Abstract

The aim of this project is to provide a clinical evaluation of the accuracy of retrospective techniques for the intermodality registration of volume images of the human head.

The goal of retrospective image registration is to provide a non-invasive avenue for the visualization of function (PET) in the context of anatomy (MR) and soft tissue (MR) in the context of bone (CT). Retrospective systems have been under development at many sites for many years, but rigorous evaluation has been limited to phantoms. In this project several retrospective CT-to-MR and PET-to-MR image registration techniques will be applied to images of ten or more patients to determine a rigid transformation to achieve alignment. The accuracy of the transformation will be evaluated for each retrospective technique by comparing it with the transformation determined on the same image sets by a prospective system.

The retrospective techniques rely on the localization of anatomical features, while the prospective system is based on the localization of fiducial markers which are implanted in the skull prior to imaging. Because the markers, unlike anatomical features, are tailored to permit localization at a measurably high level of accuracy and because their registration can be effected and checked by deterministic algorithms, the prospective system provides a standard against which the accuracy of the retrospective techniques can be evaluated.

The patient images with all traces of the markers removed will be made available at Vanderbilt via electronic transfer to several other sites. Each such site, operating independently, will apply its registration technique to the images and will communicate its transformation parameters back to Vanderbilt for comparison with the standard transformation. The error in positioning relative to the standard will be assessed over the entire visible portion of the brain and also within specific pertinent regions of the brain. To determine the effect of geometric distortion in MR on this error, geometrically corrected MR images will be included with each image set. The accuracy of registrations involving these corrected images will be compared with that for the uncorrected images.

The objective assessment provided by this project should help to establish the level of confidence with which neuroradiologists and neurosurgeons can approach retrospective image registration.

1 Specific Aims

Our aim is to evaluate the accuracy of non-invasive, retrospective, intermodality image registration techniques for images of the human head. In particular we will be concerned with CT-to-MR and PET-to-MR registration.

Our study will focus on Spin Echo MR images—proton density, T1-weighted, and T2-weighted and on fluorodeoxyglucose PET images.

To accomplish this goal we will provide a set of CT, MR, and PET images for which the correct registration parameters are known. We determine the correct parameters by means of an invasive, prospective technique involving markers and stereotactic frames attached by implantation to the patient's skull. After the correct parameters have been determined, altered copies of the images will be made in which all traces of the markers and frames will be removed. These altered images will then be placed into a database at Vanderbilt University. This database will include a minimum of ten patients.

This database of images will be accessed through the international electronic network by investigators at other sites. These investigators will calculate registration parameters for these images using their respective retrospective techniques, and they will communicate their parameters back to Vanderbilt, again via the network. Because the success of registration depends on the geometrical accuracy of the images, and because there is distortion of varying degrees in all MR images, we will include in addition to the three MR images for each patient, three images that have been corrected for geometrical distortion. The registration parameters will be determined separately for the corrected and the uncorrected images to determine whether the geometrical correction has a statistically significant effect.

After the registration parameters have been received, we will compare the registrations from each site to the correct registrations. We will analyze and publish the results.

2 Background and Significance

Recent improvements in tomography—CT, MR, and PET—have given the physician a wealth of image information for the diagnosis and treatment of brain disease. By means of these three imaging modalities information is provided on bone and soft tissue anatomy and on function. In current practice several images may be ordered for a given patient. Each acquired image will typically comprise a set of slices, often contiguous, spanning the region of interest. T1-weighted, Proton Density, and T2-weighted MR images may be obtained, and both contrast-enhanced and unenhanced CT as well. Each slice of each image in this collection will then be transferred to film and examined side-by-side in the traditional light box and, if PET is included, color hardcopy of its slices may be used as well, to indicate areas of hyper or hypoactivity, or they may in rare cases be examined on a computer screen, where window and level adjustments can be made interactively. Unfortunately, because of differences in the positioning and orientation in the scanners, the correspondence between points in the films can be difficult to determine. During the examination of the images the information from the various image modalities is combined in the physician's mind to produce a mapping of points from one image space to another. This mapping relies on experience that allows the physician to recognize homologous anatomical features in CT and MR, despite their different brightness patterns. This combined image information is then used in making a diagnosis and, possibly, in planning for surgical intervention. If the diagnosis leads to surgical intervention, a different process of recognition must be employed. The surgeon must mentally combine image information with the physical view of the surfaces of exposed anatomy to recognize homologous features in image space and physical space so as to establish landmarks for navigation. If the radiotherapy or radiosurgery is indicated, a mapping must be determined between the images and the physical space of the radiation source.

2.1 Image registration

In both the examination of images for diagnosis or surgical planning and the reference to images during surgical navigation, there is uncertainty in the mental mapping from one space to another. The uncertainty is caused by the ambiguity in the intensity patterns, the variability between patients, the intensity changes due to disease, and the limits of resolution of the images. For three-dimensional imaging modalities, there exists over almost all the image space, an exact one-to-one mapping [1] between two images of the same patient. The determination of this one-to-one mapping is called "image registration". Because the brain is enclosed in and attached to the rigid skull, supine images of the head involve transformations that can be considered to be rigid body transformations. If there have been anatomical changes between scans due to resection or the progression of disease, non-rigid motion will be take place as well, but in order to determine the non-rigid component of this motion, it is still necessary to determine the rigid transformation caused by the difference in positioning in the scanners. If this transformation is known, it is possible with digital image displays to show the physician which points correspond in, for example, CT and MR images, or PET and MR images, of a patient.

