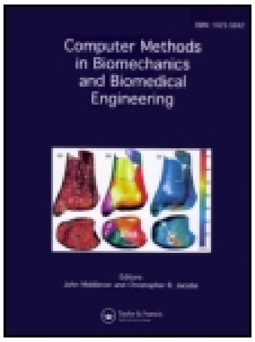

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Medical image registration: a review

Francisco P.M. Oliveira and João Manuel R.S. Tavares*

Instituto de Engenharia Mecânica e Gestão Industrial, Faculdade de Engenharia, Universidade do Porto, Rua Dr. Roberto Frias, 4200-465 Porto, Portugal

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This paper presents a review of automated image registration methodologies that have been used in the medical field. The aim of this paper is to be an introduction to the field, provide knowledge on the work that has been developed and to be a suitable reference for those who are looking for registration methods for a specific application. The registration methodologies under review are classified into intensity or feature based. The main steps of these methodologies, the common geometric transformations, the similarity measures and accuracy assessment techniques are introduced and described.

Keywords: computational methods; image analysis; image alignment, matching, warping; geometrical transformations; similarity measures; optimisation

1. Introduction

Image registration, also known as image fusion, matching or warping, can be defined as the process of aligning two or more images. The goal of an image registration method is to find the optimal transformation that best aligns the structures of interest in the input images. Image registration is a crucial step for image analysis in which valuable information is conveyed in more than one image; i.e. images acquired at different times, from distinct viewpoints or by different sensors can be complementary. Therefore, accurate integration (or fusion) of the useful information from two or more images is very important.

Much of the research that has been developed for medical image analysis was devoted to image registration (Pluim and Fitzpatrick 2003). Applications of image registration in the medical field include fusion of anatomical images from computerized tomography (CT) or magnetic resonance imaging (MRI) images with functional images from positron emission tomography (PET), single-photon emission computed tomography (SPECT) or functional magnetic resonance imaging; intervention and treatment planning (Gering et al. 1999; Gering et al. 2001; Staring et al. 2009); computer-aided diagnosis and disease following-up (Huang et al. 2009); surgery simulation (Miller et al. 2010); atlas building and comparison (Freeborough and Fox 1998; Ganser et al. 2004; Joshi et al. 2004; Leow et al. 2006; Wu et al. 2009; Gooya et al. 2011); radiation therapy (Lavely et al. 2004; Foskey et al. 2005); assisted/guided surgery (Maurer et al. 1997; Hurvitz and Joskowicz 2008; Huang et al. 2009; King et al. 2010); anatomy segmentation (Collins and Evans 1997; Frangi et al. 2003; Dornheim et al. 2005; Martin et al. 2008; Isgum et al. 2009; Gao et al. 2010; Zhuang et al. 2010; Oliveira et al. 2011b); computational model building (Grosland et al. 2009) and image subtraction for contrast enhanced images (Maksimov et al. 2009). For PET and SPECT images, registration has also been useful for correct scatter attenuation and partial volume corrections based on CT images (Hajnal et al. 2001; Bai and Brady 2011).

Medical image registration has been developed for almost all anatomic parts or organs of the human body: brain (Kassam and Wood 1996; Collignon et al. 1997; Studholme et al. 1997; Itti et al. 1997; Gering et al. 2001; Guimond et al. 2001; Shen and Davatzikos 2002; Zhu and Cochoff 2002; Hipwell et al. 2003; Xie and Farin 2004; Shen 2004, 2007; Wu et al. 2006b; Ashburner 2007; Duay et al. 2008; Bhagalia et al. 2009; Postelnicu et al. 2009; Xu et al. 2009; Liao and Chung 2010; Auzias et al. 2011; Cho et al. 2011; Mayer et al. 2011), retina (Cideciyan 1995; Stewart et al. 2003; Fischer and Modersitzki 2004; Matsopoulos et al. 2004; Lin and Medioni 2008; Tsai et al. 2010), chest/lung (Mattes et al. 2003; Bhagalia et al. 2009), whole thorax (Loeckx et al. 2003), breast (Rueckert et al. 1999; Rohlfing et al. 2003; Schnabel et al. 2003; Washington and Miga 2004; Karaçali 2007; Serifovic-Trbalic et al. 2008), abdomen (liver, kidney and spleen) (Brock et al. 2005), prostate (Foskey et al. 2005; Alterovitza et al. 2006), entire body (Shekhar et al. 2005), cervical (Staring et al. 2009), heart (Dey et al. 1999; Shekhar and Zagrodsky 2002; Rhode et al. 2003; Shekhar et al. 2004; Ledesma-Carbayo et al. 2005; Grau et al. 2007; Huang et al. 2009), pelvis (Hamilton et al. 1999; Shen 2004, 2007), wrist (Giessen et al. 2009), vascular structures (Hipwell et al. 2003; Groher et al. 2009; Ruijters et al. 2009), bones

*Corresponding author. Email: tavares@fe.up.pt

(Andreetto et al. 2004; Heger et al. 2005; Tang et al. 2006; Hurvitz and Joskowicz 2008), knee (Mahfouz et al. 2003; Yamazaki et al. 2004) and spine (Tomazevic et al. 2003).

Recent improvements in medical imaging have allowed the acquisition of temporal image sequences. In comparison to static images, these sequences offer additional information about the motion of the imaged organs, such as the heart. Examples of spatiotemporal image registration of the heart can be found in Grau et al. (2007), Ledesma-Carbayo et al. (2005), Perperidis et al. (2005), Peyrat et al. (2010), and a solution for temporal plantar pressure image sequences registration is presented in Oliveira et al. (2011a).

In the literature, several reviews on image registration methods can be found: overall image registration in Brown (1992), Salvi et al. (2007), Wyawahare et al. (2009), Zitová and Flusser (2003), medical image registration in general (Elsen et al. 1993; Maintz and Viergever 1998; Bronzino 2000; Hajnal et al. 2001; Hill et al. 2001; Modersitzki 2004; Goshtasby 2005; Fischer and Modersitzki 2008; Slomka and Baum 2009) and hierarchical non-linear medical image registration (Lester and Arridge 1999). Also there are reviews that focus on specific anatomical parts, such as cardiac (Mäkelä et al. 2002), retina (Laliberté et al. 2003), breast (Guo et al. 2006) and brain (West et al. 1997). Other surveys focus on the image similarity measure in Penney et al. (1998), Pluim et al. (2003, 2004).

A large number of software solutions have been presented for medical image registration; examples of free-open-source software packages include: FAIR (Modersitzki 2009) – source code in Matlab; AIR (Woods, Grafton, Holmes, et al. 1998; Woods, Grafton, Watson, et al. 1998) – source code in C; ITK (Ibáñez et al. 2005) – source code in C++; 3D Slicer (Gering et al. 1999; Pieper et al. 2004; Pieper et al. 2006) – almost all source code in C++; FLIRT (Jenkinson and Smith 2001) – source code in C++ and Elastix (Klein et al. 2010) – source code in C++. Both 3D Slicer and Elastix are based on the ITK library. ART is also a free software package distributed as binary files for Linux and Mac operating systems. The well-known statistical parametric mapping (SPM) (Friston, Holmes et al. 1995; Ashburner and Friston 1999) software package has been designed for the analysis of brain imaging data sequences, but it also includes a registration tool. An extended list of free software solutions for medical image analysis can be found on the Neuroimaging Informatics Tools and Resources Clearinghouse webpage.

