the manual

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Chapter 1

Introduction

This manual describes a software package for image registration: `elastix`. The software consists of a collection of algorithms that are commonly used to solve medical image registration problems. A large part of the code is based on the Insight Toolkit (ITK). The modular design of `elastix` allows the user to quickly test and compare different registration methods for his/her specific application. The command-line interface simplifies the processing of large amounts of data sets, using scripting.

1.1 Outline of this manual

In Chapter 2 quite an extensive introduction to some general theory of image registration is given. Also, the different components of which a registration method consists, are treated. In Chapter 3, `elastix` is described and its usage is explained. Chapter 4 is dedicated to `transformix`, a program accompanying `elastix`. A tutorial is given in Chapter 5, including many recommendations based on the authors' experiences. More advanced registration topics are covered in Chapter 6. The final chapter provides more details for those interested in the setup of the source code, gives information on how to implement your own additions to `elastix`, and describes the use of `elastix` as a library instead of a command line program. In the Appendices A and B example (transform) parameter files are given. Appendix D contains the software license and disclaimer under which `elastix` is currently distributed.

1.2 Quick start

- Download `elastix` from http://elastix.isi.uu.nl/download.php. See Section 3.2 for details about the installation. Do not forget to subscribe to the `elastix` mailing list, which is the main forum for questions and announcements.
- Read some basics about the program at http://elastix.isi.uu.nl/about.php and in this manual.
- Try the example of usage. It can be found in the *About* section of the website. If you don't get the example running at your computer take a look at the FAQ in the general section:

  http://elastix.isi.uu.nl/FAQ.php

- Read the complete manual if you are the type of person that first wants to know.
- Get started with your own application. If you need more information at this point you can now start reading the manual. You can find more information on tuning the parameters in Chapter 5. A list of all available parameters can be found at http://elastix.isi.uu.nl/doxygen/pages.html. Also take

a look at the *parameter file database* at http://elastix.isi.uu.nl/wiki.php, for many example parameter files.

- When you are stuck, don't miss the tutorial in Chapter 5 of this manual. Also, take a look at the FAQ again for some common problems.
- When you are still stuck, do not hesitate to send an e-mail to the `elastix` mailing list. In general, you will soon get an answer. To subscribe visit http://lists.bigr.nl/mailman/listinfo/elastix.

1.3 Acknowledgements

The first version of this manual has been written while the authors worked at the Image Sciences Institute (ISI, http://www.isi.uu.nl), Utrecht, The Netherlands. We thank the users of `elastix`, whose questions and remarks helped improving the usability and documentation of `elastix`. Specifically, we want to thank the following people for proofreading (parts of) this manual when we constructed a first version: Josien Pluim, Keelin Murphy, Martijn van der Bom, Sascha Münzing, Jeroen de Bresser, Bram van Ginneken, Kajo van der Marel, Adriënne Mendrik (in no specific order). Over the years several users have contributed their work as new components in `elastix`, see the website for a list.

Chapter 2

Image registration

This chapter introduces primary registration concepts that are at the base of `elastix`. More advanced registration topics are covered in Chapter 6.

Image registration is an important tool in the field of medical imaging. In many clinical situations several images of a patient are made in order to analyse the patient's situation. These images are acquired with, for example, X-ray scanners, Magnetic Resonance Imaging (MRI) scanners, Computed Tomography (CT) scanners, and Ultrasound scanners, which provide knowledge about the anatomy of the subject. Combination of patient data, mono- or multi-modal, often yields additional clinical information not apparent in the separate images. For this purpose, the spatial relation between the images has to be found. Image registration is the task of finding a spatial one-to-one mapping from voxels in one image to voxels in the other image, see Figure 2.1. Good reviews on the subject are given in Maintz and Viergever [1998], Lester and Arridge [1999], Hill et al. [2001], Hajnal et al. [2001], Zitová and Flusser [2003], Modersitzki [2004].

The following section introduces the mathematical formulation of the registration process and gives an overview of the components of which a general registration method consists. After that, in Sections 2.3-2.8, each component is discussed in more detail. For each component, the name used by `elastix` is given, in `typewriter` style. In Section 2.9, methods to evaluate the registration results are discussed.

2.1 Registration framework

Two images are involved in the registration process. One image, the *moving image* $I_M(\boldsymbol{x})$, is deformed to fit the other image, the *fixed image* $I_F(\boldsymbol{x})$. The fixed and moving image are of dimension d and are each defined on their own spatial domain: $\Omega_F \subset \mathbb{R}^d$ and $\Omega_M \subset \mathbb{R}^d$, respectively. Registration is the problem of finding a *displacement* $\boldsymbol{u}(\boldsymbol{x})$ that makes $I_M(\boldsymbol{x}+\boldsymbol{u}(\boldsymbol{x}))$ spatially aligned to $I_F(\boldsymbol{x})$. An equivalent formulation is to say that registration is the problem of finding a *transformation* $\boldsymbol{T}(\boldsymbol{x}) = \boldsymbol{x}+\boldsymbol{u}(\boldsymbol{x})$ that makes $I_M(\boldsymbol{T}(\boldsymbol{x}))$ spatially aligned to $I_F(\boldsymbol{x})$. The transformation is defined as a mapping from the fixed image to the moving image, i.e. $\boldsymbol{T} : \Omega_F \subset \mathbb{R}^d \rightarrow \Omega_M \subset \mathbb{R}^d$. The quality of alignment is defined by a distance or similarity measure $\mathcal{S}$,

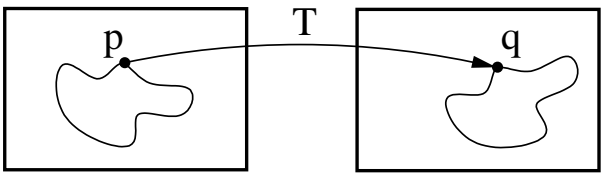


Figure 2.1: Image registration is the task of finding a spatial transformation mapping one image to another. Left is the fixed image and right the moving image. Adopted from Ibáñez et al. [2005].

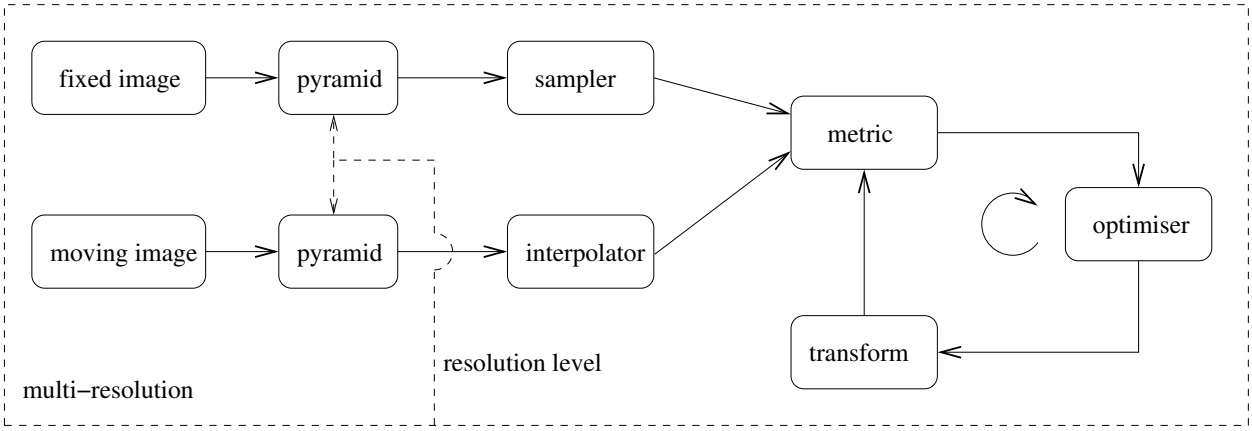


Figure 2.2: The basic registration components.

such as the sum of squared differences (SSD), the correlation ratio, or the mutual information (MI) measure. Because this problem is ill-posed for nonrigid transformations $\boldsymbol{T}$, a regularisation or penalty term $\mathcal{P}$ is often introduced that constrains $\boldsymbol{T}$.

Commonly, the registration problem is formulated as an optimisation problem in which the cost function $\mathcal{C}$ is minimised w.r.t. $\boldsymbol{T}$:

$$\hat{\boldsymbol{T}} = \arg\min_{\boldsymbol{T}} \mathcal{C}(\boldsymbol{T}; I_F, I_M), \qquad \text{with} \tag{2.1}$$

$$\mathcal{C}(\boldsymbol{T}; I_F, I_M) = -\mathcal{S}(\boldsymbol{T}; I_F, I_M) + \gamma \mathcal{P}(\boldsymbol{T}), \tag{2.2}$$

where γ weighs similarity against regularity. To solve the above minimisation problem, there are basically two approaches: parametric and nonparametric. The reader is referred to Fischer and Modersitzki [2004] for an overview on nonparametric methods, which are not discussed in this manual. The `elastix` software is based on the parametric approach. In parametric methods, the number of possible transformations is limited by introducing a parametrisation (model) of the transformation. The original optimisation problem thus becomes:

$$\hat{\boldsymbol{T}}_{\boldsymbol{\mu}} = \arg\min_{\boldsymbol{T}_{\boldsymbol{\mu}}} \mathcal{C}(\boldsymbol{T}_{\boldsymbol{\mu}}; I_F, I_M), \tag{2.3}$$

where the subscript $\boldsymbol{\mu}$ indicates that the transform has been parameterised. The vector $\boldsymbol{\mu}$ contains the values of the "transformation parameters". For example, when the transformation is modelled as a 2D rigid transformation, the parameter vector $\boldsymbol{\mu}$ contains one rotation angle and the translations in x and y direction. We may write Equation (2.3) also as:

$$\hat{\boldsymbol{\mu}} = \arg\min_{\boldsymbol{\mu}} \mathcal{C}(\boldsymbol{\mu}; I_F, I_M). \tag{2.4}$$

From this equation it becomes clear that the original problem (2.1) has been simplified. Instead of optimising over a "space of functions $\boldsymbol{T}$", we now optimise over the elements of $\boldsymbol{\mu}$. Examples of other transformation models are given in Section 2.6.

Figure 2.2 shows the general components of a parametric registration algorithm in a block scheme. The scheme is a slightly extended version of the scheme introduced in Ibáñez et al. [2005]. Several components can be recognised from Equations (2.1)-(2.4); some will be introduced later. First of all, we have the images. The concept of an image needs to be defined. This is done in Section 2.2. Then we have the cost function $\mathcal{C}$, or "metric", which defines the quality of alignment. As mentioned earlier, the cost function consists of a similarity measure $\mathcal{S}$ and a regularisation term $\mathcal{P}$. The regularisation term $\mathcal{P}$ is not discussed in this

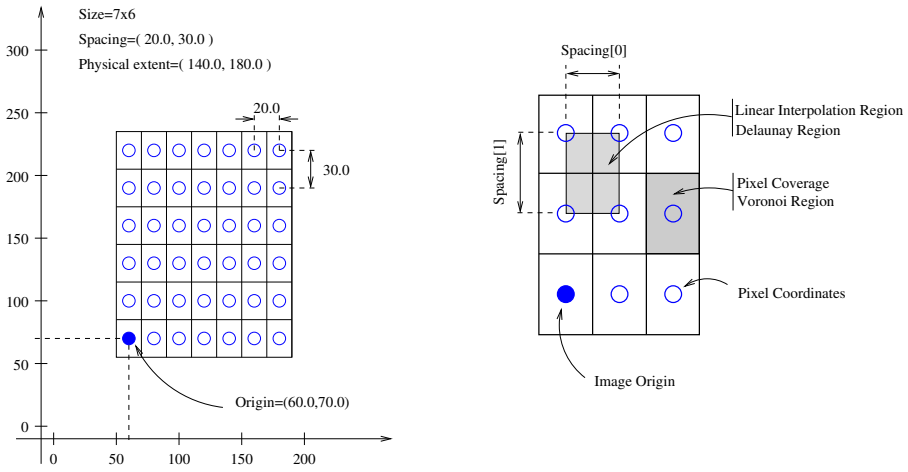


Figure 2.3: Geometrical concepts associated with the ITK image. Adopted from Ibáñez et al. [2005].

chapter, but in Chapter 6. The similarity measure $\mathcal{S}$ is discussed in Section 2.3. The definition of the similarity measure introduces the sampler component, which is treated in Section 2.4. Some examples of transformation models $\boldsymbol{T}_{\boldsymbol{\mu}}$ are given in Section 2.6. The optimisation procedure to actually solve the problem (2.4) is explained in Section 2.7. During the optimisation, the value $I_M(\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}))$ is evaluated at non-voxel positions, for which intensity interpolation is needed. Choices for the interpolator are described in Section 2.5. Another thing, not immediately clear from Equations (2.1)-(2.4), is the use of multi-resolution strategies to speed-up registration, and to make it more robust, see Section 2.8.

2.2 Images

Since image registration is all about images, we have to be careful with what is meant by an image. We adopt the notion of an image from the Insight Toolkit [Ibáñez et al., 2005, p. 40]:

> Additional information about the images is considered mandatory. In particular the information associated with the physical spacing between pixels and the position of the image in space with respect to some world coordinate system are extremely important. Image origin and spacing are fundamental to many applications. Registration, for example, is performed in physical coordinates. Improperly defined spacing and origins will result in inconsistent results in such processes. Medical images with no spatial information should not be used for medical diagnosis, image analysis, feature extraction, assisted radiation therapy or image guided surgery. In other words, medical images lacking spatial information are not only useless but also hazardous.
>
> Figure 2.3 illustrates the main geometrical concepts associated with the itk::Image. In this figure, circles are used to represent the centre of pixels. The value of the pixel is assumed to exist as a Dirac Delta Function located at the pixel centre. Pixel spacing is measured between the pixel centres and can be different along each dimension. The image origin is associated with the coordinates of the first pixel in the image. A pixel is considered to be the rectangular region surrounding the pixel centre holding the data value. This can be viewed as the Voronoi region of the image grid, as illustrated in the right side of the figure. Linear interpolation of image values is performed inside the Delaunay region whose corners are pixel centres.

Therefore, you should take care that you use an image format that is able to store the relevant information (e.g. `mhd`, DICOM). Some image formats, like `vpx`, do not store the origin and spacing. This may cause serious problems!

Up to `elastix` version 4.2, the image orientation (direction cosines) was not yet fully supported in `elastix`. From `elastix` 4.3, image orientation is fully supported, but can be disabled for backward compatibility reasons.

2.3 Metrics

Several choices for the similarity measure can be found in the literature. Some common choices are described below. Between brackets the name of the metric in `elastix` is given:

Sum of Squared Differences (SSD): (`AdvancedMeanSquares`) The SSD is defined as:

$$\mathrm{SSD}(\boldsymbol{\mu}; I_F, I_M) = \frac{1}{|\Omega_F|} \sum_{\boldsymbol{x}_i \in \Omega_F} \left(I_F(\boldsymbol{x}_i) - I_M(\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}_i))\right)^2, \tag{2.5}$$

with Ω_F the domain of the fixed image I_F, and $|\Omega_F|$ the number of voxels. Given a transformation $\boldsymbol{T}$, this measure can easily be implemented by looping over the voxels in the fixed image, taking $I_F(\boldsymbol{x}_i)$, calculating $I_M(\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}_i))$ by interpolation, and adding the squared difference to the sum.

Normalised Correlation Coefficient (NCC): (`AdvancedNormalizedCorrelation`) The NCC is defined as:

$$\mathrm{NCC}(\boldsymbol{\mu}; I_F, I_M) = \frac{\sum_{\boldsymbol{x}_i \in \Omega_F} \left(I_F(\boldsymbol{x}_i) - \overline{I_F}\right)\left(I_M(\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}_i)) - \overline{I_M}\right)}{\sqrt{\sum_{\boldsymbol{x}_i \in \Omega_F} \left(I_F(\boldsymbol{x}_i) - \overline{I_F}\right)^2 \sum_{\boldsymbol{x}_i \in \Omega_F} \left(I_M(\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}_i)) - \overline{I_M}\right)^2}}, \tag{2.6}$$

with the average grey-values $\overline{I_F} = \frac{1}{|\Omega_F|} \sum_{\boldsymbol{x}_i \in \Omega_F} I_F(\boldsymbol{x}_i)$ and $\overline{I_M} = \frac{1}{|\Omega_F|} \sum_{\boldsymbol{x}_i \in \Omega_F} I_M(\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}_i))$.

