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Integration of functional and anatomical brain images

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Abstract

This article concerns the integration of functional and anatomical volumetric brain images. Integration consists of two steps: matching or registration, where the images are brought into spatial agreement, and fusion or simultaneous display where the registered multimodal image information is presented in an integrated fashion. Approaches to register multiple images are divided into extrinsic methods based on artificial markers, and intrinsic matching methods based solely on the patient related image data. The various methods are compared by a number of characteristics, which leads to a clear preference for one class of intrinsic methods, viz. voxel-based matching. Furthermore, two- and three-dimensional techniques to display multimodality image information are outlined. © 1997 Elsevier Science B.V.

Keywords: Brain imaging; Multimodality registration; Multimodality visualization; Functional–anatomical integration

1. Introduction: purpose and scope

Integration of images from multiple modalities has rapidly evolved into a substantial area of research in medical imaging. There are two major causes for this development.

First, performing the calculations involved in registering two three-dimensional (3D) datasets has become feasible on present-day computers. This has paved the way for novel matching approaches that are based on the full contents of the images rather than on just a few points from artificial markers or anatomical landmarks.

Second, there is a steadily growing demand from the clinic for multimodality integration, in particular in neurosurgery and radiation treatment planning and evaluation.

In Van den Elsen et al. [1] a classification of image registration methods is given according to a number of discerning criteria. The main criteria are:

Dimensionality: 2D/3D/4D. In 2D methods, projection images or tomographic slices of different recordings are aligned, under the — often implicit — assumption that the images are in the same plane relative to the patient. Spatial 3D methods bring a volumetric data set into spatial agreement with another — 2D or 3D — image. Spatiotemporal registration of time series of 2D images also is a 3D matching problem and, likewise, matching of series of 3D images is a 4D approach.

Nature of matched properties: extrinsic/intrinsic. Extrinsic methods use artificial objects as stereotactic frames, head or dental moulds, or skin markers for the registration. Intrinsic matching methods work with image data only. Properties used include the pixel or voxel intensities, (scaled) differential invari-

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ants, anatomical landmark points, and object features like contours (for 2D images) or surfaces (for 3D images).

Elasticity of the transformations: rigid/affine/projective/curved. A transformation is rigid if the distance between any two points in the image is preserved, affine when any straight line is mapped onto a straight line while parallelism is preserved, projective when the constraint of parallelism is dropped in the latter definition, and curved if straightness of lines is generally not preserved. Rigid transformations are a subset of affine transformations, affine of projective, and projective of curved transformations. Transformations are generically categorized in the most specific class.

Interaction: interactive, semi-automatic, automatic. The amount of interaction required for a certain method is not readily measured. A simple classification is obtained by defining methods as interactive if they require human interference in determining the transformation, as semi-automatic if user interaction is required only for starting, guidance, and/or stopping of the matching procedure, while automatic methods can do without any interaction.

The scope of the present paper is now outlined.

As the title indicates, only integration of functional and anatomical brain images, a subclass of multimodal image-to-image matching, will be covered. This excludes image-to-image matching of single modality image data and image-to-atlas matching. Image-to-image matching generally deals with data from the same patient, whence it is natural to consider only rigid transformations (translations and rotations).

The survey will furthermore be limited to registration of two volumetric images: matching of a 3D image with a 2D image and matching of time series of images are not dealt with. Brain imaging modalities that produce anatomic volumetric data are computed tomography (CT), CT angiography (CTA), magnetic resonance imaging (MRI), and MR angiography (MRA). Functional volumetric brain imaging modalities are perfusion weighted MRI (PWI), diffusion weighted MRI (DWI), MR spectroscopic imaging (MRSI), functional MRI (fMRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT). In addition, functional volumetric information may be inferred from electro-encephalography (EEG) or magneto-encephalography (MEG) by means of mathematical modelling (source localization). These modalities are included in the study.

Intrinsic and extrinsic methods will both be discussed. The emphasis will be on intrinsic methods, however, since evidence is accumulating that these are superior to extrinsic methods. This categorization will be discussed in more detail in the next section.

