Demons deformable registration for CBCT-guided procedures in the head and neck: Convergence and accuracy

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Purpose: The accuracy and convergence behavior of a variant of the Demons deformable registration algorithm were investigated for use in cone-beam CT (CBCT)-guided procedures of the head and neck. Online use of deformable registration for guidance of therapeutic procedures such as image-guided surgery or radiation therapy places trade-offs on accuracy and computational expense. This work describes a convergence criterion for Demons registration developed to balance these demands; the accuracy of a multiscale Demons implementation using this convergence criterion is quantified in CBCT images of the head and neck.

Methods: Using an open-source “symmetric” Demons registration algorithm, a convergence criterion based on the change in the deformation field between iterations was developed to advance among multiple levels of a multiscale image pyramid in a manner that optimized accuracy and computation time. The convergence criterion was optimized in cadaver studies involving CBCT images acquired using a surgical C-arm prototype modified for 3D intraoperative imaging. CBCT-to-CBCT registration was performed and accuracy was quantified in terms of the normalized cross-correlation (NCC) and target registration error (TRE). The accuracy and robustness of the algorithm were then tested in clinical CBCT images of ten patients undergoing radiation therapy of the head and neck.

Results: The cadaver model allowed optimization of the convergence factor and initial measurements of registration accuracy: Demons registration exhibited $TRE=(0.8\pm0.3)$ mm and $NCC=0.99$ in the cadaveric head compared to $TRE=(2.6\pm1.0)$ mm and $NCC=0.93$ with rigid registration. Similarly for the patient data, Demons registration gave mean $TRE=(1.6\pm0.9)$ mm compared to rigid registration $TRE=(3.6\pm1.9)$ mm, suggesting registration accuracy at or near the voxel size of the patient images ($1\times1\times2$ mm³). The multiscale implementation based on optimal convergence criteria completed registration in 52 s for the cadaveric head and in an average time of 270 s for the larger FOV patient images.

Conclusions: Appropriate selection of convergence and multiscale parameters in Demons registration was shown to reduce computational expense without sacrificing registration performance. For intraoperative CBCT imaging with deformable registration, the ability to perform accurate registration within the stringent time requirements of the operating environment could offer a useful clinical tool allowing integration of preoperative information while accurately reflecting changes in the patient anatomy. Similarly for CBCT-guided radiation therapy, fast accurate deformable registration could further augment high-precision treatment strategies. © 2009 American Association of Physicists in Medicine. [DOI: [10.1118/1.3223631](https://doi.org/10.1118/1.3223631)]

Key words: deformable image registration, Demons algorithm, cone-beam CT, flat-panel detector, head and neck, image-guided interventions, image-guided surgery, image-guided radiation therapy

I. INTRODUCTION

Advances in cone-beam CT (CBCT) imaging technology have enabled the application of image guidance in a broad spectrum of interventional procedures. CBCT is well suited to image-guided interventions as it is a fast, noninvasive, low dose, 3D imaging modality that does not require the patient to be moved for acquisition of volumetric data. The availability of high-quality 3D images, showing both soft tissue and bony anatomy, acquired at the time of the procedure allows the most up-to-date patient-specific information to be used to guide the procedure. Treatment of head and neck disease presents particular challenges that may be addressed with the aid of CBCT: complex 3D anatomy, infiltrative disease in close proximity to critical structures, and high cost associated with normal tissue complications. CBCT-guided therapies for head and neck disease include radiation therapy with daily online imaging to verify patient positioning¹⁻³ and, more recently, the primary motivation for this work, intraoperative CBCT-guided surgery,⁴⁻⁸ which allows surgeons to acquire 3D images during the procedure to precisely localize target and normal structures and visualize the progress of target resection.

Ideally, the most recent CBCT image could be visualized with respect to any previously acquired information—e.g., diagnostic CT and MRI, previous CBCT images, and planning and segmentation of targets, critical tissues, and nearby anatomical landmarks. As such prior information exists in different spatial and anatomical frames of reference, image registration is required to place all available image-based information within a common reference frame. As physically invasive procedures, such as image-guided surgery, induce local deformations both as the goal and as an unavoidable by-product of the intervention, deformable image registration could offer an important means of geometrically resolving and integrating CBCT with images acquired during or before the procedure in a manner that accounts for complex morphological change.

