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Registration of MRI to Intraoperative Radiographs for Target Localization in Spinal Interventions

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Abstract

Purpose—Decision support to assist in target vertebra localization could provide a useful aid to safe and effective spine surgery. Previous solutions have shown 3D-2D registration of preoperative CT to intraoperative radiographs to reliably annotate vertebral labels for assistance during level localization. We present an algorithm (referred to as MR-LevelCheck) to perform 3D-2D registration based on a preoperative MRI to accommodate the increasingly common clinical scenario in which MRI is used instead of CT for preoperative planning.

Methods—Straightforward adaptation of gradient/intensity-based methods appropriate to CT-to-radiograph registration is confounded by large mismatch and noncorrespondence in image intensity between MRI and radiographs. The proposed method overcomes such challenges with a simple vertebrae segmentation step using vertebra centroids as seed points (automatically defined within existing workflow). Forwards projections are computed using segmented MRI and registered to radiographs via gradient orientation (GO) similarity and the CMA-ES (Covariance-Matrix-Adaptation Evolutionary-Strategy) optimizer. The method was tested in an IRB-approved study involving 10 patients undergoing cervical, thoracic, or lumbar spine surgery following preoperative MRI.

Results—The method successfully registered each preoperative MRI to intraoperative radiographs and maintained desirable properties of robustness against image content mismatch and large capture range. Robust registration performance was achieved with projection distance error (PDE) (median $\pm$ iqr) = 4.3 ± 2.6 mm (median $\pm$ iqr) and 0% failure rate. Segmentation accuracy for the continuous max-flow method yielded Dice coefficient = 88.1 ± 5.2 , Accuracy = 90.6 ± 5.7 , RMSE = 1.8 ± 0.6 mm, and contour affinity ratio (CAR) = 0.82 ± 0.08 . Registration performance was found to be robust for segmentation methods exhibiting RMSE < 3 mm and CAR > 0.50.

Conclusion—The MR-LevelCheck method provides a potentially valuable extension to a previously developed decision support tool for spine surgery target localization by extending its utility to preoperative MRI while maintaining characteristics of accuracy and robustness.

A Introduction

Vertebra level localization using intraoperative imaging can be a challenging task in spine interventions and carries uncertainty in surgical decision-making. Decision support systems to facilitate accurate vertebra localization could provide clinical utility in improved confidence and savings in time, radiation dose, and resources in the operating room. Such solutions could even help prevent wrong-level errors that have been reported to occur in 1 in 3110 spine surgery procedures (Mody *et al* 2008). Previous solutions (Otake *et al* 2012, Lo *et al* 2015, De Silva *et al* 2016) achieved decision support for vertebra localization via 3D-2D registration of preoperative computed tomography (CT) images and intraoperative radiographs. Similar capability based on preoperative MRI would be very valuable, since MRI is increasingly important in the diagnosis and planning of spine pathology. MRI exhibits soft-tissue imaging characteristics that are well suited to diagnosis of spinal disease (including degenerative disease, deformity, infection, congenital conditions, trauma, and tumor) and planning of surgery. Compared to CT, MRI exhibits superior soft-tissue contrast resolution for delineation of discs, foramina, epidural fat, nerve roots, and cerebrospinal fluid (Abul-Kasim *et al* 2008, Green and Saifuddin 2004, Go ci ski *et al* 2001). As of 1999, MRI constituted ~75% of diagnostic 3D spinal imaging as reported in Maitino *et al* 2003 and, as a consequence, an increasingly large percentage of patients present to surgery with preoperative MRI. Spine interventions for pain management (Airaksinen *et al* 2006, Boswell *et al* 2007) are conducted with even higher frequency and could similarly benefit from a solution for automatic vertebra localization based on MRI to identify target vertebrae faster with less fluoroscopy time. Sagittal T2-weighted MRI is the most commonly acquired imaging protocol for preoperative diagnosis (providing clear visualization of the spinal canal and cerebrospinal fluid), and lateral radiographs are the common view for intraoperative localization (providing a view of individual levels without bringing the x-ray detector over the surgical field). Accurate alignment of vertebrae between MRI and radiography would provide decision support for level localization to a broader patient population who undergo spine interventions.

Previous work on the LevelCheck algorithm (Otake *et al* 2012, 2013, 2015, De Silva *et al* 2016) addressed several challenges to achieve fast, accurate CT-radiograph registration for vertebra localization. Such work included the basic gradient-based 3D-2D registration framework (Otake *et al* 2012) with parallel implementations for digitally reconstructed radiograph (DRR) generation and similarity metric computation as well as a robust multi-start search technique based on the covariance-matrix-adaptation–evolution-strategy (CMA-ES) optimizer to mitigate local optima in the search space (Otake *et al* 2013). The framework was extended to improve robustness in handling content mismatch between intraoperative radiographs and DRRs caused by strong gradient magnitudes in the presence of interventional instruments and implants via a gradient orientation (GO) based similarity metric (De Silva *et al* 2016). The method has been extended to accommodate spinal deformation occurring between the preoperative CT and intraoperative radiograph (Ketcha *et*

et al 2016a) and has been tested in pilot (Lo *et al* 2015) and larger scale (De Silva 2016) clinical studies.