The purpose of the paper is to give a state-of-the-art survey of methods for integration of volumetric brain images from multiple modalities, with an emphasis on functional–anatomical integration. Approaches to image registration are described and compared by a number of characteristics. It will be shown that these criteria are appropriate to clearly select a class of approaches as being superior. The second issue, multimodal visualization of the registered data, does not readily admit of such an outspoken conclusion. We will give an overview and a brief description of approaches to integrated image presentation. However, the question of which display technique is the most suitable is strongly task dependent, which prevents a general evaluation of visualization methods.

2. Multimodality image registration

This section discusses rigid registration of multimodal volumetric brain images. In keeping with the categorization of the preceding section, the approaches are divided into extrinsic and intrinsic matching. Extrinsic registration methods are subdivided according to the type of artificial marker employed, intrinsic methods according to the property of the image data used for matching. This yields the following classification:

Extrinsic matching:

- Stereotactic frame/skull screws
- Non-invasively fixated mould or frame
- Skin markers

Intrinsic matching:

- Anatomical landmarks
- Structures/objects
- Voxel properties

We will briefly discuss each of these classes of image matching methods, taking into account criteria as accuracy of the match, patient-friendliness, reproducibility, labour-extensiveness, feasibility of doing the match retrospectively, extensibility to curved matching, and applicability to all clinically accepted brain imaging methods. At the end of the section, a tabular overview of the matching methods vs. these quality criteria is presented.

2.1. Extrinsic matching

The three approaches classified under extrinsic matching have in common that they do not admit of retrospective matching, which entails that the clinical protocols must take account of the requirements of the matching procedures. Consequently, an image that was acquired before the necessity of multimodality integration is recognized, cannot be included in the matching procedure if extrinsic approaches are used.

2.1.1. Stereotactic frame / skull screws

In stereotactic neurosurgery, a rigid frame is attached to the head of the patient to guide the surgical instruments. In the image acquisition stage, localizer frames containing point markers or line markers (rods) are attached to the sterotactic frame in order to provide a reference system for all imaging modalities. Consequently, an accurate registration of all multimodal images for surgery planning is ensured. We use the terminology stereotactic frame exclusively for a frame which is fixated to the skull by screws [2,3]. Non-invasive moulds and adapters are treated under the next heading.

Stereotactic frame based registration is the least patient-friendly of all image integration approaches. It has a high degree of reproducibility, and applying it is rather labour-intensive. The use of stereotactic frames for image registration is restricted, firstly since the frame cannot be attached to all patients and secondly because the size of the frame is prohibitively large to be used in imaging devices as some head coils of MRI scanners and multiple headed SPECT cameras. The latter drawback can be avoided by just employing skull screws rather than the entire frame [4,5]. This set-up still allows the use of the thus obtained image information as a guidance in neurosurgery, provided one has the disposal of a surgical microscope that can combine — upon registration of the coordinates — the pre-operatively acquired image data with the intra-operative microscope image. Such microscopes are now commercially available.

For a long time, stereotactic frame based matching has been the gold standard for image integration. This no longer holds true. Even though the accuracy of stereotactic frame based methods can be increased by knowledge-based methods [6], there is increasing evidence that intrinsic methods can attain a higher accuracy, while they are also more attractive by any other of the criteria used. This issue will be further discussed below.

2.1.2. Non-invasively fixated mould or frame

Non-invasively fixated alternatives to the stereotactic frame are a thermoplastic mask [7], a dental mould [8], a combination of these [9], and an adapter with a nasion support and ear plugs [10]. These devices are all slightly less accurate than the stereotactic frame, generally more labour-intensive because individual moulds have to be made for each patient, and provide less reproducible matching results. On the other hand, the methods are more patient-friendly and more generally applicable; both limitations to general application of the stereotactic frame hold to a lesser extent for these devices.

Non-invasive frames are suited primarily for radiotherapy purposes (registration of CT with treatment beams); they have little use in functional imaging, and thus in functional–anatomical image integration.

2.1.3. Skin markers

Image registration using skin markers is patient-friendly and applicable to all clinical imaging modalities. The reproducibility is good for brief time intervals, in which case the reference points of the markers can be marked with (if necessary, invisible) ink; for long time intervals, the reproducibility is at best fair.

The accuracy of point marker based matching may be quite good under ideal circumstances, i.e., when the tomographic image slices are thin and interslice gaps are narrow or absent, and when the reference points are inside the scanned volume. The method is not very labour-intensive if the number of markers is limited to four or five [11]. For image protocols with thick slices and/or large interslice gaps, the accuracy of point marker based registration is poor.