Clinical use of online deformable registration in image-guided procedures is hampered by the long computation times required for many algorithms, and the difficult but necessary task of validating registration accuracy and robustness. The “Demons” family of algorithms offers a form of deformable registration with relatively low computational expense.⁹ Previous work has shown the original Demons algorithm to be a good choice for registration of head and neck images when compared to other intensity-based algorithms.¹⁰ It has been shown both experimentally^{11,12} and theoretically¹³ that modifications to the standard Demons algorithm are an important means of obtaining faster convergence, with equivalent or improved registration performance.

Previously, the difficulty in finding a robust convergence criterion for Demons registration has been noted and left as an area of future research.^{13,14} In this work, we introduce a novel convergence criterion for Demons registration and describe its optimization for the task of CBCT-guided head and neck interventions. The accuracy of a multiscale implementation of the “symmetric” Demons algorithm using this con-

vergence criterion for registration of CBCT head and neck images is quantified both in terms of image similarity and accuracy [target registration error (TRE)]. Performance is compared to that of rigid registration alone to evaluate the necessity of deformable registration in image-guided head and neck interventions.

II. METHODS

II.A. The Demons algorithm

II.A.1. Initialization by rigid bony registration

The algorithm was evaluated with respect to registration of CBCT images acquired on a mobile C-arm⁵ and IGRT linac² as detailed below. In all cases, a previous CBCT image, denoted I_0 , was registered “forward” to match the “current” CBCT image, I_1 , thereby geometrically resolving the prior image to reflect the most up-to-date anatomical information.

Rigid registration of bony anatomy is used as a first step in the registration process to resolve gross translation and rotation errors. The rigid registration method (as well as the deformable registration method, below) was implemented in C++ using components of the open source insight segmentation and registration toolkit (ITK).¹⁵ For rigid registration, bony anatomy in both I_0 and I_1 were segmented using an intensity threshold applied across a given region of interest (ROI). The default threshold and ROI could be interactively adjusted to account for HU variations, avoid image artifacts (e.g., streaks or truncation), and exclude areas of the anatomy undergoing known deformation (e.g., jaw flexion). Using a multiresolution approach, a regular step gradient descent optimizer was used to find the transformation (rotation and translation) that minimizes the dissimilarity of the two images [i.e., maximize the normalized cross correlation (NCC)]. Using markers affixed rigidly to cadaveric specimens, we found this method to be accurate for points displaced rigidly to within the voxel size of surgical C-arm CBCT reconstructions (~ 0.8 mm). This rigid transformation provided the basic initialization for subsequent Demons deformable registration.

II.A.2. Symmetric Demons deformable registration

Demons registration operates iteratively, repeating two major steps: (i) calculation of a displacement vector at various points in the image and (ii) smoothing of the resulting vectors to form a regularized deformation field. In the most popular Demons method, an update field is generated at each iteration with a displacement vector, $\vec{d}$, given by

$$\vec{d}(x) = \frac{[I_0(x) - I_1(x)]\vec{\nabla}I_1(x)}{\|\vec{\nabla}I_1(x)\|^2 + [I_0(x) - I_1(x)]^2/K} \quad (1)$$

at every position x in the images;⁹ the normalization factor K , not included in Thirion’s original description, is computed as the mean squared value of the image voxel sizes. This form of normalization accounts for unit imbalance, results in a force that scales with changing voxel size, such as during

FIG. 1. Flowchart of multiscale Demons algorithm with illustration of convergence criterion.

multiscale registration, and has theoretical justification when viewing Demons as an optimization problem.¹⁶ The update field for the current iteration, U_n , is added to the existing deformation field D_{n-1} and then regularized to give the output deformation field for the current iteration

$$D_n = G_\sigma * (D_{n-1} + U_n), \quad (2)$$

where G_σ is a Gaussian kernel of width σ and $*$ denotes 3D convolution. In our study, σ was fixed to 1 mm, a value equal or similar to that used by other investigators.^{11,10,13,17}