Straightforward adaptation of the previous LevelCheck solution to MR-radiograph registration is challenged by the mismatch observed in multi-modality image intensities and tissue noncorrespondence. Cerebrospinal fluid, anterior/posterior longitudinal ligaments, and muscles surrounding the spinous processes are conspicuous in MRI but exhibit minimal contrast in radiographs, thus presenting a challenging level of mismatch for an image-intensity-based registration algorithm. To overcome such strong mismatch, Harmouche *et al* 2012 previously proposed a MR-radiograph registration solution using an articulated spine model for scoliotic patients. The registration relied upon accurate detection of vertebra landmark points in the images to be registered with the articulated model, and a model specific to scoliotic curvature could limit applicability to a broader spectrum of spine shape and/or pathology. Other registration methods have been developed (Tomazevic *et al* 2003, 2006) by matching 3D surface-normals with back projected 2D gradients and using robust similarity metrics; however, the performance of these methods was compromised when strong content mismatch was observed between MR and radiograph images, and multiple radiographic views (as many as nine) per registration were required for robust registration. Alternatively, methods have been proposed that simulate pseudo-CT data (van der Bom *et al* 2011, Torrado-Carvajal *et al* 2016) from multi-spectral MRI and subsequently used in a mono-modality 3D-2D registration framework. The major drawback of this approach is the requirement of specialized MRI pulse sequences that are not within the standard diagnostic imaging protocols for spine, in order to robustly synthesize a simulated CT image.

To mitigate the degree of mismatch and focus the registration to aligning relevant vertebra anatomy, we propose a relatively simple vertebra segmentation step in the registration process. Vertebra segmentation in MRI can be seeded using the vertebra centroids that are already (automatically) defined within the standard LevelCheck workflow. Registration methods that rely upon a pre-segmentation step have been previously applied for CT-radiograph registration in spine to perform a surface-to-contour registration in segmented CT and radiographs (Hamadeh *et al* 1998). In this method, the segmentation is performed in both 3D and 2D images while an entirely contour-based registration is implemented via backprojecting the 2D contours onto the space of 3D surfaces. The method described below performs segmentation only in the 3D image and subsequently uses forward projections of the segmentation to align with relevant anatomical structures in 2D radiographic images.

We propose a solution, henceforth referred to as "MR-LevelCheck," for registering T2-weighted sagittal MR images with lateral radiographs using a simple segmentation of vertebrae. The segmentation output is subsequently provided as input to the previously developed 3D-2D "LevelCheck" registration framework with a few adjustments to operating parameters. Note that the method maintains other desirable features of LevelCheck, including robustness to content mismatch (via the gradient orientation (GO) similarity measure) (De Silva *et al* 2016) and is extensible to deformable registration (as in the msLevelCheck method of (Ketcha *et al* 2016b)). The sections below describe an example implementation of vertebra segmentation in MR images using continuous max-flow (Yuan *et al* 2010) and integration within the 3D-2D registration pipeline. The sensitivity of the 3D-2D

registration result to the quality of 3D segmentation is also investigated, and the sensitivity to the quality of segmentation is evaluated in terms that are fairly agnostic of a particular segmentation algorithm. Finally, the method is evaluated in clinical data for patients undergoing surgery of the cervical, thoracic, or lumbar spine.

B Methods

Registration of an MR image to a radiograph requires anatomical structures with non-linear, non-monotonic image intensity correspondence to be accurately aligned. To drive the registration according to relevant anatomical structures and to reduce the large mismatch in image content between the two modalities, we introduced a segmentation step to emphasize the vertebrae and/or vertebral cortex, which are the relevant, conspicuous, salient features in radiographs for purposes of target localization. The registration is not tied to a particular segmentation method, and alternative segmentation techniques (Michopoulou *et al* 2009, Neubert *et al* 2012, Kadoury *et al* 2013) could be incorporated. In this work, we use a simple implementation for vertebra segmentation with publicly available software for continuous max-flow optimization (Yuan *et al* 2010).

