Evaluation of CT-MR Image Registration Methodologies for 3D Preoperative Planning of Forearm Surgeries

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Abstract:

Computerised surgical planning for forearm procedures that considers both soft and bony tissue, requires alignment of preoperatively acquired computed tomography (CT) and magnetic resonance (MR) images by image registration. Normalised mutual information (NMI) registration techniques have been researched to improve efficiency and to eliminate the user dependency associated with manual alignment. While successfully applied in various medical fields, application of NMI registration to images of the forearm, for which the relative pose of the radius and ulna likely differs between CT and MR acquisitions, is yet to be described. To enable the alignment of CT and MR forearm data, we propose an NMI-based registration pipeline, which allows manual steering of the registration algorithm to the desired image subregion and is, thus, applicable to the forearm. Successive automated registration is proposed to enable planning incorporating multiple target anatomical structures such as the radius and ulna. With respect to gold-standard manual registration, the proposed registration methodology achieved mean accuracies of 0.08 ± 0.09 mm (0.01 – 0.41 mm range) in comparison to 0.28 ± 0.23 mm (0.03 – 0.99 mm range) associated with a landmark-based registration when tested on 40 patient datasets. Application of the proposed registration pipeline required less than 10 minutes on average compared to 20 minutes required by the landmark-based registration. The clinical feasibility and relevance of the method were tested on two different clinical applications, a forearm tumour resection and radioulnar joint instability analysis, obtaining accurate and robust CT-MR image alignment for both cases.

Keywords: image-to-image registration, mutual information, surgical planning, forearm

Introduction

Preoperative computerised surgical planning can improve diagnostic quality and treatment outcome[1]. For the treatment of forearm bone injuries and pathologies such as instability[2,3], fractures[4] and tumours[5], the need for computerised planning has been widely reported[6–14]. However, to date, its application has been greatly limited to patient-specific planning on computed tomography (CT) data, considering only bony structures such as for corrective osteotomies[15] and the design of patient-specific instruments[16]. The inclusion of soft tissue analysis based on magnetic resonance (MR) images (MRI) would allow a wider range of forearm treatments to benefit from computerised surgical planning. However, MR's relatively low image resolution, in addition to the lack of signal produced by the cortical bone (due to the very short transverse relaxation time used in conventional MRI sequences[17]) renders the delineation of anatomical structures or the definition of surgical resection margins more challenging and error-prone, compared to CT. The overlay of preoperatively acquired CT and MR images would provide a possible solution for augmenting high-resolution cortical bone anatomy with crucial soft tissue information[18]; however, to date, no methodology for the automatic alignment of MRI and CT data of the forearm has been proposed.

Image-to-image registration[19] is the process of finding a transformation that best aligns both image datasets. Following registration by image fusion[19] would allow the integration of information from unimodal or multimodal images into a single dataset that has the maximum information content. Currently, the clinical gold-standard for image registration of CT and MRI is still described as a time-consuming manual process typically performed by a radiologist[18], where the 3D volumes of the CT and MR datasets have to be matched by successive manual rotations and translations under visual supervision. To automate this operator-dependent process, a variety of image registration algorithms and methodologies have been widely researched[20,21].

One of the earliest such methods, anatomical landmark point-based registration, derives an alignment transformation from a set of corresponding 3D points in the images to be aligned[22]. Although simple and relatively efficient, the accuracy of the method relies on how well a user can identify corresponding landmarks in both image data sets. As an alternative, fully automatic algorithms that reduce or eliminate the effect of user variability have been developed. Particularly, normalised mutual information[23] (NMI) has become one of the most investigated measures for automatic medical image registration of multimodal images[20]. NMI registration has been successfully applied to align CT and MR images in various medical fields such as radiotherapy[24], neurosurgery[25,26], spinal surgery[27] and others[28–31]; however, its application to the forearm has yet to be described. NMI registration methodologies are typically applied on the whole CT and MR image volumes. Nevertheless, because the relative pose between the radius and ulna most certainly differs between CT and MR acquisitions, direct application on the entire forearm images is likely to produce poor results. Additionally, the alignment procedure with NMI registration is reliable only when the initial image pose (position and orientation) is close to the “correct” pose[32] and therefore requires a robust pre-alignment initialisation. Thus, a method for localisation of the anatomical structures of the forearm is also required.

