Computational Anatomy: Simple Statistics on Interesting Spaces

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Computation Anatomy

- Precise *Computational* study of *Anatomical* Variability.
- First attempts to bring mathematical insight were made by D'Arcy Wentworth Thompson (1860-1948)

"In a very large part of morphology, our essential task lies in the comparison of related forms rather than precise definition of each; and the deformation of a complicated figure may be a phenomenon of easy comprehension though the figure itself have to be left unanalyzed and undefined" ---1917 D. W. Thompson: "On Growth and Form"

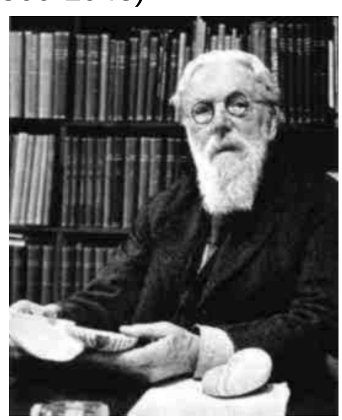
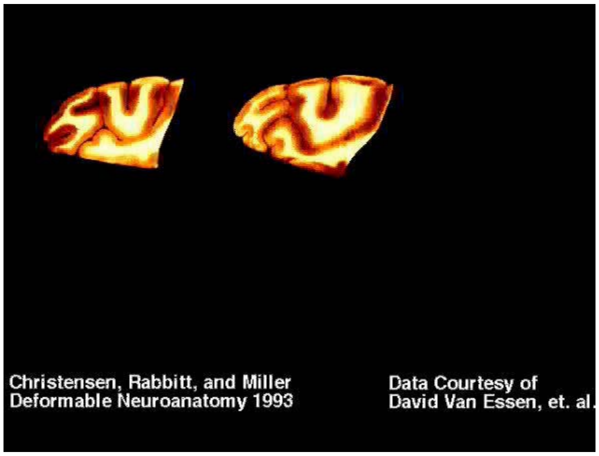
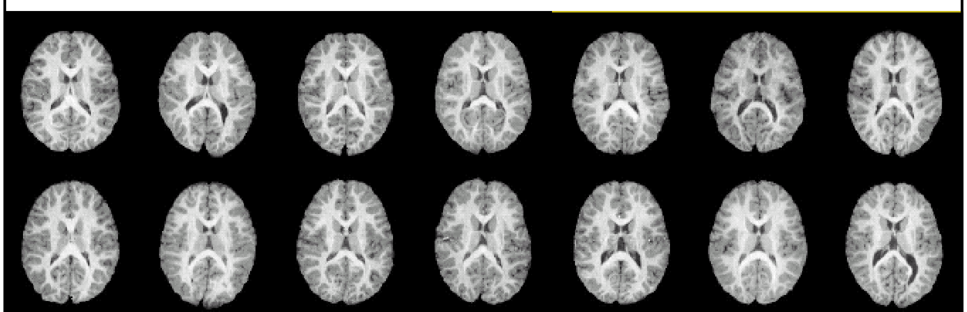


Image Understanding Via Computational Anatomy



•Deformable Image Registration. Map a family of images to a single Template Image

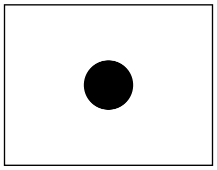
Motivation:A Natural Question

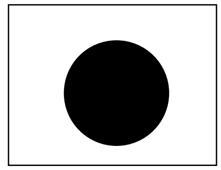


- Given a collection of Anatomical Images what is the Image of the “Average Anatomy”

Motivation: A Natural Question

Consider two simple images of circles:

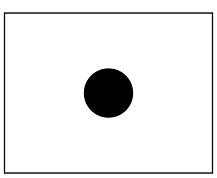


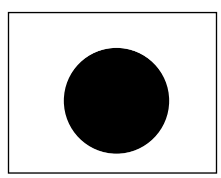


What is the Average?

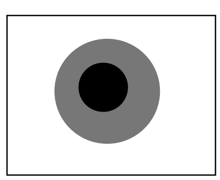
Motivation: A Natural Question

Consider two simple images of circles:



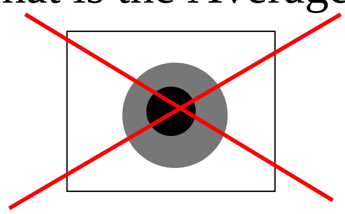


What is the Average?



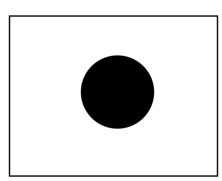
Motivation: A Natural Question

What is the Average?