2.2 Prospective and retrospective systems

Image registration can in principle remove the uncertainty in the mind of the physician when comparing two images of the same patient, but, in fact, there is always some uncertainty in any registration. To achieve a high degree of accuracy in the registration of image space to physical space Horsley and Clark developed the stereotactic frame systems [2]. These systems, which were first used on humans

in 1947, achieve their accuracy by means of an invasive procedure in which a head frame, parts of which are visible in the images of the patient, is attached to the head via pins implanted into the skull. The advent of three dimensional tomograms in the 70's and subsequent improvement in CT have led to an increase in their accuracy to a level today of about two millimeters [3]. Other invasive systems have followed, including a system developed at Vanderbilt based on small fiducial markers attached to the skull, which achieves accuracies of one millimeter or better [4, 5]. These systems achieve their accuracy by adding to the image an easily localized object that is rigidly attached to the skull. While this invasive approach is easily justified when precise surgical navigation or radiosurgery is to be involved, it is rarely justifiable as an aid to diagnosis and non-surgical treatment. A host of other less invasive approaches involve the non-invasive attachment of markers to the skin. (All the approaches discussed here are compared in detail in a book chapter, entitled "A review of medical image registration" [6], a copy of which is provided in the appendix to this proposal.) Because the use of such markers implies that specially planned procedures were undertaken, techniques for image registration that rely on them are referred to as "prospective" techniques.

About ten years ago, beginning with the efforts of Noz and Maguire to register PET and CT images [7], techniques for "retrospective" registration of tomographic began to appear. These techniques, which have now been developed at many sites, rely on the increasingly common acquisition of "volume images", which are sets of contiguous tomograms that span a large portion of the head. They achieve registration without markers or frames by aligning corresponding anatomical features in the two images. A major example is the surface-matching technique first demonstrated in 1987 by Pelizzari's group in Chicago [8, 9] and now pursued by many others, including Robb's group at the Mayo clinic [10], which distributes its technique in their commercial image processing system *Analyze*, and many others [6, 11]. In this technique a surface in one image, for example the outer surface of the head, is matched to the corresponding surface in the other image. The surface is identified using semi-automated algorithms and some user interaction. In another prominent technique, anatomically identified points are identified in the two spaces and a transformation is found that brings the points into approximate coincidence [7, 12, 13]. Many other retrospective techniques have been tried including principal axis transformations [14, 15], ridge matching [16], and others [6]. These researchers have assessed the accuracy of these systems by means of anecdotal visual evaluation and phantom studies but have not had the benefit of clinical data with known registration parameters for their evaluation.

2.3 The need for evaluation

In February 1993 Fitzpatrick and Maciunas attended the NSF "Workshop on Computer-Assisted Surgery" organized by Russell Taylor and George Bekey. The meeting was attended by sixty-five invited participants including radiologists, surgeons, physicists, engineers, computer scientists, and others representing academics, industry, and foundations, each of which was experienced in some aspect of computer-assisted surgery. The participants were organized into working groups that were assigned the task of establishing "Research priorities". All five groups identified "registration" as a major clinical need. The primary application identified was the registration of images to the patient in the OR, but it was clear that image-to-image registration, for putting soft tissue (MR) into the context of bone (CT), for putting function (PET) in the context of anatomy (MR) and for long term monitoring of tumor growth, was considered important as well [17]. These latter applications lend themselves to the retrospective techniques, and the establishment of some "gold standard" to evaluate their accuracy was included as a specific recommendation. After Maciunas presented our preliminary results on prospective image registration, the idea of Vanderbilt's providing some sort

of test bed for these techniques was suggested in informal discussions near the end of the meeting. Since this meeting we have discussed this possibility with more researchers at more institutions and have received constantly growing encouragement to undertake the task of setting up a database of images and standard registrations and overseeing the evaluation of retrospective image registration techniques based on that database. In this further discussion it came to light that the interconnection of so many research institutions via the Internet means that we would not need to ship magnetic tapes. At the recent SPIE Medical Imaging '94 meeting upon being urged by several groups active in this area to go forward, we resolved to try to find the support to fund such an evaluation. After this meeting we formally contacted the dozen or so most prominent groups in the field of retrospective image registration and described our plan for evaluation. Most of them will be able to take part and have formally accepted the responsibility to join us in this work. We have formulated a plan for what we believe will be an objective and meaningful evalutation. This proposal describes our plan.

3 Preliminary Studies

Image registration has been the central area of research for the principal investigator, Fitzpatrick, since 1981, when he began work on the registration X-ray images of the heart for the enhancement of digital subtraction radiography. In 1988 he and co-investigator, Maciunas, began a collaboration on the problem of registration of CT and MR images of the brain. This collaboration was funded by Codman & Shurtleff, Inc., the subsidiary of Johnson & Johnson that manufactures neurosurgical equipment. That company has recently been renamed, Johnson & Johnson Professional, Inc. The purpose of that collaboration was to explore the limits of accuracy that could be achieved through the implantation into the skull of markers that are visible in both modalities. That funding began in July of 1988 and continues today. A third investigator, Robert L. Galloway of Vanderbilt's Biomedical Engineering joined the project soon after its beginning. The research has been followed by the development of a product named the "ACUSTAR I[1] Advanced Surgical Navigation System," which, subject to FDA approval of the current clinical trials, will soon be sold for use on neurosurgical patients.

