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Registration of Multimodal Medical Images

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Abstract

Medical images are increasingly being used within healthcare for diagnosis, planning treatment, guiding treatment and monitoring disease progression. Within medical research (e.g. neuroscience research) they are used to investigate disease processes and understand normal development and ageing. Technically, medical imaging mainly processes missing, ambiguous, complementary, redundant and distorted data. In this paper, we propose a set of MR-CT image registration methods by using spatial models like rigid, affine and projective transformations. The registered and fused image contains the properties and details of both MR and CT images and can efficiently be used in clinical medicine.

Keywords: medical MR/CT imaging, image registration, linear transformations.

1 Introduction

Image registration (*IR*) is a fundamental task in computer vision used to finding either a spatial transformation (e.g., rotation, translation, etc.) or a correspondence (matching of similar image entities) among two (or more) images taken under different conditions (at different times, using different sensors, from different viewpoints, or a combination of them), with the aim of overlaying such images into a common one.

IR methods can be classified in two groups according to the nature of images: *voxel*-based IR methods (also called *intensity*-based), where the whole image is considered for the registration process; and, on the other side, *feature*-based methods, which consider prominent information extracted from the images, being a reduced subset of them. The latter methods take advantage of the lesser amount of information managed in order to overcome the problems when the images present some looses to deal with, for example, regardless of changes in the geometry of the images, radiometric conditions, and appearance of noise and occlusion. The features correspond to *geometric primitives* (points, lines, surfaces, etc.) which are invariant to the transformation to be considered between the input images. Moreover, the latter methods perform faster than the former ones due to the reduced amount of data they take into account, at the expense of achieving coarse results.

Likewise, IR is the process of finding the optimal spatial transformation (e.g., rigid, similarity, affine, etc.) achieving the best fitting/overlaying between two (or more) different images named *scene* and *model* images (Figure 1). They both are related with the latter transformation, measured by a *similarity metric* function. Such transformation estimation is interpreted into an iterative optimization procedure in order to properly explore the search space. Two search approaches have been considered in the IR literature: (i) *matching-based*, where the optimization problem is intended to look for a set of correspondences of pairs of those more similar image entities in both the scene and the model images; (ii) the *transformation parameter-based*, where the strategy is to try to directly explore inside each range of the transformation parameters. Both strategies can be used with either a voxel-based or a feature-based approach.

2 Medical imaging

Medical imaging is a vital component of a large number of applications. Such applications occur throughout the clinical track of events, *i.e.* not only within clinical diagnostic settings, but prominently so in the area of planning, consummation, and evaluation of surgical and radiotherapeutical procedures.

The imaging modalities employed can be divided into two global categories: *anatomical* and *functional*. Anatomical modalities include X-ray, CT (computed tomography), MRI (magnetic resonance imaging), US (ultrasound), and (video) sequences obtained by various catheter "scopes", *e.g.*, by laparoscopy or laryngoscopy. Some prominent derivative techniques are so detached from the original modalities that they appear under a separate name, *e.g.*, MRA (magnetic resonance angiography), DSA (digital subtraction angiography, derived from X-ray), CTA (computed tomography angiography), and *Doppler* (derived from US, referring to the Doppler effect measured).

Functional modalities, *i.e.*, depicting primarily information on the metabolism of the underlying anatomy, include (planar) scintigraphy, SPECT (single photon emission computed tomography), PET (positron emission tomography), which together make up the *nuclear medicine* imaging modalities, and fMRI (functional MRI). With a little imagination, spatially sparse techniques like, EEG (electroencephalography), and MEG (magneto-encephalography) can also be named functional imaging techniques.

Since information gained from two images acquired in the clinical track of events is usually of a complementary nature, proper *integration* of useful data obtained from the separate images is often desired. A first step in this integration process is to bring the modalities involved into spatial alignment, a procedure referred to as *registration*. After registration, a *fusion* step is required for the integrated display of the data involved.

A prominent example concerns *radiotherapy treatment*, where both CT and MR can be employed. The former is needed to accurately compute the radiation dose, while the latter is usually better suited for precise delineation of tumor tissue. This is the main raison for our approach – to deploy a (semi)automatic procedure for registration of MR and CT images.

