



# Development and applications of a software for Functional Image Registration (FIRE)

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**Summary** Image registration with anatomical modalities, such as CT and MRI, facilitates the anatomical identification and localization in the interpretation of nuclear medicine images that lack anatomical information. The implementation of Functional Image Registration (FIRE), an operating system (OS) and platform independent multimodal image registration software is reported. In order to register the images without an operator's interaction, several automatic algorithms were implemented. These include principal axes matching and maximization of the mutual information methods. The user interface was designed to support the manual registration of the images. Fused images were composed by overlaying one image with the other one transparently, in which the opacity of the overlaid image was interactively controlled. FIRE was successfully applied to many clinical cases for which automatic and/or manual registration was required. An OS and platform independent program for image registration developed in this study will be useful for the clinical application of image registration techniques.

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## 1. Introduction

Image registration techniques have been used in the areas of diagnosis, pre-operative evaluation, image guided surgery, functional brain mapping, and the planning of radiotherapy [1–3]. In particular, image registration of functional images from

nuclear medicine, such as PET and SPECT, which lack detailed structural information, with anatomical modalities, such as CT and MRI, facilitates the anatomical localization and interpretation.

However, registration software is not routinely used in most nuclear medicine clinics. This is despite the fact that the clinical demand for image registration and fusion is high and its clinical relevance in several areas has been proved [4–6]. This is mainly because registration software is not available through the commercial suppliers of PET

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or SPECT scanners [7], and very limited type of files with simple header information are recognized in most of the currently available software, such as Automatic Image Registration (AIR) and Statistical Parametric Mapping (SPM) [8,9]. The transfer and storage of image data has been standardized through DICOM in radiology and INTERFILE in the nuclear medicine field. However, many companies still adhere to their own file formats. Therefore, image registration software that supplies as many various file formats as possible would be welcome in the nuclear medicine community.

## 2. Functional requirements and design considerations

The lack of commercial software where both automatic and manual matching of the images is done with a convenient graphic user-interface is another reason hindering the use of the registration technique. The ability of manual registration is specially needed in the nuclear medicine community because of the specific problems associated with nuclear medicine data, where the anatomical information provided is insufficient and the signal to noise ratio is very low compared to anatomical images. These undesirable properties of nuclear medicine images frequently result in the failure of fully automatic registration algorithms.

For these reasons, an operating system (OS) and platform independent multimodal image registration software, called Functional Image Registration (FIRE), was developed where (1) the automatic and user-interactive manual matching of the images is possible, (2) various file formats of medical images are supported and (3) the realistic fusion of registered images is performed.

This article describes the features of the FIRE software and presents the exemplar cases where the software was successfully applied.

## 3. Program description

FIRE was developed using the IDL (Research Systems Inc., Boulder, CO) language in order to allow easy transfer of the program to various operating systems and platforms.

### 3.1. Input and output specifications

FIRE can read images in various file formats including DICOM, INTERFILE, and ANALYZE (Mayo Foundation, Rochester, MN). Image files from Siemens-CTI

PET (Siemens-CTI, Knoxville, TN), Picker/Marconi SPECT (Picker International, Cleveland, OH), and ADAC SPECT (ADAC Laboratories, Milpitas, CA) scanners are also supported. The registered images are saved in the ANALYZE format, and the fused static images are captured from the monitor screen and saved in JPEG format with their color-tables without compression so as to maintain the image quality. In addition, the cine of a fused image can be saved as an MPEG movie file.