There is an asymmetry in Eq. (1) arising from only the gradient of the fixed image (I_1) being considered. To overcome this, Thirion also proposed a modified, symmetric displacement calculation,

$$\tilde{d}(x) = \frac{2[I_0(x) - I_1(x)][\tilde{\nabla}I_1(x) + \tilde{\nabla}I_0(x)]}{\|\tilde{\nabla}I_1(x) + \tilde{\nabla}I_0(x)\|^2 + [I_0(x) - I_1(x)]^2/K}, \quad (3)$$

where the gradient of the deformed moving image is included in the displacement calculation.¹⁸ This symmetric form of Demons registration has not been studied in as much depth as the original until recently. Symmetric Demons is similar in form to the “accelerated” Demons algorithm of Wang *et al.*,¹¹ who found it to converge faster than the original Demons force calculation. As it has been shown that different implementations of similar algorithms can exhibit significant variation,¹⁹ we focus on a readily available open-source implementation. In previous work,¹² we investigated four ITK based Demons algorithms implementing both Eqs. (1) and (2) and found the symmetric Demons implementation by Vercauteren,²⁰ now available in ITK version 3.10, to be the most suitable for intraoperative CBCT-guided head and neck surgery in terms of registration performance, image quality, and convergence behavior—results consistent with Vercauteren’s recent verification of the performance advantage of the symmetric form over the original.¹³ Based on these results, all experiments described below were carried out using this symmetric Demons implementation, referred to hereafter simply as “Demons” for conciseness.

II.A.3. Multiscale registration and convergence

The registration algorithm was implemented using a multiscale approach, as illustrated in Fig. 1. A morphological

pyramid is created by repeatedly downsampling the original images—e.g., nominal downsampling factors of 8, 4, 2, and 1, denoted as DS₈-DS₄-DS₂-DS₁, and registration is performed iteratively starting with images at the coarsest level of the pyramid. When registration has completed (converged) at each pyramid level, the resulting deformation field is used to initialize registration at the next coarsest level.

An important consideration for multiscale Demons registration is how to determine when to stop registration at a given level and ultimately when to halt registration overall. A convergence criterion is required that allows enough iterations to be performed for accurate registration while terminating registration before the point beyond which computational effort is wasted. A convergence criterion was developed based on the histogram of the difference between successive deformation fields (after smoothing). At each level of the multiscale pyramid, registration is terminated when the change between successive deformation fields is small enough that the current deformation field can be considered stable. At each iteration, the difference between the current and previous deformation field is calculated by voxelwise vector subtraction,

$$\Delta D_n = D_n - D_{n-1}. \quad (4)$$

Next, the fraction of difference vectors in ΔD_n that exhibit a magnitude below a specific threshold

$$D_{\text{thresh}} = ka_{\text{vox}} \quad (5)$$

is calculated, where a_{vox} is the voxel size (at the current pyramid level), k is a scalar fraction, and D_{thresh} is the threshold distance. When the fraction of difference vectors with magnitude less than D_{thresh} is sufficiently large (e.g., 99% described below), registration is halted as the deformation field and thus registration can be considered to have reached a stable state (i.e., “convergent”). The number of iterations required to reach convergence is strongly affected by the value of k : selecting k too large will terminate registration prematurely, while too small a value will cause extra iterations that do not improve the result.

II.A.3.a. Masking to exclude artifact and noise. When calculating convergence, an image mask (defined once) was used to exclude air and truncation artifact at the periphery of the image. The use of the mask is not essential, but helpful

when large amounts of air, noise, or artifact are present in certain areas of the image. A cylindrical mask (~ 16 cm diameter $\times$ length of image) occupying the central field of view was chosen to restrict the ROI to regions of head and neck anatomy and minimize the effect of surrounding noise and reconstruction artifact. The use of the mask for convergence testing was motivated by the possibility that large changes in displacements are still possible in areas of the image containing artifact or noise after “convergence” has been achieved in internal anatomy. This same mask was used to exclude artifact and noise in the calculation of image similarity for performance evaluation, for similar reasons of excluding regions dominated by artifact or noise (rather than anatomy). Masking could be used during registration, but such an approach would require a more robust mask than a simple cylinder so as not to inadvertently exclude relevant anatomy during the registration process.

II.B. Parameter selection and performance evaluation

Images drawn from two clinical applications of CBCT-guided therapies were used to optimize the proposed convergence criterion and to evaluate the accuracy of symmetric Demons: (i) A cadaveric head imaged with a prototype CBCT capable surgical C-arm to simulate intraoperative image-guided head and neck surgery and (ii) CBCT images of patients undergoing radiation therapy of head and neck cancer with daily online imaging. For both studies, inpatient registration was performed on two CBCT images to match the previous image, I_0 , to the current image I_1 . Registration accuracy was quantified in terms of normalized cross-correlation (NCC) and TRE. All studies were performed on a Dell dual-processor (2 Xeon 5140) $\times$ dual core 2.33 GHz PC running Windows XP with 2 Gbytes of RAM. While the Demons implementation (i.e., calculation of the deformation field at each iteration) exploited the parallelism of the dual multicore CPU, the current implementation of the convergence criterion (i.e., calculation of deformation field differences) did not.