We hypothesise that registering CT and MRI data, based on an isolated anatomical subsection of the forearm (e.g. radius or ulna), would enable an automated, accurate and robust alignment. Such registration would facilitate the generation of a multimodal fused display to aid in surgical planning in cases such as bony tumour resection or radioulnar joint instability analysis, with an accuracy within millimetres[18]. Additionally, such data fusion could be utilised during image-guided navigation, which provides notable intraoperative support to the surgeon[33,34].

Towards this end, we herein propose and evaluate a clinically applicable and user-independent rigid CT-MR image registration pipeline for the forearm, which includes the isolation of the targeted anatomy for pre-alignment to steer the registration algorithm to the desired region. In cases where registration information from several anatomical structures is required, the proposed registration pipeline can be applied to each structure successively. The proposed pipeline was validated on clinical data and its accuracy and efficiency were compared to a landmark-based registration methodology with respect to the gold-standard manual registration. Feasibility for use in 3D preoperative surgical planning was further demonstrated on a clinical case of tumour resection on the radius and on the surgical planning of a distal radioulnar joint instability which requires successive registration of both the radius and ulna.

Methods

A pipeline for the automated registration of T1-weighted MRI and CT data was developed for the forearm based on the normalised mutual information (NMI) metric. Custom-made software was designed to implement the proposed pipeline, which comprises an interactive coarse pre-alignment of the CT image to the MR image, the isolation of the targeted anatomy, and the execution of an automatic registration algorithm based on NMI. The methodology was evaluated on N=40 image datasets of healthy and pathological anatomies and retrospectively tested on two clinical cases.

Registration Pipeline

The proposed registration pipeline is aimed at finding an optimal transformation T that transforms a voxel position x_{CT} of the CT image I_{CT} to a voxel position x_{MR} of the MR image I_{MR}.

$$T: x_{CT} \longmapsto x_{MR} \Leftrightarrow T(x_{CT}) = x_{MR}$$

The pipeline, summarised in Figure 1, involves: 1) the extraction of an isosurface S_{CT} from I_{CT} representing roughly the radius bone; 2) an interactive coarse pre-alignment of S_{CT} to I_{MR} resulting in the transformation T_c; 3) isolation of the targeted anatomy using S_{CT} and execution of an automatic registration algorithm based on NMI producing the optimised transformation $\hat{T}_{NMI}$; 4) the concatenation of the transformations T_c and $\hat{T}_{NMI}$ to obtain the final optimised transformation $\hat{T}$ mapping the CT to the MR space. The pre-alignment described in steps 1) and 2) is required to prevent the automatic registration algorithm from converging to an incorrect local minimum. A detailed description of each pipeline step is provided thereafter.

A custom-made C++ software application was built to implement the proposed registration pipeline. The following libraries are used in the software: Qt (version 5.3.2, https://www.qt.io) for the graphical user interface; Coin3D (version 3.1.3, https://bibucket.org/Coin3D/coin) and SoQt (version 1.5.0, https://bitbucket.org/Coin3D/soqt) for the 2D and 3D rendering; ITK (Insight Segmentation and Registration Toolkit, version 4.8.2, https://itk.org) for image processing; VTK (The Visualization Toolkit, version 6.1.0, https://vtk.org) for 3D surface generation and smoothing; and elastix[35,36] (version 4.8, http://elastix.isi.uu.nl) for image registration.

