Diss. ETH No. 23289

Development of a novel micro-structural finite element approach to model fracture fixation in osteoporotic human bone

A thesis submitted to attain the degree of
DOCTOR OF SCIENCES of ETH ZURICH
(Dr. sc. ETH Zurich)

presented by
Juri Alexis Steiner
M.Sc. Human Movement Sciences, ETH Zurich
born on 18.11.1983
citizen of Ringgenberg BE

accepted on the recommendation of
Prof. Dr. J. Stephen Ferguson, examiner
Prof. Dr. G. Harry van Lenthe, co-examiner

2016
To my wife Barbara and my parents.
"C’est par la logique qu’on démontre, c’est par l’intuition qu’on invente. Savoir critiquer est bon, savoir créer est mieux." Henri Poincaré
# Table of Contents

**Acknowledgements** iii  
**Summary** vii  
**Zusammenfassung** xi  

1. **Introduction** 1  
   1.1. Thesis motivation 2  
   1.2. Thesis aims 5  
   1.3. Thesis outline 6  

2. **Background** 13  
   2.1. Computational analysis of primary implant stability in trabecular bone 15  

3. **Assessing peri-implant bone damage** 41  
   3.1. Screw insertion in trabecular bone causes peri-implant bone damage 43  

4. **Primary stability of single fracture fixation screws** 61  
   4.1. A novel *in silico* method to quantify primary stability of screws in trabecular bone 63  

5. **Primary stability of a multi-screw fracture fixation system** 83  
   5.1. Towards a clinically oriented patient-specific *in silico* model to quantify primary implant stability in human osteoporotic bone 85  

6. **Synthesis** 99  
   6.1. Assessing peri-implant bone damage 101  
   6.2. Primary stability of single fracture fixation screws 101  
   6.3. Primary stability of a multi-screw fracture fixation system 102  
   6.4. Limitations and future research 102  
   6.5. Conclusion 104
A. Validation of an optical motion tracking method
   A.1. An optical motion tracking method to measure displacements of bone
        fragments and implants during mechanical loading

Curriculum Vitae
Acknowledgements

The work presented in this thesis was carried out at the Institute for Biomechanics, ETH Zurich and I would like to express my profound gratitude to all those who contributed to my work and who have helped to make my grad student experience in academia one for which I will be thankful forever.

First of all, my most sincere appreciation goes to my two advisors who made this versatile Ph.D. project possible. There were days when I would put on surgical scrubs at 6 a.m. to dissect human specimens in the wet lab, conduct micro-CT scans and mechanical experiments during the day and then write programs for image processing and finite element analyses till late in the evening. For this, special thanks go to Prof. Harry van Lenthe who, during my research assistance days, encouraged me to stay for a few more years as a Ph.D. student at the Institute and supported me in obtaining the necessary funding. Given that he has been stationed in Leuven, Belgium, throughout my entire Ph.D. period, I have very much appreciated his quick and reliable feedback at all stages of my work. His perceptive input, constructive criticism and discerning ideas to complex problems were invaluable for the successful completion of my doctoral work. Likewise I would like to say many thanks to Prof. Stephen Ferguson with whom I had the honor to start my employment as a Ph.D. candidate on the same day as he started his professorship at the Institute for Biomechanics. Stephen’s ability to quickly grasp new concepts and his openness to share his extensive lab experience were crucial in the success of this work.

I owe special thanks to Dr. Jean Favre, head of the visualization group at the Swiss National Supercomputer Center in Lugano and his team. Thanks to their superb efforts and support I was able to visualize even my largest datasets. Their visualization work made it very easy to spot potential modeling errors and to explain even to people outside of the field what we were doing.

As one of the last members of the former “Implant Fixation Group” I would like to give special thanks to Dr. Samuel Basler with whom I shared the office during my research assistance and at the beginning of my Ph.D. His work ethic, collegiality and activities outside of research were a great example to me on how to combine hard work, friendship and leisure time in a well-balanced way. Further thanks go to the
Acknowledgements

other members of the Implant Fixation Group; in particular Prof. Davide Ruffoni and Dr. Andreas Wirth who both supervised me during my 3 months internship and made sure that I felt welcome in their group right from the start. Also many thanks go to Dr. Thomas Müller whose working attitude and sense of humor even during stressful times was inspiring. Thank you guys - you all substantially contributed towards my decision to pursue my own Ph.D. studies.

The projects that I appreciated the most were the ones realized in a team effort with the people I had the pleasure to work with. Particularly, I would like to thank Jessica Crabb, Remo Affentranger, Florian Bolliger, Dr. Alex Zwahlen, Dr. Sandro Badilatti, Duncan Betts and especially Dr. Patrik Christen for their contributions to the successful completion of my thesis. At this point, very special thanks go to Remo, whose reliability as a helpful co-worker and most eager table soccer companion I will always warmly recall. Moreover, further thanks go to Jochen Walser, with whom I had the pleasure of sitting side-by-side in the office thus creating valuable occasions for exchanging new concepts and ideas. For all the experimental work I received important assistance and guidance from the technical staff, namely Peter Schwilch and Marco Hitz who always kept an open door and were happy to share their workshop expertise with me.

Further thanks go to Ilsoo Koh, Gregor Spreiter, William Enns-Bray, Dr. Ben Helgason, Dr. Jolanda Vetsch, Helen Greutert, Olga Krupkova, Oddný Björgvinsdóttir, Patrick Wettenschwiler, Thomas Zumbrunn and Alexeev Dmitriy who always offered a helping hand whether relating to computer issues or hands-on lab/kitchen work. As in the past years, I had the honor to organize a running team in our group for the famous SOLA relay foot race taking place every year in May, it is now my pleasure to thank everyone for participating so selflessly, and also of course, for beating the Müller group each time. Many thanks go to the Italian delegation, namely, Dr. Antonia Torcasio, Dr. Giacomo Marini, Fabio D’Isidoro and Enrico De Pieri with whom I had the pleasure to practice my humble Italian skills from time to time - Grazie mille ragazzi! Last but not least I also would like thank Dominika Ignasiak, Yabin Wu and Dr. Junichi Handa with whom I shared the office during the last few very intense months of my Ph.D. and endured my emotional ups and downs during that time - thanks for sharing!

I also feel very much indebted to Sofia Delamanis and Catherine Palmer for their kind and professional support in administrative issues. Special thanks go to Catherine for proof-reading my Acknowledgements. I would also like to express my gratitude towards our industrial partner, in particular Dr. André Weber from DePuy Synthes, whose inputs from an industrial and clinical perspective were helpful for
the design of clinically relevant experiments and computer models.

The dedication required to complete this doctoral thesis would have not been possible without the support from my friends and family. Words cannot describe my gratitude for the unconditional support and love from my parents that I received during my childhood and entire education. I am also sincerely grateful to my in-laws for their warm welcome into their family. My most profound thanks go to my wife Barbara who has always been at my side since we got together almost 14 years ago. Her loving support and understanding in both good and bad times, despite her own intense working hours as a medical doctor, have never ceased to amaze me. Thank you for proof-reading the German translation of the summary and more importantly, thank you sharing your life with me! Finally, I would like to gratefully acknowledge the financial support of CTI, DePuy Synthes and ETH Zurich.

January 2016
Juri Steiner
In daily life, our bones fulfill various vital tasks to keep our body functioning properly: They protect delicate organs, produce red blood cells, provide a mineral reservoir to keep for instance calcium and phosphate blood levels in essential balance; and last but not least they provide structural and mechanical support during daily activities. With increasing age however, bones lose their structural integrity. The underlying disease is called osteoporosis and is defined as a systemic bone disease causing decreased bone density and altered bone micro-architecture, which inevitably leads to an increased fracture risk. Despite the advances made in the diagnosis and pharmacological treatment of osteoporosis, the prevalence of osteoporotic fractures is still increasing because the proportion of the elderly in our population is constantly growing. When osteoporotic fractures occur, immediate treatment is required, because in many cases they are very painful and, if left untreated, they can severely limit the individual’s mobility for a lifetime. The primary goal of fracture fixation is to obtain secure primary implant stability, in order to reduce the potential risk of fixation failure requiring revision surgery. In osteoporosis, however, fracture treatment is hindered because it is more difficult to obtain a secure, mechanically stable, screw fixation in low quality bone compared to a healthy bone stock. Consequently, the treatment of osteoporotic fractures is sub-optimal.

