3D Deformable Registration for Monitoring Radiotherapy Treatment in Prostate Cancer

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Abstract. Two deformable registration methods, the Demons and the Morphon algorithms, have been used for registration of CT datasets to evaluate their usability in radiotherapy planning for prostate cancer. These methods were chosen because they can perform deformable registration in a fully automated way. The experiments show that for in-patient registration both of the methods give useful results, although some differences exist in the way they deform the template. The Morphon method has, however, some advantages compared to the Demons method. It is invariant to the image intensity and it does not distort the deformed data. The conclusion is therefore to recommend the Morphon method as a registration tool for this application. A more flexible regularization model is needed, though, in order to be able to catch the full range of deformations required to match the datasets.

1 Introduction

Prostate cancer is the third most common cause of death from cancer in men of all ages and it is the most common cause of death from cancer in men over the age of 75 [8]. External beam radiotherapy has shown to be an effective treatment for localized prostate cancer in early stages. Radiation dose to the prostate was earlier very limited because of concern about normal tissue toxicity. Now three-dimensional conformal radiotherapy has allowed safe dose escalation to treat prostate cancer, which makes it possible to apply higher radiation doses on cancerous tissues and, at the same time, reduce the dose in healthy tissues [7]. There are several side effects associated with radiation therapy, including for example rectal bleeding and hematuria (blood in urine), basically derived from the undesired but unavoidable radiation of rectum and bladder [2]. This implies that careful consideration must be taken to the dose-volume histograms of normal tissues to avoid excessive toxicity in these regions.

Before beginning radiotherapy treatment CT scans have to be obtained for computerized treatment planning, to determine the most appropriate way to deliver radiation therapy. The radiotherapy team selects the target volume and

computes security margins using the CT scan and thereby obtains the volume to be radiated. External beam radiation therapy is usually performed 5 days a week for 6-8 weeks, and during this time there are some displacements and deformations of the prostate and high-risk organs that demand monitoring [1].

One of the problems to solve in the reduction of the radiated volume is the significant daily change in position of the prostate. The use of for example affine or projective registration algorithms, nowadays available in commercial radiotherapy software, allow quantification of the displacements of the prostate and reduction of the radiated volume considerably. However, the deformations of high-risk organs, such as rectum and bladder, where the dose evaluation is very important, remain an obstacle for the additional reduction of the margin. In addition, daily deformations pose a challenge in accurate tracking of the dose radiated to each point of the pelvis anatomy since it is not possible to quantify exactly the total radiation dose administered in several sessions. The use of deformable registration algorithms would allow setting an anatomical correspondence between the planning CT scan and the monitoring CT scan, and simulating the deformation of the anatomy more accurately.

The monitoring process is controlled with CT scans of the patient in different stages of the treatment, so the registration algorithm will be inpatient and will match small deformations. The next step of our research is to perform the planning of a patient using a planning template and the CT scans, which involves interpatient registration with larger deformations. One example of this has been included in this evaluation.

2 Methods

There are numerous algorithms for medical image registration in the literature, normally oriented to a concrete clinical application and to the type of images implicated in the process, see for example [4]. In this work two selected deformable registration algorithms have been employed and evaluated for the radiotherapy planning application. The methods are fully automatic and work on 3D data. The first one is the Demons algorithm [5], previously tested on e.g. inter-patient MRI brain and SPECT cardiac images and already used in radiotherapy planning by e.g. Wang et al. [10]. The second one is the Morphon algorithm [6], which is a relatively new method that has shown to work well for automatic segmentation of for example hip fractures and the hippocampus [9,11].

2.1 The Demons Method

The Demons algorithm, proposed by J.P.Thirion [5], is a method to perform iterative deformable matching of two 3D medical images fully automatic. The Demons method presumes that the boundaries of an object in the reference image can be simulated as a semi-permeable membrane, while the template image is a deformable grid whose junctions are two kind of particles: inside or outside. Each demon acts locally, to push the deformable model particles perpendicularly to the contour, but the direction of the push depends on the nature (inside or outside) of the current estimate of the model at that point.

There are some different ways to perform the algorithm, depending on the voxels considered to be demons, on the type of deformations allowed and on the way to compute the magnitude and direction of the demons forces. The implementation of the Demons method used in this work is characterized by the use of demons in all the voxels of the reference image. Since for medical images, iso-intensity contours are closely related to the shapes of the objects, one demon can be associated to each voxel of the reference image where the gradient norm is not null and hence a 3D grid of demons acts to deform the image.