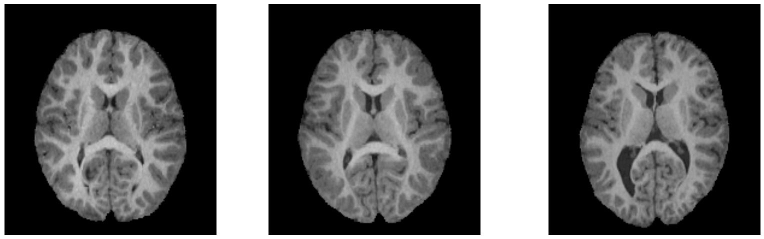
Motivation: A Natural Question

Average considering "Geometric Structure"

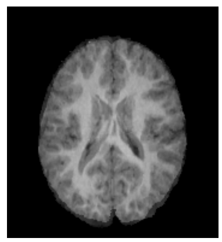


A circle with "average radius"

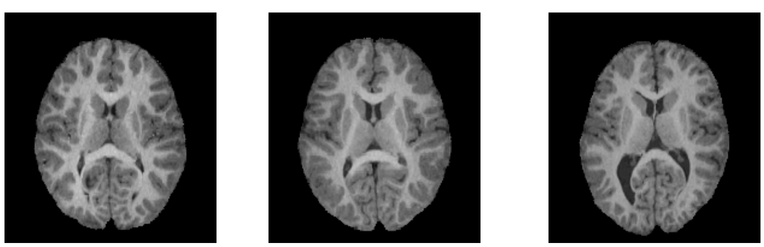
Motivation: A Natural Question



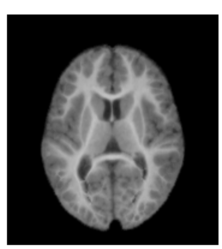
Simple average:



Motivation: A Natural Question

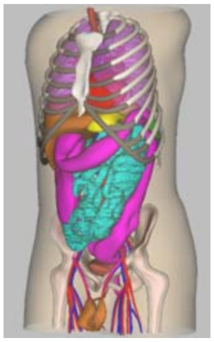


Average considering "Geometric Structure"



Mathematical Foundations Computational Anatomy

- Homogeneous Anatomy characterized by $(\Omega, \mathcal{H}, \mathcal{I}, P)$.
- Ω::The underlying coordinate system with a collection of 0,1,2 and 3 dimensional compact manifolds of
  0-Dimensional –Landmark points
  1-Dimensional –Lines
  2-Dimensional –Surfaces
  3-Dimensional –Sub-Volumes
- $\mathcal{H}$: A set of transformation of Ω accommodating biological variability.
  $$h \in \mathcal{H} : \Omega \leftrightarrow \Omega$$
- *I* Set of anatomical Imagery (CT, MRI, PET, US etc…)
  $$I_\alpha \in \mathcal{I} : \Omega \to I\!R^N$$
- P: A probability measure on the set of transformation $\mathcal{H}$:



Interesting Spaces

- Image intensities I well represented by elements of flat spaces:
  - L^2 :Square integrable functions.
- Structure in Images represented by transformation groups:
  - For circles simple multiplicative group of positive real's (R^+)
  - Scale and Orientation: Finite dimensional Lie Groups such as Rotations, Similarity and Affine Transforms.
  - High dimensional anatomical structural variation: Infinite dimensional Group of Diffeomorphisms

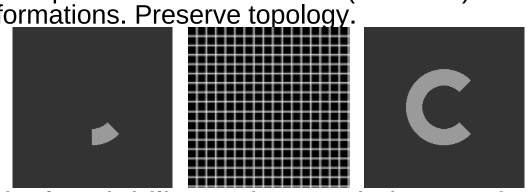
Space of Images and Anatomical Structure

- Images as function of a underlying coordinate space Ω
- Image intensities $L^2(\Omega)$
- $\mathcal{H}$: Space of structural transformations: $Diff(\Omega)$ diffeomorphisms of the underlying coordinate space Ω
- Space of Images and Transformations a *semi-direct* product of the two spaces.

$$L^2(\Omega) \otimes Diff(\Omega)$$

Mathematical Foundations of Computational Anatomy

- $h \in \mathcal{H}$ transformations constructed from the group of diffeomorphisms of the underlying coordinate system Ω:
  - Diffeomorphisms: one-to-one onto (invertible) and differential transformations. Preserve topology.



- Anatomical variability understood via transformations $\mathcal{H}$:
  - Traditional approach: Given a family of images $\{I_0, I_1, \cdots, I_N\}$ construct "registration" transformations $\{h_i, i = 1, \cdots, N\}, h_i \in \mathcal{H}$ that map all the images to a single template image or the Atlas.
- How can we define an "Average anatomy" in this framework: The Atlas estimation problem!!

Large deformation diffeomorphisms

- Space of all Diffeomorphisms $Diff(\Omega)$ forms a group under composition:

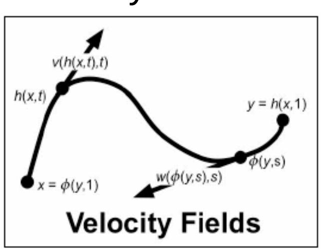
$$\forall h_1, h_2 \in Diff(\Omega) : h = h_1 \circ h_2 \in Diff(\Omega)$$

- Space of diffeomorphisms not a vector space.

$$\forall h_1, h_2 \in Diff(\Omega) : h = h_1 + h_2 \notin Diff(\Omega)$$

Large deformation diffeomorphisms.