II.B.1. Quantification of registration performance

The two metrics of registration accuracy used in these experiments are summarized as follows. The NCC between images I_0 and I_1 is

$$\text{NCC} = \frac{\sum_{\text{image}} I_0 \cdot I_1}{\sqrt{\sum_{\text{image}} I_0^2 \cdot \sum_{\text{image}} I_1^2}} \quad (6)$$

calculated over every voxel in the image. The NCC ranges from zero (completely uncorrelated images) to one (perfectly registered images). NCC is limited in that it, like any image similarity metric, does not describe the registration performance with respect to any specific anatomical feature (instead describing similarity overall) and does not provide a physical measure of accuracy (e.g., units of displacement).

For a voxel intensity-based algorithm like Demons, it is important to verify the performance indicated by an image

similarity metric with an independent measure of accuracy. TRE describes the accuracy in matching anatomical points between the two images.²¹ The TRE was measured by localizing concordant anatomical target points in both images by an observer before registration. The points selected in I_0 were transformed through the rigid transformation and the deformation field to obtain the location of the anatomical points after registration. The difference between the deformed point location $[x_{\text{target}}(I_{0\text{reg}})]$ and the fixed point location $[x_{\text{target}}(I_1)]$ yields the TRE,

$$\text{TRE} = \|\vec{x}_{\text{target}}(I_{0\text{reg}}) - \vec{x}_{\text{target}}(I_1)\|. \quad (7)$$

TRE carries units of distance and is zero for perfectly registered images (and perfectly localized points). The specific anatomical points selected are detailed below for each study. To avoid biasing comparison, all methods investigated used the same set of points as input; the points were selected on the original images prior to registration and without any knowledge of the location of the points after registration. As each point was selected in the original image and all methods investigated use the same input points, observer variability does not bias comparison, and a single observer was sufficient to evaluate registration performance. Blinded reselection of the same anatomical points in the cadaveric head images showed the mean intraobserver variability to be ~ 0.7 mm, on the order of the voxel size for these images, as expected.

The smoothness of the deformation field was measured in terms of harmonic energy²²

$$E_h(D) = \frac{1}{2} \int \sum_{i=1}^3 \sum_{j=1}^3 \left(\frac{\partial D_j(x)}{\partial x_i} \right)^2 dV \quad (8)$$

averaged over the number of voxels in the deformation field, a measure inversely related to the smoothness of the deformation field.

II.B.2. Parameter optimization: Cadaver study

Deformations analogous to those occurring during head and neck surgery were simulated in a cadaveric head between two scans acquired using a surgical C-arm modified to perform intraoperative CBCT.⁵ The experimental setup is shown in Fig. 2(a). The motorized orbit of the C-arm allows collection of projection images over $\sim 178^\circ$ using a large FOV flat-panel detector. The projection images are then reconstructed to form a CBCT volume with 3D image quality sufficient to target bone and soft-tissue structures in the head and neck. Images were acquired in 60 s at 100 kV_p, delivering a dose of 10 mGy (0.35 mSv).²³ CBCT images illustrated in Fig. 2(b) were acquired before and after intervention. Under endoscopic guidance, the inferior turbinates, medial orbital walls, and nasal septum were displaced by a surgeon, and the jaw was exercised (mouth open in I_0 , closed in I_1). The magnitude of the induced deformations was as large as ~ 15 mm, most evident in the nose, jaw, turbinates, and oropharynx. To a smaller extent, flexion of the cervical spine is evident.

FIG. 2. Cadaver study: Experimental setup and example images. (a) Photograph of the surgical C-arm modified for intraoperative CBCT showing a cadaveric specimen undergoing endoscopic intervention in the sinuses and oral cavity. [(b)–(d)] Central sagittal slice of CBCT images before and after intervention with differences overlaid (yellow-green difference image) and superposition of 3D renderings: (b) No registration, (c) rigid registration alone (note large differences in the jaw, nose and sinuses), and (d) after registration with Demons deformable registration.

