A Useful Implementation of Medical Image Registration for Brain Tumor Growth Investigation in a Three Dimensional Manner

Emrah Irmak[1], **Mustafa Burak TÜRKÖZ**[2]
[1,2]Karabuk University / Electrical and Electronics Engineering Department, Karabuk, 78050, Turkey

Abstract
Image registration or as sometimes called image matching is the operation of geometrically taking two or more than two images to the same coordinate system. Image registration is a fundamental job used to match two or more than two images acquired, for example, at different times, from different machines or sensors, or from different viewpoints. Aligning medical images for neurologic research, diagnosis and treatment can be considered as a specific example of image registration. Magnetic Resonance (MR) images of the brain contain anatomic sense for neurologic research, diagnosis and treatment. Therefore to evaluate changes in serial scans of MR images becomes an important issue in medical image registration field. In this paper an objective application of registration of multiple brain imaging scans is used to investigate brain tumor growth in a 3 dimensional (3D) manner. Using 3D medical image registration algorithm, multiple scans of MR images of a patient who has brain tumor are registered with different MR images of the same patient acquired at a different time so that growth of the tumor inside the patient's brain can be investigated. MR images are registered with 3D accuracy on the order of two corresponding images. Technique is implemented to 19 patients and satisfactory results are obtained. This study is a critical application for correlation of anatomic information obtained by MR for clinical and research purposes. This paper is intended to provide a comprehensive reference source for researchers involved in medical image registration and tumor growth investigation.

Keywords:
Geometrical Transformation, 3D Medical Image Registration, Optimization, Tumor Growth

1. Introduction

A wide range of medical image techniques have been presented with the developments in medical image processing field over the years. As these techniques were independently studied, a large body of research is evolved. Fortunately, techniques differ in information on which registration relies. To put it briefly, connection between the changes of the images and type of the registration method that is most appropriate should be established by the researchers or scientists [1]. Changes refer to the volumetric differences in values and locations of pixels between the two images [2]. Value changes are generally differences in intensity. The changes in question can be classified in three major types.

The first type is the changes which result in misalignment of the images such as the differences in acquisition. For registering images, a spatial transformation is used to remove these changes. The type of transformations that should be sought to find the optimal transformation is established by gain insight about the changes of this type. The transformation type then affects the general method which should be used. The second type of changes is quite similar to first type because they are also due to changes in acquisition. One of the difference between them is that they cannot be modeled easily, for the sake of example; lighting and atmospheric conditions. Another difference is that this type usually changes intensity value. The third type is changes in the nature of the images, for example tumor growths, or other scene changes. For the medical purposes such as, diagnosis, treatment or neurologic research changes of the third type must not be removed by registration. Therefore they make registration more difficult since an exact match is not possible anymore [3]. The characteristics of the each type of changes should be taken into account since knowledge about the characteristics of each type of change establishes the choice of feature space, similarity metric, search space, and search strategy. Ultimately these all together will establish the main method to be used for registration process for the sake of neurologic research, treatment, diagnosis, etc. This course of action is quite practical for understanding relationships between the wide variety of existing methods and to be helpful to choose the most appropriate method for the specific purpose.

The first widely-used method is point-based (fiducial markers) registration method. Aforementioned registration method is achieved by finding the rigid transformation that brings the fiducial points in the two spaces into alignment [4]. Advantage of point-based registration is that it is fast, accurate and robust. However it requires fixation of fiducial markers to rigid structures, which is not always possible or is too invasive to be acceptable.

Second widely-used method is surface-based registration method. This method is based on a description of the shape of an anatomical structure. This anatomical

Manuscript received June 5, 2017
Manuscript revised June 20, 2017

structure may be skin or outer bone surface. To be able to estimate registration transformation minimizing points-to-surface or surface-to-surface distances is used. Unfortunately skin is not a rigid structure and that bone surface has to be exposed during the procedure.

