THREE-DIMENSIONAL RECONSTRUCTION AND DESIGN OF PATIENT-SPECIFIC IMPLANT USING OPEN-SOURCE SOFTWARE

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THREE-DIMENSIONAL RECONSTRUCTION AND DESIGN OF PATIENT-SPECIFIC IMPLANT USING OPEN-SOURCE SOFTWARE

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LIST OF ABBREVIATIONS

2D	Two-dimensional
3D	Three-dimensional
AM	Additive manufacturing
ANOVA	Analysis of variance
CAD	Computer-aided design
CAD/CAM	Computer-aided design/computer-aided manufacturing
CBCT	Cone beam computed tomography
CT	Computed tomography
DC	Decompressive craniectomy
DICOM	Digital Imaging and Communication in Medicine
DSC	Dice similarity coefficient
HD	Hausdorff distance
HU	Hounsfield unit
ICC	Intra-class correlation coefficient
MIROS	Malaysian Institute of Road Safety Research
MITK	Medical Imaging Interaction Toolkit
MRI	Magnetic resonance imaging

MVA	Motor vehicle accident
NURBS	Non-uniform rational B-spline
PACS	Picture Archiving and Communication System
PMMA	Polymethylmethacrylate
STL	Standard tessellation language

REKONSTRUKSI TIGA DIMENSI DAN MEREKA BENTUK IMPLAN SPESIFIK PESAKIT MENGGUNAKAN PERISIAN SUMBER TERBUKA

ABSTRAK

Perisian komersial bagi pengimejan perubatan kebiasaannya mahal. Malahan, kajian berkaitan rekonstruksi tiga dimensi (3D) tengkorak dan mereka bentuk implant spesifik pesakit menggunakan perisian sumber terbuka yang percuma adalah terlalu sedikit. Kajian ini bertujuan membandingkan model tengkorak 3D dan implant spesifik pesakit yang direkonstruksi daripada imej tomografi berkomputer (CT) menggunakan perisian sumber terbuka dengan perisian komersial. Pada peringkat pertama kajian ini, perisian komersial Mimics v17.0 telah digunakan untuk mengrekonstruksi model tengkorak 3D dari 58 orang peserta yang menjalani imbasan CT di Hospital USM. Seterusnya, tiga perisian sumber terbuka, MITK Workbench 2016.11, 3D Slicer 4.8.1 dan InVesalius 3.1, telah digunakan untuk mengrekonstruksi model tengkorak 3D dari peserta yang sama. Model tengkorak 3D yang dihasilkan dari perisian komersial dan sumber terbuka kemudiannya dieksport dalam format s*tandard tessellation language* (STL) ke perisian 3-matic v9.0 dan *CloudCompare* untuk dianalisis. Perisian SPSS versi 24.0 digunakan bagi analisis statistik. ANOVA satu hala menunjukkan tiada perbezaan yang bererti bagi analisis kraniometri yang dijalankan ke atas model tengkorak 3D yang direkonstruksi menggunakan perisian komersial dan tiga perisian sumber terbuka, $p > .05$. Analisis *Hausdorff distance* (HD) menunjukkan purata jarak titik di antara Mimics dengan MITK adalah 0.25 mm. Manakala, bagi Mimics dengan 3D Slicer, dan Mimics dengan InVesalius, hampir tiada perbezaan di antara dua model tengkorak 3D yang bertindih, iaitu purata jarak titik adalah 0.01 mm. Dengan menggunakan analisis *Dice similarity coefficient* (DSC), persamaan di antara Mimics dan MITK, Mimics dan 3D Slicer, dan Mimics dan InVesalius adalah masing-masing 94.1%, 98.8%, and 98.3%. Pada peringkat kedua kajian ini, implan spesifik pesakit telah direka bentuk menggunakan perisian komersial 3-matic v9.0 dan perisian sumber terbuka MITK Workbench 2016.11 untuk 10 orang pesakit *decompressive craniectomy*. Kaedah interpolasi berasaskan bentuk digunakan, di mana teknik segmentasi setiap hirisan kelima dan kesepuluh data CT dilakukan. Reka bentuk akhir implan spesifik pesakit dari kedua-dua perisian dieksport ke format STL ke perisian *CloudCompare* untuk dianalisis. Hasil ujian Kruskal-Wallis bagi luas permukaan dan isipadu implan spesifik pesakit yang direka bentuk menggunakan 3-matic dan dua teknik MITK menunjukkan tiada perbezaan yang bererti, $p > .05$. Hasil analisis HD bagi implan spesifik pesakit yang direka bentuk menggunakan 3-matic dan dua teknik MITK menunjukkan purata jarak titik untuk 3-matic dengan MITK pada setiap hirisan kesepuluh adalah 0.28 mm dan bagi 3-matic dengan MITK pada setiap hirisan kelima adalah 0.15 mm. Hasil analisis DSC bagi implan spesifik pesakit yang direka bentuk menggunakan 3-matic dan dua teknik MITK menunjukkan persamaan di antara 3-matic dan MITK pada setiap hirisan kesepuluh dan kelima adalah masing-masing 85.1% dan 89.7%. Sebagai kesimpulan, perisian sumber terbuka yang dikaji dalam kajian ini adalah setanding dengan perisian komersial untuk rekonstruksi 3D berasaskan imej CT dan juga mereka bentuk implan spesifik pesakit. Ini adalah kajian pertama dalam mereka bentuk implan spesifik pesakit dari imej CT menggunakan kaedah interpolasi berasaskan bentuk dengan perisian sumber terbuka yang percuma.

