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Deformable Image Registration with Local Rigidity Constraints for Cone-Beam CT Guided Spine Surgery

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Abstract

Image-guided spine surgery is associated with reduced co-morbidity and improved surgical outcome. However, precise localization of target anatomy and adjacent nerves and vessels relative to planning information (e.g., device trajectories) can be challenged by anatomical deformation. Rigid registration alone fails to account for deformation associated with changes in spine curvature, and conventional deformable registration fails to account for rigidity of the vertebrae, causing unrealistic distortions in the registered image that can confound high-precision surgery. We developed and evaluated a deformable registration method capable of preserving rigidity of bones while resolving the deformation of surrounding soft tissue. The method aligns preoperative CT to intraoperative CBCT using free-form deformation (FFD) with constraints on rigid body motion imposed according to a simple intensity threshold of bone intensities. The constraints enforced 3 properties of a rigid transformation – namely, constraints on affinity (AC), orthogonality (OC), and properness (PC). The method also incorporated an injectivity constraint (IC) to preserve topology. Physical experiments involving phantoms, an ovine spine, and a human cadaver as well as digital simulations were performed to evaluate the sensitivity to registration parameters, preservation of rigid body morphology, and overall registration accuracy of constrained FFD in comparison to conventional unconstrained FFD (denoted uFFD) and Demons registration. FFD with orthogonality and injectivity constraints (denoted FFD+OC+IC) demonstrated improved performance compared to uFFD and Demons. Affinity and properness constraints offered little or no additional improvement. The FFD+OC+IC method preserved rigid body morphology at near-ideal values of zero dilatation ($\mathcal{D} = 0.05$, compared to 0.39 and 0.56 for uFFD and Demons, respectively) and shear ($\mathcal{S} = 0.08$, compared to 0.36 and 0.44 for uFFD and Demons, respectively). Target registration error (TRE) was similarly improved for FFD+OC+IC (0.7 mm), compared to 1.4 and 1.8 mm for uFFD and Demons. Results were validated in human cadaver studies using CT and CBCT images, with FFD+OC+IC providing excellent preservation of rigid morphology and equivalent or improved TRE. The approach therefore overcomes distortions intrinsic to unconstrained FFD and could better facilitate high-precision image-guided spine surgery.

Keywords

deformable registration; Demons registration; free-form deformation; cone-beam CT; image-guided surgery

1. INTRODUCTION

Spinal pathologies are among the most common causes of severe disabilities and death. For example, the prevalence of scoliosis ranges from 1–2% in children (age < 15), to 2–32% in adults, and to 68% in elderly (age 60–90) (Trobisch et al., 2010, Kotwal et al., 2011, Smith et al., 2011). Additionally, spinal injury is found in 25% of trauma victims in North America (Fehlings and Wilson, 2010, Whang et al., 2011), and spine metastases are identified in 10% of patients with malignant tumors (Delank et al., 2011). Such pathologies, i.e., spinal deformity, trauma, and neoplasm, can be addressed by surgical intervention (Lis et al., 2004, Tormenti et al., 2010, Schouten et al., 2012). However, spine surgery can present significant clinical challenges due to complexity of spinal anatomy and surrounding neuro-vascular structures. Therefore, precise localization of vertebral levels and target anatomy (e.g., the tumor and adjacent nerves and vessels) are important to surgical outcomes. Conventional methods of spinal localization based on the surgeon's knowledge of spine anatomy, preoperatively acquired images (CT and/or MR), and intraoperative fluoroscopy have significant shortcomings. For example, clinical studies have shown misplacement in lumbar pedicle screw insertion at a rate of 10–40% (Castro et al., 1996, Laine et al., 2000). Image-guided spine surgery (IGSS) is associated with improved localization, increased safety to patients, and reduced radiation exposure. For example, (Kamimura et al., 1999) and (Amiot et al., 2000) reported improved accuracy in CT-guided pedicle screw placement. However, precise localization of target anatomy with respect to planning data (e.g., device trajectories) can be challenged by anatomical deformation induced by variability in intraoperative setup and the procedure itself.

Recent advancement in IGSS alleviates such limitation by incorporation of high-quality intraoperative imaging which provides up-to-date 3D cone-beam CT (CBCT) images that properly capture the deformation and provide a basis for registration of preoperative planning information to the current view of the patient. Various studies investigated application of intraoperative CBCT in IGSS. For example, the O-arm based navigation systems demonstrated improved surgical accuracy in pedicle screw insertion (Silbermann et al., 2011, Baaj et al., 2013) and spinal trauma surgery (Schouten et al., 2012). Also, intraoperative CBCT using a mobile C-arm exhibited image quality suitable to IGSS with improved soft-tissue visibility and the potential to reduce fluoroscopy exposure to patient and staff, providing improved surgical performance in preclinical studies (Siewerdsen et al., 2005, Schafer et al., 2011). A potential clinical workflow for CBCT-guided spine surgery is illustrated in figure 1, where CBCT can be acquired at various points during the procedure to visualize progress and/or verify the quality of surgical outcome. Because the definition of planning data in the intraoperative images can be challenging and time-consuming due to limitations in soft-tissue visibility and image quality, registration of preoperative planning data to the intraoperative patient pose provides a more streamlined workflow. The

registration process (figure 1(IV)) conventionally relies on rigid registration, which is unable to account for changes in spine curvature and deformation of adjacent soft tissue. Moreover, typical deformable registration fails to discern differences in elasticity properties of tissue, which can result in unrealistic deformation of the spine (e.g., distortion about the pedicle and/or spinal dura) that can confound high-precision spinal surgery, which has an accuracy requirement of 1–3 mm (Cleary et al., 2000, Shahidi et al., 2001).

Previous registration methods incorporating elasticity of tissues can be classified into three broad categories including piece-wise rigid registration, locally-rigid registration, and constrained volumetric registration. Piece-wise rigid registration methods can provide perfect preservation of rigid bone morphology; however, deformation of soft-tissue might not be accurately modeled. Examples of piece-wise registration methods include: i) a point interpolation weighted by a distance function of rigid structures (Little et al., 1996, Moreno et al., 2008) or rigidity coefficients (Wei et al., 2008); ii) articulated models of the spine to estimate piecewise-rigid deformation from a rigid transformation of each vertebra (du Bois d'Aische et al., 2007, Harmouche et al., 2010, Harmouche et al., 2012); and iii) constrained group-wise registrations that concurrently estimate a rigid transformation of each rigid body (van de Giessen et al., 2009, Gill et al., 2012). The methods (i,ii) require accurate definition of rigid structures and/or landmark feature points, which could be difficult to achieve in clinical workflow. Giessen et al (van de Giessen et al., 2009) and Gill et al (Gill et al., 2012) proposed methods (iii) to simultaneously estimate a rigid transformation of each bone in an optimization framework that applies physiological constraints representing the spatial relation of each wrist bone and vertebra, respectively. The former did not explicitly address soft-tissue deformation, and the latter might not provide accurate deformation of soft-tissue, since soft-tissue surrounding each vertebra is transformed using its corresponding estimated rigid mapping. Alternatively, locally-rigid registration as proposed by Arsigny et al (Arsigny et al., 2005) estimates a polyrigid transformation with the potential ability to model deformation of articulated structures, where the degree to which rigidity is preserved depends on the parameters defining a region of influence of each rigid transformation. Application in clinical workflow may be challenged due to the required knowledge of a rigid transformation and centroid of each vertebra in computing the polyrigid transformation from a weighted average of logarithms of rotations (of rigid transformations). On the other hand, constrained fully volumetric registration methods are capable of minimizing unrealistic deformation of bones and resolving soft-tissue deformation. The constraints can be applied as a tissue-dependent filter of deformation (Staring et al., 2007a, Baluwala et al., 2011) or regularization within an optimization framework to penalize deviations from rigid-body motion (Loeckx et al., 2004, Ruan et al., 2006, Keeling, 2006, Staring et al., 2007b). Filtering a deformation field according to stiffness of tissue can involve fine-tuning of parameters controlling the width of the filter (varying per iteration and per registration process). The authors also noted sharp transitions in the deformation field at the boundary of rigid and non-rigid tissues that do not represent realistic physical shear or sliding motion. On the other hand, constrained optimization of an image similarity metric typically uses image intensities to automatically compute registration without reliance on pre-computed transformations or accurate definition of landmark features and/or bony structures, therefore offering more streamlined workflow potentially suitable to IGSS. Loeckx et al. applied this

technique to estimate constrained free-form deformation (FFD) by imposing orthogonality of the spatial derivative of a deformation in bony structures, where the spatial derivative was computed analytically (Loeckx et al., 2004). Ruan et al. similarly estimated FFD between inhale and exhale thorax CT images by imposing the orthogonality constraint in bones through use of tissue stiffness defined using a hyperbolic tangent function of image intensities (Ruan et al., 2006). Besides the orthogonality constraint, Staring et al. incorporated affinity and properness constraints in a FFD-based method to preserve rigidity of bones and/or structures of interest (e.g., for analysis of disease progress) (Staring et al., 2007b). The method demonstrated the ability to preserve morphology of lung tumors for inspection of tumor growth using CT thorax data. However, application of the method in registration of CT and CBCT images of articulated structures such as the spine has not been investigated. Also, since no explicit constraint on smoothness of deformation was imposed, violation of topology can occur (including folding and tearing of tissues).

