Image registration for assessment of Crohn's disease severity
Image registration for assessment of Crohn's disease severity

PROEFSCHRIFT

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Contents

1 Introduction ................................................................................................... 1
  1.1 Magnetic resonance imaging ................................................................. 4
  1.2 Assessment of Crohn’s disease using MRI ........................................... 5
  1.3 Medical Image registration .................................................................... 6
  1.4 Objectives ................................................................................................. 7
  1.5 Thesis outline .......................................................................................... 10

2 Expiration-phase Template-based Motion Correction of Free-Breathing Abdominal Dynamic Contrast Enhanced MRI .......................................................... 14
  2.1 Introduction ............................................................................................. 15
    2.1.1 Related work ..................................................................................... 16
    2.1.2 Objective and approach .................................................................... 18
  2.2 Methods .................................................................................................. 19
    2.2.1 Data ..................................................................................................... 20
    2.2.2 Unbiased retrospective gating to the expiration-phase ................. 22
    2.2.3 Non-rigid registration ........................................................................ 25
    2.2.4 Experimental design ......................................................................... 27
  2.3 Results ..................................................................................................... 29
    2.3.1 Visual inspection ................................................................................ 29
    2.3.2 Numbers of subsets and random reference selection .................... 32
    2.3.3 B-Spline node spacing ...................................................................... 32
    2.3.4 Respiration phase selection and registration performance ............ 33
    2.3.5 Registration accuracy based on landmarks and comparison to a state-of-the-art method ................................................................. 36
    2.3.6 Correlation of relative contrast enhancement to CDEIS ............... 38
  2.4 Conclusion .............................................................................................. 40

3 Image registration based on autocorrelation of local structure ................. 47
  3.1 Introduction ............................................................................................. 48
3.1.1 Related work ................................................................. 48
3.1.2 Objective ................................................................. 51
3.2 Methods ........................................................................ 51
3.2.1 The analytic and monogenic signal ......................... 51
3.2.2 The band-pass filter and representation of local structure .... 54
3.2.3 Autocorrelation of local structure ......................... 57
3.2.4 Image registration pipeline ................................ 60
3.3 Results and Discussion .................................................. 60
3.3.1 Synthetic data ......................................................... 61
3.3.2 Registration of thoracic CT images ....................... 64
3.3.3 Registration of abdominal MR images ............... 66
3.4 Conclusion ................................................................ 75

4 A hybrid optimization strategy for registering images with large local deformations and intensity variations ................................................................. 81
4.1 Introduction ................................................................ 82
4.2 Methods ................................................................... 84
4.2.1 Preliminaries........................................................... 86
4.2.2 Definition of the data term .......................................................... 87
4.2.3 Definition of the bowel region term ....................... 89
4.2.4 Definition of the descriptor matching and coupling terms ... 90
4.2.5 Optimization procedure ........................................... 92
4.3 Results....................................................................... 92
4.3.1 Comparison of descriptor matching on intensity and mean phase 92
4.3.2 Registration performance on synthetic abdominal images .... 93
4.3.3 Registration of thoracic CT images with large deformations ...... 97
4.3.4 Abdominal MR image pre- to post-contrast registration ...... 99
4.4 Conclusion .............................................................. 109

5 Image registration based on the structure tensor of the local phase .... 115
5.1 Introduction .............................................................. 116
5.2 Methods ................................................................. 116
1 Introduction
Inflammatory bowel diseases (IBDs) constitute a substantial healthcare problem in the Western World. Crohn’s disease is a chronic IBD with a prevalence of 3.2 in 1000 [1] in North America and Europe. The disease is caused by a disorder of the immune system and manifests itself by inflammation of one or more segments of the gastrointestinal tract.

Grading of Crohn’s disease severity is important to determine the treatment strategy and to quantify the response to treatment. Ideally, a disease severity score should be objective, reproducible, quantifiable, non-invasive and comprehensive. In clinical practice, the Crohn’s Disease Endoscopic Index of Severity (CDEIS) [2] is an often used disease severity score that is acquired during ileocolonoscopy. However, this procedure is invasive and not very comprehensive. Other disease severity scores such as Crohn's Disease Activity Index (CDAI) [3] and the D’Haens index [4] also have their own drawbacks: they either lack objectivity or are not quantitative. Obtaining a reliable indication of the current disease severity is not straightforward. This difficulty is illustrated by the fact that patient questionnaires and symptoms correlate poorly with findings obtained by ileocolonoscopy [5]. To overcome all these drawbacks, the Virtual Gastrointestinal Tract (VIGOR++) project aims to propose a better

Table 1.1 Synopsis of Crohn’s disease indices. A qualitative comparison between the different scores show that VIGOR++ is the most promising score to assess the severity of Crohn’s disease. Notice that CDAI, CDEIS and D’Haens are existing scores. The VIGOR++ score is the aim of the project (Table from www.vigorpp.eu/facts.php).

<table>
<thead>
<tr>
<th>Index\requirement</th>
<th>Objective</th>
<th>Reproducible</th>
<th>Quantifiable</th>
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<tr>
<td>CDAI</td>
<td>-</td>
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<td>CDEIS</td>
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<tr>
<td>D’Haens</td>
<td>+/-</td>
<td>+</td>
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<tr>
<td>VIGOR++ score</td>
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Chapter 1. Introduction

score (see Table 1.1) for assessing Crohn’s disease severity.

The VIGOR++ project has investigated the use of MRI for obtaining a quantitative assessment of the amount of inflammation in patients with Crohn’s disease. An example comparing ileocolonoscopy and MRI can be seen in Figure 1.1. MRI is non-invasive imaging technique and it examines bowel wall and extraenteric soft tissues rather than only bowel surface as in ileocolonoscopy. MRI has already been used to objectively assess Crohn’s disease and a large number of features were proposed to evaluate disease activities [2] [3] [4]. The VIGOR++ project involved a suit of MRI modalities to be able to quantify the extent of inflammation through automatic MRI measurements rather than only manually measured features [2][3][4].

Automatic tools for measuring parameters that quantify disease severity require accurate as well as precise spatial alignment of all image data (inter- and intra-modalities). This spatial alignment is often referred to as image registration. For abdominal imaging with MRI, image registration is challenging because of respiratory motion, peristalsis and susceptibility artifacts. These give rise to large space-variant deformations in regions dominated by fine details. The

Figure 1.1 A representative example of Ileocolonoscopy and MR images showing the same part of bowel wall affected by Crohn’s disease as pointed out by the arrows. (Images from www.vigorpp.eu)
problem is further complicated by the administration of an intravenous contrast agent, which causes space-variant signal fluctuations due to a highly varying uptake and release of the contrast agent.

1.1 Magnetic resonance imaging

Magnetic resonance imaging (MRI), or nuclear magnetic resonance image (NMRI) is a medical imaging technique used in radiology to investigate the anatomy and physiology of the body in both health and disease [6]. MRI was first introduced by Lauterbur and Mansfield in 1973 [7]. Thirty years later they were awarded the Nobel prize in Physiology or Medicine for “their discoveries concerning magnetic resonance imaging”.

MRI uses magnetic fields at radio frequencies to generate a signal rather than using ionizing radiation like in computed tomography (CT). Different types of MR images are standardly used for differential diagnoses. Typically, T1 weighed MRI typical show a bright signal in fat tissue and a dark signal in water. Reversely, T2 weighed MRI typically registers a bright signal from water and dark signal from fat tissue.

In our study, we only focused on 3T T1-weighted MRI, particularly 3D+t Dynamic Contrast Enhanced MR imaging (DCE-MRI). A typical example is shown in Figure 1.1. During dynamic contrast enhanced MRI (DCE-MRI), a contrast agent is injected into the patient to enhance the signal by shortening the

![Figure 1.2 T1-weighted MR images from VIGOR++ patient. From left to right: pre-contrast MR image (a), DCE MR image (b) and post-contrast MR image (c). The red arrow in (c) points out the diseased bowel and the green arrow points out the bladder.](image)
Chapter 1. Introduction

T1 time. Usually, it yields a brighter signal in diseased bowel wall than in normal bowel wall (See Figure 1.2 (a) and (c)). This is because the tissue affected by inflammation has a higher degree of vascularization and leakier vessel walls, than normal tissue. As such, the contrast medium accumulates in the interstitium of the inflamed tissue. Practically, radiologists use this as one of the methods to identify the diseased bowel wall.

1.2 Assessment of Crohn’s disease using MRI

A wide variety of MR imaging features were used for determining disease activity, with different weight given by different researchers [8]. To increase consistency and optimize accuracy, quantitative scores have been developed including those imaging features that best determine disease activity. Recent results using MRI for assessing Crohn’s disease [9] [10] showed that a quantitative score called the MR Index of Activity has high correlation with CDEIS (e.g. in [9], r=0.82, p<0.001). Therefore, MRI is widely studied as an alternative to ileocolonoscopy. The MR Index of Activity consists of several features (derived by image-based measurements): wall thickness, post-contrast wall signal intensity, relative contrast enhancement (RCE), presence of edema, ulceration, pseudo polyps, and lymph node enlargement. Each of these measurements has to be determined manually, which is a time consuming task for radiologists. Furthermore, the intra- and inter-observer variability might make it an imprecise technique. Therefore, we would prefer to have a more objective measurement tool, which generates those features automatically. This is nontrivial, though, and it will require various new image processing techniques to produce those features. For instance, automatic image segmentation is needed for deriving the thickness of the bowel wall. Furthermore, image registration is required to align the pre-contrast and post-contrast MR images to produce an RCE measurement. In this thesis, we are focusing on the role of image registration to support assessment of the severity of Crohn’s disease using MRI.
Chapter 1. Introduction

1.3 Medical Image registration

Image registration aims to achieve spatial alignment of partially overlapping images acquired by a single or different imaging modalities at a single or multiple time points. Image registration has been an active field of research in medical image analysis for more than a decade, but it remains challenging for many practical cases. A recent survey summarizes the current state-of-the-art [11]. Practically, a registration procedure searches for the “best” deformation parameters $\mu$ between two images and is often formulated by means of an optimization problem:

$$
\arg\min_{\mu} D(F, M \circ T(\mu)) + R(T(\mu)),
$$

in which the first term, $D$, quantifies the goodness of alignment between the images $F$ (fixed image) and $M$ (moving image) under the parameterized transformation $T$. Because of the ill-posedness of image registration, a second term, $R$ is added to regularize the transformation and prevent non-physical deformations, such as folding.

Figure 1.3 A representative DCE-MRI dataset: (a) DCE-MRI series; (b) intensity as a function of time along the yellow and the red lines from (a).
Essentially, the goal of medical image registration is to map different images into a common coordinate system to establish anatomical correspondences between images. It is a standard tool in many specializations, such as neuroimaging and cardiovascular imaging. A typical application of image registration is the spatial alignment in longitudinal brain studies [12]. Here, detected changes may relate to the neurological disorders such as Alzheimer’s disease. Another example of image registration is to estimate spatiotemporal behavior of cardiac images [13] [14]. For instance, myocardial ischemia reduces the capacity of the heart to eject blood into the aorta. This disease can be diagnosed by assessing the myocardial contractile function generated from image registration of cardiac MR images.

In principle, a registration method consists of three core components [11]: 1) a deformation model that defines how one image is transformed towards another, 2) an objective function that includes the similarity between two images as well as a regularization term to penalize the non-physical deformations, and 3) an optimization strategy that searches for the values of the transformation parameters that maximize the objective function. Various aspects of these core components will be studied in this thesis for solving different challenges.

1.4 Objectives

In the VIGOR++ project, image registration is a crucial step to automatically generate MRI-based image features for assessing the severity of Crohn’s disease. To our experience, directly applying state-of-the-art image registration techniques, without any pre-processing, give an implausible alignment [15]. Therefore, we had different challenges to overcome:

**DCE-MRI to DCE-MRI: discontinuities due to breathing effects**

State-of-the-art DCE-MRI has a high temporal resolution (less than 1 second per volume) which allows data acquisition while the subject is freely breathing. Time intensity curves (TICs) obtained from the DCE-MRI contain important information on the degree of inflammation of the bowel wall. In order to facilitate TIC analysis, image registration is required to compensate for missing correspondence of the bowel wall caused by respiration-induced motion. However, the discontinuities in the deformation field complicate the image registration task. Figure 1.3 demonstrates how the respiration-induced motion affects the bowel wall movement by showing the intensities of the bowel wall as
Chapter 1. Introduction

a function of time. One can observe that the intensity profile of the bowel wall fluctuates dramatically over time.

In this thesis, we propose an expiration-phase, template-based motion correction method to solve the abovementioned problem. It consists of two steps: (1) expiration-phase template construction and retrospective gating of the DCE-MRI to the template using a rigid transform, and (2) non-rigid registration of the gated DCE-MRI. Retrospective gating to the expiration-phase in the step (1) reduces discontinuities in the deformation field to a large extent after which the remaining deformation is estimated by non-rigid registration in step (2).

**DCE-MRI to post-contrast MRI: different contrast**

Automatically deriving features from DCE-MRI such as TICs rely on the annotation of ROIs indicating diseased bowel wall. However, these ROIs are typically delineated on post-contrast images because of the higher resolution and signal to noise ratio (SNR). Therefore, alignment of DCE-MRI and post-contrast MRI is essential to map the ROIs from post-contrast MRI to DCE-MRI. The post-contrast MRI was acquired in a breath-hold (taking about 10 seconds) but the subject is freely breathing during the DCE-MRI scan. That causes misalignments of the bowel wall (see Figure 1.2(b) and (c)) between both scans. One can also observe that the contrast is different between DCE-MRI and post-contrast MRI. That is because the administration of the contrast agent causes space-variant signal fluctuations due to a spatially variant uptake and release of this contrast agent. Furthermore, DCE-MRI uses a fast imaging technique (in the order of 1 volume/second) compared to post-contrast MRI, which contributes to the low contrast in the images.

Various methods were investigated to solve abovementioned problems. One of the most representative methods to tackle the contrast difference is image registration using mutual information (MI) in the objective function [16] [17]. However, MI is a global measurement, which lacks local, i.e. spatial information on the local structure. Therefore, it cannot cope with local contrast variations in the data. Although follow-up studies have tried to incorporate local information such as gradient orientation [18] and regional information [19] [20], it has been noticed [21] that finding accurate correspondences remains difficult. In order to overcome the difficulties of registration hampered by different contrast, we propose a novel measure of the local image structure based on the monogenic signal, which is intrinsically insensitive to the changing contrast. We integrate
Chapter 1. Introduction

this measure into the modality independent neighborhood descriptor (MIND) registration framework [21]. The new framework, which we call autocorrelation of local structural information (ALOST), is evaluated based on different image registration tasks including DCE-MRI and post-contrast MRI.

**Pre-contrast to Post-contrast: different contrast, large deformations**

Another important feature called relative contrast enhancement (RCE) has been often used in MR scoring of Crohn’s disease. The RCE was measured by using the following equation:

\[
RCE = \frac{100((I_{\text{post}} - I_{\text{pre}})/I_{\text{pre}})}{\text{std}(I_{\text{post}})/\text{std}(I_{\text{pre}})},
\]

in which \((I_{\text{pre}}, I_{\text{post}})\) are the averaged bowel wall signal intensities measured over manually annotated regions of interest (ROI's) in pre- and post-contrast T1-weighted MRI; each ROI must be placed at approximately the same location in the pre- and post-contrast images; furthermore, \{\text{std}(I_{\text{pre}}),\text{std}(I_{\text{post}})\} are the standard deviations of the noise measured in manually annotated ROI's containing air outside the body in the pre- and post-contrast MR images.

One can easily see from Figure 1.2 (a) and (c) that the contrast between the pre- and post-contrast MR images is very different due to the uptake of the contrast agent. Additionally, large deformations are present emanating from the different depths of breath-hold during the scans, combined with different organ positions and peristalsis. It is even far from trivial to manually generate an RCE measurement from pre- and post-contrast MR images since the correspondences are hard to find. Image registration can aid the RCE measurement based on the annotation in the post-contrast scan, though. A crucial challenge in this problem is the large deformation of highly structured regions. These regions cannot be processed by the traditional course-to-fine strategy employing a multi-resolution approach to avoid getting trapped in a local minimum. Therefore, we propose a new registration framework based on a hybrid optimization method, which involves discrete descriptor matching combined with continuous optimization. The descriptor is insensitive to the contrast difference and used at the original resolution to avoid local minima. The continuous optimization is the same as our ALOST framework, which is used for refining the registration result as obtained from the discrete descriptor matching.
1.5 Thesis outline

Matching the aforementioned objectives, this thesis is organized as follows.

In Chapter 2 a new registration method is presented to achieve spatial alignment in free-breathing DCE-MRI. The extracted TICs are modelled by a tri-exponential model. The model parameter $A_1$, corresponding to the amount of enhancement, is further correlated to the CDEIS. Thirty retrospectively included datasets from the Academic Medical Center (AMC) of Amsterdam are used in this study for evaluation purposes. This data is also used to test the methods presented in chapters 3 to 5. The method of chapter 2 is particularly designed for registering DCE-MRI. It may be less suited for registering data with large variations in local contrast or large spatial deformations.

In Chapter 3 a new method called autocorrelation of local structural information (ALOST) is proposed to register images with different variations in local contrast. The method is tested by registering DCE-MRI to post-contrast MRI. The method of this chapter is applied after the technique from chapter 2 has processed the data. We use the registered DCE-MRI from chapter 2 to derive the $A_1$ feature. Other publicly available datasets (e.g. DIR-Lab lung study http://www.dir-lab.com/) are also used to evaluate the algorithm.

In Chapter 4 a hybrid optimization framework is presented to register images with large deformations in highly structured regions that are also hampered by different variations in local contrast. Extending the work from chapter 3, this hybrid optimization framework solves the large deformation problem in registering pre-contrast to post-contrast MR images. Automatic RCE measurements are generated from the registered data to test the method. The method is also evaluated using synthetic data and the DIR-Lab lung study.

In Chapter 5 an alternative method called Structure Tensor of the LoCal Phase (STOP) is proposed to solve different contrast problem. It incorporates local information into the structure tensor rather than in the autocorrelation function discussed in Chapter 3. This method is also tested by registering DCE-MRI to post-contrast MRI.

References
Chapter 1. Introduction


Chapter 1. Introduction


2 Expiration-phase Template-based Motion Correction of Free-Breathing Abdominal Dynamic Contrast Enhanced MRI

This paper studies a novel method to compensate for respiratory and peristaltic motions in abdominal Dynamic Contrast Enhanced MRI. The method consists of two steps: (1) expiration-phase ‘template’ construction and retrospective gating of the data to the template; (2) non-rigid registration of the gated volumes. Landmarks annotated by three experts were used to directly assess the registration performance. A tri-exponential function fit to time intensity curves from regions of interest was used to indirectly assess the performance. One of the parameters of the tri-exponential fit was used to quantify the contrast enhancement. Our method achieved a mean target registration error (MTRE) of 2.12 mm, 2.27 mm and 2.33 mm with respect to annotations by expert, which was close to the average inter-observer variability (2.07 mm). A state-of-the-art registration method achieved a MTRE of 2.83–3.10 mm. The correlation coefficient of the contrast enhancement parameter to the Crohn’s Disease Endoscopic Index of Severity (r = 0.60, \( p = 0.004 \)) was higher than the correlation coefficient for the Relative Contrast Enhancement measurements values of two observers (\( r(\text{Observer 1}) = 0.29, \ p =0.2 \); \( r(\text{Observer 2}) = 0.45, \ p = 0.04 \)). Direct and indirect assessments show that the expiration-based gating and a non-rigid registration approach effectively corrects for respiratory motion and peristalsis. The method facilitates improved enhancement measurement in the bowel wall in patients with Crohn’s disease.

Chapter 2. Expiration Phase Template-based Motion Correction for Free-Breathing Abdominal DCE-MRI

2.1 Introduction

Inflammatory bowel diseases (IBD) are a substantial healthcare problem in the Western World. They affect over 1 million citizens in the United States, of which 565,000 suffer from Crohn's disease [1]. Grading of Crohn's disease severity is important to determine treatment and to quantify drug response. Ileocolonoscopy in combination with the assessment of biopsy samples is mostly used for diagnosis and assessment of all IBD. However, this procedure is invasive and requires extensive bowel preparation, which is considered very burdensome by most patients. Moreover, it primarily gives information on mucosal abnormalities and only little information on the transmural and extraintestinal extent of the disease while only the colon and a small part of the small bowel is examined.

Therefore, abdominal Magnetic Resonance Imaging (MRI) is now widely studied for diagnosing and grading luminal Crohn's disease (CD). Various imaging features are used to determine the presence and extent of disease activity, including enhancement after intravenous injection of a contrast medium [2]. In a recent study, Rimola et al [3] used multivariate analyses correlating radiological features to the Crohn's Disease Endoscopic Index of Severity (CDEIS) [4] which is often considered the reference standard. The study reported that the radiologic features to be evaluated, include wall signal intensity and relative contrast enhancement (RCE) after intravenous injection of a contrast medium.

Several other previous studies indicate that the Time Intensity Curves (TICs) obtained from Dynamic Contrast Enhanced MRI (DCE-MRI) contain important information on the degree of inflammation of the bowel wall [5], [6]. The aforementioned papers achieved a temporal resolution in the order of 5 seconds, making motion artefacts inevitable [5]. Advances in high temporal resolution MRI scanning protocols have opened the way to extract TIC-measurements from free-breathing DCE-MRI. Unfortunately, respiratory and peristaltic motions complicate an easy analysis of such curves since spatial correspondence over time is lost. Direct registration of DCE-MRI fails if the bowel is subject to large, locally discontinuous deformations caused by organs “sliding” along each other due to breathing.

This paper presents a novel method to compensate for such motion and facilitates quantitative analysis of TICs extracted from the bowel wall. As such,
a solution is presented for a crucial and challenging problem: to obtain accurate, quantitative features for assessing Crohn's disease severity from DCE-MRI. Actually, the method is also applicable to other abdominal diseases, but our focus is on Crohn's disease.

2.1.1 Related work

Much work has been done to correct for motion during image acquisition in cardiac imaging applications, particularly, by means of gating techniques using various physiological signals [7], [8]. Early work on DCE-MRI registration was related to breast imaging [9]. It involved a non-rigid, B-spline transformation and employed Normalized Mutual Information (NMI) as similarity metric. Unfortunately, NMI appeared not well suited for the substantial intensity differences between pre- and post-contrast images particularly when an inappropriate deformation model is applied. It led to undesirable shrinkage or expansion in certain regions [10], [11]. Therefore, volume preserving non-rigid registration methods were introduced [10], [11]. Later, Song et al. [12] proposed a registration method based on a dyadic wavelet and Fourier transforms for renal imaging, but they only dealt with rigid motion.

