REVIEW ARTICLE

3D dental image registration using exhaustive deformable models: a comparative study

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Objectives: Image registration is commonly used in dental applications for aligning imaging data sets, which is particularly useful when assessing the progression or regression of particular pathomorphologic conditions. However, due to the nature of the processed data or the data acquisition process itself, rigid body registration may be insufficient to accurately align the processed data sets. In such cases, deformable models are employed. This study presents a comparison of four well-established deformable models for aligning CBCT volumes.

Methods: The compared models include the original Demons algorithm, symmetric forces Demons, diffeomorphic Demons and level-set motion. The compared techniques are incorporated into a general image registration scheme featuring two distinct stages: a common, fast, rigid-based alignment for pre-registering the data and a finer elastic registration phase, based on the four compared deformation models.

Results: The proposed framework was applied to a total of 40 CBCT volume pairs with known and unknown initial differences.

Conclusions: After both qualitative and quantitative assessment of the produced aligned data, it was concluded that the level-set motion method outperformed all other techniques for data pairs with both unknown initial differences, as well as with known elastic deviations based on fixed sinusoidal models and B-splines.

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Introduction

The accurate alignment of imaging data is often a strong requirement in numerous medical applications.^{1–3} Commonly, the alignment of imaging data allows medical experts to compare different snapshots in time of a specific anatomical region, hence evaluate the progression or regression of certain pathomorphologic conditions or the success rate of a followed treatment scheme.⁴ This can be achieved by applying digital subtraction radiography techniques for revealing the differences in the anatomical region of interest, using images of the same modality

acquired over different time intervals.^{5–7} In addition, aligned data from different modalities (CT/MRI, CT/single-photon emission CT etc.) can be used for combining multiple levels of information concerning the examined anatomical region of interest. In both cases, accurate image alignment is required, as poorly aligned images may hinder the evaluation process, by introducing undesired artefacts or noise.^{8,9}

Image alignment has been proven to be especially advantageous in the evaluation of dental images. By applying digital subtraction radiography techniques, diagnosis of certain dental, oral or dentomaxillofacial conditions, such as carries, deformities or tumours, can be automated to a great extent.^{1,4} In addition, the

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analysis of dental images can help experts plan and evaluate complex operative procedures or treatment schemes, such as bone augmentation, by comparing oral radiographs of the patients in different time intervals (*e.g.* prior to and after surgery).⁴ As a result, numerous registration techniques focusing exclusively on dental applications have been proposed.¹⁰ Most of them concern two-dimensional (2D) dental radiographs or panoramic images, which are extensively used for the assessment of various dentomaxillofacial conditions.^{11,12} Recently, the combination of dental imaging data from different modalities has been explored, in an attempt to maximize the available information and hence the accuracy of the registration scheme.¹³ Moreover, the registration of three-dimensional (3D) dental data volumes was considered, using rigid-body semi-automatic or fully automatic techniques.^{14,15} Similar to 2D imaging, the alignment of 3D dental data, such as CBCT volumes, allows dentistry experts to readily compare two or more imaging data sets from various viewing angles, thus aiding clinical assessment.

In general, image alignment can be achieved through a repetitive trial-and-error procedure called registration.^{3,7,9} Through image registration, a floating imaging data set is spatially aligned according to a reference data set according to a selected transformation model. In every step of the iterative procedure, a new set of transformation parameters is introduced by a suitable optimization technique.^{16–18} The aforementioned transformation parameters are applied to the floating imaging data set and the transformed set is compared with the reference one, using a specified measure of match, which quantifies the alignment success rate.^{17,18} Usually, after several iterations of the registration scheme, the floating data set is spatially aligned to the reference data set. To maximize accuracy, all data points (pixels) of the two data sets are considered. Alternatively, registration can be based on a selected subset of the overall data points, thus dramatically improving processing time at the cost of reduced alignment accuracy.^{19,20}

In most cases, a rigid transformation model is sufficient for transforming the floating data set. A rigid model may transform an object by introducing translations and rotations along the axes of the reference system.³ However, if elastic deformations are present in either of the subject data sets, rigid models cannot fully describe the required transformation function, thus introducing misaligned regions along the boundaries of the elastic deformations.²¹ This case is quite common in medical imaging data, where elastic deformations may be caused by the nature of the data itself (soft tissue, breathing etc.) or be due to abnormalities in the acquisition process (CT beam deflection, patient movement etc.).^{21–23} Elastic (or non-rigid) models are usually defined by a large number of parameters, which describe the magnitude and direction of the virtual forces applied to the objects for deforming them globally or in particular regions.^{22,23}

Numerous elastic transformation models have been proposed over the years. Owing to the increased

complexity and computation time required by such models, most of them are based on processing a limited set of selected data points throughout the data.²⁴ The most popular elastic models for non-rigid registration are the spline-based approaches which are commonly used for interpolation and smoothing, including thin-plate splines, B-splines, T-splines and cubic splines.^{24–26} However, medical data usually require increased accuracy which is difficult to achieve using point-based models.²⁷ Therefore, exhaustive models are preferred in this case, where all data points of the processed data sets are considered.^{28,29} The most commonly employed exhaustive, elastic registration schemes are based on the Demons algorithm.³⁰ Several derivatives of the particular algorithm have been developed over the years, some of which are optimized for increased accuracy while others for reduced processing time, which is a common issue for Demons-based techniques.^{31,32}

In this article, a comparative study is presented for examining four of the most common elastic deformation models, which are incorporated into a common, two-stage registration scheme. More specifically, Demons, symmetric Demons, diffeomorphic Demons and level-set motion have been considered.^{30–33} All compared models were applied to 3D CBCT data with both known and unknown spatial differences. Their performance was evaluated in terms of the achieved registration accuracy as well as the required processing time.

The rest of the article is organized as follows: in the Materials and methods section, the proposed elastic registration framework is presented, along with the compared elastic deformable models. In the Results section, the comparative results are presented and, finally, the Discussion section examines some of the key aspects of the compared elastic registration techniques.

Methods and materials

This study is concerned with the comparison of four exhaustive deformable models for aligning 3D CBCT data sets. More specifically, the original Demons algorithm, symmetric forces Demons, diffeomorphic Demons and level-set motion were examined using a common registration framework consisting of two distinct processing stages. According to the proposed framework, the reference and floating data sets are initially pre-aligned using a rigid-based registration scheme. Then, the pre-aligned data sets are accurately registered, using an elastic scheme, based on the four compared deformable models. The overall registration methodology is summarized in [Figure 1](#).

