

MIND: Modality Independent Neighbourhood Descriptor for Multi-Modal Deformable Registration

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Abstract

Deformable registration of images obtained from different modalities remains a challenging task in medical image analysis. This paper addresses this important problem and proposes a modality independent neighbourhood descriptor (MIND) for both linear and deformable multi-modal registration. Based on the similarity of small image patches within one image, it aims to extract the distinctive structure in a local neighbourhood, which is preserved across modalities. The descriptor is based on the concept of image self-similarity, which has been introduced for non-local means filtering for image denoising. It is able to distinguish between different types of features such as corners, edges and homogeneously textured regions. MIND is robust to the most considerable differences between modalities: non-functional intensity relations, image noise and non-uniform bias fields. The multi-dimensional descriptor can be efficiently computed in a dense fashion across the whole image and provides point-wise local similarity across modalities based on the absolute or squared difference between descriptors, making it applicable for a wide range of transformation models and optimisation algorithms. We use the sum of squared differences of the MIND representations of the images as a similarity metric within a symmetric non-parametric Gauss-Newton registration framework. In principle, MIND would be applicable to the registration of arbitrary modalities. In this work, we apply and validate it for the registration of clinical 3D thoracic CT scans between inhale and exhale as well as the alignment of 3D CT and MRI scans. Experimental results show the advantages of MIND over state-of-the-art techniques such as conditional mutual information and entropy images, with respect to clinically annotated landmark locations.

Keywords: Non-rigid registration, multi-modal similarity metric, self-similarity, non-local means, computed tomography, magnetic resonance imaging, pulmonary images

1. Introduction

The aim of medical image registration is to find the correct spatial mapping of corresponding anatomical or functional structures between images. Patient motion, due to different positioning or breathing level, and pathological changes between scans may cause non-rigid deformations, which need to be compensated for. Advances in recent years have resulted in a number of robust and accurate methods for deformable registration techniques for scans of the same modality, with registration accuracies close to the scan resolution (as demonstrated in an evaluation study of lung registration, Murphy et al. (2011)). However, the registration of images from different modalities remains a challenging and active area of research. Alignment of multi-modal images helps to relate clinically relevant and often complementary information from different scans. For example, it can be used in image guided interventions. Using

multi-modal images can also help a clinician to make use of the complementary information present in different modalities and improve the diagnostic task. One common clinical application is the registration of computed tomography (CT) and magnetic resonance imaging (MRI), as it can combine the good spatial resolution and dense tissue contrast of a CT with the better soft tissue contrast of MRI.

In addition to the geometric distortion caused by patient motion, multi-modal registration also has to be able to deal with intensity distortions. Due to the different physical phenomena that are measured by the different modalities, there is no functional relation between the intensity mapping of corresponding anatomies. This problem can be addressed using geometric registration approaches, which aim to match a sparse set of descriptors, such as *scale invariant feature transform* (SIFT) (Lowe (1999)) or *gradient location and orientation histograms* (GLOH) (Mikolajczyk and Schmid (2005)), which are to some extent invariant to changes of intensity (or illumination) since they rely on image gradients and local orientations. However, they have not been successfully applied to multi-modal images, where the intensity variations are more severe. Voxel-wise in-

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38 intensity based registration can also be used to align multi-modal 95
39 images. This requires the use of a similarity metric derived 96
40 from the image intensities that is robust to the non-functional 97
41 intensity relationship. 98

42 Mutual information (MI), first introduced by Maes et al. 99
43 (1997) and Viola and Wells III (1997), is an information the-100
44 oretic measure, which aims to find a statistical intensity rela-101
45 tionship across images and thereby maximises the amount of-102
46 shared information between two images. For the rigid align-103
47 ment of multi-modal images, MI has been very successful and-104
48 is widely used (an overview is given in Pluim et al. (2003)).-105
49 Its application to deformable multi-modal registration comes-106
50 with many difficulties, and several weaknesses have been iden-107
51 tified. The main disadvantage is that MI is intrinsically a global-108
52 measure and therefore its local estimation is difficult, which-109
53 can lead to many false local optima in non-rigid registration.-110
54 Moreover, the optimisation of mutual information for non-rigid-111
55 registration is computationally complex and converges slower-112
56 than more simple intensity metrics, such as sum of squared dif-113
57 ferences (SSD), calculated over the intensities directly. Con-114
58 sequently, a new approach to deformable multi-modal regis-115
59 tration has emerged, which uses a different scalar represen-116
60 tation of both images based on a modality independent local-117
61 quantity, such as local phase, gradient orientation or local en-118
62 tropy (Mellor and Brady (2005), Haber and Modersitzki (2006),-119
63 Wachinger and Navab (2012)). These approaches benefit from-120
64 their attractive properties for the optimisation of the cost func-121
65 tion, since the point-wise (squared) differences can be used to-122
66 minimise differences between the image representations. For-123
67 challenging multi-modal scans it is however not always possi-124
68 ble to find a scalar representation that is sufficiently discrimina-125
69 tive. 126

70 In this article, we introduce a new concept for deformable-127
71 multi-modal registration using a highly discriminative, multi-128
72 dimensional image descriptor, called the modality independent
73 neighbourhood descriptor (MIND), which can be efficiently
74 computed in a dense manner over the images and optimised-129
75 using SSD. We make use of the concept of local self-similarity,
76 which has been exploited in many different areas of image anal-130
77 ysis, such as denoising (Buades et al. (2005)), super-resolution-131
78 (Manjon et al. (2008)), image retrieval (Hörster and Lienhart-132
79 (2008)), detection (Shechtman and Irani (2007)) and segmenta-133
80 tion (Coupé et al. (2010)). It allows the formulation of an image-134
81 descriptor, which is independent of the particular intensity dis-135
82 tribution across two images and still provides a very good rep-136
83 resentation of the local shape of an image feature. It is based-137
84 on the assumption that even though the intensity distribution of-138
85 an anatomical structure may not correspond across modalities,-139
86 it is reliable within a local neighbourhood in the same image.-140
87 Therefore descriptors based on a simple intensity based met-141
88 ric, like SSD, can be extracted for each modality separately and-142
89 then directly compared across images. The overview of our ap-143
90 proach is schematically shown in Fig. 1. We first extract a dense-144
91 set of high-dimensional image descriptors for both images in-145
92 dependently based on the intensity differences within a search-146
93 region around each voxel in the same modality. We embed this-147
94 in a standard non-rigid registration framework to optimise the-148

transformation parameters using a single-modal similarity met-
ric (SSD), in order to compare descriptors across the two im-
ages.

This article extends our earlier work (Heinrich et al. (2011))
by using a more principled derivation of this image descriptor,
thus making it more robust to changes in local noise and con-
trast and therefore allowing for the use of the L2 norm to com-
pare descriptors across modalities. We also present a more thor-
ough evaluation including quantitative comparisons to more re-
cent multi-modal similarity metrics.

This paper is structured as follows: Section 2 presents an
overview of related work in deformable multi-modal registra-
tion, as well as examples of the use of image self-similarity in
literature. This includes a brief review of two recent techniques:
conditional mutual information and entropy images, against
which the proposed technique will be compared. Section 3 de-
scribes the formulation and implementation of MIND, demon-
strating its sensitivity to different types of image features, such
as corner points, edges and homogenous areas, and their lo-
cal orientation. Details of its efficient implementation are pre-
sented, which greatly reduces the computational complexity by
using convolution filters. The rigid and deformable registration
framework used in the experiments, which is based on a multi-
resolution Gauss-Newton optimisation, is presented in Section
4. Section 5 shows an evaluation of the robustness and accuracy
of the presented method, first for the task of landmark detection
in multi-modal 3D datasets under the influence of intensity dis-
tortions, then for deformable registration of CT lung scans, and
finally on the clinical application of the alignment of volumetric
CT and MRI scans of patients suffering from the lung disease
empyema. The method's performance is quantitatively evalu-
ated using gold standard landmarks localised by a clinical ra-
diologist. Finally, the results are discussed and future research
directions are given.

2. Background

2.1. Mutual information

Mutual information (MI) is derived from information theory
and measures the statistical dependency of two random vari-
ables. It was first introduced to medical image registration
for the rigid alignment of multi-modal scans by Maes et al.
(1997) and Viola and Wells III (1997), and later used success-
fully in a variety of applications, including deformable registra-
tion (Rueckert et al. (1999), Meyer et al. (1997)). Studholme
et al. (1999) introduced normalised mutual information (NMI)
to cope with the effect of changing image overlap on MI. It is
based on the assumption that a lower entropy of the joint inten-
sity distribution corresponds to a better alignment.