Seven anatomical points were chosen for calculation of TRE in the cadaver data: the posterior-inferior aspect of the clivus at midline, anterior-superior tip of the lower jaw at midline, center of a 4 mm hole drilled in the left cribriform plate, center of a 4 mm hole in the right cribriform plate, superior aspect of the C1 vertebra, lateral tip of the right mandible, and lateral tip of the left mandible. Both TRE and NCC were calculated at each iteration of Demons registration for various settings of the convergence factor k and various morphological pyramids. Pyramids investigated included the nominal four-level pyramid (DS₈-DS₄-DS₂-DS₁), three-level pyramids created by excluding any single level in the nominal pyramid (namely, DS₈-DS₄-DS₂, DS₈-DS₄-DS₁, DS₈-DS₂-DS₁, and DS₄-DS₂-DS₁), and one five-level pyramid (DS₁₆-DS₈-DS₄-DS₂-DS₁).

The effect of the convergence criterion on registration time and accuracy was compared to approaches in which the number of iterations was fixed. The first fixed iteration scheme was comparable to that selected by trial and error in other work,¹⁰ performed using 50 iterations at DS₈, 100 iterations at DS₄, 10 iterations at DS₂, and 10 iterations at DS₁ [denoted as (DS₈N₅₀-DS₄N₁₀₀-DS₂N₁₀-DS₁N₁₀)]. We also investigated an approach in which the number of iterations was fixed at the value determined to be “optimal” according to the convergence criterion in order to measure the extra time associated with the convergence calculation.

II.B.3. Performance evaluation: Patient images

A second study employed the optimal convergence factor determined in the cadaver data to evaluate registration accuracy in CBCT images of ten patients undergoing fractionated head and neck radiation therapy treatment with daily online imaging. The patients exhibited “significant deformation” during the course of their treatment, as assessed by a radiation therapist, including one case that was replanned due to

excessive weight loss. For each patient, two CBCT volumes were used: one from the beginning of treatment (I_0) and the second from the end of treatment (I_1). The time between images ranged from 30 to 50 days. A description of each case is given in Table I. TRE was measured using eight anatomical points: the inferior aspect of the left and right temporal bones, tip of the left and right coronoid mandible process, inferior aspect of specific cervical vertebrae, and soft-tissue targets in the oropharynx (epiglottis or uvula), and in the left and right external auditory canals. Performance was evaluated in terms of NCC and TRE for Demons registration and compared to rigid registration alone across all patients and across all anatomical targets (80 points in total).

III. RESULTS

III.A. Selection of convergence criterion: Cadaver study

Figures 3 and 4 illustrate the convergence behavior of Demons deformable registration in cadaver data and provide initial evaluation of registration accuracy in CBCT imaging of the head and neck. Figure 3 highlights the advantages conferred by a multiscale approach with a robust convergence criterion that can be used across all levels of the pyramid. Each curve corresponds to registration performed with a different setting of k —i.e., a different fraction of the voxel size used to determine advancement of the algorithm to the next pyramid level. At each change in pyramid level, convergence is evident as a sudden increase in the NCC between two iterations. Long plateaus suggest too stringent a convergence criterion, as for $k = \frac{1}{16}$, thus wasting iterations—i.e., computation time spent performing registration without measurable increase in accuracy. In some cases, performance was actually degraded by performing registration for too long—e.g., for $k = \frac{1}{16}$ at pyramid level 1, where NCC actually de-

TABLE I. Summary of cases studied and registration performance for four-level multiscale registration with convergence factor $k = \frac{1}{10}$. (Note: Voxel size was $(0.8 \times 0.8 \times 0.8) \text{ mm}^3$ for the cadaver images and $(1.0 \times 1.0 \times 2.0) \text{ mm}^3$ for patient images.)

Patient No.	Description	Rigid NCC	Demons NCC	Rigid TRE (mm)		Demons TRE (mm)	
				Range	Mean	Range	Mean
Cadaver	Surgically induced soft-tissue deformation; jaw exercised	0.931	0.991	0.8–6.7	2.6 ± 1.0	0.4–2.0	0.8 ± 0.3
1	Neck flexion	0.946	0.994	1.4–7.0	3.1 ± 1.7	0.4–2.3	1.2 ± 0.6
2	Large anatomical changes due to weight loss	0.910	0.986	1.3–6.1	3.1 ± 1.7	0.7–3.4	1.6 ± 0.9
3	Weight loss	0.924	0.992	1.5–4.6	2.6 ± 1.2	0.7–4.4	2.1 ± 1.2
4	Neck flexion	0.889	0.993	1.0–4.3	2.6 ± 1.0	0.7–3.7	1.6 ± 1.0
5	Weight loss	0.922	0.989	1.8–6.5	4.3 ± 1.5	0.6–3.4	1.8 ± 1.0
6	Neck flexion, shrinkage, and weight loss	0.915	0.993	3.7–6.9	5.5 ± 1.0	1.0–1.7	1.4 ± 0.2
7	Weight loss	0.910	0.994	2.4–7.9	5.1 ± 2.0	0.8–3.0	1.6 ± 0.8
8	Shrinkage/weight loss & setup variations	0.936	0.991	1.5–5.5	3.0 ± 1.7	0.5–2.7	1.4 ± 0.7
9	Spinal flexion and deformation in pharynx	0.969	0.995	1.0–2.2	1.7 ± 0.5	0.7–2.3	1.6 ± 0.6
10	Weight loss and poor mask fitting; case replanned	0.901	0.992	1.5–8.6	4.2 ± 2.1	0.5–3.0	1.5 ± 0.8