Arrow-shaped skin markers were introduced in Van den Elsen et al. [12] to combine EEG or MEG derived 3D dipole data with tomographic (CT, MRI) image data of the same patient. Subsequently, this type of marker was used for various image-to-image matching procedures [13,14]. The main advantage of arrow-shaped markers over point-shaped markers is that they can be located in tomographic images with subslice accuracy, which makes them superior especially in matching data sets with an inferior sampling in the axial direction. Furthermore, the markers can indicate points slightly outside of the scanned volume.

2.2. Intrinsic matching

The three methods classified under intrinsic matching have two properties in common. The first is the retrospective nature of the match; the imaging protocols need not make provisions for the matching procedure. The second common property is, accordingly, the extreme patient-friendliness of the approaches. The key problem of intrinsic matching methods is the selection of the image properties on which the match is based. These have to be derived from quite dissimilar images, which poses a challenging task.

2.2.1. Anatomical landmarks

Image registration using anatomical landmarks is generally a rather labour-intensive process, since the landmarks have to be pointed out interactively (e.g., [15–17]). While a first guess may be provided by automatic means, no fully automated landmark extraction algorithms have been reported. Consequently, the approach has a low degree of reproducibility. The accuracy is fair and increases with the number of landmarks used until a certain limit is reached (typically at around 20–25 landmarks [18]). Landmark matching is applicable to all tomographic imaging modalities and can readily be extended to nonlinear (curved) matching. This latter property is shared only by voxel-based methods.

2.2.2. Structures / objects

Object-based image matching has become popular by the work of Pelizzari and coworkers [19–21]. Their method defines objects by contour detection in the 2D slices of the tomographic set; most commonly the external surface of the skin is used for registration. In one image modality (the one covering the larger volume of the patient), these contours are stacked to generate a surface, the 'head', onto which a 'hat', consisting of a set of points derived from the contours in the other modality, is fitted by means of an optimization procedure. The method is quite accurate and applicable to all tomographic imaging modalities (although for application to PET and SPECT the availability of a transmission scan is desirable); the robustness is questionable, though, owing to the dependency on a high-level object definition. The main disadvantage of the method is that user interaction is required to steer the optimization process, both by identifying the parts of the 'head' and 'hat' to be used and by selecting and adapting the transformation parameters.

Several attempts have been made to improve upon the original concept of Pelizzari. For example, Jiang et al. [22] increased the accuracy of the match by removing outliers which result from imperfect segmentation of the surfaces in a threshold-based approach. Collignon et al. [23] proposed a more flexible method for outlier removal. Furthermore, they combined their concepts of object matching and anatomical landmark matching into one algorithm. Van Herk and Kooy [24] succeeded in rendering object matching free of user interaction by basing it on automatic segmentation; however, they did not include any outlier removal procedure.

Object definition is a high-level task, which is difficult to automate without endangering the accuracy. Instead, multimodality matching may be based on low-level binary feature images. Such images may be robustly produced by differentiation of the original grey scale image in a scale space setting [25].

Given natural symmetry constraints, it can be shown that the unique linear blurring kernel to construct a scale space is the Gaussian function [26]. The family of Gaussian derivatives provides a framework to define geometric invariants for, e.g., spatial orthogonal transformations [27].

Van den Elsen et al. [28] used a second order invariant, evaluated by Maintz et al. [29], to extract ridge-like structures (i.e., structures medially located in image objects) from CT and MR images. The resulting feature images were thresholded to yield binary images which were registered by means of a hierarchical chamfer matching algorithm [30]. The method compares favourably with registration using arrow-shaped markers, but later proved to be inferior to registering the full feature images, which will be discussed below.

A theoretically promising intrinsic registration method based on higher order geometrical properties is core matching [31]. The core was earlier referred to as the multiscale medical axis, which can be thought of as a set of curves that represent the approximate middle of image objects. The adjective 'multiscale' refers to the fact that the medial axis has an additional parameter indicative of the local width of the object it represents. Cores extracted from multimodal images are attractive structures for registration, since their multiscale nature is more comprehensive than the single scale ridges and edges discussed above. The practical results of method are not yet convincing, both because of the size of the registration errors and because of the highly interactive nature of the method [32].

