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Deformable registration of CT and cone-beam CT with local intensity matching

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Abstract

Cone-beam CT (CBCT) is a widely used intra-operative imaging modality in image-guided radiotherapy and surgery. A short scan followed by a filtered-backprojection is typically used for CBCT reconstruction. While data on the mid-plane (plane of source-detector rotation) is complete, off-mid-planes undergo different information deficiency and the computed reconstructions are approximate. This causes different reconstruction artifacts at off-mid-planes depending on slice locations, and therefore impedes accurate registration between CT and CBCT. In this paper, we propose a method to accurately register CT and CBCT by iteratively matching local CT and CBCT intensities. We correct CBCT intensities by matching local intensity histograms slice by slice in conjunction with intensity-based deformable registration. The correction-registration steps are repeated in alternating way until the result image converges. We integrate the intensity matching into three different deformable registration methods, B-spline, demons, and optical flow that are widely used for CT-CBCT registration. All three registration methods were implemented on a graphics processing unit (GPU) for efficient parallel computation. We tested the proposed methods on twenty five head and neck cancer cases and compared the performance with state-of-the-art registration methods. Normalized cross correlation (NCC), structural similarity index (SSIM), and target registration error (TRE) were computed to evaluate the registration performance. Our method produced overall NCC of 0.96, SSIM of 0.94, and TRE of 2.26mm, outperforming existing methods by 9%, 12%, and 27%, respectively. Experimental results also show that our method performs consistently and is more accurate than existing algorithms, and also computationally efficient.

1. Introduction

Recent advances in medical imaging technology make 3D intra-operative imaging possible. Cone-beam CT (CBCT) is one of effective in-room 3D imaging modalities due to its cost-effective nature and lower radiation dose to the patient. It can be realized as a mobile system such as mobile C-arm or can be combined with an existing system, e.g., linear accelerator for radiation therapy (Oelfke *et al* 2006, Xing *et al* 2006, Yang *et al* 2007). Intra-operative CBCT is especially useful as it represents the patient anatomy at the time of treatment.

Pre-operative imaging is typically performed before the surgical procedure or treatment, and the physician identifies the target and determines the surgical/treatment plan. CT is widely used as a reference planning volume for most CBCT-guided procedures such as orthopedic surgery and radiation therapy. Registration between the planning CT and the intra-operative CBCT is crucial to match the plan and the structures of interest between two time points, i.e., planning and surgery/treatment, for accurate delivery of the planned treatment. It also allows us to detect and assess anatomical changes during and/or after the treatment. CT-CBCT registration is also useful to improve the CBCT reconstruction. The registered CT provides valuable patient-specific prior knowledge to regularize the CBCT reconstruction, and many studies demonstrate that prior-constrained iterative reconstruction techniques significantly improve the CBCT reconstruction quality (Stayman *et al* 2011, Zhang *et al* 2013).

Even though CT and CBCT use the same imaging modality, X-ray, CBCT intensity is inconsistent with CT due to artifacts from various sources such as scatter, truncation, and incomplete data in Radon space. Some artifacts may also come from discrepancies between the image processing used in reconstruction and the actual physical property (Schulze *et al* 2011). To accurately reconstruct CBCT images using a filtered-backprojection (Feldkamp *et al* 1984), at least a short scan (180° plus fan angle) is necessary. As shown in figure 1, the mid-plane can be reconstructed exactly (if there is no truncation) as every pixel on this plane within the field of view satisfies Tuy's condition (Tuy 1983). However, off-mid-planes undergo different information deficiency depending on slice locations and the reconstruction is approximate, resulting in different reconstruction artifacts (Ramamurthi 2006, Sadowsky *et al* 2011). This implies that CBCT image intensities may not be accurately transformed to CT intensities using a global intensity matching approach.

Artifacts in CBCT reconstruction often cause undesirable errors when performing intensity-based deformable registration. Figure 2 shows an example of CT and CBCT images of the same patient. As shown in this example, the CBCT reconstruction quality is spatially varying, and some regions may exhibit significant degradation, e.g., lower neck and shoulder regions in this case. Therefore, registration strategy based on direct intensity comparison such as sum of squared differences (SSD) is likely to produce incorrect results (Zhen *et al* 2012) due to significant intensity mismatch between CT and CBCT.

Alternatively, CT-CBCT registration can be considered as a multimodal registration (Greene *et al* 2009). In this approach, mutual information (MI), normalized mutual information (NMI), or normalized cross-correlation (NCC) are widely used as a similarity metric (Sotiras *et al* 2013). If the images are well aligned, corresponding anatomical structures overlap. The underlying assumption of MI- or NCC-based approaches is that the better structural overlay leads less dispersion in the joint histogram (Pluim *et al* 2003) or higher intensity correlation. Therefore, two images can be registered by sharpening the dispersed joint histogram or maximizing their intensity correlation. However, this assumption may not hold well for CT-CBCT registration because CBCT intensity of the same tissue significantly varies due to various artifacts.

Recently, a few groups tried to resolve this issue by incorporating CT-CBCT intensity matching into the registration process. Hou *et al.* (Hou *et al* 2011) proposed to correct CBCT intensity by applying global histogram matching between CBCT and CT. However, the global matching cannot produce accurate intensity matching because it does not take into account the spatially-varying intensity distortion in CBCT reconstruction at off-mid plane slices. Nithiananthan *et al.* (Nithiananthan *et al* 2011) classified the CBCT volumes into four regions (air, two soft tissue regions, and bone) and matched the intensity for each region by linear regression during the registration in an alternating fashion. This method requires division of CBCT intensity ranges into four regions to fit different linear models, and they used fixed range values. Such piecewise linear fitting with fixed ranges often fails as the CBCT intensity distribution varies depending on the subject, field of view, and scanning parameters.

