

# Deformable Registrations for Head and Neck Cancer Adaptive Radiotherapy

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**Abstract.** Preliminary tests and results are described to evaluate the accuracy and robustness of a FFD voxel-based deformable registration algorithm in registering planning CTs to CBCTs from head and neck patients. Similarity measures, computation time and visual inspection are used to assess the effect of different registration parameters in the results and to find a promising interval of parameters' values.

## 1 Motivation

Developments in radiotherapy techniques aim at delivering increasingly more conformal doses to the target volumes while sparing the surrounding healthy tissues. However, the steeper the dose gradients become the more important it is to precisely set up the patient. This includes accurate positioning of the internal organs [1]. Inaccuracy in positioning can cause underdosage of the target volume and overdosage of normal tissues, which can result in increased risk of tumour recurrence and complications [2].

The incorporation of daily setup images taken on the treatment site into the radiotherapy process can facilitate adaptive radiation therapy (ART). In ART the treatment is evaluated periodically using in-room imaging, such as cone-beam computed tomography (CBCT), and the plan is adaptively modified to take in consideration changes in dose due to changes in patient setup and anatomy [3].

ART could be particularly useful for head and neck (HN) patients due to the complexity of the surrounding anatomy and the proximity to several radiosensitive critical structures. Conventionally, it is assumed that the targets in the HN region are quite rigidly attached to the bony anatomy [4] and so organ motion is minimal. However, recent studies report progressive changes in the patient anatomy during the course of the treatment and relate them to dosimetric changes from the original plan [2][5][6]. The reasons for anatomical changes are multifactorial and can be related with the decrease of tumour and nodal volumes, weight loss (due to difficulties in swallowing), alteration in muscle mass and fat distribution, fluid shift within the body [7] and resolving postoperative changes/edema [2]. Studies done on mid-treatment re-planning of HN patients show that there is benefit to some patients, but there is no method to identify the ones that will benefit more from replanning and the optimal timeframe for it to take place.

For some HN patients at least one replanning is necessary. Currently replanning is done in University College London Hospital (UCLH) in Intensity Modulated Radiation Therapy (IMRT) treatments only when absolutely necessary, usually mid-way through the treatment when considerable anatomical changes take place and the patient no longer fits in their personal immobilizing thermo-plastic mask. The new plan is built from scratch by acquiring a new planning CT and without accurately knowing the dosimetric consequences so far. It may be more beneficial to replan the patients earlier in their treatment, but there is no evaluation method to assess the necessity and timing for replanning.

UCLH and University College London (UCL) are currently developing a clinical proton therapy facility, expecting to treat its first patients in 2017. In Proton Therapy (PT) accounting for setup and anatomical changes becomes even more important as more conformal doses are delivered and the dose distribution is more sensitive to the patient's anatomy. Therefore, the question of if and when to replan is even more relevant in PT.

It is widely accepted in literature that the future of ART depends on the use of accurate deformable registration algorithms [7][8][9]. A deformable registration resolves the major challenges in ART: planning CT scans warped to match the daily CBCT can be used for reliable dose calculations, regions of interest can be propagated from the planning CT and daily dose distributions can be warped back to the planning CT to calculate the accumulated delivered dose [6]. The main challenge is in how to properly validate deformable registrations on clinical data, so for now they must be used with care.

In this work we investigate a deformable registration algorithm to register the planning CT and weekly CBCT images taken from HN patients. These findings will be useful for developing and validating a future ART protocol for HN patients.

## 2 Methods and Materials

NiftyTK software was developed by the Centre of Medical Image Computing (CMIC), at the Department of Medical Physics and Bioengineering of UCL. The software is in constant development and contains several tools for image registration and visualization. It combines a set of different toolkits, including the open-source NiftyReg (<http://cmic.cs.ucl.ac.uk/home/software>) for rigid and deformable image registration, and a viewer (NiftyView).