grades after a certain number of iterations. Conversely, too loose a convergence criterion (large k) tends to advance the algorithm to higher levels in the pyramid while improvement is still possible at the current (less computationally expensive) level; moreover, registration is halted prematurely, leading to reduced registration performance overall. The results span a broad range in k , with $k < \sim \frac{1}{3}$ overly loose, $k > \sim \frac{1}{16}$ too stringent, and intermediate values ($\frac{1}{6} < k < \frac{1}{12}$) suggesting reasonable convergence criteria.

The accuracy and computational expense associated with changing the convergence criterion, k , is highlighted in Fig. 4(a), which shows the total number of iterations required

across all four pyramid levels and the final value of NCC as a function of k . As k decreases, the total number of iterations increases sharply; furthermore, a slight reduction in performance is observed at the lowest k values due to excessive iterations of Demons registration.

Registration time is directly related to the number of iterations, as illustrated by the measured registration time in Fig. 4(a). The NCC is observed to peak about an optimal value of $k \sim 0.1$, which appears to balance the requirements of speed and accuracy. This value of the convergence factor was used in subsequent studies of registration accuracy [as summarized in Table I and illustrated in the images shown in Fig. 2(d)].

At $k=0.1$, the extra computations associated with the proposed convergence criterion accounted for an additional ~ 10 s in the entire registration process. The results obtained with a fixed number of iterations (viz., DS_8N_{50} - $\text{DS}_4\text{N}_{100}$ - DS_2N_{10} - DS_1N_{10}) provided approximately equivalent accuracy to the “optimal” scheme ($\text{NCC}=0.989$ compared to 0.991) but required a larger amount of time (82 s, compared to 52 s), indicative of excess iterations being performed. In this sense, the k convergence approach “adapts” to the optimal number of iterations within a given level of the morphological pyramid (at the cost of ~ 10 s computation time in the initial implementation).

As shown in Table I, the cadaver study demonstrated Demons deformable registration in CBCT-guided procedures of the head and neck to yield $\text{NCC} > 0.99$ compared to $\text{NCC} \sim 0.93$ for rigid registration alone. Furthermore, the TRE evaluated in seven anatomical points was 0.8 ± 0.3 mm (on the order of the voxel size) for Demons registration compared to 2.6 ± 1.0 mm for rigid registration alone. The differences are evident in the difference images of Figs. 2(c)

FIG. 3. Convergence behavior of Demons algorithm in cadaver data for varying values of k . Four levels of the morphological pyramid are labeled with spatial resolution increasing at each level according to the binning (downsampling, DS) factors $\frac{1}{8}$, $\frac{1}{4}$, $\frac{1}{2}$, and 1, respectively.

FIG. 4. Cadaver study: Parameter selection and registration accuracy. (a) Accuracy and computational expense of multiscale Demons registration as a function of convergence factor, k . The left axis shows the total number of iterations required to reach convergence. The right axis shows the corresponding NCC at convergence for the cadaver data. The value selected for further studies is highlighted by the vertical bar ($k=\frac{1}{10}$). (b) Evolution of Demons registration accuracy in terms of TRE and NCC with optimal value for k .

and 2(d) where rigid registration accurately aligns the bulk bony anatomy of the spine and skull but does not correct for the closing of the jaw and the displacement of the soft tissue in the sinus and oropharynx. Demons registration successfully accounted for such deformations.

The deformation field output for the cadaver study with $k=0.10$ and $\sigma=1.0$ had a harmonic energy of $E_h=0.38$. Increasing the size of the smoothing kernel to $\sigma=2.0$ and $\sigma=3.0$ yielded smoother deformation fields with harmonic energy of $E_h=0.08$ and 0.02 , respectively, but degraded TRE to 1.3 ± 0.6 and 1.6 ± 0.8 mm.