Third widely-used method is intensity-based registration method. This technique works directly with image data. Like many other image processing applications, to be able to record medical images in the registration process, the concerned medical images have to be in digital form rather than analogue form. In other words, the images must be coded into numbers that indeed represent the intensity of the images. The intensity of the images in each point is the color of each location within the images [5]. Recently intensity-based registration method has grown compare to other methods. There are a few reasons for this situation. Firstly, twenty years ago it was taking hours or even days of computers for registering two image volumes if intensity-based registration method is used. At the present time, a few minutes or even seconds in some situations is enough for a simple computer to be able solve the same intensity-based registration problems. Therefore advance in terms of computational resources, processing speed has led intensity-based registration method over other methods. Secondly, before introduction of similarity measures in intensity-based methods there was not a robust similarity metric to compare the interpolated image as the result of registration process. Namely, with introduction and development of similarity measure, especially mutual information (MI), there has been a considerable development in usage of intensity-based image registration as well. Thirdly, the growing importance of the intensity-based registration methods is also a consequence of their simplicity, because there is no need for image segmentation which is generally subject to errors and image segmentation can usually be complex [1].

Looking at literature of medical analysis it can be easily seen that image registration builds up much of the research. Li et al. [6] is worth to be read to consider medical image registration using mathematical tools. Most of the work related to medical image registration is about registration of functional medical images with anatomical medical images. Positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) is functional medical images which give information about functionality of the human body. On the other hand magnetic resonance imaging (MRI) and computed tomography (CT) are anatomical medical images which give information about anatomy of the human body. By registering two different images a new medical image which contains both anatomical and functional information about human body is much more informative and useful. There are a lot of works in literature about this issue: Gering et al. [7] and Pereira et al. [8] are must read paper for intervention and treatment planning. Chang et al. [9] studied a good case for computer-aided diagnosis and disease following-up. For guided surgery on the other hand, Hurvitz and Joskowicz [10], Huang et al. [11] and Galloway et al. [12] are some the best papers. Ozsavas et al. [13], Mendrik et al. [14] , Zhuang [15] and Oliveira et al. [16] made a great effort about anatomy segmentation. Recent improvements have been more on monomodal medical image registration rather than multimodal medical image registration. Acquisition of temporal image sequences contains much of the monomodal image registration research. Compared to multimodal images, mentioned sequences propose additional information about the changes of the imaged organs, such as tumor growths in any part of human body. Object lessons of temporal image registration of the heart can be found in Perperidis et al. [17], Marinelli et al. [18] and Peyrat et al. [19]. Despite that nearly entire anatomic parts and organs of the human body have been studied, much of the research of monomodal image registration has been done on brain. Duay et al. [20], Studhole et al. [21] , Liao and Chung [22], Cho et al. [23].

2. Methods and Materials

To summarize registration process, Figure 1 is an ideal illustration of how process works. It should be stated that the objective is to seek iteratively for a geometrical transformation that, when applied to moving images, optimizes (in other words minimizes) the similarity metric. Image which is not changed during registration is called fixed image, the image which is changed, i.e. transformed during registration is called moving image. The purpose of a similarity metric is to return a value indicating how well two images match. Role of optimizer is to define search strategy for the process. Interpolator takes pixel intensities to the new coordinate system according to the geometric transformation that has been found. Interpolator measures the value of intensity difference between the images in the new positions.

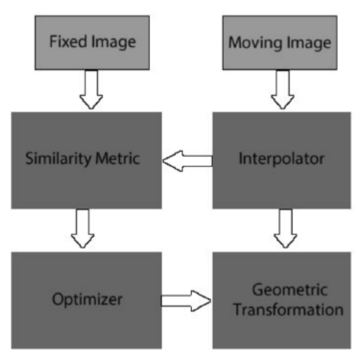

Figure 1. Visual Representation of Image Registration

2.1. Geometric Transformation

Image registration process has a variety of characteristics. Transformation type is one of the basic characteristic of the image registration in order to properly overlay fixed and moving images. In this section of the paper procedure of selecting the transformation type for our specific application is explained. Affine transformation is an efficient transformation type for this problem. Now that an affine transformation is composed of a combination of a translation, a rotation, a scale and a shear change. Possible misalignment for MR images taken at different type with the same sensors are translation, rotation scale and shear change. The most commonly used registration transformation is the affine transformation which is sufficient to match two images of a scene taken from the same viewing angle but at different times.

