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Survey of Medical Image Registration

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Abstract Computerized Image Registration approaches can offer automatic and accurate image alignments without extensive user involvement and provide tools for visualizing combined images. The aim of this survey is to present a review of publications related to Medical Image Registration. This paper paints a comprehensive picture of image registration methods and their applications. This paper is an introduction for those new to the field, an overview for those working in the field and a reference for those searching for literature on a specific application. Methods are classified according to the different aspects of Medical Image Registration.

Keywords: *image registration, deformable model, multimodal, extrinsic, elastic, rigid; non rigid, voxel based, feature based*

1. Introduction

Image Registration is an important preprocessing step in Medical image analysis. Medical images are used for diagnosis, treatment planning, disease monitoring and image guided surgery and are acquired using a variety of imaging modalities like Computer Tomography (CT), X-ray, Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), Ultrasound, etc. So images obtained using different modalities need to be compared to one another and/or combined for analysis and decision making. To monitor disease progress and growth of abnormal structures, images are acquired from subjects at different times or with different imaging modalities. Misalignment between images is inevitable and this reduces the accuracy of further analysis. Image registration is a task to reliably estimate the geometric transformation such that two images can be precisely aligned. Any registration technique can be described by three components: a transformation which relates the target and source images, a similarity measure which measures the similarity between target and source image, and an optimization which determines the optimal transformation parameters as a function of the similarity measure. Image Registration plays an important role in medical image analysis, group analysis and statistical parametric mapping. Because of its importance in both research and medical applications, Medical Image Registration has been intensively investigated for almost three decades [1] and numerous algorithms have been proposed. Much of the early work in medical image registration was in registering brain images of the same subject acquired with different modalities (e.g. MRI and CT or PET) [2-10]. For these applications a rigid change in brain shape or position within the skull over the relatively short periods between scans. Today rigid registration is often extended to include affine registration, which includes scale factors and shears, and can partially correct for calibration differences across scanners or gross differences in scale between subjects.

Now complex non-rigid medical image registration techniques are developed for modeling soft-tissue deformation during imaging or surgery [11,12] and to model changes in anatomy of the object of interest [13-18].Researchers interested in more specific aspects of Medical Image Registration, can refer publications of Makela et al, for Cardiac Applications [19], Hutton et al., for Nuclear Medicine [20], Rosenman et al., for Radiation Therapy [21], Meijering et al., for Digital Subtraction Angiography [22] and Toga and Thompson [23] and Thompson et al. [24] for brain warping applications.

This paper starts with an overview of Medical Image Registration in Section 1. Section 2 deals with the classification of various Registration techniques .Section 3 deals with registration based on Dimensionality of the images. Section 4 is based on nature of the images. Section 5 describes registration methods based on the Domain of registration. Section 6 discusses techniques based on various levels of interaction .Section 7 deals with different Optimization techniques used in image registration. Section 8 discusses about the different Modalities involved. Section 9 deals with the different Subjects and Section 10 discusses about registration of different Objects. Finally Conclusion regarding the different aspects is provided in the last section.

2. Classification of Registration Methods

The registration methods can be classified based on the criteria formulated by Vanden Elsen, Pol and Viergever (17). Nine basic criteria are used, each of which is again subdivided on one or two levels.

The nine criteria and primary subdivisions are: represented in the following tree diagram.

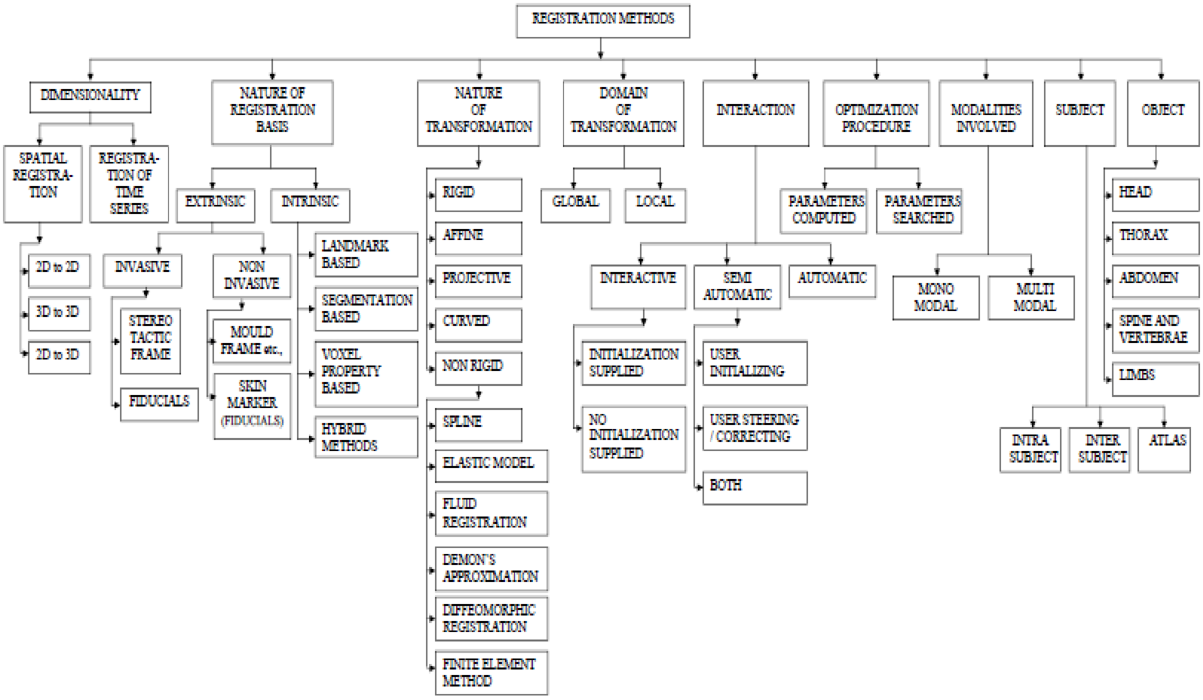
3. Dimensionality

3.1. Spatial Dimensions

The process of registration involves computation of a transformation between the coordinate systems of the images or between an image and physical space.

3.1.1. 2D-to-2D

2D images may be registered using rotation and two orthogonal translations. Changes in scale may also be corrected. *2D/2D* registration can be used to align 2D slices from tomography data. Compared to *3D/3D* registration, *2D/2D* registration is less complex, so obtaining a registration is easier and faster than in the *3D/3D* case.



3.1.2. 3D-to-3D

Accurate registration of multiple 3D MR and CT volumes is the most common and fully developed method. The spatial relationship between the internal organs of the patient has not distorted or changed and the imaged organ behaves as a “rigid body.” In 3D Rigid registration three translations and three rotations are sufficient to bring the images into accurate alignment. The scanning devices must be calibrated to determine image scaling, i.e., the size of the voxels in each modality must be known. *3D/3D* registration is used to accurately register tomographic datasets, or to register a single tomography image to any spatially defined information.