An important disadvantage of mutual information for image
registration is that it ignores the spatial neighbourhood of a par-
ticular voxel within one image and consequently, it does not
use the spatial information shared across images. In the pres-
ence of image intensity distortions, such as a non-stationary
bias field in an MRI scan, this can deteriorate the quality of
the alignment, especially in the case of non-rigid registration

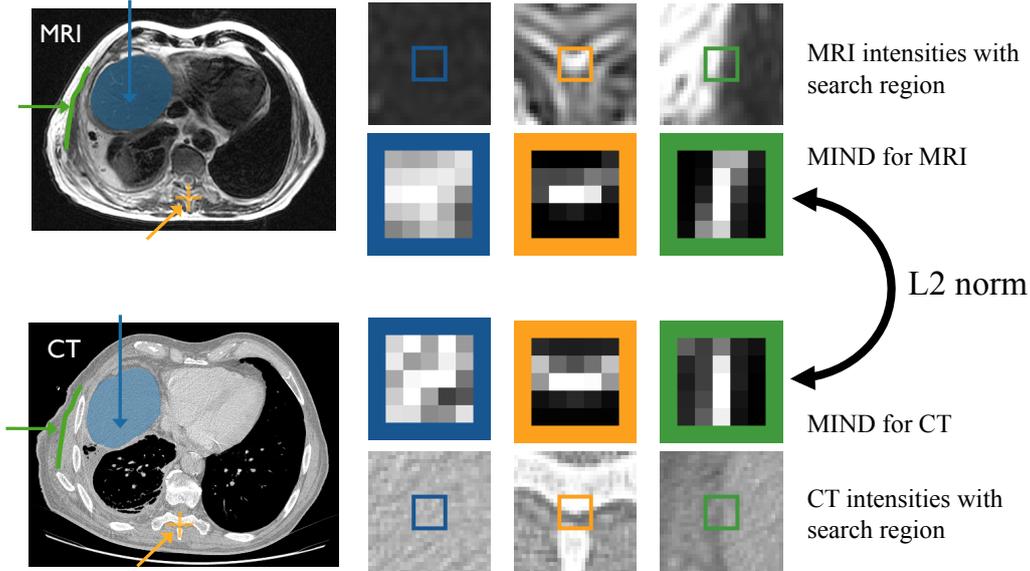


Figure 1: Proposed concept for the use of MIND for multimodal registration. MIND is calculated in a dense manner in CT and MRI. Three exemplary locations with different image features: ■ homogenous intensities (liver), ■ corner points at one vertebra and ■ image gradients at the boundary between fat and non-fat tissue are shown. The corresponding descriptors (in coloured boxes, high intensities correspond to small patch distances) are independent of the respective modality and can be easily compared using the L2 norm.

149 where the geometric constraints of the transformation are relaxed compared to rigid body alignment. One approach to overcome this problem is to include spatial information into the joint and marginal histogram computation. In Rueckert et al. (2000) a second-order mutual information measure is defined, which extends the joint entropy estimation to the spatial neighbours of a voxel and therefore uses a 4D histogram, where the third and fourth dimensions define the probability of the spatial neighbours of a voxel to have a certain intensity. A problem that arises here is the curse of dimensionality, meaning that a lot of samples are needed to populate the higher-dimensional histogram. The authors therefore limit the number of intensity bins to 16, which might again decrease the accuracy. Three more recent approaches of MI including spatial context can be found in (Yi and Soatto (2011)), (Heinrich et al. (2012)) and (Zhuang et al. (2011)).

2.1.1. Pointwise normalised mutual information

165 In (Hermosillo et al. (2002), Rogelj et al. (2003)), variants of mutual information to obtain a pointwise similarity metric have been proposed. For the implementation of NMI as comparison method, the approach of (Rogelj et al. (2003)) is used in this work. The joint and marginal histograms p of two images I and J are obtained in a conventional manner by summing up the contribution of all intensity pairs to one global histogram. The local contribution $NMI(\mathbf{x})$ for each voxel can then be obtained using:

$$NMI(\mathbf{x}) = \log \left(\frac{p(I(\mathbf{x}), J(\mathbf{x}))}{p(I(\mathbf{x}))p(J(\mathbf{x}))} \right) \frac{1}{\sum_{\Omega} p(I(\mathbf{x})) \log p(I(\mathbf{x}))} \quad (1)$$

175 Alternatively, a local joint histogram estimation could be used, which however would limit the number of samples and

would require more sophisticated histogram strategies like non-parametric windows (Dowson et al. (2008)), which are computationally extremely demanding for 3D volumes. A simplified computation for this technique was recently presented by Joshi et al. (2011).

2.1.2. Conditional mutual information

192 A number of disadvantages of using the traditional global MI approach have been analysed by Loeckx et al. (2010), Haber and Modersitzki (2006), and Studholme et al. (2006). These lie mainly in the sensitivity of MI (or NMI) to non-uniform bias fields in MRI. These can be often explained by the lack of spatial information in the joint histogram calculation. Different approaches have been proposed to include spatial context into MI as mentioned above. Studholme et al. (2006) introduce a third channel to the joint histogram containing a spatial or regional label. In this work, the recent approach called conditional mutual information (CMI), as introduced by Loeckx et al. (2010) is used for comparison purposes. In this technique, a third dimension is added to the joint histogram and a second dimension is added to the marginals representing the regional location of an intensity pair. The image is subdivided into a number of overlapping regions and each intensity pair only contributes to its specific regional histograms. A number of anchor points are evenly distributed on the image grid. Each voxel in a 3D volume is then attributed to its 8 nearest anchor points, and its contribution to this regional label $r(\mathbf{x})$ is weighted by the reciprocal spatial distance $w(I(\mathbf{x}), J(\mathbf{x}), \mathbf{x})$ to it. CMI is then defined as:

$$CMI(\mathbf{x}) = - \sum_{\mathbf{x} \in \Omega} w(I(\mathbf{x}), J(\mathbf{x}), r(\mathbf{x})) \log \left(\frac{p(I(\mathbf{x}), J(\mathbf{x}))}{p(I(\mathbf{x}))p(J(\mathbf{x}))} \right) \quad (2)$$

In (Loeckx et al. (2010)) it was shown that this reduces the negative influence of bias fields and yields a higher registration accuracy for a small number of realistic test cases. The drawbacks lie again in the difficulty of populating this 3D histogram, and in the fact that corresponding anatomical structures, which are spatially further apart, are ignored.

2.2. Structural representation

A very different approach to multi-modal image registration is the use of a structural representation, which is assumed to be independent of a certain modality. One can then use a simple intensity-based measure across image representations. Using image gradients directly would be not representative across modalities, but the use of the local gradient orientation is possible and has been used in (Pluim et al. (2000)) for rigid registration and in (Haber and Modersitzki (2006), Heinrich et al. (2010)) and (De Nigris et al. (2010)) for deformable registration. In (Mellor and Brady (2005)), the local phase of the image was extracted using a technique called the monogenic signal, and further used for registration. However, in their work mutual information was used between phase images, which implies that there was still no direct dependency between the representations of different modalities. Our approach is different in that not a scalar representation, but a vector-valued image descriptor is derived for each voxel.

2.2.1. Entropy images

Local patch-based entropy images have been proposed by Wachinger and Navab (2012), which were then minimised using SSD across modalities, achieving similar registration accuracy as mutual information for rigid multimodal registration, and some synthetic non-rigid experiments. The basic assumption that drives the registration based on entropy images is that intensity changes occur at the same locations in different modalities. An entropy image is produced by firstly calculating histograms of small image patches. The size p and weighting C_{σ} of the local patches is of great importance. The entropy value $E(\mathbf{x})$ for each voxel is then obtained using a Parzen Window smoothing of the histogram from which the Shannon entropy is calculated.

According to (Wachinger and Navab (2012)), the number of intensity bins for non-rigid registration should be sufficiently small to ensure a well populated local histogram, which however reduces the sensitivity to small intensity changes. A problem with this approach can be a changing level of noise within and across images - which in turn would influence the entropy calculation. The high complexity (p^d per voxel, where d is the dimension of the image) of the entropy image calculation could potentially be reduced using a convolution kernel for the contribution of each individual voxel to all neighbouring voxels within the size of a patch.

2.3. Self-similarity

Our approach uses the principle of self-similarity, a concept which has first been introduced in the domain of image denoising by Buades et al. (2005). These authors make use of similar

image patches across a noisy image to obtain a noise-free pixel, which is computed as a weighted average of all other pixels in the image. The weights $w(i, j)$ used for the averaging are based on the sum of squared differences between the patch, which surrounds the pixel of interest, and all other patches in the image. The denoised pixels $NL(i, J)$ are then calculated using the following equation:

$$NL(i, J) = \sum_{j \in N} w(i, j) J(j) \quad (3)$$

where N is the neighbourhood of i . The approach demonstrated a very good performance for image denoising. The use of patches to measure similarity based on the weights $w(i, j)$ within the same image can easily capture a variety of image features, because it treats regions, edges, corners and textures in a unified way and is thus much more meaningful than using single intensities. In subsequent work, this approach was simplified to search for similar patches only within a smaller non-local search region (Coupé et al. (2006)). Figure 1 gives an example of how well the self-similarity pattern can describe the local structure around an image location. Mainly because of this property, the concept has been used later on in a variety of applications. Of particular interest is the application to object localisation by Shechtman and Irani (2007). Here, a correlation surface is extracted using colour patch distances and then stored in a log-polar histogram, which can be matched across images using the L1 norm.

3. Modality independent neighbourhood descriptor

In this section we will present the modality independent neighbourhood descriptor (MIND) and its use to define the similarity between two images based on the SSD of their descriptors. First we motivate the use of image self-similarity for the construction of an image descriptor. We will then propose the definition of self-similarity by using a Gaussian-weighted patch-distance and explain the spatial capture range of the descriptor.