Therefore, to preserve topology and rigidity of the vertebrae while accurately resolving deformation, we developed a deformable registration method incorporating injectivity (Choi and Lee, 2000) and rigidity constraints (Staring et al., 2007b) for CBCT-guided spine surgery. The method estimated free-form deformation (FFD) that aligned 3D preoperative CT/CBCT and intraoperative CBCT using mutual information (MI). Physical experiments involving phantoms, an ovine spine, and a human cadaver as well as digital simulations were performed to evaluate sensitivity to registration parameters, preservation of rigid body morphology, and overall registration accuracy of constrained FFD in comparison to conventional unconstrained FFD (denoted uFFD) and Demons registration. The various registration methods evaluated in this work are detailed in Section 2. Detailed analysis of the sensitivity of registration performance to algorithm parameters and image noise is given in Sections 3, 4, and appendix. Finally, Section 5 discusses the advantages and limitations of the constrained registration method and delineates future work for clinical translation.

2. REGISTRATION METHODS

Registration estimates the transformation that aligns a moving image (I_0) to a fixed image (I_1). The transformation can be classified according to its degrees of freedom (DOF). Rigid and/or affine transformations with a few DOF are typically used for initial alignment, whereas deformation with higher DOF is used to capture complex spatial differences. In this work, a rigid transformation estimated by maximizing normalized mutual information (NMI) between I_0 and I_1 using a gradient descent optimization was used as an initialization. Three deformable registration methods were subsequently evaluated: i) the Demons algorithm described in Section 2.1; ii) conventional, unconstrained FFD (uFFD) detailed in Section 2.2; and iii) a collection of FFD variants incorporating constraints on topology and rigidity detailed in Section 2.3.

2.1 Demons Registration

The Demons method estimates a nonparametric deformation represented by a dense displacement field. The optimization framework for the Demons method as proposed by Vercauteren et al. incorporates an intermediate displacement field which allows the

optimization to be decoupled into two steps (Vercauteren et al., 2009). First, an update field comprising update vectors is estimated by minimizing the mean square intensity difference (MSD) between I_0 and I_1 under a maximum update step length (MSL) constraint. Linearization of a cost function leads to parallelizable, voxel-wise computation of an update vector as:

$$\mathbf{u}(\mathbf{x}) = - \frac{2 \left[I_1(\mathbf{x}) - I_0^{(i)}(\mathbf{x}) \right] \left[\nabla I_1(\mathbf{x}) + \nabla I_0^{(i)}(\mathbf{x}) \right]}{K \left[I_1(\mathbf{x}) - I_0^{(i)}(\mathbf{x}) \right]^2 + \left\| \nabla I_1(\mathbf{x}) + \nabla I_0^{(i)}(\mathbf{x}) \right\|^2} \quad (1)$$

where i represents an iteration number, ∇I_0 and ∇I_1 denote the gradients of I_0 and I_1 , and $K = 3/(MSL^2 \|\text{voxel size}\|^2)$ constrains the update vector by $\|\mathbf{u}(\mathbf{x})\| < 1/(2\sqrt{K})$ (Vercauteren et al., 2009).

The second step involves composition and regularization of motion fields as:

$$D_{Demos}^{(i)} = G_{\sigma_D} * \left[D_{Demos}^{(i-1)} \circ \left(Id + G_{\sigma_U} * U_{Demos}^{(i)} \right) \right], \quad (2)$$

where $\circ$ denotes a compositive operation, $U_{Demos}^{(i)}$ represents the update field, $D_{Demos}^{(i)}$ is the displacement field, Id represents an identity map, and G_{σ_U} and G_{σ_D} denote Gaussian filters of width σ_U and σ_D to smooth the update and the displacement fields, respectively. Variation of the smoothing filters yields different deformation models with varying capabilities (Cachier et al., 2003). For example, smoothing only the update field yields a fluid model, smoothing only the displacement field yields an elastic model, and smoothing both fields yields a viscoelastic model. In this work, Demons optimization was performed in a morphological image pyramid in which I_0 and I_1 were repeatedly downsampled to coarser resolution by a factor of 2 (e.g., downsampling factors of 8, 4, 2, and 1). The MSL was fixed at 0.5 voxels based on previous work and additional analysis (not shown for brevity) (Reaungamornrat et al., 2013). The convergence criterion was based on diminishing change in MSD as in previous work (Reaungamornrat et al., 2013). The compositive form in equation (2) was favored over the diffeomorphic form, since exponentiation of the motion field was found to accumulate numerical errors in the deformation estimate (Arsigny et al., 2006, Vercauteren et al., 2009).

2.2. Unconstrained Free-Form Deformable Registration (uFFD)

Free-form deformation was based on cubic B-splines (Mattes et al., 2003). Accounting for an initial rigid transformation, the free-form deformation was defined as:

$$\mathbf{T}_{\mu}(\mathbf{x}) = \mathbf{T}_{Rigid}(\mathbf{x}) + \sum_{i=1}^N \mu_i \beta^{(3)} \left(\frac{\mathbf{x} - \mathbf{x}_i}{\sigma} \right), \quad (3)$$

where $\mathbf{T}_{Rigid}$ denotes the rigid transformation, $\mathbf{T}_{\mu}$ is the free-form deformation with deformation parameters μ , N is the number of control points in the support of B-splines of $\mathbf{x}$, $\mu_i = (\mu_{i,x}, \mu_{i,y}, \mu_{i,z}) \in \mu$ is a displacement defined at a control point $\mathbf{x}_i$, and $\beta^{(3)}(\mathbf{x}) = \beta^{(3)}(x)\beta^{(3)}(y)\beta^{(3)}(z)$ denotes the 3D tensor product of the 1D cubic B-splines, where $\sigma = (\sigma_x,$

σ_y, σ_z) is the grid spacing. The deformation parameter (μ) was estimated by maximizing mutual information (MI) between the warped moving image I_0 and the fixed image I_1 as

$$E(T_\mu; I_0, I_1) = MI(T_\mu[I_0], I_1). \quad (4)$$

The derivative of MI with respect to μ was derived as described in (Mattes et al., 2003), and the gradient of I_0 was computed based on its cubic B-spline interpolation representation. The limited-memory, quasi-Newton optimizer with bound constraints (LBFGS-B) (Zhu et al., 1997) was used to maximize equation (4) in a multi-resolution scheme of both the images and the lattice of control points to improve computational efficiency and robustness. A morphological image pyramid was constructed in a manner similar to the Demons method, and a lattice pyramid was constructed such that the number of control points in the image was upsampled by a factor of 2 in the next finer level of the pyramid. Specifically, the number of the control points in each image dimension (x, y, z -directions) at level ℓ was $n_{\ell+3}$, where n_{ℓ} is the number of control points in the image, and the 3 control points are added to allow estimation of the displacements on the first and the last control points in the image. The number of control points in the image at each subsequent level was then $n_{\ell+1} = 2n_{\ell}$. The convergence criterion was based on reduction in the cost function (equation (4)) of less than 10^4 times that of machine precision (e.g., 2.22045×10^{-16} for double precision) between successive iterations, with a maximum of 800 iterations. Registration computed in this manner is referred to as conventional unconstrained free-form deformation (uFFD).

2.2 Constrained Free-Form Deformable Registration (FFD)

Since an optimization based on image similarity as in equation (4) could lead to an ill-posed problem (Bernd and Jan, 2008), priors are typically added to constrain the deformation, such as smoothness (Terzopoulos, 1986; Rueckert et al., 1999), diffeomorphism (Rueckert et al., 2006; Se Young and Fessler, 2009), consistency in direction of registration (Christensen and Johnson, 2001; Modat et al., 2012), and conformity with tissue characteristics (Rohlfing et al., 2003; Loeckx et al., 2004; Ruan et al., 2006; Staring et al., 2007b). Such constraints can be incorporated as “hard” constraints to be exactly satisfied or as “soft” constraints (regularization) to be approximately satisfied as:

$$E(T_\mu; I_0, I_1) = MI(I_1, T_\mu[I_0]) + \lambda_{Reg} Reg(T_\mu) \text{ subject to } Constraint(\mu), \quad (5)$$

where λ_{Reg} denotes a regularization parameter, $Reg(T_\mu)$ is the regularization applied on T_μ , and $Constraint(\mu)$ denotes a hard constraint on μ . As described below, we imposed injectivity as a hard constraint to assure smoothness of the deformation, and we imposed local rigidity as a soft constraint controlled by a regularization parameter to enforce rigid body motion (bones) within a deformable surrounding (soft tissue).

