Non-Rigid Registration of Medical Images: Theory, Methods and Applications

Daniel Rueckert Paul Aljabar

Medical image registration [1] plays an increasingly important role in many clinical applications including the detection and diagnosis of diseases, the planning of therapy, the guidance of interventions and the follow-up and monitoring of patients. The primary goal of image registration is to find corresponding anatomical or functional locations in two or more images. This has many applications: Registration can be applied to images from the same subject acquired by different imaging modalities (*multi-modal* image registration) or at different time points (*serial* image registration). Both cases are examples of *intra-subject* registration since the images are acquired from the same subject. Another application area for image registration is *inter-subject* registration where the aim is to align images acquired from different subjects, e.g. to study the anatomical variability within or across populations.

While rigid registration has become a widely used tool in clinical practice, non-rigid registration has not yet achieved the same level of clinical acceptance. Much recent progress has been made, however, in developing improved non-rigid registration techniques. In this article we will illustrate some of the advances which have been made over the last decades. We will discuss some of the theoretical aspects of non-rigid registration and describe methods for their implementation. Finally, we will illustrate how common problems in medical imaging, such as motion correction and image segmentation, can be solved using image registration.

METHODS

In general, the process of image registration involves finding the optimal geometric transformation which maximizes the correspondences across the images. This involves several components (see Figure 1):

- *A transformation model* which defines a geometric transformation between the images. There are several classes of non-rigid transformations including parametric and non-parametric models. Some of these models are well suited for small deformations while others can represent large deformations.
- *A similarity metric* which measures the degree of alignment between the images. In cases where features such as landmarks, edges or surfaces are available, the distances between corresponding features can be used to measure the alignment. In other cases the image intensities can be directly used to measure the alignment.
- *An optimization method* which maximizes the similarity metric. Like many other problems in medical imaging, non-rigid registration can be formulated as an optimisation problem whose goal it is to maximize an associated objective function.

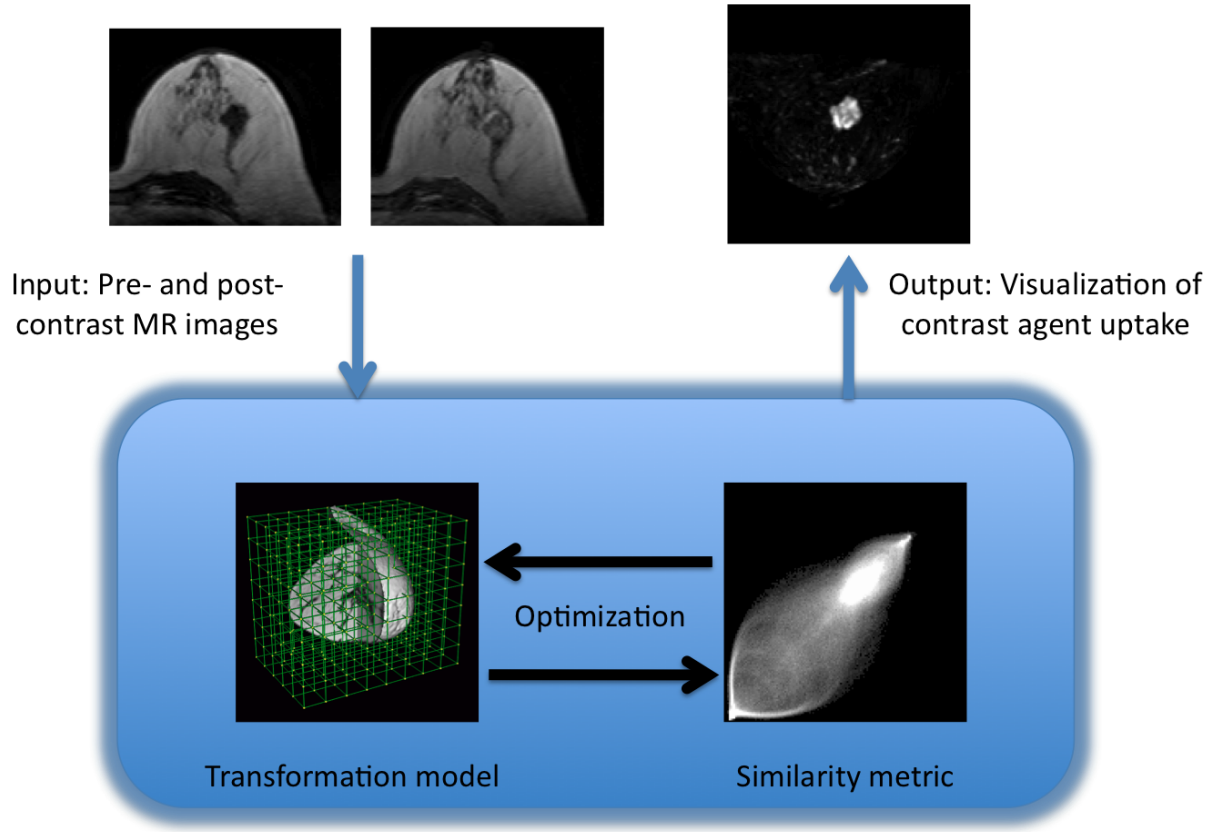

Figure 1: Illustration of the components of a generic non-rigid image registration algorithm: The transformation model, the similarity metric and the optimisation technique. This example shows the application of non-rigid registration for the motion correction of contrast-enhanced MR images [2].

