An Entropy Measure to Assess Nonrigid Registration Algorithms for Statistical Atlas Construction

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Abstract

Assessment of normal and abnormal anatomical variability requires a coordinate system enabling inter-subject comparison. We present a minimum entropy criterion to assess affine and nonrigid transformations bringing a group of subject scans into alignment. This measure is a data-driven measure allowing the identification of an intrinsic coordinate system of a particular group of subjects. We assessed two statistical atlases derived from magnetic resonance imaging of newborn infants with gestational age ranging from 24 to 40 weeks. Over this age range major structural changes occur in the human brain and existing atlases are inadequate to capture the resulting anatomical variability. The entropy measure we propose allows an objective choice between competing registration algorithms to be made.

Key words: nonrigid registration, entropy, statistical atlas construction.

1 Introduction

Assessment of normal and abnormal anatomical variability requires a coordinate system enabling inter-subject comparison [1–3]. Several nonrigid registration algorithms have been proposed for comparing anatomy or for the construction of statistical atlases [4–13], and each has advantages that make it attractive for these applications in some circumstances but also disadvantages that potentially may limit the applicability.

We restrict our consideration here to only those nonrigid registration algorithms that attempt to project anatomy from a source to a target with a plausible model of deformation. If we allow arbitrary nonrigid transformations then anatomically implausible deformations can be constructed to generate arbitrarily good alignments. For example, one construction to achieve perfect intensity matching of two volumes is the following: for each voxel of the target, scan across the source until a voxel with matching intensity is found, and then project this voxel from the source into the target. As long as the source has the same or larger intensity range as the target this will result in a perfect intensity match but will tell us nothing useful about how to project the anatomy of the source to match the target.

We propose below an objective criterion for comparing the quality of a statistical atlas. We define a statistical atlas of anatomy as a group of acquisitions in a common coordinate system. Typical measures available in a statistical atlas are the mean and variance of the underlying acquisition signal intensity at each voxel, and very often, a segmentation of each acquisition is also carried out. In order to assess the quality of the alignment, we require a tissue segmentation of some type be available. The segmentation allows us to compare the spatial distribution of the structures of interest for the particular application or anatomy for which such an atlas is intended.

We define perfect alignment as every voxel of an acquisition being in correspondence with precisely the same anatomy in each scan. Under these circumstances, comparing the segmentations of each scan we would find the same structure identified at each voxel. Variability between the acquisitions can be considered encoded by the transformations that bring them into alignment. For example, a scan of the brain might be brought into alignment with a group of scans, first by an affine transformation correcting for rotation, translation and scale differences, and then a nonrigid transformation correcting for local shape variations. In this case the interesting anatomical variability of the scan is encoded by the nonrigid transformation that brings it into the common coordinate system.

In information theory, the information (or uncertainty) associated with a signal is referred to as the entropy of the signal [14]. Entropy-based methods were first used in medical image registration by [15–17]. Recently Miller et al. [18] proposed using pixelwise entropies across a set of binary images as a measure of their joint alignment. Here, we apply this technique to multi-valued volumes in three-dimensions with the goal of constructing a probabilistic anatomical atlas in an *intrinsic* coordinate system in order to describe anatomical variability. We propose computing the voxelwise entropy of the segmentations of each structure of the scans (as defined below). This measure of entropy is zero for a set of scans in perfect alignment as described above. Under these circumstances, a perfect nonrigid registration algorithm has been able to capture all of the anatomical variability and encode it in the nonrigid transformation, leaving the uncertainty of the atlas (or coordinate system) as zero. For a practical nonrigid registration algorithm, we may expect that

the entropy of the atlas does not reach the desirable value of zero, in which case the anatomical variability that the nonrigid registration can capture is encoded in the set of transformations bringing the scans into alignment, and crucially the amount of anatomical variability not captured by the nonrigid registration algorithm is indicated by the entropy of the aligned segmentations.

Therefore, we propose to assess a statistical atlas by measuring the entropy of the aligned segmentations voxelwise. We consider the minimum entropy statistical atlas as defining an intrinsic coordinate system for the anatomy under consideration.

2 Method

We consider here the application of constructing a statistical atlas of magnetic resonance images of newborn infants with a gestation age ranging from 24 to 40 weeks. Over this period major developmental changes in the human brain take place [19].