THREE-DIMENSIONAL RECONSTRUCTION AND DESIGN OF PATIENT-SPECIFIC IMPLANT USING OPEN-SOURCE SOFTWARE

ABSTRACT

The commercial medical imaging software is typically expensive. Moreover, studies on three-dimensional (3D) skull reconstruction and design of patient-specific implant using free open-source software are scanty. This study aimed to compare the 3D skull models and patient-specific implants reconstructed from computed tomography (CT) images using the open-source software with commercial software. In the first stage of the study, the commercial Mimics v17.0 software was used to reconstruct the 3D skull models from 58 subjects who underwent CT scan at Hospital USM. Next, three open-source software, MITK Workbench 2016.11, 3D Slicer 4.8.1, and InVesalius 3.1, were used to reconstruct the 3D skull models from the same subjects. The 3D skull models from the commercial and open-source software were exported in standard tessellation language (STL) format into 3-matic v9.0 and CloudCompare software for analyses. SPSS version 24.0 was used for statistical analyses. For the first stage of the study, one-way ANOVA demonstrated that no significant difference was found on the craniometric analyses performed on 3D skull models reconstructed using the commercial software and the three open-source software, $p > .05$. Hausdorff distance (HD) analysis demonstrated the average points distance of Mimics versus MITK was 0.25 mm. Meanwhile, for Mimics versus 3D Slicer and Mimics versus InVesalius, there were almost no differences between the two superimposed 3D skull models with average points distance of 0.01 mm. Based on Dice similarity coefficient (DSC) analysis, the similarity between Mimics and MITK, Mimics and 3D Slicer, and Mimics and InVesalius were 94.1%, 98.8%, and 98.3%, respectively. In the second stage of the study, patient-specific implants were designed using the commercial 3-matic v9.0 software and open-source MITK Workbench 2016.11 software for ten decompressive craniectomy patients. The shape-based interpolation method was used, in which the technique of segmenting every fifth and tenth slices of CT data were performed. The final design of patient-specific implants from both software was exported to STL format into CloudCompare software for analyses. Results of Kruskal-Wallis test for the surface and volume of patient-specific implants designed using 3-matic and the two MITK techniques showed no significant difference, $p > .05$. Results of HD analysis for patient-specific implants designed using 3-matic software and the two different MITK techniques showed the average points distance for 3-matic versus MITK on every tenth slice was 0.28 mm and for 3-matic versus MITK on every fifth slice was 0.15 mm. Results of DSC analysis for patient-specific implants designed using 3-matic and the two different MITK techniques showed the similarity between 3-matic and MITK on every tenth and fifth slices were 85.1% and 89.7%, respectively. In conclusion, the open-source software investigated in this study are comparable with the commercial software for 3D reconstruction of CT images as well as designing the patient-specific implants. This is the first study on designing patient-specific implant based on CT images applying shape-based interpolation method using the free open-source software.

CHAPTER 1

INTRODUCTION

Craniofacial fractures are commonly caused by motor vehicle accidents (MVA) including motorcycle, automobile, bicycle, and pedestrian hit (Naveen Shankar *et al.*, 2012; Pohchi *et al.*, 2013). MVA cases are also increasing in Malaysia (MIROS, 2017) and it costs Malaysia RM 9.2 billion in 2016 (Gan, 2017). Utilisation of three-dimensional (3D) reconstruction of the skull is a method to design a patient-specific cranial implant to improve management of patients with craniofacial fractures. The data obtained from the diagnostic imaging tools which were reconstructed in 3D with better resolution aid in the diagnosis to improve patient management.

1.1 Background of the Study

Our society places high regard on physical and facial beauty; no matter how loving, intelligent, or courageous a person may become, most will look no further than the face. Patients with craniofacial fractures and deformity normally have facial distortion. Apart from that, they may also suffer from other disabilities such as speech and visual impairment, eating and breathing disorders, and even brain dysfunction. Therefore, the impact of craniofacial fractures often causes its victim to have a lower quality of life, which may lead to isolation and rejection.

Craniofacial region of the human body is made up of various bones integrated in a complex fashion. Fractures of the craniofacial region can occur due to many factors such as sports-related injuries, gunshot trauma, and MVA. Reportedly, MVA-related was the most common (Hoppe *et al.*, 2014; Naveen Shankar *et al.*, 2012; Rivera-Barrios *et al.*, 2015). Different diagnostic imaging tools are being used to diagnose fractures of the craniofacial region such as x-rays, computed tomography (CT) scan, and magnetic resonance imaging (MRI). As explained earlier, the craniofacial region has a complex anatomical setting and disruption in the bony continuity of this region is detrimental to both aesthetics and functionality. Due to these factors, it is always challenging to diagnose fractures of the craniofacial region. Most of the time, clinical examination is insufficient and requires radiological imaging tools to diagnose these fractures. With the advance in computer technology, 3D reconstruction of the craniofacial region can be achieved with the aim to get better visualization of the fractures to aid in diagnosis and management of the patients.

Cranial vault reconstruction is surgically performed to cover the defected bone in the skull which may be caused by congenital defects, diseases, accidents, infections, or tumours (Saldarriaga *et al.*, 2011). It is a complicated and risky endeavour involving intricate procedures that demand the skills and experience of oral and maxillofacial surgeons as well as plastic and reconstructive surgeons. The reconstruction of cranial defects is one of the few areas of reconstructive surgery where precision in pre-operative planning is vastly important.

Previously, surgical procedure for managing large defect of the skull is complicated as it has to be done manually based on two-dimensional (2D) imaging, namely the shaping, modelling, and placement of the implant, which is made of bone grafts, bone cements, or titanium meshes. Using this conventional method resulted in long and complex operations with poor aesthetic results. The manual process is very labour-intensive and expensive (Salmi *et al.*, 2012). With the advance in the computer and additive manufacturing (AM) technology, an implant that exactly fits the defect can be manufactured pre-operatively from the radiographic data obtained from CT scan.

Poukens *et al.* (2008) highlighted the difficulties in cranial implants reconstruction if the injuries cross the midline of the skull. Designing an implant that involves part of the orbit is more complicated (Senck *et al.*, 2013) due to the curvature of the orbital area and the need for mirroring of the other side. Studies have reported the advantages of using several different computer-aided design and computer-aided manufacturing (CAD/CAM) platforms (Drstvensek *et al.*, 2008), which resulted in the perfectly fit implant, less surgery time, and better aesthetic results (Mazzoli *et al.*, 2009).

Cranial reconstruction of a very large defect in a skull is a challenge, as it normally involves the use of sophisticated proprietary image processing and expensive CAD software. As an alternative, open-source software is developed by a non-profit community or research organisation. It is free to use, distribute, and modify. Among the advantages of open-source software are its flexibility to modify features to fit the needs of the research and the ability to run experiments at a lower cost.

1.2 Gap Statement and Justification of Study

Following an extensive injury, surgical reconstruction can be very challenging due to limited 3D visualization. Visualizing these fractures in a form of a skull model would help in pre-operative planning of the case. In developed countries, 3D reconstruction was extensively applied in clinical setting unlike in Malaysia, where there is not many computer experts in 3D reconstruction to produce printed 3D models and patient-specific implants.

There are limited studies in comparing several open-source software with the commercial software in Malaysia. Therefore, the aim and scope of this study was to investigate, apply, and expand the application of several open-source software for 3D reconstruction of skull model and the design of patient-specific cranial implant.

1.3 Objectives of the Study

1.3.1 General Objective

The general objective of this study was to investigate and develop methods in using open-source software for 3D reconstruction and design of patient-specific cranial implant based on CT imaging and computer technology, and later to apply this method in clinical applications. Three different open-source software was compared with the commercial software on its accuracy in producing the 3D skull models. Later, the commercial and open-source software were utilised to design patient-specific cranial implants to be used in clinical cases.