Data acquisition

For the purposes of this study, 20 CBCT data sets were employed from a study examining a novel periodontal bone augmentation surgical procedure.⁴ 20 patients

Figure 1 Diagram of the proposed two-stage registration scheme used to compare the four deformable models.

were treated in a two-stage surgical approach. The first stage involved an augmentation procedure, using a partial thickness flap design. If possible, implants were simultaneously placed during this stage. The edentulous ridge was augmented vertically and horizontally with non-resorbable bovine mineral and locally retrieved autogenous bone chips. After grafting, a non-resorbable titanium membrane or a resorbable membrane was trimmed and adapted over the grafted area. The membrane was fixed by titanium pins. Re-entry was performed after 9–12 months post-operatively. By this time, implant surfaces were covered by newly formed hard tissue. Fixation screws and cover screws were then removed to allow access for abutment connection. Finally, healing abutments were inserted. As a result, a total of 20 data pairs was produced, one for each patient, from an initial pre-operative acquisition and a subsequent post-operative acquisition. All data sets consist of 325 slices, each of which has a size of 400×400 pixels. In all cases, the pixel size was fixed at 0.4×0.4 mm, and the interslice distance was fixed at 0.4 mm.

In the aforementioned data sets, the initial spatial difference between the reference and floating data is unknown. Therefore, due to the acquisition process and equipment, those pre-operative and post-operative pairs exhibited both rigid and elastic deviations of unknown magnitude. The primary source of those deviations was mandible movement during acquisition, which cannot be modelled accurately using a conventional rigid transformation approach. 20 additional data pairs were constructed from manually transforming 20 reference data sets, by applying known, strictly elastic transforms (no rigid component), based on 2 fixed sinusoidal

models and B-splines. Specifically, for the two sinusoidal transforms, a 2D sinusoidal model and a 3D sinusoidal model were employed. In the first case, each slice of the original CBCT data was transformed according to Equation (1). As can be seen in Equation (1), each pixel with initial coordinates (x, y) is displaced to its new coordinates (x', y') using the parameters a and T which control the amount of elastic deformation.

$$\begin{aligned} x' &= x + a \sin\left(\frac{y}{T}\right) \\ y' &= y + a \cos\left(\frac{x}{T}\right) \end{aligned} \quad (1)$$

This transformation was employed to produce two data pairs using the parameter values $a = 8$, $T = 128$ and $a = 12$, $T = 64$, for simulating a small and a large initial deformation, respectively.

The employed 3D sinusoidal model is shown in Equation (2). In this case, the transformation is applied to the entire CBCT set and each pixel with the initial coordinates (x, y, z) is displaced to its new co-ordinates (x', y', z') . Again, the amount of elastic deformation is controlled by parameters a_x, a_y, a_z in the three axes of the 3D space and the parameter T which is common to all axes.

$$\begin{aligned} x' &= x + a_x \sin\left(\frac{\pi x}{T}\right) \\ y' &= y + a_y \sin\left(\frac{\pi y}{T}\right) \\ z' &= z + a_z \sin\left(\frac{\pi z}{T}\right) \end{aligned} \quad (2)$$

In this case, three data pairs were produced: a pair with small initial deformation with $(a_x, a_y, a_z, T) = (2, 2, 1, 16)$ a pair with mild initial deformation with $(a_x, a_y, a_z, T) = (5, 5, 2, 32)$ and a pair with large initial deformation with $(a_x, a_y, a_z, T) = (10, 10, 5, 32)$.

The rest of the data sets with known elastic differences were produced using the well-established B-splines model. In each case, the reference data set was transformed using B-spline curves defined by random parameters with fixed lower and upper limits. A B-spline of k order is defined by joining several polynomial segments of degree $k - 1$. The spline's basic function is defined by a knot vector $T = (t_0, t_1, \dots, t_m)$, which determines the m parameters of the curve. In our case, the B-spline curves of the third order were employed.

Pre-registration

The data pairs used in our study exhibited both rigid and elastic initial spatial deviations. As a result, it was necessary to apply a preliminary pre-registration technique for correcting all rigid displacements, before applying the compared deformation models. In addition, the processing time of the elastic registration stage of the

proposed methodology can be dramatically improved if the reference and floating data sets are roughly aligned.²⁹ Because any possible misalignment issues should be addressed by the finer elastic registration stage, the accuracy of the pre-registration can be compromised, in favour of reduced the processing time. Therefore in this study, a coarse, fast pre-registration method was applied for reducing the initial spatial differences of the reference and floating data sets. As a result, the overall processing time of the entire registration scheme was not greatly affected, whereas its final accuracy was dramatically improved. The preferred pre-registration scheme is summarized in Figure 2.

As can be seen in Figure 2, a classic intensity-based, rigid registration technique was employed. In each iteration of the registration process, the floating data set is transformed according to the parameters of a 3D affine transformation, as described in Equation (3), where (a_i, b_i, c_i) , $i = 1, 2, 3$ and (d_x, d_y, d_z) are its 12 independent parameters.³⁴

$$\begin{bmatrix} x' \\ y' \\ z' \end{bmatrix} = \begin{bmatrix} a_1 & a_2 & a_3 \\ b_1 & b_2 & b_3 \\ c_1 & c_2 & c_3 \end{bmatrix} \begin{bmatrix} x \\ y \\ z \end{bmatrix} + \begin{bmatrix} d_x \\ d_y \\ d_z \end{bmatrix} \quad (3)$$

Those parameters are calculated according to an optimization method, which in our case is the Nelder–Mead approach (Downhill Simplex), which is a widely used optimizer in image processing.³⁴ The preferred

Figure 2 Flow chart of the preferred pre-registration method.

measure of match, indicating the similarity of the reference and the transformed floating data set after each iteration, is Matte's mutual information (MMI).³⁵ The particular metric quantifies the negative mutual information between the reference and the floating data set, as a function of the transform parameters t and can be calculated using Equation (4), where p , p_T , p_R are the joint, marginal floating and marginal reference probability distributions, respectively. The probability distributions are calculated using Parzen histograms over all r and f histogram bins of the reference and floating data sets.

$$\text{MMI} = - \sum_f \sum_r p(f, r|t) \log \frac{p(f, r|t)}{p_T(f|t)p_R(r)} \quad (4)$$

Because only a rough alignment estimate is required for the pre-registration procedure, a simple linear interpolation scheme was employed for approximating real co-ordinate values.³⁴

