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The Role of Registration in Accurate Surgical Guidance

J. Michael Fitzpatrick, PhD
Department of Electrical Engineering and Computer Science, Vanderbilt University, Nashville, Tennessee

Abstract

Registration is presented as the central issue of surgical guidance. The focus is on the accuracy of approaches employed today, all of which use pre-operative images to guide surgery on rigid anatomy. The three most well established approaches to guidance—the stereotactic frame, point fiducials, and surface matching—are examined in detail, along with two new approaches based on microstereotactic frames. It is shown that each method relies on the registration of points in the image to corresponding points in the operating room, and therefore that the error patterns associated with point registration are similar for all of them. Three types of registration error—fiducial localization error (FLE), fiducial registration error (FRE), and target registration error (TRE) are highlighted, as well as two additional guidance errors—target localization error, and total targeting error, the latter of which is the overall error of the guidance system. Statistical relationships between TRE and FLE, between FRE and FLE, and among TRE, TLE and TTE are given. Finally some myths concerning fiducial registration are highlighted.

Keywords

surgical guidance; navigation; registration; registration error; fiducials; stereotactic frames; microstereotactic frames

1. Introduction

Registration is the central operation required when surgical guidance is based on pre-operative images, and if it is not done well, then a guidance system may be worse than useless. It may in fact be dangerous. The danger arises from the illusion promoted by guidance systems that there is a physical relationship between the position of a probe1, as it is continually moved by the surgeon, and the position of that probe as depicted on the display screen. The illusion is enhanced by navigational systems that track a hand-held probe, for which movement of the depicted probe closely mimics the movement of the physical one. Because of the strong similarity in movement, the surgeon may naturally become subliminally convinced that there is a high similarity position as well. Of course, there should be a high similarity, but unless an accurate registration has been performed, both the probe depicted by the system and the surgeon's faith in that system may be misplaced.

[1]A "probe" may be an inert pointer, a scalpel, an electrocautery tool, a surgical microscope, a biopsy needle, or any other instrument or device used to probe physical anatomy.

In this work, we examine the role of registration in surgical guidance and its effect on the accuracy of that guidance. We will show that registration is the common denominator among all the most popular guidance approaches and, further, that only one type of registration underlies all of them—point registration. We begin with a general definition: Registration is the determination of a geometrical transformation that aligns one view of an object with another, where a "view" can be an image, such as CT or MR, but it can also be the physical object itself [1]. In the subject that we treat here—surgical guidance—the two views always comprise an image and a physical object. The resulting registration of interest is termed "image-to-physical" registration, and the physical object involved is always some part of the anatomy of a patient. The geometrical transformation determined by the registration process is a mathematical function that maps each point in the space of one view onto the corresponding point in the other, and it is the accuracy of this correspondence that determines the value of the guidance.

A basic assumption made by the designers of the typical guidance systems is that the anatomy captured in the pre-operative image remains rigid from image acquisition to surgical procedure. While non-rigid registration is feasible for image-to-image registration [2, 3], its use for image-to-physical registration remains a subject of research [4]. Thus, for image guidance, "registration" typically means "rigid registration", and in this article we focus on rigid registration methods. We show that rigid, point registration lies at the heart of all the most popular navigational systems, and we examine issues that affect its accuracy. Such an examination quickly reveals that point registration requires the determination of fiducial points before registration is performed. The form and number of fiducials varies from system to system, but their role as the foundation of accuracy does not. In what follows, we study the most popular guidance systems, describe their dependence on fiducial registration, and carefully examine the errors that affect their accuracy.

2. History

Surgical procedures have been guided by pre-operative images since a mere two weeks after the discovery of x-rays. In December 1895, a radiograph was aligned, or "registered", with a patient's hand to guide the removal of an embedded broken needle—[5]. Since that day, both the quality of medical imaging and the quality of the registration of image to patient have increased dramatically. The first major breakthrough occurred in 1947, when a stereotactic frame was first used to guide surgery in humans by registering plain films to anatomy [6]. The stereotactic frame is a fixture that attaches rigidly to the patient, primarily on the head. The head frame is a metal structure made large enough to fit around the head and equipped typically with sharpened pins that pierce the scalp and indent the skull with sufficient pressure to hold it in place throughout the interval from the beginning of imaging to the end of the surgical procedure. An example is shown below in Figure 4a. The frame is equipped with a holder (Figure 4b) that can be adjusted intra-operatively by geometrical triangulation relative to the frame so that the surgeon can employ it to advance a probe to an internal target while avoiding vital anatomy. In 1973, imaging took its greatest leap forward when Hounsfield demonstrated computerized tomography (CT) [7], and Lauterbur demonstrated a primitive version of magnetic resonance imaging (MR) [8], which became clinically available in about five years. The 3D nature of these images greatly enhanced the capability

of the frame [9]. In the early 1980s, a new approach to image guidance based on the frame became possible with the advent of real-time updating of images displayed on computer screens. Kelly and colleagues displayed tumor outlines in the operating room updated in response to the movement of a surgical microscope [10, 11], and Roberts and colleagues displayed similar images through a microscope while it was being tracked sonically [12]. Tracking is the determination of the geometrical position of an object in the operating room. Mechanical tracking, such as that employed by Kelly, and sonic tracking, used by Roberts, have given way to today to optical, infrared, or magnetic detection, but, regardless of the means, it is a critical component of all guidance systems. By incorporating tracking and image-updating, Kelly and Roberts launched the field that has come to be known as “computer-aided surgery”, “image-guided surgery”, or simply “surgical guidance”.

In 1987, Allen proposed to abandon the frame entirely and to use instead “fiducial implants” [13]. These implants, known today as “fiducial markers”, or simply “fiducials” or “markers”, are small (no more than a centimeter across), discrete objects designed to be screwed into the skull and to be visible in both CT and MR. In effect, the fiducial markers together with the skull itself play the role of the frame. In 1997, researchers at Vanderbilt University conducted the world's first major clinical trial of a fully functional image-guidance system based on fiducial markers. This system, trademarked “Acustar”, was the first guidance system to receive FDA clearance, and it introduced for the first time a configuration that is now commonplace among commercial systems: a computer display, an infrared tracking system, a specially designed set of fiducial markers, and trackable probes that mate with those markers. Acustar also introduced a method for tracking the motion of the head holder that allowed the infrared tracker and the surgical bed to be moved independently. This innovation has also become standard. Its implementation and its effect on accuracy are described in Section 4 below.

The Acustar trial demonstrated for the first time that neurosurgical guidance with accuracy at the level of one millimeter was possible [14], surpassing (even today) the accuracy achieved by the stereotactic frame, and it marked the beginning of the “frameless” revolution. In the subsequent dozen years since that historic trial, frameless guidance systems based on the Acustar model using either bone-implanted or skin-affixed markers, have become a standard in both neurosurgery and sinus surgery, with many commercial choices readily available [15].

3. Registration methods

Regardless of the system being used, when pre-operative images are used to guide surgery, some registration method must be employed. No method is perfect, and we begin this section by introducing the most commonly accepted true measure of imperfection. While there are many possible approaches to registration, a few have emerged as more popular alternatives—point fiducials, also known as fiducial markers, surface matching, and stereotactic frames. We consider these approaches one-by-one, treating point fiducials first because of the dependence of the other methods on the point-fiducial registration algorithm. After we consider these popular methods, we describe two new methods based on fixtures

that we term “microstereotactic frames” because of their similarity to the stereotactic frames and their considerably smaller size.

