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A Survey of Medical Image Registration

J. B. Antoine Maintz* and Max A. Viergever

Image Sciences Institute, Utrecht University Hospital, Utrecht, the Netherlands

Abstract
The purpose of this chapter is to present a survey of recent publications concerning medical image registration techniques. These publications 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.

Keywords: registration, matching

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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. The imaging modalities employed can be divided into two global categories: *anatomical* and *functional*. Anatomical modalities, *i.e.,* depicting primarily morphology, include X-ray, CT (computed tomography[a]), MRI (magnetic resonance imaging[b]), US (ultrasound[c]), portal images, and (video) sequences obtained by various catheter "scopes", *e.g.,* by laparoscopy or laryngoscopy. Some prominent derivative techniques are so detached from the original modalities that they appear under a separate name, *e.g.,* MRA (magnetic resonance angiography), DSA (digital subtraction angiography, derived from X-ray), CTA (computed tomography angiography), and *Doppler* (derived from US, referring to the Doppler effect measured). Functional modalities, *i.e.,* depicting primarily information on the metabolism of the underlying anatomy, include (planar) scintigraphy, SPECT (single photon emission computed tomography[d]), PET (positron emission tomography[e]), which together make up the *nuclear medicine* imaging modalities, and fMRI (functional MRI). With a little imagination, spatially sparse techniques like, EEG (electro encephalography), and MEG (magneto encephalography) can also be named functional *imaging* techniques. Many more functional modalities can be named, but these are either little used, or still in the pre-clinical research stage, *e.g.,* pMRI (perfusion MRI), fCT (functional CT), EIT (electrical impedance tomography), and MRE (magnetic resonance elastography).

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. Unfortunately, the terms *registration* and *fusion*, as well as *matching*, *integration*, *correlation*, and others, appear polysemously in literature, either referring to a single step or to the whole of the modality integration process. In this paper, only the definitions of registration and fusion as defined above will be used.

An eminent example of the use of registering different modalities can be found in the area of epilepsy surgery. Patients may undergo various MR, CT, and DSA studies

*Corresponding author
(e-mail: Twan.Maintz@cv.ruu.nl)
[a] Also formerly and popularly CAT, computed axial tomography.
[b] Also referred to as NMR, nuclear magnetic resonance, spin imaging, and various other names.
[c] Also echo(graphy).
[d] Also SPET, single photon emission tomography.
[e] SPECT and PET together are sometimes referred to as ECAT (emission computerized axial tomography).

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. A second example concerns radiotherapy treatment, where both CT and MR can be employed. The former is needed to accurately compute the radiation dose, while the latter is usually better suited for delineation of tumor tissue.

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

This paper aims to provide a survey of recent literature concerning medical image registration. Because of the sheer volume of available papers, the material presented is by necessity heavily condensed, and –except for a few interesting and "classic" cases– no papers written before 1993 are referred to. Concerning publications pre-dating 1993, we refer the reader to review papers such as van den Elsen, Pol & Viergever (1993) and Maurer, McCrory, & Fitzpatrick (1993). No complete review papers of a later date exist to our knowledge, except for the field of computer aided surgery (Lavallée, 1996). To narrow the field of available publications in such a way does not, however, impede us in reaching our primary goal, which is to paint a comprehensive picture of current medical image registration methods.

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 (1993). A version considerably augmented and detailed is presented. Nine basic criteria are used, each of which is again subdivided on one or two levels. The nine criteria and primary subdivisions are:

I. Dimensionality

II. Nature of registration basis

- **a.** Extrinsic
- **b.** Intrinsic
- **c.** Non-image based

III. Nature of transformation

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

IV. Domain of transformation

V. Interaction

VI. Optimization procedure

VII. Modalities involved

- **a.** Monomodal
- **b.** Multimodal
- **c.** Modality to model
- **d.** Patient to modality

VIII. Subject

- **a.** Intrasubject
- **b.** Intersubject
- **c.** Atlas

IX. Object

A registration procedure can always be decomposed into three major pillars: the *problem statement*, the *registration paradigm*, and the *optimization procedure*. The problem statement and the choice of paradigm and optimization procedure together provide a unique classification according to the nine criteria mentioned. Although pillars and criteria are heavily intertwined and have many cross-influences, it can be said that the problem statement determines the classification according to criteria **VII**, **VIII**, and **IX**, and has a direct bearing on the criteria **I** and **III**. The paradigm influences the criteria **II**, **III**, **IV**, and **V** most directly, while the optimization procedure influences criterion **V** and controls **VI**. It is often helpful to remember the three pillars are independent, since many papers do not describe them as such, often presenting problem statement, paradigm, and optimization procedure in a compounded way.

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

3. DIMENSIONALITY

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

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 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 of a single tomographic slice to spatial data. Some applications register multiple 2D projection images to a 3D image, but since a usual preprocessing step is to construct a 3D image from the 2D projection images, such applications are best categorized as *3D/3D* applications. 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 some 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

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)

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* (Lunsford, 1988; Vandermeulen, 1991; Lemieux *et al.*, 1994b; Lemieux and Jagoe, 1994; Strother *et al.*, 1994; Hemler *et al.*, 1995c; Vandermeulen *et al.*, 1995; Peters *et al.*, 1996) screwed rigidly to the patient's outer skull table, a device which until recently provided the "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 (Gall and Verhey, 1993; Leung Lam *et al.*, 1993; Maurer *et al.*, 1993; Li *et al.*, 1994b; Maurer *et al.*, 1994; Maurer *et al.*, 1995b; Maurer *et al.*, 1995a; Simon *et al.*, 1995b; Ellis *et al.*, 1996), but usually non-invasive marking devices are reverted to. Most popular amongst these are markers glued to the skin (Evans *et al.*, 1991; Maguire *et al.*, 1991; Malison *et al.*, 1993; Wang *et al.*, 1994b; Wahl *et al.*, 1993; Bucholz *et al.*, 1994; Li *et al.*, 1994b; Edwards *et al.*, 1995a; Edwards *et al.*, 1995b; Leslie *et al.*, 1995; Stapleton *et al.*, 1995; Wang *et al.*, 1995; Fuchs *et al.*, 1996), 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 (Greitz *et al.*, 1980; Laitinen *et al.*, 1985; Schad *et al.*, 1987; Hawkes *et al.*, 1992; Evans *et al.*, 1989; Evans *et al.*, 1991).

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 (Simon *et al.*, 1995b; Ellis *et al.*, 1996) 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 (Evans *et al.*, 1989; Evans *et al.*, 1991; Hill *et al.*, 1991a; Hill *et al.*, 1991b; Maguire *et al.*, 1991; Zubal *et al.*, 1991; Henri *et al.*, 1992; Bijhold, 1993; Ding *et al.*, 1993; Fright and Linney, 1993; Gluhchev and Shalev, 1993; Hill *et al.*, 1993b; Morris *et al.*, 1993; Neelin *et al.*, 1993; Wahl *et al.*, 1993; Ge *et al.*, 1994; Harmon *et al.*, 1994; Moseley and Munro, 1994; Pietrzyk *et al.*, 1994; Strother *et al.*, 1994; Edwards *et al.*, 1995a; Edwards *et al.*, 1995b; Ge *et al.*, 1995; Hamadeh *et al.*, 1995b; Hamadeh *et al.*, 1995c; Leslie *et al.*, 1995; Meyer *et al.*, 1995; McParland and Kumaradas, 1995; Soltys *et al.*, 1995; Savi *et al.*, 1995; Stapleton *et al.*, 1995; Vandermeulen *et al.*, 1995; Zubal *et al.*, 1995; Christensen *et al.*, 1996; Evans *et al.*, 1996b; Evans *et al.*, 1996a; Erbe *et al.*, 1996; Fang *et al.*, 1996; Peters *et al.*, 1996; Rubinstein *et al.*, 1996), 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 (He *et al.*, 1991; Fontana *et al.*, 1993; Ault and Siegel, 1994; Eilertsen *et al.*, 1994; Thirion, 1994; Ault and Siegel, 1995; Uenohara and Kanade, 1995; Amit and Kong, 1996; Chua and Jarvis, 1996; Thirion, 1996a). 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 (Evans *et al.*, 1989; Evans *et al.*, 1991; Wahl *et al.*, 1993; Moseley and Munro, 1994; Hamadeh *et al.*, 1995c; McParland and Kumaradas, 1995; Zubal *et al.*, 1995; Christensen *et al.*, 1996; Evans *et al.*, 1996b): 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 (Besl and McKay, 1992) 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 (1987), 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* (Chen *et al.*, 1987; Levin *et al.*, 1988; Guéziec and Ayache, 1992; Jiang *et al.*, 1992b; Ayache *et al.*, 1993; Collignon *et al.*, 1993a; Fritsch, 1993; Gee *et al.*, 1993; Gee *et al.*, 1994; Gee *et al.*, 1995a; Gee *et al.*, 1995b; Gee and Haynor, 1996; Gilhuijs and van Herk, 1993; Hill *et al.*, 1993a; Kittler *et al.*, 1993; Miller *et al.*, 1993; Rusinek *et al.*, 1993; Tsui *et al.*, 1993; Turkington *et al.*, 1993; Zhao *et al.*, 1993; Collignon *et al.*, 1994; Ettinger *et al.*, 1994b; Ettinger *et al.*, 1994a; Feldmar and Ayache, 1994; Fritsch *et al.*, 1994b; Fritsch *et al.*, 1994a; Grimson *et al.*, 1994a; Grimson *et al.*, 1994b; Grimson *et al.*, 1994c; Hemler *et al.*, 1994a; Hemler *et al.*, 1994b; Huang and Cohen, 1994; Hata *et al.*, 1994; Henderson *et al.*, 1994; van Herk and Kooy, 1994; Kanatani, 1994; Krattenthaler *et al.*, 1994; Kooy *et al.*, 1994; Lavallée *et al.*, 1994; Liu *et al.*, 1994; Maurer *et al.*, 1994; Mendonça *et al.*, 1994; Péria *et al.*, 1994; Philips, 1994; Petti *et al.*, 1994; Simon *et al.*, 1994; Serra and Berthod, 1994; Szelisky and Lavallée, 1994; Szeliski and Lavallée, 1994; Scott *et al.*, 1994; Strother *et al.*, 1994; Staib and Xianzhang, 1994; Taneja *et al.*, 1994; Wang *et al.*, 1994a; Zuk *et al.*, 1994; Ardekani *et al.*, 1995; Andersson *et al.*, 1995; Andersson, 1995; Betting and Feldmar, 1995; Betting *et al.*, 1995; Burel *et al.*, 1995; Christmas *et al.*, 1995; Feldmar *et al.*, 1995; Grimson *et al.*, 1995; Henri *et al.*, 1995; Hemler *et al.*, 1995c; Hemler *et al.*, 1995b; Hemler *et al.*, 1995a; Hamadeh *et al.*, 1995b; Hamadeh *et al.*, 1995c; Hamadeh *et al.*, 1995a; Kruggel and Bartenstein, 1995; Lavallée and Szeliski, 1995; Leszczynski *et al.*, 1995; Maurer *et al.*, 1995a; Pellot *et al.*, 1995; Pallotta *et al.*, 1995; Pajdla and van Gool, 1995; Pennec and Thirion, 1995; Ryan *et al.*, 1995; Rizzo *et al.*, 1995; Simon *et al.*, 1995b; Simon *et al.*, 1995a; Serra and Berthod, 1995; Scott *et al.*, 1995; Sull and Ahuja, 1995; Troccaz *et al.*, 1995; Turkington *et al.*, 1995; Vassal *et al.*, 1995; Vandermeulen *et al.*, 1995; Xiao and Jackson, 1995; Zubal *et al.*, 1995; Declerc *et al.*, 1996; Evans *et al.*, 1996b; Ettinger *et al.*, 1996; Feldmar and Ayache, 1996; Grimson *et al.*, 1996; Gilhuijs *et al.*, 1996; Ge *et al.*, 1996; Goris *et al.*, 1996; Hemler *et al.*, 1996; Jain *et al.*, 1996; Lavallée *et al.*, 1996b; Lavallée *et al.*, 1996a; Qian *et al.*, 1996; Szeliski and Lavallée, 1996; Wang *et al.*, 1996c), 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* (Bajcsy *et al.*, 1983; Guéziec, 1993; Taubin, 1993; Davatzikos and Prince, 1994; MacDonald *et al.*, 1994; Sandor and Leahy, 1994; Tom *et al.*, 1994; Bro-nielsen, 1995; Bainville *et al.*, 1995; Mangin *et al.*, 1995; Sandor and Leahy, 1995; Thirion, 1995; Cuisenaire *et al.*, 1996; Davatzikos *et al.*, 1996; Davatzikos, 1996; McInerney and Terzopoulos, 1996; Thirion, 1996b), 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 (Chen *et al.*, 1987; Levin *et al.*, 1988; Pelizzari *et al.*, 1989; Chen and Pelizzari, 1989), 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 (1988). 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 (Taubin, 1993; Davatzikos and Prince, 1994; Sandor and Leahy, 1994; Tom *et al.*, 1994; Bro-nielsen, 1995; Bainville *et al.*, 1995; Sandor and Leahy, 1995; Thirion, 1995; Cuisenaire *et al.*, 1996; Davatzikos *et al.*, 1996; Davatzikos, 1996; Thirion, 1996b), or the second image is used *unsegmented* (Bajcsy *et al.*, 1983; Guéziec, 1993; MacDonald *et al.*, 1994). 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[a] 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 (Bro-nielsen, 1995; Little *et al.*, 1996). 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[b], and cortical registration of MR images (Bajcsy *et al.*, 1983; Davatzikos and Prince, 1994; MacDonald *et al.*, 1994; Sandor and Leahy, 1994; Sandor and Leahy, 1995; Thirion, 1995; Cuisenaire *et al.*, 1996; Davatzikos *et al.*, 1996; Davatzikos, 1996; Thirion, 1996b). 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.

