Investigation and improvement of multi-resolution mutual-information-based registration

Dilla, Handini

2006

Dilla, H. (2006). Investigation and improvement of multi-resolution mutual-information-based registration. Master's thesis, Nanyang Technological University, Singapore.

<https://hdl.handle.net/10356/5676>

<https://doi.org/10.32657/10356/5676>

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NANYANG TECHNOLOGICAL UNIVERSITY**

2006

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SCHOOL OF MECHANICAL AND AEROSPACE ENGINEERING

A thesis submitted to the Nanyang Technological University
in fulfillment of the requirement for the degree of
Master of Engineering

2006

ACKNOWLEDGEMENT

Firstly, the author would thank Almighty God for His grace, guidance, enlightenment, and for giving endurance to go through this course.

The author would also like to express her heartfelt gratitude to Associate Professor Teo Ming Yeong for all his supervision, guidance, suggestions, understanding and supports throughout the course of this project. Besides, the author would like to thank Associate Professor Michael Lau, for his time and effort to review this thesis patiently and his valuable suggestions.

The author would like to show her sincere gratitude to Mr. Charles Lo, from National Neuroscience Institute, the NeuroBot Project Officer, for providing all the required information for this project and for being a very inspiring discussions partner. The author would like to dedicate her earnest thanks to NNI surgeons and staffs for providing a very conducive and pleasant environment.

Special thanks are due to all who has helped the author in one way or another. Last but not least, the author would like to thank her family and friends for the encouragement and support.

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SUMMARY

An image-guided surgical robotic system, NeuroBot, is currently being developed by a team of researchers from Nanyang Technological University (NTU) Singapore and National Neuroscience Institute (NNI) Singapore. The system aimed to assist neurosurgeons in skull-base surgery especially in generating operative plan and drilling task. As one of the required functionalities of the system, an image registration technique was aimed to be developed in this project. Mutual-Information (MI)-based method, an acknowledged registration method for its high accuracy, was adopted in a multi-resolution scheme to improve the speed and robustness. It was intended to use multimodal images in this project. However, due to the lack of availability of public resources in multimodal datasets, the project used single modal image datasets from MRI (Magnetic Resonance Imaging). Two versions of algorithms adopting the technique were developed, and their performance were investigated for several factors which are optimization methods, number of multi-resolution levels, transformation, and acquisition modes. The speed and accuracy served as the performance indicator. The algorithms differ by their optimization methods which are Powell's and regular step gradient descent (RSGD) optimizations. ITK (Insight Toolkit) registration framework was used as the development tool kit. It was found that RSGD outperforms Powell's method – based algorithm in terms of speed, with comparable accuracy. The experimental results using RSGD-optimization registration technique showed that only two results, out of 94 results, exceeded the sub-voxel accuracy; such results are termed as outlier data (in this case, data whose error > 1 mm). Multi-resolution scheme was proven to improve the robustness and speed of registration process; and, it was found that the number of multi-resolution levels affects the registration speed. In the experiments, among the number of levels tested, three and four levels were found to be the optimum number of levels as they gave the fastest speed for RSGD-based algorithm. It was found that time spent for image resampling for every level acts as the limiting factor to the registration speed. The placement of the transformation origin was also found to affect the registration speed. The placement of transformation origin in the center (centered-origin) of an image volume gave faster registration process than the one in the image corner (normal-origin) by four times. In addition, the experiment showed

that the larger the range of the transformation, the more inaccurate the results were. This could be explained by the fact that the adopted transformation method, Euler3D transformation, assumes linearity for small range that still holds for small transformation range but deviates for larger range. It was also found that the acquisition mode affected the accuracy. Intra-acquisition-mode gave higher accuracy than inter acquisition-mode. A set of models representing multimodal image pairs were developed in this project and tested on the algorithms. The results showed that the algorithms worked well with the models. The algorithms are hence applicable for multimodal image registration.

Based on the investigation results, a technique to improve the registration performance was then proposed. The proposed method combined the optimization methods (Powell's and RSGD) in one multi-resolution scheme MI-based registration. It is a new technique, and the novelty of this project. This new technique, implemented as an algorithm referred as the Improved Algorithm, outperformed the registration speed of RSGD-based technique by 2.8 to 4.1 times. Although the accuracy of the Improved Algorithm was still outperformed by the RSGD algorithm, it still maintained its lower bound error within sub-voxel accuracy (< 1 mm). In this project, the algorithms were only tested on the head images of MR modality obtained from the BrainWeb resource. Testing of the registration algorithms being developed in this project in more cases of image pairs and multimodal images is required to confirm the general applicability of the algorithms.

CHAPTER 1

INTRODUCTION

Chapter one presents the introduction of the report elaborating the background of the project, an overview of the robotic system being developed, and a brief introduction on image registration and its significance in this project. Subsequently, the objective and scope of this project are presented, followed by the report organization.

1.1 Background

1.1.1 Surgical robotic system

The advancement of computer and robotics technology has brought the robotic systems into the operating theatre. Such robotic systems assist the surgeons in carrying out surgical procedures.

The number of robotic surgery systems is increasing; they are being developed and applied in different fields such as orthopaedic, cardiac, urology, and neurosurgeries [1]. To name some of the surgical robotic systems that are in use in operating theatre are ROBODOC (Integrated Surgical Systems Inc., Davis, CA), CASPAR (developed by ortoMAQUET Inc., Rastatt, Germany), and EVOLUTION 1 (URS Inc., Schwerin, Germany) [2]. The first two are used in orthopaedic surgery for total hip and knee replacement, whereas the last is for robotic neuro-endoscopy. These systems are considered as robots because they are freely programmable for a complete surgical task. They are different from existing (tele)manipulators such as ZEUS (ComputerMotion Inc.) and Da Vinci (Intuitive Surgical Inc.), which work under direct control of the surgeon in a master-slave fashion [2]. NeuroMate, a robotic system for stereotactic functional brain surgeries, comprises of pre-surgical planning workstation and could adapt to changes required during surgery, was developed by Integrated Surgical Systems [3].

1.1.2 Skull-Base Surgery

The skull-base refers to the area in the skull that provides the base on which the brain rests (Figure 1.1). It is one of the most complex regions in human anatomy as it contains critical features which are the eye orbits, ear canals, two carotid arteries, two vertebral arteries, 12 cranial nerves and blood drainage system of the brain.

Figure 1.1. Skull-base area. Adapted from [4].

The 12 pairs of cranial nerves are responsible for specific basic functions such as blinking, swallowing or focusing the eye, etc. A tumor existed in the skull base may affect these nerves both by the presence of the tumor and by the steps carried out during the operation.

The skull-base surgery aims to remove the tumors involving the skull-base such as acoustic schwannomas, meningiomas, pituitary tumors jugular tumors, and a variety of malignancies [5]. Using the conventional method, due to the delicate nature of this surgery, patients may be in the operating theatre for as long as 15 hours.

Normally, up to 8 hours are required to drill the skull to gain access into the skull-base. The drilling process is slowed down by the uncertainties of the location of the vital features hence requiring extra handling of the drilling tool. The length of the operation time may cause the surgeon to suffer from fatigue which may lead to hand tremor and inaccuracy of the procedure.

1.2 Overview of the NeuroBot System

In view of the difficulties in performing skull-base surgery, a team of researchers from Nanyang Technological University (NTU) Singapore and National Neuroscience Institute (NNI) Singapore aimed to develop an image-guided surgical robotic system to assist the neurosurgeons. The first phase of development started in 1998, and currently it is in the second phase of development which started in early 2005. The main aim of the system is to shorten the bone drilling time while maintaining current level of accuracy and precision. The robot is expected to reduce the drilling time from 8 hours to as low as 2 hours. The time reduction will not only benefit the surgeons but also the patient as it could reduce the patient's trauma and time under anesthesia.

The robotic system aims to assist the neurosurgeons in performing the skull-base surgeries, involving various approaches e.g. trans-temporal, middle fossa, trans-orbital approaches, etc; those approaches require intensive task of bone drilling. Particularly, the system assists the surgeons in the following tasks:

1. To generate an optimum operative plan that avoids the critical features (e.g. important nerves, major blood vessels): A cavity, from the scalp leading to the skull-base area, is required to be drilled in order to approach the lesion in the skull-base. The system is involved in generating a preoperative plan of the drill trajectory that could avoid the critical features.
2. To perform the skull drilling task: The use of robotic arm in drilling surpasses human arm in terms of stability, geometrical accuracy, steadiness, and tireless. Hence, the use of robot would ease the surgeon's task while improving the result of the surgery e.g. higher accuracy.

The schematic of the NeuroBot is illustrated in Figure 1.2. The NeuroBot comprises of a workstation, robot manipulator, and navigation (tracking) system. The workstation functions as the central processing unit of all the information and the surgeon's assistant for decision making. The tracking system enables the robotic system to recognize the physical space and relate it to the image space. The robot manipulator which comprises of a base robot and a parallel manipulator with its 7th DOF functions as the robot's arm and end-effector respectively.

Prior to the surgery, several pieces of invasive fiducial markers are screwed on the outer table of the patient's head. Subsequently, the patient goes for CT (Computed Tomography) / MRI (Magnetic Resonance Imaging) / MRA (Magnetic resonance angiography) scanning with the markers kept intact. The patient's CT/MRI datasets are then loaded into the planning system residing in the workstation. The planning system functions as the visualization and planning interface for the surgeon. The markers serve as the reference for the patient's head in the physical space. As these markers are also visible in the scanning image, they are also used to relate the physical space i.e. operating theatre and the image space i.e. where the volume image of the patient's head is defined. The relationship between the coordinate spaces is termed as physical to image space registration.

Through the planning station, the surgeon performs the surgical plan aided with the visualization of the patient's head image. The surgical plan including the area to be avoided and/or to be drilled is then translated into the manipulator's (i.e. the base robot and the parallel manipulators) action. The process of the robotic surgery is constantly monitored by the tracking system. The tracking system which comprises of 3 cameras is able to track the Infra-Red (IRED) markers. Several IRED markers are mounted on the manipulator and surgical tools. As the camera is unable to see the fiducial markers, a reference frame attached with IRED markers is established to infer the position of the patient's head; in order to establish the relationship, the fiducial markers' position needs to be calibrated prior to the surgery. The surgeon can interact with the system during the process of the surgery, to observe the process, make changes, or stop the process if the process goes wrong. The details on the NeuroBot system could be found in [6] and [7].

Figure 1.2. The schematic of the NeuroBot System.

1.3 Image Registration

In order to perform the drilling task, the robotic system needs to generate a drilling plan based on the input from the surgeon. The plan comprises of safe and shortest path from the skull surface leading to the skull-base area. During intra-operative stage, the surgeon needs to ensure that the drilling task is performed safely. The requirements cause the need of the surgical planning and navigation system to acquire comprehensive information on human head anatomy which comprises of skull bone, brain matter, lesion, and blood vessels as this task involves critical feature avoidance.

The information on the patient's head anatomy is obtained from the images of the patient's head. Several imaging modalities could be employed for this purpose. Unfortunately, one imaging modality is only good for certain characteristics of anatomy; CT imaging modality is good for imaging hard structures such as bony structures, whereas MRI is good for imaging soft tissues and lesions.

In order to obtain comprehensive information on the anatomy, there is a need to combine the information from different imaging modalities. This has led to the need of implementing image registration functionalities in this robotic system. Image registration is defined as the process of finding a transformation that could relate a point in an image to a point in the other that refers to the same object. Thus, image

registration has allowed the information contained in two images or more to be related. With the implementation of image registration functionality in the planning and navigation system, the robotic system would be able to combine the information of the skull bone (from CT image), lesion, and brain matter (from the MR image); thus could assist in avoiding the critical features during the surgical intervention.

Currently, Dextroscope from Volume Interaction (www.volumeinteractions.com), a virtual-reality-based planning system is being used to perform volume visualization and registration in NNI. The system can perform registration fast; on average it takes less than 1 minute to register two image volumes of $(128-256) \times (128 - 256) \times (128-256)$ voxels. Voxel is three dimensional (3-D) pixel. However, the system is very expensive; it costs about S\$ 80,000-100,000. Prior to the registration process, the user is required to do initialization by placing the images in a close proximity; both images have to be overlapping and within 1 mm misalignment error. It is done interactively using the virtual-reality tools.

Currently, NeuroBot only has physical to image registration system. It has not yet been equipped with image to image registration functionality. To differentiate the registration terms, image registration refers to image to image registration. It is not intended to integrate the Dextroscope's registration algorithm into the NeuroBot as Dextroscope is a patented commercial product; the license for adopting the Dextroscope's registration is very expensive. An image registration feature is hence required to be developed and integrated in NeuroBot.

1.4 Project Objectives and Scopes

There have been several image registration techniques available. However, it was mentioned in [8],[9] that Mutual-Information-based registration technique is a promising method that could give high accuracy results; even outperforming the acknowledged gold standard registration method, marker-based registration method.

The main objective of this project was to develop a registration technique adopting the Mutual-Information-based (MI-based) method that fits the usage of the NeuroBot and preferably could improve the performance of the currently available registration

techniques in general, especially in terms of speed and accuracy. The elaboration on the discussion of the selection of registration method for the NeuroBot is discussed in section 2.4. The registration technique should be able to work on multimodal images, having a good accuracy level i.e. sub-pixel accuracy and shorter processing time. It is intended to achieve the processing time of the Dextroscope's registration i.e. in the order of 1 minute. However, considering its being computationally expensive method, achieving the processing time in order of 2-3 minutes for registering two image volumes of the same size using MI method is considered fast. Thus, it is intended that the processing time to be achieved is in the range of 2-3 minutes.

Thus, in order to achieve the main objective, several sub-objectives were established, which comprised of:

1. To develop MI-based registration algorithms based on the currently existing variants of MI technique;
the technique adopted was of the MI-based technique with a multi-resolution scheme implementation.
2. To investigate the performance of the developed algorithms;
the performance was assessed based on the speed and accuracy. Several factors were investigated for its effects on the registration performance. The factors namely: the optimization methods, properties of multi-resolution scheme coupled with the optimization method, properties of transformation, and the types of the acquisition modes of the images being registered.
3. Based on the results of the investigation, to develop an improved registration technique.

1.5 Report Organization

This report is organized into 7 chapters. The first chapter elaborates the overview of the project comprising of the background, system overview, the significance of the project as well as the project's objectives and scopes. The second chapter describes the general concepts of image registration; several theories of image registration and validation techniques are presented, followed by discussions on the requirement analysis for the implementation of registration technique in the robotic system being

developed. Chapter 3 explains the Mutual-Information-based Registration concepts covering the basic underlying theory, its components, existing variations of techniques and some review on the research works by others; a discussion on the selection of techniques in MIB for the system being developed is also presented. In chapter 4, elaboration on the design of the algorithms of the multi-resolution MI-based registration as well as the design of the investigation experiments is presented.

Chapter 5 presents the results and discussions of the investigation experiments conducted as explained in chapter 4. Chapter 6 presents the design, implementation, experimental results and discussions of the developed combined optimization registration algorithms. Finally, chapter 7 concludes the report and presents suggestions for future improvement of the image registration system of the NeuroBot.

CHAPTER 2

MEDICAL IMAGE REGISTRATION

Chapter two presents the literature review on the medical image registration. It comprises of the explanation on image registration and its underlying concepts, followed by classification of registration methods, and validation techniques. The chapter concludes with a discussion on the requirement analysis of the registration application being developed for the robotic system.

2.1 General Overview

Registration is defined as “the determination of a one-to-one mapping between the coordinates in one space and those in another such that points in the two spaces that correspond to the same anatomical point are mapped to each other” [10]. Or simply, registration is the process of aligning two spaces so that corresponding features in both spaces can easily be related.

Registration establishes spatial correspondence between the spaces being registered. For that, image registration involves finding transformations that relate spatial information in one coordinate space e.g. image or physical space to those in another. It is illustrated in Figure 2.1, a spatial transform T that maps points in one image to another is the one being searched for in the registration process.

Figure 2.1. Image registration concept. It is the task of finding a spatial transform mapping one image into another. Adapted from [11].

The spaces involved could be image and/or physical spaces. Registration between image space and physical space is applied to relate an image space comprising

preoperative images and a surgical plan to a physical space i.e. the operating theatre. Registration between image spaces is also termed as image registration. The implementation of image registration enables the combination of information from multiple imaging modalities, e.g. combining bony structure of the head from the CT scan image and the brain soft tissues from MR image and monitoring of changes in an organ over time intervals. The important concepts in registration are elaborated below.

A. Transformation Type

There are four types of transformations commonly used in registration which are: *rigid*, *affine*, *projective* and *curved* transformation. *Rigid* transformation involves only translation and rotation [13]. *Affine* transformation maps parallel lines onto parallel lines. Thus, in addition to translation and rotation, affine transformation allows skewing. *Projective* transformation maps lines onto lines, whereas *curved* or *elastic* maps lines onto curves [13].

A rigid or affine 3D transformation can be described using a single constant matrix (a) equation:

$$y_i = a_{ij}x_j \quad (2.1)$$

where, x and y are the old and new coordinate vectors. In the rigid case, this equation is constrained as [12]:

$$\begin{pmatrix} y_1 \\ y_2 \\ y_3 \\ 1 \end{pmatrix} = \begin{pmatrix} & & & \\ & r & & t \\ & & & \\ 0 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ 1 \end{pmatrix} \quad (2.2)$$

where t is an arbitrary translation vector, r is 3x3 rotation matrix. In the affine case, r is unrestricted. In the projective case, a constant matrix representation can only be used if employing homogeneous coordinates:

$$\begin{aligned} y_i &= u_i / u_4 \\ u_i &= a_{ij}x_j \end{aligned} \quad (2.3)$$

where a is an arbitrary 4x4 constant matrix. Curved transformation cannot in general be represented using constant matrices. Most applications represent curved

transformations in terms of a local vector displacement (disparity) field: $y_i = x_i + t_i(x)$, or as polynomial transformations in terms of the old coordinates [13].

B. Transformation Domain

Transformation in registration could be employed in global and/or local domains. A transformation is called global if it applies to the entire image, and local if sub-sections of the image each have their own transformations defined [13]. The examples of transformation cases in terms of 2D transformations are depicted in Figure 2.2.

Figure 2.2. Examples of 2D transformations. Adapted from [13].

C. Dimensionality of Registration

Dimensionality in registration could be of *spatial* or *spatial dimension with time series* [14]. *Spatial* dimension means that all the dimensions are spatial, without time frame involved. For example: 2D/2D (from 2-D image to 2-D image) registration (e.g. CT with X-ray images), with no time involved [14]. The other one *with time series* means that time is as an added dimension. Some examples of its applications are the monitoring of bone growth in children and monitoring of tumor growth [14].

D. Nature of Features in Registration

The nature of the features contained in the image used in registration could be *extrinsic* and *intrinsic*. *Extrinsic* means foreign objects are introduced into the

imaged space, whereas *intrinsic* means it bases on the information contained in the patient's image.

Extrinsic method uses artificial object attached to the patient; the objects must be well visible and accurately detectable in all the modalities in use. The advantages of this method are fast, easy, can usually be automated, and simpler computations; there is no need for complex algorithms as the registration parameter can be computed easily (i.e. relatively easy compared to methods involving optimization) [14]. However, this method causes complication during the pre-acquisition phase and often invasive. Non invasive markers could be used, yet less accurate.

The objects commonly used in extrinsic method are stereotactic frame [15], screw-mounted markers [16], and marker glued to the skin [17]. Stereotactic frame is screwed rigidly to the patient's outer skull table; to date, it serves as the "gold standard" for registration accuracy. Such frames are used for localization and guidance purposes in neurosurgery. The method is invasive and to be used in surgery; therefore the mounting of a frame solely for registration purpose is not permissible. Screw mounted marker is also invasive, whereas skin marker is not. However, skin marker has low accuracy as skin surface is prone to shifting during acquisition.

Intrinsic methods utilize patient generated image information only. This method could be *landmarks based* i.e. a limited set of identified salient points, *segmentation based* i.e. the alignment of segmented binary structures, *voxel property based* i.e. based on the computation from the image grey values, or common object surfaces [14].

Anatomical landmarks use salient, accurately locatable points and visible in the morphology of human anatomy; the landmarks are usually identified interactively by the user [18]. Geometrical landmark use points at the locus of the optimum of some geometry property, e.g. local curvature, corners, etc; it is generally localized automatically [19]. Landmark based methods are theoretically versatile i.e. it is applicable to any images regardless of the object or subject is. Normally, it is used in conjunction with different registration method to constrain the search space.

However, the method is not automatic as it requires user interaction for landmark identification.

Rigid model based method is a type of the segmentation based registration method. It extracts the structures that are anatomically similar (e.g. surfaces) from both images to be registered, and used the structures as sole input for the alignment procedure [20]. This method is popular in clinical use [21] due to its relatively low computational complexity as segmentation is easy. However, its accuracy is limited by the accuracy of the segmentation step. The registration stage is commonly automated, but semiautomatic for the segmentation stage.

Other type of segmentation-based method is *deformable model-based* method. In this method, the extracted structures (mostly surface and curves) from one image are elastically deformed to fit the second image [22]. This method is always locally defined and computed.

Voxel property based methods operate directly on the image gray values, without the need for prior data reduction by the user or segmentation. Voxel-based method could: immediately *reduce* the image gray value content to a representative set of scalars and orientations and use the *full image content*.

Examples of reductive approach are *Principal axes* and *moments based* methods. In these methods, the image center of gravity and its principal orientation (principal axes) are computed from the image zeroth and first order moments; registration is then performed by aligning the center of gravity and the principal orientation. The principal axes methods are automatic, fast, and easy implementation, and used for application that requires no high accuracy [23]. Moments based methods are basically hybridly classified as registrations that use segmentation.

Currently, *full image content* based methods are the most popular method in research. These methods are theoretically, the most flexible registration methods as they eliminate the need to reduce gray value image, but use all available information throughout the registration process. Despite its being an accurate retrospective registration method and applicable in almost any medical application area, it is

computationally expensive. However, the availability of fast and large internal memory computer can solve this problem. A registration method belonging to this category is the *mutual-information based* registration [23].

E. Imaging Modalities

Multimodal registration involves the concepts of imaging modalities. In this case, three imaging modalities, CT, MRI, and MRA are discussed briefly as they are related to NeuroBot system as mentioned in section 1.2.

CT is a tool to diagnose a lesion in human body. The basic principle is based on the detection of X-ray (i.e. short wavelengths electromagnetic radiation) attenuation while traveling through a body or organ using a detector array [23a]. Materials of different density produce images of different brightness. For the measurement, the body or organ of interest of the patient is taken slice by slice. Each slice depicts a 2-D area of a slice of the organ/body. Special software uses the set of 2-D pictures obtained to assemble a 3-D image from them. The X-ray method is best suited for investigating solid material such as bones and bone structures; however, it is also commonly used for soft tissues [23a]. The magnetic resonance imaging (MRI) method can detect contrasts in soft tissues. The basic principle is based on the measurement of the relaxation properties of water protons in living tissue upon the exposure of a radio frequency and magnetic field gradient (MFG) pulses [23b]. For a measurement, the patient is placed into the MRI instrument and a picture of a 2-D slice is taken of the area of interest. Afterward, the location of the measurements is advanced in defined steps (e.g. slices of 2–10 mm). Upon completion of the measurements, the 2-D pictures are assembled to a 3-D image using special software [23b]. Magnetic resonance angiography (MRA) is a type of MRI scan in which a dye is injected into the bloodstream prior to the scanning [23c]. The dye makes the blood vessels easier to see on the scan. An MRA scan provides more detail than a basic MRI scan. It can help detect the arteries and veins [23c].

Images of different imaging modalities are different in terms of image resolution and grey values distribution. Image resolution is represented as the number of pixels (in 2-D image) or voxels (in 3-D image) composing the image. Using different imaging

modalities, an object of a certain dimension could result in some images of different resolution. A typical 2-D CT image datasets could have resolution of 512x512 pixels (X-, Y- dimensions), whereas a typical 2-D MRI could have 256x256 pixels [73]. Other resolution values are also possible such as higher or lower resolutions than the typical values; it depends on some considerations such as imaging time (high resolution image requires longer time to produce), imaging area and the imaging machine's capability (minimum and maximum resolution capability of the machine). As for 3-D image datasets, the resolution in Z direction is more variable; it depends on the thickness of the imaged object and the imaging machine's capability. Thus, resolution affects the pixel (in 2-D image) or voxel (in 3-D image) size. For instance, an object of a certain dimension could result in a CT dataset of 512x512x100 voxels or an MRI dataset of 256x256x100 voxels; thus, one voxel in the MRI dataset represents a physical volume of four times the one in CT dataset (i.e. $(512/256) \times (512/256) \times (100/100) = 2 \times 2 \times 1 = 4$).

Different imaging modalities could also cause different grey value distributions; it is due to different range of the grey values and different principle of acquisition techniques. Grey value range depends on the capacity of the data storage allocated for representing the grey values; it is normally represented as *pixel* or *voxel depth* in bits/pixel (for 2-D image) or bits/voxel (for 3-D image). A 2-D image with pixel depth of 8 bits/pixel has grey values ranging from 0 to 256 ($=2^8$). Pixel depth values could also be 10 bits/pixel or 12 bits/pixels, etc. The difference between CT and MRI scan images are illustrated in Figure 2.3.

Figure 2.3. Samples of CT and MRI images in axial plane. (a) Sample of 2-D CT scan image. Adapted from [24], (b) Sample of 2-D MRI scan image. Adapted from [25].

Different principle of acquisition technique could result in images of different grey value distributions. Different acquisition technique, e.g. X-ray attenuation, radio frequency, as has been explained in the beginning of this section, affects the contrast and brightness of the image.

2.2 Classifications of Registration Methods

Currently, there have been many registration methods available. Several ways of classifying the methods have been proposed by several researchers. Gerlot-Chiron et. al. [26] classified registration methods into four categories: (1) point methods, (2) edge methods, (3) moment methods, and (4) similarity criterion optimization methods. Gerlot-Chiron's classification does not involve large scope of registration methods; it only views registration methods based on the features of the images that are used in registration.

Van den Elsen et. al. [13], from the Computer Vision Research Group University of Utrecht, proposed a more extensive classification that later became a reference of classification methods by many researchers; they classified the registration methods based on a number of criteria: (1) dimensionality (2D, 3D, 4D), (2) type of features in registration (intrinsic and extrinsic), (3) transformation domain (local and global), (4) type of transformation (rigid, affine, projective, and curved), (5) determination of parameter (searched and directly computed), and (6) interaction (interactive, semi-automatic, and automatic). In [27], Chmielewski et.al. derived a classification method from [13]; they classified the methods into ten categories, which are: (1) dimensionality (2-D, 3-D), (2) transformation domain (*local* and *global*), (3) transformation type (*rigid*, *affine*, *projective*, and *non-linear*), (4) tightness of feature coupling (*interpolating* i.e. the features of objects in one image are exactly transformed into features in the other one and *approximating* i.e. a non-zero fitting error appears, spread over the overlaid features as a result of least square fitting), (5) measure of the registration quality i.e. applying measures that can be derived from the data or the data themselves e.g. quadratic mean distance and the maximum distance, (6) method of parameter determination (*directly computed* and *searched*), (7) subject (*intra-subject* and *inter-subject*), (7) data type (*raw data* i.e. raw pixels or voxels, *features of data* i.e. edges, or blobs, and *markers on data* i.e. data introduced

to the original data, for example manually marked pixels), (9) source of features (*intrinsic* and *extrinsic*), (10) automation level (*automatic* and *semi-automatic*).

A more comprehensive method of classification was proposed by Maintz et. al. in [14]; it augmented the classification by van den Elsen et.al. in [13]. Maintz's classification is more extensive than the classification by Chmielewski as the cases in each of the category cover more cases than the ones in [27]. The classification in [14] was defined as the Nine Basic criteria which are: (1) Dimensionality (*spatial* and *spatial with time series*), (2) Nature of registration (*extrinsic*, *intrinsic*, and *non-image based* i.e. involves calibration of the scanners), (3) Nature of transformation (*rigid*, *affine*, *projective* and *curved*), (4) Domain of transformation (*local* and *global*), (5) Interaction (*automatic* i.e. user only supplies the algorithm, image data and possibly information on the image acquisition, *semi-automatic* i.e. the user needs to initialize the algorithm by segmenting the data or steer the algorithm by rejecting or accepting suggested registration hypotheses and *interactive* i.e. the user does the registration manually, assisted by software supplying a visual or numerical impression of the current transformation and/or an initial transformation guess), (6) Optimization procedure (*directly computed* or *searched for* parameter), (7) modalities involved (*monomodal*, *multimodal*, *modality to model* and *patient to modality* registration), (8) Subject (*intra-subject* i.e. the registered images from a single patient, *inter-subject* i.e. the registered images from different patients, and *atlas* i.e. registration from patient to database images), (9) Object e.g. brain, skull, eye, dental, thorax.

2.3 Validation of Registration

Validation is required to assess the performance of a registration method. Validation could involve many aspects [14]: (1) robustness/stability i.e. the stability of the method in response to variations, (2) reliability i.e. the method should be able to work given the reasonable inputs, (3) resource requirements i.e. the material and effort involved in the registration process, (4) algorithm complexity i.e. clinical consideration regarding time and resource constraints, (5) assumption verification i.e. verifications of the assumptions used in the algorithm into real practice, (6) clinical use i.e. the assessment of the method in terms of need and comparison to other

available techniques, (7) precision i.e. systematic error that is introduced when the registration algorithm is supplied with idealized input; precision is a system property, and (8) accuracy i.e. actual, “true” error occurring at a specific image location; it applies in a practical scenario and occurs at a registration instance.

A method of accuracy validation was presented by Fitzpatrick in [28]; it was a project by Vanderbilt University, a project for the evaluation of image registration between prospective and retrospective registration methods. Prospective registration is the one using fiducial markers, whereas retrospective registration is the one involving the matching of intrinsic features or maximizing voxel similarity. The accuracy measurement was carried out using a “gold standard”. Gold standard refers to a method that was acknowledged to have highest accuracy among other methods. In the experiment [28], the gold standard was achieved using stereotactic frame screwed rigidly to the patient’s outer skull table; the frame is imageable in CT and MRI. The registration methods to be validated were compared with the gold standard. The measures of accuracy were: FRE (Fiducial Registration Error) and TRE (Target Registration Error). FRE is defined as “*the distance between corresponding fiducials after registration and transformation*”, whereas TRE is defined as “*the distance between corresponding points other than those used to estimate the transformation parameters*” [8]. The FRE and TRE values of the validated registration methods were compared to the ones of the gold standard. It was found that the best retrospective registration method was *Mutual Information Based Registration*.

