Editorial: Registration of Nuclear Medicine Images

The location and repositioning of subjects is of critical importance to medical imaging. In the past, it has been common for physicians to interpret data from different modalities, recorded at different times, using a poorly described yet generally understood visual alignment system. This in effect involves applying some spatial transformation between structures within an image in order to match the data. Decisions as to the progress of disease and other important medical issues are often based on this process. Such an approach is questionable, even given the high degree of spatial sense possessed by many physicians. The need exists for more objective methods of aligning image information. The slow development in this area may be attributed in part to a lack of effort by manufacturers to develop standardized immobilization and alignment hardware and methods. In addition, there are inherent difficulties in attempting to reproduce subject position well enough for projection imaging studies. There have been some notable successes. Planar imaging alignment methods are now in use in concert with digital subtraction angiography (*2*) and various nuclear medical cardiac studies (*1*).

The advent of quantitative tomographic modalities such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) in nuclear medical practice not only offers the opportunity to apply standardized alignment and image registration methods, but *requires* their use for optimal interpretation of studies. This is especially important in situations where serial comparisons in a given patient are made or where specific regions within an organ must be identified. An organ in which these issues are of particular interest is the brain because of its regional functional organization, but the reproducible identification and measurement of other tissues such as the myocardium is also important.

Identification of anatomic structures and regions in nuclear medicine images is complicated by their functional nature in the sense that organ physiology may vary with time or disease-state while the underlying anatomic landscape is fixed. This fact often makes necessary the use of a secondary source of anatomic information which must be made congruent with functional image data. Anatomic imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) may serve this purpose or, alternatively, some stylized reference such as a digitized atlas may be used.

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There have been a number of approaches to the alignment of tomographic images, including manual alignment and the derivation of transformations between images based on either edge location in combination with other fiducial landmarks (*3*) or based on area-related parameters. The latter include methods using principal axes of a uniform area defined by the image edge (*4–5*) and those using image correlation methods such as the one described by Junck et al in this issue (*6*). These methods vary in their stability depending on the amount of information used in computing the transformation. Those based on the use of edge information only tend to have some sensitivity to errors in the selection in edge points while those using an area based scheme tend to be somewhat more stable. Alignment to within a millimeter has been achieved in practice with both approaches. Experience to date has shown that such accuracy is acceptable within currently available image resolution. It should be noted that the use of slice-by-slice alignment methods require that the third dimension, usually associated with the transverse axis of the imaging device, be determined and reproduced independently. This is usually accomplished with a mechanical immobilization and alignment device (*7–10*).

The method described by Junck is directed at aligning PET slices and is based on maximizing the correlation between two images. It uses all of the available data and hence shows good stability. A limitation of this approach, however, is the implicit assumption that both images have the same structure and that the local values are the same within a global constant. These assumptions will hold when measuring the same functional parameter over short times or when the spatial distributions of two measured parameters are similar, as for example in well designed activation studies. Problems may arise, however, when distributions of parameters are different over large regions, as in regions of mismatched blood flow and metabolism in evolving strokes, or when different modalities are compared, as when MRI slices are to be used for anatomic region selection. In these cases, methods which use only the slice outline or such outline filled with constant values may be more reliable. It should be kept in mind that differences in scale and differential distortions between modalities must be accounted for. This is usually a relatively simple task requiring calibration of the imaging devices with a standard phantom object.

A problem with all approaches that align an image data set on a slice-by-slice basis is that the assumption must be made that no rotation of the structure of interest in or out of the slice has taken place. This can

be assured to some degree by immobilizing the subject but still may be a source of error in comparing aligned images. Many tomographic devices in use today provide only thick slices and therefore limit, in practice, alignment methods to planar approaches. Even if a more general alignment scheme using multiple slices is attempted, the results are still limited by partial volume effects. A related, but much smaller source of error inherent in all of the alignment methods discussed here, is that differences in the imaging system response from point to point in the image field, inherent in PET and SPECT devices, introduce a position dependent variation in quantitative values which is not dealt with by transformation alone. Fortunately, if image positions are relatively close before transformation, this error is negligible in all but the smallest structures or regions.