Deformable registration models

According to the proposed methodology, pre-registration is followed by a finer elastic registration stage. Elastic registration is based on a suitable deformable model which dictates the way in which the floating image is elastically deformed in an attempt to match the reference image as accurately as possible. In our case, four deformable exhaustive registration models were compared, namely, the original Demons algorithm, symmetric forces Demons, diffeomorphic Demons and level-set motion. Each of those models is described in the following sections:

Demons: Demons algorithm describes an optimization procedure in which an optimal displacement field is calculated.³⁰ The displacement field defines the force that needs to be applied to each pixel of the floating data set to spatially approximate the reference data set. Given a reference data set I_R and a floating data set I_F , the Demons algorithm estimates the non-parametric transformation s , which describes its displacement field. Therefore, as can be seen in Equation (5), each data point p is deformed according to s .^{36,37}

$$s : p \rightarrow p + s(p) \quad (5)$$

After the transformation is initialized, an optimal flow is calculated, which can in turn be used to estimate the direction and magnitude of the displacement force in each data point.³⁸ The particular force can be modelled as a vector and is approximated through Equation (6), where $\sigma_i(p) = |I_R(p) - I_F \circ c(p)|$, $J^p = \nabla_p^T I_R$, $\circ$ is the composition operator and σ_x controls the maximum step length.³⁷

$$u(p) = - \frac{I_R(p) - I_F \circ c(p)}{\|J^p\|^2 + \frac{\sigma_i^2(p)}{\sigma_x^2}} J^{pT} \quad (6)$$

The non-parametric transformation c approximates the spatial transformation s . Initially, $c = s$, which becomes $c \leftarrow s + u$, after a finite number of iterations. During the N th iteration, the Demons force can be calculated using Equation (7).³⁷

$$u_n(p) = u_{n-1}(p) - \frac{I_R(p) - I_{F \circ c_{n-1}}(p)}{\|J^p\|^2 + \frac{|I_R(p) - I_{F \circ c_{n-1}}(p)|^2}{\sigma_x^2}} J^{pT} \quad (7)$$

The spatial deviations between the reference and the deformed imaging data can be quantified through the definition of a global energy function, which needs to be minimized to achieve accurate registration. Initially, the global energy $E(s)$ can be calculated using Equation (8), where Sim is the similarity measure quantifying the resemblance of the compared imaging data. In this case, the similarity measure can be calculated through Equation (9).^{37,38}

$$E(s) = \frac{1}{\sigma_i^2} Sim(I_R, I_{F \circ s}) + \frac{1}{\sigma_T^2} Reg(s) \quad (8)$$

$$Sim(I_R, I_{F \circ s}) = \frac{\|I_R - I_{F \circ s}\|^2}{2} \quad (9)$$

Moreover, $Reg(s)$ is a regularization term, σ_i represents the noise on the image intensity and σ_T controls the amount of regularization, which smoothens the resulting transformed imaging data. After a finite number of iterations and taking transformation c into account, the energy function can be re-estimated using Equation (10), considering an additive Gaussian noise component on displacements.³⁹

$$E(c, s) = \left\| \frac{1}{\sigma_i} (I_R - I_{F \circ c}) \right\|^2 + \frac{1}{\sigma_T^2} Reg(s) + \frac{1}{\sigma_x^2} dist(s, c)^2 \quad (10)$$

In the particular equation, σ_x accounts for a spatial uncertainty on the transformed imaging data, $dist(s, c) = \|c - s\|$ and $Reg(s) = \|\nabla_s\|^2$.

Symmetric forces Demons: Owing to its popularity in elastic image registration, numerous variations of the original Demons algorithm have been proposed over the years. Most derivative approaches change the way the deformation forces are calculated.^{38–41} According to Equation (7), an asymmetry is introduced due to the fact that the gradient of the reference data set is taken into account. To overcome this issue, the symmetric forces Demons method was proposed.⁴⁰ The particular approach considers both the gradient of the reference and the deformed floating imaging data for calculating the local forces. In that case, the optimal flow of the scheme can be expressed using Equation (11), where $\sigma_i(p) = |I_R(p) - I_{F \circ c}(p)|$, $J^p = (\nabla_p^T I_R + \nabla_p^T (I_{F \circ s}))/2$ and σ_x controls the maximum deformation step length.⁴⁰

$$u(p) = - \frac{I_R(p) - I_{F \circ s}(p)}{\|J^p\|^2 + \frac{\sigma_i^2(p)}{\sigma_x^2}} J^{pT} \quad (11)$$

Diffeomorphic Demons: Another well-established derivative of the original Demons algorithm is the diffeomorphic Demons technique.³¹ According to the particular technique, the original optimization procedure proposed by the Demons algorithm is performed using diffeomorphic transformations. Diffeomorphisms do not form a vector space, like most spatial transformations used in medical imaging.⁴² Instead, they can be expressed using Lie groups.⁴³ As a result, the original energy function [Equation (8)] is expressed using diffeomorphisms. In that case, the primary objective of the minimization process is to estimate an update step u on the Lie algebra from a transformation s , and then use a rule on the Lie group through the exponential map. Therefore, instead of $c \leftarrow s + u$, which was applied to the original Demons algorithm, diffeomorphic Demons considers the following equation:⁴¹

$$c \leftarrow s \circ \exp(u) \quad (12)$$

In that case, the distance between two diffeomorphisms is $dist(s, c) = \|Id - \exp(u)\| \approx \|u\|$.

The algorithmic procedure of diffeomorphic Demons is similar to one of the original Demons algorithm, apart from the estimation of c , which is presented in Equation (12). As a result, the energy function in this case can be calculated using Equation (13).⁴¹

$$E_s^{corr}(u) = \|I_R - I_{F \circ s \circ \exp(u)}\|^2 + \frac{\sigma_i^2}{\sigma_x^2} dist(s, s \circ \exp(u))^2 \quad (13)$$

Level-set motion: Level-set motion is a deformable registration model, based on level-set evolution theory.³² According to the application of the particular theory in image processing, the floating image moves and evolves at a speed proportional to its difference to the reference image. Evolution terminates when that difference is minimized, which practically means that the reference and floating data sets are aligned. The evolution of the images is performed along their respective normal vectors.^{32,44}