2.4 Discussions

2.4.1 Requirement Analysis of NeuroBot Image Registration

An image registration algorithm was required to be developed in the NeuroBot system. Thus, the requirements for the registration system of the NeuroBot governed the development of the algorithm. The requirements of the image registration for the NeuroBot are listed in Table 2.1. Additional information on the currently available registration system, physical space to image space registration of NeuroBot, is listed in the third column of Table 2.1 for reference purpose as some of the information is needed for discussion in this section.

Image registration in the NeuroBot is used to align the volume information of the patient's head obtained from the medical imaging scans. The modality of the scans could be single or multiple modality involving MRI, CT and MRA as it is used to combine the information of the skull bone (from CT image), lesion, brain matter (from the MR image), and blood vessel (from MRA image). The dimensionality of registration required by the NeuroBot is 3-D. Thus, based on the modality and dimensionality involved, multimodal 3-D to 3-D image registration was chosen. A range of registration speed of 2-3 minutes is expected, considering the speed of Dextroscope registration.

Table 2.1: Requirements for the Image Registration of the NeuroBot.

No.	Image Registration (Image to image registration) Requirements	Current available registration system: Physical to Image Registration	Intended Specification of Image to Image Registration System
1	Image dimensionality	3-D (image) to 3-D (physical space)	3-D to 3-D (volume to volume images)
2	Image modality	CT of hexagonal phantom made of acrylic	CT, MRI, MRA
3	Processing Time	<1 min (the marker based method applies direct calculation of parameters, low computational complexity)	2-3 minutes
4	Usage	Intra-operative	Pre-operative planning
5	Accuracy	0.1112 mm (TRE) [29]	Sub-voxel accuracy
6	Features of registration	Marker-based (invasive, extrinsic)	Voxel-based (intrinsic)
7	User Interaction	Interactive	Automatic / interactive

Based on the nature of registration, there are three options to select from: extrinsic, intrinsic and non-image based methods. Non-image based method is suitable for registration system in intra-operative use. Image registration system of NeuroBot is to be used in the preoperative planning stage of a surgery. It hence does not need to be a non-image based registration method. The non-image option is thus dropped.

Accuracy is the most important requirement in NeuroBot's registration. Image to physical space registration is directly related to the operating theatre environment (physical space); whereas image to image registration is indirectly related to the physical space as it only deals with image space. Hence, the accuracy of image to

physical space registration is dependant on the measure in physical space, whereas image registration is dependant on voxel size, the smallest unit in the image space. Thus, the accuracy expected is less than the size of one voxel i.e. sub-voxel accuracy.

The user of the registration system would be a surgeon. It was intended that the surgeon could be relieved from complicated technical matters such as requiring the surgeon to perform segmentation or other image preprocessing prior to the registration which is required in semi-automatic method. Thus, an automatic or interactive image registration method is expected. An automatic method only requires the user to input the images and minimum information regarding the image, such as acquisition mode, to produce the result; whereas an interactive method requires the user to supply an initial transformation guess in addition to the images and some related information such as acquisition method. Keeping technical matters as minimum as possible from the user in performing image registration would not affect the flexibility of control and operation of the robotic system as image registration is basically only one of the tasks of the NeuroBot system, yet very important, of the overall tasks of the robotic system; it only performs image alignment. Being only a small task, image registration is simplified by developing it in automatic mode.

Currently, the physical to image registration system used by the NeuroBot is of marker based method in which a reference frame is used to relate between image space and physical space. A set of fiducial markers are screwed onto the patient's head to serve as the frame; it is hence invasive and extrinsic. It is expected that, in the future, the marker-based method of physical to image registration system would be replaced to a non-invasive method, so as not to add complication, such as bacterial infection, to the patient. Therefore, the image registration technique is also expected to support the change. Another extrinsic technique, non-invasive marker e.g. skin marker, is also possible. However, the use of non-invasive markers violates the accuracy requirement as non-invasive marker-based method has low accuracy. Thus, an ideal option for this problem is an intrinsic-based registration technique with high accuracy, as it would be non-invasive and be able to fulfill the accuracy requirement.

The search for a solution to fulfill all the requirements of the NeuroBot's image registration was then directed towards the intrinsic method. In a recent comparative study [8], [9], as many as 16 retrospective registration methods from 12 research groups worldwide were evaluated; the results showed that two methods based on mutual information (MI) outperformed the accuracy of all other methods and achieved approximately the same order of accuracy as the gold standard method i.e. stereotactic frame – based method. This fact indicated a potential solution for the search of a suitable method for NeuroBot. The stereotactic frame – based method, an extrinsic and invasive method, belongs to frame-based method. The method is comparable to the current method used in the physical space to image space registration of NeuroBot. As MI was proven to achieve the accuracy comparable to the gold standard [8], [9]. MI technique is expected to consequently outperform the accuracy of, or comparable to the accuracy achieved in other extrinsic and invasive methods including the screwed fiducial marker – based method used by NeuroBot.

However, MI method is computationally expensive as it involves plenty of iterations for its optimization part. The advancement of processor technology and capacity of internal memory could help solving this problem. Thus, it was decided to use the mutual-information based registration when applied to the NeuroBot system.

2.4.2 Mutual-Information Based Registration Techniques for the NeuroBot

The image registration method being developed in this project adopted the Mutual Information-based technique for registering 3-D to 3-D images. The requirements for the MI-based technique being implemented are listed in Table 2.2. The listed requirements are only general and qualitative; more technical aspects on the technique are presented in section 3.7.

For this stage, the imaging modality used in this application was MR, yet it involved different acquisition techniques which are proton density (PD) and T2 relaxation time. As this project has not had produced its own datasets on a human head, an outside resource was used. The datasets for this project were obtained from outside resource that provides free image datasets for medical image processing purpose. The resource provides datasets on human head by MRI scan; with the acquisition

mode of Proton Density (PD), T1 and T2. A combination of PD and T2 mode was chosen as it is expected to represent different grey value distributions. Other combinations are also possible, yet they could be reserved for future experiments. The details on the datasets being used in this project are presented in section 4.3.1. Although only MRI images were used in this project, a model of multimodal images was developed from the MRI images. The model was used to predict the applicability of the registration method being developed to multimodal images; as the model is still considered single modal images i.e. MRI. The verification of the model using real multimodal image sets would be reserved for future work. The model is developed by combining images of different gray value distribution (different acquisition-modes, PD and T2) and of different resolution.

Table 2.2: Requirements of MI-based Registration Techniques for NeuroBot.

No	Requirements	Current (developed in this project)	Intended (to be developed in the future)
1	Image Dimensionality	3-D to 3-D	3-D to 3-D
2	Image Modality	MRI (PD and T2 acquisition modes)	CT, MRI, MRA
3	Type of Transformation	Rigid Transformation	Rigid Transformation
4	Domain of Transformation	Global	Global
5	User Interaction	Automatic/interactive	Automatic/interactive
6	Optimization procedure	Searched for (iterative method)	Searched for (iterative method)

Among the available type of transformations: rigid, affine, projective, and curved, the transformation required in this registration application is rigid transformation, i.e. rotations and translations are allowed. It was chosen based on the assumption that the imaged brain is not deformed; as the brain is an enclosed object inside the skull and there was no intervention performed on the brain i.e. craniotomy and opening of dura mater. In that case, the intracranial pressure within the brain would be preserved and no brain deformation would have happened during the image acquisition. Thus, the use of rigid transformation was considered sufficient. The imaged regions involved in the image registration application are the global image area. An iterative method was employed to search for the optimum alignment parameters.

As discussed in the previous section, the image registration application was intended to be an automatic or interactive application so that it could minimize the complexity of operating it by the surgeon. The application was developed in two stages: the investigation and the improvement stages. In the initial stage i.e. investigation stage,

several times of tuning of parameters were required, hence the application used interactive method of interaction. The user still needed to input the initial guesses and certain parameters such as parameter scale, number of levels, and step length to the algorithm. However, in the following stage i.e. improvement stage, the application was improved towards the automatic method where only the images being registered were needed as the input. The technique resulted in the improvement stage is going to be implemented in the NeuroBot system.

A validation technique was employed to assess the registration algorithm performance in terms of speed and accuracy. In this case, as there were no fiducial markers used, the gold standard approach i.e. fiducial marker-based registration could not be employed to compare the results to obtain FRE, or TRE values. Instead, the results would be validated by comparing the spatial transformation results obtained from the registration process with the true value of the transformation employed to the images. The images being registered were transformed with a predefined value of transformation which involves rotation and translation. Upon registration, the images were expected to be aligned back, which implied that the transformation results obtained from the registration process should be similar to the transformation applied.

Thus, in this project, an image registration method as discussed in section 2.4 was developed. Basic concepts of the image registration discussed in section 2.1 and the classification of registration methods discussed in section 2.2 serve as the basis for the requirement analysis of NeuroBot's image registration system as discussed in section 2.4.1. Finally, in section 2.4.2, more specific requirements pertaining to the MI method for the NeuroBot's image registration system and the method for validation were discussed.

CHAPTER 3

MUTUAL-INFORMATION-BASED REGISTRATION

This chapter elaborates the concepts of the Mutual-Information-Based (MIB) registration technique comprising of the concepts of entropy, the concept of Mutual Information, variation of techniques in MIB and acceleration techniques. A review of MIB techniques developed by other researchers is also represented. It is concluded with a discussion on the selection of MIB techniques for the NeuroBot.

3.1. Introduction

Mutual-Information-Based (MIB) registration is a method classified under voxel property-based registration. The voxel property-based registration operates directly on the image grey values without the need to apply prior data reduction by the user or segmentation [14].

The idea of MIB was originated by Collignon and colleagues in 1994, by suggesting the use of entropy as a measure of registration [30]. Currently, this method has been commonly used in many clinical applications [31]. The definition on the entropy is elaborated in section 3.2.

Among the advantages of this method are the comparative ease of matching intensity images across modalities and the ability to discard intensity patterns in either modality that are not relevant to registration [32].

3.2. Entropy Concept

In MIB registration method, ‘Entropy’ is the measure for the registration. The term ‘Entropy’, was originated from communication theory, was basically *a measure of information* of a message [31].

The first definition of ‘Entropy’ was formulated by Hartley [33] in 1928. He defined entropy H as:

$$H = n \log s = \log s^n \quad (3.1)$$

where n is the number of symbols used in a message, and s the number of possibilities for each symbol. A message could be regarded as a string of symbols. If the message consists of n symbols, and each symbol has s different possibilities, there would be s^n different message possible (assumption: there are no syntactic rules). Hence, Hartley’s information measure depends on the number of possible outcomes: the larger the number of possible messages, the larger the amount of information that could be obtained from a certain message [31]. However, if there is only a single message possible, there is no gained information ($\log 1=0$) from it, as somebody would have known that he would receive the message. In this case, the measure could also be regarded as the measure of *uncertainty*. When there are more than one different messages that somebody could possibly receive, the person would be more uncertain about which message that the person would actually receive. Yet, if there is only one, there would be no uncertainty. A limitation of Hartley’s measure is the assumption that all symbols have equal possibilities to occur, which is not always the case.

The drawback was then corrected in 1948 by Shannon who introduced *Shannon entropy* [31] which weights the information per outcome by the probability of that occurring. Shannon entropy is defined as

$$H = \sum_i p_i \log \frac{1}{p_i} = -\sum_i p_i \log p_i \quad (3.2)$$

with events $e_1, \dots, e_m$ occurring with probabilities $p_1, \dots, p_m$.

The application of the Shannon entropy for an image, in which, instead of focusing on the probabilities of symbols occurring, it is on the distribution of the grey values of the image. The probability distribution of grey values can be estimated by counting the number of times each grey value occurs in the image and dividing those numbers by the total number of occurrences. An image with almost a single intensity will have a low entropy value which also means that it contains very little

information. A high entropy value will be yielded by an image with more or less equal quantities of many different intensities, which is an image containing a lot of information.

Thus, entropy has three interpretations which are “(1) the amount of information an event (message, grey value of a point) gives when it takes place, (2) the uncertainty about the outcome of an event, and (3) the dispersion of the probabilities with which the events take place [31].”

3.3. Mutual Information

A. Definition

The definition of the “Mutual information”, MI, could be presented in various ways. In [31] there are 3 definitions of MI, $I(A,B)$, which are:

- (1). Given two images A and B, I can be defined as

$$I(A,B) = H(B) - H(B|A) \quad (3.3)$$

where $H(B)$ is the Shannon entropy of image B, computed on the probability distribution of the grey values. $H(B|A)$ indicates the conditional entropy, which is defined that based on the conditional probabilities $p(b|a)$, the probability of grey value b in image B given that the corresponding voxel in A has grey value a. In other words, in uncertainty context of entropy, equation (3.3) translates “the amount of uncertainty about image B minus the uncertainty about B when A is known.”

In other words, MI is the amount by which the uncertainty about B decreases when A is given: the amount of information A contains about B. $I(A,B)$ also means the amount of information B contains about A, as it is *mutual* information.

Registration is assumed to correspond to maximizing mutual information: the images have to be aligned in such a manner that the amount of information they contain about each other is maximum.

(2). A definition that is closely related to joint entropy:

$$I(A,B) = H(A) + H(B) - H(A,B) \quad (3.4)$$

The term $-H(A,B)$ means that maximizing mutual information is related to minimizing joint entropy.

(3). The definition related to the Kullback-Leibler distance, which is defined as

$$\sum_i p(i) \log (p(i)/q(i)),$$

for two distributions p and q . It is a measure of the distance between two distributions. Analogues to the Kullback-Leibler measure, the mutual information of images A and B is defined as

$$I(A, B) = \sum_{a,b} p(a, b) \log \frac{p(a, b)}{p(a)p(b)} \quad (3.5)$$

The interpretation of this definition is that it measures the distance between the joint distribution of the images' grey values $p(a,b)$ and the joint distribution of the images, $p(a)p(b)$. It is a measure of *dependence* between two images.

B. Properties

The properties of the mutual information [34] are:

Independence:	$I(A, B) = 0 \Leftrightarrow p_{AB}(a, b) = p_A(a) \cdot p_B(b)$
Symmetry:	$I(A, B) = I(B, A)$
Self information:	$I(A, A) = H(A)$
Lower bound:	$I(A, B) \geq 0$
Upper bound:	$ \begin{aligned} I(A, B) &\leq \min(H(A), H(B)) \\ &\leq (H(A) + H(B))/2 \\ &\leq \max(H(A), H(B)) \\ &\leq H(A, B) \\ &\leq H(A) + H(B) \end{aligned} $
Data processing:	$I(A, B) \geq I(A, T(B))$

C. MI Registration Method and Criterion

The generic method of MIB registration is illustrated as a flowchart in Figure 3.1. As described in [35], let $p_A(a)$ be the marginal probability function of *fixed image*, or also normally called *reference image*, $p_B(b)$ the marginal probability function of

moving image, or can also be called *test image*, and $p_{AB}(a,b)$ the joint probability function of geometrically related voxels in *fixed* and *moving images*. The geometric relation that maps the moving image into the fixed image is denoted by T . The effect of applying the geometric transformation T to the moving image will change the joint probability function $p_{AB}(a,b)$. On the other hand, the reference image's marginal probability function, $p_A(a)$, is not affected, and $p_B(b)$ may suffer slight changes due to test image interpolation [35]. MI of both images upon the transformation, $I(A,B \circ T)$, is then calculated once for each geometric transformation, T , until registration is achieved. The registration criterion states that if the images are geometrically aligned, the value of MI is maximum.

Registration criterion:

$$I(A, B \circ T)_{\max} = I(A, B \circ T^*) \quad (3.6)$$

where T^* stands for the optimal registration transformation.

Figure 3.1. Flowchart of Mutual Information Based Registration Process.

3.4. Variations of Techniques

The variations of techniques in MIB arise due to the variations of techniques to approach the problem in each stage of the registration steps.

A. Density Function Estimation Techniques

The first step of the algorithm (refer to Figure 3.1), is to determine the entropy and density function of the images being registered. However, in a typical registration problem, direct access to the probability densities information is not available and hence they have to be estimated from the image data. In this case, there are several techniques available, such as:

Parzen Window Technique:

This technique [36] calculates the probability density function using Parzen window density estimation, i.e. superposition of function centered on the elements of a sample A drawn from the image z.

$$P(x) \approx p^*(z) \equiv \frac{1}{N_A} \sum_{z_j \in A} R(z - z_j) \quad (3.7)$$

where, N_A is the number of trials in the sample A, R is a window function which integrates to 1 and is generally assumed to be Gaussian.

For the MI, it calculates the $I(X,Y)$ based on Equation 3.4. The entropy is calculated using Viola's equation:

$$h(z) \approx -\frac{1}{N_B} \sum_{z_i \in B} \ln p^*(z_i) \quad (3.8)$$

where N_B is the number of trials in the second sample B.

Frequency Histogram Technique:

This technique was presented by Collignon [36]. It calculates the density function using the equation:

$$p(x, y) = \frac{1}{N} h(x, y) \quad (3.9)$$

where N is the number of samples.

It then calculates the mutual information I using Equation 3.5:

$$I(X, Y) = \sum_{x, y} p(x, y) \log \frac{p(x, y)}{p(x)p(y)} \quad (3.10)$$

where $p(x)$, $p(y)$ are marginal density.

B. Interpolation Techniques

After determining the density function p , the subsequent step is to apply transformation on the moving image. Upon transforming, the grid points of the moving image will not necessarily coincide with the grid points of the fixed image. Therefore, it requires the use of an interpolation algorithm to determine the moving image values at fixed image grid positions. Several methods of interpolations have been used in registration [34], such as: nearest neighbor (NN) interpolation, trilinear interpolation, partial volume interpolation (PV), and tri-linear partial intensity (PI) distribution interpolation.

NN method interpolates the mapped pixel value of the moving image upon the transformation by T , $T_\alpha s$, to the nearest point grid in the fixed (or reference) image. As illustrated in Figure 3.2, $r(T_\alpha s)$, the intensity value of a point from the moving image s mapped by transformation T to the fixed image grid, is equal to the intensity value of the nearest point grid in the fixed image i.e. point n_3 . NN interpolation generally is insufficient to guarantee sub-voxel accuracy, as it is insensitive to translation up to one voxel.

$$r(T_\alpha s) = r(n_3) \quad (3.11)$$

Figure 3.2. Nearest Neighbor Interpolation. Adapted from [34].

Tri-linear interpolation method, or also named as linear interpolation [9], uses weighted average of a grid area to interpolate the mapped pixel $T_\alpha s$. Figure 3.3 illustrates the tri-linear interpolation method; the mapped pixel value is interpolated using the weight w_i obtained based on the percentage of the quadrant area within a grid area; the summation of the weight w_i is one. However, tri-linear interpolation

may introduce new intensity values which have originally not existed in the fixed image leading to unpredictable changes in the marginal distribution of the fixed image for small variation of transformation T ; hence an alternative approach namely tri-linear partial volume distribution (PVI) interpolation was proposed in [30], [37]. PVI is not an interpolation method in the sense that it can be used to create and interpolate image. Yet, it is specifically designed to update the joint histogram of two images. Like linear interpolation, PVI also uses the weighted average w_i . However, instead of calculating a weighted average of the neighboring grey values, it updates the histogram entries of the neighbor points n_i ; hence, no new intensity values are created. Another interpolation method that also updates the joint histogram is tri-linear partial distribution (PI) interpolation. It computes the image intensity value by tri-linear interpolation and contribution of the sample to the joint histogram over the bins [34].

$$\begin{aligned} r(T_\alpha s) &= \sum_i w_i \cdot r(n_i) \\ \sum_i w_i \cdot (T_\alpha s) &= 1 \end{aligned}$$

Figure 3.3. Trilinear or linear interpolation. Adapted from [34].

C. Mutual Information Measure Techniques

Once the distribution been interpolated, the MI measure is to be calculated. There are several variation of techniques to calculate Mutual Information $I(A,B)$, which are:

Mutual Information – Joint Entropy Concept

The MI measure by entropy concept is the original version of MI. It is calculated based on formula in Equation 3.3 and 3.4. Given two discrete random variables A and B (i.e. image A and B), the MI is calculated as [34]:

$$\begin{aligned} I(A,B) &= H(A) + H(B) - H(A,B) \\ &= H(A) - H(A|B) \\ &= H(B) - H(B|A) \end{aligned}$$

with $H(A)$ and $H(B)$ being the entropy of A and B respectively, $H(A,B)$ their joint entropy, and $H(A|B)$ and $H(B|A)$ the conditional entropy of A given B and of B given A [34]. $H(A)$, $H(A|B)$, and $H(A,B)$ defined as:

$$H(A) = -\sum_a p_A(a) \log p_A(a) \quad (3.12)$$

$$H(A|B) = -\sum_{a,b} p_{AB}(a,b) \log p_{A|B=b}(a) \quad (3.13)$$

$$H(A,B) = -\sum_{a,b} p_{AB}(a,b) \log p_{AB}(a,b) \quad (3.14)$$

with $p_{A|B=b}(a)$ the conditional probability of A given $B = b$; $p_A(a)$ and $p_B(b)$ are the marginal probability distribution of A and B respectively; $p_{AB}(a,b)$ is the joint probability distribution of A and B .

Mutual Information – Kullback Liebler distance

It calculates the MI based on Kullback Liebler distance formula in Equation 3.5.

Normalized Mutual Information (NMI):

From the definition of mutual information it follows that a high MI value correlates to a low joint entropy value. Low entropy, in turn, means a crisp joint probability distribution and therefore alignment of the images.

Since the joint histogram and therefore the probability distributions are computed only for the overlapping part of the images, another MI measures have been proposed by Studholme [38]:

$$NMI(A, B) = \frac{H(A, B)}{H(A) + H(B)} \quad (3.15)$$

where $H(A)$, $H(B)$, $H(A,B)$ represents entropy of A , B , and joint entropy of A and B respectively.

Entropy Correlation Coefficient (ECC):

Normalized mutual information was also proposed by Maes [39]. It represents a measure of mutual information as ECC, a measure quite similar to NMI.

$$ECC(A, B) = \frac{2.I(A, B)}{H(A) + H(B)} \quad (3.16)$$

where $H(A)$, $H(B)$ represents entropy of A and B , and $I(A,B)$ represents mutual information between A and B .

Multimodal MI:

MI for multimodality is:

$$I(A,B,C) = H(A) + H(B) + H(C) - H(A,B,C) \quad (3.17)$$

where $H(A)$, $H(B)$, $H(C)$ represents entropy of A , B , and C , $H(A,B,C)$ represents joint entropy between A,B,C , whereas $I(A,B,C)$ represents mutual information between A , B , and C .

D. Optimization Techniques

If the MI value has not been maximized in the current iteration, the next step is to search for the next transformation T . The search for T is an optimization problem. There are several optimization techniques used in registration. There are methods that do not require function derivatives, in this case is of MI function, such as: Powell and Simplex methods. The ones that require derivatives are such as: gradient ascent, gradient descent, quasi-Newton, and Levenberg-Marquardt.

Powell Optimization

Given an N -dimensional search space, Powell's method performs one-dimensional optimization for each of the n dimension. The method finds the N -dimensional optimum values of a function by repeatedly optimizing the function in one dimension along a set of N different directions in turn. Each time, it starts from the optimum point found in the previous direction using a one-dimensional line minimization method as presented in Brent's [40]. The set of directions are initialized with the basis vector in each dimension in parameter space, yet after every iteration in which all directions in the set are optimized over, the overall distance moved in parameter space in that iteration is taken as a new direction.

The limitation of Powell method is that it is relatively sensitive to local optima in the registration function [31]. Powell – Brent optimization in 2-D is illustrated in Figure 3.4. D_0 is the initial direction for the first iteration i.e. basis vector in x_1 and x_2 directions; the subsequent iteration uses the overall distance moved from the

previous iteration as the new direction i.e. D1. Powell method is a popular method as it does not require gradient information and few numbers of evaluations are required [31]. Hence, it makes Powell's method relatively computationally inexpensive compared to those with derivative requiring methods.

Figure 3.4 Powell – Brent Optimization in 2-dimension parameter space. Adapted from [41].

Gradient Descent Optimization

Gradient descent optimization is performed based on the formula [41]:

$$p_{n+1} = p_n + \text{learningRate} \frac{\partial f(p_n)}{\partial (p_n)}$$

The step of the optimization process is determined by the learning rate and the gradient, which is represented as:

$$\text{step} = \text{learningRate} \cdot \frac{\partial f(p_n)}{\partial p_n}$$

$$\text{where } \frac{\partial f(p_n)}{\partial p_n} \text{ indicates the function's gradient.}$$

The optimization process using gradient descent method is depicted in Figure 3.5. The difficulty in using this method is in determining the optimum learning rate. Too large or too short learning rate will cause longer time to arrive at the optimum point as illustrated in Figure 3.6 (a) and (b). However, this limitation is solved by a variant of this method which is regular step gradient descent method which will be described in Section 4.2.4.

Figure 3.5. Optimization process using gradient descent method. Adapted from [42].

(a) Too large learning rate

(b) Too small learning rate.

Figure 3.6. Effect of learning rate in gradient descent optimization. Adapted from [42].

3.5 Acceleration Techniques

MI-based registration is a computationally costly process especially when it involves large size image volumes (images with the size more than $512 \times 512 \times 512$ voxels). Several techniques have been employed to accelerate the process. Multi-resolution schemes were often implemented to improve the speed as well as the behavior of a registration method with respect to local optima problem [43]. In multi-resolution scheme, a rough estimate of registration is found in relatively short time using down-sampled images, which is subsequently refined using the image of increasing resolution. The registration at finer resolution would be faster as a result of the initial estimate provided by the previous level of resolution. Several techniques replace costly calculations by using look up tables. In [44], a look up table is used to avoid computations for the weights of interpolation. Look up table is used in [45] to speed up the Parzen windowing process for the Gaussian functions.

3.6 Review on the Implementation of Optimization Techniques in MI-based Registration

Registration could be seen as an optimization problem (refer to elaboration in section 3.3.C and Appendix A.2). Hence, one of the affecting factors to the performance of the registration techniques is the optimization methods. This section aims to present a brief summary of some works by other researchers on the implementation of various optimization techniques in their MI-based registration methods. Several techniques implemented multi-resolution scheme in their optimization process. This mainly aims to solve the local optima problem (i.e. improve the robustness) and increase the registration speed.

There are groups of optimization methods that require gradient information of the function being optimized (gradient-based optimization techniques) and the ones that do not require gradient information (non-gradient-based optimization techniques). Optimization techniques that require gradient information are such as gradient ascent, gradient descent, Levenberg-Marquardt, Quasi-Newton; whereas the ones not requiring gradient are such as Powell and Simplex methods.

Powell optimization method was found as a popular method being used in MI-based registration. Its implementation could be found in: [37], [46], [47], [48], [49] and [50]. Implementation of Powell optimization in multi-resolution scheme could also be found in: [43], [51].

Simplex method, another non-requiring-gradient method, was implemented in [52], [53], [47]. In [47], its performance was compared with the one in Powell optimization method. Its implementation with multi-resolution scheme was found in [43]. Levenberg-Marquardt method was implemented in [43], [54]. In [55], the method was derived to specifically for use in MI registration. Its implementation in multi-resolution scheme was found in [43]. Quasi-Newton method was implemented in [56], and its implementation in multi-resolution scheme was found in [43] and [56]. Other techniques, gradient ascent was found in [57], whereas gradient descent had been implemented in [58]. Combination of optimization methods, which mostly involve Powell method, were also found in several publications: Powell and Simplex

[59]; Powell and genetic algorithm [60], Powell with topographical global optimization [61]; these combined optimization method were performed on a single resolution scheme. In [59], the technique was used to register 2-D/2-D images. The techniques in [60] and [61] combined global optimization technique, that is performed first to limit the optimization search space, and local optimization technique, that continues the optimization process within the search space found in the first step. Comparison of several optimization methods with multi-resolution scheme was presented in [43]; the comparison study showed that Powell's method performed the best for full resolution image registration, whereas Simplex, conjugate-gradient or Levenberg-Marquardt were the most efficient for two-level multi-resolution.

3.7. Discussions on Selection of Techniques in Mutual Information for NeuroBot Image Registration

A technique of MI-based registration was adopted and investigated for the NeuroBot. The discussion in this section focuses on the technical aspects of the MI method; the general aspects had been discussed in section 2.4. Specific technical details that are dependant on the image processing library i.e. ITK would be discussed in the design of algorithm sections in chapter 4 and 6. Table 3.1 presents the summary of MI aspects for the NeuroBot image registration.

Among three MI measures: joint entropy concept, Normalized Mutual Information (NMI) and Entropy Correlation Coefficient (ECC), joint entropy concept is the computationally cheapest measure. This is seen in the formulae of the respective MI measures in Table 3.1. The calculation of MI in joint entropy concept involves simpler arithmetic operations which are summation and subtraction of entropy measure H compared to NMI that involves summation and division. Division and multiplication operations are more complex than summation and subtraction in the microprocessor. The most computationally costly measure among the three is ECC as it involves the computation of mutual information, I , inside its equation in addition to division with summation of entropy H .

MI measures of joint entropy and Kullback Liebler distance concepts are equally popular methods in image registration [14]. Both methods were then considered for NeuroBot image registration. In terms of computational complexity, joint entropy concept might be slightly more costly than Kullback Liebler distance; joint entropy measure involves more logarithmic and multiplication operations than Kullback Liebler. However, joint entropy is more closely related to the original concept of entropy in information theory. Kullback Liebler distance measure is closer to statistical concept [31]; it is based on the measure of the distance between two distributions. Hence to keep the context of MI registration closer to its original concept which is the information theory, joint entropy concept was chosen.

Table 3.1: Summary of MI Aspects for the NeuroBot Image Registration.

No.	Aspects	Available Techniques	Selected Technique
1	MI measure	Joint Entropy concept $I(A,B)=H(A)+H(B)-H(A,B)$	Joint Entropy Concept
		Kullback Liebler distance $I(A, B) = \sum_{a,b} p(a, b) \log \frac{p(a, b)}{p(a)p(b)}$	
		Normalized Mutual Information (NMI) $NMI(A, B) = \frac{H(A, B)}{H(A) + H(B)}$	
		Entropy Correlation Coefficient (ECC) $ECC(A, B) = \frac{2.I(A, B)}{H(A) + H(B)}$	
2	Density Function Estimation	Parzen Windowing	Parzen Windowing
		Frequency Histogram	
3	Interpolation	Nearest Neighbor interpolation	Trilinear interpolation
		Trilinear interpolation	
		Partial Volume (PV) interpolation	
		Tri-linear Partial Intensity (PI)	
4	Transformation	Rigid	Rigid
		Affine	
		Projective	
		Curved	
5	Optimization	Non-gradient-based e.g. Powell, Simplex.	Powell's and Conjugate gradient or Levenberg-Marquardt methods.
		Gradient-based e.g. gradient ascent, gradient descent, etc.	
6	Acceleration Techniques	Multi-resolution scheme	Multi-resolution scheme
		Look up table for interpolation	
		Look up table for Parzen Windowing	

The density function estimation is related to MI measure. Hence, the selection of density function depends on the choice of MI measure. Parzen window technique is suitable for MI measure of joint entropy concept, whereas frequency histogram is for Kullback Liebler distance measure, as elaborated in section 3.4.A. Thus, Parzen window technique was chosen.