After the corresponding CT and MR data sets of each case are loaded into the developed software, as a pre-processing step, the software automatically resamples the MR image data to obtain isotropic voxel sizes. For example, an MR image with an original anisotropic voxel size of $(0.176, 0.176, 3)$ mm^3 is resampled with a sampling ratio of $(1,1,17)$ mm^3, resulting in isotropic voxel sizes of 0.176^3 mm^3. No pre-processing of the CT data set is required. Additionally, 2D slices of the MR images corresponding to the axial, coronal and sagittal anatomical planes are extracted and displayed in 2D viewers.

A 3D isosurface S_{CT} is computed from the CT data set with a threshold of 300 HU and displayed in a 3D viewer (Figure 2a). The threshold was chosen empirically to work with images of the forearm and must be adapted for the targeted anatomy. However, the threshold does not have to be accurate, as it contributes only to the process of coarse pre-alignment of the CT image to the MRI (± 100 HU is acceptable on our data). An outline of the extracted isosurface is additionally displayed on the axial, coronal and sagittal 2D planes in the graphical user interface (Figure 2b-d).

For initialisation, the 3D isosurface S_{CT} is manually aligned onto the MR image, using a manipulator that allows the user to apply rotational and translational movements in the 3D viewer (Figure 2a). A suitable alignment is visually found when the isosurface outline displayed in the axial, coronal and sagittal planes, roughly matches the MR data (Figure 2b-d). The resulting coarse transformation T_c is then applied to the CT image I_{CT}. The transformed image is denoted as $I_{CT}^{T_c}$.

As a next step, a binary mask is generated from S_{CT} to represent the region of interest on which the registration will be applied. The region of interest isolates the targeted anatomy and prevents the registration from including other bone structures of the wrist such as carpal bones, making the algorithm more robust. Hence, a binary mask of the 3D isosurface is moved to the MR space through the coarse transformation T_c and dilated by a margin adjustable in the graphical user interface of the software (15 pixels were suitable in our experiments) to include only voxels in the vicinity of the radius cortical bone layer (Figure 3).

Implementation of the whole automatic registration algorithm is carried out by means of the elastix library[35,36] with the parameters described thereafter. The automatic intensity-based registration problem is formulated in elastix as an optimisation problem

$$\hat{T}_{NMI} = \arg\min_{T_{NMI}} C\left(T_{NMI}; I_{CT}^{T_c}, I_{MR}\right)$$

in which the cost function C is minimised with respect to transformation parameters and the return value $\hat{T}_{NMI}$ approximates the optimal transformation T_{NMI}. The normalised mutual information metric[32] $I\left(I_{CT}^{T_c}, I_{MR}\right)$ is used in the cost function C to compute the image similarities:

$$I\left(I_{CT}^{T_c}, I_{MR}\right) = \frac{H\left(I_{CT}^{T_c}\right) + H(I_{MR})}{H\left(I_{CT}^{T_c}, I_{MR}\right)}$$

where $H(\cdot)$ denotes the entropy[37] of a portion of one image that overlaps with the other image volume for the given transformation and $H\left(I_{CT}^{T_c}, I_{MR}\right)$ denotes the joint entropy[37] between the images $I_{CT}^{T_c}$ and I_{MR}. To solve the optimization problem, i.e. to obtain the optimal transformation parameter vector for $\hat{T}_{NMI}$, an iterative adaptive stochastic gradient descent strategy is employed[38] with a maximum number of iterations of 3000. A relatively fast linear interpolator is used during registration iterations and a slower but more accurate higher quality third-order B-spline[39] interpolation for generating the resulting transformed CT image. To increase the chance of successful registration, several levels of Gaussian smoothing are applied to the MRI during registration iterations (Gaussian scale space[40]). For each optimization step, the standard deviation σ of the smoothing Gaussian distribution is decreased by a factor of 2, ending with $\sigma = 0.5$ in the last smoothing operation. The last registration iteration employs the full MRI without any filtering. Thus, the automatic registration process starts with blurred images allowing the algorithm to emphasise first on large and dominant structures, before focusing on details in the last registration stages.