2.2.3. Voxel properties

Multimodality registration methods based on voxel properties have only recently appeared on the scene, but they have nonetheless taken the lead in brain image matching. This type of methods shares the advantages of being retrospective, patient-friendly, and generally applicable with the other classes of intrinsic matching approaches. In addition, most voxel-based methods do not require user interaction and thus are both labour-extensive and reproducible; they can also be extended to curved (usually referred to as elastic) matching, which is a desired property in image-to-atlas matching and intersubject matching. On top of all this, early algorithms of voxel-based type already produced results of surprisingly high accuracy [1,33]. In consequence, research efforts in multimodality image registration have focused on this class of approaches. We will discuss a few of the recent methods, all of which were developed only in the last few years. Two subclasses will be considered: methods working directly on the intensities of the images to be matched and methods utilizing higher order geometrical features like gradients or ridges.

Woods et al. [33] proposed a method to register MRI and PET volumetric images based on the assumption that for any MRI grey level the variance of corresponding PET grey levels is minimum at registration. A weighted sum of the variances at all MRI grey levels then is used as a similarity measure. In other words, the scatter plot which is formed by having MRI intensities on one axis and PET intensities on the other axis, is maximized with respect to crispness. While this method generally works if it is applied to the original images, it is not robust unless the MRI and PET images have been segmented to contain only brain tissue.

Hill et al. [34] described a related method. The skewness of the 2D scatter histogram is maximized; the used measure is a normalized third order moment of the histogram. A preprocessing step in which the images are thresholded to get rid of background noise is beneficial [35].

The most recently proposed class of intensity-based methods makes use of measures taken from information theory. Initially, minimization of entropy measures was used with some success in CT–MRI matching and MRI–PET matching [35,36]. Later, maximization of the mutual information of the image histograms (the relative entropy) has been used successfully [37–41]. The use of mutual information compares favourably to other retrospective methods [42,43].

Van den Elsen et al. [44] employed the above discussed ridge detectors, based on second order scaled differential invariants, to arrive at a voxel-based approach. The feature ('ridgeness') images were cross-correlated to find the maximum, using a hierarchical algorithm. The matching accuracy was found to be very high, even in the case that parts of one image or of both images were missing. The method is automatic since the scale at which the ridgeness images are read out can be fixed robustly at a value corresponding to the thickness of the skull.

Maintz et al. [45] considered a number of scaled differential invariants for CT–MRI matching, includ-

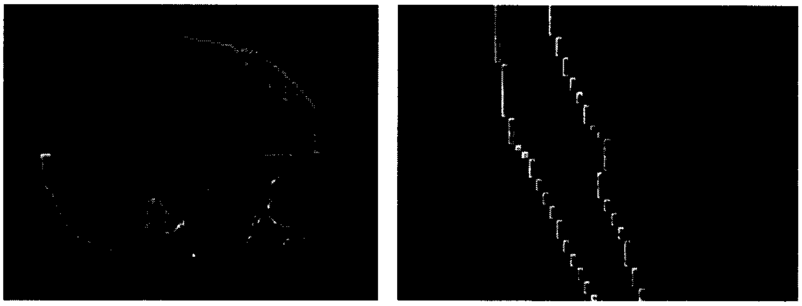

Fig. 1. Example of a CT–MRI registration based on image features. The left image shows a hybrid view of the registered images. In the right image a zoom of the MR image near the cerebellum can be seen. In this case, bone contours segmented from the CT image are overlaid, showing the accuracy of the match.

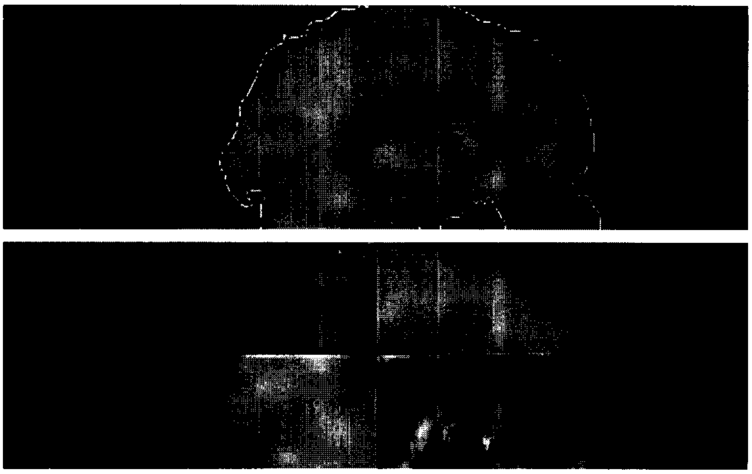

Fig. 2. Example of a PET–MRI registration based on image features. The top image shows the midsagittal slice of the registered PET volume with a contour obtained from the MR image. In the bottom image the same slice can be seen as a hybrid of MRI and registered PET data.