3.1.3. 2D-to-3D

2D-to-3D registration is used for establishing correspondence between 3D volumes and projection images like x-ray. 2D-to-3D registration is done when the position of one or more 2D slices are to be established relative to a 3D volume. The main application of these methods is in image-guided surgery. Hence their computational complexity must be reduced without affecting the accuracy. Diagnostic applications outside the Operation Theater and radiotherapy setting allow for off-line registration, and here computational complexity and speed is not an issue.

3.2. Registration of Time Series

Registration of images acquired during different time instances is used for monitoring disease progress and to assess treatment response. 3D imaging with single or multiple imaging modalities at different time intervals during and after a radiation course provide the opportunity to increase treatment accuracy and precision. During the course of radio therapy, registration is done for target delineation, to quantify patient specific physiological motion, and to assess treatment response. In cardiology, multiple images are acquired in synchronism with the heart beat, using the ECG or blood pressure waveform. Image noise is reduced by averaging, the synchronized or “gated” acquisitions over multiple cardiac cycles. Similarly, registration of x-ray images of the heart acquired before and after injection of contrast material allows synchronous subtraction of mask images. All these methods assume that the heart cycle does not change from beat to beat. Registration of images acquired at different time intervals are used to study dynamic processes such as tissue perfusion, blood flow, and metabolic or physiological processes.

4. Nature of Registration Basis

Medical Image registration can be divided into Extrinsic method i.e., based on foreign objects introduced into the imaged space, and Intrinsic methods, i.e., based on the image information generated by the patient himself.

4.1. Extrinsic Registration Methods

In *Extrinsic registration*, artificial objects are attached to the patient and they must be clearly visible and accurately detectable in all the modalities. These registration methods are computationally efficient and can be automated easily. They do not require complex optimization algorithms, since the transformation parameters are computed easily. The following external markers are commonly used in medical imaging.

- Stereo tactic frame screwed rigidly to the patient's outer skull table [14]
- Screw-mounted markers [15]
- Markers glued to the skin [16]

Extrinsic methods does not include patient related image information, the nature of the registration transformation is often restricted to be rigid (translations and rotations only). If these methods are to be used with images of low (spatial) information content such as EEG or MEG, a calibrated video image or spatial measurements are often necessary to provide spatial information for basing the registration. Because of the rigid-transformation constraint, and various practical considerations, use of extrinsic 3D/3D methods is largely limited to brain and orthopedic imaging, although markers can often be used in projective (2D) imaging of any body area (37,38). Non-rigid transformations can in some cases be obtained using markers, *e.g.*, in studies of animal heart motion, where markers can be implanted into the cardiac wall.

4.2. Intrinsic Registration Methods

In Intrinsic registration methods salient visible Landmarks, segmented binary structures, or voxel intensities of the image are used as reference.

4.2.1. Landmark Based Registration Methods

Landmark based approaches use identifiable prominent anatomical elements in each image. These elements typically include functionally important surfaces, curves and point landmarks [17] that can be matched with their counterparts in the second image. Anatomical landmarks used were sparsely distributed throughout the images. These correspondences define the transformation from one image to the other. The use of such structural information ensures that the mapping has biological validity and allows the transformation to be interpreted in terms of the underlying anatomy or physiology. Corresponding point landmarks can be used for registration [18] provided landmarks can be reliably identified in both images. Landmarks can either be defined anatomically, or geometrically [19] by analyzing how voxel intensity varies across an image. When landmarks are identified manually, it is important to incorporate measures of location accuracy into the registration .After establishing explicit correspondences between the pairs of point landmarks, interpolation is used to infer correspondence throughout the rest of the image volume in a way consistent with the matched landmarks [20].

Recent work has incorporated information about the local orientation of contours at landmark points to improve the registration accuracy further. In some algorithms, linear features called ridges or crest lines are extracted directly from three-dimensional (3D) images [21], and they are non-rigidly matched. Then, as above, interpolation extends the correspondences between lines to the rest of the volume. In some applications linear features are used as landmark structure. For instance in the brain, a large subset of the crest lines correspond to gyri and sulci and in Subsol et al.,[22] these features were extracted from different brains and registered to a reference to construct a crest-line atlas. As point and line matching is relatively fast to compute, a large number of researchers explored them [23]. Other related applications include the registration of vascular images where the structures of interest are “tubes” [24]. Surfaces of 3D structures like shape of left ventricle can be used as landmarks in non-rigid registration methods based on 3D geometric features.

4.2.2. Segmentation Based

Segmentation based registration methods are based on *rigid models or deformable models*. If rigid models are used surfaces are extracted from both the source and target image and they are used as input for the registration process. If deformable *models are used* surfaces or curves are segmented from one image and are elastically deformed to fit the second image [26].Deformable model based methods are complex since some regularization terms are included in the cost function. The *rigid model based* approaches are simple and hence they are the most popular methods currently in clinical use. The popularity of this method is due to the success of the “head-hat” method introduced by Pelizzari et al. [27], which relies on the segmentation of the skin surface from CT, MR and PET images of the head. Since the segmentation task is fairly easy to perform, and the computational complexity is relatively low, the method has remained popular, and many follow-up papers aimed at automating the segmentation step, improving the optimization performance, or otherwise extending the method have been published. Another popular segmentation based approach is the fast *Chamfer matching* technique for alignment of binary structures by means of a distance transform, introduced by Borgefors [28]. In segmentation based methods the registration accuracy depends on the accuracy of the segmentation step. Several algorithms have been developed for detecting the features and aligning images simultaneously. In 2001, the first segmentation and registration framework was proposed in L.Zollei et al., [29], which utilizes multi-channel Chan-Vese active contour to segment the desired edge features and find the optimal Euclidean transformation between images. In 2002, Moelich improved this framework by substituting the Chan-Vese active contour with logic models that allow better control of the segmentation and richer context information about dissimilarity of images [30]. In 2004, Chen presented a joint framework of classification and registration for MR data [31]. This was achieved by Maximizing Aposteriori (MAP) model. In 2005, Young introduced a method that combines partial differential equations based on morphing active contours with Yezzi and Zollei’s algorithms for joint segmentation and registration [29]. In the same year, a statistical framework using an Expectation Maximization based algorithm appeared in K. M. Pohl et al. [32]. The approach simultaneously estimates image in homogeneities, anatomical label-map and a mapping from the atlas to the image space. Most of the existing approaches are restricted to lower dimensional rigid transformations for image registration. Recently, M. Droske et al. [33] proposed a novel method of non- rigid registration using edge alignment. The key idea of this work is to modify the Ambrosio-Tortorelli approximation of the Mumford-Shah model, which is traditionally used for image segmentation, so that the new functional can also estimate the spatial transformation between images.