- ✓ *Translation transformation moves a set of points a fixed distance in x and y,*
- ✓ *Scale transformation scales a set of points up or down in the x and y directions,*
- ✓ *Rotate transformation rotates a set of points about the origin,*
- ✓ *Shear transformation offsets a set of points a distance proportional to their x and y coordinates.*

It is convenient to start by considering linear functions x, y and transformations defined by x and y functions. These transformations might be applied to a point P(x, y) within a plane. All linear transformations T might be represented using following equations:

$$x' = ax + by + e \qquad (1)$$

$$y' = cx + dy + f \qquad (2)$$

The point Q(x´, y´) is called image of P under the transformation T. It is written as, Q = T(P). Two equations can be written in matrix form as follow:

$$\begin{bmatrix} x' \\ y' \end{bmatrix} = \begin{bmatrix} a & b \\ c & d \end{bmatrix} \begin{bmatrix} x \\ y \end{bmatrix} + \begin{bmatrix} e \\ f \end{bmatrix} \qquad (3)$$

Two equations can also be written as $Q = MP + \vec{v}$, where M and $\vec{v}$ are:

$$M = \begin{bmatrix} a & b \\ c & d \end{bmatrix}, \quad \vec{v} = \begin{bmatrix} e \\ f \end{bmatrix} \qquad (4)$$

Therefore the product of the matrix M and point P yields MP, and the addition of vector $\vec{v}$ and product MP results in a point that is geometrically the transportation of the point by the magnitude and orientation of the vector. Figure 2 shows fixed image, moving image and transformed image. By registering fixed and moving image, moving image is taken to the coordinate system of the fixed image.

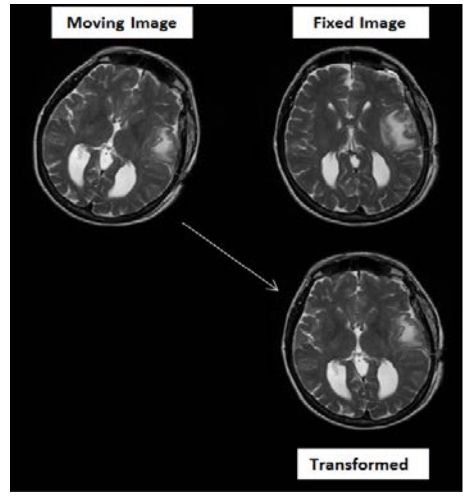

Figure 2. Transformed Moving Image (at the bottom)

2.2. Similarity Measure

The similarity metric used in this problem is sum of squared differences (SSD) similarity metric. This metric, which is one of the most commonly used metrics with monomodal intensity based problems, is based on pixel intensity difference. The key idea behind the SSD is that similar images must have similar pixel intensities when registered accurately. The purpose of a similarity measure is to return a value indicating how well two images match.

2.2.1. Sum of Squared Differences (SSD)

For Fixed Image A and Moving Image B, SSD can be expressed as

$$SSD = \frac{1}{N} \sum_{i}^{N} \left| A(I) - B'(I) \right|^2 , \qquad \forall i \in A \cap B'. \qquad (5)$$

where A(i), B´(i), and N represent pixel intensity value of the fixed image for the ith pixel, pixel intensity value of the transformed moving image for the ith pixel, and number of pixels of the images, respectively.

It has been conditioned that the fixed image and moving image are identical in some degree. There are just misalignments to be minimized. SSD must theoretically be close to zero when the images are correctly registered. Therefore, the golden rule is that the lower the SSD, the better registration process is. The SSD technique is a restricted method. As it has been mentioned before, the images must be identical. In this study MR images of the brain which are identical except for misalignments are used; therefore the SSD technique is ideal for this study.

2.3. Optimizer

The intention of optimization is to seek the minimum value of similarity metric. The optimization process is finished when the similarity metric gets its minimum value. For this reason, registration process can be mathematically summarized as:

$\min_T D[A(i), T(B(i))]$ (6)

where
D = Similarity Metric (Cost Function),
A(i) = Fixed Image,
B(i) = Moving Image,
T = Transformation.

2.3.1. Regular Step Gradient Descent

Regular Step Gradient Method is used as the optimization type at this study. This method was established by Cauchy (1847). This optimization type is one of the simplest method along optimization types adopted for image registration purposes. Cauchy was the first to make use of the negative gradient direction in 1847 for minimization problems. In this method an initial trial point X_1 is chosen, which is iteratively moved along the steepest descent direction until the optimum point is found. See Figure 3. Theoretically this method will not terminate unless a stationary point is found. The method is a hill-climbing technique which begins with an initial estimate X_k of the SSD. Another guess (X_{k+1}) is made from the current guess X_k. We calculate the difference function at all points in a small (say, 3x3) neighborhood of X_k and takes as the next guess X_{k+1} that point which minimizes the difference function.