3.1. Motivation and Concept

Our aim is to find an image descriptor, which is independent of the modality, contrast and noise level of images from different modalities and at the same time sensitive to different types of image features. Our approach is based on the assumption that a local representation of image structure, which can be estimated through the similarity of small image patches within one modality, is shared across modalities. As mentioned before, many different features may be used to derive a similarity cost function for image registration, such as corner points, edges, gradients, textures or intensity values. Figure 1 shows some examples on two slices of a CT and MRI volume.

Most intensity based similarity metrics employ only one of these features or need to define a specific combination of different features and a weighting between them. Image patches have been shown to be sensitive to very different types of image features including edges, points and texture. Using patches

for similarity calculations also removes the need for a feature-specific weighting scheme. However, they are limited to single-modal images. In our approach, a multi-dimensional image descriptor, which represents the distinctive image structure in a local neighbourhood, is extracted based on patch distances for both modalities separately and afterwards compared using simple single-modal similarity measures.

MIND can be generally defined by a distance D_p , a variance estimate V and a spatial search region R :

$$\text{MIND}(I, \mathbf{x}, \mathbf{r}) = \frac{1}{n} \exp\left(-\frac{D_p(I, \mathbf{x}, \mathbf{x} + \mathbf{r})}{V(I, \mathbf{x})}\right) \quad \mathbf{r} \in R \quad (4)$$

where n is a normalisation constant (so that the maximum value is 1) and $\mathbf{r} \in R$ defines the search region. By using MIND, an image will be represented by a vector of size $|R|$ at each location \mathbf{x} .

3.1.1. Patch-based distance

To evaluate Eq. 4 we need to define a distance measure between two voxels within the same image. As mentioned before, image patches offer attractive properties and are sensitive to the three main image features: points, gradients and uniformly textured regions. Therefore the straightforward choice of a distance measure $D_p(\mathbf{x}_1, \mathbf{x}_2)$ between two voxels \mathbf{x}_1 and \mathbf{x}_2 is the sum of squared differences (SSD) of all voxels between the two patches P of size $(2p + 1)^d$ (with image dimension d) centred at \mathbf{x}_1 and \mathbf{x}_2 .

$$D_p(I, \mathbf{x}_1, \mathbf{x}_2) = \sum_{\mathbf{p} \in P} (I(\mathbf{x}_1 + \mathbf{p}) - I(\mathbf{x}_2 + \mathbf{p}))^2 \quad (5)$$

The distance value defined in Eq. 5 has to be calculated for all voxels \mathbf{x} in the image I and all search positions $\mathbf{r} \in R$. The naïve solution (which is e.g. used in Coupé et al. (2006)) would require $3(2p + 1)^d$ operations per voxel and is therefore computationally very expensive.

We propose an alternative solution to calculate the exact patch-distance very efficiently using a convolution filter C of size $(2p + 1)^d$. First a copy of the image I' is translated by \mathbf{r} yielding $I'(\mathbf{r})$. Then the point-wise squared difference between I and $I'(\mathbf{r})$ is calculated. Finally, these intermediate values are convolved with the kernel C , which effectively substitutes the SSD summation in Eq. 5:

$$D_p(I, \mathbf{x}, \mathbf{x} + \mathbf{r}) = C \star (I - I'(\mathbf{r}))^2 \quad (6)$$

This procedure is now repeated for all search positions $\mathbf{r} \in R$. The solution of Eq. 6 is equivalent to the one obtained using Eq. 5. Using this method it is also easily possible to include a Gaussian weighting of the patches by using a Gaussian kernel C_σ of size $(2p + 1)^d$. The computational complexity per patch distance calculation is therefore reduced from $(2p + 1)^d$ to $d(2p + 1)$ for an arbitrary separable kernel and $3d$ for a uniform patch weighting. A similar procedure has been proposed in the context of windowed SSD aggregation by Scharstein and Szeliski (1996).

3.2. Variance measure for Gaussian function

We want to obtain a high response for MIND for patches that are similar to the patch around the voxel of interest, and a low response for everything that is dissimilar. A Gaussian function (see Eq. 4) is used for this purpose. The denominator $V(I, \mathbf{x})$ in Eq. 4 is an estimation of the local variance. A smaller value for V yields a sharply decaying function, and higher values indicate a broader response. The parameter has to be related to the amount of noise in the image. The variance of the image noise can be estimated via pseudo-residuals ϵ calculated using a six-neighbourhood \mathcal{N} (see Coupé et al. (2008)):

$$\epsilon_i = \sqrt{\frac{7}{6}} \left(I(\mathbf{x}_i) - \frac{1}{6} \sum_{\mathbf{x}_j \in \mathcal{N}} I(\mathbf{x}_j) \right) \quad (7)$$

ϵ is averaged over the whole image domain Ω to obtain a constant variance measure $V(I, \mathbf{x}) = \frac{1}{|\Omega|} \sum_{i \in \Omega} \epsilon_i^2$. This however increases the sensitivity of the image descriptors to spatially varying noise. Therefore a locally varying function would be beneficial. A better way of determining $V(I, \mathbf{x})$ is to use the mean of the patch distances themselves within a six-neighbourhood $\mathbf{n} \in \mathcal{N}$:

$$V(I, \mathbf{x}) = \frac{1}{6} \sum_{\mathbf{n} \in \mathcal{N}} D_p(I, \mathbf{x}, \mathbf{x} + \mathbf{n}) \quad (8)$$

Using this approach (Eq. 8), MIND can be automatically calculated without the need for any additional parameters.

Exemplary responses of the obtained descriptors for three different image features for both CT and MRI are shown in Fig. 1 (second and third row on the right), where a high intensity corresponds to a small patch distance. Fig. 1 demonstrates how well descriptors represent these features independent of modality.

3.3. Spatial search region

An important issue using MIND is the spatial extent of the search region (see R in Eq. 4) for which the descriptor is calculated. In the original work of Buades et al. (2005), self-similarity was defined across the whole image domain, thus coining the term: "non-local filtering". For the use in object detection, Shechtman and Irani (2007) used a sparse ensemble of self-similarity descriptors calculated with a search radius of 40 pixels, which was stored in a log-polar histogram. For the use of MIND in image registration, however, a smaller search region is sufficient. This can be explained by the prior knowledge of smooth deformations, which are enforced by the regularisation term of most deformable registration algorithms. We will define three different types of spatial sampling for the spatial search region R : dense sampling, sparse sampling (rays of 45 degrees), and a six-neighbourhood. Figure 2 illustrates these configurations, where the red voxel in the centre is the voxel of interest, and all gray voxels define R . The computational complexity is directly proportional to the number of sampled displacements, therefore the six-neighbourhood clearly offers the best time efficiency. If the neighbourhood is chosen too large, the resulting descriptor might be affected by non-rigid deformations.

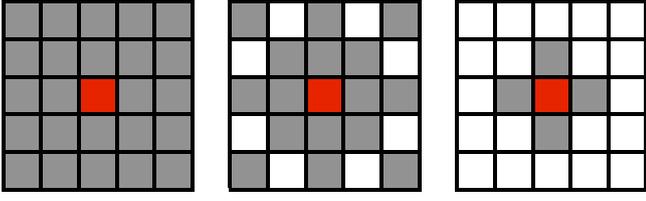


Figure 2: Different samplings of the search region: (a) dense, (b) sparse and (c) six-neighbourhood. Red voxel is the voxel of interest, gray voxels are being sampled $\mathbf{r} \in R$.

An evaluation of the influence of both patch-size (and weighting) and search region will be given in Section 5.2.1. A basic MATLAB implementation for the efficient calculation of MIND can be found in the electronic appendix.

3.4. Multi-modal similarity metric using MIND

One motivation for the use of MIND is that it allows to align multi-modal images using a simple similarity metric across modalities. Once the descriptors are extracted for both images, yielding a vector for each voxel, the similarity metric between two images is defined as the SSD between their corresponding descriptors. Therefore efficient optimisation algorithms, which converge rapidly can be used without further modification. We employ Gauss-Newton optimisation, which minimises the linearised error term in a least-square sense (Madsen et al. (1999)). In order to optimise the SSD of MIND, the similarity term $S(\mathbf{x})$ of two images I and J at voxel \mathbf{x} can be defined as the sum of absolute differences between descriptors:

$$S(\mathbf{x}) = \frac{1}{|R|} \sum_{\mathbf{r} \in R} |\text{MIND}(I, \mathbf{x}, \mathbf{r}) - \text{MIND}(J, \mathbf{x}, \mathbf{r})| \quad (9)$$

This requires $|R|$ computations to evaluate the similarity at one voxel. Some algorithms, especially discrete optimisation techniques (Glocker et al. (2008), Shekhovtsov et al. (2008)) use many cost function evaluations per voxel. In order to speed-up these computations the descriptor can be quantised to only 4 bit, without significant loss of accuracy. For $|R| = 6$ all possible distances between descriptors can be pre-computed and stored in a lookup-table.

The similarity S yields an intuitive display of the difference image after registration. Enabling single-modal similarity metrics by using an intermediate image representation is also the motivation in (Wachinger and Navab (2012)); in contrast to our work they reduce the alternative image representation to a single scalar value per voxel.