Besides *multimodality registration*, important application areas exist in *monomodality registration*. Examples include treatment verification by comparison of pre- and post-intervention images, comparison of ictal and inter-ictal (during and between seizures) SPECT images, and growth monitoring, *e.g.*, using time series of MR scans on tumors, or X-ray time series on specific bones. Because of the high degree of similarity between these images, solving the registration is usually an order of magnitude easier than in the multimodality applications.

3 The image registration problem

Different taxonomies have been established to classify the IR methods presented so far, considering different criteria: the image acquisition procedure, the search strategy, the type of transformation relating the images, and so forth.

There is not a universal design for an IR method that could be applicable to all registration tasks, since various considerations on the particular application must be taken into account. However, IR methods usually require the four following components (Figure 1): two input *Images*, named as Scene $Is = \{p_1, p_2, ..., p_n\}$ and Model $Im = \{p_1, p_2, ..., p_m\}$, with p_i and p_j being image points; a *registration transformation* f being a parametric function relating the two images; a *similarity metric function* F in order to measure a qualitative value of closeness or degree of fitting between the transformed scene image, denoted by $f'(Is)$, and the model image; and an *optimizer* which looks for the optimal transformation, f, inside the defined solution search space.

Hence, the key idea of the IR process is focused on determining the unknown parametric *transformation* that relates both images, by placing them in a common coordinate system bringing the points as close as possible. Because of the uncertainty underlying such transformation, the IR task arises as a *nonlinear problem* that cannot be solved by a direct method (e.g., resolution of a simple system of linear equations). It should be solved by means of an iterative procedure searching for the *optimal estimation* of f, following a specific search space optimization scheme aiming at minimizing the error of a given *similarity metric* of resemblance. Classical local optimizers can be used for this task although their main drawback is that they usually get trapped in a local minima solution. The main reasons for such behavior are related to both the nature of the problem to be tackled and the greedy/local search features of these methods. So, the interest on the application of soft-computing and Artificial Intelligence in general to the IR optimization process has increased in the last decade due to their global optimization nature.

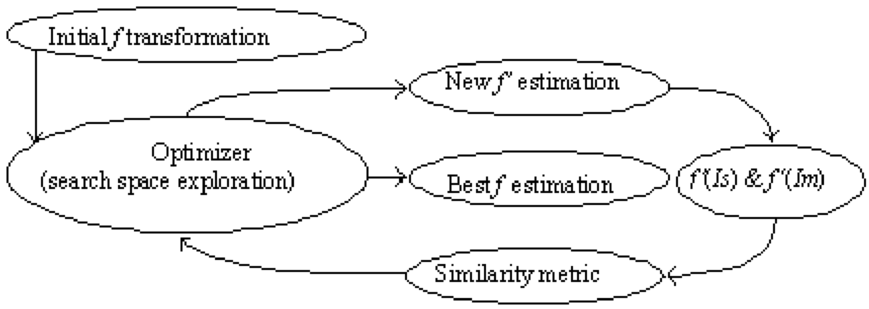


Figure 1. Image registration optimization process.

According to the nature of images, IR methods can be classified as *voxel*-based (or *intensity*-based) and *feature*-based. While the former directly operate with the whole raw images, the latter approaches introduce a previous step: before the application of the registration process, a reduced subset of the most relevant features are extracted from the images. Since voxel-based methods can deal with a major amount of image information, they are often considered as *fine-tuning* registration processes, while feature-based methods typically achieve a *coarser* approximation due to the reduced data they take into account. One important drawback of voxel-based approaches relies on the commonly used rectangular window for the correspondence estimation. If the images are deformed by complex transformations, this type of window will not be able to cover the same parts of the transformed scene and model images. Moreover, if the window contains a smooth image region without any prominent detail, it will probably be incorrectly matched to other smooth image region in the model image. Nevertheless, the principal disadvantage of voxel-based methods comes from situations where there are changes in illumination during the acquisition of the scene and the model images. In that case, the similarity metric offers unreliable measurements and induces the optimization process to be trapped in local minima. With the intention of avoiding many of the drawbacks related to voxel-based methods, the second IR approach is based on the extraction of prominent geometric primitives (*features*) from the images. The proper comparison of feature sets will be possible using a reliable feature detector that confronts the accurate extraction of invariant features, that is, regardless of changes in the geometry of the images, radiometric conditions, and appearance of noise. There are many different features that can be considered, for example, *region features*, *line features*, and *point features*, among which corners are widely used due to their invariance to the image geometry.