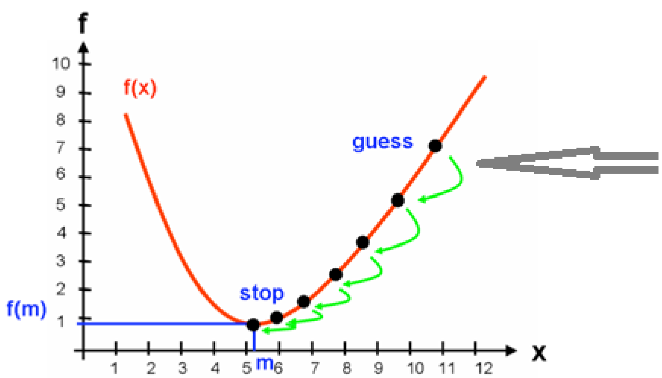

Figure 3. Regular Step Gradient Descent Optimizer

3. Experimental Results

Figures 4 (Fixed Image) and 5 (Moving Image) are MR images of a patient brain that has brain tumor. Tumors are marked with red arrows in the associated images. These MR images are taken at two different times. Figure 4 and 5 are just one scan of the patient acquired at different times. However registration process has been applied to all scans which have brain tumor. In this patient 30 scans of the patient brain have brain tumor. Slices thickness between scans is 1mm which is a perfect thickness for tumor analysis. It has been investigated experimentally how the brain tumor grows, specifically which part of the brain tumor grows, diminishes, or un-changes with time.

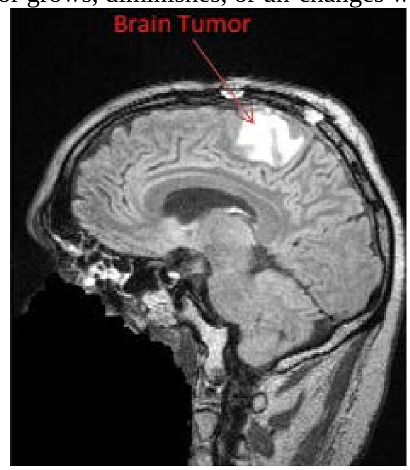

Figure 4. Fixed Image

Figure 5. Moving Image

Figure 6 is just overlapping of two scans. Misregistration of the scans is quite obvious. Misregistration between two scans is marked with red arrows as well. Figure 7 is registration result. In figure 7, it can be seen that distortions which is called misregistration is removed. The remaining variations are changes which are of interest; they are therefore not distortions, they are tumor changes which are desired to be detected. These important changes are marked with red arrows. Green parts shows tumor which has been growing with time. Magenta parts, on the other hand, shows tumor which has been diminishing parts with time and lastly white parts are unchanged brain tumors. This process has been applied to all 30 scans and results can be seen in Figure 10 and Figure 11.

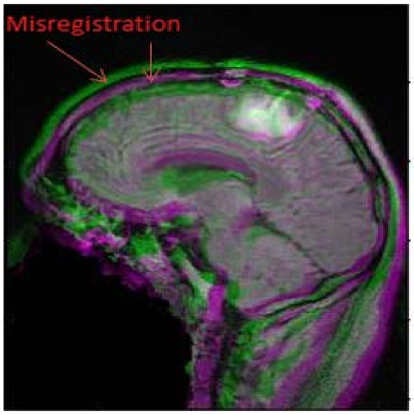

Figure 6. Overlapping Result

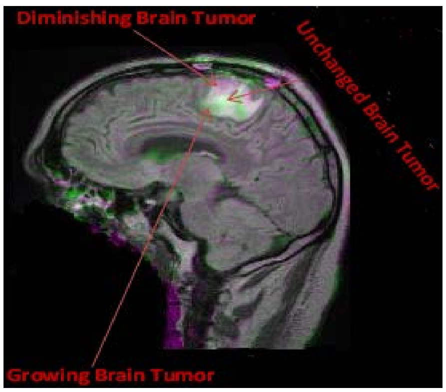

Figure 7. Registration Result

Segmented tumor after registration process is individually indicated in Figure 8. Figure 9 is filtering result of segmented tumor image. Figure 9 is necessary to compute area (hence volume) of diminished tumor part, growing tumor part and unchanged tumor part on an individual basis.