Among four methods of interpolation: nearest neighbor (NN), tri-linear, partial volume (PV), and partial interpolation distribution (PI), tri-linear was selected. NN is the simplest among all; however, it is insufficient to guarantee sub-voxel accuracy. PV and PI methods do not really interpolate the images, instead, they update the joint histogram of the images. As the MI measure does not use frequency histogram technique, these interpolation techniques are not suitable. Thus, tri-linear was chosen.

There were several factors to be considered for improving registration performance. In this project, improvements were focused on the speed and accuracy. As registration process can be seen as an optimization process, the implementation of optimization method is an important factor to the registration performance. In addition, multi-resolution scheme was proven to improve the robustness and speed of registration. Thus, the combinations of optimization methods and multi-resolution scheme were chosen to be investigated for their effect in registration performance. Thereafter, based on the investigation, an improved technique was then proposed and implemented. The technique could then be combined with other acceleration techniques proposed by other researchers such as the use of look-up-table for interpolation and Parzen window techniques for future work.

In this project, it was intended to investigate the performance of both gradient-based and non-gradient-based optimization techniques separately, then assessing the possibility of combining both techniques to improve registration performance. Thus, two optimization methods, each representing gradient-based and non-gradient-based techniques were chosen.

Powell's optimization, a non-gradient-based technique, is a popular technique implemented in image registration, and it yielded the optimum result in a

comparative study presented in [43]. However, in multi-resolution registration, Conjugate gradient and Levenberg-Marquardt, of gradient-based technique outperformed Powell's method [43]. Thus, it was decided to adopt Powell's technique, a non-gradient technique, and conjugate gradient or Levenberg-Marquardt, a gradient technique.

In this project, the optimization techniques were implemented and investigated separately in multi-resolution scheme of MI-based image registration. Thereafter, both techniques were combined; the performance was then investigated and compared with the ones of separate implementations of the optimization methods. Based on the author's review, a registration technique combining Powell's method with gradient-based method in multi-resolution scheme had not been found. The combination of optimization methods mentioned in [59] was different from the one being developed in this project; they differ in terms of the type of the optimization methods being combined (technique in [59] combined two non-gradient methods), and their image dimensionality (technique in [59] was applied to 2-D/2-D images). The techniques used in [60] and [61] are also different from the one in this project. One of the optimization techniques being combined in [60] and [61] was neither from gradient nor non-gradient based optimization techniques. This project focused on investigating the combination of gradient and non-gradient based optimization techniques. Thus, the combination between Powell's and gradient-based optimization methods in registration application might be the novelty of this project.

CHAPTER 4

MULTI-RESOLUTION MI-BASED REGISTRATION ALGORITHMS AND EXPERIMENTS

This chapter presents the design of the algorithms of the multi-resolution MI-based registration as well as the design of the investigation experiments. It begins with a brief introduction encompassing the summary of the requirement analysis for the selection of techniques for the NeuroBot system from the previous chapters, followed by the design of the registration algorithms for use in the investigation stage. Subsequently, the datasets specifications being used in the investigation as well as the error calculation method are presented. Eventually, the design of experiments is elaborated; it is started by enlisting the investigated factors, followed by the elaboration on the procedures and concepts of every experiment.

4.1 Image Registration Technique for the NeuroBot

In this project, an image registration technique for NeuroBot system was developed. The requirement analysis of the NeuroBot image registration system presented in section 2.4.1 concluded that MI-based technique is suitable for the NeuroBot system. General aspects of the MI-based registration for the NeuroBot were presented in section 2.4.2, whereas the technical aspects of the MI technique were discussed in section 3.7.

The method being developed in this project would be the first version of the image registration application for the NeuroBot, hence the outcome of this project would be used as a ground work for the development of the registration application in the future. The project consisted of two stages: investigation and improvement stages. In the first stage, investigation, two algorithms based on the specifications elaborated in section 3.7 were developed. Both algorithms differed by their optimization techniques: Powell's and Regular Step Gradient Descent (RSGD) techniques.

Investigation was carried out to assess the performance of the algorithms with respect to the variations of several factors which are: the optimization methods, properties of multi-resolution scheme coupled with the optimization method, properties of transformation, and the types of the acquisition-modes of the images being registered. Accuracy and speed were used as the measures of the performance.

In the second stage, improvement, algorithms having combination of two optimization methods, Powell and RSGD with multi-resolution scheme were developed and investigated.

4.2 Design of Registration Algorithm

Registration algorithms being implemented in this project were developed using ITK (stands for the Insight Toolkit) an open-source software toolkit for registration and segmentation registration framework. Please refer to Appendix A for the technical specifications of ITK. It is a convenient tool kit to implement registration algorithm as it provides a framework that allows easy replacement of the methods of the registration components i.e. *transform*, *interpolator*, *metric*, and *optimizer*.

The selection of techniques discussed in section 3.7 was based more on the theoretical considerations, whereas the design of algorithm discussed in this section emphasized more on the software and hardware implementation considerations. Software considerations are such as the availability of the required techniques as listed in section 3.7 in the ITK library and the success of the function implementation in the real code, whereas hardware consideration is such as the computational cost of the selected technique. All of the above mentioned considerations serve as the basis in designing the algorithm. The specifications of the algorithms for the investigation stage are listed in Table 4.1; the column “ITK Components” refers to the objects in ITK for the respective registration aspects, whereas “ITK Methods” refers to the techniques associated with the ITK components for the respective selected techniques.

MI measure and density function estimation are implemented as *metric* object in ITK. *Metric* can be regarded as the cost function to be maximized or minimized

Chapter 5 Results and Discussions of Investigation of Multi-Resolution MI-Based Registration Algorithms

during the registration process depending on the method of registration. In this case, the metric used was *mutual information metric*. There are two types of metric implementation for MI: *Viola and Well* algorithm and *Mattes* algorithm. The difference between *Viola and Well's* and *Mattes'* implementation is in the number of samples drawn in each iteration. *Viola and Well's* implementation draws 50-100 pixels/voxels samples in each iteration whereas *Mattes'* draws only 5-10% of the image pixels/voxels once throughout the registration process [62]. Hence, *Mattes'* implementation was chosen to save computational cost.

Table 4.1: Specifications of ITK Implementation of Registration Algorithm.

No.	Registration Aspects	Selected Techniques (From Table 3.1)	ITK Components	ITK Methods
1	MI Measure and Density Function Estimation	Joint Entropy Concept and Parzen Windowing	<i>metric</i>	Mutual Information Metric: <i>Mattes'</i> Implementation
2	Interpolation	Tri-linear (linear) interpolation	<i>interpolator</i>	<i>Linear</i> interpolator
3	Transformation	Rigid Transformation	<i>transform</i>	<i>Euler3D</i> transformation
4	Origin of transformation	n.a.	n.a.	<i>Centered origin</i>
5	Optimization	Powell's and Conjugate gradient or Levenberg-Marquardt methods.	<i>optimizer</i>	Non-gradient based: Powell's optimization
				Gradient based: Regular step gradient descent optimization
6	Acceleration Technique	Multi-resolution	Registration Framework	Multi-resolution framework

Interpolation is handled by *interpolator* object in ITK. Section 3.7 discussed the selection of tri-linear (linear) interpolation technique over other techniques based on the suitability with the selected MI measure and the probability density function. ITK provides several techniques of interpolation such as: nearest neighbor (NN), linear and B-Spline interpolation methods (please refer to Appendix A, section A.2.2). The required technique, linear interpolation, is available. However, it would be compared with other available techniques in ITK in terms of implementation. Although nearest neighbor scheme performs faster than linear and B-spline, it may suffer from the roughness of the image metric. B-spline interpolation performs better in creating the smoothest metric space among the three, but it is computationally costly. The

optimum choice among the three could be the linear interpolation scheme as it combines moderate computational load and moderate smoothness of the metric it generates. Thus, linear interpolation scheme was then chosen as the interpolation method.

The ITK component handling transformation technique is *transform* object (refer to Appendix A, section A.2.1). The technique selected in section 3.7 was rigid transformation. ITK provides several transformation methods such as *Affine*, *Euler3D*, and *quaternion rigid transform* objects. Affine transformation would not be considered; only *Euler3D* and *quaternion rigid* transformation are considered as both provide rigid transformation (rotation and translation) functionality in 3-dimensions. In the context of registration, *transform* parameters define the search space for *optimizers*. Thus, the goal of the optimization is to find the set of parameters defining a transformation that result in the best possible value of an image metric. The more number of parameters a *transform* has, the longer its computational time in a registration process as the dimension of the search space is equal to the number of the transform parameters to be optimized. Compared to quaternion, the number of parameters in Euler3D (6 parameters) is fewer than the one in quaternion (7 parameters). Thus, the Euler3D transformation was chosen to save the computational speed.

Transformation depends on the origin of the reference frame. The placement of transformation origin affects the speed of the registration process. Normally, the origin is shifted to the center of the image or volume to speed-up the registration process (Appendix A, section A.2.1, last paragraph). Centered-origin transformation will likely to speed-up the registration process as normally the object's image is concentrated in the center of the image area / volume. Thus, centered-origin based transformation was chosen as fewer spatial transformations are required to align the images than in the normal origin – based transformation.

Based on the discussion in section 3.7, it was intended to implement algorithms with Powell's and conjugate gradient or Levenberg-Marquardt optimization methods. However, preliminary tests on the implementation of the Powell's, conjugate

gradient and Levenberg-Marquardt optimizations using ITK library had resulted that Powell's technique worked well, whereas the two others failed to generate any results. The failure might be due to wrong settings of certain parameters or existence of bugs in the source code of the optimization function in the ITK library by the software developer. ITK is a developing image processing library that certain functions are still not well developed yet [67]. Thus, another gradient-based technique was chosen as a replacement. It was chosen from one of the well developed optimization functions in ITK, a variant of gradient descent optimization which is regular step gradient descent. For non-gradient-based, Powell's optimization was selected.

Powell's and Regular Step Gradient Descent *optimizers* were chosen as the optimization components. In the investigation stage, they were implemented in separate algorithms. Powell *optimizer* has the advantage of requiring no derivative of the *metric*. Regular Step Gradient Descent *optimizer* has the advantage over the Gradient Descent *optimizer* that it eliminates the problem of determining the learning rate (please refer to Appendix A, section A.2.4). The performance of both optimizers in the registration algorithm was observed and compared in terms of speed and accuracy.

Multi-resolution registration framework was selected as the base framework of the algorithms. It was chosen for its ability to improve the performance of a registration process in terms of speed, robustness and accuracy. Two image pyramids were created each for fixed and moving images. The resolution scheme to down sample the image in every level of resolution follows the formula:

$$\text{shrink factor} = 2^{L-(i+1)} \quad (4.1)$$

where, L is the number of levels, i is the level's number. Please refer to Appendix A, section A.3.

There are several properties need to be defined by the user when using optimizer. Each optimizer has different sets of properties as elaborated in Appendix A, section A.2.4. The properties affect the process of optimization, which are:

- a) In regular step gradient descent optimizer:
 - *Step length*; it governs the optimization step during the optimization. It is initialized by specifying the *maximum step length*.
 - *Minimum step length*; it serves as the stopping criterion.
- b) In Powell optimizer:
 - *Step length*; it governs the optimization step during the optimization.
 - *Step tolerance*; it functions as the convergence criterion or stopping condition.

In case the stopping criteria (i.e. *minimum step length* or *step tolerance*) fail to perform, *maximum iterations* and *number of iterations* set in Powell and regular step gradient descent optimizers respectively would take over. *Step length* refers to the value increment of the parameter during the optimization process, whereas convergence/stopping criteria refer to conditions to indicate the end of a series of iterations based on the difference between the results of two consecutive iterations.

Two sets of algorithms were developed. The algorithms differ by their optimization methods i.e. regular step gradient descent and Powell's methods. In the multi-resolution scheme being implemented, more progressive step length (e.g. 10 – 30 step units) and relaxed convergent criteria (e.g. 0.1 step units) were set for coarse resolution level (i.e. level zero is the coarsest resolution); reduced steps (e.g. step length from the previous level divided by two) and more stringent convergent criteria (e.g. the convergent criteria from the previous level divided by ten) were then set in subsequent finer resolutions. The pseudo code for updating the variables in the program implementing regular step gradient descent method is presented as follows:

```

IF (multiresolution_level == 0)
  THEN
    Step_length = Max_step_length
    Min_step_length = t
  ELSE
    Step_length = Step_length/x

```

/*The program's flow goes to THEN block when the registration works in level 0 i.e. coarsest resolution*/
 /*Max_step_length is the initial step length, step length in the coarsest resolution, i.e. level 0; it is defined by the user*/
 /*t is the minimum step length indicating the stop condition in the coarsest level; it is defined by user.*/
 /*ELSE block is when the registration works in other levels than 0*/
 /*x is the factor to reduce the step length in the

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$\text{Min_step_length} = \text{Min_step_length} / y$	subsequent resolution level; e.g. if $x = 5$, the new step length for the current level is the step length in the previous level divided by 5.*/ /*y is the factor to reduce the minimum step length in the subsequent resolution level; it terminates the optimization in the level when it is met; for example, if $y = 5$, the new stopping condition i.e. the Min_step_length for the current level is the Min_step_length in the previous level divided by y.*/
---	---

The pseudo code for updating of the variables in the program implementing Powell's method is:

IF (multiresolution_level == 0) THEN	/*The program's flow goes to THEN block when the registration works in level 0 i.e. coarsest resolution*/
$\text{Step_length} = n$	/*n is the initial step length, step length in the coarsest resolution, i.e. level 0; n is defined by the user*/
$\text{Step_tolerance} = t$	/*t is the step tolerance in the coarsest level, defined by user; it terminates the optimization process in the first level*/
ELSE	/*ELSE block is when the registration works in other levels than 0*/
$\text{Step_length} = \text{Step_length} / x$	/*x is the factor to reduce the step length in the subsequent resolution level; e.g. if $x = 5$, the new step length for the current level is the step length in the previous level divided by 5.*/
$\text{Step_tolerance} = \text{Step_tolerance} / y$	/*y is the factor to reduce the step tolerance in the subsequent resolution level; it terminates the optimization in the level when the tolerance is met; for example, if $y = 5$, the new tolerance for the current level is the step tolerance in the previous level divided by y.*/

4.3 Registration Datasets Specifications and Error Calculation Method

4.3.1. Image Datasets

Two sets of 3-D images were used in this experiment. The images are volume images of the same object i.e. upper part of a head. They were acquired using the same imaging modality, MR, yet of different acquisition-modes i.e. PD (Proton density) and T2 relaxation time. The reason for choosing both datasets had been explained in section 2.4.2. The datasets were obtained from [63]. These datasets were provided by ITK developer and meant to test on the registration algorithm. The specifications of the datasets are presented in Table 4.2. Due to different acquisition-modes i.e. PD

and T2, both sets have different grey values. The visualization of the datasets is attached in Appendix F.

Table 4.2: Specification of datasets.

Dataset Label	Brain1Set	Brain3Set
Modality	MRI PD (Proton density)	MRI T2
Voxel value type	Signed short 0 to 4095	Signed short 0 to 4095
Noise (specified)	3%	3%
Image size (voxel) (x,y,z)	181 x 217 x 181	181 x 217 x 181
Voxel size (mm ³) – in physical space	1 x 1 x 1	1 x 1 x 1

Magnetic Resonance Imaging (MRI) produces images of the body using nuclear magnetic resonance properties of tissues. Unlike X-ray, MRI does not use ionizing radiation. It produces contrast between different tissues based on a variety of physical parameters. Therefore a great variety of information can be obtained by appropriate selection of imaging parameters. The properties of the physical body being imaged are controlled by several parameters: TR (repetition time of a sequence of radio-frequency pulses), TE (spin-echo delay time) and TI (inversion time). Some weighting commonly used in MRI acquisition are T1, T2, and PD. T1 is acquired using short TR (< 800 ms) and usually short TE (<20 ms) times. Due to the short acquisition time, T1 images tend to contain little noise. T2 is acquired using long TE (>70 ms) and usually long TR (>1500 ms) times. They tend to be noisier than PD and T1 images. PD combines a relatively long TR with a relatively short TE time.

There are three types of images in each of the BrainSet. The first is the original image; whereas the second and third were obtained from the application of two different sets of transformations to the original image. The two transformation sets are: (a) translation in x-direction of 15 mm and rotation w.r.t. z-axis of 10 degrees, (b) translation in positive x-direction of 20 mm and clock wise rotation w.r.t z-axis of 20 degree. The transformation sets (a) and (b) were specified by the ITK developer to provide different ranges of transformation; the set (a) represents small range of transformation (i.e. 15 mm translation and 10 degree rotation), the set (b) represents larger range of transformation (i.e. 20 mm translation and 20 degree

rotation). In this project, the original image was labeled as Brain[No]Normal ([No] indicates the number of the set, i.e. 1 or 3). The Brain1Normal dataset being transformed by the first transformation set was labeled as Brain1R10T15, whereas by the second transformation set was Brain1R20T20. Similarly for Brain3Normal dataset, Brain3R10T15, Brain3R20T20 were the dataset being applied with the first and second set of transformation respectively.

The visualization of the images in Appendix F shows that Brain3Set has higher contrast compared to the Brain1Set. Contrast indicates the span of the ranges of the grey values contained by the image. High contrast indicates that large varieties of grey values are contained in an image, or in other words, a large span of the grey values. Low contrast indicates that small varieties of grey values are contained in the image, or a narrow span of grey values range. Thus, in high contrast image, different areas in the image are easily identifiable, unlike in low contrast image.

4.3.2 True Value of Registration Results

In this project, the registration results in a set of transformation, consisting of translational and rotational components. Assessment to the results was conducted based on the comparisons between the results with the true value of the transformation. The representation of the true value is dependant on the origin of the transformation being adopted i.e. normal-origin based and centered-origin based transformation (refers to Appendix A, section A.2.1). Both cases are discussed separately.

Normal-origin based transformation

In normal-origin based transformation, a transformation is represented with respect to the origin (0,0,0). Brain[No]R10T15 was generated by rotating 10° w.r.t z-axis ccw and translating +15 mm in x-direction (transformation: $\theta_x = 0, \theta_y = 0, \theta_z = 10, t_x = 15, t_y = 0, t_z = 0$) the Brain[No]Normal image. In registration between Brain[No]Normal (as fixed image) and Brain[No]R10T15 (as moving image), the result is the opposite transformation i.e. 10° rotation w.r.t z-axis cw and -15 mm translation in x-direction of the moving image $\{\theta_x = 0, \theta_y = 0, \theta_z = -10, t_x = -15, t_y = 0, t_z = 0\}$.

It is similarly between Brain[No]Normal and Brain[No]R20T20; the later was generated from the earlier with the transformation of $\{\theta_x = 0, \theta_y = 0, \theta_z = 20, t_x = 20, t_y = 0, t_z = 0\}$. Hence, the registration result between Brain[No]Normal (fixed) and Brain[No]R20T20 (moving) is $\{\theta_x = 0, \theta_y = 0, \theta_z = -20, t_x = -20, t_y = 0, t_z = 0\}$.

Centered-origin based transformation

In centered-origin based transformation (refers to Appendix A, section A.2.1), a transformation is represented with respect to the center of the origin ($x = \text{length}/2, y = \text{width}/2, z = \text{thickness}/2$).

The conversion between the *normal-origin* and *centered-origin* based transformation could be solved using transformation matrix method. However, in this project, it was solved using geometrical method as this method could better illustrate the translation and rotation process in aligning the images than the matrix method. In this case, the conversion only involves calculation of the translational components, as the rotational components between the two bases are conserved. Calculation to convert the translational component from the normal- to the centered- based, could be done by applying the transformation (that is represented in normal origin) to the coordinate of the center of the volume/image; the translational component of the transformation is the vector resulted from the difference between the initial and the new coordinate of the volume's/image's center.

To convert the registration result between Brain[No]Normal (fixed) and Brain[No]R[A]T[L] (moving) ([A] indicating the angle, i.e. $10^\circ, 20^\circ$, [L] the translation component, i.e. 15, 20 mm) the computation is as follows (for illustration, please refer to Figure 4.1):

$$x' = S \cos(\alpha - A) - L \quad (5.1)$$

$$y' = S \sin(\alpha - A) \quad (5.2)$$

$$\text{where, } S = \sqrt{x^2 + y^2} \quad (5.3)$$

$$\alpha = \tan^{-1} \frac{y}{x} \quad (5.4)$$

The calculation of x' and y' for both cases of registration are presented in Table 4.3.

Figure 4.1. Illustration for calculation of conversion of transformation bases from center normal-origin to centered-origin based transformation in registration of Brain[No]Normal and Brain[No]R[A]T[L].

Table 4.3: Calculation of the new center coordinates for registration of Brain[No]Normal (fixed) and Brain[No]R[A]T[L] (moving).

Registered Images	A	L	Init center coord.		α (deg.)	S	New center coord.	
			x	y			x'	y'
Brain[No]Normal and Brain[No]R10T15	10	15	90.5	108.5	50.1685	141.2887	92.9659	91.1365
Brain[No]Normal and Brain[No]R20T20	20	20					102.1514	71.0038

In this case, z' is constant, as the transformation only occurs in x-y plane. It can be seen that A is in cw direction (-ve sign of θ_z), L is in negative x-direction (-ve sign of t_x). Thus, the conversion of transformation is calculated as:

$$\begin{Bmatrix} \theta_x' \\ \theta_y' \\ \theta_z' \\ t_x' \\ t_y' \\ t_z' \end{Bmatrix} = \begin{Bmatrix} \theta_x \\ \theta_y \\ \theta_z \\ x' \\ y' \\ z' \end{Bmatrix} - \begin{Bmatrix} 0 \\ 0 \\ 0 \\ x \\ y \\ z \end{Bmatrix}$$

where $\{\theta_x, \theta_y, \theta_z, t_x, t_y, t_z\}$ is the representation of transformation in normal-origin based and $\{\theta_x', \theta_y', \theta_z', t_x', t_y', t_z'\}$ is its representation in centered-origin based

transformation. The conversions of the transformations (or the true value of transformation) are summarized in Table 4.4.

Table 4.4: Summary of the true values of the registration results (transformations) for registration between Brain[No]Normal (fixed) and Brain[No]R[A]T[L] (moving).

Registered Images	Registration Result (transformation)	
	In normal-origin based $\{\theta_x, \theta_y, \theta_z, t_x, t_y, t_z\}$	In centered-origin based $\{\theta'_x, \theta'_y, \theta'_z, t'_x, t'_y, t'_z\}$
Brain[No]Normal and Brain[No]R10T15	$\{0, 0, -10, -15, 0, 0\}$	$\{0, 0, -10, 2.4659, -17.3635, 0\}$
Brain[No]Normal and Brain[No]R20T20	$\{0, 0, -20, -20, 0, 0\}$	$\{0, 0, -20, 11.6514, -37.4962, 0\}$

4.3.3 Error Calculations Method

In this project, accuracy validation of the registration results adopted the accuracy validation method presented in [28] with some adjustments. As had been elaborated in section 2.3, the validation method in [28] could not be fully adopted as the datasets being used in this experiment have no markers information. Hence, the comparisons with the results of the gold standard registration method i.e. marker-based registration could not be calculated. However, the true values of the transformation between the registered images were known. Thus, these true values were then used to replace the registration result of the gold standard.

In [28], the TRE values were obtained by calculating the error based on the difference between the mapped points using the transformation result of the registration being assessed and the ones of the gold standard. The points for mapping were selected on several areas of interest. The areas of interest were chosen based on anatomical/medical consideration that they are easily identifiable both in the image and, physically, on the patient's head anatomy; for example, a sharp corner, a certain contour, or a unique shape identifiable both in the image and in the physical anatomy. The differences were then summed up to get the average value of the error. However, the locations of the assessed points with respect to the origin of the transformation's reference frame affect the error distribution; as has been elaborated in [64], the further the location of the points from the origin of the transformation's

reference frame, the larger the resulted error. Thus, error is not evenly distributed throughout the area. The distribution is only even if only translational components existed. However, in real case, rotational components always exist, causing the uneven distribution of errors. The further from the center of rotation, the larger the error. It follows the fact that the displacement contributed by rotation equals to the angle of rotation multiplied by the distance between the point of interest and the center of rotation ($s = \theta r$).

Thus, in this experiment, to eliminate the problem of determining the area of interest in error calculation, only one point was used to be mapped and used to calculate the error; the point used was the center of the volume (i.e. the origin of the transformation reference frame). The error was calculated by measuring the difference (i.e. distance) between the mapped point by the registration result being assessed and the one by the true value transformation. Despite being simpler than using TRE method, this error measure could only serve as a lower bound of the error values; it is due to the fact that this error measure only takes the translational components into account, excluding the rotational component (the rotational component does not make any effect when the point being mapped is in the center of the transformation origin). Nevertheless, its disadvantage, i.e. its being only as a lower bound error measure, has brought advantages. It has made the error measure become more independent from any area of interest; thus, it has also made the measure become a more general error measure. The error was calculated as follows:

$$error = \sqrt{(t_x'' - t_x')^2 + (t_y'' - t_y')^2 + (t_z'' - t_z')^2}$$

where t_x'' , t_y'' , t_z'' are the translational component of a transformation being assessed, t_x' , t_y' , t_z' are the translational component of the true value of transformation.

As the voxel size is $1 \times 1 \times 1 \text{ mm}^3$, the error measure less than 1 mm is considered as having sub-voxel accuracy. As far as the results in this experiment were concerned, all errors fell in sub-voxel accuracy but some outliers. In this case, outlier is defined as the result whose accuracy exceeds sub-voxel accuracy ($> 1 \text{ mm}$). The details of experimental results are presented in chapter 5.

4.4 Design of Experiments

4.4.1 Investigated Factors

For the second objective of the project (section 1.4) i.e. to investigate the performance of the developed algorithms, several investigations were performed. Accuracy and speed were used as the measure of performance. Investigations were carried out to assess the performance of the algorithms with respect to the variations of several investigated factors. The investigated factors comprise:

- a) Optimization Methods
- b) Properties of multi-resolution registration together with the properties of the optimization methods, which comprise of:
 - Parameter scales
 - Number of multi-resolution levels
 - *Step length* and *step tolerance* in Powell's method.
 - *Maximum step length* and *minimum step length* in regular step gradient descent method.
- c) Properties of transformation methods which comprise of:
 - Centered-origin vs. normal-origin –based transformation
 - Ranges of Transformation
- d) Type of the acquisition-modes which comprises of:
 - Intra-acquisition-mode
 - Inter-acquisition-mode

The experimental procedures to investigate the above mentioned factors are described in section 4.4.2 - 7.

The datasets used in this project were of mono-modal images i.e. MRI as has been elaborated in section 2.4.2. As the registration technique being developed in this project is to be applied for multimodal image registration, a theoretical model of multi-modal image was developed and tested using the technique. The modeling of multimodal images and the experiment using the model are described in section 4.4.8.

4.4.2 Experiment on Parameter-Scales Tuning

An issue pertaining to the implementation of MI-based Registration using ITK is the tuning of the parameters scales; it was elaborated in Appendix A, section A.2.4.D. This is the first and an important step that has to be performed in registration process in order to ensure the validity of the result. These parameter scales are dependant on the methods used by the transform and optimizer components. Different methods may need different parameter scales. This requires observation to the behavior of the algorithm with respect to the variations of the parameter scales coupled with the number of multi-resolution levels and optimization properties e.g. step length, etc.

Parameter tuning experiment aimed to get the best parameter scales for the translation and rotational components. The goodness of the parameter scales is determined based on the following criteria:

- a) It does not fail the registration process regardless of the variations of the number of multi-resolution levels and optimization properties. It was assessed by looking at the results; *fail* means the registration stops midway without giving any results. In the program, an error message is displayed when a failure happens.
- b) The results show *correctness* and *consistency* regardless of the variations of the number of multi-resolution levels and optimization properties. Correctness is indicated by the error values and the values of the rotational components. A result is considered correct if its error value is smaller than the voxel size (i.e. < 1 mm) AND the rotational components are close to the rotational components of the true value transformation (i.e. ± 1 degree from the true value of rotational components). Tolerance of ± 1 degree ($= 0.0174$ radian) for the rotational was chosen for its being the smallest unit of angle easily discernable in both physical and image spaces while considering that misalignment of 1 degree in the center of rotation would be magnified to 1.58 mm at the perimeter of the image (i.e. $0.0174 \text{ rad} \times 90.5 \text{ mm} = 1.58 \text{ mm}$, only exceeds 0.58 mm from sub-voxel accuracy). Consistency is indicated by the tendency of the results to follow a trend. Combining consistency and

correctness requirements, the results are expected to constantly follow a trend of correct results.

There are six parameters being optimized when Euler3D is adopted (Appendix A, section A.2.1, Table A.1). The first three parameters represent the rotational components of the transformation, whereas the last three the translational components. Thus, two types of scale were defined, one each for rotational and translational components. In this case, the scale for rotation was fixed to 1.0, whereas the scale for translation became the investigated variable. As rule of thumb, a scaling factor of $1/\text{image_size}$ was applied for the translational component; the `image_size` is rounded to the nearest power of ten in physical space unit. Thus, the variable for the parameter tuning experiment was varied, starting from the scaling value of $1/\text{image_size}$ up to 100 for Powell optimizer, to $1/100$ for regular step gradient descent optimizer. The image size of $181 \times 217 \times 181 \text{ mm}^3$ ($= 181 \times 217 \times 181$ voxels) was approximated as $100 \times 100 \times 100 \text{ mm}^3$ ($= 100 \times 100 \times 100$ voxels) in physical space. The flow chart of the experimental procedure is illustrated in Figure 4.2. The steps are basically to vary the parameter sets, executing the program, and then assessing the generated results using the abovementioned criteria. Each set of parameter scale was tested by varying the number of multi-resolution levels and the optimization's properties e.g. maximum and minimum step lengths. The optimization's properties were varied for each number of multi-resolution levels.