An alternative way was to de-enhance the DCE images prior to registration [13]. Thereafter, methods addressed the contrast change by estimating the intensity enhancement during the registration procedure. This was accomplished by incorporating the intensity enhancement in the regularization term [14]. Also, a progressive principal component registration method (PPCR) was proposed [15] in order to use enhancement information from an entire dataset to drive the registration procedure (illustrated on liver images). This method relied on principal component analysis (PCA) and did not require the selection of a reference image. The PCA aimed to separate contrast enhancement from motion before registration, assuming that the contrast enhancement appears earlier in the sorted list of principal components than organ motion. Similar ideas based on data decomposition were also used in other studies [16] [17]. In [16], independent component analysis (ICA) was used for separating the various sources of data variability in free-breathing cardiac MRI. Recently, a method called robust data decomposition registration (RDDR) [17] was proposed for registering DCE-MRI images. They used robust principal component analysis (RPCA) to decompose DCE-MRI into low- rank and sparse components. The low- rank components were shown to correspond to smooth deformations and slowly varying changes, while the sparse components represented rapid and
local intensity changes. The low-rank components were insensitive to intensity changes and therefore used for registration.

Lately, the aforementioned PPCR method was compared with a model-based technique and a sequential elastic registration (SER) approach on a synthetic DCE-MRI phantom and a variety of clinical cases [18]. It was concluded that the SER method was superior in small, but important ROI's such as the tumor core. However, a limitation of this paper is that the comparison was done on breath-hold DCE-MRI data.

Furthermore, a number of methods incorporated a pharmacokinetic model such as the Tofts model [19] into the registration procedure for improving the registration accuracy. An example is an iterative registration procedure that was proposed by Buonaccorsi et al. [20], aiming to register motion deformed liver images to synthetic images. Therefore, pharmacokinetic models were first fit to each voxel in the deformed data. Subsequently, synthetic images were generated corresponding to the model values for each time point in the dynamic series. The synthetic maps were used as fixed reference volumes to drive the registration of the raw time point images. More recently, a Bayesian framework was introduced to jointly estimate the parameters of a pharmacokinetic model and the motion of the colon [21]. Alternatively, a combined image segmentation and registration method was established [22].

Some prospective methods use respiratory tracking based on navigator echos during imaging to impose a priori correspondence. A navigator echo samples a small column of tissue in the craniocaudal direction, typically across the diaphragm. The result is a one-dimensional image of the tissue boundary between the thorax and abdomen, with the temporal change in signal intensity providing a reference for the position of the diaphragm. A limitation of the method is that it requires uniform and regular respiration cycles for optimal image correspondence [23]. Clearly, registration techniques could be used for fine tuning. More importantly, however, is that the navigator approach requires that a well-defined reference area is available. This is not the case in the lower part of the abdomen (notice that the diaphragm is outside the field of view in Figure 2.1(a)). Recently, a generalized image reconstruction method in k-space for motion compensation was presented [24]. Here, a linear non-rigid motion model was assumed. However, the combined respiratory and bowel motion of our application has non-linear characteristics, for which this technique was not designed.
The aforementioned studies paid specific attention to breast, cardiac, liver and renal DCE-MRI. Abdominal DCE-MRI poses additional challenges. None of the aforementioned methods address the problems induced by respiratory and peristaltic motion combined with potential susceptibility variations that are inherently associated with DCE-MRI of the bowel.

### 2.1.2 Objective and approach

State-of-the-art DCE-MRI has a high temporal resolution (less than 1 second per volume) which facilitates data acquisition while the subject is freely breathing. However, quantification of contrast enhancement is hampered by a substantial spatial mismatch due to respiratory motion, potentially associated susceptibility variations and peristaltic movement. To overcome these problems we present a new ‘template’-based registration (motion correction) scheme for compensating the aforementioned effects, which leads to an unbiased registration result.

Volumetric images are obtained during contrast injection, while the subject is freely breathing. Since abdominal scans lack a well-defined reference area like the diaphragm, the conventional navigator echo gating cannot be applied. To eliminate the dominating respiratory motion, we apply a retrospective gating scheme instead. In our earlier work [25], we first randomly picked a reference image from the DCE-MRI data. Then we gated the DCE-MRI to that reference image through rigid registration. However, this random reference may not coincide with a stable phase of the respiratory cycle [26]. Therefore, it may contain large breathing artefacts. In such a case, a poor registration outcome was obtained.

In the current paper, we avoid the randomness of the algorithm’s performance as well as a potential bias by building an expiration-phase reference instead. After selection of the expiration-phase images, we align these data by a B-spline transformation that maximizes the NMI. The poor performance of NMI in previous DCE-MRI applications was caused by discontinuities in the deformation field and the sudden appearance of structures due to the inflowing contrast medium. In our application, the former is tackled by gating and the latter does not occur. The bowel wall is merely enhanced as it was already visible prior to contrast injection. We chose NMI as our cost function for its robustness to intensity alterations. The registration compensates for the residual mismatch due to varying breathing depth and remaining peristalsis.
The choice for expiration-phase gating will be compared to using other phases of the respiratory cycle such as the inspiration-phase and the arbitrary-phase. Moreover, the efficiency of our approach is studied by comparison to a state-of-the-art method [17]. This evaluation includes an assessment by means of manually annotated landmarks. Finally, enhancement measurements from the TICs are correlated to colonoscopic measurements of disease activity.

### 2.2 Methods

We will first describe the DCE-MRI data and the annotation procedure used in our work. Then, we present the two main steps that our method comprises: (1) expiration-phase template construction and retrospective gating to the template...
(2.2.2), and (2) non-rigid registration using B-splines (2.2.3). Finally, validation experiments are described.

2.2.1 Data
The MRI data employed in this paper were taken from a prior study of consecutively included patients with luminal Crohn's disease [27] that has been approved by the local Medical Ethics Committee. All 33 patients had given informed consent to the prior study. Furthermore, 30 out of 33 patients have given written consent to usage of their data for future investigations. The data of the latter 30 patients were used for this study.

Patients drank 1600ml of a hyperosmolar fluid (Mannitol, 2.5%, Baxter, Utrecht, The Netherlands) 1 hour before acquiring the MRI scans to achieve bowel distention. MR imaging included T2-weighted single shot fast spin echo (SSFSE) sequences and a high resolution, 3D T1-weighted spoiled gradient echo sequence with fat saturation, followed by a free-breathing 3D+t DCE-MRI data acquisition on a 3.0T MRI scanner (Intera, Philips Healthcare, Best, The Netherlands) by a 3D spoiled gradient echo sequence. Fourteen coronal slices were obtained with a pixel size of 1.78 × 1.78 × 2.5mm³, TE = 1.8ms, TR = 2.9ms, and a flip angle of 6°. In 6.1 minutes, 450 3D image volumes were acquired at a rate of 0.8 second/volume. The patients were instructed to breathe regularly at a low frequency. A bowel relaxant (20 mg, Buscopan, Boehringer, Ingelheim, Germany) was administered to the patients immediately prior to the start of the DCE sequence to minimize bowel movement. A contrast agent (Gadovist 1.0 mmol/ml, Bayer Schering Pharma, Berlin, Germany) was injected (0.1 ml/kg bodyweight) after the 10th image volume was acquired. The dynamic volume was located in a visibly inflamed area of the bowel, or in the terminal ileum when a visibly inflamed area was absent, based on the T2-weighted SSFSE sequences. The DCE sequence was also succeeded by a high resolution, 3D T1-weighted spoiled gradient echo sequence with fat saturation. A routine radiological report was made for each patient by an experienced abdominal radiologist.

Two observers with respectively 17 years (1100 small bowel MRI) and 18 years (700 small bowel MRI) experience in reading abdominal MRI, evaluated the MRI scans as described in [28]. In 7 of the 30 cases, one of the scoring radiologists had already seen the MR previously during routine patient care (see above). However, the elapsed time between the initial evaluation and the current scoring was at least one year (ranging from 357 to 622 days, median of 481
Each observer measured the relative contrast enhancement (RCE) from the pre- and post-contrast T1 weighted MR images. The RCE was calculated as:

$$RCE = \frac{100((I_{post} - I_{pre}) / I_{pre})}{\text{std}(I_{post})/\text{std}(I_{pre})}$$

(2.1)

in which \((I_{pre}, I_{post})\) are the averaged bowel wall signal intensities measured over manually annotated regions of interest (ROI's) in pre- and post-contrast T1-weighted MRI; each ROI was placed at approximately the same location in the pre and post-contrast images; \(\{\text{std}(I_{pre}), \text{std}(I_{post})\}\) are the standard deviations of the noise measured in manually annotated ROI's with air outside the body in the pre- and post-contrast MR images. The bowel was visually classified into five different segments: rectum, left colon (sigmoid plus colon descendens), transverse colon, right colon (cecum plus colon ascendens), and terminal ileum. The observers delineated per segment a ROI in the bowel wall that was identified to contain the most disease activity [27]. If a bowel segment did not contain disease activity a bowel wall region was randomly selected.

A research fellow with a background in image analysis of Crohn's disease made manual annotations in the DCE-MRI expiration-phase template, as well as in other templates to be evaluated (see below) based on the radiological report of the patient. In each slice all 2D regions signifying Crohn's disease were identified by a polygon. Additionally, the bowel segment was indicated. For each positive annotation, i.e. a single polygon, a nearby region was annotated that was deemed healthy. Additionally, for each positive annotation, a region outside the body was annotated. All these annotations were checked by an abdominal radiologist with extensive experience in assessing luminal Crohn's disease in MRI (i.e. the radiologist with 17 years of experience).

All previously mentioned observers (including the research fellow and the abdominal radiologist) were unaware of the findings from ileocolonoscopy, but were aware of the patients' surgical history. All patients underwent ileocolonoscopy within one month after the MRI scan was acquired, which served as the reference standard. During ileocolonoscopy the Crohn's disease endoscopic index of severity (CDEIS) was scored per bowel segment [27]. The endoscopist performing the scoring was blinded with respect to the MRI results.

In 2/30 patients no inflammation or other signs of Crohn's disease were detected. In the remaining 28 patients, 26 regions were identified in which the terminal
ileum was affected by Crohn's disease, 8 regions in the colon ascendens, 1 suspicious region in the transverse colon, and also 1 in the sigmoid (thus, there were 36 affected regions in total). We separated the 36 bowel segments with Crohn's disease areas into two parts. 10 segments, from 10 patients were randomly chosen for training, i.e. parameter tuning: the training set; 26 segments were left for testing to have an independent set for evaluation: the test set. In the test set no CDEIS could be obtained due to strictures in 5/26 segments. Figure 2.1 (b) illustrates the dataflow of our paper.

### 2.2.2 Unbiased retrospective gating to the expiration-phase

The focus of our investigation is on the quantification of the time-varying contrast uptake and release as reflected by the dynamic MRI signal values. During contrast uptake/release there is respiratory and bowel movement. Unfortunately, simple motion correction by means of registration of all the recorded images cannot be applied. This is because registration without gating needs to cope with the large, discontinuous deformations induced by breathing. Furthermore, varying susceptibility effects could affect the image intensity differently depending on the breathing depth. Moreover, the bowel movement may also impose a discontinuous deformation on the bowel structures, as the injected Buscopan does not fully suppress the peristalsis.

We hypothesize that retrospective gating to a certain phase of the respiratory cycle reduces the aforementioned effects to a large extent. In earlier work [25] we incorporated information about the respiratory cycle by computing the sum of squared differences (SSD) for all volumes to a selected reference volume. The middle volume of a series of DCE images was taken as reference volume. The gating was done by selecting the volumes that corresponded to the local minima of the SSD as a function of volume number. As such, we aimed that images acquired in the same respiration phase were selected. However, picking the middle volume as a reference image led to large, undesired fluctuations in the selected volumes, because the selected reference could be in any phase of the respiratory cycle. Therefore, the gated images were prone to suffer from motion artifacts, particularly as a phase right in between the inspiration and the expiration stages was accidentally selected. To solve this problem, we now rigidly register all volumes to a so-called expiration-phase template image, to avoid picking the ‘wrong’ volume. Based on the head-to-foot translation curve derived from this rigid registration, we select all local minima which represent the expiration-phase (see Figure 2.2). Essentially, our gating procedure is
inspired by the one described in [29]. We propose a method consisting of five steps for creating the template image which is adaptively formed by a weighted sum of temporal images:

**Step 1: Selection of 10 reference volumes.** Divide the 450 volumes into 10 consecutive subsets with an equal number of images, i.e. 45. Randomly select 1 reference from each subset. The 10 initial references are uniformly distributed over time and account for variations in breathing depth during acquisition.

**Step 2: Measurement of head-to-foot displacement around the reference volumes.** For each of the initial references, we pick the 10 nearest neighbors in time and apply a rigid registration to the reference volume based on the SSD. Since these 10 volumes are scanned in 8 seconds and the normal breathing frequency is about 12-20 cycles/min, this corresponds to approximately 2 to 3 respiratory cycles. We use the SSD as similarity measure, since the contrast over 10 consecutive images does not vary much in such a short time.

The head-to-foot displacement is measured by the y-coordinate of the rigid registration: a smaller y-displacement implies closer to the head.
Chapter 2. Expiration Phase Template-based Motion Correction for Free-Breathing Abdominal DCE-MRI

Figure 2.2 The head-to-foot displacement of each volume with respect to the expiration-phase template as a function of time shows oscillatory behavior due to respiration. Positive displacements indicate that the volume is shifted in foot direction compared to the template. The black circles in the inset correspond to the gated volumes that are in the expiration-phase. Since the shifts are relative compared to the template negative values arise as the subject exhales deeper.

Step 3: Detection of the expiration-phase volumes. Select from each of the 10 subsets the expiration-phase images corresponding to the local minima of the 10 head-to-foot displacement curves. This was done by picking the volumes for which the Gaussian second derivative was higher than that of its direct neighbors (i.e. a local minimum). The scale (standard deviation) of the Gaussian was set to 0.8 second (1 scan interval). Typically, this would deliver 2-3 images per subset. Again, notice that these images are rather evenly distributed over the total number of 450 images and may therefore represent varying breathing depth.

Step 4: Selection of the 'best' expiration-phase volume as the initial template. An initial template image is obtained by:

$$c = \arg \max_i \sum_{j=1, j\neq i}^N d(I_i^0, I_j^0)$$  \hspace{1cm} (2.2)

$$I_a^0 = I_c$$  \hspace{1cm} (2.3)

where \(d(I_i^0, I_j^0)\) denotes the NMI between two expiration-phase volumes from step 3, \(c\) the index to the volume with maximal cumulative NMI to all others and \(N\) the number of expiration-phase volumes selected in step 3. Thus, \(I_a^0\) is the
image which has maximal accumulated NMI with respect to all the other expiration-phase images selected in step 3. We use NMI now as the image contrast over the entire series varies significantly due to the inflow of the contrast medium.

**Step 5: Update the template volume.** Register all expiration-phase volumes from step 3 to the template $I^t_a$ ($t=0$ is starting point) based on a rigid transformation that maximizes the NMI. Adaptively weighting the expiration-phase volumes yields a new template image as follows:

$$I'_a = \sum_{i=1}^{N} W'_i I'_i$$  \hspace{1cm} (2.4)

$$W'_i = \frac{d(I^{-1}_i, I^{-1}_a)}{\sum_{i=1}^{N} d(I^{-1}_i, I^{-1}_a)}$$  \hspace{1cm} (2.5)

in which $I^t_i$ is the $i^{th}$ volume with weight factor $W'_i$, $I^t_a$ the template and $t$ denotes the iteration. We found empirically that we need five iterations of step 5 until convergence (defined as a relative change in $I^t_a$ of less than 0.1%). Since the initial expiration-phase images (step 3) are obtained around randomly picked time points in each one-tenth part of the whole sequence, the template image emanating from step 5 reflects the temporal-intensity information via the weighting procedure. It has an intensity that is somewhat in the middle of the range of intensities encountered. Notice that expiration images that were acquired when a subject did not fully exhale (for instance, as a subject started to inhale after only reaching mid-exhale), might yield poor correspondence. However, due to the involved weighting, the influence of such outliers will be minimized. As such the template retains some local sharpness (See Figure 2.3). Finally, all volumes (i.e. from the entire DCE series) are rigidly registered to the template to obtain a head-to-foot displacement curve. Subsequently, the expiration-phase images were selected by finding the local minima of this curve. Figure 2.2 illustrates the outcome of this so-called retrospective gating procedure.

**2.2.3 Non-rigid registration**
Chapter 2. Expiration Phase Template-based Motion Correction for Free-Breathing Abdominal DCE-MRI

After retrospective gating of the expiration-phase volumes, there is still some remaining misalignment due to variations between the respiratory cycles and small peristaltic movements. A non-rigid transform is used for compensating the residual misalignment. Therefore, a B-spline transform based on NMI similarity is employed. A transformation based on B-splines is widely used in non-rigid registration and is defined as:

\[
T_{\rho}(x) = x + \sum_{x_k \in N_x} \rho_k \beta_3 \left( \frac{x - x_k}{\sigma} \right)
\]

This transform is governed by a set of \( N_x \) control points \( (x_k) \); \( \beta_3(x) \) represents the cubic multi-dimensional B-spline polynomial; \( \rho_k \) is the control point displacement, and \( \sigma \) is the grid spacing of the B-spline [9].

We used the Elastix [30], a publicly available registration platform to perform the rigid and non-rigid registrations. Both registrations were applied as part of a hierarchical (coarse-to-fine) multi-resolution procedure involving three levels corresponding to down-sampling by a factor of 4, 2 and 1 respectively (1 refers to original resolution) [31]. The NMI was maximized by gradient descent in 1000 iterations for each resolution level. The bending energy of the
transformation field was used to penalize sharp variations of the transformation, i.e. to prevent folding. The weight for the bending energy in Elastix was set to 0.01, as in [9].

### 2.2.4 Experimental design

From each annotation (ROI) in the template image we extract a single TIC. Each TIC was normalized as follows: $S'(t) = \frac{S(t)}{S(0)} - 1$. Essentially, $S(0)$ is taken to represent the offset of the curve. Subsequently, a tri-exponential model $S''(t)$, which is a closed-form solution of Tofts’ model [19], was fit to $S'(t)$ to extract the global trend:

$$S''(t) = A_1 \exp(-\lambda_1 t) + A_2 \exp(-\lambda_2 t) - A_3 \exp(-\lambda_3 t) \tag{2.7}$$

The mean square residue (MSR) of the fit served as a measure for spatial alignment of the registration process. We have chosen to apply the tri-exponential model as it is often used in pharmacokinetic analysis, provides a good fit to the acquired TICs and facilitates easy interpretation.

After an initial visual inspection of the registration results, we performed two experiments in order to set the parameters of our algorithm. These experiments were based on the training set (as indicated above):

- **Number of subsets and random reference selection.** Each DCE series was partitioned into consecutive subsets to create the expiration template and from each subset a random reference volume was selected as described above. We varied the number of subsets from 1 to 50 to evaluate how it influences the registration result. We also determined the variation due to the random reference selection. Therefore, we repeated the procedure five times, while selecting different reference volumes. While doing so, we extracted TICs from the registered data and fitted a tri-exponential model to the annotated regions. The MSR after fitting was used to assess the effect of our choices.

- **B-spline node spacing.** The non-rigid registration was performed with five different B-spline node spacings: 20, 16, 12, 8 and 4 voxels, respectively (they correspond to 50mm, 40mm, 30mm, 20mm, 10mm respectively). As in the previous experiment, the TICs were extracted from the registered data and we fitted a tri-exponential model to each of them. The lowest average MSR after fitting was used to select the B-spline node spacing. The Wilcoxon signed rank test was used to compare the results. A p-value < 0.05 was considered to indicate a significant difference.
Next, we assessed the performance of the algorithm by three experiments, carried out on the test set:

_Respiration phase selection._ Our method includes retrospective gating to the expiration-phase, which intuitively seems the least susceptible to motion artifacts [32]. To support our choice, this method was compared to gating and registration to two other phases of the respiratory cycle: the inspiration-phase and an arbitrarily selected phase. Essentially, the inspiration-based framework works in a similar fashion as the proposed method except for the selection of the maxima from the displacement curves instead of the minima. To compare with our earlier, preliminary work [25], we also picked the middle volume of the DCE series as a reference. Henceforth, we will refer to it as the arbitrary-phase reference since the respiration phase is essentially randomly picked. In addition to the aforementioned choices, we also tried to register all images to the expiration-phase template, i.e. without gating. The MSR that remains after fitting the tri-exponential model to different sections of the bowel wall was used to assess the various strategies. Again, the Wilcoxon signed rank test was used to compare the results.

_Mean target registration error._ We evaluated the accuracy of our method based on manually annotated landmarks. Unfortunately, it is not a trivial task to identify salient points on the bowel wall which was subject to both intensity and spatial deformations. Therefore, five landmarks were carefully selected on organs in close proximity to the bowel wall, including the lateral caudal tip of the liver, the cranial apex of the bladder and the bifurcation of the aorta into the lower extremities. We invited three experts in abdominal image analysis to independently annotate these landmarks on ten randomly selected DCE images from each patient. The inter-observer variability was computed by the mean distance between the annotations of the experts. Subsequently, the different gating and registration methods were applied to the annotated volumes after which the mean target registration error (MTRE) was calculated for each expert. The mean MTRE was determined by averaging the Euclidean distance between the landmarks over all permutations of the ten registered DCE images. Similarly, the MTRE was computed for a state-of-the-art method for respiratory motion correction: the so-called robust data decomposition registration (RDDR) [17]. We applied the RDDR method to the original data as was proposed in [17]. Furthermore, we applied RDDR to the images remaining after expiration phase
gating to examine how gating influences the result. Once more, the Wilcoxon signed rank test was used for comparison of the outcomes.

Relative contrast enhancement. It was shown that radiological features from MRI are related to CDEIS [3]. Particularly, the relative contrast enhancement is evaluated as it is known to have significant correlation to CDEIS. A measure for DCE relative contrast enhancement (DR) was defined via (1) using for \((I_{\text{pre}}, I_{\text{post}})\) the signal intensity inside a ROI in the first respectively the last registered volume and for \{\text{std}(I_{\text{pre}}), \text{std}(I_{\text{post}})\}\) the standard deviations of the noise measured in the annotated air region outside the body in the first, respectively the last registered volume. Subsequently, we computed the Pearson correlation coefficient between the RCE measurements from the two observers and the CDEIS scores. We also computed the Pearson correlation coefficient between DR and the CDEIS scores. Finally, we determined the Pearson correlation coefficient between model fitting parameter \(A_1\) and the CDEIS, as \(A_1\) is directly related to the slope of the TIC curve and therefore to the DR measurement. All correlations were performed on measurements from diseased areas as determined on the MRI data. These data served as independent measures (in addition to the MSR of the fit) to assess the performance of our method as RCE is known to correlate with CDEIS [3]. The significance of the correlations were assessed by mapping the correlations onto a t-statistic by a Fisher transformation (MATLAB R2010b, The Math Works Inc., Natick, Massachusetts, USA).