Our new similarity metric based on the MIND can be used in any registration algorithm with little need for further modification. We show in the experimental section that it can improve accuracy for both rigid and deformable registration of multi-modal data.

4. Gauss-Newton registration framework

This section describes the rigid and deformable registration framework, which will be used for all similarity metrics that

are being compared in Section 5. We chose to use a Gauss-Newton optimisation scheme as it has an improved convergence compared to steepest descent methods (Zikic et al. (2010a)). For single-modal registration using SSD as similarity metric, Gauss-Newton optimisation is equivalent to the well known Horn-Schunck optical flow solution (Horn and Schunck (1981)) as shown in (Zikic et al. (2010b)).

4.1. Rigid registration

Rigid image registration aims to find the best transformation to align two images while constraining the deformation to be parameterised by a rigid-body (translation and rotation, 6 parameters). Extending this model to the more general affine transformation, the transformed location $\mathbf{x}' = (x', y', z')^T$ of a voxel $\mathbf{x} = (x, y, z)^T$ can be parameterised by $\mathbf{q} = (q_1, \dots, q_{12})$:

$$\begin{aligned} u = x' - x &= q_1x + q_2y + q_3z + q_{10} - x \\ v = y' - y &= q_4x + q_5y + q_6z + q_{11} - y \\ w = z' - z &= q_7x + q_8y + q_9z + q_{12} - z \end{aligned} \quad (10)$$

where $\mathbf{u} = (u, v, w)^T$ is the displacement of \mathbf{x} . For a quadratic image similarity function \mathbf{f}^2 , the Gauss-Newton method can be applied. It uses a linear approximation of the error term:

$$\begin{aligned} \mathbf{f}(\mathbf{x}') &\approx \mathbf{f}(\mathbf{x}) + \mathbf{J}(\mathbf{x})\mathbf{u} \\ (\mathbf{J}^T \mathbf{J})\mathbf{u}_{\text{gn}} &= -\mathbf{J}^T \mathbf{f} \end{aligned} \quad (11)$$

where $\mathbf{J}(\mathbf{x})$ is the derivative of the error term with respect to the transformation and \mathbf{u}_{gn} is the update step. We insert Eqs. 10 into Eq. 11 and differentiate with respect to \mathbf{q} to calculate $\mathbf{J}(\mathbf{x})$. The advantage of this method is that we can directly use the point-wise cost function derivatives with respect to \mathbf{u} to obtain an affine transformation, so that MIND has to be computed only once per image.

Parameterizing a rigid-body transformation directly is more difficult. Therefore, at each iteration the best affine matrix is first estimated and then the best rigid-body transformation is found using the solution presented in Arun et al. (1987). The Gauss-Newton step is iteratively updated while transforming the source image towards the target. In order to speed up the convergence and avoid local minima, a multi-resolution scheme (with downsampling factors of 4 and 2) is used.

4.2. Diffusion-regularised deformable registration

Within the non-rigid registration framework, we aim to minimise the following cost function with respect to the deformation field $\mathbf{u} = (u, v, w)^T$, consisting of a non-linear similarity term S (dependent on \mathbf{u}) and a diffusion regularisation term:

$$\arg \min_{\mathbf{u}} \sum_{\mathbf{x}} S(I_1(\mathbf{x}), I_2(\mathbf{x} + \mathbf{u}))^2 + \alpha \text{tr}(\nabla \mathbf{u}(\mathbf{x})^T \nabla \mathbf{u}(\mathbf{x})) \quad (12)$$

Since the objective function to be minimised is of the form $\sum_i \mathbf{f}_i^2$, we can again apply the Gauss-Newton optimisation method, where \mathbf{f} is minimised iteratively with the update rule: $(\mathbf{J}^T \mathbf{J})\mathbf{u}_{\text{gn}} = -\mathbf{J}^T \mathbf{f}$, where \mathbf{J} is the derivative of \mathbf{f} with respect to \mathbf{u} . This can be adapted to this regularised cost function. We simplify the notation to $S = S(I_1(\mathbf{x}), I_2(\mathbf{x}))$ and

483 $\nabla S = (\frac{\partial S}{\partial u}, \frac{\partial S}{\partial v}, \frac{\partial S}{\partial w})^T$ and $\Delta \mathbf{u} = \nabla(\nabla(\mathbf{u}(\mathbf{x})))$. The regularisation
 484 term is linear with respect to \mathbf{u} as the differential operator is
 485 linear. The resulting update step given an initial or previous
 486 deformation field \mathbf{u}_{prev} becomes then:

$$(487) \quad (\nabla S^T \nabla S - \alpha \Delta) \mathbf{u}_{\text{gn}} = -(\nabla S^T S - \alpha \Delta \mathbf{u}_{\text{prev}}) \quad (13)$$

487 Equation 13 is solved using successive over-relaxation (an iterative
 488 solver). The final deformation field is calculated by the
 489 addition of the update steps \mathbf{u}_{gn} . The parameter α balances the
 490 similarity term with the regulariser. The value of α has to be
 491 found empirically. This choice will be further discussed in Section
 492 5.2.

4.3. Symmetric and inverse-consistent approach

494 For many deformable registration algorithms, there is a
 495 choice for one image to be the target and the other to be the
 496 source image. This places a bias on the registration outcome
 497 and may additionally introduce an inverse consistency error
 498 (ICE). The ICE has been defined by (Christensen and Johnson
 499 (2001)) for a forward transform A and a backward transform B
 500 to be the difference between AB^{-1} and the identity. In (Avants
 501 et al. (2008)) a symmetric deformable registration is presented,
 502 which calculates a transform from both images to a common in-
 503 termediate image and also ensures that the forward transform is
 504 the inverse of the backward transform. The full forward trans-
 505 form transformation is calculated by $A(0.5) \circ B(0.5)^{-1}$, where
 506 0.5 describes a transformation of half length (or with half the in-
 507 tegration time, if velocity fields are used). We follow the same
 508 approach and estimate both A and B . We then use a fast it-
 509 erative inversion method, as presented in (Chen et al. (2007)),
 510 to obtain $A(0.5)^{-1}$ and $B(0.5)^{-1}$. This approach helps to obtain
 511 diffeomorphic transformations, which means that no physically
 512 implausible folding of volume occurs. We use this symmetric
 513 approach in all deformable registration experiments.

5. Experiments

515 In this section we perform a number of challenging registra-
 516 tion experiments to demonstrate the capabilities of MIND in
 517 medical image registration. We compare our new descriptor to
 518 state-of-the-art multi-modal similarity metrics: normalised mutual
 519 information (NMI), conditional mutual information (CMI),
 520 and SSD of entropy images (eSSD) within the same registration
 521 framework. We evaluate our findings based on the target registra-
 522 tion error (TRE) of anatomical landmarks. The TRE for a
 523 given transformation \mathbf{u} and an anatomical landmark pair $(\mathbf{x}, \mathbf{x}')$
 524 is defined by (Maurer et al. (1997)):

$$(525) \quad \text{TRE} = \sqrt{(x + u(\mathbf{x}) - x')^2 + (y + v(\mathbf{x}) - y')^2 + (z + w(\mathbf{x}) - z')^2} \quad (14)$$

525 We first apply the different methods to landmark localisation
 526 within an aligned pair of T1 and PD weighted MRI scans of the
 527 Visible Human dataset. We then perform deformable registra-
 528 tions on ten CT datasets of lung cancer patients, and finally we
 529 register CT and MRI scans of patients with emphyema.

5.1. Landmark localisation in visible human dataset

Evaluating multi-modal image registration in a controlled
 manner is not a trivial task. Finding and accurately marking
 corresponding anatomical landmarks across modalities is
 a difficult task even for a clinical expert. Random deformation
 experiments, as they are usually performed in the literature
 for multi-modal registration (e.g. in D'Agostino et al. (2003),
 Glocker et al. (2008), Mellor and Brady (2005), Wachinger
 and Navab (2012)), are mostly unrealistic. In order to per-
 form a simulated deformation on multi-modal data, an aligned
 scan pair must be available, which is only usually possible for
 brain scans. Here the number of different tissue classes is a
 lot smaller than for chest scans, thus these experiments do not
 generalise very well. Moreover, simulated deformations hardly
 ever capture the complexity and physical realism of patient
 motion. To address these problems, we perform an alterna-
 tive experiment: regional landmark localisation. For this pur-
 pose, we employ the less regularly used Visible Human dataset
 (VHD) (Ackerman (1998))¹. Because the scans were taken
 post-mortem, no motion is present and different modalities are
 consequently in perfect alignment. We selected two MRI se-
 quences, T1 and PD weighted volumes, as they offer a suffi-
 cient amount of cross-modality variations. The images are up-
 sampled from their original resolution of 1.875x4x1.875 mm
 to form isotropic voxels of size 1.875 mm³.

