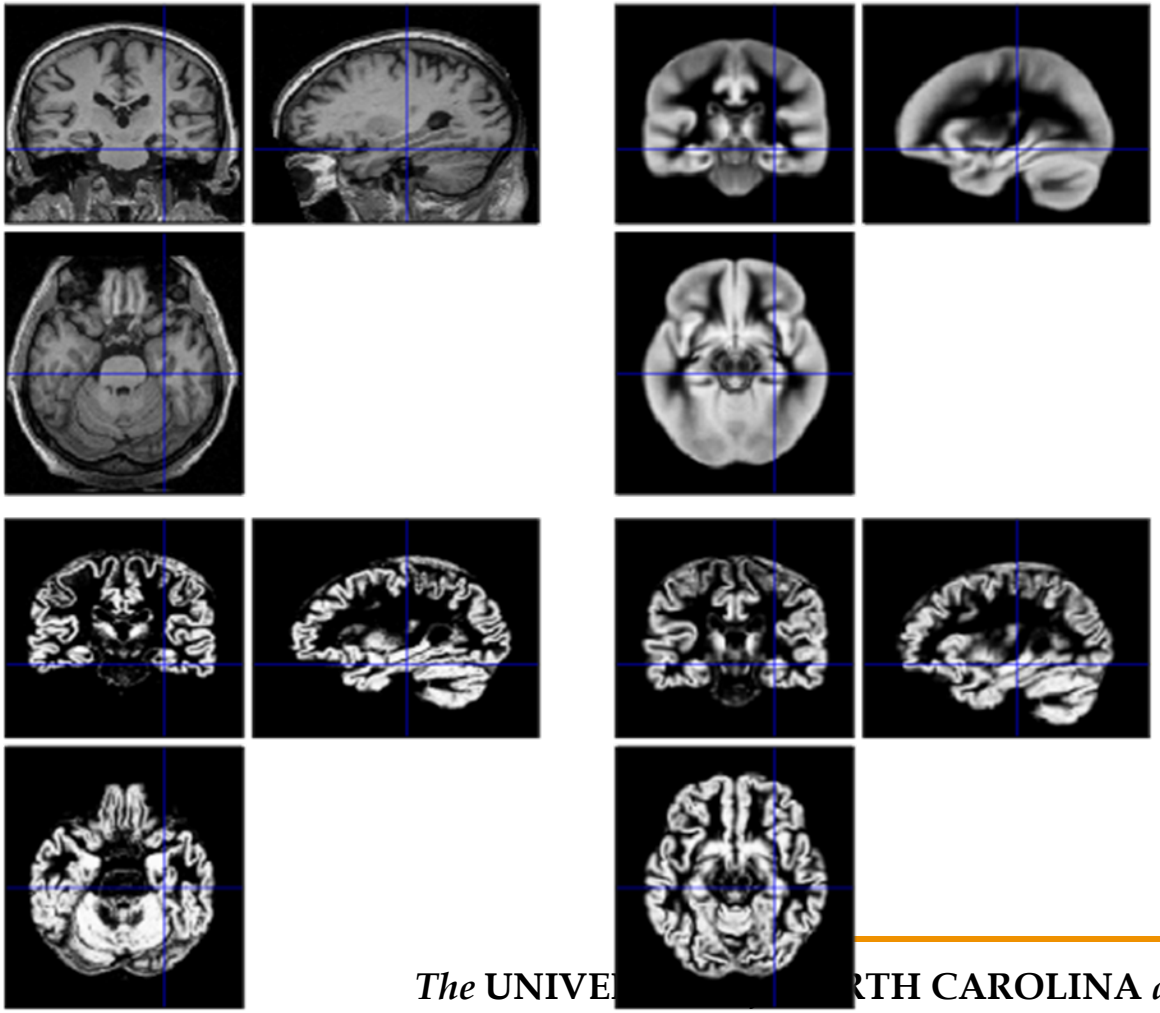
$$E(f) = E_{smooth}(f) + E_{data}(f)$$

Looking at it on a pixel-by-pixel basis (where f is the labeling):

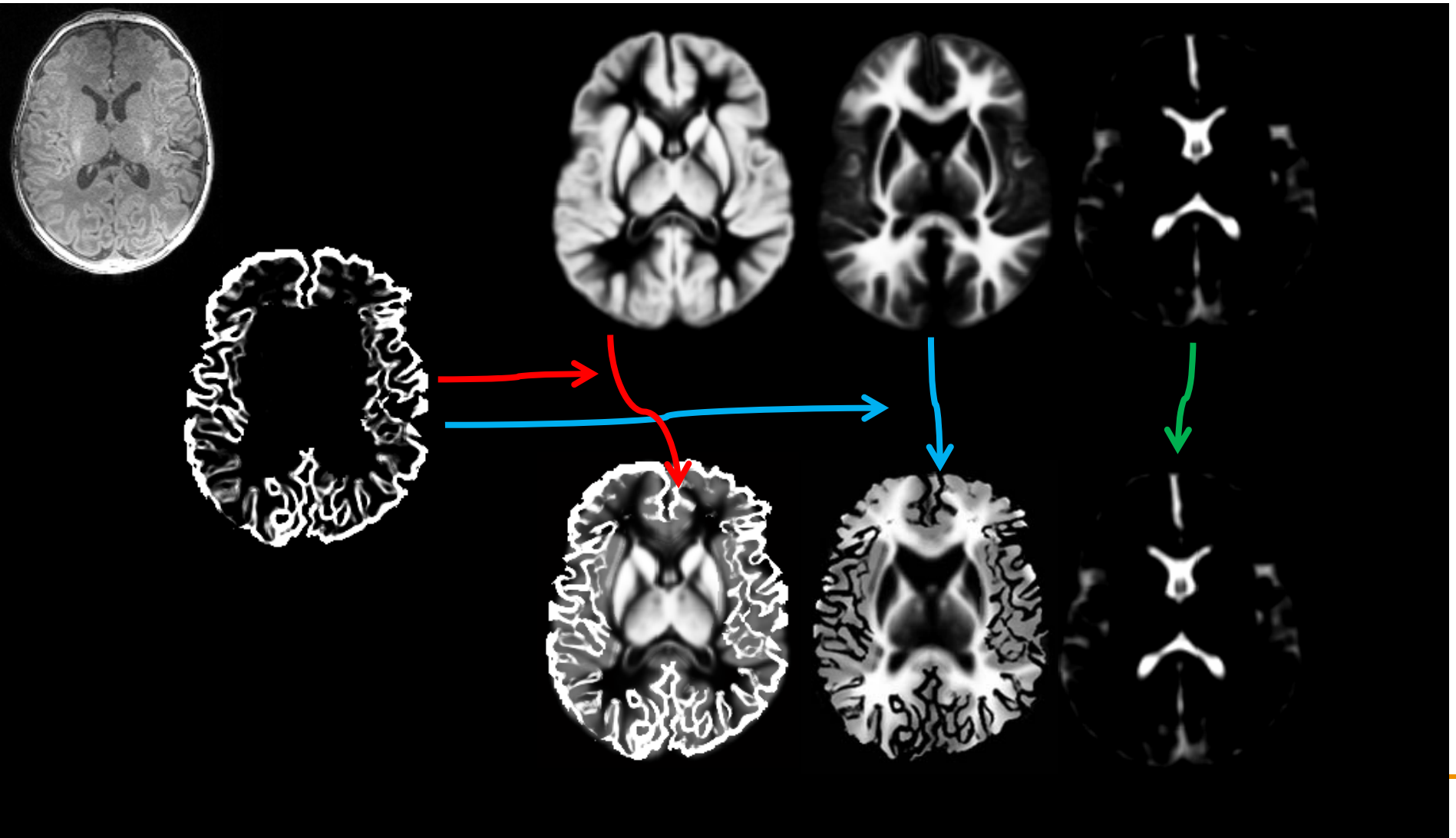
$$E(f) = \sum_{\{p,q\} \in \mathcal{N}} V_{p,q}(f_p, f_q) + \sum_{p \in \mathcal{P}} D_p(f_p)$$

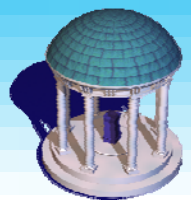
Problem: We cannot try all possible pairings for the labels f.
Need an efficient algorithm to solve this problem.

Segmentation ⟷ Registration



Hybrid Atlas



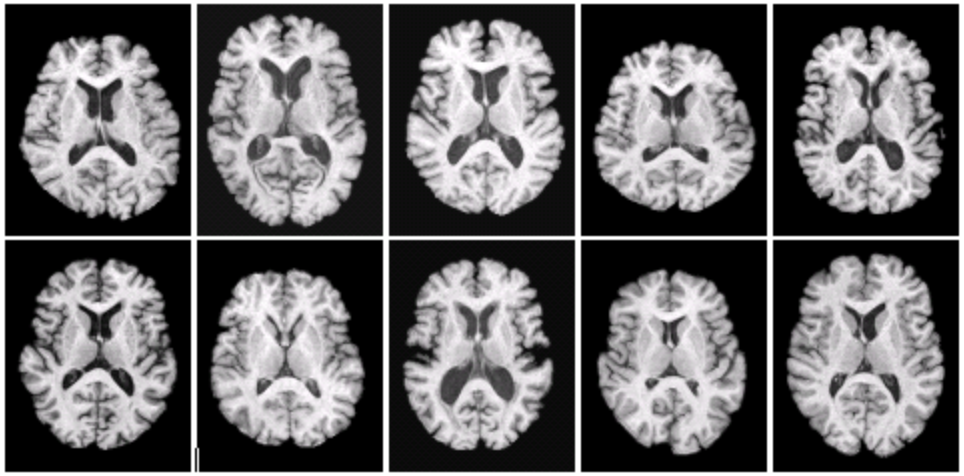


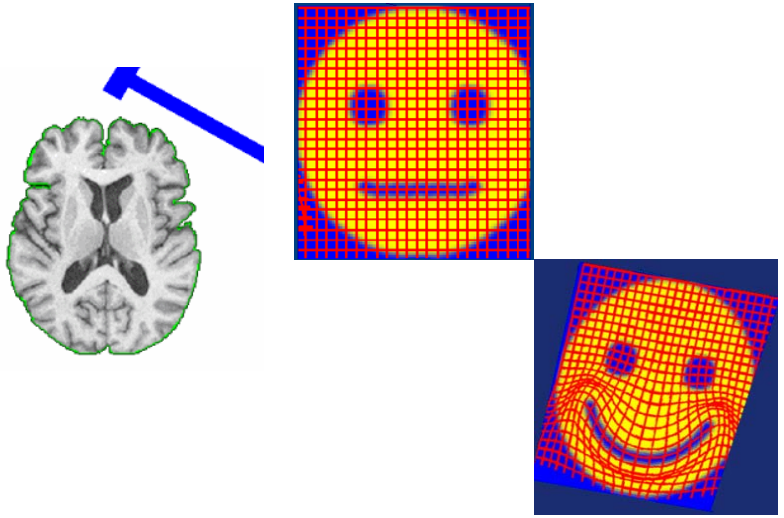
Imaging Registration

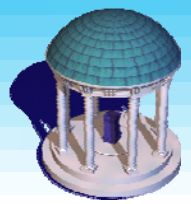
Regression Methods
Infinite-dimensional Statistics