In order to improve the treatment of fractures in osteoporotic bone, more detailed and quantitative understanding on the role of peri-implant bone for implant (i.e. orthopedic fracture fixation screw) stability is needed. However, systematic mechanical in vitro testing on a wide variety of human bone specimens is very costly in terms of material and time. Alternatively, a computational approach, more specifically finite element (FE) modeling, has been proposed as an alternative strategy. In most FE studies that investigate the mechanical competence of bone-screw systems, bone has been treated as a continuum material with homogenous material properties, while only a few actually considered the anisotropic micro-architecture of bone. A high potential is seen in high-resolution micro-computed tomography (µCT) based finite element (µFE) analysis; a technique that has been verified and validated for quantifying stiffness and strength of trabecular bone. However, regarding in silico
modeling of screws in trabecular bone, a considerable remaining challenge lies in the
description of the implant-bone interface. So far, no single computational study has
been performed that fully takes both the bone micro-architecture and the complex
mechanical properties of the bone-screw interface into account. Therefore, the aims
of this thesis were (i) to develop an imaging method that localizes and quantifies
bone damage due to screw insertion, (ii) to improve the \textit{in silico} quantification of
the apparent stiffness of screws in human trabecular bone, and (iii) to establish a
proof of concept towards a patient-specific organ level \textit{in silico} model to quantify
primary implant stability of a fracture fixation device in human osteoporotic bone.

For the first aim, we developed a method that localizes and quantifies bone dam-
age, non-invasively and in three dimensions, along the entire length of the screw. We
could show that the trabecular bone structure is affected by screw insertion and that
bone damage occurs close to the implant only ($< 1.0$ mm). We also showed that
screws with large threads had a slightly greater impact on the peri-implant bone
than screws with small threads. It is the first study to localize and quantify bone
damage caused by screw insertion based on a non-invasive, three-dimensional, $\mu$CT
imaging technique. We clearly demonstrated that peri-implant bone damage already
occurs during screw insertion. We hypothesized that the strong over-predictions of
the primary implant stability in screw-bone systems, as seen with state-of-the-art
computational models, is related to the fact that perfectly intact bone-screw inter-
faces were assumed. Hence, we recommended that our findings on bone damage
should be taken into consideration to further improve primary implant stability, es-
pecially in low quality osteoporotic bone. We believe that this technique could be
a promising method to assess more systematically the effect of peri-implant bone
damage on primary implant stability.

For the second aim, we developed a novel \textit{in silico} method to accurately quan-
tify primary implant stability of screws in trabecular bone. In short, we developed
a patient-specific computational model that can quantify the apparent stiffness of
screws in bone with an accuracy of 12 % for both uniaxial compressive loading
as well as shear loading. The approach uses $\mu$FE analysis in combination with a
statistical modeling technique that links the tissue modulus of the damaged peri-
implant bone to the native bone micro-architecture in a specimen-specific manner.
We confirmed our hypothesis that by modeling interface detachment between screw
and bone and by considering insertion-related bone damage it is possible to obtain
a more accurate prediction of the primary stability of screws in bone. The effects
of insertion-related bone damage appear to be stronger than that of interface de-
tachment. In conclusion, we have brought further evidence that screw insertion
causes peri-implant bone damage; a phenomenon that should be considered in the future for any computational analysis of primary implant stability of bone-implant systems. We believe that this novel technique provides an important step towards a better understanding of the detailed mechanisms of primary implant stability in human trabecular bone.

For the third aim, we established a proof of concept for a patient-specific in silico model to quantify primary implant stability of a complex plate and screw system in human osteoporotic bone. Furthermore, we put in place a methodology to validate such a patient-specific µFE model using in vitro biomechanical tests combined with a motion tracking system that measures displacements on various sites of the specimen. We confirmed the hypothesis that the consideration of peri-implant bone damage due to screw insertion improves the accuracy of the prediction of the apparent implant-bone stiffness. Based on this demonstration case, the predictive power of the proposed method can be further validated by including more specimens.

In conclusion, this thesis showed clear evidence for peri-implant bone damage due to screw insertion as well as the need to simulate this damage in computational models in order to achieve a more accurate prediction of the mechanical competence of bone screws in human trabecular bone. Furthermore, the proposed modeling technique shows the potential to also accurately quantify, at the organ level, the mechanical competence of complex fracture fixation systems in human osteoporotic bone.
Zusammenfassung


Für die erste Zielsetzung haben wir eine Methode entwickelt, welche Knochenläsionen nicht-invasiv und in allen drei Dimensionen entlang der ganzen Schraubenlänge lokalisiert und quantifiziert. Wir konnten zeigen, dass die trabekuläre Struktur durch die Schraubensetzung beeinträchtigt wird und Läsionen nur sehr nah (< 1.0 mm) am Implantat entstehen. Des Weiteren konnten wir zeigen, dass grössere Schraubengewinde mehr Auswirkungen auf die Knochenstruktur haben als kleinere Schraubengewinde. Wir konnten klar aufzeigen, dass Knochenläsionen am Schrauben-Knochen-Übergang bereits während der Schraubensetzung entstehen. Aufgrund dessen vermuteten wir, dass die zu hohen Steifigkeitswerte in den klassischen FE Modellen darauf zurückzuführen sind, dass für deren Berechnung eine komplett intakte Knochenstruktur in Implantatnahe angenommen wurde. Wir empfehlen daher, unsere Erkenntnisse betreffend Knochenläsionen im osteoporotischen Knochen bei der Verbesserung der Implantatstabilität zukünftig zu berücksichtigen. Wir glauben, dass diese Methode ein vielversprechendes Verfahren ist, um die Auswirkungen der durch Schraubensetzung verursachten Knochenläsionen auf die Primärstabilität systematisch zu untersuchen.

Für die zweite Zielsetzung haben wir einen neuartige in silico Methode entwickelt um genaue Voraussagen über die Primärstabilität von Schrauben im trabekulären Knochen zu machen. Dazu haben wir ein patientenspezifisches Modell entwickelt, welches die Steifigkeit von Schrauben im menschlichen Knochen in uniaxialer Richtung (parallel zur Schraubenlängsachse) und vertikal dazu mit einer Genauigkeit von

Chapter 1

Introduction
1.1. Thesis motivation

Socio-economic relevance of osteoporotic fractures

Over the past century, mankind has been remarkably successful in treating many life threatening diseases [1] as well as in spotting numerous risk factors (e.g. unsafe drinking water and sanitation infrastructure, obesity, tobacco and alcohol abuse) associated with increased morbidity and mortality [2]. Consequently, this has led to an increased life expectancy worldwide [1] and is expected to continue increasing for the next few decades [3] along with a steadily improving socio-economic status. The increase in socio-economic status (i.e. income per capita and education) has led to a shift from ‘years of life lost due to premature mortality’ (YLLs) to ‘years lived with disability’ (YLDs) [1]. The increase in YLDs is associated to the increasing prevalence of age-related neurological disorders, mental disorders and last but not least also to musculoskeletal disorders [1]. In other words, as the proportion of elderly people continues to grow, the prevalence of age-related diseases (e.g. Alzheimer, Parkinson, osteoporosis) increases as well. Among the musculoskeletal disorders, the systemic metabolic bone disease osteoporosis is considered to be one of the most serious health issues worldwide. A common way to measure this is by assessing the number of life years lost due to ill-health, disability or early death and is referred to as disability-adjusted life-years (DALYs) [1]. In 2006, it has been shown that osteoporosis worldwide accounted for more DALYs than for instance hypertensive heart disease and rheumatoid arthritis did [4]. Furthermore, when considering neoplastic disorders, the number DALYs due to osteoporosis was higher than for all sites of cancer, with the exception of lung cancers [4].

Osteoporotic bone is defined as a systemic bone disease causing low bone density and impaired bone micro-architecture which inevitably leads to an increased risk of fractures [5]. Statistics in 2002 reported a total of 9.0 million osteoporotic fractures worldwide; 1.6 million (18.2 %) were at the hip, 1.7 million (18.5 %) at the forearm and 0.7 (7.9 %) million at the humerus [4]. Considering the ongoing growth of the elderly population, the future trend of osteoporotic fractures is clear. For instance, predictive models for 2050 have estimated 1.4 million yearly hip fractures in men, and even 3.1 million in women; this corresponds roughly to an increase of 230 % and 190 %, respectively [6]. It can be assumed that similar trends exist for other anatomical sites. Currently, every second woman and every fourth man above 50 years of age suffers from an osteoporotic fracture [7]. The total annual costs have been estimated to be US$20 billion and even US$30 billion in the USA and in the European Union, respectively [8,9]. In Switzerland, osteoporotic fractures have been
found to result in more hospital bed days and therefore higher health care costs than myocardial infarction and stroke [10, 11].

**Challenges in the treatment of osteoporotic fractures**

The treatment regime of long bone fractures depends, among others, on the severity of the fracture. This can vary from conservative treatment, in which the fragments can be realigned easily and supported externally by conventional plaster casting or splinting [12, 13] to surgical intervention for open reduction and internal fixation with trauma implants for more complex fracture patterns. Typically, the invasiveness of the surgical procedure increases with the complexity of the fracture [12]. Irrespective of the surgical intervention, the primary goal is to obtain secure implant fixation for internal fixation, as to provide the necessary condition for biological fracture healing (i.e. secondary implant stability) and thus to reduce the potential risk of revision surgery.