3.1. Target registration error

Each guidance system relies on some registration method, and with any registration method, an algorithm processes information obtained from physical devices to produce an optimal transformation. However, the fact that the transformation is optimal does not mean that it is ideal. An ideal transformation maps every point in the image space onto its correct counterpart in physical space and vice versa. It is perfectly accurate. An optimal transformation, on the other hand, is the best guess, given the available information, but it is rarely ideal. For example, with an ideal transformation, when a depicted probe touches an anatomical target point on the computer screen, the actual probe will be touching the actual anatomical target on the patient. If the optimal transformation is not ideal, however, then the actual probe will be displaced some distance from the actual target. The standard term in the literature for this displacement is “target registration error” (TRE) [1], and it is the commonly accepted true measure of the accuracy of a registration process. We can state the situation mathematically as follows: If the optimal transformation produced by a registration process is specified by T, then a target point $\mathbf{p}$ in the image will be mapped into a physical point $\mathbf{p}' = T(\mathbf{p})$.[2] If the ideal transformation maps $\mathbf{p}$ to $\mathbf{q}$ (i.e., $\mathbf{q}$ is the perfect transformed point) then the error vector, $\mathbf{TRE}(\mathbf{p})$ is equal to $\mathbf{p}' - \mathbf{q}$. $\mathbf{TRE}(\mathbf{p})$has three components—in the x, y, and z directions, but the size of the error at that point, which we denote $\mathrm{TRE}(\mathbf{p})$ (i.e., with TRE not in the bold font), is equal to the length, $|\mathbf{p}' - \mathbf{q}|$, of the displacement vector. TRE is the dual of registration accuracy. A registration with high accuracy is one with low TRE.

3.2. Point fiducials

Point fiducials are points that can be reliably identified in the two spaces to be registered. The most accurate point fiducials are provided by fiducial markers, and since Maurer reported on their remarkable accuracy in 1998 [14], fiducial markers have steadily grown in importance in neurosurgical guidance with two competing versions of the markers in use—bone-implanted and skin-affixed. The former, which were the subject of Maurer's paper, has the advantage of high accuracy but the disadvantage of invasiveness, while the latter has the advantage that they are non-invasive but the disadvantage of reduced accuracy. The invasiveness of the bone-implanted version involves a scalp incision for each marker, followed by the screwing of a threaded post into exposed bone. Such relatively minor invasiveness may seem to be a petty concern when brain surgery is involved. Indeed, if intra-operative imaging is available, then the procedure can be carried out under general anesthesia, and the only possible concern is the added time required in the operating room for the implantations, which may be more than recouped, if the guidance reduces the time for the initial exploration or the time for resection. However, if the image must be acquired pre-operatively, then a separate procedure is required outside the operating room, requiring local anesthesia, and a hence more complex workflow. With skin-affixed markers the

[2]The problem can be stated the other way around as well, with $\mathbf{p}$ corresponding to the physical point (i.e., in the operating room), but for consistency we will use $\mathbf{p}$ as the image point throughout this work.

procedure is much easier and quicker and generally does not require even hair removal. However, the skin is movable, and as a result these fiducials may be in different positions relative to the skull during imaging and during surgery. This problem may be exacerbated by changes in the skin and subcutaneous fat due to drugs administered peri-operatively to reduce brain swelling, and due to stretching of the skin by the pinning of the head in a head clamp.

Regardless of the type of fiducials used and regardless of where the image is acquired or when the fiducials are attached, fiducials will be subject to localization error. Fiducial localization is the process of estimating the geometrical position of a fiducial point, such as the centroid of a fiducial marker. Localization must be carried out for each fiducial both in the preoperative image after scanning and on the physical patient at the beginning of the surgical procedure. The fiducial's position is always reckoned relative to some coordinate system—the scanner's coordinate system in the image and the tracker's coordinate system in the operating room. Because images and trackers are imperfect, the fiducial localizations are imperfect. As a result, there is error in the determination of the centroids of the fiducials. We call this error fiducial localization error (FLE). Figure 1 depicts the situation. In (a) the small circles represent the true centroids of fiducials in an image. These true points are unknowable, but by algorithmic means or by interactive selection the points are localized. The dots are the resulting localized points. In (b) (far right) the circles again represent true centroids of the fiducials, this time in the operating room, and the “plus signs” (+) represent the localized points. Localization error here is due not only to limitations in the tracking of the probe used to localize the fiducials but also to motion of the fiducials relative to the anatomy between the time of imaging and the time of operating room localization. For skin-affixed markers, this fiducial motion includes that due to skin motion. By comparing the numbers in (a) and (b), it can be seen that, as is typical, the orientation of the fiducial configuration has changed from image to operating room. In this case there has been a counter-clockwise rotation of 80 degrees. In (c) (middle) we see the result of registration. The localized positions (dots) in (a) have been subjected to a rigid transformation, T, indicated by the large arrow, which is a rotation by 73 degrees, so that they are aligned as closely as possible with the localized positions (plus signs) from (b). As a result a target point in (a), indicated by the cross (×) is transformed to a position very close to the true target in (b), indicated by the diamond (◊). The displacement between the transformed target and the true target is the TRE (small arrows).

Systems that provide image guidance based on fiducials typically utilize registration algorithms predicated on the assumption that FLE is statistically independent for each fiducial in the image. This assumption is likely to be true for fiducials implanted in bone. For bone markers, FLE in the image is due to the random effects of noise and pseudorandom error produced both by imaging artifacts and by the discrete nature of reconstructed images produced by tomography (e.g. CT, PET, or SPECT) or by MR, while FLE in the operating room is due to noise and pseudorandom error produce by the discrete nature of the signals recorded by optical or electromagnetic devices that provide tracking. Skin-affixed markers suffer from these same errors, but are subject to the additional, and typically much larger error associated with changes in, and movement of the skin. The assumption of FLE independence is highly questionable for skin-affixed fiducials, since fiducials near each

other will to some extent move similarly when the skin moves or when skin swells or shrinks. However, FLE among the markers is typically treated as approximately independent, and it is also assumed that the distributions of their three vector components are normal with zero mean. Registration algorithms are based on these assumptions, and we will adopt them henceforth as well. The assumptions of independence and normality, coupled with maximum likelihood analysis leads, through maximum likelihood analysis [16, 17], to a minimization of the "fiducial registration error" (FRE), which is the root-mean-square (rms) error in the fit of the fiducials after registration. The resulting transformation is the optimal one. Here is the mathematical description of the optimization process:

