Multi-class Posterior Atlas Formation via Unbiased Kullback-Leibler Template Estimation

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Abstract. Many medical image analysis problems that involve multi-modal image lend themselves to solutions that involve class posterior density function images. This paper presents a method for large deformation exemplar class posterior density template estimation. This method generates a representative anatomical template from an arbitrary number of topologically similar multi-modal image sets using large deformation minimum Kullback-Leibler divergence registration. The template that we generate is the class posterior that requires the least amount of deformation energy to be transformed into every class posterior density (each characterizing a multi-modal image set). This method is computationally practical; computation times grows linearly with the number of image sets. Template estimation results are presented for a set of five 3D class posterior images representing structures of the human brain.

1 Introduction

Computational anatomy, the study of anatomical variation, is an active area of research in medical image analysis. An important problem in computation anatomy is the construction of an exemplar template (or atlas) from a population of medical images. This template represents the anatomical variation present in the population [1,2,3]. Understanding anatomical variability requires robust high-dimensional image registration methods where the number of parameters used to describe the mappings between images is on the order of the number of voxels describing the space of the images.

Modern imaging techniques provide an array of imaging modalities which enable the acquisition of complementary information representing an underlying anatomy. Most image registration algorithms find a mapping between two scalar images. In order to utilize multi-modal images of a single anatomy we define the notation of a multi-modal image set, $\bar{I}$, as a collection of m co-registered multi-modal images, $\bar{I}(x) \in \mathbb{R}^m$. For example, $\bar{I}(x)$ might represent a CT image, a T1-weighted MR image, and a PET image of a single anatomy.

Most image registration algorithms find a mapping between two scalar images. If the images are of different modalities, mutual information is typically used to register them. High-dimensional image registration in the context of mutual information and other dissimilarity measures frameworks has been studied extensively. A thorough investigation of these dissimilarity measures in high-dimensional image registration is presented in [4]. A multi-modal free-form registration algorithm that matches voxel class labels, rather than image intensities, via minimizing Kullback-Leibler divergence is presented in [5,6]. This method finds correspondences between two multi-modal scalar images. A method that minimizing Kullback-Leibler divergence between expected and observed joint class histograms is presented in [7]. This technique, however, estimates class labels as preprocessing step and is used only for rigid registration between scalar images. The method presented in this paper is more general in that registration is performed on sets of images, of arbitrary number. The method is not also constrained by an initial class labeling. Although inter-subject high-dimensional image registration has received much attention [8,9,10,11], to our knowledge, little attention has been given to using multi-modal image sets of subjects to estimate registration transformations.

1.1 Model Based Multi-modal Image Set Registration

Across image sets, the number of constituent images may vary, thus registration based on an intensity similarity measure is not possible in this setting. While mutual information can be extended to multiple random variables, its extension to registration involving three or more images is problematic in that it requires maintaining an impractical number of histogram bins whose number, additionally, is orders of magnitude greater than the number of spatial elements of a typical medical image <<**ref**>>. Given these difficulties we move to a model based approach where the registration is performed using underlying anatomical structures. We incorporate anatomical structures as a prior in a Bayesian framework as described in [12].

This framework is based on the assumption that human brain anatomy consists of finitely enumerable structures such as grey matter, white matter, and cerebrospinal fluid. These structures present with varying radiometric intensity values across disparate image modalities. Given a collection of multi-modal image sets representing the atlas population, we capture the underlying structures by estimating, for each image set, the class posterior densities associated with each of the structures. These class posterior densities are then used to produce the multi-class posterior atlas by estimating high-dimensional diffeomorphic registration maps relating the coordinate spaces of the densities. The Kullback-Leibler divergence is used as a metric for the posterior densities to estimate the transformation. The use of the class posterior densities provides an image intensity independent approach to image registration. As the number of structures in our method approaches the number of voxels in the image space, we lose the benefit of geometry from the prior and are, thus, left with the impractical mutual information setting.