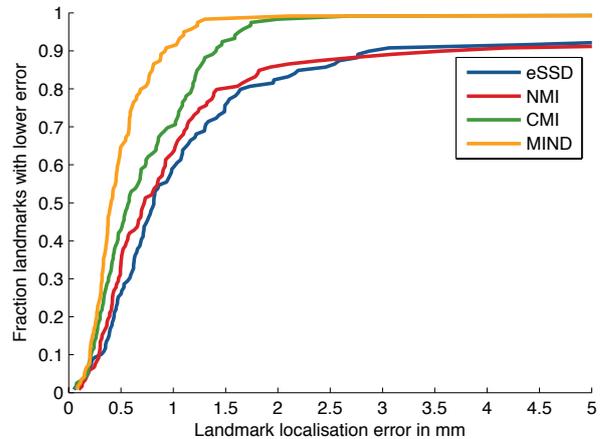


Figure 4: Cumulative distribution of landmark localisation error in mm for 119 landmarks located in the original T1/PD MRI scan of the Visible Human dataset. MIND achieves a significantly higher localisation accuracy.

In our tests we automatically select a large number (119) of
 geometric landmarks using the 3D version of the Harris corner
 detector (Rohr (2000)). Cross-sections of both sequences are
 shown in Fig. 3. For each landmark of the MRI-PD scan,
 we perform an exhaustive calculation of the similarity metric
 within a search window of 39x39x39 mm of the T1 image
 around the respective location. Since no regularisation is used
 in this experiment, we average the cost function over a local

¹The Visible Human dataset is obtainable from http://www.nlm.nih.gov/research/visible/getting_data.html

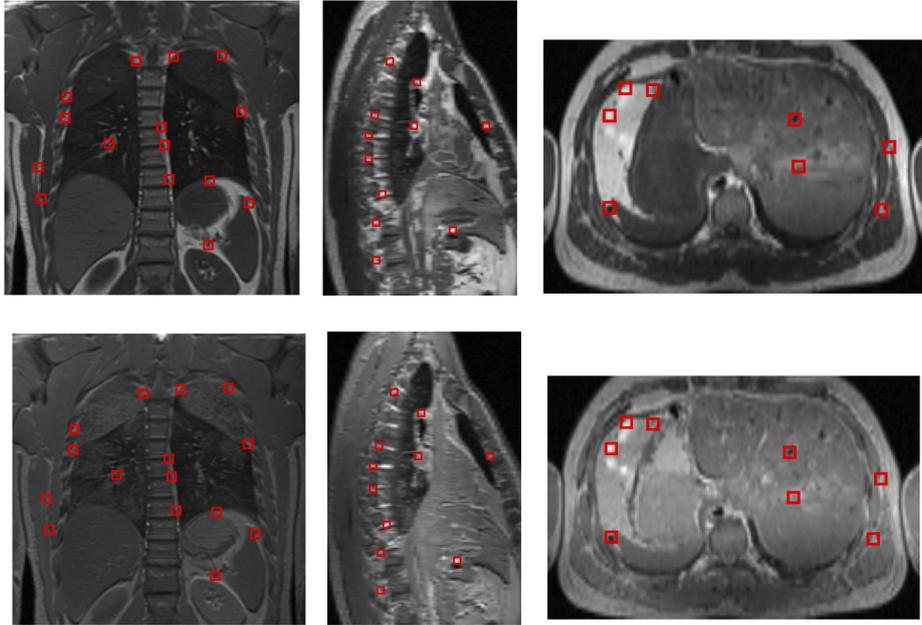


Figure 3: Visible Human Dataset used for landmark localisation experiment. T1 and PD MRI scan of post-mortem human are intrinsically aligned. The landmarks, which were used for evaluation are plotted with red squares.

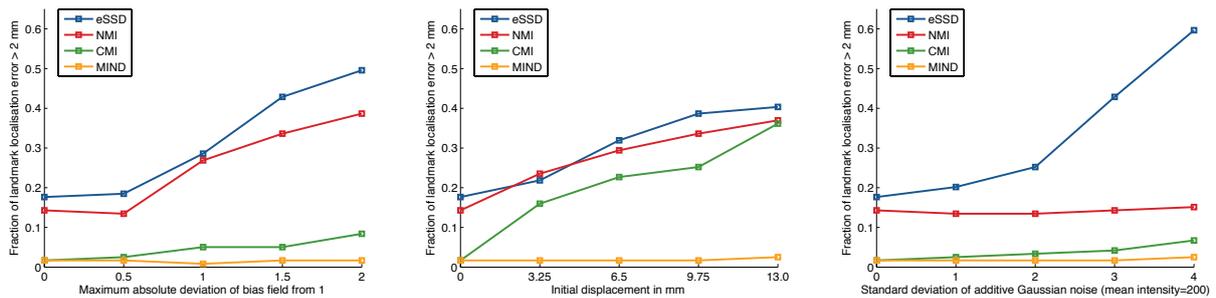


Figure 5: Fraction of falsely located landmarks (error > 2mm) for increasing bias field, initial misalignment (translation), and additive Gaussian noise in multi-modal pair of T1/PD MRI scan of Visible Human dataset. The resulting localisation deteriorates for NMI and eSSD with increased bias. NMI, CMI and eSSD have a high localisation error for initially misaligned volumes. eSSD shows a high sensitivity to Gaussian noise.

neighbourhood with a radius 5 voxels. The optimal position⁵⁸¹ (highest similarity) is calculated (up to subpixel accuracy) and⁵⁸² compared to the known ground truth location. The Euclidean⁵⁸³ distance serves as localisation error. If the similarity metric is⁵⁸⁴ sufficiently discriminative, no other local optimum should ap-⁵⁸⁵pear within the search region. The distribution of the resulting⁵⁸⁶ error for all compared similarity metrics is shown in Fig. 4.⁵⁸⁷ MIND achieves a significantly lower localisation error than all⁵⁸⁸ other similarity metrics. We subsequently apply a non-uniform⁵⁸⁹ bias field (multiplicative linear gradient in y-direction), a trans-⁵⁹⁰lation, or additive Gaussian noise to the T1 scan. The fraction⁵⁹¹ of falsely located landmarks with increasing image distortion⁵⁹² is plotted in Fig. 5. MIND clearly outperforms both NMI and⁵⁹³ eSSD by achieving a consistently lower landmark localisation⁵⁹⁴ error. CMI is, as expected, not affected by the non-uniform bias⁵⁹⁵ field, however for an initial misalignment of the scan pair the⁵⁹⁶ joint histogram estimation becomes less reliable and the locali-⁵⁹⁷sation accuracy deteriorates.

5.2. Deformable registration of inhale and exhale CT scans

We performed deformable registration on ten CT scan pairs between inhale and exhale phase of the breathing cycle, provided by the DIR-Lab at the University of Texas (Castillo et al. (2009))². The patients were treated for esophagus cancer, and a breathing cycle CT scan of thorax and upper abdomen was obtained, with slice thickness of 2.5 mm, and an in-plane resolution ranging from 0.97 to 1.16 mm. Even though this stipulates a single-modal registration problem, directly intensity based similarity criteria such as SSD may fail in some cases SSD may fail in some cases due to the changing appearance between inhale and exhale scans. Particular challenges for these registration tasks are the changing contrast between tissue and air, because the gas density changes due to compression (Castillo et al. (2010b)), discontinuous sliding motion between lung lobes and the lung rib cage interface, and large deformations of small features (lung vessels, airways). For each image 300 anatomical

²This dataset is freely available at <http://www.dir-lab.com>

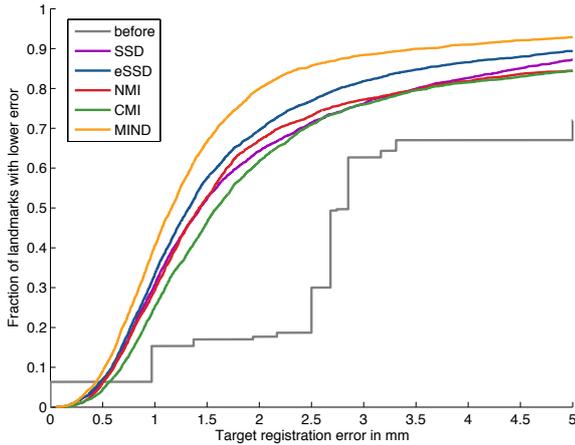


Figure 6: Deformable registration of 10 cases of CT scans evaluated with 300 expert landmarks per case. Registrations are performed between maximum inhale and exhale. The plot shows the cumulative distribution of target registration error, in mm. A significant improvement using MIND compared to all other methods has been found using a Wilcoxon rank sum test ($p < 0.0001$). The staircase effect of TRE before registration is due to the voxel based landmark annotation.

landmarks have been carefully annotated by thoracic imaging experts with inter-observer errors of less than 1 mm. The maximum average landmark error before registration is 15 mm (for Case 8), the maximum displacement of a single landmark is 30 mm.

The cumulative distributions of target registration error (TRE) for all 3000 landmarks (all 300 landmarks for all 10 cases) after registration are shown in Figure 6. MIND achieves the lowest average and median TRE among all methods. The average error of the second best metric (eSSD) is more than a third higher. The Wilcoxon rank-sum test was used to compare the TRE between the different similarity metrics across all cases and for each case individually. We found a significant improvement for MIND compared to all other metrics. Entropy SSD could significantly improve the accuracy compared to NMI. A summary of the registration results is given in Table 1. The range of Jacobian values of the transformations are all positive, thus all deformation fields are free from singularities. An example of the registration outcome using our proposed method along with the magnitude of the deformation field is shown in Figure 7.