[a]Intersubject and atlas registration is covered in section 9.
[b]*e.g.*, see (Fang *et al.*, 1996).

4.2.3. Voxel property based registration methods

The *voxel property based* registration methods stand apart from the other intrinsic methods[c] 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 (Alpert *et al.*, 1990; Banerjee and Toga, 1994; Ettinger *et al.*, 1994b; Ettinger *et al.*, 1994a; Pavía *et al.*, 1994; Wang and Fallone, 1994; Slomka *et al.*, 1995; Dong and Boyer, 1996; Wang *et al.*, 1996a). 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) (Slomka *et al.*, 1995), and as a coarse pre-registration in various other registration areas (Banerjee and Toga, 1994; Ettinger *et al.*, 1994b; Ettinger *et al.*, 1994a; Pavía *et al.*, 1994; Slomka *et al.*, 1995; Dong and Boyer, 1996). 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

[c]Except some instances of geometric landmark registration.

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. 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 (Studholme *et al.*, 1996). 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) (Junck *et al.*, 1990; Bacharach *et al.*, 1993; Bettinardi *et al.*, 1993; van den Elsen and Viergever, 1993; Hill, 1993; Hua and Fram, 1993; Münch and Rüegsegger, 1993; Radcliffe *et al.*, 1993; Banerjee and Toga, 1994; Collins *et al.*, 1994a; Collins *et al.*, 1994b; van den Elsen, 1994; van den Elsen *et al.*, 1994; Lemieux *et al.*, 1994a; Moseley and Munro, 1994; Maintz *et al.*, 1994; Maintz *et al.*, 1996c; Pavía *et al.*, 1994; Radcliffe *et al.*, 1994; Andersson, 1995; Andersson *et al.*, 1995; Cideciyan, 1995; Collins *et al.*, 1995; van den Elsen *et al.*, 1995; Hemler *et al.*, 1995c; McParland and Kumaradas, 1995; Maintz *et al.*, 1995; Perault *et al.*, 1995; Studholme *et al.*, 1995b; Studholme *et al.*, 1995a; Dong and Boyer, 1996; Gottesfeld Brown and Boult, 1996; Hristov and Fallone, 1996; Lehmann *et al.*, 1996; Maintz *et al.*, 1996b).
- Fourier domain based cross-correlation, and phase-only correlation (de Castro and Morandi, 1987; Leclerc and Benchimol, 1987; Chen, 1993; Lehmann *et al.*, 1996; Shekarforoush *et al.*, 1996; Wang *et al.*, 1996b).
- Minimization of variance of intensity ratios (Hill, 1993; Hill *et al.*, 1993a; Woods *et al.*, 1993; Ardekani *et al.*, 1994; Studholme *et al.*, 1995b; Studholme *et al.*, 1995a; Zuo *et al.*, 1996).
- Minimization of variance of grey values within segments (Cox and de Jager, 1994; Ardekani *et al.*, 1995).

$*$ Minimization of the histogram entropy of difference images (Buzug and Weese, 1996).

- Histogram clustering and minimization of histogram dispersion (Hill, 1993; Hill *et al.*, 1994; Hill and Hawkes, 1994; Collignon *et al.*, 1995b; Hawkes *et al.*, 1995; Studholme *et al.*, 1995b; Studholme *et al.*, 1995a; Lehmann *et al.*, 1996).
- Maximization of mutual information (relative entropy) of the histogram (Collignon *et al.*, 1995a; Viola and Wells III, 1995; Viola, 1995; Wells III *et al.*, 1995; Maes *et al.*, 1996; Pokrandt, 1996; Studholme *et al.*, 1996; Viola *et al.*, 1996; Wells III *et al.*, 1996).

$*$ Maximization of zero crossings in difference images (Stochastic sign change (SSC), and Deterministic sign change (DSC) criterion) (Venot *et al.*, 1983; Venot *et al.*, 1984; Venot and Leclerc, 1984; Hua and Fram, 1993; Hoh *et al.*, 1993; Venot *et al.*, 1994; Perault *et al.*, 1995; Bani-Hashemi *et al.*, 1996).

$*$ Cepstral echo filtering (Bandari *et al.*, 1994).

$*$ Determination of the optic flow field (Barber *et al.*, 1995; Meunier *et al.*, 1996).

$*$ Minimization of the absolute or squared intensity differences (Hoh *et al.*, 1993; Lange *et al.*, 1993; Zhao *et al.*, 1993; Moseley and Munro, 1994; Yeung *et al.*, 1994; Christensen *et al.*, 1995b; Christensen *et al.*, 1995a; Haller *et al.*, 1995; Hajnal *et al.*, 1995a; Hajnal *et al.*, 1995b; Jacq and Roux, 1995; Kruggel and Bartenstein, 1995; Slomka *et al.*, 1995; Unser *et al.*, 1995; Christensen *et al.*, 1996; Eberl *et al.*, 1996; Haller *et al.*, 1996).

$*$ Matching local low-order Taylor expansions determined by the image grey values (Shields *et al.*, 1993).

- Implicitly using surface registration by interpreting a 3D image as an instance of a surface in 4D space (Feldmar *et al.*, 1996).

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 (Hata *et al.*, 1994; Péria *et al.*, 1995; Erbe *et al.*, 1996). 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[a].

5. NATURE AND DOMAIN OF THE TRANSFORMATION

III. Nature of transformation

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

IV. Domain of transformation

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

5.1. Nature of the transformation

An image coordinate transformation is called *rigid*, when only translations and rotations[b] 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:

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

[a] For instance (Potamianos *et al.*, 1995; Peters *et al.*, 1996). See computer aided surgery literature (Lavallée, 1996) for more complete references.
[b] and, technically, reflections, but this is disregarded in our formulation, since they do not apply to the general medical image registration problem.

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 1 shows examples of all transformation types mentioned.

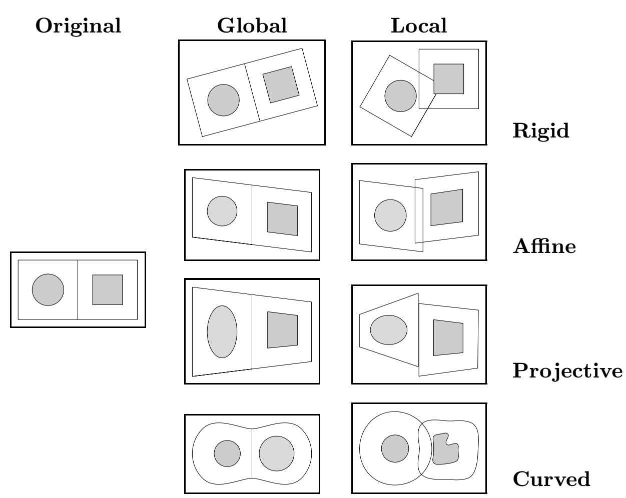

Figure 1. Examples of 2D transformations.

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 (Bro-nielsen, 1995; Little *et al.*, 1996). Some problems that are intrinsically locally rigid (such as the registering of individual vertebrae from images of the spinal column) are in registration tasks often solved by splitting the image in images meeting the global rigid body constraint.