Image Registration

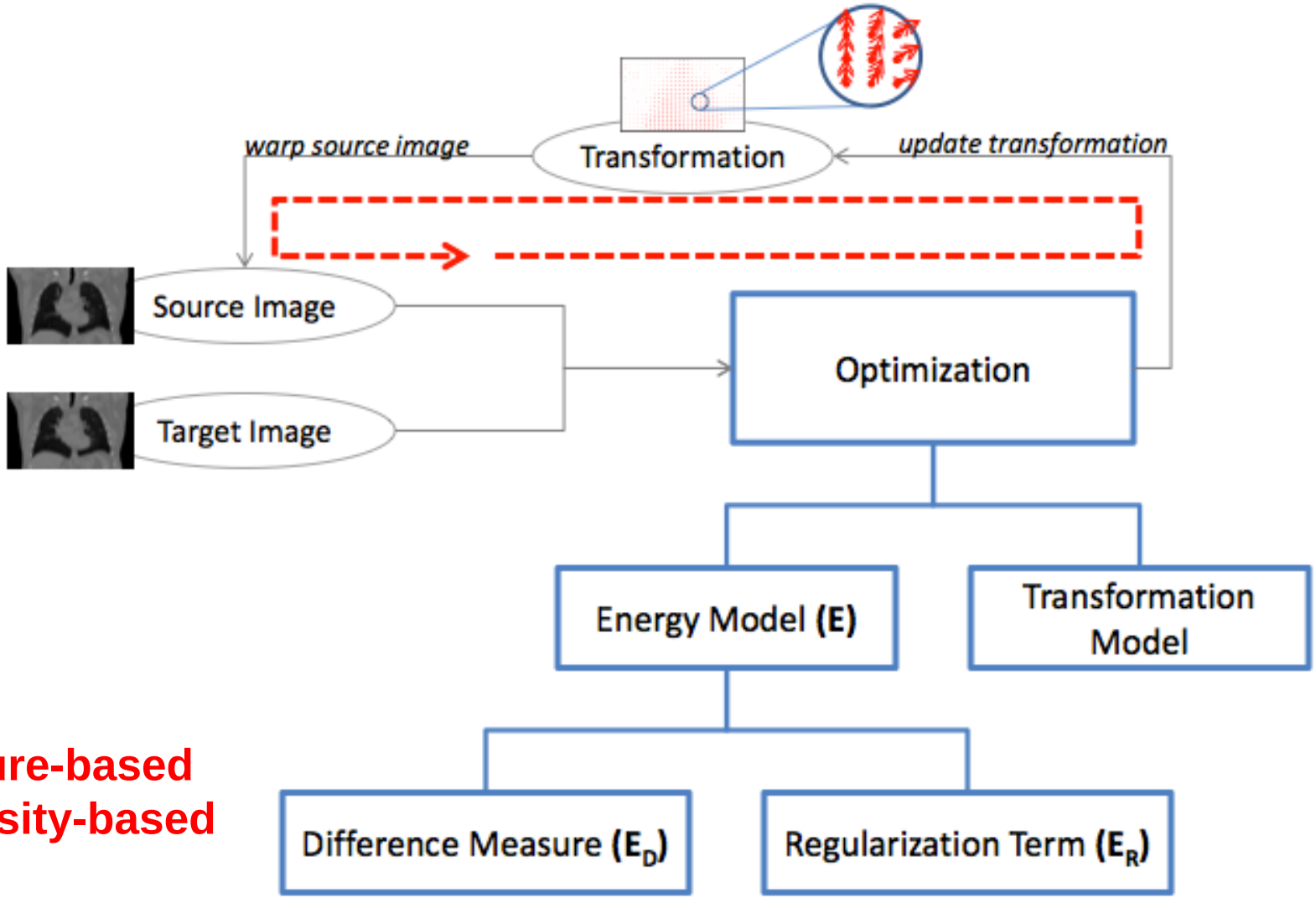
Image registration is the process of transforming different sets of data into ***one coordinate system***. Data may be multiple photographs, data from different sensors, from different times, or from different viewpoints.



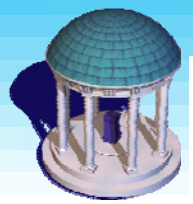




Deformable Registration: General Framework



Feature-based
Intensity-based



Minimization Problem

Images (target I_T, source I_S): $I : \Omega \to \mathbb{R}$

Image domain: $\Omega \subset \mathbb{R}^d$, $d=2,3$

Warped Source Image

$$u' = \arg\min_{u \in \mathrm{H}} E_D(I_T, I_S(\varphi)) + \lambda E_R(u)$$

Displacements are elements of a Hilbert space H, e.g.: $u \in \mathrm{L}^2$

Deformation: $\varphi = \mathrm{Id} + u$, $\varphi : \Omega \to \mathbb{R}^d$

or point-wise: $\varphi(x) = x + u(x)$

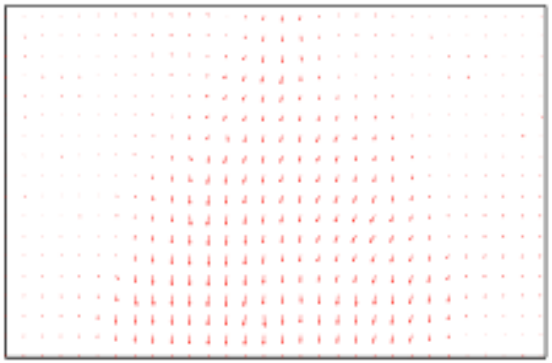
Please note: Highly heterogeneous notation in the field

Displacement:

$u : \Omega \to \mathbb{R}^d$

e.g. $u = [u_x, u_y, u_z]$

difference between original position of a point x and its transformation φ(x)

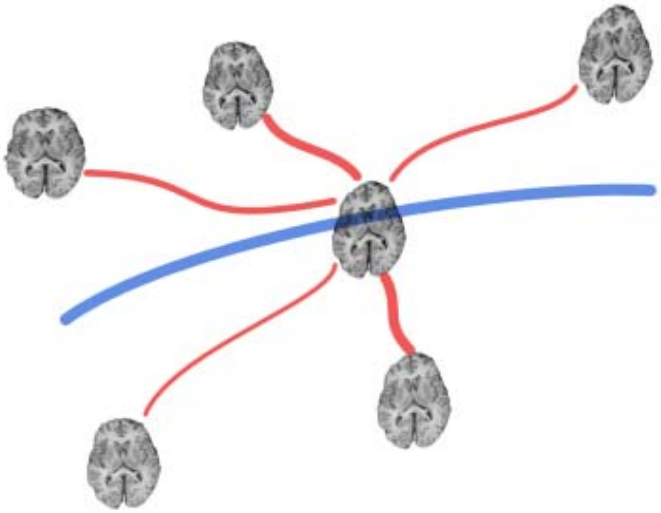


Large Deformation Diffeomorphic Metric Mapping

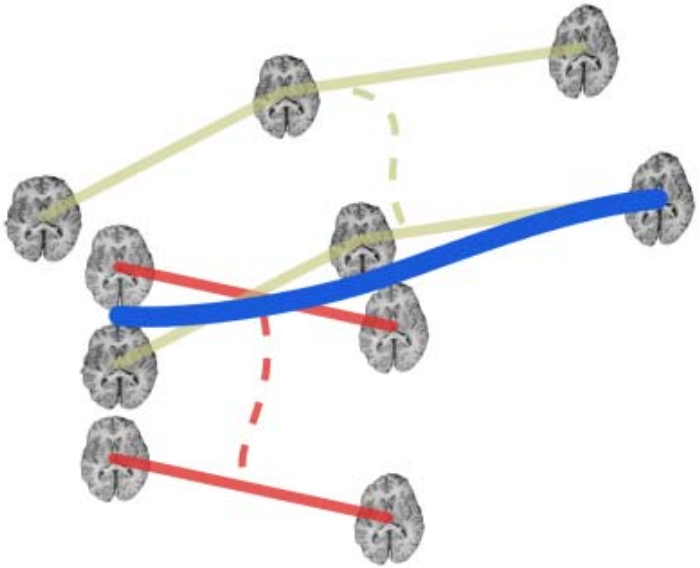
Nonparametric Local Linear Model

Atlas-Building

Davis et al. [2007]



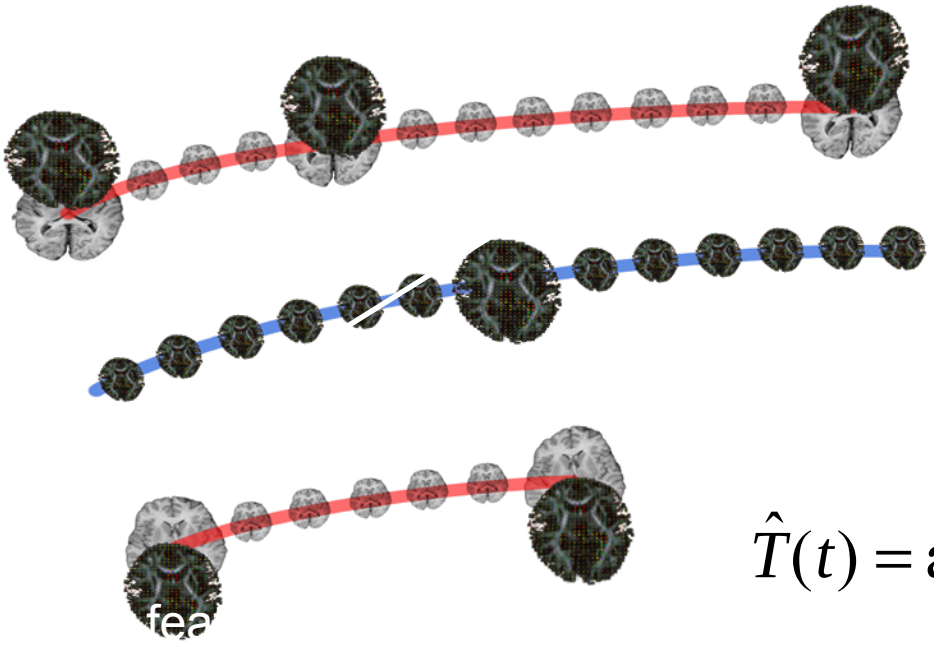
Durrleman et al. [2009]



$$\hat{T} = \arg\min_T \sum_{i=1}^{n} w_i g(B_i, T)^2$$

Longitudinal Atlas-Building

Objective: Obtain an estimate of an average temporal trajectory and its variation from a set of subjects each imaged at multiple time-points.

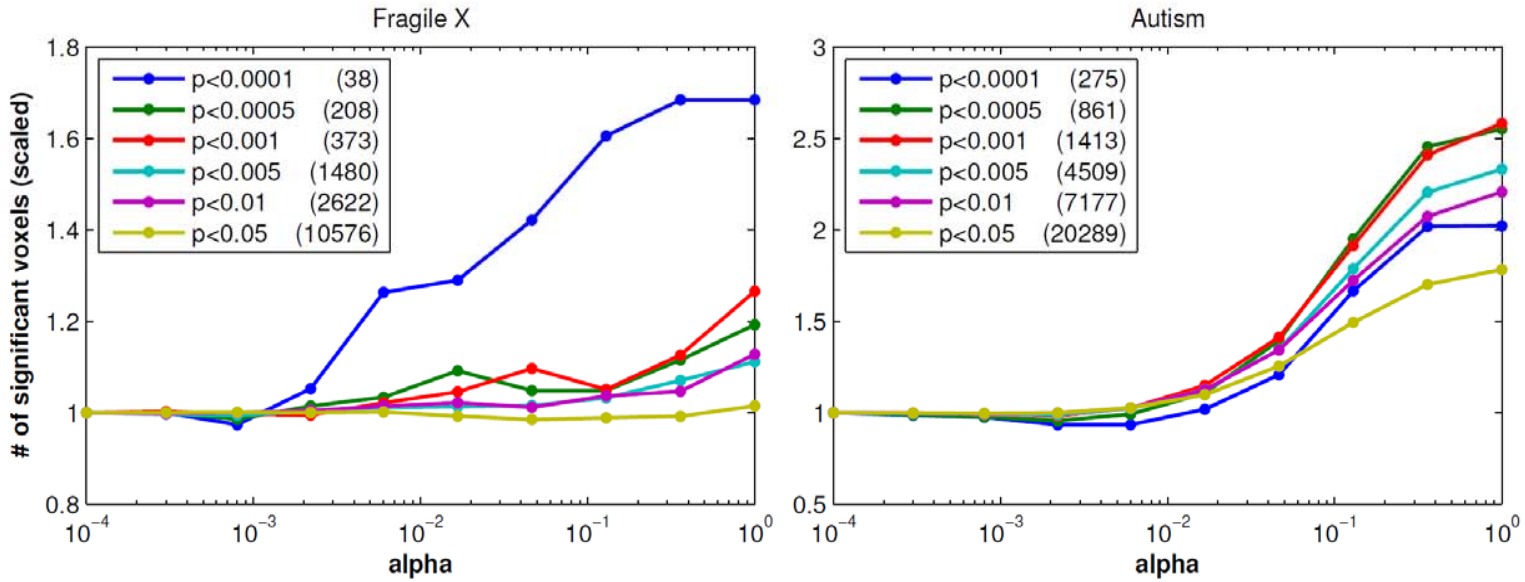


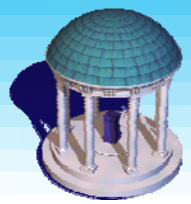
$$\hat{T}(t) = \arg\min_T \sum_{i=1}^{n} \sum_{j=1}^{m_i} w(t_{ij}, t) g(B_i(t_{ij}), T(t))^2$$

Effect of Registration and Atlas-Building on Statistics

$$E(\{v^i\}, I^\tau) = \sum_{i=1}^{N} \left(\int_0^1 \langle L^\dagger L v^i, v^i \rangle + \frac{1}{\sigma^2} \| I^i \circ \Phi^i - I^\tau \|^2 \right)$$

$$L = \gamma + \beta \nabla \nabla + \alpha \nabla^2; \ \alpha, \ \beta, \ \gamma > 0$$

