Medical image registration is a challenging problem, especially when there is large anatomical variation in the anatomies. Geodesic registration methods have been proposed to solve the large deformation registration problem. However, analytically defined geodesic paths may not coincide with biologically plausible paths of registration, since the manifold of diffeomorphisms is immensely broader than the manifold spanned by diffeomorphisms between real anatomies. In this paper, we propose a novel framework for large deformation registration using the learned manifold of anatomical variation in the data. In this framework, a large deformation between two images is decomposed into a series of small deformations along the shortest path on an empirical manifold that represents anatomical variation. Using a manifold learning technique, the major variation of the data can be visualized by a low-dimensional embedding, and the optimal group template is chosen as the geodesic mean on the manifold. We demonstrate the advantages of the proposed framework over direct registration with both simulated and real databases of brain images.
dealing with an analytical manifold of diffeomorphisms. In partic-

ular we borrow an idea from Isomap algorithm (Tenenbaum et al., 2000), which replaces the geodesic path of the analytical manifold by the shortest path on a k-nearest-neighbor (kNN) graph that approximates the metric structure of the empirical manifold. We refer to our approach as a framework for Geodesic Registration on Anatomical Manifolds (GRAM).

The GRAM has the following beneficial properties:

1. Learning of anatomical manifolds: GRAM computes the geodesics path from the observed anatomical variation of the actual data, which is the key difference to the previous approaches to the large deformation problem. The anatomical manifold learned from a database is reusable: to register test images from a new database to a template image in the old database, we can compute the new registration paths by utilizing the learned deformations.

2. Efficiency: Since in this framework the deformations are computed between two close images, we can use simpler and faster registration algorithms such as Diffeomorphic Demons algorithm (Vercauteren et al., 2007), rather than more elaborate algorithms such as Large Deformation Diffeomorphic Metric Mapping (LDDMM) (Beg et al., 2005). In GRAM framework, a registration algorithm is an interchangeable component, and therefore different kinds of registration algorithms may be used in the framework (more will be discussed in Section 4). The only requirement is that the component registration algorithm results in diffeomorphic deformation fields for two similar images.

3. Visualization and automatic template selection: From the analysis of the shortest paths, GRAM computes a Euclidean embedding of the data which allows us to preview the overall structure of the data such as existence of multiple clusters or the major mode of variation. It also finds an optimal template among the samples for groupwise registration.

1.4. Related work

This paper builds on our previous work (Hamm et al., 2009) and has been extended by new experiments and in-depth analysis of the algorithm. In this framework we adopt the Isomap algorithm (Tenenbaum et al., 2000) to compute and visualize the Euclidean embedding of the metric structure of the data after pairwise registration. Several authors have proposed related algorithms to analyze metric structure of the data and visualize them. Blezek and Miller (2006) proposed Atlas Stratification, which finds multiple modes of the images by mean-shift and visualizes the distribution of the data by Multidimensional Scaling. Images are affinely registered, using Mutual Information as a metric between two images, although it is not a metric, strictly speaking. Sabuncu et al. (2008) proposed an algorithm that also finds the multiple modes of the images by Generalized Expectation-Maximization-based clustering. Images are registered by B-spline, and the membership probability of an image belonging to multiple templates are calculated iteratively. The use of geodesic distances to discover the manifold structure of data, has been proposed by Rohde et al. (2008) and Gerber et al. (2009). These two papers commonly use LDDMM and Multidimensional Scaling to visualize the manifold structure of data, and the latter further uses a kernel regression to reconstruct unseen images from the manifold. However, the two methods directly register all image pairs, which can be difficult and slow for image pairs that are very dissimilar. Our framework distinguishes itself from the aforementioned methods by the following facts: we not only compute the low-dimensional embeddings to visualize the data, but we also compute actual large deformation from each image to a common template for groupwise registration. Furthermore, these large deformations are computed efficiently via the shortest path on a k-nearest-neighbor (kNN) graph that approximates the metric structure of the empirical manifold.
sequences of small deformations on the anatomical manifold learned from data.

