Software for Image Registration: Algorithms, Accuracy, Efficacy

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Image registration is finding increased clinical use both in aiding diagnosis and guiding therapy. There are numerous algorithms for registration, which all involve maximizing a measure of similarity between a transformed floating image and a fixed reference image. The choice of the similarity measure depends, to some extent, on the application. Methods based on the use of the joint intensity histogram have become popular because of their flexibility and robustness. A distinction is made between rigid-body and non-rigid transformations. The latter are needed for inter-subject registration or intra-subject registration in cases where the region of the body of interest is not considered rigid. Non-rigid transformation is normally achieved using a global model of the deformation but can also be defined by a set of locally rigid transformations, each constrained to a small block in the image. There is scope for further research on the incorporation of appropriate constraints, especially for the application of non-rigid transformations to nuclear medicine studies. Most of the initial practical concerns regarding image registration have been overcome and there is increasing availability of commercial software. There are several approaches to the validation of registration software, with validation of non-rigid algorithms being particularly difficult. Studies have demonstrated the accuracy on the order of half a pixel for both intra- and inter-modality registration (typically 2 to 3 mm). Although hardware-based registration has now become possible by using dual-modality instruments, software-based registration will continue to play an important role in nuclear medicine.

THE COMPLEMENTARY NATURE of information provided by different imaging modalities is well understood by nuclear medicine practitioners, but it is only recent software and hardware developments that have enabled this to be exploited in a clinical setting. Increasingly, reporting stations provide access to data from multiple modalities, and various forms of fused display are becoming available for viewing spatially registered images. Aside from multi-modality fusion, availability of registration software improves the utility of serial nuclear medicine studies. The availability of registered data has also prompted the development of improved quantitative tools for image analysis.

To a large extent, the availability of image fusion based on registration software has been limited to sites with on-site technical expertise. This is not surprising given the rapid evolution of algorithms and the slow adoption of standards for image transfer. The advent of dual-modality instrumentation has provided a direct fusion capability, prompting demand that has exceeded expectation. It has become clear that high quality fusion can provide important additional diagnostic information, although the full impact on clinical management has yet to be scientifically demonstrated. The unprecedented interest in image fusion has itself created a demand for software solutions that can complement the hardware approach. There are many studies performed on conventional single-modality equipment that can benefit from image fusion. Even with dual-modality instrumentation, there are important applications that require software approaches. These include serial studies, fusion with a modality not available in a dual-modality instrument, and inter-subject studies. Furthermore, hardware-based fusion cannot account for differences caused by deviations from ideal imaging conditions, such as the effects of field non-uniformities in magnetic resonance imaging (MRI), and differences caused by discrepancies in acquisition times, such as respiratory motion blurring. It is clear that the demand for effective fusion software will increase as the clinical impact of image fusion and associated techniques is more fully demonstrated.

The adoption of software registration has been hampered by limitations in the ease of image transfer and the profusion of poorly validated algorithms. It is only relatively recently that fairly robust algorithms have become available and, indeed, the development of algorithms continues, particularly for the more complex problem of non-rigid registration. The objectives here are to review software approaches to registration, to comment on the accuracy of registration algorithms, and to discuss limitations and potential future directions in the development of software registration in the nuclear medicine context. The interested reader is referred to Hajnal et al.[1] for a more extensive coverage. There are also useful reviews covering various aspects of medical image registration.[2-14]

GENERAL ALGORITHMS FOR IMAGE REGISTRATION

Distinction is made between image fusion and image registration. In broad terms, image fusion denotes synergistic exploitation of spatially related images. Examples include not only the combined display of registered

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0001-2998/03/3303-0013$30.00/0
doi:10.1053.2003.127309

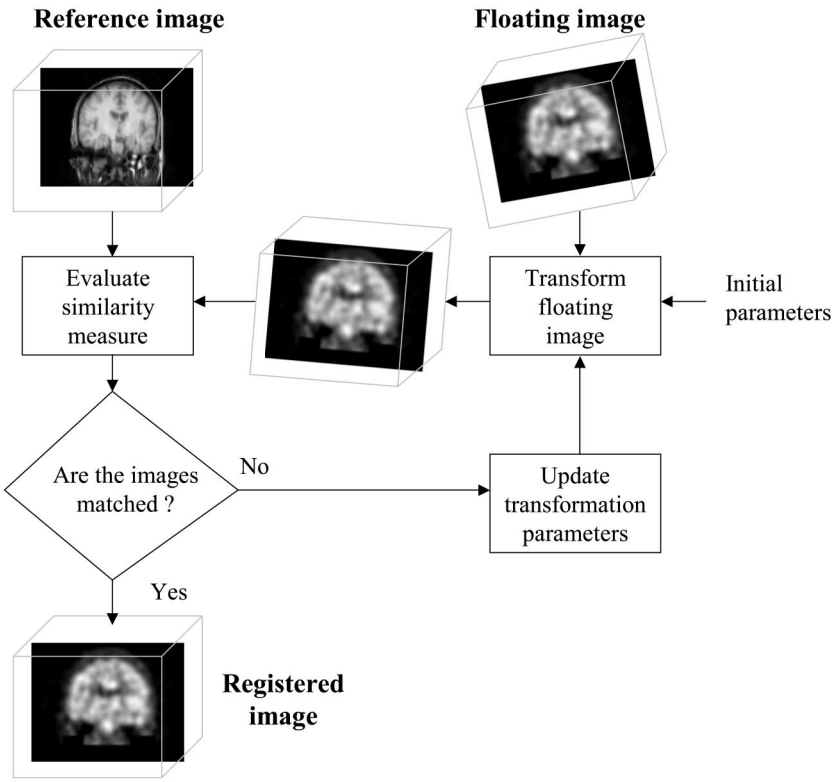

Fig 1. Schematic of a general image registration algorithm. An initial set of transformation parameters is applied to the floating image. The transformed floating image is then compared with the reference image by assessing the similarity between the two images. The algorithm iteratively updates the transformation parameters and reassesses the similarity measure until alignment is achieved.

studies, but also the use of registered data for region-of-interest definition, for correction of attenuation or partial volume effects, and for incorporation of anatomical information in tomographic reconstruction of emission data. Underlying all fusion applications are algorithms for the spatial registration of images. This review focuses on registration algorithms and on the evaluation of their performance.