2.3 Results

2.3.1 Visual inspection
Intensity profiles as a function of time are visualized in Figure 2.4(b)-(e). The original profiles show jagged, periodic fluctuations of the bowel surface, see Figure 2.4 (b). Figure 2.4 (c) shows that these disturbances largely remain after registering all data to the expiration template. (pointed to by the red arrow). Likewise, the fluctuations are not completely removed from the gated data Figure 2.4 (d). After gating and non-rigid registration, the intensity profiles are
smooth: Figure 2.4 (e). It nicely illustrates that our registration procedure could deal with the effects of varying breathing depth and the (limited) peristalsis movement that needed to be compensated after gating.
2.3.2 Numbers of subsets and random reference selection
First, we investigate how the number of subsets influences the registration result on the training set. Table 2.1 collates the average MSR of the tri-exponential fit over the diseased respectively normal regions as a function of the number of subsets. It demonstrates that the MSR stabilizes as the number of subsets is 2 or larger (for each such pair, p > 0.05). Therefore, it shows that the number of subsets is not a critical parameter. Additionally, we repeated the random reference selection 5 times while employing 10 subsets. The MSR results are shown in Table 2.2. It demonstrates that the random pick also does not influence the average MSR value.

2.3.3 B-Spline node spacing
Figure 2.5 shows the average MSR of the tri-exponential fit over the training set as a function of the B-spline node spacing. It involved the diseased as well as the healthy regions in each subject. The red curve was derived from all regions containing inflamed bowel. The green curve was extracted from the control regions containing healthy bowel. We presume that a lower average MSR

Table 2.2 Average mean squared residue (MSR) after fitting the tri-exponential model to TIC’s from diseased and healthy regions in 10 patients for five randomly selected reference images (number of subsets is 10).

<table>
<thead>
<tr>
<th>Reference image no.:</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseased, n = 10</td>
<td>0.0020</td>
<td>0.0020</td>
<td>0.0022</td>
<td>0.0023</td>
<td>0.0021</td>
</tr>
<tr>
<td>Normal, n = 10</td>
<td>0.0011</td>
<td>0.0011</td>
<td>0.0011</td>
<td>0.0011</td>
<td>0.0011</td>
</tr>
</tbody>
</table>
indicates a better registration. Setting the node spacing to eight voxels appears to be optimal for our registration task. Although the differences are small, this setting yields a significantly lower MSR compared to the other spacings (p < 0.05).

2.3.4 Respiration phase selection and registration performance

Figure 2.6 collates the outcome of different correction schemes on the test set. The original number of 3D volumes per DCE-MRI dataset was 450. The gated expiration-phase sets contained 70-140 volumes (in all 28 patients with regions affected by Crohn's disease). Figure 2.6 (a) depicts annotated regions of interest (ROI's): red indicates a diseased region and green a healthy reference region. TICs of the ROIs extracted from the original, gated, and registered data are shown in Figure 2.6 (b)-(f). Notice that in Figure 2.6 (b), the fluctuations of the green curve are much more severe than those of the red curve. This is because the bowel segment in the green region is closer to the lungs. As a consequence, it suffers more from respiratory motion. Figure 2.6 (c) contains TICs that result from registering all 450 volume to the expiration-phase template. Clearly, the TICs after gating and registration display reduced fluctuations: Figure 2.6 (d) - (f). Observe especially the noise reduction of the green curve, which is typical for the whole dataset.
Figure 2.6 Comparison of TICs. (a) a representative data set containing two annotations: a bowel segment affected by Crohn’s disease (red) and a region representing a healthy area (green). The remaining images show the TICs extracted from ROIs in the original data (b), after registering all 450 volumes to the expiration-phase template (c), after gating to an arbitrary selected respiratory phase and registration (d), after inspiration-based gating and registration (e) and after expiration-based gating and registration (f). The black lines in Figures (d),(e),(f) result from fitting the tri-exponential function. The mean squared residuals (MSRs) of the red TICs from (b) to (f) are: 0.0037, 0.0030, 0.0025, 0.0020 and 0.0020; the MSRs of the green TICs from (b) to (f) are: 0.0155, 0.0091, 0.0031, 0.0033 and 0.0011.
Table 2.3 Mean square residue (MSR) after fitting the tri-exponential model to the TIC’s in various ROI’s, averaged over all patients. The first column indicates the bowel section in which the ROI was placed: TI = Terminal Ileum, CA = Colon Ascendens, TC = Transverse Colon, SIG = Sigmoid colon. The first four rows are averages over diseased areas, the last 4 rows are over normal bowel regions. The six labels #1 - #6 denote averaged MSR values without gating or registration (#1), after expiration-phase gating (#2), after registration of all data to the expiration-phase template (#3), after gating and registration to an arbitrary (#4), inspiration (#5), and expiration-phase template (#6). The numbers in bold are the lowest per row. The worst cases encountered are shown between brackets. Abbreviations E-phase, A-Phase R and I-Phase stand for expiration-phase, arbitrary-phase and inspiration-phase, respectively. The suffix '-all' means registration of all images and suffix R reflects registration of those images in a particular respiration phase.

<table>
<thead>
<tr>
<th>Case</th>
<th>#1 Original data</th>
<th>#2 E-Phase</th>
<th>#3 E-Phase R-all</th>
<th>#4 A-Phase R</th>
<th>#5 I-Phase R</th>
<th>#6 E-Phase R</th>
</tr>
</thead>
<tbody>
<tr>
<td>TI(diseased, n=16)</td>
<td>0.0047(0.0114)</td>
<td>0.0039(0.0087)</td>
<td>0.0021(0.0061)</td>
<td>0.0024(0.0044)</td>
<td>0.0021(0.0037)</td>
<td><strong>0.0019</strong>(0.0027)</td>
</tr>
<tr>
<td>CA(diseased, n=8)</td>
<td>0.0047(0.0194)</td>
<td>0.0051(0.0111)</td>
<td>0.0029(0.0047)</td>
<td>0.0040(0.0069)</td>
<td>0.0031(0.0059)</td>
<td><strong>0.0021</strong>(0.0031)</td>
</tr>
<tr>
<td>TC(diseased, n=1)</td>
<td>0.0114</td>
<td>0.0119</td>
<td>0.0024</td>
<td>0.0030</td>
<td>0.0025</td>
<td><strong>0.0016</strong></td>
</tr>
<tr>
<td>SIG(diseased, n=1)</td>
<td>0.0013</td>
<td>0.0020</td>
<td>0.0013</td>
<td>0.0019</td>
<td>0.0019</td>
<td><strong>0.0013</strong></td>
</tr>
<tr>
<td>TI(normal, n=16)</td>
<td>0.0116(0.0536)</td>
<td>0.0047(0.0073)</td>
<td>0.0023(0.0037)</td>
<td>0.0030(0.0075)</td>
<td>0.0020(0.0034)</td>
<td><strong>0.0013</strong>(0.0019)</td>
</tr>
<tr>
<td>CA(normal, n=8)</td>
<td>0.0126(0.0177)</td>
<td>0.0071(0.0113)</td>
<td>0.0018(0.0047)</td>
<td>0.0023(0.0041)</td>
<td>0.0019(0.0025)</td>
<td><strong>0.0011</strong>(0.0028)</td>
</tr>
<tr>
<td>TC(normal, n=1)</td>
<td>0.0814</td>
<td>0.0476</td>
<td>0.0057</td>
<td>0.0079</td>
<td>0.0052</td>
<td><strong>0.0037</strong></td>
</tr>
<tr>
<td>SIG(normal, n=1)</td>
<td>0.0129</td>
<td>0.0156</td>
<td>0.0092</td>
<td>0.0100</td>
<td><strong>0.0080</strong></td>
<td>0.0087</td>
</tr>
</tbody>
</table>
Also, notice that the expiration-phase approach renders the smoothest TIC curves (Figure 2.6 (f)).

Table 2.3 gives the average MSR values over different segments of the bowel wall in the test set. A smaller MSR indicates a better fit and corresponds to a smoother TIC. The MSR values were calculated over regions of interest separately indicated in the expiration-phase template (for #1,#2,#3,#6), in the arbitrary-phase template (#4) and the inspiration-phase template (#5), respectively. Notice that there are 450 time points in the original data (#1) and after registration of all data to the expiration-phase template (#3). Gating reduces the original 450 time points to approximately 100. The effect of having different numbers of data points was taken into account by uniformly down-sampling the TICs extracted from all 450 time points (#1 and #3) to the number of data points after gating (#5). In former experiments [26], it was already shown that expiration-phase images are more reproducible than inspiration-phase images. However, we still include inspiration-phase selection if only to confirm the previous results and make our experiments comprehensive.

Apparently, the MSR values in Table 2.3 for the methods that also involve registration are, always smaller than the MSR values for the original and gated-only data. Furthermore, Table 2.3 shows that expiration-phase based registration gave the best result among all the registration procedures. In fact, the Wilcoxon signed rank test yields that the MSR in column #6 is significantly lower than all the other approaches in the cases with more than one sample (p < 0.05).

2.3.5 Registration accuracy based on landmarks and comparison to a state-of-the-art method

The inter-observer variation in the annotations was calculated to be 2.07 mm. Table 2.4 demonstrates that gating alone reduced the magnitude of misregistration by a factor of two (see #2 compared to #1). Furthermore, the expiration-based approach (#6) yields a significantly smaller MTRE (p < 0.05) than the other registration and gating approaches (#1 - #5). Essentially, this finding confirms the conclusions from 2.3.4 that the expiration-phase is the most stable respiratory phase for registration. Observe that the errors of expiration-based gating and registration (#6) approximate the inter-observer variability of the annotations. Notice also that RDDR applied to the images after expiration phase gating (#8) outperforms
Table 2.4 Mean target registration error (MTRE) of landmarks. The eight labels #1 - #8 denote averaged MTRE values without gating or registration (#1), after expiration-phase gating (#2), after registration of all data to the expiration-phase template (#3), after gating and registration to an arbitrary (#4), inspiration (#5), and expiration-phase template (#6) and registration using RDDR without gating (#7) and using RDDR on expiration-phase gated data (#8). The standard deviation of the target registration error of all landmarks are shown between brackets. The numbers in bold are the lowest in the different categories (i.e. for our proposed methods and the RDDR based methods). The unit for all reported values is mm.

<table>
<thead>
<tr>
<th>Case</th>
<th>#1 Original data</th>
<th>#2 E-Phase</th>
<th>#3 E-Phase R-all</th>
<th>#4 A-Phase R</th>
<th>#5 I-Phase R</th>
<th>#6 E-Phase R</th>
<th>#7 RDDR-all</th>
<th>#8 RDDR-gated</th>
</tr>
</thead>
<tbody>
<tr>
<td>OB1</td>
<td>5.01 (2.65)</td>
<td>2.22 (0.67)</td>
<td>4.41 (2.84)</td>
<td>2.66 (1.93)</td>
<td>2.60 (1.53)</td>
<td><strong>2.12</strong> (0.56)</td>
<td>4.44 (0.91)</td>
<td><strong>3.08</strong> (1.25)</td>
</tr>
<tr>
<td>OB2</td>
<td>5.62 (2.60)</td>
<td>3.40 (1.77)</td>
<td>3.71 (2.42)</td>
<td>2.48 (1.57)</td>
<td>2.53 (1.24)</td>
<td><strong>2.27</strong> (1.13)</td>
<td>3.32 (1.92)</td>
<td><strong>2.83</strong> (1.23)</td>
</tr>
<tr>
<td>OB3</td>
<td>6.32 (1.06)</td>
<td>2.48 (0.77)</td>
<td>5.35 (1.00)</td>
<td>2.34 (0.71)</td>
<td>2.60 (0.92)</td>
<td><strong>2.33</strong> (0.73)</td>
<td>5.27 (1.04)</td>
<td><strong>3.10</strong> (1.17)</td>
</tr>
</tbody>
</table>

Table 2.5 Pearson correlation of enhancement measurements (DR, $A_1$) to CDEIS. r and p denote the correlation coefficient and p-value, respectively. DR was obtained from the first and last DCE volumes. $A_1$ is a parameter from the tri-exponential model that captures the contrast enhancement. The six labels #1 - #6 denote correlation between CDEIS and (DR, $A_1$) parameters from the data without gating or registration (#1), after expiration-phase gating (#2), after registration of all data to the expiration-phase template (#3), after gating and registration to an arbitrary (#4), inspiration (#5), and expiration-phase template (#6). The numbers in bold are the best correlations per case.

<table>
<thead>
<tr>
<th>Case</th>
<th>parameters</th>
<th>#1 Original data</th>
<th>#2 E-Phase</th>
<th>#3 E-Phase R-all</th>
<th>#4 A-Phase R</th>
<th>#5 I-Phase R</th>
<th>#6 E-Phase R</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR</td>
<td>r</td>
<td>0.16</td>
<td>0.22</td>
<td>0.33</td>
<td>0.50</td>
<td>0.50</td>
<td><strong>0.55</strong></td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.48</td>
<td>0.32</td>
<td>0.14</td>
<td>0.02</td>
<td>0.02</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>$A_1$</td>
<td>r</td>
<td>0.18</td>
<td>0.21</td>
<td>0.39</td>
<td>0.36</td>
<td>0.40</td>
<td><strong>0.60</strong></td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.43</td>
<td>0.35</td>
<td>0.08</td>
<td>0.11</td>
<td>0.09</td>
<td><strong>0.004</strong></td>
</tr>
</tbody>
</table>
Chapter 2. Expiration Phase Template-based Motion Correction for Free-Breathing Abdominal DCE-MRI

RDDR directly applied to the original data (#7). It once more confirms that gating is an important step to achieve high registration accuracy. Finally, observe that our expiration-based approach (#6) yields a significantly lower MTRE than RDDR applied to the same data (#8) (p < 0.05).

2.3.6 Correlation of relative contrast enhancement to CDEIS

Table 2.5 shows the correlation of our measures for relative contrast enhancement (DR and $A_1$) with the CDEIS score. These correlations concern 21 out of 26 diseased segments, since in 5 segments the CDEIS could not be scored during colonoscopy due to strictures. The DR and $A_1$ parameters based on expiration-phase gating and registration yield the best correlation. Furthermore,
DR improves over observers 1 and 2. Parameter $A_1$ based on expiration-phase gating and registration shows an even better correlation with CDEIS ($r = 0.60$, $p = 0.004$) than DR. The result is further illustrated in Figure 2.7.

Finally, Figure 2.8 contains representative colormaps of DR and $A_1$ illustrating the differentiating power of the proposed methods. Notice particularly how in the diseased regions the signal is stronger after gating and registration. Furthermore, observe that the $A_1$ color maps display a slightly sharper response than the manual RCE. There are some ‘false positive’ regions in the colormaps. These regions are outside of the radiologist’s annotations indicating diseased
Chapter 2. Expiration Phase Template-based Motion Correction for Free-Breathing Abdominal DCE-MRI

bowl. This only emphasizes that Crohn’s disease severity cannot be based on a single feature, which is well known [3].

2.4 Conclusion

We developed a method for compensating the spatial mismatch due to the motion inherent to free-breathing DCE-MRI of the abdomen. This problem is especially hard because adjacent organs may slide along each other, causing large, discontinuities in the deformation field. Our method applies a retrospective gating to the expiration breathing phase after which residual misalignment is removed by a non-rigid registration. Effectively, the gating makes that image volumes are already almost in correspondence and that the remaining deformation field is continuous. As such the confounding effects of breathing motion, and potentially varying susceptibility are already limited.

We performed a quantitative assessment of the registration accuracy using manually annotated landmarks made by three image analysis experts. Our expiration-based approach showed the lowest MTRE for each expert and the results were close to the average inter-observe variation (2.07mm). We also found that our method performed significantly better than a state-of-the-art methods for registering DCE-MRI called RDDR. We also quantitatively assessed the registration performance by an application-specific task. Therefore, we first compared the mean square residue emanating from fitting a tri-exponential model to the extracted TICs in diseased and healthy regions. We compared retrospective gating of the expiration-phase to the inspiration-phase as well as to a randomly selected phase. The expiration-based approach proved to produce the best result. We also quantitatively evaluated the motion correction procedure by correlating the DCE based RCE measurement (DR) and the fit parameter $A_1$ with the CDEIS score. Again, the expiration-based approach gave the best result. A simpler expiration-based approach which only choses one expiration-phase image from all 450 images may give worse outcome (confirmed in Table 2.1). Essentially, it was shown that our weighted expiration template gives the best outcome.

We also found that the DR measure derived from the expiration-phase DCE data correlates significantly with the CDEIS score. The result is better than the correlations between manual RCE measurements and CDEIS. Even stronger, the model parameter $A_1$, which was obtained by fitting a tri-exponential model to
the TIC, showed a better correlation than all other RCE based correlations. Parameter $A_1$ represents the amplitude of exponential signal enhancement.

A limitation of our work is that the regions of interest were manually drawn by one expert. As such, a differently drawn region could result in a different TIC. Notice, that in Table 2.3 all six methods essentially involved the same regions albeit separately annotated in different templates by the same expert to enable a proper comparison. Moreover, in order to reduce variability due to inclusion of boundary regions we instructed the expert to carefully make the annotations.

Another limitation of our work is that retrospective gating excludes a large part of the data. However, we hypothesize that the loss of data due to retrospective gating hardly affects the TICs from tissue and subsequent pharmacokinetic modeling. Such TICs reflect the time-varying concentrations of contrast agent in the blood pool and intercellular space. These two compartments are related by linear diffusion equations for which the arterial input function acts as input. In our ongoing research we derive the AIF for pharmacokinetic modeling from the aorta, prior to gating and registration. The aorta is firmly connected to the spine, so that it is not affected by respiratory motion. As such, the AIF is optimally sampled. The aforementioned diffusion acts as a low-pass filter on the time-varying AIF and yields a smoothed TIC in response to the AIF. As such the effects of gating (subsampling) are limited. An AIF derived from a different artery than the aorta that is suffering from respiration movement might be affected by the loss of data. We consider an investigation of this topic beyond the scope of the current paper. Primarily, our results demonstrated that gating is an important step to improve the registration of free-breathing abdominal MR images (2.3.4, 2.3.5 and 2.3.6). Due to the relative large discontinuous deformation caused by breathing it is not easy to estimate the displacement by a conventional registration technique. Essentially, the gating procedure reduces the breathing effects to a large extent. Alternatively, we may consider using a discrete optimization technique such as Markov random fields to improve the registration results without using gating.

All the results demonstrate that our expiration-based, retrospective gating and a non-rigid registration approach effectively corrects for respiratory motion and remaining peristalsis. We consider as future work combining DCE features with other MRI features for optimal CDEIS prediction.
References


Chapter 2. Expiration Phase Template-based Motion Correction for Free-Breathing Abdominal DCE-MRI


Chapter 2. Expiration Phase Template-based Motion Correction for Free-Breathing Abdominal DCE-MRI


Registration of images in the presence of intra-image signal fluctuations is a challenging task. The definition of an appropriate objective function measuring the similarity between the images is crucial for accurate registration. This paper introduces an objective function that embeds local phase features derived from the monogenic signal in the modality independent neighborhood descriptor (MIND). The image similarity relies on the autocorrelation of local structure (ALOST) which has two important properties: (1) low sensitivity to space-variant intensity distortions (e.g. differences in contrast enhancement in MRI); (2) high distinctiveness for ‘salient’ image features such as edges. The ALOST method is quantitatively compared to the MIND approach based on three different datasets: thoracic CT images, synthetic and real abdominal MR images. The proposed method outperformed the existing techniques on all these datasets. The registration of dynamic contrast enhanced and post-contrast MR images of patients with Crohn’s disease led to relative contrast enhancement measures with the highest correlation (r=0.56) to the Crohn’s disease endoscopic index of severity.

3.1 Introduction

Image registration has been one of the main topics of research in the medical imaging community over the past decades. Typically, a registration method consists of three core components [1]: 1) a deformation model that defines how one image is transformed towards another, 2) an objective function that determines the similarity between two images, and 3) an optimization strategy that searches for the values of the transformation parameters that maximize the objective function. A recent survey of the research into image registration approaches can be found in Sotiras et al. [1].

An appropriate objective function is pivotal to achieve accurate correspondence after registration. The choice of objective function has proven especially challenging for medical image registration. Ultimately, our focus is on registering magnetic resonance (MR) images of the gastrointestinal tract for the assessment of inflammatory bowel diseases (IBD). This registration problem is further complicated by fluctuating tissue intensity over the field of view (e.g. due to differences in contrast enhancement and the MRI bias field) as well as large deformations between corresponding structures in both images (e.g. due to respiration and peristaltic bowel movement). To be successful in registering MR images that exhibit a large intra-image signal variation, we need an objective function that is especially sensitive to the phase of the local image structures and avoid the confounding effect from the fluctuating signal intensity. We will introduce a novel criterion function based on the mean and standard deviation of the local phase derived from a multi-scale representation of its monogenic signal.

3.1.1 Related work

Generally speaking, there are two different perspectives for looking at the objective function: global and local. From a global point of view, the objective function can be defined based on the statistical relationship between the image intensities. An example is mutual information (MI), one of the most studied registration metrics (e.g. [2] [3]). It has been widely and successfully used in both mono- and multi-modal image registration problems, e.g. [4] [5] [6]. However, originally being a global objective function, it lacks local, i.e. spatial, information on the local structure and cannot cope with large signal and contrast variations. Several methods were proposed addressing this problem. Initially, Pluim et al. [7] combined gradient information with MI in order to capture the local structure. They proposed a term, which seeks to align locations with high gradient magnitude and similar orientation. Recently, Rivaz et al. [8] proposed
the so-called SeSaMI method, which also uses gradient information. A self-similarity weighted graph-based implementation is introduced using $\alpha$-Mutual Information ($\alpha$-MI) for nonrigid image registration. The method employs a self-similarity measure based on local structural information, which is invariant to rotation and to local affine intensity distortions. However, the method comes with a rather high computation cost because multi-dimensional features are involved to build SeSaMI. Alternatively, Studholme et al. [9] introduced a regional label as an extra “channel” to the intensity joint histogram to compute the so-called regional mutual information (RMI). The RMI was shown robust to local contrast variations over diseased brain tissue. Recently, Loeckx et al. [10] proposed a measure called conditional mutual information (CMI) which extends the intensity joint histogram with a third channel containing spatial information. Although these methods introduce local information into a global objective function, it has been noticed [11] that finding an accurate correspondence remains difficult, especially due to the many local optima that generally accompany most non-rigid deformation models.

From a local point of view, the objective function is usually defined based on a sum of point-to-point or (small) region-to-region correspondences between images. Sum of squared differences (SSD) and cross correlation (CC) are exemplary methods to do so. However, they are only reliable under the assumption that the intensity relationship between the images is linear. For many registration problems, especially concerning mono-modal images with space-variant intensity distortions and multi-modal images, this assumption is not correct.