The remainder of the paper is organized as follows. Section 2 describes the proposed algorithm in detail. Section 3 demonstrates the proposed framework with several simulated and real databases, including simulated 2D images, 3D cortical surfaces from OASIS database, and 3D Fractional Anisotropy map of mouse brains. Section 4 discusses the limitations and extensions of the proposed method, and Section 5 concludes the paper with discussion on the future work.

2. Methods

In this section we provide the algorithmic details of the GRAM framework. The overall training procedure consists of three stages. First, we analyze the data structure by coarse registrations between all image pairs. From this we find a kNN graph structure and a low-dimensional embedding of the data. In the second stage, we choose a template automatically from the graph structure, and identify geodesic paths from the template to other images on anatomical manifolds. In the third stage, we compute the large deformations between adjacent images along the paths. In addition to the training procedures, we also describe how to use the trained manifold to register a new set of images by updating the previously computed deformations between adjacent images along the paths. In addition to the training procedures, we also describe how to use the trained manifold to register a new set of images by updating the previously found geodesic paths. Each stage is described in more detail in the following sections.

Throughout the paper, let us assume the dataset \( X \) consists of \( n \) images \( I_1, \ldots, I_n \) and each image is a nonnegative real function on a 2D or a 3D domain \( \Omega \).

2.1. Construction of empirical manifolds

In the first stage we construct the empirical manifold of data by investigating its metric structure. For this purpose we represent the data as a graph whose vertices correspond to the image samples. Below is the summary of the required steps.

1. Perform coarse registrations between all pair of images. The edge \( d_{ij} \) is assigned a weight equal to the distance \( d_{ij} \) between two images after registration. The definition of distance \( d_{ij} \) is dependent on the specific algorithm used for registration, and we use a weighted sum of a similarity term and a smoothness term.

2. Construct a connected kNN or \( \epsilon \)-NN graph based on the edge lengths.

3. Find the geodesics (=shortest paths on the graph) between all pairs of vertices, e.g., by Dijkstra’s or Floyd-Warshall algorithm. The length \( g_{ij} \) of a geodesic is the sum of its edge lengths \( d_{ij} \) along the path.

4. (Optional) Visualize the Euclidean embedding of the data by solving eigenvalue problems (refer to Tenenbaum et al. (2000) for details).

The distance \( d_{ij} \) is asymmetric in general, that is \( d_{ij} \neq d_{ji} \). To make it symmetric we can use the average \( 0.5(d_{ij} + d_{ji}) \), or we can compute \( d_{ij} \) for \( i < j \) and \( j = 1, 2, \ldots, n \) and assign \( d_{ji} = d_{ij} \) to reduce the computation to a half. The latter is possible since \( d_{ij} \) and \( d_{ji} \) are usually highly correlated. By enforcing symmetry the shortest path length \( g_{ij} \) becomes a valid metric, since triangle inequality is fulfilled by the definition of shortest paths.

\[ d_{ij} = \begin{cases} 0 & \text{if } i = j, \\ \text{minimum distance} & \text{if } i \neq j \end{cases} \]

The size of the neighborhood \( k \) in kNN is a parameter the user should select. For a small value of \( k \), the graph is not connected and has multiple disjoint subgraphs. For a too large value of \( k \), the graph becomes completely connected and the shortest path is the same as the direct path. A convenient heuristic is to choose the smallest value that makes the kNN graph connected. More will be discussed in Section 4. An alternative to kNN selection is \( \epsilon \)-neighbor selection, in which two images \( I_i \) and \( I_j \) are considered neighbors of each other if \( d_{ij} < \epsilon \) for some \( \epsilon > 0 \). The advantage of this method is that we can strictly set an upperbound to the distance of the edges that will be used for registration. However, finding the smallest \( \epsilon \) that makes the whole graph connected still requires searching through all values of \( \epsilon \).