In addition, a careful validation must be performed to assess measures of performance such as accuracy and robustness as well as in application-specific terms such as clinical utility. In the following we will describe the individual components of non-rigid registration techniques in more detail.

TRANSFORMATION MODELS

The transformation model used in the registration defines how the coordinates of two images are related. For a pair of images $\mathscr{I}_A$ and $\mathscr{I}_B$, this is often expressed as a single coordinate transformation $\mathbf{T}$ mapping each point $\mathbf{x}$ in $\mathscr{I}_A$ to an anatomically corresponding location $\mathbf{T}(\mathbf{x})$ in $\mathscr{I}_B$. Some transformations require only translation, rotation or scaling and, in this case, the output coordinates of $\mathbf{T}(\mathbf{x})$ can be written as a linear combination the input coordinates for some fixed global set of linear weights. In the case of non-rigid registration, no such global linear model can be formulated, and it is common to optimise a spatially varying displacement field $\mathbf{u}$ to express the transformation, i.e. $\mathbf{T}(\mathbf{x}) = \mathbf{x} + \mathbf{u}(\mathbf{x})$. Typical requirements of a non-rigid transformation are that it is smooth and invertible, i.e. that it does not lead to effects such as tearing or collapsing regions to a point. Such requirements reflect the variations in anatomy where changes in size and shape are common but changes in topology are rare.

As an illustration of some of the aspects of non-rigid transformation models, we describe the widely used free-form deformations (FFDs) which were developed within the computer graphics

and computer aided design communities and now also have an established role in medical image registration [2]. A FFD is defined by a set of displacement vectors associated with the points of a discrete 3-D lattice. A blend of the vectors is used to define the displacement at a general location in the image with nearer vectors having a greater influence. The blending weights are determined by a weighting function and spline functions, such as B-splines, are often used.

FFDs are an example of parametric transformations and contrast with non-parametric transformations where a displacement vector is associated with every voxel[1] in the image. FFDs are geometric in their construction but it is possible to derive transformations from more physical models such as fluid [3], diffusion [4] or elastic models [5]. FFDs are also an example of small deformation models which are suitable for modelling, say, gradual changes in anatomy. In some applications, such as the deformations of cardiac muscle, a large deformation model, such as that derived from a flow field, can be more appropriate.

In the case of fluid-based transformations models, the registration no longer seeks to optimise the displacements at each location directly but instead estimates a velocity field which is used to provide the displacement. In this case the corresponding points $\mathbf{x}$ and $\mathbf{T}(x)$ represent the start and end points of a flow determined by the velocity. This can be a challenge to optimise, especially given that the velocity field may be allowed to vary over time as well as spatially.

SIMILARITY METRICS

The second component of a registration algorithm is the registration basis which measures the degree of alignment of the images. The two main approaches are feature-based and voxel-based similarity measures. Feature-based registration approaches usually utilise points, lines or surfaces and aim to minimize the distance between the corresponding features in the images. An advantage of feature-based registration is that it can be used for both mono- and multi-modality registration but the need for a feature extraction step, in form of landmark detection or segmentation, can be onerous. Moreover, any error during the feature extraction stage, whether manual or automated, will adversely affect the registration and cannot be recovered at a later stage. It is possible to avoid such errors by using the image intensities directly without the need for feature extraction. This relies on voxel-based similarity measures which aim to measure the degree of shared information in the image intensities. This is relatively simple in the case of mono-modality registration but more complex for multi-modality registration. Over the last decade, voxel-similarity measures have become the method of choice for measuring image alignment, largely due to their robustness and accuracy.

The simplest statistical measure of image similarity is based on the squared sum of intensity differences (SSD) between images $\mathscr{I}_A$ and $\mathscr{I}_B$,

$$\mathscr{S}_{SSD} = -\frac{1}{n}\sum(\mathscr{I}_A(\mathbf{p}) - \mathscr{I}_B(\mathbf{T}(\mathbf{p})))^2 \tag{1}$$

where $\mathbf{p}$ is a point in image $\mathscr{I}_A$, $\mathbf{T}(\mathbf{p})$ is the corresponding location in $\mathscr{I}_b$ and n is the number of voxels in the overlap region. This measure is based on the assumption that both imaging modalities have the same characteristics. If the images are correctly aligned, the difference between them should be zero except for noise and the SSD measure can be shown to be optimal if this noise is Gaussian. Since this similarity measure assumes that the imaging modalities are identical, their application is restricted to mono-modal applications.