3.1 The ACUSTAR system

The primary goal of the ACUSTAR system is to provide intra-operative guidance to the neurosurgeon based on volume images of the patient. Before these images are obtained the surgeon implants four plastic posts into the outer table of the skull of the patient. The posts are located over the convexity with the specific locations being determined by individual clinical circumstances. This procedure involves draping the patient and, for each post, which is about three millimeters in diameter and a centimeter long, applying a local anesthetic, making a scalp incision, drilling a shallow hole in the outer table of the skull, inserting the post through the incision and twisting its threaded end into the hole. The other end of the post remains outside the skin. The posts themselves are invisible in MR and PET images and are only faintly visible in CT. The markers that provide the fiducial points for registration are attached to these posts after the posts have been implanted. The external end of the post is fitted at the top with a machined keyhole with grooves to accept a mating portion of the marker. One marker is attached to each post before imaging takes place. The marker, which is shown schematically in Figure 1 attached to a post, is also constructed of plastic. The dotted rectangle in the marker shows a cross section of a hollow cylindrical interior with an inside diameter of 7 mm and an inside height of 5 mm. This hollow interior is filled with a liquid which shows up bright in the scan.

Once the markers have been attached, the patient is sent to the imaging suites for scanning, and volume images are acquired for each modality which has been ordered. A volume image is a set of contiguous tomographic slices, which in the current project are of constant thickness within a given volume. There are two types of markers. The difference lies is in the liquid which is inside. One type of marker is designed to be bright in both CT and MR. The other is bright in PET. Example of CT, MR, and PET images of patients in which these markers have been implanted can be seen in Figures 3(a), 4(a), and 5(a). In the case of the particular patient whose images are shown, it happened that three markers appeared within one slice in all three modalities. The markers are the three small bright marks that can be seen close to the head. The bright marks near the periphery of the image arise from a stereotactic frame, which was also attached to the patient. After the images have been acquired, but before surgery begins, the images are analyzed. The primary purpose of this

[1] Trademark of Johnson & Johnson, Professional, Inc.

anaylsis is to determine the location of fiducial points for image registration (the secondary purpose being surgical planning). A fiducial point is a geometrical point within the marker. The coordinates of that point must be known for every marker for every image that is to be used in registration. The coordinates are three, possibly non-integral, numbers (x, y, z) which have units of millimeters.

The accuracy of the registrations depends on the consistency of the determination of these coordinates: They should specify the same position within the marker for all positions, all orientations, and all imaging modalities. Our team has worked on the problem of the accurate determination of such a point for five years. Our current technique is described in a recent paper, "An automatic technique for localizing externally attached markers in MR and CT volume images of the head" [18], a copy of which is included in the Appendix. This technique consists of two parts—Part One, in which candidate positions are determined for an entire volume image and Part Two, in which exact positions are determined from the candidate positions. Only the second step works for PET images. For PET images candidates must still be identified interactively, which means that someone must scan through the PET slices for each patient and click somewhere in the interior of each of the four markers. While the need for interaction is a drawback for the Acustar system, it does not affect the current project. The centroid of the marker is used as the fiducial point. The centroid is found by taking a weighted average of the intensities within the marker image. Because of the extra information available from this distribution of intensities, it is possible to get sub-voxel localization accuracy with this technique [19].

Once the locations of the fiducials have been determined in a pair of images, it is possible to find the rigid body transformation that best aligns the corresponding fiducials in the least squares sense [20, 21]. The determination of this transformation is done with a completely deterministic algorithm. There is no search required. The problem is a member of the *Procrustes* family of problems, which have been well studied. We use the closed-form solution developed by Arun, Huang & Blostein that is based on the singular value decomposition of the covariance matrix of the position vectors in the two spaces [22].

In addition to providing the means for image registration just described, the ACUSTAR system provides the means for the registration of the images directly to the patient during surgery. While this image-to-physical-space registration does not bear on the currently proposed evaluation of retrospective image registration, it is the primary reason for the development of the ACUSTAR system and the purpose that justifies its invasiveness. Once imaging is completed the markers serve no further purpose and can thus be removed. In the surgical suite, before surgery begins, a new piece, called a "localization cap" is attached to each post. This cap is designed to mate with the tip of a wand which can be used to localize a point in the cap that is coincident with the centroid of the marker that was attached to that post. Once all the caps have been localized, the ACUSTAR system applies the same algorithm to determine for each image volume the transformation that best aligns the volume with the patient's head. Once this transformation is known it is possible for the system to display on a monitor screen the changing position of the tip of the wand within each image volume simultaneously as it is moved by the surgeon through the brain. It is this latter display to which the "Surgical Navigation" in the product's name refers.

3.2 Correcting geometrical distortion in MR images

Fitzpatrick has been working on the problem of correcting geometrical distortion in MR images since 1987 when Maciunas pointed out the problem to him. At that time Maciunas was hoping to use MR images for stereotactic surgery but was aware that its geometrical fidelity was not nearly

as trustworthy as that of CT. Geometrical accuracy in MR requires precise control of the static magnetic field in which the patient being imaged is immersed. If the static coils are not properly shimmed to produce a sufficiently homogeneous field and/or if the gradient coils are not calibrated correctly, the resulting image will be distorted. Improvements in MR imagers have reduced the magnitude of the problem somewhat, but there is a residual problem that cannot be addressed by improvements in the machine: Even a perfectly homogeneous field is rendered inhomogeneous by the presence of the patient. Because the patient is composed of material, primarily water, which is itself susceptible to magnetization, the field will be changed when the patient is introduced into the magnet. Furthermore, the change varies spatially, is nonlinear, and is dependent on the particular shape of the patient's head and his sinuses. Therefore, it is not possible to correct for the distortion by calibration with phantoms. The resulting geometrical distortion is typically only one to three millimeters on a perfect scanner, but for stereotactic surgery such error is not acceptable.