2.2.1 Local Injectivity Constraint (IC)—Since a B-spline deformation does not guarantee preservation of topology of deformed tissues, various studies have incorporated constraints to impose invertibility of B-splines (Rueckert et al., 2006; Se Young and Fessler, 2009). We imposed local invertibility of the cubic B-splines using the sufficient condition proposed by Choi and Lee (Choi and Lee, 2000). Denoting $\delta_x = \max|\mu_{x,i}|, \delta_y = \max|\mu_{y,i}|$ and

$\delta_z = \max|\mu_{z,i}|$, the cubic B-splines are then locally injective if $\delta_x < \sigma_x/K_{3D}$, $\delta_y < \sigma_y/K_{3D}$ and $\delta_z < \sigma_z/K_{3D}$, where $K_{3D} \approx 2.48$. A displacement vector is therefore bounded in magnitude by approximately 0.40 times the control point spacing. Similarly, the constraint in 2D was given by $K_{2D} \approx 2.05$ (for experiment #2, below). The constraint was imposed as a bounding box of μ using the bounding constraints of LBFGS-B.

2.2.2 Rigidity Constraints—A deformation of rigid bodies can be constrained according to properties of a rigid mapping – for example, the spatial Jacobian matrix of the deformation must be affine, orthogonal, and proper. Rigidity constraints based on these 3 properties were imposed on deformation in bones through use of a tissue stiffness map derived once prior to registration from the preoperative image I_0 by simple intensity thresholding of bone intensities for CT and/or CBCT images. Bones and soft tissue were thereby assigned stiffness values of 1 and 0, respectively. A threshold value of 200 HU in CT (0.024 mm⁻¹ in CBCT) was used in results reported below, and as detailed in the appendix the sensitivity of the results to the selection of threshold value was found to be low provided a reasonable selection of threshold value (i.e., a value separating soft tissue and bone intensities) due to local support of cubic B-splines, relatively and spatially dense application of penalties, and sparse configuration of control points, as well as use of a fill-hole operation and morphological shape opening to refine the stiffness map. Despite the reduced contrast and presence of artifacts typical of CBCT, the simple threshold-based segmentation plus automatic hole filling was sufficient for all experiments described below. Advanced segmentation methods or functions of image intensities (e.g., sigmoid and hyperbolic tangent functions) could be applied to define tissue stiffness, but the current work considered a simple threshold for CT and CBCT images. To improve computational efficiency, the constraints were applied on 50% uniform samples of voxels in bones. The

derivative of $T_\mu(x)$ was derived using $\dot{\beta}^{(d)}(x) = \beta^{(d-1)}\left(x + \frac{1}{2}\right) - \beta^{(d-1)}\left(x - \frac{1}{2}\right)$, where d is a degree of the B-splines (Mattes et al., 2003, Loeckx et al., 2004, Staring et al., 2007b).

Affinity Constraint: Since a rigid mapping is affine (e.g., parallel lines remain parallel.), and the second derivative of an affine transformation with respect to the spatial position is $\mathbf{0}$, departure of the deformation from an affine transformation can be measured in terms of the bending energy as:

$$AC(T_\mu; x) = \|\ddot{T}_\mu(x)\|_F^2 \quad (6)$$

where the double-dot notation implies a second spatial derivative and $\|\cdot\|_F$ is the Frobenius norm. The expression evaluates to zero for affine transformations.

Orthogonality Constraint: Since the spatial Jacobian matrix of a rigid mapping is orthogonal, departure of the deformation from a rigid mapping can be measured using orthogonality as:

$$OC(T_\mu; x) = \|\dot{T}_\mu(x)\dot{T}_\mu(x)^T - \mathbf{I}\|_F^2 \quad (7)$$

where the dot notation implies a first spatial derivative, and $\mathbf{I}$ is an identity matrix. The term evaluates to zero if $\dot{\mathbf{T}}_{\mu}(\mathbf{x})$ represents a rotation or a reflection (determinant equal to 1 and -1 , respectively). Conceptually, OC penalizes changes in volume (e.g., scaling) and shape (e.g., shear). However, if $\dot{\mathbf{T}}_{\mu}(\mathbf{x})$ is a reflection, changes in topology can occur (e.g., folding, tearing, or the appearance or disappearance of structures) which cannot be detected by OC.

Properness Constraint: Since the spatial Jacobian matrix of a rigid mapping is proper (i.e., determinant = 1), deformations comprising reflection and/or scaling were penalized using:

$$PC(\mathbf{T}_{\mu}; \mathbf{x}) = \left(\det(\dot{\mathbf{T}}_{\mu}(\mathbf{x})) - 1 \right)^2 \quad (8)$$

where $\det(\cdot)$ denotes a matrix determinant. The expression evaluates to 0 for rigid transformations and deformation involving simple and/or pure shear (for which the change in volume is 0). Since $\det(\dot{\mathbf{T}}_{\mu}(\mathbf{x}))$ is related to change in local volume, the term $\det(\dot{\mathbf{T}}_{\mu}(\mathbf{x})) = 0$ implies a violation of topology within an Eulerian description of the deformation (Yang et al., 2011). Similarly, $0 < \det(\dot{\mathbf{T}}_{\mu}(\mathbf{x})) < 1$ implies volume expansion, $\det(\dot{\mathbf{T}}_{\mu}(\mathbf{x})) > 1$ implies volume contraction, and $\det(\dot{\mathbf{T}}_{\mu}(\mathbf{x})) = 1$ implies no volume change (Christensen et al., 2007). The constraint is therefore equivalent to preservation of volume and/or incompressibility (Rohlfing et al., 2003). Equation (8) could lead to asymmetric penalization of expansion and contraction; however, since a symmetric form, $[\log(\det(\dot{\mathbf{T}}_{\mu}(\mathbf{x})))^2]$, can cause unstable evaluation of the cost function and its derivative as $\det(\dot{\mathbf{T}}_{\mu}(\mathbf{x}))$ approaches 0, equation (8) was used.

2.2.3 Constrained Approach—Incorporating injectivity as a hard constraint and rigidity as regularization gives a cost function for constrained FFD as:

$$E(\mathbf{T}_{\mu}; I_0, I_1) = \text{MI}(\mathbf{T}_{\mu}[I_0], I_1) - \frac{1}{\sum_{\mathbf{x}} c(\mathbf{x}|\mathbf{T}_{\mu})} \sum_{\mathbf{x}} c(\mathbf{x}|\mathbf{T}_{\mu}) \times \left\{ \lambda_A \|\ddot{\mathbf{T}}_{\mu}(\mathbf{x})\|_F^2 + \lambda_O \|\dot{\mathbf{T}}_{\mu}(\mathbf{x}) \dot{\mathbf{T}}_{\mu}(\mathbf{x})^T - \mathbf{I}\|_F^2 + \lambda_P \left(\det(\dot{\mathbf{T}}_{\mu}(\mathbf{x})) - 1 \right)^2 \right\} \quad (9)$$

subject to $|\mu_{i,x}| < \sigma_x / K_{3D}$, $|\mu_{i,y}| < \sigma_y / K_{3D}$, and $|\mu_{i,z}| < \sigma_z / K_{3D}$

where $c(\mathbf{x}|\mathbf{T}_{\mu})$ denotes the tissue stiffness in I_0 after deformation $\mathbf{T}_{\mu}$, and the parameters λ_A , λ_O , and λ_P are the regularization strength of AC, OC, and PC, respectively. Similar to the unconstrained FFD method, equation (9) was optimized using LBFGS-B in a multi-resolution scheme, and the convergence criterion was met when the same reduction in cost function (less than 10^4 times that of machine precision) was achieved. The gradient of the cost function with respect to μ can be explicitly evaluated due to the $\mathcal{C}^2$ continuity of cubic