- $Diff(\Omega)$ infinite dimensional "Lei Group" (Almost).
- Tangent space: The space of smooth velocity fields.
- Construct deformations by integrating flows of velocity fields.



$$\frac{d}{dt}h(t,x) = v(h(t,x),t), \qquad h(0,x) = x \ .$$

$$\begin{aligned} y &= h(x,1) = x + \int_0^1 v(h(x,\tau),\tau)d\tau \\ x &= \phi(y,1) = y + \int_0^1 w(\phi(y,\tau),\tau)d\tau \end{aligned}$$

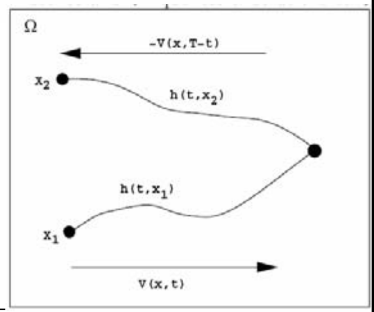
Large deformation diffeomorphisms.

Theorem 1 *If $v(\cdot, t)$ continuously differentiable and compact support, and let $h(t, \cdot)$ be the solution to the ODE*

$$\frac{d}{dt}h(t,x) = v(h(t,x),t), \qquad h(0,x) = x \ .$$

The solution exists and for each t, $h(t, \cdot)$ is a diffeomorphism of $\Omega \leftrightarrow \Omega$ for each $t \in [0,1]$

- Proof: Existence and Uniqueness of solutions of ODE's.
- One-to-one: Uniqueness
- Differentiability: Smooth dependence on initial condition.



Relationship to Fluid Deformations

- Newtonian fluid flows generate diffeomorphisms: John P. Heller "An Unmixing Demonstration," *American Journal of Physics*, **28**, 348-353 (1960).

Simple Statistics on Interesting Spaces: 'Average Anatomy'

- Use the notion of Fréchet mean to define the "Average Anatomical" image.
- The "Average Anatomical" image: The image that minimizes the mean squared metric on the *semi-direct* product space

$$L^2(\Omega) \otimes Diff(\Omega)$$

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Metric on the Group of Diffeomorphisms: LDMM

- Induce a metric via a Sobolev norm on the velocity fields. Distance defined as the length of Geodesics under this norm.
- Distance between *e*, the identity and any diffeomorphism φ is de

$$D^2(e,\varphi) = \min_{v:\dot{\phi}(t)=v(\phi^v,t)} \int_0^1 ||Lv(t)||_V^2 dt.$$

- Left invariant distance between any two is defined as:

$$D(\varphi_1,\varphi_2) = D(e,\varphi_1^{-1} \circ \varphi_2).$$

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Simple Statistics on Interesting Spaces: ‘Averaging Anatomies’

- The average anatomical image is the Image that requires “Least Energy to deform and match to all the Images in a population”:

$$\{\hat{\varphi}_i, \hat{I}\} = \operatorname*{argmin}_{v_i:\dot{\phi}(t)=v(\phi^v,t),I} \sum_{i=1}^{N} \left(\frac{1}{\sigma^2} ||I - I_i \circ \varphi_i||^2_{L^2} + \int_0^1 ||Lv_i(t)||^2_V dt \right)$$

•Not as intractable as it looks!!

•Efficient alternating algorithm:

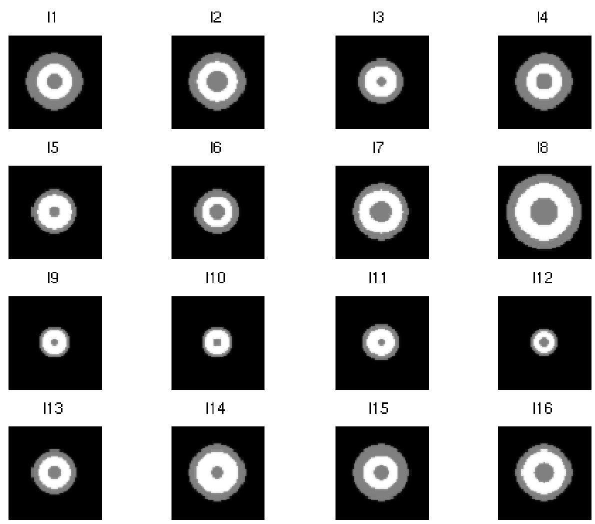
Simple Statistics on Interesting Spaces: ‘Averaging Images’

$$\{\hat{\varphi}_i, \hat{I}\} = \operatorname*{argmin}_{v_i:\dot{\phi}(t)=v(\phi^v,t),I} \sum_{i=1}^{N} \left(\frac{1}{\sigma^2} ||I - I_i \circ \varphi_i||^2_{L^2} + \int_0^1 ||Lv_i(t)||^2_V dt \right)$$

•If the transformations are fixed than the average image is simply the average of the deformed images!!

•Alternate until convergence between estimating the average and the transformations.

