Diffeomorphic Diffusion Registration of Lung CT Images

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Abstract. Registration of the lungs in thoracic CT images is required in many fields of application in medical imaging, for example for motion estimation, analysis of pathology progression or the generation of shape atlases.
In this paper, we present a robust registration approach that has been optimized for the registration of thoracic CT data. The algorithm consists of an initial shape-based adjustment of lung surfaces followed by an intensity-based diffeomorphic image registration.
The approach is evaluated based on 20 CT scans provided for the EMPIRE10 study for pulmonary image registration. A fourth place out of 34 participants suggests a good applicability for the registration of lung CT images.

Keywords: registration, thin plate splines, diffeomorphisms, EMPIRE10

1 Introduction

Lung registration on the base of thoracic CT data is an essential part of many applications in medical imaging and used for example for estimation of respiratory motion [16], image reconstruction [7], analysis of tumor or nodule growth in follow-up examinations or the generation of shape and motion atlases of the lung [8]. Its clinical relevance is underlined by the huge number of recent publications dealing with this topic.

With the aim of establishing a platform for in-depth validation of different registration approaches, the challenge "Evaluation of Methods for Pulmonary Image Registration 2010" - EMPIRE10 was initiated in the course of MICCAI 2010 conference. An objective comparison of registration approaches is realized by applying the algorithms on the same set of 20 CT images and evaluating the results with the same criteria. These criteria include the alignment of lung boundaries and fissures, average landmark distances and analysis of singularities in the displacement field.

In this paper, a fully automatic registration approach is presented and evaluated using the EMPIRE10 platform. The algorithm consists of two steps. First, a coarse pre-registration is performed combining a registration of surface points

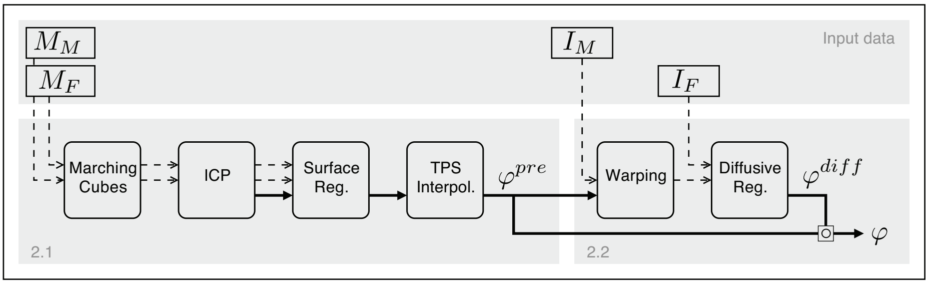

Fig. 1. Outline of the algorithm.

with a thin plate spline interpolation. Second, an image-based diffeomorphic registration algorithm is applied.

In the EMPIRE10 study, the approach reached a final placement of four out of 34 participating algorithms, which demonstrates its applicability for the registration of lung CT images.

This paper is organized as follows: In section 2, pre-registration (Sect. 2.1) and diffeomprohic registration (Sect. 2.2) are introduced. Some details of the implementation and the required parameters are explained in section 2.3. The results of the EMPIRE10 evaluation are presented in section 3 and the paper concludes with a discussion in section 4.

2 Methods

The goal of image registration is to calculate a transformation $\boldsymbol{\varphi} : \Omega_F \to \Omega_M$ that deforms a moving image $I_M : \Omega_M \to \mathbb{R}$ to match a fixed image $I_F : \Omega_F \to \mathbb{R}$, where $\Omega_M, \Omega_F \subset \mathbb{R}^3$ denote the domains of fixed and moving image, respectively. In the context of EMPIRE10, the transformation is specified by a displacement field $\boldsymbol{u}(\boldsymbol{x})$ with $\boldsymbol{\varphi}(\boldsymbol{x}) = \boldsymbol{x} + \boldsymbol{u}(\boldsymbol{x})$ and $\boldsymbol{x} \in \Omega_F$.

The registration method presented in this paper is outlined in figure 1 and basically consists of two steps. First, a surface-based pre-registration is performed combining a coarse affine alignment with a following nonlinear registration of the lung surfaces. In a second step, a dense diffeomorphic registration of the CT data is performed.

These steps are detailed in the following.

2.1 Pre-registration

Pre-registration is based on binary lung masks $M_F : \Omega_F \to \{0, 1\}$ and $M_M : \Omega_M \to \{0, 1\}$ of fixed and moving image. While these are provided for the EMPIRE10 study and therefore assumed to be known in this work, several applicable approaches for automatic lung segmentation have been proposed in the past [10, 13].