There are many instances of image registration being used for modalities other than nuclear medicine. Here, the discussion will focus particularly on the software approaches that are relevant to nuclear medicine. In most cases, data sets to be aligned are three-dimensional (3D), although applications of 2D-3D,[15] as well as 2D-2D registration have been described, for example, in the context of correction for patient motion.[16-18]

Given two image data sets (normally 3D but, for simplicity, referred to as "images"), registration requires the determination of a *transformation* (T) that can be applied to one image (referred to as the floating image) to bring it into alignment with the second image (referred to as the reference image). Determining the necessary transformation normally requires an iterative search in which a measure of *similarity* between the transformed floating image and the reference image is maximized. This is usually achieved by using an iterative, automatic *optimization* algorithm (Fig 1).

There are two basic types of transformation that can be applied in aligning images:

- *Rigid body*: This assumes that only translation and/or rotation are necessary. The relative scale factors along the axes are usually determined independently, based on the known voxel dimensions.
- *Non-rigid body*: This is applicable where rigidity cannot be assumed. A non-rigid transformation may take the form of an affine transformation (which allows for shape change via a shearing action) or more complex transformations where shape change is accommodated either globally or locally.

It is useful at the outset to define different classes of application and to outline the different demands they place on the registration algorithms. In practice, three classes of image registration problem are distinguished:[2,8,14]

- *Intra-modality, intra-subject.* In the comparison of serial studies in the same modality, assumptions made regarding the similarity between images favor the choice of relatively simple algorithms that are well suited to rigid-body transformations. Comparison of ictal and interictal brain single photon emission computed tomography (SPECT) studies in

an individual patient is an example.

- *Intra-modality, inter-subject.* Aligning studies from multiple patients is quite common in establishing normal ranges or in performing group analysis. However, matching images across individuals is not trivial and requires non-rigid transformations. Assessment of activation in patient groups by using statistical parametric mapping (SPM) is an example.
- *Inter-modality, intra-subject.* Probably the area of most interest is the alignment of images from different modalities, where the underlying image values can be quite different in the two images to be aligned. This requires algorithms more sophisticated than those relying on a direct comparison of values. A rigid-body or non-rigid model is assumed, depending on the application. Clearly, registration of a positron emission tomography (PET) or SPECT image with a computed tomography (CT) or MR image falls into this category. Registration of images of the head is usually adequately defined by a rigid-body transformation, whereas images of other regions of the body may require a non-rigid transformation.

Inter-modality, inter-subject registration falls outside the problems of interest in clinical practice and, in any case, is not practical in a clinical setting.

SIMILARITY MEASURES

A measure of similarity between images is central to the registration algorithm. In the main, it determines the robustness and flexibility of the algorithm. A number of similarity measures have been suggested, generally falling into three categories: landmark-based measures, surface or edge measures, and voxel intensity measures.

Landmark Measures

Registration can be achieved by identifying unique landmarks, either anatomically defined or fixed externally to the patient, that appear in the two images to be aligned. Relatively simple and well-developed algorithms[19,20] can then be used to find the transformation that minimizes the average distance between the corresponding imaged landmarks. In general, nuclear medicine images lack anatomical detail and identification of specific anatomical landmarks[21,22] tends to be difficult, if not impossible. Instead, external fiducial markers are attached to the skin, made visible in both images by means of radioactivity and/or contrast material.[23-26] Use of external fiducial markers is generally inconvenient and impractical for routine use, although it is useful for validation of registration techniques (see section on validation). As an alternative to the anatomical landmarks, which typically require significant user input, geometrical features can be automatically identified,[27] but again this tends to be limited to high-resolution modalities. Landmarks can provide a basis for both rigid and non-rigid transformations (as in commercially available morphing programs). However, this relies on accurate landmark identification. Moreover, the complexity and fidelity of the transformation is determined by the number of landmarks. Landmark techniques are, therefore, even less well suited to non-rigid registrations of nuclear medicine data.

Surface and Edge Measures

Two images can be aligned by minimizing the average distance between corresponding surfaces or edges, identified by preprocessing the images.[28-31] An alternative is to match surface points in one image to the identified surface in the second image.[32] This particular technique was among the first to be successfully applied in matching nuclear medicine data to other modalities by using the "head and hat" algorithm, where alignment is likened to moving a hat to best fit a person's head. The technique was designed for use in brain studies, but has been adapted for other applications.[33,34] However, the accuracy of the technique is poor in low-resolution studies, and the presence of a suitable surface is not always guaranteed. Like the landmark measures, the surface/edge measures are better suited to high-resolution anatomical modalities.

Voxel Intensity Measures

In nuclear medicine, similarity measures based directly on voxel intensities have the greatest appeal and are most widely used. The simplest measures compare intensity values in the images to be aligned. However, intensities obtained with different modalities are usually poorly correlated. More general measures that do not rely on intensity correlations are better suited to inter-modality registration. Similarity measures based on analysis of the joint intensity histogram (representing the co-occurrence of intensity values in the two images) have become particularly popular.