Results: Sample of 16 Bull's eye Images



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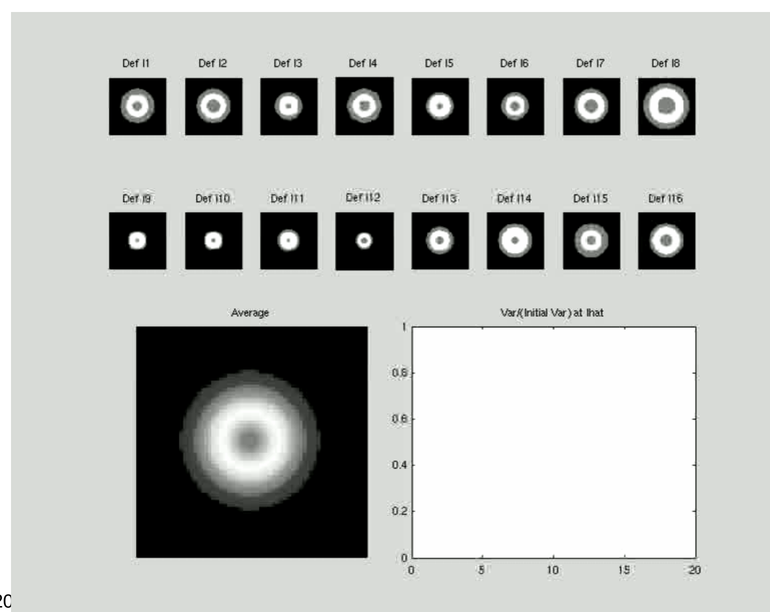
Averaging of 16 Bull's eye images



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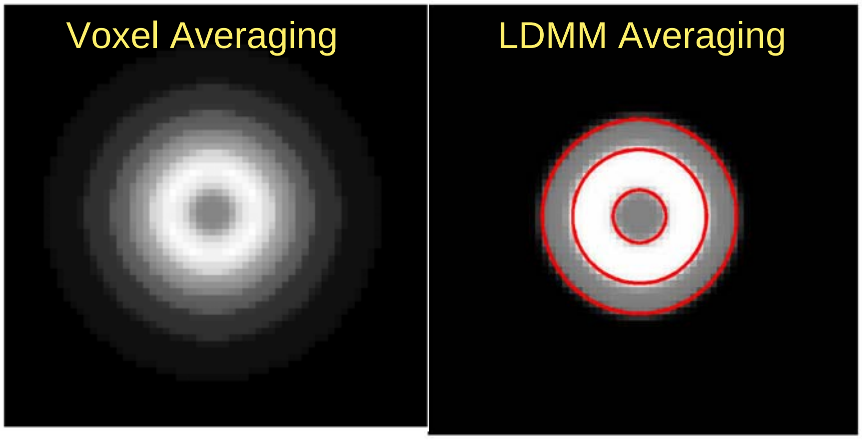
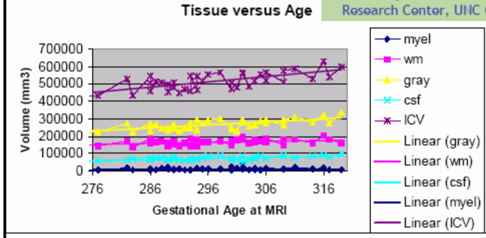
Averaging of 16 Bull's eye images



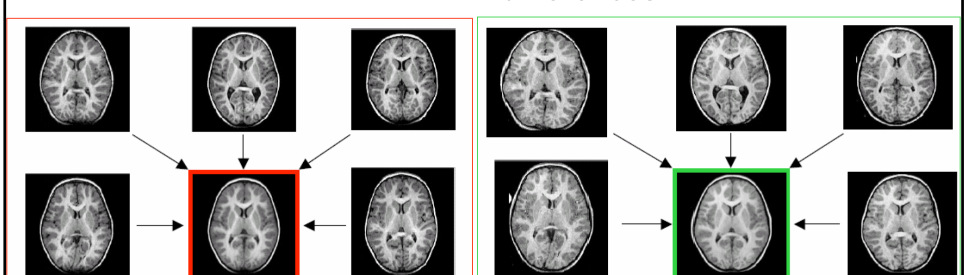
Numerical average of the radii of the individual circles forming the bulls eye sample.

Applications: Early Brain Development Assessed by structural MRI

Current unpublished work of Guido Gerig, Matthieu Jomier, and Joe Piven, UNC Schizophrenia Research Center, UNC Chapel Hill

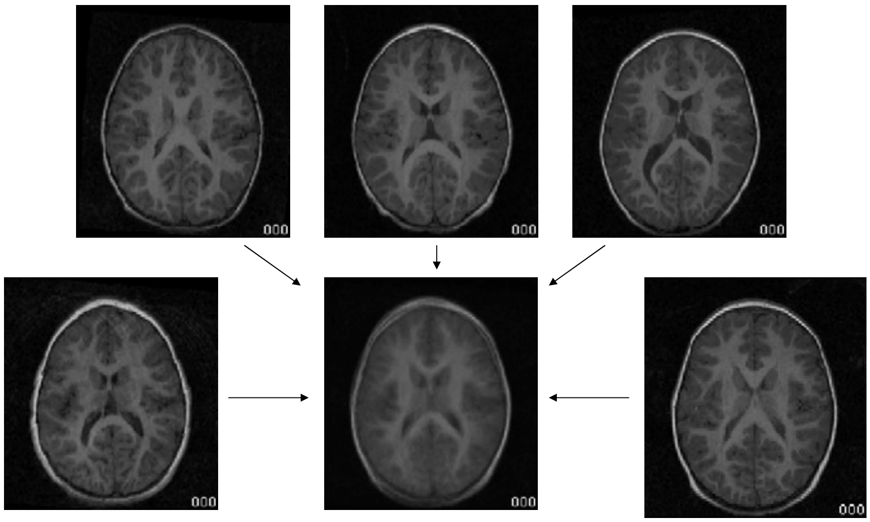


- Longitudinal study of Brain Growth from 2 Years to 4 Years.
- Quantify details Structural differences.