4.2.3. Voxel Property Based

Voxel property based approaches match intensity patterns in each image using mathematical or statistical criteria. They define a measure of intensity similarity between the source and the target and adjust the transformation until the similarity measure is maximized. They assume that the images will be most similar at the correct registration. Commonly used voxel based similarity measures are the [2] Mean Squared Difference (MSD), Normalized Correlation (NC)], Mutual Information (MI) , and Normalized Mutual Information (NMI).For monomodal registration tasks the Sum of Squared Grey value differences (SSD) can be applied, since it assumes the same grey value structure in both images. If this pre requisite is not fulfilled, but at least a linear dependency between the grey values can be assumed, Cross Correlation (CC) can be used. If even this linear dependency is not given, as it is the case in multimodal registration tasks, entropy-based measures like Mutual Information (MI) [1] has to be chosen. Among the different similarity measures that have been proposed, Mutual Information (MI) and Normalized Mutual Information (NMI) are the most commonly used since they produce satisfactory results in terms of accuracy, robustness and reliability. However, MI-based methods are very sensitive to implementation decisions. In particular, the way of estimating the probability distributions and the choice of the interpolator have a great influence in the accuracy and robustness of the registration results. Most commonly used intensity-based similarity measures, including Sum-of-Squared-Differences (SSD), Correlation Coefficient (CC), Correlation Ratio (CR) and Mutual Information (MI), rely on the assumption of independence and stationarity of the intensities from pixel to pixel [1]. These similarity measures are defined only between the corresponding pixels without considering their spatial dependencies. Further, the intensity relationship is assumed to be spatially stationary. As a result, such measures tend to fail when registering two images corrupted by spatially-varying intensity distortion. All these measures are discussed at greater length in Hajnal et al. [2].

4.2.4. Hybrid Methods

Combining geometric features and intensity features in registration result in more robust methods. Hybrid algorithms combine intensity-based and model-based criteria to establish more accurate correspondences in difficult registration problems. Sulcal information can be used to constrain intensity-based brain registration [35,36] or cortical surface with a volumetric approach [37]. Surfaces are also used to drive volumetric registration in Thompson et al. [38], and to analyze normal and Alzheimer brains with respect to an anatomical image database. In Christensen et al. [39] the registration task is to correct for large displacement and deformation of pelvic organs induced when intra cavity CT images are used to treat advanced cancer of the cervix. Anatomical landmarks are used to initialize an intensity driven fluid registration with both stages using the same model for tissue deformation. In this application the more robust but less flexible landmark registration produces a robust starting position for the less robust but more flexible fluid registration and the two steps run serially (there is further discussion of fluid registration in the next section). Other researchers have attempted true hybrid solutions where intensity and feature information are incorporated into a single similarity measure, e.g. in Russakoff et al. [40] a rigid registration is computed between a pre-operative spinal CT and an intra operative X-ray by maximizing the difference of mutual information based intensity measure and a distance between corresponding landmarks. As is often the case, an additional parameter has to be chosen empirically to appropriately weight the intensity and landmark parts of the similarity measure. A more sophisticated approach built on the same principles is used in PASHA (Pair And Smooth Hybrid Algorithm) [41] where the similarity measure is the weighted sum of an intensity similarity, a term expressing the difference between the landmark correspondence and the volumetric deformation field, and a smoothing term. In Hellier and Barillot [36] a framework for incorporating landmark constraints with image-based non-rigid registration is described for the application of inter subject brain image registration where the constraints ensure that homologous sulci are well matched. Traditional mutual information function aligns two multimodality images with intensity information, lacking spatial information, so that it usually presents many local maxima that can lead to inaccurate registration. Liu et al. [42] proposed an algorithm using adaptive combination of intensity and gradient field mutual information (ACMI). Gradient code maps (GCM) are constructed by coding gradient field information of corresponding original images. The gradient field MI, calculated from GCM, can provide complementary properties to intensity MI. ACMI combines intensity MI and gradient field MI with a nonlinear weight function, which can automatically adjust the proportion between two types of MI to improve registration. Experimental results demonstrate that ACMI outperforms the traditional MI and it is much less sensitive to reduced resolution or overlap of images.

5. Nature of the Transformation

5.1. Rigid

Translations and rotations suffice to register images of rigid objects. Examples include registration of bone or of the brain when neither skull nor dura has been opened. .Rigid registration is also used to approximately align images that show small changes in object shape (for example, successive histological sections [43] and serial MR images) or small changes in object intensity, as in functional MR time series images. The global rigid transformation is used most frequently in registration applications. It is popular because in many common medical images the rigid body constraint leads to a good approximation. Furthermore, it has relatively few parameters to be determined, and many registration techniques are not equipped to supply a more complex transformation. The most common application area is the human head.

5.2. Affine

The affine transformation preserves the parallelism of lines, but not their lengths or their angles. It extends the degrees of freedom of the rigid transformation with a scaling factor for each image dimension and additionally, a shearing in each dimension [44,45,46]. In P. Viola et al. [47] and in, M. Jenkinson et al. [48], an affine registration with nine degrees of freedom is performed to correct calibration errors in the voxel dimensions. Holden et al. [49], further more measured the relative scaling error between scans. R.Shekhar et al. [50] compared registration accuracies of ultrasound images using transformations of increasing complexity (rigid, rigid with uniform scaling, rigid with non uniform scaling and fully affine).

5.3. Projective

Projective transformation is used when the scene appears tilted. Straight lines remain straight, but parallel lines converge toward vanishing points. The projective transformation requires that straight lines in the reference image remain straight in the sensed image. The projective transformation type has no real physical basis in image registration except for *2D/3D* registration. It is sometimes used as a "constrained-elastic" transformation, when a fully elastic transformation behaves inadequately or has too many parameters to solve for. The projective transformation is not always used in *2D/3D* applications, even though projections will always figure in the problem, the transformation itself is not necessarily projective but may be rigid, if it applies to the 3D image prior to its projection to the 2D image.

5.4. Curved

Several algorithms adapted from computer vision have been proposed and used over time .Gueziec matches the crest lines using a combination of geometric hashing and Hough transform. A 2D-to-3D non-rigid intensity-based planar-to-curved-surface image alignment algorithm was proposed by Smarder Gefan et al. .This algorithm matches experimental data of two dimensional images with their corresponding images overlaid on a curved-surface within a volumetric image [51]. This PDE-based 2D-to-3D registration technique allows for inter-modality matching of sectional data with a volumetric image of homologous objects.

5.5. Non Rigid

Clearly most of the human body does not conform to a rigid or even an affine approximation [1] and much of the most interesting work in registration today involves the development of non-rigid registration techniques for applications ranging from modeling, tissue deformations to variability in anatomical structures, Non Rigid registration remains a challenging research problem due to its smoothness requirement and high degree of freedoms in the deformation process. Numerous algorithms have emerged to nonlinearly register medical images to one another. They require a great deal of computation time, which is a major drawback for many clinical applications, accordingly how to improve the precision and how to increase the speed and how to evaluate the registered results need further research [13].

