An Overview of Medical Image Registration Methods

J. B. Antoine Maintz[1] and Max A. Viergever

Imaging Science Department, Imaging Center Utrecht

Abstract

The purpose of this paper is to present an overview of existing medical image registration methods. These methods will be classified according to a model based on nine salient criteria, the main dichotomy of which is *extrinsic* versus *intrinsic* methods. The statistics of the classification show definite trends in the evolving registration techniques, which will be discussed. At this moment, the bulk of interesting intrinsic methods is either based on segmented points or surfaces, or on techniques endeavoring to use the full information content of the images involved.

1 Introduction

Within the current clinical setting, medical imaging is a vital component of a large number of applications. Such applications occur throughout the clinical track of events; not only within clinical diagnostis settings, but prominently so in the area of planning, consummation, and evaluation of surgical and radiotherapeutical procedures.

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

An example of the use of registering different modalities can be found in radiotherapy treatment planning, where currently CT is used almost exclusively. However, the use of MR and CT combined would be beneficial, as the former is better suited for delineation of tumor tissue (and has in general better soft tissue contrast), while the latter is needed for accurate computation of the radiation dose. Another eminent example is in the area of epilepsy surgery. Patients may undergo various MR, CT, and DSA studies for anatomical reference; ictal and interictal SPECT studies; MEG and extra and/or intra-cranial (subdural or depth) EEG, as well as ^{18}FDG and/or ^{11}C-Flumazenil PET studies. Registration of the images from practically any combination will benefit the surgeon.

In this paper, our aim is to classify registration methods, and give an overview of current techniques.

2 Classification of registration methods

The classification of registration methods used in this chapter is based on the criteria formulated by van den Elsen, Pol & and Viergever [1]. A version considerably augmented and detailed is presented. Nine basic criteria are used, which can each be subdivided again. The nine criteria and primary subdivisions are given is figure 1.

In the following sections, we will discuss the separate criteria in more detail.

3 Dimensionality

3.1 Spatial registration methods

The main division here is whether all dimensions are spatial, or that time is an added dimension. In either case, the problem can be further categorized depending on the number of spatial dimensions involved. Most current papers focus on the *3D/3D* registration of two images (no time involved). *3D/3D* registration normally applies to the registration of two tomographic datasets, or the registration of a single tomographic image to any spatially defined information, *e.g.*, a vector obtained from EEG data. *2D/2D* registration may apply to separate slices from tomographic data, or intrinsically 2D images like portal images. Compared to *3D/3D* registration, *2D/2D* registration is less complex by

[1]Corresponding author: J.B.A. Maintz, University Hospital Utrecht, Room E.01.334, Heidelberglaan 100, NL-3584 CX, Utrecht, the Netherlands. email: twan@cv.ruu.nl

Classification for medical registration methods

I. Dimensionality

- **a.** Spatial dimensions only:
  1. 2D/2D
  2. 2D/3D
  3. 3D/3D
- **b.** Time series (more than two images), with spatial dimensions:
  1. 2D/2D
  2. 2D/3D
  3. 3D/3D

II. Nature of registration basis

- **a.** Extrinsic
  1. Invasive
     - **A.** Stereotactic frame
     - **B.** Fiducials (screw markers)
  2. Non-invasive
     - **A.** Mould, frame, dental adapter, *etc.*
     - **B.** Fiducials (skin markers)
- **b.** Intrinsic
  1. Landmark based
     - **A.** Anatomical
     - **B.** Geometrical
  2. Segmentation based
     - **A.** Rigid models (points, curves, surfaces)
     - **B.** Deformable models (snakes, nets)
  3. Voxel property based
     - **A.** Reduction to scalars/vectors (moments, principal axes)
     - **B.** Using full image content
- **c.** Non-image based (calibrated coordinate systems)

III. Nature of transformation

- **a.** Rigid
- **b.** Affine
- **c.** Projective
- **d.** Curved

IV. Domain of transformation

- **a.** Local
- **b.** Global

V. Interaction

- **a.** Interactive
  1. Initialization supplied
  2. No initialization supplied
- **b.** Semi-automatic
  1. User initializing
  2. User steering/correcting
  3. Both
- **c.** Automatic

VI. Optimization procedure

- **a.** Parameters computed
- **b.** Parameters searched for

VII. Modalities involved

- **a.** Mono-modal
  1. Autoradiographic
  2. CT or CTA
  3. MR
  4. PET
  5. Portal
  6. SPECT
  7. US
  8. Video
  9. X-ray or DSA
- **b.** Multi-modal
  1. CT—MR
  2. CT—PET
  3. CT—SPECT
  4. DSA—MR
  5. PET—MR
  6. PET—US
  7. SPECT—MR
  8. SPECT—US
  9. TMS—MR
  10. US—CT
  11. US—MR
  12. X-ray—CT
  13. X-ray—MR
  14. X-ray—portal
  15. X-ray—US
  16. Video—CT
  17. Video—MR
- **c.** Modality to model
  1. CT
  2. MR
  3. SPECT
  4. X-ray
- **d.** Patient to modality
  1. CT
  2. MR
  3. PET
  4. Portal
  5. X-ray