Mutual Information (MI): (`AdvancedMattesMutualInformation`) For MI [Maes et al., 1997, Viola and Wells III, 1997, Mattes et al., 2003] we use a definition given by Thévenaz and Unser [2000]:

$$\mathrm{MI}(\boldsymbol{\mu}; I_F, I_M) = \sum_{m \in L_M} \sum_{f \in L_F} p(f, m; \boldsymbol{\mu}) \log_2 \left(\frac{p(f, m; \boldsymbol{\mu})}{p_F(f) p_M(m; \boldsymbol{\mu})} \right), \tag{2.7}$$

where L_F and L_M are sets of regularly spaced intensity bin centres, p is the discrete joint probability, and p_F and p_M are the marginal discrete probabilities of the fixed and moving image, obtained by summing p over m and f, respectively. The joint probabilities are estimated using B-spline Parzen windows:

$$\begin{aligned} p(f, m; \boldsymbol{\mu}) = \frac{1}{|\Omega_F|} \sum_{\boldsymbol{x}_i \in \Omega_F} & w_F(f/\sigma_F - I_F(\boldsymbol{x}_i)/\sigma_F) \\ & \times w_M(m/\sigma_M - I_M(\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}_i))/\sigma_M), \end{aligned} \tag{2.8}$$

where w_F and w_M represent the fixed and moving B-spline Parzen windows. The scaling constants σ_F and σ_M must equal the intensity bin widths defined by L_F and L_M. These follow directly from the grey-value ranges of I_F and I_M and the user-specified number of histogram bins $|L_F|$ and $|L_M|$.

Normalized Mutual Information (NMI): (`NormalizedMutualInformation`)
NMI is defined by $\mathrm{NMI} = (H(I_F) + H(I_M))/H(I_F, I_M)$, with H denoting entropy. This expression can be compared to the definition of MI in terms of H: $\mathrm{MI} = H(I_F) + H(I_M) - H(I_F, I_M)$. Again,

with the joint probabilities defined by 2.8 (using B-spline Parzen windows), NMI can be written as:

$$\mathrm{NMI}(\boldsymbol{\mu}; I_F, I_M) = \frac{\sum_{f \in L_F} p_F(f) \log_2 p_F(f) + \sum_{m \in L_M} p_M(m;\boldsymbol{\mu}) \log_2 p_M(m;\boldsymbol{\mu})}{\sum_{m \in L_M} \sum_{f \in L_F} p(f,m;\boldsymbol{\mu}) \log_2 p(f,m;\boldsymbol{\mu})}$$

$$= \frac{\sum_{m \in L_M} \sum_{f \in L_F} p(f,m;\boldsymbol{\mu}) \log_2 \left(p_F(f) p_M(m;\boldsymbol{\mu})\right)}{\sum_{m \in L_M} \sum_{f \in L_F} p(f,m;\boldsymbol{\mu}) \log_2 p(f,m;\boldsymbol{\mu})}. \tag{2.9}$$

Kappa Statistic (KS): (`AdvancedKappaStatistic`) KS is defined as:

$$\mathrm{KS}(\boldsymbol{\mu}; I_F, I_M) = \frac{2 \sum_{\boldsymbol{x}_i \in \Omega_F} \mathbf{1}_{I_F(\boldsymbol{x}_i)=f, I_M(\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}_i))=f}}{\sum_{\boldsymbol{x}_i \in \Omega_F} \mathbf{1}_{I_F(\boldsymbol{x}_i)=f} + \mathbf{1}_{I_M(\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}_i))=f}}, \tag{2.10}$$

where $\mathbf{1}$ is the indicator function, and f a user-defined foreground value that defaults to 1.

The SSD measure is a measure that is only suited for two images with an equal intensity distribution, i.e. for images from the same modality. NCC is less strict, it assumes a linear relation between the intensity values of the fixed and moving image, and can therefore be used more often. The MI measure is even more general: only a relation between the probability distributions of the intensities of the fixed and moving image is assumed. For MI it is well-known that it is suited not only for mono-modal, but also for multi-modal image pairs. This measure is often a good choice for image registration. The NMI measure is, just like MI, suitable for mono- and multi-modality registration. Studholme et al. [1999] seems to indicate better performance than MI in some cases. The KS measure is specifically meant to register binary images (segmentations). It measures the "overlap" of the segmentations.

2.4 Image samplers

In Equations (2.5)-(2.8) we observe a loop over the fixed image: $\sum_{\boldsymbol{x}_i \in \Omega_F}$. Until now, we assumed that the loop goes over *all* voxels of the fixed image. In general, this is not necessary. A subset may suffice [Thévenaz and Unser, 2000, Klein et al., 2007]. The subset may be selected in different ways: random, on a grid, etc. The sampler component represents this process.

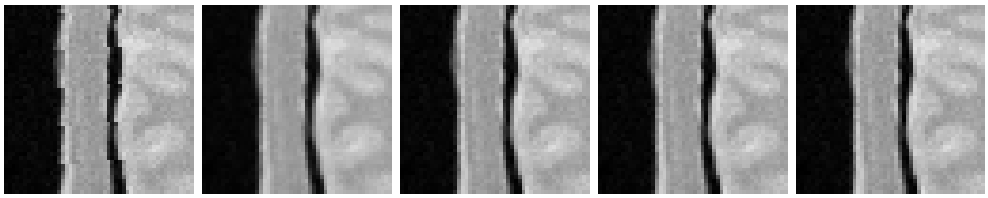
The following samplers are often used:

Full: (`Full`) A full sampler simply selects all voxel coordinates $\boldsymbol{x}_i$ of the fixed image.

Grid: (`Grid`) The grid sampler defines a regular grid on the fixed image and selects the coordinates $\boldsymbol{x}_i$ on the grid. Effectively, the grid sampler thus downsamples the fixed image (not preceded by smoothing). The size of the grid (or equivalently, the downsampling factor, which is the original fixed image size divided by the grid size) is a user input.

Random: (`Random`) A random sampler randomly selects a user-specified number of voxels from the fixed image, whose coordinates form $\boldsymbol{x}_i$. Every voxel has equal chance to be selected. A sample is not necessarily selected only once.

Random Coordinate: (`RandomCoordinate`) A random coordinate sampler is similar to a random sampler. It also randomly selects a user-specified number of coordinates $\boldsymbol{x}_i$. However, the random coordinate sampler is not limited to voxel positions. Coordinates *between* voxels can also be selected. The grey-value $I_F(\boldsymbol{x}_i)$ at those locations must of course be obtained by interpolation.



(a) (b) (c) (d) (e)

Figure 2.4: Interpolation. (a) nearest neighbour, (b) linear, (c) B-spline $N = 2$, (d) B-spline $N = 3$, (e) B-spline $N = 5$.

While at first sight the full sampler seems the most obvious choice, in practice it is not always used, because of its computational costs in large images. The random samplers are especially useful in combination with a stochastic optimisation method [Klein et al., 2007]. See also Section 2.7. The use of the random coordinate sampler makes the cost function $\mathcal{C}$ a more smooth function of $\boldsymbol{\mu}$, which makes the optimisation problem (2.4) easier to solve. This has been shown in Thévenaz and Unser [2008].

2.5 Interpolators

As stated previously, during the optimisation the value $I_M(\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}))$ is evaluated at non-voxel positions, for which intensity interpolation is needed. Several methods for interpolation exist, varying in quality and speed. Some examples are given in Figure 2.4.

Nearest neighbour: (`NearestNeighborInterpolator`) This is the most simple technique, low in quality, requiring little resources. The intensity of the voxel nearest in distance is returned.

Linear: (`LinearInterpolator`) The returned value is a weighted average of the surrounding voxels, with the distance to each voxel taken as weight.

N-th order B-spline: (`BSplineInterpolator` or `BSplineInterpolatorFloat` for a memory efficient version) The higher the order, the better the quality, but also requiring more computation time. In fact, nearest neighbour ($N = 0$) and linear interpolation ($N = 1$) also fall in this category. See Unser [1999] for more details.

During registration a first-order B-spline interpolation, i.e. linear interpolation, often gives satisfactory results. It is a good trade-off between quality and speed. To generate the final result, i.e. the deformed result of the registration, a higher-order interpolation is usually required, for which we recommend $N = 3$. The final result is generated in `elastix` by a so-called `ResampleInterpolator`. Any one of the above can be used, but you need to prepend the name with `Final`, for example: `FinalLinearInterpolator`.

2.6 Transforms

A frequent confusion about the transformation is its direction. In `elastix` the transformation is defined as a **coordinate mapping from the fixed image domain to the moving image domain**: $\boldsymbol{T} : \Omega_F \subset \mathbb{R}^d \rightarrow \Omega_M \subset \mathbb{R}^d$. The confusion usually stems from the phrase: "the moving image is deformed to fit the fixed image". Although one can speak about image registration like this, such a phrase is not meant to reflect mathematical underlyings: one deforms the moving image, but the transformation is still defined from fixed to moving image. The reason for this becomes clear when trying to compute the deformed moving image (the registration result) $I_M(\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}))$ (this process is frequently called *resampling*). If the transformation would be defined from moving to fixed image, not all voxels in the fixed image domain would be mapped to (e.g. in

case of a scaling), and holes would occur in the deformed moving image. With the transformation defined as it is, resampling is quite simple: loop over all voxels $\boldsymbol{x}$ in the fixed image domain Ω_F, compute its mapped position $\boldsymbol{y} = \boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x})$, interpolate the moving image at $\boldsymbol{y}$, and fill in this value at $\boldsymbol{x}$ in the output image.

The transformation model used for $\boldsymbol{T}_{\boldsymbol{\mu}}$ determines what type of deformations between the fixed and moving image you can handle. In order of increasing flexibility, these are the translation, the rigid, the similarity, the affine, the nonrigid B-spline and the nonrigid thin-plate spline like transformations.

Translation: (`TranslationTransform`) The translation is defined as:

$$\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}) = \boldsymbol{x} + \boldsymbol{t}, \tag{2.11}$$

with $\boldsymbol{t}$ the translation vector. The parameter vector is simply defined by $\boldsymbol{\mu} = \boldsymbol{t}$.

Rigid: (`EulerTransform`) A rigid transformation is defined as:

$$\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}) = R(\boldsymbol{x} - \boldsymbol{c}) + \boldsymbol{t} + \boldsymbol{c}, \tag{2.12}$$

with the matrix R a rotation matrix (i.e. orthonormal and proper), $\boldsymbol{c}$ the centre of rotation, and $\boldsymbol{t}$ translation again. The image is treated as a rigid body, which can translate and rotate, but cannot be scaled/stretched. The rotation matrix is parameterised by the Euler angles (one in 2D, three in 3D). The parameter vector $\boldsymbol{\mu}$ consists of the Euler angles (in rad) and the translation vector. In 2D, this gives a vector of length 3: $\boldsymbol{\mu} = (\theta_z, t_x, t_y)^T$, where θ_z denotes the rotation around the axis normal to the image. In 3D, this gives a vector of length 6: $\boldsymbol{\mu} = (\theta_x, \theta_y, \theta_z, t_x, t_y, t_z)^T$. The centre of rotation is not part of $\boldsymbol{\mu}$; it is a fixed setting, usually the centre of the image.

Similarity: (`SimilarityTransform`) A similarity transformation is defined as

$$\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}) = s\boldsymbol{R}(\boldsymbol{x} - \boldsymbol{c}) + \boldsymbol{t} + \boldsymbol{c}, \tag{2.13}$$

with s a scalar and $\boldsymbol{R}$ a rotation matrix. This means that the image is treated as an object, which can translate, rotate, and scale isotropically. The rotation matrix is parameterised by an angle in 2D, and by a so-called "versor" in 3D (Euler angles could have been used as well). The parameter vector $\boldsymbol{\mu}$ consists of the angle/versor, the translation vector, and the isotropic scaling factor. In 2D, this gives a vector of length 4: $\boldsymbol{\mu} = (s, \theta_z, t_x, t_y)^T$. In 3D, this gives a vector of length 7: $\boldsymbol{\mu} = (q_1, q_2, q_3, t_x, t_y, t_z, s)^T$, where q_1, q_2, and q_3 are the elements of the versor. There are few cases when you need this transform.

Affine: (`AffineTransform`) An affine transformation is defined as:

$$\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}) = \boldsymbol{A}(\boldsymbol{x} - \boldsymbol{c}) + \boldsymbol{t} + \boldsymbol{c}, \tag{2.14}$$

where the matrix $\boldsymbol{A}$ has no restrictions. This means that the image can be translated, rotated, scaled, and sheared. The parameter vector $\boldsymbol{\mu}$ is formed by the matrix elements a_{ij} and the translation vector. In 2D, this gives a vector of length 6: $\boldsymbol{\mu} = (a_{11}, a_{12}, a_{21}, a_{22}, t_x, t_y)^T$. In 3D, this gives a vector of length 12.

We also have implemented another flavor of the affine transformation, with identical meaning, but using another parametrization. Instead of having $\boldsymbol{\mu}$ formed by the matrix elements + translation, it is formed by d rotations, d shear factors, d scales, and d translations. The definition reads:

$$\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}) = \boldsymbol{RGS}(\boldsymbol{x} - \boldsymbol{c}) + \boldsymbol{t} + \boldsymbol{c}, \tag{2.15}$$

with $\boldsymbol{R}$, $\boldsymbol{G}$ and $\boldsymbol{S}$ the rotation, shear and scaling matrix, respectively. It can be selected using `AffineDTITransform`, as it was first made with DTI imaging in mind, although it can be used anywhere else as well. It is currently only implemented in 3D, and also has 12 parameters.

B-splines: (`BSplineTransform`) For the category of non-rigid transformations, B-splines [Rueckert et al., 1999] are often used as a parameterisation:

$$\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}) = \boldsymbol{x} + \sum_{\boldsymbol{x}_k \in \mathcal{N}_{\boldsymbol{x}}} \boldsymbol{p}_k \boldsymbol{\beta}^3 \left(\frac{\boldsymbol{x} - \boldsymbol{x}_k}{\boldsymbol{\sigma}} \right), \tag{2.16}$$

with $\boldsymbol{x}_k$ the control points, $\boldsymbol{\beta}^3(x)$ the cubic multidimensional B-spline polynomial [Unser, 1999], $\boldsymbol{p}_k$ the B-spline coefficient vectors (loosely speaking, the control point displacements), $\boldsymbol{\sigma}$ the B-spline control point spacing, and $\mathcal{N}_{\boldsymbol{x}}$ the set of all control points within the compact support of the B-spline at $\boldsymbol{x}$. The control points $\boldsymbol{x}_k$ are defined on a regular grid, overlayed on the fixed image. In this context we talk about 'the control point grid that is put on the fixed image', and about 'control points that are moved around'. Note that $\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}_k) \neq \boldsymbol{x}_k + \boldsymbol{p}_k$, a common misunderstanding. Calling $\boldsymbol{p}_k$ the control point displacements is, therefore, actually somewhat misleading. Also note that the control point grid is entirely unrelated to the grid used by the Grid image sampler, see Section 2.4.

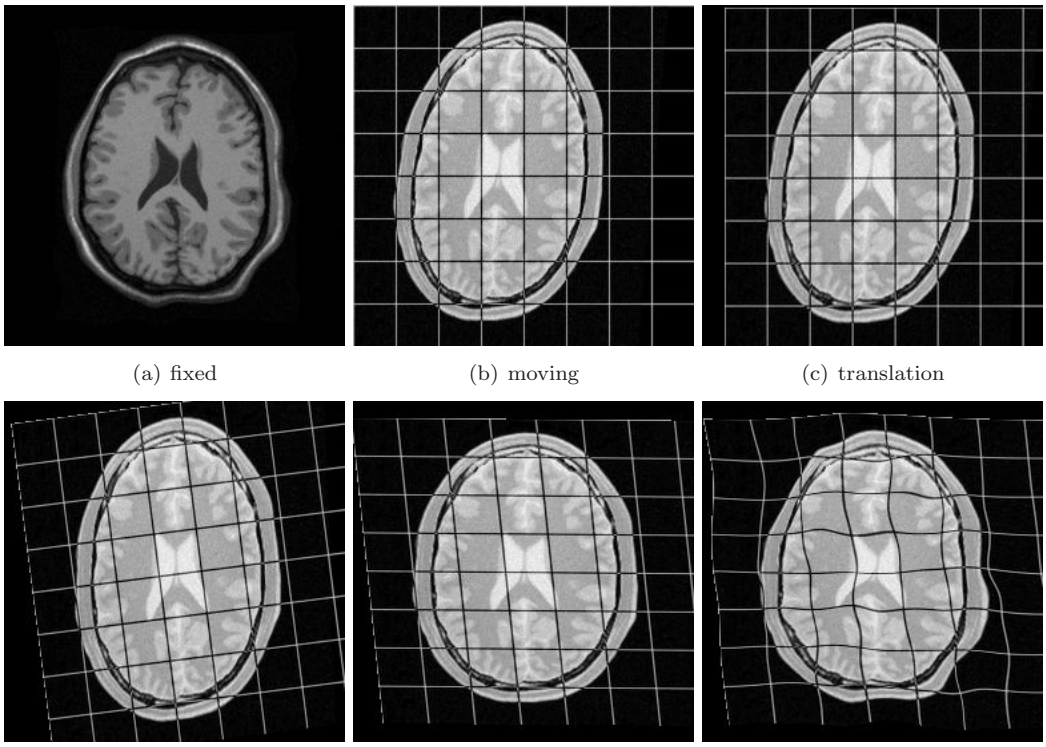
The control point grid is defined by the amount of space between the control points $\boldsymbol{\sigma} = (\sigma_1, \ldots, \sigma_d)$ (with d the image dimension), which can be different for each direction. B-splines have local support ($|\mathcal{N}_{\boldsymbol{x}}|$ is small), which means that the transformation of a point can be computed from only a couple of surrounding control points. This is beneficial both for modelling local transformations, and for fast computation. The parameters $\boldsymbol{\mu}$ are formed by the B-spline coefficients $\boldsymbol{p}_k$. The number of control points $\boldsymbol{P} = (P_1, \ldots, P_d)$ determines the number of parameters M, by $M = (P_1 \times \ldots \times P_d) \times d$. P_i in turn is determined by the image size $\boldsymbol{s}$ and the B-spline grid spacing, i.e. $P_i \approx s_i/\sigma_i$ (where we use $\approx$ since some additional control points are placed just outside the image). For 3D images, $M \approx 10000$ parameters is not an unusual case, and M can easily grow to $10^5 - 10^6$. The parameter vector (for 2D images) is composed as follows: $\boldsymbol{\mu} = (p_{1x}, p_{2x}, \ldots, p_{P_1}, p_{1y}, p_{2y}, \ldots, p_{P_2})^T$.

