COMBINING REGIONAL METRICS FOR DISEASE-RELATED BRAIN POPULATION ANALYSIS

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ABSTRACT

In this paper, we present a new metric combining regional measurements to improve image based population studies that use manifold learning techniques. These studies currently rely on a single score over the whole brain image domain. Thus, they require large amount of training data to uncover spatially complex variation in the whole brain impacted by diseases. We reduce the impact of this issue by first computing pairwise measurements in local regions separately and then combining regional measurements into a single pairwise metric. We apply the new metric to learn the manifold of ADNI data and evaluate the resulting morphological representation by fitting multiple linear regression models to the mini-mental state examination (MMSE) score. The regression models show that the morphological representations from the proposed metric achieves higher estimation accuracy of MMSE score compared to those from the conventional global scores.

Index Terms— Alzheimer's disease, Manifold learning, Brain MRI

1. INTRODUCTION

Image based population studies become more significant part for analysis of the brain thanks to large databases of brain images. A necessary tool in image based brain population analysis is to construct a model to represent a large population of brain images preferably with respect to clinical variables. Manifold learning methods have recently gained increasing attentions for modeling brain images due to efficient low-dimensional representations [1, 2, 3, 4, 5, 6]. However, current brain population studies using manifold learning techniques rely on scores uniformly evaluating the entire image domain, which requires large amount of training data. We address this issue in this paper by proposing a new metric that first computes metrics in specific brain regions and then combine them into a single metric.

Manifold learning methods encode the pairwise relations between samples in the high-dimensional image space into the low-dimensional embedding. Therefore, they are largely impacted by the underlying pairwise measurements between data points. In general, image based brain population studies use a single score for the whole brain image as pairwise measurements. For example, Jia et,al. [4] measures the pairwise distances based on intensity differences in the global image domain. In addition, Aljabar et,al. [5] measures global shape and appearance pairwise similarities and combine them into a single pairwise score. However, the drawback of manifold learning from conventional global scores is that it requires large dataset to reveal the anatomical variation of the whole brain due to curse of dimensionality issue. If we do not have enough samples for very high-dimensional manifold, the resulting embedding is likely to be a poor approximation of the true manifold structure. Therefore, large number of samples are necessary to learn spatially complex patterns of morphological changes impacted by brain diseases. However, typical number of images in a study is limited to a few hundreds which are not sufficient to uncover spatially complex anatomical variation in the whole brain.

To reduce the impact of the limited samples, we propose a new metric which independently measures the pairwise metric in specific brain regions. Since the anatomical variation in the specific region has lower degree of freedom compared to the whole brain, the region-specific metric requires smaller number of samples. We then combine multiple regional metrics into the single metric with preserving the pairwise relations in specific regions to generate morphological representations of brain population. The new metric is used for a manifold learning of a subset of ADNI dataset and validated by estimating mini-mental state examination (MMSE) scores via multiple linear regression. Our new metric finds more precise representations of the morphology that is relevant to this clinical score compared to using a conventional global score.

2. COMBINED METRIC FROM LOCAL REGIONS FOR MANIFOLD LEARNING

Our framework of combining regional measurements for manifold learning is summarized in Figure1. We first divide the image into multiple regions and then separately measure the pairwise metric between small regions. We define the regional pairwise metric based on the global deformation fields. We then combine these regional metrics into a single global

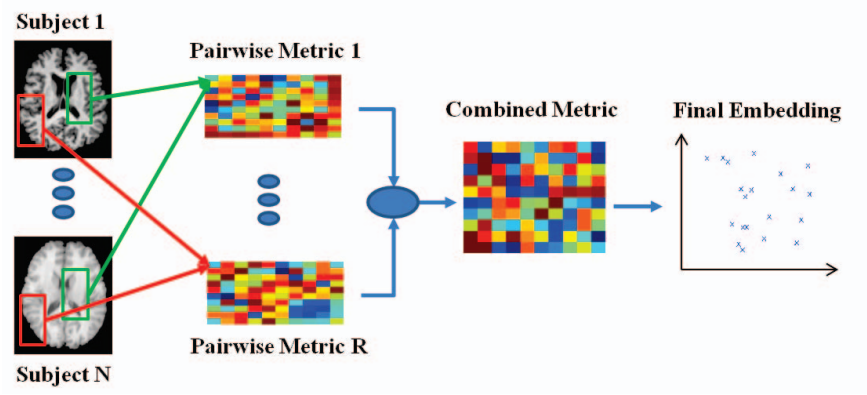


Fig. 1. An overview of the framework to combine regional measurements for manifold learning

metric. Finally, we feed the combined metric into a manifold learning step to generate a low-dimensional embedding coordinates that can be used to find correlation with clinical variables.

