Automated Comparison of Scintigraphic Images

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New algorithms for automated comparison of scintigraphic images have been developed and are described here. The first step presented here is the registration of the images, performed by optimizing, with respect to the registration parameters (two translational shifts, one angle of rotation, the two parameters of a linear transformation of the gray levels), the stochastic sign change (SSC) criterion. The optimization of this criterion is demonstrated to be efficiently performed using the adaptative random search strategy; a more limited but less time-consuming method is also presented. The second step described is the point-by-point comparison of the registered images. The pixel-by-pixel application of Poisson variable statistical tests permits the generation of the significant image differences. From such images it is possible to detect modifications which escape visual inspection. Examples of applications are given in controlled and routine conditions. These algorithms are useful for the processing of many investigations and are proposed for implementation on all nuclear medicine data processing systems.

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A nuclear medicine physician frequently has to compare two scintigraphic images of the same organ. These images may have been acquired at different times according to the same protocol in order to follow the course of a disease and assess the efficiency of a treatment (e.g., sequential perfusion lung scan after therapy). They can also result from double tracer studies (e.g., thallium-technetium parathyroid scan or perfusion-ventilation lung scan) or from acquisitions performed before and after physiologic interventions (e.g., stress and redistribution thallium myocardial scan). The visual comparison of such pairs of images is not an easy task: The statistical fluctuations, the changes in cross-talk, and the variations of gray scale on films can mask or simulate significant differences. Simple procedures such as the subtraction of images are often carried out in order to visualize the changes and to increase the sensitivity and specificity of their detection (*1,2*). This image processing necessitates either a complete lack of patient motion between the acquisition of the two images or a preliminary realignment of the images. For this purpose, automated methods based on correlation measures are available; most of them have been developed in the context of Landsat imaging (*3*). Simpler methods have been developed for scintigraphic images (*4*). All these methods, however, have a major disadvantage: their lack of robustness can lead to misregistrations when the images strongly differ in certain parts. Moreover, even if the registration procedure is valid, the subtraction images can be difficult to interpret because they contain both the significant differences to be detected and the noise.

In a preliminary paper (*5*), we presented the application of a new similarity measure between images for the automated normalization of even dissimilar scintigraphic images. The theoretical background of this methodology has now been extensively developed. First, it concerns the automated registration of images with respect to both geometric and gray-level registration parameters (*5–10*) and, second, the pixel-by-pixel comparison of scintigraphic images (*8,10*). This paper shows how some of these methods can be selected and implemented in order to provide an automated scintigraphic image comparison software that would be useful for every nuclear medicine department. These methods are presented and two different implementations are described for a fast and standard data processing system, in controlled and routine conditions.

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MATERIALS AND METHODS

The scintigraphic images to be compared differ because of different acquisition conditions (e.g., position of the patient under the sensor, acquisition times and activities, responses of the detector to various tracers, noise). They are also different because of the changes to be detected. The proposed two-step methodology consists first of applying a robust registration procedure which makes it possible to correct for the different acquisition conditions independently of the changes to detect and, second, of visualizing these changes after a pixel-by-pixel comparison of the registered images.

Registration Step

The image registration can be reduced to a parameter estimation problem (the registration parameters) in the presence of outliers (the changes to be detected) (*10*). It is, therefore, possible to register the images by optimizing, with respect to the registration model parameters, a similarity measure which has been selected for its robustness in the presence of outliers. This approach requires the selection of: (a) the structure of the registration model, (b) the similarity measure, and (c) the optimization method.

Registration Model

The goal of the registration model is to correct for all the nonsignificant differences. This model includes geometric and gray-level transformations which are based on the following assumptions:

1. The differences due to the variable patient positions under the scintillation camera are corrected by the product of a two-dimensional translation T (with shifts Dx and Dy) and a rotation R (with angle r).

