MUTUAL INFORMATION BASED NON-RIGID MOUSE REGISTRATION USING A SCALE-SPACE APPROACH

Sangeetha Somayajula, Anand A. Joshi, and Richard M. Leahy

Signal and Image Processing Institute, Univ. of Southern California, Los Angeles, CA 90089

ABSTRACT

We propose a scale-space based approach to non-rigid small animal image registration. Scale-space theory is based on generating a family of images by blurring an image with Gaussian kernels of increasing width. This approach can be used to extract features at varying levels of detail from an image. We define the scale-space feature vector at each voxel of an image as a vector of intensities of the scale-space images at that voxel. We generate scale-space images of the target and template images, and extract their corresponding scale-space feature vectors at each voxel. The extracted feature vectors are aligned using mutual information based non-rigid registration to simultaneously align global structure as well as detail in the images. We represent the displacement field in terms of the discrete cosine transform (DCT) basis, and use the Laplacian of the displacement field as a regularizing term. The DCT representation of the displacement field simplifies the Laplacian regularization term to a diagonal, thus reducing computational cost. We apply the scale-space registration algorithm on mouse images obtained from two time points of a longitudinal study, and compare its performance with that of a hierarchical multi-scale approach. The results indicate that scale-space based registration gives better skeletal as well as soft tissue alignment compared to the hierarchical multi-scale approach.

Index Terms— Image registration, non-rigid registration, mutual information, scale-space, small animal registration.

1. INTRODUCTION

Longitudinal and inter-subject studies are often performed in small animal imaging in order to study changes in mouse anatomy and function over a period of time, or across populations. Changes in animal posture, tissue growth, organ movement and other anatomical changes during longitudinal studies require non-rigid registration of the acquired images for accurate analysis. Normalization of anatomical variability across populations in inter-subject studies also requires non-rigid registration. Several non-rigid registration algorithms have been developed, most of which have been applied to brain registration. A review of these methods can be found in [1], [2]. The registration of small animal images is challenging because of the presence of rigid structures like the skeleton within non-rigid soft tissue. It has been observed that though the existing non-rigid registration algorithms have been applied successfully to brain imaging, these methods do not perform well for small animal registration [3] -[5].

In [3] and [4] mouse registration was performed using piecewise rigid registration of anatomical structures, which were defined in a segmentation step prior to registration. In [5] a fully automated method was proposed for whole body registration, where they first aligned the skeleton using a point based method, after which they imposed stiffness constraints at the skeleton to align the whole body images using intensity based non rigid registration with mutual information as the similarity metric.

In this paper, we describe a Gaussian scalespace theory based approach to simultaneously align global structure such as overall shape, as well as detail such as the skeleton, in small animals. Scale space theory provides a framework for the analysis of images at different levels of detail [6]. It is based on generating a one parameter family of images by blurring an image with Gaussian kernels of increasing width (the scale parameter), and analyzing these blurred images (the scale-space images) to extract structural features, which can be used in image registration [7]. We extract scale-space feature vectors at each voxel of the target and template images that are to be registered. We define the scale-space feature vectors at each voxel of an image as a vector of the intensities of its scale-space images at that voxel. We align the scale-space feature vectors with the goal of finding a common mapping that aligns the fine structure that appears in the images at lower scales, as well as the global structure that remains in the images at higher scales. We do not explicitly impose any rigidity constraints near the skeleton. We use mutual information (MI) as a similarity metric between the target and template images since it measures the similarity between distributions of intensities rather than actual values of intensities in the image, thus being more robust to intensity differences in these images [8]. This multi-scale approach has the additional advantage of having a cost function that is less prone to local minima [2], and hence is able to perform large non-linear deformations accurately.