Average 2yrs Average 4yrs

Applications: Early Brain Development Assessed by structural MRI



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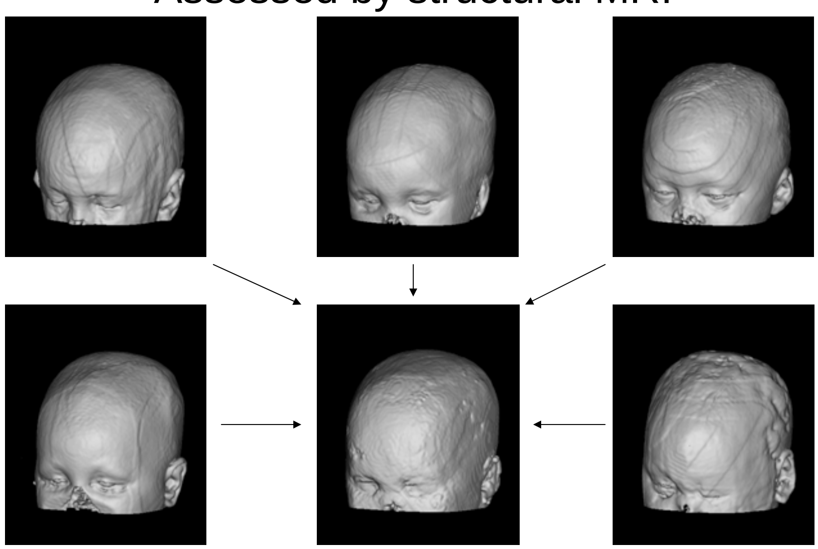

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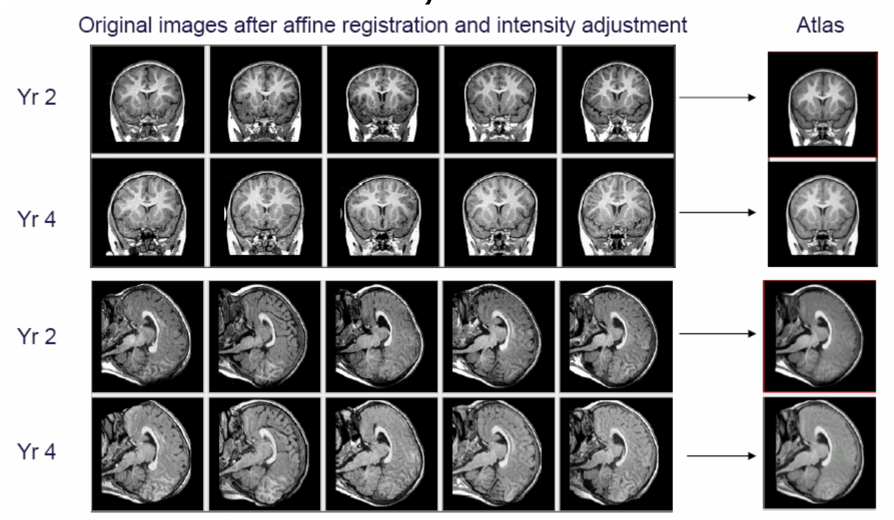

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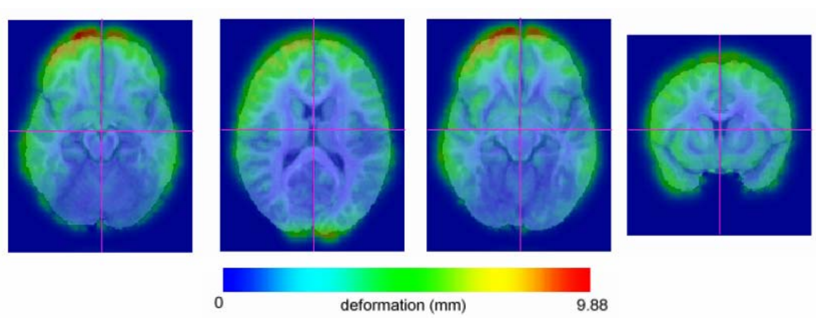

- Deformation between 2 Year Average and 4 Year Average.