The following discusses some of the available voxel intensity similarity measures:

- *Principal axes:* The center of mass (counts) and orientation (principal axes) of each image set can be determined[35,36] and used to align the floating image to the reference image. Although relatively fast, the technique is limited to situations where the imaged area and intensity distributions are similar. It is also limited to rigid-body transformations.
- *Minimum intensity difference:* A simple approach for intra-modality registration is to use the sum of either absolute or squared intensity differences between the two images.[37-39] In the case of images that differ in intensity only due to Gaussian noise, this can be shown to provide optimum registration.[40] Although the technique is limited to the registration of similar images, it has found numerous applications in nuclear medicine.[39] The technique can be considered the method of choice for intra-modality registration in nuclear medicine.
- *Cross-correlation:* Cross-correlation is a useful technique that has been applied to both inter- and intra-modality registration,[41-43] either directly to

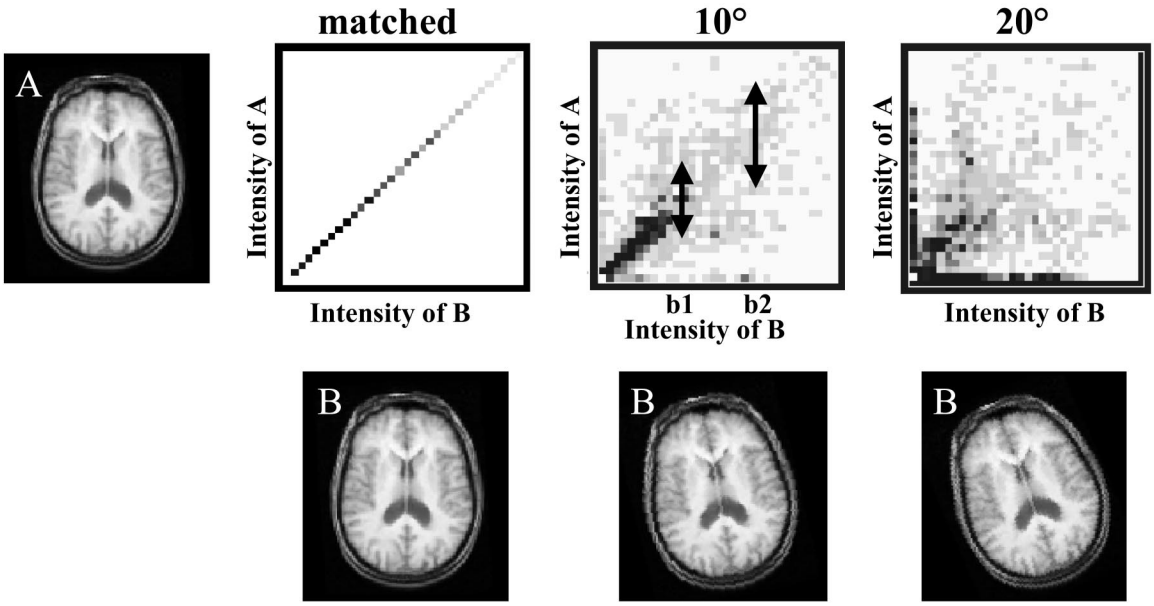

Fig 2. Joint intensity histogram. For two images, a joint intensity histogram is constructed by plotting the relative frequency of each pair of intensities. For voxels with a given intensity in B, the proportion of corresponding voxels in A with a particular intensity is plotted. The histogram approximates the joint probability density function and, therefore, the value in each cell estimates the probability of occurrence of a particular pair of intensities in the two images. For the special case of identical images (illustrated), the joint histogram forms a single line when the images are aligned, but disperses from this line as image B is reoriented. One approach to estimating dispersion is by measuring or standard deviation of voxel intensities in A for specific intensities in B (as illustrated for intensities b1 and b2).

images or extracted features.

- *Minimum variance:* This measure is well suited to the registration of nuclear medicine data with high-resolution modalities. It defines a transformation that minimizes the variance in those regions of the functional study that are aligned with "single tissue" regions defined by segmentation of the anatomical image. At its simplest, the algorithm defines a segment as a set of voxels sharing the same intensity value.[44] A more sophisticated segmentation that accounts for spatial correlations among neighboring voxels has also been reported.[45] Both approaches have been demonstrated to be accurate and robust.
- *Voxel intensity histogram:* Most of the above techniques imply a spatial correspondence between intensity values in the images to be aligned. A separate class of similarity measures can be defined that rely only on the co-occurrence of specific intensity pairs, independent of location.[46] A joint intensity histogram can be constructed for a pair of images to estimate the probability of occurrence of each intensity pair (Fig 2). At correct alignment, a reduction in the dispersion of the joint histogram values is observed. This dispersion can be analyzed either in terms of variance reduction[47,48] or by using information theory.[49-52] The main attraction of these algorithms is that they do not rely on a direct correlation between image intensities in the two images. Therefore, they can be applied in inter-modality registration where the images to be aligned can be quite different. These algorithms have been successfully applied in a wide range of situations, with rigid-body and non-rigid transformations. A more detailed description is, therefore, warranted.

REGISTRATION BASED ON THE JOINT INTENSITY HISTOGRAM

It is useful to adopt an intuitive view of the joint intensity histogram. As can be seen in Fig 2, when identical images are correctly aligned, the knowledge of the intensity in one image provides maximum information about the other, allowing perfect prediction of the intensity in the second image. This information is known as the *mutual information* (MI). In the more general case, where the images differ, registration is still achieved by maximizing the MI, but there will be residual uncertainty in the prediction of intensity in the second image. The maximization of MI has been demonstrated to be extremely robust[53] even though explicit dependence on spatial correspondence is absent from the relationship between intensity values.

The information available in an image can be measured by entropy H (or uncertainty in the intensity values),

$$H = -\sum_i p_i \log p_i , \qquad (1)$$

where p_i is the probability of finding intensity *i.* Based on information theory, MI(A,B), between images A and

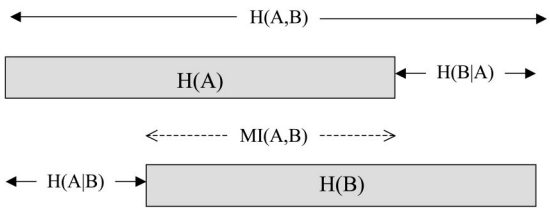

Fig 3. Mutual information. We denote the entropy or uncertainty associated with images A and B as H(A) and H(B) and their joint entropy as H(A,B). The area of overlap defines the mutual information, MI(A,B), where image A can be predicted from image B. Aligning the two images maximizes MI. The relationship between MI and the conditional entropies H(A|B) or H(B|A) is illustrated (see text).