It has been shown that for some registration algorithms increases in image similarity can be associated with decreased spatial alignment.²⁴ In Fig. 4(b), NCC and TRE are seen to evolve together as Demons registration proceeds iteratively from rigid registration at the extreme left, through each level of the multiscale image pyramid. In this study, both metrics of registration performance suggest a gradual increase in registration accuracy iteration by iteration, showing that the improvements in registration performance as measured by NCC also suggest an increase in spatial alignment. For the cadaver data, the results suggest submillimeter TRE for $NCC > 0.98$, with little improvement in targeting accuracy to be gained for $NCC > 0.99$. TRE appears to reach a stable minimum value a bit earlier in registration (i.e., in the third pyramid level) than NCC, which continues to improve slightly in the fourth pyramid level.

Consistent with the above observation, the three-level pyramid DS_8 - DS_4 - DS_2 registration scheme was the only variation from the nominal pyramid that showed substantial benefit. Eliminating the most computationally expensive pyramid level provided approximately equal registration accuracy ($NCC=0.988$) with a reduction in registration time (~ 25 s total compared to 52 s). In contrast, the DS_8 - DS_4 - DS_1 pyramid provided equivalent accuracy, but greatly increased registration time ($NCC=0.991$ in 135 s). The other downsampling schemes investigated all performed approximately equally to the nominal scheme both in terms of registration accuracy ($NCC=0.990$ – 0.991) and time (ranging from ~ 50 to 60 s).

III.B. Performance evaluation: Patient study

In the ten radiation therapy patients, rigid registration yielded a mean TRE and standard deviation of 3.5 ± 1.8 mm, while Demons deformable registration improved TRE to 1.6 ± 0.8 mm (by comparison, TRE with no registration was 6 mm, on average, and ranged as high as 25 mm). The results suggest targeting accuracy at or near the voxel size of the patient images ($1 \times 1 \times 2$ mm³). The lower TRE achieved with deformable registration was statistically significant ($p < 0.001$) based on a two-tailed, paired t-test. The results highlight the nonrigid anatomical changes that can occur in the head and neck over the course of a therapeutic procedure.

Analysis of the TRE for individual anatomical points is shown in Fig. 5. As might be expected, and consistent with the motivation of this work for surgical targeting of soft-

FIG. 5. Registration accuracy by anatomical point as measured in patient images for rigid and symmetric Demons registration. Box-and-whisker plots represent: The median TRE (horizontal line), the 25th and 75th percentiles (edges of the box), and total range (extent of whiskers) excluding outliers (+ symbols), with outliers defined as greater than $1.5 \times$ interquartile range below the first or above the third quartile.

tissue tumors, the largest improvement over rigid registration is achieved for the soft-tissue targets. Consistent improvement is also observed for all the bony anatomy points, highlighting the necessity of deformable registration even for accurate alignment of bony anatomy, an important feature in tasks such as surgical navigation where such points are often used as anatomical landmarks. An example of the need for deformable registration for accurate alignment of bony anatomy is given by the left and right temporal bones: while they are rigid with respect to each other, they are not rigid with respect to other bony anatomy, such as the mandible and spine. Independent motion of the jaw and flexion of the neck are possible as indicated by both the higher median TRE for rigid registration of bony anatomy as well as the larger observed range.

For the patient data, TRE on the order of the slice thickness was still achieved when Demons registration omitted the final level of the image pyramid—specifically TRE = 1.9 ± 0.9 mm for registration with the DS₈-DS₄-DS₂ pyramid. Eliminating the last multi-scale level, in which full-resolution (nondownsampling) images are registered, may make deformable registration for image-guided procedures more feasible. Using only the first three levels of the image period decreased the average registration time from 270 to 45 s. (The increased registration time for the radiation therapy patient images compared to surgical C-arm cadaver data is due to a larger FOV).

IV. DISCUSSION AND CONCLUSIONS

The range and magnitude of deformations observed in head and neck procedures suggest that rigid registration alone is not sufficient to account accurately for the motion of multiple bony structures (e.g., spine, cranium, and mandible) or—especially—soft-tissue targets. Anatomical changes arising from jaw and neck flexion, weight loss, and the procedure itself necessitate nonrigid, deformable registration for accurate resolution of geometric discrepancies. Multiscale Demons registration is a well-known technique for fast intensity-based deformable registration with proven utility in a variety of applications.^{25,26,11} For use in CBCT-guided procedures (e.g., surgery and radiation therapy), considerations of speed and accuracy present equally important challenges to practicality and performance. The convergence criterion invoked to terminate registration at a given level affects both speed and accuracy.