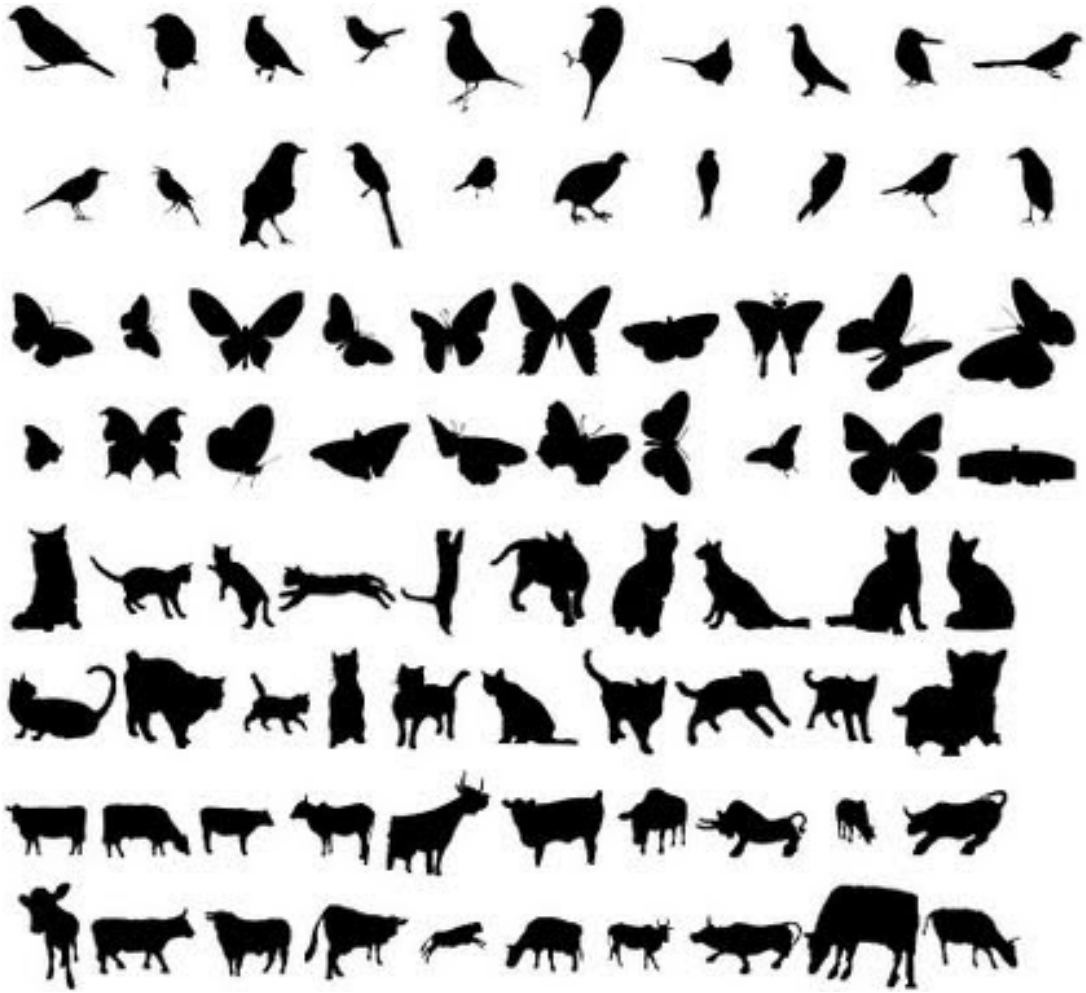




Shape Analysis

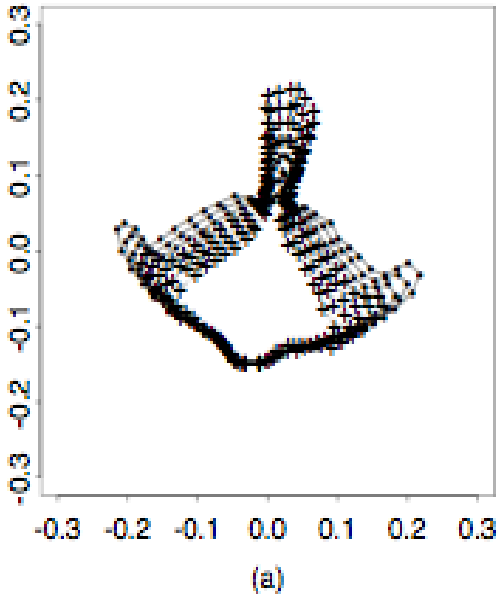
Differential Geometry
Statistical Shape Theory
Nonparametric Methods

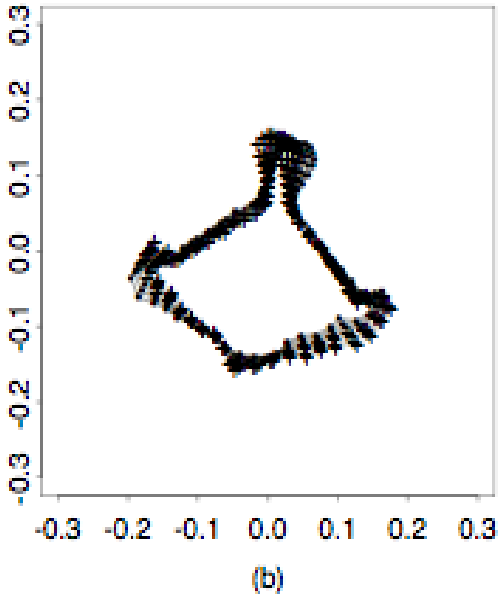
What is Shape?

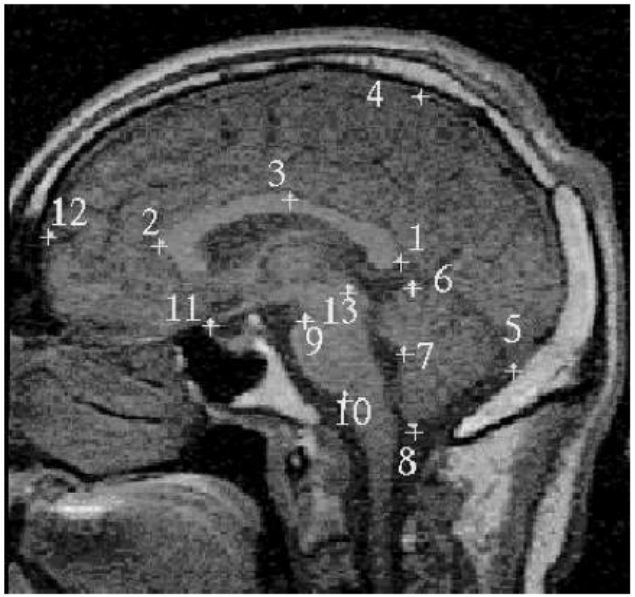


Kendall/Dryden & Mardia:

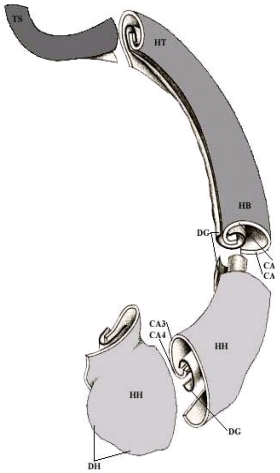
Shape is all the geometrical information that remains when location, scale and rotational effects are filtered out from an object.

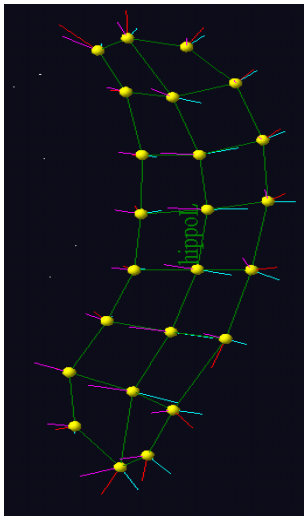


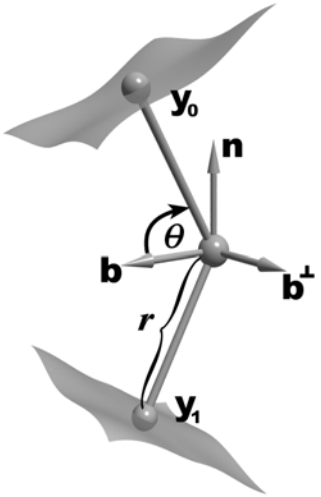




Medial Representation

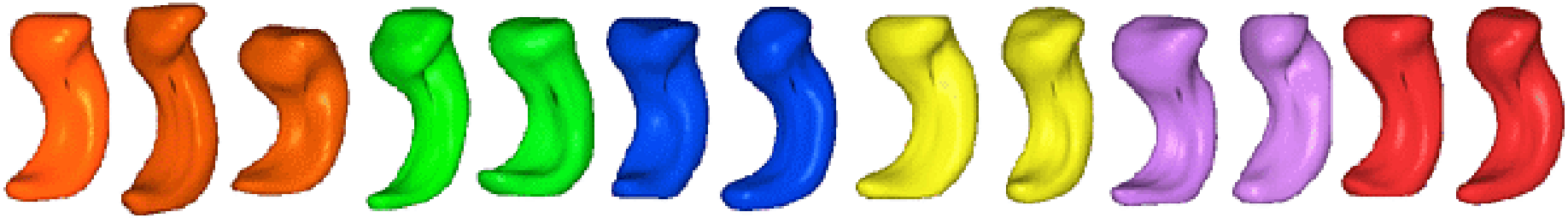


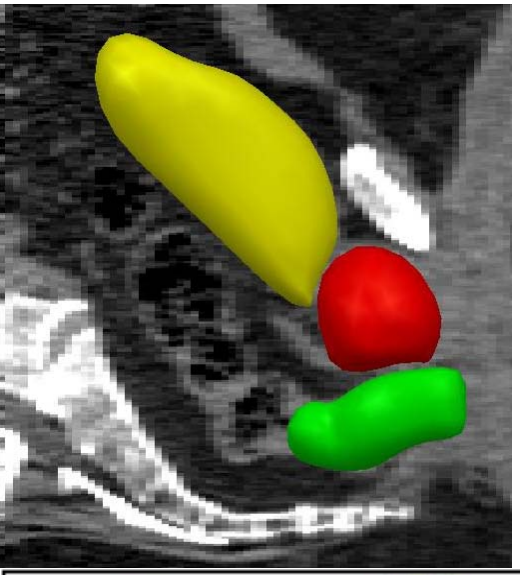


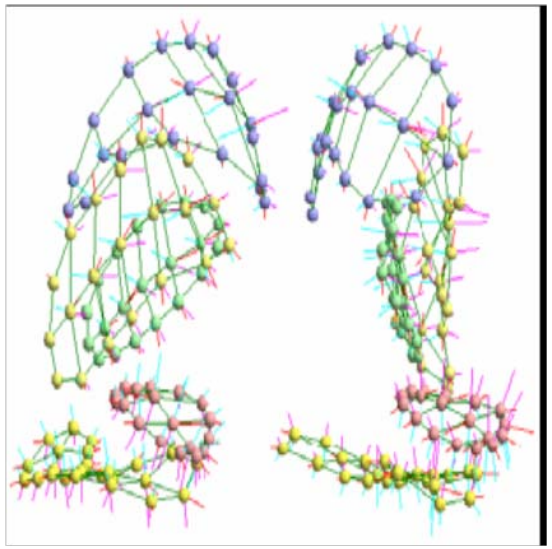


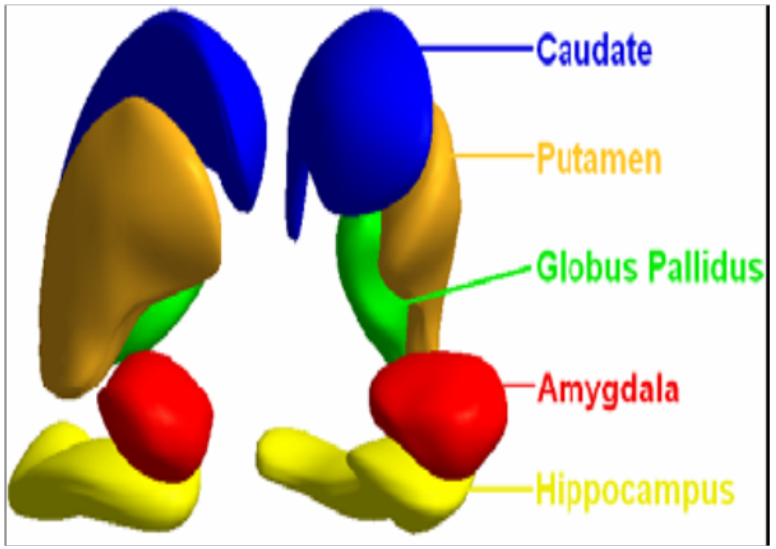
$$M(1)=(p,r,n_0,n_1)\in R^3\times R_+\times S(2)\times S(2)$$