The rigid/affine registration code uses a Block Matching algorithm [10], while the deformable registration code is a re-factoring of Rueckert et al. (1999) Free-Form Deformation (FFD), based on B-Splines and a voxel-based similarity measurement - Normalized Mutual Information (NMI) [11]. The major differences from the original paper are in the calculation of the gradient and joint histogram, introduction of other penalty terms, and a GPU implementation, which make the code faster and more robust [12].

In this preliminary study we aim to evaluate the image registration algorithm on a small set of data to find a set of promising parameters to use in further

studies. This set of parameters should give good results for any HN registration by minimizing the computation time and keeping acceptable values for the similarity measures. Since high values of similarity measurements do not necessarily mean a better registration the analysis is aided with visual assessment of the registered images. The similarity measure used was the NMI,

$$\text{NMI}(A, B) = \frac{H(A) + H(B)}{H(A, B)} \quad (1)$$

where  $H(A)$  and  $H(B)$  are the entropy of the images  $A$  and  $B$ . NMI can take any value between 0 and 2, where higher values correspond to higher similarity and values of  $\text{NMI} > 1$  typically represent a good agreement between images. Initial tests using SSD as similarity measure showed that it did not perform well due to the intensity differences between CT and CBCT images.

This study can then be divided in two parts based on the input parameters of the registrations:

1. Optimization of the rigid transformation
  - Effect of masking the reference image;
  - Effect of ignoring the last level of resolution;
2. Optimization of the deformable transformation
  - Effect of the bending energy weight (BE): the bending energy is a penalty term introduced in the cost function to constrain the transformation to be smooth.

$$\begin{aligned} \text{BE} = \int \int \int_{\Omega} & \left( \frac{\partial^2 \mathbf{T}}{\partial x^2} \right)^2 + \left( \frac{\partial^2 \mathbf{T}}{\partial y^2} \right)^2 + \left( \frac{\partial^2 \mathbf{T}}{\partial z^2} \right)^2 \\ & + 2 \left[ \left( \frac{\partial^2 \mathbf{T}}{\partial xy} \right)^2 + \left( \frac{\partial^2 \mathbf{T}}{\partial xz} \right)^2 + \left( \frac{\partial^2 \mathbf{T}}{\partial yz} \right)^2 \right] \end{aligned} \quad (2)$$

- Effect of the logarithm of the jacobian weight (JL): the logarithm of the jacobian penalty penalizes large local volume changes and prevents folding.

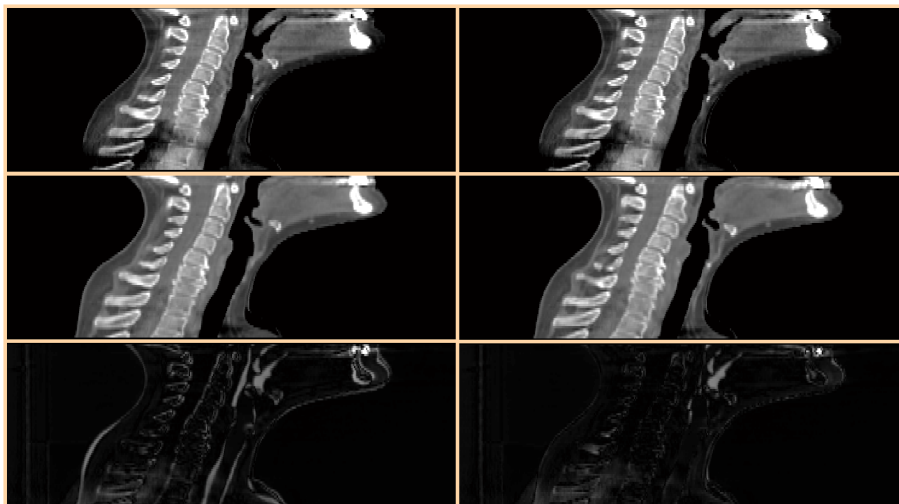
$$\text{JL} = \frac{1}{n} \sum |\log(\det(\nabla \mathbf{T}))| \quad (3)$$

- Number of histogram bins used to calculate the joint histogram;
- Effect of thresholding the reference and floating images;
- Maximum number of iterations used;
- Control Point (CP) spacing;
- Effect of masking the reference image;
- Effect that the choice of rigid transformation has on the deformable registration results;

Registrations were repeated changing the parameters of interest for two clinical datasets from HN patients.