Several methods [12] [13] [14] were proposed for tackling this non-linear intensity relationship by relying on features based on local orientation rather than intensities. The first two methods [12] [13] use the gradient orientation in a multi-scale fashion, but restricted to voxels with a high gradient magnitude. The third method [14] employs the local orientation as obtained by the local structure tensor (LST) [15] [16]. Here, the eigenvector corresponding to the largest eigenvalue of the structure tensor points in the dominant orientation of the local signal. This feature was shown to yield a more consistent registration for small image features (e.g. thin lines). A limitation of these methods is that the local orientation is ill-defined in areas where two or more unimodal oriented patterns come together (e.g. bifurcations of vessels).
One might also consider the local entropy as measures of the local image structure. Following up on that idea, local entropy was introduced [17]. The intensity histogram was first calculated over a small patch centered at each voxel in the image. Then, the Shannon entropy for each voxel was calculated over the smoothed histograms in which discretization errors were suppressed by use of a Parzen kernel. The assumption behind using the entropy image was that intensity variations would occur at corresponding locations in the different images. Accordingly, the SSD of entropy images was used as the objective function. However, this method is sensitive to noise when calculating the histogram over small patches. Also, the assumption of equivalent entropy is not valid if two images exhibit large structural differences (e.g. between PET and MRI).

Alternatively, local phase and local amplitude from the monogenic signal were proposed to represent local image structure [18] [19]. The local amplitude of the monogenic signal represents the local (square-root of the) energy of the signal and the local phase is a signature determining the balance between the even and the odd components of the local signal. Image registration steered by similarity in local phase and local amplitude was introduced [20] [21] [22]. However, these registration methods used a voxel-wise representation of structure, without particularly emphasizing the structural resemblance in the surrounding neighborhood. Another drawback of merely using a voxel-wise phase representation is the sensitivity to noise. It was already mentioned in [20] that noise can only be dealt with by carefully choosing certain parameters.

Recently, a local image descriptor based on neighborhood information called MIND (modality independent neighborhood descriptor) was proposed [11]. The method was derived from the concept of self-similarity, which was first proposed by Buades et al [23]. MIND embeds the local structure in a vector representation for each voxel. This descriptor essentially comprises the local autocorrelation function (see also section 3.2.3). It has resulted in better registration results compared to other, state-of-the-art methods. MIND was reported to be a “distinctive” descriptor, which might be important for registering images with many degrees of freedom [11]. One may notice, however, that small image patches by themselves are not a good representation of the local structure. Such patches capture not only true structure information originating from signal differences across organ boundaries, but also undesired information. For instance, differences in contrast enhancement are
‘uncharacteristic’. MIND does not fully suppress such influences. Fortunately, one can use a band-pass filter to calculate the local phase for image patches. The phase information primarily describes the desired structure that is related to sharp edges. Complimentary, the contrast difference is contained in the local amplitude. By neglecting the local amplitude information, the information left (local phase) is insensitive to differences in contrast enhancement.

3.1.2 Objective
In this paper we present a novel measure of the local image structure based on the monogenic signal, which is insensitive to “uncharacteristic” information such as differences in contrast enhancement and the MRI bias field. Subsequently, we integrate this measure in the aforementioned MIND principle. As such, we exploit the autocorrelation of local structural information (ALOST) rather than the autocorrelation of intensity (MIND). We demonstrate the benefit of image registration using ALOST by applying it to images that have space-variant intensity distortions.

3.2 Methods
The ALOST method is designed to register images distorted by contrast variations, e.g. by the MRI bias field or fluctuating gadolinium uptake. The method involves several image processing techniques. The monogenic signal [18] is introduced to measure the local image structure of 3D images. The monogenic signal is an extension of the analytic signal to higher dimensions (3.2.1). It is calculated using specific band-pass filters. Two complementary features are derived from the monogenic signal: local phase and phase congruency (3.2.2). We integrate these features in a patch-based representation called ALOST (3.2.3). Finally, the image registration pipeline is described (3.2.4).

3.2.1 The analytic and monogenic signal
The analytic representation of a signal is based on the concept that negative frequency components of a real-valued signal are essentially superfluous due to the Hermitian symmetry of its Fourier spectrum. Specifically, if \( f(x) \) is a real-valued signal and \( \mathcal{F}(\omega) \) its Fourier transform, then the Fourier spectrum

\[
\mathcal{F}_A(\omega) = \mathcal{F}(\omega)(1 + \text{sgn}(\omega))
\]  

(3.1)
contains only positive frequency components and is reversible into $\mathcal{F}(\omega)$. The inverse Fourier transform of $\mathcal{F}_A(\omega)$ is called the analytic signal [15]

$$f_A(x) = f(x) - if_H(x), \quad (3.2)$$

where $f_H(x)$ is Hilbert transform of $f(x)$:

$$f_H(x) = H(f(x)) = \frac{1}{\pi} \int_{-\infty}^{\infty} \frac{f(\tau)}{\tau - x} d\tau. \quad (3.3)$$

Without loss of information the negative frequency components of a real-valued signal are discarded, but instead one has to deal with a complex-valued signal. Incidentally, notice that the conversion from the complex-valued analytic signal back to the underlying real-valued signal is just a matter of discarding the imaginary part from (3.2). The analytic signal representation makes certain attributes of the signal more accessible. Typically, the analytic signal is described by the local amplitude $|f_A(x)|$ and local phase $\varphi(x)$ defined as:

$$|f_A(x)| = \sqrt{f_A(x)f_A^*(x)} = \sqrt{f^2(x) + f_H^2(x)}, \quad (3.4)$$

$$\varphi(x) = \arctan\left(\frac{f_H(x)}{f(x)}\right). \quad (3.5)$$

Generally, direct calculation of these quantities cannot be done, because the Hilbert transform requires an infinite support filter, see (3.3). Therefore, the local amplitude and phase are conventionally estimated based on a band-pass filtered version of the signal. If $q_e(x)$ represents the band-pass filter, we have that the analytic signal is approximated by:

$$\hat{f}_A(x) = f_A(x) * q_e(x) = [f(x) - if_H(x)] * q_e(x)$$

$$= f(x) * q_e(x) - iH(f(x) * q_e(x)) = f_e(x) - if_{o}(x), \quad (3.6)$$

where $q_o(x)$ is the Hilbert transform of $q_e(x)$, so that these filters form a quadrature-pair. In particular, we choose $q_e(x)$ to be an even, real-valued, band-pass filter (hence the subscript $e$) with zero DC-value to be invariant to an arbitrary chosen amplitude offset. Furthermore, its real-valuedness and even
symmetry implies that there is no change of phase information if we choose $q_e(x)$ such that its Fourier transform satisfies $Q_e(x) \geq 0$. In turn, $q_o(x)$ is odd. Observe that the response of the signal to $q_e(x)$ gives the local real-and-even component of the approximated analytic signal and that the response to $-q_o(x)$ yields the local imaginary-and-odd component of it.

The monogenic signal [18] extends the analytic signal from 1 dimensional to $N$ dimensional by means of the Riesz transform. We restrict ourselves to 3D images for illustration purposes. The monogenic signal relies on a rotationally symmetric, real-valued, zero-mean band-pass filter whose Fourier transform is non-negative to avoid phase flipping. This filter is used to extract the even component of the signal:

$$f_e(x) = f(x) * q_e(x),$$

where $f(x)$ is a 3-D image and $q_e(x)$ is an isotropic band-pass filter [18]. The choice of the band-pass filter is not a trivial task. We will discuss it in the next section.

Three filters are constructed to extract the three odd components (i.e. one per image dimension) from the signal by applying the 3-D Riesz transform to the isotropic band-pass filter. The frequency responses of the filters are given in the 3D Fourier domain by:

$$Q_R(u) = Q_o(u) = \frac{u}{|u|} Q_e(u),$$

in which $Q_e(u)$ represents the Fourier transform of $q_e(x)$. Notice that the term $(u/|u|)$ yields the same frequency response along its primary axes as the 1-D Hilbert transform. Also, while $u$ represents a basis vector of the Fourier space, there are three odd components for a 3D image. The response to (3.8) yields the Riesz transform of $f(x)$ defined as:

$$f_R(x) = F^{-1}\{F\{f_e(x)\} \cdot Q_R\}.$$  

Finally, the monogenic signal (expressed in quaternions) is:

$$f_M(x) = f_e(x) - (i,j,k)f_R(x).$$
The local amplitude and phase of the monogenic signal are defined as:

\[ A(x) = |f_M(x)| = \sqrt{f_c(x)^2 + |f_R(x)|^2}, \quad (3.11) \]

and

\[ \varphi(x) = \text{atan} \left( \frac{f_R(x)}{f_c(x)} \right). \quad (3.12) \]

Notice that with this definition the phase \( \varphi(x) \) ranges from \(-\pi/2\) to \(\pi/2\). Although the orientation of the phase can be expressed in two angles, these are not used in the proposed registration method.

### 3.2.2 The band-pass filter and representation of local structure

The choice of band-pass filter is important in obtaining some key properties [24]. We choose a log-Gabor filter which is essentially a shifted Gaussian function on a logarithmic scale in the frequency domain. We opt to do so because it is a zero DC filter with a tunable bandwidth. Furthermore, log-Gabor filters are invariant to an additive polynomial function of order \( n < \infty \).

The filter \( q_\omega(x) \) is defined in the frequency domain as:

\[ Q_\omega(\omega) = n_c \exp \left(-\ln^2 \left( \frac{\omega}{\omega_0} \right) / 2 \ln^2 (k_\beta) \right), \quad (3.13) \]

where \( n_c \) is a normalization constant, \( \omega_0 \) the central (tuning) frequency and \( k_\beta \) \((0 < k_\beta < 1)\) a parameter related to the bandwidth \( \beta \) of the filter:

\[ \beta = -\frac{2\sqrt{2}}{\sqrt{\ln 2}} \ln(k_\beta). \quad (3.14) \]

In our experiments the log-Gabor filter was applied to four scales \((\omega_0 = 3, 9, 27 \text{ and } 81) \) [22]. Using \( k_\beta = 0.47 \) yields a log-Gabor filter with 2.6 octaves in bandwidth which is the smallest bandwidth of edge operators without significant aliasing [24].

At each scale, we compute the local amplitude \( A_i(x) \) and local phase \( \varphi_i(x) \) using (3.11) and (3.12). The local energy model postulates that features are perceived at points in an image where the Fourier components are in phase [25].
As such, congruency of phase at any angle produces a clearly perceived feature [26]. The angle at which the congruency occurs dictates the feature type, for example, a step corresponds to $\varphi = 0$ and a peak to $\varphi = \frac{1}{2} \pi$.

Initially, a measure for phase congruency (PC) was developed by Morone and Owens [25]:

$$PC_1(x) = \frac{|E(x)|}{\sum_{i=1}^{n} A_i(x)}, \quad (3.15)$$

where $E(x)$ is defined as the scale accumulated monogenic signal:

$$E(x) = \sum_{i=1}^{n} f_{M,i}(x), \quad (3.16)$$

and (for our 3D image space), $|E(x)|$ is given by:

$$|E(x)| = \sqrt{\left( \sum_{i=1}^{n} f_{c,i}(x) \right)^2 + \left( \sum_{i=1}^{n} f_{R1,i}(x) \right)^2 + \left( \sum_{i=1}^{n} f_{R2,i}(x) \right)^2 + \left( \sum_{i=1}^{n} f_{R3,i}(x) \right)^2}, \quad (3.17)$$

with $A_i$ the local amplitude (3.11) and $f_{R1,i}$, $f_{R2,i}$ and $f_{R3,i}$ the three components originating from Riesz transform $f_{R,i}(x)$ (3.9) at scale $i$.

$$PC_1(x) = \frac{\sum_{i=1}^{n} A_i(x) \cos(\varphi_i(x) - \bar{\varphi}(x))}{\sum_{i=1}^{n} A_i(x)}$$ can be written as a weighted sum of cosines, where the $\bar{\varphi}(x)$ is the phase of $E(x)$ henceforth referred to as the mean phase:

$$\bar{\varphi}(x) = \arctan(\frac{\sum_{i=1}^{n} |f_{R,i}(x)|}{\sum_{i=1}^{n} f_{c,i}(x)}). \quad (3.18)$$

If all scale components are in phase, the complex vectors would be aligned and the phase congruency would be 1. Alternatively, if there is no coherence of phase, the phase congruency becomes zero. Phase congruency provides a measure that is independent of the magnitude, making it invariant to global trends in the signal and variations in contrast. Moreover, averaging over different scales decreases the influence of noise on the estimated phase.

Later, Kovesi [27] developed a modified phase congruency measure which subtracted the sine of the phase deviation to produce a more localized response:
where the factor $W(x)$ reflects the spread in frequency. $T$ is a threshold ensuring that only values exceeding the noise floor are taken into account. Therefore, the symbols $[ ]$ denote that the quantity enclosed is equal to itself when larger than $T$ and zero otherwise. Finally, $\varepsilon$ is a small positive constant to avoid division by zero. More details can be found in the work by Kovesi [27].

Figure 3.1 shows the mean phase and phase congruency ($PC_2$) applied to an image with an simulated, spatially-varying intensity distortion [28]. The red profiles show that the mean phase is not sensitive to the applied signal distortion and that the phase congruency is high for both edges and peaks. The blue profiles shows the results from the undistorted images for comparison. It can be seen that the profiles from the distorted image and undistorted image show a strong resemblance, both for the mean phase and phase congruency. Notice also that particularly larger features exhibiting a sharp intensity transition such as the skull yield a high phase congruency, whereas smaller features e.g. in the cerebellum have a low phase congruency.
3.2.3 Autocorrelation of local structure

The mean phase and phase congruency are voxel-wise descriptors of the local structure that are not sensitive to global trends [20]. They have also limited sensitivity to noise if one chooses the band-pass filters carefully (i.e. by applying appropriate cut-off frequencies). Indeed, a mere phase based method can still suffer from noise. Neither mean phase nor phase congruency by itself captures the coherence of structural information in a neighborhood. A patch-based method [11] [29] solves this issue and simultaneously suppresses the sensitivity to noise even further. One way to do so is using a local autocorrelation (AC) function which is embedded in the local sum of squared differences (SSD) between two patches of size $P$ in image $I$: 
Chapter 3. Image registration based on autocorrelation of local structure

\[ D_p(I, x_1, x_2) = \sum_{p \in P} \left( I(x_1 + p) - I(x_2 + p) \right)^2 \]

\[ = \sum_{p \in P} I^2(x_1 + p) - 2 \sum_{p \in P} I(x_1 + p)I(x_2 + p) + \sum_{p \in P} I^2(x_2 + p) \]

where \(x_1\) and \(x_2\) are the centers of the two image patches \(P\) of size \(D \times D \times D\) (in 3-D case). \(D_p\) gives a small value when the local autocorrelation function \(AC_p\) yields a high value. As such the modality independent neighborhood descriptor (MIND) [11] incorporates the \(AC_p\) as follows:

\[
\text{MIND}(I, x, r) = \frac{1}{n} \exp \left( \frac{-D_p(I, x, x + r)}{V(I, x)} \right),
\]

with \(r\) an offset in a predefined neighborhood \(R\) of size \(R \times R \times R\) around position \(x\), \(n\) a normalization constant (chosen such that the maximum value of MIND at position \(x\) is 1) and \(V(I, x)\) represents the average SSD in a small neighborhood \(N\) around \(x\):

\[
V(I, x) = \frac{1}{\text{size}(N)} \sum_{n \in N} D_p(I, x, x + n).
\]

In other words, MIND returns an 1-D vector of length \(R^3 - 1\) which represents all correlations between a neighborhood \(P\) centered at voxel \((x)\) and a neighborhood \(P\) centered at a voxel around it \((x + r)\). Three parameters have to be defined in MIND: the patch size \(D\), the search neighborhood size \(R\), and the size of the variance calculation neighborhood \(N\). We followed the same setup as [11]: \(N = N_6\) which means a six-connected neighborhood and patch size \(D = 3\). Only the size of the search region \(R\) is a free parameter and was trained for different datasets. More details for choosing \(R\) can be found in section 3.3.
The original MIND descriptor is applied to the image intensity itself, which makes it sensitive to global trends (e.g. intensity distortions, see Figure 3.1(a)). We propose to combine the best of two worlds: (1) the structural measures of local phase and phase congruency and (2) the neighborhood description of MIND. This is captured in our new descriptor – henceforth referred to as Autocorrelation of the LOcal Structure (ALOST). ALOST describes the local structure for each image voxel as a $2(R^3 - 1)$ dimensional vector:

$$\text{ALOST}(I, x, r) = [\text{MIND}(\bar{\phi}(I), x, r), \text{MIND}(\text{PC}(I), x, r)],$$

(3.23)

where $\bar{\phi}(x)$ and $\text{PC}(x)$ are the mean phase and phase congruency from, respectively, equations (3.18) and (3.19). Thus, the phase information over all scales is represented by a mean value, encoding for the type of structure (e.g. ridge, slope, etc.), and a value reflecting the spread of the scale-dependent phases around the mean phase, signifying the reliability of such a feature. It will be shown that the proposed ALOST descriptor enhances the distinctiveness of image features over separate representations based on either mean phase or
Chapter 3. Image registration based on autocorrelation of local structure

phase congruency. In order to visualize the distinctiveness of the descriptors we measure the self-similarity of the local structure descriptors as:

\[
\text{SELFSIM}(\text{DESCRIPTOR}, I, x, r, m) = 1 - \frac{1}{M} \| \text{DESCRIPTOR}(I, x, r) - \text{DESCRIPTOR}(I, x + m, r) \|, \tag{3.24}
\]

where \(\text{DESCRIPTOR}\) is either MIND or ALOST, input image \(I\) either the intensity, the mean phase or the phase congruency and \(M\) the region size over which the self-similarity is measured. This gives rise to four descriptors denoted as ALOST, MIND-I, MIND_MP, MIND_PC. Figure 3.2 shows the self-similarity of the various descriptors in a region-of-interest of a brain image corrupted by a simulated intensity distortion. Clearly, Figure 3.2(e) shows the “distinctiveness” of ALOST around the voxel that we picked. Note that MIND applied to the mean phase shows the least distinctiveness among all descriptors.

### 3.2.4 Image registration pipeline

We implemented the registration pipeline as used in MIND [11]. The objective function which is going to be minimized consists of a data term and a regularization term:

\[
\arg\min_{u_m} \left\{ \sum_x \left( \frac{1}{|R|} \sum_{r \in R} |\text{ALOST}(I_f, x, r) - \text{ALOST}(I_m, x + u_m, r)|^2 \right) + \alpha \text{tr} \left( \nabla u_m(x)^T \nabla u_m(x) \right)^2 \right\}, \tag{3.25}
\]

where \(u_m = (u, v, w)\) is the deformation field for each voxel in the moving image and \(u_m^*\) the optimal transformation. The data term of the objective function is defined as the sum of absolute descriptor differences. The regularization term penalizes the total variation of the deformation. The objective function is then optimized by means of the Gaussian-Newton method. While doing so a multi-resolution procedure was followed involving three levels corresponding to down-sampling by a factor of 4, 2 and 1 respectively (1 refer to original resolution). More implementation details can be found in [11].

### 3.3 Results and Discussion

The four descriptors (MIND_I, MIND_MP, MIND_PC, and ALOST) were evaluated on several datasets: abdominal MRI data with synthetic spatially-
variant intensity distortions and synthetic spatial deformations (3.3.1), thoracic CT images (3.3.2), and abdominal MR images (3.3.3). The computation time for each descriptor depends linearly on the number of voxels. The average registration time for the largest dataset (thoracic images of size 256×256×94) was less than 10 minutes on a personal computer equipped with an Intel® Core™2 Quad Processor Q8400 clocked at 2.66 GHz and 4GB RAM memory.

3.3.1 Synthetic data
We simulated a corrupted image by applying an intensity distortion to abdominal MR image data as described by Myronenko et al. [28]. Firstly, a spatially-varying intensity distortion was applied to an abdominal MR image to create the fixed image (see Figure 3.3 (a)). Second, another intensity distortion was applied to the same (initial) abdominal image in a comparable manner. Thereafter, a geometric distortion with a thin-plate spline (TPS) model was applied to this image to get a second image, used as the moving image (see Figure 3.3 (a)). The intensity distorted regions are contained in the dashed red box of the moving image. Subsequently, we used the Normalized Mutual Information (NMI) [5] as a baseline metric as well as the four approaches described in II.C to register these data: MIND_I, MIND_MP, MIND_PC and ALOST (see the first row of Figure 3.3 (b)-(f)). Enlarged versions of the regions corresponding to the aforementioned dashed red boxes after registration are shown in respectively the second row of Figure 3.3 (b)-(f). The fixed image is displayed in green and the registered moving image in magenta. A perfect registration yields a grey-scale image. Any color denotes misregistration. For display purposes, the color-coding was applied to the images without intensity distortion.

It can be seen that MIND_MP, MIND_PC and ALOST gave better registration results in the region with intensity distortions than NMI and MIND_I. Particularly, one can see from Figure 3.3 (b) and (c) that the registration is off in the regions pointed out by the yellow arrows. This illustrates that NMI and MIND_I are sensitive to intensity fluctuations. Furthermore, ALOST yielded better results than registration only based on MIND_MP or MIND_PC in the areas again denoted by the yellow arrows. Registration based on the MIND_MP descriptor particularly failed in a region that was subject to a large deformation (Figure 3.3 (d)) as MIND_MP is not sufficiently distinctive (see Figure 3.2 (c)) to register this part. Registration based on the MIND_PC descriptor also caused misregistration in the region indicated in Figure 3.3 (e). This happened because
Chapter 3. Image registration based on autocorrelation of local structure

MIND_PC merely emphasizes ‘larger’ features with a strong intensity transition (see Figure 3.1 (c)) and does not perform well in complex regions in which small details are relevant. Such regions only give a reliable phase response on the smallest scale. Essentially, ALOST combines the merits of MIND_MP and MIND_PC Therefore, it facilitates enhanced distinction and is insensitive to intensity distortions. This experiment shows that ALOST has the potential to register images suffering from large spatial deformations and strong intensity distortions.

We generated 100 synthetic abdominal MR images with a random spatial deformation and a random intensity distortion (as above) to quantitatively compare our method to the other techniques. The NMI method was taken from the elastix toolbox [30] using a B-spline transform with a histogram bins setting of 64. This setting was used in all the following experiments. The other four methods were tested using the MIND_I registration framework, which needs careful tuning of the search region $R$. Therefore, we first used 20 pairs of synthetic images to identify the best $R$ for each method. The average root mean square error (RMSE) of the estimated deformation field with each method for varying $R$ is shown in Figure 3.4. Apparently, all four methods gave the lowest average RMSE at $R = 3$. Notice also that the ALOST method gave the lowest average RMSE for all settings. We subsequently used $R = 3$ to test the methods on the remaining 80 datasets. The results are contained in Table 3.1. One can see that the phase-based methods MIND_MP, MIND_PC and ALOST gave better results than NMI and MIND. This is because these three methods are insensitive to the intensity distortion. One can also see that the ALOST method gave the lowest average RMSE among the phase-based methods because of the better distinctiveness. A two-sided signed rank test demonstrated that ALOST had a significantly better outcome than all other methods (p<0.05).
Figure 3.3(a) An abdominal MR image with a simulated space-variant intensity distortion (fixed image) and the same abdominal MR image affected by a different simulated intensity distortion and a spatial deformation (moving image); (b)-(f) the top images show the moving image after registration based on respectively NMI, MIND_I, MIND_MP, MIND_PC and ALOST; the bottom image contain the fixed image in the green channel and the registered, moving image in the red and blue channels: proper registration gives grey tone and misregistration results in green or magenta tones; the yellow arrows indicate misregistration in the regions with large contrast variation and spatial deformation in the moving image.
3.3.2 Registration of thoracic CT images

The MIND_I method was evaluated on publicly available 4D thoracic CT scans of ten patients [31]. Each scan has 300 anatomical landmarks annotated by thoracic imaging experts in both the inhale and exhale scans. The inter-observer error is less than 1 mm. The registration of inhale and exhale scans can be seen as a mono-modal registration problem. However, due to gas density differences between inhale and exhale scans, an objective function based on minimizing the sum of squared differences failed in several cases [11].