Besides free software for image registration, there are free medical images available for study purposes. For instance, on the BrainWeb project webpage, a simulated brain database with three MRI sequences (T1, T2 and proton density) is available; and on the PET-SORTEO project webpage, simulated PET images are accessible.

Several comparisons of image registration methodologies have been published. For instance, in West et al. (1997), 12 registration methodologies, some fully automated and others with user interaction, were compared. Those methodologies were compared for the registration of CT, PET and MRI brain volumes. The accuracy of the methodologies under comparison was assessed by relating the geometric transformation found with a gold standard obtained based on fiducial markers attached to the skull. In Zhilkin and Alexander (2004), the *Patch Algorithm* (PA; Zhilkin and Alexander 2000) is compared with the AIR 3.0, COCGV, FLIRT–FMRIB's, IR and SPM algorithms on monomodal registration by using affine geometric transformations. Regarding non-rigid registration, 14 algorithms were compared in the registration of brains in Klein et al. (2009), namely: AIR, ANIMAL, ART, Diffeomorphic Demons, FNIRT, IRTK, JRD-fluid, ROMEO, SICLE, SyN and four different SPM5 algorithms ('SPM2-type' and regular Normalization, Unified Segmentation, and the DARTEL Toolbox). Other comparisons can be found in Ardekani et al. (2005), Economopoulos et al. (2010), Hellier et al. (2003), McLaughlin et al. (2005), West et al. (1999), Yassa and Stark (2009).

Image registration is often referred to as image fusion, image matching or image warping; however, to avoid any ambiguities these terms will be designated the following definitions for the rest of this paper: image fusion is used to designate the process of combining two or more images into a single image; image matching, as the process of establishing the correspondences among the structures in input images without explicitly aligning them and image warping, as the application of a geometric transformation on an input image. Also, 'fixed image' is designated as the image that remains unchanged, and 'moving image' as the image that is transformed using the 'fixed image' as a reference.

The main goals of this paper are to introduce the works done on medical image registration, and identify and introduce the key guidelines that have been defined and addressed.

Although several reviews on medical image registration can be found (e.g. Slomka and Baum 2009), this review has a wide coverage and is very general, as no particular attention is given to a specific multimodality image registration application; however, detailed information concerning the main steps of common registration algorithms is given.

The paper is organised as follows: In the next section, the image registration methodologies are classified. Afterwards, common registration methodologies are introduced and explained, focusing on their main features, such as: geometric transformations, similarity measures and optimisers. Then, in Section 4, the current techniques for accuracy assessment are presented and, finally, in the last section, a discussion is addressed.

2. Registration methodologies – classification

Basically, the registration of input images requires the selection of the feature space, a similarity measure or alignment quality, a transformation type and a search strategy. A great number of medical image registration methodologies have been presented, and several criteria have been proposed to classify them. Elsen et al. (1993) classified the registration methodologies by the data dimensionality (1D, 2D, 3D, 4D, ...), source of the image features used to make the registration (intrinsic or extrinsic properties of patients), transformation domain (local or global), transformation elasticity (rigid, affine, projective or curved), tightness of property coupling (interpolating or approximating), parameter determination (direct or search oriented) and interaction (interactive, semi-automatic or automatic). This classification scheme was further detailed and extended to nine fundamental criteria by Maintz and Viergever (1998), where each criterion was divided into one or more sub-criteria (Table 1).

The registration of images from the same modality, but obtained using different acquisition parameters, such as, the registration of T1-MRI images with T2-MRI or proton density MRI images, are often classified as multimodal.

Registration methodologies are also commonly classified using the feature space image information. This information may be the intensity of the raw voxels, the intensity gradient, statistical information related to the voxel intensity or structures extracted from the images to be registered, such as, sets of points, edges, contours, graphs, surfaces and volumes.

Registration methodologies based on voxel intensity are commonly known as intensity based, and those based on the geometrical structures extracted from the images as feature based or geometrical based (Hawkes 2001). Other methodologies use the images in the frequency domain or the Fourier transform properties to achieve optimal registration, and are known as frequency or Fourier based.

Another common classification criterion for registration is based on the amount of image information that is used in the process. A methodology is classified as global, if all voxels presented in the region of the interest (ROI) are used. On the other hand, it is classified as local, if only a part of the voxels in the ROI is used. Usually, the intensity-based methods are global and the feature-based methods are local.

A common medical image, I, can be defined as a function$I : D \subset R^3 \rightarrow R$; that is, I is defined in a subset of a 3D space and has values in R. However, in some imaging modalities, like diffusion tensor magnet resonance imaging (DT-MRI), the image can have values in a multidimensional space. In this case, the images are also known as multichannel images, vector images or tensor images. In this work, no distinction has been made for this feature, and all images are assumed to be defined in a 3D space, since volumetric images are the most common image data type in medical imaging and 2D images can always be considered in a 3D space.

3. Registration methodologies

Most of the intensity-based registration methodologies can be illustrated by the diagram in Figure 1. The main idea is to search iteratively for the geometric transformation that, when applied to the moving image, optimises i.e. minimises or maximises a similarity measure, also known as the cost function. The similarity measure is related to voxel intensity and is computed in the overlapped regions of the input images. The optimiser has the function of defining the search strategy. The aim of the interpolator is to resample the voxel intensity into the new coordinate system according to the geometric transformation found.

Whenever possible, a pre-registration transformation, which makes the moving images closer to the fixed images in terms of the similarity measure, is used as an initial solution for the registration algorithm. A good pre-registration allows a faster convergence of the optimiser and decreases the likelihood of convergence to a local optimum.

For the feature-based registration methodologies, there are two main approaches to search for the optimal transformation after the feature segmentation process in the input images: (1) the matching among features is established using some criterion, e.g. based on geometrical, physical or statistical properties. Then, the geometric transformation is established based on the matching found (Figure 2). An example of such approach is when the features extracted, i.e. segmented, from the input images, are sets of points and each point is represented by a descriptor. Then, the 'corresponding costs' are the 'distances' between the descriptors of the possible point pairs, and the similarity measure between the input images is usually given by the sum of all the 'corresponding costs' established (Bastos and Tavares 2004; Oliveira and Tavares 2009; Oliveira et al. 2009a). As such, this approach is reliable when the descriptors used are invariant to the geometric transformations to be assessed. (2) The matching and the transformation are defined concurrently based on the optimisation of a similarity measure between the features extracted from the input images. The algorithm of this registration approach is quite similar to the algorithm in Figure 1; however, in this case, rather than the original intensity images, the features extracted are used to define the registration result.

The registration methodologies based on image moments, such as the principal axes technique (Faber and Stokely 1988; Alpert et al. 1990; Dhawan et al. 1995), can be classified as feature based, since the basis of the registration is a set of image descriptors extracted from the input images. However, the algorithm used is different from the ones previously presented. Briefly, in this methodology, the translational component of the transform

Table 1. Medical image registration classification criteria proposed by Maintz and Viergever (1998).