### 3 Results

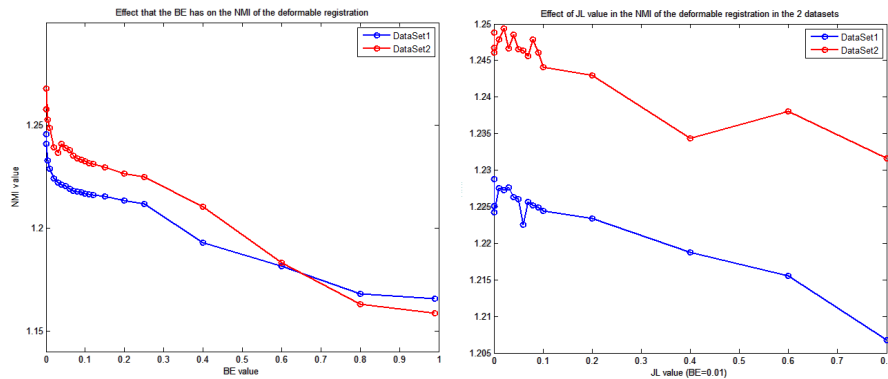
Rigid only transformations were applied to describe the global motion, as it is an intra-subject registration. Mask usage in the rigid registration improved the global alignment results and reduced significantly the computation time. Ignoring the last level of registration has no visual effect if masks are used, which reduces the computation time even further. The rigid registrations took approximately 1 minute to compute.



**Fig. 1.** Sagittal slices of the CBCT, registered image and difference image between the two. The first column refers to a rigid-only transformation, and the second to the deformable transformation. Gray areas show where the CBCT and registered image disagree. Even though the anatomy of the HN is conventionally considered rigid, a rigid-only registration cannot fully capture all the changes. A rigid registration shows considerable disagreement in the bone and external contours alignment. Using deformable registration the matching is improved. Near the throat there are still discrepancies due to swallowing.

Regarding the deformable registration,

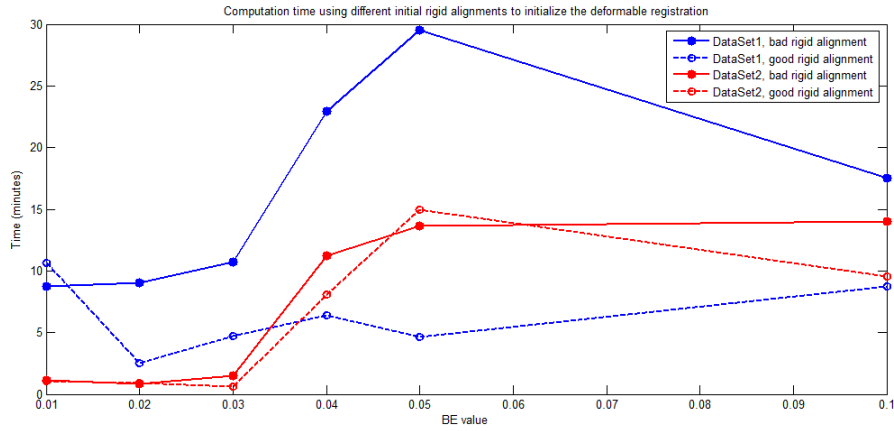
1. Values of BE within the interval  $[0.01, 0.10]$  seem to produce acceptable results. For these two datasets the best visual results are produced by a narrower range  $([0.02, 0.06])$ . Low values of BE may give good NMI values, but visually the alignment is incorrect (Fig. 2).
2. In general, using the jacobian penalty term only causes dramatic visual changes for low values of BE, where folding is more likely to occur. The introduction of this parameter appears to smooth the effect that other parameters changes have. Thus values within  $[0.01, 0.10]$  seem like a good



**Fig. 2.** Decreasing of the NMI value with increasing BE/JL value. Increasing values of BE and JL overall decrease the similarity measure as the code is built to maximize it and penalty terms constrain that maximization.

compromise between constrain of the transformation and stopping folding from occurring.