In this work, excellent results were achieved through use of a convergence criterion that considered the change in the distance by which voxels are displaced from one iteration to the next as a fraction of the voxel size. An optimal convergence factor ($k=0.1$) was identified in a cadaver study and found to provide robust performance when applied to registration of ten sets of patient images exhibiting a broad range of deformations (see Table I).

The use of this convergence factor requires additional computations—for example, contributing ~10 s computation time to the 50 s registration process (in the nonmultithreaded initial implementation). A less computationally ex-

pensive approach would be to examine the root mean square change value of the update field, U_n , to determine whether the update is sufficiently “small” to halt registration; this value can essentially be computed for “free” as part of the Demons force calculation and is available as part of the default ITK Demons implementation. Application of this less computationally expensive method in the cadaver studies described above showed this approach to be nonrobust and unsuitable to a large number of datasets. We believe the problems with this convergence criterion arise from (i) examining U_n as opposed to the regularized deformation field D_n and (ii) deciding convergence based on a single number distilled from the large number of elements in the update field.

An alternative implementation of our convergence criterion could allow k to vary at each level of the morphological pyramid—for example, a smaller value at the less computationally expensive levels and a larger value at the final level to force the most computationally intensive step to finish sooner. Initial investigation of such an approach using the same data as above suggested no significant performance advantage. Too many iterations at the coarsest level may degrade registration performance, and too few at the final level does not take full advantage of the high resolution information in the image. In the ten patient datasets, we observed that the total number of iterations required for convergence varied by over 40% from one dataset to another, and by almost 80% (ranging from 9 to 16) at the final, most time-consuming level of multiscale registration, highlighting the difficulty in picking a fixed number of iterations in a manner that could account for the range of relevant deformations.

The degradation of registration performance observed for an excessive number of iterations is likely associated with the algorithm attempting to align random noise fluctuations between the two images. As Demons can only be considered an *approximation* of an optimization process,¹⁶ beyond a certain point the displacements calculated by the Demons algorithm may be inaccurate. For example, even with “perfect alignment” of structures in the images, stochastic variations associated with quantum noise could cause nonzero displacement, subsequently misaligning the images overall.

A relatively small (1 mm) smoothing kernel was used in this study since in the context of image registration for CBCT-guided head and neck surgery, we wanted to allow for sharp transitions in deformation—e.g., at an interface of bone and soft tissue or in the presence of surgical intervention and excised tissue. For applications in which increased smoothness of the deformation field is desired, recently proposed modifications to the Demons algorithm can produce smoother deformation fields at the expense of extra computation.¹³

Ongoing work in our laboratory includes adaptation of this approach to the registration of diagnostic, preoperative CT images with intraoperative CBCT, recognizing the importance of CT for planning in image-guided surgery and radiation therapy of the head and neck. It can be expected that the deformations encountered will be as large (or larger)

than those found in this study. A necessary preprocessing step for application of the algorithm to CT-to-CBCT registration is normalization of voxel intensity values. Such preprocessing is under investigation using histogram matching and equalization as well as the wealth of ongoing research in accurately converting CBCT voxel values to Hounsfield units.^{27–29} Other challenges include the presence of image artifacts that are common in CBCT. Foremost of these were dental fillings (absent from the current study) and truncation artifacts (excluded from the convergence calculation in the current work by means of the cylindrical mask), each the subject of ongoing effort in the field of CBCT image quality. Future investigation includes adaptation and evaluation of this registration method in a broader spectrum of CBCT-guided head and neck surgery patient images, specifically considering the challenges posed by surgically excised tissue upon registration accuracy.

CBCT guidance appears to offer an important modality for improving the accuracy and precision of therapeutic procedures by resolving geometric and anatomical uncertainties at the time of treatment. The ability to register images and planning information acquired at earlier times during therapy could play an important role in augmenting CBCT guidance. While the focus of the current work is CBCT-guided surgery, implications for the (currently more prevalent) application of IGRT are clear and consistent with a broad spectrum of research in deformable registration for radiation therapy. Demons deformable registration was found to provide fast updates of anatomical changes in head and neck procedures with accuracy (TRE) at or near the intrinsic spatial resolution of the underlying images.

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