B, can be determined from the entropy of the individual images H(A) and H(B) and their joint entropy H(A,B),

$$MI(A,B) = H(A) + H(B) - H(A,B)\,. \qquad (2)$$

All three terms rely only on the probability of occurrence of the various intensities, independent of their spatial distribution (Fig 3). Because one of the images is rotated, or otherwise transformed, the definition of the MI is valid only over the area of overlap of the two images. Alternatively, it can be shown that

$$MI(A,B) = H(B) - H(A|B)\,, \qquad (3)$$

where H(B|A) represents the conditional entropy of image B given image A.

It can be seen in this definition that maximizing the MI can be achieved by minimizing the conditional entropy. When identical images are correctly aligned, the conditional entropy will be zero, i.e., knowing the intensity values in A, the intensity values of B should be predicted perfectly. A problem arises because of the possible variation in the area of overlap of the two images. A variation of MI referred to as the *normalized MI* accounts for the area of overlap and provides a more robust similarity measure.[52,54] The reader is referred to the excellent review by Hill et al.[13] for a more detailed discussion on information theoretic approaches.

An alternative similarity measure for the joint histogram involves estimation of the variance in the intensities of those voxels in one image (A) that are spatially aligned with voxels of a specific intensity (b) in the second image (B). Referring to Fig 2, the variance of intensities of A can be seen to vary for different intensities of B. The weighted sum of these variances is compared with the overall variance of intensities of A as a measure of the dispersion. The defined statistic is the *correlation ratio* (CR)[47] given by

$$CR_A = 1 - \Big(\sum_b var(A_b)\,N_b/N\Big)/var(A)\,, \qquad (4)$$

where A_b refers to the intensity values in image A that correspond to intensity b in image B, var(A) is the variance of all intensity values in A, N_b is the number of voxels with intensity b in image B, N is the total number of voxels in image B.

It can be easily recognized that a complementary version of the correlation ratio (CR_B) can be defined, in which the roles of images A and B are swapped, leading to a different outcome. To remove the dependence on the order of images, a *symmetric CR* is defined as the sum CR_A+CR_B[48] or average $(CR_A+CR_B)/2$ of the two asymmetric terms. The behavior of the normalized MI and the symmetric CR is very similar, with the latter proving more robust when sparse sampling is used to improve the speed of computation.[48,55]

NON-RIGID REGISTRATION

As outlined earlier, there are two main types of transformation: rigid-body and non-rigid. A rigid-body transformation, which permits only rotations and translations, or a slightly more general affine transformation,[56] which additionally permits zooming and shearing deformations, can be expressed as a matrix that acts on the coordinates of every voxel in the image. However, in some cases, neither rigid-body nor affine transformations adequately describe the necessary alignment. In particular, inter-subject registration requires more complex transformations to account for the many anatomical differences between individuals. In addition, non-rigid registration may be necessary to account for differences in posture or organ size and position in serial studies (eg, pre- and post-therapy). Most non-rigid algorithms use a smooth transformation, often based on a physical process. For reasons of computational efficiency, the transformation is computed at a subset of voxels and interpolation is used to propagate the transformation throughout the image volume. One approach is to use a set of basis functions[57-59] or shape descriptors[60] to describe the transformation. Alternatively, various physical models have been suggested, including a thin metal plate,[61] elastic solid,[62,63] and viscous fluid.[64,65]

The choice of voxels where the transformation should be computed and how far the transformation is to propagate from these voxels poses problems in nuclear medicine. To illustrate the problem, consider the hypothetical situation illustrated in Fig 4 where the two images represent a functional and an anatomical study. Each image consists of a large organ (or the whole body) with an embedded lesion. Comparing the two images shows that both the organ and the lesion differ in shape and size, but the distortion is different. A global non-rigid transformation will give the best average match for all parts of the image. Because the organ is much larger than the lesion, the transformation will be biased toward correcting the organ distortion and may not adequately correct for lesion distortions. Use of a locally non-rigid algorithm may better adapt to local shape change, but introduces a potentially serious problem. These algorithms seek to match local regions and would, therefore,