Secure implant fixation is more challenging when osteoporosis is the underlying cause of a fracture. Osteoporosis does not only increase the risk for fractures, it also increases the risk for non-union and revision surgery. In osteoporosis, treatment is hindered because it is more difficult to obtain a secure, mechanically stable, implant fixation in low quality bone compared to a healthy bone stock [14, 15]. Numerous experimental biomechanical studies have provided strong evidence that fracture fixation screws show a reduced mechanical competence right after implantation (i.e. primary implant stability) in patients affected by osteoporosis [16–19]. These findings have been supported by several clinical studies, where a low cortical and cancellous bone mass resulted in decreased implant stability [20, 21]. Despite these findings, the detailed mechanisms behind decreased implant stability in osteoporotic bone are still not well understood. Consequently, the treatment of fractures and osteoporotic fractures in particular may be sub-optimal.

**Need for improved assessment techniques of primary implant stability in osteoporotic fractures**

In order to improve the treatment of fractures in osteoporotic bone, more detailed and quantitative understanding on the role of peri-implant bone for implant stability is needed. Ideally, a systematic investigation of the mechanical stability in bones with a wide range of microstructures should be performed. However, such *in vitro* experimental testing on human bone is very costly in terms of material (especially human bone) and time. This is due to several factors. First, bone possess a highly
Chapter 1. Introduction

heterogeneous structure and thus anisotropic mechanical properties [22] that not only differ between individuals [23] but also among different sites of the same individual [23] and even within the same bone of a specific individual [24,25]. Second, implants are highly variable, in terms of design, depending on their function and anatomical location. Third, systematic and independent parametric analyses based on different implants that could be tested in the same bone specimen at the exact same location are obviously not possible, because each mechanical test will influence the following one.

In view of these limitations, a computational approach, more specifically finite element (FE) modeling, has been proposed as an alternative strategy, provided that these models are properly verified (i.e. how numerically accurate is the model?) and validated (i.e. how precise is the model prediction compared to in vitro measurement?) [26–28]. The FE method is the most commonly used numerical technique in engineering. It has been used for at least 45 years in mechanical and civil engineering for the mechanical analysis of all kinds of materials and constructs such as machines and bridges. Likewise, it has been used in biomechanics [26–28], among others to optimize the mechanical performance of bone implants. In most computational studies that investigate the mechanical competence of bone-screw composites, bone is treated as a continuum material with homogenous material properties while only a few actually considered the anisotropic micro-architecture of bone [29–32]. A high potential is seen in high-resolution CT (µCT) images; a technique that has been verified and validated on trabecular bone structures [33,34]. The µCT images provide an accurate representation of the trabecular bone that can be used for FE models (µFE) to investigate varying loads both on a macro- and micro-structural level.

A great challenge regarding in silico modeling of implant-bone constructs lies in the description of the implant-bone interface. In continuum FE, several attempts have been made to model the interface by implementing frictional effects, cohesive forces, detachment and sliding [35–37]. Only a few µFE studies are available in which the interface representation could partially account for such complex mechanical behavior [25,31]. Reported methods include removal of elements at specific sites [25] and decreasing Young’s moduli of bone elements close to the implant.
1.2. Thesis aims

The overall aim of this thesis was to create a patient-specific computational model to quantify the primary implant stability of fracture fixation devices in osteoporotic bone.

Specifically, the following aims have been defined:

Aim 1: Development of an imaging method that localizes and quantifies the presence of peri-implant bone damage due to screw insertion. So far, different modes of micro-damage have been localized and quantified using microscope-based 2D approaches on histomorphometric slices. However, none of these methods have been able to capture and/or quantify peri-implant damage fully in three dimensions (3D). Furthermore, histomorphometry is invasive per se and, consequently, does not allow for a direct comparison between the 'before' and 'after' screw insertion state within the same specimen. We hypothesize that bone damage occurs close to the implant only, and that it is affected by the screw thread design.

Aim 2: Improve the quantification of apparent stiffness of single screws in human trabecular bone using $\mu$FE. $\mu$FE models are able to capture the microstructural variation in trabecular bone and have been put forward as a more advanced technique to conventional continuum FE. However, state-of-the-art $\mu$FE models of bone-screw systems overestimate the experimentally measured mechanical response. We hypothesize that a more accurate prediction of primary implant stability of screws in bone is possible (i) by modeling interface detachment between screw and bone and (ii) by considering insertion-related bone damage.

Aim 3: Improve the quantification of apparent stiffness of multi locking-screw plate system in the human proximal humerus using $\mu$FE. Based on the results of aim 1 and aim 2, a clinically oriented computer model is put in place in which the primary implant stability of a fractured humerus fixed with a locking-screw plate system is assessed. We hypothesize, that the consideration of bone-implant detachment during primary implant stability and peri-implant bone damage due to screw insertion will improve the accuracy for the prediction of the apparent implant-bone stiffness. Therefore, the third aim of this thesis is to develop and validate a patient-specific $\mu$FE model with a corresponding experimental setup that targets a clinically oriented fracture fixation scenario.
1.3. Thesis outline

The thesis is structured into 6 chapters. The first chapter gives an overview of the motivation, aims and outline of the thesis. The second chapter provides background information on the computational analysis of primary implant stability in osteoporotic bone. Chapters 3, 4 and 5 reflect the aims mentioned above. An overall summary of the thesis is provided in chapter 6.

Chapter 1 consists of the motivation, the aims and the outline of this thesis.

Chapter 2 provides an introduction and critical review of the topic of computational analysis of primary implant stability in osteoporotic bone. More specifically, the limitations of the currently available computer methods are listed in detail. Furthermore, alternative and potentially promising modeling approaches to address these issues are mentioned and thoroughly discussed.

Chapter 3 refers to aim 1 and describes a novel method for the non-invasive assessment of peri-implant bone damage due to screw insertion. This method is based on µCT scans taken of human trabecular bone cores before and after screw insertion. After image registration of the pre- and post-insertion scans, changes in the bone micro-architecture are identified and quantified. The results of this method show that peri-implant bone damage already occurs during screw insertion and that its occurrence remains close to the implant within a fraction of 1 mm. In summary, we quantified peri-implant bone damage at the bone microstructural level in three dimensions. The occurrence of peri-implant bone damage should be taken into consideration to further improve primary implant stability, especially in low quality osteoporotic bone.

Chapter 4 refers to aim 2 and presents a novel computational method to improve current state-of-the-art µFE models of bone-screw systems in their prediction of the experimentally measured mechanical response. The results of this work show that the inclusion of peri-implant bone damage improves the prediction of the apparent stiffness of single screws fixed in human trabecular bone measured in vitro. While unbonded interfaces play only a minor role, the reduced mechanical competence of damaged peri-implant bone has a considerable effect on the accurate estimation of apparent stiffness in bone-screw systems. Interestingly, this damage region is specimen-specific and its mechanical properties can be estimated well, and uniquely, based on the morphometric characteristics of the bone in which the screw had been placed. In summary, we quantified the reduced mechanical competence of peri-implant bone damage which is linked
1.3. Thesis outline

to the underlying morphometry of the trabecular bone microstructure at the screw insertion site.

Chapter 5 refers to aim 3 and is based on the outcomes described in chapter 3 and 4. This chapter describes how these crucial findings are applied onto a clinically oriented fracture fixation scenario. Specifically, the primary implant stability of a fractured humerus fixed with a locking-screw plate system was assessed by developing a patient-specific $\mu$FE model that was compared to corresponding in vitro data. We could show that the consideration of peri-implant bone damage improves the accuracy for the prediction of the apparent implant-bone system when compared to current state-of-the-art $\mu$FE models.

Chapter 6 provides a summary of the entire thesis with its most important findings, major contributions to the research community and limitations of the proposed methods as well as an outlook on future relevant research niches.

References


Chapter 1. Introduction


[15] E. Schneider, J. Goldhahn, P. Burckhardt. The challenge: fracture treatment in osteoporotic bone. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National*
1.3. Thesis outline

Osteoporosis Foundation of the USA, 16 Suppl 2(September 2002):S1–2, mar 2005.


Chapter 1. Introduction


1.3 Thesis outline


Chapter 2

Background
2.1. Computational analysis of primary implant stability in trabecular bone

Juri A. Steiner¹, Stephen J. Ferguson¹ and G. Harry van Lenthe¹,²

¹Institute for Biomechanics, ETH Zurich, 8093 Zurich, Switzerland
²Biomechanics Section, KU Leuven - University of Leuven, Celestijnenlaan 300, 3001 Leuven, Belgium

Published as:
Reprinted with permission and in compliance with the publisher copyright policy.