The most time-consuming part in practice is the pairwise registration between all images which requires \( O(n^2) \) number of registrations. To reduce the overhead we can perform the registration on coarse-resolution images of the original data and also use fewer number of iterations than the final registration in the later stage. Although such approximation is not ideal, it may be necessary to keep the computation time practical for databases with a large number of images. To further speed up the pairwise registration, we can distribute the registration tasks over multiple CPUs, since the registration of one pair is independent of the other pairs.

2.2. Automatic template selection

An unbiased template of the given data can be defined as the geodesic mean of the data (Joshi et al., 2004; Avants and Gee, 2004). From the graph derived in the previous section, we can choose a template from the population that is closest to the geodesic mean:

\[ I_T = \arg \min_i \sum_j g^2(I_i, I_j), \]

where \( g \) is the shortest path length. Since the shortest path length is only an approximation, the chosen template is different from those of Joshi et al. (2004) and Avants and Gee (2004). However, the advantage of this approach is that, the template is chosen with little additional computation. Since we have already computed the geodesic lengths \( g_{ij} \), the template can be chosen by looking up the values.

Two other variants to the mean are the center

\[ I_T = \arg \min_i \max_j g(I_i, I_j), \]

and the median

\[ I_T = \arg \min_i \sum_j g(I_i, I_j). \]

The three templates look similar in our experiments, but we choose the median as the template due to its resilience to outlying samples in the data.

2.3. Computation of large deformations

We compute the large deformation from the template \( I_T \) to any node \( I_i \) by a recursive composition of the small deformations from its edges along the geodesic path. Let \( f_{ij}: \Omega \rightarrow \Omega \) denote the deformation field computed from the registration of \( I_i \) to \( I_j \). Given the two fields \( f_{ij} \) and \( f_{jk} \), we can easily compute the composition field \( f_{jk} = f_{jk} \cdot f_{ij} \) by resampling and interpolating the two fields. The final deformation \( f_{ij} \) is the refinement on the composed field \( f_{ij} \) by a few additional iterations of registration. Below is the summary of the procedure.

1. Identify \( n \) geodesic paths from \( I_T \) to the rest \( I_j \), \( \forall j \in 1, \ldots, n \).
2. Enumerate all edges $\varepsilon$ used in any of the shortest paths. Perform accurate registration between $(i, j)$, $\forall e_{ij} \in \varepsilon$.

3. For each $j \in 1, \ldots, n$,
   (a) Let $s = (s_1 = T, \ldots, s_n = j)$ be the geodesic path from $I_T$ to $I_j$.
   (b) If $f_{s_j}$ is already computed then exit.
   (c) Otherwise, recursively compute $f_{s_{j-1} s_j} = f_{s_{j-1} s_{j-2}} \cdot f_{s_{j-2} s_{j}}$.
   (d) Fine-tune $f_{i, s_n}$ by additional iterations of registration.

Note that we needed only coarse registration results in the previous stages, and this stage is where we actually perform accurate registrations. Step 2 may seem to be a huge computational burden at first since the number of all the edges in a graph can be as large as $n^2$. In fact, we only need to update the registration for $n - 1$ edges, that is, no more than the number of direct registration for a conventional approach. This is due to property of the graph that the shortest paths from the template to the rest forms a spanning tree. Furthermore, the registration converges faster since the two adjacent images are similar by construction. The condition that each deformation field of the edge being diffeomorphic is sufficient for the composed field to be diffeomorphic as well.

The fine-tuning is a crucial part of the procedure. It is required since the transitivity (Christensen and Johnson, 2003) is not guaranteed for registration algorithms in general, that is, the composed field $f_{i, k} \cdot f_{k, j}$ of the two registration results is not the same as the field $f_{i, j}$ computed directly from the registration between $I_i$ and $I_k$. In summary, the composed field serves as the initial field to start the registration which helps to avoid the local minimum of direct registration path, and the fine-tuning serves as the minimization of the transitive error.

2.4. Registration of new data

The learned manifold of training images can be used to facilitate the registration of new test images not included in the training database. When the new images are introduced, the manifold can be reused without recomputing the geodesic paths from the beginning. The geodesic deformation for the test image can be computed by registering the new image to the closest image in the training database and then composing the field with the known learned deformation field of the closest image to the template. Below is the summary of the procedure.