Verification Study Design

To determine the accuracy and efficiency of the proposed automated image registration pipeline, we conducted a study on clinical MR and CT datasets of the forearm, applying the proposed pipeline retrospectively to corresponding pairs of CT and MR datasets. We compared the results to those achieved using a standard anatomical landmark point-based image registration with respect to a gold-standard manual registration. With the approval of the local institutional review board (ethics commission of the canton of Zürich, Switzerland, BASEC-No. 2016-00282), N=40 patients with healthy and pathological radius anatomy were included in this retrospective study. The inclusion criteria were the presence of both a clinical CT scan and an MR scan of the forearm. The acquired images thus contained CT scans with 1 mm slice thickness (120 kV, Philips Brilliance 64 CT, Philips Healthcare, The Netherlands) and MR scans with 2 to 4 mm slice thickness (coronal T1-weighted sequence; 1.5 Tesla system Siemens Medical Solutions, Erlangen, Germany). The field of view as defined in the standard clinical protocol contained at least 8 cm of the distal radius. The final CT and MR data sets were exported from the picture archiving systems as anonymised DICOM files.

Landmark-Based Registration Methodology

For comparison, we employed a standard landmark-based registration methodology, with which the correspondence between the CT image and the MR image is calculated based on manually-placed anatomical landmarks using a commercial software (Mimics Medical, Version 19.0). An expert technician scrolled through the stack of 2D axial, coronal and sagittal CT slices and selected the following anatomical landmarks $L_{CT} = \{x_{CT}\}$: (1) radius styloid, (2) dorsal distal edge of the sigmoid notch, (3) palmar distal edge of the sigmoid notch and (4) Lister's tubercle (Figure 4). Similarly, the corresponding anatomical landmarks $L_{MR} = \{x_{MR}\}$ were selected through the stack of 2D axial, coronal and sagittal MR image slices. Once point-pair correspondence was established, a point-pair matching algorithm using a closed-form solution to the least-squares problem[41] was applied to minimize the misalignment between the set of points by solving the equation

$$T_L(R_L, t_L) = \arg\min_{R_L, t_L} \sum_{x_{CT} \in L_{CT}} d^2\big(R_L x_{CT} + t_L, x_{MR}^*(x_{CT})\big)$$

where $T_L(R_L, t_L)$ is the optimal alignment transformation and $x_{MR}^*(x_{CT})$ is the point in the set L_{MR} corresponding to the point x_{CT} in the set L_{CT}, and $d^2(\cdot,\cdot)$ is the squared Euclidean distance between two points: $d^2(p_1, p_2) = \|p_1 - p_2\|_2^2$.

Gold-Standard Manual Registration

The manual registration approach used to align the MR and CT images was originally developed for the 3D preoperative planning of tumour resection surgery at the pelvis[18]. The 3D surface models S_{CT} and S_{MRI} of the radii were constructed by manual segmentation of the cortical bone layers in the CT and MR images, respectively. A commercial image processing software (Mimics Medical Version 19.0, Materialise, Belgium) was used for the segmentation task. The resulting 3D surface models S_{CT} and S_{MRI} were then imported into the preoperative planning software CASPA (Balgrist CARD AG, Switzerland). The surface registration functionality of CASPA relies on the iterative closest point (ICP) algorithm[42] and was applied to calculate the transformation T_{ICP}, which aligns S_{CT} to S_{MRI} by minimizing the point-to-point distances between the surfaces in a least square sense. The ICP algorithm was configured to stop when either the average root mean squared error was below 0.01 mm or when 100 iterations were reached. Lastly, the gold-standard transformation T_{GS} was obtained in CASPA by a manual fine-tuning process, in which $S_{CT}^{T_{ICP}}$ is interactively translated and rotated to match S_{MRI}. Special care was taken to visually align the distal joint surfaces of the radii, as they are very relevant to surgical procedures around the wrist.