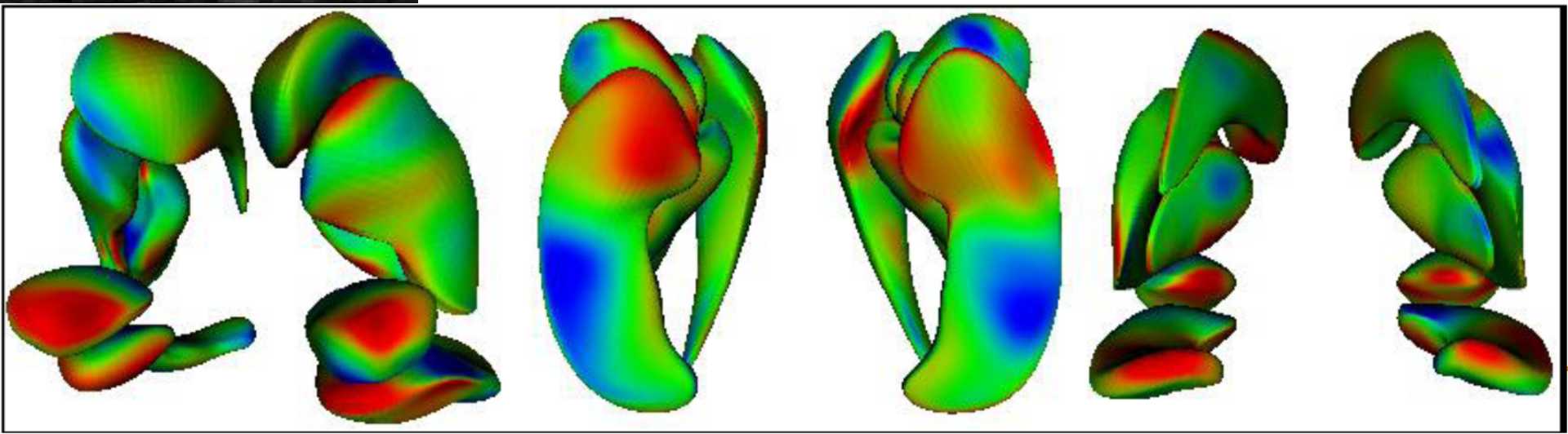
$$M(k)=\prod_{k=1}^{K}M(1)$$



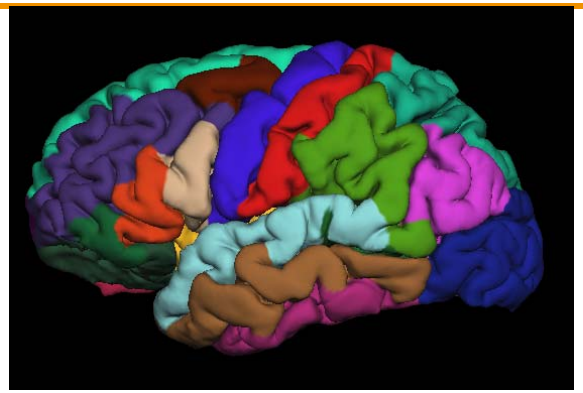




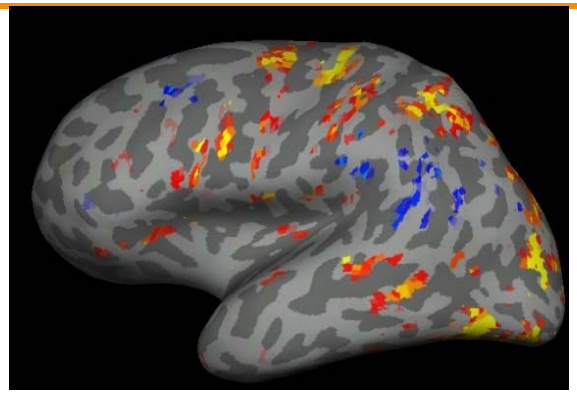

Caudate
Putamen
Globus Pallidus
Amygdala
Hippocampus



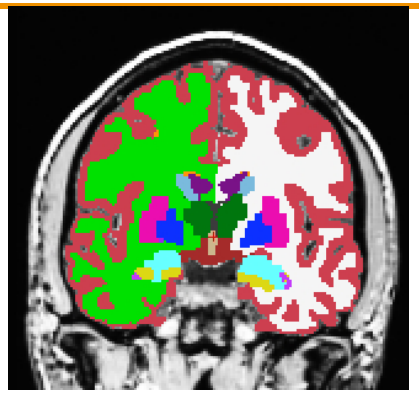
FreeSurfer



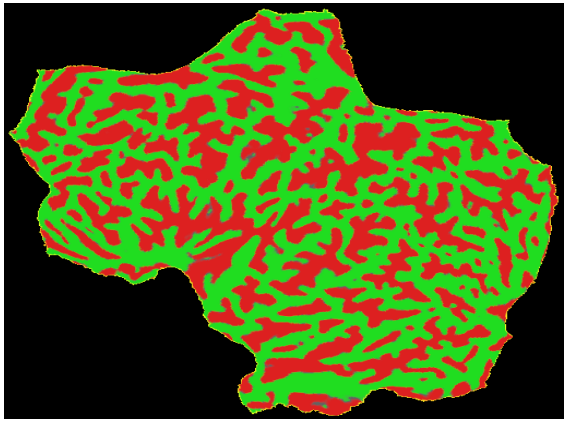
Cortical Reconstruction and Automatic Labeling



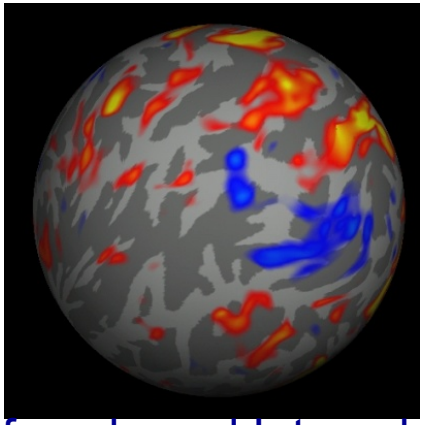
Inflation and Functional Mapping



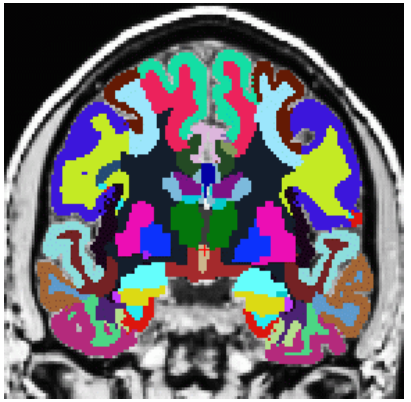
Automatic Subcortical Gray Matter Labeling



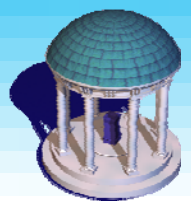
Surface Flattening



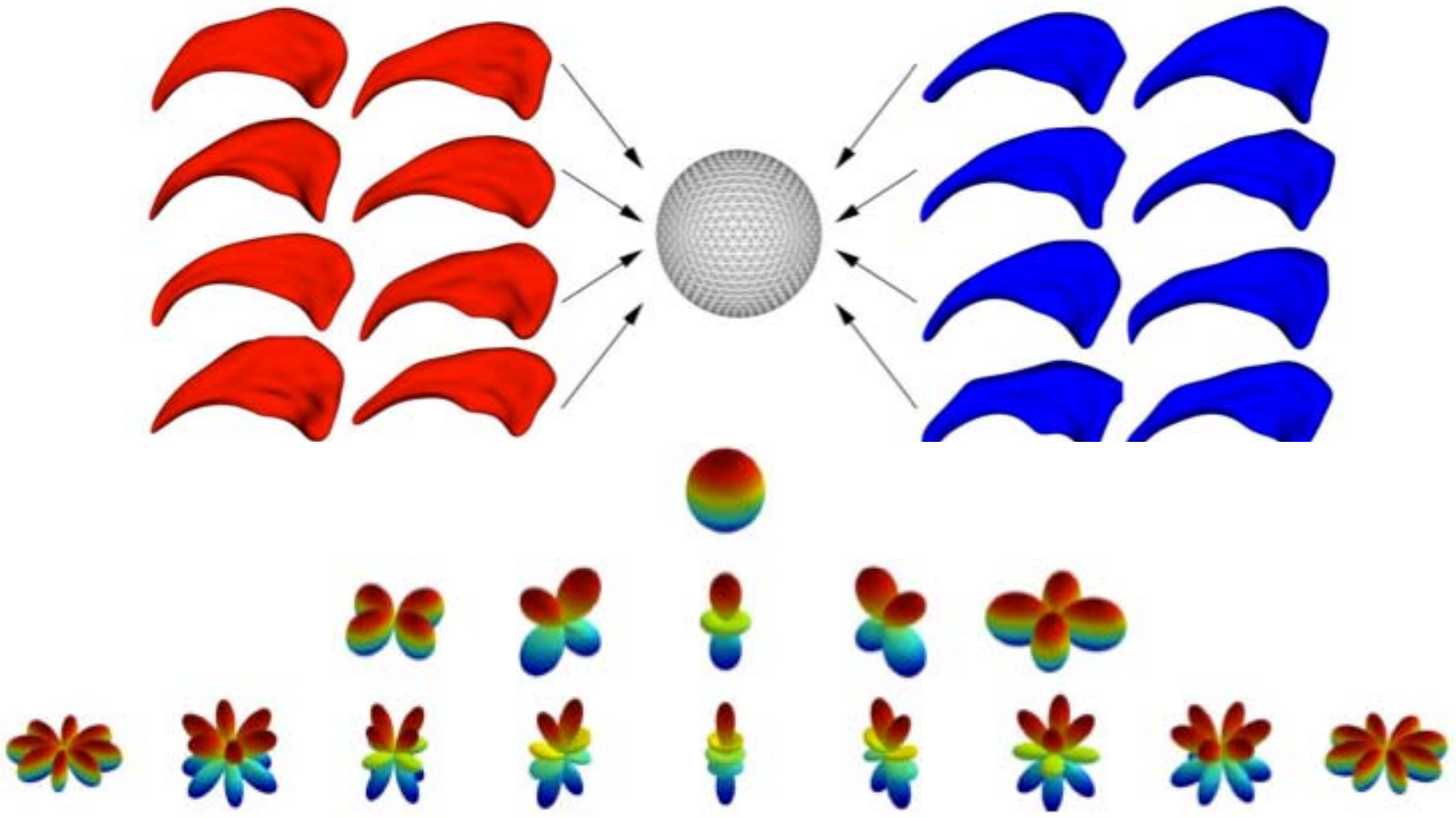
Surface-based Intersubject Alignment and Statistics