1.3.2 Specific Objectives

The specific objectives for this study were:

1. To reconstruct 3D skull models using commercial software (Mimics v17.0) as the gold standard.
2. To investigate and develop methods to reconstruct 3D skull models using three open-source software:
    a. MITK Workbench 2016.11 (German Cancer Research Center, http://www.mitk.org)
    b. 3D Slicer 4.8.1 (National Institutes of Health, United States of America, http://www.slicer.org)

c. InVesalius 3.1 (Centre for Information Technology, Ministry of Science and Technology, Brazil, https://www.cti.gov.br/invesalius)

3. To compare the craniometric and geometric measurements of 3D skull models reconstructed using Mimics software with MITK, 3D Slicer, and InVesalius software.
4. To design and fabricate patient-specific cranial implants using commercial software (3-matic v9.0) based on clinical cases from Neurosurgery Department, for insertion in patients with decompressive craniectomy (DC).
5. To design patient-specific cranial implants using open-source software (MITK) based on clinical cases from Neurosurgery Department.
6. To compare geometric measurements of patient-specific cranial implants produced using commercial software (3-matic) with open-source software (MITK).

1.4 Significance of the Study

As part of Universiti Sains Malaysia (USM) Research University Team (RUT) project, the author had investigated and applied several open-source software to perform image processing of CT data, to segment the region of interest of anatomical structures, to create 3D skull models, and finally to convert the 3D skull models to a format that is compatible for 3D printing platform.

Commercial software is expensive and not many hospitals or institutions have the budget to purchase them. Meanwhile, in-house software needs to be developed by the institution itself, which means they may need to hire an expert for this purpose. Thus, the use of open-source software to construct the 3D skull models and design of patient-specific cranial implants will reduce the cost of purchasing commercial software as well as paying yearly licensing fee to maintain the software. Furthermore, it can benefit patients as their treatment time and cost would be much lower, apart from the more aesthetic results.

Research comparing open-source software with commercial software in their ability to reconstruct 3D skull models and design of patient-specific cranial implants is scanty. This study aimed to investigate this aspect to strengthen the concept that similarly accurate 3D skull models and good quality patient-specific cranial implants can be constructed using open-source software. Moreover, similar study to the present study can be replicated by other researchers from other health institutions or universities as the open-source software is freely available and the steps involved in using them were clearly outlined in this thesis.

Other ongoing research related to this topic which fall under the Craniofacial Imaging Research Cluster at USM involving inter-disciplinary team has produced significant benefits to the present patient management. Furthermore, there is an opportunity to enrich the training to other specialities using these data to demonstrate the importance of life-long learning. This study contributed to knowledge in medical imaging, open-source software technology, and clinical applications.

CHAPTER 2

LITERATURE REVIEW

The main goal of this chapter is to provide current concept of cranio- and maxillo-facial imaging of craniofacial fractures, the technology in 3D reconstruction of the skull based on CT scan data, and the design of cranial implant. The explanations include a review about the technology of imaging, the software for 3D reconstruction of the skull, and the software for implant design.

2.1 Craniofacial Region

Fractures of the craniofacial region can occur due to trauma, falls, and sports injury. A number of small bones join together to form the craniofacial region, adding to its complexity; thus, leading to difficulty in diagnosing and treating the fractures (Pickrell *et al.*, 2017; Shah *et al.*, 2016). The bones of the craniofacial region include bones around the eyes (orbital bones), cheekbones (zygoma), cranial bones (the top portion of the skull that protects the brain), frontal bone, lower jaw (mandible), nasal bones, upper jaw (maxilla), and parietal bones (Craven, 2014). Figures 2.1 and 2.2 show the anterior and lateral views of the skull, respectively.

Due to the complexity of this region (Patel *et al.*, 2016), having a good diagnostic tool to view these bones is helpful in clinical management. Different diagnostic imaging tools are being used to diagnose fractures of the craniofacial region such as x-rays, CT scans, cone beam computed tomography (CBCT) scans, and MRI. However, these images can only be viewed on a computer screen, which may limit a surgeon’s perspective on the prognosis of repairing the fracture. Therefore, having a

3D model which can be derived from these data would greatly benefit surgeons in managing these fractures, especially when the fracture involved multiple small bones.

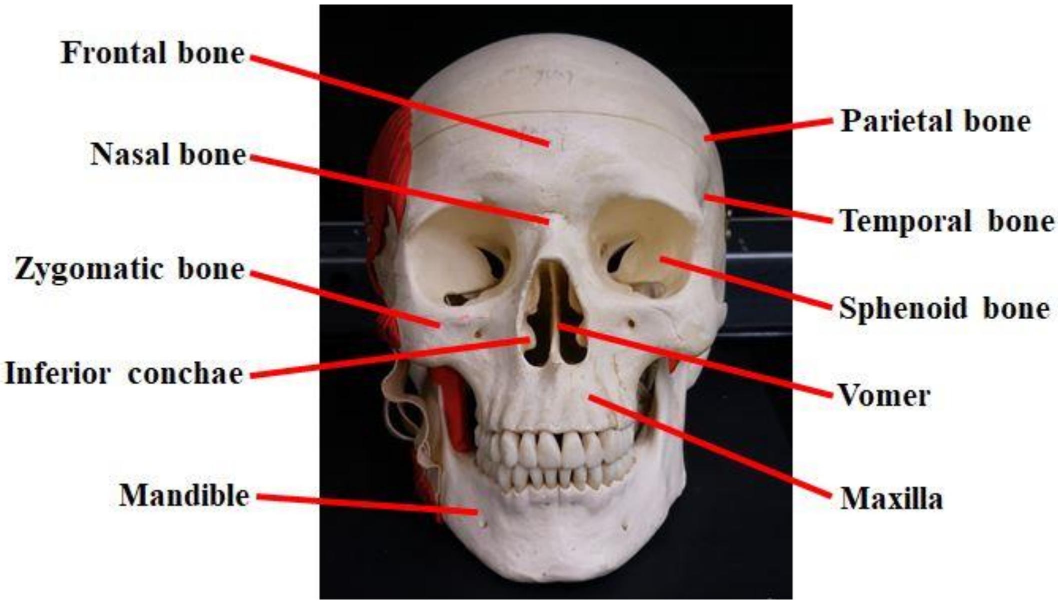

Figure 2.1 Anterior view of the skull.