3. The number of bins used in the joint histogram calculations affects the overall results. Unexpectedly, increasing the number of bins does not seem to increase the computation time but it degrades the final registration. It is possible that a higher binning value makes the code more sensitive to noise in the images. Also, CBCT intensity values for the same type of tissue may vary in different areas of the image so smaller binning intervals may lead to the same tissue being separated in different bins on different zones of the image. Considering NMI values and visual assessment, a binning of 64 was found as acceptable in all tests done.
4. A thresholding may be advisable to remove “padding” values (voxels with intensities inferior to -1000HU) and to deal with high-intensity artefacts. The thresholding conducted showed no improvement in image alignment and computation time. However, since the effect of threshold is similar to the effect of increasing the binning of the joint histogram, for thresholding to have a positive effect the choice of binning must be adjusted properly. We are still to find the best combination of both.
5. Reducing the maximum number of iterations reduces the computation time by forcing the algorithm to finish before it reaches a convergence value. Overall it looks like a good compromise to use a maximum of 1000 iterations at, which limits the maximum computation time to approximately 5 minutes.
6. Good results were achieved when using CP spacing between 5 and 10 voxels. For lower values it is difficult to sufficiently constrain the registration and the algorithm loses the capture range of bigger deformations.
7. The choice of rigid registration parameters does have an impact in the following deformable registration. In general initializing the deformable registration with a better rigid alignment reduces the time spent to reach con-



**Fig. 3.** Computation time using different initial rigid alignments.

vergence (Fig. 3). The final results are visually similar while overall the NMI value is slightly improved.

- Masking the reference image in the deformable transformation reduces the computation time to 1 minute, but can make the registrations more sensitive to other parameters.

Combining all these results, overall the deformable registration takes around 1 minute if a mask is used, and up to a maximum of 5 minutes if none is used.

## 4 Conclusions

The code used is fairly robust as small changes in the parameters do not cause dramatic changes in the registration results, particularly when the jacobian penalty term is used. For the parameters investigated there are intervals of values that give promising results.

For rigid registrations the best results were achieved using a mask and ignoring the last level of resolution. The optimal parameters found for the deformable registration are:  $BE=[0.02, 0.06]$ ,  $JL=[0.01, 0.10]$ , a maximum number of 1000 iterations, a binning of 64 for the joint histogram calculation, no thresholding and a control point spacing between 5 and 10 voxels. Such registrations can take up to a maximum of 5 minutes to finish; using a mask this time can be reduced to less than 1 minute.

## 5 Future Work

On this preliminary work we focused only on two datasets. We will use our findings on more datasets to narrow this range of parameters to a single value,

valid for all HN images produced in UCLH. On this next step we will also include more quantitative analysis of the registration.

Future quantitative checks must assess accuracy, robustness and consistency. They can include jacobian analysis of the deformation field and calculation of other similarity measures that are not maximized by the algorithm, such as the Sum of the Square Distances (SSD). The output of the deformable registration is a deformation field that relates each point in the CT to the CBCT image. This information can be used to deform the contours delineated in the CT to the CBCT space. A quantitative analysis of the registration can be done by comparing the automatically generated contours with the ones drawn by a trained physician (generally considered as gold-standard) by using quantities such as Dice Similarity Index (DSI), Pearson's correlation coefficient (CC) [7], Overlap Index [8] and Distance Transformation (DT).

We will also investigate whether image pre-processing to reduce noise and enhance contrast can improve the registrations.

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