### 3.2. User interface

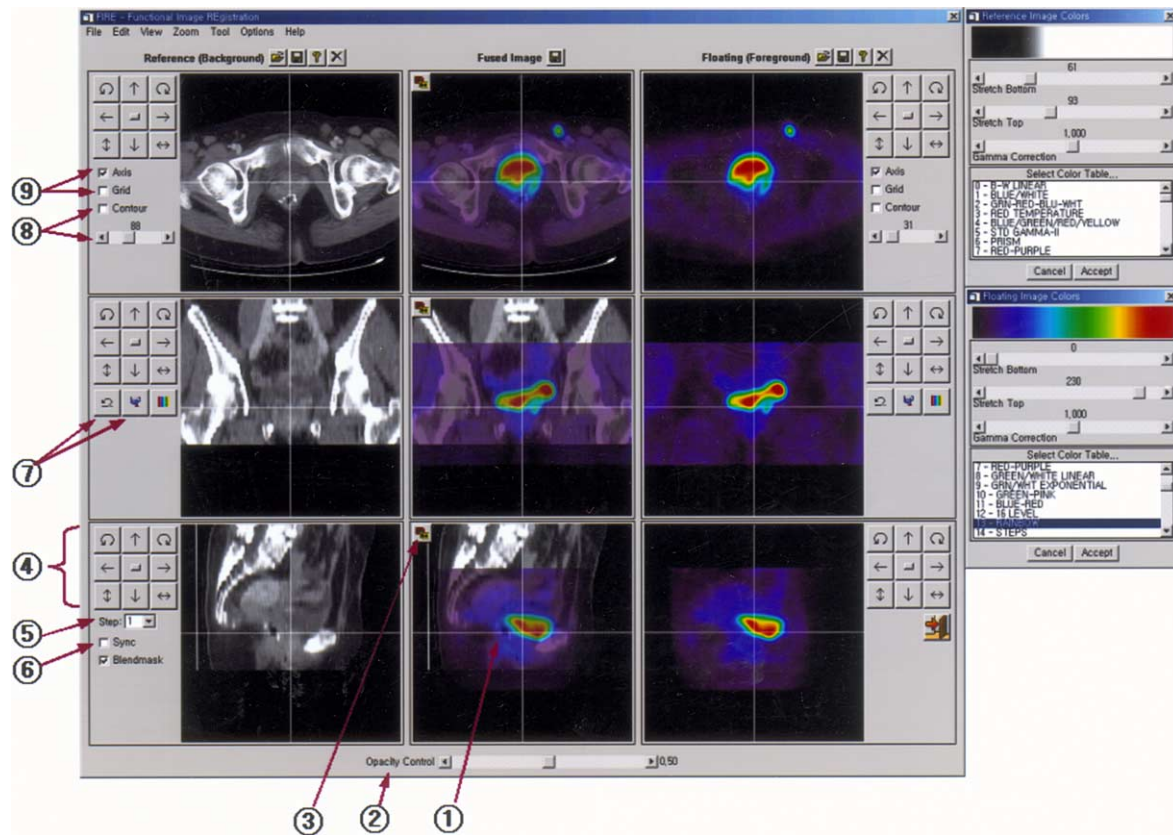
The user interface was designed to support user-interactive manual registration and the real-time display of fused images. Fig. 1 shows the graphic user interface used in FIRE. When the reference and floating images are loaded, three cross-reference views (axial, coronal, and sagittal) of each image are displayed in the left and right column. Initially, the center of each view is set to be the origin of the image volume.

If both the reference and floating images are displayed, cross-reference views of their fused image are composed analytically, and are presented in the middle column (① in Fig. 1). The opacity of the overlaid floating image can be interactively controlled (②). Clicking the animation button (③) results in a cine of the fused image to be run with varying opacity. Fig. 2 shows the fused images of the T1-weighted brain MR and F-18-FDG PET images with variable opacities ranging from 0 (fully transparent) to 1.0 (fully opaque).

The reference and floating images are presented with different color scales that can be managed in parallel using the independent color bars. Forty-six different color-tables including Rainbow, Hot-metal, Warm, and Cool, which are the favorite colors in nuclear medicine, are supported in this software.

### 3.3. Computational methods and algorithms

The images can be rotated and translated by pushing the control buttons. Using the control buttons (④) located on the side of individual images, the images can be rotated along three axes (x, y, and z) and translated in three directions according to the selected button. The magnitude of the rotation angle and translation distance can be varied from 0.1 to 270 degrees and mm, respectively (⑤). The mirroring and flipping of images are also supported since the left and right sides or the top and bottom sides can be switched during the acquisition, storage, and translation of the images.



**Fig. 1** User interface of FIRE program. (1) Semi-transparent overlay of the floating image over reference image. (2) Interactive control of the opacity of the overlaid floating image. (3) Animation button to run a cine of the fused images with varying opacity. (4) Control buttons to translate, rotate, mirror, and flip the image. (5) Magnitude of the rotation angle and translation distance. (6) Reference and floating images can be transformed synchronously or not. (7) Undo and reset buttons of the image transformation. (8) Contour of each image can be derived using a thresholding method, and overlaid on the opposite image. (9) Axis and grid buttons.