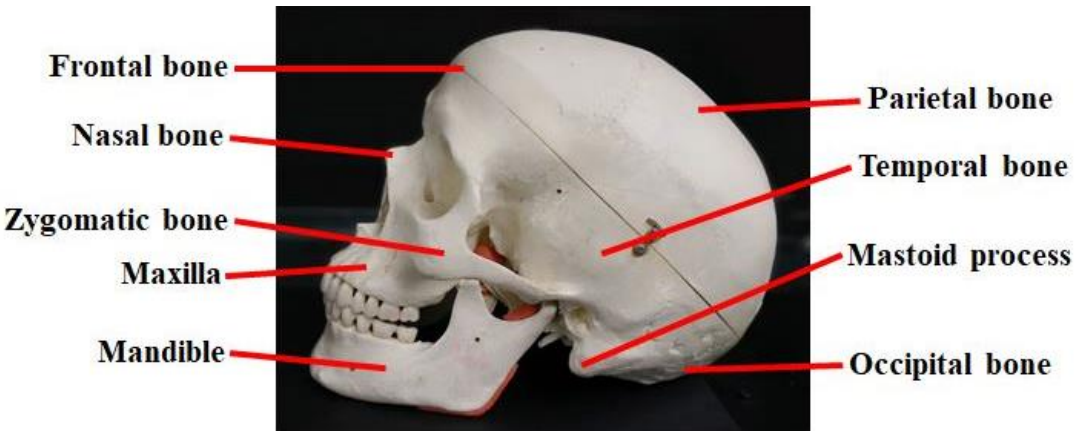

Figure 2.2 Lateral view of the skull.

3D anatomical models from medical imaging data provide the added benefit of allowing anatomist or anthropologist to avoid handling fragile “real” specimens. Often in forensic cases, there is residual soft tissue attached to the bony specimen that cannot be removed or defleshed. This soft tissue can obscure critical landmarks and features used in establishing the biological profile or evidence of trauma. On the other hand, cadaveric dissection has always been associated with ethical concerns (Gunderman, 2008; Hasan, 2011), difficulties and potential risks of preservation, and disposal of specimens (Schmitt *et al.*, 2014). Furthermore, shortage of donors is another limitation associated with cadaveric dissection in some countries. With the 3D models, the soft tissue can be virtually removed or made transparent for analysis. Due to its precise reconstruction of intricate anatomical structures, there is an increasing use of 3D printing in medicine, ranging from basic anatomy to surgical practice and advanced research application (Chen *et al.*, 2017).

Detailed anatomical models replicated using 3D printers are best for teaching and learning of anatomy as they allow teachers and lecturers to introduce diverse specimens into classrooms (Thomas *et al.*, 2016). The printed 3D models are also useful to assist in diagnosis, surgical planning, implant design, and patient management (Giannopoulos *et al.*, 2016). Clinically, the 3D model is useful in management of craniofacial fractures.

2.2 Craniofacial Fractures

Common aetiological factors for craniofacial fractures include sports-related injuries, gunshot trauma, and MVA. Craniofacial fractures range from mild to severe. The primary goals in repairing complex craniofacial fractures are restoration of occlusion and mastication, and anatomic reconstruction of a symmetrical facial skeleton (Morrison *et al.*, 2014).

According to the report by Malaysian Institute of Road Safety Research (MIROS), 2012 Annual Report, the number of road accidents in Malaysia has increased year by year, from 279,711 in 2002 to 462,423 in 2012. Furthermore, vehicle registration has also increased from 12 million in 2002 to 22.7 million in 2012. Although no specific study has been conducted on the relationship between the number of vehicles on the road and accident cases, common causes of craniofacial fractures were reportedly MVA-related, including motorcycle, automobile, bicycle, and pedestrian hit (Hoppe *et al.*, 2014; Naveen Shankar *et al.*, 2012; Rivera-Barrios *et al.*, 2015). Studies conducted by Pohchi *et al*. (2013) on maxillofacial fractures at Hospital Universiti Sains Malaysia (Hospital USM) also showed similar results.

Motorcycles crashes contributed to more than 60% of accidents in Malaysia, with overall fatality index of 22 /100,000 in the population in 2014, according to MIROS 2016 Annual Report (MIROS, 2017). Additionally, the report mentioned a statement from Malaysian Ministry of Transport in 2014 which stated that accidents involving commercial vehicles such as lorry, bus, and taxi are increasing, with the total of 57,430 road accidents in 2014 alone. All these accidents could potentially contribute to increased number of patients with craniofacial fractures.

Patients with craniofacial fractures often present with facial deformity and other physiological disorders such as impairment in speech, vision, eating, breathing, and brain dysfunction. For this reason, imaging of craniofacial fractures is very important to provide accurate and reliable information for a successful patient management.

2.3 Imaging of Craniofacial Area

Apart from clinical expertise, sophisticated radiological imaging is required to aid in the diagnosis of craniofacial fractures. Normally, craniofacial fractures are diagnosed from plain x-ray films, CT scan, and/or CBCT scan (Casselman *et al.*, 2013; Johari *et* *al.*, 2016; Li *et al.*, 2016). Commonly, CT scan is the chosen method for patients with craniofacial fractures (Bellamy *et al.*, 2013; Kennedy *et al.*, 2014; Mundinger *et al.*, 2016; Righi *et al.*, 2015) as it can show the bones clearly. The output of these CT scan's data is in the Digital Imaging and Communications in Medicine (DICOM) format, which is the international standard to transmit, store, retrieve, print, process, and display medical imaging information.

2.3.1 Conventional Radiograph

Imaging of anatomical structures for medicine began with the discovery of x-radiation by Wilhelm Roentgen in 1895 (Linet *et al.*, 2012). For the first time, images of the internal body could be taken of living individuals. Marie Curie, who had just a few years before won a Nobel Prize for her research into radiation, drove a truck with portable x-ray equipment near the battlefields of France. This mobile unit allowed shattered bones to be visualized (Scatliff and Morris, 2014).

X-ray imaging involves taking a piece of film in a cassette and placing it between the object being imaged (body part) and the x-ray emission device or source. The film (or image capture receptor) detects the x-ray's waves and creates an image of the anatomy that it passed through. X-ray images are known to be effective at capturing bone and other dense structures but are less useful in distinguishing soft tissues. Although today's technology offers images of higher quality, more information can sometimes lead to diagnostic confusion (Scatliff and Morris, 2014). Not much information can be seen in a 2D modality; therefore, CT scan is more favourable for imaging of the craniofacial fractures because of its ability to visualise the fractures in 3D.

2.3.2 Computed Tomography Scan

CT scan was developed in the 1970s by Sir Godfrey Hounsfield and Allan MacLeod Cormack, and has become a critical diagnostic and imaging tool in both research and clinical settings (Wathen *et al.*, 2013). The technology works by acquiring planar x-ray images (or projections) taken at various degrees of rotation around a patient or specimen. These data are then reconstructed, typically with a filtered back projection algorithm, to produce a 3D array of radio-density values. The linear attenuation coefficient for each object at the selected effective energy was converted to Hounsfield Units (HU) using the standard equation (Reeves *et al.*, 2012):

$$\frac{\mu_x - \mu_{water}}{\mu_{water}} \text{ X } 1000 = HU$$

where μ is the linear attenuation coefficient and HU is the Hounsfield Unit. The Hounsfield number specifies the attenuation in relation to the attenuation in water. Each HU is equivalent to 0.1% of the attenuation of water, which represent the numerical value that is assigned to each pixel in a CT image.