2 Bayesian Framework

From a population of N multi-modal image sets $\{\bar{I}_i\}_{i=1}^N$, for each class c_j we first estimate the class posterior densities $p_j^i(x) = p(c_j(x)|\bar{I}_i)$ for each image set i where $c_j(x)$ is the class associated with the voxel at position $x \in \Omega \subset \mathbb{R}^3$. Again, this method is independent of the choice of the number of images comprising each image set. These class posterior densities are produced using the expectation maximization method described in [13,14]. Following [14,15], for each class c_j the associated data likelihood, $p(\bar{I}_i(x)|c_j(x), \mu_j, \Sigma_j)$, is modeled as a normal distribution with mean, μ_j, and covariance, Σ_j. The class posteriors are computed using a new atlas developed at UNC's department of psychiatry for two year old children. This atlas is based on fourteen subjects using the same concepts as used in the construction of the Montreal Neurological Institute (MNI) International Consortium for Brain Mapping (ICBM) atlas [16].

In this paper we focus on the construction of an exemplar templates from a population of anatomical class posterior densities. We use the method developed in [17] which provides an unbiased technique for atlas construction using large deformation diffeomorphic registration.

3 Exemplar Templates

We consider the problem of estimating a template class posterior $\hat{p}$ that is the best representative for a population of N class posteriors, $\{p^i\}_{i=1}^N$, representing the N individual image sets $\{\bar{I}_i\}_{i=1}^N$. The template $\hat{p}$ is not a member of the $\{p^i\}$. To this end, we consider the problem of constructing a mapping between $\hat{p}$ and each class posterior in the set $\{p^i\}$. That is, we estimate the mappings $h_i : \Omega \rightarrow \Omega_i$ where $\Omega \subset \mathbb{R}^3$ and $\Omega_i \subset \mathbb{R}^3$ are the coordinate systems of the class posteriors $\hat{p}$ and p^i respectively. Again, Ω is independent of any of the population class posterior coordinate systems. This framework is depicted in Figure 1.

Following the template construction framework developed in [17] we seek the representative template class posterior $\hat{p}$ that requires the minimum amount of energy to deform into every population class posterior p^i. More precisely, given a transformation group S with associated metric $D : \mathcal{S}^2 \rightarrow \mathbb{R}$, along with a probability density dissimilarity measure $E(p, q)$, we wish to find the class posterior density $\hat{p}$ such that

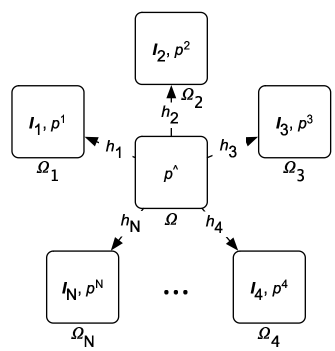

Fig. 1. Template Construction Framework

$$\{\hat{h}_i, \hat{p}\} = \underset{h_i \in \mathcal{S}, p}{\operatorname{argmin}} \sum_{i=1}^{N} E(p^i \circ h_i, p) + D(e, h_i) \quad (1)$$

where e is the identity transformation.

In this paper we focus on the infinite dimensional group of diffeomorphisms $\mathcal{H}$ as described in [17]. We apply the theory of large deformation diffeomorphisms [18] to generate deformations h that are solutions to the Lagrangian ODEs $\frac{d}{dt}h(x,t) = v(h(x,t),t)$.

We induce a metric on the space of diffeomorphisms by using a Sobolev norm (a norm that involves derivatives of a function) via a partial differential operator L on the velocity fields v. Let h be a diffeomorphism isotopic to the identity transformation e. We define the distance $D(e,h)$ as

$$D(e,h) = \min_{v} \int_0^1 \int_{\Omega} ||Lv(x,t)||^2 dxdt$$

subject to

$$h(x) = x + \int_0^1 v(h(x,t),t)dt.$$

The distance between any two diffeomorphisms is defined by

$$D(h_1, h_2) = D(e, h_1^{-1}, h_2).$$

The construction of h and h^{-1}, as well as the properties of D, are described in [17].