Thin-plate splines: (`SplineKernelTransform`) Thin-plate splines are another well-known representation for nonrigid transformations. The thin-plate spline is an instance of the more general class of kernel-based transforms Davis et al. [1997], Brooks and Arbel [2007]. The transformation is based on a set of K corresponding landmarks in the fixed and moving image: $\boldsymbol{x}_k^{\text{fix}}$ and $\boldsymbol{x}_k^{\text{mov}}, k = 1, \ldots, K$, respectively. The transformation is expressed as a sum of an affine component and a nonrigid component:

$$\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}) = \boldsymbol{x} + A\boldsymbol{x} + \boldsymbol{t} + \sum_{\boldsymbol{x}_k^{\text{fix}}} \boldsymbol{c}_k \boldsymbol{G}(\boldsymbol{x} - \boldsymbol{x}_k^{\text{fix}}), \tag{2.17}$$

where $\boldsymbol{G}(\boldsymbol{r})$ is a basis function and $\boldsymbol{c}_k$ are the coefficients corresponding to each landmark. The coefficients $\boldsymbol{c}_k$ and the elements of $\boldsymbol{A}$ and $\boldsymbol{t}$ are computed from the landmark displacements $\boldsymbol{d}_k = \boldsymbol{x}_k^{\text{mov}} - \boldsymbol{x}_k^{\text{fix}}$. The specific choice of basis function $\boldsymbol{G}(\boldsymbol{r})$ determines the "physical behaviour". The most often used choice of $\boldsymbol{G}(\boldsymbol{r})$ leads to the thin-plate spline, but another useful alternative is the elastic-body spline Davis et al. [1997]. The spline kernel transforms are often less efficient than the B-splines (because they lack the compact support property of the B-splines), but they allow for more flexibility in placing the control points $\boldsymbol{x}_k^{\text{fix}}$. The moving landmarks form the parameter vector $\boldsymbol{\mu}$. Both landmark sets are needed to define a transformation. Note that in order to perform a registration, only the fixed landmark positions are given by the user; the moving landmarks are initialized to equal the fixed landmarks, corresponding to the identity transformation, and are subsequently optimized. The parameter vector is (for 2D images) composed as follows: $\boldsymbol{\mu} = (x_{1x}^{\text{mov}}, x_{1y}^{\text{mov}}, x_{2x}^{\text{mov}}, x_{2y}^{\text{mov}}, \ldots, x_{Kx}^{\text{mov}}, x_{Ky}^{\text{mov}})^T$. Note the difference in ordering of $\boldsymbol{\mu}$ compared to the B-splines transform.

See Figure 2.5 for an illustration of different transforms. Choose the transformation that fits your needs: only choose a nonrigid transformation if you expect that the underlying problem contains local deformations, choose a rigid transformation if you only need to compensate for differences in pose. To initialise a nonrigid



(a) fixed (b) moving (c) translation

(d) rigid (e) affine (f) B-spline

Figure 2.5: Different transformations. (a) the fixed image, (b) the moving image with a grid overlayed, (c) the deformed moving image $I_M(\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}))$ with a translation transformation, (d) a rigid transformation, (e) an affine transformation, and (f) a B-spline transformation. The deformed moving image nicely resembles the fixed image $I_F(\boldsymbol{x})$ using the B-spline transformation. The overlay grids give an indication of the deformations imposed on the moving image. NB: the overlayed grid in (f) is NOT the B-spline control point grid, since that one is defined on the fixed image!

registration problem, perform a rigid or affine one first. The result of the initial rigid or affine registration $\boldsymbol{T}_{\hat{\boldsymbol{\mu}}_0}$ is combined with a nonrigid transformation $\boldsymbol{T}_{\boldsymbol{\mu}}^{\mathrm{NR}}$ in one of the following two ways:

$$\text{addition:} \quad \boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}) = \boldsymbol{T}_{\boldsymbol{\mu}}^{\mathrm{NR}}(\boldsymbol{x}) + \boldsymbol{T}_{\hat{\boldsymbol{\mu}}_0}(\boldsymbol{x}) - \boldsymbol{x} \tag{2.18}$$

$$\text{composition:} \quad \boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}) = \boldsymbol{T}_{\boldsymbol{\mu}}^{\mathrm{NR}}\left(\boldsymbol{T}_{\hat{\boldsymbol{\mu}}_0}(\boldsymbol{x})\right) = (\boldsymbol{T}_{\boldsymbol{\mu}}^{\mathrm{NR}} \circ \boldsymbol{T}_{\hat{\boldsymbol{\mu}}_0})(\boldsymbol{x}) \tag{2.19}$$

The latter method is in general to be preferred, because it makes several postregistration analysis tasks somewhat more straightforward.

2.7 Optimisers

To solve the optimisation problem (2.4), i.e. to obtain the optimal transformation parameter vector $\hat{\boldsymbol{\mu}}$, commonly an iterative optimisation strategy is employed:

$$\boldsymbol{\mu}_{k+1} = \boldsymbol{\mu}_k + a_k \boldsymbol{d}_k, \quad k = 0, 1, 2, \cdots, \tag{2.20}$$

with $\boldsymbol{d}_k$ the 'search direction' at iteration k, a_k a scalar gain factor controlling the step size along the search direction. The optimisation process is illustrated in Figure 2.6. Klein et al. [2007] give an overview of various optimisation routines the literature offers. Examples are quasi-Newton (QN), nonlinear conjugate

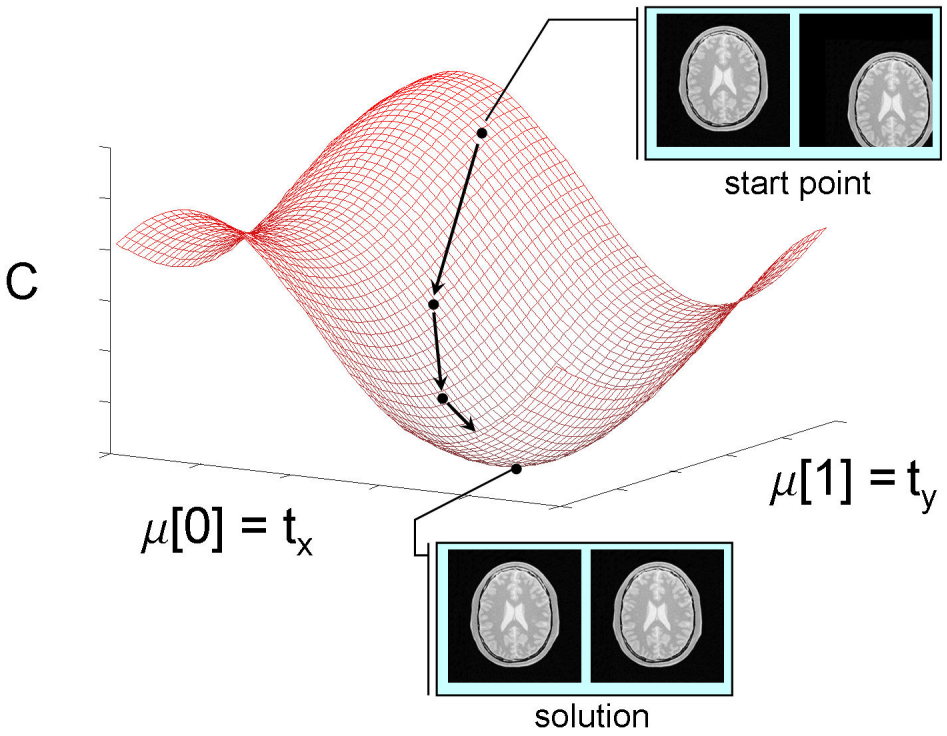


Figure 2.6: Iterative optimisation. Example for registration with a translation transformation model. The arrows indicate the steps $a_k \boldsymbol{d}_k$ taken in the direction of the optimum, which is the minimum of the cost function.

gradient (NCG), gradient descent (GD), and Robbins-Monro (RM). Gradient descent and Robbins-Monro are discussed below. For details on other optimisation methods we refer to [Klein et al., 2007, Nocedal and Wright, 1999].

Gradient descent (GD): (`StandardGradientDescent` or `RegularStepGradientDescent`) Gradient descent optimisation methods take the search direction as the negative gradient of the cost function:

$$\boldsymbol{\mu}_{k+1} = \boldsymbol{\mu}_k - a_k \boldsymbol{g}(\boldsymbol{\mu}_k), \tag{2.21}$$

with $\boldsymbol{g}(\boldsymbol{\mu}_k) = \partial \mathcal{C} / \partial \boldsymbol{\mu}$ evaluated at the current position $\boldsymbol{\mu}_k$. Several choices exist for the gain factor a_k. It can for example be determined by a line search or by using a predefined function of k.

Robbins-Monro (RM): (`StandardGradientDescent` or `FiniteDifferenceGradientDescent`) The RM optimisation method replaces the calculation of the derivative of the cost function $\boldsymbol{g}(\boldsymbol{\mu}_k)$ by an approximation $\widetilde{\boldsymbol{g}}_k$.

$$\boldsymbol{\mu}_{k+1} = \boldsymbol{\mu}_k - a_k \widetilde{\boldsymbol{g}}_k, \tag{2.22}$$

The approximation is potentially faster to compute, but might deteriorate convergence properties of the GD scheme, since every iteration an approximation error $\boldsymbol{g}(\boldsymbol{\mu}_k) - \widetilde{\boldsymbol{g}}_k$ is made. Klein et al. [2007] showed that using only a small random subset of voxels (≈ 2000) from the fixed image accelerates registration significantly, without compromising registration accuracy. The Random or RandomCoordinate samplers, described in Section 2.4, are examples of samplers that pick voxels randomly. It is important that a new subset of fixed image voxels is selected every iteration k, so that the approximation error

has zero mean. The RM method is usually combined with a_k as a predefined decaying function of k:

$$a_k = \frac{a}{(k+A)^\alpha}, \tag{2.23}$$

where $a > 0$, $A \geq 1$, and $0 \leq \alpha \leq 1$ are user-defined constants. In our experience, a reasonable choice is $\alpha \approx 0.6$ and A approximately 10% of the user-defined maximum number of iterations, or less. The choice of the overall gain, a, depends on the expected ranges of $\boldsymbol{\mu}$ and $\boldsymbol{g}$ and is thus problem-specific. In our experience, the registration result is not very sensitive to small perturbations of these parameters. Section 5.3.6 gives some more advice.

Note that GD and RM are in fact very similar. Running RM with a Full sampler (see Section 2.4), instead of a Random sampler, is equivalent to performing GD. We recommend the use of RM over GD, since it is so much faster, without compromising on accuracy. In that case, the parameter a is the parameter that is to be tuned for your application. A more advanced version of the `StandardGradientDescent` is the `AdaptiveStochasticGradientDescent`, which requires less parameters to be set and tends to be more robust Klein et al. [2009].

Other optimisers available in `elastix` are: `FullSearch`, `ConjugateGradient`, `ConjugateGradientFRPR`, `QuasiNewtonLBFGS`, `RSGDEachParameterApart`, `SimultaneousPerturbation`, `CMAEvolutionStrategy`.

2.8 Multi-resolution

For a good overview of multi-resolution strategies see Lester and Arridge [1999]. Two hierarchical methods are distinguished: reduction of data complexity, and reduction of transformation complexity.

2.8.1 Data complexity

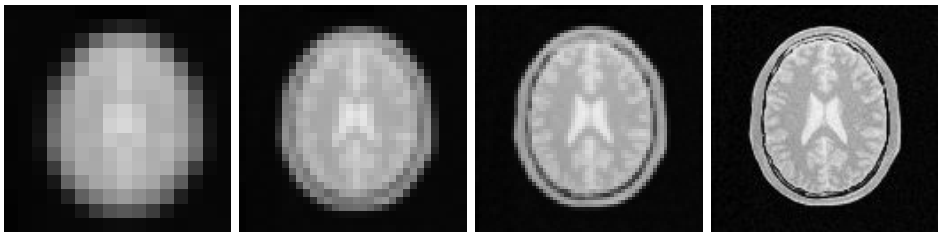
It is common to start the registration process using images that have lower complexity, e.g., images that are smoothed and possibly downsampled. This increases the chance of successful registration. A series of images with increasing amount of smoothing is called a scale space. If the images are not only smoothed, but also downsampled, the data is not only less complex, but the *amount* of data is actually reduced. In that case, we talk about a "pyramid". However, confusingly, the word pyramid is used by us also to refer to a scale space. Several scale spaces or pyramids are found in the literature, amongst others Gaussian and Laplacian pyramids, morphological scale space, and spline and wavelet pyramids. The Gaussian pyramid is the most common one. In `elastix` we have:

Gaussian pyramid: (`FixedRecursiveImagePyramid` and `MovingRecursiveImagePyramid`) Applies smoothing and down-sampling.

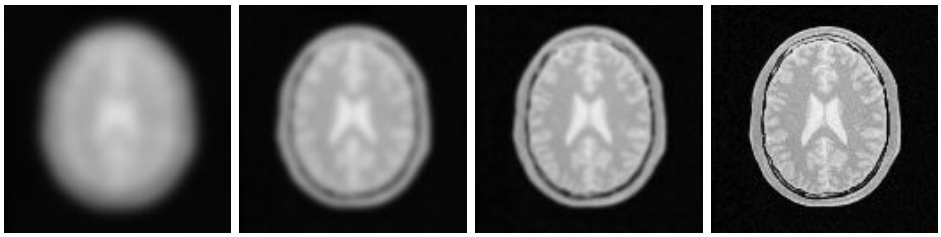
Gaussian scale space: (`FixedSmoothingImagePyramid` and `MovingSmoothingImagePyramid`) Applies smoothing and *no* down-sampling.

Shrinking pyramid: (`FixedShrinkingImagePyramid` and `MovingShrinkingImagePyramid`) Applies *no* smoothing, but only down-sampling.

Figure 2.7 shows the Gaussian pyramid with and without downsampling. In combination with a Full sampler (see Section 2.4), using a pyramid with downsampling will save a lot of time in the first resolution levels, because the image contains much fewer voxels. In combination with a Random sampler, or RandomCoordinate, the downsampling step is not necessary, since the random samplers select a user-defined number of samples anyway, independent of the image size.



(a) resolution 0 (b) resolution 1 (c) resolution 2 (d) original



(e) resolution 0 (f) resolution 1 (g) resolution 2 (h) original

Figure 2.7: Two multi-resolution strategies using a Gaussian pyramid ($\sigma = 8.0, 4.0, 2.0$ voxels). The first row shows multi-resolution with down-sampling (`FixedRecursiveImagePyramid`), the second row without (`FixedSmoothingImagePyramid`). Note that in the first row, for each dimension, the image size is halved every resolution, but that the voxel size increases with a factor 2, so physically the images are of the same size every resolution.

2.8.2 Transformation complexity

The second multiresolution strategy is to start the registration with fewer degrees of freedom for the transformation model. The degrees of freedom of the transformation equals the length (number of elements) of the parameter vector $\boldsymbol{\mu}$.

An example of this was already mentioned in Section 2.6: the use of a rigid transformation prior to nonrigid (B-spline) registration. We may even use a three-level strategy: first rigid, then affine, then nonrigid B-spline.

Another example is to increase the number of degrees of freedom within the transformation model. With a B-spline transformation, it is often good practice to start registration with a coarse control point grid, only capable of modelling coarse deformations. In subsequent resolutions the B-spline grid is gradually refined, thereby introducing the capability to match smaller structures. See Section 5.3.5.