Given a floating image $I_F(X)$ and reference image $I_R(X')$, where $X = V(X')$ and $X, X' \in R^3$ for the 3D imaging data used in this study, the floating image needs to be evolved in such a way that, in the end of the process, it will spatially match the reference image. This can be achieved by estimating an optimal transformation V which describes the spatial differences of the subject images. The particular transformation is estimated through a recursive procedure, resembling the evolution of living cells.³² The evolution from I_F to I_R can be described by a motion field, which can be calculated using Equation (14), where $I(X, 0) = I_F(X)$.

$$I_t(X, t) = (I_R(X) - I(X, t)) \nabla(I(X, t)) \quad (14)$$

Then, the transformation motion field V , can be estimated through Equation (15), where $\vec{V}(X, 0) = \vec{0}$.

$$\frac{dV}{dt} = \left(I_R(X) - I_F(\vec{V}(X)) \right) \frac{\nabla(I_F(\vec{V}(X)))}{\|\nabla(I_F(\vec{V}(X)))\|} \quad (15)$$

After each iteration of the algorithm, the transformation is updated according to Equation (16), where t is the time, dV is the incremental motion field and Δt is the selected time step.⁴⁴

$$V_{n+1} = V_n + \left(\frac{dV}{dt} \right) \Delta t \quad (16)$$

The aforementioned evolutionary procedure stops when $S = I_R(X) - I(X, t)$ is minimized or when $\nabla(I(X, t)) = 0$.

However, the above estimation procedure is very sensitive to noise in the image. To minimize noise interference, $I(X, t)$ is convolved with a Gaussian kernel.⁴⁴ In that case, Equations (13) and (14) are suitably modified according to Equations (17) and (18), respectively, where G_σ is a Gaussian kernel with standard deviation σ and $\times$ is the convolution operator.

$$I_t(X, t) = (I_R(X) - I(X, t)) \nabla(G_\sigma \times I(X, t)) \quad (17)$$

To stabilize the computation of the transformation when $\nabla(G_\sigma \times I_F(\vec{V}(X)))$ is close to zero, a small positive constant α is added, as can be seen in Equation (18).^{32,44}

$$\frac{dV}{dt} = \left(I_R(X) - I_F(\vec{V}(X)) \right) \frac{\nabla(G_\sigma \times I_F(\vec{V}(X)))}{\nabla(G_\sigma \times I_F(\vec{V}(X))) + \alpha} \quad (18)$$

Level-set motion has two basic differences compared with the Demons algorithm. In level-set motion, the magnitude of the motion vector is a function of the differences in intensity between the respective pixels from the reference and floating data sets. As a result, motion vectors should be proportional to the respective gradients. On the other hand, in the Demons algorithm, the motion vector is defined as a function of both the intensity differences and gradient magnitude between the corresponding pixels of the reference and floating data sets, leading to an unstable vector field. In addition, in level-set motion the gradients are calculated using Minmod finite differences instead of central differences, as is the case in Demons.⁴⁴

Results

The four exhaustive deformation models described in the Materials and methods section were assessed both qualitatively and quantitatively, as far as their registration accuracy is concerned. To accomplish this, a custom image CBCT registration application was implemented using the Insight Segmentation and Registration Toolkit.⁴⁵ All available data pairs, namely 20 pairs with unknown and 20 more pairs with known initial spatial differences, were aligned using the proposed two-stage registration scheme and the four featured deformable models. In each case, the alignment accuracy was examined and quantified. All relevant results are presented in the following subsections:

Qualitatively evaluation

Qualitative evaluation was performed by means of visual assessment. To accomplish this, the reference, floating and aligned floating data sets were reconstructed, using a specialized volume visualization library.⁴⁶ In all cases, the produced volumes were fused before and after registration, which provided an immediate estimate of the achieved alignment accuracy. For better clarity of the presented results, only hard tissue was modelled, by applying a simple intensity-based threshold filter. Some examples of the above visual assessment scheme are presented in Figure 3, which concerns a data set with unknown initial spatial deviations, and Figure 4 which showcases a data pair with known elastic deviations (3D sinusoidal with $a_x = 10$, $a_y = 10$, $a_z = 5$ and $T = 32$). Figures 3a and 4a show the fused volumes prior to registration while Figures 3b and 4b depict the intermediate results obtained after the application of the pre-registration method described in the Materials and methods section. The aligned volumes obtained using the Demons algorithm are presented in Figures 3c and 4c while the results obtained after applying the symmetric forces and diffeomorphic Demons implementations are shown in Figures 3d, 4d, 3e and 4e, respectively. Finally, the fused aligned volumes obtained using the level-set motion model are illustrated in Figure 3f and 4f.

A different visual assessment approach is presented in Figure 5. The particular comparative scheme utilizes the edges of the depicted reference objects for quantifying the accuracy of registration. In this case, a data pair with unknown initial spatial differences is employed. Firstly, the edges of the reference preoperative data set are extracted, using a simple 3×3 Sobel operator.⁴⁷ Then, a single slice of the reference data and its corresponding slices from the floating, pre-registered and fully registered data sets were extracted. The calculated edges were superimposed into all extracted slice images, thus providing a visual estimation of the achieved registration accuracy in each step of the proposed scheme and for each compared deformable model. As can be seen in Figure 5, significant improvement was achieved after pre-registration (Figure 5b), compared with the

Figure 3 Registration results of a data pair with unknown initial differences (Pair 3). Fusion of three-dimensional CBCT pre-operative and post-operative volumes (a) before registration, (b) after pre-registration and after full registration using (c) Demons algorithm, (d) symmetric forces Demons, (e) diffeomorphic Demons and (f) level-set motion.

unregistered slices (Figure 5a). However, it is quite clear that the linear alignment method featured in the pre-registration process is insufficient for accurately registering the particular data pair. Accuracy is dramatically improved after the application of any of the four compared deformation models, as can be seen in Figure 5c–f, where the results of the original Demons algorithm, symmetric forces Demons, diffeomorphic Demons and level-set motion are presented, respectively.

As can be seen in all presented examples in Figures 3–5, it is evident that the pre-registration phase dramatically improves the spatial alignment of the reference and floating data sets. Moreover, further improvement is achieved by applying any of the four compared elastic deformation techniques. However, it is very difficult to visually perceive the difference in the obtained alignment accuracy, when comparing the fused volumes produced by applying the four compared deformation models. Consequently, quantitative evaluation of the results is necessary.

Quantitative evaluation

Quantitative analysis of the results was performed by means of quantizing the alignment accuracy using a well-defined similarity metric. In our case, the MMI metric was used. The particular metric was also used in the fast pre-registration stage of the proposed registration scheme and can be calculated using Equation (4).