Accuracy Evaluation

For accuracy evaluation, we considered the registered gold-standard surface model $S_{CT}^{T_{GS}}$ as the ground truth and compared it to the surface models S_{CT}^{T} and $S_{CT}^{T_L}$ obtained from the proposed registration pipeline and the landmark-based registration, respectively. The mean distance surface metric $d_{mean}(\cdot,\cdot)$, implemented as the mean of all minimum vertex-to-vertex Euclidean distances between the surfaces, was used to quantify a technical registration error and the Hausdorff surface[43] distance metric $d_{HD}(\cdot,\cdot)$ to provide a more clinically relevant measure. Consequently, the errors $e_{mean} = d_{mean}\left(S_{CT}^{T},\, S_{CT}^{T_{GS}}\right)$ and $e_{mean} = d_{mean}\left(S_{CT}^{T},\, S_{CT}^{T_{GS}}\right)$ were computed for the proposed registration pipeline and the errors $e_{mean}^{L} = d_{mean}\left(S_{CT}^{T_L},\, S_{CT}^{T_{GS}}\right)$ and $e_{HD}^{L} = d_{HD}\left(S_{CT}^{T_L},\, S_{CT}^{T_{GS}}\right)$ were computed for the landmark-based registration.

Finally, we performed a statistical evaluation on the alignment error values obtained from both the landmark-based registration and our proposed registration pipeline. First, an ANOVA F-test was conducted to determine whether the variance between the means of the two methodologies was significantly different. Subsequently, a two-tail t-test was performed to determine the level of significance of the observed results.

Results

From the N=40 patient data sets, four data sets were excluded from the study due to the non-conform protocol performed at other institutions. The proposed registration pipeline was successfully applied to all remaining N=36 patient data sets.

The proposed registration pipeline and the landmark-based registration had mean registration errors of $e_{mean} = 0.08 \pm 0.09$ mm (0.01 – 0.41 mm range) and $e_{mean}^{L} = 0.28 \pm 0.23$ mm (0.03 – 0.99 mm range), respectively (Figure 5a). The ANOVA F-test confirmed that the difference between the two registration methodologies was statistically significant ($F(45) = 6.9$, $p < 0.05$). Additionally, the two-tail t-test analysis confirmed that the mean registration error of the proposed pipeline was significantly smaller than that of the landmark-based methodology ($t(45) = 4.89$, $p < 0.05$). Similarly, the clinically relevant registration errors based on the Hausdorff distances were $e_{HD} = 0.37 \pm 0.38$ mm (0.02 – 1.72 mm range) for the proposed registration pipeline and $e_{HD}^{L} = 1.14 \pm 1.23$ mm (0.01 – 4.24 mm range) for the landmark-based registration (Figure 5b), with a statistically significant difference confirmed by ANOVA F-test ($F(45) = 10.28$, $p < 0.05$). The results of the two-tail t-test analysis on the Hausdorff distances metric also confirmed that the registration error of the proposed registration pipeline was significantly smaller than the landmark-based methodology ($t(42) = 3.55$, $p < 0.05$). The proposed registration pipeline is therefore approximately three times more accurate than the landmark-based methodology.

Qualitative representation of the results for one case is depicted in Figure 6. Colour-encoded Euclidean error distances were mapped onto the 3D surface of the distal radius extracted from the CT data for the proposed registration pipeline (Figure 6a) and for the landmark-based methodology (Figure 6b), to illustrate the location of errors on the cortical layer of the distal radius joint. White to red colour gradient maps the absolute error distances [0.0 – 1.3] in millimetres. Additionally, the outline of the 3D radius surface extracted from the aligned CT was shown on the MR image data in coronal, axial and sagittal planes (Figure 6c-e). Moreover, the MR image was colour-encoded and overlaid onto the registered CT image (Figure 6f) where red to yellow colour gradient maps to the intensity value range of [0 – 270] on our data sets, to include soft tissue while excluding cortical bone.

