

A TWO-STAGE MINIMUM SPANNING TREE (MST) BASED CLUSTERING ALGORITHM FOR 2D DEFORMABLE REGISTRATION OF TIME SEQUENCED IMAGES

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ABSTRACT

Significant cardiac and respiratory motion of the living subject, occasional spells of defocus, drifts in the field of view, and long image sequences make the registration of *in-vivo* microscopy image sequences used in atherosclerosis study an onerous task. In this study we developed and implemented a novel Minimum Spanning Tree (MST)-based clustering method for image sequence registration that first constructs a minimum spanning tree for the input image sequence. The spanning tree re-orders the images in such a way where poor quality images appear at the end of the sequence. Then the spanning tree is clustered into several groups based on the similarity of the images. Subsequently deformable registration is conducted locally within the group with respect to the local anchor image selected automatically from the images in the group. After that coarse registration is performed to find the global anchor and then a deformable registration is performed globally to incorporate larger drift and distortion. Two-stage deformable registration incrementally incorporates larger drifts and distortions present in the longer sequence. Our algorithm involves very few tuning parameters, the optimal value of these parameters can be easily learned from data. Our method outperforms other methods on microscopy image sequences of mouse arteries.

Index Terms— Microscopic image registration, minimum spanning tree, time sequence imaging, graph clustering, *In-vivo* image analysis for atherosclerosis study.

1. INTRODUCTION

Automated registration or alignment of time-sequenced images is an essential image processing task for microscopy image analysis and various image registration models (2D or 3D) are available in the literature, that can be categorized into different groups, such as elastic models [1, 2], spine-based models [3, 4], feature detection-based methods [5, 6], and in-

tensity based methods [7]. Manual or semi-automatic registration specially for longer sequences is an extremely tedious task which demands for automation.

In this research we focus on the automation of the 2D registration of longer image sequences that may contain substantial amount of poor quality images. Most of the previous studies allow the user to select the anchor image, while few of them choose the anchor automatically [6] and some of them choose the anchor image randomly from the middle of the sequence [5], one of the other approaches selects the anchor image by maximizing the correlation with the remaining frames [8, 9]. Once the anchor image is selected, then the registration is performed by aligning the rest of the images of the sequence sequentially or recursively with respect to the anchor image. However, these methods perform poorly for the image sequence if the image sequence contains subsequence of poor quality images which is very common to microscopy images where images are often distorted by tissue motion as well as in sequential alignment registration error in each stage accumulates over the process.

In this paper, we developed and implemented an automated deformable registration algorithm for a long image sequence by tailoring minimum weighted spanning tree from coarse image alignment (MISTICA) [10] towards 2D image registration. The research contribution in this research is as follows. (i) minimum weighted spanning tree (MST) based image sequence registration performs re-ordering the images using shorter sequences which mitigate the error propagation by de-evaluating the poor quality image subsequence through sending them back in the sequence during the registration process; thus bad images are registered at the end. (ii) This algorithm selects an anchor image automatically and thus avoids the user interaction during the longer registration process; (iii) It has only two tuning parameters, graph width and number of clusters in the graph, making it more user friendly than many existing techniques. Previous studies show that for a number of image sequences, the registration performance is robust to changes of graph width value within a wide range. Furthermore, the number of clusters in the graph can be se-

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lected automatically or through cross validation [11]. (iv) The two-stage registration process can incrementally register larger drift and distortion and thus perform better than single stage registration. We conducted our experiment on *in-vivo* microscopy image sequences dedicated for the study of atherosclerosis [12]. The datasets pose several technical challenges to image sequence alignment such as (a) these sequences are often long, exceeding 1000 images; (ii) the motion artifacts are significant due to the cardiac and the respiratory motions; (iii) there are occasional changes in focal plane and drifts in the field of view; (iv) these factors, mixed together, create considerable challenges for the existing techniques available for image sequence alignment. Experimental results demonstrate that we outperform competitive methods.