3.1 Transformations

We can classify IR methods according to the registration transformation model used to relate both the scene and the model images. The first category of transformation models includes *linear transformations*, which preserves the operations of vector addition and scalar multiplication, being a combination of translation, rotation, global scaling, and shear components. The most common linear transformations are rigid, similarity, affine, projective, and curved. Linear transformations are global in nature, thus not being able to model local deformations. The second category of transformation models includes *"elastic"* or *"non-rigid"* transformations. These transformations allow local warping of image features, thus providing support for local deformations.

3.2 Similarity metric

One of the most important components of any IR method is the similarity metric. This is considered as a function F that measures the goodness of a given registration solution, that is, of a registration transformation f. The final performance of any IR method will depend on its accurate estimation. Each solution is evaluated by F applying such transformation f to one of the two images, usually to the scene image ($f(I_s)$). Next, the degree of closeness or fitting between the transformed scene and the model images, $\Psi(\cdot)$ must be determined,

$$F(I_s, I_m, f) = \Psi(f(I_s), I_m). \tag{1}$$

There are many approaches trying to estimate such function $\Psi(\cdot)$ depending on the dimensionality (2D or 3D) and the nature of the considered images. For example:

(a) voxel-based approach: sum of squared differences, normalized cross-correlation (i.e., correlation coefficient or phase correlation), and mutual information;

(b) feature-based approach: feature values-based metrics (i.e., registration based on the curvature) and distance between corresponding geometric primitives.

It is useful to mention that the F function is affected by both the discretization of images and the presence of noise, causing worse estimations and favoring the IR method to get trapped in local minima.

3.3 Search space strategies

The IR process performs an iterative exploration to obtain that optimal transformation f (introduced in Figure 1). So, the closer f to the unknown global optimum, the better the fitting (measured by the similarity metric F) between scene and model. The optimization process considered to obtain those solutions can be deterministic or stochastic (either a global or a local one). Although the final registration problem solution consists of the right values for the parameters which determine f, we can distinguish two different strategies to solve the problem, each of them working in a different solution space: (i) the first approach searches in the *matching* space to obtain a set of correspondences of pairs of the most similar image entities in both the scene and the model images, from which the registration transformation is derived; and (ii) the second directly makes a search in the space of the f parameters guided by the F function, called *transformation parameters* space.

Concerning the CT — MR images registration topic, some valuable attempts were made in the past. Some *full image content* based methods using cross-correlation were proposed in [14], using the entire image, where the CT grey values are remapped in a local linear fashion to improve correspondence with the MR image. In [28] there are used *invasive fiducial markers*, which are compared to the *segmented surface* registration. Various authors used *surface based* registrations in comparisons to other methods. Hemler [17] compared it to a *frame* based method, and optimization of the cross-correlation of remapped grey values. Besides the above mentioned cross-correlation methods, other *full image content* based methods were proposed in [6] and used clustering of the joint histogram to find the optimal transformation.

In recent years, the application of several well-known evolutionary algorithms (EAs) to the IR optimization process has introduced an outstanding interest in order to solve those problems due to their global optimization techniques nature. The first attempts to solve IR using evolutionary computation [4] can be found in the early eighties, when Fitzpatrick et al. [16] proposed such approach based on a genetic algorithm for the 2D case and applied it to angiographic images. Since then, several evolutionary approaches have been proposed to solve the IR problem [8].

4 Proposed method of MR-CT image registration using linear transformations

4.1 Spatial Transformation Models

Spatial transformation models play a central role in any medical image registration procedure. These models impose mathematical constraints on the types of geometric distortions that can be imposed during the process of registration. The registration process cannot be accomplished without some type of spatial transformation model. A variety of linear models can be used, ranging from *rigid-body transformations* that preserve all internal angles and distances to perspective models that distort all distances and angles while preserving colinearity. All linear spatial transformations can be expressed using matrix notation.

Rigid-Body Model

For medical imaging, the most constrained spatial transformation model is the rigid-body model. This model asserts that distances and internal angles within the images cannot be changed during registration. As the name implies, this model assumes that the object behaves in the real world as a rigid body, susceptible to global rotations and translations, but internally immutable. This model is well suited to objects such as individual bones, which cannot be deformed. To a reasonable approximation, this model is also applicable to the brain, which is encased in bones that protect it from forces that might lead to deformations.