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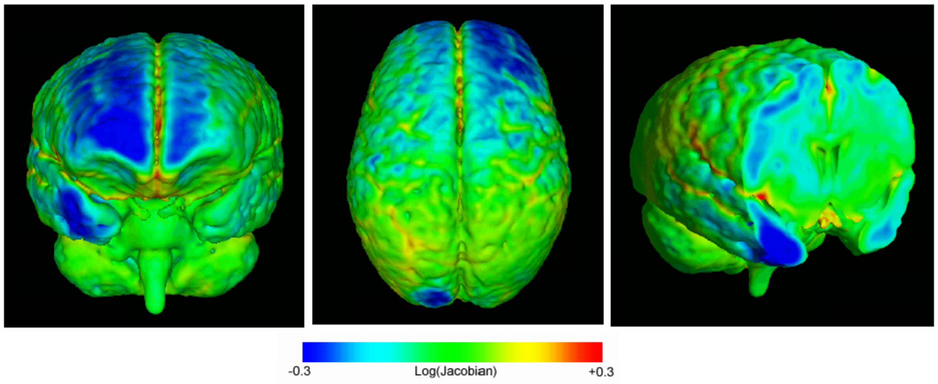
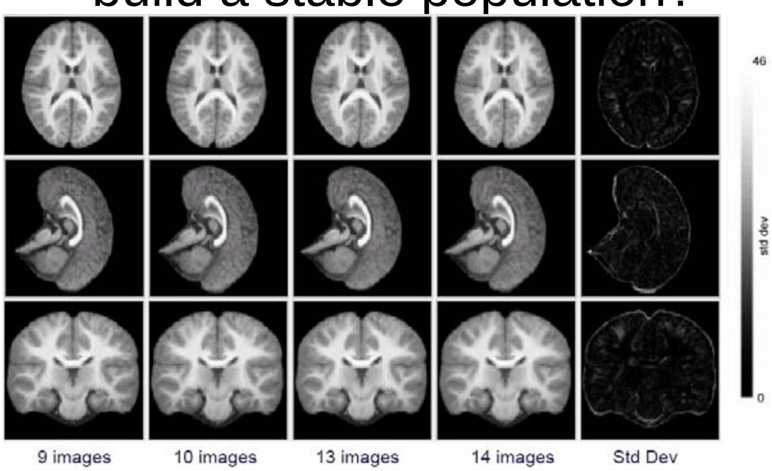
Applications: Early Brain Development Assessed by structural MRI

- Full volumetric analysis of Brain Growth.



•Use Log-Jacobian to study local volumetric changes.

How many images do we need to build a stable population?



For more details see: *P. Lorenzen*, B. Davis, and S. Joshi, "Unbiased Atlas Formation via Large Deformations Metric Mapping", in *MICCAI 2005* , Pages 411-418.

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  - *G. E. Christensen, S. C. Joshi, and M. I. Miller, "Volumetric Transformation of Brain Anatomy," IEEE Transactions on Medical Imaging, vol. 16, no. 6, pp. 864-877, Dec. 1997.*
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  - *M.I. Miller and L. Younes, "Group Actions, Homeomorphisms, and Matching: A General Framework", International Journal of Computer Vision, Volume 41, No 1/2, pages 61-84, 2001*
- *Atlas Construction*
  - *Sarang Joshi, Brad Davis, Matthieu Jomier, and Guido Gerig, "Unbiased Diffeomorphic Atlas Construction for Computational Anatomy," NeuroImage; Supplement issue on Mathematics in Brain Imaging, vol. 23, no. Supplement1, pp. S151-S160, Elsevier, Inc, 2004.*
  - *P. Lorenzen*, B. Davis, and S. Joshi, "Unbiased Atlas Formation via Large Deformations Metric Mapping", in *MICCAI 2005* , Pages 411-418.

Hypothesis Testing with Nonlinear Shape Models

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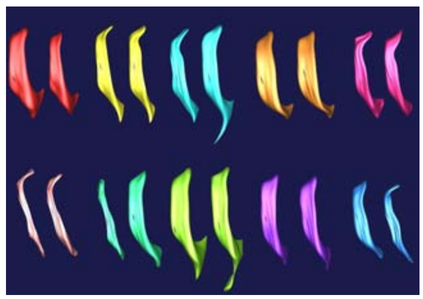
Hypothesis Testing

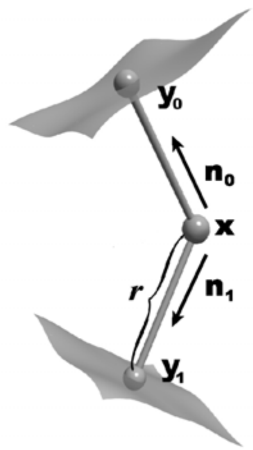
- The goal: To determine if two different populations of objects have significant shape differences



Hypothesis Testing

- The challenges:
  - –High dimension, low sample size
  - –Shape parameters live in non-Euclidean spaces
  - –Different variables are not commensurate
  - –Neighboring sites are correlated

Shape Model: M-reps



- 8 dimensions per medial atom
  - **x (3), *r* (1), n_0 (2), n_1 (2)**
- Riemannian symmetric space
  - $\mathbf{R}^3 \times \mathbf{R}^+ \times S^2 \times S^2$ (Fletcher et al. 2003)
  - Nonlinear, except $\mathbf{R}^3$

Metric Space

- Each parameter has a metric invariant to geometric transformations
  - R^3 - Euclidean metric (invariant to translation)
  - R^+ - $|\log(r_1) - \log(r_2)|$ (invariant to scale)
  - S^2 - Distance on sphere (invariant to rotation)
- Can define the Fréchet *mean of populations via the metric.*

$$\hat{\mu} = \arg\min_{x \in M} \sum_i d(x, x_i)^2$$

- *Cannot do statistical testing on the tangent space as the two populations have different means and hence different tangent spaces*
  - *No way to intrinsically transform covariance structure from one tangent space to another especially if the manifold is not parallizable.*