In all examined data pairs, the MMI values were obtained prior to registration, after the completion of the pre-registration stage and after the application of all four compared deformation models. The results for all data pairs with unknown initial spatial differences are shown in Table 1. As can be seen in Table 1, significant improvement (up to 40%) was achieved after the pairs were pre-registered and additional accuracy was achieved after applying any of the four compared deformation models (up to 136%). Because MMI is a measure of similarity, higher values of the metric correspond to a better match between the reference and aligned data sets. According to the recorded MMI

Figure 4 Registration results of a data pair known three-dimensional (3D) sinusoidal initial differences described by $(a_x, a_y, a_z, T) = (10, 10, 5, 32)$. Fusion of 3D CBCT reference and floating volumes (a) before registration, (b) after pre-registration and after full registration using (c) Demons algorithm, (d) symmetric forces Demons, (e) diffeomorphic Demons and (f) level-set motion.

values of Table 1, in 14 out of 20 cases, the level-set motion method achieves superior accuracy than the three other deformation models, closely followed by the original Demons implementation. The symmetric forces and diffeomorphic Demons algorithms seem to perform similarly. All techniques achieved consistent performance, which is indicated by the relatively low standard deviation values.

The superiority of the level-set motion method on the particular data sets was confirmed by conducting several paired *t*-tests for level-set motion and the rest of the compared deformation models. The null hypothesis that the performance of the compared methods in terms of MMI did not differ significantly was rejected, as a maximum $p = 0.043$ was recorded when pairing level-set motion with the original Demons algorithm. This practically means that level-set motion performs consistently better than the compared deformation models for the particular data sets, with a confidence level of 95%.

The same quantitative evaluation scheme was applied to the 20 additional data pairs with known initial spatial deviations, which were produced using the two sinusoidal models described in Equation (1) and

Equation (2), as well as the B-splines model. The results for this case are presented in Table 2. As can be seen in Table 2, pre-registration in this case has a lesser effect on the overall registration accuracy. The reason for this is that the applied sinusoidal and B-splines deformation models are purely elastic, with no or very limited rigid components. On the other hand, the proposed pre-registration method is designed to correct only rigid deviations, as it features a rigid-based affine transformation, which is unable to cope with elastic deformations. Nevertheless, the minor improvement achieved in all cases is enough to allow the subsequent elastic registration stage to align the data properly. According to the results shown in Table 2, the level-set motion algorithm seems to outperform on average all other deformation models for data sets with known initial deviations. This practically means that the particular approach is better suited for dealing with extreme elastic deformations on the processed imaging data. For the particular data sets, the performance of all examined Demons-based techniques is quite close, with the original Demons implementation having an edge over symmetric forces and diffeomorphic Demons.

Figure 5 Registration results of a data pair with unknown initial differences (Pair 1) on a single common data slice (193). Superposition of the edges of the slice from the reference data set on the corresponding slice from the floating data set (a) before registration, (b) after pre-registration and after full registration using (c) Demons algorithm, (d) symmetric forces Demons, (e) diffeomorphic Demons and (f) level-set motion.

A statistical two-tailed, paired *t*-test was performed on the values shown in Table 2, with the null hypothesis that the pairwise-compared models do not produce aligned data that differ significantly in terms of the measured MMI. The null hypothesis was rejected when comparing the level-set motion algorithm with any of the Demons-based approaches ($p = 1.548 \times 10^{-4}$, $p = 1.096 \times 10^{-4}$ and $p = 1.613 \times 10^{-7}$ for Demons, symmetric forces Demons and diffeomorphic Demons, respectively), indicating that level-set motion systematically outperforms all other compared methods for the particular data sets with known initial elastic deviations.

Discussion

In this study, four exhaustive deformable models were compared, namely the original Demons algorithm,

symmetric forces Demons, diffeomorphic Demons and level-set motion. The four compared techniques were incorporated into a common 3D registration scheme which consisted of two stages: a rigid pre-registration stage and an elastic fine registration stage. The proposed registration scheme was applied to 20 pre-operative and post-operative CBCT volume pairs. The volumes in each pair were aligned, using the pre-operative data set as the reference. In addition, the proposed registration scheme was applied to 20 more volume pairs featuring data sets with known elastic initial deformations (sinusoidal and B-splines). In all cases, the alignment accuracy was assessed both qualitatively and quantitatively. According to the obtained MMI measurements, the level-set motion model systematically outperformed all other techniques for the pre-operative and post-operative volume pairs with unknown initial differences. The same pattern was recorded for the examined cases with known initial

Table 1 Quantitative results in terms of Matte's mutual information for all data pairs with unknown initial differences

Data pair	Before registration	Pre-registration	Demons	Symmetric forces Demons	Diffeomorphic Demons	Level-set motion
1	0.084	0.106	0.199	0.170	0.180	0.250
2	0.242	0.280	0.450	0.441	0.440	0.440
3	0.138	0.153	0.238	0.210	0.213	0.296
4	0.137	0.138	0.224	0.212	0.205	0.251
5	0.191	0.214	0.340	0.272	0.255	0.413
6	0.199	0.208	0.381	0.322	0.310	0.410
7	0.253	0.291	0.510	0.450	0.443	0.555
8	0.127	0.163	0.340	0.288	0.315	0.322
9	0.234	0.325	0.447	0.426	0.426	0.420
10	0.093	0.094	0.126	0.110	0.112	0.167
11	0.440	0.537	0.642	0.599	0.590	0.700
12	0.215	0.238	0.377	0.365	0.383	0.500
13	0.343	0.479	0.629	0.522	0.546	0.677
14	0.458	0.632	0.790	0.668	0.675	0.641
15	0.516	0.560	0.717	0.687	0.682	0.820
16	0.511	0.628	0.855	0.787	0.790	0.836
17	0.538	0.550	0.820	0.754	0.755	0.881
18	0.476	0.540	0.676	0.634	0.631	0.653
19	0.794	0.823	0.917	0.894	0.894	0.953
20	0.388	0.540	0.680	0.600	0.570	0.740
$\mu \pm \sigma$	0.319 ± 0.189	0.375 ± 0.215	0.518 ± 0.239	0.471 ± 0.226	0.471 ± 0.225	0.546 ± 0.233

Bold values correspond to the best achieved measure of match (MMI in this case). In our case the higher the value of the MMI, the more accurate the achieved registration quality.

elastic deformations, where again, level-set motion systematically outperformed all Demons-based approaches. In all cases, the original Demons algorithm was by far the slowest method.