Medical images often consist of voxels that differ in the realworld distances that they represent along the x-, y-, and z-axes. For example, it is common for the slice thickness in magnetic resonance imaging data to be larger than the size of individual pixels within each slice. If ignored, these anisotropics in voxel size will clearly lead to apparent violations of the rigid-body model, even for solid structures that accurately follow the rigid-body assumptions in the real world. Consequently, any implementation of a rigid-body model must explicitly correct for voxel sizes to ensure that the real-world distances and angles that are being represented do not change.

Two of the parameters that specify a two-dimensional rigid-body transformation can be viewed as translations along the primary axes, and the third can be viewed as a pure rotation around the origin. Although this particular parameterization is not unique, translations along each axis and rotations around the origin will be referred to here as elementary transformations.

If a two-dimensional point (x, y) is to be transformed by one of these elementary transformations to some new point (x', y') , the following equations describe the elementary transformations:

$$\begin{vmatrix} x' \\ y' \end{vmatrix} = A \times \begin{vmatrix} x \\ y \end{vmatrix} + B, \text{ where}$$

$$\begin{aligned} x' &= x + p \\ y' &= y + q \end{aligned} \quad - \text{ Translation}$$

$$\begin{aligned} x' &= x \cdot \cos(\theta) + y \cdot \sin(\theta) \\ y' &= -x \cdot \sin(\theta) + y \cdot \cos(\theta) \end{aligned} \quad - \text{ Rotation}$$

The MATLAB programming language provides several routines that can be used to generate a variety of complex spatial transformations such as image projections or specialized distortions. These transformations can be particularly useful when trying to register images of the same structure taken at different times or with different modalities (e.g., CT scans and MRI images). While MATLAB's spatial transformations routines allow any type of transformation, only two types of transformation are most used: affine transformations and projective transformations. Affine transformations are defined as transformations in which straight lines remain straight and parallel lines remain parallel, but rectangles may become parallelograms. These transformations include rotation, scaling, stretching, and shearing. In projective translations, straight lines still remain straight, but parallel lines often converge.

Affine Transformations

The MATLAB provides a procedure [29] described below for implementing any affine transformation (Figure 2); however, some of these transformations are so popular they are supported by separate routines. These include image resizing, cropping, and rotation.

Image resizing and cropping are both techniques to change the dimensions of an image: the latter is interactive using the mouse and display while the former is under program control.

To change the size of an image, the MATLAB provides the 'imresize' command given below.

```
I_resize = imresize(I, arg or [M N], method),
```

where I is the original image and I_resize is the resized image. If the second argument is a scalar arg, then it gives a magnification factor,

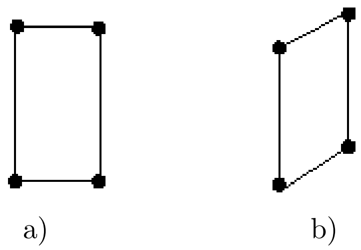


Figure 2. Affine Transformation: a) Before; b) After

and if it is a vector, [M N], it indicates the desired new dimensions in vertical and horizontal pixels, M, N. If arg > 1, then the image is increased (magnified) in size proportionally and if arg < 1, it is reduced in size (minified). This will change image size proportionally. If the vector [M N] is used to specify the output size, image proportions can be modified: the image can be stretched or compressed along a given dimension. The argument method specifies the type of interpolation to be used and can be either '*nearest*', '*bilinear*', or '*bicubic*', referring to the three interpolation methods described above. The nearest neighbor is the default. If image size is reduced, then *imresize* automatically applies an anti-aliasing, lowpass filter.

Image cropping is an interactive command:

```
I_resize = imcrop;
```

The *imcrop* routine waits for the user to draw an on-screen cropping rectangle using the mouse. The current image is resized to include only the image within the rectangle.

Image rotation is straightforward using the *imrotate* command:

```
I_rotate = imrotate(I, deg, method, bbox),
```

where I is the input image, I_rotate is the rotated image, deg is the degrees of rotation (counterclockwise if positive, and clockwise if negative), and method describes the interpolation method as in *imresize*. The nearest neighbour method is the default even though the other methods are preferred except for indexed images. After rotation, the image will not, in general, fit into the same rectangular boundary as the original image. In this situation, the rotated image can be cropped to fit within the original boundaries or the image size can be increased to fit the rotated image. Specifying the *bbox* argument as 'crop' will produce a cropped image having the dimensions of the original image, while setting *bbox* to 'loose' will produce a larger image that contains the entire original, unrotated, image. The loose option is the default. In either case, additional pixels will be required to fit the rotated image into a rectangular space (except for orthogonal rotations), and *imrotate* pads these with zeros producing a black background to the rotated image.

