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Research Article

Single versus Multi-step Non-Rigid Medical Image Registration of 3D Medical Images

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Abstract: Multi-model medical image registration is very important in medical image analysis and computer assisted surgery. Accuracy and speed are the two crucial factor of any registration algorithm. A Fast Radial Basis Function algorithm for non-rigid medical image registration with improved accuracy is presented in this article. The accuracy of the technique is improved by converting the one-step registration algorithm to multi-step i.e. three-step registration algorithm. The global transformation accuracy of this technique has been evaluated by using two different anatomical landmarks sets. The former is to calculate the model parameters, and the later is used to assess registration accuracy. Finally, we demonstrate that the multi-step technique yields better accuracy (using NMI) as compared to the one-step approach and target registration errors of about 2.91mm on the registration of CT with its synthetically deformed version obtained from the Vanderbilt database. Our study shows that the multi-step fast RBF based registration is more effective in recovering larger deformation and do kept transformation smoothness than the one-step fast RBF based registration.

Keywords: Medical image registration, deformations, radial basis functions, computer assisted surgery, radiotherapy

1. BACKGROUND

Research done so far on non-rigid medical image registration methods for radiotherapy indicates that it gives better results than rigid registration. Non-rigid registration techniques used in radiotherapy are usually divided into two main categories: feature based [1] and intensity based [2]. Feature based techniques require the identification (either manually or partially automated) of a sparse set of corresponding feature points, contours or even surfaces between images, to map one image onto the other. Therefore, it is usually tedious and prone to errors due to manual involvement in locating corresponding features. This often happened in 3D medical image registration where a large number of corresponding anatomical landmark points needs to be identified. On the other hand, intensity based techniques directly operate on image intensity values but require optimization criteria like mutual information (MI) to find the best possible mapping. It is also subject to intensity variations caused by different imaging artefacts. Such methods are accurate but computationally expensive. In landmark based techniques, a single

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misplaced landmark point results into unrealistic deformations in certain situations where large number of accurate anatomical point landmarks placement is difficult. Unlike intensity based registration methods, landmark based registration is less dependent on the underlying image content and need to have a set of reliable corresponding anatomical point landmarks. However, defining a set of large number of anatomical point landmark across two images is time consuming, prone to errors and also needs expert knowledge of the area. This makes the whole registration process complicated but also need expert knowledge.

In order to improve the accuracy and robustness of the deformable method we have proposed a multi-step fast RBF based registration technique and compare its results to the single step fast RBF based registration method. In this paper, we present a non-rigid, feature based registration method aimed at pre- or intra-operative registration of medical images during radiotherapy or surgery. Therefore, the method needs to be fast whilst maintaining acceptable accuracy. The method employs radial basis functions (RBFs), and more specifically the biharmonic spline (BHS), to define a non-linear mapping functions between images to be registered.

In our previous work [3, 4], we developed a point-based algorithm for fast medical registration using RBFs and showed that the warp speed reduced to less than a minute for a size 256^3 dataset (CT/MRI) of the Vanderbilt Database using 8-44 manually defined landmarks. During experiments, it is ob- served that the biharmonic spline (BHS) is the most optimum and theoretically correct RBF function to use in 3D instead of the widely used and the 'popular' thin-plate spline, which is only optimal in 2D. Our proposed work shows that the multi-step fast RBF based registration is more effective and robust in recovering larger deformation and insensitive to the parameters used during registration than the one-step fast RBF based registration.

2. METHODS AND ALGORITHMS

2.1. Fast Radial Basis Functions Technique

The Radial Basis Function (RBF) technique [5] is one of the most widely used technique to approximate or interpolate data scattered in more than one dimensions. The purpose of interpolation is to approximate a real-valued function $f(\mathrm{x})$ over a finite set of values $f = (f_1, \ldots, f_N)$ at the distinct points $X = \{\mathrm{x}_1, \ldots, \mathrm{x}_N\} \subset \mathbf{R}^d$. In similar situation, one chooses an RBF, $s(\mathrm{x})$, for representing such approximations, normally of the following general form:

$$s(\mathrm{x}_i) = p(\mathrm{x}_i) + \sum_{i=1}^{N} \lambda_i \varphi(\|\mathrm{x} - \mathrm{x}_i\|), \mathrm{x} \in \mathbf{R}^d \tag{1}$$

Where $p(\mathrm{x})$ is a polynomial, λ_i is a real-valued weight [1] ϕ is the (radial) basis function and $\|\mathrm{x} - \mathrm{x}_i\| = r$ is the Euclidean distance between x and x_i. So, an RBF might be defined as a weighted sum of a radially-symmetric basis function, added together with a polynomial term.