As this experiment only aimed to tune the parameter scales for the translation and rotational components, any combination of the available datasets can be used. In this case, the datasets being used were of the same modality and acquisition-mode i.e. Brain1Normal and Brain1R10T15. The results and discussions of this experiment are presented in section 5.1. The results generated in this experiment were also used for other experiments described in section 4.4.3 – 4.

Figure 4.2. Flow Chart of the Parameter-Scales Tuning Experiment.

4.4.3 Experiment on Optimization Methods

The aim of this experiment was to investigate the effect of variations in optimization methods to the registration performance. The optimization methods being investigated were Powell's and regular step gradient descent (RSGD) methods. In this experiment, the results generated by two algorithms implementing different optimization techniques were compared. As the parameter tuning experiment had varied not only the optimization methods but also other parameters such as parameter scale, step length, the procedure of this experiment was hence overlapped by the procedure of parameter tuning experiment. The results of the parameter tuning experiment would then be used to compare the effect of different optimization methods. The results and discussions on this experiment are presented in section 5.2.

4.4.4 Experiment on Optimum Combinations of Multi-resolution Properties and Optimization Method Properties

Upon determining the best set of parameter scales, it was to be investigated about the combination of the properties of the multi-resolution scheme (i.e. the number of levels) and the properties of the optimization methods that could give good registration performance. The properties of the optimization methods comprised of optimum number of levels, maximum and minimum step length (in RSGD) and step length and step tolerance (in Powell's). The number of multi-resolution levels was investigated starting from three levels. It was not started from two levels as its level-0 image resolution is still considered too fine to represent multi-resolution registration with the default ITK multi-resolution shrink factor (refer to Appendix A, section A.3); using two levels, level-0 shrink factor = $2^{2-(0+1)} = 2$, level-0 resolution = $(181/2) \times (217/2) \times (181/2)$ voxels. The datasets being used were of the same modality and the same acquisition-mode i.e. Brain1Normal and Brain1R10T15. The procedure of this experiment was also overlapped by the procedure of the parameter tuning experiment. Hence, the discussion for this experiment would also base on the same experimental results generated from the parameter tuning; however it was looked from a different aspect i.e. the optimum combinations of the parameter sets. The results and discussions on this experiment are presented in section 5.3. The

results of this experiment i.e. the optimum combination of factors were to be used in the subsequent experiments i.e. experiments described in section 4.4.6 - 7.

4.4.5 Experiment on the Effects of Transformation-Origin Placements

This experiment aimed to investigate one of the properties of the transformation method which is the placement of transformation origin. The difference of registration performance in normal-origin and centered-origin – based transformation was to be investigated using parameter scale of (1:1/10000) and 3-level. The algorithm used for the experiment would be of RSGD optimization-based. The images used were of the same acquisition-mode i.e. Brain1Normal and Brain1R20T20. The results and discussions on this experiment are presented in section 5.4.

4.4.6 Experiment on the Effects of Transformation Range

This experiment aimed to investigate a property of the transformation method which is the transformation range i.e. translation and rotation. There are two transformation sets specified to the sets of images which are 10° rotation – 15 mm translation and 20° rotation – 20 mm translation. Thus, the effect of the transformation range difference to the registration performance was investigated. The optimization method used in this experiment was regular step gradient descent optimizer. The results and discussions of this experiment are presented in section 5.5.

4.4.7 Experiment on the Effects of Acquisition-Modes

The datasets being used in the experiments were obtained from MR imaging with two different acquisition-modes, PD and T2. The effect of the acquisition-modes in the registration was investigated: both the effect by the same acquisition-mode and different modes. The optimizer being used in this experiment was regular step gradient descent optimizer.

The investigation for the effect of the same acquisition-mode was carried out to the images within PD-mode datasets (Brain1set) and within T2-mode datasets (Brain3set). The results and discussions on this experiment are presented in section 5.6.

The mode difference causes difference in grey values distribution of the images. Thus, the effect of the grey values difference to the performance of registration was investigated. The effect of different acquisition-modes was investigated by mixing the images of different modes. The registration results from images of different mode would then be compared to the ones of the same mode. The results and discussions for this experiment are presented in section 5.7.

4.4.8 Experiment and Modeling of Multimodal Image Registration

A set of theoretical models of multimodal images was developed from mono-modal image datasets of MRI in PD and T2 acquisition-modes. Some experiments were then conducted to test the models using the registration algorithm being developed in this project. The experiment aimed to verify if the algorithm is also applicable for multimodal images. Thus, this section elaborates two issues: the modeling of multimodal image datasets and experimental approach for verification of algorithms using the models.

Registration involves a pair of image datasets. As elaborated in section 2.1.E, different imaging modalities are characterized by the difference in grey value distributions and image resolution. Hence, some pairs of images differing by grey value distribution and resolution were modeled.

The available datasets are MRI images using PD and T2 acquisition-modes as specified in Table 4.1. Different gray value distribution was achieved by combining the images of different acquisition-modes; in this case, the image pairs were combined from Brain1Set (PD) and Brain3Set (T2). Both sets have different contrast and brightness.

Different resolution was achieved by combining the images of different voxel sizes. In this experiment, the voxel size of one of the pair, i.e. fixed image, was left unchanged, whereas the voxel size of its pair was varied in its X, Y, and Z dimensions. To alter the voxel size, an ITK-based program was developed to resample the image datasets; the pseudo code of the program is presented below.

Chapter 5 Results and Discussions of Investigation of Multi-Resolution MI-Based Registration Algorithms

```

Output: resized_image = Function Resize(input: input_image, factor_X, factor_Y, factor_Z)
/*Function Resize changes the resolution of an image by altering the voxel size of the
image*/
/*Input parameter: */
/*    input_image: image whose voxel size to be resized*/
/*    factor_X, factor_Y, factor_Z: multiplication factors for X, Y, Z dimensions */
/*    respectively to multiply the size of the voxel in X, Y, and Z -dimensions;1 is identity */
/*Output parameter: */
/*    resized_image: image whose voxel size has been resized*/

Initialization of variables
Read the image
Apply Gaussian filter
Image Smoothing
Resample the image using new size after multiplication by multiplication factors (factor_X,
factor_Y, factor_Z)
Write resampled image to resized_image

```

The program requires the user to specify a set of multiplication factors (for X, Y, Z dimensions) to multiply the size of the voxel in X, Y, and Z -dimensions. For example, the voxel size of the dataset was originally 1 mm x 1 mm x 1 mm (X, Y, Z); to alter the voxel size into 1.5 mm x 1.5 mm x 1 mm (X,Y,Z), the multiplication factors were set as (factor-X=1.5; factor-Y=1.5; factor-Z=1). Several combinations of image pairs representing multi-modal image model were then defined as presented in Table 4.5.

Table 4.5: Combination of Multimodal Image Model Pairs.

Pair No.	Fixed Image: Brain1Normal			Moving Image: Brain3R10T15		
	Voxel Size			Voxel Size		
	X (mm)	Y (mm)	Z (mm)	X (mm)	Y (mm)	Z (mm)
1	1	1	1	1.5	1.5	1.5
2	1	1	1	1.5	1.5	1
3	1	1	1	1	1.5	1.5

Model image from Brain1Normal was chosen as the fixed image, whereas model image from Brain3R10T15 as the moving image. The experimental results using the models were compared with the results of registration between the original Brain[No]Normal and Brain[No]R10T15, especially between Brain1Normal and Brain3R10T15. Transformation set of 10° rotation and 15 mm translation was chosen, although the set of 20° and 20 mm was also possible as transformation range was not an important factor in this experiment, the use of one of the available transformation sets was sufficient.

Changing resolution, i.e. increasing/decreasing voxel size of an image, means reforming its voxels to a new size; it involves merging and blending of grey values of several neighboring original voxels. It would cause blurring effect to the image, which eventually causes loss of image information. In this experiment, the multiplication factor was chosen from a range between 1 and 2. Multiplication factor between 0 and 1 was considered inefficient as it causes not only loss of image content but also increase in resolution which eventually increases the registration computational time. Increase in resolution, i.e. smaller voxel size, causes more number of voxels needed to be processed, which consequently increases the computational time. Range 0 to 1 was then excluded. Multiplication factor of 2 was deemed as the maximum, considering the dataset's original resolution, $181 \times 217 \times 181$ voxels. The factor of 2 would change the image's resolution to $90.5 \times 108.5 \times 90.5$ voxels, which is too rough to represent an object of $181 \times 217 \times 181 \text{ mm}^3$ for medical registration. Typical high resolution MRI image could reach $256 \times 256 \times 100$ voxels to represent the same size of object $181 \times 217 \times 181 \text{ mm}^3$. With the aforementioned considerations, a mid point value between 1 and 2 i.e. 1.5 was chosen to be the multiplication factor as it was considered sufficient to represent the difference in resolution between the registered images while maintaining the information content of the image.

The chosen multiplication factor was then applied to change the resolution of the moving image. In the first pair, the factor was applied in all three dimensions of X, Y, Z of the moving image resulting in a cube-shape voxel larger than the one of the fixed image. The second pair images have different resolution in X-Y plane, the same in Z-dimension; the moving image's voxel shape is rectangular-prism. The third pair images have different resolution in Y-Z plane, the same in X dimension; the moving image's voxel shape is rectangular-prism.

The algorithm used for this experiment was the multi-resolution algorithm with RSGD optimization technique. The one with Powell's optimization was not used as it was considered inefficient to produce the same level of accuracy in a much longer time (as discussed in section 5.2). The experiment intended to verify if the algorithm could work for the multimodal image models. To conclude that the registration

algorithm being developed in this project is applicable to multimodal images, the algorithm should fulfill the following conditions:

- a). The algorithm should be able to generate results using the model images.

This aimed to find out if there were any problems with the algorithm when used in images of different voxel size and grey value distribution.

- b). The algorithm should be able to generate *acceptable* results.

The acceptability of the results is determined by the accuracy and speed values. The accuracy is considered acceptable if its value falls within sub-voxel accuracy i.e. $< \text{size of the smallest voxel} (=1 \text{ mm})$. Basically, registration speed varies with the complexity of the registration cases; thus the ability of the algorithm to produce registration result basically indicates that the speed is acceptable. However, the results from registration experiments of the original Brain[No]Normal and Brain[No]R10T15 would be used as the values to compare with.

The results and discussions for this experiment are presented in section 5.8.

CHAPTER 5

RESULTS AND DISCUSSIONS OF INVESTIGATION OF MULTI-RESOLUTION MI-BASED REGISTRATION ALGORITHMS

This chapter elaborates the results and discussions of the experiments conducted using the algorithms and the datasets as explained in chapter 4. Visualization of the registration results is presented in the last section of this chapter.

5.1 Parameter Tuning

This section presents the results and discussion for the experiment described in section 4.4.2. Parameter tuning experiment aimed to find out the good parameter scale sets for the RSGD and Powell's optimization methods.

Regular Step Gradient Descent (RSGD) Optimizer

The complete results of parameter tuning experiment for the algorithm using RSGD optimizer are presented in Appendix B, Table B.A.1 – 5. The first combination of parameter scale tested was (rotational scale = 1, translational scale = 1/1000000); Figure 5.1 shows the results of the experiment. The results show no failure; it hence fulfills criterion (a) (refer to section 4.4.2). The Rx, Ry, Rz and error values show consistency that they follow a trend (the differences between the values within each series of Rx, Ry, Rz, and error are close). However, the results do not fulfill correctness criterion as its Rz values are very far from its true value, -10° . Thus, criterion (b) is not fulfilled. Thus, the first combination of parameter scale cannot be used.

The second combination of parameter scale is (rotational scale=1, translational scale = 1/100000). The results are presented in Appendix B, Table B.A.2. The results fulfill criterion (a). The Rx, Ry, and error values show consistency, whereas the ones of Rz

do not. Moreover, its R_z values are incorrect i.e. very far from its true value, -10° . Criterion (b) is hence not fulfilled. Thus, the combination of parameter scale cannot be used.

Figure 5.1. Graphs of: (a) Rotational Components and (b) Error Trend of parameter tuning experiment using parameter scale:

Rotation = 1, Translation = $1/1000000$. Plotted from the data in Appendix B, Table B.A.1.

The third and fourth combination of parameter scale are (rotational scale=1, translational scale = $1/10000$) and (rotational scale=1, translational scale = $1/1000$) respectively; Figure 5.2 and 5.3 show the results of the respective experiments. These results fulfill criterion (a). All R_x , R_y , R_z , and error values show consistency and correctness. Thus, criterion (b) is also fulfilled. Both sets of parameter scale are hence considered good parameter scale, and can be used.

Only one result was generated using the fifth combination of parameter scale (rotational scale=1, translational scale = $1/100$); it gave incorrect result (refer to Appendix B, Table B.A.5). Although the experiment was not done for other parameter sets, it has indicated that one of its results violated criterion (b) of correctness. Thus, the combination of parameter scale would not fulfill one of the criteria; it hence cannot be used.

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Figure 5.2. Graphs of: (a), (b) Rotational Components and (c) Error Trend of Parameter Tuning Experiment using Parameter Scale:
Rotation = 1, Translation = 1/10000. Plotted from the data in Appendix B, Table B.A.3.

Figure 5.3. Graphs of: (a), (b) Rotational Components and (c) Error Trend of Parameter Tuning Experiment using Parameter Scale:

Rotation = 1, Translation = 1/1000. Plotted from the data in Appendix B, Table B.A.4.

The summary of observations for the variations of the parameter scale is presented in Table 5.1. Hence, based on the criteria mentioned in section 4.4.2, over the variations of the combined factors of the multi-resolution levels, maximum, and minimum step lengths, good parameter scale sets were found:

{rotational scale = 1, translational scale = 1/10000} and

{rotational scale = 1, translational scale = 1/1000}.

Thereafter, these scale sets were used as the parameter scales throughout the experiments using RSGD optimizer.

Table 5.1: Summary of Parameter-Scales-Tuning Experimental Results for Regular Step Gradient Descent Optimizer based Algorithm.

Parameter scales	Consistency and correctness of results	Speed of convergence
1/1000000	Inconsistent and incorrect results; Especially for the rotational component of the transformation	n.a. because it converges wrongly i.e. incorrect results.
1/100000	Inconsistent and incorrect results; Especially for the rotational component of the transformation	n.a. because it converges wrongly i.e. incorrect results.
1/10000	Consistent and correct results	Converges correctly i.e. correct results. Reasonable speed for correct convergence. Average time = 1267 s.
1/1000	Consistent and correct results	Converges correctly i.e. correct results. Reasonable speed for correct convergence. Average time = 1718 s.
1/100	Incorrect results	n.a. because it converges wrongly i.e. incorrect results.

Powell's Optimizer

The complete results of parameter tuning experiment for the algorithm using Powell's optimizer are presented in Appendix D, Table D.1 – 6. Unlike in RSGD method, Powell's implementation did not always succeed to give a final result. The process stops midway and gave error message whenever the optimization process goes to the wrong way; this is termed as 'failed'. However, all the results that were successfully generated were all considerably close to the true values. Parameter scale set (rotation = 1, translation = 1) produced results with no failure (Appendix D, Table D.4.); they are hence considered as the candidates of good parameter scale sets.

Basically, the assessment of parameter scale for multi-resolution Powell's method does not require trials on the whole range of the *number of levels*; instead, by inputting the *number of levels* to small values (e.g. 2, 3, 4 levels) and then observing the result. Generally, if the chosen scale-set works for small number of levels, it will work for higher number of levels; and, it means it works for all cases. The scale-set that is not right cannot work on small number of levels; whereas the right one will work for the whole range of levels, step length and step tolerance. The observations to the variations of parameter scales for Powell's optimizer are summarized in Table 5.2.

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Based on the criteria in section 4.4.2, the candidates of good parameter scales were found to be 1, 10, and 100. However, considering the speed of convergence, parameter scale 1 was considered as the best parameter scale. The experiments on the algorithm implementing Powell's optimizer were not conducted as many experiments as with the RSGD optimizer due to the fact that Powell's method takes very long time to converge. Thus, it was only conducted on few selected cases.

Table 5.2: Summary of Parameter-Scales-Tuning Experimental Results for Powell's Optimizer based Algorithm.

Parameter scales	Consistency and correctness of results	Speed of convergence
1/1000000	Always failed	n.a.
1/100	Inconsistent results: Some were failed, some were successful. The successful results are always correct. Higher chance to fail in small number of levels, i.e. mostly successful when using 6 levels.	Considerably long time to converge. Average time of the correct results = 7394 s.
1/10	Inconsistent results: some were failed, some were successful. The successful results are always correct.	Considerably long time to converge, yet faster than the ones of 1/100. Average time of the correct results = 6462 s.
1	Consistent and correct results. Never failed even for small number of levels which were difficult to be achieved when using smaller scales.	Considerably long time to converge, yet slightly better than ones of 1/10 or lower. Average time = 5821 s.
10	Consistent and correct results. Never failed even for small number of levels which were difficult to be achieved when using smaller scales than 1.	Considerably long time to converge. Slightly slower than ones of 1. Average time = 4466 s.
100	Consistent and correct results. Never failed even for small number of levels which were difficult to be achieved when using smaller scales than 1.	Considerably long time to converge. Slightly slower than ones of 1. Average time = 4707 s.

Failure often happened in Powell's algorithm during the preliminary experiment. It happens when the current transformation guess has mapped the moving image (in ITK: fixed image) too far away such that less overlap area resulted. Less overlap area between fixed and moving images causes the MI calculation to fail. The fact that Powell method easily fails is related with its optimization method; it updates the parameters in turn based on the sequence of the parameter (section 3.4.D). Thus, when the first turn of the optimization process has resulted with the transformation

leading to wrong direction, the registration process would fail shortly. This situation worsens with the improper selection of parameter scale. Improper selection of parameter scale makes the parameter space become un-proportional, so that a small step length in wrong direction would cause the parameter fall out of range. For example, rotational range is between 0-1.57 radian vs. translation's range between 0-180 mm; step length 2 in angle's parameter would cause the process to fall out of range compared to step length 2 in translation's parameter. If the first turn of the iteration firstly updates the rotational component, the optimization process would fail in the first iteration as it has fallen out of range. Hence, the parameter scale tuning is very important in Powell's method.

5.2 Comparisons of Performance between Powell's and Regular Step Gradient Descent Optimization

This section presents results and discussion of the experiment as elaborated in section 4.4.3. Compared to Powell's, RSGD method never failed the process. The difference is in the way the parameters are taken into account in determining the step length. In Powell's, the parameters are taken into account separately i.e. being optimized in turn, one by one. This caused every parameter to contribute great impact in determining the step length in every iteration; moreover when it leads to the wrong direction i.e. out of range direction. On the other hand, in RSGD, the step length is determined by the gradient of the function; gradient evaluation takes all parameters into account simultaneously. Thus, the impact of all parameters is averaged out; even if there is a large value of a parameter leading to a wrong direction, the effect would be averaged out with the others. It, hence, avoids the step leading to an out of range situation. This may explain the reason why regular step gradient descent method seldom fails in spite of improper choice of parameter scales; its proper scale is indicated by the consistency of the result instead of failure or successfulness as in Powell's.

The accuracy of both optimization methods is comparable as shown in Figure 5.4. The error values are sub-voxel accurate i.e. < 1 mm. In terms of speed, Figure 5.5 shows that Powell's optimizer performs far slower compared to the RSGD optimizer

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in achieving a comparable accuracy level. One advantage of Powell's method is that it is fast to approach the solution area, yet it gets slow in achieving small convergence. In the multi-resolution scheme, Powell's method performs fast in coarse resolution level, yet gets slower in finer resolution.

Due to its very slow performance in multi-resolution scheme registration, in this experiment, further investigations on the performance of multi-resolution algorithm were only performed using RSGD method. It was considered inefficient, comparing results with a slow performing method to achieve the same level of accuracy.

Figure 5.4. Comparison of Error between Regular Step Gradient Descent - and Powell's Optimization – Based Algorithms. The plots were extracted from results in Table B.A.3-4 (Appendix B, Regular Step Gradient Descent Optimization Results) and Table D.4-6 (Appendix D, Powell's Optimization Results). *Experiment No* indicates the sequence number of the data within its series (Reg. Step Grad. Desc. Opt. or Powell's Opt series) from the collated tables.

Figure 5.5. Comparison of Speed between Regular Step Gradient Descent - and Powell's Optimization – Based Algorithms. The plots were extracted from results in Table B.A.3-4 (Appendix B, Regular Step Gradient Descent Optimization Results) and Table D.4-6 (Appendix D, Powell's Optimization Results). *Experiment No* indicates the sequence number of the data within its series (Reg. Step Grad. Desc. Opt. or Powell's Opt series) from the collated tables.

5.3 Optimum Combinations of Multi-resolution Properties and Optimization Method Properties

This section presents the results and discussions for the experiment as described in section 4.4.4.

Regular step gradient descent Optimizer

In the use of parameter scale of (rot = 1:trans. = 1/10000) (refer to Appendix B, Table B.A.3), the accuracy and speed results differing in the number of multi-resolution levels are plotted in Figure 5.6 and 5.7 respectively. Figure 5.6 shows that the best accuracy is achieved by the results of 3-level, with its average error of 0.0193 mm, followed by 4-level with average error of 0.0236 mm and 1-level with average error of 0.0245 mm; the lowest accuracy is by 5-level with average error of 0.0259 mm. In terms of processing time (Figure 5.7), the best average processing time is achieved by 1-level, 799 s, followed by 3-level, 1041 s, and 4-level, 1142 s. The slowest average processing time is by 5-level, 2767 s. Thus, based on collective observation i.e. based on the average value, the candidates for optimum combination of accuracy and speed are achieved by 3- and 4-levels. They made the highest-two accurate results, yet the second and third in speed respectively; in this case, accuracy is given more priority than speed.

Figure 5.6. Comparison of Error between the results of Regular Step Gradient Descent Optimization differing in the number of levels, using transformation range 10° rotation and 15 mm translation; Parameter scale: rotation = 1, translation = 1/10000. The plots were extracted from results in Appendix B, Table B.A.3. *Experiment No* indicates the sequence number of the data within its series (1, 3, 4, or 5 – Level series).

Figure 5.7. Comparison of Speed between the results of Regular Step Gradient Descent Optimization differing in the number of levels, using transformation range 10° rotation and 15 mm translation; Parameter scale: rotation = 1, translation = 1/10000. The plots were extracted from results in Appendix B, Table B.A.3. *Experiment No* indicates the sequence number of the data within its series (1, 3, 4, or 5 – Level series).

To find out the optimum combination of the parameter set (multi-resolution's and optimization method's properties), the results are observed individually. Individually, the best result, in terms of speed, is the one with 3-level, 10-max-length, and 1-min-step-length (Figure 5.7-8, 3-level series, and experiment no. 8). Its accuracy (error = 0.0177 mm) is also the second best after 0.0174 mm error (Figure 5.7-8, 3-level series, and experiment no.3). The experiment no. 8 is only 0.0003 mm larger in error but 1.5 times faster than the no. 3. Other results from other multi-resolution levels with comparable accuracy give speed performance of almost 1.5 times slower than experiment no. 8. Experiment no. 8 also outperforms the accuracy and speed in 1-level registration (i.e. finest resolution); 1-level's best speed is 567 s and best accuracy is 0.0187 mm. This has shown that multi-resolution scheme does increase the speed and accuracy of registration. However, the increase of the number of level from three to four has made the speed become slower without any improvement in accuracy. Hence, for parameter scale (1:1/10000), the optimum number of levels is found to be three; it agrees with the findings in the collective observation elaborated in the previous paragraph that 3-level is one of the candidates for the optimum performance. More specifically, 3-level, with max step length of ten and min step length of one made the optimum combination.

Figure 5.8. Comparison of: (a) Error and (b) Speed between the results of Regular Step Gradient Descent Optimization differing in the number of levels, using transformation range 10° rotation and 15 mm translation; Parameter scale: rotation = 1, translation = 1/1000. The plots were extracted from results in Appendix B, Table B.A.4. *Experiment No* indicates the sequence number of the data within its series (3, 4, or 5 – Level series).

With parameter scale of (1:1/1000) (refer to Appendix B, Table B.A.4), the accuracy and speed are plotted in Figure 5.8 (a) and (b) respectively. Figure 5.8 (a) shows that the best accuracy is achieved by the results of 4-level, with its average error of 0.0182 mm, followed by 3-level with average error of 0.0255 mm and 5-level with average error of 0.0258 mm. In terms of processing time (Figure 5.8 (b)), the best average processing time is achieved by 3-level, 657 s, followed by 4-level, 1045 s, and 5-level, 3804 s. Thus, based on collective observation, an optimum combination between accuracy and speed is achieved by 4-level. It gives the best accuracy yet the second in speed; in this case, accuracy is given more priority than speed.

Individually, the best result is achieved by 3-level, 10-max-step-length, and 1-min-step-length (Figure 5.8, 3-level series, and experiment no.2); it gives 0.0177 mm error and 455 s processing speed. It is the best combination of accuracy and speed. The finding is inline with the one in scale (1:1/10000). It even outperforms the best result in scale (1:1/10000). The second best result is achieved by 4-level, 20-max-step-length, and 1-min-step-length (Figure 5.8, 4-level series, experiment no. 1); it is only 7 seconds slower to achieve the same accuracy than the best result in

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(1:1/10000). The increase to 5-level does not improve the performance of the registration, both in terms of accuracy and speed. Thus, for parameter scale (1:1/1000), optimum combinations of (number of levels, max. step length and min. step length) are (3, 10, 1) and (4, 20, 1).

In theory, the increase in the number of levels in multi-resolution scheme could improve both speed and accuracy. However, in practice, it does not seem so. This is due to the fact that images need to be resampled in every level of registration. The resampling time increases as the image resolution gets finer. It may explain why 3-level of registration performs faster than registration in 1-level (no multi-resolution) as in theory; yet, it is still the fastest compared to 4- and 5- level multi-resolution. Summarizing the results, the sets of optimum combination of factors for regular step gradient descent – based algorithm, were:

Scale: (1:1/10000) and (1:1/1000)

Number of levels: 3 and 4

Maximum step length and minimum step length: (20, 1) and (10, 1).

Thus, these combinations of the values of the factors were then used in the subsequent experiments.

Powell's Optimizer

The investigation on the registration technique implementing Powell's method was conducted by observing the results in Table D.4 and D.5 of Appendix D. The experiments conducted for Powell's optimization method were not as many as the ones for Regular Step Gradient Descent method with the reason as explained in section 5.1. Due to limited number of data resulted in the experiment using Powell's method, conclusion on the effect of number of levels to registration speed and error was not able to be deduced. However, it was possible to draw general conclusion in terms of processing time and accuracy between Powell's and regular step gradient descent-based algorithms.

Compared to regular step gradient descent-based algorithm, Powell's-based algorithm performs much slower. Thus, the experiment on Powell's merely aimed to observe the basic performance of the registration. Further investigation on the

registration performance, e.g. the effect of normal-origin and centered-origin transformation, the effect of different acquisition-mode in the registration process, used regular step gradient descent optimizer.

5.4 The Effect of Transformation-Origin Placements

This section presents the results and discussions for the experiment as described in section 4.4.5. The results of the experiment on the difference of registration performance between normal-origin and centered-origin – based transformation are presented in Table 5.3. It is shown that the centered-origin outperforms the normal-origin based transformation in both accuracy and speed; as had been predicted based on the explanation on Appendix A, section A.2.1. This happens as the image of the object is concentrated in the center of the volume; hence the alignment process is faster when adopting centered-origin transformation than in normal origin.

Table 5.3: Results of Transformation Origin Placement Experiment; Parameter Set: Parameter Scale - Rotation = 1, Translation = 1/10000, No. of Level = 3, Max. Step Length = 30, Min Step Length = 1 (Appendix B, Table B.B.1a).

Origin Placement	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	Time (s)	Error (mm)
Centered	-0.0526	-0.0542	-19.6398	11.6812	-37.5188	-0.0089	997	0.0384
Un-centered	-0.0036	-0.4244	-19.4223	-18.6048	-1.5836	-0.7909	4351	2.2539

Actually, the accuracy of the normal-origin based method could be improved by increasing the number of iterations for convergence. However, as the aim of this experiment was merely to compare both methods, the number of iterations in the algorithm implementing both methods was set the same.

5.5 The Effect of Transformation Range

This section presents the results and discussions for the experiment as described in section 4.4.6. To investigate the effect of the rotational and translational ranges, comparisons were made between the registration results from different transformation values. Table 5.4 presents the summary of accuracy and speed of the registration results; the values in the table were obtained by eliminating outlier data. Outlier data is the result whose error exceeds the sub-voxel accuracy criteria. The outlier data could be found highlighted in the results of registration between

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Brain3Normal and Brain3R20T20 (Appendix B, Table B.D.1) as well as Brain1Normal and Brain3R20T20 (Appendix C, Table C.B.1); they are also depicted in Figure 5.11 and 5.13. The outlier is probably caused by improper combinations of parameter scales, number of level, minimum and maximum step lengths. The considerations on eliminating outlier data from the error calculations are described in section 5.6.

Table 5.4: Summary of Accuracy and Speed of Registration Results in the Regular Step Gradient Descent Optimization-based Algorithm.

Combinations	Average Time (s)	Average Error (mm)	Min. Error (mm)	Max. Error (mm)
Brain1Normal - Brain1R10T15	580	0.0213	0.0177	0.0330
Brain1Normal - Brain1R20T20	790	0.0327	0.0245	0.0712
Brain3Normal - Brain3R10T15	640	0.0079	0.0025	0.0180
Brain3Normal - Brain3R20T20	731	0.0087	0.0054	0.0146
Brain1Normal - Brain3R10T15	625	0.0425	0.0370	0.0450
Brain1Normal - Brain3R20T20	820	0.0471	0.0451	0.0512
Brain3Normal - Brain1R10T15	656	0.0460	0.0426	0.0618
Brain3Normal - Brain1R20T20	679	0.0571	0.0534	0.0702

From the results presented in Table 5.4, it is shown that the average errors of 10° rotation – 15 mm translation are less than the ones of its counterpart, 20° rotation – 20 mm translation (i.e. Brain[No]R10T15 vs. Brain[No]R20T20). Thus, the accuracies of the registration in the 10° rotation and 15 mm translation are slightly better than the ones in the 20° rotation and 20 mm translation.