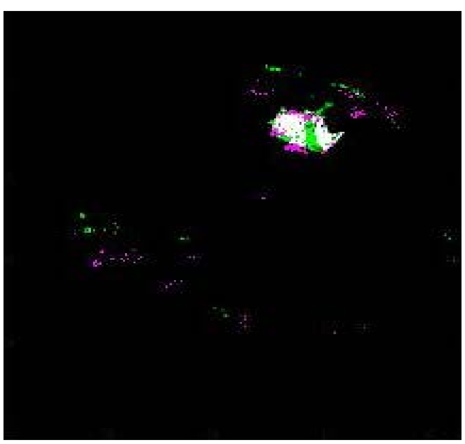

Figure 8. Segmented Tumor

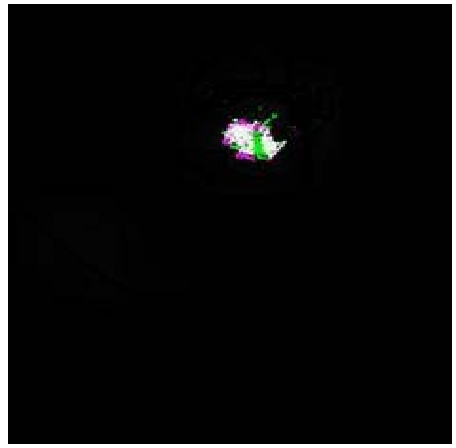

Figure 9. Segmented Tumor after Filtering

As stated before the process explained until this point has been implemented to all tumor associated part of the brain. For first patient this number was 30 scans. For demonstration, result of 16 scans is shown in Figure 10 and corresponding tumors are shown in Figure 11.

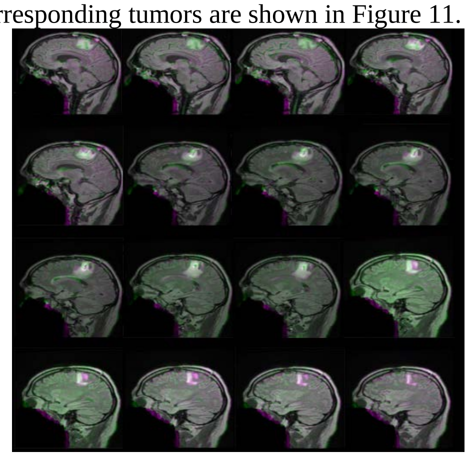

Figure 10. Segmented Tumor (first patient)

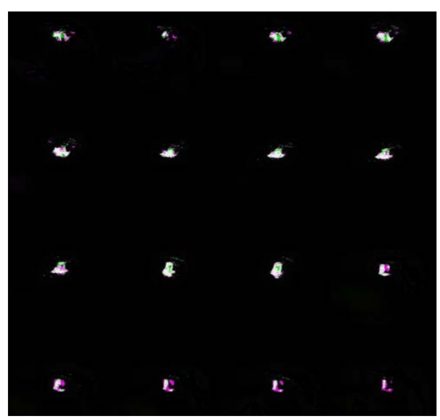

Figure 11. Segmented Tumor (first patient)

Results for the second patient are shown in Figure 12 and Figure 13. For second patient, number of scans which are tumor associated part of the brain was 24. Registration process has been applied to 24 scans. For demonstration, result of 16 scans is shown in Figure 12 and corresponding tumors are shown in Figure 13.

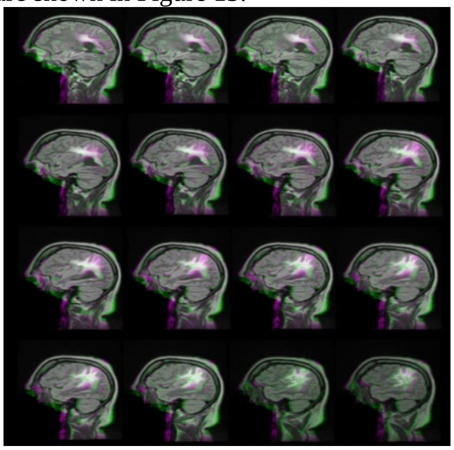

Figure 12. Segmented Tumor (second patient)