4 Large Deformation Class Posterior Template Construction

Having defined a metric on the space of diffeomorphisms, the minimum energy template estimation problem described in Equation 1 is formulated as

$$\{\hat{h}_i, \hat{p}\} = \underset{h_i, p}{\operatorname{argmin}} \sum_{i=1}^{N} E(p^i \circ h_i, p) + \int_0^1 \int_{\Omega} ||Lv_i(x,t)||^2 dxtd$$

subject to

$$h_i(x) = \int_0^1 v_i(h_i(x,t),t)dt.$$

As a measure of dissimilarity between two probability density functions $p(x)$ and $q(x)$, we use the Kullback-Leibler divergence (relative entropy),

$$D_{KL}(p(x), q(x)) = \sum_{j=1}^{C} p_j(x) \log \frac{p_j(x)}{q_j(x)},$$

where C is the number of anatomical structure classes. From an information theoretic viewpoint [19], this dissimilarity can be interpreted as the inefficiency of assuming that an observation $q(x)$ is true when $p(x)$ is true. That is, we can use Kullback-Leibler divergence to measure how much the deformed class posteriors, $\{p^i(h_i(x))\}_{i=1}^N$, deviate from the atlas $p(x)$.

Under the Kullback-Leibler divergence measure the template estimation problem becomes

$$\hat{h}_i, \hat{p} = \underset{h_i, p}{\operatorname{argmin}} \sum_{i=1}^{N} \int_{\Omega} D_{KL}(p(x), p^i(h_i(x)))dx + \int_0^1 \int_{\Omega} ||Lv_i(x,t)||^2 dx dt. \quad (2)$$

This minimization problem can be simplified by noticing that for fixed transformations h_i, the $\hat{p}$ that minimizes Equation 2 is given by normalized geometric mean of the deformed class posteriors, $p^i(x)$,

$$\hat{p}_j(x) = \frac{\left(\prod_{i=1}^{N} p_j^i(h_i(x))\right)^{\frac{1}{N}}}{\sum_{k=1}^{C} \left(\prod_{i=1}^{N} p_k^i(h_i(x))\right)^{\frac{1}{N}}}. \quad (3)$$

Combining Equations 2 and 3 results in the following minimization problem

$$\hat{h}_i = \underset{h_i}{\operatorname{argmin}} \sum_{i=1}^{N} \int_{\Omega} D_{KL}(\hat{p}(x), p^i(h_i(x)))dx + \int_0^1 \int_{\Omega} ||Lv_i(x,t)||^2 dx dt. \quad (4)$$

Note that the solution to this minimization problem is independent of the ordering of the N image sets and increases linearly as image sets are added, thus, making the algorithm scalable.

5 Implementation

Following Christensen's algorithm for propagating templates described in [20], we approximate the solution to the minimization problem described in Equation 4 using an iteratively greedy method. At each iteration n, the updated transformation h_i^{n+1}, for each class posterior p^i, is computed using the update rule $h_i^{n+1} = h_i^n(x + \epsilon v_i^n(x))$. The fields h_i^n and v_i^n are the current estimated transformations and the velocity for the ith class posterior, and ϵ is the time step size. That is, each final transformation h_i is built form the composition of n transformations.

The velocity v_i^n for each iteration n is computed as follows. First, compute the updated template estimate (i.e. the normalized geometric mean)

$$\hat{p}_j^n(x) = \frac{\left(\prod_{i=1}^{N} p_j^i(h_i^n(x))\right)^{\frac{1}{N}}}{\sum_{k=1}^{C} \left(\prod_{i=1}^{N} p_k^i(h_i^n(x))\right)^{\frac{1}{N}}}$$

for each class component j. Next, following the second order approximation to Kullback-Leibler divergence described in [12] define the body force functions

$$F_i^n(x) = \sum_{k=1}^{C} \left[\frac{p_k^i(h_i(x))}{\hat{p}_k(x)} - 2 \right] \nabla p_k^i \Big|_{h_i(x)}^T$$

This is the variation of the class posterior dissimilarity term in Equation 4 with respect to the transformation h_i. The velocity field v_i^n is computed at each iteration by applying the inverse of the differential operator L to the body force function, i.e. $v_i^n(x) = L^{-1} F_i^n(x)$, where $L = \alpha\nabla^2 + \beta\nabla\cdot\nabla + \gamma$ is the Navier-Stokes operator. This computation is performed in the Fourier domain [21].