We parameterize the displacement field using the DCT basis, and use the Laplacian of the field as a regularizing term. The DCT bases are eigen functions of the discrete Laplacian, so using the DCT representation of the displacement field in conjunction with Laplacian regularization simplifies the regularization term to a diagonal matrix. Moreover, the DCT basis gives an efficient representation of the displacement field, allowing us to represent the field using only a few coefficients. Fast implementations of DCT are readily available, and can be used to further reduce the computation time.

In this paper, we apply the scale-space registration algorithm to CT images from a longitudinal mouse study. We compare the results of this scale-space approach with those obtained by a hierarchical multi-scale approach that is commonly used in brain registration, where images at each scale are aligned hierarchically, starting at the highest scale and ending at the lowest scale.

2. METHODS AND RESULTS

2.1. Mutual information based non-rigid registration

Let $i_1(\mathbf{x})$ and $i_2(\mathbf{x})$ represent the intensities of target and template images respectively at position $\mathbf{x}$. Let the transformation that maps the target to the template be $T(\mathbf{x}) = \mathbf{x} - \mathbf{u}(\mathbf{x})$, where $\mathbf{u}(\mathbf{x})$ is the displacement field.

Let the feature vectors extracted from the target and template images at voxel $\mathbf{x}$ be $\mathbf{i}_1(\mathbf{x})$ and $\mathbf{i}_2(\mathbf{x})$ respectively. These can be considered as realizations of the random vectors $\mathbf{I}_1$ and $\mathbf{I}_2$. Let N_s be the number of features in each feature vector such that $\mathbf{I}_1 = [I_1^1, I_1^2, \cdots, I_1^{N_s}]^T$, where I_1^j is the random variable corresponding to feature j of the target image. Then, the mutual information between feature vectors of the target and deformed template, $D_{\mathbf{u}}(\mathbf{I}_1, \mathbf{I}_2)$ is defined as [9],

$$D_{\mathbf{u}}(\mathbf{I}_1, \mathbf{I}_2) = \int p_{\mathbf{u}}(\mathbf{I}_1, \mathbf{I}_2) \log \frac{p_{\mathbf{u}}(\mathbf{I}_1, \mathbf{I}_2)}{p(\mathbf{I}_1) p_{\mathbf{u}}(\mathbf{I}_2)} d\mathbf{I}_1 d\mathbf{I}_2. \quad (1)$$

A differentiable estimate of the density can be obtained using Parzen windows given by [10],

$$p_{\mathbf{u}}(\mathbf{I}_1, \mathbf{I}_2) = \sum_{\mathbf{x}} \phi\left(\frac{\mathbf{I}_1 - \mathbf{i}_1(\mathbf{x})}{\rho}\right) \phi\left(\frac{\mathbf{I}_2 - \mathbf{i}_2(\mathbf{x} - \mathbf{u}(\mathbf{x}))}{\rho}\right), \quad (2)$$

where ϕ is a Gaussian window and ρ determines the width of the window.

We use the Laplacian of the displacement field as a regularizing term. The objective function is given by

$$\max_{\mathbf{u}} D_{\mathbf{u}}(\mathbf{I}_1, \mathbf{I}_2) - \mu \left|\left|\nabla^2 \mathbf{u}(\mathbf{x})\right|\right|^2, \quad (3)$$

where μ is a hyperparameter that controls the weight on the regularizing term.

For simplicity, we assume independence between features so that MI between the feature vectors simplifies to the sum of MI between the individual features.

$$D_{\mathbf{u}}(\mathbf{I}_1, \mathbf{I}_2) = \sum_{j=1}^{N_s} D_{\mathbf{u}}(I_1^j, {I_2}^j). \quad (4)$$