[1] A volume element, the 3-D analogy of a 'pixel'.

The assumption of identical imaging modalities can, however, be too restrictive. A more general approach assumes a linear relationship between the image intensities. In this case, the similarity between both images can be expressed by the normalised cross correlation (NCC)

$$\mathscr{S}_{CC} = \frac{\sum(\mathscr{I}_A(\mathbf{p}) - \mu_A)(\mathscr{I}_B(\mathbf{T}(\mathbf{p})) - \mu_B)}{\sqrt{(\sum \mathscr{I}_A(\mathbf{p}) - \mu_A)^2 (\sum \mathscr{I}_B(\mathbf{T}(\mathbf{p})) - \mu_B)^2}} \tag{2}$$

where μ_A and μ_B correspond to the average voxel intensities in each image. While more flexible than SSD, the application of this similarity measure is nevertheless largely restricted to mono-modal registration tasks.

There has been significant interest in measures of alignment based on the information content or entropy of the registered images. An important component of these methods is the feature space of the image intensities which may be interpreted as a joint probability distribution. A simple way of visualizing this feature space is by accumulating a two-dimensional histogram of the co-occurrences of intensities in the two images for each trial alignment. By varying the degree to which the images are aligned, it can be shown that the feature space disperses as misalignment increases and that each image pair has a distinctive feature space signature at alignment.

In an information theoretic framework, the information content of images $\mathscr{I}_A$ and $\mathscr{I}_B$ can be defined by their Shannon-Wiener entropy:

$$H(\mathscr{I}_A) = -\sum_a p(a) \log p(a) \tag{3}$$

and

$$H(\mathscr{I}_B) = -\sum_b p(b) \log p(b) \tag{4}$$

where $p(a)$ is the probability that a voxel in image $\mathscr{I}_A$ has intensity a and $p(b)$ is the probability that a voxel in image $\mathscr{I}_B$ has intensity b. The joint entropy $H(\mathscr{I}_A, \mathscr{I}_B)$ of the overlapping region of images $\mathscr{I}_A$ and $\mathscr{I}_B$ may be defined by

$$H(\mathscr{I}_A, \mathscr{I}_B) = -\sum_a \sum_b p(a,b) \log p(a,b) \tag{5}$$

where $p(a,b)$ is the joint probability that a voxel in the overlapping region of image $\mathscr{I}_A$ and $\mathscr{I}_B$ has values a and b, respectively.

In order to quantify image alignment one can use measures from information theory such as mutual information [6, 7]. Mutual information (MI) is defined in term of entropies as

$$\mathscr{S}_{MI}(\mathscr{I}_A; \mathscr{I}_B) = H(\mathscr{I}_A) + H(\mathscr{I}_B) - H(\mathscr{I}_A, \mathscr{I}_B) \tag{6}$$

and should be maximal at alignment. Mutual information is a measure of how one image "explains" the other but makes no assumption of the functional form or relationship between image intensities in the two images. Studholme [8] showed that mutual information can be affected by the degree of overlap between two images. Studholme [8] and Maes et al. [6] suggested the use of normalised mutual information (NMI) as an alternative measure one form of which may be written:

$$\mathscr{S}_{NMI}(\mathscr{I}_A; \mathscr{I}_B) = \frac{H(\mathscr{I}_A) + H(\mathscr{I}_B)}{H(\mathscr{I}_A, \mathscr{I}_B)}. \tag{7}$$

IMPLEMENTATION: OPTIMISATION AND INTERPOLATION

The registration task seeks to identify the transformation parameters that maximise the similarity measure derived from the two images. In certain special cases, such as the rigid registration of pairs of corresponding landmarks, it is possible to analytically estimate the optimal transformation (in a least squares sense). Such an example is, however, exceptional as the majority of registrations are voxel-based registrations and these typically rely on numerical methods to find the optimal parameters.

In the case of non-rigid transformations, the number of parameters or degrees of freedom can be very high: For example, a FFD with a cubic control point lattice and 10 control points along each side has $10 \times 10 \times 10 \times 3 = 3000$ parameters to optimise with respect to the similarity metric. Many optimisation methods, such as Newton or conjugate descent approaches, require the estimation of the similarity measure's gradient with respect to the parameters and second order methods may also require an estimate of its Hessian. For some similarity measures, such as $\mathscr{S}_{SSD}$ or $\mathscr{S}_{CC}$, an explicit expression for the gradient may be derived. This can remain possible for more complex entropy-based measures such as $\mathscr{S}_{MI}$, but the computational overhead of evaluating them can make numerical schemes of gradient approximation more attractive. In the case of the Hessian, even numerical estimation can be computationally expensive for every iteration and techniques for avoiding its direct estimation are often exploited.

