Aus der Abteilung für Zahnärztliche Prothetik, Alterszahnheilkunde und medizinische Werkstoffkunde
(Direktor: Prof. Dr. Reiner Biffar)

im Zentrum für Zahn-, Mund- und Kieferheilkunde
(Geschäftsführender Direktor: Prof. Dr. Georg Meyer)

der Universitätsmedizin der Ernst-Moritz-Arndt-Universität Greifswald

Assessment of Frankfort Horizontal plane Reproduction on MRI

INAUGURAL – KUMULATIVE DISSERTATION

zur

Erlangung des akademischen

Grades
Doktor der Zahnmedizin
(Dr. med. dent.)

der

Universitätsmedizin

der

Ernst-Moritz-Arndt-Universität

Greifswald

2013

vorgelegt von: Amro A Daboul

geb. am: 22.07.1982

in: Damaskus/ Syrien

Dekan: Prof. Dr. med. dent. Reiner Biffar

1. Gutachter: Prof. Dr. med. dent. Reiner Biffar

2. Gutachter: Prof. Dr. med. dent. Harald Küppe

Ort, Raum: Greifswald, Hörsaal der neuen Zahnklinik

Tag der Disputation: 14. Oct 2013

Dedication

My previous, current and future work is dedicated with love and gratitude to my mom and dad for their extraordinary commitment to my education. Without your constant encouragement and support, I would not have had the courage to pursue my education up to this level.

List of contents

List of abbreviations

CI: Confidence interval

CT: Computed Tomography

CSA: Cross sectional area

DICOM: Digital imaging and communication in medicine format

FH: Frankfort Horizontal

HOR: True horizontal plane

ICC: Intra class correlation

MRI: Magnetic resonance imaging

SD: standard deviation

SHIP: Study of health in pomerania

VER: Vertical plane

Chapter 1: Introduction

Diagnostic imaging in dentistry depends mainly on conventional x-ray based techniques that convey some acknowledgeable limitations and risks such as the inability to visualize soft tissues and the exposure to invasive radiation and its associated increased risk of cancer.

Since its development, magnetic resonance imaging (MRI) has been increasingly used for medical diagnosis as an imaging modality with no ionizing radiation. In dentistry, MRI has been used to evaluate the temporomandibular joint, orofacial tissues, implant planning and in longitudinal studies analyzing craniofacial structures. MRI has been shown to enable accurate and reproducible three-dimensional measurements of the craniofacial skeleton due to the contrast between the bone and the surrounding soft tissue, which allows the evaluation of craniofacial morphology that is difficult to identify with cephalometric radiography

In most of the studies concerned with measuring or comparing craniofacial structures, a reference plane was always incorporated into the method to either allocate the craniofacial structures, or to perform comparative analysis on craniofacial morphology among subjects (longitudinal inter-individual comparison) or within the same subject (intra-individual comparison of craniofacial morphology). Both forms of analysis are dependent on the reliability of the reference plane and the subsequent measurement accuracy of the craniofacial structures.

With the broad range of reference planes that are used within different imaging modalities, a valid reference plane, ideally, should have the following features: good reliability (low method error), low intra and inter-individual variability, and an average orientation close to true horizontal (HOR) or vertical (VER) planes.[1] Therefore, it is evident that without a standardized reference plane with good reliability and low variability, analysis and comparison of craniofacial structures is questionable.

In this study, we evaluated the reproducibility of Frankfort Horizontal plane, which is one of the most common reference planes used in MRI We determined that this is important prior to its selection as a reference for cranial measurements, particularly in a population based study such as SHIP, where normative data for various craniofacial structures are measured, and any misjudgment in the reference plane may lead to inaccurate data and false conclusions.

Chapter 2: Aims and Objectives

The present study aimed to determine the accuracy and reliability of Frankfort horizontal plane identification using displays of multi-planar reconstructed MRI images and assess the reproducibility of its landmarks.

The specific aims were:

1. To provide a critical literature review toward the significance and use of Frankfort Horizontal as a craniofacial reference plane.
2. To apply new statistical methods to evaluate the Inter and Intra-Observer reliability of Frankfort Horizontal identification in terms of distance and plane orientation and to identify the error patterns.
3. To propose Frankfort Horizontal as a standardized reference plane for further craniofacial measurements in MRI.