5.5.1. Spline

One of the most important non linear transformations is the family of splines that have been used in various forms for around 15 years [52]. Many registration techniques using splines are based on the assumption that a set of corresponding points or landmarks can be identified in the source and target images. Spline-based registration algorithms use corresponding control points, in the source and target image and a spline function to define correspondences away from these points. The ''thin-plate'' spline [52,53] has been used extensively to investigate subtle morphometric variation in schizophrenia [54]. Each control point belonging to a thin-plate spline has a global influence on the transformation in that, if its position is perturbed, all other points in the transformed image change. This can be a disadvantage because it limits the ability to model complex and localized deformations and because, as the number of control points increases, the computational cost associated with moving a single point rises steeply. By contrast, B-splines are only defined in the vicinity of each control point; perturbing the position of one control point, only affects the transformation in the neighborhood of the point. Because of this property, B-splines are often referred to as having ''local support''. B-spline based non-rigid registration techniques are popular due to their general applicability, transparency and computational efficiency. Their main disadvantage is that special measures are sometimes required to prevent folding of the deformation field and these measures become more difficult to enforce at finer resolutions. Such problems have not prevented these techniques finding widespread use in the brain [54], the chest [55] the heart [56,57], the liver [58], the breast [59,60] etc.

5.5.2. Elastic Models

Non Rigid registration using Elastic models have been introduced by Broit [61] and extended by Bajcsy and Kovacic [62,63].in the early 1980s to delineate low contrast anatomical brain structures in Positron Emission Tomography (PET) and CT images. These models are nowadays used by various authors [64-69]. The estimated deformation field should basically obey the rule of the Navier equation:

$$\mu\nabla^2 u + (\lambda + \mu)\nabla\left(div(u)\right) + F = 0$$

where u is the deformation field to estimate, λ and μ are the Lame coefficients and F is the sum of forces that are applied on the system. The problem is to specify the forces F that will lead to a correct registration. Elastic models treat the source image as a linear, elastic solid and deform it using forces derived from an image similarity measure. The image is deformed until the forces reach equilibrium [69-74]. Bajcsy computed these forces so as to match the contours [63]. Davatzikos [69] did not compute any forces but segmented the brain surface and the ventricles using two different methods. The matching of these surfaces provides boundary conditions that make it possible to solve the problem. These two approaches are therefore sensitive to segmentation errors. The values of Lame coefficients influence the deformation. Earliest work proposed that $\lambda = 0$ but it appear nowadays to be a limitation. Elastic modeling cannot handle large deformations. As a matter of fact, the equation of Navier is only valid for small displacements. To solve this problem, two kinds of approaches can be used. A rigid registration can provide a good initialization Bajcsy [63] uses principal inertia axes and Davatzikos [69] uses the stereotaxic space. Another way is to solve the problem iteratively using a multi resolution approach. The topology of present structures will be preserved. This may be interesting in some applications but more questionable when matching brains of different subjects, since cortical structures are not topologically equivalent among subjects indeed [63].

Elastic registration algorithms that use parametric models represent the deformation by a moderate number of parameters, in the multi scale setting. Specific examples include hierarchical basis functions by Moulin et al. [76], quadtree-splines [77], multi resolution subspaces [78] and wavelets [79]. Splines are well suited for this kind of problems. Kybic et al. [80] used a multi resolution B-spline representation, as was initially suggested in the pioneering work of Szeliski et al. [77]. Elastic models treat the source image as a linear, elastic solid and deform it using forces derived from an image similarity measure. The elastic model [76,77,78,79,80] results in an internal force that opposes the external image matching force. The image is deformed until the forces reach equilibrium. Since the linear elasticity assumption is only valid for small deformations it is hard to recover large image differences with these techniques.

5.5.3. Fluid Registration

Registration based on elastic transformations is limited by the fact that highly localized deformations cannot be modeled, since the deformation energy caused by stress increases proportionally with the strength of the deformation. In fluid registration these constraints are relaxed over time, which enables the modeling of highly localized deformations including corners. This makes fluid registration especially attractive for inter subject registration tasks (including atlas matching) which have to accommodate large deformations and large degrees of variability. At the same time the scope for mis registration increases, as fluid transformations have a vast number of degrees of freedom replacing the elastic model by a viscous fluid model [81,82] allows large and highly localized deformations. The higher flexibility increases the opportunity for mis registration, generally involving the growth of one region instead of shifting or distorting another.

5.5.4. Demons Algorithm

Thirion proposed another non-rigid technique, the “demons” algorithm [83] which can be thought of as an approximation to fluid registration. The main limitations of the demons algorithm are that it does not provide diffeomorphic transformations. More recently, the “demons” optical flow based non rigid registration algorithm has been used to quantify change in volume of brain structures over time and to quantify the difference in volume of brain structures. It requires a great deal of computation time, which is a major drawback for many clinical applications, accordingly improving the precision ,speed and evaluating the registered results need further research.

5.5.5. Diffeomorphic Registration

Diffeomorphisms preserve the topology of the objects and prevent folding which is often physically impossible. They are considered to be a good working framework when no additional information about the spatial transformation is available. The early diffeomorphic registration approaches were based on the “viscous fluid” registration method of Christensen et al [81]. In these models, finite difference methods are used to solve the differential equations that model one image as it “flows” to match the shape of the other. At the time, the advantage of these methods was that they were able to account for large displacements while ensuring that the topology of the warped image was preserved. They also provided a useful foundation from which later methods arose. Viscous fluid methods require the solutions to large sets of partial differential equations. The earliest implementations were computationally expensive because solving the equations used successive over-relaxation. Such relaxation methods are inefficient when there are large low frequency components to estimate. Since then, a number of faster ways of solving the differential equations have been devised. These include the use of Fourier transforms to convolve with the impulse response of the linear regularisation operator, [83] or by convolving with a separable approximation [84]. More recent algorithms for large deformation registration aim to find the smoothest possible solution. For example, the LDDMM (large deformation diffeomorphic metric mapping) algorithm [85], does not fix the deformation parameters once they have been estimated. It continues to update them using a gradient descent algorithm such that a geodesic distance measure is minimized. In principle, such models could be parameterized by an initial “momentum” field, which fully specifies how the velocities - and hence the deformations evolve over unit time. Unfortunately though, the differential equations involved are difficult to solve, and it is easier to parameterize them using a number of velocity fields corresponding to different time periods over the course of the evolution of the diffeomorphism.

The basics of diffeomorphic transformations are detailed in Glaunes et al. [86]. Image registration is usually defned as a variational problem involving the metric that measures the image matching after registration and a regularization constraint in the geometric transformation that maps the source into the target .In diffeomorphic registration, transformations are usually assumed to belong to a Riemannian manifold of diffeomorphisms. The majority of the approaches have focused on the characterization of the diffeomorphic transformations in the Large Deformation Diffeomorphic Metric Mapping (LDDMM) framework [85,86]. Much less attention has been paid to the optimization strategy where classical gradient descent method is often used.