2.1. Measuring Pairwise Scores for Image Regions

We now describe our approach to measure pairwise scores between two images with respect to a specific region. Suppose we have N whole brain images $\{I_i : i = 1, 2, ..., N\}$ and each image I_i is on a 3D discrete domain Ω. We assume that images are linearly registered to the common template and the bias field is removed. To measure the regional pairwise score between I_i and I_j, we first non-rigidly register I_i to I_j resulting in transformation $\phi_{ij} : \Omega \rightarrow \Omega$. We choose the Diffeomorphic Demons [7] for this task due to its efficiency. Then, we divide the image domain Ω into R disjoint regions $\{\Omega_r : r = 1, 2, ..., R\}$ so that $\cup_{r=1}^{r=R}\Omega_r = \Omega$ and $\cap_{r=1}^{r=R}\Omega_r = \emptyset$. In practice, we divide $160 \times 200 \times 136$ whole brain image into sixty-four $40 \times 50 \times 34$ blocks. Then, we define a dissimilarity pairwise score $d_r(I_i, I_j)$ between two subject i and j with respect to region Ω^r as the weighted sum of intensity difference and field smoothness [2]:

$$d_r(I_i, I_j) = \sum_{\vec{p} \in \Omega^r} ||I_i(\vec{p} + \phi_{ij}(\vec{p})) - I_j(\vec{p})||_2^2 + \lambda || \bigtriangledown \phi_{ij}(\vec{p})||_2^2$$

where $\vec{p}$ is the voxel location, λ is a weighting parameter between intensity difference and field smoothness term, and $||\dots||_2$ is the $L2$ norm.

It is worth noting that $N(N-1)$ registrations need to be performed to compute $d_r(I_i, I_j)$ for all pairs of images. To reduce the computational burden, we assume here that our registration is symmetric and compute $d_r(I_i, I_j)$ only for $i < j, i, j = 1, 2, ..., N$ and assign $d_r(I_i, I_j)$=$d_r(I_j, I_i)$. Also, we empirically set λ so that two terms have the same maximum value over all pairs of images.

2.2. Combining Regional Metrics

After measuring the multiple regional pairwise scores, we combine them into a single pairwise measurement for manifold learning. We do so by first pointing out that $d_r(I_i, I_j)$ is an approximation of the metric on the diffeomorphism space only for two similar images. Hence, for faraway points, the metric needs to be approximated by adding up a sequence of short metric between neighboring points. Therefore, we use the geodesic distance $g_r(I_i, I_j)$ (sum of short distance between neighboring points) for each region that best preserves the pairwise relationship for combination instead of $d_r(I_i, I_j)$ [2]. In order to find $g_r(I_i, I_j)$, we separately represent the image regions as a graph whose node corresponds to the subject. We assign the edge length between two nodes to $d_r(I_i, I_j)$. Then, we construct a sparse k nearest neighbor (kNN) graph in which edges of only k nearest neighbors are retained. Heuristically, we set the smallest value that makes the kNN graph connected as k. From the kNN graph, we find the shortest path on the graph using Dijkstra algorithm [8]. Then, we define $g_r(I_i, I_j)$ as the sum of the edge length along the shortest path on the graph:

$$g_r(I_i, I_j) = \sum_{(a,b) \in l_r(i,j)} d_r(I_a, I_b),$$

where $l_r(i, j)$ is the shortest path between subjects i and j in the kNN graph with respect to the region Ω_r. Here, we measure regional geodesic distances thereby allowing each region to have its own representation of underlying regional morphological change.