5.2.1. Choice of parameters

We used a symmetric three-level multiresolution scheme within the presented Gauss-Newton framework for all compared methods. The best parameters were carefully chosen based on the TRE obtained for Case 5. An overview is given in Table A.4 in the electronic appendix. The regularisation was chosen sufficiently high to ensure physically plausible transformations with no singularities (negative Jacobians). For CMI the spatial size of each regional label was set to be between 25^3 and 50^3 voxels, as suggested in (Loeckx et al. (2010)). The computation time for each 3D registration was between 4 and 5 min-

Table 1: Target registration error in mm for deformable registration of ten CT scans between inhale and exhale. Evaluation based on 300 manual landmark per case. Inter-observer error for landmark selection < 1 mm. A Wilcoxon rank test is performed between MIND and each comparison method. Cases, for which a significant improvement ($p < 0.05$) was found are depicted below. As additional comparison, the results reported in the literature for two other techniques are shown below.

Metric	TRE (in mm)	
before	mean±std	8.46±6.58
	quantiles [0.25, 0.5, 0.75]	[3.11, 6.97, 12.55]
	cases for which $p < 0.05$	all
SSD	mean±std	2.73±3.72
	quantiles [0.25, 0.5, 0.75]	[0.89, 1.44, 2.85]
	cases for which $p < 0.05$	all except 1,2
eSSD	mean±std	2.86±4.91
	quantiles [0.25, 0.5, 0.75]	[0.86, 1.33, 2.33]
	cases for which $p < 0.05$	all except 1,2,4
NMI	mean±std	2.97±4.22
	quantiles [0.25, 0.5, 0.75]	[0.91, 1.42, 2.67]
	cases for which $p < 0.05$	all except 2
CMI	mean±std	3.06±4.10
	quantiles [0.25, 0.5, 0.75]	[1.00, 1.59, 2.85]
	cases for which $p < 0.05$	all
MIND	mean±std	2.14±3.71
	quantiles [0.25, 0.5, 0.75]	[0.77, 1.16, 1.79]
Results reported in literature		TRE (in mm)
Schmidt-Richberg et al. (2012)		
direction-dependend		2.13±1.82
diffusion regularisation		3.02±2.79
Castillo et al. (2010a)		1.35±1.43*

*These results are not directly comparable, as all frames of the 4D CT cycles are used during registration and more landmarks are evaluated.

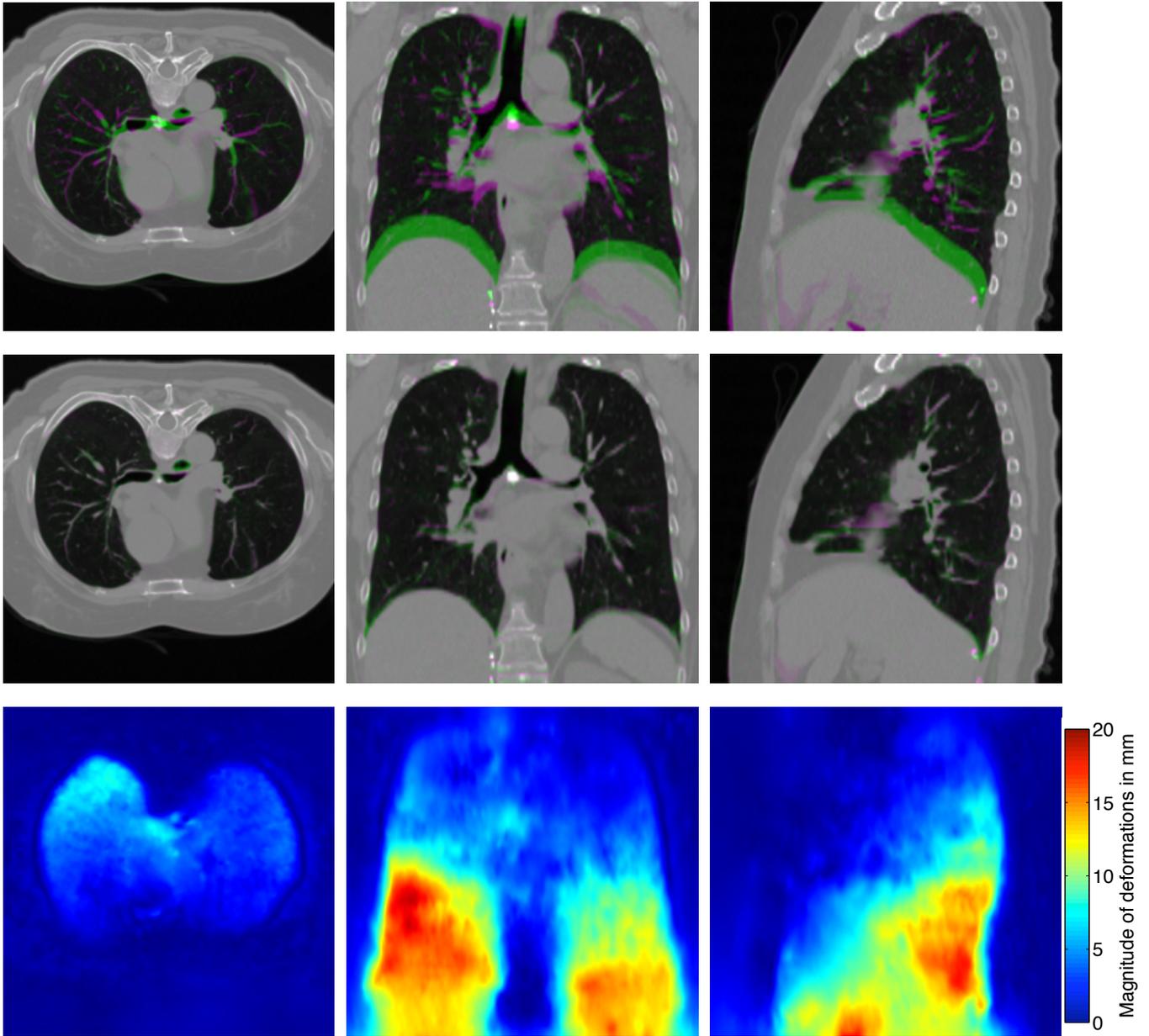


Figure 7: Deformable registration result for Case 5 of the CT dataset. Left: axial, middle: sagittal and right: coronal plane. Top row: before registration and centre row: after registration, using the proposed MIND technique. The target image is displayed in magenta and the source image in green (complementary colour). Bottom row shows the magnitude of the deformation field (red for large deformations) in mm.

630 utes for all methods (see Table 2). The influence of the choice of
 631 patch-size and search region for MIND has been evaluated us-
 632 ing both single-modal and multi-modal registration tasks. Fig.
 633 8 gives an overview of the obtained TRE. It can be generally
 634 seen that a Gaussian weighting $\sigma \approx 0.5$ (with a corresponding
 635 patch-size of $3 \times 3 \times 3$) as well as a very small search region (six-
 636 neighbourhoo) yield a very high accuracy. For other applica-
 637 tions with stronger image distortion and noise (e.g. ultrasound),
 638 we expect that larger patches and search regions would provide
 more robustness.

Table 2: Computation time (in seconds) for presented methods for Case 5 of CT dataset. For all metrics the SOR-solver for the Gauss-Newton optimisation takes 92 secs. The image dimensions are $256 \times 256 \times 106$.

Metric	preprocessing (for each GN iteration)	similarity term	full registration
eSSD	33.38	2.25	283.5
NMI	0.74	6.82	261.4
CMI	4.23	49.84	383.5
MIND	20.25	9.78	320.4

639

640 5.3. Multi-modal registration of CT/MRI lung scans

641 Deformable multi-modal registration is important for a range
 642 of clinical applications. We applied our proposed technique to
 643 a clinical dataset of eleven patients, which were scanned with
 644 both CT and MRI. Different scanning protocols were employed
 645 for these clinical datasets. The CT volumes include scans with
 646 contrast, without contrast, and a CTPA (CT Pulmonary An-
 647 giogram) protocol. For the MRI scans, both T1-weighted and
 648 T2-weighted FSE-XL sequences within a single breath-hold
 649 were employed. All patients suffered from empyema, a lung
 650 disease characterised by infection of the pleura and excess fluid
 651 within the pleural space. The extra fluid may progress into an
 652 abscess and additionally, cause the adjacent lung to collapse
 653 and/or consolidate. Both modalities are useful for detecting this
 654 pathology, but because the patients are scanned in two different
 655 sessions and at different levels of breath-hold, there are non-
 656 rigid deformations, which makes it difficult for the clinician to
 657 relate the scans. The quality of the MRI scans is comparatively
 658 poor, due to motion artefacts, bias fields and a slice thickness
 659 of around 8 mm.

660 We asked a clinical expert to select manual landmarks for
 661 all eleven cases. 12 corresponding landmarks were selected in
 662 all image pairs, containing both normal anatomical locations
 663 and disease-specific places. It must be noted that some of the
 664 landmarks are very challenging to locate, both due to low scan
 665 quality and changes of the pathology in the diseased areas be-
 666 tween scans. The intra-observer error has been measured to be
 667 5.8 mm within the MRI and 3.0 mm within a CT scan.