VIII. Subject

- **a.** Intrasubject (1)
- **b.** Intersubject
- **c.** Atlas

IX. Object

- **a.** Head
  1. Brain or skull
  2. Eye
  3. Dental
- **b.** Thorax
  1. Entire
  2. Cardiac
  3. Breast
- **c.** Abdomen
  1. General
  2. Kidney
  3. Liver
- **d.** Pelvis and perineum
- **e.** Limbs (orthopedic)
  1. General
  2. Femur
  3. Humerus
  4. Hand
- **f.** Spine and vertebrae

- brief registration criterion description
- brief optimization procedure description
- validation (if any) used

Registration:
1. Problem statement (I,III,VII,VIII,IX)
2. Criterion (paradigm) (II,III,IV,V)
3. Optimization (V,VI)

Related:
- Validation
- Visualization/fusion

Figure 1: *Classification of registration methods. See text for details.*

an order of magnitude both where the number of parameters and the volume of the data are concerned, so obtaining a registration is in many cases easier and faster than in the *3D/3D* case. We reserve *2D/3D* registration for the direct alignment of spatial data to projective data, (*e.g.,* a pre-operative CT image to an intra-operative X-ray image), or the alignment a single tomographic slice to spatial data. Since most *2D/3D* applications concern intra-operative procedures within the operating theater, they are heavily time-constrained and consequently have a strong focus on speed issues connected to the computation of the paradigm and the optimization. The majority of applications outside the operating theater and radiotherapy setting allow for off-line registration, so speed issues need only be addressed as constrained by clinical routine.

3.2 Registration of time series

Time series of images are acquired for various reasons, such as monitoring of bone growth in children (long time interval), monitoring of tumor growth (medium interval), post-operative monitoring of healing (short interval), or observing the passing of an injected bolus trough a vessel tree (ultra-short interval). If two images need to be compared, registration will be necessary except in instances of ultra-short time series, where the patient does not leave the scanner between the acquisition of two images. The same observations as for spatial-only registrations apply.

4 Nature of registration basis

4.1 Extrinsic registration methods

Image based registration can be divided into *extrinsic*, *i.e.,* based on foreign objects introduced into the imaged space, and *intrinsic* methods, *i.e.,* based on the image information as generated by the patient.

Extrinsic methods rely on artificial objects attached to the patient, objects which are designed to be well visible and accurately detectable in all of the pertinent modalities. As such, the registration of the acquired images is comparatively easy, fast, can usually be automated, and, since the registration parameters can often be computed explicitly, has no need for complex optimization algorithms. The main drawbacks of extrinsic registration are the prospective character, *i.e.,* provisions must be made in the pre-acquisition phase, and the often invasive character of the marker objects. Non-invasive markers can be used, but as a rule are less accurate. A commonly used fiducial object is a *stereotactic frame* [2, 3, 4, 5, 6, 7, 8, 9] screwed rigidly to the patient's outer skull table, a device which until recently provided the best "gold standard" for registration accuracy. Such frames are used for localization and guidance purposes in neurosurgery. Since neurosurgery is one of the main application areas of registration, the use of a stereotactic frame in the registration task does not add an additional invasive strain to the patient. However, the mounting of a frame for the sole purpose of registration is not permissible. Sometimes other invasive objects are used, such as screw-mounted markers [10, 11, 12, 13, 14, 15, 16, 17, 18], but usually non-invasive marking devices are reverted to. Most popular amongst these are markers glued to the skin [19, 20, 21, 22, 23, 24, 13, 25, 26, 27, 28, 29, 30], but larger devices that can be fitted snugly to the patient, like individualized foam moulds, head holder frames, and dental adapters have also been used, although they are little reported on in recent literature [31, 32, 33, 34, 35, 19].

Since extrinsic methods by definition cannot include patient related image information, the nature of the registration transformation is often restricted to be rigid (translations and rotations only). Furthermore, if they 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 on. Because of the rigid-transformation constraint, and various practical considerations, use of extrinsic 3D/3D methods is largely limited to brain and orthopedic [17, 18] imaging, although markers can often be used in projective (2D) imaging of any body area. 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

Intrinsic methods rely on patient generated image content only. Registration can be based on a limited set of identified salient points *(landmarks)*, on the alignment of segmented binary structures *(segmentation based)*, most commonly object surfaces, or directly onto measures computed from the image grey values *(voxel property based)*.