Localization in the image and in the physical space of the operating room produces two sets of corresponding fiducial points, $\mathbf{p}_i$ and $\mathbf{q}_i$ for $i = 1 \ldots N$, which are the localized image points and the localized physical points, respectively. A rigid transformation is sought of the form $\mathbf{p}_i = R\mathbf{p}_i + \mathbf{t}$, where R is a 3-by-3 rotation matrix, which means that R^tR must equal the identity matrix, and $\mathbf{t}$ is a 3-element column vector whose elements are the components of translation along the x, y, and z axes. This optimum R and $\mathbf{t}$ are found, meaning that they maximize the goodness of fit of the fiducials by minimizing a weighted sum of the squares of the distances, $|\mathbf{p}_i' - \mathbf{q}_i|$, between corresponding fiducials after the transformation has been applied. In particular, the quantity,

$$\mathrm{FRE}^2 = \frac{1}{N}\sum_{i=1}^{N}\left|W_i\left(\mathbf{p}_i' - \mathbf{q}_i\right)\right|^2, \quad (1)$$

is minimized, where each W_i is a 3-by-3 weighting matrix for fiducial i. W_i is equal to the inverse of the cross-covariance matrix of the statistical distribution of localization errors for fiducial i [17], which may differ from point to point (hence the subscript i) and may also depend on spatial direction as well. Directional dependence means that FLE is anisotropic. The anisotropic problem has no closed-form solution and must be solved approximately by iterative approaches [17–20]. Typically, however, the anisotropy is small and is ignored, leading to the isotropic problem, for which W_i is simply a scalar. For the isotropic problem, fiducial-registration algorithms that are provably optimal have been available since 1966 [1]. For two given sets of corresponding points, $\mathbf{p}_i$ and $\mathbf{q}_i$, these algorithms all produce the same rigid transformation, which is optimal in the least-square sense, meaning that FRE in Eq. (1) is reduced to a minimum. Thus they are all equally accurate. Virtually every frameless system provides the option of bone-implanted fiducials or skin-affixed fiducials. Not surprisingly, studies of accuracy for these systems in the clinical setting find a statistically significant difference with bone-implantation achieving intracranial means of 1.0 mm to 1.5 mm [14, 21, 22], while skin-affixed fiducials exhibit a wide range from 1.3 mm to 4 mm [21, 23, 24].

3.3. Surface matching

When the attachment of fiducials is not feasible or is considered to be too much effort, anatomical features may tried instead. Discrete anatomical points can be selected as fiducials, such as the tip of the nose, the tragus or the nasion, but there are few localizable points available on the surface of the anatomy, and furthermore such anatomical points do

not provide the accuracy of fiducial markers, because there is no clear cut point associated with such features. The "tip" of the nose, for example, is difficult to define consistently between image and physical space. Furthermore, all such features tend to be subject to skin movement, which can cause large errors. An alternative is the skin's surface. This surface, like any surface, admits localization only in the direction perpendicular to itself, and therefore skin movement, which is primarily along the surface (i.e., sliding of skin along bone), has a much smaller effect on the accuracy of localization than it does for discrete points. Therefore, typical guidance systems provide a surface-matching option. Algorithms are included for defining a surface or surfaces in the image—typically the surface between air and skin. Then, in the operating room, the surgeon touches the surface at multiple points with a probe to determine a set of points on the same surface, as, for example, with the StealthStation (Medtronic, Inc., Minneapolis, MN), or uses an infrared probe to determine such points, as with the VectorVision system (BrainLAB AG, Feldkirchen, German). Then an optimal transformation is sought that minimizes the distance between the surface points found in the operating room and the surfaces identified in the image.

The most popular algorithm for surface matching is called the "Iterative Closest Point" (ICP) algorithm [25]. As its name implies, ICP is an iterative algorithm, and at each iteration three substeps are carried out: (1) For each surface point $\mathbf{q}_i$ that has been localized with the probe, the closest point $\mathbf{p}_i$ on the image surface is identified. (2) Point registration is performed, as described above in Section 3.2, to minimize FRE in Eq. (1) with W_i defined such that a weight of zero is given to components along the surface at point *i*. (3) Each $\mathbf{q}_i$ is replaced by $\mathbf{q}_i' = R^t(\mathbf{q}_i - \mathbf{t})$. The size of FRE is noted at each step, and when the change in FRE from one step to another is less than some set threshold, the iteration is halted and the registration is complete. ICP does not perform well if the two surfaces are grossly misregistered, so the ICP algorithm is typically preceded by a rough initial registration process. ICP then "fine tunes" the initial registration. Guidance systems typically provide surface registration as an option alongside point registration, and recent patient studies have consistently measured accuracies in neurosurgical procedures of two to five millimeters [21, 22, 24]. One of these studies [24] found that with phantoms the error fell below two millimeters, suggesting that changes in the skin surface between imaging and surgery is a serious problem.

3.4. Stereotactic Frames

Stereotactic frames were first used on humans in the 1950s, long before the development of tomographic imaging. Not long after CT became widely available in the late 1970s, however, Russell Brown patented an adjunct to the frame for accurate registration with CT. It comprised a novel set of localizing rods, which are often termed *N-bars*[3], because they are arranged in sets that form the letter "N" [9, 26], as shown in Figure 2. These N-bars serve as fiducials for the registration of image space to physical space, and they are attached to a ring, called a "base ring", which is attached rigidly to the patient from imaging to surgery and serves both to hold the head stationary via fixation to the scanner bed during imaging and to provide a base of support for instruments during the procedure. Brown designed the N-bars to overcome scanning artifacts that were prevalent in CT scanners at the time. The

[3]or "*Z-bars*"

artifacts comprised erroneous, inconsistent, and unknown shifts, tilts and rotations of image slices relative to one another during acquisition, and heroic efforts were required to overcome them. In Figure 2 an image slice is shown that is canted relative to the base ring. Because of arbitrary orientation of the patient on the scanner bed, this orientation is arbitrary regardless of the quality of the CT scan, but in early scanners the orientation of slices relative to each other was also arbitrary and, more importantly, unknown. As a result, discrete fiducial markers could not be used to perform an accurate registration. Brown's N-bars overcame this problem by providing a means to perform an independent registration of each slice individually to the ring.

The registration of an image slice via N-bars is carried out as follows: First the centroids of the intersections of the bars with the image slice are determined in scanner coordinates. Seven such intersections are depicted by ellipsoids in Figure 2; three intersections associated with one N-bar are depicted in Figure 3. A simple geometric analysis involving similar triangles gives the following relationship:

$$L_{bc}=\frac{L_{ac}d_{bc}}{d_{ac}} \quad (2)$$

The value of L_{bc}, coupled with knowledge of the physical lengths of the vertical rods and the spacings between them and simple geometry, again involving similar triangles, gives us the position, $\mathbf{q}_1$, of the intersection B in terms of coordinates fixed in the base ring. Thus, we have determined two corresponding points: the image point $\mathbf{p}_1$, which comprises the scanner coordinates of the centroid of ellipse B, and $\mathbf{q}_1$, which is the physical point. Repeating this process for the other two N-bars gives three such point pairs. From this point forward, the registration problem reduces to the registration of three point fiducials. Thus, it is possible to utilize the minimization of FRE in Eq. (1) with $N = 3$, to find a transformation from image space to physical space. Here Brown compensated for scaling errors in the scanner by omitting the restriction that R in Eq. (1) be a rotation matrix. Mathematically speaking, he used an affine transformation instead of a rigid one, which allows stretching or squeezing. As a result FRE can be easily minimized to zero by linear algebra. With the excellent geometric fidelity of modern CT scanners, however, the requirement that R is orthogonal can be reinstated, and one of the standard algorithms used for rigid point fiducials can be (and usually should be) employed [1].

Brown's N-bar solution is geometrically, mathematically, and physically elegant, but in practical terms it requires that a cumbersome and somewhat frightening cage be in place around the patient's head during scanning, and, because it cannot be removed and re-attached in the same reliably in the same position, the base ring (with the N-bars removed) must be left in place until the surgery is complete. The patient is subjected to prolonged discomfort and, in order to minimize it, workflow must be constrained so that imaging and surgery can take place on the same day. Subsequent improvements in CT scanners have eliminated the problems to which Brown supplied such a clever solution, and hence there is no longer a need to compensate for them. Studies published over the past 15 years have found that stereotactic frames provide an accuracy level between one and two millimeters [27–30], which fails to match the level of even the very first frameless system. Yet the frame

has become such an entrenched tradition among neurosurgeons that it remains today as the most common approach for biopsies, for placing electrodes, and for any other application where a single trajectory or point, or a limited set of trajectories or points is involved.