B-splines. Since the Frobenius norm of a matrix A is $\|A\|_F = \sqrt{\sum_{i,j} |A_{i,j}|^2}$, the gradient of AC with respect to μ using the chain rule was given by:

$$\frac{\partial}{\partial \mu} \|\ddot{\mathbf{T}}_{\mu}(\mathbf{x})\|_F^2 = \sum_{k=1}^{\dim} \sum_{i,j=1}^{\dim} 2 \left(\ddot{\mathbf{T}}_{\mu,k}(\mathbf{x}) \right)_{i,j} \frac{\partial}{\partial \mu} \left(\ddot{\mathbf{T}}_{\mu,k}(\mathbf{x}) \right)_{i,j} \quad (10)$$

where dim denotes a spatial dimension, and i, j and k are indices of the spatial Hessian of T_{μ}

at a point $\mathbf{x}$ corresponding to $\frac{\partial T_{\mu,k}}{\partial x_i \partial x_j}$. Similarly the derivative of OC was given by:

$$\frac{\partial}{\partial \mu} \|\dot{T}_{\mu}(\mathbf{x}) \dot{T}_{\mu}(\mathbf{x})^T - I\|_F^2 = \sum_{i,j=1}^{dim} 2 \left(\dot{T}_{\mu}(\mathbf{x}) \dot{T}_{\mu}(\mathbf{x})^T - I \right)_{i,j} \left(\frac{\partial}{\partial \mu} \dot{T}_{\mu}(\mathbf{x}) \dot{T}_{\mu}(\mathbf{x})^T + \dot{T}_{\mu}(\mathbf{x}) \frac{\partial}{\partial \mu} \dot{T}_{\mu}(\mathbf{x})^T \right)_{i,j} \quad (11)$$

and the derivative of PC evaluated using Jacobi's formula was given by:

$$\frac{\partial}{\partial \mu} \left(\det \left(\dot{T}_{\mu}(\mathbf{x}) \right) - 1 \right)^2 = 2 \left(\det \left(\dot{T}_{\mu}(\mathbf{x}) \right) - 1 \right) \text{tr} \left(\text{adj} \left(\dot{T}_{\mu}(\mathbf{x}) \right) \frac{\partial}{\partial \mu} \dot{T}_{\mu}(\mathbf{x}) \right) \quad (12)$$

where $\text{tr}(\cdot)$ denotes a trace of a matrix, and $\text{adj}(\cdot)$ is an adjugate of a matrix.

We therefore have three deformable registration methods, each of which carries implicit or explicit priors or regularization - Demons via smoothing of the update and/or deformation fields, uFFD via implicit smoothing from a finite number of B-spline control points, and FFD with various explicit rigidity constraints. The first two, however, can introduce non-physical warping of rigid bodies, such as the vertebrae and impart non-physical distortion (e.g., warping of the tumor volume and/or device trajectories) within such rigid bodies. Such observation motivated the explicit constraints in (9), with FFD variants denoted FFD+IC (injectivity only) and a host of alternatives (denoted FFD+AC, FFD+PC, FFD+OC, FFD+OC+AC+PC, etc.) to improve preservation of rigid morphology. Table 1 summarizes the various methods and registration parameters associated with each.

3. EXPERIMENTAL METHODS

Four experiments were performed to evaluate performance of the various deformable registration methods as illustrated in figure 2. Experiment #1 first identified nominal (optimal) values of the Demons parameters capable of preserving rigidity while still solving large deformations. Experiment #2 then investigated the necessary and sufficient rigidity constraints for the FFD method. Experiment #3 evaluated the sensitivity of the FFD method to its intrinsic registration parameters, and the overall findings were validated in Experiment #4 involving a human cadaver. A different phantom was used in each experiment to differentiate data used for optimization, sensitivity analysis, and evaluation.

3.1. Analysis of Registration Performance

For each experiment, registration performance was quantified by the degree to which rigidity was maintained within rigid bodies as well as geometric accuracy, and assessed qualitatively by visualizing square grid images and straight-line planning trajectories after deformable registration. It was important to select metrics distinct from the cost function so that the performance of each registration method could be justified and compared.

3.1.1 Preservation of Rigidity—Preservation of rigidity was assessed quantitatively in terms of local dilatation and shear, and qualitatively by visualization of square grid images and straight-line planning trajectories. The local dilatation and shear were analyzed from the

displacement vectors defined in rigid bodies. A displacement field of free-form deformation was computed using equation (3).

Local changes in volume and/or shape due to deformation can be measured using strain (Lur'e, 2005, Gould, 2013, Dixit, 2008). The strain-displacement relations from the theory of elasticity give a strain tensor ($\boldsymbol{\varepsilon}(\mathbf{x})$) describing deformation based on an assumption of linear elasticity (i.e., elements of $\mathbf{u}(\dot{\mathbf{x}})$ are small in comparison to unity) as:

$$\boldsymbol{\varepsilon}(\mathbf{x}) = \frac{1}{2} [\dot{\mathbf{u}}(\mathbf{x}) + (\dot{\mathbf{u}}(\mathbf{x}))^T] \quad (13)$$

where $\mathbf{u}(\dot{\mathbf{x}})$ denotes a spatial Jacobian matrix of a displacement vector $\mathbf{u}(\mathbf{x})$.

Dilatation: The dilatation represented local changes in volume as a sum of extensional strains,

$$\mathcal{D}(\mathbf{x}) = \text{tr} [\boldsymbol{\varepsilon}(\mathbf{x})], \quad (14)$$

equal to the divergence of the displacement vector $\nabla \cdot \mathbf{u}(\mathbf{x})$. Using an Eulerian description of the deformation, $\mathcal{D} < 0$ implies expansion, $\mathcal{D} = 0$ implies no volume change, and $\mathcal{D} > 0$ implies compression. The term evaluates to 0 for rigid transformations as well as deformations involving simple and/or pure shear.

Maximum Shear Angle: Since the off-diagonal elements of $\boldsymbol{\varepsilon}(\mathbf{x})$ represent one-half of the change in angle between two originally orthogonal directions, the local maximum shear angle was described as

$$\mathcal{S}(\mathbf{x}) = \|\boldsymbol{\gamma}\|_{\infty} \quad (15)$$

where $\|\cdot\|_{\infty}$ denotes the infinity norm, and $\boldsymbol{\gamma}$ denotes a vector of $2\varepsilon_{i,j}$ for $i \neq j$ since $\boldsymbol{\varepsilon}(\mathbf{x}) = [\varepsilon_{i,j}]$ is a symmetric matrix. The term evaluates to 0 for rigid, scale, and similarity transformations (i.e., any combination of a rigid transformation and a uniform scale). To reiterate, $\mathcal{S}$ and $\mathcal{D}$ are both 0 only when the transformation is a rigid-body motion.

Visualization of Grid Images and Planning Trajectories: The degree to which rigidity was maintained within vertebrae following deformable registration was also qualitatively assessed through visualization of grid images and linear trajectories. Since a rigid transformation preserves distances between points and spatial orientation (i.e., does not include reflection), a deformation that preserves shape and volume of square grids and linear trajectories is associated with rigid motion.

3.1.2 Target Registration Error—The geometric accuracy of the registration methods was evaluated in terms of target registration error (TRE), as the distance between each corresponding target point in I_0 and I_1 after registration:

$$TRE = \|\mathbf{x}_1^{target} - \mathbf{x}_0^{target}\| \quad (16)$$

where x_1^{target} is a target point in I_1 , x_0^{target} is a target point in I_0 after registration, and $\|\cdot\|$ denotes the Euclidean norm.

3.2. Experiment #1: Optimization of Demons parameters

The nominal values of the Demons deformation-field smoothing parameters (σ_D and σ_U) were identified by optimizing dilatation (optimal $\mathcal{D} = 0$), maximum shear angle (optimal $\mathcal{S} = 0$), and TRE using the balloon phantom illustrated in figure 2(a). The phantom consisted of twenty-six 9.5 mm diameter Delrin spheres attached to an air-filled balloon (approximate diameter ~ 10 cm), and submerged in water to simulate piecewise-rigid motions in an otherwise highly deformable context. The balloon phantom was selected in this experiment since it provided non-uniform rigid motion of the individual spheres and facilitated unambiguous analysis of rigidity maintained in each sphere after deformation of the balloon. The phantom was first imaged with the balloon partially deflated for I_0 , followed by I_1 with the balloon inflated. A CBCT imaging bench in the geometry of a surgical C-arm was used (100 kVp, 360 mAs), and example images are shown in figure 2(a). Reconstruction was performed at a voxel size of 0.4^3 mm^3 for I_0 and I_1 of size $(300 \times 300 \times 300)$ voxels. The overall motion between I_0 and I_1 due to inflation of the balloon was 6.3 ± 2.5 mm (maximum deformation of 13.5 mm) following rigid registration. The centroids of the 26 Delrin spheres were used as the target points for TRE measurement. The optimization was performed by varying σ_D and σ_U , while MSL was fixed at 0.5 voxels to constrain irregularity of deformation from image noise. The range of filter widths investigated was $\sigma_D = 0-2$ voxels (in increments of 0.1 voxels) and $\sigma_U = 0-8$ voxels (in increments of 0.5 voxels). The morphological pyramid used in the analysis was constructed with downsampling factors of [4,2,1] voxels. The parameter values jointly minimizing $\mathcal{D}$, $\mathcal{S}$, and TRE were used in subsequent experiments. We also performed an evaluation of Demons registration accuracy in comparison to uFFD, where the latter used the B-spline lattice with $n_0=7$ points to capture non-uniform movement of each rigid sphere.