Chapter 3: Background and literature review

3.1 Frankfort Horizontal plane

Frankfort Horizontal was developed over a decade-long period as anthropologists attempted to present it more suitably. In 1872, Merkel and Von Ihering [2] suggested a reference plane passing from the lowest point of the orbit through the midpoint of the porus acousticus externus. Subsequently in 1882, at the Craniometrical Conferences in Munich and Berlin, Von Ihering's line was modified. Porion was selected as a more suitable landmark dorsally, and the plane was labeled German Horizontal. It was introduced as Frankfort Horizontal (FH) in 1884, after its adoption at an anthropological conference in Frankfurt. It was defined as a plane extending from the left Orbitale to both Porion points. [3]

Since then, the plane has been widely recognized as a reference plane for the skull and has proved to be of great value in craniofacial studies and orthodontics. It has been presented in several studies as an adequate cranial base reference and was incorporated in anthropological studies, maxillofacial surgery planning and descriptive communications between clinicians. [4–7] However, in many of the previous studies in the craniofacial area, anatomical areas were studied based on FH plane visual estimation rather than landmark identification, FH landmark identification errors were not evaluated on images. And no data have been published on its reproducibility.

3.2 Craniofacial landmarks reproducibility

Since the development of 3D CT and MRI, many methods were proposed to analyze the craniofacial area. They have been useful in describing the position, orientation and shape of different craniofacial structures in individual subjects, or comparing between subjects suffering from any dysmorphic variation and the population norms. The notion behind most methods analyzing the craniofacial area is that different structures are measured with regard to lines or reference planes. Those reference planes rely mainly on the individual identification of craniofacial landmarks that are traditionally used for cephalometric analysis. Furthermore, since the validity of craniofacial analysis and measurements depend highly on the accuracy and reliability of the reference plane used, the identification and reproducibility of the landmarks that form the plane should be verified in each imaging modality. Additionally, it was recommended in the literature that every study should include an assessment of reproducibility [8], [9].

McClure et al [10] examined the reproducibility of 19 landmarks including porion and orbitale on cephalmetric images. They concluded that the inter-examiner errors on 2D images were generally low. In another study conducted by Kragskov et al [11], it was suggested that landmarks detection on 3D CT images has less reliability than traditional 2D cephalometric images. Kragskov argued that the reason behind these findings was that distances calculated between points on 2D cephalograms consisted of two coordinates only in comparison to three coordinates for 3D CT images, thus adding an extra deviation. On the contrary, other studies have reported good reproducibility of craniofacial landmarks in 3D CT using aids such as phantoms and metallic markers. [12], [13] However, this approach would demonstrate the accuracy of the imaging but does not simulate the clinical situation in which precision is influenced by the difficulty in identifying landmarks.

Olszewski et al [14] identified 22 craniofacial landmarks on CT images and classified them into 4 groups based on their reproducibility. In their study, Porion was classified under mean inter-examiner reproducibility and Orbitale with low inter-examiner reproducibility. In a later study conducted on 3D CT by Lagravere et al [15], Porion showed relatively high intra and inter-examiner mean differences and Orbitale showed high inter-examiner differences.

Nonetheless, although differences in imaging modules, techniques and measurement methods make direct comparison of results reported in the literature on FH landmarks reproducibility rather unreliable, a general estimation on the 3D complexity of these landmarks can be concluded.

3.3 Frankfort Horizontal as a standardized reference plane in MRI.

The ideal positioning of the patients prior any MRI scan would be that in which the Frankfort Horizontal plane is parallel to the scan direction. Studying craniofacial components based on this estimation is, however, riddled with several limitations. Limitations such as difficulty to maintain a fixed position of the head during the scan, the presence of any dysmorphic abnormality and anatomical variations between subjects would make it difficult to compare measurements between subjects or obtain correct analysis values of the studied structures.

Related to that fact, it is suggested that discrepancies in reported values of the same measured craniofacial structures (i.e. Masticatory Muscles) among different studies in the literature are in fact, due to methodological differences and inadequate standardization among subjects.