668 First a rigid registration of all cases using the proposed
 669 Gauss-Newton framework with the respective similarity met-
 670 rics is performed. The resulting landmark errors are shown in
 671 Figure 9. MIND achieves a lower TRE of 9.3 mm, on average,
 672 compared to NMI (10.8 mm). We additionally calculated the
 673 optimal rigid body transformation using a least square fit of the

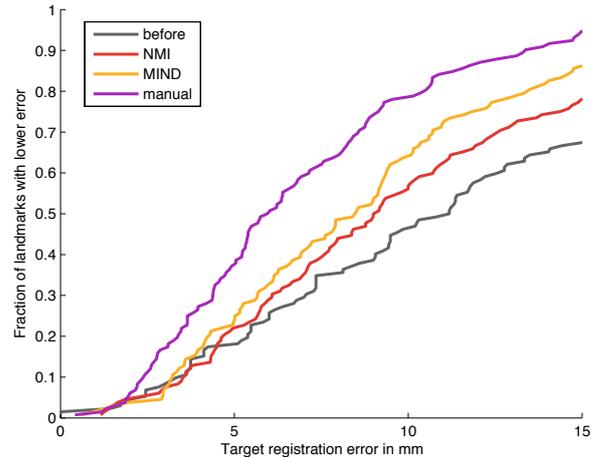


Figure 9: Rigid multi-modal registration of 11 cases of CT/MRI scans of empyema patients. Evaluated with 12 expert landmarks per case. The plot shows the cumulative distribution of target registration error, in mm. The manual registration error shows the residual error after a least square fit using a rigid transformation model to the ground truth landmark locations. MIND achieves an overall better performance than NMI.

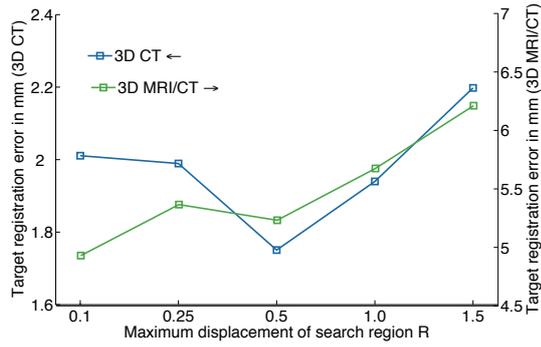
674 ground truth landmark locations. We were not able to use en-
 675 tropy images for this multi-modal experiment as the structural
 676 representation is not sufficient to allow for the large variations
 677 in appearance and distortion between the CT and MRI scans
 678 and the registration fails for most cases (increased landmark er-
 679 ror compared to ground truth after registration).

680 We use the rigid transformations obtained from the linear
 681 registration as initialisation of the subsequent deformable reg-
 682 istration. For eSSD, the rigid transformations obtained using
 683 MIND, are employed as initialisation. The parameter choice
 684 for all compared methods can be found in Table A.5 in the elec-
 685 tronic appendix.

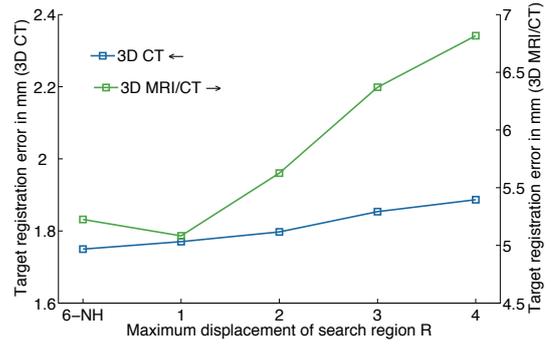
686 The obtained average TRE is 7.1 mm for MIND, 8.8 mm for
 687 CMI, 9.2 mm for NMI and 10.5 mm for eSSD. Even though
 688 the error for MIND is higher than what can be expected for
 689 a CT-to-CT registration, it is lower than the spatial resolution
 690 of the MRI scans and close to the intra-observer error. The
 691 distribution of landmark errors is shown in Fig. 10. Using a
 692 Wilcoxon rank test, a statistically significant improvement of
 693 MIND compared to NMI ($p=0.019$) and CMI ($p=0.023$) was
 694 found. An overview of the registration results is given in Table
 695 3. The Jacobian values are all positive, thus no transformations
 696 contained any singularities. An example registration outcome
 697 for MIND and NMI is shown in Figure 11.

6. Discussion and Conclusion

698 We have presented a novel modality independent neighbour-
 699 hood descriptor (MIND) for volumetric medical image registra-
 700 tion. The descriptor can be efficiently computed locally across
 701 the whole image, and it allows for accurate and reliable align-
 702 ment in a variety of registration tasks. Compared to mutual in-
 703 formation it does not rely on the assumption of a global (or re-



(a) Increasing Gaussian weighting σ for patch-distance (see Sec. 3.1.1), the half-size of the patch is $p = \lceil 1.5\sigma \rceil$



(b) The maximum displacement r_{\max} of the search region R (see Sec. 3.3). 6-NH stands for a six-neighbourhood.

Figure 8: Parameter variation for MIND to determine the best choice of (a) σ in patch-distance D_p and (b) the spatial search region R . The TRE is evaluated for one single-modal (3D CT) case (left y-axis) and one multi-modal (3D MRI/CT) registration (right y-axis). Based on these tests, we choose $\sigma = 0.5$ and a six-neighbourhood for all experiments.

Table 3: Target registration error in mm for deformable registration of eleven CT/MRI scan pairs of empyema patients. Evaluation based on 12 manual landmarks per case. Slice thickness of MRI scans is 8 mm (in-plane resolution ≈ 1 mm), intra-observer error for landmark localisation is 5.8 mm in MRI scans. A Wilcoxon rank test has been performed between presented methods. Significant improvements using MIND are found compared any other method (using all 132 landmarks).

Metric	TRE (in mm)
before	mean \pm std
	quantiles [0.25, 0.5, 0.75]
	p-value
eSSD	mean \pm std
	quantiles [0.25, 0.5, 0.75]
	p-value
NMI	mean \pm std
	quantiles [0.25, 0.5, 0.75]
	p-value
CMI	mean \pm std
	quantiles [0.25, 0.5, 0.75]
	p-value
MIND	mean \pm std
	quantiles [0.25, 0.5, 0.75]

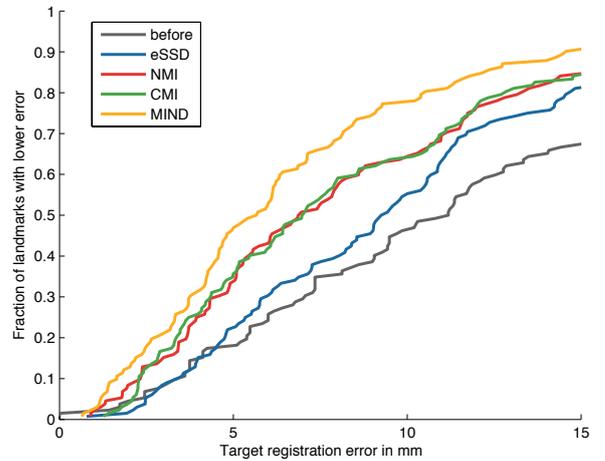
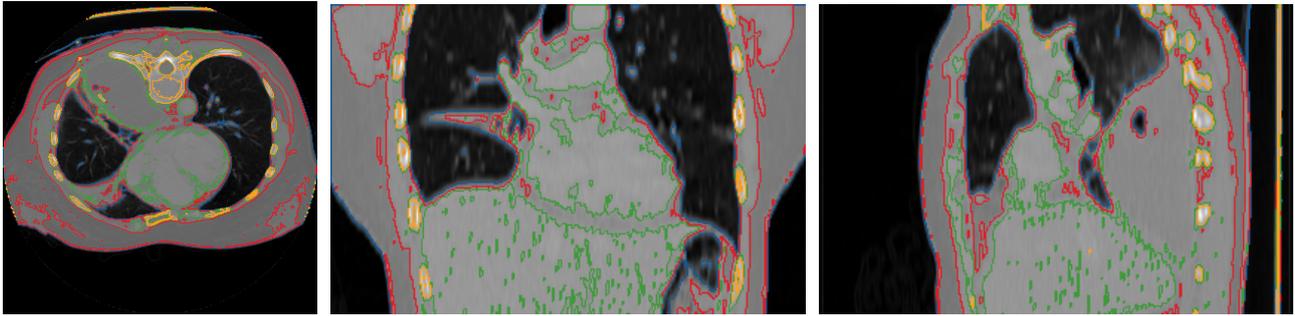
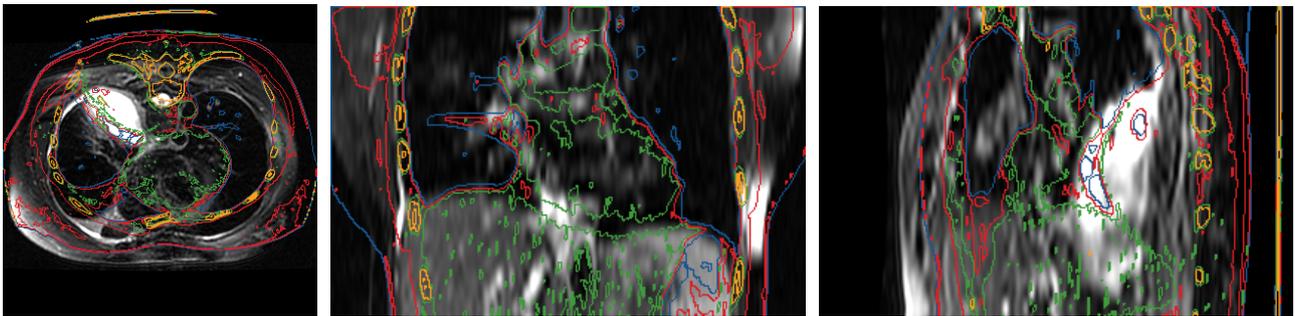


Figure 10: Deformable multi-modal registration of 11 cases of CT/MRI scans of empyema patients, evaluated with 12 expert landmarks per case. The plot shows the cumulative distribution of target registration error, in mm. MIND achieves a statistically significant ($p < 0.023$) better result than all other methods. The comparatively high residual error is due to both low scan quality, (in-plane resolution is ≈ 1 mm, but the slice thickness up to 8 mm) and the challenging landmark selection for the clinical expert (intraobserver error is 5.8 mm).