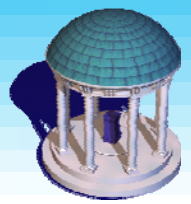


Automatic Gyral White Matter Labeling



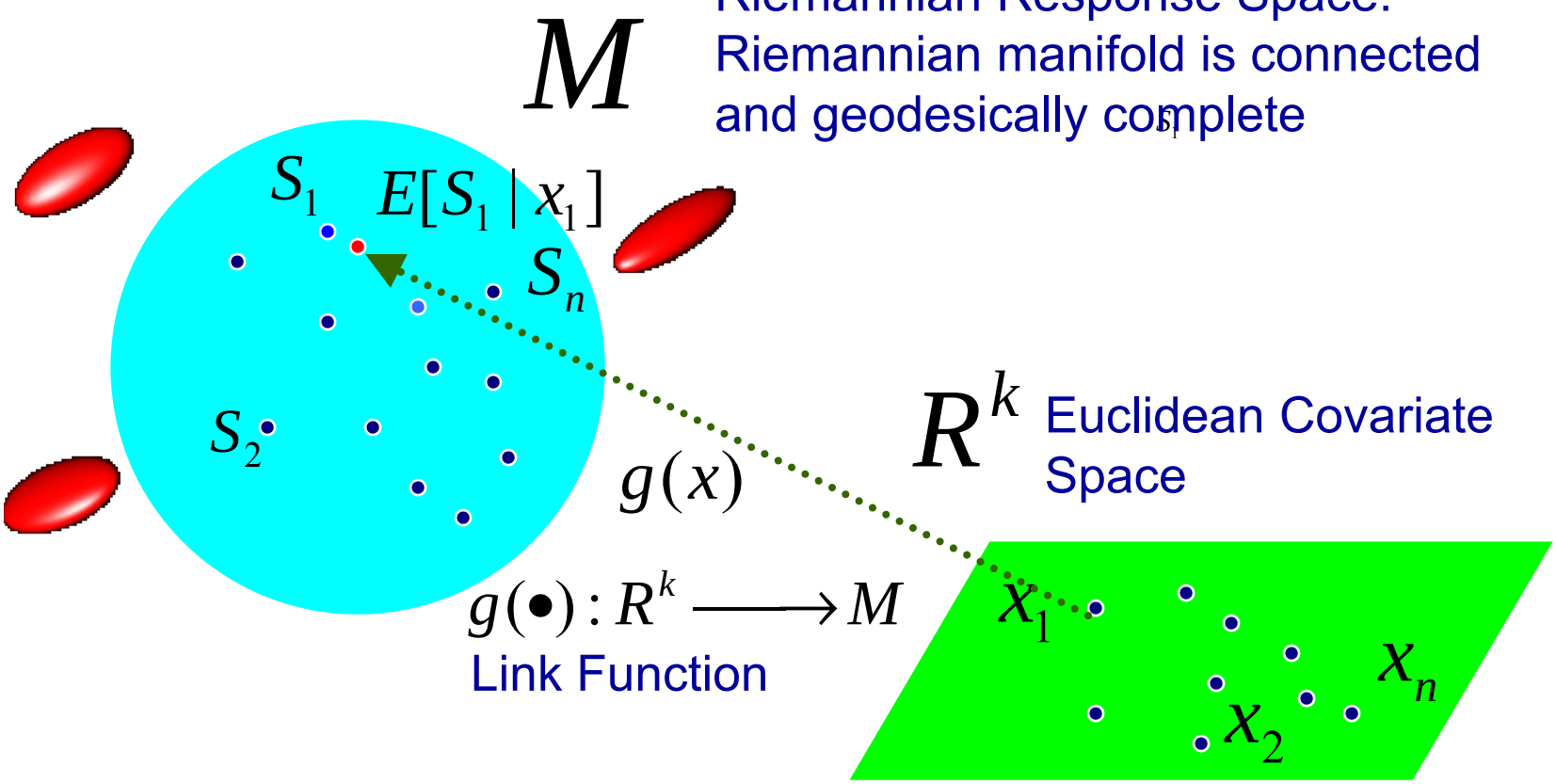
Shape Representation using Basis functions



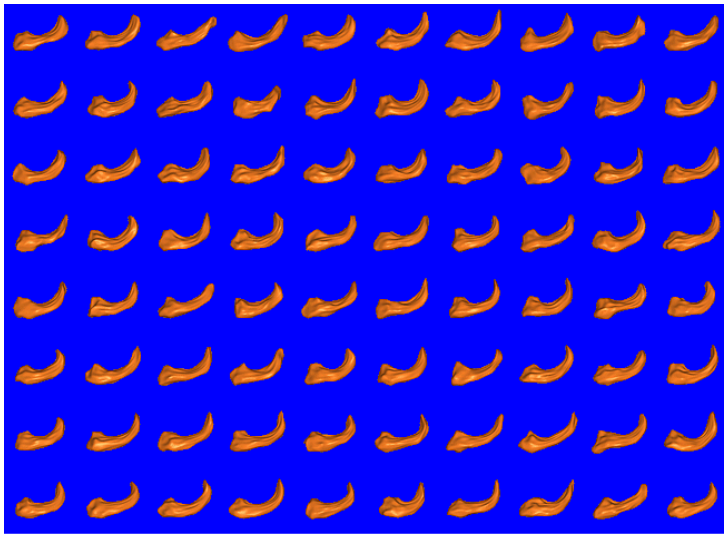


Manifold Data

Manifold-valued Data



Semiparametric and Nonparametric Regression for Manifold-valued Response from Cross-sectional, Longitudinal and Family-based Neuroimaging Studies



M

$$= g(x, \theta, f) \oplus \varepsilon$$

$$x \in R^k, \theta \in \Theta \subset R^p, f \in F$$

$$g : R^k \times R^p \times F \to M$$

Population Statistics

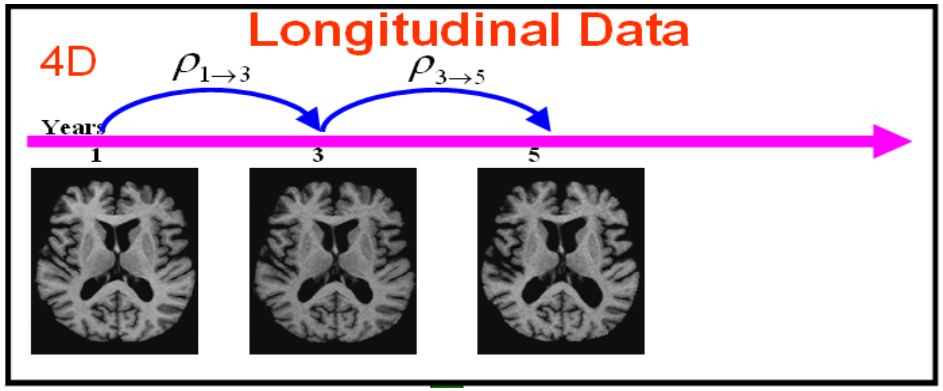
Regression Analysis
Longitudinal Data Analysis
Multivariate Data Analysis
Functional Data Analysis
Nonparametric Smoothing Methods

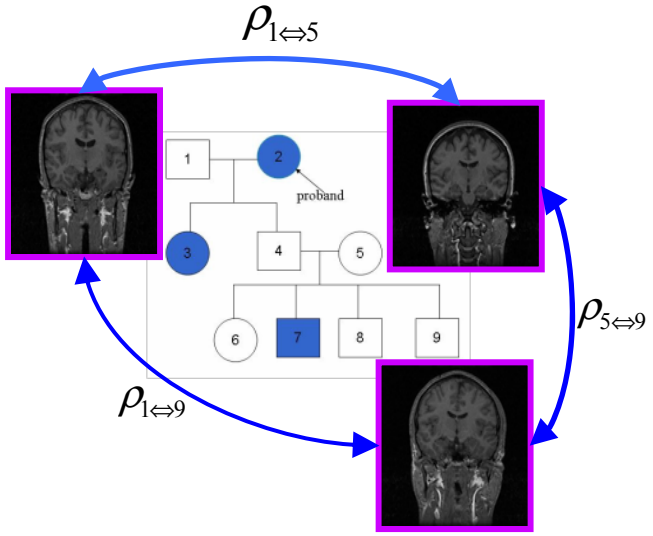
Complex Study Design:

cross-sectional studies;

clustered studies including

longitudinal and twin/familial studies;





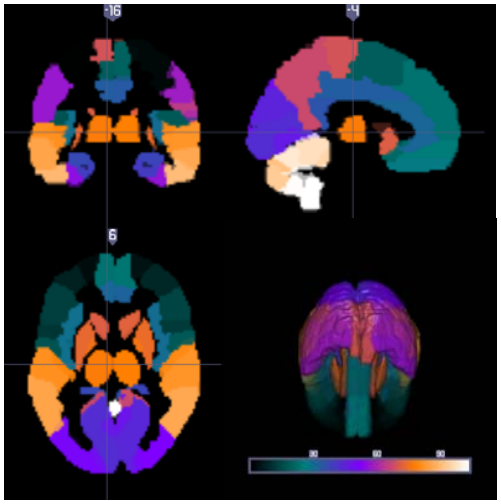
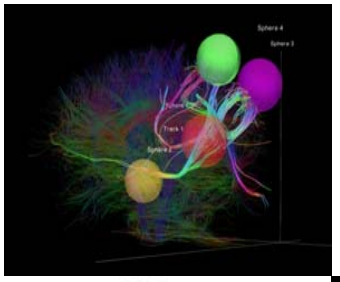
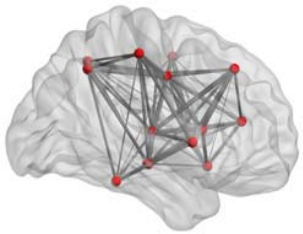
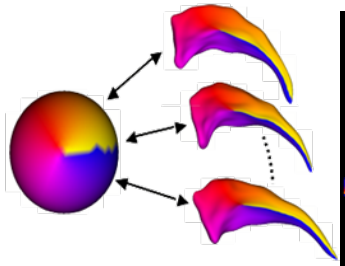
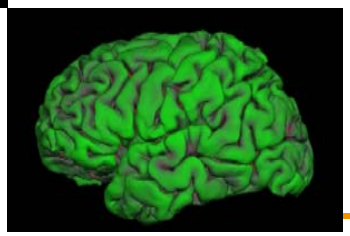
Complex Data Structure