The experimental results implied that the larger the transformation values i.e. rotation and translation, the larger magnitude of error is introduced. This might be due to the effect of transformation method being adopted, Euler3D transform, which assumes linear transformation. In small range of transformation, i.e. small translation and rotation, the linear assumption might be correct, yet, the assumption would not hold for larger range; it deviates more as the transformation involves larger range. The use of better transformation method such as affine transformation might give better accuracy for large values of transformation, yet it would reduce the speed of the registration process; as calculation for better accuracy is more time consuming. In real implementation, this finding suggests that to get better accuracy using the registration application being developed in this project, the patient's head should only be allowed to displace as small displacement as possible, preferably within the

range of 10° rotation and 15 mm translation between the image acquisitions. Head clamp and a reference frame could be used to constrain the movement of the patient's head during acquisition.

In terms of speed, the average processing time results show that the larger the transformation values, the longer it takes to converge to the solution. This is related to the initial guess of the solution applied. In this experiment, the initial guess of the solution i.e. transformation was defined as ($R_x=0$, $R_y=0$, $R_z=0$, $t_x=0$, $t_y=0$, $t_z=0$). The distance between the initial guess to the optimum solution, i.e. true value of transformation, determines the time taken for convergence. The distance between the initial guess to 10° rotation – 15 mm translation is closer than the ones of 20° rotation – 20 mm translation; thus the earlier takes shorter time for convergence than the later. Hence, it could be concluded that the speed of convergence is affected by the distance between the initial guess of the transformation to the optimum solution. The further the solution from the initial guesses, the slower the convergence to be achieved. However, this could be sped up by finding the right step length and choosing the closer initial guess.

5.6 Intra-Acquisition-Mode Registration

This section presents the results and discussions for the investigation as described in section 4.4.7. Registration results between images within-T2 acquisition-mode, i.e. Brain3Set datasets, show better accuracy compared to the ones of within-PD mode i.e. Brain1Set datasets. This could be observed by comparing the results in Appendix B, Table B.A.3 – 4 and Table B.C.1-2 for within Brain1 and Brain3 datasets rotated 10° and translated 15 mm for parameter scale 1/10000 and 1/1000 respectively; Table B.B.1-2 and Table B.D.1-2 for within Brain1 and Brain3 datasets rotated 20° and translated 20 mm for parameter scale 1/10000 and 1/1000 respectively. In terms of speed, both modes do not show much difference. The data are plotted in Figure 5.9 – 5.12.

Figure 5.9. Error Comparison between within-Brain1Set and within-Brain3Set for 10 degree rotation and 15 mm translation set; plotted from Appendix B, Table B.A.3 – 4 (Brain1Set) and Table B.C.1-2 (Brain3Set).

Figure 5.10. Speed Comparison between within-Brain1Set and within-Brain3Set for 10 degree rotation and 15 mm translation set; plotted from Appendix B, Table B.A.3 – 4 (Brain1Set) and Table B.C.1-2 (Brain3Set).

Figure 5.9 shows the error comparison of within-Brain1Set and Brain3Set for 10° rotation and 15 mm translation. For within-Brain1Set, its average error is 0.0213 mm, minimum error 0.0177 mm and maximum error 0.033 mm. As for the results of within-Brain3Set datasets registration, its average error is 0.0079 mm, minimum error 0.0025 mm and maximum error 0.018 mm. Thus, the average error from within-Brain1Set registration is higher than within-Brain3Set. In terms of speed,

Figure 5.10 shows that the average processing time of within-Brain1Set is faster than within-Brain3Set by 60 s. It is considered a slight difference in speed for 0.0134 mm error difference.

The results for the other transformation values, 20° rotation and 20 mm translation are presented in Figure 5.11 and 5.12 for error and speed respectively. For within-Brain1, its average error is 0.0327 mm, minimum error 0.0245 mm and maximum error 0.0712 mm; whereas for within-Brain3Set datasets, its average error is 0.1484 mm, minimum error 0.0054 mm and maximum error 1.1258 mm. It is depicted in Figure 5.11. Its bad result is contributed by the maximum error of 1.1258 which is considered as the outlier data. If the outlier were excluded, the average error would be 0.0087 mm. The exclusion of the outlier data makes the results more appropriate as this outlier is probably caused by improper combination between the parameter scale, number of levels and the step length. Such improper combinations may cause invalid data i.e. outlier data. Thus, it is more appropriate to eliminate the outlier. Hence, in this case, the accuracy of within Brain3Set registration is better than within Brain1Set; this agrees with the previous findings. Thus, it is concluded that within Brain3Set registration gives better accuracy than within Brain1Set datasets. In terms of speed, Figure 5.12 shows that the average processing time of within-Brain3Set is faster than within-Brain3Set by only 30 s. This finding is the opposite of the one in 10° rotation and 15 mm translation. However, the difference is considered insignificant as it is only a slight difference in speed for 0.024 mm error difference.

Figure 5.11. Error Comparison between within-Brain1Set and within-Brain3Set for 20 degree rotation and 20 mm translation set; plotted from Appendix B, Table B.B.1 – 2 (Brain1Set) and Table B.D.1-2 (Brain3Set).

This accuracy difference might be caused by the difference in grey value intensity distribution created by different acquisition-modes. Appendix F shows that Brain1Set datasets (PD mode) show less contrast compared to Brain3Set (T2 mode). High contrast image means that the gray values of the image involve wide range of gray values; in other words, different areas within the image are better distinguishable in high contrast image; hence, it implies that the intensity values could also serve as the area label in high contrast image. Thus, in registration between two images of high contrast, the grey values do not only serve as intensity distribution but also as area label information. Thus, this could improve the accuracy of the registration result. Whereas in low contrast image, the grey values do not contain area label information; as the areas within the image are hardly distinguishable by the grey values. Thus, registration results of low contrast images are not as good as in the ones of high contrast.

Figure 5.12. Speed Comparison between within-Brain1Set and within-Brain3Set for 20 degree rotation and 20 mm translation set; plotted from Appendix B, Table B.B.1 – 2 (Brain1Set) and Table B.D.1-2 (Brain3Set).

5.7 Inter-Acquisition-Mode Registration

This section elaborates the results and discussions of the investigation as explained in section 4.4.7. Basically, there are two groups of experimental results on the investigation of the effect of different acquisition-mode to the registration result, which are: Brain1Normal (fixed) vs. Brain3R[A]T[L] (moving) datasets and Brain3Normal (fixed) vs. Brain1R[A]T[L] (moving) datasets. The results are presented in Figure 5.11 – 5.16.

The results of the registration between Brain1Normal and Brain3R[A]T[L] are presented in Figure 5.13 and 5.14 for accuracy and speed respectively. It is shown in Figure 5.13 that for Brain1Normal and Brain3R10T15, the average error is 0.0425 mm with minimum error 0.037 mm and maximum error 0.045 mm. For Brain1Normal and Brain3R20T20, its average error is 0.1925 mm. However, there is an outlier error of 1.21 mm. This outlier is eliminated with the same reason as explained in section 5.6. Eliminating outlier, the average error is then 0.0471 mm, with minimum error of 0.0451 mm and maximum error of 0.0512 mm. The errors between the two only differ slightly; 20° rotation - 20 mm translation makes more error than 10° rotation – 15 mm translation. In terms of speed, 10° rotation – 15 mm translation performs faster than 20° rotation - 20 mm translation as shown in Figure 5.14. This finding agrees with the findings in the effect of the transformation range

as discussed in section 5.5. In addition, in both cases, the speed of 3-level performed faster than the one of 4-level.

Figure 5.13. Error Comparison between Brain1Normal vs. Brain3R10T15 and Brain1Normal vs. Brain3R20T20; plotted from Appendix C, Table C.A.1 – 2 (Brain1Normal vs. Brain3R10T15) and Table C.B.1-2 (Brain1Normal vs. Brain3R20T20).

Figure 5.14. Speed Comparison between Brain1Normal vs. Brain3R[Angle]T[Displacement]; plotted from Appendix C, Table C.A.1 – 2 (Brain1Normal vs. Brain3R10T15) and Table C.B.1-2 (Brain1Normal vs. Brain3R20T20).

The results of the registration between Brain3Normal and Brain1R[A]T[L] are presented in Figure 5.15 and 5.16 for accuracy and speed respectively. It is shown in Figure 5.15 that for Brain3Normal and Brain1R10T15, its average error is 0.046 mm, with the minimum error of 0.0426 mm and the maximum error of 0.0618 mm; whereas for Brain3Normal and Brain1R20T20, its average error is 0.0571 mm, with the minimum and maximum error of 0.0534 mm and 0.0702 mm respectively. Thus, the accuracies of the registration in the 10° rotation and 15 mm translation are slightly better than the ones in the 20° rotation and 20 mm translation. It agrees with the previous findings. As shown in Figure 5.16, the speed in 3-level is faster than in 4-level. This fact also agrees with the previous findings. The fact that the longer time taken for 4-level than in 3-level was explained by the reason presented in section 5.3. In addition, the speed of 10° rotation – 15 mm translation is slightly faster than 20° rotation - 20 mm translation. It agrees with the previous finding as well as the finding as discussed in section 5.5.

Figure 5.15. Error Comparison between Brain3Normal vs. Brain1R[Angle]T[Displacement]; plotted from Appendix C, Table C.C.1 – 2 (Brain3Normal vs. Brain1R10T15) and Table C.D.1-2 (Brain3Normal vs. Brain1R20T20).

Figure 5.16. Speed Comparison between Brain3Normal vs. Brain1R[Angle]T[Displacement]; plotted from Appendix C, Table C.C.1 – 2 (Brain3Normal vs. Brain1R10T15) and Table C.D.1-2 (Brain3Normal vs. Brain1R20T20).

Table 5.5 shows that the overall accuracy of registration results in the inter-acquisition-mode are worse compared to the ones of the intra-acquisition-mode; the first four ranks of average error are occupied by the image pairs of the same acquisition-mode. In terms of speed, the rank is governed by the transformation range; 10° rotation and 15 mm translation gives faster speed than 20° rotation and 20 mm translation. The fact that the accuracy of inter-acquisition-mode registration is less than ones of intra-acquisition-mode would be described using the joint

histogram. A joint histogram is a 2-D histogram plotting the frequency of occurrence of grey level value combinations between two overlapping images; one axis provides the range of grey level values for one image e.g. 0-255 in 8 bit grey level, the other axis is for the range of the other image; a very dark pixel in the joint histogram indicates zero occurrence, whereas a very bright pixel indicates high occurrence e.g. 255. An example of joint histogram is presented in Figure 5.17. The joint histograms generated in this project were produced using a program developed using ITK library; the pseudo code of the program is as follows:

```
Output: joint_histogram_image = Function JointHist (input: fixedImage, movingImage)
/*Function JointHist generates the joint histogram of two images which are fixedImage and
movingImage, and write the generated histogram into 2-D image file (*.png) i.e.
joint_histogram_image */
```

Initialization of parameters and variables.

Read the images.

Define the number of bins of the joint histogram (the range of the grey values).

Generate the joint histogram.

Write the generated joint histogram into joint_histogram_image.

Table 5.5: Comparison of Average Errors and Speeds.

Rank	Average-Error Comparison		Average-Speed Comparison	
	Image Combination	Error (mm)	Image Combination	Processing Time (s)
1	Brain3Normal-Brain3R10T15	0.0079	Brain1Normal-Brain1R10T15	580
2	Brain3Normal-Brain3R20T20	0.0087	Brain1Normal-Brain3R10T15	625
3	Brain1Normal-Brain1R10T15	0.0213	Brain3Normal-Brain3R10T15	640
4	Brain1Normal-Brain1R20T20	0.0327	Brain3Normal-Brain1R10T15	656
5	Brain1Normal-Brain3R10T15	0.0425	Brain3Normal-Brain1R20T20	679
6	Brain3Normal-Brain1R10T15	0.046	Brain3Normal-Brain3R20T20	731
7	Brain1Normal-Brain3R20T20	0.0471	Brain1Normal-Brain1R20T20	790
8	Brain3Normal-Brain1R20T20	0.0571	Brain1Normal-Brain3R20T20	820

The joint histogram of two misaligned images appears as a dispersed distribution, whereas aligned images produce a sharper joint histogram distribution; dispersed distribution means a high entropy value. As the aim of MI method is to maximize the MI $I(A,B)$ i.e. minimizing joint entropy (refer to Equation 3.4), the registered images joint entropy would appear as a sharper distribution than its prior-registration joint entropy. The examples of joint histogram from the combination of images are presented in Figure 5.18. Examples of the joint histograms adopted from [31] depicted in Figure 5.19 also show that misalignment between the image pairs creates more dispersed joint histogram.

Figure 5.17. Examples of joint histograms.

Figure 5.18. Joint Histogram of Aligned and Misaligned Images.

Figure 5.19. Joint histogram of a 2-D MR image with itself.

(a) Histogram of the images when registered perfectly. As the image is identical, all grey value correspondences lie on the diagonal; (b), (c), (d) The joint histogram when one of the MR images is rotated with respect to the other by angles of 2° , 5° , and 10° . Adopted from [31]

Images of different modality would have different range of grey values. Difference in the grey values ranges may affect the symmetry of the joint histogram. When the registered images have different range of grey values, its joint histogram is of unsymmetrical shape; on the other hand, the same grey value range creates a symmetrical shape. It agrees with the joint histograms found in [31] generated from CT and MR image pairs that is unsymmetrical (refer to Figure 5.20) and the ones generated from MR image pairs of different alignments that are symmetrical (refer to

Figure 5.19); unsymmetrical joint histogram from CT and MR image pair is caused by different gray values range of CT and MR modality images. A comparison table of joint histograms generated from the image pairs used in this project between intra- and inter- acquisition-mode is presented in Figure 5.21. Brain1Set and Brain3Set images were acquired using the same modality, MRI, yet of different acquisition-modes as has been elaborated in Section 4.3.1 and 4.4.8. The joint histogram of the aligned images in Figure 5.19 appears as a single line whereas in Figure 5.18 appears as a symmetrical area of shades. Both pairs differ by the image dimensionality; the one in Figure 5.19 was generated from 2-D images whereas in Figure 5.18 was from 3-D images.

Figure 5.20. Example of joint histogram of multimodal images.

(a) A CT image, (b) an MR image, (c) the occurrences of the grey values combinations between the overlapping images is plotted: x-axis for the grey values of CT image and y-axis for MR image. Adapted from [31].

The fact that the intra-acquisition-mode gives better accuracy than inter-acquisition-mode might be caused by the difference in the grey value range between the images in the pair. The same grey value range creates a symmetrical joint histogram, whereas different range creates unsymmetrical joint histogram. Unsymmetrical distribution tends to be more dispersed than the symmetrical one; thus, it is inherently dispersed. The joint histograms of aligned image pairs from intra- and inter- acquisition-mode are illustrated in Figure 5.22. The joint histograms of inter-acquisition-mode image pairs are unsymmetrical and more dispersed than the ones of intra-acquisition-mode; it shows that they inherently contain a predetermined entropy value. The value hence serves as a minimum threshold value of entropy in the joint entropy minimization process during registration between the image pairs of different gray value range. The minimum threshold value causes the joint entropy could not be fully minimized; consequently, it limits the accuracy of image

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alignment. It may hence explain the reason of lower accuracy in images of inter-acquisition-mode compared to of the one of the intra-acquisition-mode.

Intra-acquisition-mode Images		Inter-acquisition-mode Images	
Misaligned	Aligned	Misaligned	Aligned
Brain1Normal and Brain1R10T15		Brain1Normal and Brain3R10T15	
Brain1Normal and Brain1R20T20		Brain1Normal and Brain3R20T20	
Brain3Normal and Brain3R10T15		Brain3Normal and Brain1R10T15	
Brain3Normal and Brain3R20T20		Brain3Normal and Brain1R20T20	

Figure 5.21. Joint Histograms of Intra- and Inter- Acquisition-Mode Image Pairs.

Figure 5.22. Joint histograms of aligned image pairs: intra- and inter- acquisition-modes.

5.8 Verification of Algorithm using Multimodal-Image Model

The experiment was conducted using the multi-resolution algorithm implementing RSGD optimization. The parameters used for the experiment were: *parameter scale - rotation* of 1 and *translation* 1/10000, *number of level* 3, *maximum step length* of 10, and *minimum step length* of 1. This parameter set was chosen based on the experimental result of registration between Brain1Normal and Brain3R10T15 (refer to Appendix C, Section A, Table C.A.1-2) that has shortest processing time, i.e. 434 sec. with an acceptable error value of 0.0436 mm (<1.0 mm, sub-voxel accuracy). The experimental result of the registration of the multimodal image registration model is presented in Table 5.6.

Table 5.6: Results of multi-resolution registration algorithm verification experiment using multimodal image models.

Pair No.	Results							Error (mm)
	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	Time (s)	
1	-0.0845	0.0385	-10.014	2.4435	-17.3834	0.1650	518	0.1677
2	-0.0582	0.0244	-10.053	2.4172	-17.4156	0.0752	428	0.1036
3	-0.0778	0.0206	-9.9587	2.4396	-17.3889	0.1641	532	0.1681

To verify the applicability of the algorithm being developed in this project for multimodal image registration, the experimental results would be assessed based on the conditions described in section 4.4.8. The first condition was fulfilled: the algorithm was able to produce results using the model. There was no faulty occurred during the execution of the program. This is related to the ITK's transformation concept and the choice of image alignment measure (i.e. metric object) of ITK adopted in the program. As had been explained in Appendix A, section A.2.1, ITK performs registration in physical space, instead of in image space; hence, voxel size difference between the registered images would not affect the registration performance as all information in image space is translated into physical space. In addition, the choice of MI measure affects the applicability of the algorithm for multimodal images. As has been described in Appendix A, section A.2.3, not all metric objects in ITK is applicable for multimodal image registration; however, MI metric is applicable for multimodal registration. Thus, as expected, the program ran free-of-faulty for the pairs of multimodal image models.

The second condition for the applicability of the algorithm to multimodal images is the acceptability of the generated results. The acceptability is assessed based on two aspects: speed (processing time) and accuracy. Basically, the ability of the algorithm to produce result implies that the resulted speed is acceptable. Table 5.6 shows that the processing time ranges from 428 – 532 seconds; it shows that the speed is acceptable. Comparing with the average speed of experiments between Brain[No]Normal and Brain[No]R10T15 (Table 5.5), the experiments on the models performs slightly faster; the maximum processing time of the models, 532 s, is still shorter than the minimum average time of the results between Brain[No]Normal and Brain[No]R10T15, 580 s. It might be due to the lower resolution of the model than of the original images involved in the registration; the lower the image resolution, the smaller amount of voxels need to be processed during registration.

The results in Table 5.6 show that the error values are sub-voxel accurate. The errors are less than the size of the smallest dimension of the smallest voxel size i.e. 1 mm; the smallest voxel among the pairs is the fixed image voxel, $1 \times 1 \times 1 \text{ mm}^3$. Thus, the accuracy of the results is considered acceptable. As the algorithm being tested has fulfilled both conditions stipulated in section 4.4.8, it is then concluded that the algorithm is applicable for multimodal image registration.

Figure 5.23 shows that the errors resulted from the registration of model images, Brain1Normal and Brain3R10T15 pairs, are larger than the ones from the original Brain[No]Normal and Brain[No]R10T15 pairs. The pairs are as presented in Table 4.5. The images of the model pairs involve images of lower resolution; the model images have larger voxel size than the one of the original image. Image resolution affects the information content of an image. High resolution image contains more information than the one of low resolution. Consequently, the accuracy of the registration involving images of low resolution would be lower than the one of high resolution. The lowest error among the model pairs is achieved by the second pair that has difference of resolution in X-Y plane. The errors in the first and third pairs are almost equally high compared to the second pair; both involved resolution difference in X-Y-Z and Y-Z dimensions respectively. Low error in the second pair is probably related to the fact that the transformation set (10 degree rotation and 15

mm translation) was only applied in X-Y dimension whereas Z-dimension was left unaltered with no transformation applied. Altering resolution in Z-dimension would introduce some loss of image contents in Z direction; it then added some amount of misalignment in Z-dimension in addition to misalignment in X-Y dimensions introduced by the defined transformation. Thus, changing the resolution of the Z-dimension would cause more error, as can be seen in pair 1 and 3.

Figure 5.23. Error Comparison of Multimodal Image Models and Mono-modal Image Registration Results. The algorithm used is Regular Step Gradient Descent-based Algorithm.

5.9 Visualization

The visualization of the overall volume was performed using free 3-D visualization software VolView [65]. The visualization of the original datasets volumes is attached in Appendix F. Typically, registration results for 2-D images are visualized as a checkerboard that the two images are superimposed and shown in squares of alternating sequence. In that way, the alignment between the two images can be assessed based on how good the images are joined at the periphery of the composing squares. For 3-D image, visualization of registration result might be done by

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superimposing the two volumes on the screen. However, rarely that free visualization software provides functionality for visualizing two volumes at the same time, as in the case of Volview. In view of the situation, the checkerboard method was hence adopted for 3-D case. Several corresponding slices were sampled from the pair of registered volume image and visualized as a checkerboard.

In this project, the result of registration algorithm was as a set of transformation values. For this to be visualized, the transformation set was then used to map the moving image to the coordinate space of the fixed image; the mapped moving image was subsequently written to a volume. A program to perform the mapping and writing to a volume was developed using ITK library. The pseudo code of the program is listed below:

```

/*Algorithm name: ImageMapping*/
output: mappedmovingImage Function ImageMapping (input: fixedImage, movingImage,
mapping_transformation)
/*****
/*Description: function ImageMapping maps the moving image (movingImage) to
/*          the reference frame of fixed image (fixedImage) using the transformation
/*          as defined by mapping_transformation.
/*mapping_transformation consists of transformation parameters represented as
/*a set of transformation parameters according to the adopted transformation
/*method (Euler3D transform); the mapping_transform is a set of parameters
/*consists of 6 parameters which are Rx, Ry, Rz, Tx, Ty, Tz.
/*Rx, Ry, Rz define rotational transformation, whereas Tx, Ty, Tz define
/*translational transformation
/*The mapped moving image is then written to an image volume
/*named mappedmovingImage.
*****/
Initialization of variables and parameters
Set transform = Euler3DTransform
Set interpolator = LinearInterpolator

Read the fixedImage and movingImage.
Measure image size, spacing size and origin of the fixedImage in x, y, z dimension.
Define the reference frame of the fixed image based on the measurement to the fixedImage
space above.
Map the moving image (movingImage) to the reference frame of fixed image using the input
transform parameters i.e. mapping_transformation.
Write the mapped moving image to an image volume (mappedmovingImage).

```

Upon the mapping, the moving image would align with the fixed image; the alignment could be observed by comparing the images slice by slice. Volview assisted in visualizing the image volume in its volumetric view as well as axial, sagittal and coronal views.

A closer observation to the registration result could be performed by making the checkerboard of every pair of corresponding slices of the registered volumes. However, for demonstration purpose in this report, the checkerboards were only generated for selected slices. A matlab program was developed to generate checkerboard image; the source code is attached in Appendix I. Some samples of slices were chosen arbitrarily along axial, sagittal and coronal views. In this case, the slice number chosen were 40 (axial), 80 (sagittal), and 142 (coronal/Frontal); they represented front, middle and rear slices. The concept of visualization used in this project is illustrated in Figure 5.24. The example of implementation of visualization concept is depicted in Figure 5.25. It is illustrated for the registration between Brain1Normal and Brain3R20T20; the difference between the checkerboards of the slices before and after registration is noticeable. The checkerboard visualizations of selected cases from the results of the RSGD-based algorithm are presented in Appendix G.

Figure 5.24. Illustration of Visualization of Registration Results.

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Figure 5.25. Illustration of Visualization for Registration between Brain1Normal and Brain3R20T20.

CHAPTER 6

COMBINED OPTIMIZATION TECHNIQUE IN MULTI-RESOLUTION MI-BASED REGISTRATION

This chapter begins with summary of the investigation findings and considerations for improving the performance of registration by the algorithms presented in chapter 4 and 5. Subsequently, two algorithms, and their experimental results and discussions are presented. It is concluded with the discussion on the performance of the two algorithms and the comparison with other researchers' work.

6.1 Problem Statement and Considerations

In the previous chapters, the advantages of implementing multi-resolution scheme in registration had been elaborated. The investigation of two registration algorithms implementing multi-resolution schemes was presented in chapter 4 and 5. Both algorithms differed by the optimization methods i.e. regular step gradient descent and Powell's method.

The performance of the algorithms was assessed based on the accuracy and speed. The registration results of the experiment was considered having sub-voxel accuracy. However, in terms of speed, the algorithms' performance still needed to be improved to achieve the requirement as mentioned in section 2.4.1, Table 2.1, point 3. This improvement was required as the registration algorithm is to be implemented as a part of surgical planning and navigation system; fast registration contributes to fast completion of the surgery. Thus, a registration algorithm that could improve the speed while maintaining high accuracy level was needed. A technique that could achieve registration speed in the order of one to three minutes is desired and acceptable as has been discussed in section 1.4.

Based on the experimental results discussed in chapter 5, the range of the average registration speed was found to be between 580 and 790 seconds (from Table 5.4). The fastest processing time among all results was 391 seconds (Appendix B, Table B.C.2) with error value of 0.0106 mm in physical space. It is expected that the processing time could be increased up to the order of two minutes.

In view of the situation, an approach was suggested to improve the performance of the registration algorithms based on the experimental results. The results had shown that: in general, regular step gradient descent based algorithm outperforms Powell's based algorithm in terms of processing time. However, one of the concerns in regular step gradient descent method is that its speed of convergence depends on the initial guess of the solution (section 5.5). The closer the initial guess to the solution, the faster the convergence could be achieved. Hence, to improve the performance of the regular step gradient descent based algorithm, a method to provide a good initial guess is required. On the other side, Powell's method has the advantage of its being fast to approach the solution area (section 5.2) and perform fast in coarse (low) resolution. Thus, considering the advantages of Powell's optimization, a method to provide a good initial guess for the regular step gradient descent was proposed: to use Powell's optimization in the coarse level within the multi-resolution scheme. Thus, the suggested approach is to develop a registration algorithm using multi-resolution scheme combining two optimization methods: Powell's method in the coarse resolution level and regular step gradient descent method in the finer resolution.

6.2 Test-Algorithm

6.2.1 Design of Algorithm and Experiments

In the first stage of the realization of the proposed method, a test version of the algorithm was developed. The aim of the development of the test algorithm was as a means to find out the optimum number of levels of multi-resolution scheme to be used and to study the behavior of the algorithm.

The algorithm was implemented using ITK registration framework. However, ITK multi-resolution registration framework does not provide a way to change the optimization method in the middle of the registration process. Thus, an iteration process was employed together with the common registration framework (Appendix A, section A.2) i.e. one level registration; hence, manual resampling and registration process were carried out in each level. By using this approach, the change of any registration component in the middle of the multi-resolution registration process was made possible.

The methods adopted for the registration components were the same as the ones described in section 4.2. The approach to replace the multi-resolution framework in ITK involved placing the registration process inside iteration; the flowchart implementing the approach and the comparison with the multi-registration framework are illustrated in Figure 6.1. The image pyramid is replaced by iteratively resampling the images prior to the registration process inside each iteration. The resampling process involves downsizing and smoothing by Gaussian filter. The downsizing process reduces the resolution of the image by the downsizing factor for the respective level. In the top level of the multi-resolution, the downsizing factor is the largest as the coarsest resolution image is generated. Smoothing process using Gaussian filter is employed to avoid aliasing problem during resampling. The image datasets being used were the combinations of Brain[No]Normal and Brain[No]R[A]T[L].

Figure 6.1. Flowcharts of multi-resolution registration algorithms implementing multi-resolution registration framework and common registration framework inside iteration.

The first version of the algorithm, named Test-Algorithm, was made as a multi-resolution scheme with 3 levels; its top level (i.e. level 0, the coarsest) implemented Powell's optimizer, whereas the subsequent levels (i.e. level 1 and 2) implemented regular step gradient descent optimizer. The decision to allocate one level for Powell's method and two levels for regular step gradient descent was due to the considerations of the advantages and limitations of each of the optimization method as well as the required sampling time if many levels were to be used. As the aim of placing Powell's method at the top level was to search for the best initial guess for the subsequent level, it was enough to allocate one level for this purpose. Allocating more levels for Powell's would only add time spent for image resampling while getting no significant improvement in terms of closeness of the initial guess to the solution; as had been explained in section 5.2, it is fast in approaching the area confining the solution yet slow in getting small convergence. The task of approaching the solution was then assigned to the regular step gradient descent

method; as it is considerably fast in working with fine resolution image. Two levels were chosen; it was then observed as to whether there was a need to reduce or add another level.

The shrink factor in each level in this adapted multi-resolution scheme did not follow the one as in ITK multi-resolution registration. Instead of using the ITK's shrink factor (Appendix A, section A.3), the shrink factors for the levels were customized as:

$$\text{Shrink factor for level 0} = 2^5$$

$$\text{Shrink factor for level 1} = 2$$

$$\text{Shrink factor for level 2} = 1$$

In this case, the shrink factor was only defined as the power of two to make the downsizing of the images comparable to the ones by image pyramid. The image resolution in the level was thus downsized by the shrink factor applied in each 3-dimension. For instance, for the 3-D volume, the number of pixels along x, y, and z were downsized by dividing them with the shrink factor. The datasets used has 181x217x181 voxels. In level-0, the volume's size was downsized to (181/32 x 217/32 x 181/32) voxels. Yet, the down sizing does not affect the physical size of the volume; it remains 181 x 217 x 181 mm³. The resampling process only changes the image's resolution. In the last level, the registration works in the full resolution of the image as the shrink factor is 1. The set of shrink factors was chosen so that the level-0 of registration has coarse image resolution for the Powell's optimization to perform fast. Its shrink factor was chosen to be 2⁵ among the possible factors starting from 2²; as 2⁰ (finest resolution) and 2¹ are reserved for level-2 and -1 respectively. Factor 2⁵ was chosen arbitrarily, considering that this value would only be the starting point to find out if this factor was appropriate; if the experimental results suggested that the resolution using this factor was still considered too coarse for the Powell's method to work optimally, the factor could be decreased to e.g. 2⁴ to 2², or otherwise. The findings would then be used to perform rectification in the improved algorithm. For the intended application in real implementation, the shrinking factor would be calculated based on the size of the registered images. The findings in this experiment would serve as the guideline to calculate a proper shrinking factor. For instance, if

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factor 2^5 was found to be a proper shrinking factor for an image size of $181 \times 217 \times 181 \text{ mm}^3$, an image of twice its size would require factor of 2×2^5 . The pseudo code of adapted multi-resolution algorithm, referred as “*Test Algorithm*”, is presented as follows:

```

/*Algorithm name: Test Algorithm*/
/*initialization*/
Read the images
Set transform = Euler3DTransform
Set interpolator = LinearInterpolator
Set metric = MattesMutualInformationMetric
i = 0 /*i indicates the level number i.e. level iterator*/
/* starting from 0, the coarsest level*/

WHILE (i < Number of Levels)
DO

    Resample the images by resizing using shrink factor and smoothing factor for level i.

    IF(i == 0) /*if in level 0*/
    THEN

        /*initialization for Powell's optimizer*/
        Set optimizer = PowellOptimizer
        Set optimizer's scales for PowellOptimizer
        Set Step Length = a
        Set Step Tolerance = b

    ELSE /*i ≠ 0*/

        Set optimizer = RegularStepGradientDescentOptimizer
        Set optimizer's scales for RegularStepGradientDescentOptimizer
        IF (i == 1)
        THEN
            Set Maximum Step Length = c
            Set Minimum Step Length = d
        ELSE /*i > 1*/
            Set Maximum Step Length = Step Length from previous level
            Set Minimum Step Length = (minimum step length in prev. lvl)/10
        /*end of IF (i == 1) block*/

    /*end of IF (i == 0) block*/

    Start Registering
    i = i+ 1 /*increment level iterator*/

/*end of WHILE loop*/

```

In the initialization stage, the registration components: transform, interpolator and metric are set up. The level iterator, i , is initialized to zero; indicating the level zero of multi-resolution level. Subsequently, the algorithm flow proceeds into the loop.