A totally free-form deformation is allowed, but a low pass filter of the deformation vector field is used to control the deformability of the model. With the assumption that the intensity of an object is constant along time over small displacements, we used a modification of the classic optical flow equation to compute the displacement field:

$$\mathbf{v}^T \left(\frac{\nabla f + \nabla m}{2} \right) = m - f \quad (1)$$

where f is the intensity of the reference image, m is the intensity of the template image, ∇f and ∇m are their corresponding gradients, and $\mathbf{v}$ is the motion which brings m closer to f .

From eq. 1, only the projection of $\mathbf{v}$ on $(\nabla f + \nabla m)$ is determined, so we have:

$$\mathbf{v} = \frac{2(m - f)(\nabla f + \nabla m)}{\|\nabla f + \nabla m\|^2} \quad (2)$$

In order to avoid very large deformation forces that can distort the template image, the forces of the demons are needed to be close to zero when one of the gradient norms is close to zero, but the expression in eq. 2 tends towards zero only when both gradients are small at the same time. Furthermore, eq. 2 is unstable when the gradient norms are small. In this case, a small variation of the intensity can push the end point of $\mathbf{v}$ to infinity in any direction. The solution proposed by Thirion is to multiply $\mathbf{v}$ with a similarity coefficient s , resulting in $\mathbf{d} = \mathbf{v} \cdot s$, where s is defined by:

$$s = \begin{cases} 0 & \text{if } \nabla f^T \nabla m \leq 0 \\ \frac{2 \cdot \nabla f^T \nabla m}{\|\nabla f\|^2 + \|\nabla m\|^2 + 2(m - f)^2} & \text{if } \nabla f^T \nabla m > 0 \end{cases} \quad (3)$$

By applying this regularization the displacement field, when $\nabla f^T \nabla m > 0$, is given by the iterative equation:

$$\mathbf{d}' = \mathbf{d} + \frac{4(T_n(m) - f)(\nabla f + \nabla T_n(m))(\nabla f^T \nabla T_n(m))}{(\|\nabla f + \nabla T_n(m)\|^2)(\|\nabla f\|^2 + \|\nabla T_n(m)\|^2 + 2(T_n(m) - f)^2)} \quad (4)$$

where $T_n(m)$ is the deformed template image after n iterations.

This expression tends to zero when one of the gradients norms tends to zero and also when the two gradients are very dissimilar. It is important to notice that this expression requires the computation of $\nabla T_n(m)$ for each point and at each iteration.

Since this method uses the intensity difference between the images, in addition to the gradient of the intensity of the images, it is sensitive to intensity variations of the same anatomic point in different images. We have assumed that the intensity of an object is constant over time for small displacements, which is not always true for CT scans. Two images taken with the same device can have different values of intensity due to the noise in acquisition and reconstruction of CT scans. We have implemented a preprocessing that equalizes the histograms of both images in order to decrease the effect of this.

2.2 The Morphon Method

The Morphon algorithm has previously been presented in e.g. [6,11]. It is a non-rigid registration method in which a template is iteratively deformed to match a target in 2D or 3D using phase information. A dense deformation field is accumulated in each iteration under the influence of certainty measures. These certainty measures are associated with the displacement estimates found in each iteration and assure that the accumulated field is built from the most reliable estimates. The displacement estimates are derived using local image phase, which makes the method invariant to intensity variations between the template and target. Unlike the demons method, where the intensity values are considered to be consistent between the images, no preprocessing of the data is needed in the Morphon method.