Zhen *et al.* (Zhen *et al* 2012) applied a patch-based CBCT intensity correction to address the spatially-varying CBCT reconstruction artifacts. They used a linear intensity mapping for every patch, and computed the first two moments to find a linear model. Lou *et al.* (Lou *et al* 2013) solved global optimization based on mutual information with a regularization term to minimize the sum of intensity differences between CT and intensity-corrected CBCT. As a result, they find displacement vector fields and intensity-correction terms by minimizing MI and SSD between CT and intensity-corrected CBCT in one framework. Compared to (Hou *et al* 2011) and (Nithiananthan *et al* 2011) which use global matching models, Zhen *et al.* and Lou *et al.* compare and match CT and CBCT intensities locally using a small cubic patch (Zhen *et al* 2012) or each voxel (Lou *et al* 2013). In (Zhen *et al* 2012), a mask is created to find voxels at different tissue types between CT and CBCT, the moments of the voxels are computed by averaging the values of neighboring voxels. However, structures within a small patch region, e.g., in their case, $3 \times 3 \times 3$ voxels, are unlikely to be well matched until the later iterations of the registration, which leads to unstable moments of intensity distribution, yielding erroneous intensity matching. Additionally, additional interpolation/extrapolation step is necessary to obtain globally smooth intensity mapping. Simultaneous optimization of voxel-by-voxel intensity correction with deformable registration (Lou *et al* 2013) increases degrees of freedom of the problem, which may easily lead to a local optimum and hinder convergence.

This paper proposes a new strategy to improve CT-CBCT registration. We use local CT-CBCT intensity matching strategy to address spatially-varying CBCT artifacts. Unlike other approaches, our local intensity matching is performed on anisotropic patch regions by considering the CBCT reconstruction process and resulting systematic artifacts. Specifically, our method combines a local CT-CBCT intensity matching and deformable registration, and iteratively solves both problems in an alternating fashion. At each iteration, local CBCT intensity is matched to the corresponding CT by intensity histogram matching within each patch region, in our case, each slice. We match individual slice intensities rather than using small patches to accommodate the different image intensity distortion caused by slice-dependent information deficiency. Since the intensity matching is independent of registration algorithm, we combine the local intensity matching with three different popular registration methods, B-spline, demons, and optical flow algorithms, and compare the performance. All registrations are performed in 3D regardless of the patch size of intensity matching.

Furthermore, both intensity matching and deformable registration are implemented on a graphics processing unit (GPU) to enable fast and efficient computation. The initial concept of our method has been presented in (Park *et al* 2015) with preliminary results. In the current paper, we have significantly updated our initial concept by improving algorithms, implementing more efficient GPU modules, and extensively testing our methods on larger number of patient data.

The remainder of this paper is organized as follows. In section 2, we describe the key methods and each step of our combined CT-CBCT intensity matching-registration process. Numerical results based on 25 head and neck cancer patient data sets are presented in section 3. In section 4, we further discuss the performance and the effect of patch size, and finally conclude the paper in section 5.

2. Methods

We first perform rigid registration of planning CT to CBCT images using MI as the similarity metric to obtain reasonable initial alignment for the successive intensity matching and deformable registration. We do not attempt to match CT-CBCT intensities during the rigid registration step as the two volumes are not initially aligned and therefore the intensity matching is inaccurate. Rigid registration is sufficient for intra-subject CT-CBCT registration, which is the case for most image-guided surgery or radiation therapy. However, when registering CT and CBCT images taken from different subjects, an affine registration is preferred to achieve better initial alignment. Herein, we use rigid registration as the first step as we test our method on head and neck radiation therapy cases.

After the initial rigid registration, we simultaneously compute the intensity matching and deformable registration. Since images cannot be perfectly aligned by initial rigid registration, the initial intensity matching may not provide sufficient accuracy. Therefore, we perform the intensity matching and the registration in an alternating fashion as the iteration proceeds rather than finding the intensity mapping as a onetime process before the registration. Notice that the intensity matching is performed at every iteration of the deformable registration in a similar way as in (Nithiananthan *et al* 2011, Zhen *et al* 2012). Because the reconstruction fields of view (FOV) are different between CT and CBCT, we detect the region of interest (ROI) by thresholding the CBCT images using the Otsu's method (Otsu 1979) and create a mask for the deformable registration. We particularly use CBCT images to determine the ROI as the CBCT has smaller FOV than the planning CT. Figure 3 shows the overall procedure of our algorithm.

Because the intensity matching and deformable registration alternate in our framework, the intensity matching can be combined with any deformable registration algorithm. In this paper, we combine the intensity matching with three widely-used deformable registration methods, B-spline, demons, and optical flow, and compare their performances. We now describe the details of our algorithms.

2.1. Intensity matching

CBCT has various artifacts originated from different sources. Most common artifacts include metal artifacts, scatter, truncation, and intensity inconsistency at off-mid planes due to approximate reconstruction. In general, these artifacts are spatially varying, and especially, the intensity inconsistency varies slice by slice as each slice parallel to the plane of source-detection rotation undergoes different information deficiency.

Figure 4 shows an example of joint histograms between CT and CBCT slices at different slice locations. As shown in this figure, the joint histogram between CT and CBCT intensities becomes more dispersed as the slice location is farther from the mid-plane. This happens because the farther the CBCT reconstruction plane is from the mid-plane, the more missing information in the Radon space, i.e., the CBCT reconstruction is more approximate (Ramamurthi *et al* 2006). Therefore, global intensity correction should not be used to properly address these spatially-varying characteristics. In our approach, we perform local intensity matching using each slice as our patch. We particularly chose a slice-by-slice approach because CBCT reconstruction artifacts vary depending on slice locations. If the patch size is too large (especially along the direction perpendicular to the mid plane), intensity matching becomes less accurate for the same reason as the global matching. On the other hand, intensity matching with a patch smaller than a slice often leads to inconsistent matching between different patch regions, producing discontinuous boundaries. Such non-smooth boundaries may cause significant registration errors unless they are properly smoothed before registration, which requires additional computation. Performance comparison results for different methods based on global matching (can be considered as a large patch-based matching) and smaller patch-based matching, and our slice-based local matching are provided in section 3. We also added additional discussions on different patch sizes and their effect on the registration quality in section 4.