2. MINIMUM SPANNING TREE BASED CLUSTERING ALGORITHM FOR 2D DEFORMABLE REGISTRATION

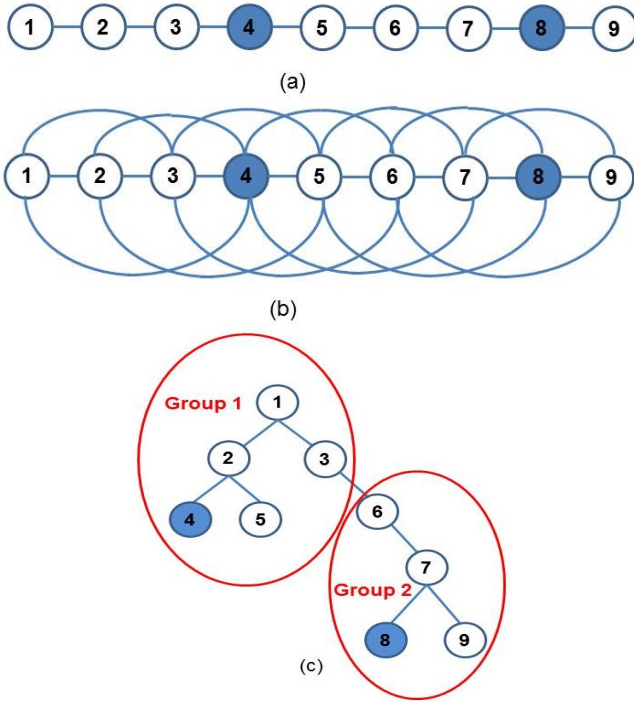


Fig. 1. (a) A time-sequenced set of nine images. Shaded circles represent poor quality images. (b) A graph constructed on the image sequence. (c) An example of clustering minimum weighted spanning tree.

The algorithm is illustrated in Algorithm 1. Our MST based clustering algorithm for 2D registration consists of three sequential major steps:

Step 1: MST based graph construction. Construct a graph for the input image sequence as shown in Fig. 1(a)

Algorithm 1 MST based 2D deformable registration algorithm

- 1: Run the MST algorithm to reorder the image sequence so that poor quality images lie at the end of the sequence.
 - 2: Cluster the MST into M groups, $\mathbf{G}_1, \dots, \mathbf{G}_M$ using normalized graph cut.
 - 3: **for** $k = 1, \dots, M$ **do**
 - 4: Compute the feature (say entropy) for each image, $h(I_u), u \in G_k$;
 - 5: **(Anchor Selection)** Select anchor in each group having the highest entropies $j_k = \operatorname{argmax}_{u \in G_k} \{h(I_u)\}$.
 - 6: Align each image $\{i | i \neq j_k\}$ of group k into Anchor j_k according to MST traversal order using rigid registration and compute MSE_{i,j_k} for each group k .
 - 7: **Anchor reselection**
 - 8: Find the image having minimum MSE_{i,j_k} of group k , $j^* = \operatorname{argmin}_{i \neq j_k \in G_k} (MSE_{i,j_k})$.
 - 9: Align anchor I_{j_k} into image I_{j^*} using rigid registration and compute the registration error MSE_{j_k,j^*} .
 - 10: Replace Anchor I_{j_k} by I_{j^*} if $MSE_{j_k,j^*} < MSE_{j^*,j_k}$.
 - 11: Perform **deformable** registration of images in group k with respect to the Anchor Image.
 - 12: **end for**
 - 13: Set the number of groups to one, run (4-9) to obtain the final Anchor Image AI_{final} .
 - 14: Align each image of the sequence to the target AI_{final} using **deformable** registration.
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and (b). Then construct a minimum weighted spanning tree (MST) [13] as shown in Fig. 1(c). The edge weights for the graph are constructed as follows:

$$E(I_i, I_j) = \begin{cases} \|I_i - R(I_i, I_j)\| & \text{if } i \neq j \text{ and } |i - j| \leq \delta \\ \infty, & \text{otherwise,} \end{cases}$$

where the function $R(X, Y)$ denotes the registered source image Y with respect to the target image X . The norm $(\|\cdot\|)$ represents the sum of absolute differences of pixel values between two images. By convention, no edge with infinite weight is constructed. The value of the parameter δ controls the sparsity of the graph. A smaller value of δ illustrates greater sparsity. For a complete graph, $\delta = n - 1$. The computational complexity of MST-based registration is dominated by graph construction, which is $O(\delta n)$, while the computational complexity of registration with adaptive template matching is $O(n)$.

Step 2: Graph clustering. Cluster MST into M groups as shown in Fig. 1(c). Users can select the value of M or the value of M can be chosen automatically as well [14].