We applied affine (translation, rotation and scale parameters only, no shear parameters were considered) and nonrigid registration to construct a statistical atlas from tissue classifications of the above subjects. We used a minimum entropy criterion as an objective measure of the quality of the statistical atlas generated by affine transformation alone and by affine and nonrigid registration together.

2.1 MRI Acquisition

Spoiled Gradient Recalled Acquisitions in the Steady state (SPGR) with a voxel size of 0.7x0.7x1.5 mm^3 (coronal T1w) and Conventional Spin Echo (axial PDw and T2w) MR acquisitions with a voxel size of 0.7x0.7x3.0 mm^3 of newborn infants are acquired under a protocol with IRB approval. Twenty two acquisitions of subjects with gestational age (GA) < 34 weeks were analysed. For each subject, T2w and PDw volumes were resampled to align with and have the same voxel size and acquisition order as the T1w volumes.

2.2 Tissue Classification

A sequence of image processing algorithms was used to segment each of the MRI acquisitions into separate tissue classes: cortical graymatter (GM), subcortical GM, unmyelinated white matter (WM), myelinated WM and cerebrospinal fluid (CSF). These algorithms were designed to reduce imaging system noise, and to classify tissue types on the basis of MR intensity and expected anatomy derived from a

template. Anisotropic diffusion filtering was used to smooth noise without blurring fine details. Supervised spatially varying template moderated classification was used to identify tissue classes [20]. This analysis is a supervised nonparametric multispectral classification algorithm which identifies tissue classes in the data set by comparison to a set of prototype tissue values selected by an expert operator, knowledgeable in both developmental neuronanatomy and pediatric MR-imaging.

2.3 Minimum Entropy Affine Alignment

Generalizing from [18], we define the joint voxelwise entropy of a collection of J volumetric segmentations, S_j, $j \in 1...J$, each brought into alignment by a transform T_j, as

$$H(T_1(S_1), T_2(S_2), ...T_J(S_J)) = \sum_{i=1}^{N} H(v_i)$$

where N is the number of voxels of the volumes, v_i is the random variable defined by the values of voxel i across the images and $H(\cdot)$ is the discrete entropy function.

Consider each volumetric image consisting of N voxels. We define a random variable V at each voxel on the lattice of the aligned scans (as determined by the MRI acquisition — this can be generalized to sub-voxel resolution, the only constraint necessary is that sub-voxel accurate segmentations be available). Denote the value of the value of random variable V_i at voxel i by v_i. The joint entropy of the random variables defined at each voxel is then $H(T_1(S_1), T_2(S_2), ...T_J(S_J))$. If we assume that the observations of anatomy (tissue class) at each voxel are independent of the neighboring voxels then the joint entropy is the sum of the entropy of each voxel i.e. $H(T_1(S_1), T_2(S_2), ...T_J(S_J)) = \sum_{i=1}^{N} H(V_i)$, which gives us Equation 2.3. The value of $H(V_i)$ is determined by the relative frequency of the label of the segmentation at voxel i. A natural generalization would be to relax the assumption of independence between observations at each voxel by defining a Markov random field to represent the probability over a neighborhood at each voxel of the tissue classifications, and hence capturing to some degree the true spatial coherence of normal anatomy.

A minimum entropy alignment seeks to identify the set of transforms T_j which minimizes the entropy of the collection i.e.

$$\arg \min_{T_1,...,T_J} H(T_1(S_1), T_2(S_2), ..., T_J(S_J)).$$

A local optimization method has been proposed to solve this optimization simultaneously for each transform [18]. However, here we propose to approximate this by fixing one volume and computing the minimum entropy transform between this and

the other tissue classifications using a previously described fast, robust and accurate affine registration method suitable for tissue classifications [21]. We therefore solve the optimization problem :

$$\arg\min_{T_k'} E(I(S_1), T_k'(S_k)), \forall k \in 2...J,$$

where $I(\cdot)$ is the identity transform, and hence we construct the atlas with entropy

$$H(I(S_1), T_2'(S_2), ..., T_J'(S_J)).$$

2.4 Nonrigid Registration

We describe in this section the nonrigid registration algorithm we used for the experiments reported below. However, the primary focus of this work is to describe the method for evaluating any particular nonrigid registration algorithm, and the method we apply here (which is quite successful) is simply one of many that should be evaluated and compared.