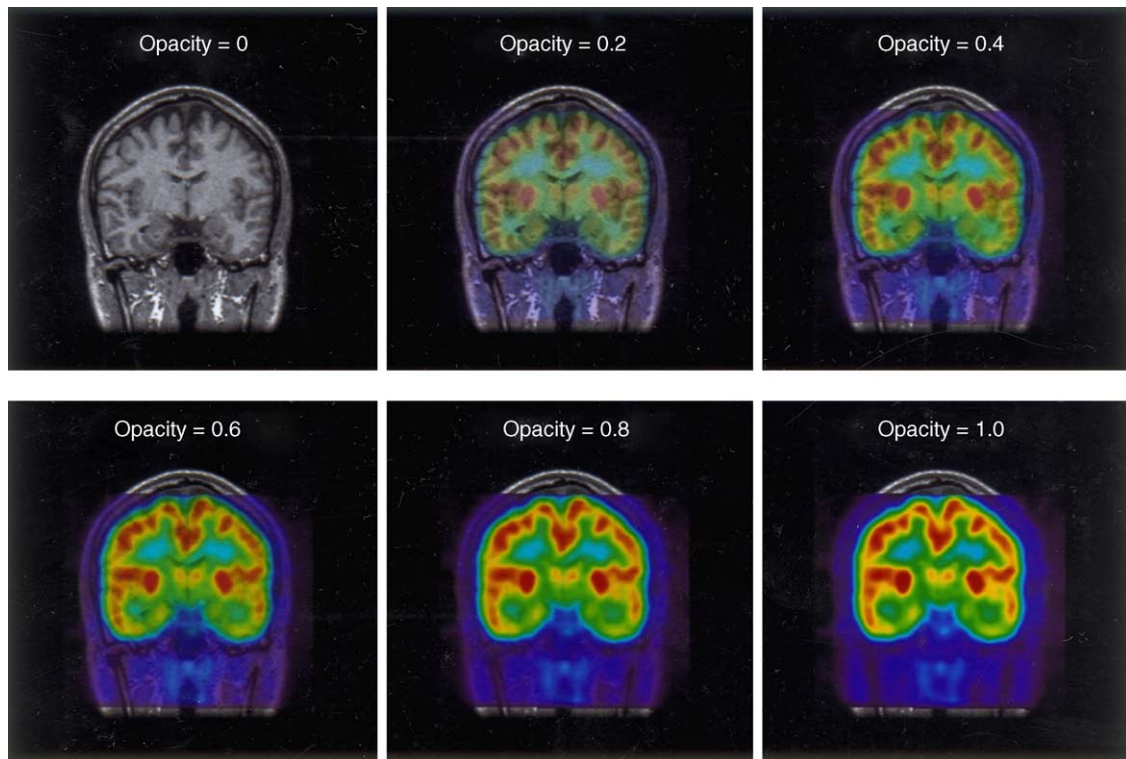
In addition, the images can be re-oriented by clicking the cursor or drawing a line on the images directly. When clicking the cursor on either of the images using the left mouse button, the image is translated so that the selected point will be moved to the axis origin (center of each view). If a line is drawn using the right mouse button, first, the image is translated so that the center of the selected line will be moved to the origin of the axis and it is then rotated so that the line will be overlaid on either the vertical or horizontal axis of the selected view (the close axis from the selected line is selected). The reference and floating images can be transformed either synchronously or not (6). Undo and reset (7) of the image reorientation is also possible to correct a user's error.

For accurate and easy manual registration, the contours of the reference and floating images can be overlaid on the opposite images (8). The contours of each image are derived using a thresholding method, and the threshold can be varied

interactively using a slider. The axes and grids (9) as well as the contours can be shown when required.

For the registration without an operator's interaction, several automatic algorithms were implemented. These include principal axes matching, minimization of the squared intensity difference, maximization of the correlation coefficient of the intensity, and maximization of the mutual information methods [10,11]. Principal axes matching algorithm is based on the moments of the objects and matches the center of mass and principal axes of the images automatically. For the principal axes matching, the target objects to be registered are defined at first using thresholding method, and their centers of mass and inertia matrices are computed. The rotation angles are derived from the eigenvectors of the inertia matrix to match the three principal axes of the object to the x-, y-, and z-axes of world coordinate.

The other three algorithms are based on the similarity of the image intensity. Sum of absolute differences, correlation coefficient, and mutual



**Fig. 2** Fused images of the T1-weighted brain MR and F-18-FDG PET images with variable opacities ranging from 0 (fully transparent) to 1.0 (fully opaque).

information of the intensity histogram are the similarity criteria used for each method. Mutual information of the two random variables represents the degree of dependence of the variables and is maximized when the amount of information that one variable contains about the other is maximum. We would say that such mutual information between two images reaches to maximum when they are exactly registered. Mutual information maximization is also associated with the minimization of the variance of intensity ratio.