2.9 Evaluating registration

How do you verify that your registration was successful? This is a difficult problem. In general, you don't know for each voxel where it should map to. Here are some hints:

- The deformed moving image $I_M(\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}))$ should look similar to the fixed image $I_F(\boldsymbol{x})$. So, compare images side by side in a viewer. You can also display the two images on top of each other with a checkerboard view or a dragable cross. Besides looking similar, also check that the deformed moving image has the same texture as the moving image. Sudden blurred areas in the deformed image may indicate that the deformation at that region is too large.
- For mono-modal image data you can inspect the difference image. Perfect registration would result in a difference image without any edges, just noise.

- Compute the overlap of segmented anatomical structures after registration. The better the overlap, the better the registration. Note that this requires you to (manually) segment structures in your data. To measure overlap, commonly the Dice similarity coefficient (DSC) is used:

$$\mathrm{DSC}(X,Y) = \frac{2|X \cap Y|}{|X| + |Y|}, \tag{2.24}$$

  where X and Y represent the binary label images, and $|\cdot|$ denotes the number of voxels that equal 1. A higher DSC indicates a better correspondence. A value of 1 indicates perfect overlap, a value of 0 means no overlap at all. Also the Tannimoto coefficient (TC) is used often. It is related to the DSC by $\mathrm{DSC} = 2\mathrm{TC}/(\mathrm{TC}+1)$. See also Crum et al. [2006]. It is important to realise that the surface-volume ratio of the segmented structures influences the overlap values you typically get [Rohlfing et al., 2004]. A value of DSC $= 0.8$ would be very good for the overlap of complex vessel structures. For large spherical objects though, an overlap < 0.9 is in general not very good. What is good enough depends of course on your application.

- Compute the distance after registration between points that you know correspond. You can obtain corresponding points by manually clicking them in the fixed and the moving image. A less time-consuming option is the semi-automated approach of Murphy *et al.* Murphy et al. [2008], which is designed for finding corresponding points in the lung. Ideally, the registration has found the same correspondence as the ground truth.

- Inspect the deformation field by looking at the determinant of the Jacobian of $\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x})$. Values smaller than 1 indicate local compression, values larger than 1 indicate local expansion, and 1 means volume preservation. The measure is quantitative: a value of 1.1 means a 10% increase in volume. If this value deviates substantially from 1, you may be worried (but maybe not if this is what you expect for your application). In case it is negative you have "foldings" in your transformation, and you definitely should be worried.

- Inspect the convergence, by computing for each iteration the exact metric value (and not an approximated value, when you do random sampling), and plot it. For example for the SSD measure, the lower the metric value, the better the registration.

- Do not use image similarity as a way to evaluate your registration. Torsten Rohlfing can explain why Rohlfing [2012].

2.10 Visualizing registration

`elastix` is a command line program and does not do visualization. It takes the input fixed and moving image and at the end of the registration generates an output (result) image. Usually, however, you will need to inspect the end result visually. For this you can use an external viewer. Such a viewer does not come with the `elastix` package, but is a stand-alone application, with dedicated functionality for visualization. We have listed a number of visualization tools in Table 2.1. All of them are freely available, sometimes even as open source. The list is not exhaustive.

Tool	Open source?	Platforms	url and comments
MeVisLab	✗	✓✓✓	http://www.mevislab.de/ MeVisLab has modular framework for the development of image processing algorithms and visualization and interaction methods, with a special focus on medical imaging. Quite easy in use.
ITK-SNAP	✓	✓✓✓	http://www.itksnap.org Visualization, mostly targeted to segmentation.
ParaView	✓	✓✓✓	http://www.paraview.org/ Data analysis, exploration and visualization application. Renderings are nice. Sometimes difficult in use.
3DSlicer	✓	✓✓✓	http://www.slicer.org/ Application and framework for medical image analysis, visualization, and surgical navigation.
VV	✓	✓✓✓	http://www.creatis.insa-lyon.fr/rio/vv The 4D Slicer, a fast and simple viewer. VV is more specifically designed for qualitative evaluation of image registration and deformation field visualization. A tutorial on the use of VV in combination with `elastix` can be found in Appendix C of this manual.

Table 2.1: A number of visualization tools. The three marks for the platforms column denote Windows, Linux and Mac OSX support, respectively.

Chapter 3

elastix

3.1 Introduction

The development of **elastix** started half to late 2003, and was intended to facilitate our registration research. After some initial versions we decided to put the separate components of **elastix** in separate libraries. This resulted in major version 3.0 in November 2004. **elastix** 3.0 was also the first version that was made publicly available on the **elastix** website, around the same time. The continued development brings us today (February 12, 2014) to version 4.7.

what	where
Website	http://elastix.isi.uu.nl
SVN repository	https://svn.bigr.nl/elastix/trunkpublic
Dashboard	http://my.cdash.org/index.php?project=elastix
WIKI	http://elastix.isi.uu.nl/wiki.php
FAQ	http://elastix.isi.uu.nl/FAQ.php
Mailing list subscription	http://lists.bigr.nl/mailman/listinfo/elastix
Mailing list	elastix@bigr.nl

The website also contains a **doxygen**[1] generated part that provides documentation of the source code. An overview of all available classes can be found at

http://elastix.isi.uu.nl/doxygen/classes.html.

For each class a description of this class is given, together with information on how to use it in **elastix**. See

http://elastix.isi.uu.nl/doxygen/modules.html

for an overview of all available components.

3.1.1 Key features

elastix is

- open source, freely available from http://elastix.isi.uu.nl;
- based on the ITK, so the code base is thoroughly tested. Quite some modifications/additions are made to the original ITK code though, such as the use of samplers, a transformation class that combines multiple transformation using composition or addition, and more.

[1] http://www.doxygen.org

- suitable for many image formats. The use of ITK implies that all image formats supported by ITK are supported by `elastix`. Some often used (medical) image formats are: .mhd (MetaIO), .hdr (Analyze), .nii (NIfTI), .gipl, .dcm (DICOM slices). DICOM directories are not directly supported by `elastix`;
- multi-platform (at least Windows, Linux and Mac OS), multi-compiler (at least Visual C++ 2008, 2010, gcc 4.x, clang 3.3+), and supports 32 and 64 bit systems. The underlying ITK code builds on many more platforms, see www.itk.org/Wiki/ITK_Prerequisites. So, it is highly portable to the platform of the user's choice;
- highly configurable: there is a lot of choice for all the registration components. Choosing the configuration that suits your needs is easy thanks to human readable and editable parameter file;
- easy to use for large amounts of data, since `elastix` can be called easily in a script;
- fast, thanks to stochastic subsampling Klein et al. [2007], and thanks to multi-threading and code optimizations Shamonin et al. [2014];
- relatively easy to extend, i.e. to add new components, so it is very suited for research also.

3.2 Getting started

This section describes how you can install `elastix`, either directly from the binaries, or by compiling `elastix` yourself.

3.2.1 Getting started the really easy way

The easiest way to get started with `elastix` is to use the pre-compiled binaries.

1. Download the compressed archive from the website:

   http://elastix.isi.uu.nl/download.php

2. Extract the archive to a `folder` of your choice.
3. Make sure your operating system can find the program:
   (a) Windows 7: Go to the control panel, go to "System", go to "Advanced system settings", click "Environmental variables", add `folder` to the variable "path".
   (b) Linux: Add the following lines to your `.bashrc` file:

   ```
   export PATH=folder/bin:$PATH
   export LD_LIBRARY_PATH=folder/lib:$LD_LIBRARY_PATH
   ```

   or call `elastix` with the full path: `fullPathToFolder\elastix`. Note that in Linux, you will have to set the `LD_LIBRARY_PATH` anyway.

3.2.2 Getting started the easy way

It is also possible to compile `elastix` yourself, since the source code is freely available. In this section, we assume you use the Microsoft Visual C++ 2008 (or higher) compiler under Windows, and the GCC compiler under Linux/MacOS.

1. Download and install CMake: www.cmake.org.

2. Download and compile the ITK version 4.5.0: www.itk.org. Make sure to set the following (advanced) CMake variable to ON: Module_ITKReview, and optionally ITK_USE_64BITS_IDS and ITK_LEGACY_REMOVE. For faster building of ITK you can switch off BUILD_EXAMPLES and BUILD_TESTING.

3. Obtain the sources. There are three possibilities:

   (a) Download the compressed sources from the website. Extract the archive to <your-elastix-folder> of your choice.

   (b) Use subversion (https://subversion.tigris.org) to check out the release from the subversion repository:

   ```
   svn co --username elastixguest --password elastixguest
     https://svn.bigr.nl/elastix/tagspublic/elastix_XX_X <your-elastix-folder>
   ```

   where XX_X is the major version number (first 2 digits) and the minor version number (1 digit). So, for example, for version 4.7 this would be 04_7.

   (c) Use subversion to check out the latest development version. NB: this version might be unstable!

   ```
   svn co --username elastixguest --password elastixguest
     https://svn.bigr.nl/elastix/trunkpublic <your-elastix-folder>
   ```

4. Run CMake for elastix:

   (a) Windows: start CMake. Find the src folder with the source code. Set the folder where you want the binaries to be created. Click "Configure" and select the compiler that you use. Set the CMAKE_INSTALL_PREFIX to the directory where you want elastix installed. Click "Configure" until all cache values are no longer red, and click "Generate".

   (b) Linux: run CMake from the folder where you want the binaries to be created, with as command line argument the folder in which the sources were extracted: ccmake <src-folder>. Set the CMAKE_BUILD_TYPE to "Release" and the CMAKE_INSTALL_PREFIX to the directory where you want elastix installed.

   CMake will create a project or solution or make file for your compiler.

5. Compile elastix by opening the project and selecting "compile" in release mode, or on Linux by running make install. Your compiler will now create the elastix binaries. On Windows you can perform the installation step (which copies the binaries to the CMAKE_INSTALL_PREFIX directory) by also 'compiling' the INSTALL project.

6. Make sure your operating system can find the program, see above.

For developers: When running CMake, you may toggle the display of the "advanced" options. In this list you will find several options like USE_BSplineTransform ON/OFF. By default only the most commonly used components are ON. To reduce compilation time, you may turn some components OFF, which you do not plan to use anyway. Be careful though to not turn off essential components. The released binaries are compiled with all components ON.

3.3 How to call elastix

elastix is a command line program, although since version 4.7 (February 2014) initial support for a library interface is available, see Section 7.3.2. This means that you have to open a command line interface (a DOS-box, a shell) and type in an appropriate elastix command. This also means that there is no graphical user interface. Help on using the program can be acquired as follows:

```
elastix --help
```

which will give a list of mandatory and optional arguments. The most basic command to run a registration is as follows:

```
elastix -f fixedImage.ext -m movingImage.ext -out outputDirectory -p parameterFile.txt
```

where '`ext`' is the extension of the image files. The above arguments are mandatory. These are minimally needed to run `elastix`. The parameter file is an important file: it contains, in normal text, what kind of registration is performed (i.e. what metric, optimiser, etc.) and what the parameters are that define the registration. It gives a high amount of flexibility and control over the process. More information about the parameter file is given in Section 3.4. All output of `elastix` is written to the output directory, which needs to be created before running `elastix`. The output consists of a log file (`elastix.log`), the parameters of the transformation $\boldsymbol{T}_{\boldsymbol{\mu}}$ that relates the fixed and the moving image (`TransformParameters.?.txt`), and, optionally, the resulting registered image $I_M(\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}))$ (`result.?.mhd`). The log file contains all messages that were print to screen during registration. Also the `parameterFile.txt` is copied into the log file, and the contents of the `TransformParameters.?.txt` files are included. The log file is thus especially useful for trouble shooting.

Besides the mandatory arguments, there are some optional arguments. Mask images can be provided by adding `-fMask fixedMask.ext` and/or `-mMask movingMask.ext` to the command line. An initial transformation can be provided with a valid transform parameter file by adding `-t0 TransformParameters.txt` to the command line. With the command line option `-threads unsigned_int` the user can specify the maximum number of threads that `elastix` will use.

Running multiple registrations in succession, each possibly of a different type, and with the output of a previous registration as input to the next, can be done with `elastix` in several ways. The first one is to run `elastix` once with the first registration, and use its output (the `TransformParameter.0.txt` that can be found in the output directory) as input for a new run of `elastix` with the command line argument `-t0`. So:

```
elastix -f ...  -m ...  -out out1 -p param1.txt
elastix -f ...  -m ...  -out out2 -p param2.txt -t0 out1/TransformParameters.0.txt
elastix -f ...  -m ...  -out out3 -p param3.txt -t0 out2/TransformParameters.0.txt
```

and so on. Another possibility is combine the registrations with one run of `elastix`:

```
elastix ...  -p param1.txt -p param2.txt -p param3.txt
```

The transformations from each of the registrations are automatically combined, using one of the equations (2.18) and (2.19).

On the `elastix`-website, in the 'About' section, you can find an example on how to use the program. Maybe now is the time to try the example and see a registration in action.

3.4 The parameter file

The parameter file is a text file that defines the components of the registration and their parameter values. Supplying a parameter works as follows:

```
(ParameterName value(s))
```

So parameters are provided between brackets, first the name, followed by one or more values. If the value is of type string then the values need to be quoted:

```
(ParameterName "value1" ...  "valueN")
```

Comments can be provided by starting the line with '//'. A minimal example of a valid parameter file is given in Appendix A. A list of available parameters for each class is given at http://elastix.isi.uu.nl/doxygen/parameter.html. Examples of parameter files can be found at the wiki: http://elastix.bigr.nl/wiki/index.php/Parameter_file_database.

Since the choice of the several components and the parameter values define the registration, it is very important to set them wisely. These choices are what make the registration a success or a disaster. Therefore, a separate chapter is dedicated to the fine art of tuning a registration, see Chapter 5.

Chapter 4

transformix

4.1 Introduction

By now you are able to at least run a registration, by calling `elastix` correctly. It is often also useful to apply the transformation as found by the registration to another image. Maybe you want to apply the transformation to an original (larger) image to gain resolution. Or maybe you need the transformation to apply it to a label image (segmentation). For those purposes a program called `transformix` is available. It was developed simultaneously with `elastix`.

4.2 How to call `transformix`

Like `elastix`, `transformix` is a command line driven program. You can get basic help on how to call it, by:

```
transformix --help
```

which will give a list of mandatory and optional arguments.

The most basic command is as follows:

```
transformix -in inputImage.ext -out outputDirectory -tp TransformParameters.txt
```

This call will transform the input image and write it, together with a log file `transformix.log`, to the output directory. The transformation you want to apply is defined in the transform parameter file. The transform parameter file could be the result of a previous run of `elastix` (see Section 3.3), but may also be written by yourself. Section 4.3 explains the structure and contents that a transform parameter file should have.

Besides using `transformix` for deforming images, you can also use `transformix` to evaluate the transformation $\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x})$ at some points $\boldsymbol{x} \in \Omega_F$. This means that the input points are specified in the fixed image domain (!), since the transformation direction is from fixed to moving image, as explained in Section 2.6. If you want to deform a set of user-specified points, the appropriate call is:

```
transformix -def inputPoints.txt -out outputDirectory -tp TransformParameters.txt
```

This will create a file `outputpoints.txt` containing the input points $\boldsymbol{x}$ and the transformed points $\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x})$ (given as voxel indices of the fixed image and additionally as physical coordinates), the displacement vector $\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}) - \boldsymbol{x}$ (in physical coordinates), and, if `-in inputImage.ext` is also specified, the transformed output points as indices of the input image[1]. The `inputPoints.txt` file should have the following structure:

[1] The downside of this is that the input image is also deformed, which consumes time and may not be needed by the user. If this is a problem, just run `transformix` without `-in` and compute the voxel indices yourself, based on the $\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x})$ physical coordinate data.

```
<index, point>
<number of points>
point1_x point1_y [point1_z]
point2_x point2_y [point2_z]
...
```

The first line indicates whether the points are given as "indices" (of the fixed image), or as "points" (in physical coordinates). The second line stores the number of points that will be specified. After that the point data is given.

Instead of the custom `.txt` format for the input points, `transformix` also supports `.vtk` files:

```
transformix -def inputPoints.vtk -out outputDirectory -tp TransformParameters.txt
```

The output is then saved as `outputpoints.vtk`. The support for `.vtk` files is still a bit limited. Currently, only ASCII files are supported, with triangle meshes. Any meta point data is lost in the output file.

If you want to know the deformation at all voxels of the fixed image, simply use `-def all`:

```
transformix -def all -out outputDirectory -tp TransformParameters.txt
```

The deformation field is stored as a vector image `deformationField.mhd`. Each voxel contains the displacement vector $\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}) - \boldsymbol{x}$ in physical coordinates. The elements of the vectors are stored as `float` values.