The calibrated Hounsfield scale will have values of -1,000 HU to represent air, 0 HU to denote water, and up to 3,000 HU for dense bone. Soft tissues, which are primarily composed of water and protein, will have densities in the range of 100 to 300 HU (Bushberg *et al.*, 2012). However, it can be difficult to differentiate soft tissues via CT due to their low radio-opacity. On the other hand, the range for bone is either around 300 to 3000 HU (Schreiber *et al.*, 2011) or 150 to 2000 HU (Sogo *et al.*, 2012). The high range of bone HU is depending on the bone density. Hiasa *et al.* (2011) considered normal bone as having HU around 400 to 1000 HU.

The primary limitation of CT is its inability to distinguish many soft tissues based on native contrast. While bone has high contrast within a CT image due to its material density from calcium phosphate, soft tissue is less dense, and many are homogenous in density. This presents a challenge in distinguishing one type of soft tissue from another (Wathen *et al.*, 2013).

However, CT scans are good to project the bony contours of the anatomical location, and the 1-mm resolution is sufficient for diagnosis (Coolens *et al.*, 2009). The fractures site can be reconstructed to 3D images that makes it easier for both the radiologists and surgeons to diagnose and plan for treatment of the fractures.

2.4 Significance of the 3D Skull Models

Advances in craniofacial medical imaging have placed an importance of the 3D reconstruction of the skull model for medical applications. This technology has provided new possibilities to visualize complex medical data through generation of 3D skull models which were used for basic cranial education for medical students (Chen *et al.*, 2017), surgical training for surgeons (de Notaris *et al.*, 2014), pre-operative planning (Giannopoulos *et al.*, 2016), facial contouring surgery (Yim *et al.*, 2015), forensic medicine and dentistry (Katsumura *et al.*, 2016), computer-assisted surgery (Ritacco *et al.*, 2015), maxillofacial prosthesis (Jazayeri *et al.*, 2018), and craniofacial reconstruction (Jardini *et al.*, 2014; Maduri *et al.*, 2017; Park *et al.*, 2016; Schebesch *et al.*, 2013).

Craniofacial reconstruction is commonly performed following head or facial trauma and on cancer patients who have lost part of the bony structures following tumour surgery. In current practice, the reconstruction of craniofacial defects is normally based on bone graft which is shaped to fit the defect. However, clinically, bone graft is limited to a small defect as the graft is taken from the patient's own bone. With 3D skull model derived from CT data, pre-surgical planning can be done to fabricate an implant from compatible biomaterials such as titanium mesh or methylmethacrylate (Jalbert *et al.*, 2014). Using this technique, bigger and complex defect of the skull can be repaired.

Sex determination from the unidentified human remains is now possible from the assessment of the 3D model of the skull. Results of studies by Dereli *et al.* (2018) on 85 3D skull models from archive of CT data and Shearer *et al.* (2012) on scanned 3D models of 128 dry skulls, showed that sex can be determined from morphological features in volume-rendered CT 3D images. Results from these studies, which rely only on the digital images without the need for maceration processes, and the transfer of digital data in place of physical material, will make it possible to gain expert opinions in forensic anthropology (Dereli *et al.*, 2018). This would hugely benefit the forensic community as the digital format would save cost and time.

Apart from forensic application, 3D model of the skulls could be used for teaching of difficult anatomical concepts (Pujol *et al.*, 2016) to medical and health sciences students (Chen *et al.*, 2017). With the 3D skull models, students will be able to place the models in their hands and have better understanding of the anatomical landmarks and their spatial relationship with other structures. Additionally, these 3D models are also helpful to illustrate anatomical variations among patients.

In summary, the 3D model of the skull can be used in pre-operative planning in maxillofacial-, neuro-, and plastic-surgery and its related disciplines, orthodontics, forensics medicine, anthropology, surgical simulation, face recognition, and many other applications. In the medical imaging field, to find the most accurate, reliable, and yet low-cost 3D imaging software for 3D reconstruction of the skull is very important as it would have an impact on patient management. Therefore, it is important to find the best software for skull segmentation.

2.5 Software for Skull Segmentation

Most of the skull segmentation studies have utilised commercial software to create the meshed model or 3D model of the skull from patients' CT data; for example, Mimics software (Moiduddin *et al.*, 2017; Phanindra Bogu *et al.*, 2017; Rotaru *et al.*, 2012), CATIA software (Chrzan *et al.*, 2012), and Maxilim® software (Jonkergouw *et al.*, 2016). The 3D models created using skull segmentation software can be used for pre-operative planning or to design cranial implants (Kim *et al.*, 2012a). However, most of the software mentioned in the literatures are either commercial software or built in-house which were out of reach to researchers without big budgets or facilities.

Several studies have used open-source software, but no detailed steps were given as guidelines for other researchers to reproduce similar studies. Therefore, it was difficult to replicate these studies without proper tools or methods. Studies with detailed steps, particularly in the methodology of using certain open-source software would encourage other researchers to reproduce similar studies; therefore, encouraging more knowledge to be shared. Thus, this study was aimed to fill this gap.

Prior to the start of the study, apart from the commercial Mimics software available in Hospital USM, several open-source medical imaging software were downloaded and tested. Three open-source software, Medical Imaging Interaction Toolkit (MITK), 3D Slicer, and InVesalius, were finally selected for the analysis based on their robustness, visualizations, reliability, and ease of use. Furthermore, these software were able to segment the 2D images and reconstructed them into 3D exportable models that is in STL files. An STL file describes the surface geometry of an object which can be sent to the 3D printers for printing of the skull.

2.5.1 Mimics v17.0 Software

Mimics software (Materialise NV, Heverlee, Belgium), has been widely used for reconstruction of 3D skull models and has been mentioned in many studies (Park *et al.*, 2016; Yuan *et al.*, 2017; Zhang *et al.*, 2018). Mimics is the shortened form for Materialise's Interactive Medical Image Control System, an interactive tool for the visualization and segmentation of CT images as well as MRI images and 3D rendering of objects.

This software is a fully-integrated, user-friendly 3D image processing and editing software based on various scanner data. It imports scanner data in a wide variety of formats and offers extended visualization and segmentation functions. The software is specially developed for image processing which converts the DICOM files into a 3D model. The obtained 3D model contains information about the patient’s hard and soft tissues. Segmentation and region growing techniques were applied with different range of HU for the segregation of hard and soft tissues, making it suitable for the segmentation of the skull with craniofacial defect prior to craniofacial surgery (Moiduddin *et al.*, 2017). The software is also used for the 3D cephalometry analysis (Olmez *et al.*, 2011), reconstruction of 3D model of the skull (Bogu *et al.*, 2017; Decker *et al.*, 2013) and reconstruction of 3D model of the face (Decker *et al.*, 2013)

Most studies have used Mimics as a gold standard such as to evaluate the accuracy of image segmentation from the in-house computer-aided surgical simulation system for the orthognathic surgery (Yuan *et al.*, 2017). Similarly, Zale *et al.* (2018) studied the inter-departmental imaging protocol for 3D data of 30 CT scans by measuring glenoid version and they used Mimics software as the gold standard. The graphical user interface of Mimics software is shown in Figure 2.3.