It is noteworthy that MST based graph clustering algorithm decomposes the original image sequence into smaller sub-sequences and these smaller sub-sequences contain poor

quality images toward their end. Thus, registration error propagation is minimized. Simple template matching method lies into one extreme in that it subdivides the input sequence into the largest number sub-sequences and prevents the error propagation due to poor quality images. Since the sequences are long, the anchor image in simple template matching cannot adapt to the illumination changes and drifts. The sequential methods, such as StackReg [15], lies on the other extreme end in that it divides the input sequence into at most two sub-sequences. So, they can handle the drift and change of illumination; however, they fail to tackle occurrences of poor quality images. Our MST based graph clustering algorithm achieves a balance between these two extremities.

Another important issue regarding image registration involves user interaction to choose an anchor image. A number of the existing algorithms require the user to choose an anchor image. Our toy example illustrates that suitable anchor image can mitigate the registration error propagation. For example, the choice of 2 and 7 over 3 and 6 for group 1 and 2 respectively in Fig. 1(c) would most likely yield a better registration. In practice, browsing through images and looking for the anchor in longer image sequences can be tedious and error-prone. We adopt an automatic anchor selection algorithm in our method that is described below.

Step 3: Anchor Selection and image registration. In contrast to available methods which pick either first or middle image randomly as an anchor image, we select the anchor image through an iterative assesment of image entropy and Mean Square Error (MSE) of the registration process. Normally structural similarity measure is exploited for registration purposes. However, due to distortions, structural similarity cannot always be maintained even for consecutive slices. MSE is a useful tool to check whether the slices are distorted or not. High MSE values indicate a high probability of distorted and noisy slices while low MSE values indicate strong similarity between consecutive images. However, there is a strong possibility that substantial amount of slices (specifically initial and end slices) exist among long time sequenced slices which contain little information due to the topology of the animal organs and MSE-based registration error may become small even if these slices are not suitable candidates for reference slices. To alleviate selecting these slices, similar to [16], we incorporate entropy information along with MSE for anchor selection. Entropy measures the mutual information and high mutual information in consecutive slices illustrate high similarity and vice versa.

In our registration algorithm, we first select one image from each group select as the anchor image that possess the highest entropies in the group. Then align each image in the group according to MST traversal order using rigid registration and compute the corresponding MSE with the associated anchor image. Subsequently we find the image having the minimum MSE. Let denote the image as I and the corresponding MSE as M . Align the associated anchor image with

I and compute MSE, say M_1 . Replace anchor image with I if $M_1 < M$. Then we implement a standard deformable registration algorithm for each group with respect to the associated anchor image. For deformable registration, we implement diffeomorphic image registration [17]. For rigid registration, we use MISTICA [10] that is as follows:

Step a. Compute the path between the first and last images on the MST in the input image sequence. An image that is midway on this path is selected as the anchor image.

Step b. Perform a breadth (or depth) first traversal of the MST starting at the anchor image (root node). Store identity transformation at the root node.

While there are nodes in MST yet to visit, do

 Get the next node C in the traversal order.

 Get the parent node P of C .

 Get the image I_C stored at C .

 Get the image I_P stored at P .

 Compute a transformation T to register I_C to I_P .

 Get the transformation T_P stored at P .

 Update T by composing T_P with T : $T \leftarrow T_P \circ T$.

 Store T at C .

End While

Step c. Visit each node of the MST in any order to transform the image stored at the node by the corresponding transformation stored at the same node.

We perform deformable registration twice: once with respect to the local anchor (anchor selected within the group images) and other with respect to the global anchor (anchor selected for the whole sequence). For a longer sequence, normally the topology of the anchor image is quite different from many images located far away from it due to larger drift and change of illumination. In two-stage registration, first images are registered with the local anchor, the topology of which is closer to the candidate images than the final anchor image. Then images are registered with the final anchor image. Thus in the two-stage registration, the amount of total drifts and distortions present in the sequence are divided into several parts and each part is handled separately through local registration conducted inside the group. Incremental adjustment of the two-stage deformable registration towards large distortion of the structures and artifacts tends to avoid the failure of conventional one shot deformable registration process.