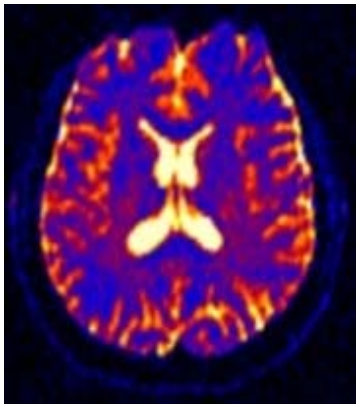
Multivariate Imaging Measures

Smoothed Functional Imaging Measures

Whole-brain Imaging Measures

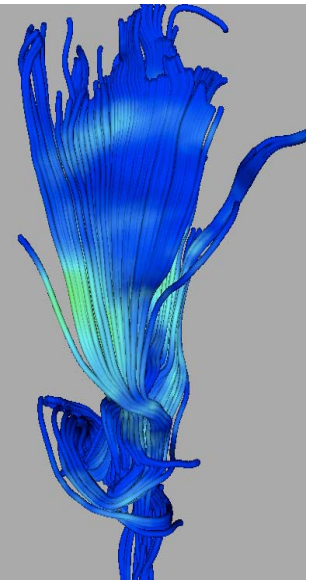
Time Series Imaging Measures

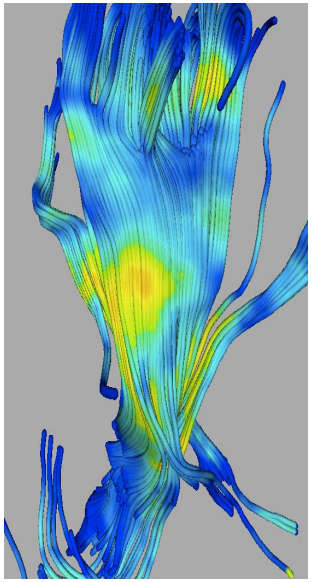


Functional Data

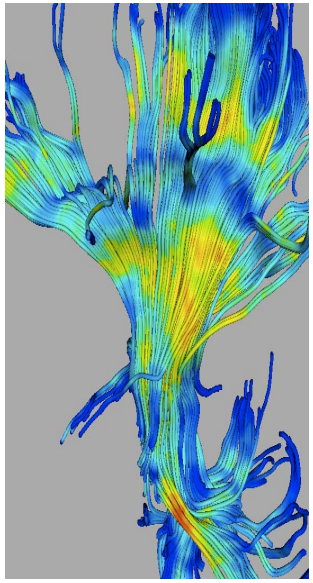
White Matter Maturation



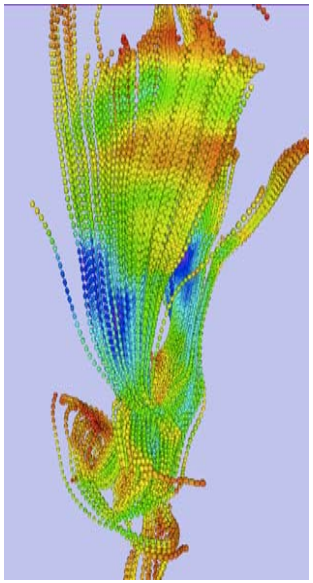
Week 2



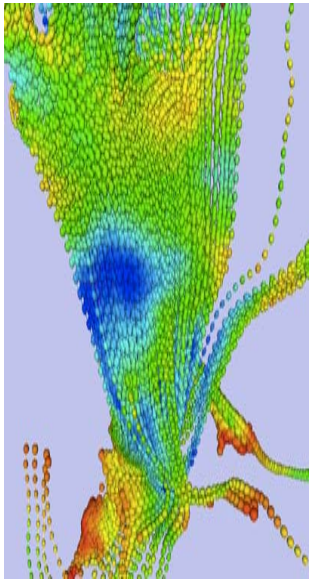
Year 1



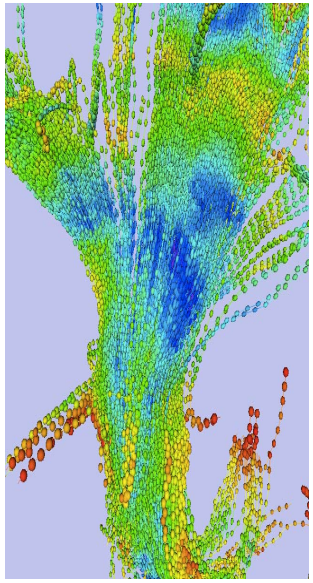
Year 2



Week 2

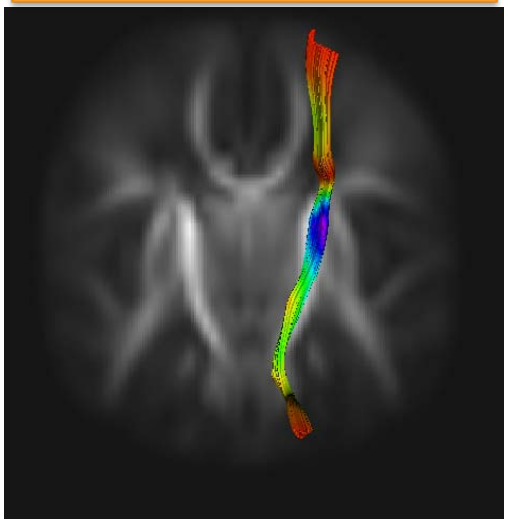


Year 1



Year 2

Sample Data



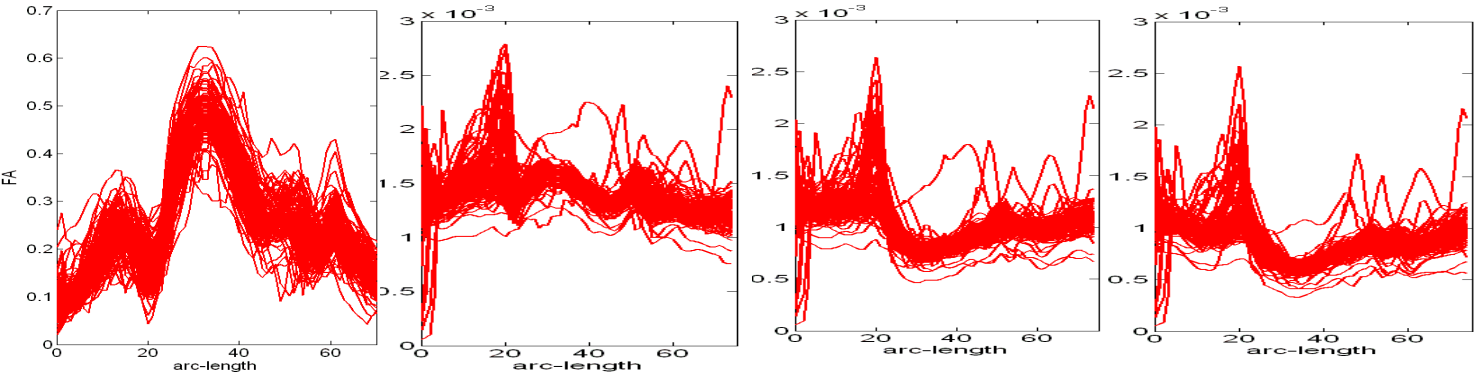
Right internal capsule: a collection of axons connecting the cerebral cortex and the brain stem

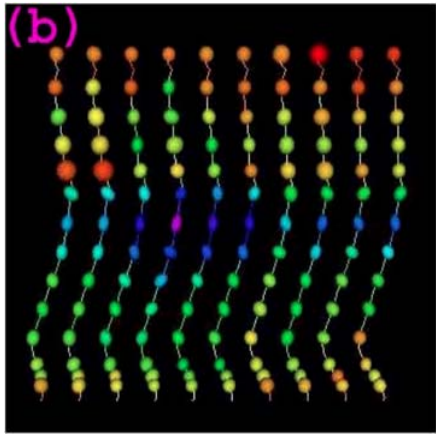
diffusion properties or diffusion tensors

$$Y_i(s_j) = (y_{i,1}(s_j), \cdots, y_{i,m}(s_j))^T$$

grids $\{s_1, \cdots, s_{n_G}\}$

covariates $x_1, \cdots, x_n$





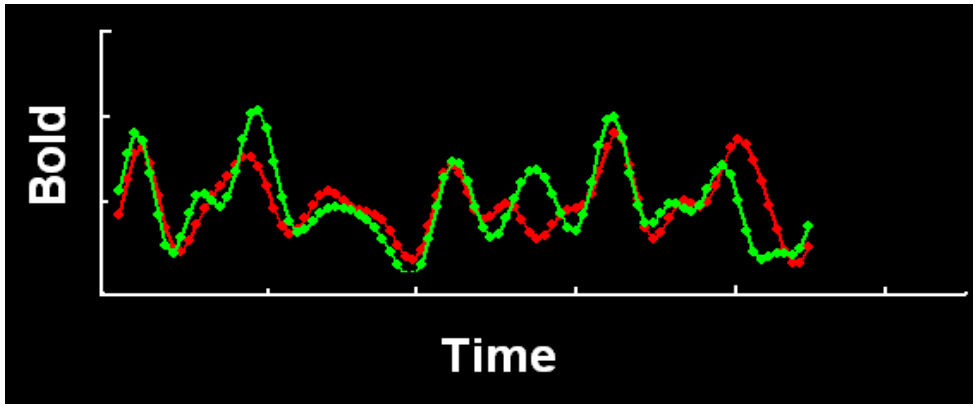
Functional Data

- Image-on-Image
  Image-on-Scalar
  Scalar-on-Image
- Functional Smoothness
- Spatial-temporal Covariance Operators
- Large Subject Heterogeneity
- Design-related Statistical Issues

Network Statistics

Random Graph Models

Functional Connectivity



is the mechanism for the coordination of activity between different neural assemblies in order to achieve a complex cognitive task or perceptual process. (Fingelkurts, Fingelkurts, Seppo Kahkonen, Fingelkurts, 2005)

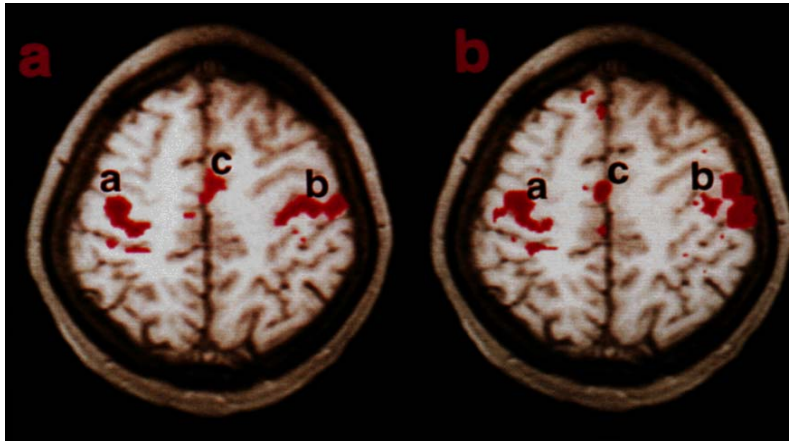
Resting-State Network

fMRI for finger tapping task;

fcMRI:

- **contralateral motor cortex showed activation and low frequency (<0.1 Hz) fluctuations in the signal of the resting brain, revealing a high degree of temporal correlation.**

fMRI fcMRI

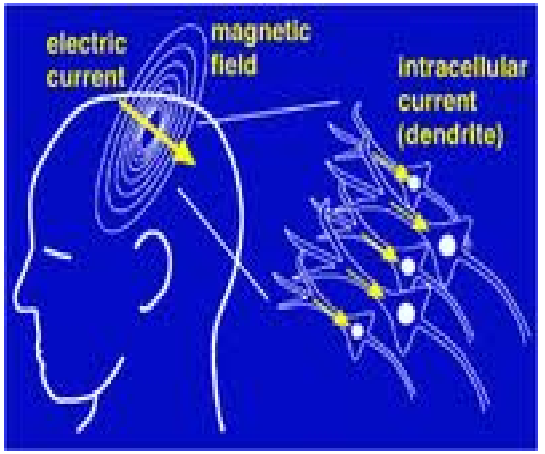


Biswal et al, JCBFM, 17:301-308, 1997

Functional Connectivity

Magnetoencephalography (**MEG**) is a technique for mapping brain activity by recording magnetic fields produced by electrical currents in the brain using very sensitive magnetometers.

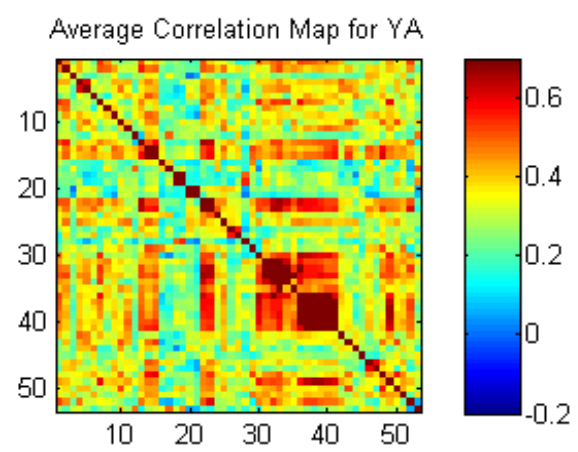
Electroencephalography (**EEG**) is the recording of electrical activity along the scalp. EEG measures voltage fluctuations resulting from ionic current flows within the neurons of the brain.

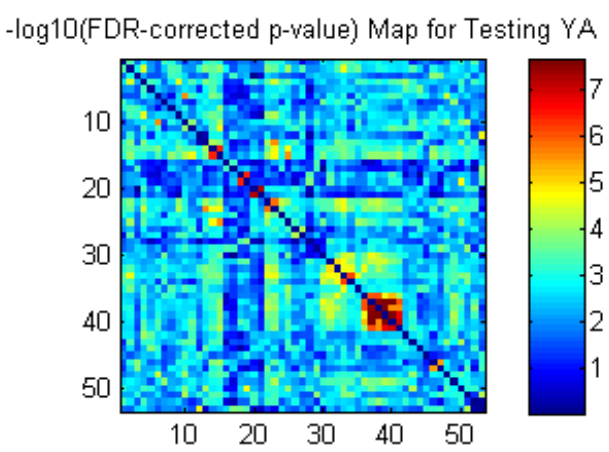


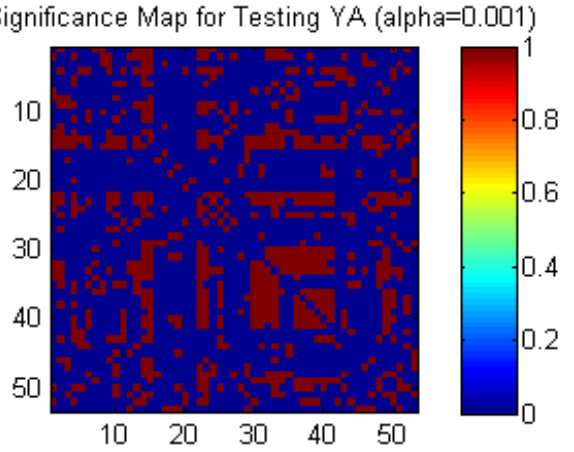
Functional Connectivity

- is to make inferences on the structure of relationships among brain regions and across groups or time.
- Interesting scientific questions include
  - ♦ "These ROIs form a network."
  - ♦ "ROIs are more connected during task A than B."
  - ♦ "Quantify the emergence and development of some brain networks."
  - ♦ "Connectivity pattern differs between groups A and B."