4.2.1 Landmark based registration methods

Landmarks can be *anatomical*, *i.e.*, salient and accurately locatable points of the morphology of the visible anatomy, usually identified interactively by the user [35, 19, 36, 37, 20, 38, 39, 40, 41, 42, 43, 44, 45, 46, 23, 47, 48, 49, 50, 6, 25, 26, 51, 52, 53, 27, 54, 55, 56, 57, 28, 8, 58, 59, 60, 61, 62, 63, 9, 64], or *geometrical*, *i.e.*, points at the locus of the optimum of some geometric property, *e.g.*, local curvature extrema, corners, *etc*, generally localized in an automatic fashion [65, 66, 67, 68, 69, 70, 71, 72, 73, 74]. Technically, the identification of landmark points is a segmentation procedure, but we reserve the classification *segmentation based* registration for methods relating to segmentation of structures of higher order, *i.e.*, curves, surfaces, and volumes. Landmark based registration is versatile in the sense that it –at least in theory– can be applied to any image, no matter what the object or subject is. Landmark based methods are mostly used to find rigid or affine transformations. If the sets of points are large enough, they can theoretically be used for more complex transformations. Anatomical landmarks are also often used in combination with an entirely different registration basis [35, 19, 23, 49, 53, 55, 58, 59, 60]: methods that rely on optimization of a parameter space that is not quasi-convex are prone to sometimes get stuck in local optima, possibly resulting in a large mismatch. By constraining the search space according to anatomical landmarks, such mismatches are unlikely to occur. Moreover, the search procedure can be sped up considerably. A drawback is that user interaction is usually required for the identification of the landmarks.

In landmark based registration, the set of identified points is sparse compared to the original image content, which makes for relatively fast optimization procedures. Such algorithms optimize measures such as the average distance (L_2 norm) between each landmark and its closest counterpart (the *Procrustean* metric), or iterated minimal landmark distances. For the optimization of the latter measure the *Iterative closest point* (ICP) algorithm [75] and derived methods are popular. Its popularity can be accredited to its versatility –it can be used for point sets, and implicitly and explicitly defined curves, surfaces and volumes–, computational speed, and ease of implementation. The Procrustean optimum can sometimes be computed, using *e.g.*, Arun's method [76], but is more commonly searched for using general optimization techniques. Such techniques are referred to in section 7. Yet other methods perform landmark registration by testing a number of likely transformation hypotheses, which can, *e.g.*, be formulated by aligning three randomly picked points from each point set involved. Common optimization methods here are quasi-exhaustive searches, graph matching and dynamic programming approaches.

4.2.2 Segmentation based registration methods

Segmentation based registration methods can be *rigid model based* [77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 14, 117, 118, 119, 120, 121, 122, 123, 124, 125, 6, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 7, 140, 141, 52, 53, 142, 143, 144, 145, 16, 146, 147, 148, 149, 150, 151, 17, 152, 153, 154, 155, 156, 157, 158, 8, 159, 58, 160, 60, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173], where anatomically the same structures (mostly surfaces) are extracted from both images to be registered, and used as sole input for the alignment procedure. They can also be *deformable model based* [174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190], where an extracted structure (also mostly surfaces, and curves) from one image is elastically deformed to fit the second image. The *rigid model based* approaches are probably the most popular methods currently in clinical use. Their popularity relative to other approaches is probably for a large part due to the success of the "head-hat" method as introduced by Pelizzari and co-workers [77, 78, 191, 192], 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 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 popularity cause is the fast *Chamfer matching* technique for alignment of binary structures by means of a distance transform, introduced by Borgefors [193]. A drawback of segmentation based methods is that the registration accuracy is limited to the accuracy of the segmentation step. In theory, segmentation based registration is applicable to images of many areas of the body, yet in practice the application areas have largely been limited to neuroimaging and orthopedic imaging. The methods are commonly automated but for the segmentation step, which is performed semi-automatically most of the times.

With *deformable models* however, the optimization criterion is different: it is always locally defined and computed, and the deformation is constrained by elastic modeling constraints (by a regularization term) imposed onto the segmented curve or surface. Deformable curves appear in literature as *snakes* or *active contours*; 3D deformable models are sometimes referred to as *nets*. To ease the physical modeling, the data structure of deformable models is not commonly a point set. Instead, it is often represented using localized functions such as splines. The deformation process is always done iteratively, small deformations at a time. Deformable model approaches are based on a *template model* that needs to be defined in one image. After this, two types of approaches can be identified: the template is either deformed to match a segmented structure in the second image [176, 177, 179, 180, 181, 182, 184, 185, 186, 187, 188, 190], or the second image is used *unsegmented* [174, 175, 178]. In the latter case, the fit criterion of the template can be, *e.g.*, to lie on an edge region in the second image. Opposed to registration based on extracted rigid models, which is mainly suited for intrasubject registration, deformable models are in theory very well suited for intersubject and atlas[1] registration, as well as for registration of a template obtained from a patient to a mathematically defined general model of the templated anatomy. A drawback of deformable models is that they often need a good initial position in order to properly converge, which is generally realized by (rigid) pre-registration of the images involved. Another disadvantage is that the local deformation of the template can be unpredictably erratic if the target structure differs sufficiently from the template structure. A typical error is that the deformable model matches the anatomy perfectly, except in the one interesting image area where a large tumor growth has appeared. In intrasubject matching of, *e.g.*, the cortical surface, this may result in entire gyri being missed or misplaced. The solution may lie in locally adapting the elasticity constraints [181, 194]. Deformable models are best suited to find local curved transformations between images, and less so for finding (global) rigid or affine transformations. They can be used on almost any anatomical area or modality, and are usually automated but for the segmentation step. In the current literature the major applications are registration of bone contours obtained from CT[2], and cortical registration of MR images [174, 177, 178, 179, 184, 185, 186, 187, 188, 190]. Deformable models are ideally suited for the former application, as the bone contours are easily extracted from the CT, and there are often no other contours near that disturb the proper deformation convergence. The latter application is important because if a cortical registration between two brains can be found, a segmentation of one cortex can be instantly transfered to the other.