To match CBCT and CT intensities within a patch region, we perform histogram matching between two histograms for each slice. Let $I_F(\mathbf{x})$ and $I_M(\mathbf{X}): \mathbb{R}^3 \rightarrow \mathbb{R}$ be CBCT and CT volumes, respectively. And let p_F and p_M be the probability mass functions for I_F and I_M , respectively, and W be the width of the intensity range of two volumes. For the k^{th} iteration, the intensity value at location $\mathbf{x}$ on the j^{th} slice $i_{F,j}^k = I_{F,j}^k(\mathbf{x})$ can be computed as

$$i_{F,j}^k = G^{-1}[T(i_{M,j}^{k-1})] \quad (1)$$

where $G(i_F) = (W - 1) \int_{-\infty}^{i_F} p_F(t) dt$ and $T(i_M) = (W - 1) \int_{-\infty}^{i_M} p_M(t) dt$. An algorithm for discrete version can be found in (Gonzalez *et al* 2007).

2.2. Registration

In this paper, we focus on intra-subject CT-CBCT registration, which is the key step for most CBCT image-guided surgery and radiation therapy procedures. Note that our intensity matching can be combined with various deformable image registration methods. We combine our intensity matching with B-spline free-form deformation, demons, and optical

flow-based methods that are widely used for CT-CT or CT-CBCT registration and are computationally efficient. All these algorithms are implemented on GPU for faster computation.

2.2.1. Hierarchical B-spline—A free form deformation (FFD) is widely used in medical image registration (Rueckert *et al* 1999, Mattes *et al* 2003, Sotiras *et al* 2013). In image registration applications, uniformly spaced knot vectors and parameters are commonly used because the volume data structure is represented as voxels. Typical deformations using B-spline use uniformly spaced control points, and cardinal splines are used as the interpolant (Unser 1999, Thevenaz *et al* 2000, Mattes *et al* 2003, Klein *et al* 2007), which is reasonable in many cases. However, uniform grid may not be suitable if there are larger local deformations than the maximum displacement possibly represented by one grid size. Finer grid requires increased computation time and memory space. To overcome such limitations of uniform grid, hierarchical B-splines have been widely used in shape modeling (Forsley *et al* 1988), and also applied to medical image registration problems (Xie and Farin 2004). In these approaches, local refinement is performed by subdivision of a patch. The original grid is not replaced by the refined control points, but sub-grids are stored in a hierarchical way to represent the target volume by *overlay*. Figure 5 shows an example of 2D refinement of a bicubic B-spline patch (for only conceptual explanation, but note that our registration computation is performed in 3D). The white dots in this figure are the original control points and the corresponding surface patches are shown with solid lines. To refine the central region, control points described as black dots connected by dashed lines are created and overlaid on the original grids as shown in figure 5(b). The deformation and grid refinement are performed in a hierarchical and alternating way during the registration process.

In our CT-CBCT registration, we first make volume pyramids for CT and CBCT, and perform the registration hierarchically using uniform control points for each level. We then compute differences between CBCT and deformed CT within local patches to identify regions where deformations need to be refined. If SSD value of a local patch is larger than the (mean + standard deviation) of the entire patches at the same level, the local patch is refined and deformable registration is performed locally using the refined grids. For more details of the algorithm, we refer readers to (Xie and Farin 2004). We use SSD as the similarity metric because the CBCT intensity is matched to CT by the iterative intensity matching in our approach.

One of advantages of using SSD similarity metric is its computational efficiency of finding the optimal solution. By applying optical flow approach to find optimal positions of the grid points (Xie and Farin 2004), iterative steps require computing only gradients of volume intensities as shown in the following equation, which can be easily parallelized.

$$\mathbf{v}(\mathbf{p})^k = \frac{\left(I_M^{k-1}(\mathbf{p}) - I_F(\mathbf{p})\right) \times \nabla(I_F(\mathbf{p}))}{\|I_F(\mathbf{p})\|^2 + \left(I_M^{k-1}(\mathbf{p}) - I_F(\mathbf{p})\right)^2} \quad (2)$$

where $\mathbf{v}(\mathbf{p})^k$ is the displacement vector for a point $\mathbf{p}$ at the k^{th} iteration, and it is computed for every control point. We apply a fast B-spline transform (Unser, 1999) to interpolate the volume before registration.

2.2.2. Demons—While B-spline registration is a parametric approach with degrees of freedom determined by the number of control points, demons and optical flow directly compute the displacement vector at each voxel by minimizing intensity differences between two volumes. Since Thirion (Thirion 1998) introduced the diffusion process with Maxwell's demons to the registration problem, it has been widely used in medical image registration due to its computational efficiency and robustness. Among many variations (Pennec *et al* 1999, Wang *et al* 2005, Vercuteren *et al* 2009, Gu *et al* 2010), we use the double force algorithm (Wang *et al* 2005) that gives stable and robust computation results in our case. In this approach, the displacement vector $\mathbf{v}$ at each voxel at the k^{th} iteration is computed as

$$\mathbf{v}^k = (I_M \circ T^{k-1} - I_F) \times \left(\frac{\nabla I_F}{\|I_F\|^2 + \alpha (I_M \circ T^{k-1} - I_F)^2} + \frac{\nabla I_M \circ T^{k-1}}{\|I_M \circ T^{k-1}\|^2 + \alpha (I_M \circ T^{k-1} - I_F)^2} \right) \quad (3)$$

where $T^k: \mathbb{R}^3 \rightarrow \mathbb{R}^3$ is a transformation function of the deformable registration at the k^{th} iteration, and $I_M \circ T^k = I_M^k$ is the transformed moving volume. Note that T corresponds to the displacement vector field of the CT images in our problem, and we use $\alpha = 2.5$ chosen by experiments. In every step, the incremental displacement vector field $\{\mathbf{v}^k\}$ is smoothened by a Gaussian kernel. To preserve rigidity of hard tissues and to allow flexibility for soft tissue and air regions, we multiply an additional regularization term,