For registration by the minimization of the squared intensity difference and maximization of the correlation coefficient of the intensity, the pixel values of each image are normalized to the mean pixel value of the objects to be registered, and both the rotation angles and translation distances are searched using the Levenberg–Marquardt algorithm.

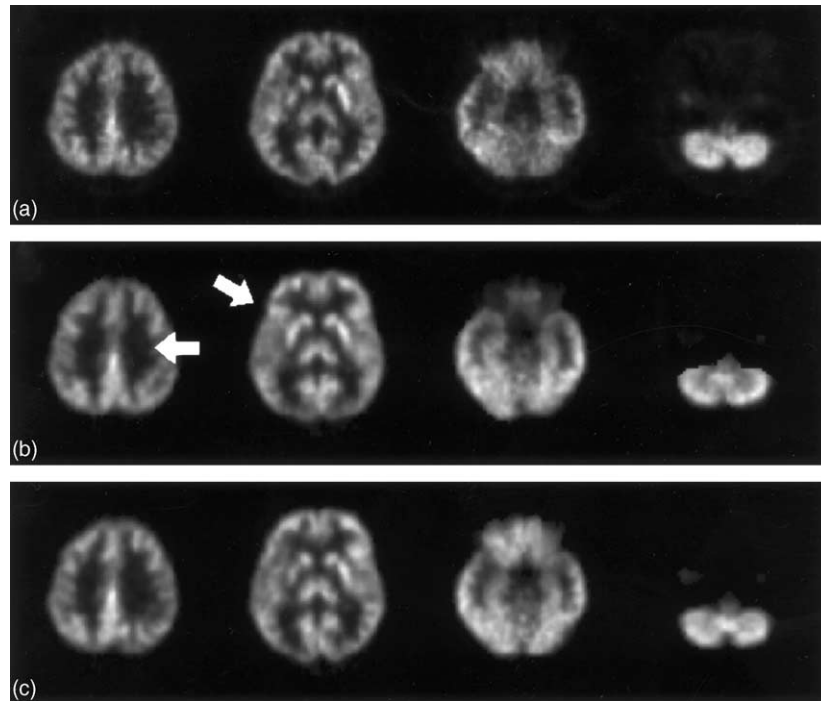
#### 4. Sample runs

FIRE was applied to many clinical cases for which automatic and/or manual registration was required. Fig. 3 shows the F-18-FDG brain PET images

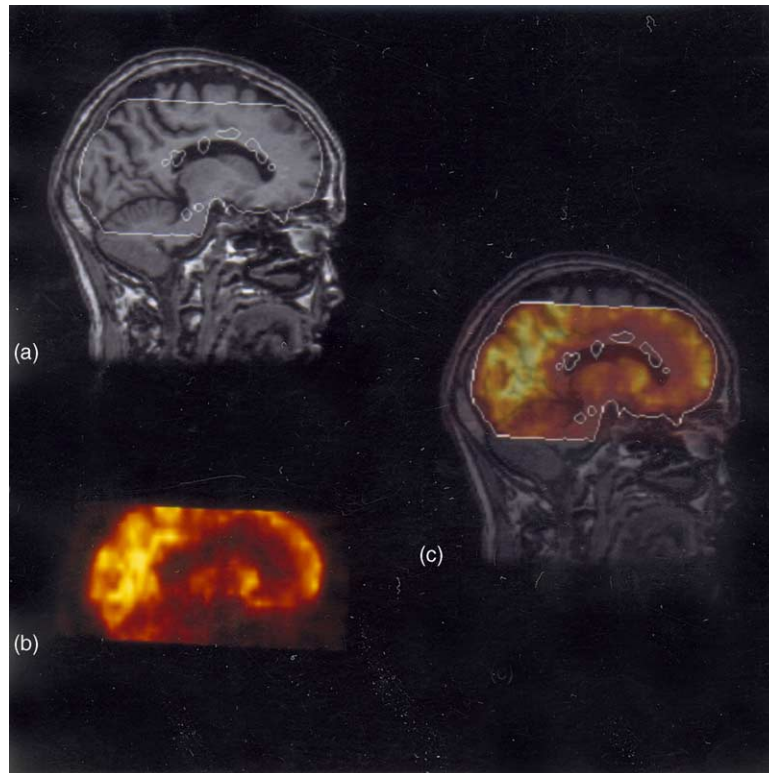
of a patient with obsessive-compulsive disorder before and after medical treatment, which were registered with FIRE using automatic algorithms. The reference image (a) was the PET image acquired prior to treatment. Initially, the PET image acquired after treatment was registered on the reference image using the principal axis matching method for coarse registration (b). The images were slightly misaligned. The arrows shown in Fig. 3(b) indicated an observable difference in white matter in left hemisphere (smaller in floating image) and right sylvian fissure. After a refine registration using the maximization of mutual information method, these differences disappeared (c).