2. The differences in the gray-levels are corrected by a two parameter linear transformation. The normalization of two scintigraphic images is generally considered as a multiplicative process with a single parameter NF (normalization factor) (*5, 11*). Such a normalization permits correction for the differences in acquisition times and injected activities but it does not take into account differences in backgrounds. For example, when different radiopharmaceuticals are used, the circulating blood activities may be different and therefore a correction by a more sophisticated model is required. Such differences are modeled here, by the addition of a parameter BG (background) to every pixel of one of the images.

If F1(i, j) and F2(i, j) are the two original images, the registration model can be defined by the following equations:

$$F1(i, j) = F3(i, j) + C(i, j) \quad (1)$$

$$F3(i, j) = R_r * T_{Dx,Dy}(NF(F2(i, j) + BG)). \quad (2)$$

F3(i, j) is the result of R and T on F2(i, j); C(i, j) includes the true differences to be detected and the noise effect.

Similarity Measure

The determination of the five registration parameters requires the selection of a similarity measure which allows the minimization of C(i, j) everywhere but in regions where true differences exist. For this purpose, we have developed a new class of similarity measures that are well suited for the registration of images that may strongly differ in certain parts. In this class, the stochastic sign change (SSC) criterion is convenient for scintigraphic images. Consider that the two images F1(i, j) and F2(i, j) only differ because of the noise measurement which is assumed to be additive, zero mean with a symmetric density function. Let D(i, j) = F1(i, j) − F3(i, j) be the subtraction image. If there were no noise, the D(i, j) pixel values would be null. In the presence of noise, the D(i, j) pixel values fluctuate around 0. There are many sign changes in the sequence of a D(i, j) line. Suppose that F1(i, j) and F3(i, j) strongly differ in a zone. In this zone, the D(i, j) pixel values are all negative or all positive and there is no sign change in this part of D(i, j). The more similar the images are, the larger the sign change number. The SSC criterion is therefore defined as the number of sign changes in the sequence of the subtraction image F1(i, j) − F3(i, j), scanned line by line or column by column (*5,6*). The registration parameter values are the ones which maximize the SSC criterion value. Each parameter cannot be estimated independently of the others so that a multidimensional method must be found for the SSC criterion maximization.

Optimization Methods

Many numerical optimization methods are available for maximizing a function with respect to several parameters (*12*) but the registration model and the SSC criterion have characteristics which make this optimization problem a nonclassic one. First, the function to optimize only takes integer values so that it is not differentiable. Second, some parameters are integers (e.g., Dx,Dy) while others are reals (e.g., NF). Third, the function to optimize may be multimodal (with local maxima). Probabilistic methods are appropriate in such cases because they provide global optimizers and do not necessitate the calculation of the criterion derivatives. Their basic principle is the calculation of the criterion for randomly chosen sets of parameter values. Among these methods, the Adaptative Random Search (ARS) strategy was selected for its efficiency (*7,13*). In this method, two phases are repeated alternatively. The first one consists of finding the variances of a multinormal distribution which lead to the maximum SSC criterion value. During the second phase, these variances are used a fixed number of times and the parameter values which correspond to the maximum of the criterion are selected. A complete description and evaluation of this algorithm can be found in (*7*). This fully automated method is efficient but requires numerous evaluations of the criterion; its implementation necessitates the use of an array processor and therefore we have also developed a more limited but less time-consuming procedure that can be used on standard computer systems if no rotation is considered. In this second procedure, the gray-level registration is performed at each step of the geometric registration, accomplished by using an integer version of the Steepest Descent (SD) method (*12*), while the Simplex algorithm (*12*) is used for the gray-level registration.