4.2.3 Voxel property based registration methods

The *voxel property based* registration methods stand apart from the other intrinsic methods[3] by the fact that they operate directly on the image grey values, without prior data reduction by the user or segmentation. There are two distinct approaches: the first is to immediately *reduce* the image grey value content to a representative set of scalars and orientations, the second is to use the full image content throughout the registration process.

Principal axes and moments based methods are the prime examples of *reductive* registration methods. Within these methods the image center of gravity and its principal orientations (principal axes) are computed from the image zeroth and first order moments. Registration is then performed by aligning the center of gravity and the principal orientations [195, 196, 98, 99, 197, 198, 199, 200, 201]. Sometimes, higher order moments are also computed and used in the process. The result is usually not very accurate, and the method is not equipped to handle differences in scanned volume well, although some authors attempt to remedy this latter problem. Despite its drawbacks, principal axes methods are widely used in registration problems that require no high accuracy, because of the automatic and very fast nature of its use, and the easy implementation. The method is used primarily in the re-alignment of scintigraphic cardiac studies (even intersubject) [199], and as a coarse pre-registration in various other registration areas [196, 98, 99, 197, 199, 200]. Moment based methods also appear as hybridly classified registration methods that use segmented or binarized image data for input. In many applications, pre-segmentation is mandatory in order for moment based methods to produce acceptable results.

Voxel property based methods using the full image content are the most interesting methods researched currently. Theoretically, these are the most flexible of registration methods, since they –unlike all other methods mentioned– do not start with reducing the grey valued image to relatively sparse extracted information, but use all of the available information throughout the registration process. Although voxel property based methods have been around a long time, their use in extensive 3D/3D clinical applications has been limited by the considerable computational costs. An increasing clinical call for accurate and retrospective registration, along with the development of ever-faster computers with large internal memories, have enabled full-image-content methods to be used in clinical practice, although they have not yet been introduced in time-constrained applications such as intra-operative 2D/3D registration. Methods using the full image content can be applied in almost any medical application area, using any type of transformation.

[1] Intersubject and atlas registration is covered in section9.

[2] *e.g.*, see [63]

[3] Except some instances of geometric landmark registration.

However, such a statement is largely merited by the fact that “full-image-content based” is a very gross classifier. The real versatility of a method can only be established on an individual basis. Many recent papers report on applications that are tailored for rigid or affine global registration of 3D images of the head. Nearly all presented methods are automatic, although hybrid approaches (*e.g.*, including an interactive landmark based pre-registration) are being suggested [202]. While the methods theoretically support curved transformations and intersubject registration, we have encountered only few publications on this.

As concerns full-image-content based voxel property registration methods, literature reports on the following paradigms being used ($*$ = most likely restricted to monomodal applications)

- Cross-correlation (of original images or extracted feature images) [203, 204, 205, 206, 207, 208, 209, 210, 196, 211, 212, 213, 214, 215, 49, 216, 217, 197, 218, 132, 131, 219, 220, 221, 7, 55, 222, 223, 224, 225, 200, 226, 227, 228, 229].
- Fourier domain based cross-correlation, and phase-only correlation [230, 231, 232, 228, 233, 234].
- Minimization of variance of intensity ratios [207, 90, 235, 236, 224, 225, 237].
- Minimization of variance of grey values within segments [238, 130].
- $*$ Minimization of the histogram entropy of difference images [239].
- Histogram clustering and minimization of histogram dispersion [207, 240, 241, 242, 243, 224, 225, 228].
- Maximization of mutual information (relative entropy) of the histogram [244, 245, 246, 247, 248, 249, 202, 250, 251].
- $*$ Maximization of zero crossings in difference images (Stochastic sign change (SSC), and Deterministic sign change (DSC) criterion) [252, 253, 254, 208, 255, 256, 223, 257].
- $*$ Cepstral echo filtering [258].
- $*$ Determination of the optic flow field [259, 260].
- $*$ Minimization of the absolute or squared intensity differences [255, 261, 96, 49, 262, 263, 264, 265, 266, 267, 268, 143, 199, 269, 59, 270, 271].
- $*$ Matching local low-order Taylor expansions determined by the image grey values [272].
- Implicitly using surface registration by interpreting a 3D image as an instance of a surface in 4D space [273].