This seemingly insurmountable problem yielded in 1989 to a self-calibration idea developed at Vanderbilt in which two images are acquired of the same patient—one with a forward readout gradient and a second one with a reverse gradient. The resulting images differ in subtle ways that reveal the distortion pattern. This distortion can be corrected by means of an automatic numerical algorithm applied to the two images as input to produce one output image in which distortions due to both shimming errors and the magnetic susceptibility of the patient are removed. We have published both phantom and clinical studies that verify the efficacy of this technique [23, 24, 25, 5]. While removal of the distortion from shimming and susceptibility has been a difficult problem to solve, it is on the other hand a fairly simple matter to correct for the distortion that arises from gradient errors (this correction is already routine on some GE scanners, for example). These errors are not dependent on the patient and thus can be corrected by phantom calibration. We refer to the correction for geometrical distortion as "rectification", and we have found that fully rectified images (corrected both for static field inhomogeneity and for gradient errors) show a significant ($p = 0.05$) [5] improvement in geometrical fidelity over unrectified images (see below).

3.3 Retrospective image registration

The idea of implantation of markers to provide fiducials for image registration is simple and it provides an obvious advantage over techniques that rely on natural landmarks: The marker can be tailored to serve the purpose of image registration accuracy and it is the same for every patient. The disadvantage, however, is quite serious: It is highly invasive. The implantation of the marker is a surgical procedure. It is, to be sure, relatively minor surgery for a patient who is about to undergo a craniotomy or even a biopsy, but it is unacceptable when its only purpose is to enhance the usefulness of diagnostic imaging. For this latter case a non-invasive technique is needed. During the six years that we have been pushing further and further in the direction of increasing the accuracy of our invasive, prospective system, other institutions have been working in the direction of non-invasive, retrospective systems. We have outlined the progress in retrospective registration in Section 2 of this proposal, and we have included in the Appendix a copy of an article, entitled "A Review of Medical Image Registration" [6], which discusses these techniques among others.

The need for noninvasive registration techniques has been felt at Vanderbilt as well. During the last two years two independent techniques have been pursued here. A novel technique developed by Yaorong Ge (System Analyst in Psychiatry and Ph.D. candidate in Computer Science) under the direction of Fitzpatrick, Maciunas, Kessler, and Richard A. Margolin (M.D., Psychiatry) is designed to provide a simple, efficient PET-to-MR registration. This technique is similar to one developed by

Kapouleas *et al.* [26], and like that technique it is heavily interactive. A second technique, based on Pelizzari's approach has been developed under the direction of Dawant [5]. Both of these technique produce image registrations that are visually compelling, but in both cases it was felt that a more objective measure of accuracy was needed. The presence of so much experience, expertise, and software for prospective registration here led naturally to the evaluation of the accuracy of both systems using both stereotactic frames and the ACUSTAR markers [27, 5]. It was this work that led to the idea of setting up a similar evaluation for others' retrospective registration techniques.

3.4 Evaluation of accuracy

An image registration system is accurate to the extent that it maps a point in one image to the corresponding point in a second image. If it maps a point to a position that is, say, one millimeter from the corresponding point, then it has made a one millimeter error for that point. In order to evaluate the accuracy of the system it is necessary to establish the correct mapping. One way to establish the correct mapping, at least for a few points, is to include in the imaged object a few markers with fiducial points that can be accurately localized in the two images. A fiducial point can be localized in a first image, that point can be mapped by the registration system to the second image, and the mapped point can be compared with the fiducial point that is independently localized in the second image. If the mapped point is one millimeter from the independently localized point the system is charged with a one millimeter error for that point. Because these markers represent targets of interest to the surgeon or the diagnostician, we call the error in their mapping, "target registration error".

We used this technique to demonstrate to the FDA that ACUSTAR is at least as accurate as the most accurate stereotactic frame (significance level $p = 0.05$), which was found in earlier trials conducted by Maciunas to be the COMPASS system (Stereotactic Medical Systems, Inc., Seneca, NY) [28]. We found in phantom studies for CT-to-CT a mean target registration error over 40 samples of 0.27 mm with standard error of the mean of 0.04 mm and a maximum error of 0.87 mm. For CT-to-MR we found a mean error over 40 samples of 1.00 mm with standard error of the mean of 0.06 mm and a maximum of 2.00 mm [29]. When we incorporate full image rectification for MR we find that the CT-to-MR mean error drops to 0.60 mm with standard error of the mean of 0.035 mm and a maximum of 1.11 mm. [These latter, rectified results are not yet published]. We are currently using this technique in our ongoing clinical FDA trials of ACUSTAR. Of the eleven patients for which data has been gathered so far, the CT-to-MR mean error is 0.85 mm with a maximum error of 1.2 mm. [These are as yet, unpublished results.]

We also used this technique in an evaluation of Dawant's implementation of Pelizzari's registration. The results are given in the paper "Evaluation of geometrical distortion correction in MR on image registration accuracy," a paper presented at the SPIE Medical Imaging '94 Conference [5] and included in the Appendix. In this work we examined the effect of MR distortion upon registration accuracy. As discussed above there are two components to this distortion—static field inhomogeneity and gradient errors. We acquired both forward and reverse gradient images and applied our numerical algorithm to produce an image corrected for inhomogeneity. Rather than use phantom calibration to correct for gradient errors, however, we took advantage of the fact that the visible portion of the stereotactic frame could be measured and its dimensions compared with the apparent dimensions in the image. Figure 2 shows a schematic depiction of a stereotactic frame as it is situated around the patient's head (not shown in this figure are the pins that attach the frame percutaneously to the patient's skull). The frame has a set of "N-bars" attached to it. Each of these N-bars intersects