The basis function ϕ can take several forms, but three of them have a common property of minimizing specific quantities of energy [1], which makes them suitable for use in 2D and 3D non-rigid medical image registration techniques. Rohr [1] further shows that the biharmonic spline (BHS): $\phi(r) = r$ and the thin- plate spline (TPS): $\phi(r) = r^2 \log r$, both minimize a bending energy potential of order two in three and two dimensional space respectively. Thus to warp 3D image data, the BHS is therefore the choice to be preferred. Rowland et al. [6] confirmed its theoretical optimality in 3D as shown by Rohr experimentally.

Rowland et al. [6] rewritten the Equation 1 without the linear polynomial part (for sake of

[1] The λ weights are determined in the 'calculation' step using a least mean squares approach. This step is followed by the 'evaluation' step which applies the RBF to (usually) all voxels. The latter step is much more time-consuming than the former.

clarity), and extend it to 3D for evaluation of $i = 1 \ldots m$ evaluation points/voxels (targets) represented by the target vector x_i, after having found the spline parameters λ_j for $j = 1 \ldots n$ landmarks represented by the source (landmark) vector y_j:

$$s(x_i) = \sum_{j=0}^{n} \lambda(y_j)\varphi(\|x_i - y_j\|), i = 0,\ldots,m \qquad (2)$$

Livne and Wright [7] described a new technique for fast multilevel evaluation of RBF expansions. The main idea of the fast RBF technique is to represent a smooth RBF, ϕ, accurately on a regular coarse grid having few nodes as compare to the full voxel set and thus the expensive summation in Equation 2 need to be performed only at these few nodes while the remaining voxel values can finally be determined using a less expensive formulation based on the values calculated for the surrounding nodes. Unlike the grid based approach by Levin et al. [8], it is the RBF coefficients that are interpolated within the grid and not the intensity values of the voxels. The main principle of the fast RBF technique is to encapsulate source and target points in separate grids of size H. It results in a two stage process conversion of the RBF in Equation 2. The first stage replaced the original **source** points with their corresponding grid points by using a centered ***p***th order tensor product interpolation:

$$\varphi(\|x_i - Y_J\|) = \sum_{j:J_k \in \sigma_j^{(k)}} \omega_{jJ_3}\omega_{jJ_3}\omega_{jJ_3}\varphi(\|x_i - Y_{(J_3,J_2,J_1)}\|) \qquad (3)$$

where $j = 0, 1, \ldots, n$ and for dimension $k = 1, 2, 3$:

$\sigma_j^{(k)} := \{J_k : \|Y_{J_k}^{(k)} - y_j^{(k)}\| < pH/2\}$, where ω_{jJ_k} are the new centered ***p***th order interpolation weights from the coarse $Y_{J_k}^{(k)}$ centres $y_j^{(k)}$ to the landmark positions. The second stage replaced the original **target** points with their corresponding grid points using the same approach:

$$\varphi(\|x_i - Y_J\|) = \sum_{I_k \in \overline{\sigma}_i^{(k)}} \overline{\omega}_{iI_3}\overline{\omega}_{iI_2}\overline{\omega}_{iI_1}\varphi(\|X_{(I_3,I_2,I_1)} - Y_J\|) \qquad (4)$$

where $i = 0, 1, \ldots, m$, $\mathbf{J} = (J_1\ J_2,\ J_3)$, and for dimension $k = 1, 2, 3$: $\overline{\sigma}_i^{(k)} := \{I_k : \|X_{I_k}^{(k)} - x_i^{(k)}\| < pH/2\}$,

where $\overline{\omega}_{iI_k}$ are the centered pth-order interpolation weights from the coarse evaluation point $X_{I_k}^{(k)}$ to the level h (original image grid size) evaluation point $x_i^{(k)}$. The method used to distribute the known RBF coefficients $\lambda(\mathbf{y}_j)$ at each landmark position to the surrounding nodes of grid $\mathbf{Y}$ is called *anterpolation*. Further in depth detail of the technique in 1D and 2D can be found in [7] and its 3D extension in [9].

2.2. Multi-step Registration Using Fast RBF

In order to avoid cross-over of structures (unrealistic deformation) during large deformation recovery using landmark based registration, we proposed the multi- step approach with an affordable computation time instead of solving a tight topological preservation map. This is just like divide and conquer rule to recover large deformation while keeping locality of transformation.

Initially, a few corresponding landmarks are selected in both images which roughly represents the corresponding deformation from one image to the other. Registration using the source and target landmarks directly is the one-step fast RBF registration technique but sometimes results into unrealistic deformation due to violation of transformation locality. In order to minimize this unrealistic deformation, we used multi-step fast RBF technique. Each step of our multi-step approach is the application of single-step fast RBF method. We introduced programmatically new virtual landmarks between the source and target landmarks as shown in Fig. 1.