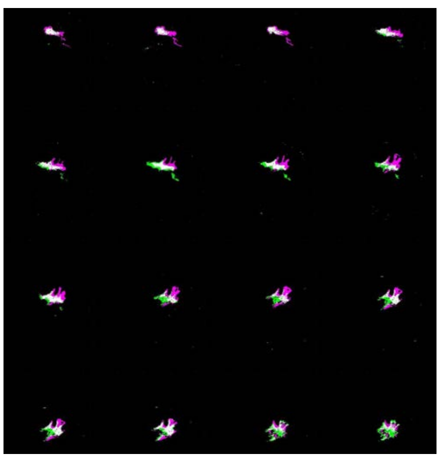

Figure 13. Segmented Tumor (second patient)

4. Conclusion

An exciting and rewarding application of medical image registration is presented in this paper. Tumor growthiness inside the patient's brain is successfully investigated. In this study, intensity based image registration method is used. Sum of squared differences metric is used as similarity metric and regular step gradient descent optimizer is used as optimization technique. The data has been used from The Cancer Imaging Archieve (TCIA) database. Brain MR image of the patient (Figure 4) is properly registered with another brain MR image (Figure 5) acquired at a later time for the same patient to investigate tumor growth within the time. Registration result is shown in Figure 7. Associated tumor parts are segmented and taken out as shown in Figure 8. This image in figure 8 is gone under filtering to get rid of noisy parts and result is shown in Figure 9. This process is implemented to all tumor associated slices of the patient to compute the volume of grown brain tumor, diminished brain tumor and unchanged brain tumor individually. Technique is implemented to 19 patients and satisfactory results are obtained. A challenge of this paper is that grown, diminished, and unchanged brain tumor parts of the patients are investigated and computed on an individual basis in a three-dimensional manner (3D) within the time.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] F. P. M. M. Oliveira and J. M. R. S. S. Tavares, "Medical Image Registration: a Review", Comput. Methods Biomech. Biomed. Engin., vol. 17, no. 2, pp. 73–93, 2014.

[2] L. G. Brown, "A Survey of Image Registration", ACM Comput. Surv., vol. 24, no. 4, pp. 325–376, 1992.

[3] X. Gao, C. Wang, W. Zhang, J. Wu, and H. Liu, "The Analysis and Application of Spline Interpolation for Multi-Sensor and Multi-Resolution Image Registration", Int. Geosci. Remote Sens. Symp., vol. 2, no. 2001, pp. 7929–7931, 2003.

[4] J. M. Fitzpatrick, J. B. West, and C. R. Maurer, "Derivation of Expected Registration Error for Point-based Rigid-body Registration", Proc. SPIE Medical Imaging, vol. 3338, no. February, pp. 16–27, 1998.

[5] E. Irmak, E. Ercelebi, and A. H. Ertas, "Brain Tumor Detection using Monomodal Intensity based Medical Image Registration and MATLAB", Turkish J. Electr. Eng. Comput. Sci., vol. 24, pp. 2730–2746, 2016.

[6] L. Li, T. Niu, and Y. Gao, "Mathematical Methods and Applications in Medical Imaging 2014", Computational and Mathematical Methods in Medicine, vol. 2015, pp. 2–4, 2015.

[7] D. T. Gering et al., "An Integrated Visualization System for Surgical Planning and Guidance using Image Fusion and an Open MR", J. Magn. Reson. Imaging, vol. 13, pp. 967–975, 2001.

[8] G. C. Pereira, M. Traughber, and R. F. M. Jr, "The Role of Imaging in Radiation Therapy Planning : Past , Present , and Future", Biomed Res. Int., vol. 2014, no. 2, 2014.

[9] C. J. Chang, G. L. Lin, A. Tse, H. Y. Chu, and C. S. Tseng, "Registration of 2D C-Arm and 3D CT Images for a C-Arm Image-Assisted Navigation System for Spinal Surgery", Appl. Bionics Biomech., vol. 2015, 2015.

[10] A. Hurvitz and L. Joskowicz, "Registration of a CT-like Atlas to Fluoroscopic X-ray Images using Intensity Correspondences", Int. J. Comput. Assist. Radiol. Surg., vol. 3, no. 6, pp. 493–504, 2008.

