

Chapter 2

Current methods for lung registration

The determination of correspondences between two or more images is required in almost every field of medical image processing. Consequently, a vast diversity of registration algorithms has been developed in the past, which is documented by several review articles [Brown 1992; Maintz and Viergever 1998; Hill et al. 2001; Zitova and Flusser 2003; Oliveira and Tavares 2012; Sotiras et al. 2012] and books [Hajnal et al. 2001; Modersitzki 2004; Goshtasby 2012a] published on this topic.

As initially detailed, an important field of application of registration techniques is the correspondence analysis in lung CT images. Focussing on this field, the domain of algorithms can be restricted to monomodal 3D-3D registration methods, but it still offers a variety of different approaches. To assess and compare their accuracy, the demand for common evaluation platforms has emerged in recent years. As a consequence, two international evaluation studies have been conducted in 2009 and 2010.

On the one hand, several academic and commercial institutions were invited to participate at the *Multi-Institution Deformable Registration Accuracy Study* (MIDRAS), with the purpose “to assess the accuracy, reproducibility, and computational performance of deformable image registration algorithms under development at multiple institutions on common datasets.” [Brock et al. 2010]. Altogether, twenty-one groups submitted their results. In addition to thoracic 4D CT scans, CT and MR images of liver and prostate were considered in this study.

On the other hand, the *Evaluation of Methods for Pulmonary Image REgistration 2010* (EMPIRE10) challenge is an ongoing study and was initiated in conjunction with the MICCAI 2010 conference at Beijing, China [Murphy et al. 2011b]. Focussing on lung registration, it is aimed at registering 30 thoracic CT scan pairs covering different fields of intra-patient registration. Results are then evaluated with a common set of criteria. Here, initially twenty-three groups submitted thirty-four algorithms to compete in the challenge.

Moreover, with the publically available POPI model [Vandemeulebroucke et al. 2007] and the DIR-lab data [Castillo et al. 2009], several 4D CT scans have been provided together with manually determined corresponding points to enable the quantitative evaluation of registration algorithms for motion estimation. These images are referred to in many recent publications dealing with lung registration to provide a more meaningful

comparison. For more details on POPI, DIR-lab and the EMPIRE challenge, the reader is referred to Sections 7.1.2 and 7.2.3.

In this chapter, an overview on current methods for the registration of thoracic CT images is given. Since collating a comprehensive survey on lung registration techniques would surpass the scope of this work, the focus is on methods participating in one of the aforementioned challenges as well as very recent developments in this field. These algorithms are listed in Table 2.1. In Section 2.1, the approaches are categorized and different possibilities for the definition of their fundamental components highlighted.¹ Available open-source implementations are introduced in Section 2.2 and the implications on this thesis derived in Section 2.3.

2.1 Intensity-based registration techniques

Let T and R denote two images (for example, two time points of a 4D sequence), called template and reference image. The goal of image registration is finding a transformation φ that warps a template image to match a reference image, such that $T \circ \varphi \approx R$. A commonly persuaded approach to find φ is by minimization of an energy functional

$$\mathcal{J}[\varphi] := \mathcal{D}[T \circ \varphi, R],$$

where \mathcal{D} is a distance measure that quantifies the dissimilarity between reference and transformed template image. In this formulation, two components have to be determined: the distance measure to precisely define the sense of similarity and the transformation model. However, depending on the degrees of freedom of the transformation, an additional condition is often required to restrain it to be physiologically plausible. Since the lung can be described as an elastic body [Tustison et al. 2011], a certain smoothness of the transformation is expected and can be achieved by adding a regularization condition \mathcal{S} to the energy functional:

$$\mathcal{J}[\varphi] := \mathcal{D}[T \circ \varphi, R] + \mathcal{S}[\varphi]. \quad (2.1)$$

In the following Sections 2.1.1 to 2.1.3, an overview on different transformation models, regularizers and distance measures that are currently used in the literature is given. From a computational point of view, the optimization strategy for finding the minimum of the functional is also of eminent importance. Different approaches for this purpose are described in Section 2.1.4.