Figs. 4 and 5 shows the exemplar cases where the intensity information was partially available and manual registration using FIRE was required. The SPGR brain MR and F-18-FDG PET images shown in Fig. 4 were not accurately matched when they were registered using the automatic registration algorithm (maximization of mutual information). This might be because the field of view (FOV) of the PET scanner was not sufficient to contain the whole brain. Therefore, a part of the superior frontal and parietal lobes and the cerebellum was not included in the PET image. The misalignments were corrected user-interactively using FIRE for

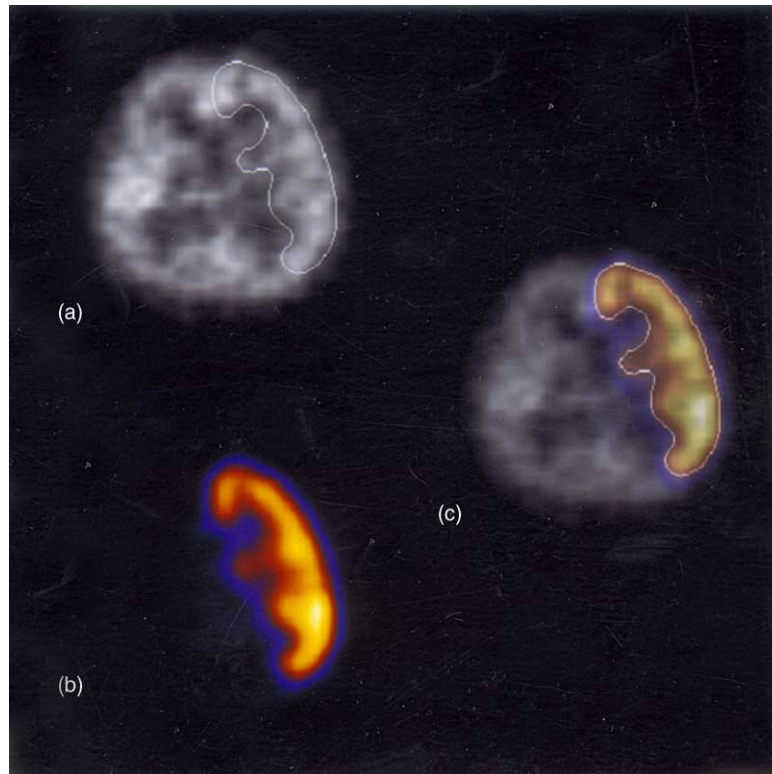




**Fig. 3** F-18-FDG brain PET images registered using the automatic algorithms. (a) PET image acquired prior to treatment (reference). (b) and (c) PET image acquired after treatment and registered on the reference image using the principal axis matching (b) and maximization of mutual information (c) methods.



**Fig. 4** SPGR MR and F-18-FDG PET images registered initially using an automatic registration and further corrected user-interactively. (a) SPGR brain MR image (reference) with a PET contour. (b) F-18-FDG PET (floating). (c) Fused image with the PET contour.



**Fig. 5** Brain SPECT images registered user-interactively. (a) SPECT image acquired after an intra-venous injection of Tc-99m-HMPAO. (b) SPECT image acquired after a Tc-99m-HMPAO injection into the left internal carotid artery during the intracarotid amobarbital procedure. (c) Fused image.

more than 100 cases, which were performed for the MR-based partial volume correction of the brain PET images [12].