B.1 Segmentation

As with conventional LevelCheck, the method is implemented in a manner consistent with fairly streamlined workflow, requiring only the definition of “true” vertebral locations in the 3D image as input. Definition of such point locations (referred to as vertebral centroids, c_i) can be done automatically in CT (Dikmen *et al* 2008) and MR (Zhan *et al* 2012). Taking these locations as seed points for the segmentation, we formulated a spatially continuous min-cut problem with the objective function:

$$S = \min_{u(x) \in \{0,1\}} \int [(1-u) \cdot D_1(x) + u \cdot D_2(x)] dx + \int g(x) |\nabla u(x)| dx \quad (1)$$

where $u(x)$ is a membership function defining whether each pixel x lies outside ($u(x) = 0$) or inside ($u(x) = 1$) the vertebrae. The term $D_1(x)$ yields a lower cost to pixels within a neighborhood about the centroid with intensity close to the mean intensity $\overline{I_{Ac}}$ to be included in the segmentation and the term $D_2(x)$ encourages pixels with large gradient-weighted distance from the vertebra centroid to be excluded from the segmentation.

$$D_1(x) = |I(x) - \overline{I_{Ac}}| \quad (2)$$

$$D_2(x) = \int_{c_i}^x \nabla I(x) dx \quad (3)$$

where $I(x)$ is the pixel x in image I and $\overline{I_{A_c}}$ is the mean over the neighborhood A_c . The term $\nabla I(x)$ represents the gradient image. The second term in Eq. (1) enforces smoothness according to:

$$g(x) = \lambda(1 + \exp(-\nabla I(x))) \quad (4)$$

where λ is a regularization parameter with value selected according to the sensitivity analysis detailed below. The regularization term $g(x)$ decreases with increasing gradient magnitude $\nabla I(x)$ to encourage the alignment of image gradients with the segmentation ($\nabla u(x)$) during the minimization of S in Eq. (1).

The objective function in Eq. (1) was solved globally and exactly using a continuous max-flow model as described in (Yuan *et al* 2010) to obtain the segmentation output. The optimization is performed in a spatially continuous form by solving a sequence of convex-relaxed optimization problems in discrete time steps. The solution at each time step is the globally optimal solution computed efficiently according to the algorithm in (Yuan *et al* 2010). While the segmentations, in principle, can be directly solved in 3D, in the current work they were computed in each sagittal plane of the MR image and resampled with the same spacing as the original volume to obtain the segmented 3D image.

B.2 3D-2D Registration

Registration of a 3D CT image to a 2D radiograph commonly operates according to iterative alignment of a digitally reconstructed radiograph (DRR, computed by forward projection of the CT image) with the radiograph. The physical basis for such rationale is simple: forward projection of CT voxel values (attenuation coefficient, μ) emulates the physical process of attenuation yielding a radiograph (line integrals). Registration of an MR image to a radiograph challenges such an approach in that the forward projection likely does not yield a quantity with strong correspondence to the radiograph, depending strongly on the MR pulse sequence, etc. A lack of correspondence between MR and radiograph image intensities therefore presents an obvious challenge to registration based on forward projection. A variety of MR acquisition pulse sequences may present a solution – e.g., the ultrashort echo time (UTE) pulse sequence, which gives stronger correspondence to CT images than T1 or T2 weighted images (Keereman *et al* 2010). Alternatively, a CT-like image could be *synthesized* from the MR image according to various methods (Torrado-Carvajal *et al* 2016, van der Bom *et al* 2011) and thereby fold more naturally into the usual CT-to-radiograph registration process. To facilitate broader clinical applicability, however, and without the requirement of special pulse sequences, the method below was developed to operate somewhat irrespective of the MR image type, and the work below used the most common MR image type acquired for diagnosis and/or planning of spinal intervention – namely, T2-weighted images in which the spinal cord and cerebrospinal fluid (CSF) are conspicuous.

B.2.1 Segmentation variants—With the vertebral level annotations and segmentation described in Section B.1 as input, we investigated several variations of the segmentation to generate a projection of the MR image that reliably co-registers with a radiograph. The

methods are illustrated in Figure 1. The first projection method, denoted s_0 , simply forward projects the MR image intensities (without segmentation) analogous to the process in CT-radiograph registration. Various volumetric masking methods as in (Ketcha *et al* 2016b) could also be employed in the s_0 method to reduce the influence of anatomical structures/soft tissues distal to the spine. The s_1 method instead projects only the segmented region defined by the method in Section B.1, including the MR image intensities within the segmented region. For T2-weighted images, cortical bone appears dark and is therefore not usually captured within the segmented region; therefore, the s_1 method amounts to a projection of the MR image of the inner bone. The s_2 method addresses this point by dilating the segmentation (by a distance d mm) to include a region approximating the bony cortex and then projecting the MR image intensity values. Alternatively, the s_3 method treats the undilated segmentation (as in s_1) simply as a binary region (interior constant value k) and forward projects the segmentation without regard for interior image features and intensity inhomogeneity within the vertebrae, focusing instead on the vertebra bulk and boundaries. The s_4 method in turn projects only the dilated region defined in s_4 , focusing entirely on the vertebral “cortex” as the salient feature in registration. The $s_0 - s_4$ methods thus span a progression in feature reduction from the MR image itself to progressively simplified representation of features within.