Facial and masticatory muscles measurements are extensively reported in the literature through MRI, as their length, cross-sectional areas CSA and relationships with craniofacial morphology reflect their force-producing properties and manifest various illnesses. However, the reported values in the literature were inconsistent, and it was assumed that this variation is due to differences in the studied populations. Nonetheless, it is difficult to clarify possible population differences without using standardized methods. For instance, while some studies [16,17] estimated FH prior to the scan, and then measured the CSA of the masseter and medial pterygoid muscle at 30-degree angle to FH, other studies [18] measured the muscles CSA parallel to FH. It was later ascertained that for CSA in each muscle to be determined correctly, it must be measured at an angle perpendicular to the muscle's long axis. To define this long axis in the masseter and medial pterygoid muscles, the muscle's medio-lateral inclination relative to Frankfort horizontal plane must be measured. [19]
The variations in CSA values among previous studies revealed that this parameter could differ considerably depending on the methods and subjects. Since FH is used as a reference plane in those studies, a standardized method is necessary for its detection on subjects, and in order to obtain reliable results, FH detection needs to be landmark-based rather than visually estimated prior to the scan.

Chapter 4: Materials and Methods

4.1 Subjects and MRI Data Acquisition

MRI scans of 43 subjects (26 f, 17 m), age 26–78 years old with normal skull shape were randomly selected from the longitudinal population based sub-cohort study SHIP- 2.

Scans were performed in the SHIP center for clinical magnetic resonance research at the university of Greifswald using a whole-body 1.5 Tesla MR system (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany). The protocol was identical for all participants and included axial T1-weighted ultra-fast gradient echo sequence (1.9/3.4 [repetition time ms/ echo time ms]; flip angle 15, 256mm field of view, 1.0x1.0x1.0 mm voxel size and 176x256x176 acquisition matrix).

4.2 Landmark Detection

FH landmarks were detected and recorded using the open source dicom viewer Osirix. 3D coordinates for each image were calculated from the DICOM headers, which were based on the MRI scanner coordinates. The center of coordinates (x0, y0, z0) provided by the headers was the center of the highest point on the subjects head. Osirix then determined the coordinates (x, y, z) for each subsequent voxel and converted the actual calculated size of voxels to millimeters. This insured that the coordinates of each landmark remain the same with any subsequent magnification changes.

To procure a wide range of views for each image set, Multi-planar reconstruction (MPR) was used to accurately identify the three landmarks that define FH plane. Sagittal, axial, and coronal rendered slices, as well as 3D image reconstructions were used to determine the 3D positional coordinates of Left and right porion (Po) and left orbitale (Or) based on their anatomical position.

The color coded locaters in both coronal and axial view ports were used simultaneously to detect the most inferior point on the infraorbital rim,orbitale landmark was then located on the sagittal view port. In the same manner, the locater in the coronal view port was used to outline the soft tissue and bone above the external auditory meatus, porion landmark was then located on the corresponding sagittal view port as the most lateral point in a low signal intensity area.

The synchronized color-coded axis locaters on the three planar views were used for further view angle adjustments to permit locating the landmarks accurately.

4.3 Evaluation of Reproducibility

The main examiner obtained landmark coordinates for each image set two times in different sessions, and 1 time by 4 other examiners over a period of two weeks each, one week apart.

Intra-examiner reproducibility was assessed using intraclass correlation coefficients (ICC) for the main examiner measurements. ICC was also used to calculate inter-examiner reliability by comparing the main examiner mean trial with the measurements of the other 4 examiners. Additionally, paired mean difference (D), standard deviation (SD), coefficient of variability and Bland-Altman plots were used as described and recommended by Szklo & Nieto. [20] The analyses and plots were performed using STATA/SE software, version 12.1 (StataCorp LP, College Station, Tex.).

To assess the reliability of the plane in terms of distance, the spherical distance d between two readings of the same point was calculated (square root from $(x1- x2)^2 + (y1- y2)^2 + (z1- z2)^2$ with indices for the two readings). To assess the reliability of the plane in terms of angulation, the dihedral angle between the planes from two readings was calculated.

Chapter 5: Results

The intra-examiner Reproducibility for each coordinate was greater than 0.94 in terms of ICC. The 95% CIs were small with a lower limit of 0.85 indicating an excellent reproducibility. The coefficients of variability were fairly low. The absolute systematic error (mean difference between both readings) for each Cartesian coordinate was lower than 1 mm. Systematic bias other than absolute error, such as proportional error, was graphically examined using Bland-Altman plots. Intra-examiner reproducibility of the three landmarks in terms of distance showed mean differences between 1.3 to 2.4 mm. Intra-examiner difference in the dihedral angle of FH was less than 3° for 97.7% of the readings with a mean of 1°.