The updated accumulated deformation field, $\mathbf{d}_{n+1}$, is found in each iteration by adding the displacement estimates from the current iteration, $\mathbf{d}$, to the accumulated deformation field from the previous iteration, $\mathbf{d}_n$. This sum is weighted with certainty measures associated with the accumulated field, c_n , and certainty measures associated with the displacement field from this iteration, c .

$$\mathbf{d}_{n+1} = \mathbf{d}_n + \frac{c}{c_n + c} \mathbf{d} \quad (5)$$

The displacement estimates are found from local phase difference. The local image phase can be derived using so called quadrature filters [3]. Quadrature filters are onedimensional and must be associated to a specific direction when used for multidimensional data. Therefore a set of quadrature filters, each one sensitive to structures in a certain direction, is applied to the target and template respectively. The output when convolving one quadrature filter f with the signal s is:

$$q = (f * s)(\mathbf{x}) = A(\mathbf{x})e^{i\phi(\mathbf{x})} \quad (6)$$

The phase difference between two signals can be found from the complex valued product between the filter output from the first signal, the target, and the complex conjugate (denoted by $*$) of the output from the second signal, the template:

$$q_1 q_2^* = A_1 A_2 e^{i\Delta\phi(\mathbf{x})} \quad (7)$$

The local displacement estimate d_i in a certain filter direction i is proportional to the local phase difference in that direction, which is found as the argument of this product, $\Delta\phi(\mathbf{x}) = \phi_1(\mathbf{x}) - \phi_2(\mathbf{x})$.

A displacement estimate is found for each pixel and for each filter in the filter set. Thus, a displacement field is obtained for each filter direction $\hat{\mathbf{n}}_i$. These fields are combined into one displacement field, covering all directions, by solving the following least square problem:

$$\min_{\mathbf{d}} \sum_i [c_i(\hat{\mathbf{n}}_i^T \mathbf{d} - d_i)]^2 \quad (8)$$

where $\mathbf{d}$ is the sought displacement field, $\hat{\mathbf{n}}$ is the direction of filter i , and c_i is the certainty measure (equal to the magnitude of the product in equation 7).

3 Results

Two CT scans of four different patients have been available for evaluating the deformable registration. For each patient intrapatient registration has been performed using the two deformable registration methods. Each one of the two patient scans has been used as template resulting in two registrations per patient and per method. In one scan of one of the patients contrast agent has been injected, which affects the registration process. This case is not comparable with the other datasets and is therefore handled separately in the discussion of the results.

To get an overview of the registration results we start by showing the correlation between the datasets before and after registration with the different methods. The graph in figure 1 shows the mean correlation per slice for the three datasets without contrast, before and after registration with the Demons and the Morphon respectively. The correlation has been computed for the edge information in the data instead of the original intensity information. This was chosen to obtain a measure that does not vary depending on the intensities in the homogeneous areas. Instead it reflects the deformation of the structures in the data better. From the graph we can see that there is not much difference between the two registration methods, they give similarly good results and have improved the alignment of the datasets considerably. While this gives an idea of how well the datasets have matched, one must also validate the deformed data visually to see how the algorithms have deformed the data. 2D slices from two of the registrations are shown in figure 2. These have been chosen to illustrate the result of the registration as well as the differences between the methods.

The Demons and the Morphon method deform the data in somewhat different ways. The implementation of Demons that has been used computes the displacement field based on the gradients of both reference and deformed template image. This makes it possible to avoid extremely large deformations that might destroy the structures and to e.g. fill holes that are not too big, as can be seen in figure 2 (a)-(e). This, however, often results in distortions of the data, which is demonstrated in the enlarged parts of the examples shown in figure 3. These images also show that the Morphon method gives a smoother deformation, keeping the structures of the template image. The Morphon method has, however, failed to deform the template sufficiently in parts of the soft tissue areas as can be seen in figure 2 (f)-(j).

Fig. 1. Mean correlation per slice based on the edge information in each slice. The Demons and the Morphon method generate similar results.

A slice of the dataset with the contrast agent is shown in figure 4. The problem with this dataset is that the contrast agent that fills the urinary bladder makes the edge between this tissue and the surrounding tissue much stronger than in the dataset without contrast agent. For the Demons algorithm this causes problems in the whole process. The Demons method assumes the same anatomical point having the same intensity level in both images, and a histogram equalization is performed before the registration starts trying to obtain this. The contrast agent corresponds to a completely new intensity level in this datasets, not present in the other scan of the patient. The Demons preprocessing step tries to match the histograms of the two datasets anyway, which in the worst case may increase the intensity differences instead of decreasing it. This, in turn, deteriorates the registration result. The Morphon method is invariant to the intensity levels in the datasets since it uses the local image phase to estimate the displacements. The stronger edge in the contrast dataset is however recognized by the filters used for phase estimation, which makes the Morphon registration responsive to the contrast as well, although only in the neighborhood around this edge. In the Morphon result it is difficult to say how well the datasets have matched in the area covered by the contrast agent, although the rest of the image has matched well, figure 4(c). For the Demons result parts of the anatomy, such as the hip bones, have completely lost their shape. The soft tissue, such as the bladder, has not been registered correctly either, figure 4(d).