Then, we define the metric over the entire image domain $c(I_i, I_j)$ between I_i and I_j by combining the regional geodesic distance:

$$c(I_i, I_j) = \sqrt{\sum_{r=1}^{R} g_r^2(I_i, I_j)}$$

It is worth noting that the region which has more anatomical variation will contribute more on $c(I_i, I_j)$ because $g_r(I_i, I_j)$ will be larger on such region.

2.3. Deriving Embeddings from Combined Metric

Now, we have a single combined pairwise metric for image dataset. To derive embedding coordinates from this combined metric, we apply ISOMAP [9] algorithm. In order to use the ISOMAP algorithm, we again represent the data as a graph whose node corresponds to the image samples. Then, we assign the edge length as $c(I_i, I_j)$ and construct a connected kNN graph. By solving eigenvalue problems, we can find a low-dimensional embedding of image data. This embedding coordinates can be used to represent the brain population. The dimension of embedding is less than the number of subjects. To further reduce the dimensionality of representations, we choose the first 20-dimensional embedding coordinates resulting in a residual variance of less than 0.1.

3. ESTIMATING CLINICAL VARIABLES

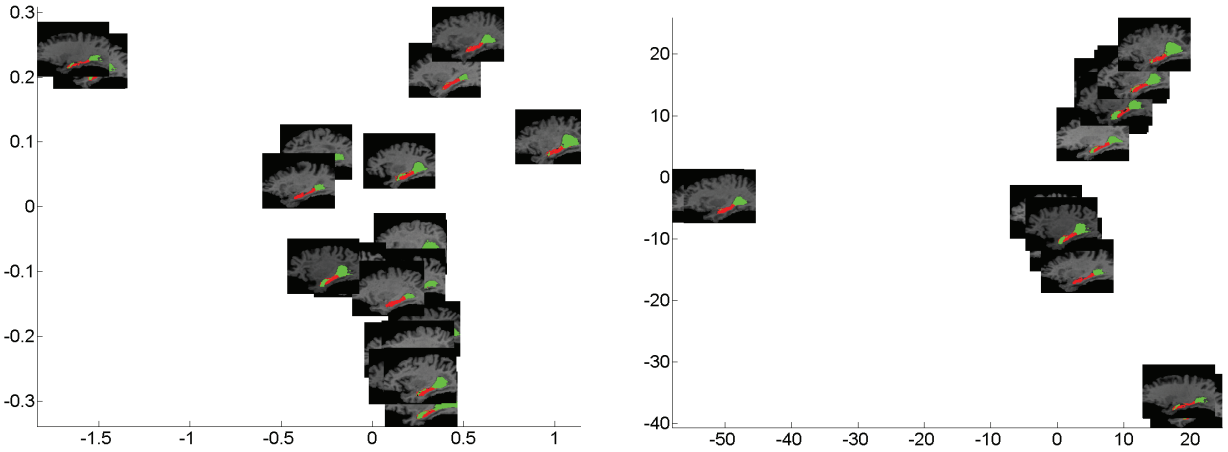
We use our combined metric to generate the representation of a subset of ADNI dataset. The dataset consisted of structural MRI scans of 100 Mild Cognitive Impairment (MCI) subjects. The resulting representation is evaluated by estimating MMSE scores via multiple linear regression model. To have a reference point, we also generate the representation using a conventional global score which is the deformation based distance in the whole image domain. (i.e. $R = 1$)

3.1. Visualizing the Embeddings

First, we plotted the embedding coordinates for ADNI dataset in Figure2. We used the first two embedding coordinates for visualization purpose. The sagittal slice for chosen subjects is displayed with highlighted ventricle (green) and hippocampus (red). Figure2(a) and Figure2(b) shows the embeddings from conventional global scores and combined regional metrics, respectively. Compared to Figure2(a), ventricle size and hippocampus volume are the most significant changes observable along the vertical axis in Figure2(b). This indicates that combined regional metrics can better characterize the gradual shape change in ventricle and hippocampus regions. This implies that combined regional metric can better capture the anatomical variation in specific brain regions with the small number of samples. Since ventricles and hippocampus regions are related to cognitive declines in Alzheimer's disease, embedding coordinates from combined regional metrics can have high correlation with clinical variables such as MMSE scores.