Classification criteria	Subdivision	
Dimensionality	Spatial dimension: 2D/2D, 2D/3D, 3D/3D	
	Temporal series	
Nature of the registration basis	Extrinsic (based on foreign objects introduced into the imaged space)	
	Invasive	Stereotactic frame
		Fiducials (screw markers)
	Non-invasive	Mould, frame, dental adapter, etc.
		Fiducials (skin markers)
	Intrinsic (based on patient)	
	Landmark based	Anatomical
		Geometrical
	Segmentation based	Rigid models (points, curves, surfaces, volumes)
		Deformable models (snakes, nets)
	Voxel property based	Reduction to scalars/vectors (moments, principal axes)
		Using full image content
	Non-image based (calibrated coordinate systems)	
Nature of transformation	Rigid (only rotation and translations)	
	Affine (translation, rotation, scaling and shearing)	
	Projective	
	Curved	
Domain of transformation	Local	
	Global	
Interaction	Interactive	Initialisation supplied
		No initialisation supplied
	Semi-automatic	User initialising
		User steering/correcting
		Both
	Automatic	
Optimisation procedure	Parameters computed (the transformation parameters are computed directly)	
	Parameters searched for (the transformation parameters are computed using optimisation algorithms)	
Modalities involved in the registration	Monomodal (CT-CT, MRI-MRI, PET-PET, CTA, etc.)	
	Multimodal (CT-MRI, CT-PET, CT-SPECT, PET-MRI, MRI-US, etc.)	
	Modality to model	
	Patient to modality (register the patient with the coordinate system of the imaging equipment)	
Subject	Intrasubject (same subject)	
	Intersubject (different subjects)	
	Atlas	
Object	Head (brain, eye, dental, etc.)	
	Thorax (entire, cardiac, breast, etc.)	
	Abdomen (general, kidney, liver, etc.)	
	Limbs	
	Pelvis and perineum	
	Spine and vertebrae	

is based on the centres of mass of the images; and the rotational component is based on the eigenvectors of the second-order central moments matrix of the images.

In the next sections, the registration algorithms illustrated in Figures 1 and 2 are described.

3.1 Geometric transformations

The choice of the geometric transformation model used is crucial to the success of a registration algorithm, and is highly dependent on the nature of the data to be registered. Usually, the geometric transformations are divided into rigid and non-rigid classes. The rigid transformation is the simplest one, and in a 3D space, it can be defined by six parameters or degrees-of-freedom: three translational and three rotational parameters. The non-rigid transformation class includes the similarity transformation (translation, rotation and uniform scaling), affine (translation, rotation, scaling and shear), projective and curved. The curved transformation is also commonly referred to as a deformable, elastic or fluid transformation. The rigid and similarity geometric transformations are subsets of the affine transformation.

A 3D affine transformation $T : R^3 \rightarrow R^3$ is given by $T(X) = DX + S$, where D is a 3×3 matrix representing the rotation, scaling and shearing, and S is a 3×1 vector

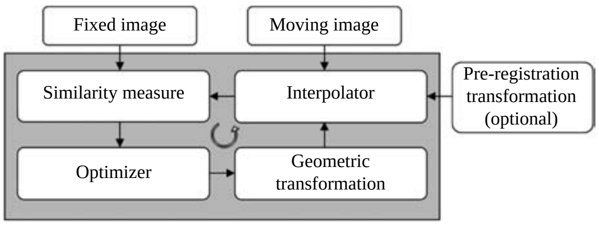

Figure 1. Diagram of the typical algorithms used in the intensity-based registration methodologies.

representing the translation or shift. Sometimes, affine transformations are classified as linear; however, such classification is not mathematically correct, since the function T is linear if, and only if, $T(aX + bY) = aT(X) + bT(Y)$, which implies that the translational component S of the transformation be null. The affine geometric transformation is usually represented with homogeneous coordinates, which has the advantage of using only a 4×4 matrix to represent the whole transformation.

According to the literature, a rigid geometric transformation is mainly applied in two situations. One is in the registration of rigid structures, such as bones (Livyatan et al. 2003; Andreetto et al. 2004; Heger et al. 2005; Tang et al. 2006) and the other is in pre-registration before a more complex geometric transformation (Lötjönen and Mäkelä 2001; Mattes et al. 2003; Hellier and Barillot 2004; Auer et al. 2005). The use of affine non-rigid transformations in the final image registration is not common; but, some examples can be found in Butz and Thiran (2001), Jenkinson and Smith (2001), Meyer et al. (1997), Zhilkin and Alexander (2000), Zvitia et al. (2010). Like the rigid transformation, the affine non-rigid transformation is also sometimes used in a pre-registration for a final curve registration (Balci et al. 2007; Karaçali 2007; Zhuang et al. 2010). The affine transformations, both rigid and non-rigid,

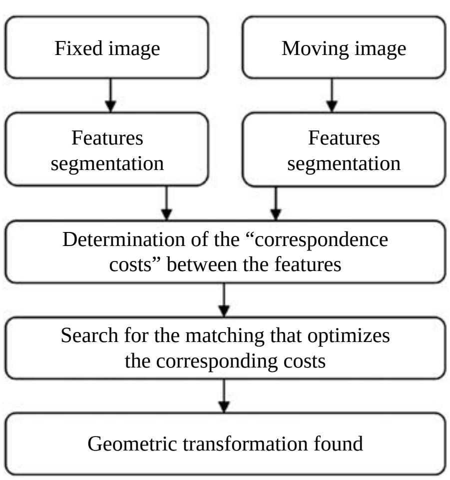

Figure 2. Diagram of a typical feature-based registration algorithm.

have been used in the registration of ultrasound images (Meyer et al. 1999; Roche et al. 2001; Shekhar and Zagrodsky 2002; Shekhar et al. 2004; King et al. 2010), since the low resolution and low signal-to-noise ratio of the ultrasound images make the accurate registration difficult when more complex transformations are used.

Most approaches for medical image registration are based on curved transformations, since the almost all anatomical parts, or organs, of the human body are, in fact, deformable structures. The simplest curved transformations are based on polynomials of a degree superior to one, and, in a similar way to the affine transformations. Their implementation is very simple as they can be defined by a deformation matrix and a translation vector. However, these transformations are rarely used since they do not usually represent the real deformations involved in the medical images.

Basically, two kinds of curved deformations have been used in medical image registration: free-form transformations, in which any deformation is allowed; and guided deformations, in which the deformation is controlled by a physical model that has taken into account the material properties, such as tissue elasticity or fluid flow. It should be noted that sometimes the registration algorithms based on fluid flow are classified as free-form, since they are able to address almost any deformation.

In many free-form deformation models, a grid of control points is defined in order to determine the deformation involved. The points of such a grid are moved individually in the direction that optimises the similarity measure, defining local deformations. Transformation between control points is propagated by interpolation; for example, using linear interpolation (Kjems et al. 1999) or other convex kernels (Gaens et al. 1998; Lötjönen and Mäkelä 2001). The most popular interpolator used for free-form deformation is probably the cubic B-spline (Rueckert et al. 1999; Studholme et al. 2000; Rohlfing and Maurer 2001; Rohlfing et al. 2003; Kybic and Unser 2003; Mattes et al. 2003; Kabus et al. 2004; Xie and Farin 2004; Balci et al. 2007; Bhagalia et al. 2009; Bai and Brady 2011; Khader and Hamza 2011); but, B-splines of other degrees can also be used (Loeckx et al. 2010).

Originally, the free-form deformation based on the cubic B-spline was defined in a regular grid of points. Lately, in Schnabel et al. (2001), a new framework was proposed by extending and generalising the technique previously presented in Rueckert et al. (1999). On the other hand, some authors have developed a deformable registration method by defining the global transformation as a series of locally affine transformations (Periaswamy and Farid 2003; Shekhar et al. 2005).