3.3. Experiment #2 : Investigation of FFD Constraints

The influence of each rigidity constraint (OC, AC, and PC) was investigated by evaluating the performance of FFD registration using the variants FFD+OC, FFD+AC, FFD+PC, and each possible combination. The studies involved a 2D simulation facilitating analysis in a large number of studies and computations. Figure 2(b) shows the I_0 and I_1 images (each 1500×1500 pixels, 0.25 mm pixel size) comprising 5 rigid bodies (simulated vertebrae), each with a hypodense target (tumor), and adjacent fasciae of simulated muscle, fat, and blood. A predefined rigid transformation for each vertebra in I_1 was interpolated to generate the scoliotic curvature in I_0 with the deformation extent of 24.0 ± 12.0 mm (maximum deformation of 42.8 mm) while preserving rigidity of the vertebrae (Moreno et al., 2008). Simulated correlated noise $G_\sigma * \mathcal{N}$ was added to each image, where G_σ is a Gaussian filter of width 2 pixels and $\mathcal{N}$ is a Gaussian white noise with zero mean and standard deviation of 200 HU (the highest differences in intensities of soft-tissues). Although not a completely accurate simulation of CBCT image quality and noise, the simulations were nonetheless considered fair approximations to CBCT of the spine. As depicted in figure 2(b), 25 target points were defined at the corners of the simulated vertebrae and the centroids of the target

tumors for TRE measurement. Figure 2(b) also depicts the linear planning trajectories defined in I_0 . A five-level hierarchical image pyramid with downsampling factors of [32, 16, 8, 4, 2] pixels was used for the large deformation.

3.4. Experiment #3 : Sensitivity Analysis of FFD Parameters

The sensitivity of FFD registration performance to the intrinsic parameters was investigated in terms of $\mathcal{D}$, $\mathcal{S}$, and TRE using an ovine spine phantom (vertebrae within surrounding natural soft tissue, diameter ~14 cm, depicted in figure 2(c)). The ovine spine was positioned in a CBCT-compatible frame and imaged first in a preoperative setup with scoliotic curvature for I_0 , followed by an intraoperative I_1 image with the spine straightened to natural posture. The CBCT imaging bench in the geometry of a surgical C-arm was used as in Experiment #1 (100 kVp, 360 mAs). Reconstruction was performed at a voxel size of 0.6^3 mm³ for I_0 and I_1 of size (256×256×256) voxels. The extent of deformation between I_0 and I_1 was 20.9 ± 4.7 mm (maximum deformation of 32.3 mm). Figure 2(c) shows 40 target points manually identified from unambiguous anatomical features of the ovine spine (spinous and transverse process). The sensitivity of FFD registration was analyzed as a function of the number of control points at the registration level $\ell=0$ (n_0) and the regularization parameter λ_O . (Only the orthogonality constraint was included, since – as detailed below – Experiment #2 showed OC to be the sufficient constraint, with little or no benefit from addition of AC and/or PC.) The operating range and the nominal value of n_0 were investigated by varying n_0 over the range of 2–11 points using uFFD, and those for λ_O were identified by varying λ_O by factors of 2× over the range $\lambda_O = 0.0$ to 3276.8 using FFD +OC and FFD+OC+IC. A three-level hierarchical image pyramid with downsampling factors of [8,4,2] voxels was used in each case. The value of n_0 and λ_O identified in this experiment provided the nominal value in other experiments. In addition, the sensitivity of registration performance to image noise was analyzed as detailed in the appendix.

3.5. Experiment #4: Validation of Constrained FFD (Cadaver Neck Flexion)

FFD registration incorporating the rigidity constraints and parameters identified in experiments above was validated in a cadaver study simulating neck flexion (applicable to image-guided surgery of the cervical spine as well as radiotherapy of the head and neck). Performance of the constrained FFD method was compared to uFFD and Demons. Three image guidance scenarios were investigated: (i) CT-to-CT registration (i.e., preoperative CT and intraoperative CT); (ii) CBCT-to-CBCT registration (i.e., successive intraoperative CBCT scans); and (iii) CT-to-CBCT (i.e., preoperative CT and intraoperative CBCT, including differences in image intensity, artifacts, etc.). Unambiguous target points were identified manually for TRE measurement from prominent features on the skull and the cervical spine (e.g., spinous and transverse process, and anterior and posterior tubercle). As depicted in figure 2(d), transpedicle planning trajectories were defined in I_0 for qualitative visualization of the extent to which rigidity was preserved within the vertebral bodies.

3.5.1 CT-to-CT Registration—The cadaveric head was positioned in a CT-compatible frame, and a preoperative CT (I_0) was acquired with the neck in a natural pose, followed by intraoperative CT (I_1) with neck flexion (cervical lordosis). Each CT scan was acquired with a standard head protocol [Somatom Definition Flash, Siemens, Erlangen, Germany] (120

kVp, 220 mAs). Reconstruction was performed at a voxel size of 0.5^3 mm^3 for I_0 and I_1 of size ($512 \times 512 \times 473$) voxels. The extent of deformation was $12.6 \pm 6.5 \text{ mm}$ (maximum deformation 26.2 mm). Figure 2(d) shows the 29 target points defined in I_0 and I_1 . Morphological pyramids were constructed with downsampling factors [16, 8, 4, 2] voxels for more stable convergence under large deformation. The B-spline lattice used $n_0=5$ points for the large field-of-view.

3.5.2 CBCT-to-CBCT Registration—As in figure 2(d), preoperative CBCT (I_0) and intraoperative CBCT (I_1) were acquired with the neck in the natural pose and flexed simulating the surgical setup using a prototype mobile C-arm (100 kVp, 410 mAs) (Siewerdsen et al., 2005, Siewerdsen, 2011). Reconstruction was performed at a voxel size of 0.6^3 mm^3 for I_0 and I_1 of size ($256 \times 256 \times 256$) voxels. The deformation extent was $11.6 \pm 6.6 \text{ mm}$ with maximum deformation of 29.9 mm. Twenty-six target points were defined in I_0 and I_1 . Image pyramids involved downsampling of [8, 4, 2, 1] voxels.

3.5.3 CT-to-CBCT Registration—The preoperative CT I_0 and the intraoperative CBCT I_1 were acquired as described above. The deformation extent between I_0 and I_1 was $12.0 \pm 6.1 \text{ mm}$ (maximum deformation 38.3 mm). Registration was performed in the region of mutual support (i.e., that shared by both I_0 and I_1). Since registration using Demons required pre-processing of the images and/or an alternative Demons with intensity matching (Nithiananthan et al., 2011), Demons was not included in Experiment #4(c), since the topic of image intensity mismatch is outside the scope of the current work. Thirty-two target points were identified in I_0 and I_1 . The hierarchical image pyramid involved downsampling of [8, 4, 2, 1] voxels.

4. RESULTS

4.1. Experiment#1: Optimization of Demons Parameters

Figure 3 summarizes the results of Experiment #1 in optimizing the Demons parameters by minimizing the mean absolute values of dilatation ($|\overline{\mathcal{D}}|$), shear ($\overline{\mathcal{S}}$), and TRE ($\overline{TRE}$). The fluid and elastic models (σ_D and σ_U equal to zero, respectively) were unable to both preserve rigidity and achieve accurate registration, although the fluid model demonstrated better ability to resolve deformation than the elastic model. Smoothing the update field guarantees smoothness of the displacement field but does not impose direct constraints on the magnitude of the displacements. The fluid model therefore offers capability to resolve large deformation but has a tendency to distort rigid objects. On the other hand, smoothing the displacement field does limit the magnitude of displacements, and the larger the kernel, the smoother and more coherent motions are achieved (but the less able to resolve large deformation). Figure 3 demonstrates the ranges of viscoelastic models that were capable of optimizing (minimizing) $|\overline{\mathcal{D}}|$, $\overline{\mathcal{S}}$, and $\overline{TRE}$. The viscoelastic models with small values of σ_D and σ_U were capable of capturing local spatial differences but were susceptible to image noise and irregularity of the deformation; therefore, they resulted in increased distortion and TRE. Alternatively, large values of σ_D and σ_U improved the ability to preserve rigidity but decreased the capability of resolving deformation. The operating ranges were, therefore,

$\sigma_D=0.6\text{--}0.8$ voxels and $\sigma_U=2\text{--}3$ voxels, with a nominal value of $\sigma_D=0.6$ voxel and $\sigma_U=2.7$ voxels computed as the value that jointly minimized $|\mathcal{D}|$, $\mathcal{S}$, and TRE .