B.2.2 Similarity metric—Using the MR segmentation variants described above, 3D-2D registration was performed by optimization of a gradient-based similarity metric in a rigid 6 degree-of-freedom transformation space as shown in Figure 2. The basic framework is the same as LevelCheck (Otake *et al* 2012, De Silva *et al* 2016) and is extensible to a deformable transformation of annotations as described in (Ketcha *et al* 2016a). The presence of interventional tools and implants within the radiographic field of view can introduce strong mismatch in content between the 3D and 2D images that challenges accurate registration. As shown by (De Silva *et al* 2016), robust registration in the presence of such mismatch can be achieved using the gradient orientation (GO) similarity metric:

$$GO = \frac{1}{\max(N, N_{LB})} \sum_{x \in \{\nabla I_1 > t_1 \cap \nabla I_2 > \delta\}} w(x) \quad (5)$$

where N denotes the total number of overlap pixels between the two images being evaluated. The term $\max(N, N_{LB})$ enforces image overlap (using the lower bound term N_{LB} , which is set to 30% of the total number of pixels in the 2D image in our experiments) by penalizing degenerate solutions that produce a large metric value with small image overlap. The term $w(x)$ denotes a mapping of the angle θ between two gradient vectors at each pixel x according to:

$$w(x) = \frac{2 - (\ln(|\theta| + 1))}{2} \quad (6)$$

Within the overlap region, gradient orientation was evaluated if the pixels exceed the median gradient intensity (t_1) in the radiographic image ∇I_1 and if there exists a segmented

boundary location in the projection image ∇I_2 . The segmented boundaries were defined in ∇I_2 as pixels exceeding the threshold δ , with a value selected to provide a reasonably reliable vertebral boundary in forward projecting the segmented 3D image. Image gradients were calculated in 2D images using a modified Sobel kernel in a 3×3 neighborhood. In the work reported below, the threshold and lower bounds were set to $t_1 = \text{median}$, $k = 1$, and $\delta = 5$. In this setting, forward projecting with $k = 1$ within a vertebra region >5 mm in size produces $\nabla I_2 > 5$, thereby satisfying the condition for metric evaluation at that pixel location.

B.2.3 Optimization method—The GO metric was optimized using the multi-start covariance-matrix-adaptation evolution-strategy (CMA-ES) optimizer as adapted from (Hansen and Ostermeier 1997) and described in (Otake *et al* 2013). CMA-ES is a derivative-free evolutionary optimizer with robustness to a non-convex, rugged search space, as often the case in multi-modality images with mismatching gradients. The multi-start strategy involves a simultaneous registration based upon multiple initial seed points positioned according to a k-d tree partitioning of the six-dimensional search space and helps to further avoid local optima. The number of multi-starts was set to 50 as in previous work, and the population size was set to 500 (increasing from 100 in previous work on CT-radiograph registration) to more fully sample the steep objective function space associated with sparse features in projection of segmentations.

B.3 Experiments

B.3.1 Clinical study—Clinical images were retrospectively analyzed in an institutional review board (IRB)-approved study involving 10 patients who had undergone cervical, thoracic, and lumbar spine surgery. There were no changes to the standard-of-care imaging protocols in the images analyzed in the study. The MR images for each patient were exemplary of diagnostic / preoperative planning data for patients undergoing spinal intervention – specifically, T2-weighted MR images with in-plane (sagittal) image spacing ranging from (0.48×0.48) mm² to (0.98×0.98) mm², slice thickness ranging from 3.0 to 5.2 mm, and number of sagittal slices ranging from 13 to 22. The MR images were acquired on scanners with magnetic field strength 0.35 T – 3 T from variety of scanner manufacturers and models: Siemens Espree, Aera, Symphony, Skyra (Siemens Healthcare, Erlangen, Germany); Philips Intera (Philips Healthcare, Cleveland OH, USA); GE Signa HDxt (GE Healthcare, Little Chalfont, UK); Toshiba Opact (Toshiba Corporation, Tokyo, Japan). Intraoperative radiographs acquired for purposes of target localization were also commonplace in clinical practice – specifically, lateral radiographs acquired during the procedure with a mobile radiography system (DRX-1, Carestream Health, Rochester, NY) with (0.14×0.14) mm² pixel size and manufacturer reported exposure index ranging from 1102 to 2169.

Annotation of the vertebral centroid positions was performed manually with the assistance of a neuroradiologist according to standard designations (C1–C7, T1–T12, and L1–L5) in both the MR and intraoperative radiographs – taken as definition of “true” location. Automatic labeling of vertebrae in the MR image (Zhan *et al* 2012, Dikmen *et al* 2008) could be alternatively used to improve workflow.