$1 / \left(\|I_M^{k-1}(\mathbf{p})\|^2 + \alpha \|I_M^{k-1}(\mathbf{p}) - I_M^{k-1}(\mathbf{q})\|^2 \right)$, to the Gaussian kernel when smoothening $\{\mathbf{v}^k\}$. $\mathbf{q}$ represents a neighboring voxel position of $\mathbf{p}$, and we use 26-neighbor scheme. In this weighted averaging, all the weights are normalized at each voxel again. In addition, multi-resolution approach using 4 volume pyramids is applied for computational efficiency and robustness.

2.2.3. Optical flow—Since Horn and Schunck (Horn *et al* 1981) introduced the optical flow concept to computer vision problems, deformable registration based on optical flow algorithm and its variations (Cornelius and Kanade 1986, Urschler *et al* 2010, Hermann *et al* 2014) including a GPU-based implementation (Noe *et al* 2008) have been studied. We use the Cornelius and Kanade method (Cornelius and Kanade 1986), which has been applied to CT-CBCT registration in (Noe *et al* 2008). They modified the original optical flow approach (Horn *et al* 1981) by introducing additional terms to make spatially-smooth velocity fields and smooth pattern changes as well as the basic term to minimize intensity differences. This method is preferred as it allows the change of intensities between matched points while the original optical flow model by (Horn *et al* 1981) assumes intensity consistency of matched points between two images. We incorporate our intensity matching step into the registration

iteration step used in (Noe *et al* 2008). In our implementation, we generate the final deformed volume by only applying the transformation vector fields to the original CT. Similar to demons, the incremental displacement vector fields are smoothened using the Gaussian kernel with tissue-dependent regularization term for every iteration.

2.2.4 GPU parallelization and computation—For efficient computation, we parallelized both the intensity matching and deformable registration process using GPU. All three registration algorithms are computed within a similar framework as shown in figure 6. The *host* represents CPU and main memory (RAM) and the *device* represents the graphics card including GPU and its memory. To avoid unnecessary data transfer between the host and device, both fixed and moving volumes are copied from the host and allocated to the device before starting iterations. In our implementation, we allocate a thread of the device per slice for intensity matching and per unit (i.e., one voxel) for the registration. Each thread of the device executes the same function, called as *kernel*, at a time. The host sequentially calls kernel functions K1 and K2 to perform intensity matching and deformable registration, respectively, during iterations. The intensity-matched CBCT and the deformed CT are finally copied from the device to the host as the output.

The main difference of B-spline deformation from the other two is that the deformation is computed based on control grids while each voxel is used for demons and optical flow methods. In addition, the direct B-spline transformation (Unser, 1999) is applied as a preprocessing to compute coefficients for the B-spline interpolation. This step is also parallelized and computed efficiently at each x , y , and z -direction by sequential kernel calling using GPU.

3. Experiments and results

We evaluated our methods on 25 head and neck cancer cases treated by intensity-modulated radiation therapy. For each case, a treatment planning CT was acquired on a Philips Brilliance Big Bore CT scanner (Philips Medical Systems, Cleveland, OH, USA), and daily CBCT images were acquired using an Elekta Synergy on-board imager (Elekta Inc., Maryland Heights, MO, USA). The CBCT images were exported as DICOM images using Elekta XVI imaging software. CT images have an image size of $512 \times 512 \times (129-161)$ with a voxel size of $1.236 \times 1.236 \times 3 \text{ mm}^3$. CBCT images have an image size of $270 \times 270 \times 88$ with a voxel size of $1 \times 1 \times 3 \text{ mm}^3$. For evaluation, we registered the planning CT to the last treatment day CBCT that showed the largest anatomical changes. All registration methods with intensity matching were implemented using C++ for CPU and NVidia CUDA SDK for GPU, and ran on a desktop computer with Intel Xeon E5-2630 2.4GHz CPU, 32GB main memory, and NVIDIA GeForce GTX 980.

3.1. Performance comparison with/without intensity matching

To evaluate the effect of the proposed intensity matching, we combined the intensity matching with three registration methods as described in section 2, and performed CT-CBCT registrations with and without the intensity matching. Figure 7 shows an example of an intensity-corrected CBCT computed by the proposed method. The proposed intensity matching significantly improves the CBCT image contrast in regions with severe intensity

distortion. In the corrected CBCT, anatomical structures are clearer in the axial plane and their intensities are more consistent along the superior-inferior direction than the original CBCT as shown in Figure 7(c).

Figure 8 shows checkerboard comparison between original CBCT and demons registration results without/with intensity matching. Our approach shows improved matching result with high fidelity even in degraded soft tissue regions as well as other structures such as the bone compared to the unregistered CT and registered CT without intensity matching.

To quantitatively evaluate the improvement of the registration quality when using the intensity matching, we computed two similarity metrics, normalized cross correlation (NCC) and structural similarity index (SSIM) (Wang *et al* 2004) between the original CBCT and registered CT with/without intensity matching. We specifically chose this metric as NCC is widely used similarity measures in image registration, and SSIM computes the structural similarity between two images and is often used to measure the quality of CBCT reconstruction in comparison to a ground truth volume (Bian *et al* 2010, Lee *et al* 2012, Sadowsky *et al* 2011). For all of these metrics, higher values imply higher similarity between the two volumes. For NCC and SSIM, similarity score of 1 means that two volumes are identical while score of 0 means that two volumes are not correlated or structurally similar. Figure 9 shows the performance comparison of three registration methods with intensity matching and Table 1 shows the summarized results of the performance comparisons with and without intensity matching.