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

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

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 desired 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[a]. 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 (Morris *et al.*, 1993; Pietrzyk *et al.*, 1994; Soltys *et al.*, 1995). Perhaps, like many methods that rely primarily on the proper use of good visualization software, they are –often undeserved– 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[b]. 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 (Levin *et al.*, 1988; Hill *et al.*, 1991b; Tsui *et al.*, 1993; Ettinger *et al.*, 1994b; Ettinger *et al.*, 1994a; Hata *et al.*, 1994; van Herk and Kooy, 1994; Kooy *et al.*, 1994; Lemieux *et al.*, 1994a; Andersson, 1995; Andersson *et al.*, 1995; Collignon *et al.*, 1995a; Leszczynski *et al.*, 1995; Bani-Hashemi *et al.*, 1996; Gilhuijs *et al.*, 1996; Gottesfeld Brown and Boult, 1996; Maes *et al.*, 1996), the Downhill Simplex method (Hill *et al.*, 1991b; Gilhuijs and van Herk, 1993; Hill *et al.*, 1993a; Hoh *et al.*, 1993; Leung Lam *et al.*, 1993; van Herk and Kooy, 1994; Kooy *et al.*, 1994; Li *et al.*, 1994b; Meyer *et al.*, 1995; Slomka *et al.*, 1995; Eberl *et al.*, 1996), Brent's method and series of one-dimensional searches (Bacharach *et al.*, 1993; Münch and Rüegsegger, 1993; Ault and Siegel, 1994; Petti *et al.*, 1994; Ault and Siegel, 1995; Ardekani *et al.*, 1995; McParland and Kumaradas, 1995; Hristov and Fallone, 1996), Levenberg-Marquardt optimization (Taubin, 1993; Hemler *et al.*, 1994a; Hemler *et al.*, 1994b; Szelisky and Lavallée, 1994; Szeliski and Lavallée, 1994; Bainville *et al.*, 1995; Hamadeh *et al.*, 1995b; Hamadeh *et al.*, 1995c; Lavallée and Szeliski, 1995; Unser *et al.*, 1995; Lavallée *et al.*, 1996a; Szeliski and Lavallée, 1996), Newton-Raphson iteration (Fright and Linney, 1993; Woods *et al.*, 1993; Zuo *et al.*, 1996), stochastic search methods (Miller *et al.*, 1993; Viola and Wells III, 1995; Viola, 1995; Wells III *et al.*, 1995; Viola *et al.*, 1996; Wells III *et al.*, 1996), gradient descent methods (Zuk *et al.*, 1994; Perault *et al.*, 1995; Buzug and Weese, 1996; Christensen *et al.*, 1996; Cuisenaire *et al.*, 1996), genetic methods (Hill *et al.*, 1993a; Hill *et al.*, 1994; Hill and Hawkes, 1994; Staib and Xianzhang, 1994; Kruggel and Bartenstein, 1995; Cross *et al.*, 1996), simulated annealing (Liu *et al.*, 1994), geometric hashing (Guéziec and Ayache, 1992; Ayache *et al.*, 1993; Pajdla and van Gool, 1995), and quasi-exhaustive search methods (Bettinardi *et al.*, 1993; van den Elsen and Viergever, 1993; Hua and Fram, 1993; Cox and de Jager, 1994; van den Elsen, 1994; van den Elsen *et al.*, 1994; Mendonça *et al.*, 1994; Maintz *et al.*, 1994; Maintz *et al.*, 1996c; van den Elsen *et al.*, 1995; Maintz *et al.*, 1995; Dong and Boyer, 1996; Maintz *et al.*, 1996b). Many of these methods are documented in (Press *et al.*, 1992). 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 (Besl and McKay, 1992; Simon *et al.*, 1994; Feldmar and Ayache, 1994; Maurer *et al.*, 1995a; Pajdla and van Gool, 1995; Simon *et al.*, 1995a; Betting and Feldmar, 1995; Betting *et al.*, 1995; Cuchet *et al.*, 1995; Feldmar *et al.*, 1995; Ellis *et al.*, 1996; Feldmar *et al.*, 1996; Feldmar and Ayache, 1996; Goris *et al.*, 1996), 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.

[a]see, *e.g.*, (Wang *et al.*, 1995)
[b]see, *e.g.*, (Arun *et al.*, 1987; Hill *et al.*, 1991a; Hill *et al.*, 1993b)

8. MODALITIES INVOLVED IN THE REGISTRATION

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

VII. Modalities involved

a. Monomodal

1. Auto-radiographic
2. CT or CTA
3. MR
4. PET
5. Portal
6. SPECT
7. US
8. Video
9. X-ray or DSA

b. Multimodal

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[a]—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

[a]Transcranial magnetic stimulation.

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 (Bucholz *et al.*, 1994; Harmon *et al.*, 1994; Henderson *et al.*, 1994; Lemieux *et al.*, 1994a; Lavallée *et al.*, 1994; Lea *et al.*, 1994; Li *et al.*, 1994b; Simon *et al.*, 1994; Wang *et al.*, 1994a; Betting *et al.*, 1995; Betting and Feldmar, 1995; Bainville *et al.*, 1995; Cuchet *et al.*, 1995; Edwards *et al.*, 1995a; Edwards *et al.*, 1995b; Hamadeh *et al.*, 1995c; Hamadeh *et al.*, 1995a; Lea *et al.*, 1995a; Lea *et al.*, 1995b; Maurer *et al.*, 1995b; Miaux *et al.*, 1995; Ryan *et al.*, 1995; Simon *et al.*, 1995b; Simon *et al.*, 1995a; Evans *et al.*, 1996b; Fuchs *et al.*, 1996; Lavallée *et al.*, 1996b; Lavallée, 1996; Peters *et al.*, 1996) and radiotherapy (Bijhold, 1993; Gall and Verhey, 1993; Leung Lam *et al.*, 1993; Troccaz *et al.*, 1995; Vassal *et al.*, 1995; Gilhuijs *et al.*, 1996) 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 (Bajcsy *et al.*, 1983; Rizzo *et al.*, 1995; Amit and Kong, 1996; Cuisenaire *et al.*, 1996; Jain *et al.*, 1996). *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[a].

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* (Bajcsy *et al.*, 1983; Gee *et al.*, 1993; Miller *et al.*, 1993; Szeliski and Lavallée, 1994; Szelisky and Lavallée, 1994; Sandor and Leahy, 1994; Collins *et al.*, 1995; Ge *et al.*, 1995; Haller *et al.*, 1995; Sandor and Leahy, 1995; Thirion, 1995; Amit and Kong, 1996; Declerc *et al.*, 1996; Fang *et al.*, 1996; Gee and Haynor, 1996; Haller *et al.*, 1996; Thirion, 1996b) and *atlas* registration (Collins *et al.*, 1994a; Collins *et al.*, 1994b; Davatzikos and Prince, 1994; MacDonald *et al.*, 1994; Barber *et al.*, 1995; Christensen *et al.*, 1995b; Christensen *et al.*, 1995a; Slomka *et al.*, 1995; Christensen *et al.*, 1996; Cuisenaire *et al.*, 1996; Davatzikos *et al.*, 1996; Feldmar *et al.*, 1996) 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 clinical use 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.

[a]References to monomodal and multimodal applications will be given in the *object* section, since they are numerous, and moreover many papers are not specific to one of the four application categories.

10. OBJECT

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

   1. General
   2. Femur
   3. Humerus
   4. Hand

f. Spine and vertebrae

The above list is, again, not theoretically complete, but composed of those imaging areas encountered in recent literature. Almost all reviewed papers will be cited in this section[a], focussing on the paradigm used. We will break down this section according to the areas mentioned in the list. Hopefully this will give an idea of the specific approaches and trends associated with each image area. Since many papers concern global head registration (177 out of over 300 reviewed papers), this subsection will be further divided according to the modalities involved. *Note that many papers may have more than one application area, even though they only demonstrate a registration method in one area.* This implies that some areas, *e.g.*, CT-SPECT registration, appear to have been poorly examined, while in fact good methods have been developed in other areas that are instantly or easily transfered to the problem at hand. Many general papers do not detail a specific medical registration application. Such papers are mentioned at the end of this section.

10.1. Registration of head images

Many possible registration tasks can be defined on images of the human head, including all types of monomodal, multimodal, model, and patient registration of a plethora of image modalities in various diagnostic and interventionist settings. This makes for the prevalence of papers concerned with registration of images of the head, possibly along with the fact that the head can be considered a rigid body in many applications, while such a constraint cannot be met in many thoracic, abdominal, pelvic, and spinal images.

10.1.1. Monomodal applications: CT

Intrasubject 3D CT registration was performed by Guéziec and Ayache (Guéziec and Ayache, 1992; Ayache *et al.*, 1993; Guéziec, 1993) by registering "crest lines" (extremal lines of the principal curvature) of surfaces. This technique was later adapted by Thirion (Thirion, 1994; Thirion, 1996a), using only the extremal points of the crest lines. Van Herk (van Herk and Kooy, 1994) and Xiao (Xiao and Jackson, 1995) employed *surfaces* for registration by Chamfer matching, a technique which uses a pre-computed distance map for fast computation of the distance between two surfaces (Borgefors, 1988). Liu (Liu *et al.*, 1994) also used a Chamfer-like technique, employing *cores* instead of surfaces, with a full scale-space distance metric. A core can be defined as a multi-scale instance of a medial axis, *i.e.*, a structure, supported by a quench-like function, that runs "in the middle" of some perceived object. Petti (Petti *et al.*, 1994) performed registration by maximizing the overlap, or, more precisely, by minimizing the "exclusive or" (XOR) overlap of *segmented* solid structures. Finally, Lemieux (Lemieux *et al.*, 1994b; Lemieux and Jagoe, 1994) studied the accuracy of *frame-based* registration relative to the accuracy of *marker* detection.

3D morphing of CT skulls was performed by Christensen (Christensen *et al.*, 1996), who *elastically* morphed infants skulls to an *atlas* by locally minimizing the intensity difference, after an initial *rigid* alignment based on *anatomical landmarks.* Fang (Fang *et al.*, 1996) performed interspecies morphing of the skull based on *anatomical landmarks*, between human and macaque skulls.

Local elastic 3D intrasubject CTA registration was performed by Bani-Hashemi (Bani-Hashemi *et al.*, 1996) and Yeung (Yeung *et al.*, 1994), by extending methods used in DSA to 3D. The former used the DSC criterion, while the latter searches for a matching voxel by finding the voxel closest (in the squared sense) in grey value.

10.1.2. Monomodal applications: rigid and affine MR registration

Fully interactive rigid registration methods are described by Morris (Morris *et al.*, 1993) and Pietrzyk (Pietrzyk *et al.*, 1994). Alpert (Alpert *et al.*, 1990) registers by alignment of the *principal axes* and the center of gravity. Ettinger (Ettinger *et al.*, 1994b; Ettinger *et al.*, 1994a) also uses these for a pre-registration, but then refines the transformation using a semi-automatically extracted intra-cranial *surface* with a Gaussian weighted distance function. Approximately the same method is implemented by Rusinek (Rusinek *et al.*, 1993), which does not weigh the distance, but supplies an *affine* instead of a rigid transformation. Their method is (an extension of) the well-known "head-hat" *surface* matching technique, minimizing the squared distance between two segmented (skin) surfaces, originally presented by Pelizzari and co-workers, including Levin (Levin *et al.*, 1988), who documented its use on the current application. *Rigid surface* based Chamfer matching was used by Jiang (Jiang *et al.*, 1992a; Jiang *et al.*, 1992b)

[a]The reader is warned that readability was not foremost in our minds at the time of writing. Rather, this section serves a reference purpose.

on *manually segmented surfaces*, and extended by Zuk (Zuk *et al.*, 1994), who added hierarchical surface point sampling. Various *surface based* methods using Besl's (Besl and McKay, 1992) ICP algorithm were implemented by Feldmar. In (Feldmar and Ayache, 1994), ICP was used directly on *segmented surfaces* to find an *affine* transformation. In (Feldmar and Ayache, 1996) the segmented surface was elaborated to an 8D structure: not only the spatial coordinates were used in the cost (distance) function computation, but also the surface normals and the principal curvatures. In (Feldmar *et al.*, 1996) the 'surface' needed no segmentation, since the entire 3D image was considered to be a surface in 4D (spatial coordinates plus intensity) space.