¹ Since the focus is on the evaluation studies, this overview is restrained to intensity-based approaches. Shape- and feature-based registration methods – usually used in a pre-processing step to overcome anatomical differences and divergences in patient positioning, especially in inter-subject registration – are not further regarded at this point.

Table 2.1: Current methods for lung CT registration. The ten best-ranked methods of the MIDRAS [Brock et al. 2010] and EMPIRE10 [Murphy et al. 2011b] studies are compared. Furthermore, some recent methods are listed that follow noteworthy ideas. **Abbreviations:** TPS: Thin-plate-splines; (N)MI: (Normalized) Mutual Information; SAD: Sum of Absolute Difference; (N)SSD: (Normalized) Sum of Squared Differences; NCC: Normalized Cross Correlation; SSTVD: Sum of Squared Tissue Volume Differences; SSVMD: Sum of Squared Vesselness Measure Differences; NGF: Normalized Gradient Field; ELE: Euler-Lagrange Equation; GD: Gradient Descent; CG: Conjugated Gradients; ASGD: Adaptive Stochastic Gradient Descent; BFGS: Broyden-Fletcher-Goldfarb-Shanno; MRF: Markov Random Fields; **References:** M1: Dong, Zhang [Wang et al. 2005]; M2: Han; M3: Dufort, Stundiza; M4: Xia, Samant; M5: El Naqa, Yang [Yang et al. 2008]; M6: Hawkes, Crum [Crum et al. 2005]; M7: Heath [Heath et al. 2007]; M8: Mageras, Hu [Lu et al. 2004]; M9: Nord; M10: Noe, Tanderup [Noe et al. 2008]; E1: [Han 2010]; E2: [Song et al. 2010]; E3: [Staring et al. 2010]; E4: [Schmidt-Richberg et al. 2010a]; E5: [Modat et al. 2010a]; E6: [Kabus and Lorenz 2010]; E7: [Cao et al. 2010b]; E8: [Muenzing et al. 2010]; E9: [Song et al. 2010]; E10: [Garcia et al. 2010]; F1: [Heinrich et al. 2012]; F2: [Rühaak et al. 2013]; F3: [Gorbunova et al. 2012]

Ref.	Transform. model	Regularizer	Distance measure	Solver
– MIDRAS STUDY –				
M1	Dense field	Gaussian	NSSD	Demons-like
M2	B-splines	not specified	SSD	GD
M3	TPS	Bending energy	SSD	Backward GD
M4	Dense field	Diffusion-based	SSD	GD
M5	Dense field	Gaussian	MSD	Gauss-Seidel
M6	Dense field	Viscous-fluid	NCC	Full Multigrid
M7	Dense field	Linear-elastic	NCC	3D Simplex
M8	Dense field	Diffusion	SSD	ELE/Gauss-Seidel
M9	Dense field	Gaussian	NSSD	Demons-like
M10	Dense field	Viscous-fluid	SSD	GD
– EMPIRE10 STUDY –				
E1	Dense field	Gaussian	MI/NSSD*	pair-and-smooth
E2	Diffeomorphic	Gaussian	NCC	ELE/GD
E3	B-splines	not specified	NCC	ASGD
E4	Diffeomorphic	Diffusion	NSSD	ELE/GD
E5	B-splines	Bending energy	NMI	CG
E6	Dense field	Linear-elastic	SSD	ELE/GD
E7	B-splines	Laplacian	SSTVD/SSVMD	Quasi-Newton (BFGS)
E8	Diffeomorphic	Diffusion	NSSD	Demons-like
E9	Diffeomorphic	Gaussian	NCC	ELE/GD
E10	Diffeomorphic	Gaussian	NSSD	Demons-like
– FURTHER APPROACHES –				
F1	Diffeomorphic	Total variation	SAD	MRF on spanning tree
F2	Dense field	Curvature	NGF	L-BFGS
F3	B-splines	not specified	Mass-preserving	ASGD

* In this approach, additional features are detected and incorporated in the registration.