each transaxial image slice at three points. At each of these intersections a fiducial mark is visible in the image. These marks can be seen in the sample images shown in Figures 3(a), 4(a), and 5(a), where sample slices are shown for the same patient for CT, MR, and PET. As can be seen from the arrangement of marks, there are three N-bars in the CT image (one above and one on either side) and four N-bars in the MR and PET images (above, below, and on the sides). The N-bars in the MR and PET images are in fact identical. They are hollow tubes that are filled with different substances to make them visible in the two modalities. The corresponding (b) figures, in which the marks are missing, are discussed in the Section 4 of this proposal. We compared registration accuracies for the cases of no-correction, partial rectification only for gradient error (called "Scaled" in the paper), correction partial rectification only for inhomogeneity (called "Rectified" in the paper), and full rectification. Employing the paired t-test (two-tailed) we found that the error is significantly ($p = 0.05$) reduced by full rectification. In that paper we used a subset of the data that will be used in this project. We consider that study to be an excellent preliminary trial of the evaluation procedure that we are suggesting in this project. The results can be summarized by the last two lines of Table 5, where the mean error and standard deviations are shown. The effect can be seen by comparing the first two means, 1.697 and 2.698, which correspond to the error in registration for the forward and reverse gradient images, respectively, to the sixth mean, 1.193, which is the mean error when the MR images have been rectified. It is equally important to note that the standard deviations have been reduced as well (1.064 and 1.516 are reduced to 0.442). The combination of mean and standard deviation enable us to make predictions about the 95%, 99%, etc. confidence levels, etc., given that we can estimate the shape of the distribution function. We are in the process of preparing this work for journal submission and are carefully examining the statistics. A comparison of these numbers with those in Table 2 (1.503 and 1.317 are reduced to 0.990) show that the fiducial marker registration system shows a smaller error. It should be noted that for this evaluation only *three* markers were used. Based on our earlier numerical simulations we can predict that the four marker system which we will be using in this project will produce errors about 20% smaller than a three marker system [21]. This prediction fits well with the clinical results of our on-going FDA study given above since 0.85 mm is 14% better than 0.99 mm and since MR distortion correction can be expected to reduce the 0.85 mm still further.

There is a subtle point to be made here. Only part of the error measured by this scheme can be attributed to the registration system; the rest is attributable to the error in target localization which is folded into the measurement. Because the calculated error is necessarily increased by this effect, we are being conservative by including it. While such conservatism is appropriate for FDA trials, we prefer scientifically to know the true registration error. This knowledge can be gained by unfolding (statistically) the localization error from the measured error. There is, however, a difficulty with this idea: The accuracy of the localization method must itself first be determined. This requirement poses a chicken-and-egg problem for systems such as ACUSTAR, which are based on fiducial markers. The difficulty lies in the unfolding of the localization error from the combination of localization error and registration error. ACUSTAR uses the best marker/localization system that we know how to build. Thus, the most accurate marker/localization system available for the evaluation of its accuracy is being used by the system itself. Furthermore, any experiment that we devise to measure the accuracy of marker localization requires that we establish a registration mapping, and the best registration system that we know how to build is ACUSTAR. It would seem that we cannot use the markers to determine the accuracy of ACUSTAR until we have used ACUSTAR to determine the accuracy of the markers! This self-referencing dilemma was solved by Calvin Maurer (Ph.D. candidate in Biomedical Engineering) under the direction of Fitzpatrick, when in 1992 he devised a statistical scheme based on maximum likelihood [19, 30]. In this scheme many markers are used

in the registration of two images acquired of the same phantom in different orientations using the same modality. The root-mean-square mapping error, which we call the "fiducial registration error" (with the localization error still folded in), is noted. A numerical simulation is then performed with the same marker configuration for many different localization error levels to determine the level that produces the same fiducial registration error. Using this method Maurer established that the markers could be localized to within ± 0.8 mm both in MR and CT images with 4 mm slices We call this number the "fiducial localization accuracy".

There is a second problem with the determination of registration error based on markers: The only useful accuracy assessment is for targets within the brain, and yet it is not possible to place markers there. To get around this problem we take advantage of our knowledge of the localization error and the rigidity of the transformations. Once we have determined the fiducial localization error, we can by means of numerical simulations estimate the error in mapping targets at any point within the brain [21].

Our experience with both prospective and retrospective registration, with accuracy evaluation, and with the correction of MR distortion gives us a strong feeling of confidence that we will be successful in carrying out the proposed research. We give the details of our research plan in the next section.

4 Research Design and Methods

We have designed an experiment that we believe will make an objective measurement of the accuracy of retrospective image registration systems based on clinical images. We are focusing on the modalities, CT, MR, and PET, and on CT-to-MR and PET-to-MR registration. Furthermore, we are focusing on Spin-Echo MR images and PET images based on the activity of ^{18}F fluorodeoxyglucose (FDG). The images are taken from other studies involving patients who, subsequently to their imaging, underwent craniotomies for resection of cerebral lesions. These patients had fiducial markers implanted in their skulls before they were imaged. The images have already been acquired for ten patients. We expect to select five to ten additional patients as well from a study that will begin in the Fall of 1995. That study will extend beyond the dates of the present project.

The retrospective registration techniques to be evaluated are implemented at, and will be applied at, sites *outside* Vanderbilt. They will be evaluated at Vanderbilt by comparing their registrations to registrations determined by a prospective technique based on the ACUSTAR system implemented at, and applied at, Vanderbilt. The prospective technique makes use of marks made in the images by the fiducial markers and stereotactic frames, each attached by implantation to the patient's skull. The investigators have concluded based on the previous studies described in Section 3 of this proposal that the prospective technique is accurate enough to serve as a standard against which the retrospective techniques can be measured. In these accuracy trials it was learned that geometrical distortion in MR can have a significant effect on registration accuracy. Therefore, "rectified" images (as explained in Section 3 above), in which the distortion has been removed, will be included in our study.

The images that the outside sites will use will have had all traces of the markers and stereotactic frame removed. All images will be communicated electronically to these sites, and they will communicate their registration parameters electronically to Vanderbilt.