The performance of all compared elastic deformation models depends on a number of parameters which determine their behaviour, processing speed and accuracy. A common parameter affecting all compared techniques is the smoothing parameter σ . In this study, the optimal

value of σ was used for each method. To determine the optimal value of the particular parameter, several trials were performed with various values of σ , using several of the available data sets. Figure 6 illustrates a typical case of how the value of σ affects the registration accuracy of the proposed registration scheme for the original Demons algorithm (Figure 6a), symmetric forces Demons (Figure 6b), diffeomorphic Demons (Figure 6c) and level-set motion (Figure 6d), in terms of

Table 2 Quantitative results in terms of Matte's Mutual Information for all data pairs with known initial elastic differences

Floating data transform	Before registration	Pre-registration	Demons	Symmetric forces Demons	Diffeomorphic Demons	Level-set notion
2D Sin. (α , T)						
(8, 128)	0.057	0.104	0.247	0.179	0.179	0.220
(12, 64)	0.044	0.056	0.210	0.139	0.137	0.188
3D Sin. (a_x , a_y , a_z , T)						
(2, 2, 1, 16)	0.125	0.127	0.161	0.151	0.150	0.170
(5, 5, 2, 32)	0.080	0.083	0.220	0.162	0.152	0.191
(10, 10, 5, 32)	0.049	0.052	0.200	0.133	0.123	0.182
B-splines ($t_{\min}$, $t_{\max}$)						
(-5, 5)	0.570	0.729	0.797	0.760	0.773	0.884
(-10, 10)	0.480	0.633	0.800	0.770	0.751	0.884
(-15, 15)	0.420	0.535	0.800	0.770	0.733	0.877
(-20, 20)	0.390	0.475	0.722	0.690	0.670	0.875
(-25, 25)	0.390	0.556	0.793	0.760	0.750	0.881
(-30, 30)	0.340	0.420	0.750	0.694	0.640	0.860
(-35, 35)	0.275	0.434	0.791	0.750	0.710	0.870
(-40, 40)	0.270	0.385	0.695	0.667	0.572	0.840
(-45, 45)	0.150	0.280	0.710	0.661	0.595	0.790
(-50, 50)	0.190	0.363	0.752	0.675	0.594	0.811
(-55, 55)	0.200	0.310	0.660	0.625	0.532	0.810
(-60, 60)	0.220	0.310	0.740	0.643	0.561	0.793
(-65, 65)	0.220	0.315	0.694	0.553	0.480	0.693
(-70, 70)	0.280	0.240	0.580	0.560	0.431	0.740
(-75, 75)	0.130	0.210	0.572	0.544	0.430	0.751
$\mu \pm \sigma$	0.244 ± 0.150	0.331 ± 0.195	0.595 ± 0.238	0.544 ± 0.242	0.498 ± 0.230	0.666 ± 0.286

2D, two-dimensional; 3D, three-dimensional; sin., sinusoidal.

Bold values correspond to the best achieved measure of match (MMI in this case). In our case the higher the value of the MMI, the more accurate the achieved registration quality.

Figure 6 Recorded accuracy of the final aligned data in terms of the Matte's mutual information for different values of σ , using (a) Demons, (b) symmetric forces Demons, (c) diffeomorphic Demons and (d) level-set motion.

the calculated MMI metric. As can be seen in Figure 6, the smoothing parameter σ plays a key role in the accuracy of the deformable model, with the exception of the level-set motion approach, which is affected to a lesser degree, compared with all Demons-based techniques.

Processing time is an important factor which determines the efficiency of any image registration method. Processing time is also of particular importance in medical applications, since alignment should be both very accurate and be achieved in reasonable time intervals. As a result, a time analysis study was

Table 3 Processing time (in seconds) for all compared deformation models on data pairs with unknown initial deviations

Data pair	Pre-registration	Demons	Symmetric forces Demons	Diffeomorphic Demons	Level-set motion
1	30	227	125	142	143
2	49	251	127	164	165
3	31	248	116	131	145
4	17	199	108	119	130
5	31	218	118	143	156
6	31	217	116	128	146
7	17	203	95	120	127
8	30	219	107	146	146
9	52	236	129	153	161
10	28	210	105	130	150
11	29	214	109	135	147
12	40	242	119	143	152
13	75	261	160	176	197
14	37	306	114	142	157
15	126	350	214	270	247
16	34	220	116	159	160
17	50	247	162	154	201
18	21	211	99	128	140
19	87	272	170	189	196
20	24	212	102	125	136
$\mu \pm \sigma$	41.950 ± 26.663	238.150 ± 37.262	125.550 ± 29.359	149.850 ± 33.702	160.100 ± 29.173

Table 4 Processing time (in seconds) for all compared deformation models on data pairs with known initial elastic deviations

<i>Data pair</i>	<i>Pre-registration</i>	<i>Demons</i>	<i>Symmetric forces Demons</i>	<i>Diffeomorphic Demons</i>	<i>Level-set Motion</i>
2D Sin. (α, T)					
(8, 128)	30	790	518	596	527
(12, 64)	36	528	240	326	274
3D Sin, (a_x, a_y, a_z, T)					
(2, 2, 1, 16)	109	570	320	377	343
(5, 5, 2, 32)	34	500	242	300	265
(10, 10, 5, 32)	40	536	243	337	271
B-splines (t_{min}, t_{max})					
(−5, 5)	180	762	354	480	650
(−10, 10)	78	625	256	381	424
(−15, 15)	76	630	253	375	391
(−20, 20)	44	561	232	350	355
(−25, 25)	59	600	249	387	407
(−30, 30)	46	590	316	345	354
(−35, 35)	85	629	272	373	388
(−40, 40)	76	620	253	373	392
(−45, 45)	66	614	241	371	378
(−50, 50)	77	641	266	371	379
(−55, 55)	85	634	262	391	402
(−60, 60)	50	615	227	352	362
(−65, 65)	51	600	235	355	356
(−70, 70)	83	660	260	386	393
(−75, 75)	50	596	238	365	410
$\mu \pm \sigma$	67.750 ± 33.893	615.050 ± 68.539	273.850 ± 66.124	379.550 ± 61.592	386.050 ± 85.299

2D, two-dimensional; 3D, three-dimensional; sin., sinusoidal.

performed for all data pairs and all compared deformation models featured in this article.