Some elastic models handle the objects represented in the images as elastic solids (Christensen et al. 1994; Davatzikos 1997; Alexander and Gee 2000; Christensen and Johnson 2001; Gefen et al. 2003). The main idea of image registration methodologies based on elastic solids is straightforward: the internal elastic forces of the solid oppose the deformation, whereas the external forces driven by the similarity measure try to deform the data to fit the body configuration. Thus, the moving image is deformed until the internal and external forces reach an equilibrium.

Other elastic-based registration methods are based on finite element models (Ferrant et al. 2002; Grosland et al. 2009). These models divide the input image into cells and assign a physical description of the tissue property to these cells.

Thin-plate splines (TPS)-based registration methodologies are also based on deformable solid properties; however, the fundamentals of the approach are different from the previous ones (Meyer et al. 1999, 1997; Auer et al. 2005). In these methodologies, a set of control points is moved along the direction that optimises the similarity measure used. The propagation of the deformation to the neighbours of the control points is defined by the thin-plate model. For point correspondence based registrations, the TPS is based on the correspondences found between the sets. TPS is an interpolation function that minimises the bending energy (Holden 2008). Some authors, as in Rohr et al. (2001), Serifovic-Trbalic et al. (2008), have used approximating TPS rather than interpolating TPS, since the former are more robust to the outliers which can occur in the landmark or point localisations.

The deformable registrations based on TPS are global, that is, when a control point is moved, its new position affects the whole deformation. The registrations based on free-form B-spline deformations are local; however, they also can be classified between a global registration model and a pure local model, since their locality can be controlled by varying the grid or mesh spacing and consequently the number of degrees-of-freedom. Since the free-form B-spline deformations are local, it is essential to correct the global misregistration before computing the deformation involved, for instance, using an affine transformation (Rueckert et al. 1999).

The expression 'elastic registration' is sometimes used as a synonym of a curved or deformable registration, however for the rest of this paper it is used just for the registration methodologies whose geometric transformation is based on the elastic properties of solid objects.

In flow-based registration algorithms, the registration problem is addressed as a motion problem. As such, the content of an image moves continually towards the other image, and this movement or deformation is driven by the minimisation of the energy of the physical model adopted.

Flow-based registration algorithms can be divided into two classes: fluid flow and optical flow. Some examples of registration algorithms based on fluid flow can be found in Ashburner (2007), Auzias et al. (2011), Bro-Nielsen and Gramkow (1996), Chiang et al. (2008), Christensen et al. (1997), Christensen et al. (1994, 1996), D'Agostino et al. (2003), Freeborough and Fox (1998), Guimond et al. (2002), Hermosillo et al. (2002), Joshi et al. (2004), Leow et al. (2005), Studholme et al. (2006), Tosun and Prince (2008).

The well-known demons algorithm and its variations (Thirion 1998; Guimond et al. 2001, 2002; Wang et al. 2005; Vercauteren et al. 2007; 2009; Yeo et al. 2010a; Gooya et al. 2011) are examples of optical flow-based registration algorithms. Other examples of optical flow-based algorithms can be found in Hellier et al. (2001), Tosun and Prince (2008). The demons algorithm is based on a diffusion process. When applied on monomodal registration, the demons-based registration is a variant of the optical flow-based approach. If instead of considering the original image intensity values, the image gradients are used, then this algorithm can also be successfully applied on some multimodal image registrations. Further details on demons algorithm can be found in Pennec et al. (1999).

The fluid-based transformations allow larger deformations than the elastic-based transformations. Thus, a low-dimensional elastic transformation is sometimes used prior to a high-dimensional fluid registration (Christensen et al. 1997).

The registration algorithms based on B-splines address the image deformations as a combination of basic functions, particularly the B-splines, but other basis functions have also been used (Friston, Ashburner, et al. 1995; Ashburner and Friston 1999). Thus, the registration problem can be seen as a problem of finding a set of coefficients for the basis functions that optimises the similarity measure.

To preserve the topology of the structures represented in the images to be registered, the geometric transformation needs to be a diffeomorphism; that is, to be invertible and differentiable mapping with differentiable inverse. The registration methodologies that use diffeomorphic transformations are known as diffeomorphic image registration methodologies. The set of elastic-solid-based registration methodologies are examples of these methodologies. The free-form and flow-based registration methodologies can also be diffeomorphic if a penalty term is added to the similarity measure or adequate constraints are used in order to avoid undesirable deformations. If not degenerated, the affine transformations are also diffeomorphic. Examples of registration algorithms that include diffeomorphic transformations can be found in Ashburner (2007), Auzias et al. (2011), Beg et al. (2005), Geng et al. (2011), Joshi and Miller (2000), Marsland and Twining (2004), Rao et al. (2004), Vercauteren et al. (2007, 2009), Yeo et al. (2009, 2010a).

A comparative study among transformation functions for non-rigid medical image registration based on points correspondence is presented in Zagorchev and Goshtasby (2006). Additionally, a study on geometric transformations for non-rigid image registration can be found in Crum et al. (2004) and a review in Holden (2008). Closely related to the medical image registration is the computational anatomy, that is, the computational models of organ deformations. A study on this subject can be found in Miller et al. (2002).

3.2 Similarity measures

The similarity measures here are divided into two classes, the intensity- and feature-based methods. Depending on the features used, some similarity measures can be included in both classes.

Normally, the similarity measure used for deformable image registration is composed of at least two terms: one related to the voxel intensity or structures similarity, and the other one to the deformation field (Collins and Evans 1997; Ashburner et al. 1999; Rueckert et al. 1999; Lötjönen and Mäkelä 2001; Rohlfing and Maurer 2001; Hermosillo et al. 2002; Rohlfing et al. 2003; Lu et al. 2004; Auzias et al. 2011). As such, the final similarity measure, or cost function, is a trade-off between the 'voxel intensity or structures similarity' and the constraints imposed on the deformation field. The constraint term is usually known as penalty or regularisation term.

Particularly in non-rigid registration, the choice of the fixed and moving images could produce distinct registration results. This is mainly a consequence of the large number of local optimums that the similarity measure used can have. Such problems are known as inverse inconsistency and indicate an error in, at least, one of the registration directions. Several solutions have been proposed to overcome this problem (Ashburner et al. 1999; Christensen and Johnson 2001; Shen and Davatzikos 2002; Rogelj and Kovacic 2006).

3.2.1. Intensity-based similarity measures

The most commonly used similarity measures are based on intensity differences, intensity cross-correlation and information theory.

The measures based on the intensity difference are usually based on the sum of squared differences (SSD) or their normalisations (Ashburner and Friston 1999; Friston, Ashburner, et al. 1995; Hajnal et al. 1995; Woods, Grafton, Holmes, et al. 1998). The assumption behind the SSD computed from the voxel intensity is that the corresponding structures in both images should have identical intensities. Thus, the lower the SSD is, the better the registered images is.

The cross-correlation and its derived measures, such as the Pearson's correlation coefficient or correlation ratio, have also been used as image similarity measures (Cideciyan 1995; Collins and Evans 1997; Roche et al. 1998; Hermosillo et al. 2002; Orchard 2007b). The cross-correlation is based on the assumption that there is a linear relation between the intensities of the corresponding structures in both images. Thus, the larger the cross-correlation is, the better the registered image is.

The SSD, the cross-correlation and their variants are similarity measures appropriate for monomodal image registration. Besides the assumptions previously referred to, these measures are also based on suppositions of independence and stationarity of the intensities from voxel to voxel. Recently, to overcome these requirements, a new similarity measure, called the residual complexity, was proposed in Myronenko and Song (2010).