The new virtual point landmarks are not the actual landmarks placed in the images but produced through coding and used to minimize distances between the source and intermediate landmarks to make the transformation local and topology preserved using the fast RBF registration equation. The final step of the multi-step fast RBF technique uses the same target landmarks identified in the image by the operator.

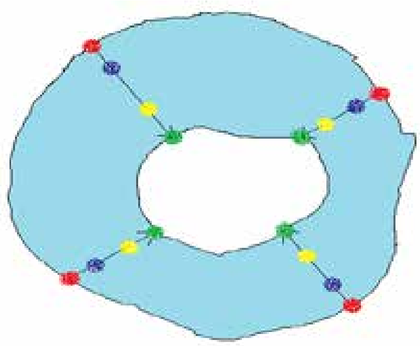

Fig. 1. A 2D representation of the proposed multi-step fast RBF registration approach using two intermediate virtual point landmarks (blue and yellow dots). The red and green dots (source and target landmarks) with the curves represent the source and target image, respectively.

Our multi-step fast RBF method first uses the source (red) and the nearest virtual landmarks (blue) for registration, then the previous virtual landmarks (blue) are considered as source landmarks and used for registration to the next virtual landmarks (yellow). This process is repeated till the final virtual land- marks (yellow in this case) are registered to the target landmarks (black). If the number of the virtual landmarks set is n the registration steps will be $n + 1$. The displacement field for every point in each step is calculated using the one-step fast RBF registration equation in the corresponding region of interest and accumulated to get the final displacement field from source to target image.

2.3. Performance Metric

To access the accuracy of our technique, we use the following two performance metrics:

2.3.1. Target Registration Error (TRE)

The TRE is the RMS error between the homologous validation landmarks after registration. To help the evaluation of global accuracy of registration we developed a set of well defined validation anatomical landmarks.

2.3.2. Normalized mutual Information (NMI)

As the NMI metric (Studholme et al. [10]) is suited to both mono-modal and multi-modal scenarios, we use this metric for image similarity measurement. In many cases it is more stable as compared to mutual information (MI) [11] and the Mattes mutual information (MMI). This metric is overlap invariant, which means that it does not depend on the degree of overlap of the two images and has an optimal value of 2.0 and a minimum value of 1.0.

The registration method was implemented using C++ programming language. All the tests were executed on an Intel Athlon Pentium IV (2.8 GHz) notebook.

3. RESULTS AND DISCUSSION

3.1. Single-step Verses Multi-Step Fast RBF Registration

The number of steps in the multi-step fast RBF registration technique is first specified by the operator which depends on the distances between source and target landmarks. For large deformation recovery, three or four step method is appropriate. In our experiments, we used the real image data obtained from the Vanderbilt database, also known as retrospective image registration evaluation (RIRE) project [12]. Though, this project is design specifically for evaluation of rigid registration techniques using fiducial markers as gold standard. It provides an online access to researchers around the globe for testing their techniques. The data base is also suitable for evaluation of non rigid registration methods as well. First, we deform the CT data using a set of manually defined 9 landmark pairs and BHS based transformation. The role of the set of landmark pairs were reversed and the one-step and multi-step algorithms were then applied to warp the deformed CT *back* to its unwarped equivalent (the ground truth) using a backward mapping approach and the BHS spline as a basis function. This allows us to compare the NMI's of a

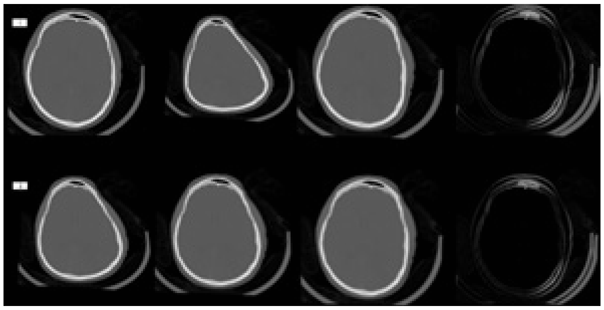

Fig. 2. Row 1 shows corresponding transverse slices from the full resolution CT dataset (Vanderbilt database) of patient P109. The first two images of Row 1 illustrate the original and deformed CT image before registration, while the last two images show corresponding registered and absolute difference images after the direct (single-step) non-rigid fast RBF registration experiment, respectively. On the other hand, the first two images of row 2 indicate the first and second step registration results of the three-step registration, while the last two images show corresponding registered and absolute difference images after the three-step non-rigid fast RBF registration experiment, respectively.