1. Register the new test image to the training images to compute the distances $d_i$ and the deformation $f_i$, where $i = 1, \ldots, n$ is the index of the training images.
2. Update the distance from the template to the test image by adding $d_i$ and $d_{r,T}$, where $d_{r,T}$ is the known distance from the template to $I_T$.
3. Choose the shortest path from above.
4. Compose the fields $f_i$ and $f_{s_{j-1}}$, where $f_{s_{j-1}}$ is the known field from the template to $I_{s_{j-1}}$.
5. Fine-tune the field by additional iterations of registration.

For this approach to work, the new dataset must not be too heterogeneous to the training dataset. Otherwise, the new data will be equally distant from all training images and gain no benefit from the learned deformations of the training data.

3. Experiments

In this section we test the proposed framework with several simulated and real databases, including simulated 2D images, 3D cortical surfaces from OASIS database, and 3D Fractional Anisotropy volume of mouse brains. To demonstrate its advantages, we compare the proposed method with the direct registration method which does not use the geodesic path. Since we do not have ground truth for the ’best’ registration for these databases, we measure the quality of the registration results in terms of MSE, Harmonic Energy (HE) and Maximum Jacobian Determinant (MJD) where maximum is computed over all voxels.

3.1. Validation with simulated data

We first test the proposed framework on a dataset of simulated 2D cortical patches. The aim of this section is to demonstrate the properties of the proposed method and to check the validity of the algorithm under varying parameters. The data consist of 60 binary 2D images of size 140 $\times$ 140 which simulate a patch of a cortex varying in the thickness and the number of folds. We use an ITK (Ibanez et al., 2005) version of the Diffeomorphic Demons by Vercauteren et al. (2007) for registration due to its fast speed. The images are registered with three levels of resolution for coarse pairwise registration, and with the original resolution for fine-tuning, with a smoothness parameter of $\sigma = 1.5$. The whole procedure takes about an hour on our cluster server (Sun Grid Engine), which has 22 multi-core nodes and 4–8 GB. Since the server is a shared resource, the exact time can vary. The computing time of the first stage, which is the dominant stage, can be estimated more accurately from the equation $0.5n(n - 1)$, where $n$ is the number of images and the $T$ is the average time to register a single image to a template under a given computing resource.

From the coarse pairwise registration we define the distance in Section 2.1 as the weighted sum of: (1) MSE between the fixed and warped images and (2) HE of the deformation field:

$$d_q = w \text{MSE} (I_i, I_j(f_{i,j})) + (1 - w) \text{HE} (f_{i,j}).$$

The smoothness parameter affects the registration results significantly. A too small value of $\sigma$ reduces the final MSE, but also increases HE and MJD significantly (over-registration). A too large value of $\sigma$ can make the final MSE many times larger than it is with a small $\sigma$ although it reduces HE and MJD (under-registration). Since the parameter selection is the choice associated with the component algorithm and not with our framework, we do not perform repeated experiments for a full range of $\sigma$. Instead, we have chosen an appropriate $\sigma$ by checking that the deformation field has no negative Jacobian, that is, the field is diffeomorphic. However, the parameter $w$ and $k$ remains to be decided.

We first show the results with a fixed value of $w = 0.75$ and $k = 16$. Fig. 2 shows the two-dimensional Euclidean embedding of the simulated data. The embedding conveniently summarizes the major shape variation of the population which have three prototypical shapes (which resemble the letter U, V, and W).

To measure improvements in registration due to the geodesic approach, we calculate the relative change of MSE

$$\delta \text{MSE} = 100 \times \frac{\text{MSE}_{\text{geodesic}} - \text{MSE}_{\text{direct}}}{\text{MSE}_{\text{direct}}}.$$

and similarly for HE and MJD.