Pixel-by-Pixel Comparison of Registered Images

Once the images are registered, the subtraction procedure becomes meaningful, but a classic subtraction image can be difficult to interpret because it contains the true differences and the fluctuations due to the noise. In a scintigraphic image, the distribution of these fluctuations is well represented by a Poisson law so that this physical knowledge can be taken into account to improve the subtraction process. It makes it possible to derive statistical tests which have to be applied pixel-by-pixel in order to decide if the values of two corresponding pixels significantly differ or are different because of the noise. If the only pixels visualized in the subtraction image are those which significantly differ, this special subtraction image will be a representation of the only true differences. Such an approach leads to the positive and negative images of the significant differences. It was already proven to make possible the detection of true differences which escape visual inspection of either the original images or the classic subtraction image (*8,11*). There is no simple statistical test for the comparison of true Poisson variables. We used the maximum likelihood ratio test approach to construct workable tests (*8,11*). Because the presented registration model includes a two-parameter linear transformation of the gray levels, the use of the following test is mandatory. Consider the values X1 and X2 of two corresponding pixels of F1(i, j) and F3(i, j) [the registered version of F2(i, j)]; let NF and BG be the values of the gray-level transformation parameters derived from the registration step. The null hypothesis is that X1 and X2 come from two Poisson distributions with means M1 and M2 such that $M1 = NF(M2 + BG)$; the alternative hypothesis is $M1 \neq NF(M2 + BG)$.

The test consists in calculating:

$$C = -2(-NF(\hat{M2} + BG) + X1 \mathrm{Log} NF + X1 \mathrm{Log}(\hat{M2} + BG) - \hat{M2} + X2 \mathrm{Log} \hat{M2} + X1 + X2 - X1 \mathrm{Log} X1 - X2 \mathrm{Log} X2),$$

where $\hat{M2}$ is the positive solution of the second order equation:

$$(NF + 1)M2^2 + ((NF + 1)BG - (X1 + X2))M2 - BG\,X2 = 0.$$

All the detailed calculations required to establish this test can be found elsewhere (*11*). Under the null hypothesis, C follows a chi-square distribution with 1° of freedom. For every pair of corresponding pixels, C must be calculated; the value of the subtraction image (positive or negative) is visualized if and only if C is greater than the tabulated value of the chi-square distribution.

IMPLEMENTATION OF ALGORITHMS

Implementation on Fast Data Processing System

All of these algorithms are implemented on a laboratory computer system* connected with an array processor†. The images to be compared (128 × 128, 64 × 64, 32 × 32) are selected. With a light-pen, the operator chooses a rectangular window that will be used for the calculations of the SSC criterion. This window may contain the differences to detect because of the robustness of the SSC criterion. A standard search domain of the registration model parameters is proposed including −15 to +15 pixels for Dx and Dy, −20 to +20 degrees for r, −50% to +50% of the ratio of the total number of counts in the window for NF, 0 to 100 counts for BG. The operator may modify each search interval if necessary. If one parameter appears a priori useless (e.g., BG), it can be fixed and excluded from the search by selecting a null search domain. The second image is registered by optimizing the SSC criterion using the ARS strategy. This algorithm is coded in FORTRAN on the minicomputer of the system but at each step the translations, rotations (nearest neighbor method), modifications of the gray-levels, and the SSC calculations are carried out in the array processor. The registration typically takes 30 sec. The generation of the positive and negative significant images is also carried out by the array processor and is immediate. It is performed either in the original format (e.g., 128 × 128) or in a reduced format (e.g., 64 × 64 or 32 × 32) in order to increase the number of counts by pixel and to increase the sensitivity in the difference detection (the power of the statistical test). At the end of these calculations, four images are displayed on a single screen: the first original image, the registered version of the second image, and the images of the positive and negative significant differences. Regions of interest can be drawn on any of these images and are reproduced on the others for an anatomic localization of the significant differences. Most of the calculation time is required by the registration procedure that typically necessitates 2 to 3,000 applications of the registration model. Therefore, the duration of the registration phase is 2 to 3,000 times the delay necessary for translating, rotating and normalizing a single image and calculating the SSC value. This permits an estimate of the calculation time corresponding to the use of any array processor.