We again evaluated five methods (NMI, MIND_I, MIND_MP, MIND_PC, ALOST) on these datasets by calculating the mean target registration error (MTRE) of the landmarks after registering the exhale to the inhale scans (see Table 3.2). While doing so, we used $R=0$ (i.e. a six-neighborhood setting) in all four methods. Note that this setting was reported in [11] to yield the best registration result for MIND_I. What is more, we empirically found that MIND_MP, MIND_PC and ALOST also gave the best registration result with $R=0$. One should notice that our registration method is not particularly designed for registration of the complete
Table 3.1 Average root mean squared error (RMSE) of the estimated deformation field prior to (Initially) and after registration using NMI, MIND_I, MIND_MP, MIND_PC and ALOST on synthetic abdominal MR images. The number printed in bold face is the minimum (best result). The standard derivation of the RMSE is given between brackets.

<table>
<thead>
<tr>
<th></th>
<th>Initially</th>
<th>NMI</th>
<th>MIND_I</th>
<th>MIND_MP</th>
<th>MIND_PC</th>
<th>ALOST</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRMSE</td>
<td>3.43 (0.29)</td>
<td>4.61 (1.02)</td>
<td>1.97 (0.27)</td>
<td>1.83 (0.30)</td>
<td>1.85 (0.24)</td>
<td><strong>1.73 (0.24)</strong></td>
</tr>
</tbody>
</table>

Table 3.2 Mean target registration error (MTRE) of 300 landmarks prior to registration (i.e. initially), and after registration using NMI, MIND_I, MIND_MP, MIND_PC and ALOST on 10 datasets made available by DIR-LAB. The number printed in bold face is the minimum (best result).

<table>
<thead>
<tr>
<th></th>
<th>Initially</th>
<th>NMI</th>
<th>MIND_I</th>
<th>MIND_MP</th>
<th>MIND_PC</th>
<th>ALOST</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTRE</td>
<td>8.46 (3.33)</td>
<td>2.90 (1.55)</td>
<td>2.00 (0.96)</td>
<td>2.26 (1.10)</td>
<td>2.46 (1.51)</td>
<td><strong>1.89 (0.89)</strong></td>
</tr>
</tbody>
</table>
Chapter 3. Image registration based on autocorrelation of local structure

For instance, we do not consider the sliding motion to the side of the lungs as [32] does. However, the annotations are more in the central part of the lungs, which our method should be able to register accurately.

Notice that NMI gave the worst registration results compared to the other methods. In this dataset, the gas density changes due to compression introduce contrast changes between tissue and air [31]. NMI is not suited to deal with this problem as was previously noticed in [11]. Furthermore, we found that MIND_PC gave the second worst result among the five methods. Again this is because important features such as the tubes of the airways are only a few pixels wide. Consequently, the phase congruency was low on these details. Since the aforementioned tubes are invisible on the larger scales, the phase is uncorrelated across scales. Consequently, the registration in MIND_PC will be dominated by the larger structures and yield an ambiguous outcome on details. Finally, a two-sided signed rank test was applied to the MTRE showing that ALOST had a significantly better outcome for all but cases 1, 7 and 10 (p<0.05). Additionally, ALOST gave the smallest mean MTRE (p < 0.05). It shows that ALOST is better in emphasizing small structures (specifically the air tubes), which leads to a better registration performance.

3.3.3 Registration of abdominal MR images

Ileocolonoscopy is considered the reference standard for the assessment of Crohn’s Disease (CD). The disease activity is expressed in the Crohn’s Disease Endoscopic Index of Severity, CDEIS [33]. This invasive procedure is considered very burdensome by many patients. Therefore, abdominal MR Imaging is studied for diagnosing and grading CD. Rimola et al [34] reported that the radiologic parameters to be evaluated include colon wall signal intensity, and relative enhancement after contrast injection. The time intensity curves (TICs) obtained from dynamic contrast enhanced MRI (DCE-MRI) were also shown to contain important information on the inflammation of the bowel wall.

The quality of registration between the DCE-MRI and the structural post-contrast MRI data by each of the five methods (NMI, MIND_I, MIND_MP, MIND_PC, ALOST) was evaluated by: 1. calculating the average dice coefficient (DC) between ROIs from DCE-MRI and post-contrast MRI; 2. measuring the correlation between the measured image features after registration and the CDEIS score. We did so because it is not feasible to reliably identify landmarks in these data.
Chapter 3. Image registration based on autocorrelation of local structure

The abdominal MRI data employed in this paper were taken from a prior study into luminal Crohn's disease [35], which has been approved by the medical ethics committee. 30 out of 33 patients from the prior study gave written consent to use their data for future investigations. MR imaging included a free breathing 3D+time DCE series and a high-resolution post-contrast scan. Both were acquired by 3D T1-weighted spoiled gradient echo sequences performed in coronal planes. The DCE volumes contained 224 × 224× 14 voxels with a size of 1.78 × 1.78 × 2.5mm³. In 6.1 minutes, 450 of such volumes were acquired at a rate of 0.8 second/volume. A contrast agent was injected after the 10th image volume was acquired. The image size of the post-contrast scans was 400 × 400× 100 voxels with a resolution of 1 × 1× 2 mm³ and was acquired in a breath-hold. All patients underwent ileocolonoscopy within one month after the MRI scan was acquired. During ileocolonoscopy the CDEIS per bowel segment was scored [35].

Figure 3.5 shows the image processing pipeline. The DCE-MRI volumes were first registered to themselves to achieve correspondence over time [36] [37]. Therefore, an expiration template was created by a weighted average of expiration-phase volumes tentatively sampled from the whole series of DCE-MRI images. Then, the DCE-MRI volumes were retrospectively gated and registered to the template (see [37] for more information). After these steps, approximately 100 out of the 450 volumes remained.

Based on a routine radiological report, an expert annotated all ROIs (polygons around the areas affected by Crohn’s disease) on the post-contrast MRI. Additionally, the affected bowel segment was identified: rectum (RT), left colon, i.e. sigmoid plus colon descendens (LC), transverse colon (TC), right colon, i.e. cecum plus colon ascendens (RC), and terminal ileum (TI).

Time intensity curves (TIC’s) of the signal on the registered DCE series in the annotated ROIs (transferred from the post-contrast MRI after registration) contain information about the inflammation activity [36] [38]. Therefore, five methods were used to register the DCE expiration template to the post-contrast scan. Subsequently, the estimated transformation was applied to the entire gated and
Figure 3.5. Image processing pipeline for the registration of the DCE series to the post-contrast abdominal image. From left to right column: DCE-MRI gating and registration, DCE-MRI to post-contrast MRI registration, and extraction of DCE-MRI features (TIC, RCE) from thresholded sub-region within the annotated ROI.
Chapter 3. Image registration based on autocorrelation of local structure

registered DCE series (Figure 3.5, right column). Thereafter, the average signal over the ROI in each image from the DCE series might be determined. However, we noticed that the ROIs sometimes covered both bowel wall and lumen due to small registration errors. Since the bowel lumen has a low intensity compared to the bowel wall, the mean signal within the ROI was determined of only those pixels that exceeded a threshold. This threshold was determined automatically by means of the isodata thresholding algorithm [39]. Next we derived TICs from this ROI and fitted a bi-exponential model:

\[ S(t) = A_1 \exp(-\lambda_1 t) + A_2 \exp(-\lambda_2 t) \]  

(3.26)

The parameters are sorted such that \( A_1 \) reflects the strong upward slope (uptake of contrast) of the TIC and \( A_2 \) the slow downward slope (wash out of contrast). We choose parameter \( A_1 \) as an alternative to the relative contrast enhancement (RCE) between pre-contrast and post-contrast MRI which has been shown to be correlated to the disease severity [34].

A visual example of DCE to post-contrast image registration

The DCE-MRI and post-contrast MRI data differ both in resolution and in slab thickness (35 mm and 200 mm, respectively). Therefore, we first down-sampled the post-contrast MRI to \( 224 \times 224 \times 80 \) voxels to get a similar voxel size as the DCE scans. We empirically found that the registration needed to be initialized close to the global optimum to avoid getting trapped in a local minimum. These local minima arise especially due to the large difference in slab thickness. To avoid this, we first rigidly registered the DCE-MRI expiration template to the post-contrast space using mutual information as the registration metric. After this initialization step, we applied NMI method and our four descriptors to register the (moving) expiration template to the (fixed) post-contrast image. A representative example is shown in Figure 3.6. Observe that there are both large intensity differences and large spatial deformations between DCE-MRI and the post-contrast MRI.

Figure 3.6 (a) shows segmented ROI affected by Crohn’s disease in red as well as a healthy region in green. In Figure 3.6 (b)-(f) show the annotations after registration by respectively NMI, MIND_I, MIND_MP, MIND_PC and ALOST. NMI (Figure 3.6 (b)) and MIND_I (Figure 3.6 (c)) support only partial registration of the bowel boundary compared to MIND_MP and MIND_PC (Figure 3.6 (d) and (e)), pointed to by the arrow in the bottom-right corner. The
size of the arrow represents the amount of misregistration. MIND_I fails to properly register this region as it is hampered by large intensity fluctuations and a large spatial deformation of the bowel. While MIND_MP and MIND_PC improve here, their registration outcomes remain unsatisfactorily in the bottom left area of the image. We attribute this to indistinctiveness of features in soft tissue (MIND_MP) and the presence of details (MIND_PC). Notice that the ALOST result (Figure 3.6 (f)) demonstrates a clear improvement compared to all other methods. Moreover, only ALOST gave good registration on both the healthy region (green) and the diseased region (red). NMI (Figure 3.6 (b)) and MIND_I (Figure 3.6 (c)) support only partial registration of the bowel boundary compared to MIND_MP and MIND_PC (Figure 3.6 (d) and (e)), pointed to by the arrow in the bottom-right corner. The size of the arrow represents the amount of misregistration. MIND_I fails to properly register this region as it is hampered by large intensity fluctuations and a large spatial deformation of the bowel. While MIND_MP and MIND_PC improve here, their registration outcomes remain unsatisfactorily in the bottom left area of the image. We attribute this to indistinctiveness of features in soft tissue (MIND_MP) and the presence of details (MIND_PC). Notice that the ALOST result (Figure 3.6 (f)) demonstrates a clear improvement compared to all other methods. Moreover, only ALOST gave good registration on both the healthy region (green) and the diseased region (red).

Evaluating registration accuracy by Dice coefficient

It was found during colonoscopy that 6 out of 30 patients did not show signs of disease activity. In the remaining 24 patients 38 segments were identified showing marked disease activity: 16 TI, 9 RC, 3 TC, 5 LC, and 5 RT segments were given positive CDEIS scores. Only 17 out of the 38 segments were contained in the DCE-MRI scan and corresponded to the annotations in the post-contrast image: 14 TI, 2 TC, 1 LC segments. This reduction of segments resulted from (1) the limited slab size of the DCE scan, so that some diseased segments were not imaged; (2) differences in interpretation of the MR and colonoscopy images:
Figure 3.6. An abdominal MR image showing a large bowel deformation in a post-contrast MR image (fixed image); DCE-MR image (moving image); (a) ROI in a sub-region of the post-contrast MR image (the red region is affected by Crohn’s disease, the green region is healthy bowl wall); (b-f) same ROIs copied to the registration based on NMI (b), MIND_I (c), MIND_MP (d), MIND_PC (e), and ALOST (f). The yellow arrows point to a misregistration area in which the size of the arrow represents the amount of misregistration.
segments were identified to harbor Crohn’s disease on one modality but not on the other, and vice versa.

We used two approaches to determine the ROIs from which TICs were generated: (1) ROI-dce: after duplicating the manual annotation to the DCE scans, we applied isodata thresholding to the annotated region for each DCE scan separately; (2) ROI-post: after applying isodata thresholding to the annotated region in the post-contrast image, we map the segmented region onto all DCE scans.

The search region $R$ was first tuned to make sure that an optimal registration result was obtained for each method (as above). Therefore, we calculated the average dice coefficient (DC) between the ROI’s-dce in the gated and registered DCE series and the ROI’s-post for eight randomly chosen segments. We consider this a measure of the registration accuracy since a higher DC reflects a more similar ROI. The outcome is shown in Figure 3.7, demonstrating that $R=3$ is the optimal search region for all methods. Observe that the ALOST method gave the largest average DC of all methods for almost each setting. Accordingly, we used $R=3$ for the methods on all 17 segments and calculated the average DC just as on the ‘tuning’ set. The outcome of this experiment is shown in Figure 3.8. A two-sided signed rank test was applied to the average DC showing that ALOST had a significantly better outcome than NMI and MIND_I (p<0.05).
ALOST also outperforms the other methods, but these differences are not significant. (p<0.05).

**TICs from DCE- to post-contrast image registration**

Figure 3.9 shows the time intensity curves from the diseased (a) and healthy (b) regions from Figure 3.6, before and after registration by the five methods. The TIC extracted from the diseased region after ALOST based registration gave the largest intensity change at the arrival of the contrast medium (Figure 3.9 (a)). The TICs extracted from the healthy region gave a similar but lower transition. Since there is only little variation in the intensity of soft tissues in this region, a misregistration is not punished (Figure 3.9 (b)). Figure 3.9 (f) showed that the diseased bowel wall is nicely covered by the ROI after ALOST based registration. This is in contrast with the other approaches (c.f. Figure 3.9 (b)-(e)). Such a misregistration clearly affects the curves extracted from the diseased region. At the same time, there is an overlap of voxels between the ROIs after applying the different registrations. As a result, the fluctuations on the curves are highly correlated.

**Correlating a contrast feature from DCE-MRI to CDEIS**
Ultimately, it is our objective to predict the CDEIS from abdominal MRI data. The relative contrast enhancement, here represented by the $A_1$ parameter (see above), is considered an important parameter to do so [34]. Accordingly, we correlated $A_1$ to CDEIS as the final means to evaluate the NMI method and four descriptors. Since we introduced two types of ROI (ROI-dce and ROI-post), TICs were generated for both. Notice that in the former approach there is enhanced adaptation to local misregistration and/or intensity fluctuation by means of thresholding each DCE scan. The $A_1$ parameters were derived from both types of TICs separately. Table 3.3 shows the correlation coefficients (CC) from the five metrics generated as such. CC-dce represents the CC generated from ROI-dce and CC-post represents the CC generated from ROI-post.

Clearly, the ALOST metric combined with the CC-dce TIC generation gave the best correlation ($p < 0.05$). Unsurprisingly, all CC-dce based correlations are slightly higher than those based on CC-post since the former suffers less from misregistration. The number 0.56 is a representative correlation value for a single feature as we used here. A similar correlation value can be found in [37]. It is well-known that for assessing Crohn’s disease in MRI, more features should be measured such as the bowel wall thickness and the diseased segment length [34]. Similarly, colonoscopy scores are also based on multiple features. In future work, we aim to generate a new MRI score, which is based on multiple features.
Chapter 3. Image registration based on autocorrelation of local structure

3.4 Conclusion

We developed a new descriptor called ALOST, which exploits the autocorrelation of the local image structure. The local structure is represented by a measure of the mean phase and the standard deviation (phase congruency) thereof. Both are derived from the monogenic signal representation. The ALOST descriptor has two important properties: (1) it is insensitive to intensity distortions; (2) it emphasizes ‘salient’ features in the image. These two properties make that image registration based on this descriptor improves compared to registration involving other measures. This is particularly the case with data hampered by strong spatially varying intensity distortions and large spatial deformations.

We quantitatively compared the performance of a NMI-based method and four different descriptors on three different datasets. For the *synthetic abdominal MR images* (1) we calculated the average root mean square error (RMSE) of the displacement field on 80 image pairs after registration. The ALOST method gave the lowest average RMSE. From the *thoracic CT images* (2) we calculated the mean target registration error (MTRE) of 300 annotated landmarks on 10 datasets after registration. The ALOST method gave the smallest mean MTRE compared to the other descriptors. In the *abdominal MR images of patients with Crohn’s disease* (3) we correlated an image feature representing the enhancement after contrast injection to an endoscopic measure of disease severity (CDEIS). It turned out that the registration by the ALOST method gave
Chapter 3. Image registration based on autocorrelation of local structure

the highest correlation with CDEIS (r=0.56, p<0.05). In all these experiments, ALOST outperformed the other methods. It shows that ALOST is a reliable technique especially to register data with space-variant intensity distortions. We expect that the method is also applicable to other images, such as retinal OCT images that suffer from luminance and contrast variations [28].

There are several limitations of our work. Our registration is based on a continuous optimization strategy. However, combining discrete optimization with a continuous one may give better registration by avoiding local minima [40]. Incorporating discrete optimization as proposed in [32] could also speed up the registration procedure. This will be required for clinical application. Sliding motion might also be a limitation for abdominal image registration, although we did not observe it in our images. If present, a potential solution might be to incorporate an explicit segmentation into our registration framework as in [40]. However, this would require accurate segmentation of the bowel, which is far from trivial. For instance, initial results by our group were reported in [36]. Another limitation of our work is in assessing the registration result of the abdominal MR data. The annotations of post-contrast MRI were drawn by only one expert. This might bias the results. Therefore, in future work, we are planning to include annotations from a second expert.

References


76


Chapter 3. Image registration based on autocorrelation of local structure


4 A hybrid optimization strategy for registering images with large local deformations and intensity variations

Large local deformations and large intensity variations hamper registration of diseased bowel segments in pre- and post-contrast abdominal MR images. Since multi-resolution strategies fail on thin bowel wall structures, a hybrid method consisting of two coupled techniques is proposed: 1) Descriptor Matching (DM) using a discrete optimization strategy to avoid getting trapped in a local minimum; 2) continuous optimization to refine the registration outcome based on Autocorrelation of LOcal image STructure (ALOST). Our method – called DM-ALOST – is made insensitive to the local uptake of contrast agent by exploiting the mean phase and the phase congruency extracted from the multi-scale monogenic signal. The method was extensively tested on abdominal MR data of 30 patients with Crohn’s disease. DM-ALOST produced significantly higher mean Dice coefficients than two state-of-the-art methods (p<0.05). The relative contrast enhancement (RCE) measured using DM-ALOST showed comparable correlation to the Crohn’s Disease Endoscopic Index of Severity as the manual measures by four human observers. Both qualitative and quantitative tests demonstrated improved registration using the proposed method compared to the state-of-the-art. It facilitates measurement of corresponding features from different abdominal MR images, which can aid in assessment of certain diseases, particularly Crohn’s Disease.


Chapter 4. A hybrid optimization strategy for registering images with large local deformations and intensity variations

4.1 Introduction

Image registration has been a key topic in the medical imaging community over the past decades. However, there are still many registration problems that remain challenging. We encountered such a challenge upon registering three-dimensional pre- to post-contrast abdominal images acquired by magnetic resonance imaging (MRI) for quantifying Crohn’s disease activity [1]. This registration is far from trivial as peristalsis of the bowel may cause large local deformations, which makes that the registration algorithm gets trapped in a local minimum [2]. Furthermore, the diseased regions of interest are composed of relatively thin bowel structures, which are easily mismatched. Moreover, there can also be large local intensity variations, a.o. due to space-varying contrast uptake and the MRI bias field.

A coarse to fine (or multi-resolution) registration strategy is often used [3] to solve the large local deformation problem and avoid local minima as much as possible. This coarse to fine fashion can be combined with discrete optimization approaches, such as graph cuts [4] and linear programming [5]. Essentially, discrete optimization involves a reduction of the search space to a limited, discrete number of potential solutions. Discrete optimization is typically less sensitive to the initial conditions [5] and suitable to deal with large deformations [2]. Large deformations can be accurately found provided that there is a sufficiently large search space, represented by a large number of so-called labels. These labels are the potential displacements of control points (e.g. the nodes of a b-spline transformation). However, due to the limited solution space with discrete optimization, one may not obtain a precise registration result.

Alternatively, continuous optimization typically produces more precise solutions than discrete approaches. However, continuous optimization is sensitive to the initial conditions and gets more easily trapped in a local minimum. A hybrid optimization strategy was recently proposed to combine the best of both worlds [6]. As such the discrete optimization strategy initially yields a coarse solution to cope with the largest deformations after which continuous optimization locally improves the result in a refined search space. The authors reported improved registration over state-of-the-art methods, which used either a discrete or a continuous optimization strategy [5] [7].

It can be foreseen that the aforementioned multi-resolution strategy removes fine structures (e.g. the bowel wall) from the image at coarse resolutions.
Chapter 4. A hybrid optimization strategy for registering images with large local deformations and intensity variations

Consequently, such a multi-resolution approach is ineffective for this task. Furthermore, local deformation due to peristalsis is in essence different from the global motion of the larger structures due to breathing. As large local deformations are not correctly estimated at a coarse scale, an ambiguous registration result will occur locally. Thus, registration based on the highest resolution is preferred without any restriction of the search space. The large displacement optical flow (LDOF) method [8] integrates rich descriptors such as the scale-invariant feature transform (SIFT) and the histograms of oriented gradients (HOG) into variational optic flow to solve the large deformation problem. SIFT and HOG are particularly useful for this approach, because they are unique enough for global matching without needing regularity constraints. The descriptor matching part applied to the original image resolution. Consequently, as there is no blurring, there is no removal of fine structures. Subsequently, continuous optimization is applied to refine the solution of descriptor matching to sub-pixel accuracy. To use descriptor matching with continuous optimization for our problem, we need an image representation and an energy function that are both not sensitive to local intensity variations.

Previously, well-known rich descriptors such as SIFT [9], SURF [10] and HOG [11] were studied for representing image structure. However, none of these can fully handle intensity and contrast variations. Alternatively, images may be transformed into a representation that is insensitive to these signal variations. An example of such a representation for multi-dimensional signals is the monogenic signal [12]. Thus, a rich descriptor could be calculated on the monogenic signal representation of these images.

Likewise, there are many energy functions for image registration that tackle the intensity inhomogeneity problem. For example, mutual information (MI) [13] [14] is one of the most widely used energy functions. However, originally being a global objective function, it lacks local, i.e. spatial, information on the local structure and cannot cope with large space-variant signal and contrast differences. Although several methods introduce local information into a global objective function [15] [16], it has been noticed [17] that finding an accurate correspondence remains difficult, especially due to the many local minima that generally accompany most non-rigid deformation models.