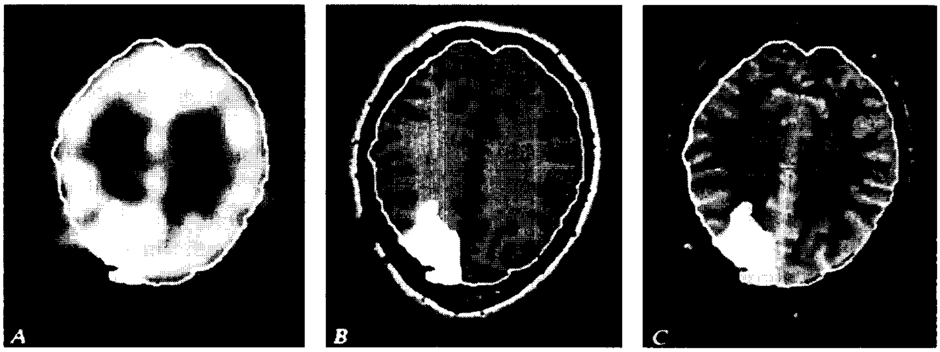

Fig. 3. 2D selective integrated display. Features, brain contour from the MR T1 image (middle) and tumour area from the MR T2 image (right) are transferred to the corresponding SPECT slice (left).

ing the gradient magnitude, several ridgeness measures, and other more exotic higher order invariants. All feature images were cross-correlated to find the optimum matching transformation. The gradient magnitude was found to perform best; it slightly outperforms the ridgeness measure, and is in addition computationally less expensive. An illustration of the accuracy that can be reached with this method is given in Fig. 1. The gradient correlation algorithm has been tried out on SPECT–MRI and PET–MRI matching [46]. Preliminary results of this approach are promising (Fig. 2), but conclusions must be postponed until a thorough evaluation has been performed.

Fig. 3 shows a 2D selective integrated display of the brain.

Table 1 gives a condensed overview of the classes of multimodality image registration techniques vs. the seven quality criteria. The latter class of methods, voxel-based intrinsic matching, clearly outperforms the other approaches.

2.3. Evaluation aspects

An issue which so far has remained undiscussed is the evaluation of registration algorithms as regards accuracy.

This poses a serious problem in clinical practice, since the best transformation is an unknown. Therefore, the accuracy can only be assessed qualitatively by visual inspection, and quantitatively by composing the found transformation to ones obtained upon employing other registration techniques. Even in the latter case the accuracy measure is not an absolute one, since it is relative to a transformation that inevitably has its own intrinsic registration error.

Van den Elsen [47] introduced a reliable method to visually inspect the accuracy of a match. The usually transaxially acquired tomographic data are reformatted to coronal and sagittal slices in which directions registration is much more error prone. By zooming in on specific structures, a detailed account of all misregistrations can be obtained. In consequence of the above, a comparison with other voxel-based algorithms provides a better basis for evaluation of the results than a comparison with extrinsic registrations. This strategy is followed now by several authors [38,45]. It allows the conclusion that a registration is accurate, but it leaves the problem of how to interpret minor differences. A novel set-up to provide an independent gold standard is the use of cadaver studies, where rigid fiducial tubes are inserted prior to imaging. This has shown to be a viable approach to evaluate CT–MRI registrations [48,49]. For instance, it clearly shows that the accuracies reported for surface based matching do not hold true for internal brain structures. An extensive evaluation technique was proposed and demonstrated by West et al. [42,43]. Here, the registration results of many different retrospective methods are compared to a gold standard based on screw-mounted markers. The differences between registration results are evaluated in clinically relevant regions only, and the images used (PET, CT, and MRI) are drawn from a large database of clinically obtained images. Although the actual accuracy of the gold standard