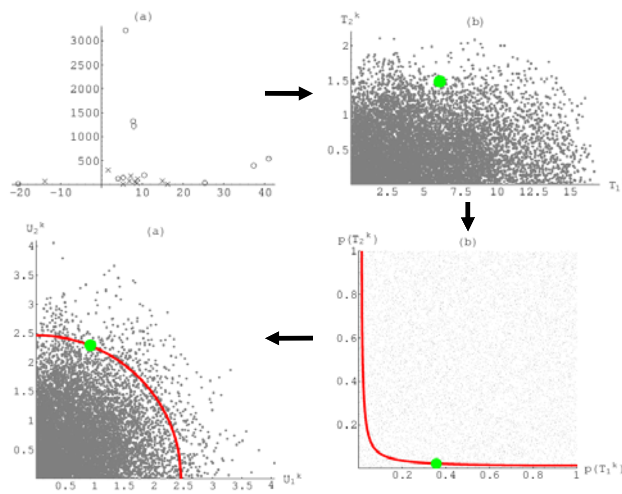
Our Approach

- Generalize permutation tests to capture desirable properties of Hotelling's test
  - Use a true multivariate permutation test framework (Pesarin 2001)
    - Perform partial tests on individual features
    - Combine the test results into a single score
  - Trivial example: Bonferroni correction
    - min p-value multiplied by number of tests
    - Too pessimistic for high-dimension data

Our Approach

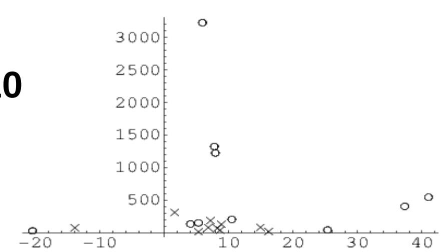
- *Marginal permutation tests on individual features generate uniformly distributed and parameterization invariant p-values*
- *Using a c.d.f., map the uniform distribution to a standard distribution, and perform tests there*
- *Gives an unbiased global test for equality of population distributions*

Our Approach In Pictures



Example

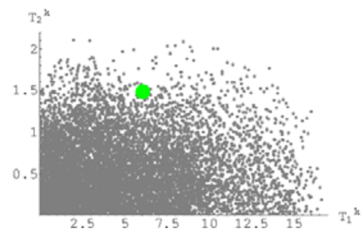
- Two data sets
  - Size $\mathbf{n_1 = n_2 = 10}$
- M=2 dimensional feature vectors
  - Position, Scale



- Drawn from multivariate normal distributions (common covariance)
  - Second parameter exponentiated
  - Then both parameters scaled by 10

Step 1: Partial Tests

- Choose N random assignments to group 1 or 2
- For each feature ***j*** and permutation ***k***
  - Compute a test statistic T_j^k , e.g. $d(\hat{\mu}_{1,j}^k, \hat{\mu}_{2,j}^k)$
  - Also compute T_j^o , the statistics for the observed data

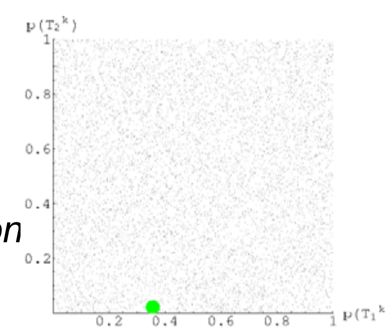


Step 2: Partial Test p-values

- For each feature ***j*** ***and permutation k***
  - *Compute a p-value using that feature's cumulative distribution*

$$p\left(T_j^k\right) = \frac{1}{N}\sum_{l=1}^{N} H\left(T_j^l, T_j^k\right)$$

$$H\left(T_j^l, T_j^k\right) = \begin{cases} 1, & T_j^k \geq T_j^l \\ 0, & T_j^k < T_j^l \end{cases}$$



- *The marginal distributions are uniform, and invariant to scale*

Step 3: Combined Test

- If the partial tests are
  - Significant for large values
  - Consistent
  - Marginally unbiased (unbiased regardless of whether or not other tests are true)
- And we choose a combining function $T'(p(T^k))$ *such that it is*
  - *Monotonically non-increasing in each p-value*
  - *Obtains its supremum* T^* *when any p-value is 0*
  - *Has finite critical values strictly smaller than* T^*

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Step 3: Combined Test

- Theorem: Then $T'(p(T^k))$ is an unbiased global test for equality of distributions (Pesarin 2001)
- What function should we use?
- One asymptotically equivalent to Hotelling's T^2 test (in linear case)
  - Uniformly most powerful, and affine invariant