In addition to computing the deformation field, `transformix` has the capability to compute the spatial Jacobian of the transformation. The determinant of the spatial Jacobian identifies the amount of local compression or expansion and can be quite useful, for example in lung ventilation studies. The determinant of the spatial Jacobian can be computed on the entire image only using:

```
transformix -jac all -out outputDirectory -tp TransformParameters.txt
```

The complete spatial Jacobian matrix can also be computed:

```
transformix -jacmat all -out outputDirectory -tp TransformParameters.txt
```

where each voxel is filled with a $d \times d$ matrix, with d the image dimension, instead of a simply a scalar value.

With the command-line option `-threads unsigned_int` the user can specify the maximum number of threads that `transformix` will use.

4.3 The transform parameter file

The result of a registration is the transformation $\boldsymbol{T}_{\boldsymbol{\mu}}$ relating the fixed and moving image. The parameters of this transformation are stored in a `TransformParameters.?.txt`-file. An example of its structure for a 2D rigid transformation is given in Appendix B. The text file contains all information necessary to resample an input image (the moving image) to the region specified in the file (by default the fixed image region).

The transform parameter file can be manually edited or created as is convenient for the user. Multiple transformations are composed by iteratively supplying another transform parameter file with the `InitialTransformParametersFileName` tag. The last transformation will be the one where the initial transform parameter file name is set to `"NoInitialTransform"`.

An important parameter in the transform parameter files is the `FinalBSplineInterpolationOrder`. Usually it is set to 3, because that produces the best quality result image after registration, see Sec 5.3.4. However, if you use `transformix` to deform a *segmentation* of the moving image (so, a binary image), you need to manually change the `FinalBSplineInterpolationOrder` to 0. This will make sure that the deformed segmentation is still a binary label image. If third order interpolation is used, the deformed segmentation image will contain garbage. This is related to the "overshoot-property" of higher-order B-spline interpolation.

4.4 Some details

4.4.1 Run-time

The run-time of `transformix` is built up of the following parts:

1. Computing the B-spline decomposition of the input image (in case you selected the `FinalBSplineInterpolator`);
2. Computing the transformation for each voxel;
3. Interpolating the input image for each voxel.

We have never performed tests to measure the computational complexity of each step, but we think that step 1 is the least time-consuming task. This step can obviously be avoided by using a nearest neighbour or linear interpolator. Step 2 is dependent on the choice of the transformation, where linear transformations, such as the rigid and affine transform, are substantially faster than nonlinear transforms, such as the B-spline transform. Step 3 depends on the specific interpolator. In order of increasing complexity: nearest neighbour, linear, 1st-order B-spline, 2nd-order B-spline, etc.

4.4.2 Memory consumption

For more information about memory consumption, see Section 5.5.3 and also:

http://elastix.bigr.nl/wiki/index.php/Memory_consumption_transformix

Chapter 5

Tutorial

5.1 Selecting the registration components

When performing registration one carefully has to choose the several components, as specified in Chapter 2. The components must be specified in the parameter file. For example:

```
(Transform "BSplineTransform")
(Metric "AdvancedMattesMutualInformation")
...
```

In Table 5.1 a list of the components that need to be specified is given, with some recommendations. The "Registration" component was not mentioned in Chapter 2. The registration component serves to connect all other components and implements the multiresolution aspect of registration. So, one may say that it actually implements the block scheme of Figure 2.2. Also the "Resampler" component was not explicitly mentioned in Chapter 2. It simply serves to generate the deformed moving image after registration. Currently there is only one Resampler available in `elastix`: the `DefaultResampler`. The component is therefore not further discussed.

Component	**Recommendation**
Registration	`MultiResolutionRegistration`
Metric	`AdvancedMattesMutualInformation`
Sampler	`RandomCoordinate`
Interpolator	`LinearInterpolator`
ResampleInterpolator	`FinalBSplineInterpolator`
Resampler	`DefaultResampler`
Transform	Depends on the application
Optimizer	`AdaptiveStochasticGradientDescent`
FixedImagePyramid	`FixedSmoothingImagePyramid`
MovingImagePyramid	`MovingSmoothingImagePyramid`

Table 5.1: Some recommendations for the several components.

5.2 Overview of all parameters

A list of all available components of `elastix` can be found at:

http://elastix.isi.uu.nl/doxygen/modules.html

A list of all parameters that can be specified for each registration component can be found at the `elastix` website:

http://elastix.isi.uu.nl/doxygen/parameter.html

At that site you can find how to specify a parameter and what the default value is. We have tried to come up with sensible defaults, although the defaults will certainly not work in all cases. A collection of successful parameter files can be found at the wiki:

http://elastix.bigr.nl/wiki/index.php/Parameter_file_database

This may get you started with your particular application.

5.3 Important parameters

In the same order as in Section 2.3 we discuss the important parameters for each component and explain the recommendations made in Table 5.1.

5.3.1 Registration

Just use the `MultiResolutionRegistration` method, since multi-resolution is a good idea. And if you still think you don't need all this multi-resolution, you can always set the `NumberOfResolutions` to 1. You don't have to set anything else. Section 5.3.7 discusses the number of resolutions in more detail.

5.3.2 Metric

The `AdvancedMattesMutualInformation` usually works well, both for mono- and multi-modal images. It supports fast computation of the metric value and derivative in case the transform is a B-spline by exploiting its compact support. You need to set the number of histogram bins, which is needed to compute the joint histogram. A good value for this depends on the dynamic range of your input images, but in our experience 32 is usually ok:

```
(NumberOfHistogramBins 32)
```

5.3.3 Sampler

The `RandomCoordinate` sampler works well in conjunction with the `StandardGradientDescent` and `AdaptiveStochasticGradientDescent` optimisers, which are the recommended optimisation routines. These optimisation methods can be used with a small amount of samples, randomly selected in every iteration, see Section 2.7, which significantly decreases registration time. Set the `NumberOfSpatialSamples` to 3000. Don't go lower than 2000. Compared to samplers that draw samples on the voxel-grid (such as the `Random` sampler), the `RandomCoordinate` sampler avoids what is known as the grid-effect [Thévenaz and Unser, 2008].

An important option for the random samplers, discussed in Section 5.3.6 is:

```
(NewSamplesEveryIteration "true")
```

which enforces the selection of new samples in every iteration.

An interesting option for the `RandomCoordinate` sampler is the `UseRandomSampleRegion` parameter, used in combination with the `SampleRegionSize` parameter. If `UseRandomSampleRegion` is set to `"false"` (the default), the sampler draws samples from the entire image domain. When set to `"true"`, the sampler randomly selects one voxel, and then selects the remaining samples in a square neighbourhood around that voxel. The size of the neighbourhood is determined by the `SampleRegionSize` (in physical coordinates). An example for 3D images:

```
(ImageSampler "RandomCoordinate")
(NewSamplesEveryIteration "true")
(UseRandomSampleRegion "true")
(SampleRegionSize 50.0 50.0 50.0)
(NumberOfSpatialSamples 2000)
```

In every iteration, a square region of 50^3 mm is randomly selected. In that region, 2000 samples are selected according to a uniform distribution. Effectively, a kind of *localised* similarity measure is obtained, which sometimes gives better registration results. See Klein et al. [2008] for more information on this approach. For the sample region size a reasonable value to try is $\approx 1/3$ of the image size.

5.3.4 Interpolator

During the registration, use the `LinearInterpolator`. In our current implementation it is much faster than the first order B-spline interpolator, even though they are theoretically the same thing.

We recommend a higher quality third order B-spline interpolator for generating the resulting deformed moving image:

```
(ResampleInterpolator "FinalBSplineInterpolator")
(FinalBSplineInterpolationOrder 3)
```

5.3.5 Transform

This choice depends on the application at hand. For images of the same patient where you expect no nonrigid deformation, you can consider a rigid transformation, i.e. choose the `EulerTransform`. If you want to compensate for differences in scale, consider the affine transformation: `AffineTransform`. These two transformations require a centre of rotation, which can be set by the user. By default the geometric centre of the fixed image is taken, which is recommended. Another parameter that needs to be set is the `Scales`. The scales define for each element of the transformation parameters $\boldsymbol{\mu}$ a scaling value, which is used during optimisation. The scaling serves to bring the elements of $\boldsymbol{\mu}$ in the same range (parameters corresponding to rotation have in general a much smaller range than parameters corresponding to translation). We recommend to let `elastix` compute it automatically: `(AutomaticScalesEstimation "true")`[1]. Always start with a rigid or affine transformation before doing a nonrigid one, to get a good initial alignment.

For nonrigid registration problems `elastix` has the `BSplineTransform`. The B-spline nonrigid transformation is defined by a uniform grid of control points. This grid is defined by the spacing between the grid nodes. The spacing defines how dense the grid is, or what the locality is of the transformation you can model. For each resolution level you can define a different grid spacing. This is what we call multi-grid. In general, we recommend to start with a coarse B-spline grid, i.e. a more global transformation. This way the larger structures are matched first, for the same reason as why you should start with a rigid or affine transformation. In later resolutions you can refine the transformation in a stepwise fashion; the idea is that you subsequently match smaller structures, up to the final precision. The final grid spacing is specified with:

```
(FinalGridSpacingInPhysicalUnits 10.0 10.0 10.0)
```

with as much numbers as there are dimensions in your image. The spacing is in most medical images specified in millimetres. It is also possible to specify the grid in voxel units:

```
(FinalGridSpacingInVoxels 16.0 16.0 16.0)
```

[1] The implementation is given in `elastix\src\Core\ComponentBaseClasses\elxTransformBase.hxx`

If the final B-spline grid spacing is chosen high, then you cannot match small structures. On the other hand, if the grid spacing is chosen very low, then small structures can be matched, but you possibly allow the transformation to have too much freedom. This can result in irregular transformations, especially on homogenous parts of your image, since there are no edges (or other information) at such areas that can guide the registration. A penalty or regularisation term, see Equation (2.2), can help to avoid these problems. It is hard to recommend a value for the final grid spacing, since it depends on the desired accuracy. But we can try: if you are interested in somewhat larger structures, you could set it to 32 voxels, for matching smaller structures you could go down to 16 or 8 voxels, or even up to 4. The last choice will maybe require some regularisation term, unless maybe if you have carefully and gradually refined the grid spacing.

To specify a multi-grid schedule use the `GridSpacingSchedule` command:

```
(NumberOfResolutions 4)
(FinalGridSpacingInVoxels 8.0 8.0)
(GridSpacingSchedule 6.0 6.0 4.0 4.0 2.5 2.5 1.0 1.0)
```

The `GridSpacingSchedule` defines the multiplication factors for all resolution levels. In combination with the final grid spacing, the grid spacing for all resolution levels is determined. In case of 2D images, the above schedule specifies a grid spacing of $6 \times 8 = 48$ voxels in resolution level 0, via 32 and 20 voxels, to 8 voxels in the final resolution level. The default value for the `GridSpacingSchedule` uses a powers-of-2 scheme: `(GridSpacingSchedule 8.0 8.0 4.0 4.0 2.0 2.0 1.0 1.0)` (for 2D images).

As a side-note: the number of parameters that are minimised in (2.1) is determined by the size of $\boldsymbol{\mu}$, i.e. in case of the B-spline deformable transform by the control point grid spacing. If you double the spacing, the number of parameters are increased by a factor 8 for a 3D image. For a 256^3 image and a grid spacing of 16 voxels this will result in approximately $(256/16)^3 \times 3 \approx 12.000$ parameters; for a grid spacing of 8 voxels this is almost 100.000 parameters. The amount of parameters can be directly related to memory consumption and registration time, depending on the specific implementation.

In most literature, *cubic* (3^{rd}-order) B-splines are used for image registration. Other spline orders are also possible of course. You may experiment with the `BSplineTransformSplineOrder` option. Orders 1, 2, and 3 are supported. A lower order will reduce the computation time, but may cause less smooth deformations. With order 1, the deformation field is not even differentiable anymore, strictly speaking.

As an alternative to the B-spline transform, `elastix` includes the `SplineKernelTransform`, which implements a thin-plate spline type of transform. See Sections 2.6 and 6.4 for more information on this transform.

Lastly, it is wise to include the following line in every parameter file:

```
(HowToCombineTransforms "Compose")
```

Up to `elastix` version 4.2, by default, if this line was omitted, `"Add"` was used for backwards compatibility. From `elastix` version 4.3, the default has been changed to `"Compose"`, which is better in most applications. See Section 2.6, Equations (2.18) and (2.19) for explanation.

5.3.6 Optimiser

The `StandardGradientDescent` method, see Equations (2.21) and (2.23) offers the possibility to perform fast registration, see Klein et al. [2007]. The key idea is that you use a random subset of voxels (samples), newly selected in each iteration, to compute the cost function derivatives. The number of samples to use is specified using the parameter `NumberOfSpatialSamples`, see Section 5.3.3. Typically, 2000-5000 is enough. It is important to tell the optimiser to select new samples in every iteration:

```
(NewSamplesEveryIteration "true")
```

A downside of the `StandardGradientDescent` method is that you need to tune the parameters of the gain factor a_k, see Section 5.3. Equation (2.22) needs a choice for the step size a_k, which is in `elastix` defined as in Equation (2.23). Figure 5.2 gives some examples.

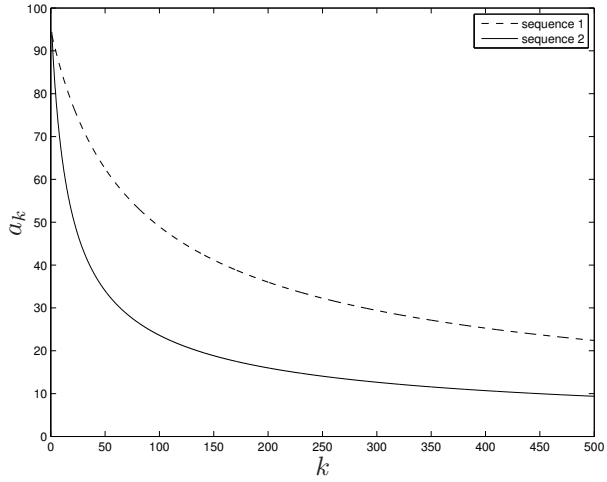


Figure 5.1: Sequence 1: $a = 1000$, $A = 50$, $\alpha = 0.602$. Sequence 2: $a = 400$, $A = 10$, $\alpha = 0.602$. Both sequences start with the same step size, but sequence 2 decays much faster.

The parameters α and A define the decay slope of the function. For the parameter α we recommend the value 0.6. For A, use something in the order of 50:

```
(SP_alpha 0.6)
(SP_A 50.0)
```

This leaves the parameter a, called `SP_a` in `elastix`, as the most important parameter to tune. And it is an important parameter, it can mean success for a good choice and failure if not! If a is set too high, the iterative solving algorithm (2.22) becomes unstable, and you may deform your image beyond recognition. If a is set too low, you will never make it to the optimum, or may get stuck in a very small nearby local optimum. Figure 5.2 illustrates this.

A good choice for a is dependent on the cost function that is used for registration: the a that will give you a good result for SSD is not the same as the one that gives a good result for MI. Finally, a also depends on the amount of deformation that you expect between the fixed and the moving image. So again, recommendations are hard to give. In general we advise you to think in orders of magnitude, if $a = 10$ is too small, try $a = 100$ and not $a = 11$. For mutual information, normalised correlation coefficient, and normalised mutual information, you could start around $a = 1000$. For the mean squared difference metric you could try something smaller than 1. If a is chosen way too big, you may encounter the error message "Too many samples map outside moving image buffer". This error may have other causes as well though. The FAQ at the `elastix` website gives more information on this error message.