Prior to computing a nonrigid registration, the above affine registration is used to remove global rotation, translation and scale differences. The nonrigid registration algorithm we used for our experiments here [22] is a generalization of the method proposed by Ferrant and co-workers [23]. In that work, displacements were estimated from segmentations of two scans by an active surface match, and the nonrigid deformation between surfaces was computed by solving a linear elastic physics-based model. Here we replace the active surface matcher with a brute force normalized cross correlation search from regions of high local structure. Again, displacements away from these regions are computed by solving a linear elastic physics-based model.

Local Structure Detection Sparsely sampled points with regions of high local structure were obtained by smoothing MR acquisitions with an edge-enhancing noise smoothing nonlinear diffusion filter, computing the magnitude of the gradient, and selecting points two standard deviations above the mean magnitude of the gradient.

Correspondence Measurement The normalized cross-correlation function allows comparison of regions of two scans. The function peaks for the displacement that best aligns the two regions. We use a brute force search in a limited search range to identify the best local match for each point of high local structure.

Interpolation with a Linear Elasticity Model The above two procedures identify sparse estimates across the image with known displacements. These are applied as boundary conditions in a linear elastic solver [22,23].

3 Results

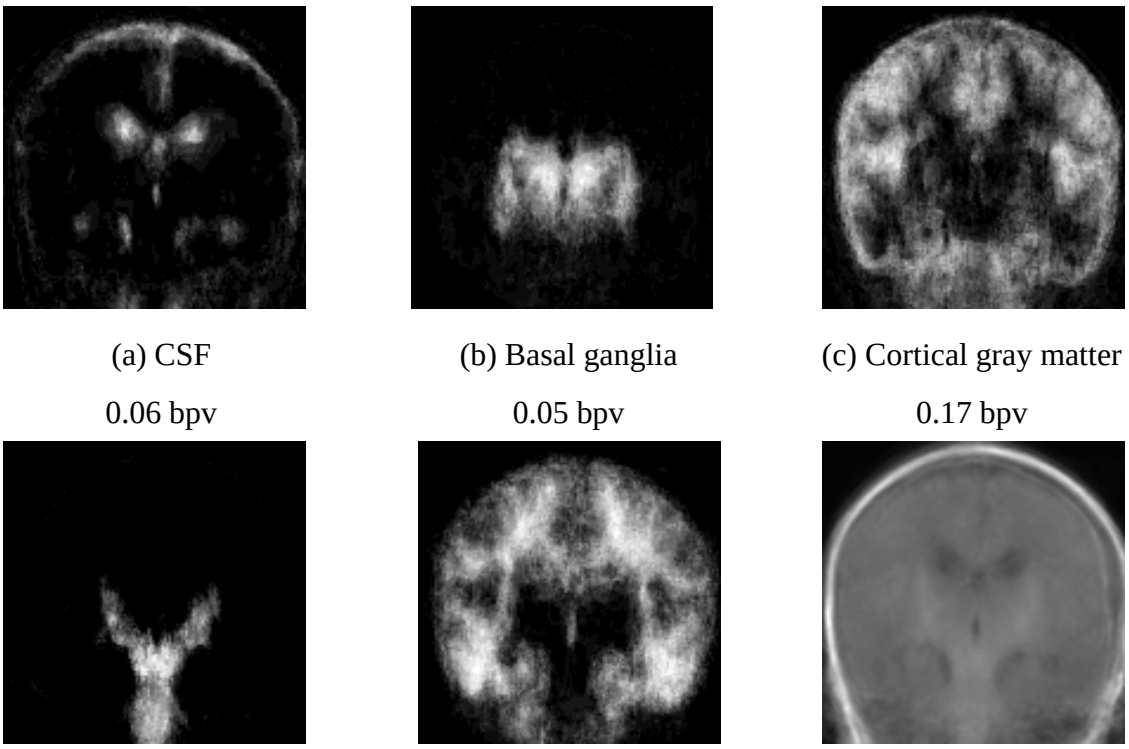
Figure 1 and Figure 2 illustrate the construction of statistical atlases using affine only and affine and nonrigid registration. Five tissue class atlases and the corresponding mean SPGR intensity for the recovered transformations are shown. We can observe that the nonrigid registration produces a spatial distribution of tissue classes that is better localized, and indeed, has a lower entropy (measured in bits per voxel) for each of the well-aligned tissue classes (CSF, cortical gray matter, myelinated white matter), and an equivalent entropy for the two tissue classes which remain difficult to spatially localize — unmyelinated white matter and basal ganglia (for which the nonrigid registration produces a better spatial alignment, but due to their small size is not different in the first two decimal places of the entropy measure).

