ISMRM Tutorial, Montreal 2011
Computational Anatomy for Subcortical Population Brain Analysis at 1mm resolution

http://www.cis.jhu.edu/education/tutorials.php

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Outline

• Bijective correspondence: Populations studied via 1-1 mappings to atlas coordinates (LDDMM)
• Atlas’s: Individual and Population
• Statistics: Gaussian Random Fields
• Representation in anatomical coordinates: PCA and surface harmonics
• P-values, clustering, LDA in diseased cohorts
• Ma, Miller, Trouve, Younes, Template Estimation via EM Algorithm, Neuroimage, 2008.
• Miller, Trouve, Younes, On the Metrics and Euler Lagrange Equations of Computational Anatomy, Annual Review of Biomedical Engineering, 2002
• Smith, Wang, Cronenwett, Mamah, Barch, Csernansky (2011) Thalamic morphology in schizophrenia and schizoaffective disorder. J. Psychiatric Research, 45: 378-385
• Vaillant, Miller, Trouve, Younes, Neuroimage 2005
Computational Functional Anatomy is the study of structure and function response variables in populations.

Populations are studied via statistics in the template coordinate systems.

Bijective correspondences are used to carry information from one coordinate system to another - we call these bijections diffeomorphisms.
Populations often involve many modalities: B0, FA, T1, T2, Segmentations,…

**Atlas:** Electronic form of anatomical knowledge

Bijective correspondence via diffeomorphic mapping

**Patient data**
Bijective mapping goes forwards and backwards.

Subject Space

- Gray matter analysis
- White matter
- CSF
- Superimposed in the original Image
- Segmentation

Original Image

- Atlas-based analysis
- Image linearly normalized by LDDMM
- Image normalized by LDDMM

Single Subject Template

Atlas

Atlas-based analysis

Bijective mapping goes forwards and backwards.
The current state of the art structural validity for subcortical structures in 1mm scale MRI.
Kappa $\sim 0.8$ Overlap of Subcortical Structures
Blue=LDDMM
Volume Bias ~10%
Blue=LDDMM
Populations are studied via templates with statistics encoded in template coordinates.
Templates encode populations via bijections.
Bijective correspondences are generated via large deformation metric mapping (LDDMM) which are flows of the Euler-Lagrange equations.

-bijection is generalization of translations, rotations, scales to infinite dimensions
Bijections are computed via Euler-Lagrange flow equations.

Lagrangian \[ \dot{\varphi}_t(x) = \nu_t(\varphi_t(x)), \varphi_0 = id \]

Eulerian \[ \dot{\varphi}^{-1}_t(x) = -D\varphi^{-1}_t(x)\nu_t(x), \varphi_0^{-1} = id \]

\[ D = \text{Jacobian matrix} \begin{pmatrix} \frac{\delta \nu_i}{\delta x_j} \end{pmatrix} \]
\[
\dot{\phi}_t(x) = v_t(\phi_t(x))
\]
The Euler-Lagrange equations are used to constrain the generation of bijections because they support large – high dimensional - deformations which carry structures consistently:

- subvolumes to connected subvolumes
- surfaces to surfaces
- sulcal curves to sulcal curves
Bijective Euler-Lagrange Flows (Diffeomorphisms)

No Euler equation flow  Euler equation flow
Simple example of large deformations in human anatomy

Closed lateral ventricles

Expanded lateral ventricles
Bijective Mapping Available via MRIStudio
www.mristudio.org

Registered MRIStudio Users

Cumulative

Yearly

LDDMM calls monthly

Jan 2010
Feb
Mar
Apr
May
Jun
July
Aug
Sep
Oct
Nov
Dec
Jan 2011
Individual Templates and Population Templates
• Full segmentation (200 structures)
• Stereotaxic (MNI and Talairach)
• Gray / white matter assignment
• Modern Brodmann’s map
• Population-averaged tract coordinates

JHU-MNI Atlas
www.mristudio.org
Building Population Atlases

Population Atlas
Population based template generation via EM Algorithm

The template to be estimated is an unknown deformation of an anatomy in the “center” of a collection of human anatomies - indistinguishable from other anatomical configurations - not an arithmetic average.

The complete data are the deformations generating the (unknown) template mapping to the population data.

• E-step: generates the conditional mean deformations given the previous iterate template-old and the observed MRI imagery.

• M-step: generates template-new maximizing the complete-data posterior distribution with respect to the unknown deformation of template-old.
EM Algorithm - Iteration 1

\[ I^1_{temp} \rightarrow M^1_0 \rightarrow I^0 \]
EM Algorithm: Iteration $n$
EM Algorithm: Convergence

$I_{\text{temp}}^\infty\rightarrow M_0^\infty\rightarrow I^0$
LDDMM Subcortical Atlas: An Example

https://caportal.cis.jhu.edu/pipelines/atlases/human

The atlas was built based on the manually labeled image volumes of 41 subjects using large deformation diffeomorphic metric template mapping algorithm. The population includes 10 young adults, 10 middle age adults, 10 healthy elders, and 11 Alzheimer’s patients.
Statistics for Populations
Statistics

Statistics are computed using Gaussian random fields on the response variables and complete orthonormal bases indexed over the anatomical coordinates.
Statistics are studied as pairs \((F, M)\) of function \(F\) on manifolds \(M\):

\[
(F, M) \quad \text{Hilbert Space } \quad H(M)
\]

with a \(\text{CON}\) base.