As a function of the transformation parameters, the similarity metric defines a hypersurface in a typically high-dimensional space (3000 dimensions in the earlier example). This presents a challenge to the optimisation as the surface is likely to be highly non-convex with multiple local maxima and a number of approaches have been developed to help identify a globally optimal set of parameters. Notable examples include coarse to fine approaches in which image pyramids at different scales are used instead of the original images with transformations at coarser levels of detail optimised first and used as an initialization for the subsequent stages with finer details. As an alternative to gradient-based optimization methods, it is also possible to discretize the parameter space entirely and apply techniques such as linear programming.

One aspect of many registration approaches is that they are expressed asymmetrically. In order to evaluate the similarity measure for the images, it is common to loop over the voxels in the first ('target') image, identifying the corresponding locations in the second ('source') image under the current transformation estimate. Each target-source intensity pair is then used to estimate the similarity. It is unlikely for each location in the target voxel lattice to correspond directly to a source voxel and it is much more likely to correspond to an intermediate location within the source voxel lattice. This necessitates the interpolation of one of the images (the source), hence the asymmetry in the model.

If, for example, a linear interpolation scheme is applied, the source image effectively undergoes a low-pass filtering step and the associated loss of detail can have an effect on the registration. In practice however, such effects are small, especially if an image pyramid is used in a multi-resolution scheme. Other more complex interpolation schemes can of course be applied, such as sinc interpolation or higher order splines, but there is a trade-off between interpolation accuracy and computational burden that needs to be taken into account.

Some approaches attempt to symmetrise the registration by looping over both source and target voxels, using the inverse transformation to obtain interpolated values from the target image. Again computational load becomes an issue here as there may be a significant cost to inverting the transformation and it may be difficult to accurately estimate its inverse.

VALIDATION OF REGISTRATION

Prior to clinical use, medical image registration algorithms need to be validated in terms of their accuracy in establishing correspondence between images. However, the validation of registration performance usually suffers from the lack of knowledge as to whether, how much, and where patient movement has occurred between and even during scanning procedures, and whether such movement affects the clinical usefulness of the data. To maintain clinical usefulness, and to inherently improve patient treatment and health care, it is therefore vital to ensure that registration is successful.

A registration method can be assessed by independent evaluation in the absence of a ground truth correspondence estimate. An initial visual inspection allows for a qualitative assessment of registration performance, which can be complemented by quantitative checks for robustness and consistency. Robustness checks establish the measurement precision by testing the bias and sensitivity after, for example, adding noise or choosing different starting estimates. Consistency checks assess the capability of a registration technique to find circular transformations based on a registration circuit, but can be sensitive to bias and may not be applicable to non-invertible transformations generated by many nonrigid registration methods. Nonetheless, consistency checks have been successfully used for intra-modality rigid body registration applications, e.g., for serial magnetic resonance (MR) imaging of the brain. The methods available to an expert observer performing a visual assessment of registration performance include the inspection of subtraction images, contour or segmentation overlays, alternate pixel displays, or viewing anatomical landmarks. These approaches have been applied to rigid registration, and since they involve inspection of the entire volume domain of the image pair, can be extended to nonrigid registration. For non-rigid registration, expert visual assessment is an important step toward clinical acceptance and routine use but locally implausible deformations, not readily picked up by observers, represent a significant challenge. Nonetheless, visual assessment often forms the first and last line of defence of any image registration validation.

In the absence of a ground truth transformation, registration accuracy can be studied by setting up a gold standard transformation. For example, the retrospective registration evaluation project (RREP) used skull-implanted markers in patients undergoing brain surgery to derive a gold standard transformation for multi-modality rigid-body image registration of the head to compare different established rigid registration methods [9]. For non-rigid registration validation, extrinsic markers cannot easily be used as they would need to be implanted into soft tissue. In an alternative approach [10], a biomechanical motion simulator was introduced which modelled physically plausible deformations of soft tissue for clinically realistic motion scenarios in an application to contrast-enhanced MR mammography. This motion simulator was designed to be independent of the image registration and transformation model used.

Finally, the segmentation of anatomical structures provide the means to measure structure overlap or surface distances before and after registration, but cannot provide insight into the registration accuracy away from the structure's boundary, or along its outline. If, however, the objective of the registration is to propagate (and hence automate) segmentation, segmentation quality can be used as a surrogate measurement. For example in [11] a number of non-rigid registration methods were compared for inter-subject brain alignment based on their segmentation quality and a number of carefully annotated image databases[2] are becoming available that can be used to establish the accuracy of non-rigid registration methods on the basis of carefully delineated image structures.