We perform the groupwise registration using the automatically chosen template with the proposed method and the direct method. The registration results are shown in Fig. 3 which shows the paths and the final warped images of the five samples which has the largest decrease in MSE. The image warped by the proposed method is

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1. Harmonic Energy is the mean Frobenius norm of the Jacobian of the deformation field.
2. We report the 99 percentile of the Jacobian Determinant instead of the maximum since the maximum is prone to noise.
3. The $w$ here is not an absolute value but a relative weight between the similarity term and the smoothness term. We normalize the two term to have a unit $l_2$ norm summed over all images.
In this figure legend, the reader is referred to the web version of this article.

In the three prototypical shapes, the template marked by the green box is chosen from the median of the geodesic distances. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 2. Two-dimensional embedding of the manifold of simulated shapes. Only a subset of the samples is shown to avoid clutter. The template determined to be the median of the graph is marked by a green box, and the red lines denote the nearest-neighbor relationship. The embedding reveals that there are three major variants (which resemble the letters U, V, and W) and the rest of the images lie in-between the three prototypical shapes. The template marked by the green box is chosen from the median of the geodesic distances. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1 summarizes the relative changes in MSE, HE and MJD. Although the decrease in MSE is of our main concern, HE also decreases significantly. This shows us that our framework can achieve more accurate and smoother registration simultaneously on average. Also note that in the worst case, geodesic method results in higher errors than direct method. The explanation for this is as follows. The registration errors from geodesic method have two opposing factors. One is the desirable decrement due to the avoidance of the local minimum of direct registration, and the other is the undesirable increment from the transitive error of the composition of deformation fields. Our experiment shows that the summed effect of the two factors is beneficial on average, but it can be negative for a fraction of the whole samples. In practice, we can always register images using both direct and geodesic methods and choose the better of the two methods for each sample, since direct registration using Demons is computationally inexpensive.

To check the robustness of the framework to the change of parameters, we repeat the experiments with three values of w (0.25, 0.5, 0.75). As we mentioned in Section 2.1, a heuristic of choosing k is to find the smallest value c that makes the kNN graph connected. We also repeat the experiments with k = 0, c = 2, c = 4. The w and k change the topology of kNN graph and subsequently the paths and the template. Fig. 4 shows two-dimensional Euclidean embeddings with these parameters. The overall shape of the embedding and the chosen templates seems to be affected by the parameters. However, the groupwise registration results of Table 2 shows that the improvements in MSE, HE and MJD vary within a small range. Note that MSE and HE decrease consistently whereas the average MJD increases sometimes, which may be due to the fact that HE and MJD measure different aspects of ‘smoothness’. From these experiments we conclude tentatively that a small difference in the parameters does not adversely affect the final outcome.

3.2. Registration of new data

We demonstrate the capability of our method described in Section 2.4: the learned manifold of the training samples can be used to facilitate the registration of new test images not included in the training database. For this purpose we generate additional simulated images that are similar to but different from the training images.

To visualize the test images along with the training images, we need to compute the coordinates of the new test points in the embedding of the training images. To do this, we first register the test images to the training images and compute the distances from (2). Using these new distances, and the known embedding and pairwise distances of the training images, we compute the coordinates from the algorithm described in (de Silva and Tenenbaum, 2002). Fig. 5 shows the two-dimensional Euclidean embedding of four test images superimposed on the embedding of the trained simulated data. The embedding provides information on the homogeneity (or heterogeneity) of the test data to the training data. One of the test images is slightly apart from the training population due to its relatively distinctive shape, whereas the remaining test images blend well into the population.

We register the test images to the template determined from the training data, using the method in Section 2.4. The registration results are shown in Fig. 6 which shows the paths and the final warped images of the test images. Compared with the MSE obtained by registering the test images to the template directly, the MSE obtained from the proposed method has a decrease of 3.4%, 34.6%, 3.2%, and 38.8%, for the four test images, respectively.