Table 3 shows the obtained processing times for all data pairs with unknown initial spatial differences. As can be seen in Table 3, the fastest approach is the symmetric forces implementation of the Demons algorithm, closely followed by the diffeomorphic Demons and level-set motion. The original Demons algorithm was by far the slowest deformation model when used to register the pre-aligned pre-operative and post-operative CBCT volumes featured in this study.

Likewise, Table 4 illustrates the obtained processing times for all data pairs with known initial deviations, based on sinusoidal and B-splines models. Again, the symmetric forces Demons method was faster than both diffeomorphic Demons and level-set motion. Once more, the original Demons algorithm was the slowest of the four compared elastic registration models. In addition, the processing time for the data pairs with purely elastic initial differences is increased, compared with that of the data pairs with unknown initial spatial deviations (Table 3), which contain both rigid and elastic components. The reason for this is the reduced efficiency of the pre-registration stage in those cases, which causes the elastic registration stage to perform an increased number of iterations for compensating for the poorly aligned pre-registered data.

The proposed registration methodology, including the four compared deformation models, was implemented in a custom console application coded in the C++ programming language. The implementation of all registration routines, including the four deformable models, was based on the Insight Segmentation and

Registration Toolkit library. The data volumes were reconstructed and presented using the specialized volume visualization library. All processing was performed on a common reference system (Dual core processor running at 2.2GHz with 2GB of Random Access Memory, running on a 64-bit Linux operating system).

Conclusions

In this article, four exhaustive, elastic deformation models were compared for registering 3D CBCT volumes. The original Demons algorithm, symmetric forces Demons, diffeomorphic Demons and level-set motion were all incorporated into the proposed two-stage registration scheme and applied to 20 volume pairs of pre-operative and post-operative CBCT volumes with unknown initial differences and 20 volume pairs featuring known initial elastic sinusoidal and B-spline deformations. After qualitative and quantitative assessment, it was concluded that the level-set motion method achieved the best accuracy on average for all examined cases. In all cases, pre-registration improved the initial spatial alignment of the processed data. Additional accuracy improvement was achieved by applying any of the four compared deformation models.