The inter-examiner reliability for each coordinate was greater than 0.90 in terms of ICC. The 95% CIs were small with a lower limit of 0.90, indicating an excellent reliability. The coefficients of variability were fairly low. The absolute systematic error (mean difference to the first examiner) for each Cartesian coordinate in the three points was lower than 1.52 mm. Bland- Altman plots showed no conspicuous pattern except for the expected digit preference in the x coordinate. This digit preference for a whole number reflects clearly the slice thickness of 1 mm and was absent in y and z coordinates. The 95% CIs (dashed lines) for the lines of ±2 SD (solid lines) were small, reflecting the sufficient sample size and the relatively small variation of the differences. Inter-examiner reliability of the three landmarks in terms of distance showed mean differences between 1.3 to 2.9 mm. Differences in the dihedral angle between each examiner and the first examiner readings of FH was less than 3° for 88.4% of the readings with mean differences between 1.1° to 1.5°.

Chapter 6: Discussion

With the absence of a fixed extra-cranial reference that would aid in the standardization of the head position among subjects in MRI, It is necessary to adjust head orientation through intra-cranial references such as Frankfort Horizontal. A significant advantage of MRI and 3D imaging in general, is the ability to re-create reference planes intra-cranially that otherwise are hard to define or recognize directly on subjects.

This is distinctly important in population-based studies that measure craniofacial structures. In previously mentioned literature, FH plane was either estimated prior to MRI scans on the subject head while in supine position, or it was estimated perpendicular to the floor prior to CT scans. This approach might result in estimation errors and affect the accuracy of FH detection and the subsequent analysis, mainly because a simple head rotation would be enough to disturb the planned position of the head, making it difficult to maintain a horizontal plane orientation during scanning. Another shortcoming of FH estimation directly on subjects is the difference between the palpable landmarks and real landmarks on images. It was observed that the palpable soft tissue Frankfort plane (tragus-orbitale) was not parallel to the hard tissue Frankfort plane (porion-orbitale) and that the 2 planes show a deviation of 6 ° on average. [21] Our study was based on this consideration, since the majority of studies advocate the use of FH as a reference plane without questioning the differences between its detection on subject's heads and images and the consequent influence it carries on measuring craniofacial structures later on images.

The results of our investigation showed that the examiner variability in detecting Porion (R/L) was slightly larger in the Sagittal plane than in the Axial and coronal planes. This observation demonstrates the Medio-Lateral complexity of Porion in the MPR view due to its location on a widely curved bone. According to Ludlow et al [22] this variability in identifying porion is probably related to the inadequate definition of this landmark in the third dimension, they noted that while some examiners localized porion in the soft tissues of the ear canal, others localized it on the bone/soft tissue margin.

6.1 Reproducibility

We attempted in this study to measure the variation in FH landmarks detection and the effect it carries on FH plane orientation. Differences in the 3D location of one of the landmarks caused up to 3° deviation of FH plane between examiners. Since variation in each of the three axes of each landmark will not contribute equally to the plane location, we reported the differences in each axis separately and the subsequent differences in the plane orientation by means of distance and angulation. It is important to distinguish between the primary analysis, which is based on the original values, and the secondary analysis, which is based on calculated and derived quantities such as the distance, hence the initial ICC was calculated for each landmark axis separately and then distance and angulation. The ICC is one of the most frequently used indices of reliability and it is a true measure of agreement that combines information on both the correlation and the systematic differences between readings. [20] Moreover, the ICC has the advantage that it can estimate the reliability of more than two sets of readings, whereas the difference is restricted to those between two sets of readings.

Additionally, Bland-Altman plots were used to expose any patterns in the landmarks detection among observers. The digit preference of 1 mm, which was found in the x-axis of all 3 landmarks, reflects clearly the slice thickness of the MRI images. This issue was not discussed in previous literature and it reflects the importance of the slice thickness parameter on the quality of readings, especially when slices of 2 mm thickness or more are used.

In our study, we used the axial, coronal and sagittal slices along with the corresponding colored axes to view and determine the landmark location and mark it on the sagittal port. The 1 mm digit preference would appear when 2 examiners agree on the anterio-posterior and superio-inferior location of a landmark on the same subject and they differ in the medio-lateral location, this leads each to select the landmark on 2 different sagittal slices and therefore the difference sagittaly will be in course millimeters. (i.e. with Orbitale point, examiners would agree on the depth and height of its location, and differ in deciding the greatest diameter of the globe)

6.2 Multi-Planar reconstruction

3D MPR has the advantage of generating slices in any position and orientation through cubic interpolation, which in comparison to the 3 fixed view ports of 2D orthogonal MPR, provides much more needed precision in detecting landmarks in complex areas such as the temporal bone and the infraorbital margin (using the axial, coronal and sagittal view ports to obtain a sagittal-oblique view helps in depicting areas where landmarks are located).