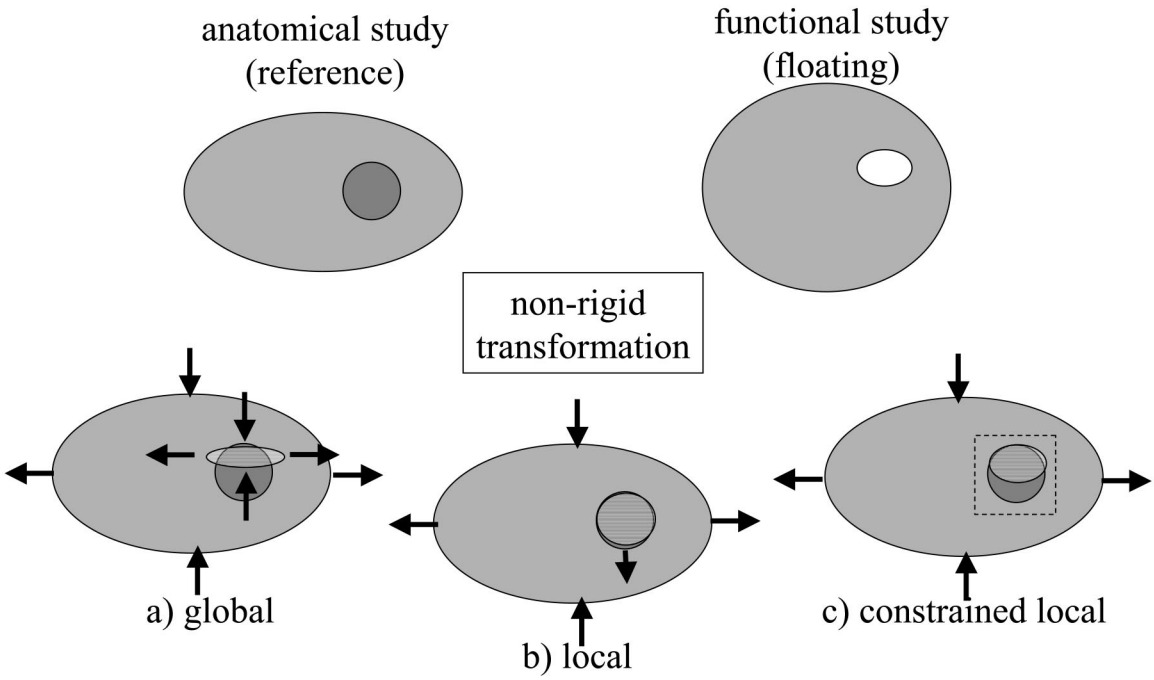

Fig 4. Limitations of non-rigid transformations. Alignment of a functional image with an anatomical image may be expressed as a global (non-rigid) transformation to account for change in shape between the two studies. (a) However, this transformation will reflect the average deformation across the image and may fail to account adequately for local changes in shape, size, and location of internal structures. (b) A locally non-rigid algorithm may be better suited resulting in a match for both body outline and internal structures. (c) Care needs to be taken to constrain the transformation (eg, avoiding local transformation within the defined area) to preserve anatomical/functional differences of diagnostic importance.

ideally match the shape and size of the lesion in the anatomical and functional images. Such a transformation may essentially destroy the relevant diagnostic information, which distinguishes functional and anatomical extent of disease. Without appropriate constraints, a non-rigid registration algorithm can be quite misleading. There is, therefore, a need to incorporate "intelligent" constraints as part of a non-rigid model, for example, limiting the extent of the local non-rigid transformation. A limited amount of work has been done to develop appropriate constraints, for example, accounting for rigid structures such as bone.[66] This is an area of continuing research.

An alternative approach to non-rigid registration implements a set of local transformations, which individually can be rigid but collectively define a non-rigid displacement field (Fig 5). These algorithms usually work by using a multi-resolution approach, where the algorithm commences with fairly coarse resolution (large blocks), progressing to finer resolution (small blocks) in subsequent iterations.[67-72] Interpolation is used to determine the transformation at points intermediate to the points where displacement vectors were calculated, with the local transformation encouraged to change smoothly from point to point, for example, by median filtering.[70] Simply removing obvious outliers may not be sufficient, so additional constraints may still be necessary.

PRACTICAL CONSIDERATIONS

Image Transfer

Historically, the difficulty of achieving efficient image transfer between modalities (or even within nuclear medicine) has been a marked impediment to software-based registration. However, most hospitals now have fast, corporate networks linking departments and direct internet connection. Physically transferring images inside an institution or from external consultants is easily realized. It should be stressed that a simple point-to-point connection is all that is necessary if a network connection is unavailable. The simplicity of this type of connection is frequently overlooked. Similarly, the problem of translating file formats is virtually solved through the current improved version of the DICOM standard.[73] However, problems are still encountered, and care needs to be taken to ensure that the order in which slices are stored and the image orientation are well understood. The availability of manufacturer-supplied software registration tools places a greater responsibility on the supplier to provide fail-proof image transfer.

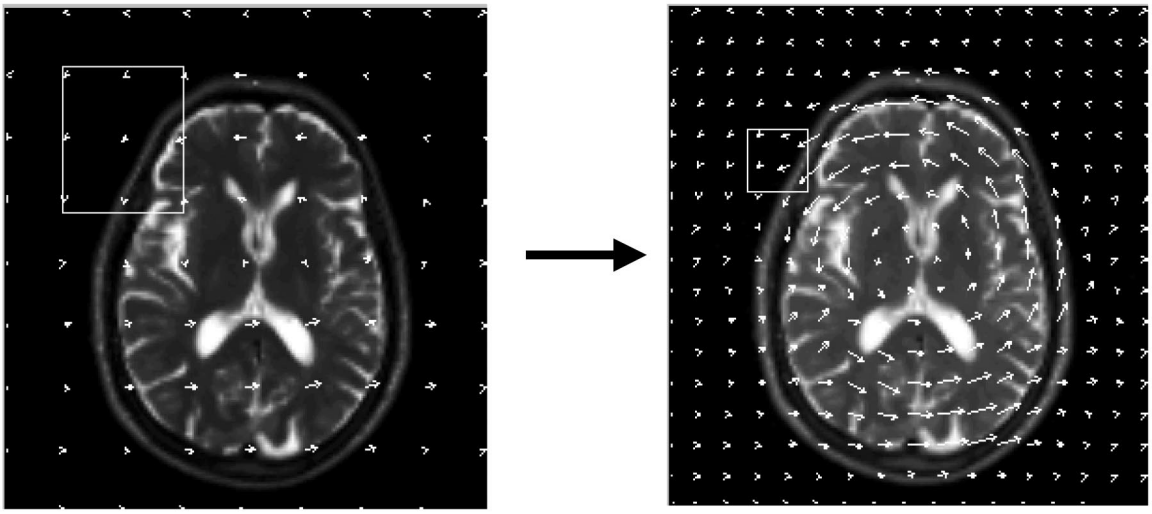

Fig 5. Non-rigid, locally implemented registration. Arbitrarily complex, non-rigid registration can be implemented by performing a series of rigid registrations in a local neighborhood (identified by the box). By moving the box to different locations, a set of displacement vectors can be defined. For computational efficiency, the algorithm usually starts with a large box, gradually reducing the box size to provide a more detailed displacement vector field. A displacement field is illustrated for a simple rotation.