General Affine Transformations

In the MATLAB Image Processing Toolbox, both affine and projective spatial transformations are defined by a *Tform* structure which is constructed using one of two routines: the routine *maketform* uses parameters supplied by the user to construct the transformation while *cp2tform* uses control points, or landmarks, placed on different images to generate the transformation. Both routines are very flexible and powerful, but that also means they are quite involved.

The basic calling structure used to implement the spatial transformation is:

```
B=imtransform(A,Tform,'Param1',value1,'Param2',value2,...);
```

where A and B are the input and output arrays, respectively, and *Tform* provides the transformation specifications as generated by *maketform* or *cp2tform*. The additional arguments are optional. The optional parameters are specified as paired arguments: a string containing the name of the optional parameter followed by the value. These parameters can specify the pixels used from the input image (the default is the entire image), permit change in pixel size, specify how to fill any extra background pixels generated by the transformation, and specify the size and range of the output array.

To specify output image range and size, parameters 'XData' and 'YData' are followed by a two-variable vector that gives the x or y coordinates of the first and last elements of the output array, B. To keep the size and range in the output image the same as the input image, simply specify the horizontal and vertical size of the input array, *i.e.*:

```
[M N] = size(A);
...
B = imtransform(A, Tform, 'Xdata', [1 N], 'Ydata', [1 M]);
```

As with the transform specification routines, *imtransform* uses the spatial coordinate system. The routine *maketform* can be used to generate the spatial transformation descriptor, Tform. There are two alternative approaches to specify the transformation, but the most straightforward uses simple geometrical objects to define the transformation. The calling structure is:

```
Tform = maketform('type', U, X);
```

where 'type' defines the type of transformation and U and X are vectors that define the specific transformation by defining the input (U) and output (X) geometries.

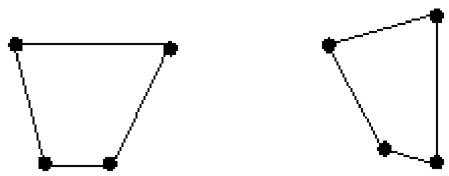
While *maketform* supports a variety of transformation types, including custom, user-defined types, affine and projective transformations.

Only three points are required to define an affine transformation, so, for this transformation type, U and X define corresponding vertices of input and output triangles. Specifically, U and X are 3 by 2 matrices where each 2-column row defines a corresponding vertex that maps input to output geometry.

Projective Transformations

In projective transformations (Figure 3), straight lines remain straight but parallel lines may converge. Projective transformations can be used to give objects perspective.

Projective transformations require four points for definition; hence, the defining geometrical objects are quadrilaterals.



a) b)

Figure 3. Projective transformation: a) before; b) after

4.2 Medical Image Registration

As presented, this procedure has become increasingly important in medical imaging as it is used for merging images acquired using different modalities or for comparing images taken of the same structure at different points in time or having different resolutions. To achieve the best alignment, it may be necessary to transform the images using any or all of the transformations described previously. Image registration can be quite challenging even when the images are identical or very similar (as will be the case in the examples and problems given here).

The difficulty in accurately aligning images that are only moderately similar presents a significant challenge to image registration algorithms, so the task is often aided by a human intervention or the use of embedded markers for reference. So, the approaches to medical image registration can be divided into two broad categories: *unassisted* image registration, where the algorithm generates the alignment without user intervention, and *interactive* registration, where a user aids the registration process.

4.3 Interactive Image Registration

Several strategies may be used to guide the registration process. In the following example, registration will depend on reference marks provided by a user. Interactive image registration is well supported by the MATLAB Image Processing Toolbox and includes a graphically based program, *cpselect*, that automates the process of establishing corresponding reference marks. Under this procedure, the user interactively identifies a number of corresponding features in the reference and input image, and a transform is constructed from these pairs of reference points. The program must specify the type of transformation to be performed (affine, projective, etc.), and the minimum number of reference pairs required will depend on the type of transformation. The number of reference pairs required is the same as the number of variables needed to define a transformation: an affine transformation will require a minimum of three reference points while a projective transformation requires four points.