The proposed registration pipeline required on average 10 minutes to be applied to a routine clinical case, where 5 minutes contributed to the manual pre-alignment and 2 minutes to the algorithm runtime (Intel Core i7-6700 3.40GHz, 32GB RAM). In contrast, the landmark-based methodology required on average 15 minutes of landmark placement and 5 minutes of alignment, resulting in a total of 20 minutes of manual work. Finally, the gold-standard (GS) manual alignment took on average slightly less than 2 hours in total, where 40 minutes were necessary to perform the alignment of CT and MR images. The proposed registration pipeline is therefore approximately twice faster than the landmark-based methodology and 15 times faster than the gold-standard (Table 1).

Clinical Applications

To demonstrate the clinical feasibility and relevance of the proposed registration pipeline, we have retrospectively applied our CT-MR image registration pipeline in two clinical cases.

First, a case of bone tumour resection illustrates the importance of aligning CT and MR data to allow delineation of accurate resection margins, to reduce the risk of local recurrence and increase the chances of patient survival[33]. Tumour excision and resection of the most proximal 16 cm radius were performed on a case of a 29 year old female with an Ewing's sarcoma in the left proximal radius. Preoperatively, the patient underwent CT acquisition (1.0 mm slice thickness, 120 kV, Somatom Definition AS, Siemens Medical Systems, Erlangen, Germany) and T1-weighted MR (3.5 mm slice thickness, 1.5 Tesla system Siemens Medical Solutions, Erlangen, Germany). The radius bone and the tumour were manually segmented in the acquired coronal T1-weighted MR image, using the Mimics software (Version 19.0, Materialise, Belgium) and aligned to the CT-reconstructed 3D model of the radius with the gold-standard registration methodology (Figure 7d). The fused 3D models of bone and tumour served as a basis for 3D preoperative planning of the tumour resection. We applied the proposed registration pipeline and the landmark-based registration retrospectively to the imaging data of this patient and found mean registration errors of $e_{mean} = 0.11 \pm 0.06$ mm (Figure 7f) and $e^{L}_{mean} = 2.47 \pm 1.94$ mm (Figure 7e), respectively. Similarly, the clinically relevant maximum registration error based on the Hausdorff distance was $e_{HD} = 0.93$ mm for the proposed registration pipeline and $e^{L}_{HD} = 10.09$ mm for the landmark-based registration. Hence, the proposed registration pipeline was significantly more accurate than the landmark-based registration for this case. The results shown in Figure 7a-c should additionally underpin the clinical feasibility of the proposed methodology.

The second clinical case underlines the significance of jointly using CT and MR data to perform dynamic preoperative surgical planning of distal radioulnar joint (DRUJ) instability. We have previously developed a motion analysis model of the forearm to study the influence of the soft tissue on the forearm motion and to identify possible actors on the DRUJ instability[44]. One of the pre-requisites for the forearm motion analysis is the corresponding insertion points of the soft tissue structures under analysis, in order to generate the 3D ligament models. This step is part of a semi-automatic pipeline that allows the generation of the bone-ligament model. An easier landmark transfer between image modalities, using our automatic CT-MR registration pipeline, could potentially enable the full automation of the forearm motion analysis. For a proof of concept of the feasibility of our method for the ligament insertion identification and transfer between MRI and CT, we have chosen the dorsal and palmar radioulnar ligaments (RUL, Figure 8) due to their proved stabilizing role on the forearm motion[3,45]. In a first step, a radiologist identified insertion points of the RUL (shown as spheres in Figure 8) and marked on the MRI the distal sigmoid notch of the radius and the ulna styloid. In a second step, the proposed registration pipeline was applied to align the marked MR images to the CT of the same patient, obtaining the reference points of the ligaments in CT for both bones. As the relative anatomical position between the radius and ulna differs between MRI and CT acquisitions, the registration pipeline was applied first to the radius, obtaining the RUL insertion points at the sigmoid notch. Subsequently, the insertion points of RUL on the ulnar styloid were obtained by applying the registration pipeline to the ulna. Finally, the denoted positions were connected using a line segment in order to obtain a 3D representation of the dorsal (shown in magenta in Figure 8) and palmar (shown in green in Figure 8) radioulnar ligaments.