twice deformed dataset with its original, using the latter as the ground truth[2]. We tested both the algorithms using 9 extra landmark pairs for *validation* in conjunction with previously defined 9 *training* (to fit the spline) landmark pairs used for obtaining the deformed CT. For experiment, we downloaded the CT dataset (P109) and resampled them to the size of 256^3 resolution and slice thicknesses of 1mm for registration. We used trilinear interpolation during resampling and during registration as well. Fig. 2 shows the corresponding slices from the one-step direct (row 1) and three-steps (row 2) non rigid fast RBF registration of the CT data with its synthetically deformed CT. The first two images in first row show the corresponding CT (patient P109 of RIRE database) and its deformed version before registration, while the last two images show corresponding registered and absolute difference images after the one-step i.e. direct registration experiment, respectively. In row 2, the first two images indicate the first and second step registration results of the three steps (multi-step) registration, while the last two images show corresponding registered and absolute difference images after the three-step non rigid fast RBF registration experiment, respectively. The deformation recovered using multi- step method (image 3 of row 2) is more reasonable and good as compared to the one-step direct method (image 3 of row 1).

Table 1. Results after applying a BHS basis function based one-step non-rigid fast RBF registration of the CT RIRE data with its synthetically deformed CT. The second column shows the evaluation time of the RBF in seconds. The third column shows the NMI after warping forwards and backwards. The third and final column shows the TRE in mm. which is evaluated on the validation landmarks (forward warp only).

Technique	**Eval. Time (Sec)**	**NMI**	**TRE (mm)**
One-step fast RBF 0.025	67.70	1.258	2.91
Three-step fast RBF 0.025	189.79	1.293	2.91

In this study, we present the non-rigid fast RBF algorithm and extended to multi-step approach for recovery of larger displacement. The multi-step approach gives reasonable results and preserves the transformation locality as compared to the one-step method. The placement of a few pairs of landmarks in source and target images using our developed software took 4 to 8 minutes on average. Table 1 shows the results for the BHS basis function based one-step and multi- step algorithms using CT data, respectively. It indicates the evaluation time and the accuracy measured using NMI and TRE in mm. The best result for the fast RBF method was obtained by setting the *H* parameter to 0.025. The RBF (BHS in this case) calculation time, which is the time required to calculate the spline parameters and of the order of a couple of milliseconds for both the methods (not shown in the table), is negligible as

[2] The TRE error was evaluated for a forward warp only.

compared to the evaluation time (second column), which is the time needed to apply the spline to each voxel of the CT data. The evaluation time (second column) of the one-step and three- step methods are 45s and 135s (45x3), respectively. The calculated TRE (third column) using the *validation*[3] landmarks for both the methods is 2.91*mm* which is due to the same set of *validation* landmark pairs used during experiments. The TRE 2.91mm is greater than the expected (< 2mm) which involve placement error that is difficult to assess but will be smaller if an experienced radiologist has placed the landmarks. Now looking at the accuracy using the NMI metric, we see that the NMI (1.33) of the three-step method is good as compared to the NMI (1.33) of the one-step method. Furthermore, Fig. 3 which shows the visual results of the deformation field obtained using one-step registration (image 3) versus three-step registration (image 4) with same set of landmark pairs.

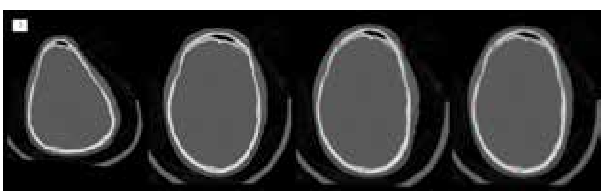

Fig. 3. Selected corresponding transverse slices from the full resolution deformed CT- to-CT dataset from the Vanderbilt database, before (image 1 and 2) the registration experiment, (image 3) the one-step and (image 4) the three-step after the fast RBF registration experiment. The registered CT slice shows numbered landmarks (colour version of the paper): red: training landmark; blue: original test landmark; green: test landmark after registration; the distance between the latter two defines the TRE which should be as minimum as possible.

The three-step registration produced more reasonable mapping of the transformation as compared to the one-step registration mapping. Result of the three-step registration (image 4) also show this, where the bones and other anatomy is better matched with the ground truth data (image 2) as compared to the one-step registration (image 3).

4. CONCLUSIONS

We have presented an optimised fast non-rigid registration method for medical imaging data using a set of manually identified anatomical landmark pairs. Also, we extend the non-rigid fast RBF algorithm to multi-step approach for recovery of larger displacement. The multi-step approach gave reasonable results and preserves the transformation locality as compared to the one-step method. Keeping the number of steps 3 or 4 in the multi-step algorithm was good enough to produce good results and it made the technique favourable for applications where both speed and accuracy were of importance, such as in image guided surgery (IGS).

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