[2]E.g. http://www.nirep.org/

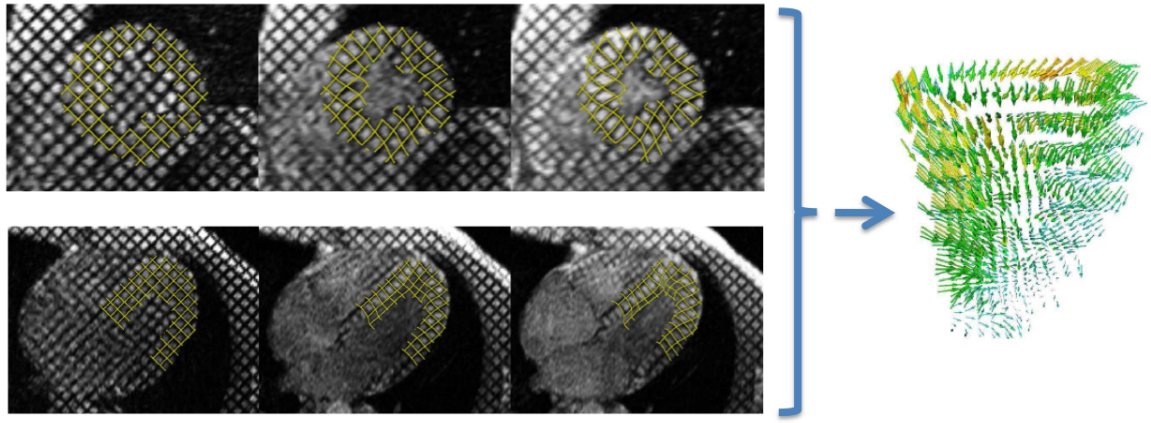

Figure 2: Tracking change over time in a sequence of tagged MR images for the 4D estimation of myocardial motion.

APPLICATIONS OF NON-RIGID REGISTRATION

TRACKING CHANGE OVER TIME

It is possible to apply the registration of medical images to identify changes in anatomies over time. The changes studied may last for short time intervals, such as muscle deformations in a cardiac cycle, or they may last for years, such gradual atrophy in an aging brain. Neural atrophy is an example of change that is diffuse and subtle compared with, say, the rapid and dramatic growth of organs during fetal development. Each of these scenarios presents its own challenges when registration is used to characterise the associated change. In a longitudinal approach to measuring change, serially acquired images of a single individual may be registered to identify changes in the anatomy that may be of clinical interest. This approach is in routine use for identifying atrophy of the brain due to aging or disease.

In the case of serial images of the head, rigid registration and subtraction can provide a good indication of changes. Other forms of serial images, such as sequences of a beating heart, require non-rigid registration to characterise the deformation of tissue of time (see Figure 2). In the case of serial brain MR images of elderly subjects, non-rigid registration may still be applied and the geometric properties of the non-rigid transformation between the images, can provide quantitative local estimates of the tissue expansion or contraction that has taken place between the scans. This helps to identify which structures in the brain are most susceptible to pathology.

In a cross-sectional approach, images are acquired from a number of subjects at varying temporal stages and inter-subject registration may be used to factor out variability across subjects and to subsequently identify the salient changes in the images of the whole cohort over time. Example applications are the generation of a 4-D spatio-temporal atlas of an aging anatomy.

MORPHOMETRY AND SEGMENTATION

Morphometry can generally be described as the study of shape and, in the context of medical images, it can represent the direct comparison or modeling of the shapes of anatomical structures. D'Arcy Thompson used non-rigid coordinate transforms to compare the forms of biological organisms in his seminal work at the start of the 20th century. The computational power now available and the tools of non-rigid registration allow the comparison of anatomies in general and anatomical structures in particular to be carried out systematically and on a large scale. For example, the expected shape of an anatomical structure and its variation over a population can be estimated and this information can be used in a clinical setting to decide if a particular anatomy is representative or pathological.

Non-rigid registration also enables more indirect approaches to morphometry such as the neuroimaging methods known as voxel-based morphometry (VBM) and deformation-based morphometry (DBM). In VBM, variations in tissue density are identified across a cohort of subjects after aligning all images to the a common template. The registrations used for alignment may only be rigid or affine, but the use of non-rigid registration increases, for example, the sensitivity of the approach when detecting group differences. DBM seeks to characterise the variation in set of medical images by registering them all to a common template. This step matches that of VBM, but if sufficiently detailed transformations are used, differences between the images are removed and the variation in the group is then encoded in the aligning deformations. By studying geometric properties of the deformations, such as their locally varying Jacobian tensors, group studies may be carried out in a similar way to that described for VBM.