Registration accuracy was analyzed in terms of the projection distance error (PDE for each registered radiograph as follows:

$$PDE = \sqrt{\frac{\sum_{\nu=1}^{N_{\nu}} (x_{\text{radiograph}}^{\nu} - x_{\text{DRR}}^{\nu})^2}{N_{\nu}}} \quad (7)$$

where ν denotes an index corresponding to vertebral level and N_{ν} denotes the total number of vertebrae labeled in a given radiograph. The term $x_{\text{radiograph}}^{\nu}$ is the expert-defined, ground truth position of the vertebral centroid in the intraoperative radiograph, and x_{DRR}^{ν} is the position of the centroid in the forward-projected DRR with system pose determined by the 3D-2D registration. Note that PDE is specified in the domain of the projection data, and the corresponding distance scale within the patient is smaller by a factor of system magnification (typically $\sim 1.5 - 2.0$ for mobile radiography). A nominal value of $PDE = 30$ mm has been suggested as an upper limit for successful registration (Varnavas *et al* 2013, De Silva *et al* 2016), corresponding to $\sim 15 - 20$ mm in the patient, such that the registered anatomical label appears within the boundaries of the corresponding vertebra on the radiograph. To evaluate robustness (including sensitivity to initialization as well as stochasticity of the optimizer), 10 repeat registrations were performed for each image-pair for each of the $s_0 - s_4$ projection methods described in Section B.2.1.

B.3.2 Effect of segmentation accuracy on registration accuracy—The accuracy of registration is expected to depend on the quality of segmentation, which was investigated in this work in a manner intended to be fairly unbiased of any particular segmentation method. There are at least three considerations in this regard. First, with respect to the continuous max-flow method in particular, the analysis was performed as a function of the parameters therein to examine sensitivity and guide selection of nominal values. Second, alternative segmentation approaches may perform better than (or worse than) this particular segmentation algorithm. Therefore, rather than implementing numerous alternative approaches (and instead seeking to remain relatively impartial with respect to one segmentation method versus another), the analysis was performed as a function of segmentation quality measures (Dice Coefficient, Accuracy, etc. described below) to provide somewhat more general insight on how registration accuracy using alternative segmentation approaches might be expected to perform. Finally, the quality of segmentation depends on the quality of the input MR image (and even the type of MR image pulse sequence). In this respect as well, the analysis performed as a function of segmentation quality measures provides somewhat more general insight on how 3D-2D registration accuracy might be expected to perform given various levels of MR image quality (or MR image type) underlying the input 3D segmentation.

The quality of the segmentation was evaluated by comparing to reference segmentations that were manually defined with assistance from a neuroradiologist. Sagittal slices within ± 10 mm of the vertebra centroid were taken as input to the segmentation. We assessed the sensitivity of registration performance to the choice of regularization parameter λ and the extent of dilation d . The λ parameter was varied over a range from 0.1 (for which the

segmentation was overly smooth) to 10 (for which the segmentation was sharp but prone to noise). Unless otherwise noted, a value $\lambda = 3$ was used in the remaining experiments. For the s_2 and s_4 methods, the extent of dilation was varied over the range $d = -5$ mm to $+10$ mm, and the effect on registration accuracy was evaluated. Unless otherwise noted, a nominal value of $d = 2$ mm was used.

The quality of segmentation was evaluated in comparison to the reference in terms of Dice coefficient, Accuracy, root-mean-square error (RMSE), and contour affinity ratio (CAR) as defined below and illustrated in Figure 3:

$$\text{Dice} = \frac{2 \times TP}{2 \times TP + FN + FP} \quad (8)$$

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FN + FP} \quad (9)$$

$$\text{RMSE} = \sqrt{\frac{1}{K} \sum_{i=1}^K d(g_i, S)} \quad (10)$$

$$\text{CAR} = \frac{1}{K} \sum_{i=1}^K 1_A[d(g_i, S) > d_{\text{thresh}}] \quad (11)$$

where TP represents the number of true-positive vertebra pixels correctly segmented as vertebra, TN represents the true-negative non-vertebra pixels correctly labels as non-vertebra, FP represents the false-positive non-vertebra pixels incorrectly labelled as vertebra, and FN represents the false-negative vertebra pixels incorrectly labelled as non-vertebra. Dice Coefficient and Accuracy evaluate the degree of area-overlap, whereas RMSE and CAR assess the alignment of vertebra boundaries. For RMSE and CAR, the number K is the total number of points lying on the segmentation boundary, and $d(g_i, S)$ is the distance between ground truth segmentation and the closest point in algorithm segmentation, where d_{thresh} is a lower bound distance between the two contours (set to 2 mm in the experiments reported below).