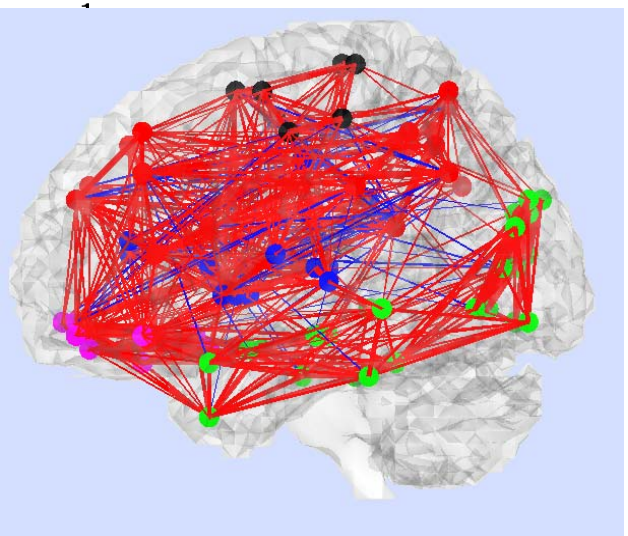
Standard Method

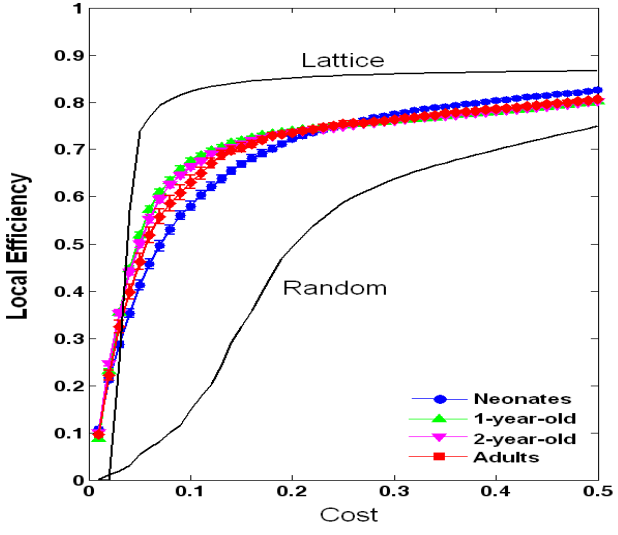


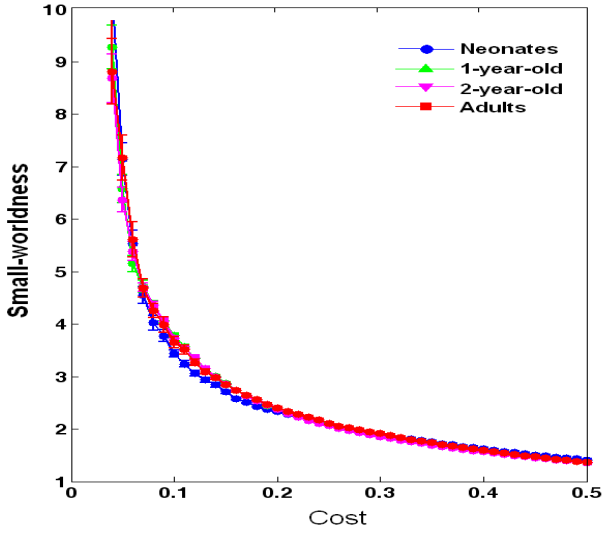




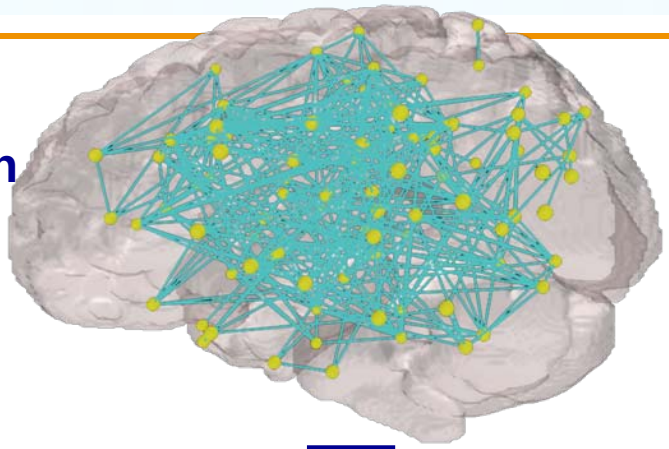
Graph







Weighted graph
Directed acyclic graph
Undirected graph



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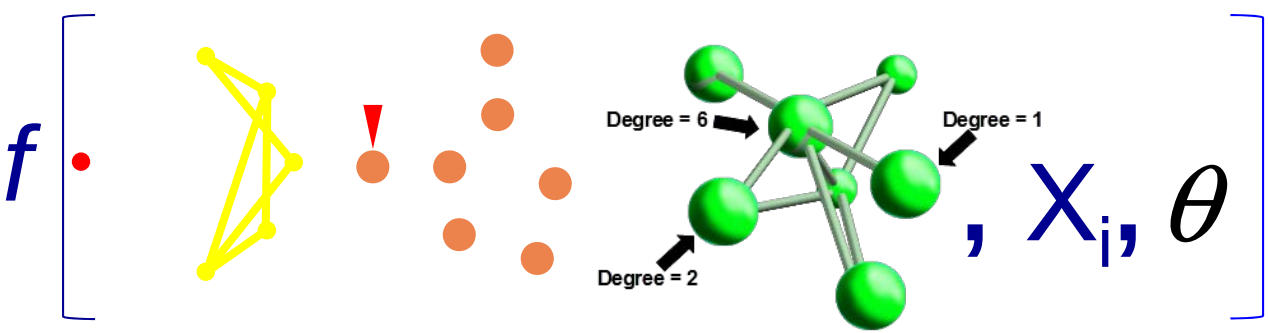
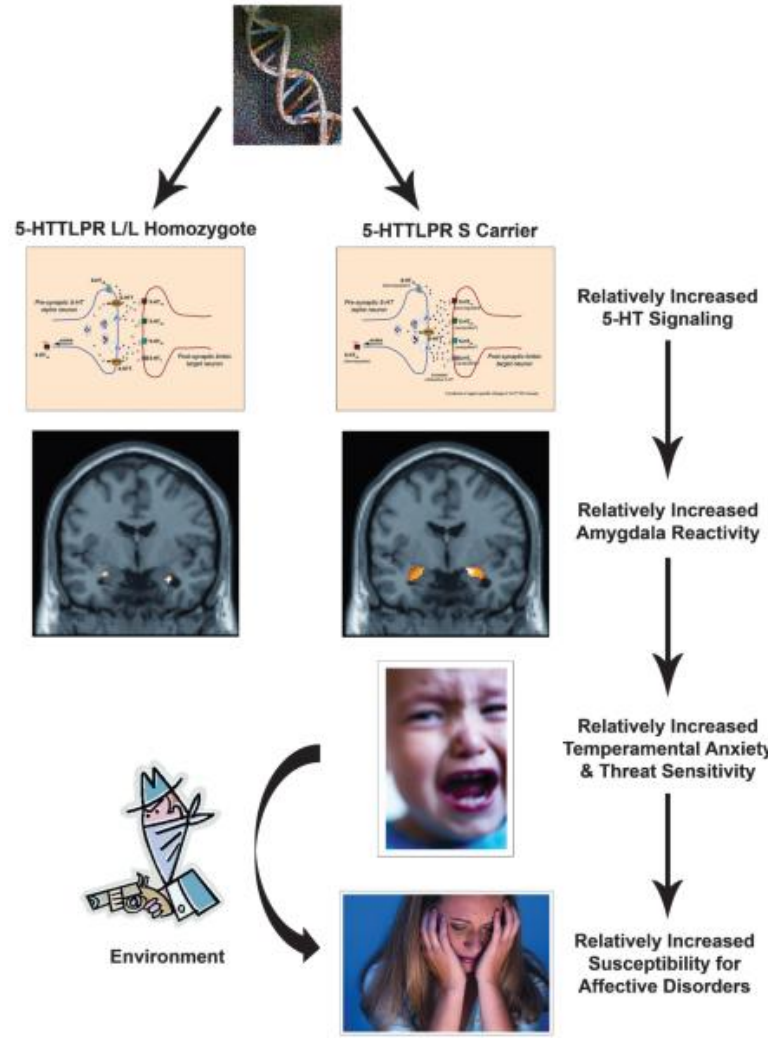


Imaging Genetics

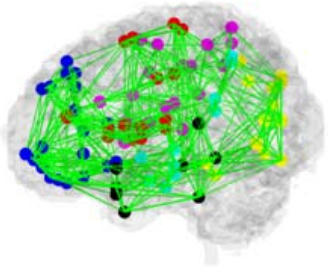
High-dimensional Problems
Causal Inference

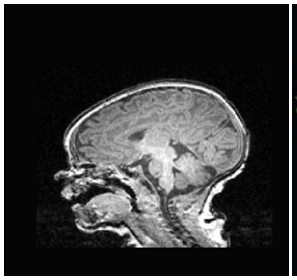


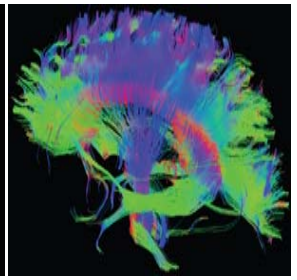
Imaging genetics allows for the identification of how common genetic polymorphisms influencing molecular processes (e.g., serotonin signaling), bias neural pathways (e.g., amygdala reactivity), mediating individual differences in complex behavioral processes (e.g., trait anxiety) related to disease risk in response to environmental adversity.

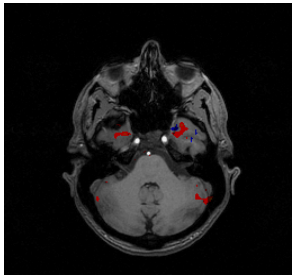
(Hariri AR, Holmes A.
Genetics of emotional regulation:
the role of the serotonin transporter in neural function.
Trends Cogn Sci. [10:182–191])

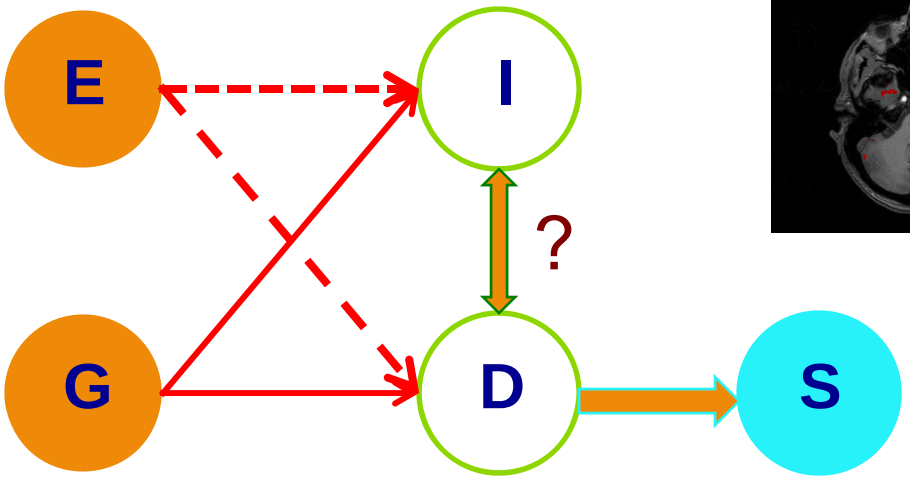
Directed Acyclic Graphs for Imaging Genetic Studies