The Demons method using the nominal values of σ_U and σ_D demonstrated better ability to preserve rigidity and compute accurate motion of the spheres than uFFD. In particular, Demons and uFFD achieved $|\mathcal{D}|$ of 0.12 ± 0.13 and 0.46 ± 0.63 , $\mathcal{S}$ of 0.16 ± 0.13 and 0.42 ± 0.34 , and TRE of 0.2 ± 0.1 and $0.6\pm0.5\text{mm}$, respectively. The Demons method yielded mean $\mathcal{D} < 0$ since regularization introduced expansion of the balloon to the motion of the spheres. On the other hand, the uFFD method yielded mean $\mathcal{D} > 0$ due to shrinking and tearing of the spheres, especially ones that were not successfully mapped to their corresponding locations in I_1 . Demons achieved improved TRE compared to uFFD (p-value = 0.0002) due to use of a dense displacement field and the characteristics of the phantom (i.e, the smooth round shape and high contrast).

4.2. Experiment #2: Investigation of FFD Constraints

Figure 4 summarizes results from the investigation of FFD constraints. Figures 4(a–c) illustrate $\mathcal{D}$, $\mathcal{S}$, and TRE using box-and-whisker plots, where measurements beyond $1.5\times$ the interquartile range were defined as outliers and omitted in these and subsequent plots of $\mathcal{D}$ and $\mathcal{S}$ to facilitate interpretation. As illustrated by the values and ranges of $\mathcal{D}$ and $\mathcal{S}$ in figures 4(a,b), Demons, uFFD and FFD+IC allowed large changes in volume and shape of the vertebrae. Use of AC and PC in FFD were similarly incapable of maintaining rigidity of the spine, demonstrating that AC and PC were neither sufficient nor necessary conditions to enforce local rigid mapping. On the other hand, OC exhibited the ability to preserve rigidity through minimization of $|\mathcal{D}|$ and $\mathcal{S}$. Since OC was capable of preserving rigidity of the vertebrae, its combinations were likewise capable of preserving rigidity. Figure 4(c) summarizes the TRE results, where the triangles denote the 95% confidence interval of the median for comparison of statistical significance in the differences observed between each method. All registration methods improved TRE after rigid registration (22.1 ± 8.5 mm), of course, with a median TRE < 1.5 mm. The large deformation and image noise posed challenges to all of the methods, especially Demons as illustrated by the TRE ranges and outliers. Figure 4(d) illustrates the ability of each method to maintain rigidity qualitatively through grid images within the region of one vertebrae and the integrity of linear planning trajectories therein. Unrealistic motions internal to rigid bodies were observed for Demons, uFFD, and FFD+IC. As illustrated by the grid images, AC penalizes local transformations unless affine, thus allowing local scale and shear. On the other hand, PC penalizes scaling but allows shear. However, OC was capable of maintaining the square grid images and linear trajectories. The ability of OC to preserve rigidity of the vertebrae was due to well-defined and high-contrast cortical bone in reliably driving registration (c.f., homogenous soft-tissue), as well as application of the penalty on fine sampling of voxels in bones. Other applications as in (Staring et al., 2007b) (e.g., analysis of disease progression or therapy response, and registration of contrast enhanced images) may benefit from the addition of AC and PC; similarly, other FFD implementations that constrain rigidity via penalties computed on control grid points such as the open-source elastix library (Staring et al., 2007b) may benefit from additional constraints. Since the studies reported here showed OC to provide a necessary and sufficient condition that enforced rigidity of the vertebrae, and the

introduction of additional penalties increased computational time and complexity in adjusting the regularization parameters, OC was selected as a sufficient rigidity constraint.

4.3. Experiment #3: Sensitivity Analysis of FFD Parameters

Results of the sensitivity analysis of parameters in FFD registration are summarized in figure 5. Figures 5(a–c) demonstrate the sensitivity of uFFD to n_0 in terms of $\mathcal{D}$, $\mathcal{S}$, and TRE. As illustrated by the values and ranges of $\mathcal{D}$ and $\mathcal{S}$, a large value of n_0 degraded the ability to preserve rigidity of the vertebrae due to increased incoherence of the deformation and susceptibility to image noise. Folding and tearing of the vertebrae was observed for n_0 5 points, resulting in $\mathcal{D} > 0$. Figure 5(c) shows the increase in TRE for larger values of n_0 due to irregularity of the deformation. Additionally, the computational cost increased with n_0 . A smaller number of control points was therefore identified to resolve the smooth deformation of the spine and to minimize $|\mathcal{D}|$, $\mathcal{S}$, and TRE, with a nominal $n_0 = 3$ points for CBCT registration (with image size $\sim 256^3$ voxels and field-of-view of $\sim 15^3$ cm³). (Still lower values – i.e., $n_0 = 2$ points – likely reduce the ability to resolve complex deformation (such as neck flexion and scoliosis with multiple curvatures)). The uFFD method with the nominal $n_0 = 3$ achieved $|\mathcal{D}| = 0.15 \pm 0.22$, $\mathcal{S} = 0.20 \pm 0.19$, and $\text{TRE} = 0.9 \pm 0.4$ mm.

The sensitivity of FFD+OC+IC to the orthogonality regularization strength (λ_O) is summarized in figures 5(d–f). The decrease in $|\mathcal{D}|$ and $\mathcal{S}$ shown in figures 5(d,e) for large values of λ_O demonstrates the ability of strong OC regularization to preserve rigidity; however, as shown in figures 5(f), TRE degrades for such strong regularization as the strength of the image matching driven by MI is superseded by the strength of the orthogonality constraint. The sensitivity of FFD+OC to λ_O was similar to that of FFD+OC+IC and is therefore not shown for reasons of brevity. Since a larger value of λ_O reduced the ability to resolve deformation, a nominal $\lambda_O = 1$ was identified as capable of preserving rigidity while achieving accurate registration (low TRE). Compared to uFFD, the FFD+OC+IC method using the nominal n_0 and λ_O improved $|\mathcal{D}| = 0.03 \pm 0.03$, $\mathcal{S} = 0.05 \pm 0.03$, and $\text{TRE} = 0.8 \pm 0.4$ mm.

4.4. Experiment #4: Validation of Constrained FFD (Cadaver Neck Flexion)

4.4.1 CT-to-CT Registration—Figure 6 summarizes results from the CT-to-CT registration scenario in the cadaver studies. Figures 6(a–c) illustrate the registration performance, where the value beside each box-and-whisker plot indicates the mean and standard deviation of $|\mathcal{D}|$, $\mathcal{S}$, and TRE. Demons exhibited a smaller range of $\mathcal{D}$ and $\mathcal{S}$ than uFFD and FFD+IC, demonstrating better ability to preserve volume and shape of the vertebrae. However, the FFD+OC method resulted in the most uniform and near optimal performance in $\mathcal{D}$ and $\mathcal{S}$, showing the ability to constrain deformation in rigid bodies within a surrounding deformable context. As illustrated in figure 6(c), all of the methods were capable of resolving the neck flexion and improving TRE beyond that of rigid registration (for which $\text{TRE} = 9.5 \pm 4.8$ mm), achieving median $\text{TRE} < 1.5$ mm in each case. Figure 6(d) demonstrates the assessment of rigidity qualitatively, where Demons, uFFD, and FFD+IC are seen to introduce distortion to the grid and planning trajectories, but incorporation of OC in the FFD methods improved the ability to maintain the square grid and the linear trajectories.

4.4.2 CBCT-to-CBCT Registration—The results of CBCT-to-CBCT registration in the cadaver studies are summarized in figure 7. The Demons, uFFD, and FFD+IC methods were unable to preserve rigidity of the vertebrae, resulting in the wide ranges of $\mathcal{D}$ and $\mathcal{S}$ in figures 7(a,b). However, imposing the rigidity constraint using FFD+OC and FFD+OC+IC successfully minimized scale and shear, improving $\mathcal{D}$ and $\mathcal{S}$ respectively. Figure 7(c) illustrates the capability of all the registration methods to resolve deformation associated with neck flexion. The TRE was improved from 7.5 ± 2.5 mm after rigid registration to a median TRE < 1.5 mm. The fairly-poor performance of Demons compared to the CT case was due to increased image noise and shading artifacts in the CBCT images. On the other hand, the improvement in TRE of the FFD-based methods was due to registration at the full-resolution level (images without downsampling). Figure 7(d) shows the distortion of the grid and trajectories introduced by all registration methods, except FFD+OC and FFD+OC+IC. Folding of soft-tissue was observed in the grid images of uFFD and FFD+IC. Spurious folding in FFD+IC could occur if the displacements violate local injectivity (Choi and Lee, 2000). For example, without loss of generality, consider the unit-space lattice with $i, j, k = \{0, 1, 2, 3\}$ denoting the indices of the control points in the support region of the cubic B-spline. The B-spline is not locally injective provided that $\mu_{x,i,j,k} = \mu_{y,i,j,k} = \mu_{z,i,j,k} = 1/K_{3D}$ if $i+j+k = 3$ and $\mu_{x,i,j} = \mu_{y,i,j} = \mu_{z,i,j,k} = -1/K_{2D}$ if $i+j+k > 3$. However, IC still provided a tight bound on the displacements and reduced folding of soft-tissue. Application of OC enforced coherence in the motions of the vertebrae and simultaneously improved smoothness of the deformation.