Rigid registration based on *segmented curves* was done by Guéziec (Guéziec, 1993), by using the crest lines of a surface, which was extracted by using a *deformable model.* Thirion (Thirion, 1994; Thirion, 1996a) also employed crest lines, but used only their curvature-extremal *points* in the registration process. Pennec (Pennec and Thirion, 1995) examined the precision of this method.

Collignon (Collignon *et al.*, 1994) performed *rigid* registration by using *segmentation*: each set is segmented using K-means clustering, and the registration is performed by minimizing the "fuzziness" between corresponding segments. He later used clustering of the joint histogram of the images to find the transformation in a *full image content* based method. Hill (Hill *et al.*, 1994; Hill and Hawkes, 1994) used a similar method based on minimizing the histogram dispersion using the third order moment of the histogram. Other *full image content* based methods were proposed by Hajnal and Bandari. The former (Hajnal *et al.*, 1995a; Hajnal *et al.*, 1995b) performed *rigid* registration by minimizing the squared intensity differences in the brain, which needs to be segmented first. The latter (Bandari *et al.*, 1994) finds translation between the images to be registered by gluing them together and regarding the compound as a time series. The second image is then registered to the first by finding the occurrence of the cepstral echo of the first image in the time series. Finally, Collignon (Collignon *et al.*, 1995a) and Maes (Maes *et al.*, 1996) (*rigid* transformations), simultaneously with Viola (Viola and Wells III, 1995; Viola, 1995; Viola *et al.*, 1996) (*affine* and higher order transformations) used maximization of the mutual information, *i.e.,* the relative entropy, of the joint histogram to achieve registration.

Several methods, amongst which *frame* and *mould* based registration, head-hat *segmented surface* registration, *anatomical landmark* based methods, and ratios of voxel variance based methods, where compared by Strother (Strother *et al.*, 1994).

10.1.3. Monomodal applications: curved MR registration

Elastic deformation of segmented curves or surfaces to corresponding structures was performed on two-dimensional slices by Nakazawa (Nakazawa and Saito, 1994), where the correct slices needed to be selected *manually*. The same approach, except fully in *three dimensions* was followed by Christensen and Haller (Christensen *et al.*, 1995a; Haller *et al.*, 1995; Haller *et al.*, 1996), using a fluid model morphing, Davatzikos (Davatzikos and Prince, 1994; Davatzikos *et al.*, 1996; Davatzikos, 1996), using elastic deformation of the brain and ventricular surface, Sandor (Sandor and Leahy, 1994; Sandor and Leahy, 1995), using elastic deformation of morphologically smoothed Marr-Hildreth edges, MacDonald (MacDonald *et al.*, 1994), and Thirion (Thirion, 1995; Thirion, 1996b), using elastic deformations using *demons*, where demons are particles than can either push or pull, depending on what side of the boundary they are on.

Collins (Collins *et al.*, 1994a; Collins *et al.*, 1994b; Collins *et al.*, 1995) performed *curved* registration by local optimization of the cross-correlation based on intensity and gradient values extracted at several scales of resolution. Ge (Ge *et al.*, 1995) employed *user defined* cortical traces and sub-cortical *landmarks*, and interpolated the curved transformation in undefined areas. Gee (Gee *et al.*, 1993; Gee *et al.*, 1994; Gee *et al.*, 1995a; Gee and Haynor, 1996) used Bayesian modeling applied to various *segmented* structures. Kruggel (Kruggel and Bartenstein, 1995) performed *elastic* registration by minimizing the local squared intensity differences, after an initial global Chamfer matching. Finally, Miller (Miller *et al.*, 1993) performed *curved* registration by using multi-valued MR images, (T1 weighted, T2 weighted, segment values, *etc.*) by minimizing the squared distance error and the elastic energy.

10.1.4. Monomodal applications: PET

All of the encountered PET—PET registration methods of brain images are *3D* and *rigid*, excepting Unser, who provides an *affine* registration. Pietrzyk (Pietrzyk *et al.*, 1994) designed a fully *interactive* method using graphical tools, *e.g.*, rendering, cut-planes, edges, *etc.* Zuk (Zuk *et al.*, 1994) does Chamfer matching, improved with hierarchical data sampling, on *segmented* surfaces. The remaining methods are *full image content* based: Andersson (Andersson, 1995) registers by optimizing the cross-correlation values in image areas near edges, where edges are defined by thresholding gradient images of the Gaussian filtered original. Eberl (Eberl *et al.*, 1996) and Unser (Unser *et al.*, 1995) find the optimal transformation by optimizing the SAD (sum of absolute differences of intensity values). Finally, Hoh (Hoh *et al.*, 1993) also uses the SAD, and compares it to results obtained by optimizing the SSC criterion.

10.1.5. Monomodal applications: SPECT

The method of Eberl (Eberl *et al.*, 1996) from the previous section, using the SAD, also applies to SPECT registration. A similar *3D rigid, using full image content* method, based on minimizing the sum of squared intensity differences, was suggested by Lange (Lange *et al.*, 1993). Other *full image content* based methods were implemented by Barber, Junck, Maintz, Meunier, and Pavía. Barber (Barber *et al.*, 1995) finds an *global affine* transformation by minimizing the optic flow field. Meunier also uses minimizes the optic flow field, but finds a *local curved* transformation. For a pre-registration, he uses the optic flow method global *rigidly*. Junck (Junck *et al.*, 1990) finds 2D *rigid* transformations by optimizing the cross-correlation. Also, the image midline in transversal images is found by optimizing the correlation between the left and mirrored right part of the image. Maintz (Maintz *et al.*, 1996a) and Pavía (Pavía *et al.*, 1994) also directly use the cross-correlation, but in a *3D rigid* manner. The former uses an hierarchical approach to optimization, the latter employs a pre-registration using principal axes. Zubal (Zubal *et al.*, 1995) uses the head-hat method on *segmented surfaces*, possibly combined with *user defined anatomical landmarks* to find a *3D rigid* transformation. *3D rigid* methods based solely on *user defined anatomical landmarks* are compared with methods based on *external markers* (both *automatically* and *semi-automatically* detected) by Leslie (Leslie *et al.*, 1995). Finally, two *interactive 3D rigid* methods are reported on: Rubinstein (Rubinstein *et al.*, 1996), who uses *anatomical landmarks*, and Stapleton (Stapleton *et al.*, 1995), where the user defines the Tailarach coordinate system by pointing out the midline, the AP (anterior-posterior) center line, and the OM (orbitomeatal) line, in the latter case aided by a single lead marker.

10.1.6. Monomodal applications: portal images

Since portal imaging appears exclusively in radiotherapy treatment settings (in fact, a portal image is obtained by measuring the transmission of the radiation beam, and hence is a 2D image), applications are only found in this specific field. Only three method instances were found: Dong (Dong and Boyer, 1996) and Hristov (Hristov and Fallone, 1996) find respectively a *global affine* and a *global rigid* transformation by optimizing the cross-correlation. Radcliffe (Radcliffe *et al.*, 1993; Radcliffe *et al.*, 1994) uses basically the same method, but speeds it up by using pseudo-correlation, which limits the computations to randomly selected small regions.

10.1.7. Monomodal applications: DSA

Venot (Venot *et al.*, 1983; Venot *et al.*, 1984; Venot and Leclerc, 1984) introduced the DSC criterion for finding a *rigid global* registration of the X-ray images involved in DSA. Hua (Hua and Fram, 1993) compared the registration performance of DSC on original images, DSC on grey-valued edge images, and of cross-correlation optimization. Leclerc (Leclerc and Benchimol, 1987) used generalized cross-correlation for finding a *local curved* transformation, in a *computed* way by implementation in a Fourier transfer-function setting. Cox (Cox and de Jager, 1994), finally, performed *local curved* registration by locally minimizing the intensity variance.

10.1.8. Other monomodal applications

Shields (Shields *et al.*, 1993) registered *2D time series* of US carotid images in an *affine* way by locally matching the first order image grey value Taylor expansion, and validated the transformation by checking cross-correlation values. Zhao (Zhao *et al.*, 1993) *affinely* registered slices of auto-radiographic imagery (scintigraphic images of cadaver slices), by minimizing displacement of *manually segmented* contours, or directly by minimizing the intensity value differences between images.

10.1.9. Multimodal applications: CT—MR

Unless otherwise stated, all of the registrations in this section supply *global rigid* transformations.

Hill (Hill *et al.*, 1991a; Hill *et al.*, 1993b) used *user identified* anatomical landmarks, to *compute* the transformation. *Identified landmarks*, either *anatomical* or *externally marked*, were also used by Maguire (Maguire *et al.*, 1991), but coarsely, since the *affine* transformation was based on optimizing the cross-correlation in areas around the landmarks. Other *full image content* based methods using cross-correlation were proposed by van den Elsen (van den Elsen *et al.*, 1994), using the entire image, where the CT grey values are remapped in a local linear fashion to improve correspondence with the MR image, and van den Elsen (van den Elsen and Viergever, 1993; van den Elsen, 1994; van den Elsen *et al.*, 1995) and Maintz (Maintz *et al.*, 1994; Maintz *et al.*, 1996c), optimizing cross-correlation of ridgeness images extracted from the original modalities. Maintz later (Maintz *et al.*, 1995; Maintz *et al.*, 1996b) included optimization of edgeness cross-correlation and compared them.

Wang (Wang *et al.*, 1994b; Wang *et al.*, 1995) and Maurer (Maurer *et al.*, 1993; Maurer *et al.*, 1995b) used *invasive fiducial markers*, and compared them to *segmented surface* registration (Maurer *et al.*, 1994). Maurer also integrated the two methods into a single one (Maurer *et al.*, 1995a).

Other *segmented surface* based methods were implemented by Ge, Hemler, Jiang, Levin, Petti, Taneja, van Herk, and Kooy. Ge (Ge *et al.*, 1996) used an ICP variation for the optimization. Hemler (Hemler *et al.*, 1994a; Hemler *et al.*, 1994b; Hemler *et al.*, 1995b; Hemler *et al.*, 1995a; Hemler *et al.*, 1996) used an automatically extracted surface with manual correction. Levin (Levin *et al.*, 1988) used the head-hat method. Jiang (Jiang *et al.*, 1992b) and Taneja (Taneja *et al.*, 1994) used the Chamfer matching technique, which was also used by van Herk (van Herk and Kooy, 1994), and Kooy (Kooy *et al.*, 1994), except in their case the surface segmentation was *automated*. Petti (Petti *et al.*, 1994) found an *affine* transformation by minimizing the "exclusive or" overlap of segmented solids. One author implemented a non-surface based *segmentation* based method: Collignon (Collignon *et al.*, 1994) proposed the minimization of "fuzziness" in corresponding segments found by K-means clustering of the original images.