3.5. The Starfix Platform

While stereotactic frames rely on rigid fixation, they include articulating and sliding parts that must be adjusted in the operating room and then tightened in place before they can be used for guidance. These adjustments require extreme care and can be subject to human error as we point out in Section 5.1 below. In 2005, the first clinical evaluation was published of the accuracy of a revolutionary device that combined the ideas of the stereotactic frame and frameless systems but without the need for the intraoperative adjustments of the frame or the tracking and image display of the frameless systems [31]. The device, which was developed primarily for the precise placement of electrical leads for deep-brain stimulation (DBS), provides guidance for a probe, much as the frame does [32]. Like the traditional frame, this platform, whose commercial embodiment is called the “STarFix microTargeting Platform” (FHC, Inc.; Bowdoin, ME, USA), attaches rigidly to the head and requires no intra-operative tracking system, but it is much smaller and lighter than the frame, as can be appreciated by the side-by-side comparison in Figure 4.

Because of it small size, such a device is termed a “microstereotactic frame”, but we will refer to this particular microstereotactic frame as the “platform”. In addition to its smaller size, a major difference from the standard stereotactic frame is that it is not adjustable in the operating room. It is a rigid fixture, and when it arrives in the operating room, it is pre-aimed at the target.[4] A probe holder is then attached to the platform, as shown in Figure 5, that permits the surgeon to advance the probe along a path predetermined by the platform. Another difference, which is less fundamental, is that, because it does not surround the head, the platform cannot be attached via pressure on pins, so, instead, the platform is anchored to fiducials (minimum of three) that are screwed into the skull and are therefore termed fiducial “anchors”, as shown in Figure 6. Because of variations in anatomy, both the physical arrangement of the anchors and their relation to targets in the head necessarily differ from patient to patient. Because of this variation, the rigid platform, must be custom designed on the basis of a CT image that is acquired after the anchors have been implanted and then fabricated for each patient so that the foot of each of its legs fits precisely on one anchor and so that probes that are attached to it are aimed at their respective targets.

The fabrication of the platform relies on the availability of rapid-prototyping equipment, and, because of the expense of rapid-prototyping machines, the length of the prototyping process, which is an hour or more for autoclavable pieces, and the need for trained operators, the platforms are fabricated at a remote site and are delivered overnight to the medical facility, typically resulting in a forty-eight hour delay. This delay is a disadvantage relative to the traditional frame, but the platform is more comfortable for the patient, it removes the workflow constraint that the imaging and surgery must occur on the same day, and it eliminates the need for adjustments after mounting on the patient to aim the probe at the

[4]or targets. Dual-target platforms are commonly used for bi-lateral DBS implantations.

target thereby reducing the possibility of human error. Its rigid design is also likely to afford more accuracy, and a recently published phantom study indicates that the Starfix platform has the clinical potential for submillimetric accuracy [33].

3.6. The Microtable

The latest entry to surgical guidance—the "Microtable"—appeared this year. See Figure 7 and Figure 8. Like the Starfix platform, this device attaches to the head via anchors (Figure 8c), is a rigid device with no adjustments, requires no intraoperative tracking system, and is custom designed for each patient. However, it can be made much more quickly than the platform—in less than ten minutes. There is a major benefit to this high speed when intra-operative CT is available. In that case, the anchors can be placed, the CT acquired, the trajectory planned, and the microtable fabricated, all while the patient is in the operating room, resulting in a simplified workflow and less patient discomfort. The speed of construction results from a design concept that requires only that parallel holes be drilled, or milled, into a single slab of plastic (e.g. Ultem, which retains its shape when autoclaved). The plastic slab serves as a tabletop (Figure 8a). Three holes accommodate table legs (Figure 8b), which fasten to the anchors (Figure 8c), and a fourth (Figure 8e) accommodates a probe driver, this latter hole being much like that of the Starfix platform. A recently published phantom study indicates that the Microtable also has the clinical potential for submillimetric accuracy [34].

4. Statistics of intrinsic navigational error

Navigational error can be divided into extrinsic error, which is error not caused by the navigation system and intrinsic error, which is error caused by the navigation system. Extrinsic error may be caused by incorrect image parameter readings (dimensions, tilt, etc.), undetected anatomical motion in the operating room (e.g., slippage of the head in the head holder), transcription errors, or other intermittent user-generated problems, but an extrinsic error that is often present to some degree occurs whenever the anatomy undergoes nonrigid motion between imaging and surgery. To reduce the problem of nonrigid anatomy, surgeons typically employ guidance systems only on bone or on the brain, which is held rigidly inside the skull. For orthopedic surgery, spine surgery, or brain biopsy, the assumption of rigid anatomy is reasonable. However, during neurosurgical procedures, after the dura has been opened, there can be considerable movement, resulting in inaccuracy on the order of several millimeters [35, 36] or more [37].

Regardless of whether extrinsic errors are present, inherent errors are inevitable. These are the errors resulting from the system's determination of the location of features in the image and in the operating room. The only errors of interest to us are those that are unpredictable. Otherwise they can be corrected and thereby eliminated. However, even unpredictable errors typically follow a statistical pattern, and error statistics can be known, so our analysis is statistical. We begin our analysis with point fiducials because the registration of point fiducials is the basis for all guidance systems, as we will point out below. Inherent error in the registration of point fiducials arises from just one source—localization error. Considerable theoretical progress has been made in the mathematical analysis of the

statistical effects of localization error on target registration error in the last decade, beginning with the publication of this statistical relationship between TRE and FLE in 1998 [38, 39]:

$$\text{rms}\ \ \text{TRE}\left(\mathbf{p}\right)=\left(\frac{1}{N}+\frac{1}{3N}\sum_{k=1}^{3}\frac{d_k^2}{f_k^2}\right)^{1/2}\times\text{rms}\ \ \text{FLE},\quad (3)$$

Where d_k is the distance from **p** to principal axis k of the fiducial set, and f_k is the rms distance of the fiducials from that same axis. Eq. (3) is derived under the limiting assumption that FLE is small relative to the spread of the fiducials, but simulations [38] and subsequent experimental evidence [40] suggest that this assumption is excellent for typical values FLE and typical fiducial arrangements associated with medical applications. As discussed in Section 3.2 above, FLE arises from imperfections in both image localization and physical localization. These two errors combine in quadrature to produce the FLE used in Eq. (3): $\left\langle \text{FLE}^2\right\rangle=\left\langle \text{FLE}_{im}^2\right\rangle+\left\langle \text{FLE}_{ph}^2\right\rangle$ under the reasonable assumption that the errors are uncorrelated. It is important to note that Eq. (3) does not suggest that TRE can be determined for a given registration. It pertains only to the rms statistic.

