Summary Handout
Biomedical Modeling Using Imaging Data: Modeling Shape as a Biological Variable

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1 Introduction

In addition to pathology detection, an essential challenge in neuroimaging is to describe patterns of structural features: shape.

To build quantitative descriptions of shape, Computational Anatomy [1] focuses on shape differences, rather than shape descriptions. These differences are modeled by transformations, which become the objects of study.

In some applications, physical models for transformation are appropriate (e.g. deformations due to breathing). When describing shape across populations, more abstract mathematical models are necessary.

In this session we focus on answering three questions:

1. How can biological shape be described quantitatively?
2. How can we apply statistical techniques to its study?
3. How can we construct biomarkers of neurodegenerative disease?

2 The metric space of biological shape

The free form smooth and invertible transformations that preserve biological organization are called the diffeomorphism group:

$$\varphi \in \mathit{Diff}, \quad \varphi : X \subseteq \mathbb{R}^3 \to X, \quad x \mapsto \varphi(x).$$

Diffeomorphisms can be stored as a vector at each voxel, but are not vector valued. The group is closed under composition, not addition and scalar multiplication:

$$\varphi^1, \varphi^2 \in \mathit{Diff} \implies \varphi^1 \circ \varphi^2 \in \mathit{Diff}\,.$$

Computationally, diffeomorphisms are generated by integrating a smooth time varying velocity field:

$$\dot{\varphi}_t = v_t(\varphi_t), \quad \varphi_0 = id \text{ (identity)}, \quad v_t \in V\ .$$

Smoothness and invertibility are ensured by embedding velocity fields in a Hilbert space V whose norm penalizes high spatial frequencies sufficiently:

$$\langle u, v\rangle_V = \int Lu(x) \cdot Lv(x)dx, \quad L \overset{e.g.}{=} (id + a\Delta)^p, \quad \Delta : \text{Laplacian} \ .$$

Diffeomorphic transformations that relate one image, $I : X \to \mathbb{R}$, to another, $J : X \to \mathbb{R}$, can be computed using a registration algorithm such as Large Deformation Diffeomorphic Metric Mapping (LDDMM) [2]:

$$v_t^* = \arg\min_{v_t \in V} \int_0^1 \frac{1}{2}\|v_t\|_V^2 dt + \frac{1}{2\sigma^2}\|I(\varphi^{-1}) - J\|_{L^2}, \quad \varphi \doteq \varphi_1 = id + \int_0^1 v_t(\varphi_t)dt \ .$$

The Hilbert space's inner product provides the structure of a Riemannian manifold, which allows us to compute distances (giving a metric space), angles, and straight lines (geodesics). The solution to the LDDMM algorithm is always a geodesic, which obeys the *EPDiff* equation (Euler-Poincare equation on the group of diffeomorphisms) [3]:

$$\frac{d}{dt}[L^*Lv] = -(D[L^*Lv]v + [L^*Lv]\text{div}v + Dv^T[L^*Lv]) \ .$$

3 Statistical shape analysis

A distance between two shapes immediately gives us the ability to define an average: the shape that minimizies sum of square distances to a population [4]:

$$\varphi^* = \arg\min_{\varphi} \sum_{i=1}^{N} d^2(\varphi, \varphi^i) \ .$$

When data is indexed to time, geodesic regression can be used to find the curve that minimizes sum of square distance to a population [5].

The initial condition to the *EPDiff* equation lies in a vector space, and is amenable to covariance analysis techniques such as principal components [6].

These techniques can be used to analyze populations and timeseries of imaging data.

4 Biomarkers of neurodegeneration

At large scales diffeomorphic transformations can be used to define volume differences, or volume differences for specific anatomical regions.

At small scales, volume changes are decomposed into Jacobian determinants at each voxel. For cortical surfaces, they are further decomposed into normal and tangential components. This is known as morphometry [7].

In neurodegeneration, patterns of atrophy in populations are quantified using Jacobian determinants of diffeomorphisms at each voxel. These are modeled statistically, and regions where atrophy occurs more strongly than normal aging are identified. Hypothesis testing testing that controls for multiple comparisons, such as permutation testing, is essential [8].

Among other studies, we are using these techniques to quantify neurodegeneration in early Alzheimer's disease. These patterns of change can be detected in imaging in the trans entorhinal cortex, long before symptoms appear [9]. We are working to validate this biomarker of disease using post mortem imaging and histology [10].

5 Conclusion

Biological shape differences are modeled using the diffeomorphism group. Diffeomorphisms are estimated from imaging data using image registration algorithms.

Because they lie on a Riemannian manifold, statistical techniques such as averages, regression, or principal component analysis can be employed to study populations and timeseries of biological shapes.

In morphometry, Jacobian determinants are used to quantify biologically meaningful patterns of growth or atrophy.

These techniques are commonly applied to the study of neurodegeneration, where statistical models can identify regions that discriminate between disease and normal aging.

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