Recently, a method employing a local modality independent neighborhood descriptor (MIND) was proposed [17]. MIND embeds the local structure in a vector representation for each voxel. This descriptor essentially comprises the
local autocorrelation function as feature vector. The Sum of Squared Differences (SSD) was used as energy function, which was optimized by means of the Gauss-Newton approach. MIND was reported to be a “distinctive” descriptor, which was claimed to be important for registering images with many degrees of freedom [17]. However, without preprocessing by – for instance – a band-pass filter, MIND does not fully suppress intensity fluctuations such as the one caused by the MRI’s bias field. Therefore, we already proposed to embed the mean phase and a measure for phase congruency – calculated from the monogenic signal – in a registration framework based on the MIND principle because these features are invariant to large intensity inhomogeneities and are highly distinctive [18] (also described in chapter 3). However, we found that this method remains sensitive to large local deformations of an image.

Alternatively, several papers have explored joint segmentation and registration approaches. Such registration is driven by the segmented region of interest, which is implicitly refined as the registration proceeds. Examples can be found in [19] [20] [21] [22]. Essentially, the segmented region is used in all these methods to avoid getting stuck in a local minimum, but this is not guaranteed in the presence of large deformations.

In this paper, we present a hybrid registration method to facilitate the spatial alignment of pre- to post-contrast abdominal MR images. The novelty is in combining discrete optimization with a powerful data representation derived from the monogenic signal. The discrete optimization strategy is based on rich descriptors matching. The descriptor matching is used to estimate large local deformations and avoid getting trapped in a local minimum. Furthermore, the data representation exploits the phase of the monogenic signal, which gives the required invariance to large intensity distortions due to the local uptake of contrast agent and the MR scanner’s bias field. A continuous optimization approach, coupled to the discrete optimization, is used for refining the registration.

### 4.2 Methods

Image registration can be treated as an optimization problem [23]. The energy function to be optimized typically consists of two parts, namely a data term and a regularization term:

$$E(w) = E_{data}(w) + \alpha E_{regularize}(w), \quad (4.1)$$
where \( \mathbf{w} = [u,v,w] \) is the deformation field for each pixel in a 3D image and \( \alpha \) a constant which balances the two terms. A common data term is:

\[
E_{\text{data}}(\mathbf{w}) = \int_\Omega \left| I_m(x + \mathbf{w}(x)) - I_f(x) \right|^2 dx,
\]

in which \( I_m \) and \( I_f \) are the moving image and the fixed image, respectively. The assumption underlying this data term is that corresponding points have the same expected intensity, albeit corrupted by additive Gaussian noise. Unfortunately, this is not the case for our abdominal imaging problem and therefore we will introduce an intensity invariant data term: \( E_{\text{data}}(\mathbf{w}) = E_{\text{ALOST}}(\mathbf{w}) \) [18].

The regularization term allows incorporation of prior knowledge and soft constraints to solve the ill-posedness of image registration. We choose to penalize the total variation of the deformation, as defined by:

\[
E_{\text{regularize}}(\mathbf{w}) = \int_\Omega \left| \nabla u(x) \right|^2 + \left| \nabla v(x) \right|^2 + \left| \nabla w(x) \right|^2 dx.
\]

The large deformations that are prevalent in abdominal images make that a conventional optimization of (4.1) easily gets trapped in a local minimum. Therefore, we emphasize our region of interest during registration and introduce a discrete optimization strategy. First, we add to (4.1) an energy term \( E_{\text{region}}(\mathbf{w}) \) based on the likelihood that a voxel contains bowel wall to emphasize potential regions containing disease activity. Secondly, we initially perform discrete optimization, which is driven by a separate energy function \( E_{\text{descriptor}}(\mathbf{w}_2) \). To facilitate a smooth interaction between two energy functions, we add a coupling term \( E_{\text{coupling}}(\mathbf{w},\mathbf{w}_1) \) to (4.1).

In the proposed hybrid registration framework, we first find a solution to the descriptor matching term through discrete optimization: \( \mathbf{w}_1 = \arg \min_{\mathbf{w}_2} \{ E_{\text{descriptor}}(\mathbf{w}_2) \} \). Herewith, we aim to estimate the largest deformations in the presence of intensity distortions without sacrificing image resolution. Subsequently, \( \mathbf{w}_1 \) is used to initialize the minimization of the following energy function by means of a continuous optimization approach:

\[
E(\mathbf{w}) = E_{\text{ALOST}}(\mathbf{w}) + \alpha E_{\text{regularize}}(\mathbf{w}) + \beta E_{\text{region}}(\mathbf{w}) + \gamma E_{\text{coupling}}(\mathbf{w},\mathbf{w}_1),
\]
Chapter 4. A hybrid optimization strategy for registering images with large local deformations and intensity variations

in which \( \beta \) and \( \gamma \) are parameters to balance the new terms in the energy function. While searching for the deformation parameters \( \mathbf{w} \) that minimize (4.4), \( \mathbf{w}_i \) remains fixed.

The remainder of the method section is structured as follows. First, we introduce some basic theory of the monogenic signal (4.2.1) on which we will build both parts of the hybrid method. Subsequently, we will define the involved energy terms: the data term (4.2.2), the bowel region term (4.2.3), the descriptor matching and coupling terms (4.2.4). Finally, we will describe our optimization procedure (4.2.5).

### 4.2.1 Preliminaries

The analytic representation of a signal is based on the concept that negative frequency components of a 1-D, real-valued signal are essentially superfluous due to the Hermitian symmetry of its Fourier spectrum. The monogenic signal extends the analytic representation from 1-D to N-D by means of the Riesz transform [24] [25].

A crucial feature that can be derived from the monogenic signal is the local phase, \( \phi(x) \). We calculate the local phase using a log-Gabor filter as suggested by [26], because it is a zero DC filter with a tunable bandwidth, c.q. scale. Specifically, we compute the local phase \( \phi_i(x) \) at four scales, c.f. [27]. The mean phase, i.e. the average angle over all scales \( \bar{\phi}(x) \), serves as an identifier for the type of image feature. For example, a step corresponds to \( \phi = 0 \) and a peak to \( \phi = \frac{1}{2}\pi \). Furthermore, it has been recognized that salient features are perceived at points in an image where the Fourier components are in phase [28]. A measure for phase congruency (PC) was developed by Kovesi [29]: if all scale components are in phase, then this measure returns one; alternatively, if there is no coherence of phase, the phase congruency becomes zero. Essentially, the mean phase and the phase congruency provide measures that are independent of the signal’s amplitude, making them invariant to trends in the signal and variations in contrast.

A representative example is shown in Figure 4.1. Figure 4.1(a) is the original image and Figure 4.1(b) is the same image with a synthetic intensity distortion. This intensity distortion merely concerned the addition of a Gaussian intensity profile centered at a randomly selected point, just as in [30]. Figure 4.1(e) and
Figure 4.1(f) are the mean phase images calculated from Figure 4.1(a) and Figure 4.1(b), respectively. We also plot profiles along a line segment suffering from a large local intensity variation in Figure 4.1(c) and Figure 4.1(g). In Figure 4.1(c), the profiles from the original and distorted images clearly deviate because of the intensity distortion. In contrast, this is not the case in Figure 4.1(g). It illustrates that the mean phase image is insensitive to local intensity changes.

### 4.2.2 Definition of the data term

Our data term $E_{ALOST}(w)$ exploits the Autocorrelation of Local STructural information. It was inspired by the MIND concept [17], which is based on the local sum of squared differences (SSD) between two patches $P$ of image $I$:

$$D_p(I,x_1,x_2) = \sum_{p \in P} (I(x_1+p) - I(x_2+p))^2$$

$$= \sum_{p \in P} I^2(x_1+p) - 2\sum_{p \in P} I(x_1+p)I(x_2+p) + \sum_{p \in P} I^2(x_2+p)$$

where $x_1$ and $x_2$ are the centers of the two image patches $P$ of size $D \times D$. Notice that expanding the square of (4.5) reveals the inner product between the two patches, which can also be interpreted as a windowed (hence local) autocorrelation as a function of the difference $x_1 - x_2$. The local SSD’s are incorporated in a feature vector defined by:
Figure 4.1 (a) An abdominal MR image and (b) the same image deformed by a simulated local intensity distortion; (e,f) mean phase images computed from (a,b); (c) intensity profiles along the red dashed lines in (a) and (b), in red and blue respectively; (g) intensity profiles along the red dashed lines in (d) and (e), in red and blue respectively; (d) descriptor matching correspondences using HOG-I and (h) using HOG-MP between (a) (red circles) and (b) green crosses on small region in the middle left of the image.
Chapter 4. A hybrid optimization strategy for registering images with large local deformations and intensity variations

\[
F(I, x, r) = \frac{1}{n} \exp \left( -\frac{D_p(I, x, x + r)}{V(I, x)} \right),
\]

with \( r \) an offset in a predefined neighborhood \( \mathbf{R} \) of size \( R \times R \) around position \( x \), \( n \) a normalization constant (chosen such that the maximum value of the MIND feature \( F \) at position \( x \) is one) and \( V(I, x) \) represents the average SSD in a small neighborhood \( N \) around \( x \):

\[
V(I, x) = \frac{1}{\text{size}(N)} \sum_{n \in N} D_p(I, x, x + n)
\]

In words, the feature vector consists of a 1-D vector of length \( R \times R \), which represents all correlations between a neighborhood \( P \) centered at a voxel \( (x) \) and a neighborhood \( P \) centered around a voxel \( (x + r) \).

We employ the mean phase image \( I_{MP} \) and the phase congruency image \( I_{PC} \) for image \( I \) in (4.5) - (4.7) since these are both insensitive to local contrast changes. Furthermore, we concatenate the feature vectors for \( I_{MP} \) and \( I_{PC} \) to form the ALOST representation:

\[
\text{ALOST}(I, x, r) = \left[ F(I_{MP}, x, r), F(I_{PC}, x, r) \right]
\]

The ALOST representation has two important properties: (1) it is insensitive to intensity distortions; (2) it emphasizes ‘salient’ features (e.g. edges) in the image. These two properties make that image registration based on this concept improves compared to registration involving the intensity, as we will demonstrate below. This is particularly the case for data hampered by strong local variations in intensity. For the sake of simplicity, we use in the remaining text the notation \( \text{ALOST}_f(x) \) and \( \text{ALOST}_m(x) \) to represent ALOST feature vectors calculated from the fixed image and the moving image respectively. As such, the energy term \( E_{\text{ALOST}}(w) \) in (4.4) is defined as:

\[
E_{\text{ALOST}}(w) = \int_{\Omega} \left| \text{ALOST}_m(x + w(x)) - \text{ALOST}_f(x) \right|^2 \, dx.
\]

4.2.3 Definition of the bowel region term

Eventually, the focus of our work is on the assessment of disease severity of patients with Crohn’s disease. Therefore, it is important that especially the diseased parts of the bowel are correctly registered. Previously, we developed a
method to automatically segment the diseased bowel wall from post-contrast MR images [31]. It consists of two major steps: 1. Defining a volume of interest (VOI). The abdominal MR volume is firstly oversegmented using a global supervoxel segmentation approach. Then, a Random Forrest (RF) classifier identifies the supervoxels encompassing the diseased tissues based on intensity, texture and curvature features. This yields an approximate volume of interest. 2. Segmenting diseased bowel wall in the VOI. Tissue probability maps are generated using a second set of RF classifiers, again based on intensity, texture, curvature, and context features. These maps convey the probabilities that a voxel within the VOI contains diseased, normal or background tissue. Subsequently, the probability values are at the basis of a graph cut segmentation. The method achieved a high accuracy with Dice coefficient values of $0.90 \pm 0.04$ and a Hausdorff distance of $7.3 \pm 0.8$ mm with respect to reference segmentations.

Unfortunately, the pre-contrast image has a very low SNR and contrast making that automatic segmentation of the diseased tissue from the pre-contrast image is impossible. Therefore, the joint segmentation and registration as in [22] is not applicable to our task. Still, the segmentation from the post-contrast MR image may locally enhance the registration accuracy by introducing the next, regional energy term:

$$E_{\text{region}}(w) = \int_{\Omega} \left| \text{DR}_f(x) \right| ALOST_m(x + w(x)) - ALOST_f(x) |^2 dx \quad (4.10)$$

in which $ALOST_m$ and $ALOST_f$ are the intensity invariant feature vectors described in 4.2.2. $\text{DR}_f(x)$ returns a probability expressing the certainty that a region is diseased in the fixed, i.e. post-contrast MR image. Therefore, registration of the diseased region is given priority depending on the value of the associated weight factor in (4.4).

**4.2.4 Definition of the descriptor matching and coupling terms**

The registration procedure is made robust against getting stuck in a local minimum through descriptor matching in a discrete optimization scheme. To accomplish this, we densely calculate descriptors over both the fixed and moving images without down-sampling to preserve the thin bowel structures. In [8], the histograms of oriented gradients (HOG) descriptor proved to be the ‘richest’ descriptor amongst others. We largely follow this idea in using HOG. It takes two steps to calculate the HOG: (step 1) compute the HOG in $N_n \times N_n$ neighborhoods (this step is often referred to as building cells) at positions that
are $N_n/2$ voxels apart; each histogram comprises $N_o$ orientations; (step 2) concatenate the histograms of each voxel with its 8 neighbors at distances of $N_n/2$ voxels (this step is usually referred to as building blocks). As such, the HOG descriptor is derived for each voxel and consists of $N_o \times 9$ entries. Inspired by [32], we determine the true 3D HOG instead of the more conventional, ‘collated’ 2D HOG. Therefore, we first calculate 3D gradients $[G_x, G_y, G_z]$ using a coarse 1-D central difference operator in all three dimensions. Then, these 3D gradients are quantized based on a regular polyhedron with $N_o=10$ orientations (i.e. a icosahedron) to limit the computation time. Furthermore, a Gaussian filter with $\sigma=0.8\text{mm}$ is applied to smooth along the polyhedron to reduce quantization effects. The final 3D HOG descriptor for each voxel consists of 10x7 entries (10 orientations times 7 cells, the cell of the current voxel plus cells from its 6 cardinal neighbors in 3D space). We empirically set $N_n=9$ voxels.

Notice that the discrete optimization aims to simplify the registration problem such that the continuous optimization will converge to the global minimum. Therefore, a highly accurate calculation is not required. At the same time, we found that the HOG was sensitive to large local intensity variations (see 4.3). Accordingly, we propose to calculate HOG on the mean phase image ($\bar{\phi}(x)$), which describes the type of local structure. Consequently, the descriptor matching term is defined as:

$$E_{\text{descriptor}}(w_2) = \sum_i |\text{HOG-MP}_m(x_i + w_2(x_i)) - \text{HOG-MP}_f(x_i)|^2,$$  \hspace{1cm} (4.11)

where $\text{HOG-MP}_m$ and $\text{HOG-MP}_f$ denote the HOG descriptors of the mean phase images derived from the moving image and the fixed image, respectively; the summation is over all positions $x_i$ in the fixed image where a HOG descriptor was calculated; $x_j = x_i + w_2(x_i)$ is a position in the moving image with such a descriptor. We couple the discrete optimization functional to the continuous one by adding a coupling term to latter

$$E_{\text{coupling}}(w, w_1) = \int_{\Omega} \rho(x) |w_1(x) - w(x)|^2 dx.$$  \hspace{1cm} (4.12)
4.2.5 Optimization procedure

One can see from (4.11) that the descriptor matching term $E_{\text{descriptor}}(w_2)$ is independent from $w$. Descriptor matching guarantees global optimization by an exhaustive search of the deformation space. Essentially, its complexity is $O(kl)$, where $k$ and $l$ are the number of descriptors in the fixed image $I_f$ and moving image $I_m$, respectively. Such an exhaustive search is time consuming, especially as we use densely sampled 3D HOG. Therefore, we efficiently perform the optimization, using the approximate nearest neighbor (ANN) search method [33]. Typically, this ANN method allows reducing the complexity without losing too much accuracy.

A continuous optimization strategy is subsequently used for refining the deformation field, after descriptor matching, by minimizing (4.4). We apply the Gauss-Newton optimization method in order to do so. Gauss-Newton achieves quadratic convergence without calculating the second derivative of the energy function with respect to $w$. We use a multi-resolution registration procedure in order to speed up the convergence (with down-sampling factors of 4, 2 and 1 (the original resolution). The “initialization” through $w_i$ is softly favored through $E_{\text{coupling}}(w, w_1)$ (see 4.2.3), but we reduce the “influence” of $w_i$ when estimating $w$ at finer resolutions. Different from [8], the weighting parameter of $\gamma$ is not fixed but decreasing with increasing iteration number of the registration procedure: $\gamma(k) = \gamma_0 / k$, where $\gamma_0$ is the initial value (to be discussed in 4.3.3) and $k$ the iteration number.

4.3 Results

The proposed hybrid registration method will be compared against two state-of-the-art registration techniques: the Deformable Registration via Attribute Matching and Mutual-Saliency weighting (DRAMMS), [34] and the Modality Independent Neighborhood Descriptor (MIND) [17]. Both methods are based on neighborhood structure descriptors. In total, five different registration methods will be involved in the comparisons. These will referred to as DRAMMS, MIND, DM-MIND (descriptor matching plus MIND), ALOST [18] and DM-ALOST (descriptor matching plus ALOST, the hybrid method currently proposed).

4.3.1 Comparison of descriptor matching on intensity and mean phase

Figure 4.1 (d) visualizes the descriptor matching results using HOG on the intensity images, HOG-I, and Figure 4.1 (h) pictures the descriptor matching
results using HOG on the mean phase images, HOG-MP, between the same regions (middle left side) in Figure 4.1 (a) and Figure 4.1 (b). Note that Figure 4.1 (b) was generated by adding only a Gaussian-shaped intensity offset to Figure 4.1 (a). Red circles indicate the positions around which the descriptors were calculated in Figure 4.1 (a) and green crosses indicate positions in Figure 4.1 (b). Observe that for each position from one image all the points in the other image were scanned to find the optimal descriptor match. Only those links are shown that have a symmetric correspondence, i.e. the same correspondence was found from Figure 4.1 (a) to Figure 4.1 (b) and vice versa. Other than this, no regularity constraints were imposed. Since there were no spatial deformations, an identity correspondence should be found, i.e. each green cross should directly fit in a red circle, without a displacement. However, there is a clearly observable difference in the matching pairs by using the HOG-I descriptor (Figure 4.1 (d)) and the HOG-MP descriptor (Figure 4.1 (h)). Where the HOG-MP descriptor mostly finds the identity correspondence, the HOG-I descriptor finds correspondences over very large displacements. This outcome emphasizes that HOG-I is very sensitive to intensity variation, whereas HOG-MP is not.

**4.3.2 Registration performance on synthetic abdominal images**

We separately evaluated the performance of our registration framework in the presence of a local geometric deformation and a local intensity distortion. In these experiments we disabled the regional term by setting $\beta = 0$; furthermore, we empirically set $\alpha = 0.1$ for ALOST and in addition set $\gamma = 0.5$ for DM-ALOST; the default settings of DRAMMS and MIND were used.

*Effects of geometric deformation on the registration performance.* We created a geometric deformation following the recipe below. First, a global geometric deformation with a thin-plate spline (TPS) model (similar to [30], 7x7 grid size) was applied to a reference image (Figure 4.2(a)). Second, a local deformation was imposed around one randomly picked point from the image. This deformation was generated by randomly selecting a displacement between 15 to 25 pixels in x and y direction respectively. Thereafter, care was taken that the displacement field was continuous by Gaussian filtering creating a Gaussian distributed displacement field around the picked point. The width of the Gaussian was set to a randomly selected value in the range from 20 to 50 pixels, which effectively controlled the locality of the deformation. An example is shown in Figure 4.2(b).
We generated 100 different deformed images from the selected reference image. Then, the aforementioned five registration methods were used to register these data. Typical outcomes are shown in Figure 4.2, which demonstrate that DM-ALOST (Figure 4.2(g)) gave the best registration result around a large deformation (pointed to by the red arrow). Furthermore, the performance of all methods over the 100 randomly generated cases is collated in the boxplots of Figure 4.4 (a). It summarizes the distributions of the root-mean-squared error of the estimated deformation fields prior to and after application of the five registration methods.

Clearly, descriptor matching is important for registering data with large local geometric deformations since DM-MIND and DM-ALOST perform better than MIND and ALOST respectively. DM-ALOST gave the best overall result, although the difference with DM-MIND was not significant.

**Effects of geometric deformation plus intensity distortion on the registration performance.** We created the synthetic test images by adding a local intensity distortion to each of the 100 geometrically deformed images by adding a Gaussian shaped intensity offset centered around a randomly selected point (again as in [30]). We assessed the performance of the same five registration methods on these data. Typical outcomes on one of the test images are depicted in Figure 4.3. Notice in particular the good
Figure 4.2 (a) A fixed image and (b) a moving image generated by adding both a global and a large local geometric deformation to image (a); (c)-(g) registration outcomes by five different methods: DRAMMS, MIND, DM-MIND, ALOST and DM-ALOST respectively. The red arrows indicate regions with large initial local deformations.
Figure 4.3 (a) A fixed image and (b) a moving image generated by adding a geometric deformation and an intensity distortion to (a); (c)-(g) registration outcomes by DRAMMS, MIND, DM-MIND, ALOST and DM-ALOST respectively. The red arrows indicate regions with large initial geometric deformations.
performance of DM-ALOST in the heavily deformed regions indicated by the arrows. Figure 4.4 (b) collates the error distributions after registration on the full set of 100 images as boxplots. The vertical axis again presents the root-mean-square error of the estimated deformation fields. The DM-ALOST outcome performs significantly better than all other approaches as assessed by a two-sided signed rank test (p < 0.01). The plot demonstrates that DM-ALOST is highly robust against both intensity distortions and geometric deformations.

4.3.3 Registration of thoracic CT images with large deformations

In addition to quantifying the performance of DM-ALOST on abdominal MR data (see below), we also applied it to a publicly available thoracic CT dataset that shows large local geometrical deformation and intensity variation. The thoracic CT images were taken from the COPDGene Study and have been previously used for assessing image registration [35].

Like the abdominal images, these data comprise thin structures that undergo large deformations and intensity variation due to gas density differences. Consequently, an SSD based method failed to register the data [17]. In total there were 10 pairs of 3D CT scans acquired in breath-holds at maximum expiration and maximum inspiration [35]. The resolution of the images varied from 0.586×0.586×2.5 mm³ to 0.742×0.742×2.5 mm³; the number of slices ranged from 102 to 135, each consisting of 512×512 pixels. There were 300 manually annotated landmarks on each expiration/inspiration scan made by an expert. Prior to registration, we used publicly available segmentation software
Chapter 4. A hybrid optimization strategy for registering images with large local deformations and intensity variations

Figure 4.5 Mean Target Registration Error (MTRE) of 300 landmarks on 10 pairs of lung CT datasets acquired in maximum inspiration and expiration for different weightings of the coupling term $\gamma$ between discrete matching and continuous optimization.

[36] to segment the lung volume to avoid discontinuities at the borders of the lungs (just as in [35]). The registration was only applied to this region.