B.3.3 Initialization and capture range—Initialization of the projection geometry was set to source-axis distance (SAD = 550–800 mm) and source-detector distance (SDD = 1000 mm) typical of mobile radiography, with the center of the radiograph initialized within $\sim 40 - 110$ mm initial error aligned to ensure basic overlap between the two images. The capture range of the algorithm was specifically investigated by perturbing the initialization in the superior-inferior (S-I) direction of the patient (y) over a broad range from -300 mm to $+300$ mm from the true position. While other degrees of freedom exist in terms of the initialization

and degrees-of-freedom solved in registration, the S-I direction along the longitudinal axis of the spine was the most relevant in terms of identifying the accurate vertebra level and susceptibility to local optima (for example, at periodic intervals of vertebral level).

C Results

C.1 MR Projection Methods

Figure 4 shows the distributions in PDE for each of the projection methods. The s_0 method involving forward projection based on the MR image intensity directly for DRR generation leads to 100% failure (median PDE >200 mm) and was found to deviate widely from and yield a solution that was often inferior to the initialization. The reason is clear: a lack of correspondence between features of the radiograph and those producing the strongest gradients in the (T2-weighted) MR image – namely, soft tissues and CSF. Such noncorrespondence resulted in an intractable level of mismatch for the registration algorithm, and gradients associated with the vertebrae in the radiographs aligned spuriously with surrounding anatomical structures in MRI.

The $s_1 - s_4$ methods all demonstrated superior performance to s_0 , indicating the advantage of segmentation to overcome gross noncorrespondence mismatch and to better focus the registration on the alignment of vertebra boundaries. The s_1 method (which includes MR images intensities within the segmentation) yielded PDE = 18.4 ± 23.6 mm (median $\pm$ inter-quartile range [IQR]). Accuracy was improved to PDE = 8.8 ± 22.6 mm (median $\pm$ IQR) for the s_3 method, which simply binarizes the (undilated) segmentation, and suggests that MR image heterogeneities within the vertebrae are also noncorrespondent with the radiograph.

Dilation of the segmentation to include the bone cortex (methods s_2 and s_4) demonstrated superior performance to projections methods that used the raw segmentations s_1 and s_3 . Hence, a simulated cortex in MR projections via dilation of the raw segmentation better facilitated alignment with the gradients generated from cortical bone in radiographs. Overall, the s_4 method, in which projections were generated using a binary segmentation of the dilated cortex region, yielded the most accurate and robust performance, with PDE median $\pm$ iqr = 4.3 ± 2.6 mm and 100% success rate. Paired statistical testing using Wilcoxon signed rank test demonstrated that all of the distributions in Figure 4 were statistically significant in their median differences ($p < 0.05$).

The benefit of dilation to include the bone cortex is further demonstrated in Figure 5, which shows measurements of PDE (for the s_4 projection method) over a broad range of dilation distance (including no dilation, $d = 0$). Setting $d < 0$ corresponds to erosion (rather than dilation) of the segmentation. Based on these findings, a nominal value of $d = 2$ mm was selected for experiments reported below.

C.2 Sensitivity to Segmentation Error

The accuracy of the continuous max-flow based segmentation was assessed by comparing segmentation results to the manually defined reference segmentations in corresponding 2D slices. The Dice metric was $(88.1 \pm 5.2)\%$ and suggested comparable performance to other MR vertebra segmentation methods (Michopoulou *et al* 2009, Neubert *et al* 2012, Kadoury

et al 2013). The Accuracy metric further included true-negative voxels within the quality measure (i.e., voxels outside the vertebrae correctly segmented as such) and was found to be $(90.6 \pm 5.7)\%$. The RMSE between the contours arising from the max-flow and reference segmentations was (1.8 ± 0.6) mm, and CAR was 0.82 ± 0.08 .

The RMSE and CAR are likely the more relevant quality measures with respect to registration that relies on accurate delineation of vertebra gradients (i.e., the GO similarity metric). Further analyses were therefore performed to characterize the dependence of 3D-2D registration performance on segmentation quality in terms of perturbations to these two segmentation metrics. Figure 6 summarizes the registration performance as a function of segmentation accuracy, where perturbations over a broad range in RMSE and CAR were imparted by variation of the regularization parameter (λ , ranging 1–10) and dilation parameter (d , ranging 1–10 mm). In Figure 6, cases perturbed in λ are shown as open circles, and those perturbed in d are shown as solid circles. The analysis was performed in 9 patients who underwent thoracic or lumbar spine surgery. One cervical case was excluded from the analysis, because perturbations to λ resulted in small variability in RMSE and CAR due to the relatively smaller scale of anatomical structures in this region. Robust registration performance was observed for cases in which the segmentation accuracy yielded $\text{RMSE} < 3$ mm and/or $\text{CAR} > 0.50$. The segmentation accuracy of the continuous max-flow method was well within these benchmarks and supports the feasibility of using a relatively simple segmentation method for 3D-2D registration for vertebral localization.