The information theory based similarity measures are mostly based on the mutual information (MI) or derived measures. The MI was simultaneously proposed for image registration by Viola and co-workers (Viola and Wells 1995; Wells et al. 1996) and Collignon et al. (1995, 1997). A few years later, a normalised mutual information (NMI) was proposed in Studholme et al. (1999), which is less sensitive to the dimensions of the overlapped image regions. The MI is based on the Shannon entropy that is computed from the joint probability distribution of the image voxel intensity.

MI registration has received so much attention that, a few years after being proposed for image registration, a state-of-the-art image registration based on MI was presented in Pluim et al. (2003) addressing almost 200 works on that topic. A comparative study on the MI and other similarity measures based on the information theory is described in Pluim et al. (2004), and a study on medical image registration based on MI is presented in Maes et al. (2003).

MI is usually defined as $\mathrm{MI}(X,Y) = H(X) + H(Y) - H(X,Y)$, where$X$ and Y are two random variables, $H(X)$ and $H(Y)$ are the Shannon's entropy of the X and Y variables, respectively, and $H(X,Y)$ is the joint Shannon's entropy of the joint probability histogram. Other equivalent definitions of the MI exist (see, e.g. Pluim et al. 2003).

MI is a measure on how well one image explains the other image, that is, it is based on the simple assumption that there is a functional between the variables involved, e.g. between the intensities of both images. The MI can be applied for both intra and inter-modal registration, and should have the highest value when the input images are correctly registered.

Figure 3 shows a registration example based on the maximisation of MI. In this example, the MI was computed in a ROI that did not contain the frame that was supporting the heads to be registered. It should be noted that the low registration accuracy based on the affine transformation is because this kind of transformation cannot model the image deformation adequately and not because of the similarity measure used. However, better accuracy could be achieved by tuning the parameters of the registration methodology more carefully.

MI is computed on a voxel by voxel basis, thus it takes into account only the relationships between corresponding

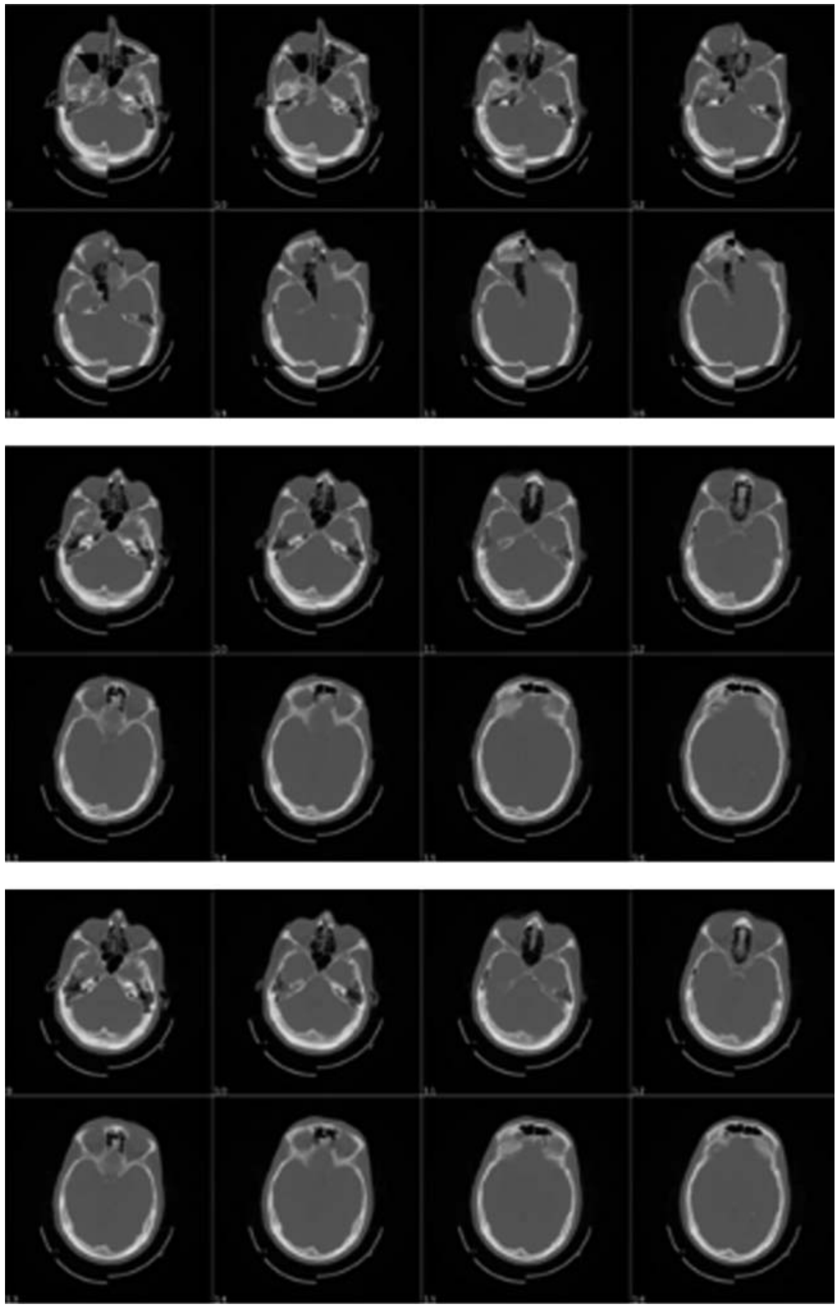

Figure 3. Registration sequence of two CT volumes of the heads of two subjects. At the top, eight slices built on a checker format (by alternating square sub-images from both original images) before registration; in the middle, the checker slices built after an affine registration; at the bottom, the checker slices built after a free-form registration using cubic B-splines.

individual voxels, and consequently does not take into consideration relevant spatial information that is inherent to the original images. To overcome this drawback, variations of the MI have been proposed. In Pluim et al. (2000), two similarity measures are suggested, one based on a combination of MI and gradient information, and the other one based on NMI and gradient information. Other solutions based on MI have also been proposed in Russakoff et al. (2004), Studholme et al. (2006), by defining a regional MI, and in Loeckx et al. (2010), using the conditional MI.

MI has proven to be a very robust and reliable similarity measure for intensity-based registration of multimodal images. However, it faces difficulties for registration of small-sized images. To overcome this limitation, for instance, in Andronache et al. (2008), the MI was used for global registration and the cross-correlation to register the small image patches.

Besides the Shannon's entropy, other divergence measures have been used, for instance, Rény's entropy (He et al. 2003; Wachowiak et al. 2003), Tsallis' entropy (Tsallis 1988; Sun et al. 2007; Khader and Hamza 2011) and Havrda-Charvat's entropy (Wachowiak et al. 2003).

The joint intensity distribution, which is the basis for the MI, is also used in the definition of other similarity measures. For example, in Chung et al. (2002), Leventon and Grimson (1998), Zhang et al. (2005), the registration methodologies described use prior information on the expected joint intensity distribution of the input images when registered to address the geometric transformation search. On the other hand, in Leventon and Grimson (1998), the log likelihood is maximised and in Chung et al. (2002) the Kullback-Leibler distance is minimised. In Orchard (2008), the geometric transformation is driven with the goal to build compact clusters of the joint intensity scatter plot.