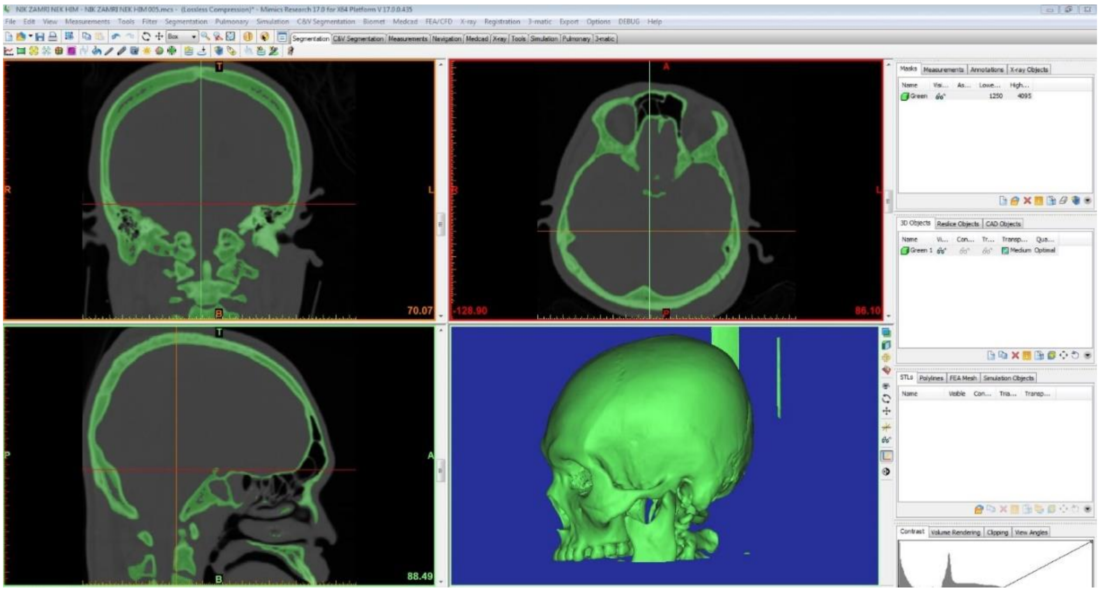

Figure 2.3 Graphical user interface of Mimics software allows researcher to view images in axial, coronal, sagittal, and 3D views.

Even though Mimics is a commercial software and the license has to be paid in order to use the software, the learning curve was quite steep to master the software interface and process. The training to use the software was also costly. Therefore, if this software can be replaced with one of the open-source software, the cost of hospital and patient management can be reduced.

2.5.2 MITK Workbench 2016.11 Software

MITK software was developed at the German Cancer Research Center (DKFZ) which can be downloaded at http://www.mitk.org. It is based on the well-established, free open-source Medical Imaging Toolkit (MITK). It is available on multiple operating systems such as Microsoft Windows, GNU/Linux, and Apple Mac OS X. The software offers several interactive 2D and 3D segmentation tools for medical imaging data. Its framework allows interactive segmentation (Maleike *et al.*, 2009; Nolden *et al.*, 2013) with simultaneous image viewing and outlining of regions in axial, sagittal, and coronal orientations.

MITK has been used in several studies for 3D skull reconstruction for pre-operative planning (Martin *et al.*, 2014; Nolden *et al.*, 2013). In another study, MITK was used to segment proximal femur manually (as gold standard) and compared with a new method of graph cut segmentation (Pauchard *et al.*, 2016). Sporns *et al.* (2018) used MITK to compare segmentation results of swallowing muscles. The graphical user interface of MITK is shown in Figure 2.4.

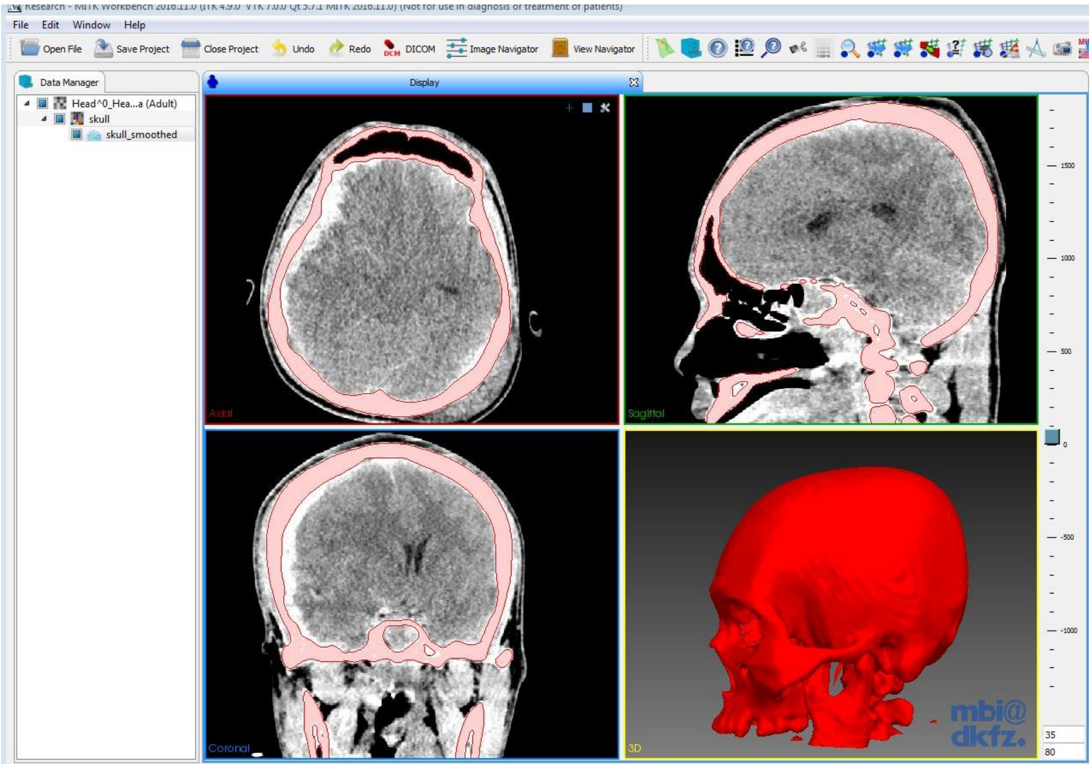

Figure 2.4 Graphical user interface of MITK software.