The transformations determined by each retrospective registration system will be compared with the prospective transformation at selected regions of interest (ROIs) within the brain. The results will be analyzed statistically over the set of patients and will be published at the end of the project.

4.1 ACUSTAR

The name of the prospective system that employs implanted fiducial markers is ACUSTAR. This system is already implemented. It provides a means to register CT and PET images to MR images and a means to register these images to the patient in the surgery. This latter registration is not used in the present proposal. The accuracy of the ACUSTAR system has been evaluated both on phantoms and on patients, as described in Section 3. These are patients who have undergone craniotomies for the resection of lesions. Images from this set of patients will be used in the present project along with images from future patients, who are part of another clinical trial of the ACUSTAR system that will get underway in the Fall of 1995. (The ACUSTAR project is funded by Johnson & Johnson, Professional, Inc. No funds are being requested in this proposal for the imaging of these patients.)

4.2 Stereotactic Frames

In addition to the markers, each of the first ten patients had a COMPASS stereotactic frame attached. This frame is rigidly attached to pins that are implanted into the skull and provides another system

for registering images. As discussed in the previous section, the frame, shown schematically in Figure 2, has a set of "N-bars" attached to it. Each of these N-bars intersects each transaxial image slice at three points. At each of these intersections a fiducial mark is visible in the image. These marks can be seen around the periphery of the sample images shown in Figures 3(a), 4(a), and 5(a), where sample slices are shown for the same patient for CT, MR, and PET. Two fiducial markers can be seen near the patient's head. The corresponding (b) images without these marks are explained below. While in principle the markers and the frame provide two redundant registration systems which can be viewed as providing primary and back-up prospective systems for this project, we prefer to use them in conjunction to provide the most accurate registration standard we can for evaluating the retrospective systems. We have briefly explained the technique in Section 3 of this proposal, and we give more detail in a published paper, "Effect of geometrical distortion correction in MR on image registration accuracy" [5], a copy of which is included in the Appendix.

4.3 Image acquisition

All ACUSTAR patients have one CT and three MR scans acquired. Of the ten patients already scanned six have in addition a PET scan. The additional set of patients will include five or more patients with PET scans and five or more without PET. The original CT volumes were acquired on a Siemens Somatom DR-H scanner; the additional CT scans will be acquired on a Siemens Somatom Plus. Each CT volume image contains between 27 and 34 contiguous slices that are 4 mm thick; each slice contains 512x512 pixels of size 0.65x0.65 mm. The MR images are acquired using a Siemens SP 1.5 Tesla scanner. Each MR image contains 20 to 26 transaxial slices that are 4 mm thick with no interslice gap; each slice contains 256x256 pixels of size 1.25x1.25 mm. T1-weighted, Proton-Density, and T2-weighted Spin-Echo MR images are acquired for each patient. The MR imaging parameters are for T1: TE= 15 ms, TR = 650 or 800 ms, four acquisitions, half Fourier reconstruction. The MR imaging parameters are for PD/T2: TE = 20/90 ms, TR = 2550 or 3000 ms, two acquisitions, half Fourier reconstruction. In addition to these three MR images, three more images are acquired with the same imaging parameters. Thus there will be a pair of T1-weighted, a pair of PD, and a pair of T2-weighted images. The only difference between two members of a pair is that the readout gradient is reversed. The PET images are acquired on a Siemens ECAT 933/08-16 system with 15 transaxial slices that are 8 mm thick. Each slice contains 128x128 pixels of size of 2.591x2.591 mm.

4.4 MR image rectification

The purpose of the additional MR acquisition is to provide information necessary for our image rectification algorithms, as explained in Section 3 above, where we also give evidence of its efficacy: There are two parts to the rectification: (1) correction for gradient errors and (2) correction for static field inhomogeneity caused both by the magnetic susceptibility of the patient and by shimming error. Correction (1) is effected by making use of the COMPASS stereotactic frame as an object of known shape and size. By measuring the position of its localizing rods both in the image and in physical space we determine the error in scale. This correction will be altered for the second set of patients, whose imaging will begin in the Fall of 1995. These patients will not have the stereotactic frame attached. Therefore, it will be necessary to image a phantom and to use the phantom measurements, instead of the frame measurements, to correct for gradient errors. We have found from our frame measurements that the gradient errors change very slowly (over days or weeks). Thus, we can use phantom data that is days old in correcting for these errors. We have not written that software, but we have already built the phantom and have experience with its imaging and analysis. We will write

the software during the project (please see the schedule below). Correction (2) is effected by means of an automatic algorithm that takes the forward and reverse-gradient images as input and produces a corrected image as output. (These algorithms are described in more detail in Section 2.4 of [5], a copy of which is included in the Appendix, and in much greater depth in [24].) We will employ this technique to produce a set of three fully rectified MR images for each patient (T1-weighted, PD, and T2-weighted).

4.5 Standard registration parameters

We register a given pair of images by calculating the translation and rotation parameters of the rigid body transformation that minimizes the mean square distance between fiducials in the two images, as described in Section 3. The result is a set of twelve numbers—the nine elements of a rotation matrix and the three components of a translation vector. These twelve numbers define the standard registration for that pair of images.