3. EXPERIMENTAL RESULTS AND DISCUSSIONS

We conducted the experiment on two microscopy datasets of mouse arteries used in atherosclerosis study as shown in Fig. 2. Fig. 2 shows the first and the last images of these sequences (from left to right column) which are denoted as (a) and (b) (from top to bottom row). The details of the image acquisition and experimental set up have been already published in [12, 18]. We compared our MST-based two-stage deformable registration with one simple template matching methods, an image stack registration method, one well-known

2D deformable registration, diffeomorphic demons [17], MST based registration method, MISTICA [10]. The simple template matching method, referred to as TM, considers the first image of the sequence as a template and matches all other images to this template. The image stack registration of [15] is referred to as StackReg. we used the optimal value of $\delta = 6$, (reported in the paper [19]) for both MISTICA and our method. We choose the value of the number of clusters in the graph as 5 for our method through cross validation [11]. The registration function $R(X, Y)$ for all the methods used translational motion. Since data are collected *in vivo*, it is practically infeasible to have ground truth registration data for the sequences. We used structural similarity index (SSIM) [20], which is a popular quality metric to compare registration algorithms. For a fair comparison, for an image sequence I_1, I_2, \dots, I_n , the first image I_1 is considered the anchor image for all the methods. All other images are compared to this anchor image by SSIM scores:

$$s_i = SSIM(I_1, I_i), \text{ for } i = 2, \dots, n,$$

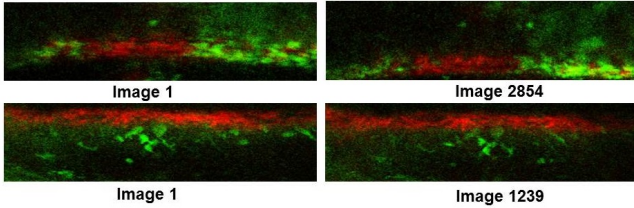


Fig. 2. Two rows from top to the bottom illustrate two datasets (a) and (b), respectively. The first and the second columns show the first and the last images in the sequences, respectively.

Table 1. Mean, SD and CV values for different registration methods, including the unregistered sequence for dataset (a).

Method	$\mu(\text{mean})$	$\sigma(\text{SD})$	$\sigma/\mu(\text{CV})$
unregistered	0.234	0.056	0.239
TM	0.307	0.063	0.205
StackReg	0.372	0.081	0.218
Diffeomorphic demons	0.401	0.072	0.179
MISTICA	0.421	0.072	0.171
MSTClust2D	0.503	0.081	0.161

where, the function $SSIM(.,.)$ measures structural similarity between two images. The value of SSIM lies between -1 and 1. Higher SSIM values demonstrate better registration between two images. For evaluating the registration of time sequenced images, we use mean and standard deviation (SD) of similarity among all pairs of registered images.

If we consider the images in a sequence as a cluster of data points, then this average similarity value μ depicts the average affinity among the data points within the cluster. We

also report the standard deviation (σ) of the SSIM values to describe the spread of the affinity of the data points within the cluster. Finally, we use coefficient of variation (CV), σ/μ , as the measure of registration for an entire image sequence. A higher value of μ and smaller value of CV implies better registration. The mean, SD and CV of the unregistered images and the four competing methods for the dataset (a) and (b) are illustrated in Table 1 and 2 respectively. From these comparisons, it is evident that the our MST-based clustering algorithm for 2D registration denoted as MSTClust2D outperforms other methods for two image sequences of significant length.

Table 2. Mean, SD and CV values for different registration methods, including the unregistered sequence for dataset (b).

Method	$\mu(\text{mean})$	$\sigma(\text{SD})$	$\sigma/\mu(\text{CV})$
unregistered	0.182	0.067	0.368
TM	0.224	0.078	0.348
StackReg	0.254	0.092	0.362
Diffeomorphic demons	0.312	0.093	0.299
MISTICA	0.342	0.089	0.260
MSTClust2D	0.412	0.096	0.233

4. CONCLUSIONS AND FUTURE WORKS

We have developed and implemented a novel two-stage 2D registration algorithm for time sequenced *in-vivo* microscopy images containing noises such as occurrences of poor quality images in long sequences, including noisy or low-intensity data, as well as images with distortion due to cardiac and respiratory motion and we achieve this by re-ordering the natural temporal order of image sequence in which they were captured. Our algorithm demotes the poor quality images by registering them at the end of the registration process and thus reduces the accumulated registration error. A computationally efficient graph clustering framework with minimum spanning trees has been developed here for 2D image sequence registration. Two-stage deformable registration incrementally accommodates larger drifts and distortion and performs better than conventional one stage deformable registration. Experimental results demonstrate that proposed algorithm outperforms competitive methods. Proposed algorithm is user friendly, because, it has only two hand tuning parameters; the graph width where graph width has an extensive range for producing robust performance and the number of clusters in the graph, the optimal value of which can be determined automatically or through cross validation. Moreover, the anchor selection procedure of the proposed method is also completely automatic. In the future, we would like to extend the proposed minimum spanning tree based graph clustering framework to temporal sequences of 3D volumes.

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