2.5.3 3D Slicer 4.8.1 Software

3D Slicer is another free open-source software which can be downloaded at http://www.slicer.org. It offers a platform for medical image informatics, image processing, and 3D visualization built through support from the National Institutes of Health, United States of America, and a worldwide developer community (Fedorov *et al.*, 2012). It is also available on multiple operating systems such as Microsoft Windows, GNU/Linux, and Apple Mac OS X with extensible plug-in for adding algorithms and applications. 3D Slicer has been used for volumetric analysis of medical images (Egger *et al.*, 2013) and reconstruction of 3D skull models (Szymor *et al.*, 2016; Tan *et al.*, 2016). The graphical user interface of 3D Slicer software is shown in Figure 2.5.

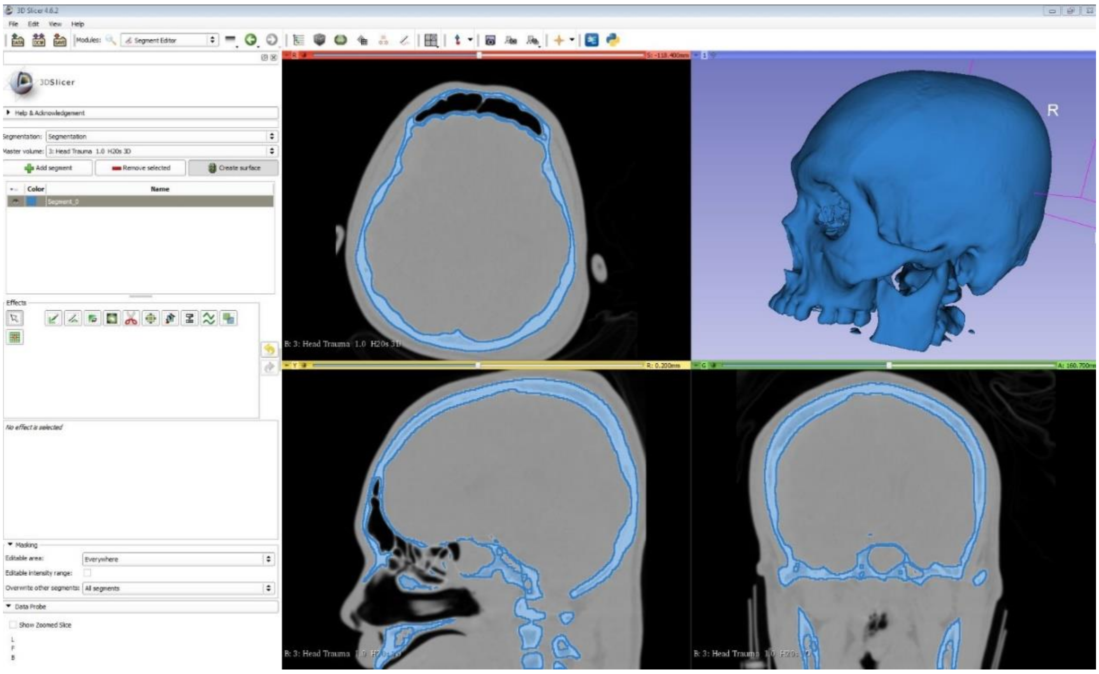

Figure 2.5 Graphical user interface of 3D Slicer software.

2.5.4 InVesalius 3.1 Software

InVesalius software is named in honour of the Belgian doctor Andreas Vesalius (1514-1564), widely considered as the father of modern anatomy. InVesalius software is developed in 2001 by the Centre for Information Technology (CTI), a unit of the Brazilian Ministry of Science and Technology. Initially, only the installation program was distributed as freeware. In November 2007 InVesalius software was made fully available as a free software and open-source via the Public Software Portal, allowing for communities of users and developers to connect. The software can be downloaded from the website https://www.cti.gov.br/invesalius.

InVesalius software is designed to run on personal computers such as desktop and notebooks, and it is compatible with various operating systems such as Microsoft Windows, GNU/Linux, and Apple Mac OS X. There are more than 10,000 people from 127 countries who are active users of InVesalius (Fazanaro *et al.*, 2016). This software has supported several surgeries in hospitals around the world for analysis and visualization of medical images. It has been used for the volumetric analysis of tumour (Gomes *et al.*, 2017), 3D reconstruction of skull model (Jardini *et al.*, 2016), and printing of anatomical structures (Coronel *et al.*, 2017).

InVesalius has been used for 3D reconstruction from CT data by many studies. Skrzat *et al.* (2016) reconstructed 3D skull models to enhance teaching of anatomy and claimed that the segmented 3D skull models were accurate; however, they did not do any comparison study to evaluate the accuracy. In another study, Ramos Verri *et al.* (2015) segmented six sets of mandible from CT data for biomechanical study of dental implant using InVesalius 3.0 and similarly, de Moraes *et al.* (2013) segmented three sets of mandible using InVesalius for finite element study of crownimplant ratio on stress distribution. Another study was the segmentation of 3D craniosynostosis model of three patients and later sent to 3D printer for surgical simulation to simulate fronto-orbital advancement and posterior distraction in the operating room environment (Ghizoni *et al.*, 2018). Based on the capability of InVesalius in segmenting 3D models of bone as reported in many literatures, this software was chosen as one of the open-source software utilised in this study. The graphical user interface of InVesalius software is shown in Figure 2.6.

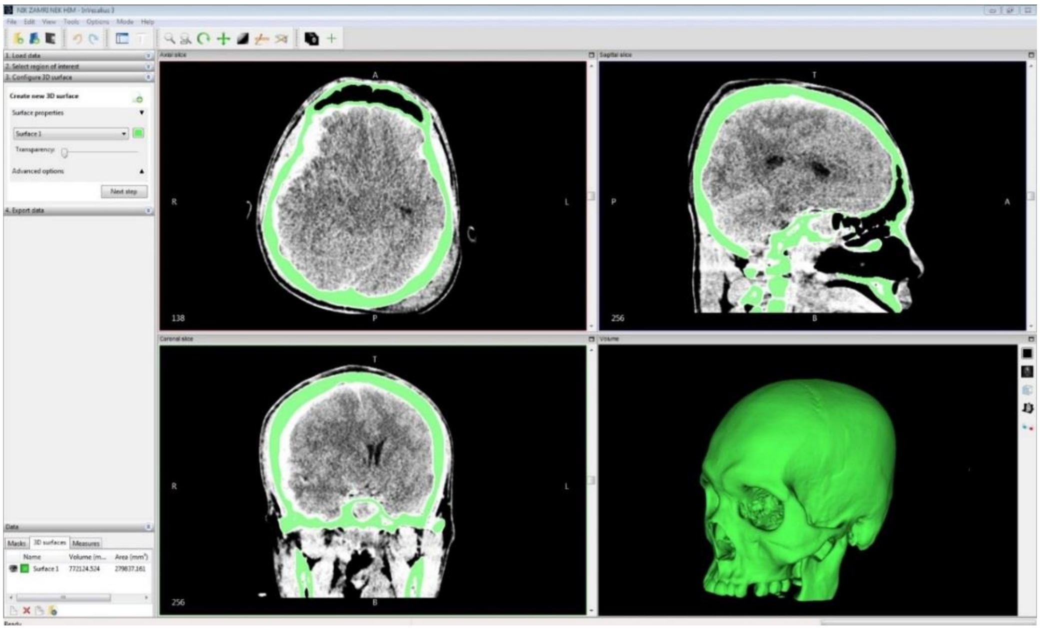

Figure 2.6 Graphical user interface of InVesalius software.