In this study, we used the axial, coronal and sagittal colored axis locaters in all three-view ports of 3D MPR to determine the landmark location and mark it on the sagittal port. This crucial functionality is not available in 2D orthogonal MPR, and it is particularly important to accurately differentiate soft tissue from bone in convex (Porion) and concave (Orbitale) areas.

Another advantage of 3D MPR is the ability to specify an axial port view that includes all the 3 landmarks of FH (Figure 3c) and the ability to export it as a new DICOM series. This is important at a later phase for obtaining correct measurements of craniofacial structures (i.e. muscle CSA).

Chapter 7: Conclusions and ongoing studies

This study revealed excellent intra- and inter-examiner reproducibility of Frankfort Horizontal plane through 3D landmark identification in MRI using freely available software Osirix. Based on these findings, a sufficiently stable landmark-based plane could be used as a standardized reference in measuring and comparing craniofacial structure.

It is important to note that this study was conducted to set the grounds on using Frankfort Horizontal as the standard reference plane on measuring masticatory muscles on SHIP-2 and SHIP-trend subjects. It is evident that any comparison of muscle size and orientation between the cohort subjects was limited by the variations in reference plane location set by the MRI machine operator. Furthermore, it would be difficult to clarify possible population differences without using a standardized method in detecting the reference plane.

References:

1. Madsen D, Sampson W, Townsend G (2008) Craniofacial reference plane variation and natural head position. Eur J Orthod 30:532-40

2. Moorrees C, Kean M (1958) Natural head position, a basic consideration in the interpretation of cephalometric radiographs. Am J Phys Anthropol: 16:213-234

3. Kollmann J, Ranke J, Virchow R (1883) Verständigung über ein gemeinsames craniometrisches Verfahren: Frankfurter Verständigung. Archiv für Anthropologie 15: 1–8.

4. Lundstro ̈m A, Lundstro ̈m F (1995) The Frankfort horizontal as a basis for cephalometric analysis. Am J Orthod Dentofacial Orthop 107: 537–540.

5. Van Eijden, Korfage JA, Brugman P (1997) Architecture of the human jaw- closing and jaw-opening muscles.Anat Rec 248: 464–474.

6. Alves PV, Mazucheli J, Vogel CJ, Bolognese AM (2008) A protocol for cranial base reference in cephalometric studies. J Craniofac Surg 19: 211–215.

7. Hirohi T, Yoshimura K (2010) Lower face reduction with full-thickness marginal ostectomy of mandibular corpus-angle followed by corticectomy. J Plast Reconstr Aesthet Surg 63: 1251–129.

8. Houston WJ (1983) The analysis of errors in orthodontic measurements. Am J Orthod 83: 382–390. 18.

9. Waitzman AA, Posnick JC, Armstrong DC, Pron GE (1992) Craniofacial skeletal measurements based on computed tomography: Part I. Accuracy and reproducibility. Cleft Palate Craniofac J 29: 112–117.

10. McClure S, Sadowsky L, Ferreira A, Jacobson A (2005) Reliability of Digital Versus Conventional Cephalometric Radiology: A Comparative Evaluation of Landmark Identification Error. Semin Orthod 11:98-110

11. Kragskov J, Bosch C, Gyldensted C, Sindet S (1997) Comparison of the reliability of craniofacial anatomic landmarks based on cephalometric radiographs and three-dimensional CT scans. Cleft Palate Craniofac J 34: 111–116.

12. Matteson SR, Bechtold W, Phillips C, Staab EV (1989) A method for three-dimensional image reformation for quantitative cephalometric analysis. J Oral Maxillofac Surg 47: 1053–1061.

13. Tyndall DA, Renner JB, Phillips C, Matteson SR (1992) Positional changes of the mandibular condyle assessed by three- dimensional computed tomography. J Oral Maxillofac Surg 50: 1164–1172.

14. Olszewski R, Tanesy O, Cosnard G, Zech F, Reychler H (2010) Reproducibility of osseous landmarks used for computed tomography based three-dimensional cephalometric analyses. J Craniomaxillofac Surg 38: 214–221.

15. Lagravere MO, Low C, Flores-Mir C, Chung R, Carey JP, et al. (2010) Intraexaminer and interexaminer reliabilities of landmark identification on digitized lateral cephalograms and formatted 3-dimensional cone-beam computerized tomography images. Am J Orthod Dentofacial Orthop 137: 598–604.