Discussion

In this study, we proposed an efficient CT to MR image registration pipeline for use in preoperative planning of forearm surgeries, showing that the approach can generate significantly more accurate results than established methodologies, such as landmark-based registration, while being considerably faster. We included several cases with deformed or non-anatomical radius shapes in the accuracy evaluation, which indicates that the proposed approach can be applied to healthy or pathological forearm bones. Finally, we demonstrated that the proposed approach is clinically feasible in two forearm applications.

Registration based on the manual alignment of reconstructed surface models can be considered as the clinical gold-standard, because it involves iterative visual inspection and correction steps controlled by a clinical expert. For manual alignment, it has been shown that experienced clinicians can reliably detect registration errors above approximately 0.2 millimeters[46]. However, manual alignment is very time-consuming, which limits the application in everyday clinical routine. In our evaluation, manual gold-standard registration took approximately two hours on average per case, including the time needed for manual segmentation of MRI data. Landmark-based registration can accelerate the alignment process, but the quality of the registration is highly dependent on the ability of the clinician to accurately identify corresponding anatomical landmarks in CT and MR images[47], which can be particularly challenging with the relatively low resolution of clinical MR images (Figure 4). Our approach has higher accuracy than the landmark-based registration, approximately three times better or 28% more accurate on average, and can also be attributed to the elimination of user-variability. These results indicate that the NMI registration used is appropriate for CT-MR registration of clinical data, as previously indicated[37].

While we performed the evaluation on clinical data retrospectively and only on one specific anatomical region, a similar accuracy is expected for the application of the registration to other forearm regions, due to similar image intensities. To apply the proposed approach to other orthopaedic surgeries, the following two parameters would need to be adapted: (1) the threshold value to create the 3D isosurface from CT data, and (2) the margin value, which controls the size of the binary mask to correctly isolate the targeted region from the rest of the image, and which enables an accurate and robust alignment. Additionally, while our pipeline performed well on relatively low-resolution MRI, its accuracy on other resolutions needs to be considered and tested. Hence, we advise readers to perform a validation of the achievable accuracies with the new image datasets and the newly-defined parameters, prior to clinical use.

A potential limitation of our work is the run time of the algorithm on relatively low-resolution MRI, which took two minutes on average, and would eventually increase considerably with the application of higher resolution image data. However, the registration could be accelerated in future by using a supervoxel-based variational framework with run time improvements reported to be up to 75%, with no negative impact on accuracy[48]. Furthermore, the pipeline requires a manual initialisation pre-alignment in order to ensure convergence of the algorithm to the correct optimum[32,37]. Techniques to find an initial coarse image alignment, including computing and aligning the centre of gravity and principal axes of images could be explored to render the proposed approach fully automatic and reduce the necessity of manual input[20].

Alternative automated registration techniques such those based on cross-correlation have also been researched; however, mutual information-based approaches are popular for MR-CT registration and have been proven to be the most accurate in other applications[20,37]. From our perspective, displaying the result of the registration to the user is highly important to permit visual verification. While we have not investigated image fusion methods in this work, approaches based on the wavelet transform could be applied to fuse multiple modalities into a single image[49].

The presented registration approach could contribute to the future development of more sophisticated preoperative planning scenarios. One area of interest could be functional planning, in which the patient-specific motion is simulated for determining the optimal preoperative plan of patients with pro-supination motion limitation or distal radius joint instability[6,44]. Such simulation models could be fit to new patient data by augmenting the CT data with soft tissue structures, such as ligaments or muscles obtained from MRI. Another interesting research direction is the calculation of synthetic CT (sCT) from MR data[50], which allows a radiation-free treatment to the patient, in addition to completely eliminating the need for multimodality registration. In future, voxel-based approaches for the generation of sCT could be a clinically viable option, if the acquisition time of multi-protocol and high-resolution MRI decreases due to technological progress in medical imaging.

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