4.4.3 CT-to-CBCT Registration—Figure 8 summarizes the results of CT-to-CBCT registration in the cadaver studies. As illustrated in figures 8(a,b), the uFFD and FFD+IC methods exhibited heterogeneity in $\mathcal{D}$ and $\mathcal{S}$, thus distorting the vertebrae. Incorporation of OC, however, improved the ability to preserve rigidity, achieving small ranges and near optimal values of $\mathcal{D}$ and $\mathcal{S}$. Figure 8(c) shows that all of the registration methods were capable of accurate registration, giving median TRE < 1.5 mm (compared to rigid registration TRE = 6.8 ± 2.5 mm). The grid images and planning trajectories depicted in figure 8(d) illustrate the ability of OC to maintain rigidity of the vertebrae. Folding in soft-tissue was observed in the grid image of all the methods except FFD+OC+IC, due to the increased challenge introduced by differences in image characteristics of CT and CBCT (i.e., smoother and more uniform for CT versus sharper and noisier for CBCT with a higher degree of shading artifacts). Figure 8(d) also illustrates that all of the registration methods except FFD+OC+IC caused tearing and folding of the occipital bone and distortion of the spinous process due to artifacts in CBCT. The combination of OC and IC was, therefore, capable of preserving rigidity, computing accurate registration, and achieving smooth deformation.

5. DISCUSSION AND CONCLUSION

A deformable registration framework accounting for the rigid nature of bones was developed using free-form deformation for CBCT-guided spinal interventions. The method (in particular, the FFD method incorporating OC and IC) was shown to outperform Demons and uFFD in preservation of rigid morphology and registration accuracy. Investigation of

various FFD constraints suggested that OC was a sufficient and necessary condition to enforce rigidity. The sensitivity analysis showed that the nominal number of control points ($n_0 = 3$ points) was capable of minimizing deformation in the spine while computing accurate deformation under conditions of fairly strong spine curvature (viz., scoliosis). Additionally, the analysis of λ_O demonstrated that over-regularization of orthogonality (setting λ_O orders of magnitude too high) prevented image matching and worsened geometric accuracy, while small values of λ_O failed to inhibit deformation of the vertebrae. Since deformation of tissues about the spine was typically smooth and coherent, the nominal settings selected in the ovine spine experiment were considered applicable (and subsequently validated) in registration of preoperative CT/CBCT and intraoperative CBCT images of the human cervical spine. The performance of the constrained method was validated in cadaver studies simulating neck flexion, demonstrating improved preservation of rigid vertebrae with mean $|D| = 0.05$ and mean $\mathcal{S} = 0.06$, reasonably accurate registration (mean TRE = 1.0 to 1.4 mm), and preservation of topology (lack of tissue folding). The method could therefore overcome the distortions of rigid body morphology that are intrinsic to unconstrained deformable registration.

Rigidity constraints similar to those used in this work have been previously applied in other frameworks such as the publicly available elastix library (Staring et al., 2007b) and the Flexible Image Registration Toolbox (FLIRT); however, FLIRT with rigidity constraints was implemented and evaluated in 2D since the required discretization of the regularizer and derivatives can be computationally expensive for large volumes (Modersitzki, 2008). While our method was also computationally expensive due to the cubic B-spline computation, the computational cost was primarily associated with the large number of control points at the full-resolution level of the volume (and not with the rigidity constraints). For example, CT-to-CBCT image registration in the cadaver study using the FFD+OC+IC method with a 4-level pyramid required 2.7 hours on a basic PC workstation (Fujitsu Celsius M270 Power, Intel Xeon E5-1620 3.60 GHz, 48 GB RAM) and yielded TRE = 1.2 ± 0.8 mm. Nevertheless, the methods for constrained FFD actually converged faster than the uFFD method and therefore required a comparable computational time (which required 2.9 hours and provided TRE = 2.1 ± 2.5 mm). The constrained FFD therefore offered not only superior registration performance and preservation of rigid bodies but also faster convergence properties. The runtime could be reduced using a 3-level pyramid (reducing run-time to 10.2 min while providing TRE = 1.6 ± 0.8 mm) or by relaxing the convergence criterion (i.e., advancing the pyramid when the change in cost function is less than a user-defined factor of machine precision). Such tradeoffs between computation time and registration accuracy are enabled by different convergence criteria and pyramid resolution schemes, which is the subject of ongoing work. Additionally, distributed and/or parallel computing could be applied in optimizing all control points concurrently to reduce computational time and improve applicability of the method (Ino et al., 2005, Modat et al., 2010).

Alternative methods for estimating rigid motion in a deformable context include a point interpolation weighted by a distance function of rigid structures (Little et al., 1996, Moreno et al., 2008) and articulated models of the spines (du Bois d'Aische et al., 2007, Harmouche et al., 2012). However, the methods require accurate definition of landmark feature points or

rigid structures in both the fixed and moving images, which could be difficult to achieve in clinical workflow. While our method avoids such user-defined input, the rigidity constraints were applied by defining tissue stiffness according to a simple thresholding of preoperative CT and/or CBCT images. The sensitivity of tissue stiffness to image intensities and noise could be reduced by utilizing more advanced techniques such as segmentation based on the contour completion method (Hu and Haynor, 2004), articulated shape models (Klinder et al., 2008), and graph cuts (Aslan et al., 2009). The use of MI enabled CT to CBCT registration without degradation due to image intensity mismatch, and the applicability of our method to registration of MR and CBCT images is the subject of future work. In addition, the use of alternate multimodal image similarity metrics that have fixed bounds, such as normalized MI, could potentially reduce complexity associated with the selection of regularization strength. We also showed that the method improved smoothness of the deformation field and preservation of topology through the use of IC; however, folding in soft-tissue could occur if the displacement violated the injectivity condition. Alternative approaches, such as consistent registration (Christensen and Johnson, 2001, Modat et al., 2012), local invertibility constraints (Se Young and Fessler, 2009), or diffeomorphic constraints (Rueckert et al., 2006), could be used to ensure smooth and invertible deformations, while alternative rigidity constraints such as strain (which evaluates to 0 for rigid transformations) could be considered (Keeling, 2006). Nevertheless, the relatively simple inclusion of IC and OC constraints performed well in the experiments reported above and provided a free-form deformation method capable of maintaining rigid bony structures and resolving soft-tissue deformation. The promising results motivate the implementation of such methods in a more parallelized computation framework for improved run-time (< 10 min) and translation to clinical feasibility studies in image-guided spine surgery.

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Appendix: Sensitivity to Threshold Selection and Image Noise

The sensitivity of the registration method to threshold selection (definition of the tissue stiffness map) and image noise (quality of the CBCT image) was investigated in terms of $\mathcal{D}$, $\mathcal{S}$, TRE, and normalized cross correlation (NCC). NCC was selected as an additional metric of registration accuracy, since it is distinct from the similarity metric in the registration algorithms. With nominal parameter settings shown in table 1, the sensitivity was analyzed for the main scenario of interest (CT-to-CBCT registration) using FFD+OC+IC, since it was the method of primary interest in best preserving rigidity and topology of the spine.

A.1 Sensitivity to Threshold Selection

The sensitivity to threshold selection (definition of tissue stiffness) was analyzed using preoperative CT and intraoperative CBCT images of the cadaver head similar to the image pair described in section 3.5.3. Definition of the stiffness mask was varied by adjusting the threshold value over the range 20 – 600 HU (increments of 20 HU). Each stiffness mask was refined in the same manner using the morphological operations of automatic hole filling (with a 3-voxel radius structural element) and shape-opening (to reduce segmentation noise). The 32 target points described in section 3.5.3 were used for TRE measurement. $\mathcal{D}$ and $\mathcal{S}$ were computed in bony structures defined through a bone segmentation derived from a nominal intensity threshold of 200 HU. NCC was computed using a sliding window of $9 \times 9 \times 9$ voxels over the entire image volume (excluding air). Similar to section 3.4, image pyramids were constructed with downsampling factors of [8, 4, 2] voxels.