3.3. 3D cortical surfaces of human brains

We test the algorithm on a database of real brain images. The Open Access Series of Imaging Studies (OASIS) databases is a

![Fig. 3. Left: geodesic paths of simulated shapes. The images are sample paths from the lefmost image (moving) to the rightmost image (fixed). The number on top of each image is the sample index. Note the gradual change of shape along each path. Right: comparison of the final warped images from the geodesic versus the direct registration using the same registration method and parameters. Warping the W-shaped images (55, 41, 57) to the fixed image (53) requires a large deformation near the middle fold in the image. The proposed method finds such path that gradually flattens the middle fold, whereas the direct registration aggressive fit the image by squeezing the middle fold towards the right side of the image, resulting in artificial fissures in the image.](image-url)
Table 1
Summary of registration results in simulated data. The decrease in Mean Square Error (MSE), Harmonic Energy (HE), and Maximum Jacobian Determinant (MJD) are shown in percentage. A higher value means a larger improvement.

<table>
<thead>
<tr>
<th>Measure</th>
<th>MSE Mean ± std (%)</th>
<th>Max (%)</th>
<th>Min (%)</th>
<th>HE Mean ± std (%)</th>
<th>Max (%)</th>
<th>Min (%)</th>
<th>MJD Mean ± std (%)</th>
<th>Max (%)</th>
<th>Min (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease</td>
<td>10.7 ± 16.1</td>
<td>43.4</td>
<td>−16.3</td>
<td>8.9 ± 8.4</td>
<td>32.4</td>
<td>−13.5</td>
<td>0.7 ± 10.8</td>
<td>30.7</td>
<td>−32.4</td>
</tr>
</tbody>
</table>

Fig. 4. Embeddings and templates under varying parameters. These nine figures looks different but they all show the gradual variation of the shapes between the three prototypical shapes (U, V, and W).

Table 2
Summary of registration results in simulated data with different parameters. The maximum and the average decrease in Mean Square Error (MSE), Harmonic Energy (HE), and Maximum Jacobian Determinant (MJD) are shown in percentage. A higher value means a larger improvement.

<table>
<thead>
<tr>
<th>Measure</th>
<th>MSE Mean (%)</th>
<th>Max (%)</th>
<th>HE Mean (%)</th>
<th>Max (%)</th>
<th>MJD Mean (%)</th>
<th>Max (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$w = 0.25, k = 11$</td>
<td>8.9</td>
<td>43.1</td>
<td>3.0</td>
<td>40.1</td>
<td>1.3</td>
<td>40.2</td>
</tr>
<tr>
<td>$w = 0.25, k = 13$</td>
<td>8.2</td>
<td>44.4</td>
<td>3.6</td>
<td>40.3</td>
<td>−2.3</td>
<td>32.8</td>
</tr>
<tr>
<td>$w = 0.25, k = 15$</td>
<td>7.8</td>
<td>43.9</td>
<td>4.2</td>
<td>40.3</td>
<td>−2.0</td>
<td>32.8</td>
</tr>
<tr>
<td>$w = 0.50, k = 11$</td>
<td>8.1</td>
<td>47.5</td>
<td>4.3</td>
<td>40.3</td>
<td>−1.4</td>
<td>41.1</td>
</tr>
<tr>
<td>$w = 0.50, k = 13$</td>
<td>8.4</td>
<td>45.8</td>
<td>4.2</td>
<td>40.3</td>
<td>−1.8</td>
<td>41.1</td>
</tr>
<tr>
<td>$w = 0.50, k = 15$</td>
<td>9.9</td>
<td>43.9</td>
<td>3.4</td>
<td>40.7</td>
<td>−2.5</td>
<td>41.1</td>
</tr>
<tr>
<td>$w = 0.75, k = 12$</td>
<td>5.5</td>
<td>39.2</td>
<td>3.7</td>
<td>33.8</td>
<td>1.1</td>
<td>19.0</td>
</tr>
<tr>
<td>$w = 0.75, k = 14$</td>
<td>10.9</td>
<td>41.4</td>
<td>8.5</td>
<td>32.4</td>
<td>0.7</td>
<td>30.7</td>
</tr>
<tr>
<td>$w = 0.75, k = 16$</td>
<td>10.7</td>
<td>41.4</td>
<td>8.9</td>
<td>32.4</td>
<td>0.7</td>
<td>30.7</td>
</tr>
</tbody>
</table>
publicly available collection of MRIs (Marcus et al., 2007). This data set consists of a cross-sectional collection of 416 subjects covering the adult lifespan aged 18–96 including individuals with neurodegeneration. The subjects are all right-handed and include both men and women. One hundred of the included subjects over the age of 60 have been clinically diagnosed with very mild to moderate Alzheimer’s disease. In this study we focus on the variation of cortical patterns in a small volume of interest (VOI). The VOI is cropped in the region that contains right superior frontopolar cortex. We use the segmentation provided with the data to extract surfaces between the gray matter and the cerebrospinal fluid. The size of each volume is resized to 68 × 56 × 72 and affinely aligned.