The loop's exiting condition is the completion of registration for all levels, i.e. indicated by i equals or bigger than the number of levels. In the loop, in the beginning of registration process of a level, the images are resampled based on the shrinking factor and the smoothing factor for the level. Afterwards, there is an IF-THEN-ELSE condition to check the current level. This condition is to differentiate the assignment of the optimization method for the current level; if the current level is 0, the flow proceeds to the THEN block, and ELSE block otherwise. In the ELSE block containing the setting up of the regular step gradient descent method, there is an IF-THEN-ELSE condition to handle the maximum and minimum step lengths assignment according to the current level; if it is in level 1, the flow proceeds to the THEN block, and ELSE block otherwise. Upon the settings of all the registration components, the registration is then carried out. At the end of the registration process, the level iterator is then incremented by one.

In the algorithm, there are four variables involved, which are a , b , c , d that represent step length and step tolerance of Powell's method, and initial maximum step length and minimum step length of regular step gradient descent method. It was to be found out the combination of the variable's value that able to give good registration result.

6.2.2 Results and Discussions

The results of the experiments using the test algorithm are presented in Table 6.1. The Powell's step tolerance, b , determines the end of optimization iteration in level-0; it also determines the proximity of the initial guess for the subsequent level's optimization method i.e. RSGD to the solution (refer to the explanation in Appendix A, section A.2.4 about step tolerance). Hence, the selection of the value of b was based on the expectation that the initial guess for the RSGD optimizer was close enough to the candidate of the true solution i.e. local extreme. Thus, it would lessen the time spent by the RSGD method to approach the solution. Hence, in this case, the value of b was set to 0.05; it means that the optimization by Powell's method will stop when local extreme is found within the proximity of 0.05 distance unit in the parameter space. Based on the preliminary experiment to calibrate the unit (not shown in the report), distance unit of 0.05 in parameter space is approximately

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equivalent to 1 mm (for translational) and 0.1 radian (for rotational). As a result, the values resulted by Powell's were close enough to the solution, within about 1 mm (for translational) and 0.1 radian (for rotational) to the true value.

The selection of the values for variable c and d (initial maximum and minimum step length respectively) was based on the level of accuracy achieved in the optimization by Powell's method in the previous level. As the optimization by Powell's method could provide a set of values for the initial guess which was within 1 mm (for translational) and 0.1 radian (for rotational) close to the true value, an initial maximum step length c of 1.5 was selected. In some of the trials, the c values were changed to 2 and 0.5 (in trial no. 4 and 2 respectively). The change was meant for observing if there was any improvement by defining longer or shorter step length; the results show that longer or shorter step length gives speed improvement when they exactly match the required distance to approach the true solution. In fact, the fastest speed is achieved by specifying 2 for the maximum step length, i.e. trial 4. The second best speed is achieved by trial 6 with maximum step length of 1.5. The third place is by trial 2, with the maximum step length set to 0.5. It is concluded that the maximum step length affects the speed to approach the true solution.

Table 6.1: Results of Trials and Tuning Experiments using Test-Algorithm.

No	Factors				Results								Error (mm)
	a	b	c	d	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time (s)	
1	0.01	0.05	1.5	0.1	0.1630	0.1234	-9.9345	2.6317	-16.9476	-0.0803	-1.610	129	0.4549
2	0.1	0.05	0.5	0.1	0.0256	0.0077	-10.1417	2.7033	-16.8763	0.5260	-1.067	105	0.7552
3	0.1	0.05	1.5	0.1	0.2160	0.0642	-9.8984	2.5694	-16.938	0.0566	-1.459	159	0.4416
4	0.07	0.05	2	0.1	0.2067	-0.1382	-9.5117	2.3154	-16.7066	-0.6208	-1.119	94	0.9163
5	0.05	0.05	1.5	0.1	-0.2067	-0.2769	-20.166	11.833	-36.3922	0.0578	-1.653	147	1.1203
6	0.02	0.05	1.5	0.1	-0.0226	0.1112	-20.4119	12.284	-36.8302	0.3115	-1.080	97	0.9700
7	0.001	0.05	1.5	0.1	0.0721	-0.2795	-19.7634	11.633	-36.46	-0.2036	-1.133	155	1.0562
8	0.001	0.05	1.5	0.1	-0.5162	-0.5455	-20.7099	12.158	-36.7155	-0.0157	-1.480	166	0.9306

In terms of speed, this algorithm outperforms the performance of the multi-resolution algorithms elaborated in chapter 4 and 5 as seen in the registration results in Appendix B and C for RSGD algorithm and Appendix D for Powell's algorithm. Compared to the result of the RSGD multi-resolution algorithm, the Test Algorithm has improved the processing speed by a minimum factor of two; the slowest result by

the test algorithm, 166 s (trial 8), performs faster than the fastest result by the regular step algorithm, 391 s (Appendix B, Table B.C.2), by a factor of 2.4 (i.e. 391/166).

Unfortunately, the Test Algorithm does not perform well in terms of accuracy. As could be seen in Table 6.1, its minimum error is 0.4416 mm which is still much larger than the maximum error resulted by regular step gradient descent algorithm, which is 0.0712 mm, excluding the outlier data (Table 5.4). The maximum error by Test Algorithm i.e. 1.1203 mm, even exceeded the voxel size. As the error definition being adopted (Section 4.3.3) is a lower bound error, having error values exceeding the voxel size is not acceptable. Thus, the Test Algorithm still needed further improvement for its accuracy.

Another drawback of this test algorithm is its being not robust as a small difference in the value of one of the parameters i.e. a causes large difference in result. The value of the Powell's step length, a , needed to be guessed to obtain convergence to the right solution. Table 6.1 only shows the values of a that could give correct convergence in the Powell's method. A small difference in the value of a could cause Powell's optimization went to wrong direction; a very large deviation. For example, if in trial 4 the value of a was changed to 0.06, the Powell's result could be as far as ($R_x = 2$, $R_y = 2$, $R_z = 5$, $T_x = 40$, $T_y = 10$, $T_z = 10$). Thus, for this algorithm to arrive at the results presented in Table 6.1, the values of variable a should follow the listed values. This drawback had rendered this algorithm not applicative. This problem was due to the limitation of Powell's optimizer that is easily trapped in local optima (Section 3.4.D). Thus, a method to avoid this 'guessing' problem was required.

6.3 Improved Algorithm

6.3.1 Considerations

The Test Algorithm (section 6.2.1) showed promising result that can improve registration speed. However, there were several critical issues that had to be resolved in order to make it perform better. These critical issues were local optimality, accuracy problems, and the optimum number of multi-resolution levels.

6.3.2 Design of Algorithm

Firstly, the problem needed to be solved was the local optima problem. It was critical for the algorithm to be applicable in all registration cases. A proposed method to solve this problem was to check the metric value at the end of the Powell's optimization. Metric value is the measure to be optimized i.e. minimized during the registration process. The metric indicates the degree of alignment between the two images, or, in other words, it indicates the closeness of the optimization result to the true solution; true solution also means global optima. Thus, in order to ensure that the Powell's optimization result is approaching the global optima instead of local optima, a check to the metric value could be performed.

Normally, a good alignment is indicated by a metric value less than -1.0. It could be seen from all the experimental results in Appendix B, C, D, and E in the column with header 'M'. The lesser the metric value, the better the accuracy. Thus, by defining a threshold value for the metric, it could be checked whether the optimization process converges to the correct direction i.e. global optima. In this case, the threshold value was defined to be -1.1 (minus 1.1). This threshold was implemented as a condition of a loop in level-0. Other problem that appeared in Powell's method is that Powell optimization is easily failed as has been discussed in section 5.2. Fortunately, ITK registration framework provides a method to detect the failure; and the error message indicating failure could be captured. Thus, in order to solve the problem related to the Powell's method, i.e. local optima and failure problems, there were two condition checks applied in level-0 prior to the passing of the optimization results to the subsequent level. The condition checks were applied to the metric values and failure error status.

Addition of several checks and iterations in level-0 of registration as elaborated above would affect the speed of the process; it would make the registration process slower. To compensate for it, the resolution of the image in level-0 were made smaller i.e. larger shrink factor was applied. It would not affect the accuracy of the final result as the registration in the top level was merely to search for the good initial guess. A refining process was handled in the lower level.

The other critical issue was accuracy. The low accuracy that has arisen in the Test Algorithm could be due to the resampling process applied even to the lowest level resolution (i.e. finest resolution, level 2). As could be seen in the pseudo code of the algorithm, the resampling process is performed on the images on every level of registration; even to the lowest level. Although the shrink factor and smoothing factor for the lowest level were set to be 1, i.e. no resizing and smoothing, the image should still go through the resampling process which may affect the images' resolution. Hence, a proposed way to handle this was to bring the registration process of the lowest level out of the iteration. This way could avoid the images being resampled; thus, it ensured that only the original images were used in the last registration, instead of the resampled ones.

Another issue was the optimum number of levels being used in the lower levels. On this matter, the time required for each resampling process should be considered. Additional number of levels would introduce additional time spent for resampling. As the Powell's method had been able to provide initial guess close to the true solution, the next process required was merely to refine the results. In refining process, the use of more than one level was not necessary as only a few steps were required for convergence provided that a close initial guess was applied. It was hence decided that only one level of registration process was used for refining process. Thus, in the last registration process, optimization was performed using regular step gradient descent on the full resolution of the images. The maximum and minimum step lengths were chosen so that it could speed up the process while maintaining considerable level of accuracy; yet, not being too stringent. In this case, maximum step length of 1 and minimum level of 0.1 were selected as this could already be able to ensure the sub-voxel accuracy.

Compiling all the proposed methods described above, a new version of the registration algorithm was developed. The algorithm has the following specifications:

- Number of multi-resolution level = 2.

- Level 0 (coarsest):

- o Resolution: $1/2^0$.

- Optimizer: Powell Optimizer
 - Step Length = Step Length + 0.01 (iterated until the close initial estimate of optimum value is met, checking based on metric value of <-1.1 .)
 - Step Tolerance = 0.005
- Level 1 (finest):
 - Resolution: full Resolution (=1) (i.e. same volume size as the original volume).
 - Optimizer: Regular Step Gradient Descent Optimizer
 - Maximum step length=1.0
 - Minimum step length=0.1

The pseudo code of the algorithm, referred as “Improved Algorithm” is presented as follows:

```

/*Algorithm name: Improved Algorithm*/
/*initialization*/
Read the images
Set transform = Euler3DTransform
Set interpolator = LinearInterpolator
Set metric = MattesMutualInformationMetric

/*Registration process in level 0*/
Resample the images by resizing using shrink factor and smoothing factor in level 0.

Set optimizer = PowellOptimizer
Set optimizer's scales for PowellOptimizer
Set Step Tolerance = 0.005

Step = 0.0 /*initialization for the step length*/

DO
    Step = Step + 0.01
    Set Step Length = Step
    Start Registering

WHILE((metric value > -1.1) or (error message is caught))

/*Registration process in level 1*/

Read image directly without resampling
Set optimizer = RegularStepGradientDescentOptimizer
Set optimizer's scales for RegularStepGradientDescentOptimizer
Set Maximum Step Length = 1.0
Set Minimum Step Length = 0.1
Start Registering

```

The registration is performed twice separately, in level- 0 and 1. The result from level-0 is passed to level-1. Upon performing initialization to set up the registration components: transform, interpolator and metric, the registration is performed for level-0. In this level, the Powell's optimizer and its parameter scales are set as well as the step tolerance value. The registration command is placed inside a DO-WHILE loop with the exiting conditions are the metric value smaller than or equal to -1.1 and no error message indicating failure is caught. The registration process in level-0 would be iterated with increasing step length until the exiting conditions are met. The results from the registration in level-0 are then passed to level-1. The optimizer is then switched to regular step gradient descent optimizer and its parameter scales are set. The maximum and minimum step lengths are set to 1.0 and 0.1 respectively prior to the registration process.

6.3.3 Experiment on the Verification of Improved Algorithm using Multimodal-Image Model

The Improved Algorithm needed to be verified for its applicability for multimodal image registration. The verification adopted the same approach as the one elaborated in section 4.4.8. It used the same multimodal image models as the ones in section 4.4.8, Table 4.5. The results and discussions for this experiment are presented in section 6.3.4.5.

6.3.4 Results and Discussions

6.3.4.1 The Effect of Transformation Range

The effect of transformation range in the Improved Algorithm was investigated based on the results generated from the combination of images from transformation set 10° rotation – 15 mm translation and 20° rotation – 20 mm translation. Figure 6.2 and 6.3 show the results of the accuracy and speed from both transformation sets.

Figure 6.2. Comparison of Accuracy between transformation ranges: 10 degree rotation - 15 mm translation and 20 degree – 20 mm translation, using Improved Algorithm.

Figure 6.2 shows that the resulted error from larger transformation value i.e. 20° rotation and 20 mm translation are smaller than the ones of smaller transformation value i.e. 10° rotation and 15 mm translation but one case for Brain1Normal – Brain1R[A]T[L]. Moreover, the average errors for both cases only differ slightly. It is unlike the result of RSGD-based algorithm that shows the trend that larger transformation value gives consistently larger error than its respective smaller transformation value (refer to Table 5.4). Hence, in Improved Algorithm, transformation range does not affect the accuracy results; a large transformation value might give larger or smaller error than a small transformation value. This implied that the adopted transformation method, i.e. Euler3D transform, affects indifferently to the transformation range in the Improved Algorithm. It might be related to the approach of determining the initial guess of the optimization. In RSGD-based algorithm, the initial guess was ($R_x=0$, $R_y=0$, $R_z=0$, $t_x=0$, $t_y=0$, $t_z=0$) for all cases. The guess is of different distance to the solution, depending on the transformation range as transformation range governs the distance between the initial guess to the true solution. In the small transformation range i.e. 10° rotation - 15 mm translation the guess is closer to the solution than the one of larger range i.e. 20° rotation – 20 mm translation. Euler3D transformation adopts linearity assumption that still holds for small range, i.e. accurate result, yet it deviates more as the

transformation range gets larger i.e. less accurate; it was as explained in section 5.5. Hence, it explains the results of the RSGD-based registration. On the other hand, the Improved Algorithm, instead of using a fix initial guess of ($R_x=0$, $R_y=0$, $R_z=0$, $t_x=0$, $t_y=0$, $t_z=0$), employs iterations checks in level-0 to search for a better initial guess to approach the true solution. The closeness of the initial guess to the solution is determined by variable *step tolerance*; it is hence of equal distance to the solution in all cases of registration regardless of the transformation range. The initial guess resulted in level-0 is then passed to the subsequent level's optimization. Thus, in the Improved Algorithm, its being of equal distance of the guess to the true solution makes the accuracy values become unaffected by the transformation range.

Figure 6.3. Comparison of speed between transformation ranges: 10 degree rotation - 15 mm translation and 20 degree – 20 mm translation, using Improved Algorithm.

The role of level-0 as a step to determine good initial guess in the Improved Algorithm also explains the relationship between the registration speed and the transformation range. Figure 6.3 shows that the speeds resulted from larger transformation range are alternately faster and slower than the ones from its respective smaller range. The speed is hence indifferent regardless of the transformation ranges. It is unlike the results by RSGD-based algorithm that shows consistently faster speed of smaller transformation range than the ones of the respective larger range (refer to Table 5.4). As RSGD applied the same initial guess for all transformation range, the distance from the guess to the true solution depends on the transformation range. It then explains the reason for slower performance of

RSGD-based algorithm in larger transformation range than in smaller range. However, in the Improved Algorithm, as explained in the previous paragraph, the distance between the initial guess to the true solution is made equal for all range by the search of good initial guess performed in level-0. This hence makes the speed of the Improved Algorithm unaffected by the difference in transformation range. In addition, the search of good initial guess in level-0 contributes to faster performance of the Improved Algorithm compared to the RSGD-based algorithm.

6.3.4.2 The Effect of Acquisition-Mode

The results depicting the effect of acquisition-mode to accuracy and speed of the Improved Algorithm are presented in Figure 6.4 and 6.5 respectively. This experiment aimed to observe the performance of registration algorithms being developed with respect to the difference in acquisition mode in MRI image datasets i.e. PD and T2 acquisition modes. In Figure 6.4, it is shown that, in average, intra-acquisition-mode has lower accuracy compared to the inter-acquisition mode. This finding is in opposite to the one in the RSGD-based algorithm that intra-acquisition-mode gives higher accuracy than the inter-acquisition-mode. The accuracy of the Improved Algorithm seems to have inconsistent pattern, unlike in the RSGD-based algorithm. It might be related to the role of level-0 to search for a good initial guess. In the parameter space, the direction of approach to the true solution could be from many directions. The direction of approach to the solution in the subsequent level i.e. level-1 depends on the direction of approach found in the level-0. Thus, the level of accuracy achieved in level-1 depends on the closeness of the guess to the solution and the specified accuracy, defined in variable *minimum step length*. Hence, sometimes the approach from the direction found in level-0 does not allow the optimization process to achieve accuracy level as expected by the *minimum step length*; in that case, the optimization would stop at the possible nearest point to the solution, yet it is not as good as the expected accuracy level. Thus, in this case, the accuracy of the result depends more on the resulted initial guess found in level-0. It is hence independent from the acquisition-mode. This explanation also complements the explanation for the independence of accuracy results from transformation range

difference in the previous section. This also explains the lower accuracy of the Improved Algorithm compared to the RSGD-based algorithm.

Figure 6.4. Comparison of accuracy between intra- and inter- acquisition-mode using Improved Algorithm.

Figure 6.5. Comparison of speed between intra- and inter- acquisition-mode using Improved Algorithm.

The speeds of the Improved Algorithm for intra- and inter- acquisition-mode are about the same values, as shown Figure 6.5. In average, the speed of both cases only differs slightly. The speed for the inter-acquisition-mode is alternately higher and lower than the respective intra-acquisition-mode; the speed for inter-acquisition-mode is slightly higher for 10° rotation - 15 mm translation, but slightly lower for 20° rotation – 20 mm translation. Although it seems to form a trend of speed values, the process of optimization as discussed in the previous paragraph suggested that the trend might only be a coincident. The speed is basically governed by the distance

between the initial guess to the solution; hence, it is independent of the acquisition-mode as well as transformation range.

6.3.4.3 Comparison between Improved Algorithm, Test Algorithm and Regular Step Gradient Descent (RSGD)-based Algorithm

The results of the experiments using the Improved Algorithm are listed in Appendix E, Table E.2 and E.3. Comparison between the accuracy and speed of the Improved Algorithm, Test Algorithm and RSGD-based algorithm are illustrated in Figure 6.6 and 6.7 respectively. RSGD-based algorithm is the algorithm as described in section 4.2. The ‘Experiment No’ in Figure 6.6 and 6.7 refers to the numbering of image pairs as listed below:

1. Brain1Normal and Brain1R10T15
2. Brain1Normal and Brain1R20T20
3. Brain3Normal and Brain3R10T15
4. Brain3Normal and Brain3R20T20
5. Brain1Normal and Brain3R10T15
6. Brain1Normal and Brain3R20T20
7. Brain3Normal and Brain1R10T15
8. Brain3Normal and Brain1R20T20

In Figure 6.6, it is shown that the Improved Algorithm generates less error than the Test Algorithm; Improved Algorithm’s maximum error, 0.2346 mm, was still less than the minimum error of the Test Algorithm results, 0.4416 mm.. Test Algorithm’s average error, 0.8306 mm, is larger than one of Improved Algorithm, 0.0884 mm. The errors of the Improved Algorithm range between 0.0188 and 0.2346 mm which are still less than the voxel size. It then fulfills sub-voxel accuracy criteria. Hence, compared to the Test Algorithm results, the accuracy of the Improved Algorithm is much better.

Figure 6.6. Comparison of Error between Improved Algorithm, Test Algorithm and RSGD Optimization – based Algorithm; plotted from Appendix E (Test and Improved Algorithms) and Table 5.4 (RSGD-based Algorithm).

Figure 6.7. Comparison of processing time between Improved Algorithm, Test Algorithm and RSGD Optimization – based Algorithm; plotted from Appendix E (Test and Improved Algorithms) and Table 5.4 (RSGD-based Algorithm).

The RSGD-based algorithm still outperforms the Improve Algorithm in accuracy. Figure 6.6 shows that the average error and the error for the respective image pair of the RSGD method are still smaller than the ones of the Improved Algorithm. In addition, as can be seen from Table 6.2, in most of the cases, the errors of the Improved Algorithm are still larger than the maximum error of the earlier but one

case i.e. Brain3Normal – Brain1R20T20. However, this accuracy level is still considered acceptable as the error is still within the voxel size.

Figure 6.7 shows that Test Algorithms performs the fastest and RSGD-based algorithm the slowest; the Improved Algorithm is in between. The longest time taken by the Improved Algorithm for the registration process is 245 s, whereas the shortest time is 140 s, the average time is 198 s. Compared to the Test Algorithm, the Improved Algorithm performs slightly slower; yet, it is much more robust. There is no guessing of variables required. Both Test and Improved Algorithm made large improvement in terms of speed from the RSGD-based algorithm. However, RSGD-based algorithm is still the best in terms of accuracy. Thus, in Test and Improved Algorithms, their fast speed is compromised by their reduced accuracy.

Table 6.2 shows comparison between the Improved and RSGD-based Algorithms. It is shown that the longest time taken by the earlier, 245 s, is still faster than the fastest in the later, 391 s. Thus, the minimum speed up factor is 1.6 ($= 391/245$). The results also show that combination between Brain1Normal and Brain1R20T20 is the most time taking in both algorithms; in the earlier algorithm, its average, minimum and maximum times are the largest; similarly in the later algorithm, its time taken is also the largest, 245 s. This implies that the alignment between Brain1Normal and Brain1R20T20 is the most complicated, as it takes the longest processing time. For the same combinations, by taking the average time in the earlier algorithm, the speed-up factors are found to be 4.1, 3.2, 3.6, 3.7, 2.9, 4.4, 2.8, and 3.6 (i.e. $580/140$, $790/245$, $640/176$, $731/195$, $625/219$, $820/187$, $656/232$, $679/188$) for the same combination order presented in Table 6.2; the values being used in the calculation are the ones highlighted. Speed up factor is calculated by dividing the time-taken between a reference result and the assessed result. In this case, the reference results are the results from the RSGD algorithm; the assessed results are the results from the Improved Algorithm.

Table 6.2: Performance comparison between regular step gradient descents –based and improved algorithms.

Combinations	Regular step Grad Desc –based Algorithm						Improved Algorithm	
	Time (s)			Error (mm)			Time (s)	Error (mm)
	Ave.	Min.	Max.	Ave.	Min.	Max.		
Brain1Normal - Brain1R10T15	580	455	712	0.0213	0.0177	0.0330	140	0.0893
Brain1Normal - Brain1R20T20	790	493	1352	0.0327	0.0245	0.0712	245	0.2346
Brain3Normal - Brain3R10T15	640	391	913	0.0079	0.0025	0.0180	176	0.0737
Brain3Normal - Brain3R20T20	731	514	872	0.0087	0.0054	0.0146	195	0.0604
Brain1Normal - Brain3R10T15	625	434	840	0.0425	0.0370	0.0450	219	0.1026
Brain1Normal - Brain3R20T20	820	516	1115	0.0471	0.0451	0.0512	187	0.0547
Brain3Normal – Brain1R10T15	656	459	956	0.0460	0.0426	0.0618	232	0.0732
Brain3Normal – Brain1R20T20	679	513	952	0.0571	0.0534	0.0702	188	0.0188

6.3.4.4 Comparison with Maes et.al. Project Result

A thorough research work on the comparison of speed and accuracy of multi-resolution scheme MI-based registration had been done by Maes et.al., presented in [43]. The comparison between the experiments conducted in [43] and this project are presented in Table 6.3. It can be seen that the speed performance of the improved algorithm occupies the lower end within the speed range of the results by Maes.et.al. A direct comparison could be made provided the same datasets were used in both projects. However, it was not the case; a direct comparison can not be done. Several adjustments and assumptions hence need to be established. The image size (in voxels) used in [43] is about twice the image size used in this project. Hence, a multiplication factor of 2.0 could be applied to the results of the improved algorithm to make the comparison between the two projects more reasonable. It is based on the assumption that the image size of twice larger might take twice the processing time longer. Upon the multiplication by 2.0, the maximum processing time by the improved algorithm i.e. 245 becomes 490 s, still falls within the range of the speed of the results in Table 6.3. However, the way of comparing speed as described can only be a rough comparison between the two projects due to its dependence on the assumptions. Another way of comparing the results, which is more independent from

assumption, is by using speed-up factor. This will be described in the subsequent paragraph.

Table 6.3: Comparison between Current Project and the Project “Performance comparisons between multi-resolution scheme MI-based Registration” by Maes et.al.

Datasets and Workstation Specifications	Project Description	Speed	Error
Head image (Vanderbilt University Data [28]): -CT: 512x512x[40-49] voxels; $[0.4-0.45]^2 \times 3.0$ $\text{mm}^3/\text{vox.}$ -MRI: 256x256x[51-52] voxels; $[0.78-0.86]^2 \times 3.0$ mm^3/voxel Workstation spec.: IRIX 6.4, R10000, 195 MHz, 17 SPECfp95.	Performance comparison between: Powell-Brent's (POW), downhill simplex's (SMP), steepest gradient descent's (STD), conjugate gradient's (CJG), quasi-Newton's (QSN), and Levenberg Marquardt's (LVM) methods.	<u>Range of mean time-taken:</u> POW: [241-764] s; SMP: [165-789] s; STD.: [327-1602] s; CJG: [195-961] s; QSN: [335-1615] s; LVM: [254-957] s. <u>Speed up factor compared to Powell's result on full resolution:</u> POW= 1.9; SMP = 2.8; STD = 1.9; CJG = 3.0; QSN = 1.9; LVM = 2.8	<u>Range of error:</u> 0.5 – 3.1 mm; mean error = 1.78 mm (< 1 CT voxel)
Head Image (BrainWeb [63]): MRI: 181 x 217 x 181 voxels; 1 $\text{mm}^3/\text{vox.}$ Workstation spec.: processor Intel Pentium 4, 3 GHz, 512 MB RAM.	Performance comparison between: Powell-Brent's (POW), Regular Step Gradient Descent (RGSD) methods, and Combined Powell's and RGSD (POW-RGSD) method (i.e. Improved Algorithm).	<u>Range of mean time-taken:</u> POW:[4010-9324]s RGSD:[391-1352]s POW-RGSD:[140-245]s <u>Speed up factor compared to RGSD's result on multi-resolution:</u> POW=[0.14-0.06]; RGSD=1; POW-RGSD=[2.8-4.4]	<u>Range of Error:</u> POW: [0.0095-0.0542]mm RGSD: [0.0025-0.0712]mm POW-RGSD: [0.0188-0.2346]mm

Another difference between the project in [43] and this project is in the specification of the workstation being used. The specification of the workstation for the implementation of the algorithms in this project is processor Intel Pentium 4, 3 GHz, 512 MB RAM. This may affect the speed difference in this comparison. The computer-specification difference made the comparison between the two projects based on speed unreasonable. Thus, it might be more appropriate to perform

comparison using a measure obtained from within each of the project; this measure is the speed-up factor. Speed-up factor is a dimensionless measure; it makes the comparison between the projects becomes independent of the computer-specification or any assumptions, as elaborated in the previous paragraph. In Maes et.al.'s project, the reference for the speed up factor was the Powell's method on full resolution i.e. non-multi-resolution scheme; in this project, the reference for the speed-up factor was the RSGD-based multi-resolution algorithm for the respective image combinations. This has made the comparison criterion more stringent than the ones in Maes et.al. as the comparison between algorithm of the same multi-resolution scheme would only expect to give small speed-up factor. However, the results show that the range of speed-up factors in this project is between 2.8 to 4.4 which are bigger than the ones in Maes et.al.'s results. This implies that the Improved Algorithm, implementing combined optimizer in multi-resolution scheme, could improve the speed of registration compared to the multi-resolution algorithm implementing only one optimizer.

In terms of accuracy, the error measures resulted by the Improved Algorithm had shown smaller values compared to Maes' results. However, the error measures method adopted in both projects are different. This project adopted lower bound error measure, whereas Maes' adopted TRE measures based on the average error of the mapping of several points. If a multiplicative factor of 10 were to be applied to the lower bound error (assuming the TRE value could be as large as 10 times the lower bound error) there would be two results by the improved algorithm that fall beyond the sub-voxel accuracy i.e. 0.2346 mm becomes 2.346 mm and 0.1026 mm becomes 1.026 mm error (Table 6.1). However, these results were still within the range of errors in Maes' experiments i.e. 0.5-3.1 mm; even if a multiplicative factor of 20 were to be used.

The difference of registration performance, i.e. speed and accuracy in both projects were affected by several factors. In addition to the abovementioned factors e.g. workstation specification, image size, another affecting factors are different image modalities involved and development software being used. Project in [43] involved registration between 3-D CT and 3-D MRI images, whereas this project involved 3-D

MR and 3-D MR images. Such difference may cause different grey value distributions and image resolution that eventually affect the accuracy of the registration result. Besides, both projects might also differ in the software library being used to develop the registration application. This project used ITK library, whereas project in [43] might use the project's proprietary library. Different library might cause different memory requirement and computational load to run the program, which eventually may affect the speed and accuracy of the registration process.