[11] X. Huang, J. Ren, G. Guiraudon, D. Boughner, and T. M. Peters, "Rapid Dynamic Image Registration of the Beating Heart for Diagnosis and Surgical Navigation", IEEE Trans. Med. Imag., vol. 28, no. 11, pp. 1802–1814, 2009.
[12] R. Galloway, S. Herrell, and M. Miga, "Image-Guided Abdominal Surgery and Therapy Delivery", J. Healthc. Eng., vol. 3, no. 2, pp. 203–228, 2012.
[13] E. E. Ozsavas, Z. Telatar, B. Dirican, Omer Saler, and M. Beyzadeollu, "Automatic Segmentation of Anatomical Structures from CT Scans of Thorax for RTP", Comput. Math. Methods Med., vol. 2014, pp. 1–15, 2014.
[14] A. M. Mendrik et al., "MRBrainS Challenge: Online Evaluation Framework for Brain Image Segmentation in 3T MRI Scans", Comput. Intell. Neurosci., vol. 2015, 2015.
[15] X. Zhuang, "Challenges and methodologies of fully automatic whole heart segmentation: a review", J. Healthc. Eng., vol. 4, no. 3, pp. 371–408, 2013.
[16] F. P. M. Oliveira, A. Sousa, R. Santos, and J. M. R. S. Tavares, "Towards an Efficient and Robust Foot Classification From Pedobarographic Images", Comput. Methods Biomech. Biomed. Engin., vol. 5842, no. February 2015, pp. 1–8, 2011.
[17] D. Perperidis, R. H. Mohiaddin, and D. Rueckert, "Spatio-temporal Free-form Registration of Cardiac MR Image Sequences", Med. Image Anal., vol. 9, no. 5 SPEC. ISS., pp. 441–456, 2005.
[18] M. Marinelli, V. Positano, F. Tucci, D. Neglia, and L. Landini, "Automatic PET-CT Image Registration Method Based on Mutual Information and Genetic Algorithms", Sci. World J., vol. 2012, pp. 1–12, 2012.
[19] J. M. Peyrat, H. Delingette, M. Sermesant, C. Xu, and N. Ayache, "Registration of 4D Cardiac CT Sequences Under Trajectory Constraints with Multichannel Diffeomorphic Demons", IEEE Trans. Med. Imaging, vol. 29, no. 7, pp. 1351–1368, 2010.
[20] V. Duay, N. Houhou, S. Gorthi, A. S. Allal, and J. P. Thiran, "Hierarchical Image Registration with an Active Contour-based Atlas Registration Model", Eur. Signal Process. Conf., 2008.
[21] C. Studholme, D. L. Hill, and D. J. Hawkes, "Automated Three-dimensional Registration of Magnetic Resonance and Positron Emission Tomography Brain Images by Multiresolution Optimization of Voxel Similarity Measures", Med. Phys., vol. 24, no. 1, pp. 25‑35, 1997.
[22] S. Liao and A. C. S. Chung, "With Symmetric Alpha Stable Filters", IEEE Transactıons on Medıcal Imaging, vol. 29, no. 1, pp. 106–119, 2010.
[23] Y. Cho et al., "A multi-resolution Scheme for Distortion-minimizing Mapping Between Human Subcortical Structures Based on Geodesic Construction on Riemannian Manifolds", Neuroimage, vol. 57, no. 4, pp. 1376–1392, 2011.
[24] S. Yazdani, R. Yusof, A. Karimian, A. H. Riazi, and M. Bennamoun, "A Unified Framework for Brain Segmentation in MR Images", Comput. Math. Methods Med., vol. 2015, 2015.
[25] J. P. W. Pluim, J. B. A. A. Maintz, and M. A. Viergever, "Mutual-information-based registration of medical images: A survey", IEEE Trans. Med. Imaging, vol. 22, no. 8, pp. 986–1004, 2003.
[26] J. Salvi, C. Matabosch, D. Fofi, and J. Forest, "A Review of Recent Range Image Registration Methods with Accuracy Evaluation", Image Vis. Comput., vol. 25, no. 5, pp. 578–596, 2007.
[27] M. V Wyawahare, P. M. Patil, and H. K. Abhyankar, "Image Registration Techniques : An overview", Int. J. Signal Process. Image Process. Pattern Recognit., vol. 2, no. 3, pp. 11–28, 2009.
[28] P. J. Slomka and R. P. Baum, "Multimodality image registration with software: State-of-the-art," Eur. J. Nucl. Med. Mol. Imaging, vol. 36, no. SUPPL. 1, pp. 44–55, 2009.
[29] X. Du, J. Dang, Y. Wang, S. Wang, and T. Lei, "A Parallel Nonrigid Registration Algorithm Based on B-Spline for Medical Images", Computational and Mathematical Methods in Medicine, vol. 2016, 2016.