Again, the same five registration methods were used to register the inspiration and expiration scans of each patient. The performance of these methods was determined by calculating the mean target registration error (MTRE) over all landmarks and all patients. We used the default settings of DRAMMS and we empirically choose $\alpha = 0.05$ and $\alpha = 0.1$ for MIND and ALOST, respectively. One might expect that a potentially important parameter in DM-MIND and DM-ALOST is the weight of the coupling term, which is determined by $\gamma_0$ (see above). Therefore, Figure 4.5 studies the registration performance on the 10 pairs of CT data with different settings of $\gamma_0$ for DM-MIND and DM-ALOST. It can be seen that the best $\gamma_0$ is around 0.5, although the differences in performance by using values in the range from $\gamma_0 = 0.1$ to $\gamma = 1$ are small. We hypothesize that this is because the descriptor matching is only needed to provide a coarse initialization, after which the continuous optimization ensures convergence to the global optimum. As such, small variations in $\gamma_0$ hardly influenced the final outcome. Accordingly, we used $\gamma_0 = 0.5$ in the remaining experiments.

Table 4.1 collates the registration outcome of the five methods. Clearly, DM-ALOST and DM-MIND outperform the other techniques. To our opinion this
indicates that descriptor matching is a crucial step to cope with large local deformations. Particularly, all differences between the descriptor matching based methods and the other techniques assessed by a two-sided signed rank test are significant (p<0.01). A visual impression of the performance of all registration methods is depicted in Figure 4.6. In these data, large deformations often occur at the bottom of the lungs [35], as indicated by the red arrows in the figure. The color-coded results combine the inspiration and expiration images in one color map in which local registration errors are emphasized by green and magenta structures and correctly registered regions are displayed in grey tones. One can observe that registration errors in this region occur only with DRAMMS, MIND and ALOST, whereas DM-MIND and DM-ALOST yield a much better registration outcome. The DM-ALOST and DM-MIND seem to perform equally well on this data, because both methods are guided by descriptor matching towards their global minimum. The absence of very large local intensity variations makes that the performance of DM-MIND is just as good as DM-ALOST.

**4.3.4 Abdominal MR image pre- to post-contrast registration**

The last series of experiments assess the suitability of the proposed method to register pre- and post-contrast abdominal MR data of patients with Crohn’s disease. We compare the five registration methods both in a qualitative and a quantitative manner. The latter will involve computation of a feature that has been shown to correlate with disease severity based on the registration. The abdominal MRI data of 30 patients were taken from a prior study into luminal Crohn's disease [37]. The local medical ethics committee approved the usage of this data. MR image acquisition included a high-resolution ‘pre-contrast’ image series, a 3D+time Dynamic Contrast Enhanced (DCE) series, and a high-resolution ‘post-contrast’ image series. A contrast agent (Gadovist 1.0 mmol/ml, Bayer Schering Pharma, Berlin, Germany; dosage: 0.1 ml/kg bodyweight) was injected during DCE imaging, i.e. between the pre-contrast and post-contrast series. The current paper focuses on registration of the pre-contrast and post-contrast MR images. This is relevant since the relative contrast enhancement (RCE) between pre-contrast and post-contrast MR images has been reported to correlate to the severity of Crohn’s disease [1].
Table 4.1 Mean target registration error (MTRE) of 300 landmarks on 10 datasets prior to registration (i.e. no registration), and after registration using DRAMMS, MIND, DM-MIND, ALOST and DM-ALOST. The numbers printed in bold face are the minima, i.e. the best results, per column. All numbers are in mm.

<table>
<thead>
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<th>Case NO.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Mean(std)</th>
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</thead>
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<td>5.33</td>
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<td>3.29</td>
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<td><strong>2.01</strong></td>
<td><strong>3.29</strong></td>
<td>3.50(1.57)</td>
</tr>
<tr>
<td>ALOST</td>
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<td>5.38</td>
<td>1.62</td>
<td>3.46</td>
<td>3.78</td>
<td>3.36</td>
<td>1.78</td>
<td>2.75</td>
<td>2.16</td>
<td>3.78</td>
<td>3.29(1.24)</td>
</tr>
<tr>
<td>DM-MIND</td>
<td><strong>2.58</strong></td>
<td>3.87</td>
<td><strong>1.53</strong></td>
<td>3.15</td>
<td>2.94</td>
<td><strong>2.81</strong></td>
<td>1.86</td>
<td>2.90</td>
<td>2.07</td>
<td>3.38</td>
<td><strong>2.71(0.72)</strong></td>
</tr>
<tr>
<td>DM-ALOST</td>
<td>2.78</td>
<td><strong>3.80</strong></td>
<td>1.61</td>
<td><strong>2.94</strong></td>
<td><strong>2.73</strong></td>
<td>3.01</td>
<td><strong>1.77</strong></td>
<td><strong>2.61</strong></td>
<td>2.07</td>
<td>3.96</td>
<td>2.72(0.77)</td>
</tr>
</tbody>
</table>
Chapter 4. A hybrid optimization strategy for registering images with large local deformations and intensity variations

Figure 4.6 (a) Fixed lung CT image (at maximum inspiration) and (b) moving image (at maximum expiration) from patient NO.1; (c)-(g) registration outcomes by DRAMMS, MIND, DM-MIND, ALOST and DM-ALOST respectively. The red arrows point to a region with a large initial deformation. The insets focus on this region and contain the fixed image in the red and blue.
Chapter 4. A hybrid optimization strategy for registering images with large local deformations and intensity variations

The pre- and post-contrast images were acquired in a breath-hold by 3D T1-weighted spoiled gradient echo sequences performed in coronal planes. Both images consisted of 400×400×100 voxels at resolutions of 1×1×2 mm³. We used the same five methods as described in 4.3.2 and 4.3.3 to register the data. The parameters were the same as in 4.3.3. These settings also proved to yield the best registration result for the abdominal images (data not shown). Figure 4.7 shows a region in the lower abdomen suffering from large local intensity variations, but without large geometric deformations (around the bladder). The upper boundary of the bladder was annotated on the post-contrast MR image (Figure 4.7 (a)). Subsequently, it was copied to the pre-contrast image prior to and after registration by means of the five approaches (Figure 4.7 (b)-(g)) to evaluate the registration accuracy. Observe that only ALOST and DM-ALOST yielded correct registration as these methods were designed to cope with the intensity variation. Figure 4.8 depicts a second region with large local intensity variation as well as large geometric deformation. The bowel segment cecum and the diseased part of it were annotated under supervision of an abdominal radiologist on the post-contrast MR image (Figure 4.8 (a)). Subsequently, these annotations were copied to the pre-contrast images prior to and after registration (Figure 4.8 (b)-(g)) to assess the registration accuracy. The top-right insets show the relative contrast enhancement (RCE) [1] measured on a per pixel basis over the diseased part. This RCE feature was calculated as \( (I_{\text{post}} - I_{\text{pre}}) / I_{\text{pre}} \times 100 \), with \( I_{\text{pre}}, I_{\text{post}} \) the pre- and post-contrast image intensities. The standard deviations of the RCE measurements were 117 (no registration), 42 (DRAMMS), 128 (MIND), 73 (DM-MIND), 145 (ALOST), 41 (DM-ALOST). As such, DRAMMS and DM-ALOST gave more constant RCE measurements; apparently because these methods yielded a better alignment of the diseased regions than the other methods.

Quantitative assessment of the registration performance

Unfortunately, it is not a trivial task to identify landmark points on the bowel wall since there is deformation due to inspiration depth and a continuous deformation over time due to peristalsis between the scans. Therefore, we decided to label relevant ‘landmark’ regions, namely the bowel segments: terminal ileum, right colon, transverse colon, left colon and rectum. A research fellow specialized in...
Chapter 4. A hybrid optimization strategy for registering images with large local deformations and intensity variations

Figure 4.7 MR images of the lower abdominal region without large local geometric deformations, but with large local intensity variations. (a) Post-contrast MR image (fixed) and (b) corresponding pre-contrast MR image (moving) prior to registration; (c)-(g) registration outcomes by DRAMMS, MIND, DM-MIND, ALOST and DM-ALOST respectively. The green curve on the upper boundary of the bladder was manually annotated on image (a) and copied to images (b)-(g) to evaluate the registration.
Figure 4.8 Region with large local geometric deformation and with large local intensity variation. (a) Post-contrast MR image (fixed) and (b) corresponding pre-contrast MR image (moving) prior to registration; (c)-(g) registration outcomes by DRAMMS, MIND, DM-MIND, ALOST and DM-ALOST respectively. A research fellow supervised by an abdominal radiologist delineated a bowel segment in the post-contrast image (a) (green contour) as well as the diseased part in this bowel piece (red). Subsequently, these annotations were copied to the pre-contrast images prior to and after registration to evaluate the registration outcome. The insets show the relative contrast enhancement calculated per pixel.
imaging Crohn’s disease supervised by a radiologist delineated each bowel segment affected by Crohn’s disease in the post-contrast MR images. Subsequently, two research fellows, both specialized in imaging Crohn’s disease, independently annotated the same region in the pre-contrast images. Polygons were drawn in coronal slices. Each lesion was delineated in all slices in which it was observed. In total 30 lesions were identified in 30 bowel segments. A typical example is shown in Figure 4.9. The mean dice coefficient calculated over the annotations in the pre-contrast MR images was 0.71, reflecting the inter-observer agreement. The dice coefficient was also computed over corresponding pairs of annotations in the pre- and post-contrast images prior to registration and after registration by each of the five methods. The results are summarized in Table 4.2. One can see that the DM-ALOST outperformed the other methods for the data of both annotators. Particularly, the Wilcoxon signed rank test demonstrated that DM-ALOST was significantly (p<0.05) better than the other methods. Notice that the mean Dice coefficients of DM-ALOST, 0.68 and 0.69, closely approximate the inter-observer agreement. Hence, the inter-observer variability puts an upper limit on the achievable correspondence between annotations and DM-ALOST.

**Correlation of manual to semi-automatic measurements of relative contrast enhancement**

The relative contrast enhancement (RCE) was calculated as defined above using the mean intensities measured over manually delineated regions in the pre- and post-contrast images. Four research fellows each supervised by a different radiologist outlined corresponding regions with the most disease activity in the pre- and post-contrast images of the 30 patients affected by the disease [38]. These regions comprised small focal areas on the order of 100 voxels, as is conventional. Moreover, one research fellow supervised by a radiologist delineated the entire region affected by the disease. The RCE was semi-automatically measured by first calculating the mean intensity over this full region in the post-contrast image and by averaging over the region in the pre-contrast image that was copied from the post-contrast image. We did so prior to and after registration by the five methods, both using $\beta = 0$ and $\beta = 100$ (see (4.4)) to study the effect of the regional weighting. These semi-automatic RCE measures were correlated to the manual RCE measures by means of Pearson’s correlation. The correlation coefficients thus obtained are
Chapter 4. A hybrid optimization strategy for registering images with large local deformations and intensity variations

Figure 4.9 Annotations on pre- and post-contrast MR images. (a)-(c) Reference annotations on the post-contrast MR images made by two research fellows; (d)-(f) corresponding annotations on the pre-contrast MR images made by the first research fellow; (g)-(i) same images as (d)-(f) but now containing the annotations by the second research fellow. Radiologists supervised the research fellows.
Table 4.2 Mean Dice Metric (MDM) between annotations on pre- and post-contrast abdominal MR images prior to registration (i.e. no registration), and after registration using respectively DRAMMS, MIND, DM-MIND, ALOST and DM-ALOST. The numbers printed in bold face are the maxima, i.e. the best results, per row. The standard deviation is shown between brackets.

<table>
<thead>
<tr>
<th></th>
<th>no registration</th>
<th>DRAMMS</th>
<th>MIND</th>
<th>DM-MIND</th>
<th>ALOST</th>
<th>DM-ALOST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fellow-1</td>
<td>0.50 (0.24)</td>
<td>0.52 (0.22)</td>
<td>0.63 (0.21)</td>
<td>0.65 (0.20)</td>
<td>0.66 (0.22)</td>
<td><strong>0.68 (0.17)</strong></td>
</tr>
<tr>
<td>Fellow-2</td>
<td>0.42 (0.27)</td>
<td>0.52 (0.23)</td>
<td>0.59 (0.21)</td>
<td>0.62 (0.19)</td>
<td>0.61 (0.21)</td>
<td><strong>0.69 (0.13)</strong></td>
</tr>
</tbody>
</table>

Table 4.3 Pearson correlation coefficients of correlations between manual and semi-automatic RCE measurements. Manual measurements were made by four research fellows supervised by four radiologists. Semi-automatic RCE measurements were performed prior to and after registration by DRAMMS, MIND, DM-MIND, ALOST and DM-ALOST. The numbers printed in boldface are the maxima, i.e. the best results, per column. The last two rows represent average correlation coefficients by correlating the semi-automatic RCE measurements to all the manual RCE measurements simultaneously without (\( \beta = 0 \)) and with (\( \beta = 100 \)) putting emphasis on the diseased region.

<table>
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<th></th>
<th>no registration</th>
<th>DRAMMS</th>
<th>MIND</th>
<th>DM-MIND</th>
<th>ALOST</th>
<th>DM-ALOST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fellow-1</td>
<td>0.29</td>
<td>0.45</td>
<td>0.45</td>
<td>0.46</td>
<td>0.45</td>
<td><strong>0.46</strong></td>
</tr>
<tr>
<td>Fellow-2</td>
<td>0.54</td>
<td>0.68</td>
<td>0.69</td>
<td>0.70</td>
<td>0.71</td>
<td><strong>0.74</strong></td>
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<tr>
<td>Fellow-3</td>
<td>0.50</td>
<td>0.50</td>
<td>0.51</td>
<td>0.52</td>
<td>0.53</td>
<td><strong>0.55</strong></td>
</tr>
<tr>
<td>Fellow-4</td>
<td>0.62</td>
<td>0.59</td>
<td>0.67</td>
<td>0.68</td>
<td>0.69</td>
<td><strong>0.71</strong></td>
</tr>
<tr>
<td>Average, ( \beta = 0 )</td>
<td>0.49</td>
<td>0.56</td>
<td>0.58</td>
<td>0.59</td>
<td>0.60</td>
<td><strong>0.62</strong></td>
</tr>
<tr>
<td>Average, ( \beta = 100 )</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>0.58</td>
<td>0.59</td>
<td>0.61</td>
<td><strong>0.62</strong></td>
</tr>
</tbody>
</table>
shown in Table 4.3, stratified by fellow for $\beta = 0$ and averaged over the fellows for $\beta = 0$ and $\beta = 100$. Notice that DM-ALOST gave a higher correlation than the other registration methods, although none of the differences were significant. Furthermore, a higher $\beta$ did not make any difference. In other words, putting more emphasis on the region of interest did not further improve the correlations. Visual inspection showed no noticeable difference between registration results with and without regional preference. Both seemed to be correct after application of DM-ALOST.

**Correlation of RCE to CDEIS**

Ileocolonoscopy is generally considered the reference standard for the assessment of Crohn’s Disease (CD). The disease activity was determined for our dataset during ileocolonoscopy by the Crohn’s Disease Endoscopic Index of Severity, CDEIS [39]. The CDEIS was measured per bowel segment (i.e. terminal ileum, right colon, transverse colon, left colon and rectum). The RCE values as obtained above were also assigned to a bowel segment by the supervising radiologist. Subsequently, the RCE values were correlated by means of Pearson’s correlation to the CDEIS values of the corresponding segment. We focused on the DM-ALOST based semi-automatic RCE measurement since we already determined from the results that this method gave the best registration outcome. The results are shown in Table 4.4. Observe that the DM-ALOST based RCE values have a similar Pearson’s correlation coefficients with CDEIS as the manual RCE values. The correlation is weak between RCE values and CDEIS. This weak correlation values were also reported previously for these data [40].
4.4 Conclusion

We developed a hybrid registration framework called DM-ALOST to register images with large local deformations combined with large local intensity variations. The main target application was the spatial alignment of 3D abdominal pre- and post-contrast MR images of patients with Crohn’s disease. Differences in inspiration depth and peristalsis cause large local geometric deformations, while the administrated contrast agent causes large spatially localized contrast variations. The developed method – DM-ALOST – combines a discrete descriptor matching at the full image resolution with continuous optimization of a powerful representation exploiting the mean phase and the phase congruency computed from the multi-scale monogenic signal. The discrete optimization enabled us to cope with local geometric deformations of small image structures and guides the continuous registration in such a way that it does not get trapped in a local minimum.

The use of the phase of the monogenic signal offers the required invariance to large intensity distortions. To emphasize a correct registration of the diseased bowel wall, we initially included a term that emphasizes potential diseased regions based on a previously developed framework employing superpixel segmentation and random forest classifiers.

We compared our method with two state-of-art registration techniques and two derived techniques on three different datasets.

1) On synthetic abdominal MR image data we calculated the root mean square error (RMSE) of the deformation field prior to and after registration. Our DM-ALOST approach gave the smallest RMSE on data with large synthetically induced local intensity variations as well as on data with both large synthetically induced intensity distortions and geometric deformations.

2) On thoracic CT images we calculated the mean target registration errors (MTRE) of 300 manually annotated landmarks on 10 datasets prior to and after registration. The DM-MIND and DM-ALOST methods both gave a smaller mean MTRE than the registration methods without descriptor matching. It proves that descriptor matching is a crucial step to register images with large local deformations.

3) On abdominal MR data we computed the mean Dice coefficient over annotated ROIs prior to and after registration. We showed that the DM-ALOST
Chapter 4. A hybrid optimization strategy for registering images with large local deformations and intensity variations

The technique performed significantly better than the other registration methods (p<0.05). Furthermore, semi-automatic RCE measurements based on the DM-ALOST approach achieved a similar weak correlation with CDEIS as the manual RCE measurements of four human observers.

The strength of the coupling term was experimentally determined to be less important. We hypothesized that initialization with the outcome of discrete descriptor matching seemed sufficient to avoid getting trapped in a local minimum. The effect of the regional term, used to emphasize diseased regions over normal tissue did not contribute to improved registration. Therefore, it should be dropped from the energy function.

There are several limitations of our work. The optimal weighting parameters were manually selected for each registration task. Although this might bias the reported figures, we found little difference between the manually tuned settings for the different data sets and the different tasks. Therefore, we do not expect that it influences the ordering of the five methods in terms of performance. Another limitation is that the HOG-MP descriptor is not invariant to non-rigid deformations. For data hampered by very large local non-rigid deformations, the descriptor matching using HOG-MP might fail. In that case, descriptors could be considered such as described in [41] [42]. However, that would go at the expense of a higher computation time. Furthermore, a more extended segmentation of the bowel (i.e. not only the diseased parts) might be useful, although the segmentation on the pre-contrast MR images is far from trivial.

References


Chapter 4. A hybrid optimization strategy for registering images with large local deformations and intensity variations


[16] C. Studholme, C. Drapaca, B. Iordanova and V. Cardenas, "Deformation-based mapping of volume change from serial brain MRI in the presence of local tissue contrast change,"
Chapter 4. A hybrid optimization strategy for registering images with large local deformations and intensity variations


Chapter 4. A hybrid optimization strategy for registering images with large local deformations and intensity variations

vol. 6, no. 5, pp. 303-313, 1987.


Chapter 4. A hybrid optimization strategy for registering images with large local deformations and intensity variations


5 Image registration based on the structure tensor of the local phase

Image registration of medical images in the presence of large intra-image signal fluctuations is a challenging task. Our paper addresses this problem by introducing a new concept based on the structure tensor of the local phase. The local phase is calculated from the monogenic signal representation of the images. The local phase image is hardly affected by unwanted signal fluctuations due to a space-variant background and a space-variant contrast. The boundary structure tensor combines the responses of edges and corners/junctions in one tensor, which has several advantages, compared to other structure tensors. We reorient the structure tensor during the registration by means of the finite-strain technique. The structure tensor is only calculated once during a preprocessing step. The results demonstrate that the proposed method effectively deals with large signal fluctuations. It performs significantly better than competing techniques.

Chapter 5. Image registration based on the structure tensor of the local phase

5.1 Introduction

Image registration is widely used for finding correspondence between medical images. The sum of squared differences (SSD), normalized cross covariance (NCC) and mutual information (MI) [1] [2] are standard (dis)similarity metrics used to measure correspondences. However, these metrics do not consider the local image structure, which may influence the robustness of non-rigid registration [3]. Several methods have integrated features of the local structure into the similarity metric [3] [4] [5] to improve the registration performance. Alternatively, the so-called MIND [6], DRAMMS [7] and ROHE [8] techniques determine structural properties of image patches and apply a simple (dis)similarity metric (e.g. SSD).

However, none of the aforementioned methods is well designed for images with large intra-image signal fluctuations. These signal fluctuations are often observed in medical images (e.g. the bias field in magnetic resonance imaging) and introduce “uncharacteristic” information. Accidentally treating this “uncharacteristic” information as local structure may give rise to incorrect registration.

We encountered this problem upon registering three-dimensional Dynamic Contrast Enhanced MR images- to post-contrast abdominal MRI data for quantifying Crohn’s disease activity. This is relevant since the two modalities contain complementary information and both suffer from large signal fluctuations [9]. We present a new, efficient structure representation based on the Structure Tensor of the Local Phase (STOP) in order to overcome the problem with the signal fluctuations. The local phase is derived from the monogenic signal representation of the image [10], which is insensitive to signal fluctuations. Furthermore, the structure tensor is a well-known concept representing the image structure. The registration results will demonstrate that this new approach outperforms other structure-based methods.

5.2 Methods

5.2.1 Monogenic signal and local phase

The mean phase of a multi-dimensional image is derived from the monogenic signal [10]. Essentially, the monogenic signal extends the analytic signal from 1-D to N-D by means of the Riesz transform. The monogenic signal for 2-D images (expressed in quaternions) is defined as:
Chapter 5. Image registration based on the structure tensor of the local phase

\[ f_M(x) = f_e(x) - (i, j)f_R(x) \]  \hspace{1cm} (5.1)

where \( f_e(x) \) is the even component of the original image calculated by convolving the original image with a rotationally symmetric, real-valued, zero-mean band-pass filter; the vector-image \( f_R(x) \) holds the odd components of the aforementioned band-pass filtered image (more details can be found in [10]). The local phase image is then calculated over multiple \( (n) \) scales of the filter [11]:

\[ \varphi(x) = \arctan \left( \frac{\sum_{i=1}^{n} f_R^i(x)}{\sum_{i=1}^{n} f_e^i(x)} \right) \]  \hspace{1cm} (5.2)

in which \( i \) denotes the scale. In our work, we use a log-Gabor filter, because it is a zero-DC filter with a tunable bandwidth. An example of a local phase image calculated from an image (Figure 5.1(a)) is shown in Figure 5.1(b). Observe that the local phase is invariant to intensity distortions.

5.2.2 Structure tensor and STOP representation

The structure tensor is often used for characterizing the local image structure. Several types of structure tensors were proposed for different applications. We choose the boundary tensor [12] for our registration framework. The boundary tensor is defined as
where $T_o$ and $T_e$ are tensors representing the odd and even image structures respectively. Effectively, this method integrates edge and corner/junction detection into a single tensor representation. Since the odd and even components of the tensor are by definition in quadrature, a boundary tensor implicitly allows us to incorporate all relevant structural information – edges (odd) and lines (even) – into a single tensor.