Implementation on Standard Data Processing System

A less complete implementation (coded in FORTRAN) of the algorithms is also made on a standard data processing system‡ (i.e., with no array processor). Compared with the previously described software, this version suffers from the following restrictions: (a) only 64 × 64 images (or 64 × 64 windows extracted from 128 × 128 images) can be processed, (b) no rotation is taken into account, and (c) the less general second optimization method is used. The initial estimates of Dx and Dy required by the SD method are provided by using the correlation coefficient as a similarity measure; those of NF and BG are the slope and intercept of the linear regression line calculated between the corresponding pixel values of the geometrically registered images (see the second example of application). Furthermore, if the initial estimates of Dx and Dy are visually correct, the SSC criterion is only used for gray-level registration. These operator interventions greatly speed up the registration process. Depending on the accuracy of the registration parameter initial estimates, the registration time ranges from 2 to 15 min.

EXAMPLES OF APPLICATION

Controlled Conditions

The performances of these algorithms are illustrated in controlled conditions by Fig. 1. Image 1A is a bone scintigram (128 × 128); image 1B was obtained by changing the position of the patient under the scintillation camera, setting five radioactive spots on the patient and modifying the acquisition time. This image was registered using the fast data processing system. Image 1c is the result of the application of the registration model to image 1B with the parameter values determined during the registration phase (Dx = −5 pixels, Dy = −8 pixels, r = 9.6°, NF = 0.68, BG = 0). Image 1d is the classical subtraction image obtained after registration. Image 1e is the image of the negative significant differences and clearly demonstrates the presence of the five superimposed