For every resolution you could specify a different value of `SP_a`, but it might be easier to start with the same value for every resolution.

```
(SP_a 1000.0 1000.0 1000.0)
```

or, equivalently:

```
(SP_a 1000.0)
```

The last important option related to the optimiser is the maximum number of iterations:

```
(MaximumNumberOfIterations 500)
```

which is, in the case of `StandardGradientDescent`, not only the maximum, but also the minimum, since there is no other stopping condition implemented for this optimiser. In general, the more iterations, the

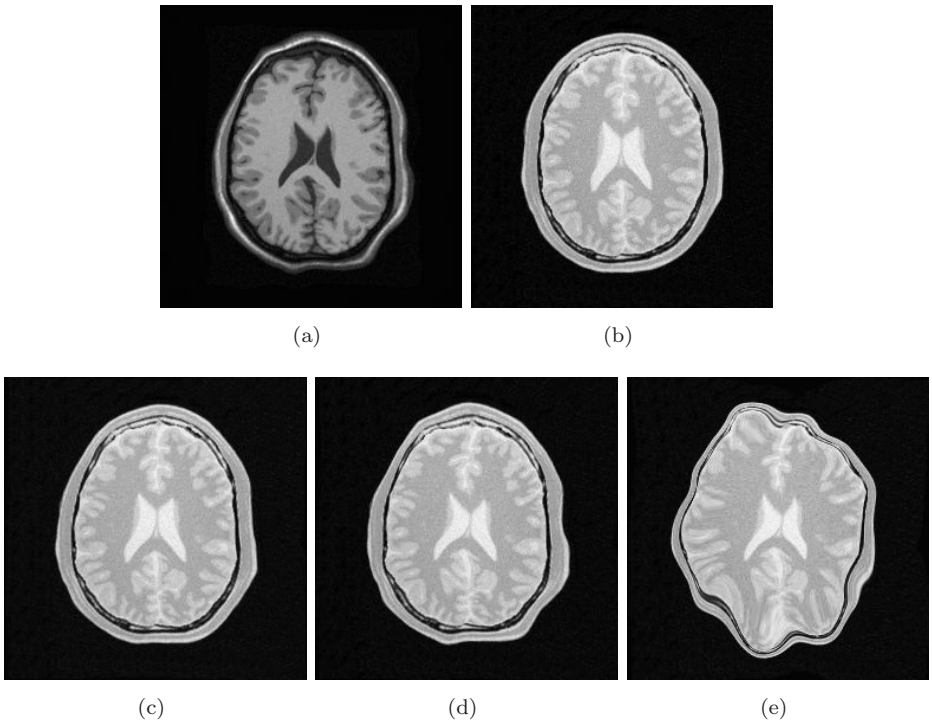


Figure 5.2: The effect of the choice of the step size a (`SP_A`). This example can be downloaded from the `elastix` website. (a) the fixed image, (b) the moving image. (c)-(e) show the registered images, with (c) $a = 320$ is too small, (d) $a = 3200$ as in the downloadable example is good, (e) $a = 32000$ is too large.

better the registration result. But, of course, more iterations take more time. A value of 500 is a good start. Use 2000 if computation time is not such an issue. You may try to go down to 200 iterations if you are in a hurry. For small 2D images, and rigid registration, even less iterations may suffice. A side benefit of using more iterations is that a wider range of `SP_a` gives good results. Tuning `SP_a` then becomes easier.

Are you getting tired of the difficulty of tuning a?

Start using the `AdaptiveStochasticGradientDescent` optimizer. This optimizer is very similar to the `StandardGradientDescent`, but estimates a proper initial value for `SP_a` *automatically*. See Klein et al. [2009] for more details. In practice this optimizer works in many applications with its default settings. Only the number of iterations must be specified by the user:

```
(Optimizer "AdaptiveStochasticGradientDescent")
(MaximumNumberOfIterations 500)
```

There are some optional extra parameters, such as `SigmoidInitialTime` and `MaximumStepLength`, which are explained in the paper [Klein et al., 2009]. In addition to automatically computing the step size, this optimizer also implements an adaptive step size mechanism, which generally makes the optimization somewhat more robust. The only downside of this optimizer is that it is relatively time-consuming to estimate a in case of a large degree of freedom (large size of $\boldsymbol{\mu}$), but we are addressing this issue [Qiao et al., 2014].

5.3.7 Image pyramids

The `FixedImagePyramid` and the `MovingImagePyramid` have identical options. What is said below about the FixedImagePyramid works similarly for the MovingImagePyramid.

Use the `FixedSmoothingImagePyramid`, since it will not throw away valuable information, and since you are not using the `FullSampler` anyway, down-sampling will not save you any time. It may consume quite some memory though for large images and many resolution levels. Two parameters have to be set to define the multi-resolution strategy: the number of resolutions (`NumberOfResolutions`) and the specific down-sampling schedule that is used in each resolution (`FixedImagePyramidSchedule`). If you only set the `NumberOfResolutions`, a default schedule will be used that smoothes the fixed image by a factor of 2 in each dimension, starting from $\sigma = 0.5$ in the last resolution. That schedule is usually fine. In case you have highly anisotropic data, you might want to blur less in the direction of the largest spacing.

In general 3 resolutions is a good starting point. If the fixed and moving image are initially far away, you can increase the number of resolution levels to, say, 5 or 6. This way the images are more blurred and more attention is paid to register large, dominant structures.

The pyramid schedule defines the amount of blurring (and down-sampling in case a `FixedRecursiveImagePyramid` is used), in each direction x, y, z and for each resolution level. It can be specified as follows:

```
(NumberOfResolutions 4)
(FixedImagePyramidSchedule 8 8 4 4 2 2 1 1)
```

In this example 4 resolutions for a 2D image are used. At resolution level 0 the image is blurred with $\sigma = 8/2$ voxels in each direction (σ is half the pyramid schedule value). At level 1 $\sigma = 4/2$ is used, and finally at the last level, level 4, the original images are used for registration. Specifying the fixed and moving image pyramids with an identical schedule can be done with one command:

```
(ImagePyramidSchedule 4 4 2 2 2 1 1 1 1)
```

for a 3D image with 3 resolution levels, where less smoothing is performed in the z-direction.

5.4 Masks

Sometimes you are specifically interested in aligning only a part of the image. A possibility to focus on this part is to crop the image. Cropping, however, restricts the region of interest (ROI) to be a square (2D) or cube (3D) only. If you need an irregular shaped ROI, you can use masks. A mask is a binary image, filled with 0's and 1's. If you use a mask, you only perform registration on the part of the image that is within the masks, i.e. where the mask has 1's.

You can/should use a mask

- when your image contains an artificial edge that has no real meaning. The registration might be tempted to align these artificial edges, thereby neglecting the meaningful edges. The conic beam edge in ultrasound images is an example of such an artificial edge.
- when the image contains structures in the neighbourhood of your ROI that may influence the registration within your ROI. This is for example the case when matching lung data. Usually, you are interested in the lungs, and not if the rib cage is well aligned. However, the ribs are structures that for example in CT can have a strong influence on the similarity metric, especially if you use the SSD metric. In that case, the rib cage may be well aligned at the cost of vessels structures near the border of the lung with the rib cage. In this case it will help you if you use a dilated lung segmentation as a mask.

Masks can be used both for the fixed and the moving image. A fixed image mask is sufficient to focus the registration on a ROI, since samples are drawn from the fixed image. You only want to use a mask for the moving image when your moving image contains nonsense grey values near the ROI.

In case you are using a mask to prevent bad karma from an artificial edge, you also need to set the parameter:

```
(ErodeMask "true")
```

If not, then when performing multi-resolution, information from the artificial edge will flow into you ROI due to the smoothing step. In case the edge around your ROI is meaningful, e.g. in the lung example, you should set it to false, because this edge will help to guide the registration.

A common exception that `elastix` throws when drawing samples is: "Could not find enough image samples within reasonable time. Probably the mask is too small." The probable cause for this is that your fixed image mask is too small. See the FAQ for more information.

5.5 Trouble shooting

5.5.1 Common errors

Some common sources of confusion and questions have been gathered in a FAQ, which can be found at

http://elastix.isi.uu.nl/FAQ.php

5.5.2 Bad initial alignment

When the initial alignment between two images is very off, you cannot start a nonrigid registration. And sometimes it can be a hassle to get it right. What factors can help to get it right?

- Start with a transformation with a low degree of freedom, i.e. the translation, rigid, similarity or affine transform. Sometimes the images are really far off, and have no overlap to begin with (NB: the position of images in physical space is determined by the origin and voxel spacing; see Section 2.2). A solution is then to add the following line to your parameter file:

  ```
  (AutomaticTransformInitialization "true")
  ```

  This parameter facilitates the automatic estimation of an initial alignment for the aforementioned transformations. Three methods to do so are supported: the default method which aligns the centres of the fixed and moving image, a method that aligns the centres of gravity, and a method that simply aligns the image origins. A method can be selected by adding one of the following lines to the parameter file:

  ```
  (AutomaticTransformInitializationMethod "GeometricalCenter")
  (AutomaticTransformInitializationMethod "CenterOfGravity")
  (AutomaticTransformInitializationMethod "Origins")
  ```

  Note that "`Origins`" is currently only available for the affine transformation.

- You need a good multi-resolution strategy, i.e. quite a bit of resolution levels. This way a lot of smoothing is going on, blurring away all the details and thereby focussing the registration on the major structures.

- Use more iterations.

- Take larger steps. Set the parameter a so high that the translation component of the transformation takes a step of several voxels in each iteration, up to 10. Maybe it will work, and in that case you will get alignment pretty quick, but the step size a is still large, so you immediately jump away from alignment again. If that happens, you should let the sequence $a_k = a/(A+k)^\alpha$ decay relatively fast. This can be achieved by setting both a and A a bit lower, see Figure 5.1.

- In case you need to find a large rotation, you might want to take larger steps for the rotation, but not for the translation. This can be achieved by modifying the scales parameter, see Section 5.3.5:

  ```
  (Scales 10000.0)
  ```

  You can set it lower to take larger rotation steps. If it is set to 1.0 you take as large steps for the rotation as for the translation (but the rotation is defined in radials). If you set it really high ($> 10^6$) you won't rotate at all. You probably don't need to go lower than 1000.0. Note that the `AutomaticScalesEstimation` option usually works fine, so specifying `Scales` is not necessary.

5.5.3 Memory consumption

The typical size of clinical images increases as a function of time. Therefore, memory efficiency will become more of an issue. `elastix` consumes $\approx$ 100 MB of memory for small images, for larger image pairs (256^3) and some common components, consumption can be about 1 - 1.5 GB. With very large images (400^3 and above) memory consumption can rise above 2 GB limit of older 32-bit Windows systems. Or perhaps you are using a laptop. Or perhaps you are using `elastix` within another memory-consuming master program. What to do with large images?

- Buy yourself a brand new computer with a lot of memory. Nowadays both the computer and the operating system will be 64 bit, so that you can actually address this much memory.
- Images in `elastix` are internally by default represented as a bunch of voxels of floating type. You can modify this to short images:

  ```
  (FixedInternalImagePixelType "short")
  (MovingInternalImagePixelType "short")
  ```

  This way you save half the amount of memory that is used to store the fixed and moving images, and their multi-resolution pyramids. This will come at the cost of a loss of precision, but may not be that harmful. This option is useful both for `elastix` and `transformix`.
- Change the interpolator that is used during registration. In case a B-spline interpolator is used, note that it stores a coefficient image internally in double type. You can also specify a float version:

  ```
  (Interpolator "BSplineInterpolatorFloat")
  ```

  which saves you another bit of memory the size of a short image. This option is useful for `elastix` only. To save even more memory, use the `LinearInterpolator`.
- Change the interpolator that is used when resampling an image:

  ```
  (ResampleInterpolator "FinalBSplineInterpolatorFloat")
  ```

  This option is useful both for `elastix` and `transformix`. However, for `elastix` it will only save you some memory at the very end of the registration.
- Use downsampled images during the registration. This probably will not effect the registration accuracy too much. After registration you can apply the resulting transformation to the original full size moving image, using `transformix`. See the FAQ for more information.

Chapter 6

Advanced topics

6.1 Metrics

6.1.1 Image registration with multiple metrics and/or images

Up till now we viewed image registration as the problem of finding the spatial relation between one fixed image and one moving image, using one similarity metric to define the fit. Sometimes, it is desirable to combine multiple metrics, or multiple fixed and moving images, or both. All these three generalisations are available in `elastix`:

multi-metric In this case the registration cost function is defined as:

$$\mathcal{C}(\boldsymbol{T_\mu}; I_F, I_M) = \frac{1}{\sum_{i=1}^{N} \omega_i} \sum_{i=1}^{N} \omega_i \mathcal{C}_i(\boldsymbol{T_\mu}; I_F, I_M), \tag{6.1}$$

with ω_i the weights. This way the same fixed and moving image is used for every sub-metric $\mathcal{C}_i$. This way one can for example simultaneously optimise the SSD and MI during a registration.

`elastix` should be called like:

```
elastix -f fixed.ext -m moving.ext -out outDir -p parameterFile.txt
```

multi-image In this case the registration cost function is defined as:

$$\mathcal{C}(\boldsymbol{T_\mu}; I_F, I_M) = \frac{1}{\sum_{i=1}^{N} \omega_i} \sum_{i=1}^{N} \omega_i \mathcal{C}(\boldsymbol{T_\mu}; I_F^i, I_M^i). \tag{6.2}$$

This way one can simultaneously register all channels of multi-spectral input data, using a single type of cost function for all channels.

`elastix` should be called like:

```
elastix -f0 fixed0.ext -f1 fixed1.ext -f<>...  -m0 moving0.ext -m1 moving1.ext
-m<>...  -out outDir -p parameterFile.txt
```

both In this case the registration cost function is defined as:

$$\mathcal{C}(\boldsymbol{T_\mu}; I_F, I_M) = \frac{1}{\sum_{i=1}^{N} \omega_i} \sum_{i=1}^{N} \omega_i \mathcal{C}_i(\boldsymbol{T_\mu}; I_F^i, I_M^i). \tag{6.3}$$

This is the most general way of registration supported by `elastix`. This will make it possible for example to register two lung CT data sets with MI, while simultaneously registering the fissure segmentations with the kappa statistic. The two may help each other in getting a better registration compared to only using a single channel.

All three scenarios use the multi-metric registration method, which is selected in the parameter file with:

```
(Registration "MultiMetricMultiResolutionRegistration")
```

Other parts of the parameter file should look like:

```
(FixedImagePyramid "FixedSmoothingImagePyramid" "FixedSmoothingImagePyramid" ...)
(MovingImagePyramid "MovingSmoothingImagePyramid" "MovingSmoothingImagePyramid" ... )
(Interpolator "BSplineInterpolator" "BSplineInterpolator" ...)
(Metric "AdvancedMattesMutualInformation" "AdvancedMeanSquareDifference" ...)
(ImageSampler "RandomCoordinate" "RandomCoordinate" ...)

(Metric0Weight 0.125)
(Metric1Weight 0.125)
(Metric2Weight 0.125)
etc
```

Another way of registering multi-spectral data is to use the α-mutual information measure, described below.

6.1.2 α-mutual information

The α-mutual information metric computes true multi-channel α-mutual information. It does not use high-dimensional joint histograms, but instead relies on k-nearest neighbour graphs to estimate α-MI. Details can be found in Staring et al. [2009]. It is specified in the parameter file with:

```
(Registration "MultiResolutionRegistrationWithFeatures")
(FixedImagePyramid "FixedSmoothingImagePyramid" "FixedSmoothingImagePyramid")
(MovingImagePyramid "MovingSmoothingImagePyramid" "MovingSmoothingImagePyramid")
(Interpolator "BSplineInterpolator" "BSplineInterpolator")
(Metric "KNNGraphAlphaMutualInformation")
(ImageSampler "MultiInputRandomCoordinate")

// KNN specific
(Alpha 0.99)
(AvoidDivisionBy 0.0000000001)
(TreeType "KDTree")
(BucketSize 50)
(SplittingRule "ANN_KD_STD")
(ShrinkingRule "ANN_BD_SIMPLE")
(TreeSearchType "Standard")
(KNearestNeighbours 20)
(ErrorBound 10.0)
```

A complete list of the available parameters can be found in the doxygen documentation → `elx::KNNGraphAlphaMutualInformationMetric`.

6.1.3 Penalty terms

This paragraph requires extension and modification.

In order to regularise the transformation $\boldsymbol{T}_{\boldsymbol{\mu}}$ often a penalty term $\mathcal{P}(\boldsymbol{\mu})$ is added to the cost function, so it becomes:

$$\mathcal{C} = \gamma_1 \mathcal{S} + \gamma_2 \mathcal{P}, \tag{6.4}$$

where γ_1, γ_2 user-defined constants that weigh similarity against regularity.

Penalty term are often based on the first or second order spatial derivatives of the transformation. An example is the bending energy of the transformation, which is arguably the most common penalty term, see Section 6.1.4.

The derivative of the similarity measure usually involves computation of the spatial derivative of the moving image: $\frac{\partial I_M}{\partial \boldsymbol{x}}$, and the derivative of the transformation to its parameters: $\frac{\partial \boldsymbol{T}}{\partial \boldsymbol{\mu}}$. In the ITK the last derivative is implemented using `transform->GetJacobian()`, i.e. the derivative to the transformation parameters $\boldsymbol{\mu}$ is referred to as 'Jacobian'.

Penalty terms usually consist of the first and second order *spatial* derivatives of the transformation, i.e. $\frac{\partial \boldsymbol{T}}{\partial \boldsymbol{x}}$ and $\frac{\partial^2 \boldsymbol{T}}{\partial \boldsymbol{x} \partial \boldsymbol{x}^T}$. We will refer to these derivatives as the 'SpatialJacobian' and the 'SpatialHessian' to clearly distinguish between these derivatives and the 'Jacobian'. In order to apply the gradient descent optimisation routine (2.21), (2.22), we additionally need the derivatives $\frac{\partial}{\partial \boldsymbol{\mu}} \frac{\partial \boldsymbol{T}}{\partial \boldsymbol{x}}$ and $\frac{\partial}{\partial \boldsymbol{\mu}} \frac{\partial^2 \boldsymbol{T}}{\partial \boldsymbol{x} \partial \boldsymbol{x}^T}$. These we call the 'JacobianOfSpatialJacobian' and 'JacobianOfSpatialHessian', respectively.