Table 1
Comparative overview of multimodality image matching approaches

	Accuracy	Patient friendly	Reproducible	Labour extensive	Retrospective	Extensible to curved matching	Extensible to intraoperative matching
Extrinsic matching							
Frame / screws	+	-	+	±	-	-	+
Mould / adapter	±	±	±	-	-	-	+
Skin markers	±	+	±	+	-	-	+
Intrinsic matching							
Anatomic landmarks	±	+	-	-	+	+	-
Surfaces / objects	±	+	±	±	+	±	±
Voxel properties	+	+	+	+	+	+	±

used cannot be ascertained, methods like these have the potential to provide a more quantitative measure of accuracy than visual inspection can.

3. Integrated image display

When the multimodality images have been matched, the question of how to optimally convey the integrated information remains. This problem is task-driven. For instance, in order to provide an anatomical frame of reference for PET, a combined MRI/PET image may be presented best by a 2D grey value or colour display of the original PET slices, with the contours of relevant structures (cortex, ventricles, lesions) as derived from the corresponding resampled MR slice outlined by a white, black, or colour overlay. If, however, for some clinical indication the MR image is the primary source of information and the PET image serves to provide additional diagnostic value, the same MRI/PET combination may be presented best by the reverse order, i.e., a 2D grey value display of original MR slices with the resampled PET distribution in the corresponding slice pasted over it by a colour overlay; alternatively, a volumetric (3D) grey value MRI display of the structure under investigation (e.g., the cortex) with a colour overlaid PET distribution may be preferred. In consequence, in evaluating a specific integrated display technique or in comparing two or more display techniques, the detection task must be well specified.

We now discuss integrated display approaches that have been proposed in the recent image processing literature and refer to the colour images on our web pages (http://www.cv.ruu.nl). We distinguish between 2D presentation methods in which one or more tomographic slices through the 3D image data set or (usually orthogonal) projections of this data set are shown, and 3D presentation methods in which a volumetric display of one or more structures is offered. Illustrations of several options for integrated image display are presented.

Note that in some of the methods the presentation is restricted to two image modalities, whereas in other methods simultaneous display of three or even more modalities is supported. Furthermore, several of the methods discussed can be advantageously combined with each other.

3.1. 2D integrated display methods

3.1.1. Juxtaposed display

Display of corresponding slices of two (or more) modalities on multiple screens — or in multiple windows on one monitor —, with separate controls for contrast and brightness in each image, and a joint cursor to indicate corresponding positions in the images [50].

3.1.2. Global or non-specific integration

All information from the images, whether relevant or not, is used so that each of the displayed pixels contains information from multiple modalities.

3.1.2.1. Arithmetic integration. This class of methods involves pixelwise addition, subtraction, multiplication, etc. of images.

3.1.2.2. 'Chessboard' and split-screen display. Alternate pixels in the display are assigned grey values and/or colours to represent the two different modalities [49,50].

3.1.2.3. Colour modelling. Colour models can be applied to more effectively convey the information of the multiple data sets to our visual system. Several authors have reported good results when applying RGB or HSV models for the integration of information from the different modalities (see, e.g., [50,51]).

3.1.3. Selective or specific integration

3.1.3.1. Windowed display. The displayed slice is divided into a number of parts, each showing the grey scale contents of one of the involved modalities [52,53]. The distinction with the chessboard display is prominent in the required user interaction for 'steering' the selection.

3.1.3.2. Feature display. A grey value presentation of one or more slices of one image modality, with relevant structures (points, contours, objects) of the second (and possibly third,...) modality overlaid in single, or multiple colours [54].

The most obvious drawback of the described 2D integrated visualization methods is the inherent lack of 3D information (see also [55,56]). The observer must study consecutive slices to mentally reconstruct the 3D picture needed for proper diagnosis, treatment planning and for communication with the referring physician or surgeon. For example, brain surface structures are generally hard to identify for lack of anatomical information when using 2D images only. With the help of a 3D rendering of the brain, gyri and sulci are much easier to trace, which alleviates the study of brain anatomy [21,58]. This demand is even more stringent for multimodal datasets, where mental 3D reconstruction of the multivariate information is nigh impossible. The following subsection will discuss techniques for 3D integrated visualization that alleviate this task.