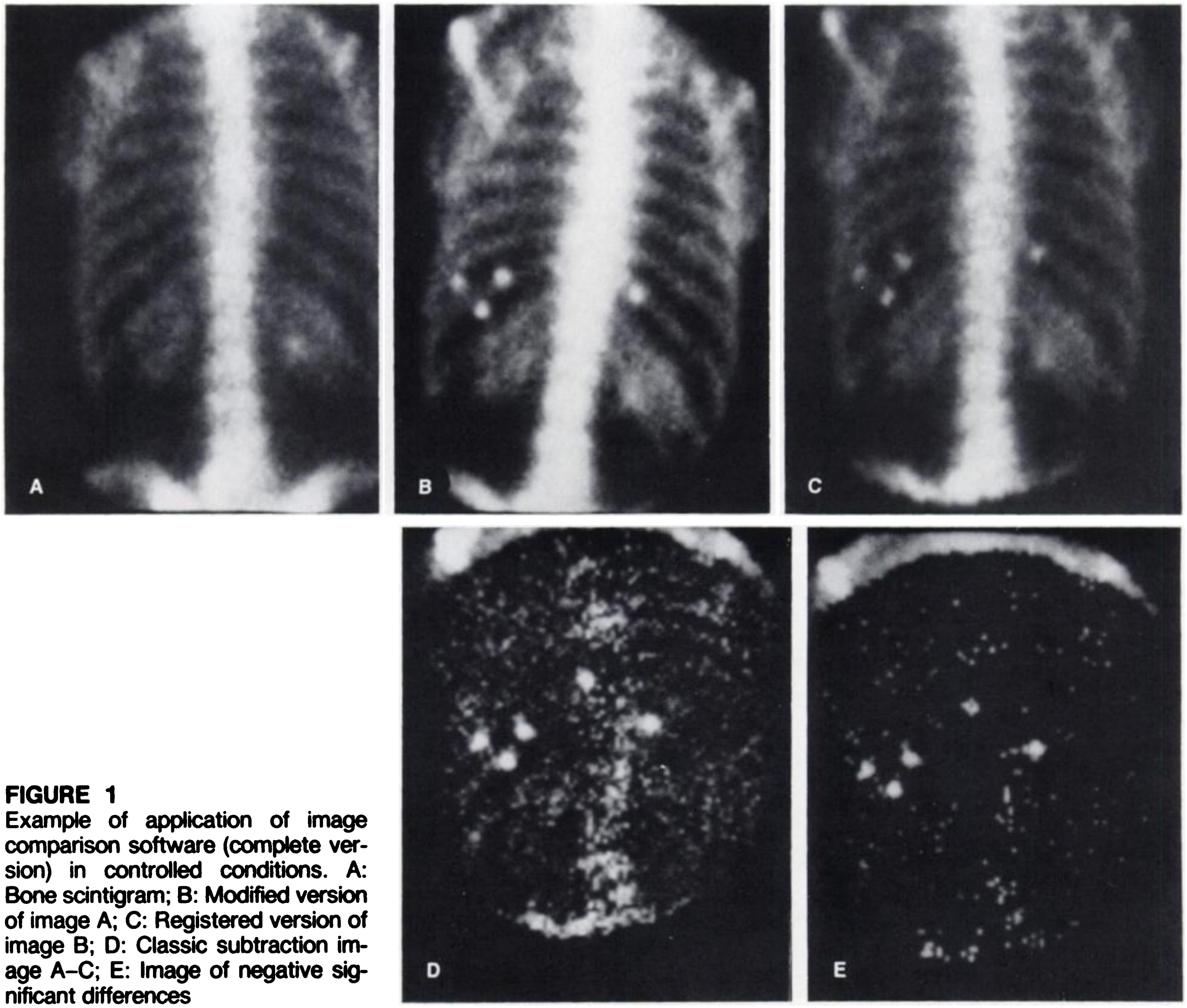

FIGURE 1
Example of application of image comparison software (complete version) in controlled conditions. A: Bone scintigram; B: Modified version of image A; C: Registered version of image B; D: Classic subtraction image A–C; E: Image of negative significant differences

spots (the one located on a vertebra is difficult to detect from the visual inspection of the original images).

Routine Conditions

This example concerns the processing of parathyroid thallium-technetium scintigraphy using the standard data processing system. The comparison of the thallium image with the pertechnetate image requires both geometric and gray-level registration. Geometric registration is necessary because patient motion can occur between the two acquisitions. Gray-level registration is necessary because the backgrounds (*14*), injected activities, and acquisition times are different. Images in Fig. 2 were obtained on a 71-yr-old woman with biologic evidence of hyperparathyroidism. An ultrasonic examination of the neck region was performed before the scintigram and demonstrated a large nodule located in the upper part of the right lobe of the thyroid gland. Image 2A is the thallium 64 × 64 window extracted from a 128 × 128 image obtained 15 min after i.v. injection of 2 mCi of thallium-201.

It was recorded for 15 min, using a pinhole collimator located 13 cm above the patient's neck. Image 2B shows the technetium image recorded for 5 min (20 min after the injection of 3 mCi of pertechnetate). During the entire test, the patient's head was kept still in a head holder. Image 2C is the registered version of image 2B ($Dx = -1$ pixel, $Dy = -1$ pixel, $NF = 0.28$ and $BG = 161$). Image 2D is the image of the significant positive differences and demonstrates the presence of two higher thallium uptake zones: a large abnormal structure located at the lower part of the left lobe and a less intense area of abnormal tissue located at the upper part of the same lobe. Image 2E is the image of the negative significant differences and shows a higher pertechnetate uptake zone. This hot nodule corresponds to the abnormal ultrasonic image. The patient was operated on 10 days after the scintigraphic test. A 2.8 g left inferior parathyroid adenoma was found behind the esophagus. The upper parathyroid gland on the same lobe was found to be enlarged. It was removed by the surgeon but was found histologically normal.

Figure 2F show the scatter diagram on which the values of the thallium image pixels are plotted compared with the corresponding values of the geometrically registered pertechnetate image. The straight line of equation $y = NF(x + BG)$ with $NF = 0.28$ and $BG = 161$ represents the model used for gray-level registration. Its intercept is $0.28 * 161 = 45$. From this example, it is clear that a simple multiplicative normalization [which would be represented by a straight line passing through the origin (i.e., with 0 intercept)] cannot correctly model the gray-level differences between the two images.