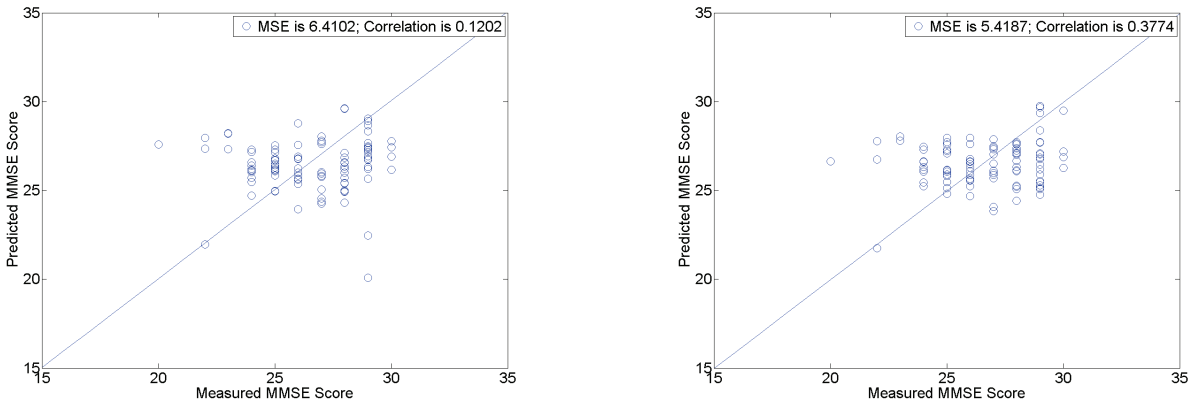
3.2. Comparison of MMSE scores

For further analysis, we conducted the multiple linear regression with MMSE score based on the resulting embedding coordinates on this dataset. We performed the cross-validation in which the subjects were divided into ten folds (9/10 for training and 1/10 for testing). The trained regression model was applied to test subjects. The estimated MMSE scores of test subjects were compared to the clinically



(a) (b)

Fig. 2. Two-dimensional embeddings of ADNI data based on (a) conventional global scores and (b) combined regional metrics. A sagittal slice is shown for selected subjects. Ventricles and hippocampus regions are highlighted in green and red, respectively. Notice the gradual shape change in ventricle and hippocampus regions in (b) compared to (a)



(a) (b)

Fig. 3. Scatter plots of clinically measured MMSE scores versus predicted MMSE scores with embedding coordinates from (a) conventional global scores and (b) combined regional metrics. The sloping solid line represents [Predicted MMSE = Measured MMSE].

measured MMSE score. Figure3(a) and 3(b) shows scatter plots of clinically measured MMSE scores versus predicted MMSE scores from the embedding based on conventional global scores and combined regional metrics, respectively. In visual inspection, the predicted MMSE score from combined regional metrics is better aligned to the line [Predicted MMSE=Measured MMSE]. In quantitative analysis, the embedding from combined regional metrics achieves lower mean squared error (5.4187 vs. 6.4102) and higher correlation (0.3774 vs. 0.1202) between clinically measured MMSE and predicted MMSE scores than the embedding from conventional global scores. This implies that embeddings from combined regional metrics outperform those from conventional global scores in terms of predictive power for MMSE scores. It is worth noting that the prediction of MMSE was not anticipated to yield high correlation in linear regression because MMSE score itself is discrete and the limited information in images alone is not sufficient to predict clinical states [1].

4. CONCLUSION

In this paper, we proposed a new metric for disease-related brain population analysis using manifold learning. The metric separately measures the pairwise scores in multiple brain regions and combines them into a single pairwise metric. The embeddings from the new metric achieved higher estimation accuracy for MMSE scores of MCI subjects than those from a conventional global score. This indicates that morphological representation from the new metric is more related to the change induced by the disease compared to those from the conventional global score. Future work will focus on finding the region specific weight on combined metric and employing the proposed metric to other medical imaging applications such as registration.

5. REFERENCES

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