The pre-registration consists of four steps. In the first step, surface models $\boldsymbol{S}_F$ and $\boldsymbol{S}_M$ of the lungs are generated from the lung segmentation masks. These surface models are constructed by the Marching Cubes algorithm, followed by a triangle decimation and a surface smoothing to obtain smooth surfaces with appropriate surface normals and to reduce the computational complexity in the following steps. Second, the surface models $\boldsymbol{S}_F$ and $\boldsymbol{S}_M$ are coarsely aligned by an affine pre-registration using the Iterative-Closest-Point (ICP) algorithm [5]. The resulting affine transformation $\boldsymbol{\varphi}^{aff}$ is used as initialization for a symmetric non-linear surface registration algorithm related to the Geometry-Constrained Diffusion presented in [1]. Finally, the resulting point correspondences are used to generate a dense transformation $\boldsymbol{\varphi}^{pre}$ based on a thin plate spline (TPS) interpolation.

Due to space constraints and to avoid redundancy, we refer to [9] for a detailed description of these steps.

2.2 Diffeomorphic Variational Registration

The intrinsic registration is done using a variational diffeomorphic approach, which has been used before in several works.

Diffeomorphic transformations $\boldsymbol{\varphi} \in Diff(\Omega)$ guarantee that the topology of the objects is preserved and they are therefore often used in computational anatomy to describe and analyze physiological processes. For the sake of efficiency, it was proposed to constrain $\boldsymbol{\varphi}$ to the subgroup of diffeomorphisms that are parametrized by a stationary velocity field $\boldsymbol{v}$ [15]. The transformation $\boldsymbol{\varphi}$ is then given by the solution of the *stationary* flow equation at time $t = 1$ [2]:

$$\frac{\partial}{\partial t}\phi(\boldsymbol{x}, t) = \boldsymbol{v}(\phi(\boldsymbol{x}, t)) \text{ and } \phi(\boldsymbol{x}, 0) = \boldsymbol{x} \ . \tag{1}$$

The solution of eq. (1) is given by the group exponential map $\boldsymbol{\varphi}(\boldsymbol{x}) = \phi(\boldsymbol{x}, 1) = \exp(\boldsymbol{v}(\boldsymbol{x}))$, which can be computed very efficiently using the scaling-and-squaring algorithm [3].

The problem of image registration can now be understood as finding a parametrizing velocity field $\boldsymbol{v}$, so that the diffeomorphic transformation $\boldsymbol{\varphi} = \exp(\boldsymbol{v})$ minimizes a distance $\mathcal{D}$ between moving and fixed image with respect to a desired smoothness $\mathcal{S}$ of the transformation:

$$\mathcal{J}[\boldsymbol{\varphi}] = \mathcal{D}[I_M, I_F; \boldsymbol{\varphi}] + \alpha\mathcal{S}[\boldsymbol{\varphi}] \ .$$

Using the diffusion regularization $\mathcal{S}[\boldsymbol{\varphi}] = \int_\Omega \|\nabla \boldsymbol{v}\|^2 d\boldsymbol{x}$ (with $\boldsymbol{\varphi} = \exp(\boldsymbol{v})$), the iterative registration algorithm 1 can be derived. The force term $\boldsymbol{f}$ is defined by:

$$\boldsymbol{f}_{I_F, I_M \circ \boldsymbol{\varphi}}(\boldsymbol{x}) = -\frac{(I_F(\boldsymbol{x}) - I_M \circ \boldsymbol{\varphi}(\boldsymbol{x}))\, \nabla I_M \circ \boldsymbol{\varphi}(\boldsymbol{x})}{\kappa^2 (I_F(\boldsymbol{x}) - I_M \circ \boldsymbol{\varphi}(\boldsymbol{x}))^2 + \|\nabla I_M \circ \boldsymbol{\varphi}(\boldsymbol{x})\|^2} \ , \tag{3}$$

with κ^2 being the reciprocal of the mean squared spacing. Even though the exact energy term $\mathcal{D}$ to this force is unknown for the particular choice of κ, previous

Algorithm 1 Diffeomorphic registration

Set $\boldsymbol{v}^0 = \boldsymbol{0}$, $\boldsymbol{\varphi}^0 = Id$ and $k = 0$
repeat
Compute the update step $\boldsymbol{f}_{I_F, I_M \circ \boldsymbol{\varphi}^k}$
Update the velocity field and perform a diffusive regularization:

$$\boldsymbol{v}^{k+1} = (Id - \tau\alpha\boldsymbol{\Delta})^{-1} \left(\boldsymbol{v}^k + \tau \boldsymbol{f}_{I_F, I_M \circ \boldsymbol{\varphi}^k} \right) \tag{2}$$