- Statistics performed in the coordinates of \(M\)

- Statistics via GRF models in \(H(M)\)

\[
F = \sum_k F_k \phi_k
\]

structure-function Laplace-Beltrami or response-variables PCA CON Basis
Statistics are obtained via template injection onto the targets. The bijection encodes in template coordinates the target shapes.
PREDICT STUDY: template structures carry a set of response variables and surface expansion functions.

\[ F = \sum_{k} F_k \phi_k \]

Five expansion functions on the template.

A response variable \( F_k \) can be generated by taking the Jacobian determinant of the template bijection onto the target and projecting onto the basis.
The Atlas to Target Statistical Pipeline

Putamen Template Injected into Targets

Shape Encoded on Template Surface Structures via Random Field Models

\[ F = \sum_{k} F_k \]

Structure-function response-variables

Laplace-Beltrami or PCA Basis
The Atlas to Target Statistical Pipeline

Caudate Template Injected into Targets

Shape Encoded on Template Surface Structures via Random Field Models

\[ F = \sum_{k} F_k \]

structure-function
response-variables

Laplace-Beltrami or PCA Basis

MRI Target

Caudate

Template

Mismatched colors in the brain diagram represent different regions such as caudate, hippocampus, pallidus, putamen, thalamus, and ventricle.
The PREDICT Study: An Example of Subcortical Shape Analysis

Human striatal studies of HD patients

Younes, Paulsen, Ross, et. All., Heterogeneous atrophy of subcortical structures in prodromal HD as revealed by statistical shape analysis, submitted.
Curved Coordinate System Representations via an Orthonormal Basis

PCA and Surface Harmonics

\[ F = \sum_{k} F_k \phi_k \]

- \( F_k \): response-variables
- \( \phi_k \): structure-function or Laplace-Beltrami or PCA Basis
PCA, one orthonormal base in Anatomical Coordinates
Principle Components are an orthonormal basis which can be used, requiring training data.

\[ F = \sum_{k} F_k \quad \text{response-variables} \quad \text{PCA Basis} \]

PCA mode 1
PCA mode 2
PCA mode 3
Laplace-Beltrami, another orthonormal base in anatomical coordinates not requiring training data (generalization of the Fourier basis)
Complete orthonormal bases via harmonics of the Laplacian operator; like the Fourier basis no training data required.

**Spherical Harmonics:**
**one example**
**Laplace-Beltrami basis for the sphere.**
\[ F = \sum_{k} F_k \]

response-variables

Laplace-Beltrami
\[ F = \sum_{k} F_k \]

\[ \phi_k \]

response-variables

Laplace-Beltrami
Laplace-Beltrami Orthonormal Base

\[ F = \sum_{k} F_k \phi_k \]
Laplace-Beltrami Surface Basis

\[ F = \sum_{k} F_k \phi_k \]

response-variables Laplace-Beltrami
Atrophy patterns: PREDICT

Rank sum tests thresholded at 5% family-wise significance (significant regions in red)

Younes, Paulsen, Ross, et. All., Heterogeneous atrophy of subcortical structures in prodromal HD as revealed by statistical shape analysis, submitted.
Atrophy pattern: Left Putamen

Two views of the atrophy pattern estimated on the left putamen

Younes, Paulsen, Ross, et. All., Heterogeneous atrophy of subcortical structures in prodromal HD as revealed by statistical shape analysis, submitted.
Atrophy pattern: Right Putamen

Two views of the atrophy pattern estimated on the right putamen

Younes, Paulsen, Ross, et. All., Heterogeneous atrophy of subcortical structures in prodromal HD as revealed by statistical shape analysis, submitted.
Atrophy Pattern: Left Caudate

Two views of the atrophy pattern estimated on the left caudate

Younes, Paulsen, Ross, et al., Heterogeneous atrophy of subcortical structures in prodromal HD as revealed by statistical shape analysis, submitted.
Atrophy Pattern: Right Caudate

Two views of the atrophy pattern estimated on the right caudate

Younes, Paulsen, Ross, et. All., Heterogeneous atrophy of subcortical structures in prodromal HD as revealed by statistical shape analysis, submitted.
Clustering
Clustering Based on Significant Discriminating Features

\[ F = \sum_{k} F_k \phi_k \]
Statistical Significance
## P-values

<table>
<thead>
<tr>
<th></th>
<th>Left putamen</th>
<th>Right putamen</th>
<th>Left Caudate</th>
<th>Right Caudate</th>
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<tbody>
<tr>
<td>Volume</td>
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<td>Jacobian</td>
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<td>.0001</td>
<td>0.011</td>
<td>.0015</td>
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<tr>
<td>Jacobian centered</td>
<td>.0011</td>
<td>.0003</td>
<td>.0014</td>
<td>.043</td>
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<td>Tangential atrophy</td>
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<td>0.0001</td>
<td>0.0024</td>
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<tr>
<td>Jacobian on harmonics</td>
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<td>.0001</td>
<td>&lt;.0001</td>
<td>.035</td>
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<td>PCA on momentum</td>
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<td>.001</td>
<td>.0034</td>
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<td>PCA on jacobian</td>
<td>.0004</td>
<td>&lt;.0001</td>
<td>.0012</td>
<td>.0013</td>
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</tbody>
</table>

p-value accuracy: .0001

Younes, Paulsen, Ross, et. All., Heterogeneous atrophy of subcortical structures in prodromal HD as revealed by statistical shape analysis, submitted.
The Locality of Shape Change in ADHD
ADHD: Basal Ganglia Shape Analysis

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>gender</th>
<th>Age(SD)</th>
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<td>CON</td>
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Basal Ganglia Template

Reconstructions in statistically significant Eigenfunctions p<.05

Subcortical Shape Analysis in Dementia

<table>
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<th>N</th>
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<th>age (mean ± SD)</th>
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<td>AD</td>
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Reconstructions in statistically significant p<.05

The End