The sensitivity of registration to threshold value is summarized in figure A.1, where the median is marked by circles, and error bars represent the 95% confident interval. Overall, the method is fairly robust over a broad range in threshold selection – for example, less than 10% variation in $\mathcal{S}$, $\mathcal{D}$, TRE, and NCC over the range 80 – 500 HU. The trends in $\mathcal{D}$ were similar to $\mathcal{S}$ and therefore not shown for reasons of brevity. A very low value of intensity threshold ($< \sim 50$ HU) yielded obviously erroneous definition of bulk soft tissue as bones, in turn applying OC in soft-tissue regions and degrading overall registration performance. This is evident as increased shear and TRE (and reduced NCC) at very low threshold values. In such cases and using the nominal value of λ_O , the magnitude of the MI term (equation 9) was an order of magnitude higher than the OC term, therefore driving the registration along directions dominated by MI and creating unrealistic shear especially at boundaries of the vertebrae. On the other hand, a very large intensity threshold ($> \sim 500$ HU) eroded bone structures (especially in subchondral trabeculae) but only slightly degraded performance. This owes primarily to the support of cubic B-splines with a dense application of the penalty (50% samples of bone voxels) and sparse control points ($n_0 = 3$ points). Overall, the method was robust across the range associated with the nominal HU of bone, with a nominal value of 200 HU selected for studies reported in section 3.

A.2 Sensitivity to Image Noise

The sensitivity of the registration method and nominal parameter settings to image noise was investigated using the studies in experiment #2 (section 3.3). Typical noise magnitude in CT is less than ~ 10 HU (e.g., noise magnitude of the CT images in experiment #4 was 6 HU), recognizing that noise also varies throughout the image according to dose, mA modulation, and the size and composition of the object. The nominal noise level in experiment #2 was conservatively chosen to be 30 HU to challenge the registration process. CBCT images, on the other hand, can exhibit a wide range of noise levels depending on the system design and acquisition / reconstruction protocols – for example, typical noise magnitude of 35 HU in the CBCT images in experiment #4. We therefore investigated the sensitivity of registration performance to image noise by adjusting the noise magnitude in the fixed image in experiment #2 (simulated CBCT) over the range $\sim 1 - 130$ HU. Other parameters, such as target points for TRE measurement and morphological image pyramids, were identical to

experiment #2. NCC was used to evaluate registration accuracy via a metric that was distinct from similarity metric in the registration technique and to provide a richer description of registration performance in areas of soft tissue. For fair and consistent comparison, NCC was computed between the noiseless fixed image and the noiseless moving image after deformation estimated from the noisy images.

The sensitivity analysis is summarized in figure A.2. Overall, registration was fairly robust up to noise levels of ~50–100 HU. $\mathcal{S}$ is insensitive to image noise, even when the registration has failed due to extremely high noise (>100 HU), since the moving image has simply not moved. Similar results were observed for $\mathcal{D}$ and not shown for brevity. The TRE in figure A.2(b) better demonstrates the extent to which the method is insensitive to image noise up to a magnitude of ~100 HU in the fixed image, beyond which TRE increases dramatically. (Note that this factor of ~3 increase in noise corresponds to a reduction in dose by a factor of ~9.) However, as illustrated by the NCC in figure A.2(c), matching of soft-tissue gradually degrades at lower levels of image noise (i.e., noise magnitude of ~40 HU), showing that registration of soft-tissue was more sensitive to noise due to the lack of features to reliably drive registration. Image denoising (Junmei et al., 2004, Buades et al., 2005, Xia et al., 2008) and/or advanced image reconstruction techniques (La Riviere and Billmire, 2005, Stayman et al., 2012, Stayman et al., 2014) could potentially improve registration accuracy, especially in soft-tissue regions.

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Figure 1. Potential clinical workflow for CBCT-guided spine surgery. (I) Preoperative 3D imaging (CT). (II) Surgical planning – e.g., definition of targets, trajectories, and/or normal tissues. (III) Patient setup and intraoperative CBCT. (IV) Deformable registration of preoperative CT (I_0) to intraoperative CBCT (I_1). (V) Surgical navigation within the geometrically resolved view of preoperative CT and planning data registered to intraoperative CBCT.

Figure 2.

Phantom and cadaver experiments. (a) Experiment #1: the CBCT moving image I_0 and fixed image I_1 of the balloon phantom with 26 rigid spheres on the surface of the balloon. (b) Experiment #2: the simulated moving image I_0 with linear planning trajectories and the fixed image I_1 , each with 25 target points. (c) Experiment #3: the CBCT moving image I_0 with planning trajectories and CBCT fixed image I_1 of an ovine spine, each with 40 anatomical target points. (d) Experiment #4: CT and CBCT images of a cadaver, including preoperative image I_0 with planning trajectories and intraoperative I_1 , each with identified anatomical target points.

Figure 3.

Experiment #1: optimization of the Demons motion-field smoothing parameters, σ_U and σ_D . (a–c) Mean $|\mathcal{D}|$, $\mathcal{S}$, and TRE measured as a function of σ_U and σ_D . Demons with $\sigma_U=2.7$ and $\sigma_D=0.6$ (each with units of voxels; 1 voxel = 0.6 mm) best preserved rigidity while achieving accurate registration (TRE < 0.3 mm). The point (0.6, 2.7) marks the nominal (optimal) parameter settings in studies below, representing the multivariate minimum in $|\mathcal{D}|$, $\mathcal{S}$, and $\overline{TRE}$. (d) Semi-transparent surface rendering of a (pink) moving sphere and its centroid with the (cyan) centroid of the corresponding fixed sphere. Note the nonrigid distortion of the sphere for parameters far from the optimal smoothing parameters.

Figure 4.

Experiment #2: investigation of constrained FFD. (a-c) $\mathcal{D}$, $\mathcal{S}$, and TRE measured as a function of the registration methods. (d) Grid images and straight-line planning trajectories relative to the moving image after registration. The OC and its various combinations improved performance in terms of $\mathcal{D}$ and $\mathcal{S}$ (both ideally 0) as well as the ability to preserve the grid and linear trajectories, while achieving low TRE. The results suggest FFD+OC as the nominal constrained registration method, with little or no benefit gained from additional AC and/or PC constraints.

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Figure 6.

Experiment #4: CT-to-CT registration. (a–c) $\mathcal{D}$, $\mathcal{S}$, and TRE measured for each of the registration methods. (d) Grid images and planning trajectories relative to the (cyan) I_1 after registration. Note the distorted linear needle trajectory in the uFFD and FFD+IC methods. Incorporation of OC with FFD demonstrated improved ability to preserve rigidity. All of the methods achieved accurate registration with median TRE < 1.5 mm, but the FFD+OC and FFD+OC+IC methods provided accurate registration and maintained rigid morphology within bony anatomy.

Figure 7.

Experiment #4: CBCT-to-CBCT registration. (a–c) $\mathcal{D}$, $\mathcal{S}$, and TRE measured for each of the registration methods. (d) Grid images and planning trajectories relative to the cyan I_1 after deformable registration. Note again the warping of linear needle trajectories for the Demons, uFFD, and FFD+IC methods. Incorporation of OC with FFD improved preservation of rigidity. All methods were capable of resolving deformation, achieving median TRE < 1.5 mm, but FFD+OC and FFD+OC+IC provided accurate registration and preservation of rigid bone morphology. They were also more robust to image noise than the Demons method.

Figure 8.

Experiment 4: CT-to-CBCT registration. (a–c) $\mathcal{D}$, $\mathcal{S}$ and TRE measured for each of the registration methods. (The Demons method was excluded from this experiment due to intensity mismatch between CT and CBCT, which is beyond the scope of the current work.) (d) Grid images, planning trajectories relative to the (cyan) I_1 , and semi-opaque overlays of I_0 and cyan I_1 after deformable registration. Arrows mark tearing and folding of the occipital bone and distortion of the spinous process. The combination of OC and IC in FFD preserved rigidity and topology of bones, preventing such tearing and folding.

Figure A.1.

Sensitivity of registration performance to selection of intensity threshold. (a–c) $\mathcal{S}$, TRE, and NCC measured as a function of threshold value. Blue arrows mark the nominal threshold value selected in section 3.

Figure A.2.

Sensitivity of the registration method to image noise. (a–c) S , TRE, and NCC measured as a function of noise in the fixed image (simulated CBCT). Blue arrows mark the noise magnitude used in section 3.3. The method was fairly robust against image noise over a fairly broad range, showing a high degree of robustness in TRE (bone features) and gradual degradation in NCC above ~40 HU.

Table 1

Summary of registration methods along with parameters and nominal values.

Methods	Parameters	Nominal Values
Demons	$(\sigma_D, \sigma_U, \text{MSL})$	(0.6, 2.7, 0.5)
uFFD	n_0	3
FFD+IC	n_0	3
FFD+AC	(n_0, λ_A)	(3, 100)
FFD+PC	(n_0, λ_P)	(3, 10)
FFD+OC	(n_0, λ_O)	(3, 1)
FFD+OC+IC	(n_0, λ_O)	(3, 1)
FFD+OC+AC	$(n_0, \lambda_O, \lambda_A)$	(3, 1, 100)
FFD+OC+PC	$(n_0, \lambda_O, \lambda_P)$	(3, 1, 10)
FFD+OC+AC+PC	$(n_0, \lambda_O, \lambda_A, \lambda_P)$	(3, 1, 10, 100)