Various authors used *surface based* registrations in comparisons to other methods. Hemler (Hemler *et al.*, 1995c) compared it to a *frame* based method, and optimization of the cross-correlation of remapped grey values. Vandermeulen (Vandermeulen *et al.*, 1995) compared surface based methods to *frame* based and *anatomical landmark* based methods. Hill (Hill *et al.*, 1993a) compared surface based registration and registration by minimizing the variance of intensity ratios.

Besides the above mentioned cross-correlation methods, other *full image content* based methods were proposed by Collignon, Maes, and Wells. Collignon (Collignon *et al.*, 1995b) used clustering of the joint histogram to find the optimal transformation. He also implemented optimizing the mutual information of the joint histogram, (Collignon *et al.*, 1995a) a method also used by Maes, (Maes *et al.*, 1996) and Wells (Wells III *et al.*, 1995; Wells III *et al.*, 1996).

West (West et al., 1996) compared many (13) *intrinsic* registration methods using a large image database with a "gold" registration standard obtained using *invasive fiducial markers*.

10.1.10. Multimodal applications: CT—PET

Rigid 3D transformations were performed by Alpert (Alpert *et al.*, 1990) using the images *principal axes* and center of gravity, by Chen (Chen *et al.*, 1987) and Levin (Levin *et al.*, 1988) using the head-hat method, and Pietrzyk (Pietrzyk *et al.*, 1994), who used a fully *interactive* method. *Affine* registration was obtained by Wahl (Wahl *et al.*, 1993), employing user identified *anatomical landmarks* and *external markers*, and Maguire (Maguire *et al.*, 1991), who optimized cross-correlation around such user identified anatomical landmarks and external markers. The latter method is also used to supply an *elastic* transformation.

10.1.11. Multimodal applications: CT—SPECT

Maguire (Maguire *et al.*, 1991) also applied his method to CT—SPECT registration. The only other instance we found was van Herk (van Herk and Kooy, 1994), who used *rigid* Chamfer matching on *automatically* extracted surfaces.

10.1.12. Multimodal applications: DSA—MR

Hill (Hill *et al.*, 1991b) used *hand drawn* structures, combined with a distance minimization which incorporated use of anatomical knowledge to *rigidly* register the DSA vessel tree to the MR surface. Henri (Henri *et al.*, 1992) performed *rigid* registration by least-squares fitting *user identified anatomical landmarks*. The landmarks identified in the MR where projected into the (DSA) plane, after applying the *rigid* transformation to the MR image.

10.1.13. Multimodal applications: PET—MR

Pietrzyk (Pietrzyk *et al.*, 1994) performs *rigid* registration by using various graphical objects like edges and cut-planes in a a fully *interactive* manner. Ge (Ge *et al.*, 1994) uses a more protocolized method, where the user identifies planes, starting with the inter-hemispheric fissure (midsagittal plane) to provide a registration. Meyer (Meyer *et al.*, 1995) performs *affine* registration using *user identified* points, lines and planes simultaneously in a weighted way. His method uses – next to Simplex optimization– distance error minimization by the BFGS (Broyden-Fletcher-Goldfarb-Shanno) approach.

Neelin (Neelin *et al.*, 1993) finds a *rigid* transformation by means of *user identified anatomical landmarks*. Evans (Evans *et al.*, 1989; Evans *et al.*, 1996a) also uses these, combined with a *foam mould* for patient immobilization. Later Evans (Evans *et al.*, 1991) used *fiducial marks* provided by a fiducial band strapped to the head, to find an *affine* transformation. Maguire (Maguire *et al.*, 1991) used *user identified anatomical landmarks* and *external markers*, and found an *affine* or *curved* transformation by optimizing the cross-correlation locally in the identified areas. Wahl (Wahl *et al.*, 1993) uses the same points directly to find an *affine* transformation.

Rigid surface based methods were employed by Chen (Chen *et al.*, 1987), Levin (Levin *et al.*, 1988), and Staib (Staib and Xianzhang, 1994) using the head-hat method. Turkington (Turkington *et al.*, 1993; Turkington *et al.*, 1995) used the same method, but *automated* the surface segmentation. Tsui (Tsui *et al.*, 1993) used the head-hat method, but computed the distance in 2D for more efficiency. Jiang (Jiang *et al.*, 1992b) uses multi-resolution Chamfer matching. Ardekani (Ardekani *et al.*, 1994; Ardekani *et al.*, 1995) uses segmentation obtained by K-means clustering applied to the MR. *Rigid* registration is then performed by minimizing the PET grey value variance in each segment.

Kruggel (Kruggel and Bartenstein, 1995) also uses Chamfer matching, but only as a pre-registration. The final transformation is *elastic* by locally finding the optimal shift minimizing the squared intensity differences. Other *full image content* based methods were implemented by Andersson, Miller, Woods, Collignon, Maes, and Wells: Andersson (Andersson *et al.*, 1995) performed *rigid* registration by simulating a PET image from the MR (by using a simple segmentation, and assigning a plausible radioactivity to each segment), and registering the simulated and real PET image using optimization of cross-correlation near edges, where the edges are obtained by thresholding a gradient image. Miller (Miller *et al.*, 1993) performed *curved* registration using multi-valued MR images, (T1 weighted, T2 weighted, segment values, *etc.*) by minimizing the squared distance error and the elastic energy. Woods performed *rigid* registration by minimizing the standard deviation of the PET values corresponding to a single MR grey value. Collignon (Collignon *et al.*, 1995a), Maes (Maes *et al.*, 1996) and Wells (Wells III *et al.*, 1995; Wells III *et al.*, 1996) performed *rigid* registration by optimizing the mutual information contained in the joint image histogram.

Studholme, Strother, and West compared a large number of *rigid* registration methods: the former (Studholme *et al.*, 1995b; Studholme *et al.*, 1995a) used optimization of cross-correlation, minimization of intensity variance, minimization of joint histogram entropy and dispersion by means of the third order moment, and manually *anatomical landmark* registration. Strother (Strother *et al.*, 1994), compared *frame* and *mould* based registration, head-hat *segmented surface* registration, *anatomical landmark* based methods, and ratios of voxel variance based methods. West (West et al., 1996) compared many (11) intrinsic methods to a registration based on *invasive fiducial markers*. Finally, Wang (Wang *et al.*, 1996a) investigated the use of registration in a clinical measurement study.

10.1.14. Multimodal applications: SPECT—MR

Rubinstein (Rubinstein *et al.*, 1996) and Malison (Malison *et al.*, 1993) performed *rigid* registration *interactively* using *anatomical landmarks.* Maguire (Maguire *et al.*, 1991) also used *user identified anatomical landmarks*, or user identified external markers, but performed *affine* or *curved* registration by locally optimizing the cross-correlation in the identified areas. Kruggel (Kruggel and Bartenstein, 1995) after an initial Chamfer match using segmented surfaces, performed *elastic* registration by minimizing the local squared intensity differences. Maintz (Maintz *et al.*, 1996d) computed a *rigid* transformation by optimizing the cross-correlation of the “edgeness” of the skin, computed using morphological operators. The other reported methods are all *rigid* and *surface based:* Turkington (Turkington *et al.*, 1993) used the head-hat method with automated surface segmentation. Jiang (Jiang *et al.*, 1992b) used multi-resolution Chamfer matching on semi-automatically segmented surfaces, as did Rizzo (Rizzo *et al.*, 1995). Finally Péria (Péria *et al.*, 1994) performed registration using the facial surface. Since such a surface is absent in a detailed way in SPECT images, a calibrated laser range facial surface was used instead.

10.1.15. Multimodal applications: US or TMS—MR

Since both TMS and US transducers can be hand-held devices, registration is often obtained using *calibrated coordinate systems*, under the assumption that strict patient immobilization can be maintained. A registration based on calibrated coordinate system is by definition *rigid*. Ettinger (Ettinger *et al.*, 1996) registered TMS to pre-TMS acquired MR via calibrating the TMS probe to a laser range scanner. The laser skin surface is then registered to the automatically segmented corresponding surface obtained from the MR. Erbe (Erbe *et al.*, 1996) registered intra-operative US to pre-operative MR via a pre-operative US calibrated to the intra-operative one. The pre-operative US (and hence, by calibration, the intra-operative one) is registered *rigidly* to the MR by means of *user identified anatomical landmarks*. Hata (Hata *et al.*, 1994) calibrated 2D US to a 3D MR system, but refined the obtained rigid registration by local Chamfer matching on semi-automatically extracted contours and surfaces.

10.1.16. Multimodal applications: X-ray

Betting (Betting and Feldmar, 1995) registered MR (or CT) to X-ray images (*2D/3D*) by a “silhouette” method: *automatic* extraction of the external contours in all involved images, followed by *3D rigidly* transforming the MR, projecting the transformed contours onto the X-ray plane, and minimizing the contour distance using a variation of the ICP algorithm. Lavallée (Lavallée and Szeliski, 1995; Lavallée *et al.*, 1996a) registered a *3D* CT to *two* X-ray images, acquired at a known angle to one another. From the X-ray planes in 3D space, the (*segmented*) external contours are projected out of plane, creating a bundle. The intersection of the two X-ray bundles defines an interior into which the CT is *rigidly* placed, minimizing the distance of the CT external surface to the bundles.

Both Betting and Lavallée aim to use their methods in a *patient to modality* intra-operative setting, using the 2D X-ray images for intermediaries. Therefore, their methods also appear in the *patient to modality* section, if experiments have been conducted using real patient data.

In radiotherapy literature, three instances of *rigid 2D/2D* X-ray to portal image registration were found. Eilertsen (Eilertsen *et al.*, 1994) finds the radiation field edges by means of a Radon transform. The X-ray (simulator) image is then registered *automatically* to the portal images by aligning the field edge corners. Ding (Ding *et al.*, 1993) also uses *landmarks*, either *geometrical* or *anatomical*, but *interactively* defined. Leszczynski (Leszczynski *et al.*, 1995) needs the field edges to be defined *interactively*, then performs Chamfer matching to find the correct transformation.

10.1.17. Modality to model registration

If models are obtained using statistics on different image data, the distinction between *modality to model* and *modality to atlas* registration is often vague. We subjectively draw the line between use of *fuzzy sets* (atlas) and *localized contours or surfaces* (models). The argument is that in the former case available information is used compounded, while in the latter case the information has been reduced to an average or modal model.

Modality to model registrations are nearly always *curved*. Bajcsy (Bajcsy *et al.*, 1983) performed elastic registration of a CT feature space (sub-images containing average intensity and edge information) to a model containing the brain and ventricular edges. Cuisenaire (Cuisenaire *et al.*, 1996) also used the brain and ventricular edges, but obtained from MR images. They were extracted from the MR by segmentation using a morphological watershed and closing algorithm. The model was obtained from a brain atlas obtained from a number of cryosectioned brains, and registration was performed by local Chamfer matching. Rizzo (Rizzo *et al.*, 1995) registered the cortical surface, obtained *semi-automatically* using edge detection, in an *elastic* fashion to a compartment model. Registration was performed on a slice-by-slice basis, after an initial manual axial correction.