4 Discussion and Conclusion

Two reports have discussed related concepts, described below, for encoding anatomical variability in a statistical atlas. These are the ideas of compact encoding of anatomical variability [13] and a "minimum variance frame" [11]. We observe that the minimum entropy criterion derived from segmentations that we propose here encapsulates both the concepts of compact encoding of anatomical variability in a formally precise fashion without the requirement of an explicit shape representation, and of maximizing the overlap of corresponding anatomical structures.

Ashburner and Friston [13] proposed a low resolution nonrigid registration algorithm optimizing over a few hundred parameters, justifying this approach as having low computational cost and being sufficiently accurate when correspondence between different individuals (and between structure and function) is not guaranteed. They noted the requirement for a compact encoding of structural variability, suitable for exploitation by a more advanced nonrigid registration algorithm.

Collins [11, pp.28–38] provides an excellent overview of the Talairach atlas and related methods, together with a summary of the primary limitations and restrictions of this form of atlas. These limitations provide motivation to search for an objective criterion with which to identify an intrinsic coordinate system in which a probabilistic atlas can be constructed. Some of these limitations include a lack of consistency in the anatomical definitions made by Talairach, lack of incorporation



(a) CSF 0.06 bpv

(b) Basal ganglia 0.05 bpv

(c) Cortical gray matter 0.17 bpv

(d) Myelinated white matter 0.05 bpv

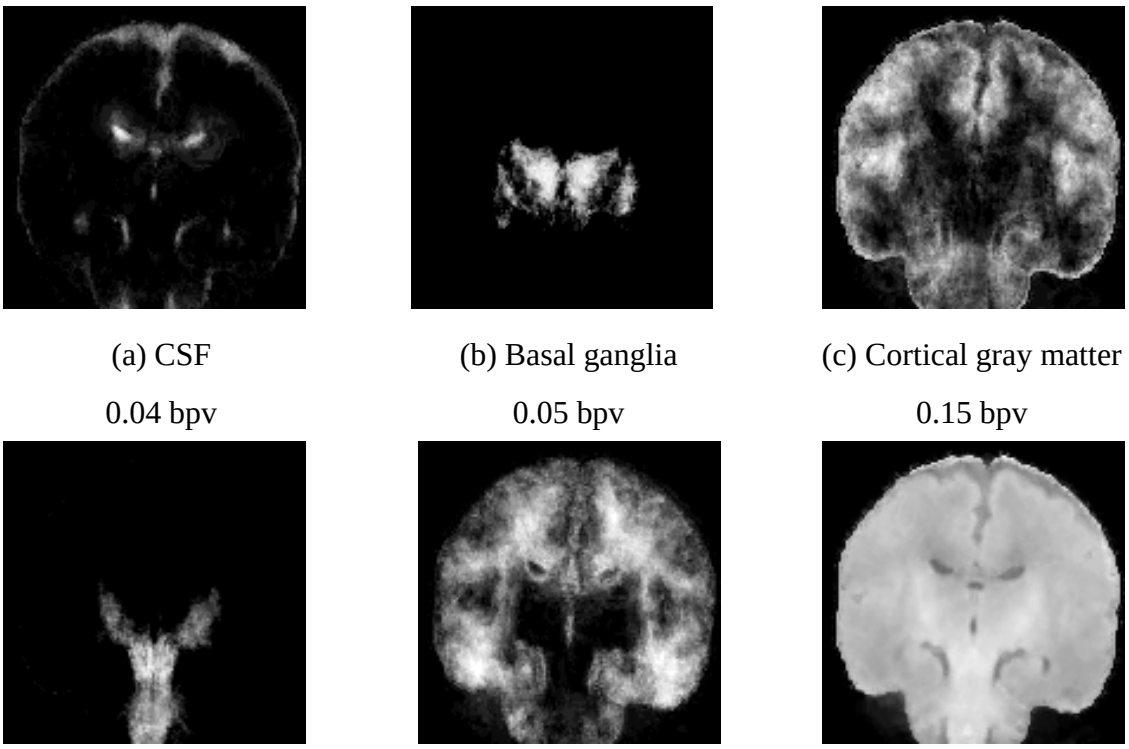
(e) Unmyelinated white matter 0.14 bpv

(f) Average SPGR intensity

Fig. 1. Minimum entropy alignment of tissue classifications from subjects with GA < 34 weeks with affine registration. The above figure shows a single slice from class atlases obtained with minimum entropy affine registration for (left to right) CSF, basal ganglia, cortical gray matter, myelinated white matter and unmyelinated white matter. The entropy per voxel for each tissue class atlas independently is noted in units of bits per voxel (bpv).

of anatomical variability (e.g. an error of 10-20mm in the localization of the central sulcus observed by Talairach [24]) and a lack of consistency between the existing but different methods of aligning new scans with any of the coordinate systems now commonly referred to as "Talairach-based". Collins constructed a mean atlas by aligning and averaging scans of 305 primarily male, primarily young subjects. He found regions of misalignment as compared to the Talairach atlas and attributed these to normal anatomical variability between the subject of the Talairach atlas and those of his cohort. Interestingly, Collins [11, p.36] proposed reconstructing a new atlas in a minimum variance frame as a mechanism for identifying a data-driven "best" coordinate system. This does not yet appear to have been done, possibly due to the difficulty of aligning cortical structures, for which the nonrigid registration algorithm of [11] is explicitly not designed.