For DT-MRI images, the similarity measure can be computed as the sum of the similarity of the individual channels. For instance, in Alexander and Gee (2000), Guimond et al. (2002), the normalised SSD computed on all the image channels was considered as the similarity measure; however, in Alexander and Gee (2000), other similarity measures were also considered. In Cao et al. (2005), the similarity measure used is based on the Euclidean distance between the principal eigenvectors of the diffusion tensors. On the other hand, in Chiang et al. (2008), the diffusion tensors are matched based on the minimisation of the symmetrised Kullback-Leibler divergence between the Gaussian probability density functions whose covariance matrices are given by the diffusion tensors.

To guarantee that the registration process is mainly influenced by the anatomical part that should be registered, or to avoid image artefacts or different fields of view (FOV) corrupting the registration process, the similarity measure can be computed over only a ROI (Huang et al. 2009; Elen et al. 2010;). Also, to increase the computational speed of the registration process, the similarity measure is frequently evaluated only on an image sample.

Several comparative studies among similarity measures have been carried out (Penney et al. 1998; Jenkinson and Smith 2001; Pluim et al. 2004). In the study presented in Pluim et al. (2004), the MI is compared against other similarity measures based on the information theory, and a survey on image registration based on MI is presented in Pluim et al. (2003).

3.2.2. Feature-based similarity measures

As aforementioned, depending on the structures extracted from the original images, the similarity measures based on intensity can be used in their registration; for example, after the segmentation of an organ from the input images, instead of using the binary images representing the organ shapes to drive the registration process, the voxel intensities of the organ can be used. A similar situation occurs when the segmentation process divides the input images into smaller image patches or volumes, and the similarity or 'distance' among those patches is assessed using intensity-based similarity measures.

As for the SSD, the similarity measure used in the feature-based registration is often computed as the sum of the 'distances' associated to each correspondence established. These distances can be related to the spatial position of the corresponding structures, or related to other attributes, as in the case of the patch segmentation described above.

For spatial distance, the Euclidean distance is a common choice. For instance, most of the iterative closest point (ICP) algorithms found in the literature use this solution. Other examples in which the Euclidean distance is used can be found in Gefen et al. (2003), Ostuni et al. (1997). Additionally, the chamfer distance has also been used in image registration solutions (Borgefors 1988; Itti et al. 1997).

In Shen and Davatzikos (2002), the distance is computed based on a set of rotation invariant moments in the neighbourhood of the voxels that drive the transformation. On the other hand, similarity measures based on the curvature have been used in surface matching (Tosun and Prince 2008).

In Zvitia et al. (2010), the correlation ratio is considered as the similarity measure used to register sets of fibres extracted from brain white matter images. The MI can also be used in feature-based registration; for instance, in Butz and Thiran (2001), the MI is computed using the image gradient fields.

3.2.3 Regularisation terms

There are several regularisation terms, but one of the most used is related to the second-order derivatives of the transformation, which are related to the bending energy of the transformation (Lötjönen and Mäkelä 2001; Shen and Davatzikos 2002; Rohlfing et al. 2003).

The Jacobian of the transformation has also been used (Christensen et al. 1997; Rohlfing and Maurer 2001; Rohlfing et al. 2003; Noblet et al. 2005); in this case, if the Jacobian is equal to 1, then the deformation is categorised as incompressible.

In Collins and Evans (1997), the regularisation term is based on the motion of each point of the moving image. On the other hand, in Kim et al. (2003), the regularisation term used is based on the sum of the squared first-order derivatives of the transformation.

3.3. Optimisation

The similarity measure can be understood as an n-dimensional function, where n is the number of degrees-of-freedom of the transformation involved. For the registration proposed, the optimum of this function is assumed to correspond to the transformation that correctly registers the input images. The goal of the optimisation algorithm used is to search for the maximum or minimum value of the similarity measure adopted. Usually, the similarity measures are defined in such a way that the optimal registration is accomplished when their value is minimised. Thus, the registration problem can be mathematically defined as: $\min_T D\left[I_0, T(I_1)\right]$, where D is the distance or similarity measure function, I_0 and I_1 are the images or structures to be registered and T is the transformation.

Several optimisation algorithms have been used in the field of medical image registration, including: the Powell's method (Collignon et al. 1997; Maes et al. 1997; Pluim et al. 2000; Lavely et al. 2004; Pluim et al. 2004; Auer et al. 2005; Meyer 2007; Sun et al. 2007; Oliveira and Tavares 2011), the downhill simplex method (Dey et al. 1999; Jenkinson and Smith 2001; Shekhar and Zagrodsky 2002; Shekhar et al. 2004), the Gauss–Newton (Ashburner and Friston 1999), the Levenberg-Marquardt (Thévenaz and Unser 2000; Kabus et al. 2004), the gradient ascent or descent (Rueckert et al. 1999; Rohlfing and Maurer 2001; Tang et al. 2006; Balci et al. 2007; Karaçali 2007), the quasi-Newton (Mattes et al. 2003; Loeckx et al. 2010; Khader and Hamza 2011), the stochastic algorithms (e.g. simulated annealing) (Nikou et al. 1999; Loeckx et al. 2003) and evolutionary algorithms (Butz and Thiran 2001; Pataky et al. 2008; Ruijters et al. 2009). Almost all the optimisation algorithms previously indicated are described in Press et al. (2007).

For deformable medical image registration, the similarity measure used is frequently addressed as the energy functional. Therefore, the goal of such registration approaches is to find the displacement field that minimises the energy functional used. The minimisation problem is frequently converted into a problem of solving a set of partial differential equations. Thus, specialised techniques, such as the finite difference method (Lu et al. 2004; Beg et al. 2005), finite element method (Brock et al. 2005; Alterovitza et al. 2006; Niculescu et al. 2009), variational method (Hermosillo et al. 2002) and Green's functions-based method (Marsland and Twining 2004), can be used.

Sometimes the optimisation problem is converted into a problem of solving a set of linear equations simultaneously. Thus, the solution can be achieved directly, for instance, by using the singular value decomposition (Zhilkin and Alexander 2000) or the least squares technique (Friston, Ashburner, et al. 1995).

Some authors have used the support vector machine (SVM) technique in their image registration algorithms (Zhang et al. 2005; Qi et al. 2008). These algorithms are frequently based on prior information obtained from the joint intensity distribution between two or more registered images. This prior knowledge is used in the registration process to estimate the similarity measure in function of the geometric transformation. Because the optimisation based on SVM is a sparse problem, this technique can be very efficient in terms of computational time.

Generally, the similarity measure as a function is not smooth, as it contains many local extremes. Some of these local extremes represent local best solutions, but others are a consequence of the approach implemented, such as interpolation imperfections and lack of robustness of the similarity measure.

The iterative optimisation algorithms are frequently implemented with a multi-resolution or pyramidal strategy. This strategy uses a coarse-to-fine approach. Usually, the process starts by defining a pair of image pyramids that are used to down-sample the fixed and moving images. Then, the registration starts by registering the images from the lower to the higher resolution images. In each step, the transformation found in the previous step is used as the new initial registration. Relatively to the methods that just use the original images, this approach has some advantages, such as higher convergence radius (also known as capture range), more robust to local optimums and usually faster. Some examples of works in which a multi-resolution strategy has been used are in Hellier and Barillot (2004), Hipwell et al. (2003), Loeckx et al. (2010), Mattes et al. (2003), Orchard (2008), Rueckert et al. (1999), Shekhar et al. (2005), Staring et al. (2009), Studholme et al. (1997), Thévenaz et al. (1998), Thévenaz and Unser (2000).