The transform class as defined in the ITK does not support the computation of spatial derivatives $\partial \boldsymbol{T} / \partial \boldsymbol{x}$ and $\partial^2 \boldsymbol{T} / \partial \boldsymbol{x}^2$, and their derivatives to $\boldsymbol{\mu}$. Initially, we created non-generic classes that combine mutual information and the mentioned penalty terms specifically (the `MattesMutualInformationWithRigidityPenalty` component in `elastix` version 4.3 and earlier). In 2010, however, we created a more advanced version of the ITK transform that does implement these spatial derivatives. Additionally, we created a bending energy regularisation class that takes advantage of these functions, see Section 6.1.4. We also reimplemented the rigidity penalty term, see Section 6.1.5; it currently however does not yet use these spatial derivatives. More detailed information can be found in Staring and Klein [2010a].

This all means that it is possible in `elastix` to combine any similarity metric with any of the available penalty terms (currently the bending energy and the rigidity penalty term).

6.1.4 Bending energy penalty

The bending energy penalty term is defined in 2D as:

$$\mathcal{P}_{\mathrm{BE}}(\boldsymbol{\mu}) = \frac{1}{P} \sum_{\widetilde{\boldsymbol{x}}_i} \left\| \frac{\partial^2 \boldsymbol{T}}{\partial \boldsymbol{x} \partial \boldsymbol{x}^T} (\widetilde{\boldsymbol{x}}_i) \right\|_F^2 \tag{6.5}$$

$$= \frac{1}{P} \sum_{\widetilde{\boldsymbol{x}}_i} \sum_{j=1}^{2} \left(\frac{\partial^2 T_j}{\partial x_1^2} (\widetilde{\boldsymbol{x}}_i) \right)^2 + 2 \left(\frac{\partial^2 T_j}{\partial x_1 \partial x_2} (\widetilde{\boldsymbol{x}}_i) \right)^2 + \left(\frac{\partial^2 T_j}{\partial x_2^2} (\widetilde{\boldsymbol{x}}_i) \right)^2, \tag{6.6}$$

where P is the number of points $\widetilde{\boldsymbol{x}}_i$, and the tilde denotes the difference between a variable and a given point over which a term is evaluated. As you can see it penalises sharp deviations of the transformation (e.g. no high compression followed by a nearby high expansion). You can use it to regularise your nonrigid transformation if you experience problems such as foldings. In our current implementation the computation time of this term is relatively large, though.

It can be selected in `elastix` using

```
(Metric "AnySimilarityMetric" "TransformBendingEnergyPenalty")
(Metric0Weight 1.0)
(Metric1Weight <weight>)
```

and has no further parameters.

6.1.5 Rigidity penalty

Some more advanced metrics, not found in the ITK, are available in `elastix`: The rigidity penalty term $\mathcal{P}^{\text{rigid}}(\boldsymbol{T}_{\boldsymbol{\mu}}; I_M)$ described in Staring et al. [2007a]. It is specified in the parameter file with:

```
(Metric "AnySimilarityMetric" "TransformRigidityPenalty")
// normal similarity metric parameters
...
// Weights
(Metric0Weight 1.0)
(Metric1Weight 0.1)

// Rigidity penalty parameters:
(OrthonormalityConditionWeight 1.0)
(PropernessConditionWeight 100.0)
(MovingRigidityImageName "movingRigidityImage.mhd")
```

A complete list of the available parameters can be found in the doxygen documentation → `elx::TransformRigidityPenalty`. See also Section 6.1.3.

6.1.6 DisplacementMagnitudePenalty: inverting transformations

The `DisplacementMagnitudePenalty` is a cost function that penalises $||\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}) - \boldsymbol{x}||^2$. You can use this to invert transforms, by setting the transform to be inverted as an initial transform (using `-t0`), setting `(HowToCombineTransforms "Compose")`, and running `elastix` with this metric, using the original fixed image set both as fixed (`-f`) and moving (`-m`) image. After that you can manually set the initial transform in the last parameter file to `"NoInitialTransform"`, and voila, you have the inverse transform! Strictly speaking, you should then also change the Size/Spacing/Origin/Index/Direction settings to match that of the moving image. Select it with:

```
(Metric "DisplacementMagnitudePenalty")
```

Note that inverting a transformation becomes conceptually very similar to performing an image registration in this way. Consequently, the same choices are relevant: optimisation algorithm, multiresolution etc...

Note that this procedure was described and evaluated in Metz et al. [2011].

6.1.7 Corresponding points: help the registration

Most of the similarity measures in `elastix` are based on corresponding characteristics of the fixed and moving image. It is possible, however, to register based on point correspondence. Therefore, in `elastix` 4.4 we introduced a metric that minimises the distance of two point sets with known correspondence. It is defined as:

$$\mathcal{S}_{\text{CP}} = \frac{1}{P} \sum_{\boldsymbol{x}_{Fi}} \|\boldsymbol{x}_{Mi} - \boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}_{Fi})\| \tag{6.7}$$

where P is the number of points $\boldsymbol{x}_i$, and $\boldsymbol{x}_{Fi}, \boldsymbol{x}_{Mi}$ corresponding points from the fixed and moving image point sets, respectively. The metric can be used to help in a difficult image registration task that fails if performed fully automatically. A user can manually click corresponding points (or maybe automatically extract), and setup `elastix` to not only minimise based on intensity, but also taking into account that some positions are known to correspond. The derivative of $\mathcal{S}_{\text{CP}}$ reads:

$$\frac{\partial}{\partial \boldsymbol{\mu}} \mathcal{S}_{\text{CP}} = -\frac{1}{P} \sum_{\boldsymbol{x}_{Fi}} \frac{1}{\|\boldsymbol{x}_{Mi} - \boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}_{Fi})\|} \left(\boldsymbol{x}_{Mi} - \boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}_{Fi})\right) \frac{\partial \boldsymbol{T}}{\partial \boldsymbol{\mu}}(\boldsymbol{x}_{Fi}). \tag{6.8}$$

In `elastix` this metric can be selected using:

```
(Metric "AnySimilarityMetric" "CorrespondingPointsEuclideanDistanceMetric")
(Metric0Weight 1.0)
(Metric1Weight <weight>)
```

Note that this metric must be specified as the last metric, due to some technical constraints. The fixed and moving point set can be specified on the command line:

```
elastix ...  -fp fixedPointSet.txt -mp movingPointSet.txt
```

The point set files have to be defined in a specific format, identical to supplying points to `transformix`, see Section 4.2.

6.1.8 VarianceOverLastDimensionMetric: aligning time series

This metric is explained in Metz et al. [2011]. Example parameter files can be found on the wiki parameter file database, entry `par0012`.

This metric should be used to estimate the motion in dynamic imaging data (time series). The variance of intensities over time is measured. Two- to four-dimensional imaging data is supported.

6.2 Image samplers

RandomSparseMask This variant of the random sampler is useful if the fixed image mask is sparse (i.e. consists of many zeros).

6.3 Interpolators

ReducedDimensionBSplineInterpolator This is a variant of the normal B-spline interpolator, which uses a 0^{th} order spline in the last dimension. This saves time when aligning time-series, when you do not have to interpolate in the last (time) dimension anyway. Its usage is illustrated in entry `par0012` of the parameter file database.

6.4 Transforms

DeformationFieldTransform This transform serves as a wrapper around existing deformation field vector images. It computes the transformation by interpolating the deformation field image. The relevant tags in the transform parameter file are as follows:

```
(Transform "DeformationFieldTransform")
(DeformationFieldFileName "deformationField.mhd")
(DeformationFieldInterpolationOrder 1)
(NumberOfParameters 0)
```

The deformation field image's pixel type should be a vector of `float` elements. It could be a deformation field that is the result of `transformix -def all` for example! Since this transform does not have any parameters (the $\boldsymbol{\mu}$ has zero length), it makes no sense to use it for registration. It can just be used as an initial transformation (supplied by the option `-t0`) or as input for `transformix`.

SplineKernelTransform As an alternative to the B-spline transform, `elastix` includes a `SplineKernelTransform`, which implements a thin-plate spline type of transform; see also Section 2.6. This transformation requires a list of fixed image landmarks (control points) to be specified with the command line option

"`-ipp ipp.txt`", by means of an input points file which has the same format as the `-def` file used by `transformix` (see Section 4.2). See the `doxygen` documentation on the website for a list of its parameters.

The moving image landmarks are optimized during the registration, and can be found in the resulting `TransformParameters.txt` file, in the parameter "`TransformParameters`". See Section 2.6 for the ordering of the parameters.

WeightedCombinationTransform This is a transformation that is modelled as a weighted combination of user-specified transformations: $\boldsymbol{T}_{\boldsymbol{\mu}}(\boldsymbol{x}) = \sum_i w_i \boldsymbol{T}_i(\boldsymbol{x})$. The weights w_i form the parameter vector $\boldsymbol{\mu}$. The sub-transforms $\boldsymbol{T}_i(\boldsymbol{x})$ may for example follow from a statistical deformation model, obtained by principal component analysis. See the `doxygen` documentation on the website for a list of its parameters.

BSplineTransformWithDiffusion This transform implements the work described in Staring et al. [2007b].

BSplineStackTransform This transformation model defines a stack of independent B-spline transformations. Its usage is illustrated in Metz et al. [2011]. Example parameter files can be found on the wiki parameter file database, entry `par0012`.

6.5 Optimisation methods

Conjugate gradient —ConjugateGradientFRPR

CMAEvolutionStrategy

FiniteDifferenceGradientDescent

Full search

Quasi Newton

RegularStepGradientDescent —RSGDEachParameterApart

SimultaneousPerturbation

Chapter 7

Developers guide

7.1 Relation to ITK

A large part of the `elastix` code is based on the ITK Ibáñez et al. [2005]. The use of the ITK implies that the low-level functionality (image classes, memory allocation etc.) is thoroughly tested. Naturally, all image formats supported by the ITK are supported by `elastix` as well. The C++ source code can be compiled on multiple operating systems (Windows XP, Linux, Mac OS X), using various compilers (MS Visual Studio, GCC), and supports both 32 and 64 bit systems.

In addition to the existing ITK image registration classes, `elastix` implements new functionality. The most important enhancements are listed in Table 7.1. Note that from version 4 ITK also has transform concatenation and supports spatial derivatives (but not their derivatives to $\boldsymbol{\mu}$ again).

7.2 Overview of the `elastix` code

The `elastix` source code consists roughly of two layers, both written in C++: A) ITK-style classes that implement image registration functionality, and B) `elastix` wrappers that take care of reading and setting parameters, instantiating and connecting components, saving (intermediate) results, and similar 'administrative' tasks. The modular design enables adding new components, without changing the `elastix` core. Adding a new component starts by creating the layer A class, which can be compiled and tested independent of layer B. Subsequently, a small layer B wrapper needs to be written, which connects the layer A class to the other parts of `elastix`.

The image samplers, for example, are implemented as ITK classes that all inherit from a base class `itk::ImageSamplerBase`. These can be found in `src/Common/ImageSamplers`. This is "layer A" in `elastix`. For each sampler (random, grid, full...) a wrapper is written, located in `src/Components/ImageSamplers`, which takes care of configuring the sampler before each new resolution of the registration process. This is "layer B" of `elastix`.

7.2.1 Directory structure

The basic directory structure is as follows:

- dox
- src/Common: ITK classes, Layer A stuff. This directory also contains some external libraries, unrelated to ITK, like xout (which is written by us) and the ANNlib.
- src/Core: this is the main `elastix` kernel, responsible for the execution flow, connecting the classes, reading parameters etc.

• A modular framework for sampling strategies. See for more details Staring and Klein [2010b].
• Several new optimisers: Kiefer-Wolfowitz, Robbins-Monro, adaptive stochastic gradient descent, evolutionary strategy. Complete rework of existing ITK optimisers, adding more user control and better error handling: quasi-Newton, nonlinear conjugate gradient.
• Several new or more flexible cost functions: (normalised) mutual information, implemented with Parzen windowing similar to Thévenaz and Unser [2000], multifeature α-mutual information, bending energy penalty term, rigidity penalty term.
• The ability to concatenate any number of geometric transformations.
• The transformations support computation of not only $\partial \boldsymbol{T}/\partial \boldsymbol{\mu}$, but also of spatial derivatives $\partial \boldsymbol{T}/\partial \boldsymbol{x}$ and $\partial^2 \boldsymbol{T}/\partial \boldsymbol{x}^2$, and their derivatives to $\boldsymbol{\mu}$, frequently required for the computation of regularisation terms. Additionally, the compact support of certain transformations is integrated more generally. See for more details Staring and Klein [2010a].
• Linear combinations of cost functions, instead of just a single cost function.

Table 7.1: The most important enhancements and additions in `elastix`, compared to the ITK.

- src/Components: this directory contains the components and their `elastix` wrappers (layer B). Very component-specific layer A code can also be found here.

In `elastix` 4.4 and later versions, it is also possible to add your own Component directories. These can be located anywhere outside the `elastix` source tree. See Section 7.4 for more details about this.

7.3 Using `elastix` in your own software

There are (at least) three ways to use `elastix` in your own software:

1. Compile the `elastix` executable and directly call it with the appropriate arguments. This is the most easy way, and Matlab and MeVisLab code exists for that.
2. Include the `elastix` source code in your own project, see Section 7.3.1.
3. Compile `elastix` as a library and link to it, see Section 7.3.2. This functionality is available as of version 4.7 (February 2014).

7.3.1 Including `elastix` code in your own software

You may find some `elastix` classes useful to integrate in your own project. For example, if you are developing a new `elastix` component and first would like to test it outside elastix (see Section 7.4. In such a case, you could of course copy the required `elastix` files to your own project, or set the include-paths manually, but this would not be very convenient.

To make it easier, a `UseElastix.cmake` file is generated in the `elastix` binary directory. You can include this in the `CMakeLists.txt` file of your own project, and CMake will make sure that all necessary include_directories are set. Also, you can link to the `elastix` libraries, such as elxCommon, to avoid recompiling code.

An example of this can be found in the directory `dox/externalproject` of the elastix source distribution.

7.3.2 Using `elastix` as a library

Introduction

`elastix` also offers the possibility to be used as dynamic or static linked library. This offers the possibility to integrate its functionality in your own software, without having to call the external `elastix` executable. The latter namely has the downside that your software, which presumably already has the fixed and moving images in memory, has to store these images to disk. `elastix` will then load them again (so they will be in memory twice), perform the registration, and write the result to disk. Your software then needs to load the result from the disk to memory. This approach obviously leads to an increase in memory use, decrease in performance due to the reading/writing overhead, and is just not very elegant. When using `elastix` as a library your software only has to pass memory pointers to the library interface, so there is no need for reading/writing or in-memory image duplication. After registration `elastix` will pass a pointer to the resulting image back to your program.

Library functionality is still quite heavily under development, but the following basic functionality is already available:

- Registration of any pair of images using any combination of `elastix` components.
- Usage of registration masks.
- Usage of multiple parameter files consecutively (similar to using the -p option of the `elastix` executable multiple times).
- Using `transformix` to transform an image.

Building `elastix` as a static or dynamic library

To build `elastix` as a library you have to disable the `ELASTIX_BUILD_EXECUTABLE` option in CMake. With this option disabled a build project for a static library will be created. If you want to create a dynamic library (not very well tested), you have to enable the `ELASTIX_BUILD_SHARED_LIBS` option.

Linking with the `elastix` library

When building your own software project, you need to link `elastix` and provide the `elastix` source directory as an include directory to your compiler. You can do this, for example, by adding the following code to your CMakeLists.txt file:

```
set( ELASTIX_BUILD_DIR "" CACHE PATH "Path to elastix build folder" )
set( ELASTIX_USE_FILE ${ELASTIX_BUILD_DIR}/UseElastix.cmake )

if( EXISTS ${ELASTIX_USE_FILE} )
  include( ${ELASTIX_USE_FILE} )
  link_libraries( param )
  link_libraries( elastix )
  link_libraries( transformix )
endif()
```

This will add a parameter to CMake, ELASTIX_BUILD_DIR, which needs to be provided by the user upon running CMake. You should provide the directory in which you have build the elastix sources (the directory having the UseElastix.cmake file). If you want to control better to which binaries you link elastix, use the CMake target_link_libraries directive instead.