4.3 Non-image based registration

It seems paradoxical that registration of multimodal images can be *non-image based*, but it is possible if the imaging coordinate systems of the two scanners involved are somehow calibrated to each other. This usually necessitates the scanners to be brought in to the same physical location, and the assumption that the patient remain motionless between both acquisitions. These are prohibitive prerequisites in nearly all applications, but they can be sufficiently met in applications involving the use of ultrasound [109, 274, 62]. Since ultrasound systems can come as hand-held devices that are equipped with a spatial (optical) localization system, they are easily calibrated, and can be used while the patient is immobilized on the CT, MR or operating gantry. The technique of calibrated coordinate systems is also often used in registering the position of surgical tools mounted on a robot arm to images[4].

[4] For instance [275, 9]. See computer aided surgery literature [276] for more complete references.

5 Nature and domain of the transformation

5.1 Nature of the transformation

An image coordinate transformation is called *rigid*, when only translations and rotations[5] are allowed. If the transformation maps parallel lines onto parallel lines it is called *affine*. If it maps lines onto lines, it is called *projective*. Finally, if it maps lines onto curves, it is called *curved* or *elastic*. Each type of transformation contains as special cases the ones described before it, *e.g.*, the rigid transformation is a special kind of affine transformation. A composition of more than one transformation can be categorized as a single transformation of the most complex type in the composition, *e.g.*, a composition of a projective and an affine transformation is a projective transformation, and a composition of rigid transformations is again a rigid transformation.

A rigid or affine 3D transformation can be described using a single constant matrix (a) equation: $y_i = a_{ij}x_j$, where x and y are the old and new coordinate vectors. In the rigid case, this equation is constrained as:

$$\begin{pmatrix} y_1 \\ y_2 \\ y_3 \\ 1 \end{pmatrix} = \left(\begin{array}{ccc|c} & r & & t \\ \hline 0 & 0 & 0 & 1 \end{array}\right) \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ 1 \end{pmatrix},$$

where t is an arbitrary translation vector, and r is a 3×3 rotation matrix defined by:

$$r_{il} = r^{(1)}_{ij} r^{(2)}_{jk} r^{(3)}_{kl}, \qquad r^{(1)} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & \cos\alpha_1 & -\sin\alpha_1 \\ 0 & \sin\alpha_1 & \cos\alpha_1 \end{pmatrix},$$

$$r^{(2)} = \begin{pmatrix} \cos\alpha_2 & 0 & -\sin\alpha_2 \\ 0 & 1 & 0 \\ \sin\alpha_2 & 0 & \cos\alpha_2 \end{pmatrix}, \quad r^{(3)} = \begin{pmatrix} \cos\alpha_3 & -\sin\alpha_3 & 0 \\ \sin\alpha_3 & \cos\alpha_3 & 0 \\ 0 & 0 & 1 \end{pmatrix},$$

i.e., $r^{(i)}$ rotates the image around axis i by an angle α_i. In the affine case, r is unrestricted. In the projective case, we can only use a constant matrix representation if employing homogeneous coordinates: $y_i = u_i/u_4, u_i = a_{ij}x_j$, where a is an arbitrary 4×4 constant matrix. Curved transformations cannot in general be represented using constant matrices. Most applications represent curved transformations in terms of a local *vector displacement* (disparity) field: $y_i = x_i + t_i(x)$, or as polynomial transformations in terms of the old coordinates.

5.2 Domain of the transformation

A transformation is called *global* if it applies to the entire image, and *local* if subsections of the image each have their own transformations defined. Figure 2 shows examples of all transformation types mentioned.

5.3 General transformation observations

Local transformations are seldom used directly, because they may violate the local continuity and bijectiveness of the transformations, which impairs straightforward image resampling when applying the transformation to the image. The term *local transformation* is reserved for transformations that are composites of *at least* two transformations determined on sub-images that cannot be generally described as a global transformation. Hence, a *single* transformation computed on some volume of interest of an image, is a *global* transformation, except that "global" now refers to the new image, which is a sub-image of the original. This definition, perhaps confusingly, does not impair a global transformation to be computed locally, *e.g.*, some applications compute a global rigid transformation of an image of the entire head based on computations done in the area of the facial surface only. Local rigid, affine, and projective transformations occur only rarely in the literature, although local rigid transformations may appear embedded in local curved transformations [181, 194]. Some problems that are intrinsically locally rigid (such as the individual vertebrae in an image of the spinal column) are in registration tasks often solved by splitting the image in images meeting the global rigid body constraint.

[5] and, technically, reflections, but this is disregarded in our formulation, since they do not apply to the general medical image registration problem.