6.3.4.5 Verification of Improved Algorithm using Multimodal-Image Model

To verify the applicability of the Improved Algorithm for multimodal image registration, the experimental results using the models are assessed based on the conditions described in Section 4.4.8. The result of the experiment is presented in Table 6.4.

Table 6.4: Results of Improved Algorithm verification experiment using multimodal image models.

Pair No.	Results							Error (mm)
	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	Time (s)	
1	0.3252	0.3182	-10.075	2.3728	-17.3252	0.1349	291	0.1683
2	0.0544	0.4233	-10.026	2.3375	-17.3863	0.0659	205	0.1461
3	-0.0094	-0.2683	-10.034	2.5365	-17.4023	0.1339	310	0.1563

The first condition that the algorithm must be able to produce results using the model images was fulfilled. There was no faulty occurred during the execution of the program. The second condition for the applicability of the algorithm to the model is the acceptability of the generated results. The acceptability is assessed on two aspects: speed and accuracy. As discussed in section 4.4.8, the ability of the algorithm to produce result implied that the resulted speed is acceptable. Figure 6.8 shows the comparison between the speed of RSGD – based algorithm and the Improved Algorithm on the original mono-modal images and multimodal image models. It is shown that the Improved Algorithm's processing time ranges 205 – 310 seconds; thus, the speed is acceptable and even outperforms with the ones of the RSGD– based algorithm.

Figure 6.8 shows that the speed of the Improved Algorithm on the multimodal image model, i.e. labeled Pair [No], is slightly slower than the one on the mono-modal image pairs i.e. labeled Brain[No]Normal and Brain[No]R10T15. It might be due to the lower resolution of the image model than of the mono-modal images; the lower the image resolution, the smaller amount of voxels need to be processed during registration. This finding agrees with the one discussed in section 5.8.

Figure 6.8. Speed Comparison of Regular Step Gradient Descent (RSGD)-based- Algorithm and Improved Algorithm (IA) on Mono-modal Images and Multimodal Image Models. Image combination ‘Brain[No]Normal-Brain[No]R10T15’ indicates label for mono-modal image, whereas ‘Pair [No]’ for multimodal image model as listed in Table 4.5.

Compared to the average speed of the RSGD-based algorithm on the pairs of mono-modal image pairs, the ones of Improved Algorithm on the multimodal image models are faster by about twice. The maximum processing time on the models, 310 s, is almost half the minimum average time of the results using mono-modal images, 580 s. Applied to the same multimodal image models, the Improved Algorithm also performs faster at almost twice the speed of the RSGD-based algorithm. The fact that the Improved Algorithm performs almost twice the speed of RSGD-based algorithm both on mono-modal image and multimodal image model is as expected due to the improvements made on the Improved Algorithm.

In terms of accuracy, Table 6.4 shows that the error values are sub-voxel accurate. The errors are less than the size of the smallest dimension of the smallest voxel size

i.e. 1 mm; the smallest voxel among the pairs is the fixed image voxel, $1 \times 1 \times 1 \text{ mm}^3$. Thus, the accuracy of the results is considered acceptable. As the algorithm being tested has fulfilled both conditions stipulated in section 4.4.8, it was then concluded that the algorithm is applicable for multimodal image registration.

Figure 6.9. Error Comparison of Regular Step Gradient Descent (RSGD)-based- Algorithm and Improved Algorithm (IA) on Mono-modal Images and Multimodal Image Models. The algorithms implemented are indicated as a prefix in the image combination label. Image pair ‘Brain[No]Normal-Brain[No]R10T15’ indicates mono-modal image, whereas ‘Pair [No]’ indicates the multimodal image model as listed in Table 4.5.

Figure 6.9 shows that, with the same algorithm, the Improved Algorithm, the errors resulted from the multimodal image model are higher than the one from mono-modal images. Its being lower accuracy when using the model might due to reduced resolution of the model compared to its original resolution i.e. mono-modal images. Low resolution image contains less information than the one of higher resolution. Consequently, the accuracy of the registration involving images of low resolution would be lower than the one of high resolution. This also explains the low accuracy

of results from the Improved Algorithm on the image model compared to the RSGD-based algorithm on the mono-modal image.

Figure 6.9 also shows that using the same multimodal image models, the results of the Improved Algorithm are of almost equal accuracy with the ones of RSGD-based algorithm. This implies that the performance of both algorithms is indifferent on registration of images of different modalities and resolution.

6.3.5 Visualization

The example of visualization of registration results by the Improved Algorithm is presented in Figure 6.10; the rests are attached in Appendix H. It is displayed as checkerboards of the registered slices in axial, sagittal and coronal (frontal) with slice number 40, 80, 142 respectively. The squares of the checkerboard are aligned well that the images of both modalities show good alignment. Despite its having larger error compared to the RSGD-based algorithm, visually, the registration results of the Improved Algorithm show as good alignment as the ones of the RSGD-based algorithm. It might be that the error values of the results are still within sub-voxel accuracy; thus, the error only contributes to small amount of misalignment which is not visually discernible.

Figure 6.10. Example of visualization of registration result between Brain1Normal and Brain3R20T20 and comparison with the result of RSGD-based Algorithm.

6.4 Conclusions

The proposed improved method i.e. Improved Algorithm shows an overall better performance than the first proposed version i.e. Test Algorithm. Although the speed of the Improved Algorithm is still slightly slower the one of the Test Algorithm, the

Improved Algorithm had improved the robustness and accuracy. Besides, it outperforms the RSGD– based algorithm in terms of robustness and speed, yet still being outperformed in terms of accuracy. However, the accuracy results achieved by the improved method fulfill the sub-voxel accuracy.

In comparison with other researcher’s results, the Improved Algorithm has shown higher speed-up factor compared to the ones in Maes et.al. Upon adjustment by imposing a reasonable multiplicative factor to compensate for the image size difference, the speed performance of the improved algorithm still fall within the range of the speed of the Maes’ results. Similarly for the error measures; upon imposing a significant multiplicative factor to compensate for the error measure method difference between the two projects, the resulted errors by the improved algorithm were still fall within the range of the errors resulted in Maes’ experiments.

The implementation of combined optimizers of regular step gradient descent and Powell’s methods in the multi-resolution scheme, as far as the knowledge of the author, has never been experimented by others before; as has been presented in the literature review in section 3.6. There were implementation on combined optimization method in image registration; however, they were not implemented in multi-resolution scheme.

The registration application being developed in this project is the part of the NeuroBot’s planning system. Other components of the planning system encompassing physical to image registration application and volume visualization are currently being developed concurrently by other team member of the NeuroBot research team. The registration algorithms being developed in this project were delivered as a library containing registration functions. Complete description of the functions encompassing the required input and the resulted output were added in the library to ease the incorporation of the registration functions to the main planning system application. The integration of the registration library to the planning system of the NeuroBot would be handled by the team member working on the main planning system.

CHAPTER 7

CONCLUSIONS AND FUTURE IMPROVEMENTS

7.1 Conclusions

In this project, four algorithms of image to image (3-D/3-D) registration were developed. The algorithms adopted Mutual Information (MI)-based registration method in multi-resolution scheme. The algorithms differ by their optimization technique. Two algorithms implemented Powell's and regular step gradient descent (RSGD) optimization methods respectively, whereas the two others implemented combined optimization of Powell's and RSGD methods. The two algorithms implementing combined optimization method were namely Test Algorithm and Improved Algorithm.

The comparison between the four registration algorithms is presented in Table 7.1. The Powell's-based and Test algorithms are not studied intensively in this project due to their limitation; Powell's method performs very slowly in full multi-resolution scheme that it is considered inefficient to conduct investigation using the method, whereas Test Algorithm is not a robust application that render the algorithm not applicable in real use.

The Improved Algorithm, the algorithm that was proposed based on the result of investigation work, has combined robustness, fast speed and considerable level of accuracy. It fulfills the intended requirements of the registration application for the NeuroBot as listed in Table 2.1. Although the algorithm was only tested with mono-modal images of MRI, the experiment using multimodal image models showed that the algorithm was successfully tested and hence was expected to be applicable for real multimodal image registration. The verification using real multimodal images is reserved for future work. In addition, as required, its speed ranges between 2 – 3 minutes and its accuracy fulfills sub-voxel accuracy (<1 mm). Besides, the Improved Algorithm is of automatic mode that it only requires the user to input the images to generate the registration result. It is hence able to minimize the technical aspects

from the user with less technical background such as a surgeon. Thus, this project had achieved its objective.

Table 7.1: Table of comparison between Powell's-based, RSGD-based, Test and Improved Algorithms.

Aspects		Registration Algorithms			
		Powell's-based Algorithm	RSGD-based Algorithm	Test Algorithm	Improved Algorithm
General Speed		Very slow. Speed range: [4010 – 9324] s.	Moderate. Speed range: [391 - 1115] sec.	Fast. Speed range: [94 - 166] s.	Fast. Speed range: [140 - 245] s.
General Accuracy		Very accurate. Error range: [0.0095 – 0.0542] mm	Very accurate. Error range: [0.0025 – 0.0712] mm	Low accuracy. Error range: [0.4416 – 1.1203] mm	Accurate. Error range: [0.0108- 0.2346] mm
Performance with respect to different ranges	Accuracy	n.a.	Small transformation range gives higher accuracy than large transformation value.	n.a.	Accuracy is independent of transformation range.
	Speed		Small transformation range gives faster speed than large transformation.		Speed is independent of transformation range.
Performance with respect to different acquisition-mode	Accuracy	n.a.	Intra-acquisition-mode gives higher accuracy than inter-acquisition-mode.	n.a.	Accuracy is independent of acquisition-mode.
	Speed		Intra-acquisition-mode gives faster speed than inter-acquisition-mode.		Speed is independent of acquisition-mode.
Applicability for multimodal images		n.a.	Tested successfully on the multimodal image models.	n.a.	Tested successfully on the multimodal image models.
Other limitations		Slow in fine resolution; easily fails in improper choice of parameter scale.	Speed of convergence depends on the initial guess of the solution.	Inapplicable in real use due to its being not robust i.e. slight difference in initial guess leads to completely wrong solution.	Less accuracy compared to RSGD-based algorithm.
Other advantages		Fast in coarse resolution.	The highest accuracy among all four algorithms.	The fastest speed among all four algorithms.	Moderate error with fast speed.

7.2 Future Improvements

A challenging issue in registration using voxel information based method lies in its computational cost. A lot of techniques have been tried to improve the speed of the registration performance. MI-based registration has shown significant result for its accuracy, yet most of the developed techniques are still time consuming.

To further speed up the registration performance, several other combinations of techniques could be investigated. It could involve the combinations of optimization, transformation, MI measures, and/or interpolation methods. Moreover, within the suggested methods, there is still large room for improvements. For example, in the MI measures calculation; this calculation involves the formation of joint histogram generation, sampling of the images, etc; the existing techniques for the joint histogram generation and sampling could still be improved to speed up the registration process.

In terms of its application, this new algorithm i.e. the Improved Algorithm could be investigated on its implementation in more cases involving various images of multimodality, such as CT, MRI, MRA, PET, etc. Also, its implementation could also be extended to various anatomical objects, such as pelvis, hip, atlas, etc. In addition, an experiment using real multimodal images is required to verify the applicability of the algorithm for multimodal registration.

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APPENDIX A

ITK REGISTRATION

A.1 Introduction

ITK, stands for the Insight Toolkit, is an open-source software toolkit for registration and segmentation. Its development started in 1999 with the funding from the US National Library of Medicine of the National Institute of Health. The complete information on the ITK can be found in ITK website <http://www.itk.org>. The following sections would present a brief description of ITK framework which is mostly extracted from the ITK user guide [11].

ITK is implemented in C++ and is cross-platform with the compilation process using CMake build environment. CMake helps in generating the native makefiles and workspaces that can be used in the compiler environment of choice [66]. Despite being in C++, it provides wrapper to interface between C++ and other programming language such as Tcl, Java and Python. This allows ITK's usage in a variety of programming language. In addition, ITK adopts generic programming style i.e. uses templated code. Such templating made the code highly efficient that many software problems are discovered at compile time, rather than at run-time during program execution [67].

A.2 ITK Registration Framework

In ITK, registration is performed within a framework of pluggable components that can easily be interchanged. This allows combinatorial variety of registration methods to be created. The ITK registration framework is depicted in Figure A.1; it comprises of the components of the registration framework and their interconnections. The input data to the registration process are two images: one defined as the fixed (reference) image $f(\mathbf{X})$ and the other one as the moving (test) image $m(\mathbf{X})$, where $\mathbf{X}$ represents a position in N-dimensional space.

Registration is regarded as an optimization problem with the goal of finding the spatial mapping that could align the moving image to the fixed image. The *transform* component $T(\mathbf{X})$ represents the spatial mapping of points from the fixed image space to points in the moving image space. The *interpolator* is used to evaluate moving image intensities at non-grid positions. The *metric* component $S(f, m \circ T)$ provides a measure of how well the fixed image is matched by the transformed moving image. This measure forms the quantitative criterion to be optimized by the *optimizer* over the search space defined by the parameters of the *transform*. Thus, in the ITK context, registration could be defined as a process of finding the set of transform parameters that result in the best value of an image similarity metric [62].

Figure A.1. Basic components of ITK registration framework: two input images, a transform, a metric, an interpolator, and an optimizer. Adapted from [11].

A.2.1 Transform

Registration in ITK is done in physical space, not in image space; hence, prior to registration, ITK maps the image space to the physical space based on the information of the pixel size and the location of the image origin in physical space. The concept of ITK registration transform is depicted in Figure A.2. Thus, the transformation being optimized in the ITK registration framework is the one that maps points from the physical space of the fixed image into the physical space of the moving image (i.e. *Space Transform*, refer to Figure A.2).

The concept of transformation adopted in ITK is *inverse transformation*. It is the reverse of the concept used in most registration concepts i.e. forward transform. Instead of transforming the moving image to the fixed image, ITK does the opposite. This implies that the *transform* component accepts the input points from the fixed image and computes the coordinates of the analogous points in the moving image.

Figure A.2. Coordinate systems involved in ITK registration. $T1$, mapping from the fixed image grid coordinate into the physical space; *Space Transform*, mapping fixed image physical coordinates into the physical space of the moving image; $T2$, mapping the physical coordinates of the moving image into the discrete grid of the moving image where the value of the pixel intensity will be computed by interpolation. Adapted from [11].

The reason of the adoption of inverse transformation in ITK is due to its fitness to the fact that the moving image is expected to be resampled using the grid of the fixed image. If the transform that maps coordinates from the moving image physical space into the fixed image physical space was used, then the resampling process could not guarantee that every pixel in the grid of the fixed image was going to receive one and only one value. In other words, the resampling will have resulted in an image with holes and with redundant or overlapped pixel value [11].

The explanation on the difference between forward and inverse transform is given in [62]. In the forward transform (Figure A.3 (a)), an input image pixel is mapped onto the output image; the output pixels with more than one hit will result in overlap i.e. the intensity value is the accumulation from the overlapping pixels; the output pixels with no hits will result in holes. On the other hand, inverse transform (Figure A.3 (b)) ensures that the output pixels are mapped back onto the input image as the output pixel value must be interpolated from a neighborhood in the input image. Hence, it avoids any holes and overlaps in the input image as all pixels are scanned sequentially.

ITK provides various transformation methods: transformation in 2-D, 3-D, N-dimension, simple translation, rotation, scaling, general affine, kernel transformation,

etc. They are implemented as classes of transformations. These transformation methods are not only used for registration, but also for other applications. Some of the transformation classes for 3-D transformations are listed in Table A.1.

Figure A.3. Forward and Inverse Transform Concept.

(a) Forward transform mapping, (b) Inverse transform mapping. Adapted from [62]

Table A.1: Transformation Methods in ITK. Adapted from [11].

Transform Method	Description	No. of parameters	Parameter Ordering	Restriction
<i>Quaternion Rigid Transform</i>	Represents a 3D rotation and a 3D translation. The rotation is specified as a quaternion, defined by a set of four numbers $\mathbf{q}$. The relationship between quaternion and rotation about vector $\mathbf{n}$ by angle q is as follows: $\mathbf{q} = (\mathbf{n}\sin(q/2), \cos(q/2))$	7	The first four parameters defines the quaternion and the last three parameters the translation in each dimension.	Only defined for 3-D input and output spaces.
<i>Euler3D Transform</i>	Represents a rigid rotation in 3D space. That is, a rotation followed by a 3D translation. The rotation is specified by three angles representing rotations to be applied around the X, Y and Z axis one after another. The translation part is represented by a Vector. Users can also specify the coordinates of the center of rotation.	6	The first three parameters are the rotation angles around X, Y and Z axis, and the last three parameters are the translations along each dimension.	Only defined for 3-dimensional input and output spaces.
<i>Affine Transform</i>	Represents an affine transform composed of rotation, scaling, shearing and translation. The transform is specified by a $N \times N$ matrix and a $N \times 1$ vector where N is the space dimension.	$(N+1) \times N$	The first $N \times N$ parameters define the matrix in column-major order (where the column index varies the fastest). The last N parameters define the translations for each dimension.	Only defined when the input and output space have the same dimension.

In the context of registration, transform parameters define the search space for *optimizers*. Thus, the goal of the optimization is to find the set of parameters defining a transform that result in the best possible value of an image metric. The more parameters a transform has, the longer its computational time when being used in a registration process; as the dimension of the search space is equal to the number of the transform parameters to be optimized.

Comparing the three transformation methods presented in Table A.1, Euler3D transform might be a good candidate for use in 3-D space as it requires fewer parameters to be optimized than the others. Hence, it could reduce the computational cost. The Euler3D transform is performed according to formula [62]:

$$\mathbf{x}' = \mathbf{R}_z \mathbf{R}_y \mathbf{R}_x \mathbf{x} + \mathbf{t}$$

or

$$\mathbf{x}' = \mathbf{R}_z \mathbf{R}_x \mathbf{R}_y \mathbf{x} + \mathbf{t}$$

where R_x , R_y , R_z , are the rotation matrices with respect to x , y , and z – axis respectively; t is the translation component of the transformation; x and x' are the original point and the transformed point respectively. The parameters optimized in Euler3D transform comprise of:

$$\{\theta_x, \theta_y, \theta_z, t_x, t_y, t_z\}$$

which are the rotation angle about x , y , z - axis and translation in x , y , z – direction respectively.

Transformation is dependant on the origin of the reference frame. The origin of the reference frame adopted affects the speed of the registration process. Normally, the origin of the reference frame is shifted in such a way that it could speed up the registration process. Normally, it is shifted to the center of the image or volume. Figure A.4(a) and (b) show the difference between the centered origin and normal origin – based transformations. Centered-origin transformation will likely to speed up the registration process as normally the object's image is concentrated in the center of the image area / volume. Thus, fewer spatial transformations are required to align the images in centered – based transformation than in the normal origin – based transformation.

Figure A.4. Origin of Transformation.

(a) Normal origin – based transformation in 2-D, (b) centered origin – based transformation. Adapted from [68]

A.2.2 Interpolator

Mostly, in mapping of a point from one space to another by a transformation, a point will be mapped to a non-grid position (Figure A.5). Thus, interpolation is required to evaluate the image intensity at the mapped position.

Some of the interpolation methods provided by ITK are: nearest neighbor interpolation, linear interpolation and B-Spline interpolation methods. Nearest neighbor interpolation method simply uses the intensity of the nearest grid position, as has been elaborated in Section 3.4.B; it is the simplest interpolation method as it does not require any floating point computations. Linear interpolation method assumes that intensity varies linearly between grid positions (refer to Section 3.4.B). B-Spline interpolation represents the image intensity using B-spline basis functions; with the B-spline coefficients computed by multiplying the B-spline coefficients with shifted B-spline kernels within a small region of the requested position [11]. ITK B-spline interpolator method provides splines of order 0 to 5. The spline of order 0 is almost the same as the nearest neighbor interpolation; order 1 is exactly the same as the linear interpolation. The use of spline may cause that the interpolated values lie outside the range of the input image intensities. Considerations when choosing the

interpolation scheme are: interpolation affects the smoothness of the metric space and interpolation is computed 1000s times in a single optimization cycle [62].

Figure A.5. Mapping of fixed image to non-grid position of the moving image. Adapted from [11].

A.2.3 Metric

Metric objects in ITK are the measure of alignment between the registered images. It measures how well the transformed moving image aligns with the fixed image by comparing the gray-scale intensity of the images; or simply, metric can be regarded as the cost function to be maximized or minimized during the registration process dependant on the method of registration used. Metric objects take basic inputs which are: the fixed and moving images, a transform and an interpolator. It then calculates the value from the inputs based on the types of the metric. There are several types of metric objects available in ITK such as mean squares, normalized correlations and mutual information metrics. However, not all could be used for multimodal image registration. Mutual information metric works for multimodal image registration. The ones related to the implementation of Mutual Information-Based registration are: Mutual Information - Viola and Well algorithm and Mutual Information - Mattes algorithm.

Mutual Information Metric

The object mutual information metric calculates the mutual information (MI) between fixed and moving images. ITK implements the mutual information, $I(A,B)$, based on the equations (3.4), (3.12) and (3.14).

As the density estimator, Parzen windowing is used. In Parzen windowing technique as given by equation (refer to Section 3.4.A):

The densities are constructed by taking intensity samples S from the image and super-positioning kernel functions $K()$ centered on the elements of S as depicted in Figure A.6. As the smoothing kernel, a variety of functions can be used, as long as they are smooth, symmetric, have zero mean and integrate to one. Examples of smoothing kernels are Gaussian and B-Spline functions.

Figure A.6. Parzen windowing. A continuous density function is constructed by superimposing kernel functions (in this case is Gaussian) centered on the intensity samples obtained from the image. Adapted from [11]

Viola and Well Implementation

One of the ITK implementation of the MI metric follows the method specified by Viola and Wells in [69]. In this implementation, two separate intensity samples S and R are drawn from the image: the first to compute the density and the second to approximate the entropy as a sample mean:

The smoothing kernel used is Gaussian density whose standard deviation σ acts as the smoothing parameter.

Mattes Implementation

Another implementation of mutual information metric follows the method defined by Mattes et. al. in [70]. In this implementation, only one set of intensity sample is drawn from the image. Using the set, the marginal and joint probability density function are evaluated at discrete positions or bins uniformly spread within the dynamic range of the images. Entropy values are then computed over the bins.

During the calculation of the probability density function (pdf), the image intensity values are linearly scaled to have a minimum of zero and maximum of one. The fixed image pdf does not contribute to the metric derivatives; hence, it does not need to be smooth. Thus, a zero order B-spline kernel is used to compute the moving image intensity pdf. Yet, to ensure smoothness, a third order B-spline kernel is used to compute the moving image intensity pdf.

The difference between Viola and Wells' and Mattes' implementation is in the number of samples drawn in each iteration. Viola and Wells' implementation draws 50-100 pixels/voxels samples in each iteration whereas Mattes' draws only 5-10% of the image pixels/voxels once throughout the registration process [62]. Hence, the use of Mattes' implementation could save computational cost.

A.2.4 Optimizer

Optimizer in ITK is a generic object that can be used for applications other than registration. In the registration framework, optimizer is used to optimize the metric criterion with respect to the transform parameters. The basic input to the optimizer is a cost function object; in this case is the metric object.

There are several optimization methods implemented in the ITK, such as:

- Amoeba optimizer, it implements Nelder-Mead Downhill simplex method.
- Conjugate Gradient optimizer, it implements Fletcher-Reeves form of the conjugate gradient with or without preconditioning.
- Gradient Descent. The advancement of the parameters is in the direction of the gradient with the step size is governed by a learning rate.

- Regular Step Gradient Descent Optimizer. The advancement of the parameters is in the direction of the gradient where a bipartition scheme is used to compute the step size.
- Powell Optimizer, it implements Powell optimization method [40]. For an N-dimensional parameter space, each iteration minimizes (or maximizes) the function in N (initially orthogonal) directions.

In this case, three optimizers being used for implementation (Chapter 4) are discussed, which were Powell, Gradient Descent, and Regular Step Gradient Descent Optimizers.

A. Powell Optimizer

Powell optimizer in ITK implements the Powell optimization method using Brent line search as elaborated in section 3.4.D. In ITK's implementation, *step length* is required to determine the initial distance for the optimization process to step in a line direction when bounding the minimum [12]. The convergence criterion could be defined using the *step tolerance* or *value tolerance*. The step tolerance criterion terminates optimization when the parameter values are known to be within this (scaled) distance of the local extreme, whereas the value tolerance criterion terminates optimization when the cost function values at the current parameters and at the local extreme are likely (within a second order approximation) to be within this tolerance [12]. *Maximum iterations* becomes the stopping condition should the step or value tolerance fails to achieve convergence.

B. Gradient Descent Optimizer

It implements a simple gradient descent optimization algorithm as described in section 3.4.D. The user needs to set the *learning rate*; it is a fixed scalar. The optimizer steps through a user defined *number of iterations*; no convergence checking is done [71]. This method requires the partial derivatives of the cost function i.e. the metric. This limitation is rectified in its variant method, Regular Step Gradient Descent Optimizer.

C. Regular Step Gradient Descent Optimizer

In this method, each time the direction of the derivative abruptly changes, the optimizer assumes that a local extreme has been passed and reacts by reducing the step length by a half [11]. Thus, in this method, learning rate is not required. The optimization process is illustrated in Figure A.7. After several reductions of the step length, the optimizer may be moving in a very restricted area of the transform parameter space. The user needs to specify the *maximum step length*, i.e. the step length in the first iteration, *minimum step length*, i.e. how small the step length should be to consider the convergence has been reached. *Number of iterations* would be the stopping condition, should the minimum step length fails to do so.

Figure A.7. Regular Step Gradient Descent Optimizer. D1 is the maximum step length, also the initial step length; the step length is halved ($D2=D1/2$) when the gradient changes direction. Optimization terminates when D_n , the current step length, gets smaller than the minimum step length defined by the user. Adapted from [42].

D. Tuning of Parameter Scales

The parameters in the optimizers need to be rescaled as some parameter spaces have different dynamic ranges. It can be seen in the case involving parameter space of rotation and translation; a unit change in rotation has greater effect on an image than one in translation. For example, the range of rotation is from 0 to 1.57 (rad), whereas the range of translation could be from 0 to, say, 180 (mm). There is a difference in the dynamic range of 1.57:180; hence a rescaling of 1:100 is required for the

translation scale to make it compatible. The difference in scale appears as long narrow valleys in the search space making the optimization problem more difficult. Hence, the rescaling of translation parameters could fix the problem.

A.3 Multi-resolution Registration Framework

Multi-resolution scheme is often incorporated in registration to improve robustness, speed and accuracy. Using multi-resolution approach, registration is performed to the images in several levels of resolution, starting from the coarsest resolution, where the images have fewer pixels/voxels, to the finest resolution. The result of the spatial transform obtained from the registration of the coarse resolution is used to initialize the registration process in the next finer resolution, thus it could speed up the registration process. Registration in the coarse level could reduce the chance for the optimizer to be trapped in the local optima; hence it could improve the robustness of the registration process.

ITK provides a framework to perform multi-resolution scheme in registration. It is almost the same as the normal registration framework as described in the previous section (Section A.2); yet, instead of performing registration to a pair of images, it performs registration to a pair of image pyramids. The multi-resolution framework is directly compatible with all the normal registration framework components. The multi-resolution framework in ITK is illustrated in Figure A.8.

Figure A.8. Components of the ITK multi-resolution registration framework.
Adapted from [11].

The input of the framework, a pair of image pyramids, are used to down-sample the fixed and moving images. The down sampling involves smoothing and sub-sampling of the images with the shrink factors that could be customized by the user.

The process of multi-resolution algorithm is illustrated in Figure A.9; it starts from level zero, which is the coarsest resolution, and passes the spatial transform result to the next finer level, level one, and so forth up to the lowest (finest) level defined by the user. One possible scheme of doing multi-resolution registration is by taking larger step sizes and more relaxed convergence criterion for the coarse level and subsequently reduces the step and increase the convergence criterion in the finer levels.

Figure A.9. Multi-resolution registration process. Adopted from [11].

By default, the shrinking factor used to down-sample the image in every level follows the following formula:

$$\text{shrink factor} = 2^{L-(i+1)}$$

where, L is the number of levels, i is the level's number. Thus, in a 5 level image pyramid, level 0 (the coarsest) sample is generated by down-sampling the original image by $\frac{1}{4}$ i.e. it only contains $\frac{1}{4}$ of the number of pixels of the original image; the shrinking factor will be applied uniformly to each dimension of the image, e.g. x, y, z , directions of an image volume. However, user may modify the shrinking factors in each level of the image pyramid, for each dimension.

APPENDIX B

Regular Step Gradient Descent Optimizer Experiment Results
(Intra-modality, the same acquisition-modes)

A. Brain1Normal and Brain1R10T15

Table B.A.1: Results using parameter scale: rotation = 1, translation = 1/1000000.

Factors			Results								Error (mm)
N o. of le v el	Max Step Leng th	Min Step Leng th	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
3	100	1	0.0326	-0.1071	-0.2491	1.9473	-17.966	-0.0071	-0.632	1404	0.7950
	10	1	-0.0204	0.0034	-0.1095	2.0103	-17.9015	-0.0001	-0.625	670	0.7050
	20	1	-0.0255	-0.0168	-0.2167	1.9932	-17.925	0.0017	-0.631	898	0.7340

Table B.A.2: Results using parameter scale: rotation = 1, translation = 1/100000.

Factors			Results								Error (mm)
N o. of le v el	Max Step Leng th	Min Step Leng th	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
3	10	1	-0.1770	-0.0078	-1.0761	1.8552	-17.6385	-0.1134	-0.654	632	0.6793
	1	0.1	-0.0885	0.0320	-2.4934	1.7381	-17.601	-0.0649	-0.694	2969	0.7684
4	0.1	0.01	-0.0577	-0.0759	-4.9933	2.2909	-17.4893	-0.1255	-0.811	16213	0.2494

Table B.A.3: Results using parameter scale: rotation = 1, translation = 1/10000.