Preparing registration parameter settings

To be able to run elastix, you need to prepare the parameter settings first. You can do this for example by reading them from file:

```
#include "elastixlib.h"
#include "itkParameterFileParser.h"
typedef ELASTIX::ParameterMapType RegistrationParametersType;
typedef itk::ParameterFileParser  ParserType;

// Create parser for transform parameters text file.
ParserType::Pointer file_parser = ParserType::New();

// Try parsing transform parameters text file.
file_parser->SetParameterFileName( "par_registration.txt" );
try
{
  file_parser->ReadParameterFile();
}
catch( itk::ExceptionObject & e )
{
  std::cout << e.what() << std::endl;
  // Do some error handling!
}

// Retrieve parameter settings as map.
RegistrationParametersType parameters = file_parser->GetParameterMap();
```

If you want to use multiple parameter files consecutively, load them one by one and add them to a vector:

```
typedef std::vector<RegistrationParametersType> RegistrationParametersContainerType;
```

Then use this vector in the code below instead of the single parameter map. You can also set up the parameter map in your C++ code. Check the typedef of ELASTIX::ParameterMapType for the exact format.

Running elastix

Once the parameter settings are loaded, run elastixusing, for example, the following code:

```
ELASTIX* elastix = new ELASTIX();
int error = 0;
try
{
  error = elastix->RegisterImages(
    static_cast<typename itk::DataObject::Pointer>( fixed_image.GetPointer() ),
    static_cast<typename itk::DataObject::Pointer>( moving_image.GetPointer() ),
    parameters,        // Parameter map read in previous code
```

```
    output_directory,  // Directory where output is written, if enabled
    write_log_file,    // Enable/disable writing of elastix.log
    output_to_console, // Enable/disable output to console
    0,                 // Provide fixed image mask (optional, 0 = no mask)
    0                  // Provide moving image mask (optional, 0 = no mask)
  );
}
catch( itk::ExceptionObject &err )
{
  // Do some error handling.
}

if( error == 0 )
{
  if( elastix ->GetResultImage().IsNotNull() )
  {
    // Typedef the ITKImageType first...
    ITKImageType * output_image = static_cast<ITKImageType *>(
      elastix->GetResultImage().GetPointer() );
}
else
{
  // Registration failure. Do some error handling.
}

// Get transform parameters of all registration steps.
RegistrationParametersContainerType transform_parameters
  = elastix->GetTransformParameterMapList();

// Clean up memory.
delete elastix;
```

Running transformix

Given the transformation parameters provided by the `ELASTIX` class, you can run `transformix`:

```
TRANSFORMIX* transformix = new TRANSFORMIX();
int error = 0;
try
{
  error = transformix->TransformImage(
    static_cast<typename itk::DataObject::Pointer>( input_image_adapter.GetPointer() ),
    transform_parameters, // Parameters resulting from elastix run
    write_log_file,       // Enable/disable writing of transformix.log
    output_to_console);   // Enable/disable output to console
}
catch( itk::ExceptionObject &err )
{
  // Do some error handling.
}
```

```
if( error == 0 )
{
  // Typedef the ITKImageType first...
  ITKImageType * output_image = static_cast<ITKImageType *>(
    transformix->GetResultImage().GetPointer() );
}
else
{
  // Do some error handling.
}

// Clean up memory.
delete transformix;
```

Alternatively, you can read the transformation parameters from file (for example, from `TransformParameters.0.txt`) using the parameter file parser in the same way as was shown for the registration parameters above.

7.4 Creating new components

If you want to create your own component, it is natural to start writing the layer A class, without bothering about `elastix`. The layer A filter should implement all basic functionality and you can test in a separate ITK program if it does what it is supposed to do. Once you got this ITK class to work, it is trivial to write the layer B wrapper in `elastix` (start by copy-pasting from existing components).

With CMake, you can tell `elastix` in which directories the source code of your new components is located, using the `ELASTIX_USER_COMPONENT_DIRS` option. `elastix` will search all subdirectories of these directories for CMakeLists.txt files that contain the command `ADD_ELXCOMPONENT( <name> ... )`. The CMakeLists.txt file that accompanies an `elastix` component looks typically like this:

```
ADD_ELXCOMPONENT( AdvancedMeanSquaresMetric
  elxAdvancedMeanSquaresMetric.h
  elxAdvancedMeanSquaresMetric.hxx
  elxAdvancedMeanSquaresMetric.cxx
  itkAdvancedMeanSquaresImageToImageMetric.h
  itkAdvancedMeanSquaresImageToImageMetric.hxx )
```

The `ADD_ELXCOMPONENT` command is a macro defined in `src/Components/CMakeLists.txt`. The first argument is the name of the layer B wrapper class, which is declared in "elxAdvancedMeanSquaresMetric.h". After that, you can specify the source files on which the component relies. In the example above, the files that start with "itk" form the layer A code. Files that start with "elx" are the layer B code. The file "elxAdvancedMeanSquaresMetric.cxx" is particularly simple. It just consists of two lines:

```
#include "elxAdvancedMeanSquaresMetric.h"
elxInstallMacro( AdvancedMeanSquaresMetric );
```

The `elxInstallMacro` is defined in `src/Core/Install/elxMacro.h`.

The files `elxAdvancedMeanSquaresMetric.h/hxx` together define the layer B wrapper class. That class inherits from the corresponding layer A class, but also from an `elx::BaseComponent`. This gives us the opportunity to add a common interface to all elastix components, regardless of the ITK classes from which they inherit. Examples of this interface are the following methods:

```
void BeforeAll(void)
void BeforeRegistration(void)
void BeforeEachResolution(void)
void AfterEachResolution(void)
void AfterEachIteration(void)
void AfterRegistration(void)
```

These methods are automatically invoked at the moments indicated by the name of the function. This gives you a chance to read/set some parameters, print some output, save some results etc.

7.5 Coding style

In order to improve code readability and consistency, which has a positive influence on maintainability we have adopted a coding style. A rough `uncrustify` configuration file is provided in `elastix` since version 4.7.

White spacing Good spacing improves code readability. Therefore,

- Don't use tabs. Tabs depend on tab size, which will make the code appearance dependent on the viewer. We use 2 spaces per tab. In Visual Studio this can be set as a preference: go to tools → options → text editor → All languages → Tabs, then tab size = indent size = 2 and mark "insert spaces". In vim you can adapt your `.vimrc` to include the lines `set ts=2; set sw=2; set expandtab`.
- No spaces at the end of a line, like in ITK. It's just ugly. To make them (very) noticeable add the following in your `.vimrc`:

  ```
  :highlight ExtraWhitespace ctermbg=red guibg=red
  :match ExtraWhitespace /\s\+$/
  ```

- Use spaces in functions, `for` loops, indices, etc. So,

  ```
  FunctionName(.void.);
  for(.i.=.0;.i.<.10;.++i.)
  vector[.i.].=.3;
  ```

Indentation l

- Not too much, not too long lines

```
namespace itk
{
^
^
/**
.* ********************* Function *****************************
.*/
^
template <class TTemplate1, class TTemplate2>
void
ClassName<TTemplate1, TTemplate2>
::Function(.void.)
{
```

```
..//Function body
..this->OtherMemberFunction(.arguments.);
..for(.i.=.0;.i.<.10;.++i.)
..{
....x.+=.i.*.i;
..}
^
} // end Function()
^
}.//.end.namespace.itk
```

- A class looks like

```
namespace itk
{
^
/**.\class.ClassName
.*.\brief.Brief.description
.*
.*.Detailed.description
.*
.*.\ingroup.Group
.*/
^
template < templateArguments >
class.ClassName:
public.SuperclassName
{
public:
^
../**.Standard.class.typedefs..*/
..typedef.ClassName.................Self;
..typedef.SuperclassName............Superclass;
```

Variable and function naming It's nice if from the name of a variable you know that it's local or a class member. Therefore,

- Member variables are prepended with `m_`, followed by a capital. In the implementation refer to them using `this->`. So, `this->m_MemberVariable` is correct.
- Local variables should start with a lower case character.
- Functions should start with a capital.
- Member functions should also be called using `this->`

Better code Some simple things to look at:

- Use const wherever you can
- For floats don't use 0, but 0.0 to avoid possible bugs.
- Use the virtual keyword when overriding a virtual function in a derived class. This is not strictly needed in C++, but when you use it, it is immediately clear that a function overridden or meant to be overridden.

- Always use opening and closing brackets. Although it is not always needed for C++, do

```
if(.condition.)
{
..valid = true;
}
```

  instead of

```
if(.condition.)
..valid = true;
```

  Also for `for`-loops.

Commenting Code is meant to be read by others, or by you in years time. So,

- Comment a lot
- End functions with `} // end FunctionName()`

Appendix A

Example parameter file

```
//ImageTypes
(FixedInternalImagePixelType "float")
(MovingInternalImagePixelType "float")
(UseDirectionCosines "true")

//Components
(Registration "MultiResolutionRegistration")
(FixedImagePyramid "FixedRecursiveImagePyramid")
(MovingImagePyramid "MovingRecursiveImagePyramid")
(Interpolator "BSplineInterpolator")
(Metric "AdvancedMattesMutualInformation")
(Optimizer "AdaptiveStochasticGradientDescent")
(ResampleInterpolator "FinalBSplineInterpolator")
(Resampler "DefaultResampler")
(Transform "EulerTransform")

// ********** Pyramid

// Total number of resolutions
(NumberOfResolutions 3)


// ********** Transform

//(CenterOfRotation 128 128) center by default
(AutomaticTransformInitialization "true")
(AutomaticScalesEstimation "true")
(HowToCombineTransforms "Compose")


// ********** Optimizer

// Maximum number of iterations in each resolution level:
(MaximumNumberOfIterations 300 300 600)

(AutomaticParameterEstimation "true")
(UseAdaptiveStepSizes "true")
```

```
// ********** Metric

//Number of grey level bins in each resolution level:
(NumberOfHistogramBins 32)
(FixedKernelBSplineOrder 1)
(MovingKernelBSplineOrder 3)


// ********** Several

(WriteTransformParametersEachIteration "false")
(WriteTransformParametersEachResolution "false")
(ShowExactMetricValue "false")
(ErodeMask "true")


// ********** ImageSampler

// Number of spatial samples used to compute the
// mutual information in each resolution level:
(ImageSampler "RandomCoordinate")
(NumberOfSpatialSamples 2048)
(NewSamplesEveryIteration "true")


// ********** Interpolator and Resampler

//Order of B-Spline interpolation used in each resolution level:
(BSplineInterpolationOrder 1)

//Order of B-Spline interpolation used for applying the final deformation:
(FinalBSplineInterpolationOrder 3)

//Default pixel value for pixels that come from outside the picture:
(DefaultPixelValue 0)
```

Appendix B

Example transform parameter file

```
(Transform "EulerTransform")
(NumberOfParameters 3)
(TransformParameters -0.000000 -4.564513 -2.091174)
(InitialTransformParametersFileName "NoInitialTransform")
(HowToCombineTransforms "Compose")

// Image specific
(FixedImageDimension 2)
(MovingImageDimension 2)
(FixedInternalImagePixelType "float")
(MovingInternalImagePixelType "float")
(Size 256 256)
(Index 0 0)
(Spacing 1.0000000000 1.0000000000)
(Origin 0.0000000000 0.0000000000)

// EulerTransform specific
(CenterOfRotationPoint 128.0000000000 128.0000000000)

// ResampleInterpolator specific
(ResampleInterpolator "FinalBSplineInterpolator")
(FinalBSplineInterpolationOrder 3)

// Resampler specific
(Resampler "DefaultResampler")
(DefaultPixelValue 0.000000)
(ResultImageFormat "mhd")
(ResultImagePixelType "short")
```

Appendix C

Practical exercise: using VV with `elastix`

This exercise has been kindly provided by Simon Rit (Creatis).

The goal of these practical exercises is to introduce you to the problem of image registration. Because software development is time consuming, you will not develop your own software but use existing open-source programs:

- `elastix` (http://elastix.isi.uu.nl/, [1]) is an open-source platform for automated image registration based on the Insight Segmentation and Registration Toolkit (www.itk.org). The development was initiated by the Image Sciences Institute of the University Medical Center of Utrecht (The Netherlands). It is command line driven with configuration settings defined in a parameter file. The user manual is available here: http://elastix.isi.uu.nl/download/elastix_manual_v4.5.pdf.
- vv (http://vv.creatis.insa-lyon.fr/), [2]) is an open-source and cross platform image viewer, designed for fast and simple visualization, based on ITK and the Visualization Toolkit (www.vtk.org). The development was initiated by the CREATIS laboratory of Lyon (France). It can also be command line driven. Command line options are accessible with `vv --help`, key shortcuts with `F1`.

To run a command window in Windows, click on `Executer` in the Windows menu and type `cmd`. In this window, you can:

- Change drive by typing, e.g., `D:` to go to drive D.
- Change folder by typing, e.g., `cd tmp` to go to subfolder *tmp*.
- Create a directory by typing, e.g., `mkdir toto` to create a *toto* subfolder.

At the end of the exercises, you should be able to do rigid (manual and automated) as well as non-rigid registrations and to visualize the results. You will write a report to answer the instructions with a bold font which will contain concise comments supported with screenshots whenever possible.

C.1 Manual rigid registration

- Download the images *ct.mha* and *cbct.mha*: http://www.creatis.insa-lyon.fr/~srit/tete.
- Open them in vv with the command line `vv ct.mha cbct.mha`. Observe them, change image on each slicer and analyze the effect of each shortcut and mouse option in the help menu (`F1`).

- Open them in vv with the command line `vv --linkall ct.mha cbct.mha` and observe the difference.
- Open them in vv with the command line `vv ct.mha --overlay cbct.mha` and observe the difference.
- In the menu `Tools`, open the manual registration tool and play with the sliders. Check that the behavior of vv manual registration is consistent with that described in the `elastix` manual, section 2.6.
- **Manually register the two images.**
- **Knowing that the convention is Euler angles with YXZ, explain how the resulting matrix is computed from the parameters.**
- The software is not robust to the gimbal lock. **Explain for which parameter(s) the gimbal lock is reached and observe the consequence in vv.**

C.2 Automated rigid registration

- Download the `elastix` parameter file *Par0005.MI.rigid.txt* which has been taken from the `elastix` database on their website.
- Create a *rigid* directory with `mkdir rigid` and run `elastix` with the command line
  `elastix -f cbct.mha -m ct.mha -p Par0005.MI.rigid.txt -out rigid`
  Observe the result with vv by typing the result parameters in the manual registration window (in the file *rigid/TransformParameters.0.txt*).
- **Detect a not so well aligned region and elaborate on the cause.**
- **Compare 3 similarity measures and plot their evolution during optimization.**

C.3 Non-rigid registration

- Download the pre-registered image *ct.mhd* and check that only deformations are left with `vv ct.mhd --overlay cbct.mha`.
- Download the `elastix` parameter file *Par0005.MI.1.txt*. The latter has been modified to account for the embedded rigid registration with the parameter `(UseDirectionCosines "true")`.
- Create a *dir* directory with `mkdir dir` and run
  `elastix -f cbct.mha -m ct.mhd -p Par0005.MI.1.txt -out dir`
- Create a *dirres* directory with `mkdir dirres` and run
  `transformix -in ct.mhd -out dirres -tp dir/TransformParameters.0.R1.txt -def all`
- **Discuss the results using the two commands:**
  `vv cbct.mha --vf dirres/deformationField.mhd`
  `vv --linkall cbct.mha --overlay ct.mhd cbct.mha --overlay dirres/result.mhd`

[1] S. Klein, M. Staring, K. Murphy, M.A. Viergever, and J.P.W. Pluim. `elastix`: a toolbox for intensity-based medical image registration. *IEEE Trans Med Imaging*, 29(1):196–205, Jan 2010.
[2] S. Rit, R. Pinho, V. Delmon, M. Pech, G. Bouilhol, J. Schaerer, B. Navalpakkam, J. Vandemeulebroucke, P. Seroul, and D. Sarrut. VV, a 4D slicer. In *Proceedings of the Fourth International Workshop on Pulmonary Image Analysis*, pages 171–175, Toronto, Canada, September 2011.

Appendix D

Software License

```
Overview:

Elastix was developed by Stefan Klein and Marius Staring under
supervision of Josien P.W. Pluim, initially under contract to the
Image Sciences Institute, University Medical Center Utrecht, The
Netherlands.

Elastix is distributed under the new and simplified BSD license
approved by the Open Source Initiative (OSI)
[http://www.opensource.org/licenses/bsd-license.php].

The software is partially derived from the Insight Segmentation and
Registration Toolkit (ITK), which is also distributed under the new
and simplified BSD licence. The ITK is required by Elastix for
compilation of the source code.

The copyright of the files in the Common/KNN/ann_1.1 subdirectory
is held by a third party, the University of Maryland. The ANN
package is distributed under the GNU Lesser Public Licence. Please
read the content of the subdirectory for specific details on this
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are met:

    * Redistributions of source code must retain the above copyright notice,
      this list of conditions and the following disclaimer.
```

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