4.6 Removing traces of the markers and frames

The markers and the stereotactic frames are designed to produce fiducial marks in the images. We use these marks in determining the standard registration parameters, but the investigators performing the retrospective registration should be blind to these marks. Fortunately, because the marks appear only in the region outside the head, they can be removed. We have already written algorithms to remove traces of the markers and frames. Examples can be seen in Figures 3, 4, and 5. The original images are labeled (a); the images in which the marks have been removed are labeled (b). The removal of the marks must be done with some care. The process should neither help nor hurt the retrospective registration. Ideally, the image would be the image that would have been obtained if no marker were there in the first place. Our technique is to replace voxels that are inside the markers with random values selected from a region that contains air. These regions exhibit background noise and reconstruction artifacts only. Because of the low level of reconstruction artifact in CT and MR, we can choose any region. We choose a region in the corner of these images. In PET images, because of the relatively large artifacts, we choose values from the immediate neighborhood of the mark. An extreme window/level has been selected for the PET image sample to show that the process is imperfect for PET. However, it appears obvious that the imperfections are small enough to have a negligible effect on the outcome of the registrations.

4.7 Communication between Vanderbilt and other sites

For each patient, the CT scan and three pairs of MR scans will be placed into a database. For some patients, as outlined above, a PET scan will be included. All patient name, number, and other identifying information will be deleted. Patient data sets will be identified only by a serial number that has meaning only in this project. "Compressed" versions of these images will be included. The compression scheme is the standard, adaptaive Lempel-Ziv coding scheme available on UNIX systems. The scheme, which is routinely used on large files (both image files and non-image files), reduces the size of typical volume image files by a factor of two and one-half to three. The filenames are given the standard extension `.Z`. The compression of the files serves to reduce the time for transfer to the remote site. The compression scheme is invertible: When the files are decompressed at the remote site they will be identical to the original file.

Each pair of MR scans will consist of the original MR scan with the "forward" gradient and the rectified image. There will be one T1-weighted, one PD, and one T2-weighted pair. These images will reside in separate directories on a disk connected to a computer at Vanderbilt which is connected to the Internet. Each single volume image will reside in a single file containing only voxel intensities. An additional, human-readable file will contain sufficient information about the image for all outside participants to effect their registrations. This information includes the shape and size of the image set, including the dimensions of the voxels, imaging parameters, etc.

Each outside investigator will be informed of the presence of the image sets and will copy them via the Internet to his or her own site. The transfer of these images will be effected via FTP ("File Transfer Protocol"). FTP is a piece of software designed to allow transfer of data between sites. To use FTP, a user must establish a connection with the remote site (host) containing the required data files. The connection is accomplished in much the same way as logging on to a local machine: The user specifies the Internet address of a host computer at the remote site which is connected to the Internet and on which FTP is implemented and supplies a username and password. Once this has been done, the user may access a limited set of directories on the host, and execute transfers, via the Internet connection between the local and host machines, of files on the host. These files are written to files of the same name on the local computer's disk. We have benchmarked this system recently by transferring a 4 Megabyte file between our site and a remote site. The transfer required 130 seconds. Thus for a typical compressed CT image, which at about 6 Megabytes is the largest image volume for each patient, the expected time for transfer is about 200 seconds, or three and one-half minutes. The total expected time for the transfer of the largest patient data set (1 CT, 6 MRs, and 1 PET) is eight and one-half minutes. The total transfer time for uncompressed images would be two to three times as long.

The investigator will perform all of the following registrations for each patient:

1. CT-to-T1
2. CT-to-rectified T1
3. CT-to-PD
4. CT-to-rectified PD
5. CT-to-T2
6. CT-to-rectified T2

and for each patient for which PET is included

1. PET-to-T1
2. PET-to-rectified T1
3. PET-to-PD
4. PET-to-rectified PD
5. PET-to-T2
6. PET-to-rectified T2

Because the PD and T2 images are obtained from two echoes following in the same excitation, the registration parameters should be the same for both. They will differ only because of registration error. The registration techniques will be applied to these modalities independently. The result of each registration will be a set of transformation parameters. The parameters can be in several forms: e.g., the translation vector and rotation matrix, translation vector and Euler angles, or untransformed and transformed positions of three noncolinear points. Each site will send electronic mail to Vanderbilt indicating the registration pair and the transformation parameters. We will allow a variety of parameter styles but will translate them to the translation vector, rotation matrix format at Vanderbilt. The translated parameters will be placed into a database at Vanderbilt for later analysis.

We are concerned that some miscommunication might occur involving image formats and transformation parameters. To reduce the chance that confusion might compromise our results, we will provide a "practice" data set, whose transformation parameters are known to everyone. This practice set will be provided before the other images are available (please see the schedule below). This set will give each site a chance to determine whether it is properly communicating with Vanderbilt.

Furthermore, to make certain that we have not erred in some way that will not be apparent with this practice set or in some way that differs in the subsequent sets, Dawant will, acting as a pilot site, apply his retrospective system to selected image sets and communicate the results by electronic mail, as would any other site. We will analyze his results informally to determine if there are errors in our protocol. Dawant will perform these registrations relatively early (please see the schedule below).

4.8 Comparison with the standard

As discussed in Section 3 above, any meaningful assessment of image registration accuracy must consider the points within the brain. Our plan is to determine the mapping errors within identified ROIs within the brain. These ROIs will be identified by Kessler and Maciunas as being of diagnostic and/or surgical importance over a large set of cases (i.e., not exclusively for these patients). Examples include the regions at or near the head of the caudate, the putamen, the temporal lobes, etc. These investigators, assisted by Dawant, and by software provided by Dawant, will outline these regions on one MR scan for each of the n patients whose images are being used in the present study. Now let us consider one such region $\mathcal{R}$. Ideally we would outline these regions on each of the other five MR scans for each patient. However, this laborious procedure is not necessary. Instead, for each patient i, we can make use of our prospective registration system, which can be used to determine a transformation between any two MR images. Using this system we can copy the region $\mathcal{R}_i$ onto each of the other five MR scans for that patient. (We should note that small errors in this transfer will not have appreciable effects on our measures of accuracy. They will cause the ROI selected on one MR scan to be slightly different from the ROI selected on another MR scan. Slight differences in ROI selection will have negligible effects on error statistics.)