Whether studying the shape properties of specific anatomical structures, or applying VBM or DBM, a segmentation step is needed. This can be used to delineate the particular anatomical structure of interest or to identify the tissue or region of interest where the analysis is to be carried out. When delineating anatomical structures, a trained human expert can provide very accurate segmentations although this is a time-consuming and costly exercise. Automated segmentation is, by contrast, much faster and easier to carry out at the expense of a loss of accuracy.

Registration can be used to bridge the gap between the manual and automatic approaches through an approach termed 'atlas-based segmentation'. An 'atlas' in this context is represented by an anatomical image together with an expert manual labelling of the structure of interest. When a new image of a different anatomy is obtained, registration can be used to align the atlas anatomy to the new image. The resulting transformation may then be used to transform the atlas label to the new image. The transformed label can then be treated as a segmentation estimate of the new image and, in a sense, the expertise of the human rater has been propagated automatically to the target image.

Atlas-based segmentation is, however, prone to errors which can arise from a variety of sources such as errors in the original labelling or errors in the estimated transformation between atlas and target. It has been shown that a multi-atlas approach to segmentation can overcome much of this error and provide very accurate structural segmentations. In this state-of-the-art approach, instead of using single atlas, a repository of atlases are stored and each is separately registered with the target. The resulting set of transformations is used to propagate the labels for each atlas to the space of the target image. After propagation, a consensus segmentation of the target is obtained by combining the propagated labels using some scheme (see Figure 3). A simple vote scheme in which the label for a voxel (in or out of the structure) is determined according to the majority of the propagated labels has been shown to be highly effective.

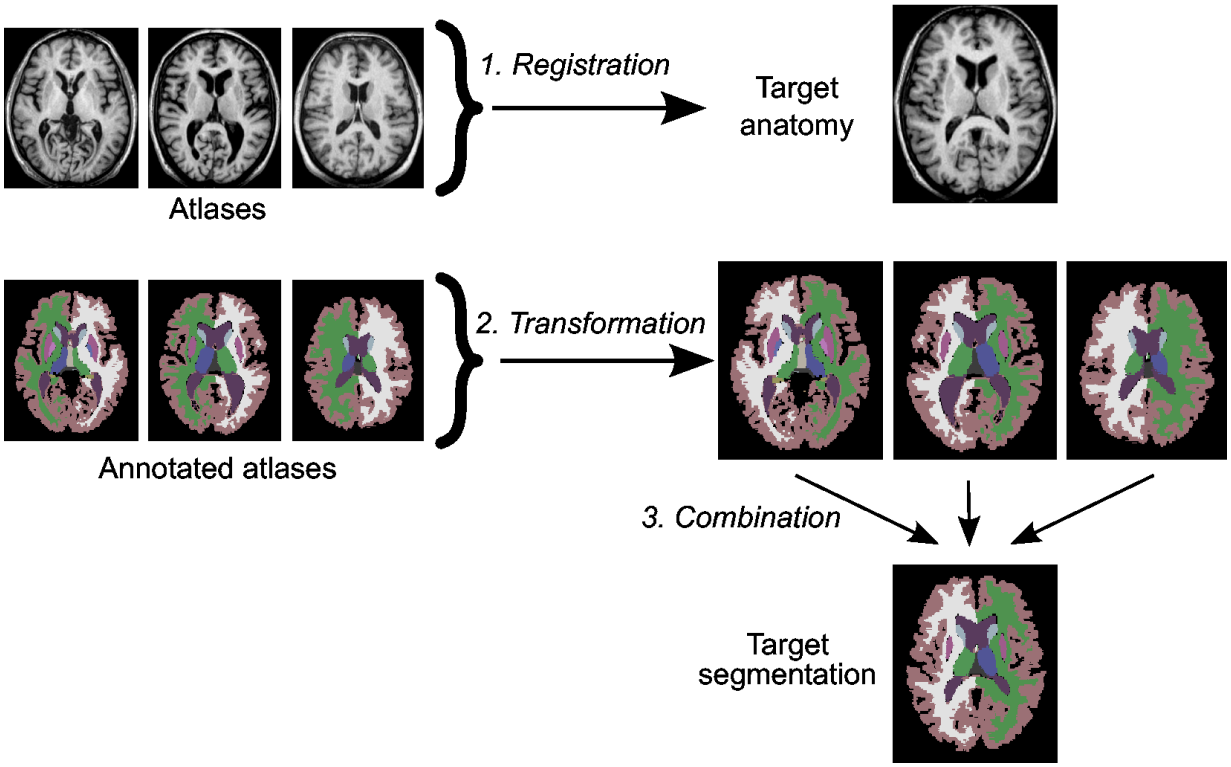

Figure 3: An example of multi-atlas segmentation of brain MR images.