Finally an example of an interpatient registration is included as a first test of the next step of our research that will involve not only the monitoring but also the planning of the process. This registration process involves larger deformations than for inpatient matching. The Morphon has shown to work well for this kind of data in previous work, for example when registering a template with a very simple description of the anatomy in the hip region to real data from a CT scan, containing a lot more structures [11]. A 2D slice of the

Fig. 2. Slice of dataset with a region of interest (roi) specified to highlight the difference in the Demons and the Morphon result. Images (a) and (f) show two different slices of the target with the roi marked with a dotted line. This region is enlarged in the right part of the figure, where (b) and (g) are the roi of the target for each slice with a bit more contrast to emphasize the structures, (c) and (h) are the roi of the template data. (d) and (i) are the deformed template resulting from Demons registration and (e) and (j), finally, are the result from Morphon registration. The Demons method has been able to better match the template compared to the Morphon method. The drawback is that it distorts the data.

Fig. 3. Enlargement of details of the result to show the distortion introduced by the Demons algorithm compared to the more smooth Morphon results

interpatient registration results for the Morphon method is shown in figure 5. The Demons algorithm, although being able to perform small interpatient deformations like in brain atlas-based registration, is not sufficient to solve this kind of

Fig. 4. Result for registration of dataset with contrast agent. (a) Target, (b) template, (c) Morphon result and (d) Demons result.

Fig. 5. Example of difference in one slice for the CT data for interpatient registration. The left image show the difference before registration and the right image show the difference after registration with the Morphon method. This image is ideally gray.

registration problems on pelvic images due to the large deformations and the intensity differences. Figure 6 shows the per slice correlation of datasets before and after registration. The Demons algorithm has not been able to match the datasets except for a few slices in the center of the stack of the data volume.

Fig. 6. The correlation (per slice) for the interpatient registration. The Demons algorithm has only been able to match a couple of slices in the center.

4 Conclusions

Two non-rigid registration methods have been used for fully automatic registration of CT volumes of the pelvic region, to evaluate their ability to catch the deformations of the anatomy between patient scans. The methods used were the Demons method and the Morphon method. They were chosen due to their capability of performing deformable registration in a fully automated way. We can conclude that the methods behave different in some aspects although the overall result is good for both of them when performing intrapatient registration. The Demons method allows a higher level of deformation of the template and may for example fill holes if it results in a better match to the target. One can discuss if this is a desirable feature in all situations, since this means that the anatomy present in the template has been modified considerably. The Demons algorithm also distorts the data to some extent, which may introduce strange artifacts in the deformed template. The Morphon method avoid the problem of distortion but has in these experiments been too stiff in some regions. Parameter settings can be changed to give the Morphon more degrees of freedom. This has been tested, and even though this results in a different deformation of the template, it did not result in a better registration of the datasets. Instead it would be usable to have different regularization models in different regions of the dataset. This feature is currently under development for the Morphon method and will be evaluated for this application in future work.

When either template or target dataset contain an intensity level not present in the other dataset, as for the dataset with contrast agent, the preprocessing step of the Demons algorithm will create an inaccurate output and the registration is misled. The Morphon method is not sensitive to the intensity levels in the same way, although the filters used for local phase estimation detects the strong edge, and the result is affected in the region of this edge.

For the experiment with interpatient registration, the Demons method was not able to give any usable result due to its sensitivity to image intensity differences between the images and the larger deformations involved in the process. The Morphon method gives adequate results, although the desire to have a more flexible regularization model exist also in this case.

Since we have used two completely different implementations of the algorithms (Matlab for the Morphon method and ITK for the Demons method) computational time is not a good measure of comparison at this stage, and is therefore left out in this discussion.

Although a more quantitative evaluation is required, the preliminary conclusion is that the Morphon method, with a more flexible regularization model, is the preferable method depending on two main causes. It is not sensitive to difference in image intensity between the datasets as is the Demons method, and it does not introduce the distortions in the deformed data seen in the Demons results.

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