The formula in Eq. (3) quantifies the effect on registration accuracy of the target's position relative to the fiducial configuration. It shows, for example that rms TRE is minimal at the centroid of the configuration, where the d_ks are each equal to zero. At that centroid, $\text{rms}\ \ \text{TRE}\left(\mathbf{p}\right)=\text{rms}\ \ \text{FLE}/\sqrt{N}$, and its value decreases as the number N of fiducials increases. For a given N, as **p** moves away from the centroid, TRE tends toward larger values, and it exhibits ellipsoidal isocontours, as illustrated in Figure 9. Two fiducial configurations are shown, and the same target position is shown for each. The two configurations are the same, except that configuration (a) has a greater vertical spread than (b). As a result of the greater spread of the fiducials in (a), **TRE**(**p**) is smaller for (a) than for (b), showing that greater fiducial spread produces more accurate registration. The shape and size of the isocontours seen in the figure are determined by the f_ks, in Eq. (3). The contours are, with only the rarest of exceptions (such as when the fiducials are placed at the vertices of a Platonic solid), never spherical, nor are their cross sections ever circular.[5]

Our description so far of the generic guidance system requires that, once the fiducials have been localized in the operating room, the anatomy must remain stationary relative to the tracker. This onerous restriction can be removed, however, if the movement of the anatomy relative to the tracker is continuously monitored by the system. This monitoring was provided in the Acustar neurosurgical system by the addition of a “coordinate reference system” (CRF), which is a set of fiducials rigidly attached to the head holder and tracked simultaneously with the surgical probe. This innovation, which has been copied in virtually every commercial system that employs infrared tracking, allows the bed to be moved and reoriented and the cart that bears the tracking system to be rolled around the room at will without compromising the registration. It adds, however, the constraint that two objects—probe and CRF—must be tracked, restricting somewhat the positioning of people and

[5]despite the fact that some commercial systems always depict navigational with circular contours

equipment so as to avoid obstructing the view of either. A second effect is that a new source of error appears—the registration of the CRF fiducials from their new position to their old position during the physical localization of the fiducials. These two errors combine in quadrature [40].

The errors, FRE and FLE, relating only to fiducials, have an even simpler statistical relationship than that of TRE and FLE [41]:

$$\mathrm{rms\ \ FRE}=\sqrt{1-2/N}\times\mathrm{rms\ \ FLE}. \quad (4)$$

An interesting feature of this relationship is that, unlike rms TRE, rms FRE is completely unaffected by the shape or size of the fiducial configuration. In Figure 9, for example, expected rms FRE is the same for (a) as for (b), and it would be the same for a third system in which the fiducials were scattered at random over the page or over a three-dimensional box of any size. Thus, the overall goodness-of-fit of fiducials is independent of the geometry of the fiducials. However, the fit of an individual fiducial, $\mathrm{FRE}_i=|\mathbf{p}_i^{\prime}-\mathbf{q}_i|$ (see Eq. (1)), depends strongly on geometry, as shown by the formula [38],

$$\mathrm{rms\ \ FRE}_i=\sqrt{(\mathrm{rms\ \ FLE})^2-(\mathrm{rms\ \ TRE}\,(\mathbf{p}_i))^2}, \quad (5)$$

which shows that the spatial dependence of the individual FRE_i is opposite that of TRE(**p**). The value tends to be larger for fiducials closer to the centroid and smaller for the more distant fiducials. The relationship between rms FRE and rms FLE in Eq. (4) provides a simple way to estimate rms FLE, which proceeds as follows: Fiducials are localized, a registration is performed, and FRE is measured, and these three steps are repeated many times so that an overall rms FRE can be calculated. Inverting the formula above then gives $\mathrm{rms\ \ FLE}=\left(N/\sqrt{N-1}\right)\times\mathrm{rms\ \ FRE}$. It is important to remember, however, that this is a relationship between statistics—in particular the root-mean-squares—not between individual measurements. Thus, FLE cannot be estimated from FRE for a single registration, but must instead be estimated from statistics gleaned from multiple measurements.

There is one other important source of inherent error in point-fiducial systems. After the registration is completed, the physical position of the probe must be determined as it is placed at one anatomical target or another. The determination of this position, whether by a tracking system, by markings on a stereotactic frame, or via readings from a mechatronic probe holder, virtually always suffers from some level of error. If the probe is placed at physical position **q**, but the system reports position **q′**, then the system is making a “target localization error” (TLE) of **q′ − q**. This error is likely to be uncorrelated with TRE and therefore will add to it in quadrature. Thus, the rms value of the total targeting error (TTE) will entail the following combination of these two errors: $(\mathrm{rmsTTE}(\mathbf{p}))^2 = (\mathrm{rmsTRE}(\mathbf{p}))^2 + (\mathrm{rmsTLE}(\mathbf{p}))^2$. This additional error may have a substantial effect on total targeting error. For example, if TLE is equal to α × FLE, then = from Eq. (3) we find that for a target at the centroid of the fiducial configuration, $\mathrm{rms\ \ TTE}=\sqrt{\alpha^2+N}\times\mathrm{rms\ \ TRE}$, which means that a TLE that is equal to FLE increases the navigational error by a factor of two or more over

that of pure registration error. Typical efforts to validate the accuracy of surgical guidance systems guard against extrinsic error. To the extent that they are successful, it is TTE that is being measured and reported.

5. Implications of point-registration errors for systems without tracking

In the previous section, in our development of point-registration error, we have focused on navigational systems that employ tracking in the operating room. However, the error statistics associated with point fiducials also have fundamentally important implications for systems without tracking, including stereotactic frames, surface-based systems, and microstereotactic frames, because the registration of point fiducials is a central feature of each. We consider the implications for each of these systems in turn.

5.1. Stereotactic frame

For the stereotactic frame, the implication would be obvious if point fiducials were attached to the base ring and used for registration. With the more common N-bar system, the relationship is less obvious, but in fact even with N-bars, a three-point registration is employed, as explained near the end of Section 3.4 above. Therefore the rms TRE can be calculated from Eq. (3) for any target point **p**. However, it is first necessary to determine the locations of the fiducials and the value of rms FLE. The positions of the fiducials are the intersections of the slanted portion of the N-bar with the slice in which **p** is centered (e.g., the "*B*" in Figure 3), or, if **p** lies between slices, the positions of the fiducials are the interpolated positions between the *B*s in the neighboring slices. The value of rms FLE can be shown to be approximately equal to 1.6 × rms FLE_{2D}, where FLE_{2D} is the in-plane fiducial localization error. Once the registration is performed, articulating components of the frame are used to place a probe at a target. Target localization error will be present to some degree in this process, and, as in the case of frameless systems based on point fiducials, it can be expected to be uncorrelated to TRE. Therefore TRE and TLE add in quadrature. An important source of TLE present with stereotactic frames but not with fiducial-marker systems is human error in the adjustment of articulating and sliding components. Up to six such adjustments must be made, and one study has found that errors in these settings occur at the rate of twelve percent and calls for a second person to check each setting before proceeding [42].

5.2. Surface registration

For surface registration systems, while point registration is indeed employed (Step 2 of ICP in Section 3.3), there is no simple relationship between fiducial localization error and target error because of the complication of the directional weighting in Eq. (1). In addition, a major source of inherent error with surface systems is an inconsistent identification of surfaces in the image versus the operating room. One problem is nonrigid motion of the skin, which destroys the point correspondence. A second problem lies in the surface delineation in the image, where the air-skin surface rarely passes exactly between voxels but instead will pass through voxels, resulting in an ambiguity of position whose size is equal to the half the longest dimension of a voxel, which may range from one to three millimeters, depending on modality and acquisition protocols. Simulations may be carried out to estimate rms TRE at a

given point for a given error in the estimate of the surface position, but the latter error is difficult to estimate reliably. Finally, as with point fiducials and frames, TLE adds in quadrature to TRE.