MOTION CORRECTION

There are a number of different imaging modalities available to medical community. MR imaging in particular has a number of attractive properties in that it can distinguish between different types of soft tissue without exposing the subject to non-ionising radiation. A drawback of MR imaging is the length of the acquisition time and, when the subject moves, this can lead to artefacts in the acquired image. The acquisition of a MR image represents a trade-off among various factors such as resolution, the quality of contrast between tissues, the signal-to-noise ratio. For example it is possible to rapidly acquire a volumetric image but the resulting SNR will be low. A high SNR volume requires a long acquisition time in which the subject is more likely to move. It is possible, however, to acquire slice data rapidly and with reasonable quality although a single slice only provides a restricted view of the anatomy.

A particular and recent application in which images are affected by motion has been the *in-utero* imaging of fetal subjects and registration may be used to correct for the resulting artefacts. In this approach, a number of parallel slices of the fetus are acquired. Each individual slice is acquired quickly enough for motion to be negligible and represents a high-resolution snapshot through the subject. The fetus is, however, likely to move during the time required to acquire all slices. This means that, while the slices are all parallel relative to the scanner, they are no longer parallel relative to the fetal anatomy. After acquisition, it is possible to use an iterative registration and reconstruction scheme to correct for the mismatch in geometry among all the slices and to estimate a 3-D volumetric reconstruction of the fetal subject's anatomy (see Figure 4).

If the head is the focus of the scan, it can be assumed that all the slices are related to the 'true'

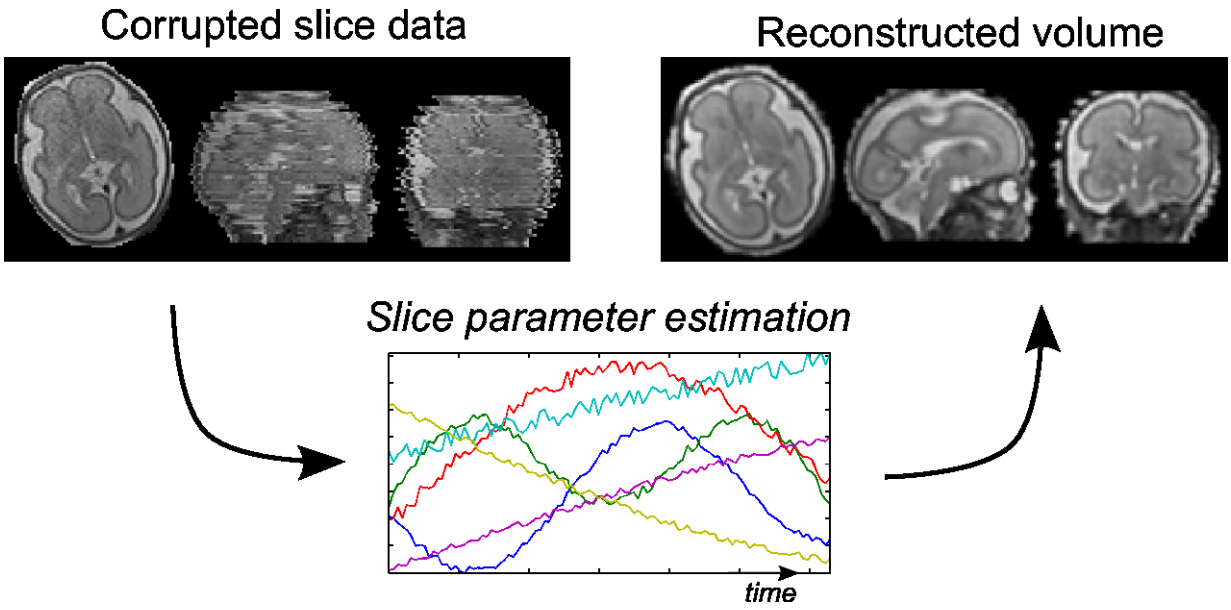

Figure 4: Registration for the correction of motion artefacts: Successively acquired slices of a moving subject are geometrically inconsistent (*left*). Registration is used to estimate the motion parameters of each slice and reconstruct a consistent volume (*right*).

underlying volume by a rigid alignment. The task is to estimate the transformation parameters for each slice. Once estimated, the relative orientations of the slices are known and it is possible to reconstruct the original signal in three dimensions using a scattered data interpolation approach. In practice the two main steps (slice parameter estimation and volume reconstruction) are carried out in an iterative and interleaved fashion. It is also possible to adopt a multi-resolution coarse-to-fine approach where the early iterations estimate the anatomy at lower spatial frequencies and more detail is recovered as the iterations proceed.