2.2. Scale-space feature vectors

We use a Gaussian scale-space theory based approach to define feature vectors that are extracted from the images. We generate images at different scales by blurring the target and template with Gaussian kernels of increasing widths. Let the width of the Gaussian kernel at each scale be σ_j, $j = 1, 2, \cdots, N_s$, such that $\sigma_j > \sigma_k$ for $j > k$. Let the smoothing kernel at scale j be represented by $S_j(\mathbf{x})$. We define the scale-space based feature vector as $\mathbf{i}_1(\mathbf{x}) = [i_1(\mathbf{x})^1, i_1(\mathbf{x})^2, \cdots, i_1(\mathbf{x})^{N_s}]$, where $i_1(\mathbf{x})^j$ is the intensity of the target image at scale j and position $\mathbf{x}$, and is given by,

$$i_1(\mathbf{x})^j = S_j(\mathbf{x}) * i_1(\mathbf{x}). \quad (5)$$

In this paper, we use N_s=2, where the first scale corresponds to no smoothing and $\sigma_2 = 3$. A coronal slice of a mouse image at these scales is shown in Fig. 1.

We generate the feature vector of the deformed template $\mathbf{i}_2(\mathbf{x} - \mathbf{u}(\mathbf{x}))$ by first applying the displacement field to the original template, and then generating the scale-space images of that deformed image. So the feature $i_2(\mathbf{x} - \mathbf{u})^j$ is given by,

$$i_2(\mathbf{x} - \mathbf{u})^j = S_j(\mathbf{x}) * (i_2(\mathbf{x} - \mathbf{u})). \quad (6)$$

We observed that this performs better than deforming the original scale-space images of the template. This could be because in our approach, we are retaining the original relationship between intensities as a function of position in the template image while computing $i_2(\mathbf{x} - \mathbf{u}(\mathbf{x}))$, and then computing the similarity metric between target and a linear transformation (smoothing) of the deformed template. In contrast, applying the displacement field to the original scale-space images will mean that we are computing the similarity metric between the target and a new function $(S_j * i_2)(\mathbf{x} - \mathbf{u})$ of the template. Though generating the scale-space feature vectors at every iteration increases the computation, we take this approach for better accuracy.

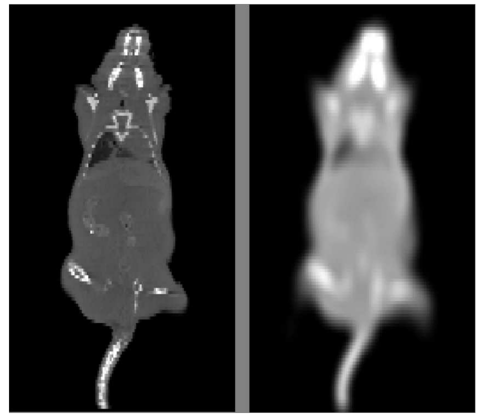

Fig. 1. Coronal slice of scale-space images of a mouse for $N_s = 2$, with scale 1 corresponding to no smoothing (left) and σ_2 =3 (right).

2.3. Displacement field and regularization

The displacement field $\mathbf{u}(\mathbf{x})$ can be represented in terms of the DCT basis. Let $\mathbf{b}_i(\mathbf{x})$ and $\beta_i(\mathbf{x})$, $i = 1, 2, \cdots, N_b$ represent the DCT basis vectors, and the DCT coefficients respectively. Then, the displacement field is given by,

$$\mathbf{u}(\mathbf{x}) = \sum_{i=1}^{N_b} \beta_i \mathbf{b}_i(\mathbf{x}) = \mathbf{B}(\mathbf{x})\beta, \quad (7)$$

where $\mathbf{B}(\mathbf{x}) = [\mathbf{b}_1(\mathbf{x}), \mathbf{b}_2(\mathbf{x}), \cdots, \mathbf{b}_{N_b}(\mathbf{x})]$, and the coefficient vector $\beta = [\beta_1, \beta_2, \cdots, \beta_{N_b}]^T$.