Calculate $\boldsymbol{\varphi}^{k+1} = \exp(\boldsymbol{v}^{k+1})$
Let $k \leftarrow k + 1$
until a stop criterion is fulfilled, i.e. the algorithm converges

studies showed a considerably better performance then with the standard sum of squared differences (SSD) [14]. This can be explained by the normalization of the gradient, which leads to a better registration of regions with low contrast. Moreover, the masks are used to restrict force calculation to the inside of the lung by setting $\boldsymbol{f}(\boldsymbol{x}) = 0$ for all $\boldsymbol{x}$ with $M_F(\boldsymbol{x}) = 0$. The update of the velocity field $\boldsymbol{v}$ is performed using (2), where τ is the step width. The term $(Id - \tau\alpha\boldsymbol{\Delta})^{-1}$ is related to the diffusion regularization $\mathcal{S}$ and can be computed efficiently using additive operator splitting (AOS) [11].

We have chosen this registration approach because of three reasons: First, in comparison to the conventional demons registration, the diffeomorphic approach prevents singularities from arising in the displacement field. Second, even though a diffeomorphic registration was not mandatory for the challenge, it is required in many applications, where for example the inverse of the transformation is needed or statistics have to be done on transformations [8]. The third reason is related to runtime and memory requirements: due to the size of the 4D CT images, diffeomorphic registration algorithms using non-stationary vector fields, e.g. [4], are not feasible.

2.3 Algorithmic and implementation details

In the following section, some details and implementation specifications of the algorithm are discussed. These considerations have been made with respect to the EMPIRE10 test data and choices may differ for other applications. For example, fixed and moving images provided for the challenge are always cropped close to the lung borders, leading to $\Omega_F \neq \Omega_M$. This aspect requires a special handling, which might not be advisable if I_F and I_M represent different time frames of a 4D data set as it is generally the case if registration is used for motion estimation. In fact, the whole pre-registration may be dispensable in this case.

Still, the number and diversity of the data sets considered for the study guarantee a certain generality of the observations and statements below.

Initialization The algorithm can be seen as the concatenation of three registration steps: an affine alignment, a surface-based adjustment and the image-based diffeomorphic registration. In principle, each step could be initialized with the results of the preceding one. However, the further velocity vectors point outside the domain Ω_F of the fixed image, the more notable extrapolation errors occur during calculation of the exponential map $\exp(\boldsymbol{v})$. This is especially considerable for the scaling-and-squaring algorithm, but also holds for other implementations, e.g. the Euler step approach [6].

As a result, the diffeomorphic registration is not initialized with the result of the pre-registration φ^{pre}. Instead, the fixed image I_F is registered with the warped image $I_M^{pre} := I_M \circ \varphi^{pre}$. By this, velocities and accordingly the extrapolation error remain comparatively small. To calculate the final displacement field, the resulting transformation φ^{diff} is concatenated with φ^{pre} using linear interpolation. However, this procedure introduces an interpolation error and is not recommended if, e.g., fixed and moving image are frames of a 4D data set.

Histogram matching A histogram matching between fixed and moving image was performed before the diffeomorphic registration to overcome gray value deviations due to different modalities or respiration-induced lung compression.

Multi resolution strategy A multi resolution strategy is applied for the diffeomorphic registration. More precisely, the image is recursively smoothed (Gaussian smoothing, $\sigma = 1.0$) and its size divided by two in each dimension. A number of three levels provided the best results on average, however, this approach could potentially be optimized depending on the actual image size and and by choosing a scaling factor independently for each dimension.

Stop-criterion The affine ICP registration stops either after a maximal number of iterations ($k^{max} = 50$) or if the mean point distance is below a threshold ($t = 0.01$). The same holds for the non-linear surface registration, where $k^{max} = 50$ and $t = 10^{-5}$ are chosen.

For the stop criterion of the variational registration, the mean squared difference (MSD) of fixed and warped moving image is considered. If no improvement of the MSD can be achieved over the last k iterations, registration is stopped (here: $k = 10$). However, on the finest level, this approach can be very time consuming due to the high computational cost of each iteration and the slow convergence of the registration. Therefore, on this level a least squares linear regression on the MSD values of the 20 most recent iterations is performed. If the slope of the fitted line is below a certain threshold (here: $t = 10^{-5}$), registration is aborted.