6 Results

To evaluate the performance of this method we applied the algorithm to a set of five class posterior densities that where derived from a population of T1-weighted, T2-weighted, and proton density 3D MR images of brains of health two year old children using an expectation maximization segmentation method [14,15]. As a preprocessing step, these images were aligned using affine transformations. An axial slice from each derived class posterior density is shown in Figure 2. There is noticeable variation between these anatomies, especially in the ventricular region.

Figure 3 shows the normalized geometric mean of the five class posterior densities and the final estimate of the template. The normalized geometric mean is blurry since it is an "average" of the varying individual neuroanatomies. Ghosting is evident around the lateral ventricles and near the boundary of the brain. In the final estimate of the template these variations have been accommodated by the high-dimensional registration.

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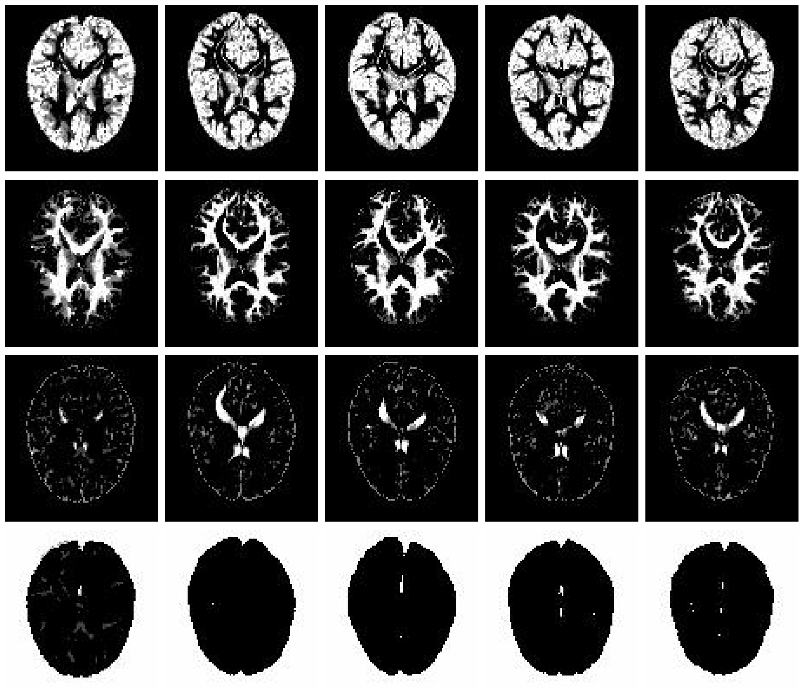

Fig. 2. Five class posteriors each with three classes and a background class. These images clearly show the large inter-subject variability, especially in the ventricular system.

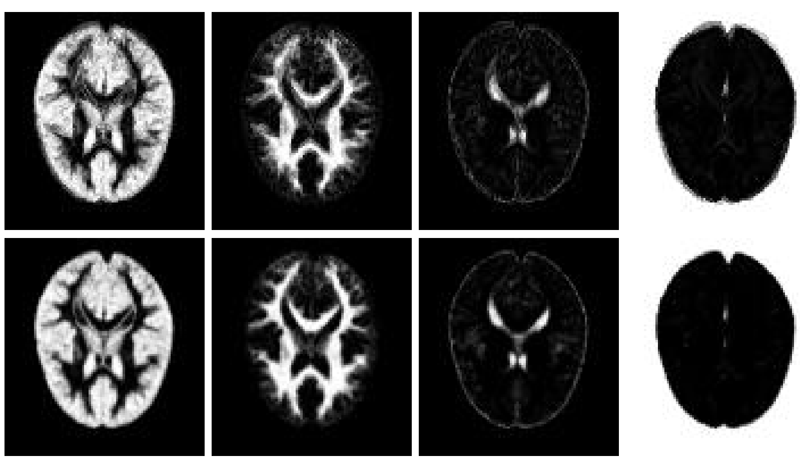

Fig. 3. Template Construction. The top row shows the normalized geometric mean class posterior density following an affine registration of all five subjects. The bottom row represents the estimated template after the final iteration of the algorithm.

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