SUMMARY AND CONCLUSIONS

As we have illustrated in this article, the non-rigid registration of medical images is a versatile tool which is widely used, both in clinical applications (e.g. motion correction and image fusion) as well as a tool for biomedical research (e.g. to study populations or disease progression in clinical trials). In contrast to rigid registration, the development of non-rigid registration techniques is very much an area of on-going research and most algorithms are still in the early stages of evaluation and validation. The speed of non-rigid registration algorithms is one drawback of most algorithms, making their clinical use difficult. However, recent advance is GPU technology have the potential to significantly accelerate non-rigid registration and offer the possibility of near real-time registration. However, another drawback is the lack of a generic gold standard for assessing and evaluating the success of non-rigid registration algorithms. Future developments in this area will need to address both issues.

Dr Daniel Rueckert is Professor of Visual Information Processing in the Department of Computing, Imperial College London.

Dr Paul Aljabar is a Senior Research Fellow in in the Department of Computing, Imperial College

London.

References

[1] J. V. Hajnal, D. L. G. Hill, and D. J. Hawkes, eds., *Medical Image Registration*. CRC Press, 2001.

[2] D. Rueckert, L. I. Sonoda, C. Hayes, D. L. G. Hill, M. O. Leach, and D. J. Hawkes, "Non-rigid registration using free-form deformations: Application to breast MR images," *IEEE Transactions on Medical Imaging*, vol. 18, no. 8, pp. 712–721, 1999.

[3] M. F. Beg, M. I. Miller, and A. T. L. Younes, "Computing metrics via geodesics on flows of diffeomorphisms," *International Journal of Computer Vision*, vol. 61, no. 2, pp. 139–157, 2005.

[4] J.-P. Thirion, "Image matching as a diffusion process: An analogy with Maxwell's demons," *Medical Image Analysis*, vol. 2, no. 3, pp. 243–260, 1998.

[5] R. Bajcsy and S. Kovačič, "Multiresolution elastic matching," *Computer Vision, Graphics, and Image Processing*, vol. 46, pp. 1–21, April 1989.

[6] F. Maes, A. Collignon, D. Vandermeulen, G. Marechal, and R. Suetens, "Multimodality image registration by maximization of mutual information," *IEEE Transactions on Medical Imaging*, vol. 16, no. 2, pp. 187–198, 1997.

[7] P. Viola and W. M. Wells, "Alignment by maximization of mutual information," *International Journal of Computer Vision*, vol. 24, no. 2, pp. 137–154, 1997.

[8] C. Studholme, D. L. G. Hill, and D. J. Hawkes, "An overlap invariant entropy measure of 3D medical image alignment," *Pattern Recognition*, vol. 32, no. 1, pp. 71–86, 1998.

[9] J. B. West, J. M. Fitzpatrick, M. Y. Wang, B. M. Dawant, C. R. Maurer, Jr., R. M. Kessler, R. J. Maciunas, C. Barillot, D. Lemoine, A. Collignon, F. Maes, P. Suetens, D. Vandermeulen, P. A. van den Elsen, S. Napel, T. S. Sumanaweera, B. Harkness, P. F. Hemler, D. L. G. Hill, D. J. Hawkes, C. Studholme, J. B. A. Maintz, M. A. Viergever, G. Malandain, X. Pennec, M. E. Noz, G. Q. Maguire, Jr., M. Pollack, C. A. Pelizzari, R. A. Robb, D. Hanson, and R. P. Woods, "Comparison and evaluation of retrospective intermodality image registration techniques," *Journal of Computer Assisted Tomography*, vol. 21, pp. 554–566, 1997.

[10] J. A. Schnabel, C. Tanner, A. D. Castellano-Smith, A. Degenhard, M. O. Leach, D. R. Hose, D. L. G. Hill, and D. J. Hawkes, "Validation of non-rigid image registration using finite element methods: Application to breast MR images," *IEEE Transactions on Medical Imaging*, vol. 22, no. 2, pp. 238–247, 2003.

[11] A. Klein, J. Andersson, B. A. Ardekani, J. Ashburner, B. Avants, M.-C. Chiang, G. E. Christensen, D. L. Collins, J. Gee, P. Hellier, J. H. Song, M. Jenkinson, C. Lepage, D. Rueckert, P. Thompson, T. Vercauteren, R. P. Woods, J. J. Mann, and R. V. Parsey, "Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration," *NeuroImage*, vol. 46, no. 3, pp. 786–802, 2009.

[12] R. Chandrashekara, R. H. Mohiaddin, and D. Rueckert, "Analysis of 3D myocardial motion in tagged MR images using nonrigid image registration," *IEEE Transactions on Medical Imaging*, vol. 23, pp. 1245–1250, October 2004.