10.1.18. Patient to modality registration

Without exception, the reported methods provide *rigid* transformations. This is not surprising, considering that it is very hard to obtain more than surface information from the patient. Paradoxically, there is often a clinical need for curved transformation in the intra-operative occurrence of the registration problem.

Many authors report on using *probes* in solving the patient to modality registration problem. A probe is a device either optically or magnetically tracked, or mounted on a robot arm, so the spatial location of the probe tip is known accurately at all times. Bucholz (Bucholz *et al.*, 1994) used CT, MR and PET images acquired with *skin markers*. After the image acquisition, the marker locations are marked with ink. During surgery, the patient wears a reference ring with LEDs clamped to the patient, which position is tracked optically. The ring is calibrated to the patient head position by probing the skin marker locations, hence the pre-operative images are calibrated to the patient. Edwards (Edwards *et al.*, 1995b; Edwards *et al.*, 1995a) used the probe in one of three registration approaches using a CT image. Either *anatomical landmarks* or *fiducials* where identified in the image and on the patient using the probe, or the skin surface was *segmented* from the CT and indicated on the patient by probing many surface points. The obtained spatial locations where subsequently registered using point or surface registration methods. The registration method using identifying *fiducials* and probing them during surgery is also used by Fuchs (Fuchs *et al.*, 1996) who used *skin markers* and a CT image, and Maurer (Maurer *et al.*, 1995b), who used an MR image and *invasive fiducials*. The method of registering a *segmented surface* from the CT image and a probed patient skin surface is also used by Henderson (Henderson *et al.*, 1994) using a CT image, and Ryan (Ryan *et al.*, 1995) and Wang (Wang *et al.*, 1994a) using an MR image.

Approaches using *stereo video* images of the patient where proposed by Evans, Betting, and Henri. Evans (Evans *et al.*, 1996b) identified *anatomical landmarks* on a stereo video image as well as in pre-operatively acquired CT or MR images to obtain registration. Betting (Betting *et al.*, 1995) and Henri (Henri *et al.*, 1995) used the skin surface extracted from the video image and a pre-operative image to find the registration transformation. Betting used either CT or MR images, Henri MR images. The registration methods use either Chamfer matching or ICP.

The extraction of the surface from stereo video images is not an easy task, and many authors use the skin surface as obtained by *laser range scanning* to obtain this surface, and register it with the skin surface *segmented* from pre-operative images. Cuchet (Cuchet *et al.*, 1995) used this method with MR images, Grimson (Grimson *et al.*, 1994a; Grimson *et al.*, 1994b; Grimson *et al.*, 1994c; Grimson *et al.*, 1995; Grimson *et al.*, 1996) used both CT or MR, and Harmon (Harmon *et al.*, 1994) and Vassal (Vassal *et al.*, 1995) only CT. The last author uses the method in a radiotherapy setting instead of the surgical theater, and also describes a different method, which is to perform the registration of patient to pre-treatment 3D CT by means of two X-ray or two portal images acquired at a known angle during the treatment. From all of the images involved contours are segmented. From the CT image, DRRs (Digitally Reconstructed Radiographs) are created, and registered to the real X-ray or portal projection images using minimization of the contour distance. Similar methods which use two acquired intra-treatment projection images for registration to a pre-treatment CT image are described by Vassal (Vassal *et al.*, 1995), Gilhuijs (Gilhuijs *et al.*, 1996), who uses bone ridges for contours, Gall (Gall and Verhey, 1993), who does not use contours, but *user identified invasive markers* (tantalum screws), Leung Lam (Leung Lam *et al.*, 1993), who used implanted and surface *markers*, and Bainville (Bainville *et al.*, 1995), who reconstructs a surface from the two radiographs. Lemieux (Lemieux *et al.*, 1994a) uses a similar method, but in a surgical setting by optimizing the cross-correlation between two intra-operative X-ray images and two DRRs from pre-operative CT.

The only truly *2D/3D* method (all the other ones are intrinsically *3D/3D*) was proposed by Betting (Betting and Feldmar, 1995) who used the silhouette method described in section 10.1.16 for registration of a single X-ray to pre-operatively acquired CT or MR.

A number of the above described methods are reported on by Hamadeh (Hamadeh *et al.*, 1995a), as used at a single site.

10.2. Registration of thoracic images

Registration of imaging of the thorax has three major application areas: *global*, *cardiac* and *breast*.

10.2.1. Registration of global thoracic images

Eberl (Eberl *et al.*, 1996) performed *3D rigid* registration of *monomodal* PET or SPECT images of the thorax by minimization of the SAD. In radiotherapy, two *2D* applications are reported. Moseley (Moseley and Munro, 1994) performed *monomodal affine* portal image registration using a two-pass approach: local translation-only registration is performed in a number of user defined regions by optimizing the cross-correlation. Then, the local shifts are combined (by least squares fitting) into a global *affine* transformation. Wang (Wang and Fallone, 1994) performed *rigid* registration of a portal to an X-ray (simulator) image by *moment* matching of the extracted radiation field edges. The edges were extracted automatically by using a morphological gradient and thresholding.

10.2.2. Registration of cardiac images

Cardiac image registration almost exclusively involves the use of *3D monomodal scintigraphic images*; we located only three exceptions. Tom (Tom *et al.*, 1994) performed *2D curved automatic* registration on series of X-ray angiographic images, by matching the skeletons of segmented arteries. Savi (Savi *et al.*, 1995) obtained *3D rigid* registration of US and PET images by aligning three *user defined anatomical landmarks*. Thirion (Thirion, 1995) performed *3D curved surface* registration on CT images using demons on segmented surfaces.

Thirion applies the same method to SPECT images. Other *curved* methods are reported by Goris and Lin. The former (Goris *et al.*, 1996) accomplishes *automatic 3D curved* SPECT-SPECT registration by using an ICP variation on extracted Canny edges in a 3-step way: first globally rigid, then affine, and finally locally *curved* by using a spline representation. The latter obtains a *3D curved* transformation between two PET sets *automatically* by a *voxel based* method on image subcubes. The actual paradigm used is not reported.

A *2D rigid* method based on *geometrical landmarks* was proposed by He (He *et al.*, 1991) for SPECT images. After the user selects the mid-ventricular slice, the algorithm finds the two local maxima along each horizontal image line, and then locates the local minimum in between them. It then least-squares fits a line trough the minima, and the resultant models the left ventricular long axis. Registration is performed by aligning the found axes from two images.

3D automatic voxel property/full image content based methods are reported by Bacharach, Bettinardi, Eberl, Hoh, Perault, and Slomka. All but Slomka's method are *rigid*. Bacharach (Bacharach *et al.*, 1993) performed PET-PET (emission) registration by optimizing the cross-correlation of the accompanying transmission scans[a]. He assumes the transmission and emission scans are internally registered. This is not always the case, as the patient is moved from the scanner bed after the transmission scan for tracer injection. Bettinardi (Bettinardi *et al.*, 1993) registers the PET transmission to the emission scan, by making a *second* transmission directly following the emission scan. He assumes the emission and second transmission scan registered, and can therefore register the first transmission to the emission scan by optimizing the cross correlation between the two transmission scans. Cross-correlation is also used for registering different PET (emission) scans by Perault (Perault *et al.*, 1995), *i.c.*, rest and stress scans of one patient. Eberl (Eberl *et al.*, 1996) finds the optimal transformation between two SPECT or PET images by optimizing the SAD. Hoh (Hoh *et al.*, 1993) also uses the SAD on PET images only, and compares the performance to optimizing the SSC. Finally, Slomka, performs *affine atlas* SPECT registration by minimization of the SAD, after an initial estimate using alignment of *principal axes*. His atlas is created by averaging a large number of normal SPECT scans registered in the same way.

Three authors report on *surface* based methods. Declerc (Declerc *et al.*, 1996) performs *affine or curved automatic* registration by a variation of ICP on two SPECT images using a surface based on pruned edges detected in a 3D polar map. Feldmar (Feldmar and Ayache, 1994; Feldmar *et al.*, 1996; Feldmar and Ayache, 1996) also used an ICP variation on SPECT images. See section 10.1.2 for a description. Pallotta (Pallotta *et al.*, 1995) obtained a *3D rigid* transformation between two (emission) PET scans by Chamfer matching of *surfaces* obtained by thresholding the accompanying transmission scans.

[a]Many PET scanners come equipped with the possibility of transmission scanning prior to tracer injection and normal emission scanning. A radioactive line source is employed for this, and the resulting transmission image has a CT-like character and is used for a tissue attenuation map in the emission image reconstruction.

10.2.3. Registration of breast images

Consensus of registration of breast images seems to be that it is archetypal to the non-rigid registration problems. Perhaps the thus induced complexity is the reason that little attempt has been made to solve the registration problem. This makes Zuo's recent publication (Zuo *et al.*, 1996) all the more surprising, since it claims that serially acquired MR images (with and without a contrast agent) of a freely suspended breast imaged using a breast coil, display only *rigid* motion, if any at all. In this chapter, *3D* motion correction is performed using the *full image content* employing Woods' (1993) minimization of variance of intensity ratios. The only other publication found (Kumar *et al.*, 1996) performed *automatic 3D curved* registration on two MR images with and without contrast agent by minimizing the sum of squared intensity differences between the images. For a pre-registration, the same procedure was first applied in an *affine* manner.

10.3. Registration of abdominal images

Registration of abdominal images appears only as applied to renal or hepatic images in the literature.

Renal images: Venot (Venot and Leclerc, 1984) applied *2D automatic rigid* registration to DSA images of the kidney by minimizing the DSC criterion. In the same application of DSA images, Buzug (Buzug and Weese, 1996) found a *2D automatic affine* transformation by combining local translations found in image subcubes by minimizing the entropy of the subtraction image. Péria (Péria *et al.*, 1995) performed *non-image based 3D automatic rigid* registration of US and SPECT images by calibrating the US scanner to the SPECT coordinate system, and acquiring the US image while the patient is still on the SPECT gantry.

Hepatic images: Venot (Venot *et al.*, 1983; Venot *et al.*, 1984) applied the same DSC strategy mentioned above to SPECT images of the liver. Hoh (Hoh *et al.*, 1993) finds a *3D rigid automatic* registration in a similar way by minimizing the SAD or SSC criterion. Scott *3D rigidly* registers CT or MR images to SPECT images by using the head-hat method on *manually* drawn contours (Scott *et al.*, 1994), or using CT external contours and contours obtained from an abdominal *fiduciary* band in SPECT (Scott *et al.*, 1995).