Subsampling

It is quite common in registration algorithms to base the alignment on only a subset of image points rather than the complete data set, mainly to improve computational speed. In some cases, the sampling is modified to refine the registration at later iterations in the optimization process (as is the case in multiresolution approaches). In the joint intensity histogram methods, care must be taken to ensure an adequate number of intensity levels (by using histogram re-binning), particularly with coarse sampling where the joint histogram becomes sparse.[52,74]

Interpolation

Interpolation is an important consideration in registration. Image transformation necessitates interpola-

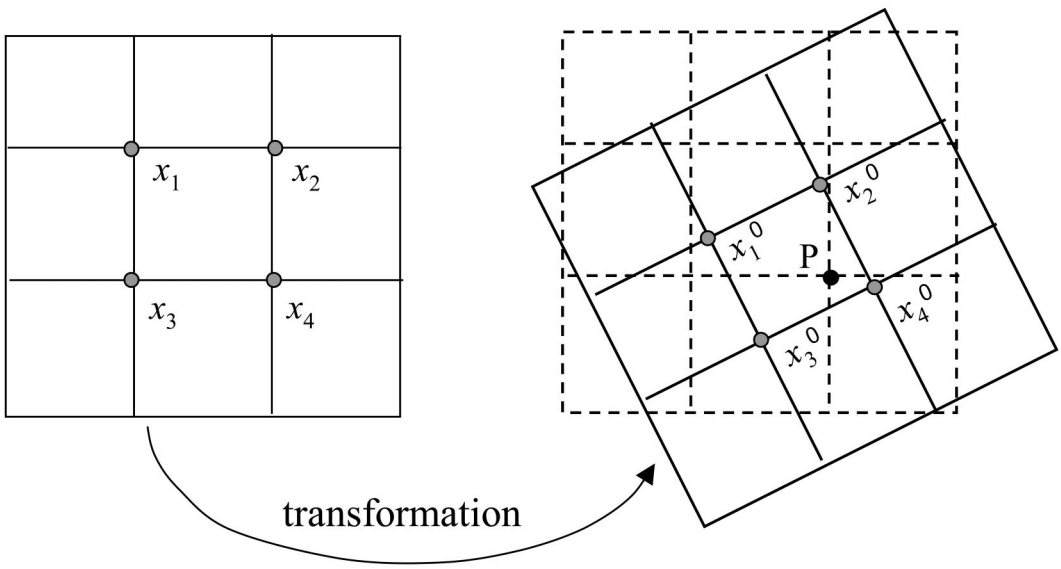

Fig 6. Interpolation associated with image registration. The transformation of an image results in the re-mapping of each voxel to a new location. For the purpose of registration, the transformed image must be re-sampled on the original grid. Determination of the intensity at each original grid point (for example point P) requires estimation based on surrounding voxel values. The resulting interpolation will result in some degree of smoothing of the original image.

Table 1. A Summary of Published Validation Results

Study	Modality	Validation Method	Reported Accuracy* (mm)
Intra-modality registration			
Eberl et al[39]	SPECT	Visual	~2.0
Woods et al[83]	MRI (inter-subject)	Consistency	~1.0
	PET (inter-subject)	Consistency	~1.5
Lau et al[77]	MRI (inter-subject)	Consistency	~1.0
Holden et al[86]	MRI*	Consistency	<0.15
Inter-modality registration			
West et al[24]	CT-MRI	Fiducials	1.0–2.5
	PET-MRI	Fiducials	2.0–3.5
Barnden et al[25]	SPECT-MRI	Fiducials	1.2–2.6
Wong et al[81]	PET-MRI	Visual	2.0–3.0
Fitzpatrick et al[82]	CT-MRI	Visual	~2.0
Ardekani et al[45]	PET-MRI	Visual	2.0–3.0

*Note that the reported accuracy is measured differently in different studies (eg, fiducial registration error versus target registration error).

tion (Fig 6), which can degrade image quality excessively if used repetitively. The simplest (and crudest) interpolator, the nearest neighbor scheme, finds a voxel nearest the point of interest and assigns the value of the voxel to that point. More sophisticated interpolators, although generally more accurate, require more voxels, estimate more parameters and, consequently, are slower. In general, insufficient attention is paid to the interpolation methods used, and the trade-off between speed and accuracy may not be optimally resolved.[13] The influence of interpolation on registration performance is well documented for algorithms based on MI.[75] Recent reviews of interpolation methods recommend the use of B-splines or a 6×6 cubic interpolator, which is easy to implement and is relatively fast.[76,77]

In non-rigid registration, interpolation is used also to provide an estimate of the displacement vectors at voxels intermediate to the calculated values. In this case, the interpolator imposes a smoothness constraint on the displacement field. The accuracy of non-rigid registration, especially along boundaries between rigid and non-rigid structures, will depend on the choice of the interpolator.

Optimization

The determination of the optimal transformation normally proceeds automatically by using well-established optimization algorithms, such as those described in *Numerical Recipes in C.*[78] The choice of the algorithm should suit the similarity measure to be maximized. In general, the algorithm should be insensitive to the presence of local maxima and should converge rapidly to the optimal solution. For registration using MI, the simplex, conjugate gradient and Levenberg Marquardt algorithms were all demonstrated to be effective.[67] Approaches such as simulated annealing,[79] designed to avoid local maxima, are slow and usually are not necessary. Problems may occur where some transformation parameters are correlated, giving rise to spurious maxima. Such problems can be avoided by removing excess parameters or constraining the optimization.

VALIDATION OF SOFTWARE APPROACHES TO REGISTRATION

For registration algorithms to be clinically useful, they must be accurate, precise, robust (adaptable to different degrees of mis-registration), and flexible (applicable to different situations). Ideally, they should also be automatic and fast. Validation of software registration is not trivial because ground truth is rarely known. A number of approaches to validation have been used and form the basis for published results on registration accuracy. Much less is published on precision, robustness, and flexibility. Validation is particularly difficult to devise for non-rigid registration algorithms.