2.1.1 Transformation models

Affine transformations Affine or rigid body transformations are frequently used for the alignment of brain images. Due to the very low number of parameters that have to be determined, linear registration is usually very performant. However, the complex deformation of an elastic organ like the lung cannot be described appropriately by such a simplistic transformation model. Therefore, affine transformations are rarely applied for lung registration aside from a pre-alignment. The same holds true for piecewise affine or poly-affine transformations [Arsigny et al. 2006b].

Spline-based transformations Spline-based transformation models are inspired by interpolation theory. The transformation is explicitly given for a set of control points and interpolated for the rest of the domain. In early approaches, radial basis functions like thin-plate-splines (TPS) [Bookstein 1989] or physically motivated elastic-body-splines [Davis et al. 1997] were applied. Free-form deformations (FFD) also gained a wide acceptance in image registration [Rueckert et al. 1999]. Here, locally controlled B-splines are used to interpolate between the control points of a rectangular grid, which entails computational benefits. In general, spline-based transformations unite a high flexibility with a (compared to dense transformations) relatively low number of parameters.

Dense displacement fields Since Thirion [1995] presented the demons-based registration, transformations are often defined by a dense vector field in which the vector attached to each voxel describes the displacement of the corresponding point. This approach is followed by 17 of the 23 methods listed in Table 2.1. Dense transformations entail increased demands on the computational resources but represent the most flexible deformation model. Due to this, they have to be employed in connection with a suitable regularizer that ensures physiologically plausible transformations.

Diffeomorphic transformations Following the argumentation of Beg et al. [2005], constraining the transformation to be a diffeomorphism is a natural choice in medical image registration as “*connected sets remain connected, disjoint sets remain disjoint [and] the smoothness of anatomical features [...] is preserved.*” From a mathematical perspective, this can be achieved by imposing additional requirements on the displacement field. For example, in the *Large Deformation Diffeomorphic Metric Mapping* (LDDMM) framework presented by Beg et al. [2005], diffeomorphic transformations are parameterized as the flow over a time-dependent velocity field. Arsigny et al. [2006a] proposed to use stationary velocity fields instead, which considerably increases computational efficiency at the expense of flexibility. Other approaches exist that guarantee, for example, diffeomorphic free-form deformations [Rueckert et al. 2006].

2.1.2 Regularization approaches

The regularization approach is closely related to the transformation model and applied to restrict the domain of valid deformations. Focussing on the regularization of dense displacement fields, the most common approaches are summarized in the following.

Gaussian/Diffusion Thirion [1995] first applied a component-wise Gaussian smoothing of the displacement field. As derived in [Modersitzki 2004], this is closely related to a diffusion regularization, in which large gradients in the field are penalized for each component independently. Both approaches can be computed very efficiently and are therefore frequently used in current registration approaches (see Table 2.1). However, they lack a physical motivation.

Elastic body In this approach, the image domain is modeled as an elastic body based on the Navier-Cauchy equation [Broit 1981]. The Lamé parameters μ and λ are used to influence the material properties. Various extensions have been proposed that tackle problems like inverse consistency [Christensen and Johnson 2001], large deformations [Pennec et al. 2005] and numerical efficiency [Fischer and Modersitzki 1999].

Viscous flow Christensen et al. [1996] first introduced viscous flow transformations into image registration. Based on the Navier-Stokes equation, the image domain is modeled as a viscous fluid. Since not the deformation but the underlying velocity field is regularized, this approach allows large deformations. However, computational inefficiency is a fundamental drawback of this model and consequently most developments concentrate on improving the numerical performance, for example based on scale-space filtering [Bro-Nielsen and Gramkow 1996] or multigrid techniques [Crum et al. 2005].