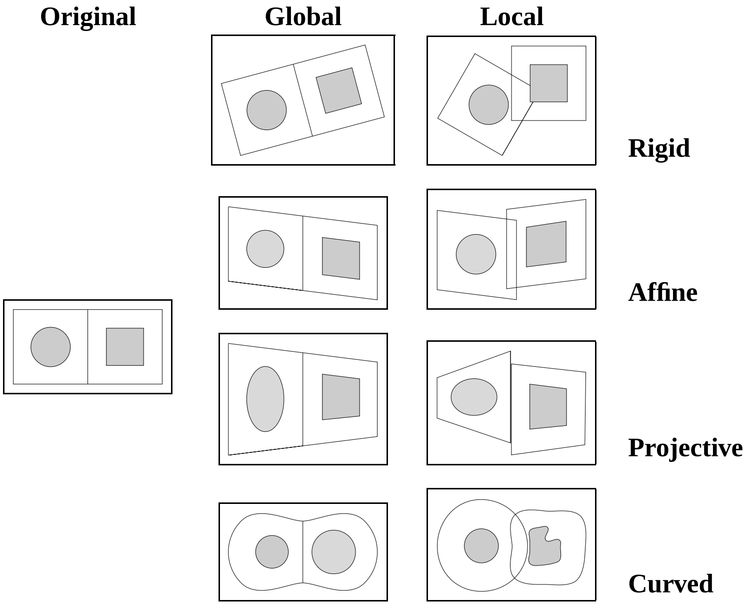

Figure 2: Examples of 2D transformations.

In recently published registration papers, as a rule, rigid and affine transformations are global, and curved transformations are local. This makes sense, given the physical model underlying the curved transformation type, and given that the rigid body constraint is –globally, or in well defined sub-images– approximately met in many common medical images. Affine transformations are typically used in instances of rigid body movement where the image scaling factors are unknown or suspected to be incorrect, (notably in MR images because of geometric distortions). The projective transformation type has no real physical basis in image registration except for *2D/3D* registration, but 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.

Since local information of the anatomy is essential to provide an accurate local curved transformation, applications are nearly always *intrinsic*, mostly *deformable model based* or *using the full image content*, and mostly semi-automatic, requiring a user-identified initialization. They appear almost solely using anatomical images (CT, MR) of the head, and are excellently suited for intersubject and image to atlas registration. Many methods require a pre-registration (initialization) using a rigid or affine transformation.

The global rigid transformation is used most frequently in registration applications. It is popular because in many common medical images the rigid body constraint is, at least to a good approximation, satisfied. 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.

6 Interaction

Concerning registration algorithms, three levels of interaction can be recognized. *Automatic*, where the user only supplies the algorithm with the image data and possibly information on the image acquisition. *Interactive*, where the user does the registration himself, assisted by software supplying a visual or numerical impression of the current transformation, and possibly an initial transformation guess. *Semi-automatic*, where the interaction required can be of two different natures: the user needs to *initialize* the algorithm, *e.g.,* by segmenting the data, or *steer* the algorithm, *e.g.,* by rejecting or accepting suggested registration hypotheses.

Many authors strive for fully automated algorithms, but it can be discussed whether this is wished for in *all* current clinical applications. The argument is that many current methods have a trade-off between minimal interaction and speed, accuracy, or robustness. Some methods would doubtlessly benefit if the user were "kept in the loop", steering the optimization, narrowing search space, or rejecting mismatches. On the other hand, many methods spent over 90% of their computation time examining registrations at a resolution level that would hardly benefit from human intervention. If they perform robustly, such methods are better left automated. Furthermore, many applications require registration algorithms to operate objectively, and thus allow no human interaction. Human interaction also complicates the validation of registration methods, inasmuch as it is a parameter not easily quantified or controlled.

Extrinsic methods are often easily *automated*, since the marker objects are designed to be well visible and detectable in the images involved[6]. Sometimes users are required to roughly point out the marker region, or supply a seed point located in the marker (*semi-automatic*). Of the *intrinsic* methods, the *anatomical landmark* and *segmentation based* methods are commonly *semi-automatic (user initializing)*, and the *geometrical landmark* and *voxel property based* methods are usually *automated*. Fully *interactive* methods are reported on very little in the recent literature [45, 50, 56]. Perhaps, like many methods that rely primarily on the proper use of good visualization software, they are considered trivial.