The DCT basis vectors are eigen functions of the discrete Laplacian. Let $\mathbf{L}$ be the discrete Laplacian matrix and γ_i, $i = 1, 2, \cdots, N_b$ be the eigen values of $\mathbf{L}$ corresponding to the basis $\mathbf{b}_i(\mathbf{x})$. Then,

$$\mathbf{L}\mathbf{u}(\mathbf{x}) = \mathbf{L} \sum_{i=1}^{N_b} \beta_i \mathbf{b}_i(\mathbf{x}) = \sum_{i=1}^{N_b} \gamma_i \beta_i \mathbf{b}_i(\mathbf{x}) \quad (8)$$

Hence, the discrete approximation of the norm of the Laplacian, $\left|\left|\nabla^2 \mathbf{u}(\mathbf{x})\right|\right|^2$ is given by,

$$||\mathbf{L}\mathbf{u}(\mathbf{x})||^2 = \sum_{i=1}^{N_b} {\gamma_i}^2 {\beta_i}^2. \quad (9)$$

Thus we save the computation cost of the matrix vector multiplication required by the left hand side of Equation 9, by reducing it to the vector norm on the right hand side. Additionally, since the DCT gives a sparse representation, we can model the displacement field with $N_c < N_b$ coefficients to reduce computation time further. Finally, the objective function is given by

$$\max_{\beta} \sum_{j=1}^{N_s} D_{\mathbf{B}\beta}(I_1^j, {I_2}^j) - \mu(\sum_{j=1}^{N_c} {\gamma_j}^2 {\beta_j}^2). \quad (10)$$

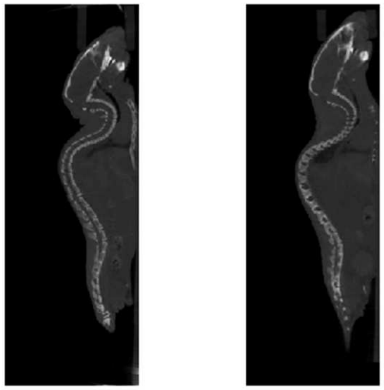

Fig. 2. Sagittal slice of target (left) and template (right) mouse images.

We optimize this objective function using a gradient descent algorithm with Armijo line search [11].

2.4. Results

We use CT images from a longitudinal mouse study. We use two time points of that study that are two months apart. The CT images were acquired using the microCT system at a resolution of $0.2 \times 0.2 \times 0.2$ mm. We first perform a MI based rigid registration on the two images using the RView software [12]. The rigidly registered images are shown in Figure 2. It can be seen that there are considerable differences in the skeleton, soft tissue, and overall shape of the images. We downsampled the CT images to size $128 \times 128 \times 64$, corresponding to a resolution of $0.4 \times 0.72 \times 0.51$ mm to reduce computation. We used these downsampled images as the target and template images in the non rigid registration algorithm. We use two scales to form our feature vectors- the unsmoothed image, and the image smoothed by a Gaussian kernel of size [7x7x7] and width $\sigma = 3$. We use $N_c = 30$ DCT bases and $\mu = 5e - 6$. We first perform the non-rigid registration at only the higher scale ($\sigma = 3$), and we use this to initialize the scale-space non rigid registration. Registration at only the lower scale (unsmoothed images) gave a local minimum that would not be a good initialization.

We compare the scale-space registration results to those of hierarchical multi-scale registration. We used the same number of DCT bases and the same scales as the scale-space registration, with $\mu = 2e - 5$. We first registered the smoothed images, and used the resulting displacement field to initialize the registration for the unsmoothed images. The overlay on the target image of the template image, and images registered using both approaches are shown in Fig. 3. We applied the displacement field resulting from both registration algorithms to the higher resolution (0.2 mm) images for display purposes. The displacement field obtained from the scale-space registration is shown in Fig. 4, for the coronal and sagittal slices shown in Fig. 3

It can be seen that the scale-space non-rigid registration algorithm gives better skeletal, limb, and soft tissue (such as liver and heart) alignment than the hierarchical multi-scale algorithm.