Abstract:
Secure fixation of fractured osteoporotic bone is a serious clinical challenge mainly because the reduced mechanical quality of low-density bone hampers proper implant fixation. Recent experimental findings have shown strong evidence for a rather complex bone-implant interface contact behavior, with frictional and non-linear mechanical properties. Furthermore, the bone microarchitecture is highly diverse even within the same anatomical site of a specific individual. Due to this intrinsic variability experimental studies that could analyze in detail the contributions of screw designs and thread geometry would require a very large amount of bone specimens; this hampers finding potential improvements for implant fixation. As a complementary approach, computational methods may overcome this limitation, since the same specimen can be tested repeatedly in numerous configurations and under various loading conditions. Recent advances in imaging techniques combined with parallel computing methods have enabled the creation of high-resolution finite-element models that are able to represent bone-implant systems in great detail. Yet, the predictive power of the mechanical competence of bone-implant systems is still limited, both on the apparent level and on the local microstructural level. The current strategy in high-resolution FE models to model the bone-implant interface, employing fully bonded cube-like elements, needs to be reconsidered, refined and validated, such that it mimics more closely the actual non-linear mechanical behavior as observed in vitro in order to exploit the full potential of
numeric models as an effective, complementary research method to physical in vitro models.

2.1.1. Introduction

On poets, nerds, and finite elements, of course

This paper presents a review on the computational analyses of implants in bone. Being part of this special Journal of Biomechanics issue, the request was made to include a paragraph providing a historical background on the topic. It is probably somewhat short to state that for computational analyses of implants in bone this history goes back to the pioneering work of Rik Huiskes; yet, current work in this area can certainly be put in his tradition. It is clear that Rik Huiskes was one of the first to use finite element (FE) approaches in orthopedic biomechanics and for sure he made his name in the analyses of implants in bone. From those early days towards current scientific practice, similar modeling strategies are still being used, albeit the size of the FE models has increased substantially. This concept of using computer simulations fits perfectly in Rik’s beliefs on present day scientific culture. More specifically, he considered himself a strong advocate of the ‘third culture’ of science [1]. Traditionally, a scientist would start using either theoretical or experimental approaches; yet, progress usually demanded the union of both a theory to make sense of the experiments and data to verify the theory [2]. In the third culture, science can be done differently by using computational models as a means to finding the ‘truth’. Such models are like theories that simultaneously produce data, or like data with a built-in theory [2]. Hence, the third culture approach to understanding how a brain works, is just to build one! As soon as the created brain behaves like a real brain, then you know how the brain works. This form of discovery of course implies that only a single unique assembly of model components yields the desired behavior. Rik taught us that the very same strategy can be used to unravel the laws of bone adaptation, which he considered to be the main focus of his work [3]. Such complex analyses typically require large computational frameworks and programs, and are executed by ‘nerds’. Evidently, Rik took pride in being a nerd.

This review shows that current modeling strategies for the analyses of bone-screw interfaces, and for bone-implant systems in general, are clear exponents of the ‘third culture’ approach. Hypotheses on bone-screw interaction are being put forward and their merits tested using computer simulations. This work is done by engineers. Or not? According to Rik Huiskes there were two kinds of people: poets and engineers.
2.1. Computational analysis of primary implant stability in trabecular bone

Poets are the ones with visionary ideas; they get the big picture and create the framework along which engineers can do their thing. With Rik we lost a great poet.

Osteoporosis increases fracture risk and affects implant stability

Osteoporosis is a key contributor to bone fractures in elderly people. Despite the advances made in the diagnosis and pharmacological treatment of osteoporosis [4–6] the prevalence of osteoporotic fractures is still increasing because the proportion of the elderly in our population is constantly growing [7,8]. It has been estimated that in the year 2000, a total of 9.0 million osteoporotic fractures occurred worldwide of which 1.6 million (18.2 %) were at the hip, 1.7 million (18.5 %) at the forearm and 0.7 (7.9 %) million at the humerus [7]. Considering the changing demographics, it has been estimated that in 2025, 800,000 hip fractures will occur yearly in men, and even 1.8 million in women; this corresponds to an increase of 89 % and 69 %, respectively [8]. It can be assumed that similar trends exist for other anatomical sites.

The treatment regime of long bone fractures depends, among others, on the severity of the fracture. Conservative treatment, using plaster casting and splints, is generally performed on fractures in which the fragments can be realigned easily. However, conservative treatment is not advised for clearly displaced and angulated multiple fragment fractures due to a high risk of malunion [9,10]. Hence, for more complex fracture patterns, surgical intervention is required. Typically, the invasiveness of the surgical procedure increases with the complexity of the fracture. This can vary from using single fracture fixation screws to plates and rods in combination with multiple cancellous and cortical screws [9]. Irrespective of the surgical intervention, the primary goal is to obtain secure implant fixation and thus to reduce the potential risk of revision surgery. 'Secure implant fixation’ or implant stability is typically divided into two consecutive phases: primary and secondary implant stability. Primary implant stability relates to a secure bone-implant fixation right after implantation and before any biologically driven bone remodeling takes place. During that time, the stability of the implant relies on interlocking and frictional bone-implant contact phenomena; this will withstand mechanical loading on the implant preventing excessive micromotion. Secondary implant stability is accompanied by a biological process called osseointegration and is initiated by lesions of the pre-existing bone matrix [11].

Despite the fact that local bone properties are known to play a major role in the fixation capacity of fracture fixation implants [12,13], a quantitative understanding of the effect of peri-implant bone quality on implant stability is still lacking. Even
less is known about the local bone properties at the bone-implant interface. A deeper understanding of their relative contribution may help to develop implants that show enhanced primary implant stability and that could consecutively improve secondary implant stability; the latter is needed for secure implant fixation over a time span of several months (e.g. fracture fixation) or even years (e.g. dental implants and joint replacements).

Secure implant fixation becomes evenmore challenging when the underlying cause of a fracture is osteoporotic bone. Osteoporosis does not only increase the risk for fractures, it also hampers positive treatment outcomes. First, appropriate treatment is hindered, because it is more difficult to obtain a secure, mechanically stable, implant fixation in low quality bone stock [14,15]. Numerous biomechanical in vitro studies have provided strong evidence that fracture fixation screws show a reduced mechanical competence right after implantation (i.e. primary implant stability) in patients affected by osteoporosis, due to their low bone density [16–19]. These findings have been supported by several clinical studies, where a low cortical and cancellous bone mass resulted in decreased implant stability [20,21]. Second, the biological fracture repair process is negatively affected. More specifically, it has been shown that in fractured osteoporotic bone the healing time is longer when compared to fractured healthy bone; hence, osteoporosis hampers osteosynthesis [22–24]. Therefore, patients suffering from an osteoporotic fracture depend for a longer period of time on reliable fracture fixation techniques than patients with normal bone stock.

In order to obtain a more detailed and quantitative understanding on the role of peri-implant bone for implant stability it would be helpful to perform in vitro a systematic investigation of the mechanical stability based on the local, patient-specific, bone structure. However, this is very difficult, because of the following:

1. Bone possesses a highly heterogeneous structure and thus anisotropic mechanical properties [25] not only differing between individuals [26] but also among different sites of the same individual [26] and even within the same bone of a specific individual [27,28] (Figure 2.1).

2. Implants are very variable in terms of design depending on their function (e.g. fracture fixation, joint replacement, etc.) and anatomic location (e.g. screw-in femoral diaphysis vs. screw-in pedicle).

3. Most clinical imaging methods are not capable of reaching the resolution required to display the discrete morphology which is necessary to determine the anisotropic mechanical properties of trabecular bone.
2.1. Computational analysis of primary implant stability in trabecular bone

Figure 2.1.: Representative cases of low, average and high density bone for different anatomical sites such as the femoral neck, the femoral trochanter and the distal radius. Adapted from Müller R. and van Lenthe G.H. (2004). 3-D Microcomputed tomography: a new method to assess bone microarchitecture. Medicographia 26 (3): 285-293.

4. Most medical imaging techniques that do reach the required resolution possess artifacts due to the presence of metal implants.

5. Systematic and independent parametric analyses based on \textit{in vitro} physical models in which different implants could be tested in the same bone specimen
at the exact same location are a priori not possible, because each mechanical
test influences the following one.

6. Fairly large sample sizes of scarce human bone material would be required in
order to reach statistical significance due to the large variance in bone quality.

In view of these limitations, a computational approach, more specifically finite
element (FE) modeling, has been proposed as an alternative strategy, provided that
these models are properly verified (i.e. how accurate is the model?) and validated
(i.e. how precise is the model compared to an in vitro model?) [29]. In a recent review
paper, the following modeling parameters have been claimed to be crucial for valid
FE models of bone-implant constructs [30]. The FE models should include the
following:

1. An adequate representation of bone and implant geometry.
2. An adequate representation of bone and implant material properties.
3. An appropriate description of the boundary conditions.
5. An appropriate representation of the failure behavior in bone-implant con-

The aim of the present review is to critically summarize the current FE modeling
techniques for predicting primary implant stability. For this purpose, we will first
summarize the most relevant structural and mechanical characteristics of trabecular
bone that are considered to be critical for implant stability. Then, current modeling
techniques will be reviewed and their individual strengths and weaknesses critically
discussed in order to propose potential areas for improvement. Within the scope
of this review, screws that are being used for fracture fixation of long bones are
specifically targeted.