Entropy is invariant to the specific label assigned to each tissue. The numeric label assigned to each tissue is irrelevant. It is only the frequency of occurrence of the tissue for a particular voxel that matters. This is not true of the variance measure,



(a) CSF 0.04 bpv

(b) Basal ganglia 0.05 bpv

(c) Cortical gray matter 0.15 bpv

(d) Myelinated white matter 0.04 bpv

(e) Unmyelinated white matter 0.14 bpv

(f) Average SPGR intensity

Fig. 2. This shows the tissue class atlases obtained with nonrigid registration for (left to right) CSF, basal ganglia, cortical gray matter, myelinated white matter and unmyelinated white matter.

which is dependent upon the values assigned to each tissue.

Since entropy is the negative of the average log likelihood, a minimum entropy method can be interpreted as a maximum likelihood method. Minimizing the entropy by transforming a single volume is equivalent to maximizing the mean log likelihood of the voxels in that volume under the distribution implied by the set of scans. So if we view our allowable transformations as being equally likely, then minimum entropy alignment can be interpreted as maximum likelihood alignment under the model implied by the set of volumes [18]. Its maximum value occurs when there is greatest disorder, i.e. an even distribution of labels over a particular voxel (not necessarily true for variance). Its minimum value occurs when there is least disorder, i.e. all labels for a particular voxel are the same. This property is shared by the variance criterion.

A minimum entropy criterion provides a means to obtain a coordinate system intrinsic to the data being studied. Anatomical variability captured by the registration algorithm is encoded in the transformations bringing subject scans into alignment, and the amount of anatomical variability not captured by the registration algorithm is indicated by the entropy of segmentations of the aligned data. We propose that

this criterion can be applied to assess the alignments obtained by affine and non-rigid registration algorithms. The minimum entropy alignment of segmentations of the subject scans represents the best encoding of the anatomical variability. Hence, this is a principled mechanism for identifying a common coordinate system for a group of subjects under study. The same reasoning applies when other anatomical structures, such as the ventricles or the hippocampal formation are to be studied — again a minimum entropy criterion allows the identification of an intrinsic coordinate system in which to study the structure.

The work described here has not dealt in detail with constraints upon the capacity of the transform aligning the anatomy. It is possible to construct transforms which minimize the entropy of the collection without meaningfully describing anatomical variability. For this reason it is desirable to study the capacity of the transforms allowed. In principle, the transforms should be selected from the group defined by normal anatomical variability, which is unfortunately unknown. An alternative may be to select a class of transforms a priori and seek the minimum entropy atlas constructed with a minimum description length constraint on the allowable transforms.

Applying this approach to scans of newborn infants grouped by age should allow the construction of a spatiotemporal atlas of the developing brain.

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