C.3 Capture Range

The susceptibility of MR-LevelCheck registration to gross errors in initialization was evaluated in terms of S-I capture range, with results summarized in Figure 7. Robust registration was found within a range (420 ± 78) mm, which represents a fairly a wide margin (approximately ± 6 vertebra levels in each direction) of initialization error. This level of robustness is consistent with that previously demonstrated for the original LevelCheck (CT-to-radiograph registration) algorithm and is attributed to the robust multi-start strategy to prevent convergence at local optima.

C.4 Clinical Study

Application of the MR-LevelCheck method to 10 patients undergoing spine surgery, with nominal parameters specified above, demonstrated successful registration in cervical, thoracic, and lumbar regions. The overall PDE was 4.3 ± 2.6 mm (median $\pm$ IQR), and there were no failed registrations. The upper bound of the 95% confidence interval in PDE was 8.5 mm. For a typical radiographic setup with a magnification of ~ 2 , this corresponds to ~ 4.2 mm error at the vertebra centroid. This compares favorably to the typical size / length of a vertebral body (~ 14 – 29 mm as reported by Busscher *et al* 2010) and implies that the labels are reliably projected onto the radiograph within the boundaries of the vertebrae. Figure 8 illustrates the MR-LevelCheck output in three example cases – one each in the cervical, thoracic, and lumbar spine regions. In each case, we see the input T2-weighted MR image, the s_4 projection (at solution), the GO map (prior to summation over u, v coordinates), and the registration result in which annotations defined in the MR image are transformed and overlaid on the radiograph. In the last column, the MR-LevelCheck results are shown as

(green) circles, and the manually annotated ground truth labels are shown as (yellow) crosses.

The images also demonstrate the robustness against image content mismatch associated with surgical instrumentation in the intraoperative radiograph (retractors and needles), largely by virtue of the GO metric. The thoracic case also shows successful registration in the presence of abnormal T5 anatomy, where the segmentation local to T5 is likely challenged (due to abnormal anatomy and signal intensity in the fractured vertebra), but reliable segmentation of adjacent vertebrae was sufficient to yield an accurate overall transformation. The cervical case also shows successful registration in the presence of poor lateral radiographic image quality in areas occluded by the shoulders. Note that all of the cases involved typical variations between the preoperative imaging setup (patient usually laying supine in the MR scanner) and the intraoperative setup (patient laying prone on the OR table). Despite corresponding deformation in spinal curvature, the method yielded reliable registration local to each vertebra. Note also that the method is extensible to a multi-stage registration approach (Ketcha *et al* 2016a) that models such deformations explicitly.

D Discussion and Conclusions

We developed a segmentation-based registration solution to overcome strong mismatch in anatomy in multi-modality images involving MRI and radiographs. Vertebra segmentation in MRI aided in the exclusion of extraneous high-contrast soft-tissue anatomy and drove the registration based on anatomical features that were salient to the radiographic features. Among the different segmentation variants investigated, the s_4 method (forward projection of the binary cortex from a dilated segmentation of the vertebral body) yielded the most accurate and robust registration performance. In CT-to-radiograph registration, image intensities from surrounding anatomical structures like spinous processes and ribs correspond well between the two modalities and could potentially help to supplement accurate alignment and increase robustness. However, in MRI the segmentation excluded such structures due to mismatch and the registration performance relies upon the remaining salient anatomical features of corresponding vertebra boundaries. In the s_4 method, dilation of the segmented vertebral body was found to assist in matching the cortical bone as appearing in the radiographs, whereas binarizing the segmentation helped to enforce the alignment of the vertebra boundaries by disregarding gradients generated due to intensity inhomogeneity within the vertebrae. These twofold variations to the original raw segmentation s_1 were desirable in emphasizing core features and demonstrated improved robustness in the s_4 method.

In the experiments described in this paper, registrations were performed using preoperative sagittal T2-weighted MR images and lateral intraoperative radiographs. While those imaging protocols are the most commonly used in spine imaging for diagnosis and treatment, the presented registration method could be sensitive to the particular acquisition protocols. For example, image features captured in the segmentation in a sagittal MRI may not provide accurate correspondence to features in an anterior-posterior (AP) radiograph; in such a scenario, a coronal MRI would presumably be better suited to the registration. Therefore, the methods presented in this paper may not be directly extensible to images acquired with

arbitrary scan or positioning protocols. However, it was shown to be well suited for the task of vertebral level localization given these two common protocols.