2.1.2. The hierarchical structure of trabecular bone

Bone is known to be a very complex multi-scale structure that is characterized by
different mechanical properties at the different hierarchical levels. Typically, five
different levels are distinguished: (1) Macro-scale [length scale: 10 mm - 500 μm]
with trabecular and cortical bone; (2) micro-scale [length scale: 10 - 500 μm] :
Haversian systems, osteons and trabeculae; (3) sub-micro-scale [length scale: 1 - 10
μm]: lamellae; (4) nano-scale [length scale: 100 nm - 1 mm]: fibrillar collagen and
2.1. Computational analysis of primary implant stability in trabecular bone

embedded mineral; (5) sub-nano-scale (length scale: <100 nm): minerals, molecular structure of collagen and non-collagenous organic proteins [31,32]. The mechanical properties of bone do not only vary as a function of the hierarchical level but they also vary among different anatomical sites. This is especially true for trabecular bone, where its discrete and porous network is composed of rods and plates [33,34]. It is known that differences in mechanical properties of cancellous bone can vary by a factor of 2-5 from bone to bone which is a much broader range than that found for cortical bone [32]. Furthermore, it can also vary across different locations within the same bone [25]. This is considered to result from a functional adaptation of bone to local mechanical loading. Beyond these variations in bone structure in space, bone can also adapt over time [35] since it is an organ that constantly thrives for homeostasis. For uncemented bone-implant systems, this process takes place during the transition from primary implant stability to secondary implant stability and is called osseointegration. Osseointegration is highly dependent on the choice of material, requiring bioinert or bio-active material and surface configurations [11] which in turn influence the degree of micromotion in the peri-implant region. Moderate micromotion has been shown to enhance bone remodelling [36–39]. However, excessive micromotion leads to the development of fibrous tissues and therefore hampers effective osseointegration and hampers secondary implant stability [40]. Secondary implant stability and its underlying osseointegration process is very relevant for implant stability; however, this review focuses on in silico modelling techniques related to primary implant stability only. This is for two reasons: first, the development of a realistic numerical model of primary implant stability should form the basis for any subsequent modeling of the osseointegration process leading to secondary implant stability; second, osseointegration is such a highly complex process itself, governed by interacting mechanical and biological factors, it would require another separate review paper to provide a sufficiently comprehensive overview.

2.1.3. In silico techniques to model primary implant stability

Computational studies of primary implant stability, such as FE modeling, allow analyzing the relative role of the peri-implant bone regions and of the implant-bone interface in a systematic and controlled manner. In FE models of bone-implant systems, a major distinction can be made in the way the mechanical characteristics of bone tissue are taken into account. Specifically, bone is either represented as a continuum material with homogenized properties representing bone at a length scale of about 1 mm, or as a discrete, cellular structure in which the bone micro-architecture is represented in detail.
Chapter 2. Background

Continuum finite element models In a typical continuum FE model, the investigated structure is treated as a continuous material without any porous features. Continuum FE models offer a great variety of modeling options ranging from perfect bonding to the inclusion of friction, cohesive forces between materials, detachment at predetermined thresholds as well as other non-linear mechanical behaviors [41–44]. The mechanical behavior of fracture fixation screws in synthetic bone has been predicted successfully with FE models treating the synthetic bone (usually polyurethane foam) as a homogenous continuum. For instance, the computed push-out strength correlated highly with the experimentally measured push-out strength for screws in high density foams ($R^2 > 0.96$). Similarly, in silico bone-screw interface stiffness, assessed by analyzing the total reaction force on screws and the total strain energy of bones, was closely related to the strength measured in the pullout tests ($R^2 > 0.72$) [45]. In these studies, the assumption of homogeneous material properties is a reasonable assumption because the porous cell structure of synthetic bone is fairly repetitive.

However, the same approach cannot be used for trabecular bone, because of its highly heterogeneous and anisotropic nature, being characterized by subject-specific and regional-specific variations in bone density [32]. These local density variations are associated with variations in the local mechanical competence [46,47], hence, are directly related to implant stability. The density variations are typically taken into account by assuming a relationship between the local CT Hounsfield numbers and the local mechanical properties, which are then included in the FE model [48]. This technique has been developed [49–51] and experimentally validated [52,53] for various bone types demonstrating that different relationships exist for different anatomical locations [47,54]. Further attempts have been made to use this technique in combination with implants. For instance, bone strain values could be accurately derived as demonstrated in a study that evaluated acetabular cups implanted in a fresh-frozen human hemi-pelvis [55].

A slightly different approach was taken in a recent continuum FE study on a rabbit bone-implant system; there, subject-specific Young’s moduli for cortical bone were selected that matched the apparent stiffness of in vitro mechanical test [42]. For the trabecular bone, a fixed E-modulus of 153 MPa was used for all specimens. Frictionless sliding contact between screw and bone was assumed combined with partial bone-screw contact (10 %) and a compliant layer (5 GPa) of 0.6mm thickness around the drilled hole to account for bone damage due to pre-drilling and screw insertion. Using this particular configuration, continuum FE axial stiffness matched the measured axial stiffness with an error of less than 8 %. Since this continuum FE model
represented bone at a length scale of 1 mm, it is questionable whether this approach could also accurately predict the mechanical behavior of implants in highly porous bone structures such as osteoporotic trabecular bone, where individual trabeculae carry more load and therefore play a more important role in mechanical stability as compared to trabeculae in high-density bone.

2.1.4. Microstructural finite element models

As shown in the previous section, continuum models can be capable of providing a reasonably accurate prediction of bone-implant behavior. Yet, it has to be realized that the continuum models are using bone material properties which are valid at a length scale of 5 mm or more in order to obtain a sufficiently representative volume of interest in which the apparent mechanical properties of such a cellular solid can be modeled as a continuum [56–58]. Hence, these models cannot accurately describe the stress and strain field at a length scale smaller than 5 mm, such as at the bone-screw interface. Consequently, it can be expected that in continuum models each specific screw needs a specific interface description, with screw-specific bonding and friction coefficients. In case a more detailed analysis is needed, such as for the precise characterization of screw geometry on the surrounding bone stresses, a more detailed description of the local geometry of the trabecular structure and of the specific shape of the implant is required.

Finite element models that include bone microstructure are typically based on data obtained from micro-computed tomography (μCT) imaging [59]. Beam and shell elements provide an elegant way to represent the trabecular struts and plates. It has been shown that such models can accurately represent the apparent mechanical behavior of bone [60,61]. Such models would have the potential to analyze the mechanical behavior of bone-implant systems as well. Yet, this has not been presented in the literature.

More recently, a purely computational strut-model has contributed to a better understanding of the mechanics underlying implant stability [62]. For this purpose, a three-dimensional beam lattice model was developed that modeled the trabecular bone structure (Figure 2.2). Microstructural features of the lattice were varied systematically. It was found that stiffness and strength were affected most by removal of trabeculae in the peri-implant region and by trabecular thinning, respectively.

More commonly, voxel-based approaches are being used to represent bone microstructure. Micro-CT based FE (μFE) modeling allows for a detailed representation of the bone micro-architecture and can be realized by a direct conversion of image voxels into hexahedral cubic elements [63,64]. This in silico approach has been
Figure 2.2.: (a) Three-dimensional cubic lattice model (edge length 17 mm) with the implant (in black) positioned in the center of the top xy-plane of the bone lattice. (b) Schematic cross section (xz-plane) of the cubic lattice. Reference implant dimensions are reported. The vertical trabeculae connecting the tip of the implant with the lattice were removed. Reproduced from Ruffoni, D., Müller, R., van Lenthe, G.H., 2012. Mechanisms of reduced implant stability in osteoporotic bone. Biomech. Model. Mechanobiol. 11, 313-23

Proven to be a robust and reliable method to quantify the mechanical behavior of trabecular bone [60,65]. Parallel computing methods with dedicated FE solver have allowed increasing the bone model size beyond 100 Mio. elements [66–68]. To the best of the authors’ knowledge, the largest linear-elastic \( \mu \)FE model so far has been run on the Jaguar at Oak Ridge National Laboratory (Cray XT5) with 388’109 degrees of freedom (DoF) using a pointer-less octree-like data structure to avoid unnecessary storage of regions where no bone mass is present (i.e. void spaces) [68]. Furthermore, non-linear \( \mu \)FE models of trabecular bone have been introduced to simulate bone strength [46,69,70]. More recently, highly complex models considering fully non-linear mechanical bone properties (i.e. material and geometry) have been applied on fairly large models containing up to 1.5x109 DoF [71,72].