3.2. Performance comparison with state-of-the-art methods

We compared our approach to state-of-the-art CT-CBCT registration methods that combined an intensity matching based on global histogram matching (Hou *et al* 2011), piecewise linear fitting (Nithiananthan *et al* 2011), and patch-based matching with a patch size of $3 \times 3 \times 3$ voxels (Zhen *et al* 2012). Since all of these methods used demons registration in combination with the intensity matching, we also used demons as the registration method with our intensity matching for a fair comparison. Figure 10 shows checkerboard comparisons between the original CBCT and registered CTs with different intensity matching algorithms. Our method produced improved registration with smoother boundary and more accurately matched internal structures compared to the other methods.

To quantitatively compare our registration performance with the other state-of-the-art methods with different intensity matching approaches, we compared NCC and SSIM scores. Because different intensity correction methods produced different CBCT intensities, we computed similarities between the deformed CT and the original CBCT (rather than the intensity-matched CBCT) for consistent comparison. Figure 11 and table 2 show the performance comparison between different intensity matching-registration algorithms including our method. For all 25 cases, our method showed the highest NCC and SSIM scores.

We performed a statistical ranking test for different intensity matching approaches with demons registration. We used an *indifference zone* $\delta (>0)$ that is widely used in statistical ranking and selection (Gibbons *et al* 1979). We computed *p*-values by testing the null

hypothesis as $(\theta_S - \theta_T) > \delta$, where θ represents the performance parameters of NCC and SSIM, and the subscripts S and T represent the proposed slice-by-slice matching and the target intensity matching method to be compared, respectively. With $\delta = 0.1\%$, the minimum significance level used to describe the NCC and SSIM in our experiments, our method shows the highest NCC with $p = 0.074, 0.059, 0.171$ and 0.096 compared to the no intensity matching, global histogram matching (Hou *et al* 2011), piecewise linear fitting (Nithiananthan *et al* 2011), and the patch-based correction (Zhen *et al* 2012), respectively. The p -values of SSIM showed $0.084, 0.053, 0.113$ and 0.091 for the same comparison. Because the test data sets are intra-subject images and NCC and SSIM measure the global intensity and structural correlation between images, their baseline values are high even without deformable registration. The score difference between different algorithms is small compared to the baseline value, and the resulting p -values of global comparison are > 0.05 .

Because our test data sets came from head and neck cancer radiotherapy cases, anatomical variation between the planning CT and the target CBCT for the whole FOV may not be large because only target tumor regions will receive high radiation dose and may noticeably change. Therefore, we repeated the similarity score comparison within the planning target volume (PTV) that included the primary and nodal tumor volumes plus margins where most significant anatomical structure change happened. As shown in Table 3, our method produced higher NCC and SSIM scores than the other three state-of-the-art methods, which is consistent with the global similarity comparison results.

NCC and SSIM can be considered as indirect measures of anatomical structural alignment accuracy because more accurate anatomical structure alignment produces higher intensity and structural similarity. However, these metrics may not be sensitive enough to measure individual anatomical structure deviation as overall scores can be high as long as intensities are similarly distributed even if structures are not aligned well. To further assess the accuracy of the registration in terms of anatomical structure alignment, we computed target registration error (TRE) using carefully chosen anatomical landmarks. To select anatomical landmarks that consistently showed up in both CT and CBCT, we first extracted candidate features using the approach proposed by (Paganelli *et al* 2013). This method uses a scale invariant feature transform (SIFT) to find a set of matching points that are consistent and matched between two scenes. Using SIFT, we first extracted 55–107 candidate landmarks from both CT and CBCT images. An expert scientist carefully reviewed the candidate landmarks and manually selected 15 best ones that were evenly distributed across the volume. The landmark positions were also adjusted by the expert if necessary to achieve high-quality correspondence. The computed deformations were applied to transform the landmark positions from the CT to the target CBCT space, and TREs were calculated by computing the Euclidean distance between the transformed landmarks and the corresponding landmarks on the target CBCT.

Table 4 shows the computed TREs for five methods including ours. For all 25 cases, our method outperformed the other methods with the smallest TREs, which is consistent with the intensity similarity comparison results. Because the lower value of TRE represent the better performance, we tested the null hypothesis as $TRE_S < TRE_T - \delta$, which becomes $(TRE_T - TRE_S) > \delta$. By testing 375 ($=15 \times 25$) sample pairs with $\delta = 0.1\text{mm}$, the proposed method

outperformed with the p -values of 0.0002, 0.0009, 0.0061 and 0.0151 compared to the no intensity matching, global histogram matching, piecewise linear fitting and the patch-based correction, respectively.

3.3. Relation of the computed deformation to anatomical changes

In our intensity matching-registration framework, target CBCT image intensities are iteratively modified during the registration, which may lead to unrealistic deformation if the intensity matching is not appropriate. Although the similarity and TRE comparison results show that our method produces better registration than conventional and state-of-the-art methods, assessment of the resulting deformation to ensure that the final deformation is consistent with the physical anatomical changes is desirable for quality assurance purpose. We therefore evaluated the deformable registration results using the Jacobian determinant of the deformation. Jacobian determinant of the deformation quantifies the volumetric change at each voxel, e.g., >1 implies volume expansion, 1 implies volume preservation, and <1 implies volume contraction.