Recently, Ashburner et al. have proposed a numerical implementation of Gauss-Newton’s method for the LDDMM variational problem [87]. The computations of the Gateaux derivatives of the objective function are performed in the space of $L2$-functions. In consequence, the action of the linear operator involved in the regularization term has to be formulated using the matrix representation of the convolution. As a result, the algorithm results into a high dimensional matrix inversion problem [88]. Although there exist well known multi grid techniques to numerically solve these problems the memory requirements for diffeomorphic registration hinder their execution in standard machines [89,90,91,92]. Moreover, multi-grid schemes need the definition of the injection and the interpolation operators associated to the elements involved in the registration, in order to compute fine-to- coarse and coarse-to-fine samplings. In the case of images, down sampling and linear interpolation are good candidates for these operators. High computational requirements have made this methodology not much attractive for clinical applications, where more efficient registration algorithms are usually preferred.

5.5.6. Finite Element Method

Finite Element Method (FEM) has been widely used in modeling biological tissues such as bone [2], myocardium , and in modeling brain deformation. A Finite Element Geometrical model is essential to predict deformation and other relevant parameters. The modeling of biomechanical tissue properties has gained considerable interest in a range of clinical and research applications. FEM can be used to model the interrelation of different tissue types by applying displacements or forces. This can help to predict mechanical or physical deformations during surgical procedures, and to derive and quantify tissue properties from observed deformations. FEM is used in brain modeling and it is used for model updation during image guided surgery procedures, for integration into non rigid registration methods [92,93] and for simulation of brain shift in interventional MR imaging [94,95,96]. In mammography, FEMs have been explored for predicting mechanical deformations during biopsy procedures [97], for simulating compressions similar to X-ray mammography in MR mammography [98], for improving and testing the reconstruction of elastic properties in elastography [99,100,101,102], and for modality-independent elastography with application to breast imaging [103].

6. Domain of Transformation

An image coordinate transformation is called Global if it is applied to the entire image and it is called local if it is applied to a small portion of the image. In the case of Global transformation the parameters of the mapping function are valid for the entire image. But Local mapping function parameters are valid only for a small patch or region around the chosen control point location.

7. Interaction

In Registration algorithms three levels of interaction can be used. In the case of Interactive algorithms the user does the registration himself with the help of software, by supplying an initial guess of the transformation parameters. In the case of automatic algorithms no interaction is involved. .In the case of semi- automatic algorithms either the user initializes the algorithm by segmenting the data or steers the algorithm to the desired solution.

Most of the authors strive to develop a fully automatic algorithm. The current registration algorithms have a trade-off between minimal interaction and speed, accuracy and robustness. In some methods the user interaction will narrow down the search space, reject the mismatch and speed up the optimization process. Further human interaction complicates the validation process since the interaction level cannot be quantified or controlled.

Extrinsic methods are often automated, since the markers are designed in such a way that they are visible and easily detectable in images involved in the registration process. Sometimes the user has to supply a seed point or to specify an initial location.

Intrinsic anatomical landmark and segmentation based methods are semi automatic. User has to initialize the process. Voxel based or Geometrical landmark based methods are fully automated. In recent literature there are only, = a few fully interactive methods.

8. Optimization Procedure

Optimization techniques are used to obtain the optimum transformation parameters required for aligning the images. Good optimization algorithms determine the transformation parameters reliably and quickly. In non-rigid registration applications choosing or designing an optimizer can be difficult because the more non-rigid (or flexible) the transformation model, the more parameters are generally required to describe it. So the optimizer take a large amount of time to determine the parameters and due to local minima problem there is more chance of choosing a set of parameters, which result in a good image match which is nevertheless not the best one. The transformation parameters are computed either directly i.e. they are determined in an explicit way from the available data, or searched for i.e., determined by finding an optimum of some cost function defined on the parameter space. The cost function determines the similarity between the two images given a certain transformation. The objective functions are less complex in mono modal registrations since there is a linear relationship between the source and the target image and the similarity metric is straight forward. The cost function also contains explicit regularization terms for smoothness and diffeomorphic constraints to preserve topology.

For optimization, the Nielder-Mead downhill simplex [1], Powell's direction set method [104], and first derivative-based methods such as conjugate gradient and Levenberg-Marquardt, have often been used [105]. The solution of the registration problem is often not considered to be Global optimum, since the feature and intensity based similarity functions and their corresponding cost functions are not optimal. Global optimization techniques such as evolutionary algorithms and simulated annealing are characterized by slow convergence rate, and have been rarely used in Medical Image registration. On the other hand, multi resolution and multi scale optimization frameworks have shown to be effective in obtaining a faster and more robust convergence toward the solution [106,107,108,109]. Maes *et al.* [106] compared various multi resolution gradient and non gradient based optimization techniques such as Powell, simplex, steepest descent, conjugate gradient, quasi-Newton, and Levenberg- Marquardt methods, and obtained a speed-up by a factor of 3 in a two-level multi resolution formulation of conjugate gradient and Levenberg-Marquardt methods for affine registration of CT and MRI images. Most of the widely used optimization algorithms, including gradient descent, quasi-Newton and Levenberg-Marquardt, require derivative calculation. Fluid and elastic transformations that can be described in terms of a partial differential equation (PDE) can be obtained using existing numerical solvers (successive over relaxation, full multi-grid etc.) [2,81].Which optimization scheme is suitable for a particular registration application depends on the cost function, the transformation, potential time-constraints, and the required accuracy of the registration.

Klein et al compared the performance of eight optimization methods: gradient descent (with two different step size selection algorithms), quasi-Newton, nonlinear conjugate gradient, Kiefer-Wolfowitz, simultaneous perturbation, Robbins-Monroe, and evolution strategy [110]. Special attention is paid to computation time reduction by using fewer voxels to calculate the cost function and its derivatives. The optimization methods were tested on manually deformed CT images of the heart, on follow-up CT chest scans, and on MR scans of the prostate acquired using a, T1 and T2 protocol. Registration accuracy is assessed by computing the overlap of segmented edges. Precision and convergence properties were studied by comparing deformation fields. The results show that the Robbins-Monroe method is the best choice in most applications. With this approach, the computation time per iteration can be lowered approximately 500 times without affecting the rate of convergence. From the other methods the quasi-Newton and the nonlinear conjugate gradient method achieve a slightly higher precision, at the price of larger computation times. Mark P. Wachowiak et al and Wang Anna et al, used Particle Swarm Optimization to register multimodal images [111,112]. They also developed two new deterministic, derivative-free, and intrinsically parallel optimization methods for image registration. Dividing RECT angles (DIRECT) is a global technique for linearly bounded problems and multidirectional search (MDS) is a recent local method [111]. The performance of DIRECT, MDS, and hybrid methods using a parallel implementation of Powell's method for local refinement, were also compared by them. Wang Anna et al., computed optimal affine transformation parameters with Niche Particle Swarm Optimization. The experimental results showed that their method has better robustness, and accuracy [112].