Other transformations require only two pairs, while other more complex transformations may require six or more point pairs. In most cases, the alignment is improved if more than the minimal number of point pairs is given.

In the Figure 4 and Figure 5 an alignment requiring the two transformations is presented. It uses the routine *cp2tform* to produce a transformation in *Tform* format, based on point pairs obtained interactively. The *cp2tform* routine has a large number of options, but the basic calling structure is:

```
Tform = cp2tform(input_points, base_points, 'type');
```

where *input_points* is a (m x 2) matrix consisting of x, y coordinates of the reference points in the input image; *base_points* is a matrix containing the same information for the reference image. This routine assumes that the points are entered in the same order, i.e., that corresponding rows in the two vectors describe corresponding points. The type variable is the same as in *maketform* and specifies the type of transform ('affine', 'projective', etc.).

5 Validation of Registration Accuracy

From the user's perspective, accuracy is one of the most important properties of a registration method. In a research setting, relative accuracy may be a basis for selecting one method over another, and in

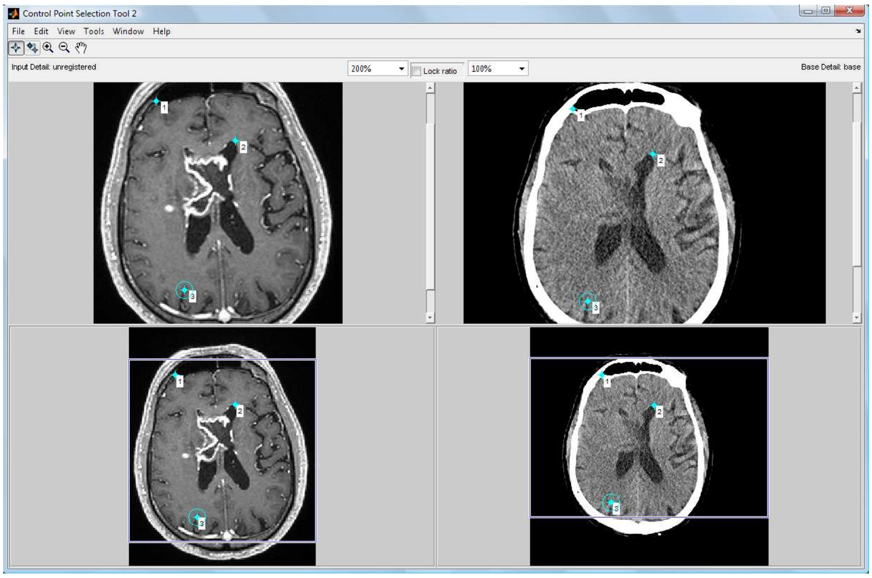
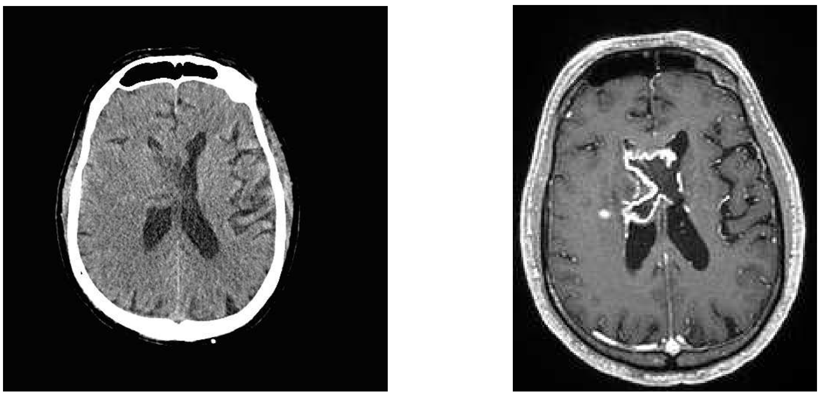
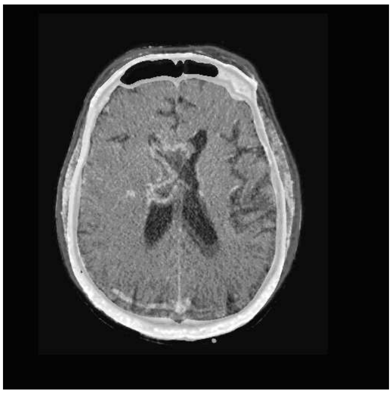