For the point correspondence-based registration algorithms, the optimal transformation between two input images can be directly determined based on the matching established. The well-known Procrustes method (Hill and Batchelor 2001) is an example of this kind of minimisation strategy. Similar solutions are the ones based on the least squares techniques. Optimisation algorithms based on assignment algorithms have also been presented (Bastos and Tavares 2004; Oliveira and Tavares 2008; Oliveira et al. 2009b).

A comparison among eight optimisation algorithms for non-rigid medical image registration based on cubic B-spline and the maximisation of the MI is described in Klein et al. (2007).

3.4. Interpolation

In the registration process, when a point is mapped from one space into another space by a transformation, it is generally allocated a non-grid position. Thus, it is necessary to evaluate the image intensity at the new mapped position. The goal of the interpolation step is to estimate the intensity at that new position.

The interpolation solution used can affect the accuracy and speed of the registration process. To increase the speed, a simple interpolation algorithm is usually used in the optimisation step, as the ones based on the nearest neighbour or linear interpolations, and then an interpolation solution of higher quality is used to obtain the final registered image, such as the ones based on cubic B-spline or windowed sinc interpolators. In cases when the smoothness or robustness of the similarity measure is significantly affected by imperfections of the interpolation solution, a superior interpolation solution should also be used during the optimisation step.

A study on image interpolation function can be found in Thévenaz et al. (2000). Additionally, in Tsao (2003), eight interpolation solutions are compared in a multimodal image registration based on maximisation of MI.

3.5 Pre-registration

A bad initial registration can compromise the registration speed or even make it worse, it can impede the convergence of the optimisation algorithm used in the registration. Thus, in most applications, it is important that the initial fixed and moving images are not badly misregistered or a good pre-registration solution should be applied to the optimisation algorithm used.

Except for the situations where the image features extracted from the images are invariant to the geometric transformations, large initial misregistrations between the input images should be avoided. An initial pre-registration can be defined manually by the user or by a fully automated approach using, for example, image moments as in Itti et al. (1997), Pan et al. (2011).

3.6 Segmentation

Image segmentation consists of extracting relevant information from the input images. This information can be simply established by sets of points, edges, lines, contours, surfaces, areas, volumes, medial axes, etc., or descriptors on the objects represented in the images, such as distances, lengths, angles, moments or shape signatures or even more complex structures containing information about the objects, such as graphs, skeletons or diagrams in the images.

In some cases, segmentation is an easy task, such as the extraction of fiducial markers placed in patients' bodies with the goal to carry out the registration based on those fiducial markers (Maurer et al. 1997), or points of high gradient magnitude (Ostuni et al. 1997). However, in the most cases, robust image segmentation is not a trivial task.

Several image segmentation techniques exist, which can be broadly classified as region or border based. Examples of region-based techniques are: thresholding methods (Wellner 1993; Otsu 1979), watershed (Beucher 1991; Grau et al. 2004) and region growing (Adams and Bischof 1994). Usual border-based segmentation techniques include edge detectors based on image gradient (Marr and Hildreth 1980; Canny 1986), corner detectors, line detectors based on the Hough transform; deformable models, like active contours, usually known as snakes (Kass et al. 1988; Cootes and Taylor 1992; McInerney and Terzopoulos 1996; Xu and Prince 1998; Gonçalves et al. 2008;) and level set methods (Wang and Wang 2006; Wang et al. 2007; Han et al. 2009).

Reviews on image segmentation techniques can be found in Gonzalez and Woods (2008), Ma, Zhen et al. (2010), Monteiro (2007), Zhang and Lu (2004), Zhang (2001).

3.7 Matching

In the intensity-based registration methodologies previously referred to, a dense matching is automatically established based on the geometric transformation found. However, in this section, the matching between the features extracted from both input images is considered sparse.

Matching can be established independently of the geometric transformation or iteratively based on it. In both cases, a similarity measure between the features to be matched is optimised. For the iterative matching optimisation, besides the optimisation algorithms previously indicated, common algorithms are the ICP (Besl and McKay 1992) and its variations (Stewart et al. 2003; Andreetto et al. 2004; Giessen et al. 2009; Tsai et al. 2010; Pan et al. 2011).

The HAMMER algorithm (Shen and Davatzikos 2002) establishes the matching in a similar fashion to the free-form deformation, that is, based on a local search for the best matching. In Wu et al. (2006a), this algorithm is integrated with a machine learning-based technique, where features are learned from different types of local image descriptors that are selected from a training set of registered images.

For the matching algorithms where the matching is established independently, the geometric transformations are also based on the optimisation of a similarity or 'distance' measure. The 'distance' among the features to be matched is based on their particular characteristics. Dedicated optimisation solutions can be used to establish the matching among features, such as self-organising maps (Matsopoulos et al. 2004), simulated annealing (Bayro-Corrochano and Rivera-Rovelo 2009), quasi-orientation maps (Wong et al. 2006), approaches based on the Procrustes method (Rangarajan et al. 1997; Hill and Batchelor 2001), fuzzy clustering (Tarel and Boujemaa 1999), homothetic boundary mapping (Davatzikos et al. 1996) or contours mapping via dynamic programming (Oliveira and Tavares 2008). To match relational structures, such as graphs, dynamic programming can be used as in Maksimov et al. (2009). Figure 4 shows an example of registration of two brain images (slices) based on contour matching and using dynamic programming.

In some matching algorithms, before the computation of the optimal geometric transformation, it is important to consider an algorithm to remove outlier matches. The random sample consensus RANSAC; Fischler and Bolles 1981) is an example of this kind of algorithm, and is

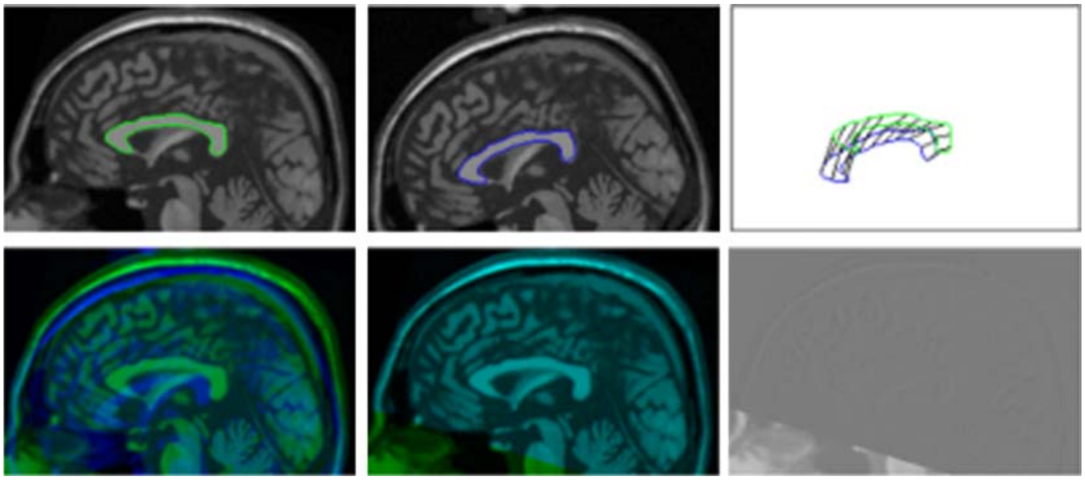

Figure 4. Matching and registration of two brain slices. At the top, fixed image overlapped by the contour segmented from the corpus callosum, moving image overlapped by the contour segmented from the corpus callosum, and the illustration of the matching established. At the bottom, input images overlapped before the registration, the same images overlapped after the registration and the difference between the input images after the registration.

applied, for example, in Wong and Orchard (2006) to enhance the robustness of the matching process.