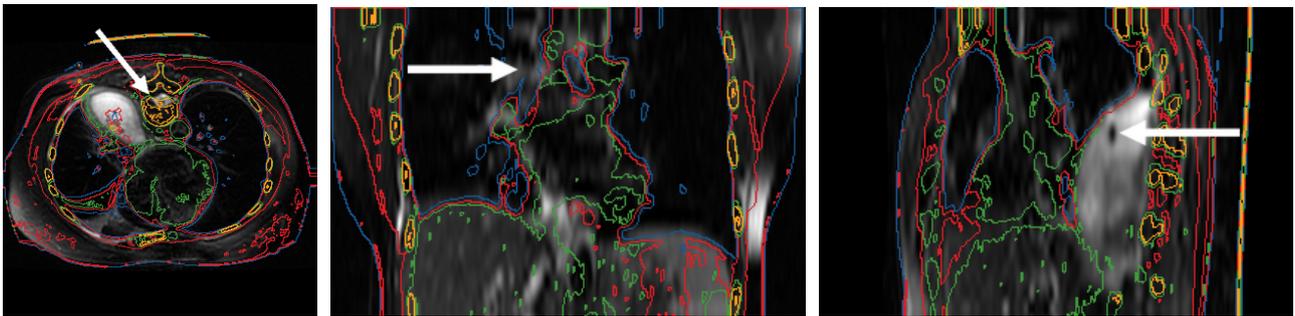
705 gional) intensity relation. The negative influence of initial mis-
706 alignment and non-uniform bias fields is massively reduced and
707 the difficult task of setting the correct parameters for the his-
708 togram calculation can be avoided. Apart from the regularisa-
709 tion parameter, a standard setting can be used for all registration
710 tasks. The descriptor is not rotationally invariant, which might
711 be a limitation in the case of strong rotations. However, the
712 sensitivity of MIND to the local orientation may in fact lead to
713 improved accuracy as suggested by the previous work of Pluim
714 et al. (2000) and Haber and Modersitzki (2006). The modal-
715 ity independent representation using a vector based on the local
716 neighbourhood (which allows it to capture orientation) instead
717 of a scalar value (used in entropy images) shows clear improve-
718 ments for real multi-modal registration experiments. The im-
719 plementation is straightforward, the running time comparable



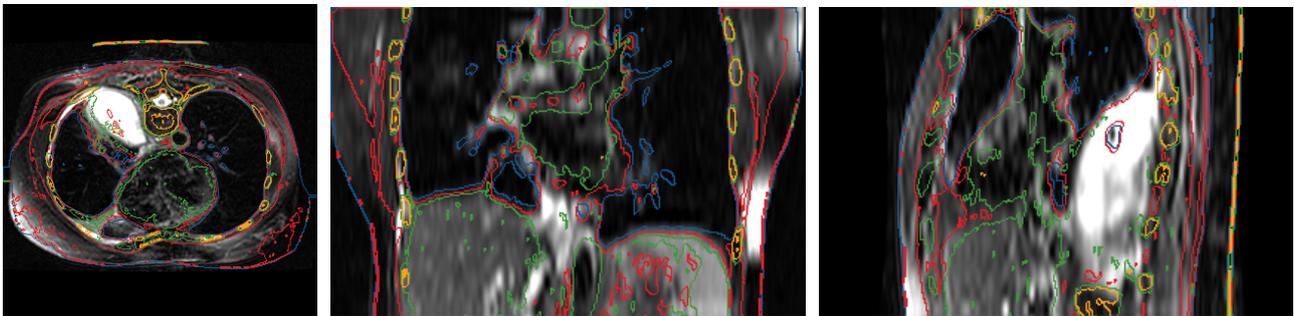
(a) CT scan of empyema patient with 4 relevant contour plots to guide the visualisation of registration results.



(b) MRI scan with identical CT contour plots before registration.



(c) Identical MRI scan with CT contour plots deformed according to non-rigid registration using NMI. The white arrows depict inaccurate registration close to one vertebrae, the inner lung boundary and gas pocket in empyema.



(d) Identical MRI scan with CT contour plots deformed according to non-rigid registration using MIND. A visually better alignment could be achieved.

Figure 11: Deformable CT/MRI registration results for Case 11 of empyema dataset. Left: axial, middle: sagittal and right: coronal plane. The third row shows the registration outcome using NMI. A better alignment is obtained when using MIND (forth row).

to other methods, and an important advantage of MIND is that it is calculated point-wise and can therefore be adapted to almost any registration algorithm.

We performed an extensive evaluation of our proposed method and three state-of-the-art multi-modal similarity metrics: entropy images, normalised and conditional mutual information. Tables 1 and 3 summarise the deformable registration results on two very challenging datasets. The results clearly demonstrate the advantages of the proposed descriptor. MIND achieves a higher accuracy and more robust correspondences for the CT dataset. The application of deformable registration to multi-modal medical images has so far remained a less sophisticated and advanced field with very few published results on clinically relevant data. Our proposed descriptor marks a novel contribution to this area. We verified its robustness to noise, field inhomogeneities and complex intensity relations in two experiments. First, the localisation of geometric landmarks was tested in an intrinsically aligned T1/PD MRI scan pair of the Visible Human dataset. Here the high discrimination and independency of bias fields has been demonstrated. Secondly for the deformable registration of clinical CT and MRI scans, we found a significant improvement over all other tested metrics.

While our validation was focused on CT and MRI modalities, we believe that our approach generalises well and further use could be made of this concept in a variety of medical image registration tasks. The application of MIND to other multi-modal registration tasks, such as registration of PET, contrast enhanced MRI and ultrasound, also to other anatomical regions, is subject for future work. A limitation of our approach is that it requires an anatomical feature to be present in both modalities, if this assumption is violated the concept of mutual-saliency (Ou et al. (2011)) could be incorporated to improve the robustness in these cases.

Further improvements might be possible. The use of more sophisticated deformation models could address application-specific challenges, such as slipping organ motion (Schmidt-Richberg et al. (2012)) and bladder filling or bowel gases (Foskey et al. (2005)). Employing a different optimisation scheme such as a registration based on MRF labelling (Glocker et al. (2011)), may allow us to find better maxima in the similarity function. In future work we will investigate the potential advantages of incorporating MIND into a discrete optimisation technique.

Acknowledgments

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Appendix A. Supplementary data

Appendix A.1. Parameters chosen for all compared methods

Table A.4: Parameter variation to obtain best results for Case 5 of CT dataset. Average target registration error (TRE) is given in mm (before registration TRE=7.10 mm). For values in brackets the transformation resulted in some negative Jacobians. Selected (fixed) settings are in bold.

Metric				
eSSD	Regularisation α	(0.1)	0.5	1.0
	TRE	(1.92)	2.06	2.22
	Gaussian patch σ	1.0	2.0	3.0
	TRE	2.06	2.19	2.23
	Histogram bins	16	32	(64)
	TRE	2.32	2.06	(1.98)
NMI	Regularisation α	(0.1)	0.25	0.5
	TRE	(2.36)	2.26	2.40
	Histogram bins	64	128	256
CMI	Regularisation α	(0.01)	0.05	0.1
	TRE	(2.37)	2.37	2.69
	Histogram bins	64	128	256
MIND	Regularisation α	(0.01)	0.05	0.1
	TRE	(2.02)	1.85	1.96
	Gaussian patch σ	0.5	1.0	1.5
MIND	TRE	1.78	1.85	2.05
	Search region	6-neighbour	sparse	dense
	TRE	1.85	1.89	1.95

Table A.5: Parameters chosen for multi-modal 3D CT/MRI registration. To account for the increased noise and more complex intensity relations across modalities, we slightly increase the regularisation parameter α .

Metric		
eSSD	Regularisation α	0.5
	Gaussian patch σ	1.0
	Histogram bins	32
NMI	Regularisation α	0.25
	Histogram bins	128
CMI	Regularisation α	0.25
	Histogram bins	32
MIND	Regularisation α	0.1
	Gaussian patch σ	1.0
	Search region	6-neighbour