5.3. Microstereotactic frames

For the microstereotactic frames, point registration is not performed algorithmically, but a form of point registration is carried out when the legs of a fixture are attached to the anchors. Ideally, the fixation point at the base of each leg should align perfectly with a point of fixation in each anchor, but, because of fiducial localization error in the image (here the anchors are the fiducials), and errors in the manufacturing of the fixture (which play the role of physical localization errors), the optimal positioning of the fixture will rarely be ideal. The positioning may involve subtle bending of the fixture or error in the mating of leg and anchor, and the distance between mating point on the anchor and nominal position of the mating point on the leg is analogous to fiducial registration error. A physical analysis of this process would be complicated, but it is clear that some sort of minimization of FRE is being done. Whether or not TRE follows the spatial pattern given by Eq. (3) and illustrated in Figure 9 is a matter of conjecture, but it is likely to be a good approximation. As with all the other systems, microstereotactic frames are also subject to TLE, which is caused by errors in the probe holder, and as with those other systems, TRE and TLE add in quadrature.

6. Stubborn myths

Because true fiducial positions and true target positions are never known in the clinical situation, it is difficult to pin down the relationships between their errors without rigorous mathematical analysis and carefully controlled studies. In the absence of knowledge of such analysis and such studies, intuition is the only remaining guide. Unfortunately, it is often a poor one. We consider here three myths that have pervaded frameless navigation since its beginnings. They are unfortunately both intuitively beguiling and false.

6.1. Myth 1: *FRE is an indicator of TRE*

In the operating room, when a frameless navigation system is used, FRE, or some measure derived from it (“zones of accuracy”, etc), may be shown to the surgeon after registration has been completed, as for example “FRE = 2.3 mm”. The surgeon must decide how to interpret this information, and at this point a common, even dangerous, misconception typically arises. It is intuitive to expect that, if FRE is smaller than usual, then TRE will be smaller than usual. This expectation is wrong. It has recently been shown mathematically that, while there is a direct relationship between their root-mean-square values, as shown in Eq. (3), there is no statistical correlation between FRE and TRE [43]. The myth that they are correlated has been part of neurosurgical lore since Acustar sparked the frameless revolution, and only recently have a few (unfortunately, very few and very recently) researchers begun to notice that it disagrees with observation [24, 44, 45]. The lack of correlation means that, for a properly working system, there is no information given by FRE or by any measure based on goodness-of-fit of the fiducials about TRE or any measure of navigational accuracy. Unfortunately, manufacturers have not yet acknowledged this fact, and, as a result, surgeons are being misled by their systems every day. There is, however,

some value in knowing FRE. An abnormally large value, 10 mm, for example, suggests that the system has been compromised in some way: Perhaps a marker has moved, a fiducial in the image was wrongly paired with a fiducial in the operating room, the localization system has failed, or undetected patient motion took place during fiducial localization. In this situation, the system should not be used for guidance, and the abnormally large FRE is the evidence. Thus, FRE may be the bearer of very bad news, but otherwise it gives no news at all.

6.2. Myth 2: *Dropping a fiducial will increase accuracy*

Most frameless guidance systems rightly encourage the surgeon to check the accuracy of the registration by touching some points of the anatomy with the probe, preferably close to the region of interest, while watching the probe as depicted on the computer screen. The distance between the depicted probe and the depicted anatomical point is a visual estimate of TRE at that point. TRE tends to vary slowly as the probe is moved from point to point, so a check of two or three points near the region of interest is a sufficient validation. If TRE appears abnormally large, then the system may be compromised, if not, then the system is likely to be operating correctly. This “sanity check” is an excellent idea. However, users may then be tempted to veer away from this sensible process by touching the fiducials themselves to make a visual estimate of FRE_i, and then concluding that the registration can be improved by relocalizing the fiducials for which FRE_i is largest. Such relocalization is misguided and is likely a waste of precious surgical time (typically while a patient is under general anesthesia!). Worse still, the surgeon may decide to omit the fiducial with the largest error! The notion that dropping that fiducial is likely to increase guidance accuracy is reinforced when the surgeon observes a concomitant reduction in FRE, and such a reduction is quite likely, because rms FRE decreases as N decreases, as can be seen from Eq. (4). However, as we learned above, rms FRE_i varies from one fiducial position to another, and fiducials nearest the centroid of the configuration are expected to exhibit the largest error when the system is working properly, so dropping them makes no sense at all. In fact it makes much more sense to keep them, because an application of the formula in Eq. (3) will, because of the presence of N in the denominator, inevitably predict that dropping a fiducial, whether its FRE_i is large or small, while it is likely to decrease FRE, will make rms TRE larger at every point in space and thus is likely to decrease navigational accuracy.

The rms values given above for TRE and FRE answer this sort of question: “What rms value should I expect for a properly working system, if I repeatedly measure TRE(**p**) or FRE?” However, they do not give the whole picture. Both TRE and FRE are statistical in nature, and thus they will rarely equal their root-mean-square values. The full statistical description requires that the probabilities of the values observed be given. Progress on this front has been made as well, with probability functions having been published for FRE [41], TRE [46], and FRE_i [47]. Each of these functions gives the probability of observing any given value of their respective error measure in proportion to rms FLE. Thus, they answer these sorts of question: “What is the probability that, if my system is working properly, TRE(**p**) is less than 5.0 mm,” and “What is the probability that my system is working, given the FRE that I observe?” The latter question is the operative one in the situation with which we ended the previous subsection and began this present one. If the probability the observed FRE is

much lower than normal, then the system is likely to be compromised and should not be used. If the probability is higher than normal, than the likelihood that the system is working correctly is higher than normal, but in neither case is it likely that dropping a fiducial will increase the accuracy.

6.3. Myth 3: *Planar fiducial configurations are bad*

When choosing the placement of the fiducials, another misconception continually arises. It is assumed that a planar configuration is somehow inferior to a non-planar one. This idea may be based on the intuitive notion that three-dimensional guidance cannot be based on a two-dimensional configuration (not true), or it may arise from experience with some (inferior) registration algorithms that fail when all the fiducials in one space or the other are planar. In any case, with the standard algorithms, planar arrangements are no worse than planar ones. Indeed, in some cases they are slightly better [40].

7. Conclusion

Surgical guidance has advanced significantly since its first use in 1895. Improvement in images, in computers, and in fiducial systems have made possible great strides in accuracy. The frameless revolution, which began in the late 1990s, when the Acustar system introduced the discrete fiducial marker as the replacement for the cumbersome frame, is gradually overtaking the stereotactic frame in popularity, and these large frames have recently been challenged on another front by microstereotactic frames, which appear to show great promise both in the areas of accuracy and workflow. While it is too early to provide a reliable assessment of the accuracy and usefulness of the microstereotactic frames, the fiducial marker appears to be emerging as the future of surgical guidance.

At the heart of each of these systems, from the stereotactic frame to the discrete marker, lies point registration. Guidance systems may differ drastically in terms of the hardware employed and the measurements made, but, as we have shown, in each case, a set of points is identified in the image, and a rigid transformation is found that aligns those points with corresponding points in the operating room. Much of the improvement in surgical guidance can be traced to improvement in the registration process, and our present work is meant to reveal both the ubiquitous role of point registration and its importance in the determination of accuracy in all the major surgical guidance systems. It is hoped that it will foster an increased understanding of the navigational approaches that depend so heavily on registration and lead ultimately to an improvement in the accuracy of surgical guidance as it is applied to patients.