The so-called STOP representation for images is obtained by first deriving the local-phase image via (5.2), after which the structure tensor (5.3) of the local-phase image is computed.

### 5.2.3 Structure tensor reorientation

Tensor reorientation has already been incorporated into the registration of diffusion tensor images [13]. It is used to adjust the tensor orientation during registration. Similar to diffusion tensor reorientation, we can also adapt the structure tensor during registration. A standard way to do so is the finite strain (FS) strategy. FS computes a rigid rotation matrix from the deformation gradient as follows:

$$ R(x) = (J(x)J(x)^T)^{-\frac{1}{2}}J(x) $$

(5.4)

where $R(x)$ is the rotation matrix in a pixel and $J(x)$ the Jacobian matrix associated with the geometric transformation at pixel $x$. Then, the structure tensor $T(x)$ is reoriented by:

$$ T'(x) = R^T(x)T(x)R(x) $$

(5.5)

where $T'(x)$ is the reoriented structure tensor. Incorporating this reorientation strategy into the registration framework allows us not only to improve the registration by incorporating structural information, it may also reduce the computational complexity because the structure tensor only needs to be calculated once during the preprocessing stage.
5.2.4 Registration framework
Since the STOP representation is invariant to local signal fluctuation, we can use the Frobenius norm to calculate a dissimilarity metric based on this tensor representation:

$\sum_x \sqrt{\text{trace}((T_f(x) - T_m(x + u_m))(T_f(x) - T_m(x + u_m))^T)}$  \hspace{1cm} (5.6)

where $T_f$ and $T_m$ are tensor representations of respectively the fixed and moving images and $u_m$ is the deformation field for each pixel. Gauss-Newton optimization is used for minimizing (5.6) with the total variation of the deformation field $u_m$ as regularization term. The tensor reorientation is embedded in the registration framework.

5.3 Results
5.3.1 Synthetic brain data
We simulated images by applying an intensity distortion to brain MRI data as described by Myronenko et al. [14]. First, a spatially varying intensity distortion was applied to a brain MR image to create the fixed image (see Figure 5.2, first column). Second, another intensity distortion was applied to the same original brain image in a comparable manner. Thereafter, a geometric distortion with a thin-plate spline (TPS) model was applied to this image to get a second image, the moving image (see Figure 5.2, second column). The registrations of the moving image to the fixed image by the three different methods are shown in the remaining images of Figure 5.2. The DRAMMS and MIND methods were applied using their default settings. One can conclude from Figure 5.2 that only the proposed method has the ability to deal with images suffering from signal fluctuation (see the regions pointed out by yellow arrows).
Chapter 5. Image registration based on the structure tensor of the local phase

We randomly generated 100 different moving images to further evaluate the methods. Subsequently, we calculated the root mean square difference (RMSD) between the imposed and estimated spatial deformations by the different registration methods. The results are shown in Table 5.1. One can see that the STOP method gave the smallest RMSD, which was significantly better than the other methods as assessed by a two-sided signed rank test ($p<0.05$).

Figure 5.2. Results of registering synthetically deformed brain images using different methods; the first row contains: fixed image, moving image, and the registration outcomes using the DRAMMS, MIND and STOP methods; the second row shows a detail with signal fluctuations. A region of interest is annotated (red contour) on the fixed image. This region is copied to the moving image and the registration outcomes by the three methods. The yellow arrows indicate the registration errors. Note that the outcome of the STOP method is highly acceptable.

We randomly generated 100 different moving images to further evaluate the methods. Subsequently, we calculated the root mean square difference (RMSD) between the imposed and estimated spatial deformations by the different registration methods. The results are shown in Table 5.1. One can see that the STOP method gave the smallest RMSD, which was significantly better than the other methods as assessed by a two-sided signed rank test ($p<0.05$).
5.3.2 Abdominal MR images
Abdominal MR datasets of 30 patients from a previous study into Crohn’s disease [15] were used to evaluate our registration method. Our aim was to register a DCE-MRI series to a post-contrast MR image. Time intensity curves (TICs) from the DCE-MRI series contain important information about the disease activity [16]. Diseased regions were delineated on the post-contrast MR image, which had higher resolution (see Figure 5.2, second and third rows). In the previous study these annotations were used to measure the thickness of the bowel wall and the length of the diseased part. Accurate registration between DCE- and post-contrast MRI allows combining complementary information within the annotated regions. The DCE-MRI series (450 volumes) were firstly registered to themselves by using the method described in [16]. This left around 100 registered volumes and one expiration phase DCE-MRI template for each patient.

Table 5.1. Evaluation of the registration performance on synthetic brain data by three methods: DRAMMS, MIND and STOP. The performance was measured by the root mean square difference (RMSD) between imposed deformations and estimated deformations over 100 cases. The numbers report the mean value and the standard deviation (std) between brackets. The unit is mm and the number printed in boldface indicates the best result.

<table>
<thead>
<tr>
<th></th>
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<th>STOP</th>
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<tbody>
<tr>
<td>RMSD</td>
<td>4.28 (0.43)</td>
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<td>1.46 (0.30)</td>
<td><strong>1.32 (0.19)</strong></td>
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</table>
Chapter 5. Image registration based on the structure tensor of the local phase

The DCE-MRI template image was registered to the post-contrast MR image to obtain spatial alignment. The three registration methods as before were used to do so. A visual comparison is shown in Figure 5.3. An experienced radiologist annotated two diseased regions on the post-contrast MR image (red polygons). The annotations were then copied to the DCE-MRI template prior to and after registration by means of the DRAMMS, MIND and STOP methods. The yellow arrows indicate registration errors.

Table 5.2. Correlation coefficients (CC) of an extracted DCE-MRI image feature for contrast enhancement and CDEIS (ground truth) prior to registration, and after registration by DRAMMS, MIND and STOP. The p-values of the correlations are shown between brackets. The number printed in boldface indicates the best result.

<table>
<thead>
<tr>
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<th>STOP</th>
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</thead>
<tbody>
<tr>
<td>CC</td>
<td>0.39 (0.12)</td>
<td>0.41 (0.10)</td>
<td>0.43 (0.08)</td>
<td><strong>0.53 (0.03)</strong></td>
</tr>
</tbody>
</table>

The DCE-MRI template image was registered to the post-contrast MR image to obtain spatial alignment. The three registration methods as before were used to do so. A visual comparison is shown in Figure 5.3. An experienced radiologist annotated two diseased regions on the post-contrast MR image (red polygons). The annotations were then copied to the DCE-MRI template prior to and after registration by DRAMMS, MIND and STOP. The yellow arrows point out the registration errors. One can see that DRAMMS failed in regions with strong signal fluctuations (e.g. second row: the bladder; third row: the bowel wall). MIND already facilitated improved registration in those regions. However, errors still occurred around the bowel wall, because MIND is not fully invariant to signal fluctuations, which makes that this method gets trapped in a local minimum. After registering the DCE-MRI template to the post-contrast MR image, we applied the found deformation field to the entire set of pre-aligned
Chapter 5. Image registration based on the structure tensor of the local phase

DCE-MR images. Subsequently, TICs were derived from the annotated diseased regions copied from the post-contrast MR image. A tri-exponential function was fit to the TIC after of which one fit parameter called $A$, reflects the strong upward slope of the TIC [16]. We correlated this feature to the Crohn’s Disease Endoscopic Index of Severity, CDEIS [17]. The results are shown in Table 5.2. It turns out that the STOP method gave the highest and one-and-only significant correlation ($r=0.53$, $p=0.03$).

5.4 Conclusion

We proposed a new local structure representation based on the structure tensor of the local phase image. It facilitates image registration in the presence of large intra-image signal fluctuations. The registration results that we obtained demonstrated that the new technique outperformed state-of-art structure-based methods. The proposed framework can be adapted to different registration purposes by using a different type of structure tensor (e.g. gradient tensor) or different measures of the local phase (e.g. phase congruency).

References


123
Chapter 5. Image registration based on the structure tensor of the local phase


6 Conclusion
Chapter 6. Conclusion

The VIGOR++ project targeted to develop methods for automatic quantification of Crohn’s disease severity based on MRI. A crucial step was to spatially align the involved MR modalities to have corresponding data for computing features related to the tissue-dependent uptake of contrast agent. In this thesis several new methods were studied for registration of the T1-weighted MRI data acquired in VIGOR++. Additionally, publically available clinical datasets were used for directly comparing the proposed methods to state-of-the-art techniques. This chapter summarizes the contributions of the previous chapters to the VIGOR++ project as well as to the outside world. Furthermore, potential future work will be briefly discussed.

6.1 Conclusions

In chapter 2, an expiration-phase template-based motion correction method was proposed for registering high temporal resolution DCE-MR images. The images particularly suffered from motion due to breathing and peristalsis. The proposed method applies retrospective gating to an unbiased expiration-phase template followed by non-rigid registration. This method achieved a lower mean target registration error (MTRE) than a state-of-the-art method for registering DCE-MRI. The MTRE was close to the inter-observer variation of manual annotations. A feature – measuring the contrast enhancement due to contrast agent uptake – was derived from a tri-exponential function fit to time-intensity curves obtained after registration. It showed a significantly better correlation (r = 0.60, p = 0.004) to the Crohn’s Disease Endoscopic Index of Severity (CDEIS) than manually measured contrast features.

In chapter 3, a new descriptor called Autocorrelation of the LOcal image STructure (ALOST) was introduced for registering images suffering from intensity variations. ALOST is insensitive to local contrast changes due to the tissue-dependent contrast agent uptake and the MR bias field. This was achieved by applying the Modality Independent Neighborhood Descriptor (MIND) to the mean phase and phase congruence computed from a multi-scale representation of the monogenic signal. The ALOST method gave the smallest MTRE in a comparison to other structure descriptors, e.g. MIND directly applied to the intensity, on chest CT images. Furthermore, a feature representing the signal enhancement in abdominal MR images after registration by the ALOST method gave the highest correlation to the CDEIS (r=0.56, p<0.05).
In chapter 4, a new registration framework called descriptor matching ALOST (DM-ALOST) was proposed for registering images with large local deformation and intensity distortion. This is particularly challenging in abdominal MRI, because the relevant bowel structures are thin and disappear in a conventional coarse-to-fine multi-resolution approach. On abdominal pre- and post-contrast T1-weighted MR images, we calculated the mean Dice coefficient of regions annotated by two observers. We showed that the DM-ALOST method performed significantly better than competing state-of-the-art methods with and without descriptor matching. Furthermore, a semi-automatic, DM-ALOST based RCE measurement was compared with fully manual RCE measurements. The DM-ALOST method gave similar correlation with CDEIS as the manual methods. Different from the ALOST approach in chapter 2, the DM-ALOST technique was designed for registering data with large spatial deformations. If there is no such problem, we would not expect differences between these two methods. Then, we would recommend to only use the ALOST method to save computation time.

In chapter 5, an alternative method was developed for efficiently registering images with intensity distortions. The method is based on the Structure Tensor to the local Phase (STOP). Similar to chapter 3, we also correlated an image feature representing the enhancement after contrast injection to CDEIS. The STOP method gave highest correlation with CDEIS \( r=0.53, p<0.05 \) in a comparison with the state of the art methods, such as MIND. The STOP method gave slightly smaller correlations compare to the ALOST method proposed in chapter 4 \( r=0.56, p<0.05 \). It showed us that a patch-based method such as ALOST might outperform pixel-based techniques such as the STOP approach for our MR images. However, choosing the patch size is a crucial step for the ALOST method. One may need to carefully tune the parameters to get optimal performance from the ALOST method.

### 6.2 Future work

Several aspects from the methods developed in this thesis could be extended:

1. **Real-time registration.** The computational time is one of the issues that was not elaborately considered in this research. Real-time performance has been one of the main challenges in medical image registration. Clearly parallel processing could be an obvious way to achieve this. Alternatively, careful tuning the
discrete optimization might reduce the processing time by initialization close to the global minimum.

2. **Method validation.** Careful evaluation has always been an issue in medical image registration, since a real ground truth is often not available. We already validated our methods on several datasets directly using landmarks annotated by experts or indirectly by means of properties from other modalities. Several methods have been recently discussed [1] [2] [3] to perform automatic or semi-automatic registration evaluation. Those methods might be useful to further assess our registration methods.

3. Combining more features via registration. The work in this thesis particularly focused on three VIGOR++ modalities: the pre-contrast, DCE and post-contrast T1-weighted MR images. However, the fat saturated T2-weighed images also contain information of Crohn’s disease, and are particularly used to identify scar tissue and wall edema. One of the commonly used T2 sequence is HASTE. The HASTE images were scanned in 2D, in two orthogonal directions. A new registration framework might exploit this by simultaneously registering the HASTE images to the other VIGOR++ data and upgrade the resolution, e.g. by employing a clever super-resolution methodology.

### 6.3 Contribution to VIGOR++ and outside world

We developed several methods for registering the VIGOR++ images. This paved the way to automatically generating corresponding features from the different MRI modalities. In particular, measures of the contrast enhancement of suspicious sites could be derived from the pre- and post-contrast images and from the dynamic MR data. These automatic features have been used in a system for improved assessment of Crohn’s disease [4] [5].

What is more, the methods developed in this thesis have a large potential to be used outside the VIGOR++ project. Particularly, the methods from chapter 2 are very useful to cope with breathing motion in other applications, e.g. in liver imaging. Furthermore, the methods from chapters 3-5 are applicable to other problems with large local geometric deformation and intensity variation, e.g. imaging Alzheimer’s disease.

### References

129
Chapter 6. Conclusion


Summary

Crohn’s disease (CD) is a chronic inflammatory bowel disease (IBD) that affects millions of people in Europe alone. It is important to accurately assess the disease severity in a safe and non-invasive manner in order to improve the treatment of patients with CD. Furthermore, the ideal assessment must be objective, reproducible, quantitative and comprehensive.

In clinical practice, ileocolonoscopy is the standard technique used for assessing CD activity, for instance by means of the Crohn’s Disease Endoscopic Index of Severity (CDEIS). However, ileocolonoscopy is invasive and the scoring is not comprehensive. To overcome these drawbacks, we investigated the use of magnetic resonance imaging (MRI) as an alternative. MRI is a non-invasive imaging technique that allows examination of the bowel wall and extraenteric soft tissues rather than only bowel surface as in ileocolonoscopy. A wide variety of MRI features has already been studied for measuring the disease activity. However, to the best of our knowledge, all the proposed MRI features were manually obtained by clinicians. Apart from being labor intensive, these measurements are inaccurate, irreproducible and non-objective due to the large intra- and inter-observer variability.

The Virtual Gastrointestinal Tract (VIGOR++) project aims to deliver a better disease scoring which fulfils all requirements of the ideal assessment of CD severity. The VIGOR++ imaging involved a suite of MRI modalities to be able to quantify the degree of disease activity based on MRI features. An accurate and precise spatial alignment of all MRI modalities is required for optimally measuring those features and have an implicit correspondence. This spatial alignment is commonly referred to as image registration.

This thesis presents four registration methods to take up three different challenges. We evaluated our method based on the VIGOR++ data, which uses the CDEIS as the reference standard.

The first challenge is related to the respiratory motion that is inherent in free-breathing DCE-MRI. The discontinuities in the deformation field caused by respiratory motion make it difficult to reliably derive features from DCE-MRI.
We proposed an expiration-phase, template-based registration method to reduce the discontinuities to the largest extend. Signal enhancement automatically derived from the registered DCE-MRI showed a significantly better correlation to CDEIS than manually measured features.

The second challenge derives from local differences in contrast between DCE-MRI and post-contrast MRI caused by tissue-specific uptake of the contrast agent and the MR bias field during imaging. We proposed a method called autocorrelation of local structural information (ALOST). This method overcomes the contrast problems by using the mean phase and phase congruency of the monogenic signal. This method produced better registration results in a comparison with state-of-the-art techniques. It facilitates combining features from post-contrast MRI (e.g. thickness of the bowel wall) and DCE-MRI (signal enhancement). As an alternative, we proposed an efficient registration pipeline based on the Structure Tensor to the local Phase (STOP) which also gave better registration result on our data in comparison with state-of-the-art methods.

The third challenge is posed by the large local deformations due to peristalsis and (depth of) respiration in combination with local contrast variations between pre- and post-contrast MRI. We designed a hybrid method coupling discrete descriptor matching with ALOST. The former solves the problem of large local deformations and the latter makes the method insensitive to local contrast changes. The technique called DM-ALOST (descriptor matching ALOST) facilitates semi-automatic extraction of features such as the relative contrast enhancement (RCE) between pre- and post-contrast MRI. The DM-ALOST method gave comparable correlation with CDEIS as the manual methods.

The proposed methods paved the way for automatically extracting MRI features for disease assessment from the different MRI modalities. These automatic features were used in a system that gave improved assessment of Crohn’s disease. What is more, the use of our methods is not limited to VIGOR++ project. Particularly, the methods are very useful to cope with breathing motion in other applications, e.g. in liver imaging. Furthermore, they are applicable to other problems that involve large local geometric deformation and intensity variation, e.g. imaging Alzheimer’s disease.
Samenvatting

De ziekte van Crohn is een chronische, inflammatoire darmziekte waaraan alleen al in Europa miljoenen mensen lijden. Het is belangrijk om de ernst van de ziekte van Crohn te kunnen beoordelen op een nauwkeurige, veilige en niet-invasieve wijze om de behandeling van patiënten te verbeteren. Bovendien is de ideale beoordeling objectief, reproduceerbaar, kwantitatief en volledig.

In de klinische praktijk is ileocolonoscopy de standaardtechniek voor de beoordeling van ziekteactiviteit, bijvoorbeeld door middel van de zogenaamde endoscopische index van ziekteactiviteit. Echter, ileocolonoscopy is invasief en de index is vaak niet volledig. Om deze nadelen te ondervangen, onderzochten wij het gebruik van magnetische resonantie imaging (MRI) als alternatief. MRI is een niet-invasieve beeldvormende techniek die onderzoek van de darmwand en zachte weefsels buiten de darm mogelijk maakt en niet alleen het darmoppervlak zoals bij ileocolonoscopy. Een grote verscheidenheid van MRI-kenmerken werd reeds bestudeerd voor het meten van de ziekteactiviteit. Echter, voor zover wij weten, werden alle voorgestelde MRI-kenmerken handmatig verkregen door clinici. Behalve dat dit arbeidsintensief is, zijn dergelijke metingen onnauwkeurig, niet goed reproduceerbaar en niet objectief, resulterend in een grote intra- en inter-observer variabiliteit.

Het virtuele tractus gastro-intestinalis project (VIGOR++) had tot doel om een betere evaluatie van de ziekte van Crohn mogelijk te maken, waarbij aan alle eisen van een ideale beoordeling zou worden voldaan. De VIGOR++ beeldvorming omvatte een reeks MRI technieken om de mate van ziekteactiviteit te kwantificeren gebaseerd op verscheidene MRI kenmerken. Een accurate en precieze ruimtelijke correspondentie van de MRI beelden is nodig om de kenmerken op optimale wijze te kunnen meten en combineren. Deze ruimtelijke uitlijning wordt gewoonlijk aangeduid als beeldregistratie.

Dit proefschrift introduceert vier nieuwe methoden voor beeldregistratie om drie verschillende problemen op te lossen. We evaluerden onze methoden met behulp van de VIGOR++ beelden, en gebruikten de endoscopische maat van ziekteactiviteit als referentiestandaard.
Het eerste probleem betreft correctie voor de continue ademhalingsbeweging tijdens DCE-MRI opnames. Discontinuïteiten in de vervorming door dit soort beweging maken het moeilijk om kenmerken op betrouwbare wijze te ontleenen aan DCE-MRI data. We stelden een registratiemethode voor op basis van een sjabloon van de uitademfase om de discontinuïteiten voor het grootste deel te verminderen. De mate van signaaltoename afgeleid van de geregistreerde DCE-MRI beelden toonde een aanzienlijk betere correlatie met colonoscopische maat voor ziekteactiviteit dan handmatig gemeten kenmerken.

De tweede uitdaging is gerelateerd aan lokale verschillen in contrast tussen de DCE-MRI en post-contrast MRI beelden veroorzaakt door weefselspecifieke opname van het contrastmiddel en globale trends in MRI beelden. We stelden een methode voor genaamd de autocorrelatie van lokale structurele informatie (ALOST). Deze werkwijze ondervangt de contrastproblemen door gebruik te maken van de gemiddelde fase en eenvormigheid van de fase van het monogenische signaal. Deze werkwijze leidt tot betere registratieresultaten in vergelijking met state-of-the-art technieken. Het maakt het mogelijk om kenmerken uit post-contrast MRI (bijvoorbeeld dikte van de darmwand) en DCE-MRI (de mate van aankleuring) te combineren. Als alternatief stelden we een efficiënte registratietechniek voor gebaseerd op de structuurtensor van de lokale fasehoek (STOP) die ook een beter registratieresultaat gaf op onze data vergeleken met state-of-the-art methoden.

Het derde probleem wordt veroorzaakt door grote plaatselijke vervorming als gevolg van peristaltiek en ademhaling alsook verschil in contrast tussen pre- en post-contrast MRI beelden. We ontwierpen een hybride methode die discrete matching op basis van een rijke signaalbeschrijving (zogenaamde descriptors) combineert met ALOST. De eerstgenoemde techniek lost het probleem van grote lokale vervormingen op en de laatste maakt de methode ongevoelig voor lokale contrastvariaties. De techniek genaamd DM-ALOST (descriptor matching ALOST) maakt extractie mogelijk van kenmerken zoals de relatieve mate van aankleuring tussen pre- en post-contrast MR beelden. De DM-ALOST methode gaf vergelijkbare correlatie met CDEIS als de handmatige methode.

De voorgestelde methoden maken de weg vrij voor automatische extractie van MRI kenmerken van de ziekte Crohn uit verschillende MRI beelden. De registratietechnieken werden gebruikt in een systeem dat een betere beoordeling van de ziekte van Crohn gaf. Bovendien is het gebruik van onze methoden niet beperkt tot het VIGOR++ project. Ze zijn bijvoorbeeld nuttig om de
ademhalingsbeweging in andere toepassingen, zoals beeldvorming van de lever, te kunnen compenseren. Ook zijn zij toepasbaar op andere problemen die grote lokale geometrische vervorming en variatie in intensiteit betreffen, zoals bijvoorbeeld beeldvorming van de ziekte van Alzheimer.
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Curriculum Vitae

Zhang Li (李璋) was born on Nov. 19, 1985 in Changsha, China. He obtained his B.E. degree in (2008) in Electronic Science and Engineering from National University of Defense Technology (NUDT), Changsha, China. In 2008, he started his Master study in National Key Laboratory of Automatic Target Recognition (ATR) in NUDT. Due to his excellent academic performance (top 5%), he was recommend by ATR lab to started his PhD program in advance in 2009. In late 2010, he moved to the Netherlands and started his PhD project at Quantitative Imaging Group, Delft University of Technology. He was involved in EU-funded VIGOR++ project, focusing on image registration.
Publications

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