3.2. 3D integrated display methods

3.2.1. Windowed display

This display method uses two volumetric visualizations of different modalities to construct an integrated presentation. One of the modalities acts as a framework into which marked parts of the second modality can be substituted [21,57,58]. Multimodal window display is hampered by problems generally encountered in volume visualization of functional data (see also [59]). On the positive side, it is a simple and fast technique (since it is essentially an integration of 2D images) to investigate functional information in an anatomical framework.

3.2.2. Cutplane volumetric display

The use of cutplanes has become a standard technique in (single modality) volume visualization. In integrated visualization, cutplanes have been used, e.g., in a volumetric visualization of skin from MRI and skull from CT, with two cutplanes representing the original CT and MRI greyvalues [16]. In Stokking et al. [60] functional data from SPECT images and anatomical features from MR images are presented on a multimodal cutplane in an anatomical framework supplied by a 3D rendering of the brain from the MR images. Since a cutplane is basically a 2D image, the results of 2D integrated visualization can be used to guide the integration of data on the cutplane.

3.2.3. Integrated data display

Volumetric structures as derived from various modalities are integrated into one dataset and subsequently displayed by standard rendering techniques, e.g., as opaque or transparent surfaces [61].

3.2.4. Surface texturing

Volumetric display of a structure from one image modality, with relevant structures (points, contours, surfaces) of the second (and possibly, third,...) modality designated by single, or multicolour overlays [12].

Fig. 4. 3D surface mapping display of SPECT and MRI data (same patient as in Fig. 3) using the normal fusion technique. The maximum intensity of the SPECT samples along the direction of the reverse gradient (normal) was used to colour encode the brain surface via a lookup table (shown on the right). Left: right hemisphere with an arrow indicating the tumour area (note the deteriorated structure of gyri and sulci). Right: left healthy hemisphere. A comparison of the left and right frontal lobes clearly shows an area of increased cerebral blood perfusion surrounding the tumour area.

3.2.5. Surface mapping

If the function of the brain is under investigation, the grey matter is the primary target and more specifically the folded surface layer (about 2–10 mm thick). Various methods that map functional activity of the grey matter onto the brain surface rendered from anatomical data have already been proposed [21,58]. These techniques share the characteristic that the functional activity below the surface is sampled along the viewing direction, which introduces (localization) artefacts. A technique, called normal fusion, overcomes these artefacts by spawning a secondary ray along the reverse gradient (normal) at a surface (in volume visualization the gradient is generally calculated to determine shading [62] to sample local functional activity and, subsequently, colour encode the sampled information onto the surface rendered from anatomical data). The approach has been quite successful in simultaneous visualization of brain SPECT and MRI; the SPECT information is integrated along the normal (i.e., inwards into the brain tissue) and the result is colour encoded onto the volume rendered cortex derived from a T1 weighted MR image (Fig. 4). Recent results have confirmed that this method adds diagnostic value to straightforward interpretation of the individual SPECT and MRI slices [63].

In closing, we remark that the techniques described in this paper can be further enhanced by making use of stereo images and/or motion display.

4. Conclusions

Multimodality image registration has made huge progress in the last few years. A previous version of this survey [61] still presented extrinsic matching using stereotactic frames or arrow-shaped skin markers as the most accurate techniques. Since then, intrinsic methods based on voxel similarity criteria have improved significantly. Both intensity based methods [14,34–36,38] and gradient based methods [45] appear to be so accurate that fiducial markers will soon be anachronistic for matching of CT, MR and PET images. For SPECT/MRI matching, intrinsic methods have not superseded extrinsic methods yet. Intrinsic SPECT/MRI registration seems feasible (Fig. 1), but additional evaluation studies will have to confirm this.

There is a wide variety of methods for integrated display. Which method is best in a specific situation depends on the image understanding task to be performed. In many applications, a 2D grey value display of one or more slices of the primary diagnostic modality, overlaid by relevant structures (points, contours, objects) from another modality in white, black, a single colour, or multiple colours, appears to be quite appropriate. Volumetric (3D) integrated display is called for in some cases, but is certainly not optimal for all interpretation tasks. For the important area of cortical SPECT/MRI and PET/MRI visualization, the normal fusion method presented by Stokking et al [60,63] is promising.

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