Curvature Curvature regularization was introduced by Fischer and Modersitzki [2004] and defined to penalize the Laplacian of the displacement field, which is an approximation of its curvature. The major advantage of this approach is that affine transformations are not penalized. Therefore, misalignments can be accounted for without an additional pre-registration step. In [Beuthien et al. 2010], curvature regularization is efficiently solved by recursive filtering based on the Green's function.

Total variation Regularization based on the total variation or the L_1 norm of the displacement field was employed for image registration in [Frohn-Schauf et al. 2007]. Since it is more robust to outliers than the diffusion approach, it is mainly used to model discontinuous motion in computer vision. However, total variation has also been applied to lung CT registration [Heinrich et al. 2012].

2.1.3 Distance measures

A comprehensive overview on distance and similarity metrics is given in [Goshtasby 2012b] and – focussing on multimodal registration – in [Hermosillo et al. 2002]. Here, only approaches frequently applied to lung registration are outlined.

Sum of Squared Differences Most intuitively, image similarity is measured by regarding the intensity differences in each voxel, which leads to the definition of the Sum of Absolute or Squared Differences (SAD and SSD) as distance measures. SSD can be shown to be the optimal measure when two images only differ by Gaussian noise [Hill et al. 2001], which leads to a frequent utilization for monomodal CT registration (see Table 2.1). Moreover, the demons-based forces introduced by Thirion [1995] are closely related to SSD [Pennec et al. 1999] and often called Normalized SSD (NSSD).

Cross Correlation If a linear relationship exists between the intensity values of reference and template image, Normalized Cross Correlation (NCC) is to be preferred as similarity measure [Hill et al. 2001]. It is therefore often used for multimodal registration but also to overcome intensity changes caused by tissue compression in lung registration [Avants et al. 2008].

Mutual Information Mutual Information (MI) as a similarity measure is adapted from information theory and was proposed for image registration by Viola and Wells [1995]. It is aimed at minimizing the joint entropy of the greyvalues of both images (interpreted as random variables) and thereby maximizing the dependency between the images. To obtain overlap invariance, an extension to Normalized MI (NMI) was proposed by Studholme et al. [1999]. Even though primarily applied to multimodal registration, it can also be used for lung alignment [Modat et al. 2010a].

Normalized Gradient Field Mutual information is highly non-convex and often has numerous local minima [Modersitzki 2004]. To overcome this drawback, Haber and Modersitzki [2006] proposed to align images based on their gradients rather than intensities. The according distance measure is called Normalized Gradient Field (NGF) and applied to lung registration in [Rühaak et al. 2013].

Task-specific constraints In several approaches, specific properties of lung anatomy are modeled as an (additional) distance metric. Cao et al. [2010a] formulate the Sum of Squared Vesselness Measure Differences (SSVMD) to explicitly align the low-contrasted vasculature of the lung. Additionally, the Sum of Squared Tissue Volume Differences (SSTVD) is used to account for the intensity variations in lung CT images during respiration. With the same purpose, a mass-preserving registration is presented in [Yin et al. 2009] and [Gorbunova et al. 2012].

2.1.4 Algorithmic solutions

For minimizing the functional (2.1), different strategies are followed in the literature, which are briefly summarized in the following. For a mathematically profound overview, the reader is referred to [Clarenz et al. 2006].

Algorithm-driven approaches In several approaches – most prominently the demons registration proposed by [Thirion 1995] – the algorithm is driven by the aim of matching images rather than explicitly solving (2.1) or a similar functional.² Here, registration is usually performed using an iterative two-step approach: First the transformation is varied a bit in a certain direction, for example inspired by the computation of the optical flow [Horn and Schunck 1981]. Second, the optimized transformation is smoothed, most commonly using a Gaussian filtering. In [Han 2010] and [Heinrich et al. 2012], similar *pair-and-smooth* procedures consisting of an iterative feature or template matching and smoothing are applied.