In our experiments, Jacobian determinants were greater than zero in all voxels for all 25 cases. The mean values of the Jacobian determinants for the whole volume are 0.99, i.e., slightly less than 1, for most cases, which is consistent with our observation that head and neck tumor often shrinks in response to radiotherapy and patients often lose their weight. The volume shrinkage is most prominent in the nodal gross tumor volume (GTV) region. As shown in figure 12, we consistently observe that the Jacobian determinant around the GTV region was less than 1, implying the volume shrinkage while other regions showed the value close to 1, implying no significant volume change. The average and standard deviation of Jacobian determinants for the nodal GTVs are 0.60 ± 0.18 , 0.59 ± 0.26 , 0.65 ± 0.22 , 0.62 ± 0.17 , 0.56 ± 0.28 , and for the 5 selected cases with the most noticeable tumor shrinkage (cases 4, 6, 8, 14, 15, respectively). This observation along with the qualitative/quantitative assessment performed above demonstrates the superior performance of our registration method to existing methods and its consistency with the actual anatomical changes. In real clinical scenario, one can use the deformation vector fields represented as arrows or grids as well as the Jacobian determinant map overlaid with the images as an assessment tool.

4. Discussion

We proposed a novel CT-CBCT deformable registration approach that iteratively corrects the CBCT intensity based on local intensity histogram matching during the registration. Our local intensity matching is performed on anisotropic patches, especially on each slice that is parallel to the plane of X-ray source-detector rotations. Our local patch-based intensity matching between CT-CBCT reduces various artifacts including scatter and inconsistent reconstruction due to approximation at off-mid-plane, and transforms the CBCT intensities to those of CT. Although it cannot perfectly remove all artifacts, it significantly improves the CBCT image contrast and produces CT-equivalent image that is sufficient enough to achieve high-quality CT-CBCT registration.

We extensively tested our method on head and neck cancer radiation therapy cases. As shown in table 1, the proposed intensity matching consistently improved the registration

performance for all three registration methods. Optical flow showed the best performance in terms of NCC and SSIM scores for most cases. The hierarchical B-spline showed the lowest performance in this experiment. Since the maximum amount of local deformations of FFD is limited by the grid size, the results may vary depending on parameter settings for the maximum refinement level and criteria. We did not try to optimize the parameters case by case but used fixed parameters that generally worked for all 25 cases with the computation time comparable to the other methods. We also used similar stopping criteria for all three registration methods for the consistent comparison.

We also compared its performance with existing state-of-the-art methods, proving its superior performance. The global histogram matching (Hou *et al* 2011) was not affected by deformable registration because it was performed in intensity domain. Therefore, local intensity variations in CBCT caused global intensity distortion at the initial stage and it was not improved during the deformable registration process. The piecewise linear fitting algorithm (Nithiananthan *et al* 2011) showed poor intensity matching, especially for the regions where the CBCT reconstruction quality was significantly degraded by truncation artifacts, e.g., lower neck and shoulder regions, resulting in inaccurate registration. The patch-based fitting (Zhen *et al* 2012) produced inconsistent intensity matching especially on the boundaries between the bone and soft tissues. On the other hand, our anisotropic patch-based, i.e., slice-based, local intensity matching produced smooth and consistent intensity matching globally and also properly matched intensities in the degraded regions, leading to more accurate registration results.

The overall computation time (mean $\pm$ standard deviation in seconds) for the initial rigid registration followed by the intensity matching-deformable registration was 12.5 ± 1.5 (hierarchical B-spline), 8.2 ± 1.7 (demons), and 10.2 ± 1.8 (optical flow). Here, we discuss a few more issues that worth further consideration.

4.1. Limitations

Although the intensity matching transforms the CBCT intensities to those of CT so that direct intensity similarity comparison is possible, severe artifacts such as metal artifacts and truncation significantly affect the intensity matching process, resulting in overestimated or inconsistent matching. A simple preprocessing step that rejects extreme values by thresholding can improve intensity matching results, and the threshold can be determined by comparing CBCT-CT histograms before the local intensity matching. More sophisticated artifact reduction methods and/or advanced reconstruction methods may be used to eliminate or reduce such artifacts and produce improved CBCT reconstruction, which may lead to better intensity matching and registration results. However, as discussed in (Lou *et al* 2013), there are already a lot of CBCT images taken by old or current generation machines and processed by conventional methods. These images cannot be easily reprocessed for artifact reduction or image quality improvement by using such recent advanced techniques. Our approach is simple and practical, and does not require any processing of the raw data, and therefore can be seamlessly integrated into the existing clinical workflow.

Another potential factor that may affect the intensity matching is the voxel resolution. In general, the planning CT and on-treatment CBCT have different reconstructed voxel

resolution. To compute the initial local intensity matching, we first resample the CBCT volume to have the same slice thickness as the CT volume after the rigid registration because CT images represent the accurate HU values. Even if the slice thickness of the CBCT and CT are the same, the initial intensity matching will only be approximately correct because two volumes cannot be accurately aligned by the initial rigid registration. As the intensity matching and registration iteration continues, both the alignment of the two volumes and the intensity matching are improved.

4.2. Patch size for local intensity matching

Since CBCT and CT image intensities are matched within local patch regions, the matching quality depends on the patch size. We compared our slice-patch-based local intensity matching with a large patch-based matching, i.e., global matching by (Hou *et al* 2011), and a small patch-based matching, i.e., (Zhen *et al* 2012) with a patch size of $3 \times 3 \times 3$ voxels. We started with a single slice-based patch and divided it into half up to $4 \times 4 \times 1$ patches. Notice that we kept the anisotropic patch shape to address the significant spatially-varying characteristics of CBCT reconstruction artifacts along the direction perpendicular to the mid-plane. We observed that local inconsistencies were alleviated in some regions (within the patch region) when using a smaller patch, but such division did not improve the overall registration accuracy and often produced poor registration performance due to the matched intensity inconsistency between different patch regions. During earlier iterations of the registration, two volumes are not well aligned, and local intensity matching becomes inaccurate especially when using a small patch. This causes intensity discontinuity on patch boundaries and incorrect SSD calculation, thus misleading the registration. We also tested our registration by varying the thickness of our anisotropic patch with more slices, i.e., 4, 8, 16 slices. We did not observe a noticeable registration performance improvement by adding more slices. Instead, we observed that the registration performance is degraded if too thick patch is used, e.g., 16 slices or whole volume. It is true that a larger patch than a single slice carries more information than a thinner or smaller patch. However, if the information in the patch is inconsistent, such inconsistent information likely influences the intensity matching process negatively. Therefore, it is desired to select the patch size and shape from which consistent information can be extracted. In our experiments on head and neck cases, a patch smaller or thicker than a slice did not improve the registration accuracy.