Voxel-based \( \mu \)FE models with a detailed representation of the peri-implant structure have revealed obvious differences in strains between continuum FE and discrete FE models, (Figure 2.3) [73] and have contributed to a better understanding of the mechanics underlying implant stability [28]. In the latter study, the bone microstructure of 12 humeral heads was assessed using \( \mu \)CT followed by digital screw insertion at 25 different locations for each humeral head. A virtual biopsy was taken prior
to insertion at each insertion site and bone structural quality was quantified based on morphometric indices. The apparent stiffness of the 300 screw-bone specimens was computed as a proxy for implant stability. While global bone density showed only moderate correlation with screw-bone stiffness ($R^2 = 0.52$), local BV/TV was a very good predictor ($R^2 = 0.91$). The prediction even improved further when local bone apparent Young’s modulus was used as a predictor for screw-bone stiffness ($R^2 = 0.97$). This clearly demonstrates that not only bone mass but also the trabecular architecture plays a key role in implant stability.

![Figure 2.3: Direct comparison of strains between continuum and discrete μCT based finite element modeling of bone-implant systems. In the left columns is low-density bone and in the right columns high-density bone. First row: 5 mm insertion depth. Second row: 10 mm insertion depth. Third row: 15 mm insertion depth. Different scales were used for the two FE models. Continuum models are not able to capture the load distribution as detailed as the discrete bone models. Reproduced from Wirth, A.J., Müller, R., van Lenthe, G.H., 2012. The discrete nature of trabecular bone microarchitecture affects implant stability. J. Biomech. 45, 1060-7](image)

The voxel-based models can be used to estimate strength. More specifically, pull-out tests have been performed on ten sheep vertebral bodies that were fixed in PMMA and into which orthopedic screws were inserted [74]. Subsequently, μFE models of the same bone-implant constructs were created based on μCT scans at a nominal voxel resolution of 25 μm. Isotropic material properties (Young’s modulus) were
assumed. Pull-out strength was derived based on the Pistoia criterion [75] in which the strength depends on the size of the volume of interest (VOI) around the implant and on the amount of highly stressed bone elements. Following this approach, in silico strength correlated highly ($R^2 = 0.87$) to measured pull-out strength. Yet, it is questionable whether the same settings would predict pull-out strength for other screw geometries or even in bones having substantially different microstructures.

Voxel-based $\mu$FE models typically assume bonded bone-implant interfaces. In case of well-osseointegrated implants [76, 77], this seems to be a reasonable modeling approach as it corresponds to an infinite coefficient of friction between bone and implant. However, frictional phenomena and non-linear behavior might play a substantial role in primary implant stability, as elucidated in the next section, and would require a more detailed representation of the bone-implant interface characteristics. A more detailed representation of the bone-implant characteristics could be accomplished by a local mesh refinement at the interface to model frictional contact as well as by an implementation of plasticity formulations to model mechanically induced bone damage. While commercial FE solvers are actually capable of modeling these features, they lack the computational power to solve models containing the required number of elements, which could easily exceed $10^8$ elements. On the other hand, $\mu$FE models do have the computational power to solve models of this size, but generally lack the capability to model complex and non-linear mechanical behavior. In the next section, more details are provided on the complexity and on the challenges to accurately model the peri-implant bone mechanics.

2.1.5. Experimental evaluation of peri-implant bone mechanics

An insightful technique to evaluate peri-implant bonemechanics is to combine biomechanical testing with imaging. This technique has seen several implementations. One straightforward approach is to evaluate first the local bone morphometry at or around the implant insertion site using $\mu$CT. Subsequently, mechanical tests are performed to retrieve relevant apparent mechanical properties of the bone-implant system that are then compared to the local bone architecture. Using this approach, Schiuma et al. found that bone volume fraction (BV/TV) and trabecular number (Tb.N.) correlated inversely with the load-induced displacement [13, 78]. Ideas exist to implement this technique into a clinical setting [79].

In a more sophisticated approach, imaging and mechanical testing are being combined in one single experimental setup. Digital Image Correlation (DIC) has been used to quantify the micro-motion of the cement-bone interface in arthroplasty [80].
In such an experiment, displacement fields are determined at discrete locations along the center line of the specimens. Additionally, relative displacements between neighboring markers are computed to track motion patterns of bone and implant and of the contact interface. This technique has been applied on \textit{in vitro} prepared cemented total hip replacements subjected to nondestructive mechanical loading. It was shown that most of the compliant responses due to mechanical loading occur at the bone-cement interface indicating highly nonlinear behavior in this region. A limitation of this technique is that DIC can be performed on exposed surfaces only. The above-mentioned limitation is not present when \(\mu\)CT is being used as the imaging technique. The combination of step-wise micro-compression in combination with time-lapsed \(\mu\)CT imaging, also referred to as image-guided failure assessment (IGFA) has been used to visualize and quantify directly in 3D the fracture initiation and progression on the microscopic level [12, 76, 81]. Recently, a custom-made automated mechanical loading device has been built that is compatible with a high-resolution peripheral quantitative computed tomography (HR-pQCT) system (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland) [81]. Using this device, it has been found that the ultimate force of dynamic hip screws (DHS) implanted in proximal human femora, correlated highly with the peri-implant bone volume fraction \((R^2 = 0.85)\). Furthermore, it was demonstrated that primary fixation failure only occurred in the peri-implant trabecular bone region. In a subsequent study, dynamic cut-out of these DHS screws was assessed [12]. It was demonstrated that, first, bone volume fraction correlated highly with implant migration \((R^2 = 0.95)\); second, the implant migration rate was inversely correlated to bone-implant contact area, and third, the bone-implant interface was significantly smaller on the experimentally tracked screw migration path compared to a hypothetical straight line in loading direction. From this, the authors concluded that implants migrate on a path of least resistance. Furthermore, the largest displacements occurred in the immediate vicinity of the implant and decreased non-linearly when moving away from the implant in radial direction [12, 76].

2.1.6. Towards improved accuracy of microstructural bone-implant models

The IGFA study (described above) on dynamic hip screws in human femoral heads has been replicated in a \(\mu\)FE study [82]. The calculated displacement fields were in good agreement with the experimentally measured displacements fields \((R^2 = 0.670.92)\); yet, the displacements in the peri-implant region were overestimated up to a factor 4 (Figure 2.4). Hence, a mismatch is present between the local displacements
as calculated from the $\mu$FE model and measured in the *in vitro* experiments.

![Figure 2.4.](image-url)

**Figure 2.4.** Visualizations of displacement fields obtained by strain mapping and micro-finite element analysis. Note the different scale bars.

The $\mu$FE models typically assume one isotropic Young’s modulus for all bone elements in the model. Although this approach does not take local variations in trabecular mineralization into account, it seems to be a valid assumption. Specifically, in a recent study, synchrotron radiationmicro-computed tomography (SR$\mu$CT) based micromechanical finite element models of trabecular bone that accounted for mineral heterogeneity were compared with homogeneous models. The comparison of the apparent stiffness tensor of both model types revealed that homogeneous models led to an overestimation of less than 3 % as compared to the heterogeneous models [83]. Furthermore, successful validation for $\mu$CT based FE models of trabecular bone, in which bone trabeculae had been modeled consisting of homogenous material properties only [60,65], indicates that other modeling features must cause the present mismatch between *in silico* and experimental data of bone-implant systems. One modeling feature that may explain the current mismatch is the presence of damage. There is histological evidence that screw insertion causes local damage to the bone tissue in immediate vicinity of the screw [84–86]. In a recent study [87] small implants were inserted at the medio-proximal site of 8 rat tibiae. While the limbs were subjected to axial compression loading strains close to the implant on the tibia surface were measured using strain gauges. Furthermore, specimen-specific $\mu$FE models were created. For each limb four models were created: one in which
the bone was assumed to be fully osseointegrated, and three additional models in which a weak peri-implant bone layer of 40 µm, 80 µm, and 160 µm was simulated (Figure 2.5). In all cases, measured and computational strains correlated very well ($R^2$ higher than 0.92 for all cases). Yet, the calculated strains varied strongly; the strains were overestimated by 69% for the fully osseointegrated case and were underestimated by 9% for the models with the 160 µm weak bone layer. Hence, it could be relevant to include weaker, ‘damaged’, bone close to an implant. However, since the strain validation took place on the cortical bone surface on rat tibiae, it is not clear if this method is also applicable and useful to human trabecular bone as well. Furthermore, a more refined understanding of the thickness and tissue modulus of the low-quality peri-implant region seems required.

Figure 2.5.: Four models corresponding to four representations of the bone implant interface were created. The first model consisted of bone and implant only (a). In the second (b), third (c), and fourth (d) models, reduced mechanical competence was modeled by assigning a Young’s modulus of 0.1 GPa to a peri-implant bony region with increasing thickness when moving from b to c. Reproduced from Torcasio, A., Zhang, X., Van Oosterwyck, H., Duyck, J., van Lenthe, G.H., 2012. Use of µCT-based finite element analysis to accurately quantify peri-implant bone strains: a validation in rat tibiae. Biomech. Model. Mechanobiol. 11, 743-50.