Rigid-Body Registration

Some published studies report using visual comparisons of anatomical landmarks relevant to the clinical application.[44,80-82] Despite inter-observer variability, these techniques have demonstrated the accuracy of approximately half a voxel in nuclear medicine registration applications. Other groups have used external fiducial markers to measure the accuracy of registration.[25,26] The markers are digitally removed from images so that they do not influence the registration, but are subsequently used to verify the registration accuracy for the fiducial points. The errors associated with this method are well documented and an extensive survey, relating to PET data and high-resolution modalities, has been published.[25] A similar study for brain SPECT/MR registration also demonstrated accuracy of about half a SPECT voxel.[26] A summary of reported values for registration accuracy is given in Table 1. It should be noted that the

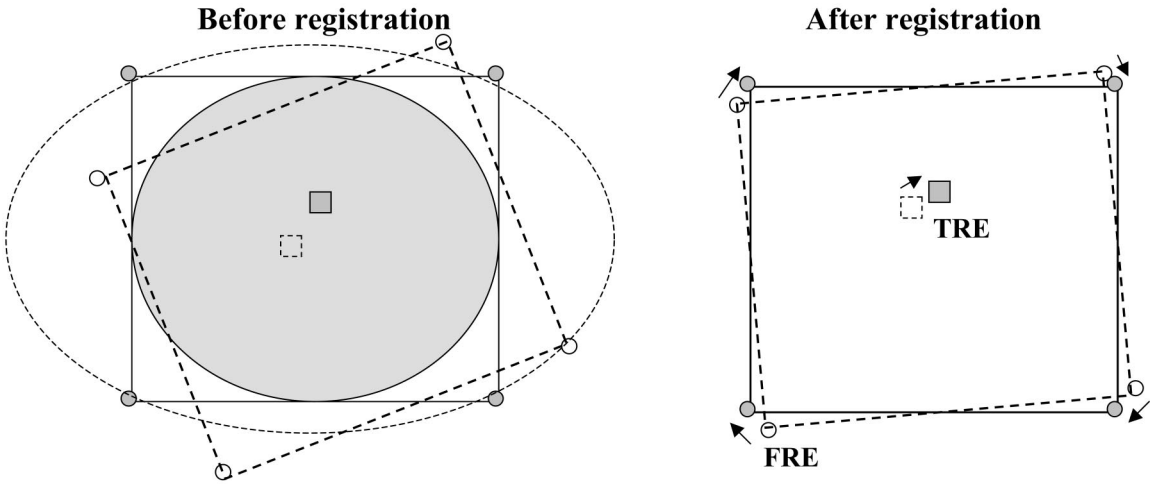

Fig 7. Estimation of registration errors. The FRE is the average distance between the corresponding fiducial markers in the reference image (shaded circles) and the floating image (open circles) after registration. Note that FRE may represent the errors on a bounding box (stereotactic frame) or at the surface of the patient (skin markers). The TRE measures the spatial distance between corresponding anatomical landmarks (squares) in the two images after registration. Note that TRE is the more clinically relevant error, provided landmarks are chosen in the area of clinical interest.

parameters used to estimate accuracy differ in these studies: for fiducial markers, the average fiducial registration error (FRE) is usually quoted instead of the more appropriate target registration error (TRE; Fig 7). Recent reports attempt to elucidate these errors.[84,85]

The consistency approach, which does not rely on landmark identification or the use of fiducial markers, requires at least three independent studies (A,B,C; Fig 8). The result of applying two successive transformations, T_{AB} followed by T_{BC}, is compared with the single transformation T_{AC}. The difference in results can be quantified, assumingthat transformation errors are random and can be attributed equally to each transformation.[83] This type of consistency approach has been demonstrated to be very sensitive when applied to high resolution images.[86] Although it has been reported in the evaluation of rigid-body algorithms, it may be applied also to assess the accuracy of non-rigid registration algorithms.

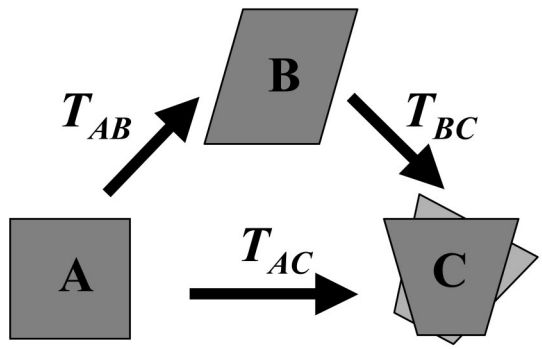

Fig 8. Use of consistency to estimate registration errors. Given three independently acquired images (A,B,C), registration of A with C can be achieved either by first transforming A to B (T_{AB}), followed by transformation from B to C (T_{BC}), or by direct transformation from A to C (T_{AC}). The two transformations ($T_{AB}T_{BC}$) and T_{AC} should be identical. The residual difference can be attributed to errors in each of the transformations.

Although most published reports describe automatic algorithms, some recent studies claim that interactive algorithms based on external markers are more accurate.[87,88] Others have demonstrated that substituting a matched transmission map for the emission image improves the robustness of PET-CT registration.[89] Error magnitude will depend on the specific application as well as on the flexibility of the software tested. Difficulties can be encountered in specific nuclear medicine applications where there may be little information that can be used by the similarity measure. There are few published reports on validation of nuclear medicine registration, despite anecdotal evidence of widespread use of registration algorithms in nuclear medicine. Further work is necessary to optimize automatic methods and to demonstrate their efficacy.