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References

1. Yoon DC. A new method for the automated alignment of dental radiographs for digital subtraction radiography. *Dentomaxillofac Radiol* 2000; **29**: 11–9. doi: <https://doi.org/10.1038/sj.dmf.4600487>
2. Matsopoulos GK, Asvestas PA, Mouravliansky NA, Delibasis KK. Multimodal registration of retinal images using self organizing maps. *IEEE Trans Med Imaging* 2004; **23**: 1557–63. doi: <https://doi.org/10.1109/tmi.2004.836547>
3. Oliveira FP, Tavares JM. Medical image registration: a review. *Comput Methods Biomech Biomed Engin* 2014; **17**: 73–93. doi: <https://doi.org/10.1080/10255842.2012.670855>
4. Economopoulos TL, Asvestas PA, Matsopoulos GK, Molnár B, Windisch P. Volumetric difference evaluation of registered three-dimensional pre-operative and post-operative CT dental data. *Dentomaxillofac Radiol* 2012; **41**: 328–39. doi: <https://doi.org/10.1259/dmfr/94040044>
5. Zacharaki EI, Matsopoulos GK, Asvestas PA, Nikita KS, Gröndahl K, Gröndahl HG. A digital subtraction radiography scheme based on automatic multiresolution registration. *Dentomaxillofac Radiol* 2004; **33**: 379–90.
6. Mol A, Dunn SM. The performance of projective standardization for digital subtraction radiography. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; **96**: 373–82. doi: [https://doi.org/10.1016/s1079-2104\(03\)00357-3](https://doi.org/10.1016/s1079-2104(03)00357-3)
7. Lehmann TM, Gröndahl HG, Benn DK. Computer-based registration for digital subtraction in dental radiology. *Dentomaxillofac Radiol* 2000; **29**: 323–46. doi: <https://doi.org/10.1038/sj.dmf.4600558>
8. Matsopoulos GK, Asvestas PA, Mouravliansky NA, Delibasis KK. Multimodal registration of retinal images using self organizing maps. *IEEE Trans Med Imaging* 2004; **23**: 1557–63. doi: <https://doi.org/10.1109/tmi.2004.836547>
9. Saxena S, Singh RK. A survey of recent and classical image registration methods. *Sig Proc Im Proc Patt Recogn* 2014; **7**: 167–76. doi: <https://doi.org/10.14257/ijsp.2014.7.4.16>
10. Mekky NE, Abou-Chadi FEZ, Kishk S. A comparison of image registration techniques in clinical dentistry. Radio Science Conference 2009.
11. Mekky NE, Abou-Chadi FEZ, Kishk S. Computer Engineering and Systems, ICCES 2010. p. 261–7.
12. Nikaido A, Ito K, Aoki T, Kosuge E, Kawamata R. A phase-based image registration algorithm for dental radiograph identification. IEEE International Conference on Image Processing 2007; Vol. 6: pp. 229–32.
13. Rathore G, Dhir V. Image registration for dental x-ray images using hybrid technique. *Int J Innov Res Sci Eng Technol* 2013; **2**: 6014–18.
14. Abduo J, Bennamoun M. Three-dimensional image registration as a tool for forensic odontology: a preliminary investigation. *Am J Forensic Med Pathol* 2013; **34**: 260–6. doi: <https://doi.org/10.1097/paf.0b013e31829f6a29>
15. Destrez R, Treuillet S, Lucas Y, Albouy-Kissi B. Semi-automatic registration of 3D orthodontic models from photographs. *Proc. SPIE* 2013; 8669.
16. Zhaoyang W, Hien K, Hieu N, Minh L. Digital image correlation in experimental mechanics and image registration in computer vision: similarities, differences and complements. *Opt Lasers Eng* 2015; **65**: 18–27.
17. Pluim JPW, Maintz JBA, Viergever MA. Mutual-information-based registration of medical images: a survey. *IEEE Trans Med Imaging* 2003; **22**: 986–1004. doi: <https://doi.org/10.1109/tmi.2003.815867>
18. Keller Y, Averbuch A. Multisensor image registration via implicit similarity. *IEEE Trans Pattern Anal Mach Intell* 2006; **28**: 794–801. doi: <https://doi.org/10.1109/tpami.2006.100>
19. Pan MS, Tang JT, Rong QS, Zhang F. Medical image registration using modified iterative closest points. *Int J Numer Method Biomed Eng* 2011; **27**: 1150–66. doi: <https://doi.org/10.1002/cnm.1421>
20. Zhang X, Li L, Tu D. Point cloud registration with 2D and 3D fusion information on mobile robot integrated vision system. IEEE International Conference on Robotics and Biomimetics (ROBIO) 2013. pp. 1187–92.
21. Sotiras A, Davatzikos C, Paragios N. Deformable medical image registration: a survey. HAL-INDIA; 2013.
22. Crum WR, Hartkens T, Hill DL. Non-rigid image registration: theory and practice. *Br J Radiol* 2004; **77**: S140–53. doi: <https://doi.org/10.1259/bjr/25329214>
23. Parraga A, Craene MD, Pettersson J, Susin A, Macq B. Non-rigid registration methods assessment of 3D CT images for head-neck radiotherapy, SPIE Medical Imaging 2007: Image Processing, San Diego, CA, USA; 2007. doi: <https://doi.org/10.1117/12.709368>
24. Bookstein FL. Principal warps: thin-plate splines and the decomposition of deformations. *IEEE Trans Pattern Anal Mach Intell* 1989; **11**: 567–85. doi: <https://doi.org/10.1109/34.24792>
25. Eilers PHC, Marx BD. Flexible smoothing with B-splines and penalties (with comments and rejoinder). *Stat Sci* 1996; **11**: 89–121. doi: <https://doi.org/10.1214/ss/1038425655>
26. Scott MA, Simpson RN, Evans JA, Lipton S, Bordas SPA, Hughes TJR, et al. Isogeometric boundary element analysis using unstructured T-splines. *Comput Methods Appl Mech Eng* 2013; **254**: 197–221. doi: <https://doi.org/10.1016/j.cma.2012.11.001>
27. Baghaie A, Yu Z, Roshan D'souza M. Fast mesh-based medical image registration. Computer Vision and Pattern Recognition. ISVC 2014.
28. Zhang J, Wang J, Wang X, Feng D. The adaptive FEM elastic model for medical image registration. *Phys Med Biol* 2014; **59**: 97–118. doi: <https://doi.org/10.1088/0031-9155/59/1/97>
29. Li B, Yang G, Coatrieux JL, Li B, Shu H. 3D nonrigid medical image registration using a new information theoretic measure. *Phys Med Biol* 2015; **60**: 8767–90. doi: <https://doi.org/10.1088/0031-9155/60/22/8767>
30. Thirion JP. Image matching as a diffusion process: an analogy with Maxwell's demons. *Med Image Anal* 1998; **2**: 243–60. doi: [https://doi.org/10.1016/s1361-8415\(98\)80022-4](https://doi.org/10.1016/s1361-8415(98)80022-4)
31. Vercauteren T, Pennec X, Perchant A, Ayache N. Diffeomorphic demons: efficient non-parametric image registration. *NeuroImage* 2009; **45**(Suppl. 1): S61–72. doi: <https://doi.org/10.1016/j.neuroimage.2008.10.040>
32. Vemuri BC, Ye J, Chen Y, Leonard CM. Image registration via level-set motion: applications to atlas-based segmentation. *Med Image Anal* 2003; **7**: 1–20. doi: [https://doi.org/10.1016/s1361-8415\(02\)00063-4](https://doi.org/10.1016/s1361-8415(02)00063-4)
33. Bieta V, Moller T. A short note on Thirions Demons algorithm. *Southeast Asian Bull Math* 2013; **37**: 813–6.
34. Goshtasby AA. *2-D and 3-D image registration for medical, remote sensing, and industrial applications*: Wiley-Interscience publication: Hoboken NJ; 2005.
35. Pluim JP, Maintz JB, Viergever MA. Image registration by maximization of combined mutual information and gradient information. *IEEE Trans Med Imaging* 2000; **19**: 809–14. doi: <https://doi.org/10.1109/42.876307>
36. Nithiananthan S, Brock KK, Daly MJ, Chan H, Irish JC, Siewersden JH. Demons deformable registration for CBCT-guided procedures in the head and neck: convergence and accuracy. *Med Phys* 2009; **36**: 4755–64. doi: <https://doi.org/10.1118/1.3223631>
37. Guimond A, Roche A, Ayache N, Meunier J. Three-dimensional multimodal brain warping using the demons algorithm and adaptive intensity corrections. *IEEE Trans Med Imaging* 2001; **20**: 58–69. doi: <https://doi.org/10.1109/42.906425>
38. Wang H, Dong L, O'Daniel J, Mohan R, Garden AS, Ang KK, et al. Validation of an accelerated 'demons' algorithm for deformable image registration in radiation therapy. *Phys Med Biol* 2005; **50**: 2887–905. doi: <https://doi.org/10.1088/0031-9155/50/12/011>

39. Lorenzi M, Ayache N, Frisoni GB, Pennec X; Alzheimer's Disease Neuroimaging Initiative (ADNI). LCC-Demons: a robust and accurate symmetric diffeomorphic registration algorithm. HAL-INRIA 2013. doi: <https://doi.org/10.1016/j.neuroimage.2013.04.114>
40. Vercauteren T, Pennec X, Perchant A, Ayache N. Diffeomorphic Demons using ITK's finite difference solver hierarchy, Asclepios Research Group, INRIA Sophia Antipolis and Mauna Kea Technologies, 2007.
41. Vercauteren T, Pennec X, Perchant A, Ayache N. Non-parametric diffeomorphic image registration with the Demons algorithm. *Proc Med Im Comp Computer Assisted Intervention* 2007; **4792**: 319–26.
42. Arsigny V, Commowick O, Pennec X, Ayache N. A Log-Euclidean framework for statistics on diffeomorphisms. In: Larsen R, Nielsen M, Sporring J, eds., *Proc. MICCAI* 2006; Vol. **4190**. pp. 924–31.
43. Hall BC. Lie groups, lie algebras, and representations: an elementary introduction. *Graduate Texts in Mathematics* 222. 2nd edn: Springer: Berlin, Germany; 2015.
44. Yang D, Deasy JO, Low DA, El Naqa I. Level set motion assisted non-rigid 3D image registration. *Proc SPIE* 2007: 6512. doi: <https://doi.org/10.1117/12.710024>
45. Johnson HJ, McCormick MM, Ibanez L. *The ITK software guide book 1: introduction and development guidelines*. Vol. **1**, 2015.
46. Schroeder W, Martin K, Lorensen B. *The visualization toolkit*: Kitware: Clifton Park, NY; 2006.
47. Danielsson PE, Seger O: Generalized and separable sobel operators. In *Machine vision for three-dimensional scenes*. H.Freeman, (ed). Academic Press, 1990.