Another modeling feature that may explain the mismatch between measured and calculated mechanical properties is micro-motion between implant and bone. This finding is supported by DIC experiments of bone-cement constructs [80]. Based on their experimental data, µFE models of a cement-bone interface specimen were produced using micro-computed tomography images of a physical specimen that was sectioned from an in vitro cemented total hip arthroplasty. Smoothed interfaces were introduced into the µFE models that are capable of simulating de-bonding and sliding between two materials. Even though the authors revealed that smooth surfaces imply frictional phenomena which in turn relate to hysteresis and not to
interface compliance, it is reasonable to assume that a smoothed interface model still can contribute to an increased ‘global’ compliance of the entire implant-bone system. Yet, a recent \( \mu \)FE study has questioned the importance of friction regarding its effect on micromotion between implant and bone \[88\]. In their study, a \( \mu \)CT-based FE model of an oral implant inserted into a Berkshire pig mandible was created to assess the relative micromotion between the implant and the surrounding trabecular bone. Non-linear contact FE analyses were performed simulating a uniaxial load applied to the top of the implant. The authors could show that friction did not have a significant effect on the magnitude of relative displacement between the implant and the bone. To sum up, where interlocking prevails (e. g. cancellous fixation screw) friction plays a minor role. On the other hand, for implants based on press fit (e.g. knee or hip arthroplasty), the frictional component is very important.

In summary, while there is experimental evidence that compliant elements at the interface are able to replicate the interface compliance observed \textit{in vitro}, it remains unclear to what extent smooth interface contact contributes to the compliance at the local level as well as at the apparent level. At first sight, it seems useful to incorporate both features into \( \mu \)FE models to investigate their relative contribution to an improved prediction of the local and global mechanical competence of implants in trabecular bone. However, it is important to note that the attempt to simulate \textit{in silico} and to validate \textit{in vitro} patient-specific implant-bone interaction in such great detail is only useful if such a detailed bone-interface description can also be directly measured in a patient in the first place.

\subsection*{2.1.7. Conclusions}

The aim of this review was to provide a critical summary on the state-of-the-art in finite element modeling of primary implant stability. Strengths and weaknesses were discussed and are summarized in Table 1, using the five criteria as listed in Section 1. In conclusion, the trabecular bone structure and composition in each patient is highly unique, site-dependent and influenced by gender, age, physical exercise and physiological condition. Due to this intrinsic variability, \textit{in vitro} biomechanical models would require a large amount of bone specimens for reliable parametrical studies in order to find potential improvements for implant fixation. Instead, \textit{in silico} methods, such as FE modeling, do not suffer from this limitation. However, it is important to note that any \textit{in silico} method requires a rigorous validation with corresponding \textit{in vitro} models as well as verification of its accuracy and robustness \[29\]. Whereas continuum FE models can provide reasonable estimates of bone-implant interaction, they cannot be used for the detailed analysis of bone-implant interface.
2.1. Computational analysis of primary implant stability in trabecular bone mechanics; hence, they are of limited value in implant shape optimizations. Alternatively, finite element models that explicitly model the bone-implant interface and peri-implant bone region can be used. While this approach has turned out to be a reliable and accurate method to assess the mechanical competence of trabecular bone, it has been less successful for bone-implant systems. Experimental data suggests that this may be related to the specific way the bone-implant interface is modeled. There is cumulating experimental evidence that bone in the peri-implant region is more compliant than in other bone regions due to local bone damage. We hypothesize that this phenomenon should be included in $\mu$FE models to further improve the accuracy of patient specific $\mu$FE models of bone-implant constructs.

Acknowledgments

This review was funded in part by the Swiss Commission for Technology and Innovation (CTI) through grant KTI-Nr. 14067.1 PFLS-LS and by Synthes GmbH.

References


Chapter 2. Background

established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 24(1):23–57, jan 2013.


2.1. Computational analysis of primary implant stability in trabecular bone


[26] F. Eckstein et al. Bone strength at clinically relevant sites displays substantial

Three-dimensional distribution of bone density in the proximal humerus. *Cal-

[28] A. J. Wirth et al. Implant stability is affected by local bone microstructural

biomechanics: the first decade. *Journal of biomechanics*, 16(6):385–409, jan
1983.

endosseous implants in osteoporotic bone. *European cells & materials*, 20:58–71,
jan 2010.

[31] L. Podshivalov and A. Fischer. Patient-Specific Diagnosis and Visualization of
number July 2011, chapter 9, pages 27–52. Springer-Verlag Berlin Heidelberg

[32] J. Y. Rho, L. Kuhn-Spearing, P. Zioupos. Mechanical properties and the hier-
1998.


[34] M. Stauber, L. Rapillard, G. H. van Lenthe, P. Zysset, R. Müller. Importance
of individual rods and plates in the assessment of bone quality and their con-
tribution to bone stiffness. *Journal of bone and mineral research : the official
2.1. Computational analysis of primary implant stability in trabecular bone


Chapter 2. Background


2.1. Computational analysis of primary implant stability in trabecular bone


Chapter 2. Background


2.1. Computational analysis of primary implant stability in trabecular bone


Chapter 2. Background


Chapter 3

Assessing peri-implant bone damage
3.1. Screw insertion in trabecular bone causes peri-implant bone damage

Juri A. Steiner¹, Stephen J. Ferguson¹ and G. Harry van Lenthe¹,²

¹Institute for Biomechanics, ETH Zurich, 8093 Zurich, Switzerland
²Biomechanics Section, KU Leuven - University of Leuven, Celestijnenlaan 300, 3001 Leuven, Belgium

Accepted as:
Juri A. Steiner, Stephen J. Ferguson and G. Harry van Lenthe. Screw insertion in trabecular bone causes peri-implant bone damage. Med Eng Phys, 2015
Reprinted with permission and in compliance with the publisher copyright policy.

Abstract:
Secure fracture fixation is still a major challenge in orthopedic surgery, especially in osteoporotic bone. While numerous studies have investigated the effect of implant loading on the peri-implant bone after screw insertion, less focus has been put on bone damage that may occur due to the screw insertion process itself. Therefore, the aim of this study was to localize and quantify peri-implant bone damage caused by screw insertion. We used non-invasive three-dimensional micro-computed tomography to scan twenty human femoral bone cores before and after screw insertion. After image registration of the pre- and post-insertion scans, changes in the bone micro-architecture were identified and quantified. This procedure was performed for screws with a small thread size of 0.3 mm (STS, N=10) and large thread size of 0.6 mm (LTS, N=10). Most bone damage occurred within a 0.3 mm radial distance of the screws. Further bone damage was observed up to 0.6 mm and 0.9 mm radial distance from the screw, for the STS and LTS groups, respectively. While a similar amount of bone damage was found within a 0.3 mm radial distance for the two screw groups, there was significantly more bone damage for the LTS group than the STS group in volumes of interest (VOIs) between 0.3-0.6 mm and 0.6-0.9 mm.

In conclusion, this is the first study to localize and quantify peri-implant bone damage caused by screw insertion based on a non-invasive, three-dimensional, µCT imaging technique. We demonstrated that peri-implant bone damage already occurs during screw insertion. This should be taken into consideration to further improve primary implant stability, especially in low quality osteoporotic bone. We believe
that this technique could be a promising method to assess more systematically the
effect of peri-implant bone damage on primary implant stability. Furthermore,
including peri-implant bone damage due to screw insertion into patient-specific
in silico models of implant-bone systems could improve the accuracy of these models.

Keywords:
Orthopedic, screw insertion, peri-implant damage, µCT, image registration

Introduction

Secure fixation of bone fragments after a fracture is mandatory to achieve proper
healing. Consequently, substantial efforts have gone towards improving fracture
fixation. It has been demonstrated that implant design, implant surface character-
istics [1, 2] and surgical technique [3–5] can all considerably influence the clinical
outcome. Not only the implant, but also the bone itself plays a role in achieving
proper fixation. Secure fracture fixation is still a major challenge, especially in
osteoporotic bone. First, primary stability is decreased because screws have less pur-
chase in osteoporotic bone [6–8]; second, secondary stability is negatively affected
because osteoporotic bone shows a diminished healing capacity [9–12]. As the el-
derly population increases and continues to age, the number of osteoporotic fracture
incidents is increasing [13, 14]. These biomechanical and demographic changes stress
the importance to further improve fracture fixation in osteoporotic bone.