Factors			Results								Error (mm)
N o. of le v el	Max Step Leng th	Min Step Leng th	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
1	30	0.001	0.0025	-0.0112	-9.9885	2.4621	-17.3739	-0.0155	-1.611	688	0.0190
	20	0.001	0.0253	0.0075	-9.9957	2.4741	-17.359	-0.0417	-1.033	635	0.0427
	10	0.001	0.0027	0.0034	-10.0064	2.4669	-17.375	-0.0154	-1.611	567	0.0192
	5	0.001	0.0019	-0.0057	-9.9816	2.4651	-17.3746	-0.0150	-1.611	760	0.0187
	1	0.001	-0.0302	-0.0316	-9.7920	2.4709	-17.3674	-0.0220	-1.580	1346	0.0229
3	30	0.1	-0.0092	-0.0495	-9.8569	2.4603	-17.3729	-0.0159	-1.594	1597	0.0193
	20	0.1	0.0035	0.0018	-10.009	2.4666	-17.3742	-0.0154	-1.611	1027	0.0188
	10	0.1	0.0025	-0.0101	-9.9793	2.4641	-17.3731	-0.0144	-1.611	753	0.0174
	5	0.1	0.0029	0.0038	-10.008	2.4666	-17.3736	-0.0149	-1.611	1172	0.0180
	1	0.1	0.0038	0.0056	-10.0209	2.4664	-17.3736	-0.0155	-1.611	980	0.0185
	60	1	-0.0341	-0.1176	-9.6287	2.4641	-17.377	-0.0161	-1.529	1605	0.0211
	20	1	0.0008	-0.0438	-9.9329	2.4631	-17.3767	-0.0188	-1.606	711	0.0232
	10	1	0.0213	0.00347	-10.029	2.4656	-17.3759	-0.0126	-1.611	480	0.0177
	4	20	0.0309	0.08238	-10.265	2.4820	-17.3795	-0.0239	-1.568	615	0.0330
	10	1	0.0058	-0.0022	-10.003	2.4647	-17.3745	-0.0156	-1.611	654	0.0191
	1	0.1	0.0031	0.0022	-10.006	2.4667	-17.3745	-0.0151	-1.611	2157	0.0187
	5	20	0.0032	0.0036	-10.008	2.4668	-17.3736	-0.0153	-1.611	947	0.0184
	10	1	0.0031	0.0032	-10.007	2.4673	-17.3746	-0.0151	-1.611	2235	0.0188
	1	0.1	0.0176	-0.0145	-9.9926	2.4580	-17.3711	-0.0389	-1.608	5120	0.0404

Table B.A.4: Results using parameter scale: rotation =1, translation = 1/1000.

Factors			Results								Error (mm)
N o. of le v el	Max Step Leng th	Min Step Leng th	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
3	20	1	-0.0375	-0.0228	-10.0583	2.476	-17.3815	-0.0121	-1.606	529	0.0239
	10	1	0.0213	0.0035	-10.0293	2.4656	-17.3759	-0.0126	-1.611	455	0.0177
	10	0.1	0.0247	0.0106	-10.0007	2.4740	-17.3592	-0.0417	-1.034	727	0.0428
	1	0.1	0.0038	0.0040	-10.0075	2.4672	-17.374	-0.0141	-1.611	918	0.0176
4	20	1	0.0213	0.0035	-10.0293	2.4656	-17.3759	-0.0126	-1.611	487	0.0177
	10	1	0.0026	0.0050	-10.0066	2.4667	-17.3741	-0.0150	-1.611	712	0.0184
	1	0.1	0.0030	0.0030	-10.0067	2.4671	-17.3745	-0.0150	-1.611	1935	0.0186
5	20	10	0.0027	0.0037	-10.0067	2.4671	-17.3743	-0.0146	-1.611	960	0.0182
	10	1	0.0028	0.0030	-10.0069	2.4671	-17.3745	-0.0150	-1.611	2116	0.0186
	1	0.1	0.0119	-0.0109	-9.9971	2.4581	-17.3709	0.0390	-1.609	8337	0.0405

Table A.A.5: Results using parameter scale: rotation =1, translation = 1/100.

Factors			Results								Error (mm)
N o. of le v el	Max Step Leng th	Min Step Leng th	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
3	10	1	-190.384	178.212	-9.0615	4.6535	-14.3207	-4.0113	-0.398	802	5.4895

B.Brain1Normal and Brain1R20T20**Table B.B.1:** Results using parameter scale: rotation =1, translation = 1/10000.

Factors			Results								Error (mm)
N o. of le v el	Max Step Leng th	Min Step Leng th	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
3	10	1	-0.1035	-0.1092	-19.3591	11.6886	-37.5557	-0.0121	-1.454	501	0.0712
	20	1	0.0143	0.0028	-20.0377	11.6588	-37.5172	-0.0102	-1.627	897	0.0245
4	10	1	0.0107	-0.0017	-19.9949	11.6534	-37.5203	-0.0124	-1.628	754	0.0272
	20	1	0.0104	-0.0068	-19.9843	11.6525	-37.5207	-0.0126	-1.628	773	0.0276

Table B.B.1a: Results using parameter scale: rotation =1, translation = 1/10000, centered and un-centered transformation.

Factors			Results								Error (mm)
N o. of le v el	Max Step Leng th	Min Step Leng th	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
3	30	1*	-0.0526	-0.0542	-19.6398	11.6812	-37.5188	-0.0089	-1.553	997	0.0384
	30	1**	-0.0036	-0.4244	-19.4223	-18.6048	-1.5836	-0.7909	-1.417	4351	2.2539

Note: * centered, ** un-centered.

Table B.B.2: Results using parameter scale: rotation =1, translation = 1/1000.

Factors			Results								Error (mm)
N o. of le v el	Max Step Leng th	Min Step Leng th	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
3	10	1	0.0067	0.0422	-19.9858	11.6452	-37.5176	-0.0140	-1.625	1352	0.0263
	20	1	0.0537	-0.0326	-20.0079	11.6653	-37.5175	-0.0110	-1.622	493	0.0277
4	10	1	0.0083	0.0018	-20	11.6551	-37.5209	-0.0124	-1.628	811	0.0279
	20	1	0.0016	-0.0020	-19.9976	11.6554	-37.5217	-0.0129	-1.628	742	0.0289

C. Brain3Normal and Brain3R10T15**Table B.C.1:** Results using parameter scale: rotation = 1, translation = 1/10000.

Factors			Results								Error (mm)
N o. of le v el	Max Step Leng th	Min Step Leng th	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
3	10	1	-0.0193	-0.0170	-9.6718	2.4681	-17.3742	-0.0033	-1.586	536	0.0114
	20	1	-0.0049	0.0059	-10.009	2.4641	-17.376	-0.0018	-1.683	547	0.0127
4	10	1	-0.0022	0.0024	-10.003	2.4655	-17.3659	-0.0002	-1.684	653	0.0025
	20	1	-0.0016	0.0045	-10.006	2.4659	-17.3662	-0.0002	-1.684	741	0.0027

Table B.C.2: Results using parameter scale: rotation = 1, translation = 1/1000.

Factors			Results								Error (mm)
N o. of le v el	Max Step Leng th	Min Step Leng th	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
3	10	1	0.0004	0.0326	-10.0028	2.4589	-17.3584	-0.0062	-1.680	391	0.0106
	20	1	-0.0587	-0.0206	-10.0995	2.4749	-17.3788	-0.0031	-1.663	581	0.0180
4	10	1	-0.0046	0.0034	-10.0057	2.4659	-17.3663	-0.0006	-1.684	913	0.0029
	20	1	-0.0010	0.0040	-10.0054	2.4659	-17.3662	-0.0005	-1.684	758	0.0027

D. Brain3Normal and Brain3R20T20**Table B.D.1:** Results using parameter scale: rotation = 1, translation = 1/10000.

Factors			Results								Error (mm)
N o. of le v el	Max Step Leng th	Min Step Leng th	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
3	10	1	-0.0744	-0.0326	-19.5963	11.6657	-37.4985	0.0021	-1.571	872	0.0146
	20	1	-1.4938	0.4208	-11.5079	10.6002	-37.3528	-0.3766	-0.577	861	1.1258
4	10	1	0.0019	0.0086	-20.0161	11.6473	-37.5017	-0.0009	-1.717	720	0.0069
	20	1	0.0042	0.0095	-20.0218	11.6483	-37.5033	-0.0021	-1.717	674	0.0080

Table B.D.2: Results using parameter scale: rotation = 1, translation = 1/1000.

Factors			Results								Error (mm)
N o. of le v el	Max Step Leng th	Min Step Leng th	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
3	10	1	0.0028	0.0026	-20.0098	11.6521	-37.5015	0.0007	-1.718	700	0.0054
	20	1	-0.0684	0.0175	-20.0111	11.6448	-37.5058	-0.0068	-1.703	514	0.0135
4	10	1	0.0049	0.0053	-20.0102	11.6497	-37.5017	-0.0013	-1.716	811	0.0059
	20	1	0.0004	0.0059	-20.0106	11.649	-37.5024	-0.0012	-1.717	828	0.0068

APPENDIX C

Regular Step Gradient Descent Optimizer Experiment Results
(Intra-modality, different acquisition-modes)

A. Brain1Normal and Brain3R10T15

Table C.A.1: Results using parameter scale: rotation = 1, translation = 1/10000.

Factors			Results								Error (mm)
N o. of le v el	Max Step Leng th	Min Step Leng th	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
3	10	1	-0.0251	0.0200	-10.0571	2.4458	-17.3756	0.0367	-1.008	434	0.0436
	20	1	-0.0163	0.0134	-9.9988	2.4561	-17.3781	0.0387	-1.008	545	0.0425
4	10	1	-0.0153	0.0115	-9.9977	2.4523	-17.3796	0.0378	-1.009	728	0.0433
	20	1	-0.0141	0.0117	-9.9971	2.4517	-17.3805	0.0372	-1.009	787	0.0433

Table C.A.2: Results using parameter scale: rotation = 1, translation = 1/1000.

Factors			Results								Error (mm)
N o. of le v el	Max Step Leng th	Min Step Leng th	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
3	10	1	0.0613	-0.0339	-10.0066	2.4698	-17.3711	0.0441	-1.006	534	0.0450
	20	1	-0.0189	-0.0185	-10.0032	2.4602	-17.382	0.0315	-1.008	451	0.0370
4	10	1	-0.0154	0.0091	-9.9981	2.4535	-17.3795	0.0374	-1.009	840	0.0425
	20	1	-0.0124	0.0145	-9.9973	2.4527	-17.3797	0.0377	-1.009	683	0.0431

B. Brain1Normal and Brain3R20T20

Table C.B.1: Results using parameter scale: rotation = 1, translation = 1/10000.

Factors			Results								Error (mm)
N o. of le v el	Max Step Leng th	Min Step Leng th	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
3	10	1	-2.9160	-1.1633	-10.318	11.1607	-36.4005	0.1507	-0.519	564	1.2100
	20	1	-0.0347	0.0195	-19.994	11.6334	-37.5044	0.0472	-1.013	870	0.0512
4	10	1	-0.0113	0.0034	-19.9942	11.6304	-37.513	0.0385	-1.013	1115	0.0470
	20	1	-0.0104	0.0018	-19.9931	11.6303	-37.5126	0.0384	-1.013	853	0.0468

Table C.B.2: Results using parameter scale: rotation = 1, translation = 1/1000.

Factors			Results								Error (mm)
N o. of le v el	Max Step Leng th	Min Step Leng th	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
3	10	1	-0.0314	-0.0303	-20.0002	11.6359	-37.5154	0.0383	-1.012	516	0.0456
	20	1	-0.0157	0.0048	-19.9978	11.6302	-37.5128	0.0362	-1.013	496	0.0451
4	10	1	-0.0112	-0.0013	-19.9921	11.6314	-37.513	0.0386	-1.013	827	0.0466
	20	1	-0.0093	0.0085	-19.9954	11.6292	-37.5123	0.0389	-1.013	1063	0.0476

C. Brain3Normal and Brain1R10T15**Table C.C.1:** Results using parameter scale: rotation = 1, translation = 1/10000.

Factors			Results								Error (mm)
N o. of level	Max Step Length	Min Step Length	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
3	10	1	0.0253	-0.0804	-9.7873	2.4351	-17.3774	-0.0517	-1.022	482	0.0618
	20	1	0.0298	0.0018	-9.9884	2.4758	-17.3617	-0.0445	-1.033	459	0.0456
4	10	1	0.0261	0.0059	-9.9942	2.4734	-17.3592	-0.0419	-1.034	860	0.0428
	20	1	0.0254	0.0079	-9.9963	2.4739	-17.3584	-0.0415	-1.034	956	0.0426

Table C.C.2: Results using parameter scale: rotation = 1, translation = 1/1000.

Factors			Results								Error (mm)
N o. of level	Max Step Length	Min Step Length	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
3	10	1	0.0120	-0.0161	-9.9889	2.4797	-17.3613	-0.0418	-1.033	493	0.0441
	20	1	-0.0065	0.0619	-9.9212	2.4583	-17.3563	-0.0446	-1.030	475	0.0458
4	10	1	0.0275	0.0089	-9.9973	2.4753	-17.3587	-0.0413	-1.034	748	0.0426
	20	1	0.0268	0.0123	-9.9974	2.4746	-17.358	-0.0414	-1.034	778	0.0427

D. Brain3Normal and Brain1R20T20**Table C.D.1:** Results using parameter scale: rotation = 1, translation = 1/10000.

Factors			Results								Error (mm)
N o. of level	Max Step Length	Min Step Length	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
3	10	1	0.0100	-0.1438	-19.6342	11.6248	-37.5129	-0.0628	-1.007	513	0.0702
	20	1	0.0480	0.0470	-20.0379	11.63	-37.5141	-0.0570	-1.034	509	0.0635
4	10	1	0.0300	0.0217	-20.0031	11.6653	-37.5011	-0.0514	-1.036	905	0.0535
	20	1	0.0288	0.0264	-20.0062	11.6676	-37.5009	-0.0512	-1.036	952	0.0539

Table C.D.2: Results using parameter scale: rotation = 1, translation = 1/1000.

Factors			Results								Error (mm)
N o. of level	Max Step Length	Min Step Length	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time(s)	
3	10	1	-0.0092	0.0500	-20.0017	11.6553	-37.5041	-0.0535	-1.034	542	0.0542
	20	1	0.0414	-0.0049	-20.006	11.6732	-37.5038	-0.0481	-1.035	519	0.0534
4	10	1	0.0275	0.0208	-20.0006	11.6664	-37.5012	-0.0518	-1.036	709	0.0542
	20	1	0.0335	0.0202	-20.0025	11.6667	-37.5009	-0.0518	-1.036	785	0.0542

APPENDIX D

Powell Optimizer Experiment Results

Using Brain1Normal and Brain1R10T15 (Intra-modality, same properties)

Table D.1: Results using parameter scale: rotation = 1, translation = 1/1000000.

Factors			Results								Error (mm)
N o. of level	Max Step Length	Min Step Length	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time (s)	
3	10	1	Failed								-
	1	0.1	Failed								-
	0.1	0.01	Failed								-
4	10	1	Failed								-
	0.1	0.01	Failed								-

Table D.2: Results using parameter scale: rotation = 1, translation = 1/100.

Factors			Results										Error (mm)
N o. of level	Step Length	Step Tolerance	Subsequent level's step length	Subsequent level's step tolerance	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time (s)	
3	5	0.05	Pre/10	Pre/10	Failed							-	-
6	10	1	Pre/10	Pre/10	Failed							-	-
	0.1	0.01	Pre/10	Pre/10	0.0093	-0.0087	-10.011	2.4651	-17.3795	-0.0085	-1.612	9324	0.0181
	0.01	0.001	Pre/10	Pre/10	-0.0261	-0.0056	-10.011	2.4687	-17.3549	0.0220	-1.610	9396	0.0238
	0.1	0.05	Pre/2	Pre/2	-0.0407	-0.0217	-9.9829	2.5008	-17.3151	0.0133	-1.604	3462	0.0612
	1	0.5	Pre/2	Pre/2	Failed							-	-

Table D.3: Results using parameter scale: rotation = 1, translation = 1/10.

Factors			Results										Error (mm)
N o. of level	Step Length	Step Tolerance	Subsequent level's step length	Subsequent level's step tolerance	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time (s)	
3	10	0.5	Pre/5	Pre/2	Failed								
	5	0.05	Pre/5	Pre/2	-0.0230	0.0295	-9.9667	2.5094	-17.3353	-0.0159	-1.607	4147	0.0542
4	5	0.5	Pre/5	Pre/5	Failed								
6	5	0.05	Pre/5	Pre/2	-0.0230	0.0295	-9.9667	2.5094	-17.3353	-0.0159	-1.607	4189	0.0542
	1	0.05	Pre/5	Pre/2	0.00169	0.00488	-10.005	2.4721	-17.3781	0.0061	-1.614	5593	0.0170
	0.1	0.01	Pre/10	Pre/10	0.01135	-0.01113	-10.009	2.4653	-17.3649	-0.0082	-1.612	11919	0.0083

Table D.4: Results using parameter scale: rotation =1, translation = 1.

Factors			Results										Error (mm)
N o. of level	Step Length	Step Tolerance	Subsequent level's step length	Subsequent level's step tolerance	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time (s)	
3	5	0.5	Pre/5	Pre/2	0.0093	-0.0087	-10.011	2.4651	-17.3795	-0.0085	-1.612	9324	0.0181
	5	0.05	Pre/5	Pre/2	-0.0229	0.0295	-9.9667	2.5094	-17.3353	-0.0159	-1.607	4130	0.0542
4	5	0.5	Pre/5	Pre/5	-0.0183	-0.0158	-10.0415	2.4618	-17.364	0.0085	-1.611	4010	0.0095

Table D.5: Results using parameter scale: rotation =1, translation = 10.

Factors			Results										Error (mm)
N o. of level	Step Length	Step Tolerance	Subsequent level's step length	Subsequent level's step tolerance	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time (s)	
3	5	0.05	Pre/10	Pre/5	0.0014	-0.0021	-10.0067	2.4679	-17.3785	0.0045	-1.614	4330	0.0158
4	5	0.5	Pre/5	Pre/5	-0.0011	0	-10.0136	2.4686	-17.3766	0.0019	-1.615	4601	0.0135

Table D.6: Results using parameter scale: rotation =1, translation = 100.

Factors			Results										Error (mm)
N o. of level	Step Length	Step Tolerance	Subsequent level's step length	Subsequent level's step tolerance	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time (s)	
3	5	0.05	Pre/10	Pre/5	-0.0029	0.0020	-10.0055	2.4701	-17.3736	0.0052	-1.614	4707	0.0121

Note:

Pre = Previous value of step length (or step tolerance).

Pre/5 = Previous value of step length (or step tolerance) divided by 5.

APPENDIX E**Combined Powell's and Regular Step Gradient Descent Optimizers
Experiment Results****A. Test Algorithm Experiment Results.**

Multiresolution level = 3 levels:

Level 0 (coarsest):

Resolution: $1/2^5$.

Optimizer: Powell Optimizer

- Step Length = a,
- Stop Tolerance = b.

Level 1:

Resolution: $\frac{1}{2}$.

Optimizer: Regular Step Gradient Descent Optimizer.

- Max step length=c,
- Min step length=d.

Level 2 (finest):

Resolution: full resolution (=1).

Optimizer: Regular Step Gradient Descent Optimizer.

- Maximum step length = last step length from previous level.
- Minimum step length = (previous minimum step length)/10

Number of image combinations:

1. Brain1Normal and Brain1R10T15
2. Brain1Normal and Brain3R10T15
3. Brain3Normal and Brain3R10T15
4. Brain3Normal and Brain1R10T15
5. Brain1Normal and Brain1R20T20
6. Brain1Normal and Brain3R20T20
7. Brain3Normal and Brain1R20T20
8. Brain3Normal and Brain3R20T20

Table E.1: Results of Trials and Tuning Experiments.

No	Factors				Results								Error (mm)
	A	b	c	d	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time (s)	
1	0.01	0.05	1.5	0.1	0.1630	0.1234	-9.9345	2.6317	-16.9476	-0.0803	-1.610	129	0.4549
2	0.1	0.05	0.5	0.1	0.0256	0.0077	-10.1417	2.7033	-16.8763	0.5260	-1.067	105	0.7552
3	0.1	0.05	1.5	0.1	0.2160	0.0642	-9.8984	2.5694	-16.938	0.0566	-1.459	159	0.4416
4	0.07	0.05	2	0.1	0.2067	-0.1382	-9.5117	2.3154	-16.7066	-0.6208	-1.119	94	0.9163
5	0.05	0.05	1.5	0.1	-0.2067	-0.2769	-20.166	11.833	-36.3922	0.0578	-1.653	147	1.1203
6	0.02	0.05	1.5	0.1	-0.0226	0.1112	-20.4119	12.284	-36.8302	0.3115	-1.080	97	0.9700
7	0.001	0.05	1.5	0.1	0.0721	-0.2795	-19.7634	11.633	-36.46	-0.2036	-1.133	155	1.0562
8	0.001	0.05	1.5	0.1	-0.5162	-0.5455	-20.7099	12.158	-36.7155	-0.0157	-1.480	166	0.9306

B. Improved Algorithm Experiment Results.

Multiresolution level = 2 levels.

Level 0 (coarsest):

Resolution: $1/2^9$.

Optimizer: Powell Optimizer

- Step Length = Step Length + 0.01 (iterated until the close initial estimate of optimum value is met, checking based on metric value of <-1.1 .)
- Step Tolerance = 0.005

Level 1 (finest):

Resolution: full Resolution (=1).

Optimizer: Regular Step Gradient Descent Optimizer

- Maximum step length=1.0
- Minimum step length=0.1

1. Brain Normal and Brain Rotated 10, Translated 15.

Table E.2: Results of Combined Optimizers Algorithm for brain normal and rotated 10, translated 15.

No	Results								Error (mm)
	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time (s)	
A.1	0.2673	0.3043	-10.3608	2.3893	-17.3478	0.0431	-1.299	140	0.0893
A.2	0.2849	-0.3181	-10.8299	2.5312	-17.441	0.0157	-0.865	219	0.1026
A.3	-0.2303	0.2984	-9.9631	2.3950	-17.3838	0.0014	-1.374	176	0.0737
A.4	0.0795	0.0992	-10.8492	2.4004	-17.3844	0.0251	-0.885	232	0.0732

2. Brain Normal and Brain Rotated 20, Translated 20.

Table E.3: Results of Combined Optimizers Algorithm for brain normal and rotated 20, translated 20.

No	Results								Error (mm)
	Rx (degrees)	Ry (degrees)	Rz (degrees)	Tx (mm)	Ty (mm)	Tz (mm)	M	Time (s)	
B.1	0.0126	-0.0217	-20.0649	11.428	-37.4287	-0.0236	-1.431	245	0.2346
B.2	0.1897	0.0064	-20.0938	11.6288	-37.4776	0.0462	-0.936	187	0.0547
B.3	-0.0524	-0.1366	-20.0198	11.6872	-37.5266	-0.0380	-0.954	195	0.0604
B.4	-0.0341	0.0457	-20.0142	11.6333	-37.4992	0.0039	-1.569	188	0.0188

Image Combinations:

- A.1. Brain1Normal and Brain1R10T15.
- A.2. Brain1Normal and Brain3R10T15.
- A.3. Brain3Normal and Brain3R10T15.
- A.4. Brain3Normal and Brain1R10T15.

- B.1. Brain1Normal and Brain1R20T20.
- B.2. Brain1Normal and Brain3R20T20.
- B.3. Brain3Normal and Brain3R20T20.
- B.4. Brain3Normal and Brain1R20T20.

APPENDIX F

Visualization of the Datasets

A. Brain1Set Datasets

A.1. Brain1Normal

A.2. Brain1R10T15

A.3. Brain1R20T20

B. Brain3Sets Datasets

B.1. Brain3Normal

B.2. Brain3R10T15

B.3. Brain3R20T20

APPENDIX G

Visualization of Mapped Moving Image using Registration Results (Regular Step Gradient Descent – based Algorithm)
Brain1Normal vs. Brain3R10T15

Result of an experiment in Table C.A.1, with the following results:

Rx = -0.0251° Ry = 0.0200° Rz = -10.0571° Tx = 2.4458 mm Ty = -17.3756 mm Tz = 0.0367 mm Time = 434 s Error = 0.0436 mm

Before Registration				After Registration		
Brain1Normal	Brain3R10T15	Checkerboard		Brain1Normal	Brain3R10T15	Checkerboard
Axial – Slice No: 40

Sagittal – Slice No: 80

Coronal – Slice: 142

Brain1Normal vs. Brain3R20T20

Result of an experiment in Table C.B.2, with the following results:
Rx = -0.0314° Ry = -0.0303° Rz = -20.0002° Tx = 11.6359 mm Ty = -37.5154 mm Tz = 0.0383 mm Time = 516 s Error = 0.0456 mm

Before Registration			After Registration		
Brain1Normal	Brain3R20T20	Checkerboard	Brain1Normal	Brain3R20T20	Brain3R20T20

			Axial – Slice No: 40		
			Sagittal – Slice No: 80		
			Coronal – Slice No: 142		

Brain3Normal vs. Brain1R10T15

Result of an experiment in Table C.C.1, with the following results:
Rx = 0.0298° Ry = 0.0018° Rz = -9.9884° Tx = 2.4758 mm Ty = -17.3617 mm Tz = -0.0445 mm Time = 459 s Error = 0.0456 mm

After Registration						
Before Registration		Brain1R10T15	Checkerboard	Brain3Normal	Brain1R10T15	Checkerboard
Brain3Normal
		Axial – Slice No: 40

		Sagittal – Slice No: 80

		Coronal – Slice No: 142				

Brain3Normal vs. Brain1R20T20

Result of an experiment in Table C.D.1, with the following results:
Rx = 0.0480° Ry = 0.0470° Rz = -20.0379° Tx = 11.63 mm Ty = -37.5141 mm Tz = -0.0570 mm Time= 509 s Error = 0.0635 mm

Before Registration				After Registration		
Brain3Normal	Brain1R20T20	Checkerboard		Brain3Normal	Brain1R20T20	Checkerboard

			Axial – Slice No: 40

			Sagittal – Slice No: 80

			Coronal – Slice No: 142			

Brain1Normal vs. Brain3R10T15

Result of an experiment in Table C.A.1, with the following results:
Rx = -0.0251° Ry = 0.0200° Rz = -10.0571° Tx = 2.4458 mm Ty = -17.3756 mm Tz = 0.0367 mm Time = 434 s Error = 0.0436 mm

After Registration						
Before Registration			After Registration			
Brain1Normal	Brain3R10T15	Checkerboard	Brain1Normal	Brain3R10T15	Checkerboard
Axial – Slice No: 40
Sagittal – Slice No: 80
Coronal – Slice: 142

Brain1Normal vs. Brain1R10T15

Result of an experiment in Table B.A.4, with the following results:
Rx = 0.0213° Ry = 0.0035° Rz = -10.0293° Tx = 2.4656 mm Ty = -17.3759 mm Tz = -0.0126 mm Time = 455 s Error = 0.0177 mm

After Registration			
Brain1Normal	Brain3R10T15	Checkerboard

Brain1Normal vs. Brain1R20T20

Result of an experiment in Table B.B.2, with the following results:

Rx = 0.0537° Ry = -0.0326° Rz = -20.0079° Tx = 11.6653 mm Ty = -37.5175 mm Tz = -0.0110 mm Time = 493 s Error = 0.0277 mm

Before Registration				After Registration		
Brain1Normal	Brain1R20T20	Checkerboard		Brain1Normal	Brain1R20T20	Checkerboard
Axial – Slice No: 40

Sagittal – Slice No: 80

Coronal – Slice: 142

Brain3Normal vs. Brain3R10T15

Result of an experiment in Table B.C.2, with the following results:
Rx = 0.0004° Ry = 0.0326° Rz = -10.0028° Tx = 2.4589 mm Ty = -17.3584 mm Tz = -0.0062 mm Time = 391 s Error = 0.0106 mm

After Registration				Before Registration		
Brain3R10T15		Checkerboard	Brain3Normal	Brain3R10T15	Checkerboard	Brain3Normal
Axial – Slice No: 40
Sagittal – Slice No: 80
Coronal – Slice: 142

Brain3Normal vs. Brain3R20T20

Result of an experiment in Table B.D.2, with the following results:
Rx = -0.0684° Ry = 0.0175° Rz = -20.0111° Tx = 11.6448 mm Ty = -37.5058 mm Tz = -0.0068 mm Time = 514 s Error = 0.0135 mm

After Registration				Before Registration		
Brain3R20T20		Checkerboard	Brain3Normal	Brain3R20T20	Checkerboard	Brain3Normal
Axial – Slice No: 40
Sagittal – Slice No: 80
Coronal – Slice: 142

Appendix H

Visualization of Mapped Moving Image using Registration Results (Combined Optimization - Improved Algorithm)

Axial – 40	Sagittal – 80	Coronal - 142
Brain1Normal and Brain1R10T15

Brain1Normal and Brain1R20T20

Brain1Normal and Brain3R10T15

Brain1Normal and Brain3R20T20

Axial – 40	Sagittal – 80	Coronal - 142
Brain1Normal and Brain3R10T15

Brain1Normal and Brain3R20T20

Brain3Normal and Brain1R10T15

Brain3Normal and Brain1R20T20

APPENDIX I**Source Code of Matlab Program for Generating Checkerboard Image**

```

%%%%%%%%%%%%%% File name: merge.m %%%%%%%%%%%%%%%
% Description: matlab function merge generates a checkerboard image from two
%              superimposed images
% Input parameter:
%   img1, img2: two images to be superimposed
%   divx, divvy : the number of partition in x and y direction respectively
%               e.g. if divx = 7, divvy = 7, then a checkerboard of 7x7 squares is
%               to be generated.
% Author      : Dilla Handini
%%%%%%%%%%%%%%

```

```
function img3 = merge(img1,img2,divx,divy)
```

```
% Reading of image-1 and image-2
```

```
f1= imread(img1);
f2 = imread(img2);
img1t = f1;
img2t = f2;
```

```
% Measuring the x, y dimension of the image, and assigning them to co1 and ro1
% respectively.
```

```
% Both images are of the same size.
[ro1,co1]= size(img2t);
```

```
%%%%%%%%%%%%%% Generating Checkerboard Image %%%%%%%%%%%%%%%
```

```
len1 = floor(ro1/divy);
wid1 = floor(co1/divx);
img3 = f1;
ctr = 1;
maxctr = divx * divy;
```

```
for ctr=1:maxctr
```

```
    ctrX = mod(ctr,divx);
    if ctrX == 0
        ctrX=divx;
    end;
```

```
    ctrY = ceil(ctr/divx);
    x1 = ((ctrX-1)*wid1) + 1;
    x2 = x1 + (wid1-1);
    y1 = ((ctrY-1)*len1) + 1;
    y2 = y1 + (len1-1);
    if (mod(ctr,2)==1)
```

```
        img3(y1:y2,x1:x2) = img1t(y1:y2,x1:x2);
```

```
    else
        img3(y1:y2,x1:x2) = img2t(y1:y2,x1:x2);
    end;
end;
```

```
imshow(img3,[]); % Showing the checkerboard as a figure.
```