5. Conclusions

We proposed a novel CT-CBCT deformable registration approach that iteratively corrects the CBCT intensity based on local histogram matching during the registration. This method particularly matches CBCT and CT intensities at individual slice level, considering the fact that the CBCT reconstruction at different off-mid-plane shows different spatially-varying artifacts due to different missing information in Radon space. The intensity matching step alternates with deformable registration, therefore can be combined with any registration algorithm. In our implementation, we tested three widely-used deformable registration methods, showing significant improvement in the registration performance regardless of the choice of the registration algorithm. Our approach is practically simple and has proved to be more robust than existing state-of-the-art algorithms, producing improved registration results

on head and neck cancer cases. Although tested on only one site, it can be easily applied to other sites where accurate image registration between pre-operative planning CT and lower quality intra-operative CBCT is necessary.

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Figure 1.
CBCT scan. (a) Cone beam CT scan geometry. (b) Lateral view of (a).

Figure 2.

(a) CT and (b) CBCT of the same patient (axial, sagittal, and coronal views). All the images are displayed using the same window level.

Figure 3.

The proposed workflow of CT-CBCT registration with intensity matching. The intensity matching and deformable registration steps (in the dashed box) are performed at every iteration. k represents the iteration number and $I^k \subset \mathbb{R}^3$ is the computed volume at the k^{th} iteration.

Figure 4.

Joint histograms of CT and CBCT at different slice locations. (a) Selected slices on CBCT – yellow line is the mid-plane. (b)–(f) joint histograms from lower to upper slices. Horizontal and vertical axes represent the CT and CBCT intensity values, respectively. Color in the joint histograms represents the frequency of the intensity pairs based on the color scale shown in the rightmost bar.

Figure 5. Local refinement and overlay of sub-grids. (a) A patch surface with 49 control points. (b) Refinement and overlay of control points. Black dots connected by dashed lines represent the refined local control points and patches.

Figure 6.
GPU parallelization of the deformable registration with intensity matching.

Figure 7. Intensity matching example. (a) Original CBCT (axial, sagittal and coronal). Orange dashed lines in the sagittal image indicate the locations of the axial and coronal images. (b) Intensity-corrected CBCT images at the same slices and with the same window level as in (a). (c) Intensity profiles of CT, CBCT and corrected CBCT along SI direction at the center of rotation.

Figure 8. Demons registration results without and with intensity matching. (From left to right) Original CBCT, checkerboard overlay of CBCT and CT before registration, CBCT and registered CT without intensity matching, and CBCT and registered CT with intensity matching. The top and the bottom rows show different cases. Red arrows indicate regions that are not accurately aligned by the conventional method (no intensity matching) but are properly registered by the proposed method (with intensity matching).

Figure 9.
Performance comparison between different registration methods with intensity matching.

Figure 10.

Checkerboard comparison between the original CBCT and registered CT with different intensity matching approaches. (From left to right) Original CBCT, global histogram matching, linear fitting, patch-based matching ($3 \times 3 \times 3$ patch), and our proposed method for (a) case 3 and (b) case 8. The lower images show the magnification of the red box region in the upper images. Images are displayed using the same window level. Red arrows indicate misregistered regions.

Figure 11.

Performance comparison for the whole volume between different intensity matching methods with demons registration.

Figure 12.

An example of the Jacobian determinant map of the deformation fields. (a) Axial, (b) sagittal and (c) coronal planes of the same patient with color scale shown on the right. The orange contour shows the nodal GTV region. The blue and the green contours in the coronal image in (b) show the right and left parotid glands, respectively.

Table 1

Mean and standard deviation of performance comparison between three different deformable registration algorithms with/without intensity matching

	Hierarchical B-spline				Demons				Optical Flow			
	NCC		SSIM		NCC		SSIM		NCC		SSIM	
	NM	M	NM	M	NM	M	NM	M	NM	M	NM	M
Mean $\pm$ STD	0.922 $\pm$ 0.034	0.947 $\pm$ 0.021	0.893 $\pm$ 0.050	0.919 $\pm$ 0.034	0.939 $\pm$ 0.030	0.962 $\pm$ 0.019	0.897 $\pm$ 0.054	0.940 $\pm$ 0.028	0.943 $\pm$ 0.030	0.967 $\pm$ 0.016	0.917 $\pm$ 0.038	0.946 $\pm$ 0.026

NM: No intensity matching

M: Intensity matching

Table 2

Performance comparison between different intensity matching-registration methods. Mean $\pm$ standard deviation of similarity scores in mm are shown. For a fair comparison, all methods used demons registration. The highest similarity score for each metric is highlighted as bold.

	NCC	SSIM
G	0.941 $\pm$ 0.027	0.901 $\pm$ 0.045
L	0.944 $\pm$ 0.031	0.909 $\pm$ 0.042
P	0.949 $\pm$ 0.022	0.917 $\pm$ 0.034
S	0.962$\pm$0.019	0.940$\pm$0.028

G: global histogram matching (Hou *et al* 2011)

L: piecewise linear fitting (Nithiananthan *et al* 2011)

P: patch-based correction (Zhen *et al* 2012)

S: proposed anisotropic patch-based matching

Table 3

Local region (PTV) comparison between different intensity matching methods with demons registration. The highest similarity score for each metric and each case is highlighted as bold.