10.4. Registration of pelvic images

Except for Venot and Studholme, all of the encountered papers appear in the context of radiotherapy. Venot (Venot and Leclerc, 1984) performed *2D rigid automatic* registration of DSA images of the iliac arteries by means of optimizing the DSC criterion. Studholme found a *3D rigid automatic* transformations between MR and PET images by optimization of the mutual information of the joint histogram.

The radiotherapy applications can be divided in *2D* applications, and *3D patient to modality* registration applications. *2D* applications where proposed by Dong, Ding, Eilertsen, Fritsch, Gilhuijs, and Wang. Dong registered portal images in a *2D affine automatic fashion* by optimization of the cross-correlation. Ding (Ding *et al.*, 1993) registered X-ray to portal images by means of *user identified landmarks*. Eilertsen (Eilertsen *et al.*, 1994), in the same application, uses alignment of the corners of the field edges, where the field edges are extracted using a Radon transform. Fritsch (Fritsch, 1993; Fritsch *et al.*, 1994b; Fritsch *et al.*, 1994a) registers portal images *rigidly* by minimizing the distance between their cores, *i.e.*, their multi-scale medial axes. Gilhuijs (Gilhuijs and van Herk, 1993) finds a *2D affine automatic* transformation by Chamfer matching extracted edges from X-ray and portal images. Finally, Wang (Wang *et al.*, 1996b) does *2D* translation-only registration of portal images based on phase-only correlation in the Fourier domain.

3D patient to modality registration was done by Troccaz (Troccaz *et al.*, 1995), who achieved this by *calibrating* a US probe to the radiotherapy system, and registering pre-treatment CT or MR to the US images by means of *user segmented* surfaces. Four other approaches to *3D patient to modality* were suggested, all of which involve the use of intra-treatment acquired portal or X-ray images. Bijhold (Bijhold, 1993) performed the registration by employing *user defined anatomical landmarks* in a pre-treatment CT image and the intra-treatment portal or X-ray images. Gall (Gall and Verhey, 1993) used a similar technique with *invasive fiducial markers* and two X-ray images. Gilhuijs (Gilhuijs *et al.*, 1996) found the transformation *automatically* using 2 X-ray or portal images using the technique described in 10.1.18. Vassal (Vassal *et al.*, 1995) used a similar technique for registration of pre-treatment CT or MR to the patient, using two portal or X-ray images, or one of two other techniques, namely a *calibrated* US probe, or *surface based* registration using a patient surface obtained by a *calibrated* laser range finder.

10.5. Registration of limb images

Registration of limb images is reported on almost exclusively in the context of orthopedic interventions, notably at the femur. Other application areas include the tibia, calcaneus and humerus, but there are usually few restrictions to adapt a certain registration method to another region. The transformations found are all *rigid*, as they concern mainly the displacement of bones. Hence, modalities always include CT or X-ray images. Since the bone contrast is very high, most methods, even those including segmentation tasks, can be automated.

X-ray to CT registration was performed by Ellis and Gottesfeld Brown. Ellis (Ellis *et al.*, 1996) finds a *2D/3D* registration between an (X-ray) röntgenstereogrammetric analysis (RSA[a]) and a CT image, by using *invasive fiducial markers* attached to the bone surface of the tibia. Gottesfeld Brown (Gottesfeld Brown and Boult, 1996) finds an *automatic 2D/3D* transformation by optimizing the cross-correlation between the X-ray and a DRR from the CT of the femur.

Monomodal 3D CT registration was done by Hemler (Hemler *et al.*, 1995b) using surface registration on *manually* corrected, automatically segmented surfaces of calcaneus. Münch (Münch and Rüegsegger, 1993) performed an *automatic* registration by optimizing the cross-correlation of femural images. Jacq (Jacq and Roux, 1995) performed *curved automatic* registration on images of the humerus by minimization of the local grey value differences.

Patient to CT modality registration was proposed by Lea, and Simon. Lea (Lea *et al.*, 1994) gives an overview of current orthopedic methods, notably applied to the femur and tibia. Simon (Simon *et al.*, 1995b) compares *invasive fiducial* and *surface based* methods on femural images, and presents an *automatic* method on the same images using an ICP variation sped up by using Kd-trees (Simon *et al.*, 1995a; Simon *et al.*, 1994).

Two other applications are reported on: Ault (Ault and Siegel, 1995; Ault and Siegel, 1994) registered US to CT images in an *automatic* fashion by means of *geometrical landmarks*, corners detected in the US and a surface model obtained from the CT. Finally, Amit (Amit and Kong, 1996) performed *2D curved automatic modality to model* registration on X-ray images of the hand by graph matching it to a model containing for nodes all anatomical flexion points.

10.6. Registration of spinal images

Except for van den Elsen, all of the reported algorithms are *surface based*. She (van den Elsen *et al.*, 1994) performs *3D rigid automatic* registration in a *full image content* based way by optimizing the cross-correlation between a CT and MR image, where the CT grey values are first remapped using localized linear transforms.

Burel and Bainville assume that the two spinal surfaces to be registered are given; no modality is named. The former (Burel *et al.*, 1995) performs *3D* rotation-only registration by decomposing each surface into its spherical harmonics. Optimization is performed by using their special geometrical invariances. Bainville (Bainville *et al.*, 1995) found a local *curved* spline deformation using the local closest point of the surfaces combined with a regularization term.

Hemler (Hemler *et al.*, 1994a; Hemler *et al.*, 1994b; Hemler *et al.*, 1995b) performs *3D rigid* registration of CT and MR images by means of an automatically extracted, user corrected surface. The surface is based on tracked Canny edges. Hamadeh (Hamadeh *et al.*, 1995b) initially suggested the use of four *user identified anatomical landmarks* for *2D/3D* registration of X-ray to CT or MR images. This technique is only used for a pre-registration in later work (Hamadeh *et al.*, 1995c), where *patient to modality* (CT) is performed using a calibrated X-ray in an intermediary step. In the pre-operative CT, a surface is segmented in a *semi-automated* way. From the intra-operative X-ray image contours are extracted by Canny-Deriche edge detection followed by hysteresis thresholding. The contour is then registered to the surface using Lavallée's "bundle" method described in section 10.1.16. Lavallée himself uses the very same method (Lavallée and Szeliski, 1995; Lavallée, 1996), but using *two* X-ray images, as described in section 10.1.16. In earlier work (Lavallée *et al.*, 1994), pre-operative CT is registered to the patient by registering probed points to a surface segmented from the CT. In later work (Lavallée *et al.*, 1996b) the probed surface can also be replaced by an US image. Szeliski (Szelisky and Lavallée, 1994; Szeliski and Lavallée, 1994; Szeliski and Lavallée, 1996), finally, performed *3D curved* registration of CT images, given segmented surfaces, using local spline deformations, where the surface distance computation is simplified using a pre-computed octree distance map.

[a]Also known as stereophotogrammetry (SPG).

10.7. General papers

Papers that cannot or cannot easily be classified in specific *object* classes, are cited in this section. Typically, such papers contain overviews of methods, general applicable registration approaches (see Maintz (Maintz, 1996)), or correspondences regarding aspects of some method.

10.7.1. Overviews

Overviews of papers concerning medical image registration were presented by Maurer (Maurer and Fitzpatrick, 1993), van den Elsen (van den Elsen *et al.*, 1993) and Viergever (Viergever *et al.*, 1995). Overviews not primarily literature oriented were given by Barillot (Barillot *et al.*, 1993; Barillot *et al.*, 1995) and Hawkes (Hawkes *et al.*, 1995). Limited Overviews were presented by Collignon (Collignon *et al.*, 1993b) (surface based methods), Lavallée (Lavallée, 1996) (computer aided surgery (CAS) methods), Lea (Lea *et al.*, 1995a; Lea *et al.*, 1995b) (CAS methods including a graph classification), and McInerney (McInerney and Terzopoulos, 1996) (deformable models used in medical imaging).

10.7.2. Correspondences regarding existing methods
Improvements to existing surface based methods are suggested by Collignon (Collignon *et al.*, 1993a). Feldmar (Feldmar *et al.*, 1995) proposes an extension to ICP to handle 2D/3D registration. Registration methods based on point sets are addressed by Kanatani (Kanatani, 1994), who proposes extensions to existing rotation only methods, and Krattenthaler (Krattenthaler *et al.*, 1994), who suggests speed up techniques. Ways to speed up optimization of mutual information based registration are suggested by Pokrandt (Pokrandt, 1996).

11. RELATED ISSUES

11.1. How to use the registration

After a registration has been obtained, two questions appear paramount: *How accurate is the computed registration?* and *How can it be used?* The latter question presents us with an entire area of research of its own: the answer may be quite simple, *e.g.*, only some statistical property of the subtracted registered images is required, to highly complex, *e.g.*, a hybrid transparent stereo rendering that needs to be projected onto an operating microscope ocular is asked for. Such complex uses invariably require non-trivial visualizations in which segmentation must figure. This creates a paradox: on the one hand, many registration applications show how intertwined the problems of registration and segmentation can be, and hence the designer of the registration algorithm is tempted to draw on his own expertise in answering the question on how the registration is to be used; indeed, this question must have figured in the registration algorithm design, which should have started out with a clinical need for registration. On the other hand, once a registration is obtained, the problem of *How to use it?* poses interdisciplinary problems of a previously unencountered nature. Be that as it may, fact is that few registration papers attempt to follow up on the use of the registration, and likewise few papers in a vast plethora of visualization papers employ registered images for input[a]. The cause for this may be found in the fact that visualization solutions are often highly specific and problem dedicated, and in the interdisciplinary nature of the problem. In other words: the areas of registration and visualization are still widely apart; not many registrations use state-of-the-art visualization, nor do many visualizations use registered input. Such solitary stances can be observed concerning other research areas too: registration and segmentation have many a common interest, yet are seldom integrated. Also, registration is rarely used in many clinical applications, even though such applications may benefit from registered images; in many cases the potential of image registration is still an unknown. This can be accredited to the fact that registration research is relatively young area where many applications are concerned, to the fact that registration often involves new visualizations that possibly come with a steep interpretation learning-curve, to the fact that registration accuracy is often very hard to quantify sufficiently, to the logistic problems involved in integrating digital (or even analog) data from different machines often departments apart, to the extra equipment and time needed, and to the interdisciplinary gap. The point of this long-winded periphrastic soliloquy is that the question *how can the registration be used* is for the most part still unanswered: even though the need for registration is born out of a clinical need, the track *after* obtaining the transformation parameters is still largely blank.

[a]Mostly the area of segmentation-free image *fusion* addresses this problem, but its applications to medical image problems are severely limited (Burt, 1993; Chou *et al.*, 1995; Li *et al.*, 1994a; Li *et al.*, 1995; Pietrzyk *et al.*, 1996; Wasserman *et al.*, 1994; Wasserman and Acharya, 1995; Wahl *et al.*, 1993; Zhou, 1994).