A logical extension of the image registration problem, especially for research studies, involves the registration of images from studies on separate individuals. This problem is more complex than the problem of registration within a given subject since variations in individual organ geometry must be taken into account. Several approaches, which have been developed for the brain, involve a combination of careful subject positioning, the collection of an anatomic reference data set (planar x-ray, CT, or MRI) in the same position as the radionuclide scan from which anatomic landmarks are determined, and the transformation to a "standard brain" geometry and location, usually based on a stereotactic atlas (*3,8,11–12*). The transformation applied may involve not only translations and rotations, but deformations to map the brain of interest onto the "standard" brain. The determination of the transformation including deformation parameters typically requires the specification of additional anatomic reference points over and above those needed for a simple alignment. To minimize the number of such determinations, transformations used to date have been limited to two- or three-fold subscalings of the characteristic dimensions of the brain. Such transformations have performed quite well in cortical brain regions, which are of primary interest in most brain studies, but have performed less well in mapping deeper-lying brain structures. To address this problem, some workers have designed semiautomated systems which allow an operator to adjust position and region size and shape (*13*) after initial alignment. Improvements may be expected if additional anatomic reference points are used along with finer subdivision of brain axes. The limit of this approach is a topological or "rubber sheet stretching" transformation which is made up of a large number of linear distortions over small areas (*14*).

The issues of alignment and anatomic region identification are separate to some degree but intersect because it is necessary to identify anatomic regions with respect to some anatomic data set in order to minimize ambiguities that may be associated with the use of functional images alone. To address the issue of region identification, the concept of transformation into stereotactic coordinates has been extended by a number of workers to include stereotactic "brain atlases" which can be superimposed upon transformed brains or alternatively may be transformed and distorted to fit a given data set in its own natural coordinate system (*2,3,8,15*). These atlases, usually based on a digitized version of a traditional atlas (*16*), allow for the identification of regions and structures in a given functional image from anatomic information and thus remove potential ambiguities associated with region selection based on functional images alone.

Newer tomographs, especially PET scanners, collect statistically valid data sets having equal resolution (on the order of 5 mm) in all dimensions. Comparable data sets may also be collected from most MRI scanners. The availability of such three-dimensional data sets makes possible the alignment of entire data volumes rather than individual tomographic planes. Such an approach would minimize or eliminate the need for mechanical alignment devices since, in principle, one volumetric data set could be rotated into another regardless of its orientation and would also minimize the partial volume errors associated with thick tomographic planes. As with the single-slice case, a number of possible approaches to the problem have been explored. These include least-squares minimization of differences between organ or bone surfaces defined from outlines in multiple planes (*11,12*), and extensions of volume-based methods such as the principal axis transformation mentioned above to three dimensions. These approaches, in addition to relaxing requirements on subject immobilization, minimize some of the partial volume errors inherent in the single-slice methods mentioned above.

The image alignment methods mentioned here work well in subjects with normal anatomy. In the case of the brain, where the organ boundaries are typically constrained by the skull, methods based either on organ outlines or areas will also work well. In other organs where organ geometry can be distorted by mass effect, the problem is more difficult and may indeed by intractable. In the case of anatomic atlases which attempt to locate subregions within an organ, normal anatomy, or at least the absence of mass effect, is a requirement. One might envision the development of organ models based on fluid mechanics which attempt to predict the displacement and distortion of tissue in disease states, but this is a very complicated problem which has received little attention to date. Thus, for the foreseeable future the application of alignment methods is limited to the brain in most circumstances and to other organs where structure is grossly normal. The more detailed anatomic atlas schemes are further limited to situations

where gross anatomy is normal in all organs. Despite this limitation, there are many situations, both research and clinical, where these techniques are useful.

We may expect that the issues surrounding region identification and alignment of image data sets will become more important as nuclear medical tomography becomes more sophisticated in both clinical and research applications. The direction of evolution, toward the use of full three-dimensional data, is already begun in many laboratories. The availability of imaging workstations and other computer hardware will make such methods available to most nuclear medicine users within the next few years providing that equipment manufacturers undertake to offer standardized immobilization and alignment hardware and software with their imaging systems. We might also expect that the development of anatomic reference aids such as computerized atlases will continue and that they will become more refined in the near future. The extension of these methods into abnormal organs is an important direction which needs to be explored before they can become generally applicable.

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