Non-Rigid Registration

The validation of non-rigid registration algorithms is difficult because there are rarely any means of direct, accurate assessment of the true alignment. Validation is particularly difficult because the extent of non-rigid misalignment can vary greatly from case to case so that no single validation model can be expected to apply in all cases. Although clearly limited, visual assessment has been successfully applied to validate registration results qualitatively.[90] Quantitative validation results can be generated with high precision and in different applica-

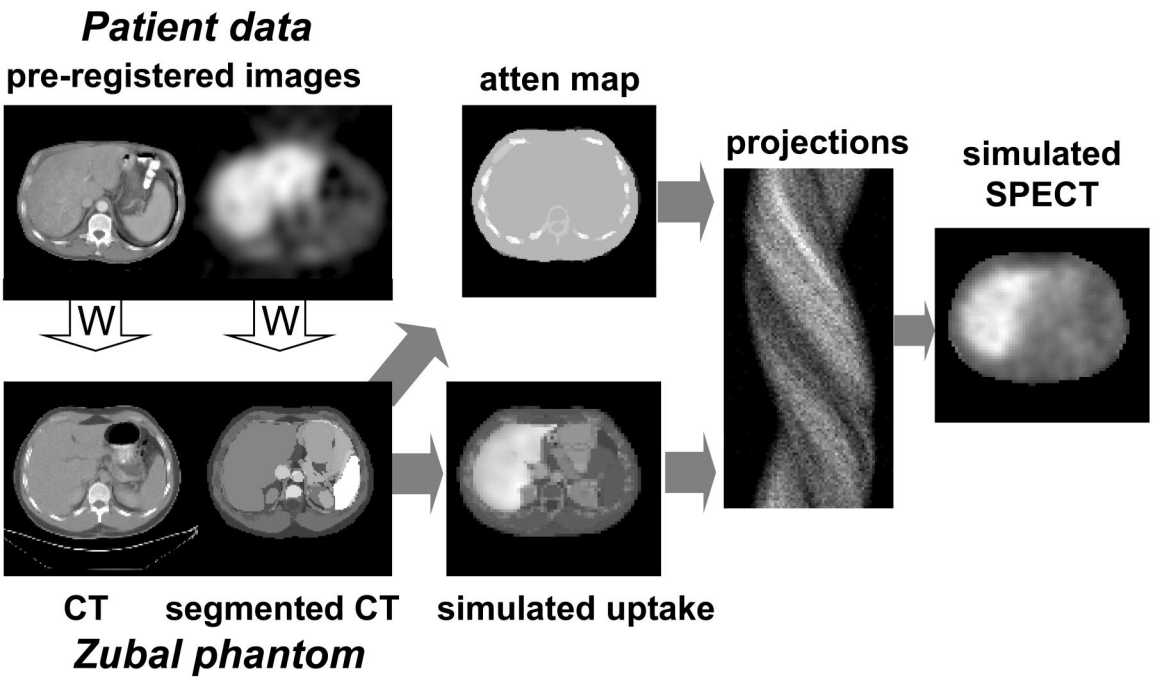

Fig 9. Modeling SPECT using the Zubal phantom. The pair of clinical images is pre-registered. The high resolution image is first non-rigidly warped (W) to register with the Zubal phantom CT, and the same transformation is applied to the functional study. The segmented Zubal phantom is then used in combination with the functional study to create a realistic activity distribution and attenuation map. These are subsequently used to create a set of projections that incorporate instrument features, such as distance-dependent resolution. The reconstructed image provides a clinically realistic image perfectly aligned with the Zubal phantom. The simulated SPECT image can subsequently be distorted to generate a bank of data for validation assessment.

tions by means of simulation. Based on independent clinical data, realistic, usually non-rigid, transformations are derived and applied to the floating image.[48,72] The algorithm being tested can then be applied, and the resultant displacement field directly compared with that obtained by simulation. An extension of this is the simulation of deformed functional studies based on an anatomical atlas (Fig 9).[91,92] In this case, both the activity distribution and the non-rigid misalignment can be modeled on clinical data, with a range of distortions applied within clinically feasible limits. The technique is useful in comparing the effectiveness of registration techniques, although results may be biased toward the type of clinical data used for simulation. There is scope for further research in this area.

EFFICACY OF IMAGE REGISTRATION IN NUCLEAR MEDICINE

Registration software faces considerable challenges in nuclear medicine. Compared with anatomical images, nuclear medicine images have a relatively poor resolution, the data are intrinsically noisy, and the distribution of activity can be functionally localized providing limited definition of organs and body boundary. Registration of nuclear medicine images with anatomical images must contend with all these differences as well as the very different intensity distributions arising from the different properties being mapped in the images. Motion blurring is a further confounding factor. This imposes restrictions on the type of registration that can be performed, particularly in some clinical studies (eg, studies of the lung acquired with and without breath holding). The studies that may benefit most from image registration are characterized by focal tracer uptake with limited visual clues regarding the anatomical localization. Such studies are also particularly difficult to register and usually need additional information to further constrain the registration. Some operator input may be required to at least define similar volumes to register (where the fields of view are different) or to constrain registration to regions where there is reasonable information content. Improvement in robustness can be demonstrated when care is taken to define sensible regions.[55] There is a need to introduce further constraints to assist registration, such as identifying specific organs or structures that can form the basis for an initial "landmark" alignment or can define a specific type of transformation. A number of approaches have been suggested, including the use of a second tracer to define specific features,[93] the use of transmission data to define the body outline and lung boundaries,[39,94,95] and incorporation of edge information[96] or tissue labeling.[97] Algorithms have been

suggested that permit the incorporation of information about rigid structures, such as bone, within a non-rigid registration context.[98] Further research should provide future improvements in this area.

The increasing volume of published work that uses image registration to illustrate diagnostic features, suggests that the acceptance of software-based image registration is increasing. Although primarily aimed at improved diagnostic interpretation, image registration also has found applications in treatment planning and interventional procedures. Furthermore, registration is an important component of fusion algorithms of considerable interest in nuclear medicine, including attenuation correction,[99] motion correction,[16-18] partial volume correction,[100-102] and tomographic reconstruction with anatomical image priors.[103-106]

ACKNOWLEDGMENTS

We wish to acknowledge the contributions to our research on image registration made by colleagues and students at the Westmead Hospital and the University of Technology, Sydney, in addition to collaborators in other centers. The following list acknowledges some of these individuals: Dennys Lau, Babak Ardekani, Seu Som, David Skerrett, Rochelle Hatton, Andre Kyme, Leighton Barnden, Stefan Eberl, Roger Fulton, Lennart Thurfjell, Iwao Kanno. Particular thanks go to Dennys Lau for providing assistance with the illustrations.

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