9. Modalities Involved

Four classes of registration tasks can be recognized based on the different modalities that are involved. In *mono modal* applications, the images to be registered belong to the same modality, as opposed to *multimodal* registration tasks [104], where the images to be registered stem from two different modalities. The other two are *modality to model* and *model to modality* registration where only one image is involved and the other modality is either a model or the patient himself. The model to modality is used frequently in intra operative registration techniques [111,113]. *Modality to model* can be applied in gathering statistics on tissue morphology [114-119].

9.1. Mono Modal

Mono modal tasks are well suited for growth monitoring, intervention verification, rest-stress comparisons, Ictal - inter Ictal comparisons, subtraction imaging (also DSA, CTA), and many other applications [120,121,122].

9.2. Multi Modal

The applications of multimodal registrations are abundant and diverse, predominantly diagnostic in nature. A coarse division would be into anatomical-anatomical registration, where images showing different aspects of tissue morphology are combined and functional-anatomical, where tissue metabolism and its spatial location relative to anatomical structures are related. Multi-modality image registration and fusion plays an increasingly important role in medicine; 3-D image reconstruction; object recognition and medical image analysis are just a few examples [123,124,125]. Medical images provide essential information for clinical diagnosis. Good image quality can yield more accurate patient information, which can then be used for better clinical decision making. .X-ray Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and Single Photon Emission Computed Tomography (SPECT) are clinically established imaging modalities [123,124,125,126]. Among them, CT and MRI images are anatomical imaging with high spatial resolutions. However their physiological information is limited. On the other hand, although SPECT and PET can provide physiological information, spatial resolutions of both are too poor, to provide clear anatomical information. Thus, it would be advantageous to combine images from different modalities, so that the resulting image can provide both physiological and anatomical information with high spatial resolution for use in clinical diagnosis and therapy [126-131]. Current multi-modal registration techniques such as those based on SSD and Mutual Information attempt to find similarities between images obtained from different modalities in a direct fashion, without a priori knowledge [1]. This is often very difficult as images acquired from different modalities can have very different intensity mappings.

Finding correspondences between the functional and anatomical images is the most important and challenging part of a multimodality registration procedure although an exact one-to-one correspondence exists between them.

10. Subject

Subject refers to the patients, whose images are to be registerd. The images to be registered may be captured from the same patient or from different patients. Based on the subject, registration algorithms can be classified into Intra subject and Inter subject Registration.

10.1. Intra Subject

In the case of intra subject registration the images involved in the registration task are captured from a single patient. It is the most common type of registration task involved in diagnostic, surgical and interventional procedures. Considerable clinical benefits were obtained by accurately aligning images of the same subject acquired with the same modality at different times. Subtle changes in intensity or shape of a structure can be detected easily. This technique is most widely used for aligning serial MR images of the brain [132]. Since the images are acquired using the same modality, an approximate linear relationship will exist between the voxel intensities in one image and voxel intensities in the other. In these cases the Correlation Coefficient (CC) is a good measure of alignment. But it basically involves multiplication of corresponding image intensities. One image is moved with respect to the other until the largest value of the correlation coefficient is found. Statistically speaking, this is where there is the strongest linear relationship between the intensities in one image and the intensities at corresponding locations in the other. Instead of multiplying corresponding intensities, we may subtract them, which lead to another measure, the Sums of Squared intensity Differences (SSD). In this case, alignment is adjusted until the smallest SSD is found. Like subtraction or multiplication the intensities can also be divided. If two images are very similar, their ratio will be most uniform at registration. This is the basis of Woods Ratio Image Uniformity (RIU) algorithm in which the variance of this ratio is calculated. Alignment is adjusted until the smallest variance is found. In early publications this was referred to as the Variance of Intensity Ratios (VIR) algorithm. These algorithms are conceptually very similar. Performance, too, is similar except when the underlying assumptions are violated due to changes in overall image brightness, shading, etc.

10.2. Inter Subject

In the case of inter subject registration the images involved in the registration task are captured from different patients. Normally used in determining changes in shape and size as well as grosser changes in topology. This remains an area of active research with several approaches under investigation. Approaches include extending the rigid-body method to incorporate deformations that follow quadratic and higher order polynomial curves, or a wide range of other, more complicated functions such as Fourier or wavelet basis functions and splines, including radial basis functions such as the thin plate spline and B-spline.

10.3. Atlas

In registration techniques based on atlas matching, one image is acquired from a single patient, and the other image is constructed from an image information database obtained using imaging of many subjects. They are used in the areas of gathering statistics on the size and shape of specific structures, finding (accordingly) anomalous structures, and transferring segmentations from one image to another [133]. A tissue growth model might be used to model differences between different individuals.

11. Object

The object in medical image registration is the part of the anatomy involved. A varied list of objects, are summarized in this section.

11.1. Head

Automatic registration of images of Head are found in G. Eggers, et al [134], Al-maveh et al., registered four head and neck images using a biomechanical model. The accuracy of the centre of mass, location of tumor and parotid glands is improved using Deformable Registration [135]. Choonik Lee et-al, .Ching-Fen et-al, Suzanne van Beek et-al Rob.H.et al, developed algorithms for registration of head and neck images for radio therapy treatment planning [136,137,138,139,140]. Weight loss, tumor shrinkage, and tissue edema induce substantial modification of patient’s anatomy during head and neck Radiotherapy or chemo-radiotherapy. These modifications may impact on the dose distribution to both Target Volumes and Organs at Risk. Adaptive radiotherapy where patients are re-imaged and re-planned several times during the treatment is a possible strategy to improve treatment delivery. It however requires the use of specific deformable registration algorithms that requires proper validation on a clinical material. Pierre Castadot et al. compared 12 deformable registration strategies in adaptive radiation therapy for the treatment of head and neck tumors [141].

11.1.1. Brain

In brain imaging, registration is used to study image variations, ranging from inter subject anatomical comparisons, intra-subject monitoring of pathological development, to matching an observed image with a reference template [1]. In cases of intra-subject or temporal variation registration, observed images could be a time series acquired in a short period of time at one occasion, or a time series acquired at several occasions. Research on the improvement of functional-to-anatomical image registration is now focused on finding appropriate correspondences through more general and reliable similarity measures based upon information theory [142]. Spatial and directional information can be incorporated into MI based similarity measure to improve the accuracy of anatomical to functional image registration . Rigid and affine transformations provide practical bases for robust and reliable functional-to-anatomical registration. However, non rigid registration has been proposed to deal with the effect of nonlinear local distortions in functional images, specifically in EPI sequences used for fMRI [143,144]. Different aspects of brain image registration were discussed in W. Crum. et al [145], P. Hellier et al. [146], S. Robbins et al. [147], M. Yassa, et al. [148], B. Ardekani et al. [149], V. A. Magnotta et al. [150], Jiangang Liu et al. [151].