7 Optimization procedure

VI. Optimization procedure

- **a.** Parameters computed
- **b.** Parameters searched for

The parameters that make up the registration transformation can either be *computed* directly, *i.e.*, determined in an explicit fashion from the available data, or *searched for*, *i.e.*, determined by finding an optimum of some function defined on the parameter space. In the former case, the manner of computation is completely determined by the paradigm. The only general remark we can make is that the use of *computation* methods is restricted almost completely to applications relying on very sparse information, *e.g.*, small point sets[7]. In the case of *searching* optimization methods, most registration methods are able to formulate the paradigm in a standard mathematical function of the transformation parameters to be optimized. This function attempts to quantify the similarity as dictated by the paradigm between two images given a certain transformation. Such functions are generally less complex in monomodal registration applications, since the similarity is more straightforward to define. Hopefully, the similarity function is well-behaved (quasi-convex) so one of the standard and well-documented optimization techniques can be used. Popular techniques are Powell's method [78, 37, 94, 98, 99, 109, 111, 114, 215, 132, 131, 244, 145, 257, 164, 226, 248], the Downhill Simplex method [37, 89, 90, 255, 11, 111, 114, 13, 54, 199, 270], Brent's method and series of one-dimensional searches [204, 209, 67, 120, 70, 130, 55, 227], Levenberg-Marquardt optimization [176, 106, 107, 123, 124, 182, 52, 53, 144, 269, 170, 172], Newton-Raphson iteration [42, 235, 237], stochastic search methods [92, 245, 246, 247, 250, 251], gradient descent methods [129, 223, 239, 59, 186], genetic methods [90, 240, 241, 126, 143, 277], simulated annealing [116], geometric hashing [79, 81, 148], and quasi-exhaustive search methods [205, 206, 208, 238, 213, 214, 117, 216, 217, 221, 222, 200, 229]. Many of these methods are documented in [278]. Frequent additions are multi-resolution (*e.g.*, pyramid) and multi-scale approaches to speed up convergence, to reduce the number of transformations to be examined (which is especially important in the quasi-exhaustive search methods) and to avoid local minima. Some registration methods employ non-standard optimization methods that are designed specifically for the similarity function at hand, such as the ICP algorithm [75, 121, 100, 16, 148, 152, 133, 134, 279, 137, 18, 273, 162, 166], created for *rigid model* based registration. Many applications use more than one optimization technique, frequently a fast but coarse technique followed by an accurate yet slow one.

8 Modalities involved in the registration

Note: The lists of modalities in figure 1, in exception, are not meant to be theoretically complete, but give the modality instances encountered in recent literature.

[6] see, *e.g.*, [29]
[7] see, *e.g.*, [76, 36, 44]

Four classes of registration tasks can be recognized based on the modalities that are involved. In *monomodal* applications, the images to be registered belong to the same modality, as opposed to *multimodal* registration tasks, where the images to be registered stem from two different modalities. In *modality to model* and *patient to modality* registration only one image is involved and the other "modality" is either a model or the patient himself. Hence we use the term "modality" in a loose sense, not only applying to acquired images, but also to mathematical models of anatomy or physiology, and even to the patient himself. Such inclusions are necessary to properly type-cast the four categories according to the actual registration task to be solved. At a first glance, this classification may seem paradoxical; *patient to modality* may seem a registration task appearing in any application. However, the classification is disjunct and closed if only the *actual coordinate systems that need to be related are considered* , *i.e.*, the coordinate systems referring to the actual modalities named in the *problem statement*. For example:

- For diagnostic purposes, two myocardial SPECT images are acquired of the patient, under rest and stress conditions. Their registration is a monomodal application.
- To relate an area of dysfunction to anatomy, a PET image is registered to an MR image. This is a multimodal application.
- To register an MR to a PET image, a PET image image is first *simulated* from the MR image, and the real and simulated PET images are registered. This is still a multimodal application.
- An example of modality to model is the registration of an MR brain image to a mathematically defined compartimental model of gross brain structures.
- In radiotherapy treatment, the patient can be positioned with the aid of registration of in-position X-ray simulator images to a pre-treatment anatomical image. Although the registration task is performed using only the images acquired, the actual task of patient positioning is clearly an example of *patient to modality* registration.

The *patient to modality* registration tasks appear almost exclusively in intra-operative [24, 48, 110, 215, 115, 280, 13, 121, 128, 134, 133, 182, 279, 25, 26, 53, 142, 281, 282, 15, 283, 150, 17, 152, 60, 30, 169, 276, 9] and radiotherapy [40, 10, 11, 156, 158, 164] applications. *Modality to model* can be applied in gathering statistics on tissue morphology (*e.g.*, for finding anomalies relative to normalized structures), and to segmentation tasks [174, 151, 72, 186, 168]. *Monomodal* tasks are well suited for growth monitoring, intervention verification, rest-stress comparisons, ictal-interictal comparisons, subtraction imaging (also DSA, CTA), and many other applications. The applications of multimodal registration 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

9 Subject

VIII. Subject

  a. Intrasubject

  b. Intersubject

  c. Atlas

When all of the images involved in a registration task are acquired of a single patient, we refer to it as *intrasubject* registration. If the registration is accomplished using two images of different patients (or a patient and a model), this is referred to as *intersubject* registration. If one image is acquired from a single patient, and the other image is somehow constructed from an image information database obtained using imaging of many subjects, we name it *atlas* registration. In literature, many instances of registration of a patient image to an image of a "normal" subject is termed atlas registration. Although this definition is as good as ours, we refer to this type of registration as *intersubject*, to keep the class distinctions clear. *Intrasubject* registration is by far the most common of the three, used in almost any type of diagnostic and interventional procedure. *Intersubject* [174, 84, 92, 124, 123, 179, 220, 51, 265, 184, 185, 72, 160, 63, 88, 271, 190] and *atlas* registration [211, 212, 177, 178, 259, 263, 264, 199, 59, 186, 187, 273] appear mostly in *3D/3D MR* *or CT brain image* applications. The nature of the registration transformation is mostly *curved*; these applications are always *intrinsic*, either *segmentation based* or *voxel property based, using the full image content.* A proper (manual) initialization is frequently desired. Some applications use *rigid* transforms, but their application is limited. Others use *anatomical landmarks* for a deformation basis of a *curved* transformation; unfortunately such applications often require the transformation in large image areas to be interpolated from the nearest landmark transformations, which may prove unreliable. The use of *intersubject* and *atlas* matching can notably be found 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.