Parameter determination Parameter values have generally been determined empirically and are chosen to be fixed for all test data sets. Test runs were not limited to the EMPIRE10 data sets, and so registration of other thoracic CT images should lead to similar registration quality using the parameter values described hereinafter.

The values of parameters introduced by the pre-registration, the histogram matching or the multi resolution strategy can be easily determined empirically. Tests showed that the algorithm is robust with respect to them.

A reasonable choice for the step with is $\tau = 1.0$, which provides fast enough convergence while maintaining stability. The latter is explained by the chosen force term (3), which restricts the maximal magnitude of the force vectors to half of the mean pixel spacing.

The most considerable choice is the value of the regularization parameter α. This usually implies a trade-off between the different validation metrics, e.g. landmark distance vs. boundary alignment. In this work, emphasis is put on the mean landmark distance, because we consider this to be the most significant metric with respect to registration accuracy. For quantifying the registration error, automatically detected landmarks where used [9]. A value of $\alpha = 0.7$ provided the best results on average.

3 Results

The evaluation criteria for pulmonary image registration in the EMPIRE10 study are (see ref. [12]):

(1) alignment of the lung boundaries,
(2) alignment of the major fissures,
(3) correspondence of annotated point pairs and
(4) analysis of singularities in the deformation field.

The results are detailed in table 1.

Computation times strongly depend on the image size and the number of iterations performed with respect to the stop criterion. For the EMPIRE10 data sets, registration was done on a Intel Xeon machine with 2.67GHz and 24GB RAM. The affine alignment took between 12 sec (dataset 17) and 65 sec (dataset 14), the surface registration between 8 min and 70 min and the diffeomorphic registration between 2 min and 150 min. Please note that the surface registration is currently realized in a very basic implementation with a huge potential for optimization.

4 Discussion

The results show that algorithm presented in this paper is highly applicable for the registration of thoracic CT images.

The pre-registration introduced in section 2.1 emerged to be essential for the success of the diffeomorphic registration. This has mainly two reasons: First, most of the image pairs show considerable differences between moving and fixed image, which results from a notable shift in patient position on the one hand and from the cropping of the images on the other hand. This demands for a well pre-alignment. The second reason is related to the usage of the masks during the

	Lung Boundaries		Fissures		Landmarks		Singularities	
Scan Pair	**Score**	**Rank**	**Score**	**Rank**	**Score**	**Rank**	**Score**	**Rank**
01	0.00	7.00	0.00	2.00	2.12	9.00	0.00	24.00
02	0.00	11.00	0.00	15.00	0.35	4.00	0.00	12.50
03	0.00	5.50	0.00	12.50	0.33	5.00	0.00	12.00
04	0.00	7.00	0.00	16.50	0.97	10.00	0.00	14.00
05	0.00	13.00	0.00	16.00	0.00	5.50	0.00	13.50
06	0.00	16.00	0.00	21.00	0.38	17.00	0.00	14.00
07	0.04	18.00	0.32	4.00	1.46	5.00	0.00	10.00
08	0.00	10.00	0.00	7.00	0.75	7.00	0.00	12.50
09	0.00	5.00	0.00	6.50	0.53	5.00	0.00	13.00
10	0.00	6.00	0.00	15.00	1.20	9.00	0.00	13.50
11	0.00	11.00	0.00	8.00	0.66	6.00	0.00	11.50
12	0.00	28.00	0.00	13.50	0.00	5.00	0.00	14.50
13	0.00	10.00	0.06	4.00	0.86	10.00	0.00	26.00
14	0.01	10.00	2.01	5.00	1.79	6.00	0.00	9.50
15	0.00	8.00	0.00	7.00	0.65	14.00	0.00	12.50
16	0.00	8.00	0.04	12.00	0.97	8.00	0.00	13.50
17	0.00	6.50	0.04	7.50	0.67	4.00	0.00	14.00
18	0.07	20.00	0.07	3.00	2.25	10.00	0.00	10.50
19	0.00	14.00	0.00	12.00	0.61	21.00	0.00	14.50
20	0.11	23.00	1.97	9.00	1.26	4.00	0.00	21.00
Avg	0.01	11.85	0.22	9.82	0.89	8.22	0.00	14.32
Average Ranking Overall								11.05
Final Placement								4

Table 1. Results for each scan pair, per category and overall. Rankings and final placement are from a total of 34 competing algorithms.

image-based registration: if fixed and moving image mask don't coincide with each other, registration errors may be introduced at the boundaries. Therefore, a simple affine alignment is not adequate.