11.2. Validation

The other question concerning a computed registration entails the accuracy. The answer is non-trivial for the simple reason that a gold standard is lacking regarding clinical practice. We can usually only supply a measure of accuracy by reference to controlled phantom studies, simulations, or other registration methods. Such measures are often lacking as concerns clinical needs: not only does a thus obtained reference accuracy require the need for an accuracy *variability* measure –since the accuracy cannot be made local in a clinical example, and therefore needs to be supplied with reliability bounds–, but neither do such measures easily transfer to particular clinical cases, *e.g.*, instances of abnormally distortive pathology.

There is a widespread quest for measures that somehow quantify registration accuracy. In our opinion, such a task is paradoxical, because of the simple fact that if such measures existed, *they would be used for registration paradigms*[b] Which brings us to a positivistic statement on accuracy: *We cannot, with absolute certainty, quantify local registration errors. However, given that we can transfer error measures obtained by reference, we can eventually say that it is* unlikely *for the error to exceed a certain bound.*

For many applications, the phase where sufficiently small errors can be ascertained has not yet been reached. In many instances, proper accuracy studies are just starting. What is particularly hampering to giving any statistics on certain methods is not only the incomparability of accuracy experiments done on particular sites–images are often

[b]As with many bold statements, this one is not entirely true, in the sense that we cannot simply use any paradigm, *e.g.*, since we are restricted in terms of computation time and convergence properties of the criterion used. Nevertheless, the gist of the statement holds.

proprietary, implementation and circumstances site specific, circumstances are different *etc.* – but also the imprecise use of the terms *accuracy, precision*, and *robustness* in many studies. The notion that public databases of representative images are to be created, and validation protocols need to be assembled, is only now emerging. The involved logistics, cost, and effort, however, make prospects Utopian for many registration applications.

11.2.1. Validation definitions

Validation of a registration embodies more than the accuracy verification. The list of items includes:

- Precision
- Accuracy
- Robustness/stability
- Reliability
- Resource requirements
- Algorithm complexity
- Assumption verification
- Clinical use

Except for the first two items (treated in the next paragraph), where the distinction is at times vague, unique definitions can be supplied. *Robustness* or *stability* refers to the basic requirement that small variations in the input should result in small variations in the output, *i.e.*, if input images are aligned in a slightly varied orientation, the algorithm should converge to approximately the same result. *Reliability* is the requirement that the algorithm should behave as expected, given a reasonable range of possible clinical input. *Resource requirements* concern the material and effort involved in the registration process. These should be reasonable relative to the clinical merit obtained from the registration. The *algorithm complexity* and related computation time should be adapted to the time and resource constraints of the clinical environment. Time can be a constraint in a two fold manner; either a single registration needs to be performed on-line because of direct clinical requirements, or multiple registrations appear in clinical *routine*, and need to be performed in a reasonable time frame so as not to cause lag in the clinical track. The *assumptions* on reality made in the paradigm and optimization modeling should be verified to hold up sufficiently in practice. Finally, the *clinical use* should be verified: does the registration provide in a clinical need, and does its use outweigh available alternatives? In ideal circumstances, all of the criteria should be satisfied. However, it is unrealistic to assume that all criteria can be met within one application; the weight attached to each criterion is application dependent, and a matter of judgment.

We have not yet defined *precision* or *accuracy*. For the problem at hand, we stray somewhat from conventional definitions. We define *precision* as the typical systematic error that can be obtained when the registration algorithm is supplied with idealized input. For example, a simple one dimensional shift optimization algorithm that does exhaustive searching with a resolution of two pixels, is expected to perform with a precision of within two pixels when given ideal input, *e.g.*, two identical images. In a more complex vein, a local error measurement obtained at an invasive fiducial marker used in the registration process can be regarded as a precision measure. Precision measures can be obtained concerning the entire registration system, or applying to specific components, like the patient (movement, artifacts), the acquisition, the paradigm, and the optimization, although we are tempted to remove the patient from the list, as modeling and quantizations are hard here. *Accuracy* is a more direct measure, referring to the actual, "true" error occuring at a specific image location. Where precision is a system property, accuracy applies to specific registration instances. Accuracy will be the property that immediately concerns the clinician: for example, the surgeon can point at the screen and say "I must make an incision *here*. How accurate can this location be determined in the patient?". Accuracy can be divided into *qualitative* and *quantitative* accuracy. The former can usually be supplied using simple visualization tools and visual inspection, *e.g.*, when registering CT and MR brain images, overlaying the segmented bone contours onto MR slices supplies the clinician with a reasonable idea of accuracy. *Quantitative* accuracy, as pointed out before, needs a ground truth that is unavailable in clinical practice, and therefore needs to be emulated by reference to another measure.

Typically, evaluations of a registration method as concerns accuracy and precision (and other criteria) may occur at a number of levels: *synthetic, phantom, pre-clinical*, and *clinical*. The *synthetic* level is entirely software-based. The images used at this level can be controlled in every aspect. If images are *simulated* emulating the clinical acquisition, we speak of a *software phantom*. The merits of software phantoms include the availability of ground truth, and the fact that realistic image degrading factors can be controlled. The (physical) *phantom* level makes use of true image acquisitions, usually imaging anthropomorphic models. At this stage, ground truth is no longer available, but it can be approximated with high accuracy by introducing markers into the phantom, by using multiple acquisitions, and the fact that phantom movements can be controlled. The *pre-clinical* level involves using real patient (or volunteer) or cadaver data. Ground truth can again only be approximated at this level, although frequently accurately so by reference to a registration based on an established registration method. Cadaver studies offer good opportunities here, as patient movement is absent or fully controlled, and patient friendliness can be disregarded in obtaining the registration standard. Studies using real patient data should optimally employ images drawn from a database containing generic as well as acquisitionally and pathologically exceptional data. Finally, at the *clinical* level the registration method is used in the clinical routine, at the intended application level. At this stage, a reference registration may or may not be available, and validation should primarily be turned over to the clinicians involved.

11.2.2. Validation: a survey

As mentioned before, validation studies are only now emerging. Many papers address some precision or accuracy validation at some level, but few extensively so, and even then is precision often restricted to the algorithmic level. Given the effort and time that needs to be expended in a complete validation study, this is not surprising, nor would it be a realistic expectation from authors presenting some new registration paradigm.

Those instances of validation we found are cited in this paragraph. We do not include robustness studies, nor precision studies not exceeding the algorithm level, *i.e.*, authors adding known transformations to input images to see if they can be recovered by the algorithm. Validation studies are frequently part of a paper presenting a new registration approach, but some papers are dedicated[a] entirely to validation.

Method validation by reference to external marker based methods can be found in (Ardekani *et al.*, 1995; Ayache *et al.*, 1993; van den Elsen and Viergever, 1993; van den Elsen *et al.*, 1994; van den Elsen *et al.*, 1995; Ge *et al.*, 1996; Leslie *et al.*, 1995; Maes *et al.*, 1996; Maurer *et al.*, 1995b; Maurer *et al.*, 1993; Maurer *et al.*, 1994; Maurer *et al.*, 1995a; Maintz *et al.*, 1994; Maintz *et al.*, 1996a; Simon *et al.*, 1995b; Turkington *et al.*, 1995; West et al., 1996; Zubal *et al.*, 1991). Validation by comparison to registration based on probed points is found in (Evans *et al.*, 1996b; Ellis *et al.*, 1996), by comparison to manually identified anatomical landmark based registration in (Andersson *et al.*, 1995; Collins *et al.*, 1994a; Collins *et al.*, 1994b; Evans *et al.*, 1989; Gee *et al.*, 1993; Gee *et al.*, 1995b; Hill *et al.*, 1993a; Leslie *et al.*, 1995; Moseley and Munro, 1994; Studholme *et al.*, 1995b; Studholme *et al.*, 1995a; Strother *et al.*, 1994), and by comparison to frame based registration in (Collignon *et al.*, 1995a; Collignon *et al.*, 1995b; Ge *et al.*, 1994; Henri *et al.*, 1992; Lemieux *et al.*, 1994b; Lemieux and Jagoe, 1994; Strother *et al.*, 1994; Woods *et al.*, 1993). Cross-method validation (reference to other intrinsic methods than the one principally used) is reported in (Andersson, 1995; Collignon *et al.*, 1995a; Eberl *et al.*, 1996; Hua and Fram, 1993; Hoh *et al.*, 1993; Lehmann *et al.*, 1996; Leszczynski *et al.*, 1995; Maurer *et al.*, 1995a; Maintz *et al.*, 1996c; Maintz *et al.*, 1995; Maintz *et al.*, 1996b; Simon *et al.*, 1995b; Studholme *et al.*, 1995b; Studholme *et al.*, 1995a; Strother *et al.*, 1994; West et al., 1996). Most popular validation techniques employ a physical phantom, possibly with controlled movement, and possibly with marking devices inserted or attached. Examples are found in (Bijhold, 1993; Betting and Feldmar, 1995; Bettinardi *et al.*, 1993; Chen *et al.*, 1987; Dong and Boyer, 1996; Ding *et al.*, 1993; Eberl *et al.*, 1996; Grimson *et al.*, 1994a; Grimson *et al.*, 1994b; Grimson *et al.*, 1994c; Grimson *et al.*, 1995; Grimson *et al.*, 1996; Gottesfeld Brown and Boult, 1996; Gluhchev and Shalev, 1993; Gall and Verhey, 1993; Holton *et al.*, 1995; Holton-Tainter *et al.*, 1995; Lemieux *et al.*, 1994a; Lavallée *et al.*, 1994; Lavallée and Szeliski, 1995; Lavallée *et al.*, 1996b; Lavallée *et al.*, 1996a; Leung Lam *et al.*, 1993; Maurer *et al.*, 1993; McParland and Kumaradas, 1995; Moseley and Munro, 1994; Péria *et al.*, 1994; Pallotta *et al.*, 1995; Petti *et al.*, 1994; Turkington *et al.*, 1993; Taneja *et al.*, 1994; Vassal *et al.*, 1995). Simulator studies, *i.e.*, studies were one modality is simulated from the other to obtain a registration standard, is found in (Cuchet *et al.*, 1995; Evans *et al.*, 1996a; Fritsch, 1993; Fritsch *et al.*, 1994b; Fritsch *et al.*, 1994a; Neelin *et al.*, 1993). Intra- and/or interobserver studies are performed in (Hill *et al.*, 1991a; Malison *et al.*, 1993; Pietrzyk *et al.*, 1994; Stapleton *et al.*, 1995). Finally, Hemler (Hemler *et al.*, 1994a; Hemler *et al.*, 1995c; Hemler *et al.*, 1995a; Hemler *et al.*, 1996) performed cadaver studies using inserted markers for reference.

[a]See, *e.g.*, (Holton *et al.*, 1995; Holton *et al.*, 1995; Lemieux *et al.*, 1994b; Lemieux and Jagoe, 1994; Maurer *et al.*, 1993; Maurer *et al.*, 1994; Neelin *et al.*, 1993; Strother *et al.*, 1994; Turkington *et al.*, 1993; Taneja *et al.*, 1994; Vassal *et al.*, 1995)

12. 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[a] However, the resolution of the images should not be used to formulate a clinically relevant level of accuracy: it is very 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.

[a]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.

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