Now let us consider one such region $\mathcal{R}_i$ for patient i in one such MR scan, and let us consider the registration transformation for one other image (CT or PET) for one retrospective method. We will use the point $(x, y, z)_{MR}$ at the center of each voxel in $\mathcal{R}_i$ as a target point. We will, using the prospective system, calculate the corresponding point (x, y, z) in CT or PET. We will apply the retrospective transformation to (x, y, z) in CT or PET to find the corresponding point $(x', y', z')_{MR}$. The target registration disparity between the retrospective technique and the prospective technique

for this voxel is

$$(\Delta x, \Delta y, \Delta z) = (x' - x, y' - y, z' - z).$$

The result will be that we know the disparity for each voxel in each region, for each registration, for each patient, and for each retrospective registration technique. These disparities are our detailed estimates of the errors of the retrospective technique relative to our standard.

4.9 Analysis of measurements

It should be apparent from our discussion in Section 3, that we have given much thought to the analysis of error measurements for image registration systems. However, we are sensitive to the need for extreme care in making claims of statistical significance, particularly when surgeons and diagnosticians may make decisions based on our conclusions. To assist us in our statistical analysis for this project we have already enlisted the aid of the Vanderbilt Medical School Faculty of Biostatistics. This faculty provides assistance in selecting the appropriate statistical tools for analyzing experimental data and determining levels of confidence. We have requested funding for continued assistance as part of this project. These experts will monitor our statistical techniques and help us to maintain rigor in our statistical claims. We will calculate the means and standard errors and we will report statistics on the length of the disparity vector, which is the commonly reported measure of registration error. We are aware of the fact that the distribution of these errors is not normal. The non-normality derives from the fact that the measured error is the euclidean distance, which is a nonnegative, nonlinear combination of the errors in x, y, and z. Furthermore, because we have not yet seen the data we cannot state the level of confidence that we can achieve for 10, 15, or 20 patients for statistics based on a knowledge of the shape, or even the approximate shape, of the distribution functions. Because of our previous experience with Dawant's implementation of the Pelizzari approach described in Section 3, wherein the variances were small enough to allow us to demonstrate significance at $p = 0.05$ with the paired t-test, we expect to be able to determine whether full rectification of MR produces a significant improvement at this same level of certainty. We can make some conservative claims before seeing the variances, however, based on order statistics. We can make predictions such as the following: For a given registration technique T and for a given region of the brain $\mathcal{R}_i$, we will determine the maximum error $e_{i,j}$ over the $\mathcal{R}_i$ for each of n patients. Let the maximum of the errors in the set $\{e_{i,j} : j = 1, n\}$ be M_i. Then for $n = 10$ we can be 90% certain that for least 79% of all patients the technique T would have a maximum error in $\mathcal{R}_i$ less than M_i. We can make similar predictions for the median and can make predictions about smallest errors as well.

4.10 Schedule

Please note that we plan to do further preparatory work before our funded work begins.

December 1, 1994—

> *Vanderbilt:* We make one practice data set available. Included with it is a file which states the standard registration parameters.

February, 1995:

> *Vanderbilt:* We make ten data sets available. No registration information is included.

February/March, 1995:

Vanderbilt: Fitzpatrick solves any start-up communication problems encountered by the outside participants.

February/March, 1995:

Vanderbilt: Dawant completes retrospective registrations for selected data sets and emails results to Fitzpatrick. Fitzpatrick corrects any protocol errors discovered.

February–July, 1995:

Outside sites: Outside investigators apply retrospective registrations to first ten data sets and email transformation parameters to Vanderbilt.

April, 1995:

Vanderbilt: Fitzpatrick completes final standard registrations for first ten data sets.

April–December 1995:

Vanderbilt: Kessler and Maciunas oversee the imaging of patients in the second set.

July 1, 1995:

Outside sites: All registrations for the first data sets are due.

June/July, 1995:

Vanderbilt: Fitzpatrick completes phantom calibration software to be used on second set of patients.

July/Aug, 1995:

Vanderbilt: Kessler, Maciunas, and Dawant complete the specification of ROIs for the first ten patients.

August, 1995:

Vanderbilt: Fitzpatrick solves communication problems for any sites that are having difficulties.

September—November, 1995:

Vanderbilt: Fitzpatrick and Dawant oversee the production of the software for determining the disparity between retrospective and prospective registration. *Other sites:* Outside investigators apply retrospective registrations to images from second set of patients and email transformation parameters to Vanderbilt.

December, 1995:

Vanderbilt: Fitzpatrick solves any remaining communication problems.

December 1995/January 1996:

Vanderbilt: Kessler, Maciunas, and Dawant complete the specification of ROIs for the second set of patients.

February/March, 1996:

Vanderbilt: Fitzpatrick and Dawant apply evaluation software to all data, organize into spread sheets, and review with Maciunas and Kessler.

February–April, 1996:

Vanderbilt: Fitzpatrick and Dawant will present preliminary analysis of results at scientific meeting.

April–August, 1996:

Vanderbilt: Fitzpatrick and Dawant complete all statistical tests, final analysis and organization of all results, write up results, and submit for journal publication.

Other sites: Each site will communicate with Fitzpatrick and Dawant to assist in the organization and write-up of the results for publication. These communications will include explanations of how their retrospective systems are applied.

Figure 1: Schematic depiction of a marker attached to a post which is implanted through the skin into the outer table of the skull.

Figure 2: A schematic representation of a stereotactic frame showing the N-bars and their relationship to the patient's head.

Figure 3:

Figure 4:

Figure 5:

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