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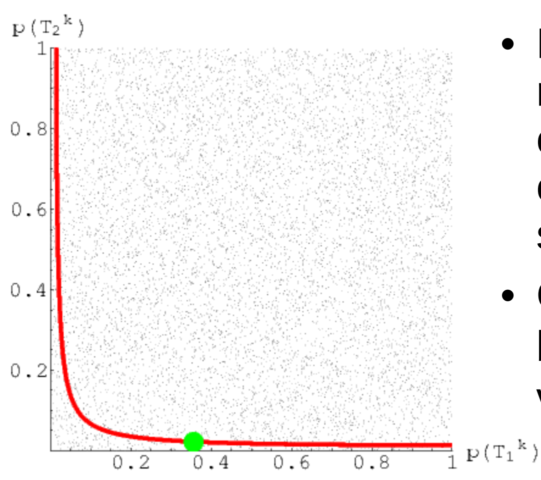
Step 3: Combined Test (2-sided)

- With signed distances, T_j^k is significant for large *and small values*
- *Map p-values for each feature to a standard normal distribution*

$$U_j^k = \Phi^{-1}(P(T_j^k) - \frac{1}{2N}), \qquad \Phi \text{ :Gaussian c.d.f.}$$

- *Compute samp. covariance* $\Sigma_U = \frac{1}{N} U^T U$
  - *Full rank even for small samples: N is large*
- *Then* $T'^k = \left(U^k\right)^T \Sigma_U^{-1} U^k$

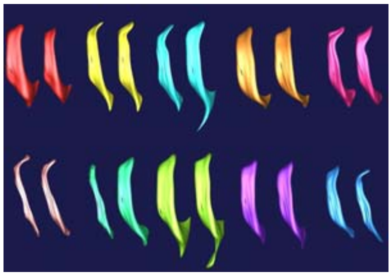
Acceptance Region



- Map critical region via c.d.f. to original space
- Contains both axes (p-value = 0)

Application: Twin Ventricles

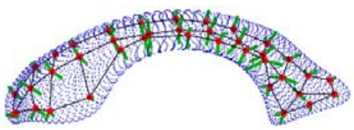
- MRI data of lateral ventricles from twin pairs
  - MZ - Healthy monozygotic: 9 pairs
  - DS - Monozygotic and discordant for schizophrenia: 9 pairs



  - DZ - Healthy dizygotic: 10 pairs
  - NR - Healthy non-related pairs: 10 pairs drawn from other healthy subjects

Application: Twin Ventricles

- Existing data set (provided by Martin Styner) includes:
  - Binary segmentations
  - PDM models of surface
  - M-rep models (3 × 13 grid, 98% volume overlap)



- All shapes volume normalized
- Aligned via m-rep extension of Procrustes (Fletcher et al. 2004)

Application: Twin Ventricles

- Test: Is shape variability between pairs related to genes? Disease?
- Test statistics for pairs ***(x_1,y_1) in group 1 and (x_2,y_2) in group 2***
- ***6 features per atom (x (3), r (1),n_0 (1), n_1(1)), 39 atoms: M = 234 tests***
- ***N = 50,000 permutations***

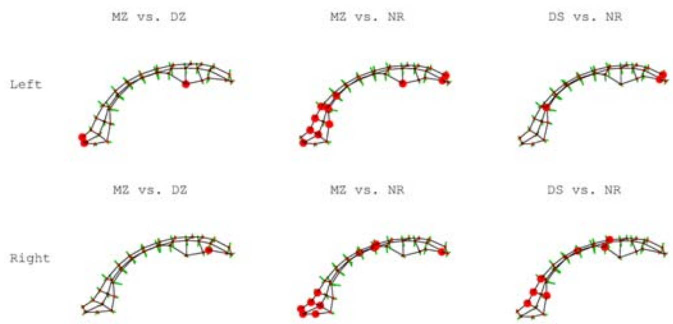
$$T_j(x_1, y_1, x_2, y_2) \;=\; \frac{1}{n_2}\sum_{i=1}^{n_2} d(x_{2,i,j}, y_{2,i,j}) - \frac{1}{n_1}\sum_{i=1}^{n_1} d(x_{1,i,j}, y_{1,i,j})$$

Global Results

	Our Study		Boundary Study	
	Left	Right	Left	Right
MZ vs. DS	0.12	0.38	0.28	0.68
MZ vs. DZ	**0.00006**	**0.0033**	**0.0082**	**0.0399**
MZ vs. NR	**0.00002**	**0.00020**	**0.0018**	**0.0006**
DS vs. DZ	**0.020**	**0.0076**	0.25	0.24
DS vs. NR	**0.0031**	**0.00026**	**0.018**	**0.0026**
DZ vs. NR	0.16	0.055	**0.05**	**0.016**

- Comparison of our results with an earlier study on the PDMs (Styner et al. 2002)
  - Tests significant at 0.05 level in bold

Local Tests



- Local tests (***M*** = 6 partial tests per atom, correction for multiple tests applied across atoms)

Conclusion

- Developed multivariate permutation test approach for hypothesis testing
- Well-defined in HDLSS case
- Requires only a metric space
- Combines features of differing scale
- Multivariate approach accounts for correlation, even without explicit correlation coefficients

References

- T Terriberry, S Joshi, and G Gerig, "Hypothesis Testing with Nonlinear Shape Models," in *Information Processing in Medical Imaging (IPMI)*, (G Christensen and M Sonka, eds.), (New York), pp. 15-26, July 2005.
- Pesarin F (2001) Multivariate permutation tests with applications in biostatistics. Wiley, Chichester, United Kingdom.