11.1.2. Retina

In the case of retinal images, area-based approaches are often used in multimodal or temporal image registration applications. Retinal images are registered by Bin Fang et al. [152] using an elastic matching algorithm with reduced computational load. Thitiporn Chanwimaluang et al. used a hybrid method to register retinal images [153]. C.V. Stewart et al used dual-bootstrap iterative closest point algorithm to register retinal images [154]. G.K. Matsopoulos et al., developed an image registration algorithm based on Global Optimization techniques [155]. A new retinal image registration method based on salient feature region was proposed by Jian Zheng et al. [156].

11.1.3. Dental

Intra-oral radiographs can be considered as images of piecewise rigid objects. teeth and jaws are rigid but can be displaced with respect to each other. Therefore MI criteria combined with affine deformations tend to fail, when teeth and jaws move with respect to each other between image acquisitions .W. Jacquet et al., registered Dental images using Focused Mutual Information [157]. Heinz-Theo Luebbers et al., compared various registration techniques used for surgical navigation in Cranio Facial surgery [158]. Vasiliki et-al developed an. Automatic Iterative Point Correspondence algorithm for registering dental sub traction radiotherapy images [159]. An automatic algorithm which is robust to noise was developed by Won-Jin Yi et- al for registering Dental radiographs [160]. Diaa Eldin et al developed an algorithm based on neural networks to match Dental Radio graph images [161]. Georg Eggers et al., used a template based technic for registering images during image guided Maxillofacial surgery [162].Techniques for registering various dental radiographs can be found in Omaima Nomir et al.[163], M. Tsuji et- al., [164]. Yu-Chih Chiang et al. [165].

11.2. Thorax

Image registration and fusion of whole-body FDG PET with thoracic CT would allow combination of anatomic detail from CT with functional PET information, which could lead to improved diagnosis. A practical and fully automated algorithm for the elastic 3-dimensional image registration of whole-body PET and CT images was proposed by Piotr J. Slomka et al. [166]. Non Rigid Registration techniques for registering thoracic images were proposed by G.K.Matsopoulos et al [167], J.S. Silva et al. [168], Thomas Köhler et al [169], A. Moreno et a [170].

11.2.1. Breast

Breast is composed entirely of soft tissues and it easily deforms, so that multimodal imaging requires non rigid registration. Physically deformable breast models are very difficult to implement because of complex patient-specific breast morphology and highly nonlinear and difficult to measure elastic properties of different types of tissues in the breast, as well as explicitly unknown boundary conditions [171]. Co registration of PET and MRI images provides additional information on morphology, vascularization and on dynamic behavior of the suspicious lesion .It also allows more accurate lesion localization, including mapping of hyper- and hypo-metabolic regions as well as better lesion-boundary definition. Such information might be of great value for assessing breast cancer accurately and assessing the need for biopsy [172,173]. Any subsequent biopsy could be precisely guided to the most metabolically active (i.e., the most malignant) region.

The task of registration and fusion of PET and MRI breast images has been addressed by different authors. Baum et al, have estimated fiducial and target registration errors *vs.* number and location of fiducials, and have shown that the steady-state heat transfer approach using external fiducial markers is accurate and it is approximately within 5mm [174,175]. L. Mainardi et al., used Complex Discrete Wavelet Transform based multi resolution algorithm for registering MRI images [176]. Non-rigid registration has also been used to correct for varying amounts of breast deformation in 3D ultrasound acquisition [178].

11.2.2. Cardiac

Cardiac image registration remains a challenge because of the numerous problems related to the different motion sources (patient, respiration, heart) and to the specificity of each imaging modality. Up to now, no general method is able to automatically register any modality with any other modality. Cardiac image registration methods always require a compromise among accuracy, precision, reliability, robustness, and issues such as automation, interactivity, speed, patient-friendliness, etc. Rigid cardiac image registration generally does not describe the spatial relationship between images adequately. Elastic (non rigid) cardiac image registration is needed especially because of cardiac motion; between end-diastole and end-systole (during cardiac cycle), the heart valvular plane moves 9 to 14mm toward the apex and the myocardial walls thicken from approximately 10 to over 15mm [178,179]. Perfusion MR imaging often takes more than three minutes. Breath holding is not possible during the imaging protocol, nor can respiratory gating be used since a high temporal resolution is needed. Therefore, dynamic gated heart images and temporal resolution are degraded by respiration-induced movements during the whole sequence [180]. Deformable model-based approaches for cardiac image registration are particularly promising for elastic 4-D registration of the cardiac images (e.g., to compensate for movement artifacts) [181]. Maria Carla Gilardi et al., proposed a surface matching registration technique based on matching, correspondent anatomical surfaces extracted from transmission (TR) SPECT and PET Cardiac images [182]. Non Rigid Registration techniques for registering Cardiac images were proposed by C.Guetter et al [183], Dimitrios et al. [184], Jasbir Sra et al. [185], and M.J. Ledesma et al. [186].

11.3. Abdomen

A normalized abdominal coordinate system independent of both the abdomen size and the respiratory motion is defined for abdominal atlas mapping in CT and MR volume images was developed by Hongkai Wang et al [187] O. Camara,et al., used a hierarchical segmentation based approach using several thoracic and abdominal structures of CT and emission PET images to initialize a non-linear registration procedure, between these complementary imaging modalities [188]. A novel neuro-fuzzy hybrid transformation model for deformable image registration in intra-operative image guided procedures involving large soft tissue deformation was proposed by Xishi Huang et al [189]. Algorithms for registering abdominal images were developed by T.Kiefer et al. [190], A.Lausch et al. [191] F.Steven et al.[192].

11.3.1. Liver

The effect of breathing motion and dose accumulation on the planned radiotherapy dose to liver tumors and normal tissues using deformable image registration was studied by Michael Velec [193]. The intra hepatic vessel system intervene the whole liver and have complex structures. In contrast to many other organs, the liver possesses not only arteries and veins, but also a third blood vessel system, the portal veins. The spatial relationship of these three kinds of vessel systems is an important issue for the liver surgery, so high quality images of the intra hepatic vessel systems may support the surgeon in planning and implementing liver surgery greatly. So if the vessels from different phases are used in one common model, the image sequences have to be aligned. Each point in one data set must match its anatomically corresponding point in the other data set. Image registration makes all corresponding points in the two images have the same anatomical structure [194]. Algorithms for registering Liver images were proposed by G.P. Penney et al. [195], He Wang et al. [196], Wen-Chi et al. [197], B. Romain et al. [198], Haytham Elhawaryet al. [199], T Böttgeret al. [200].

11.3.2. Kidney

Registration of 4D renal perfusion MR images incorporating saliency measure was done by D.Mahapatra et al. [201]. Their technique produced a better registration result than traditional entropy-based approaches. Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) is an emerging technique for a more accurate assessment of local renal function. However, the measured time intensity curves used for quantification of renal blood flow or glomerlar filtration rate are hampered by motion artefacts, mainly from respiration of the patient. A. D. Merrem et al., proposed a variational approach to image registration in DCE-MRI of the human kidney [202]. Techniques for registering kidney images were proposed by R.E.Ong, et al. [203], Francisco J. Galdames et al. [204], G. Frank et al. [205], Ting Song et al. [206], Y. Sunet al. [207].