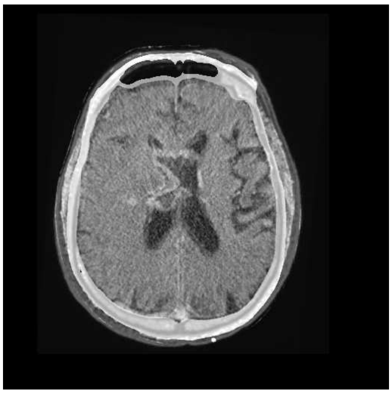
Figure 4. The use of MATLAB *cp2tform* routine



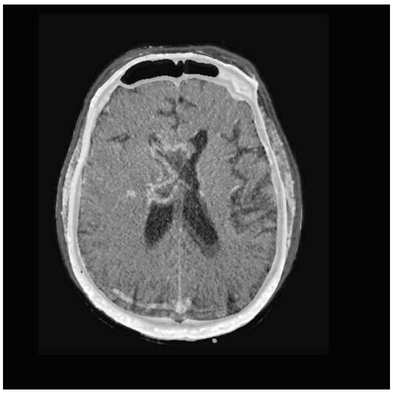
a) b)



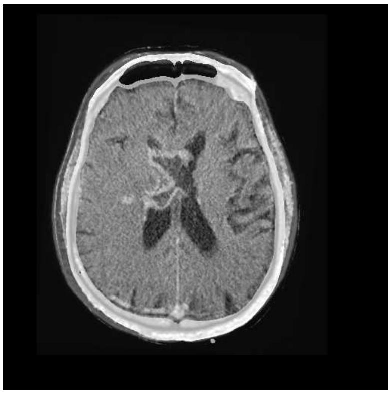
c)



d)



e)



f)

Figure 5. The image registration: a) Base image (CT); b) Unregistered image (MR); c) Registered image with affine transformation and 3 points; d) Registered image with projective transformation and 4 points; e) Registered image with projective transformation and 6 points; f) Registered image with projective transformation and 8 points

a clinical context, knowledge of absolute accuracy may be needed to make appropriate decisions. If a particular structure is of special interest, the accuracy at this particular location, as distinct from all other locations, may need to be established. To the extent that accuracy has substantial regional variations, methods used to report accuracy need to reflect these variations. Validation of registration accuracy is generally not an easy task, because the true answers (i.e., a set of gold standard answers that can serve as a basis for measuring accuracy) are generally not available. Even when estimated gold standards are available, it often turns out that uncertainty in the gold standards themselves limits the ability to assess true accuracy. In this case, strategies that at least put limits on the true accuracy are informative. Many different validation methods have been reported in the literature, and in most cases it is difficult to compare the accuracy claimed for one method with the accuracy claimed for another because of methodological incompatibilities.

5.1 Validation by Visual Inspection

One of the quickest validation methods to implement is simple visual inspection of the results. Although this may seem like an informal and potentially unreliable approach, it is possible that visual inspection to detect 2-millimeter misregistrations of brain MRI images to brain CT images quite reliably. Misregistration can be accurately identified even when one of the images is a low-resolution PET image. Whereas learning to recognize misregistration of dissimilar images requires some experience and effort, recognition of errors in similar images is fairly trivial. In general, if the images look misregistered, they probably are misregistered, and visual inspection should be used as a routine ongoing validation approach at every opportunity.

5.2 Estimation of registration accuracy

Residual registration errors after registration can also be estimated by measuring the coordinate differences along the x and y axes between a set of well-defined landmarks on CT and MR. The lateral, anterior, and posterior boundaries of the skull are well recognized on CT and MR and can be used as landmarks for estimating x and y coordinate differences.

6 Conclusions

The primary advantage of MR-CT registration and fusion technology is the ability to correlate findings from two complementary imaging modalities in a comprehensive way. As useful application, in *radiotherapy treatment*, the CT is needed to accurately compute the radiation dose, while the MR is usually better suited for a precise delineation of tumor tissue, a crucial task taking into account the big radiation doses used in general.

Our study shows that the accuracy obtained by image registration with spatial and global methods is well suited for image-guided radiotherapy. Of course, we have to extend our study to more images, both MR and CT-type.

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