Out of 416 images we discard 23 outlier images that are not connected to the rest of the data with 24-NN graph. The images are registered with three levels of resolution for the coarse pairwise registration, and with two levels of resolution for fine-tuning, with a smoothness parameter of σ = 1.0. The whole procedure takes about 24 h on our cluster server.

Fig. 7 shows the two-dimensional embedding of the OASIS data. The cortical surfaces of the VOI are rendered to aid visualization of the results, using the curvature information computed from the smoothed surface. At a glance, the OASIS data contain complex variation of cortical patterns in contrast to the simulated data. Note that in the first axis (from left to right) the embedding shows change in the depth of sulcus gyrus which may be ascribed to the atrophy of the subjects with age and the Alzheimer’s disease. The biological plausibility of the geodesic paths are demonstrated in Fig. 8 with the four samples that have the largest decrease in MSE. Since the samples 54, 52, 188, and 221 are quite different from the fixed image 108, the registration is still not perfect. However the circled areas in the figure shows that proposed method can avoid unnatural collapsing of the gyri in the direct registration method and produces more realistic patterns. The advantage is evidenced by the improvement of MSE in the four samples (17%, 16%, 14% and 14%, respectively).

We now look at the overall statistics of the data. The distribution of length of the paths (the number of vertices along the path) is as follows. The numbers of the paths of length 2, 3, 4, 5, and 6 are: 24 (6%), 196 (50%), 139 (35%), 30 (7%), and 3 (1%), respectively. The average decrease in MSE for these paths are 0%, 2.8%, 2.3%, 1.9% and −0.8%. The paths of length 2 have no change obviously since there is no intermediate sample in the path. The number of paths of length 6 are only three and shows no improvement in MSE.

Table 3 summarizes the improvements by geodesic paths. This also shows that we achieve improvements in both MSE and the smoothness measures HE and MJD, although the average amount of improvement is less significant than the simulated data. In this experiment we also use Demons algorithm with the segmented...
volumes. To study the cortical patterns better, we plan to use a surface-based registration such as Spherical Demons (Yeo et al., 2009).

3.4. Fractional Anisotropy map of mouse brains

Finally, we show that the proposed method can be applied to image database that has large variation in both shape and appearance. Data of mouse brains are collected in our lab with the aim of creating a normative atlas of a developing mouse brain. The data consist of 69 Fractional Anisotropy maps of the brains sampled at 2, 3, 4, 7, 10, 15, 20, 30, 45, and 80 days of age. Each volume is resized to $150\times150\times100$ and affinely aligned. The images are registered with three levels of resolution for coarse pairwise registration, and with the original resolution for fine-tuning, with a smoothness parameter of $\sigma = 1.5$. The whole procedure takes about 6 h on our cluster server. The images in this dataset not only have a larger number of voxels than the other experiments but they are more challenging for registration due to their large shape and appearance variation from different ages and the degrees of maturation of tracts.