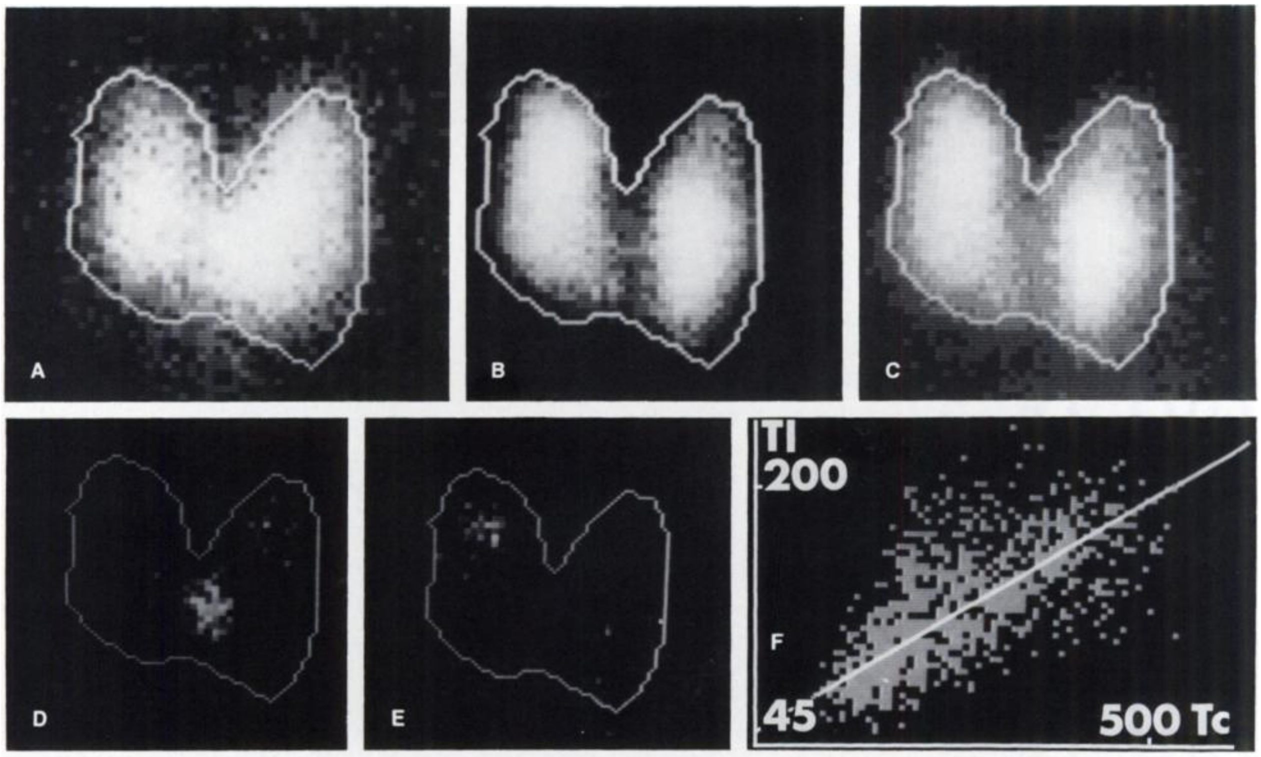

FIGURE 2
Example of application of image comparison software (simplified version) to parathyroid study. A: Thallium image; B: Original pertechnetate image; C: Registered pertechnetate image; D: Positive significant difference image; E: Negative significant difference image; F: Thallium image pixel values (T1) plotted vs. corresponding values of geometrically registered pertechnetate image (Tc)

DISCUSSION

The image comparison problem is frequently encountered in nuclear medicine. Its computerized approach has already been attempted for pancreatic (*1*, *2*), lung (*4*), myocardial (*14,15*), and parathyroid imaging (*16*). A different but related problem is the alignment of scintigraphic images and predefined standard images (*17*). Most of the proposed methods are operator dependant; some of them require the use of external landmarks; none of them solves both the geometric and the gray-level registration problems of couples of scintigraphic images.