Variational approaches Most commonly, the energy functional (2.1) is minimized using the calculus of variations. More precisely, the Euler-Lagrange equation (ELE) of the energy, which constitutes a necessary condition for a (local) minimum, is analytically derived. Then, an optimization method like the gradient descent (GD) is employed to iteratively find a transformation for which the condition is fulfilled. Finally, the derived scheme is discretized. This approach is therefore also called an *optimize-then-discretize* strategy.

Discrete optimization approaches The *discretize-then-optimize* strategy can be seen as the more intuitive one, as the images at hand are always discrete. Here, the energy functional is discretized in a first step to obtain a finite optimization problem. As a consequence, well-known numerical optimization techniques like the Gauss-Newton or Broyden-Fletcher-Goldfarb-Shanno (BFGS) methods can be applied to solve the registration problem [Nocedal and Wright 2006]. This approach is pursued for example in [Olesch et al. 2009; Rühaak et al. 2011]. Other discrete optimization techniques include Markov Random Fields (MRF), which are employed in [Heinrich et al. 2012].

2.2 Open-source implementations

The registration community is blessed with a huge number of open-source implementations, which can be utilized to solve various problems. In the following section, a brief overview is given.

² In case of demons registration, however, the ad-hoc algorithm can be reduced to minimizing (2.1), as derived in [Modersitzki 2004].

ITK The Insight Segmentation and Registration Toolkit (ITK) is a powerful C++ framework for various tasks of image processing, such as registration, segmentation and image enhancement. It provides a flexible implementation of linear registration algorithms, however, the possibilities for non-linear registration are limited. This is in the focus of current developments [Avants et al. 2012]. Major parts of the algorithms developed in this thesis are implemented as modules for the ITK framework.

ANTS The Advanced Normalization Tools (ANTS) are developed at the Penn Image Computing and Science Lab of the University of Pennsylvania, Philadelphia, US and can be accessed under <http://www.picsl.upenn.edu/ANTS/>. The framework provides flexible tools for elastic and B-spline registration with a variety of distance measures (NCC, MI, SSD, etc.). Moreover, transformations can be restricted to diffeomorphisms based on static and time-dependent velocity fields [Avants et al. 2008].

Nifty Reg The Nifty Reg package is provided by the University College London, London, UK (see <http://sourceforge.net/projects/niftyreg/>). It implements affine and FFD-based algorithms using NMI as metric. The focus is on a performant implementation using hardware acceleration [Modat et al. 2010b].

elastix The elastix framework (see <http://elastix.isi.uu.nl/>) provides multiple registration algorithms based on affine and B-spline transformations and various metrics (SSD, CC, MI, NMI, etc.) [Klein et al. 2010].

FAIR The Flexible Algorithms for Image Registration (FAIR) toolbox is a package written in MATLAB primarily thought for academic purposes [Modersitzki 2009]. Discrete optimization techniques are followed in this implementation. It can be assessed via <http://www.siam.org/books/fa06/>.

2.3 Discussion

The presented overview illustrates the widely spread possibilities to approach the task of image registration. Even though evaluation studies have been conducted to assess accuracy of different methods, it is difficult to determine superior methods because only complete algorithms are compared. Therefore, it is not possible to deduce a meaningful ranking of the single components. For example, NSSD, NCC as well as NMI have all been used in top-ranked approaches. Moreover, minor differences in the implementation, pre-processing steps and the pre-registration have a major impact on the results.

To deal with this problem, a flexible framework for image registration is employed in this work. Its modular design allows a direct comparison of the components like transformation, distance measure and regularization. The algorithm found to be optimal then serves as basis for subsequent examinations.

Registration Methods for Pulmonary Image Analysis
Integration of Morphological and Physiological
Knowledge

Schmidt-Richberg, A.

2014, XVI, 168 p. 48 illus., 14 illus. in color., Softcover

ISBN: 978-3-658-01661-6