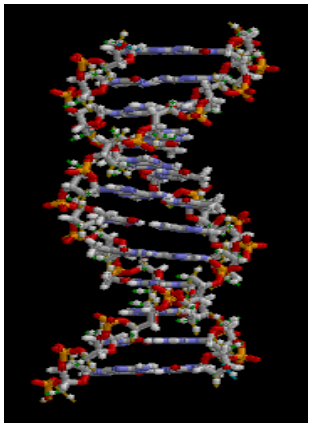


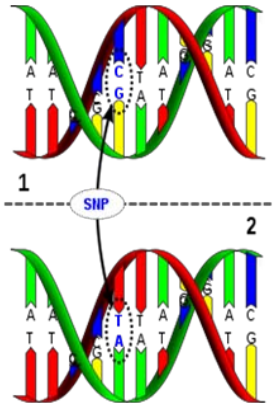






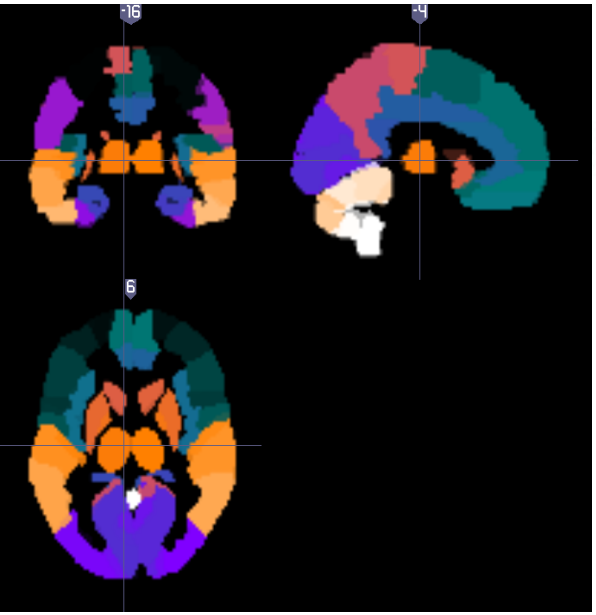


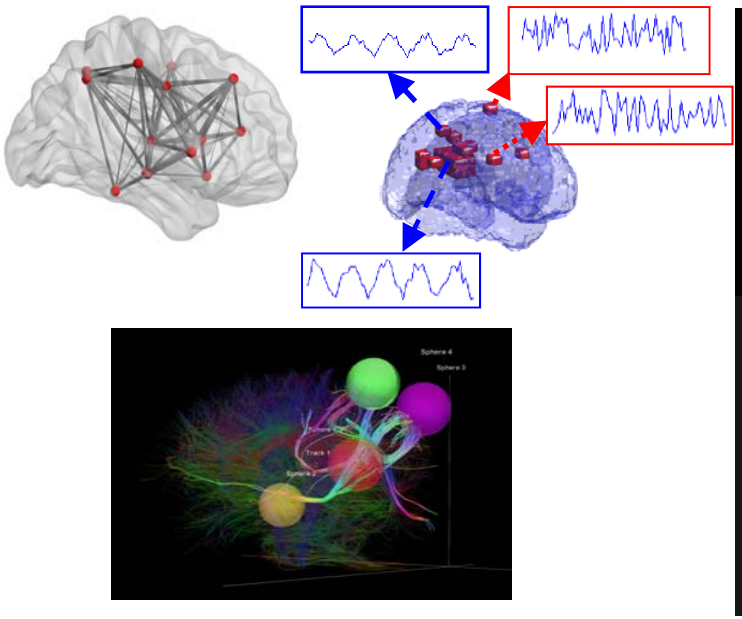


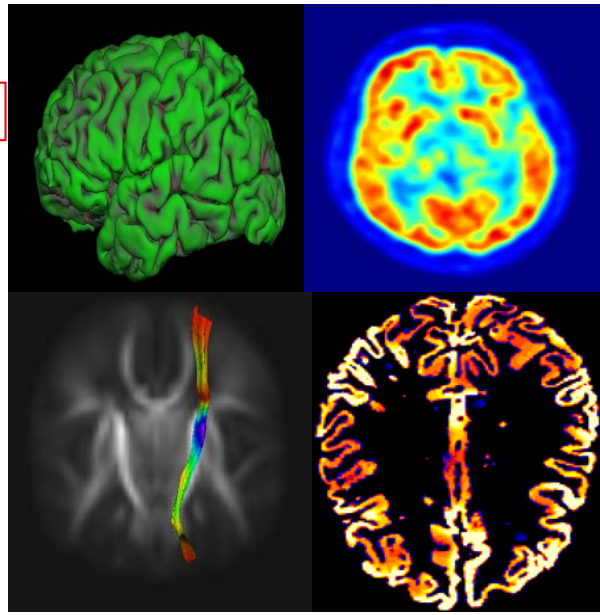


http://en.wikipedia.org/wiki/DNA_sequence

Neuroimaging Phenotype



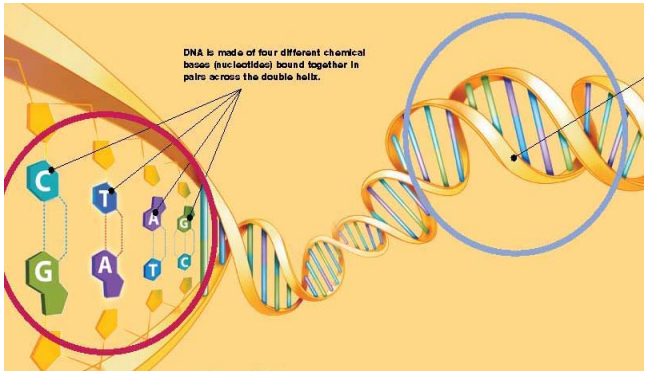


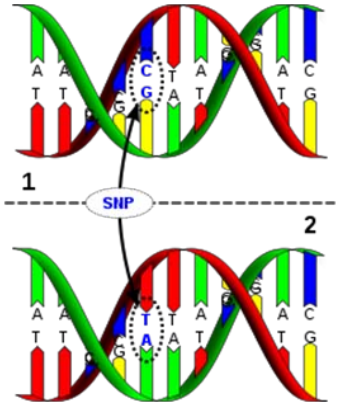


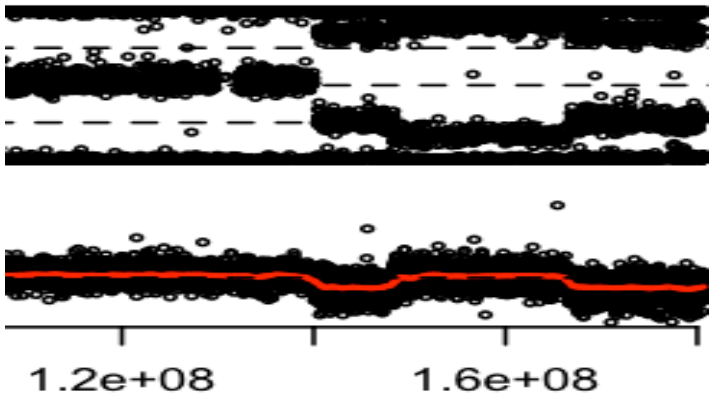
Multivariate, smoothed functions, and piecewisely smoothed functions

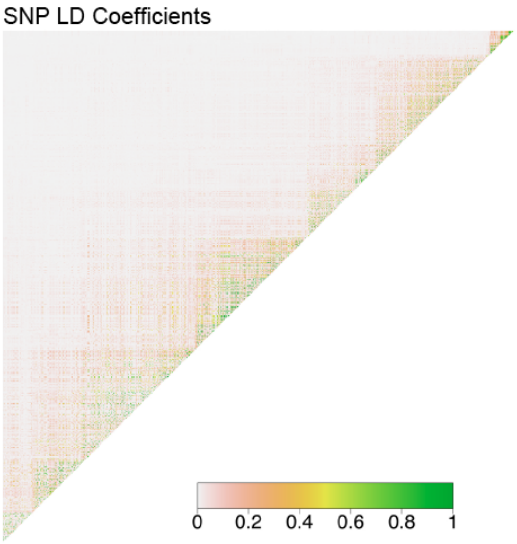
Dimension varies from 100~500,000.

Genetic Data

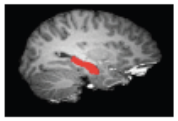
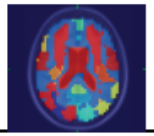
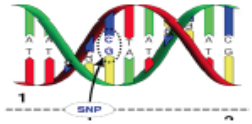
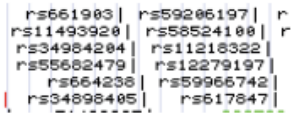
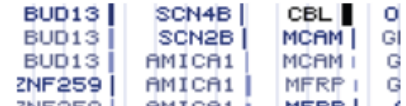




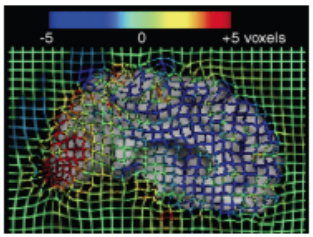




Imaging Genetics

Genetics \ Imaging	Candidate ROI 	Many ROI 	Voxelwise
Candidate SNP 	Imager	Imager	Imager
Candidate Gene	Geneticist		
Genome-wide SNP 	Geneticist		
Genome-wide Gene 	Geneticist		

Hibar, et al. HBM 2012



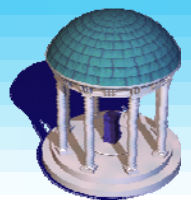
~1000 subjects

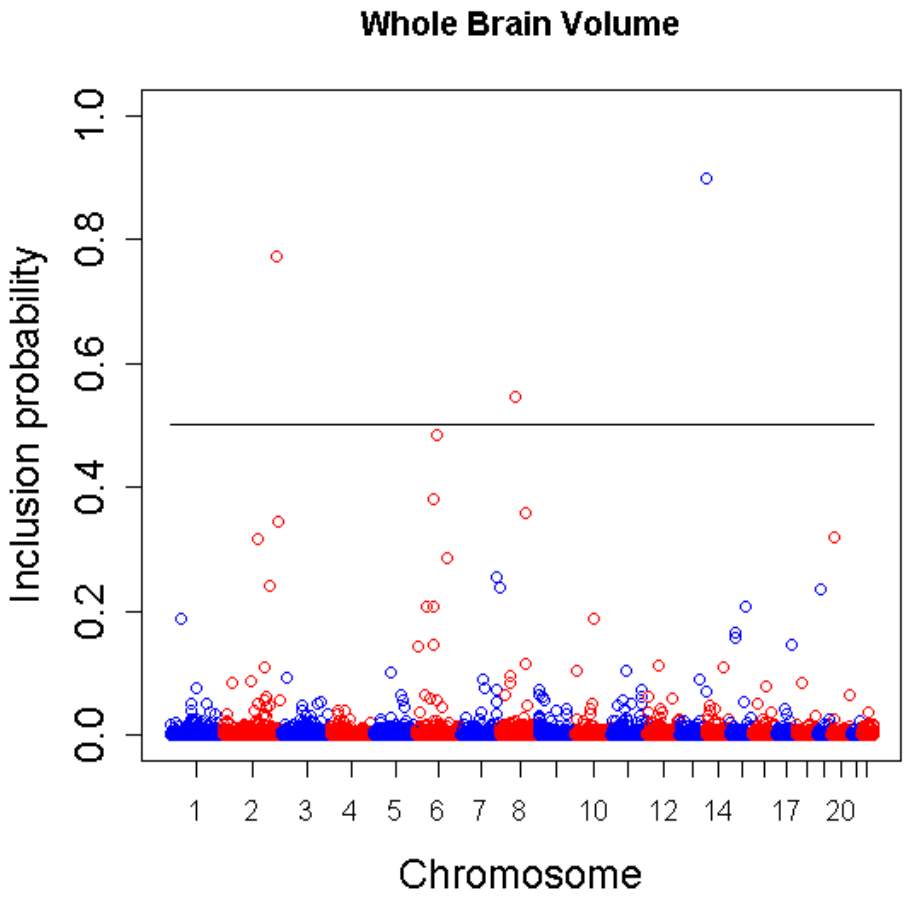
~30,000 voxels in the brain

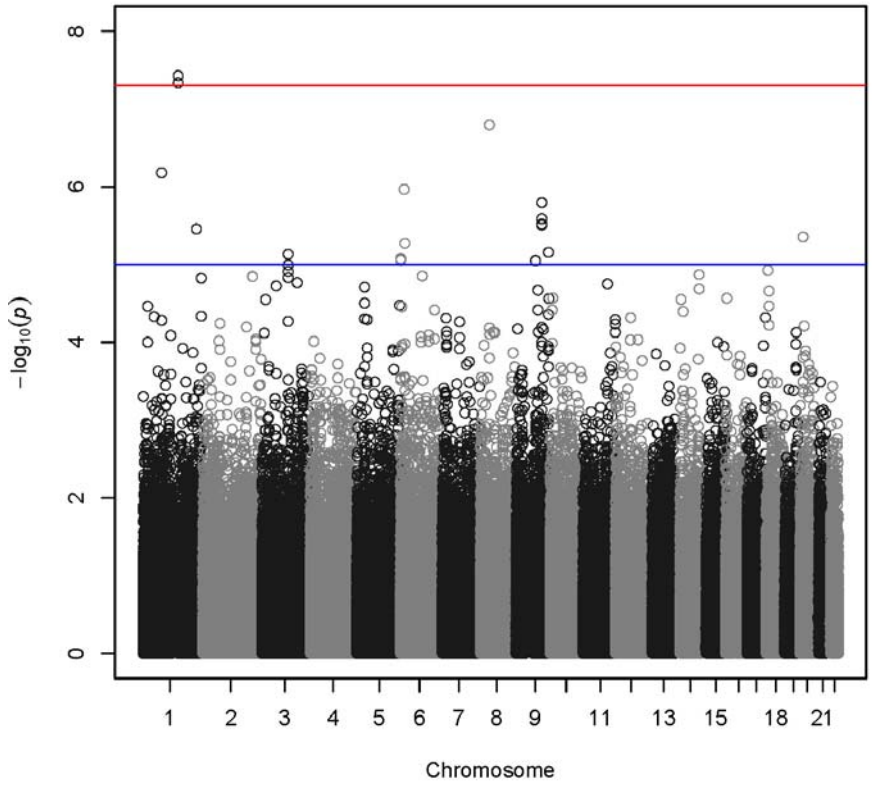
1.8×10^{10} tests!

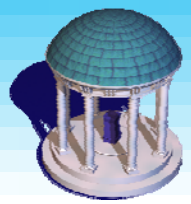
~600,000 genetic markers (SNPs)

Hibar, et al. HBM 2012




Whole Brain Volume
Inclusion probability
0.0
0.2
0.4
0.6
0.8
1.0
1
2
3
4
5
6
7
8
10
12
14
17
20
Chromosome


$-\log_{10}(p)$
0
2
4
6
8
1
2
3
4
5
6
7
8
9
11
13
15
18
21
Chromosome



Acknowledgement:

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