16. Spronsen P, Weijs W, Prahl-Andersen B, Valk J, Ginkel F (1989). Comparison of jaw muscle bite-force cross-sections obtained by means of magnetic resonance imaging and high resolution CT-scanning . J Dent Res 68:1765-1770.

17. Raadsheer M, Eijden T, Spronsen P, et al. (1994). A comparison of human masseter muscle thickness measured by ultrasonography and magnetic resonance imaging. Arch Oral Biol 39:1079-1084.

18. Goto T, Tokumori K, Nakamura Y, et al. (2002) Volume changes in human masticatory muscles between jaw closing and opening. J Dent Res 81:428-432

19. Goto TK, Yahagi M, Nakamura Y, Tokumori K, Langenbach GE, et al. (2005) vivo cross-sectional area of human jaw muscles varies with section location and jaw position. J Dent Res 84: 570–575.

20. Szklo M, Nieto JF (2007) Quality Assurance and Control In Epidemiology: Beyond the Basics. eds. M. Szklo & J. F. Nieto. 2nd edition, 297–349. Boston, Mass: Jones and Bartlett Publishers.

21 Ferrario VF, Sforza C, Germano D, Dalloca LL, Miani A Jr. (1994) Head posture and cephalometric analyses: an integrated photographic/radiographic technique. Am J Orthod Dentofacial Orthop 106: 257–266.

22, Ludlow JB, Gubler M, Cevidanes L, Mol A (2009) Precision of cephalometric landmark identification: cone-beam computed tomography vs conventional cephalometric views. Am J Orthod Dentofacial Orthop 136: 312.e1–10.

Abstract:

Objective: The purpose of this study was to determine the accuracy and reliability of Frankfort horizontal plane identification using displays of multi-planar reconstructed MRI images, and propose it as a sufficiently stable and standardized reference plane for craniofacial structures

Materials and Methods: MRI images of 43 adolescent randomly selected subjects were obtained from the longitudinal population based cohort study SHIP-2 using a T1-weighted 3D sequence. Five examiners independently identified the three landmarks that form FH plane. Intra-examiner reproducibility and inter-examiner reliability, correlation coefficients (ICC), coefficient of variability and Bland-Altman plots were obtained for all landmarks coordinates to assess reproducibility. Intra-examiner reproducibility and inter-examiner reliability in terms of location and plane angulation were also assessed.

Results: Intra- and inter-examiner reliabilities for X, Y and Z coordinates of all three landmarks were excellent with ICC values ranging from 0.914 to 0.998. Differences among examiners were more in X and Z than in Y dimensions. The Bland–Altman analysis demonstrated excellent intra- as well as inter-examiner agreement between examiners in all coordinates for all landmarks. Intra-examiner reproducibility and inter-examiner reliability of the three landmarks in terms of distance showed mean differences between 1.3 to 2.9 mm, Mean differences in plane angulation were between 1.0° to 1.5° among examiners.

Conclusion: This study revealed excellent intra-examiner and inter-examiner reproducibility of Frankfort Horizontal plane through 3D landmark identification in MRI. Sufficiently stable landmark-based reference plane could be used for different treatments and studies.

Thema: "Assessment of Frankfort Horizontal plane Reproduction on MRI"

Eidesstattliche Erklärung

Hiermit erkläre ich, dass ich die vorliegende Dissertation selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel benutzt habe.
Die Dissertation ist bisher keiner anderen Fakultät und keiner anderen wissenschaftlichen Einrichtung vorgelegt worden.
Ich erkläre, dass ich bisher kein Promotionsverfahren erfolglos beendet habe und dass eine Aberkennung eines bereits erworbenen Doktorgrades nicht vorliegt.

Amro A Daboul

Greifswald, 12/ 4/2013

Acknowledgment

I would like to express my gratitude to Prof. Dr. Reiner Biffar for his continuous support and guidance through this project. His patience and encouragement through this project is highly appreciated.

I would like to pay special thanks to Dr. Christian Schwahn for the considerable effort he exerted on this project. I am grateful to my colleagues, Dr. Klinke, Dr. Aljaghsi, Dr. Schaeffner, Dr. Soehnel, Dr. Samietz and Mr. Habes for their work and assistance. I also want to thank all the colleagues and staff at our department for 3 wonderful years of working together as a family.