Assuming a good pre-registration, the diffeomorphic approach behaves very robust and provides especially good results for fissure alignment and landmark distances.

In the tests, singularities occurred in the displacement fields for three of the test cases. These were introduced by the TPS interpolation and the point-based surface registration, which currently do not guarantee diffeomorphic transformations. This point will be adressed in future work.

References

1. Andresen, P.R., Nielsen, M.: Non-rigid registration by geometry–constrained diffusion. Medical Image Analysis 5(4), 81–88 (2001)
2. Arsigny, V.: Processing Data in Lie Groups: An Algebraic Approach. Application to Non-Linear Registration and Diffusion Tensor MRI. Ph.D. thesis, École polytechnique (2006)
3. Arsigny, V., Commowick, O., Pennec, X., Ayache, N.: A Log-Euclidean Framework for Statistics on Diffeomorphisms. In: Medical Image Computing and Computer-Assisted Intervention - MICCAI 2006. pp. 924–931 (2006)
4. Beg, M.F., Miller, M.I., Trouvé, A., Younes, L.: Computing large deformation metric mappings via geodesic flows of diffeomorphisms. International Journal of Computer Vision 61(2), 139–157 (2005)
5. Besl, P.J., McKay, N.D.: A method for registration of 3-d shapes. IEEE Trans. Pattern Anal. Mach. Intell. 14(2), 239–256 (1992)
6. Bossa, M., Zacur, E., Olmos, S.: Algorithms for computing the group exponential of diffeomorphisms: Performance evaluation. In: Computer Vision and Pattern Recognition Workshops - CVPRW 2008. pp. 1–8 (2008)
7. Ehrhardt, J., Werner, R., Säring, D., Lu, W., Low, D.A., Handels, H.: An optical flow based method for improved reconstruction of 4D CT data sets acquired during free breathing. Med Phys 34(2), 711–21 (2007)
8. Ehrhardt, J., Werner, R., Schmidt-Richberg, A., Handels, H.: Prediction of Respiratory Motion Using A Statistical 4D Mean Motion Model. In: The Second International Workshop on Pulmonary Image Analysis, Medical Image Computing and Computer-Assisted Intervention - MICCAI 2009. pp. 3–14 (2009)
9. Ehrhardt, J., Werner, R., Schmidt-Richberg, A., Handels, H.: Automatic Landmark Detection and Non-linear Landmark- and Surface-based Registration of Lung CT Images. In: Medical Image Analysis for the Clinic - A Grand Challenge, MICCAI 2010 (2010)
10. Hu, S., Hoffman, E.A., Reinhardt, J.M.: Automatic Lung Segmentation for Accurate Quantitation of Volumetric X-Ray CT Images. IEEE Trans Med Imag 20(6), 490–498 (2001)
11. Modersitzki, J.: Numerical Methods for Image Registration. Oxford Univ Press (2004)
12. Murphy, K., van Ginneken, B., Reinhardt, J., Kabus, S., Ding, K.: Evaluation of methods for pulmonary image registration: The EMPIRE10 study. In: Deng, X., Pluim, J. (eds.) Grand Challenges in Medical Image Analysis (2010)
13. van Rikxoort, E.M., de Hoop, B., Viergever, M.A., Prokop, M., van Ginneken, B.: Automatic lung segmentation from thoracic computed tomography scans using a hybrid approach with error detection. Medical Physics 36(7), 2934–2947 (2009)
14. Schmidt-Richberg, A., Ehrhardt, J., Werner, R., Handels, H.: Evaluation and Comparison of Force Terms for the Estimation of Lung Motion by Non-linear Registration of 4D-CT Image Data. In: World Congress on Medical Physics and Biomedical Engineering 2009. pp. 2128–2131 (2009)
15. Vercauteren, T., Pennec, X., Perchant, A., Ayache, N.: Symmetric log-domain diffeomorphic registration: a demons-based approach. Med Image Comput Comput Assist Interv 11(Pt 1), 754–761 (2008)
16. Werner, R., Ehrhardt, J., Schmidt-Richberg, A., Handels, H.: Validation and comparison of a biophysical modeling approach and non-linear registration for estimation of lung motion fields in thoracic 4D CT data. In: Image Processing, SPIE Medical Imaging 2009. vol. 7259, pp. 0U1–0U8 (2009)