11.3.3. Prostate

An accurate, fast, and robust algorithm for registering portal and Computed Tomographic (CT) images for radiotherapy using a combination of sparse and dense field data that complement each other was developed by Sudhakar Chelikani et al. [208]. R. Carlos et al., compared the accuracy of rigid registration with three or six degrees of freedom against elastic registration based on a deformation field modelled using B-Splines, for automated prostate localization in external beam radiotherapy. Here CT and ultrasound images are registered using Mutual information based similarity measure [209]. An almost fully automated 3D non rigid registration algorithm using mutual information and a Thin Plate Spline (TPS) transformation for MR images of the prostate and pelvis were created and evaluated by Baowei Fei et al. [210]. Algorithms for registering Prostate images used in radio therapy planning were developed by M.Jennifer et al. [211], Chao Lu et al. [212], He Wang et al. [213], M. Rex et al. [214], Hyunjin Park et al. [215], H.P. Monique et al. [216], Joakim H Jonsson et al. [217].

11.4. Spine and Vertebrae

In the registration of spine images, intensity-based methods are susceptible to local optima in the cost function and thus need initial transformations that are close to the correct transformation..Fiducial marker-based methods are fast, accurate, and robust, but marker implantation is not always possible, often is considered too invasive to be clinically acceptable, and entails risk [218]. A novel algorithm for registration of speckle-tracked freehand 3D ultrasound to preoperative CT volumes of the spine was proposed by Andrew Lang et al. [219]. A group wise ultra sound to CT registration algorithm for guiding percutaneous spinal interventions was developed by Sean Gill et al. [220]. Elias C. Papadopoulos et al., developed a multilevel registration algorithm for Image-guided, computer-assisted spine surgery, in the setting of degenerative disorders of the lumbar spine [221]. A fast and robust algorithm to register intra operative three-dimensional ultrasound data of the spine with preoperative CT data was proposed by Susanne Winter et al. [222]. A. Yezzi,et al., proposed a variational framework for integrating segmentation and registration through active contours [223].

11.5. Limbs

A new landmark-based elastic registration procedure in which individual bones are registered using Affine registration and soft tissues are elastically registered by A.Miguel et al [224]. A novel method for registering knee images using mutual information was proposed by Janet Goldenstein et al [225]. A three-dimensional magnetic resonance (MR) volume registration algorithm based on normalized cross-correlation used for monitoring hip joint disease was proposed by Masaki Takao et al. [226]. Blumenfeld et al. investigated the feasibility of automatic image registration of MR high-spatial resolution proximal femur trabecular bone images as well as the effects of gray-level interpolation and volume of interest (VOI) misalignment on MR-derived trabecular bone structure parameters. For six subjects in a short-term study, a baseline scan and a follow-up scan of the proximal femur were acquired on the same day. For ten subjects in a long-term study, a follow-up scan of the proximal femur was acquired 1 year after the baseline. An automatic image registration technique, based on mutual information, utilized a baseline and a follow-up scan to compute transform parameters that aligned the two images [227]. A 2D-3D medical image registration method was developed for 3D postoperative analysis of total knee arthroplasty by Youngjun Kim et al. [228]. A three dimensional surface registration technique for estimating knee cartilage volume was proposed by J.L. Jaremko et al. [229].

12. Conclusion

Image registration is one of the most important tasks when integrating and analyzing information from various sources. It is a key stage in image fusion, change detection, super-resolution imaging, and in building image information systems, among others. This paper gives a survey of the classical and recent registration methods, classifying them according to their nature as well as according to the four major registration steps. Although a lot of work has been done, automatic image registration still remains an open problem. Also, the problems due to imaging conditions, different movement artifacts, and elasticity of the body, lungs, and heart which cause different tissue deformations that are not possible to model using rigid registration methods. There is considerable research going on in extending the use of intensity-based registration algorithms to non rigid transformations. Registration of images with complex nonlinear and local distortions, multimodal registration, and registration of N-Dimensional images belong to the most challenging tasks at this moment. The major difficulty of N-Dimemsional image registration resides in its computational complexity. Although the speed of computers has been growing, the need to decrease the computational time of methods persists. The complexity of methods as well as the size of data still grows (the higher resolution, higher dimensionality, larger size of scanned areas). Moreover, the demand for higher robustness and accuracy of the registration usually enforces solutions utilizing the iterations or backtracking, which also produces increase of computational complexity of the method.

One of the main challenges that researchers have pointed out and developers have proposed for future research is the effect of spatial normalization on functional maps. The resolution of functional imaging and the accuracy of functional analysis techniques need to be improved, which depends on the accuracy and reliability of spatial normalization. Analysis of functional maps in studies of diseases such as dementia, in which severe anatomical differences exist between healthy and diseased brains, may lead to spurious results or invalid interpretations and conclusions, in which anatomical differences are mischaracterized as functional differences. One approach to overcome this problem is the use of subpopulation or disease-specific atlases. Cortical surface registration techniques are being incorporated for routine use in spatial normalization for functional analysis.

The convoluted structure of the cortical surface and the level of variability versus homology in sulcal and gyral patterns in the brain is a real challenge for cortical surface registration. Development of methods such as cortical reconstruction, segmentation, tissue classification, and flattening and mapping to planar, ellipsoidal or spherical surfaces, utilizes powerful tools from differential geometry, image processing and computer vision, including deformable active and statistical shape models. Topology correction in cortical reconstruction, finding appropriate correspondences in reconstructed and mapped structures, sulcal modeling, and descriptions and subsequent mapping to standard cortical structural maps are required. These techniques are expected to be used both for volumetric spatial normalization in group analysis studies, and for making automatic activation labeling tools for the last stage of functional localization. Technical advances in functional brain imaging and automatic functional localization are leading to clinical and scientific applications with higher spatial and temporal resolutions. The construction of standard and subpopulation brain atlases and brain templates, functional-to-anatomical registration, and spatial normalization through volumetric registration and cortical surface registration are deemed important fields of study in this burgeoning area of research.

Increasing use of dynamic acquisitions such as perfusion MRI will necessitate use of registration algorithms to correct for patient motion. Non-affine registration is likely to find increasing application in the study of development, ageing and monitoring changes due to disease progression and response to treatment. In these latter applications, the transformation itself may have more clinical benefit than the transformed images, as this will quantify the changes in structure in a given patient. New developments in imaging technology may open up new applications of image registration. It has recently been shown that very high field whole-body MR scanners can produce high signal to noise ratio images of the brain with $100\,\mu$m resolution .Intra modality registration of these images may open up new applications such as monitoring change in small blood vessels. Ultrasound images have been largely ignored by image registration researchers up until now, the increasing quality of ultrasound images and its low cost makes this a fertile area for both intra modality and inter modality applications.

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