In the MR-LevelCheck solution, vertebra segmentation was performed as a pre-procedure step separate from the overall registration process, as illustrated in Fig. 2. The addition of such a step falls naturally within the standard LevelCheck workflow, where it can be performed following the already existing (and automatic) workflow of annotating vertebral levels without additional time spent in the OR. The use of vertebral annotations as seeds for the automatic segmentation step would also be consistent in a streamlined workflow. The analysis indicated that reliable 3D-2D registration accuracy could be obtained when the segmentation accuracy yielded $RMSE < 3$ mm. This not only investigated the extent to which the method would perform well given a different segmentation method, but also the extent to which the method might be applicable to other MR image acquisition types (e.g., T1-weighted or UTE) for which the quality of segmentation will be different (and potentially worse). Variable image quality in MRI owing to scan time, field strength, etc. is another factor that could affect the segmentation accuracy.

The performance of image-intensity-based registration is challenged by the inherent mismatch and intensity non-correspondence between multiple modalities. In our solution, the segmentation step was devised to mitigate the mismatch in raw image features by selectively focusing on specific features that satisfy a certain objective function as given in Eq. (1). Alternatively, this could be achieved within the registration framework itself by using alternative image similarity metrics that capture descriptive image features relating to anatomical structure in local neighborhoods (Heinrich *et al* 2012, Dalal and Triggs 2005). Such similarity metrics, however, could increase the computational load of registration in an iterative optimization process. Another plausible registration approach could combine the two objective functions that in our method were optimized separately during segmentation and registration steps. With such an approach, the feature selection process (via segmentation) and feature matching process (via image-similarity criterion) could be combined and optimized in a single registration framework.

The MRI-to-radiograph registration method presented in this work could have broader clinical utility beyond spine surgery. Fluoroscopy-guided steroid needle injections for spine pain management (Wilkinson and Cohen 2013), for example, could benefit from a 3D-2D registration solution for target localization and needle guidance. While preoperative MRI also plays an increasingly vital role in pain diagnostics, visualization of surrounding soft tissues relative to the estimated needle trajectory via 3D-2D registration could provide a valuable tool to improve needle targeting accuracy, decrease radiation dose, and minimize complications in these procedures. In principle, other image-guided therapy procedures such as stereotactic body radiation therapy could also benefit from a robust, image-based registration solution for intraoperative target localization and motion tracking based on planning data defined in MRI (Brock 2007, Furtado et al 2013).

In conclusion, we demonstrated a robust MRI-to-radiograph registration solution that extends the original LevelCheck algorithm to operate based on MRI and validated the method in clinical data for spine surgery target localization. Both spine surgery and pain

management procedures in which preoperative MRI is the basis for diagnosis and planning could benefit from such decision support for level localization. Clinical studies are currently underway to further evaluate the utility of the method and demonstrate its performance in large data sets.

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Figure 1. Illustration of methods by which the MR image may be segmented and forward-projected in correspondence to the 2D radiograph: s_0 (the T2-weighted MRI itself); s_1 (the segmented regions); s_2 (the segmentation dilated to include bone cortex); s_3 (the segmentation from s_1 binarized to constant interior value); and s_4 (the dilated region from s_3).

Figure 2.

Illustration of the MR-LevelCheck process for 3D-2D registration of a preoperative MR image (and vertebral labels defined therein) to an intraoperative x-ray radiograph or fluoroscopy image.

Figure 3. Illustration of terms underlying the metrics of segmentation quality – Dice Coefficient, Accuracy, RMSE, and CAR as in equations 4 – 7.

Figure 4. Registration accuracy for 3D-2D registration based on the five variations of segmentation method ($s_0 - s_4$). The violin plots shows distributions in PDE with median value marked by the horizontal line in each case. The table shows PDE median value and IQR as well as failure rate (fraction of cases for which PDE > 30 mm).

Figure 5. Effect of the dilation parameter (d) on registration accuracy. Results shown are for the s_4 projection method. Dilation in the range $d \sim 1$ – 2 mm yielded the best performance, corresponding to the inclusion of bone cortex in the segmentation.

Figure 6.

Registration performance evaluated as a function of segmentation quality. PDE is plotted versus (a) RMSE between segmentation contours and (b) CAR for segmentations. The broad range in RMSE and CAR was achieved through perturbation of the regularization parameter (λ , open circles) and dilation distance (d , solid circles). The vertical line marks the approximate benchmark within which registration was stable and within the range of geometric accuracy required for vertebral localization (RMSE < 3 mm and CAR > 0.5).

Figure 7.

Analysis of registration capture range for the MR-LevelCheck algorithm. PDE measured as a function of initialization error along the longitudinal (SI) direction suggests robustness to gross initialization error within roughly ± 200 mm, corresponding to approximately ± 6 vertebral levels.

Figure 8. Example MR-LevelCheck registration in clinical images: (top) cervical spine; (middle) thoracic spine; and (bottom) lumbar spine. The radiographs in the right column are overlaid with the registered labels (circles) in comparison to neuroradiologist-defined truth in 2D radiographs (crosses).