We have already proposed a new normalization technique (*5*), which is extended in this paper to the simultaneous and fully automated geometric and gray-level registration of dissimilar images.

The presented algorithms form the basis of an efficient scintigraphic image comparison software. Its main characteristics result from four successive choices which must be emphasized: the structure of the registration model, the similarity measure between images, the optimization method for maximizing the similarity measure, and the statistical test for generating the images of the significant differences as an alternative to the classic subtraction images.

The registration model includes both geometric and gray-level transformations. The product of a two-dimensional translation by a rotation is assumed to efficiently correct for the different positions of the patient under the scintillation camera. This assumption implies that particular attention must be paid when repositioning the patient in order to avoid the three-dimensional uncorrectable moves. For example, the patient has to stay on his back, arms stretched along the body, without a pillow under his head. The gray-level transformation includes the well-known multiplicative normalization of the images. We have included a less classic additive correction; it was demonstrated to be of great importance (Fig. 2) especially for the generation of a subtraction image in the case of double tracer studies (*11*). The choice of a constant BG value was made for simple reasons: when BG value is large, the images of the significant differences are only meaningful in the selected window used for the registration procedure. For example, such a procedure applied to parathyroid studies can provide images of the significant differences which are only valid in the thyroid region but not in the maxillary zones if they are in the field of the camera.

A magnification was not included in the registration model. This could be a useful addition to the registration phase but it would necessitate interpolations of the image to register. This would modify the noise characteristics and would therefore invalidate the use of our statistical test which is based on a Poisson distribution.

The SSC criterion belongs to a new class of similarity measures (*6*) that we have developed for the registration of images that might be dissimilar. Scintigraphic images can be strongly different particularly because of the presence of active zones which can considerably modify the pixel values. The correlation-based registration methods would lead to severe misregistrations in this context, whereas such modifications have no influence at all on the sign-change-based methods (*6*).

The location of the similarity measure maximum is usually found by successive criterion evaluations for all the possible values of the registration parameters in a given search domain (*3*). Such an approach would lead to far too numerous calculations when applied to the five parameter registration model. Using the ARS strategy represents a breakthrough for the application of such complex registration models. This global optimizer prevents the eventuality of finding a local optimum which would lead to an incorrect registration.

The raw subtraction image obtained after registration contains both the significant differences and noise. In order to improve the specificity in the detection of abnormalities, we apply a statistical test which discards the nonsignificant differences. Figure 1 gives a pictorial illustration of the interest of the significant difference image (1E) when compared with the classic subtraction image (1D) both obtained after registration. The only active spots are visible on image 1E whereas image 1D shows both the spots and the noise fluctuations. This test was designed in order to take into account the NF and BG values estimated at the registration step. It dramatically facilitates the comparison of images with unequal signal to noise ratios.

This software is useful for the processing of many nuclear medicine investigations and makes it possible to define new efficient protocols for dual isotope studies. Classic double tracer studies necessitate the use of different energy isotopes in order to acquire the images without moving the patient. But the different absorptions of the gamma rays can generate artifacts on the subtraction image. The proposed software gives the operator the capability of efficiently registering the images so that the repositioning of the patient no longer remains a problem. It becomes possible to use radioisotopes with same or similar energies by delaying the two studies and waiting for the decay of the original isotope; the difficult absorption problems then disappear. Examples of application to monoclonal antibody studies can be found elsewhere (*11*).

This theoretically consistent methodology is routinely useful in the nuclear medicine practice and can therefore be proposed for implementation on all commercial computer systems. The inclusion of an array processor permits routine use of the most sophisticated methods, but simpler implementations are also possible on the standard systems.

FOOTNOTES

* IMAC 7300, CGR Médecine Nucléaire (French version of ADAC System 1) (Now Sopha Medicalé, Buc, France).

† AP120B, Floating Point System.

‡ SIMIS 3, Sopha Medicalé, Buc, France.

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