3.8 Frequency-based methodologies

The SSD and cross-correlation-based similarity measures can be efficiently evaluated in the frequency domain using the Fourier transform and its properties. Both measures can be directly evaluated in function of an arbitrary shift (Cideciyan 1995; Andreetto et al. 2004; Orchard 2007a; Oliveira et al. 2010), which is less time demanding than the solution based on iterative optimisation. The rotational and the scaling of 2D images can also be achieved by transforming the original image spectrums into polar or log-polar coordinate systems (Cideciyan 1995; Kassam and Wood 1996; Andreetto et al. 2004; Oliveira et al. 2010).

The well-known phase correlation technique (Kuglin and Hines 1975) can also be used to estimate the optimal registration between two images (Hoge 2003; Grau et al. 2007; Oliveira et al. 2010).

Also the Fourier transform and wavelet transforms have been used in some image registration methodologies (Gefen et al. 2003; Xu and Chen 2007).

The image registration techniques based on the optimisation of the SSD and cross-correlation in the frequency domain can be clearly classified as intensity based; however, since the computation is done in the frequency domain, they have been included in this category.

3.9. Hybrid methodologies

Various authors have combined two or more registration methodologies/strategies in their algorithms (Davatzikos et al. 1996; Christensen et al. 1997; Kim et al. 2003; Andreetto et al. 2004; Auer et al. 2005; Chen et al. 2010; Liao et al. 2011). Some use feature- and intensity-based registration methodologies concurrently. Sometimes, the similarity measure used contains information on the voxel intensity distributions and information on the features extracted from the input images simultaneously.

A common solution is the use of a feature-based algorithm for a coarse registration and then the use of an intensity-based methodology for a fine registration as described in Chen et al. (2010), Liao et al. (2011), Oliveira and Tavares (2011), Postelnicu et al. (2009). For example, in Postelnicu et al. (2009), to optimally register volumetric brain images, relevant geometrical information is initially extracted from the segmented surfaces of cortical and subcortical structures, and afterwards the surfaces are registered and the deformation found is applied to the rest of the volume data. This deformation is then refined in the non-cortical regions with an intensity driven optical flow procedure, preserving the initial registration in the cortical region.

In Christensen et al. (1997), the registration is established in two steps. First, the global transformation is determined by using a low-dimensional elastic model; then, the local higher deformation is obtained using the Navier-Stokes fluid model. On the other hand, in Auer et al. (2005), a coarse initial registration is defined by maximising the MI using the Powell's method combined with a multi-resolution strategy, and then a fine point-based registration is accomplished using an elastic TPS.

4. Registration accuracy assessment

Registration is of low value if its accuracy cannot be evaluated. To assess the registration accuracy, several approaches have been proposed. Since the image registration problem is commonly defined as an optimisation problem, the image similarity measure optimisation can be used as a crude accuracy measure. However, most similarity measures frequently used have no geometric/physical significance.

A simple and generally used approach is to apply a transformation to an image and then use the registration algorithm to re-align both images (D'Agostino et al. 2003; Wang et al. 2005; Balci et al. 2007; Bhagalia et al. 2009). Then, the applied transformation is used as ground-truth.

An approach closely related to the later is based on synthesising images by simulating the imaging acquisition physics or/and material properties and then evaluating the registration algorithm on the synthetic images produced. For example, in Schnabel et al. (2003), physically plausible biomechanical tissue deformations of the breast are simulated using the finite element method.

Other more reliable solutions are by manually identifying a set of corresponding points in both input images, e.g. fiducial markers placed into the patients or the organs, and use them to assess the registration accuracy (Collignon et al. 1997; Maes et al. 1997; West et al 1997, 1999; Penney et al. 1998; Pluim et al. 2000; Mattes et al. 2003).

The target registration error is an important measure of the accuracy of the performed registration. It evaluates the registration accuracy based on points correspondence. Since its value is given in terms of Euclidean distance between the corresponding points, it has an immediate physical meaning. Its drawback is its dependency on the fiducial localisation error (FLE). Studies evaluating the registration errors associated to this kind of registration can be found in Danilchenko and Fitzpatrick (2011), Dorst (2005), Fitzpatrick et al. (1998), Ma, Burton et al. (2010), Moghari and Abolmaesumi (2009a,b), Wiles et al. (2008).

In some studies, phantoms are used to assess the accuracy (Studholme et al. 2000; Rhode et al. 2003; Wang et al. 2005) since they allow accurate control/simulation of the patients' movements.

In Hub et al. (2009), a stochastic approach is proposed to detect areas in which the monomodal B-spline-based registration performs well and those in which the accuracy is lower. Another evaluation on the accuracy of the B-spline registration-based approach is carried out using synthetic images deformed by the finite element method in Schnabel et al. (2003).

The Dice similarity coefficient quantifies the amount of overlapping regions and has also been used to assess the registration accuracy (Alterovitza et al. 2006; Vercauteren et al. 2007; Loeckx et al. 2010).

Since the image registration task is classically formulated as an optimisation problem with a multiple set of tuneable parameters, its accuracy also depends on those parameters. Usually, such parameters are adjusted manually by observing the registration results, which does not always guarantee that the best combination is achieved. A solution to overcome this limitation is proposed in Yeo et al. (2010b).

Researchers and students can freely download the 'Vanderbilt Database' (West et al. 1997), hosted by the Retrospective Image Registration Evaluation Project, and test the accuracy of their rigid registration algorithms. This project is design to compare CT-MR and PET-MR intra-subject registration techniques using brain images from the Vanderbilt Database. The ground-truth transforms have been defined using fiducial markers.

5. Conclusions

In the last few years, the use of the intensity-based registration methods has grown considerably compared to the feature-based methods. The turning point came with the introduction of the MI as the similarity measure. Before this introduction, multimodal registration was done mainly on segmented images, since no intensity similarity measure had been proposed that could be generally and efficiently applied to multimodal registration.

Another important factor that boosted the intensity-based registration methods was the advance in terms of computational resources, particularly, processing speed and memory capacity. Ten or twenty years ago, computers needed hours or days to register two image volumes when using intensity-based methodologies. Using the same computer resources, the registration problem could be solved in less time using feature-based methods, since these methods use only a small amount of the data from the original images. Today, a simple laptop is able to solve the same intensity-based registration problem in a few seconds or minutes.

The growing importance of the intensity-based registration methods is also a consequence of their simplicity, as there is no need for image segmentation that is usually subject to errors and can be complex.

The growth in computational speed and the high accuracy of the intensity-based registration methods have stimulated many authors to use them as an initial step in image segmentation procedures, since, if the orientation and position of a structure in an input image is previously known, the segmentation task can become significantly easier. However, it should be noted that, in this case, instead of the segmentation being carried out to allow the registration afterwards, as happens in the feature-based registration methodologies, here it is the registration procedure that facilitates the segmentation task.

In the field of medical image analysis, image registration is still one of the most active topics. If the registration of static images is now well established, the registration of dynamic images still presents several difficulties, demanding significant improvements in terms of computational speed and registration accuracy.

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