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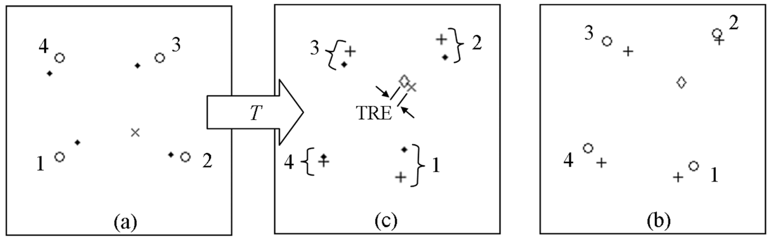

Figure 1. Depiction of fiducial registration

(a) Image space: The circles are true fiducial centroids, the dots are the localizations, and the cross is a target. (b) (at the far right) Physical space: Circles are true centroids of same fiducials, "plus" signs are the localizations, and the diamond is the same target. (c) Superposition of localized points and targets both from (a) image space after a rigid transformation *T* and from (b) physical space. The respective localizations (dots and plus signs) are imperfectly aligned, as are the target positions. The displacement between the diamond and the cross (small arrows) represents target registration error (TRE).

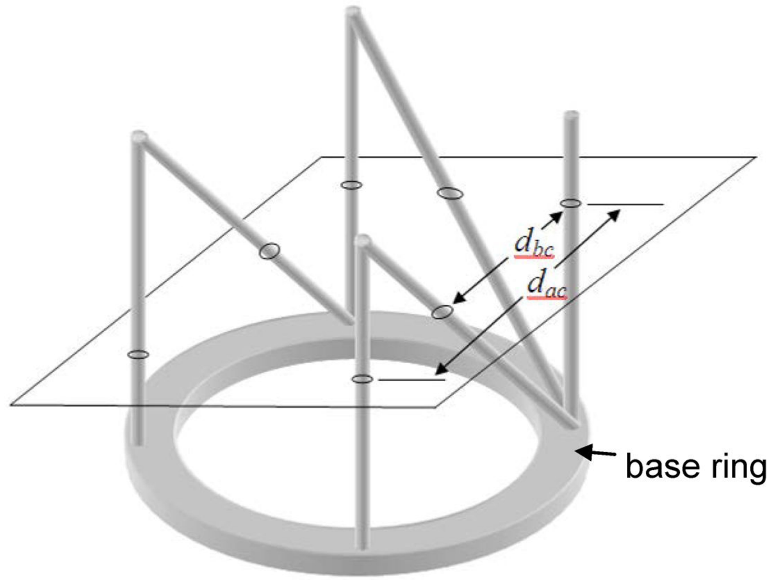

Figure 2. N-bars

Seven bars are arranged to form three N-bars. During imaging the bars are placed on a base ring, which is attached rigidly to the patient's head (attachment not shown). One CT image slice is shown. The seven ellipses represent the intersections of the bars with the slice, which need not be parallel to the base ring. The centroids of these ellipses are used to determine the position and orientation of the slice relative to the base ring. The distances d_{ac} and d_{bc} are measured in the image slice (see also Figure 3).

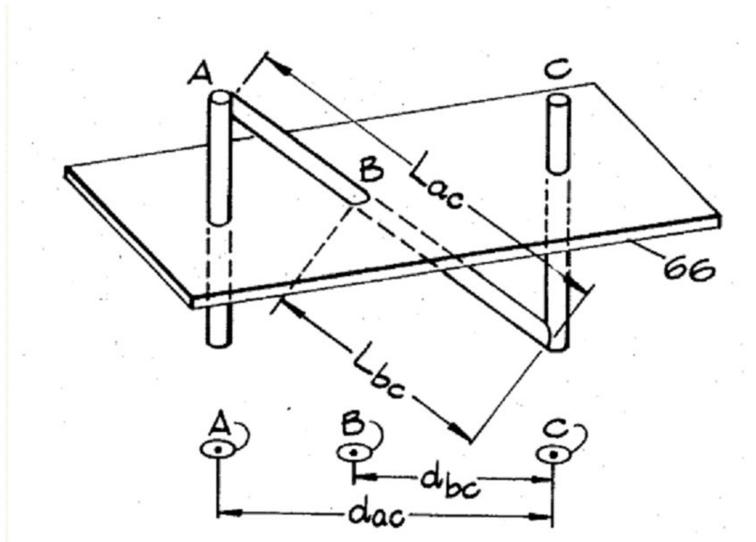

Figure 3. N-bar point determination

(copied from Brown's patent). In the upper drawing, one N-bar (A-B-C) is shown with a portion of an image slice (66). The distance L_{ac} is known from frame calibration. The distance L_{bc} is to be determined. In the lower drawing distances between the intersections of the bars with the image slice are designated as d_{ac} between A and C and d_{bc} between B and C (these same two distances are also shown in Figure 2).

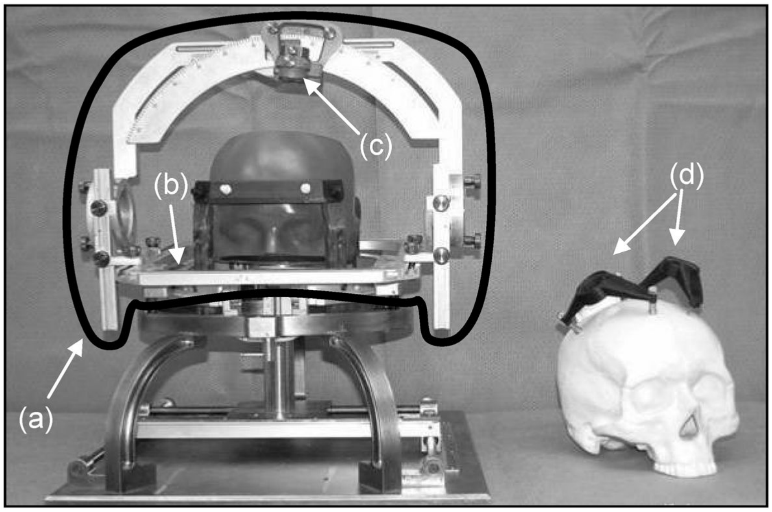

Figure 4. Comparison of a stereotactic frame and a microstereotactic frame

(a) The outline encloses a stereotactic frame (Radionics CRW, Integra Neurosciences, Burlington, MA) attached to a phantom. The N-bars (not shown) mount on base ring (b). (c) Probe holder. (d) Two STarFix microTargeting Platforms attached to a phantom. The probe holder is shown in Figure 5).

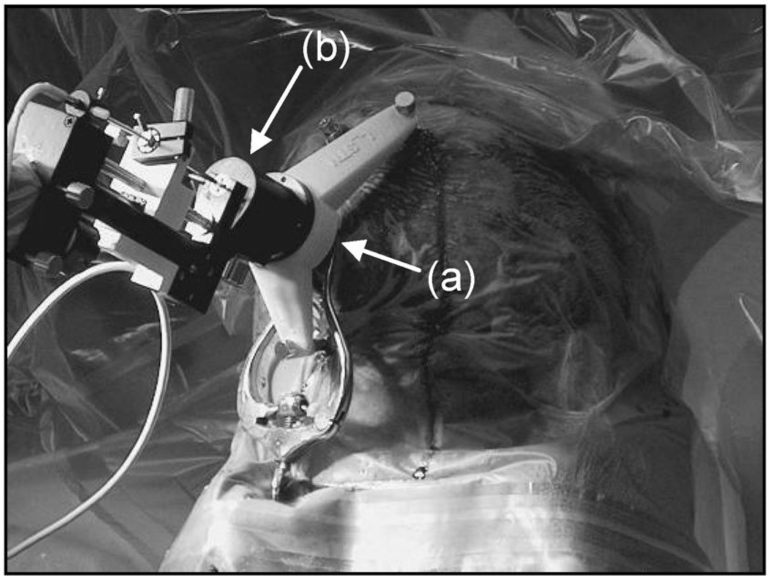

Figure 5. Driver mounted on platform

(a) Platform attached to patient's head. (b) Driver attached to platform.