Case	NCC				SSIM			
	G	L	P	S	G	L	P	S
1	0.961	0.960	0.959	0.978	0.924	0.924	0.923	0.937
2	0.953	0.964	0.959	0.979	0.888	0.893	0.906	0.935
3	0.931	0.935	0.929	0.958	0.869	0.875	0.891	0.924
4	0.969	0.973	0.973	0.976	0.864	0.886	0.893	0.916
5	0.948	0.958	0.966	0.980	0.892	0.890	0.905	0.938
6	0.904	0.903	0.913	0.926	0.836	0.858	0.875	0.891
7	0.934	0.937	0.938	0.938	0.844	0.860	0.866	0.901
8	0.921	0.916	0.929	0.956	0.882	0.885	0.898	0.910
9	0.922	0.933	0.926	0.969	0.892	0.912	0.933	0.956
10	0.906	0.904	0.911	0.923	0.883	0.885	0.899	0.927
11	0.877	0.897	0.917	0.923	0.838	0.863	0.855	0.908
12	0.924	0.917	0.935	0.964	0.870	0.874	0.874	0.934
13	0.957	0.971	0.969	0.976	0.921	0.915	0.929	0.948
14	0.875	0.886	0.908	0.910	0.743	0.795	0.826	0.840
15	0.939	0.928	0.936	0.945	0.899	0.902	0.909	0.929
16	0.887	0.858	0.924	0.940	0.859	0.824	0.901	0.922
17	0.925	0.941	0.940	0.951	0.900	0.932	0.928	0.933
18	0.938	0.954	0.958	0.959	0.925	0.935	0.935	0.947
19	0.964	0.974	0.976	0.980	0.964	0.966	0.973	0.979
20	0.924	0.918	0.910	0.935	0.899	0.903	0.895	0.927
21	0.949	0.934	0.937	0.960	0.930	0.928	0.921	0.945
22	0.975	0.978	0.979	0.980	0.965	0.963	0.965	0.974
23	0.963	0.969	0.969	0.970	0.957	0.957	0.962	0.965
24	0.915	0.932	0.926	0.933	0.911	0.931	0.921	0.933
25	0.947	0.958	0.954	0.959	0.944	0.940	0.951	0.955

Case	SSIM				NCC			
	S	P	L	G	S	P	L	G
Avg.	0.931	0.909	0.900	0.892	0.955	0.942	0.936	0.932

G: global histogram matching
L: piecewise linear fitting
P: patch-based correction
S: proposed anisotropic patch-based matching

Table 4

TRE measurements: mean±standard deviation in mm for 15 anatomical landmarks. The smallest TRE for each case is highlighted as bold.

Case	NM	G	L	P	S
1	2.79±1.92	2.75±1.53	2.50±1.32	2.63±1.31	2.39±1.25
2	2.68±1.92	2.50±1.26	2.31±1.45	2.52±1.37	2.01±1.32
3	2.93±1.76	2.68±1.57	2.53±1.43	2.42±1.57	2.38±1.43
4	2.53±1.48	2.35±1.12	2.21±1.26	2.13±1.63	1.99±1.21
5	2.67±1.74	2.45±1.21	2.41±1.02	2.35±1.21	2.05±1.31
6	2.94±1.89	2.76±1.45	2.50±1.31	2.53±1.23	2.31±0.89
7	2.91±1.59	2.63±1.57	2.47±1.53	2.43±1.45	2.27±1.12
8	3.01±1.32	2.76±1.31	2.45±1.67	2.43±1.78	2.35±0.75
9	2.71±1.32	2.54±1.42	2.35±1.29	2.38±1.32	1.98±1.32
10	3.04±1.79	2.75±1.54	2.50±1.02	2.53±1.25	2.31±1.34
11	3.21±1.67	2.89±1.87	2.65±1.58	2.65±1.76	2.45±1.78
12	2.87±1.36	2.45±1.76	2.21±1.43	2.24±1.31	1.89±1.12
13	2.65±1.89	2.56±1.21	2.34±1.42	2.25±1.57	1.97±1.34
14	3.01±1.21	2.89±1.54	2.75±1.24	2.67±1.97	2.33±1.35
15	2.98±1.72	2.69±1.67	2.45±1.28	2.43±1.65	2.25±1.07
16	2.75±1.96	2.75±1.58	2.55±1.32	2.58±1.41	2.39±1.13
17	2.68±1.92	2.50±1.26	2.41±1.45	2.52±1.37	2.18±1.30
18	2.73±1.52	2.68±1.49	2.55±1.63	2.53±1.87	2.43±1.13
19	3.21±1.63	3.02±1.52	2.95±1.76	2.97±1.63	2.72±1.20
20	2.87±1.71	2.75±1.49	2.61±1.52	2.60±1.64	2.41±1.31
21	2.88±1.89	2.80±1.52	2.50±1.31	2.53±1.23	2.36±1.28
22	2.71±1.59	2.56±1.57	2.52±1.62	2.55±1.55	2.27±1.16
23	3.01±1.32	2.76±1.31	2.45±1.67	2.49±1.78	2.25±1.25
24	2.71±1.32	2.54±1.42	2.45±1.49	2.48±1.32	2.31±1.32
25	3.01±1.38	2.86±1.54	2.68±1.52	2.73±1.32	2.50±1.24
Avg.	2.86±1.66	2.67±1.49	2.49±1.44	2.50±1.52	2.27±1.27

NM: No intensity matching

S: proposed anisotropic patch-based matching

P: patch-based correction

L: piecewise linear fitting,

G: global histogram matching

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