FIRE software was also applied to develop a probabilistic map of the blood flow distribution from the internal carotid artery (ICA) in the brain [13]. A probabilistic map of the ICA territory would be useful for an objective evaluation of the perfusion status in the ICA territory, which is necessary because the ICA is the most frequently involved vessel in cerebrovascular diseases. Brain SPECT images acquired after a Tc-99m-HMPAO injection into the ICA during the intracarotid amobarbital procedure in epilepsy patients (IAP SPECT) provide anatomical information on the blood flow distribution from the ICA [14]. However, the anatomical information is insufficient for the spatial normalization of the IAP SPECT images onto the standardized SPECT template, which is a pre-requisite for the composition of a probabilistic map. This is because Tc-99m-HMPAO is distributed only in the ICA territory in IAP SPECT. Therefore, registering the IAP SPECT images with the interictal brain SPECT images, which are routinely acquired in epilepsy patients after an intra-venous Tc-99m-HMPAO injection, is necessary to compensate

for the deficient anatomical information in IAP SPECT. Fig. 5 shows the registered interictal (a) and IAP (b) SPECT images using FIRE. No automatic algorithm could match the images precisely, and user-interactive registration was required.

## 5. Hardware and software specifications

As the FIRE was developed using the IDL language, it can be installed and run on any standard PC and Unix platform with various operating systems with which the IDL software is available. Latest version of FIRE was written for IDL 5.5, and may not work with earlier versions. Additional IDL license would be required to save the MPEG cine sequence. The FIRE ran successfully on a standard PC with Pentium III process and 512 MB RAM.

## 6. Discussion and conclusion

Although many algorithms for the fully automated registration of multi-modal images have been suggested [8–11,15,16], their use may be limited

to the registration of brain images with a normal intensity distribution. The automatic algorithms frequently fail to register pathologic images with severe anatomical deformation and abnormal image intensity. The small field of view (FOV) of the old PET scanners is also difficult. The unavailable anatomical information out of the FOV leads to a misalignment with the other modalities when automatic algorithms are used. The successful automatic registration is also difficult to achieve with receptor-ligand PET and SPECT images, as the uptake of radiopharmaceuticals is usually localized in small areas. This situation is similar when abdomen/chest F-18-FDG PET images are registered on CT images in oncology studies. In PET images, the outlines of the body and anatomical structures are blurred, and the shape and position of the organs is sometimes different from those in the CT images because of the different scan duration and position of the extremities. Therefore, a user-friendly image registration program, where user-interactive manual matching of the images is also supported, is necessary in a practical situation [7,17].

Another important requirement of the multi-modal image registration software is the capability of reading various image file formats. Although DICOM is a standard format for the storage and transfer of radiological images, INTERFILE is more popular than DICOM in the nuclear medicine field. Additionally, the ANALYZE format is commonly used due to the wide use of Statistical Parametric Mapping (SPM) software, where the ANALYZE format is adopted. In addition, as many vendor-specific file formats should be supported as possible since most scanner companies do not support the standard formats without additional charge.

The simultaneous display of geometrically registered images should be achieved so that the information from the registered images is not lost and the fused image can assist in interpreting the original images easily. The pixel interleaving method, which is used most commonly, has a disadvantage in that there is a loss of spatial resolution and an inflexibility to emphasize an interesting image [1,18,19]. Recently, the temporal interleaving method was suggested for the realistic display of fused images, in which the images were switched frame-by-frame and switching was synchronized with the vertical scanning of the monitor [19]. Although the simultaneous display of the registered images without the loss of spatial resolution and flickering effects is possible using this method, the practical application of this method is limited due to a difficulty in generating a hard-copy image that matches the image composed by this method precisely, which may be essential in a clinical situation

for later reference. In addition, implementing this method using the Windows environment is not feasible as it originally used a set of VESA extensions to the VGA ROM BIOS services, which is accessible under the DOS environment. In the FIRE software, an analytic composing method was adopted for the static combination of the registered images, which models the human visual system to render the floating image semi-transparently. The  $\alpha$ -channel composition method, in which the resulting pixel value of the fused image was obtained by a linear combination of the values for the reference and floating images, was used [20,21]. In this method, the pixel transparency was determined by the  $\alpha$ -value, which is a pre-defined property of an image object in the IDL language. The real-time composition of the fused images with a different transparency could be achieved using this method, and a cine animation of the fused images with a gradually changing transparency was possible without any feeling of dissatisfaction. Cine animation was particularly useful for a qualitative inspection of the fused images to determine any possible mismatch between the registered images, and the correlative interpretation of the registered images.

Software should be easily transplanted into any OS and platform including PC, Macintosh, and workstation. Although the use of PC and Macintosh for image acquisition and processing has increased, workstation based on a Unix environment is mainly used. In this study, an OS and platform independent program for image registration based on the IDL language was developed. This software will be useful for the clinical applications of image registration techniques.

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