10 Object

The list in figure 1 is not theoretically complete, but composed of those imaging areas encountered in recent literature. It would go beyond the scope of this paper to classify encountered papers according to object, but it is noteworthy that the majority of papers concerns global head registration, even if the registration method used could possibly be used in other image areas.

11 Discussion

What trends can be observed from the current literature? There is a definite shift in research from extrinsic to intrinsic methods, although clinically used methods are often still extrinsic. Of the intrinsic methods, the surface based methods appear most frequently, closely followed by "full image content" voxel property based methods. Instances of the latter type are slowly setting the standard for registration accuracy, a place formerly reserved for frame and invasive fiducial based registrations. The application of full image content voxel property based methods is however still largely limited in the extensive application field of intra-operative registration and radiotherapy treatment related registration (both requiring patient to modality registration). Especially in the area of intra-operative registration, surface based methods are dominant, and voxel based methods almost absent. The reasons may be clear: it is relatively easy to obtain a surface from the patient, either using laser scanning, probes, 2D imagery, *etc.* , while obtaining reliable image information for voxel property based methods is more difficult: intra-operative imaging may not even be part of the normal surgical routine. If it is, images are usually 2D, and if 3D, of a relative poor quality given common equipment and acquisition sequence constraints in the operating theater. Moreover, surface based methods are, on the average, still faster than voxel property based methods. However, a problem with surface based methods is that they cannot cope with shift of relevant anatomy relative to the surface used in the registration, which may be severely restraining to intra-operative application. This problem may be solved using voxel based methods, but given the current state of affairs considering registration methods, surgical protocol, and intra-operative imaging, this will not be done in the very near future. In the case of radiotherapy treatment related registration (patient positioning, and patient position verification), the future will certainly include more of voxel based methods: imaging (X-ray simulator images and portal images) is already part of the common clinical treatment routine; radiotherapy relies almost exclusively on imaging for (tumor) localization, unlike surgery, where the visual impression is still the most important cue. It is not unlikely that this will change soon for a number of surgical applications, given the current trend of less and less invasive surgery that requires making use of advanced imaging techniques.

Many (but not all) *monomodal* registration problems appear to have been solved satisfactorily. We can accredit this to the fact that a registration paradigm can usually be relatively simple in the monomodal problem. Furthermore, given a computed transformation, many applications do not require complex visualization techniques, but can be adequately handled using subtraction techniques. *Multimodal* applications cannot be discussed in general terms, the applications are simply too diverse. It is tempting, but incorrect, to say registration results are somewhat more satisfying in methods involving scintigraphic imaging, perhaps because the relatively blurry nature of the images allows for a slightly larger displacement. In, *e.g.,* CT to MR registration, a displacement of a pixel can sometimes be obvious to the naked eye, and to obtain an accuracy in this order of magnitude, we cannot avoid to investigate precision at the acquisition level, (*e.g.,* the distortions induced by field inhomogeneity in MR images), which are of the same order of magnitude[8] However, the resolution of the images should not be used to formulate a clinically relevant level of accuracy: it is very

[8]Distortion correcting algorithms have been proposed and are now available to a certain extent; scanners are calibrated better, and magnetic fields are adapted for minimum distortion.

well possible that a SPECT to MR registration requires a higher accuracy than some instance of CT to MR registration, even though it is likely that the smaller error is more easily assessed by the naked eye in the latter case. The actual level of accuracy needed is in many applications still an unknown, and cannot accurately be quantified, even by the clinicians involved.

Intra-operative registration and methods on patient positioning in radiotherapy are in clinical use with apparent good results at a number of sites. On the *diagnostic use* of registration (modality to modality), much less information can be found. We suspect that, bearing in mind the possible clinical potential of diagnostic registration, it is actually used very little. The reasons for this are, probably, in essence of a logistic nature: unlike in the intra-operative scene (where all imaging and operations take place in the same room), in many multimodal diagnostic settings images are acquired at different places, –often even at different departments–, by different people, at different times, often transfered to different media, and frequently evaluated by different specialist diagnosticians. Besides these logistic reasons, it is also often unclear how a registration can optimally be used in the diagnostic process. It has already been pointed out that much research can still be done in this area.

Many methods can still be considered barred from meaningful clinical application by the fact that they are as yet improperly validated. Although the proper verification methods are known in most cases, and coarsely laid out in the previous section, for most applications the painstaking work of conducting the many experiments involved is only now starting.

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