The two-dimensional embedding of the data in Fig. 9 provides a glimpse of its manifold structure. From the figure we can observe that the major variability of the data comes from age. The importance of the age factor is also observed in Fig. 10: a path that connects two brain images of different ages passes through brains of intermediate ages in a monotonic fashion. These findings are consistent with our prior knowledge of the data that the developmental stage is the major factor of the variation in the data. Fig. 10 also shows that the proposed method produces better registration results than those from the direct method. The decrease of MSE is 13.0%, 8.3%, 7.8%, 7.6%, and 6.8% for the five examples, respectively.

Table 4 summarizes the overall improvements by geodesic paths. MSE and HE decrease significantly (especially HE), and MJD remains unchanged. For mouse data we use histogram normalized intensity difference to compute MSE and geodesic distances. However, the large appearance variation in addition to the shape variation may require different model of the data manifold and revised definitions of the metric (Trouvé and Younes, 2005), which is out of the scope of this paper.

4. Discussion

In this section we discuss several aspects of the proposed framework and their practical implications for registration.

4.1. Number of samples

The proposed registration method is motivated by Isomap algorithm, which is based on the premise that the true geodesic on a convex set can be approximated well by the shortest path on the

<table>
<thead>
<tr>
<th>Measure</th>
<th>MSE</th>
<th>HE</th>
<th>MJD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± std (%)</td>
<td>Max (%)</td>
<td>Min (%)</td>
</tr>
<tr>
<td>Decrease</td>
<td>2.6 ± 4.4</td>
<td>17.0</td>
<td>−7.7</td>
</tr>
</tbody>
</table>
A higher value means a larger improvement.

### 4.3. Component registration algorithms

As we stated in the introduction, the component registration algorithm of the framework is interchangeable as long as the field it produces is diffeomorphic between two nearby images. There are many alternatives to Demons algorithm we used in this paper, including B-spline free-form deformation (Rueckert et al., 1999), elastically deformable model (Davatzikos, 1997), and feature-based algorithms such as HAMMER (Shen and Davatzikos, 2002) and DRAMMS (Ou and Davatzikos, 2009). Furthermore, the framework can be adopted for registering different representations of imagery, such as point set (of landmarks), curves, or surfaces. Depending on the component algorithm and the data types, the definition of distance between two images has to change accordingly. Note that such distance need not strictly be a true metric or a Riemannian distance since the shortest path on the graph impart the metric properties to the geodesic distance. The question of which algorithm and representation is optimal for the given data, is left to empirical studies.

### 5. Conclusion

In this paper, we propose a novel framework for Geodesic Registration on Anatomical Manifold (GRAM). The most distinguishing feature of the method is that it computes the geodesics on the manifold of the anatomical variation learned from the data, instead of computing the analytic geodesics of all diffeomorphisms. This warrants that any deformation field, as well as geodesic path, calculated in our framework represents real brain morphology, and is not merely a diffeomorphic transformation of a template, which can represent an unrealistically distorted morphologies. The learned manifold also provides a visualization of the data structure and allows us to choose an optimal template among the samples for groupwise registration. The experiments on simulated images, human cortical surfaces, and mouse FA maps show that the proposed method can achieve smaller MSES with smoother deformation fields than those computed without using the geodesic paths. This attests to the hypothesized benefits of utilizing anatomical variation of the actual data. It is left as our future work to perform cross-database tests using the framework and to compare the results with numerical geodesic registration methods.

Finally, GRAM is intended to be a meta-registration framework to efficiently compute large deformations, which allows a large class of registration algorithms to be used as its component. The code for GRAM framework will be made available on the web to encourage evaluation from the community.

### Table 4

Summary of registration results in the mouse data. The decrease in Mean Square Error (MSE), Harmonic Energy (HE), and Maximum Jacobian Determinant (MJD) are shown in percentage. A higher value means a larger improvement.

<table>
<thead>
<tr>
<th>Measure</th>
<th>MSE</th>
<th>HE</th>
<th>MJD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± std (%)</td>
<td>Max (%)</td>
<td>Min (%)</td>
</tr>
<tr>
<td>Decrease</td>
<td>3.1 ± 3.2</td>
<td>13.1</td>
<td>−4.1</td>
</tr>
</tbody>
</table>
Acknowledgments

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References