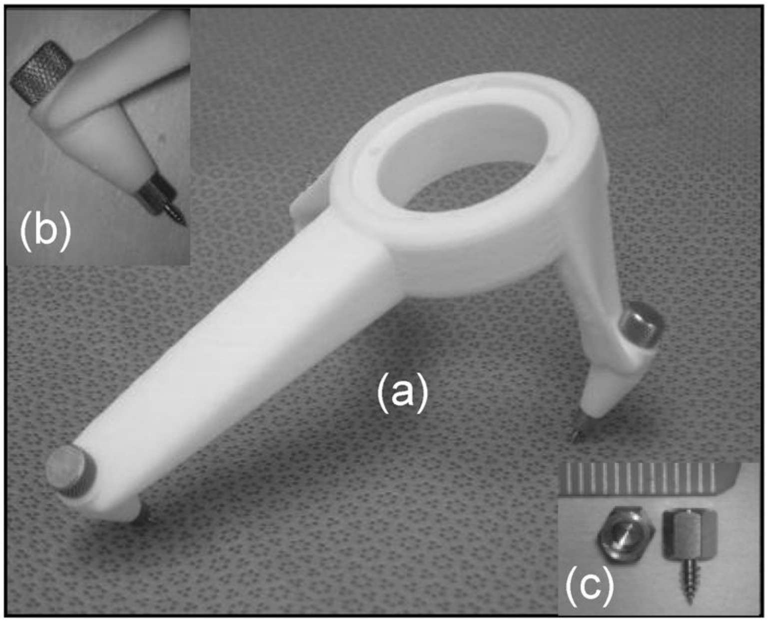

Figure 6. Platform with anchors

(a) Platform with anchors. The large hole accommodates the probe driver. (b) Close-up of one leg showing bolt attaching leg to anchor. (c) Close-up of anchors. The marks on the ruler above the anchors are millimeters.

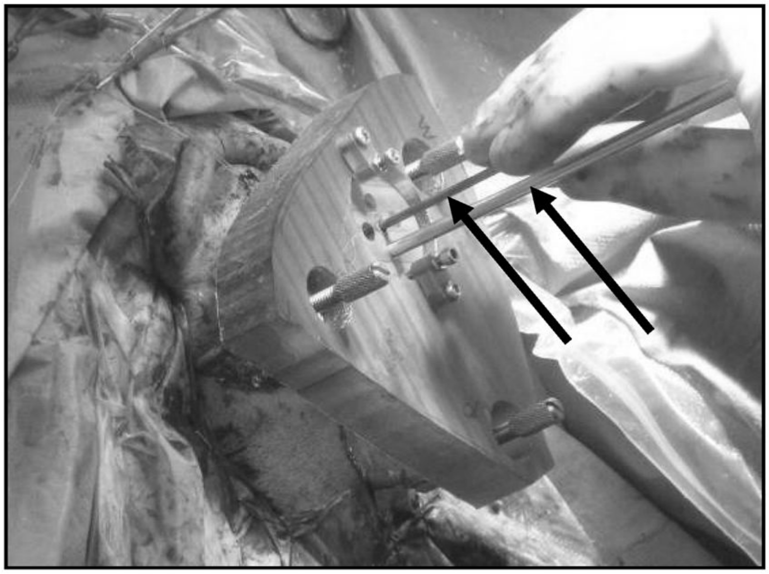

Figure 7. Microtable attached to patient

The two arrows show probes passing through a probe holder, pre-aimed at internal targets. (This image appeared previously in reference 35, is used by permission).

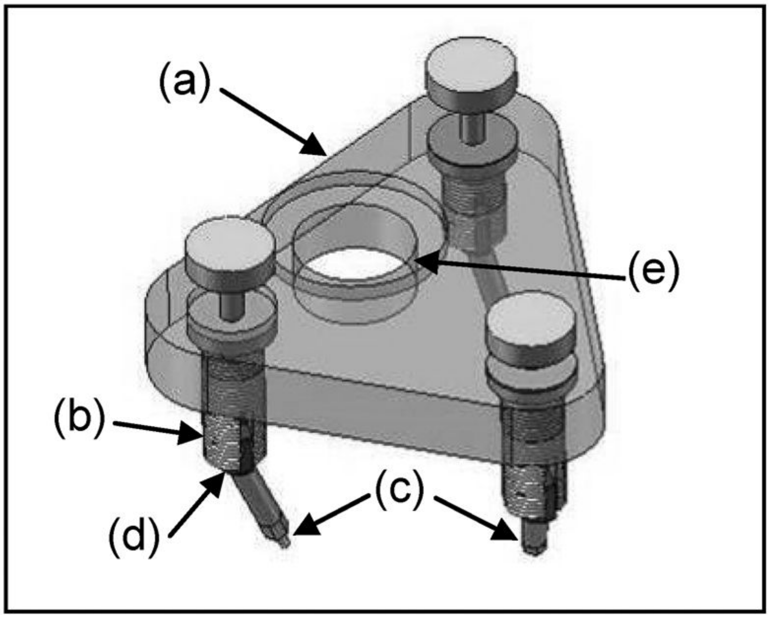

Figure 8. Microtable schematic

(a) Tabletop. (b) Table leg. (c) Anchors (similar to those shown in Figure 6c. (d) Ball-and-socket joint. (e) Hole to accommodate a probe holder.

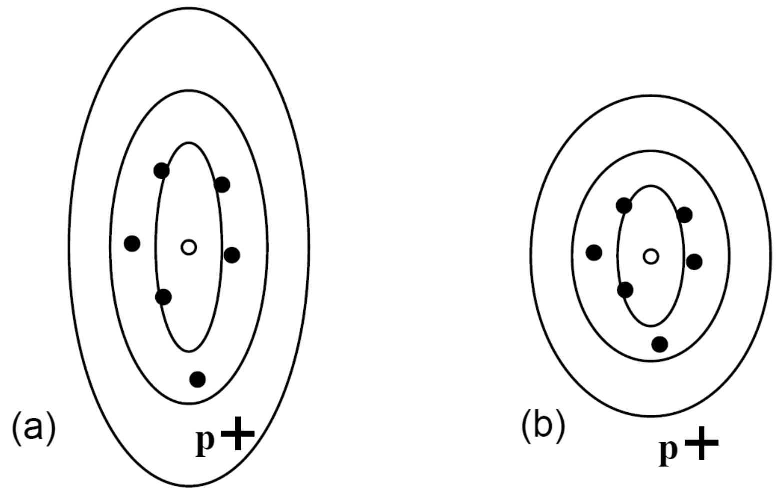

Figure 9. TRE patterns: An illustration in two dimensions

The black circles represent fiducials. (a) A configuration in which the fiducial spread is much greater vertically than horizontally. (b) A configuration in which the spread is only slightly greater vertically than horizontally. The hollow circles are placed at the respective centroids. FLE is the same for both configurations. Rms TRE at the centroid depends only on the number of fiducials, and is equal to 0.5 mm both for (a) and for (b). The ellipses are contours of constant TRE for a given FLE. In both (a) and (b), rms TRE = 1, 1.5, and 2 mm on the inner, middle and outer contour, but the contours are farther vertically from the centroid in (a) than they are in (b) **p** Thus, at position p (cross), rms TRE < 2 mm in (a), while rms TRE > 2 mm at the same position in (b), illustrating that greater spread in the fiducials leads to a greater registration accuracy.