2.5.5 Summary of 3D Reconstruction Software

There were four software for skull segmentation reviewed in this chapter, which are the commercial Mimics software, and the three open-source software: MITK, 3D Slicer, and InVesalius. Table 2.1 compares these software in terms of their cost, country of origin, system requirements, input and output files format, and type of 3D models produced.

Table 2.1 Comparisons of a commercial software (Mimics) with three open-source software (MITK, 3D Slicer, InVesalius)

	Mimics v17.0	**MITK Workbench 2016.11**	**3D Slicer 4.8.1**	**InVesalius 3.1**
Cost	USD 58,500	Free	Free	Free
Country	Belgium	Germany	USA	Brazil
System requirements	Windows 7,8,10	Windows Linux Mac OS X	Windows Linux Mac OS X	Windows 7,8,10 GNU/Linux Mac OS X
Input file	DICOM, BMP, JPEG, IGES, STL	DICOM, NRRD, VTK	DICOM, JPG, VTK, MRML, NRRD, OBJ, Analyze, NifTI	DICOM, Analyze
Output file	FEA Module e.g., Abaqus, ANSYS, COMSOL IGES, STL	VTK, VTP, PLY, STL	VTK, VTP, STL	OBJ, PLY, STL
Type of 3D models	Surface-rendered Volume-rendered	Surface-rendered Volume-rendered	Surface-rendered Volume-rendered	Surface-rendered Volume-rendered

2.6 Design of Cranial Implant

Functional and aesthetically-placed patient-specific cranial implants are extremely important for patients with large cranial defects. Therefore, pre-operative fabrication of the implants is recommended (Marreiros *et al.*, 2016) to ensure minimal adjustments during surgery, which would then translate to lower surgical cost and time, as the implants would fit nicely into the defect.

The techniques frequently used in designing cranial implants are CAD and mirror image reconstruction. However, the shape-based interpolation method may be another technique for this purpose, which was studied in this project.

2.6.1 Computer-Aided Design

Rapid developments in medical imaging and advances in CAD improved the quality of implants, resulted in improved aesthetic outcome as well as minimising operation time, blood loss, and risk of infection (Chen *et al.*, 2015; Zhao *et al.*, 2012). Patient-specific implants can be produced in any sizes with an accurate fit using this technology (Oh, 2018). The creation of the cranial implant with optimal size, shape, and mechanical properties prior to the surgical procedure reduces the operation time and complexity (Jardini *et al.*, 2014). The main advantage of using CAD is a better outcome and aesthetic of the implant; therefore, it can be successfully used in the repair of a defect (van der Meer *et al.*, 2013).

Using CAD software enables the users to automatically check if the design is within specification. It also enables users to view designs at an earlier stage in the design process. However, CAD software often consumes large amount of computer processing power. This requires a high-quality computer hardware that can be costly, on top of the price of the CAD software (Nguyen *et al.*, 2018). The cost of hardware and software is a significant disadvantage of the CAD and a major barrier to adopt this technology, particularly for institutions with limited budget.

Another disadvantage of the CAD technology is the complexity of the software. As the CAD software advances, it becomes more flexible and adaptable and could do many things. However, this comes at the cost of making the software more complex. This complexity makes it more difficult for first-time users to master the software. Combined with the cost of training personnel in CAD technologies, this complexity represents another disadvantage of CAD.

One of the examples of CAD software is 3-matic software. It comes with standard sketcher and CAD functions and can work directly on STL levels or convert CAD data to STL. The graphical user interface of 3-matic software is shown in Figure 2.7.

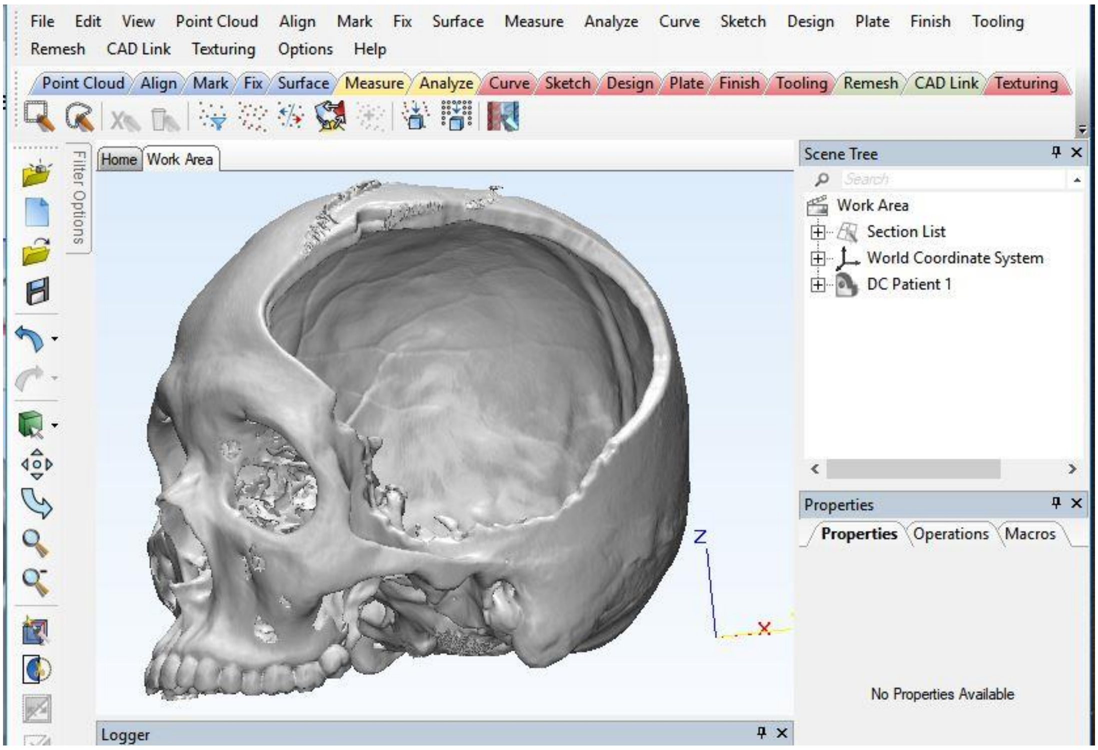

Figure 2.7 Graphical user interface of 3-matic software.