3. DISCUSSION

We used a scale-space theory based approach for non-rigid mouse registration using mutual information. We used the DCT basis to ef-

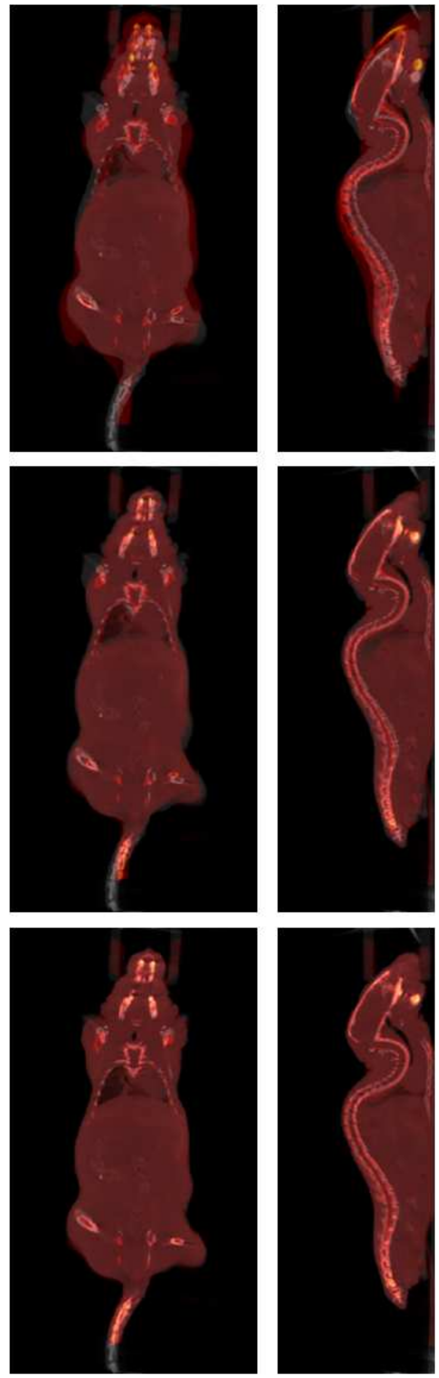

Fig. 3. Comparison of registered images: Coronal and sagittal views of overlay on target image of template (top row), hierarchical multi-scale registered image (middle row), and scale-space registered image (bottom row).

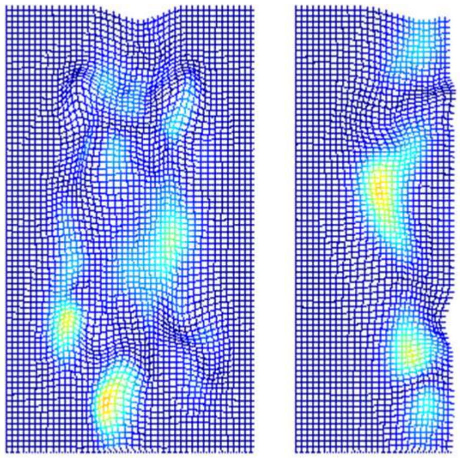

Fig. 4. Displacement field obtained from scale-space registration

ficiently represent the displacement field, as well as to simplify the Laplacian regularization term. We generated the scale-space feature vectors at each iteration after applying the displacement field to the original images, since this approach gave better accuracy. We applied this algorithm to CT images of a mouse in a longitudinal study.

By using images at different scales simultaneously, we obtained better alignment of the global structure such as the overall shape of the mouse as well as improved alignment of detail such as the skeleton, compared to the hierarchical multi-scale approach. It is encouraging to see that using this approach, we are able to get skeletal and soft tissue alignment simultaneously. In this study, we used only two scales to define the feature vectors for the target and template images. We believe that using more scales will give better performance. Though the results presented are for images of the same modality, we expect similar performance for multi-modality small animal studies as well, since mutual information is robust to intensity differences in the images to be registered. We plan more validation studies with longitudinal as well as inter-subject multi-modality data.

4. REFERENCES

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