While the effect of implant loading on the peri-implant bone has been investigated
after screw insertion [3, 15–20], less focus has been put on the bone damage caused by
screw insertion itself [1, 21–24]. At the micro-scale, different modes of micro-damage
(e.g. micro-cracks, cross hatch damage and diffuse damage) have been localized and
quantified using fluorescent microscopy based histomorphometry [1, 21, 23] and/or
laser scanning microscopy [22]. However, none of these methods have been able
to capture and/or quantify peri-implant damage fully in three dimensions (3D). Fur-
thermore, histomorphometry is invasive per se and, consequently, does not allow
for a direct comparison between the 'before' and 'after' screw insertion state within
the same specimen. Moreover, it is not clear to what extent the preparation of the
histomorphometric slices creates micro-damage in the bone. Therefore, the aim of
this study was to capture and analyze bone damage due to screw insertion and to do
so non-invasively and fully in three dimensions. We hypothesized that bone damage
would occur close to the implant only, and that it would be affected by the screw
thread design.
Methods

Twenty cylindrical trabecular bone specimens (18 mm height; 16 mm diameter) were core drilled from the epiphyseal region of twelve cadaveric human femoral heads (age 66.5 ± 10.5 years). After predrilling with a diameter of 2 mm, one self-tapping screw (length: 16 mm; core diameter: 2.1 mm) was inserted 11 mm into the center of each specimen according to the manufacturer’s guidelines. Two thread sizes, defined as 0.5 x (outer diameter - core diameter), were used. The small thread size (STS) and large thread size (LTS) were 0.3 mm and 0.6 mm, respectively. The pitch sizes of the STS and LTS groups were 0.65 and 1.31, respectively. All specimens were scanned twice with micro-computed tomography (µCT50, Scanco Medical, Brüttisellen, Switzerland) using 90 kVp energy at a nominal isotropic resolution of 20 µm; one scan was made of the intact specimen prior to screw insertion and another scan was made just after screw insertion. The screws were custom-made (DePuy Synthes, Solothurn) based on a Titanium-Aluminum alloy (TiAl_{6}Nb_{7}) that contains relatively low atomic numbers to reduce potential metal artefacts during scanning [25]. After image reconstruction, rigid image registration was performed, as described in recently published literature [26], to align the two images (Fig. 3.1a and 3.1b). Next, both images were segmented following well accepted guidelines [27] (Fig. 3.1c) based on visually distinctive grey scale values for bone and screw (arbitrary units: 200 to 400 and 800 and 1000, respectively). A visual check revealed no artificial gaps due to the segmentation. Next, the segmented screw from the physical insertion (PI) model was inserted digitally (Fig. 3.1d) into the image stack of the pre-insertion scan to obtain a digital insertion (DI) model.
Figure 3.1.: Peri-implant bone damage was assessed by conducting two sets of $\mu$CT scans; once before and once after screw insertion. Image registration was used (step a) to align $\mu$CT scan 1 with $\mu$CT scan 2 (step b). Next, both grey scale images were segmented to obtain the bone and screw structures (step c). In the last step (d), the segmented screw from the physical insertion (PI) model was copied and digitally inserted into the segmented image of $\mu$CT scan 1 to obtain the digital insertion model; the latter does not contain any peri-implant damage.
3.1. Screw insertion in trabecular bone causes peri-implant bone damage

While the PI model represents the bone core with the physically inserted screw including the peri-implant bone damage (Fig. 3.2a), the DI model represents an idealized perfect insertion without any peri-implant bone damage (Fig. 3.2b).

Figure 3.2.: The images on the left and right side show representative examples of a physical insertion (PI) and a digital insertion (DI) model, respectively. A visual comparison between the PI and DI model showed clear evidence for peri-implant bone damage due to screw insertion (representative locations shown with red arrows).

Bone debris at the outer surface of the bone sample, caused by sample preparation, was extracted by digitally removing a 0.5 mm ring of the outermost bone structure. Next, an image overlay was performed between the PI screw model and the DI screw model (Fig. 3.3). In the overlay image, two specific voxel-labeling categories were defined: (1) bone present in both images (transparent grey in Fig. 3.3) and (2) bone present in the PI image only (pink in Fig. 3.3). The bone in category 2 represents bone that has been displaced due to pre-hole drilling and screw insertion and is quantified as the bone damage volume (BDV; Fig. 3.3).
Chapter 3. Assessing peri-implant bone damage

Figure 3.3.: In an overlay procedure, the digital insertion (DI) and physical insertion (PI) image were combined to produce an overlay image. In the overlay image, two specific voxel-labeling categories were defined: (1) bone present in both images (transparent grey) and (2) bone present in the PI image only (pink). The bone in category 2 represents bone that has been displaced due to pre-hole drilling and screw insertion remains within close vicinity of the screw. The red arrows point out representative locations.

Bone damage density (BDD) was assessed by computing BDV normalized to the bone volume (BV) in hollow cylindrical VOIs around the screw (BDD = BDV/BV) of the corresponding cylindrical VOI. All VOIs had a radial thickness of 0.3 mm; their inner radius was varied in steps of 0.3 mm (up to 5.1 mm) to describe different distances to the screw (Fig. 3.4a). BV divided by the total volume (TV) in which the BV is located, was computed to calculate the average bone volume fraction (BV/TV) over all specimens as previously defined here [27]. Furthermore, BV/TV was assessed within each hollow cylindrical VOI and correlated to BDD. Most measurement techniques contain a residual noise level (i.e. precision) even though in reality no signal exists. In our case, the precision of the entire rescanning and registration process was assessed underneath the screw where no architectural changes were expected. More specifically, all bone voxels belonging to category 2 were quantified in 14 cylindrical volumes of interest (VOI; all 0.3 mm in height and 14.2 mm in diameter) underneath the screws and normalized to BV of the VOI (Fig. 3.4b). The quantified precision from the region underneath the screw (Fig. 3.4b)
3.1. Screw insertion in trabecular bone causes peri-implant bone damage

served as threshold against which BDD values in radial distance to the screw (Fig. 3.4a) were compared to detect actual bone damage that is significantly different from the precision level.

Figure 3.4.: Bone damage density was assessed in hollow cylindrical VOIs around the screw in a range from 0.0 to 5.4 mm in steps of 0.3 mm (a) by computing bone damage volume (BDV) normalized to the bone volume (BDD = BDV/BV). The precision of the entire rescanning and registration process was assessed underneath the screw where no architectural changes were expected. More specifically, all bone voxels belonging to category 2 (Fig. 3.3) were quantified in 14 cylindrical volumes of interest (VOI; all 0.3 mm in height and 14.2 mm in diameter) underneath the screws and normalized to the bone volume (BV) of the VOI (b).

Statistical analyses

ANOVA multi-comparison test with Bonferroni correction was used to determine whether BDD differed significantly ($\alpha = 0.05$) from the precision level.

Results

No significant differences in precision were found between any of the VOIs underneath the screws of the STS and LTS group. Hence, the data were pooled and served as the precision level against which all VOIs in the radial direction to the screws could be compared. For the STS and LTS group, the precision was 0.072 $\pm$ 0.02% and 0.072 $\pm$ 0.03%, respectively. A visual comparison between the PI and DI model showed clear evidence for peri-implant bone damage due to screw insertion (indicated by red arrows in Fig. 2). Further visual assessment of the computed
bone damage revealed a clear densification of BDD towards the implant site (Fig. 3.5a and 3.5b). For the STS group, BDD was significantly higher than the precision up to 0.6 mm distance from the screw (Fig. 3.5c). For the LTS group significant differences were found up to 0.9 mm radial distance from the implant (Fig. 3.5d). In both groups, we could observe that with increasing distance from the screw, BDD quickly converged towards the precision level (Fig. 3.5c and 3.5d). The LTS group showed significantly higher BDD values than the STS group in the VOIs between 0.3-0.6 and 0.6-0.9 mm distance from the implant. Highest BDD values were found in the VOI closest to the implant; no significant differences in BDD were found between the STS and LTS groups. The average BV/TV over all specimens is 27.2% ± 4.1%. BV/TV for the STS and LTS group was 25.8 ± 1.9% and 29.0 ± 4.6%, respectively (p=0.064). Within the VOIs where BDD was significantly higher than the precision, BV/TV shows no significant correlation to BDD in both groups (R² < 0.4 and p > 0.05).
3.1. Screw insertion in trabecular bone causes peri-implant bone damage

Discussion

The aim of this study was to develop a non-invasive method that would allow the qualitative and quantitative assessment of peri-implant bone damage caused by screw insertion. This goal was achieved. We could show that the trabecular bone structure is affected by screw insertion. Bone damage was found close to the implant only. We also showed that screws with large threads had a slightly larger...
impact on the peri-implant bone than screws with small threads. Bone damage does not seem to depend on bone volume fraction. Low correlation coefficients were found for other morphometric parameters, too. We assume that the accumulation of peri-implant bone damage is a complex phenomenon that depends on the underlying composition of the bone tissue. For instance, the ultrastructure of the bone (i.e. collagen content and its orientation) is known to have an influence on the mechanical properties (e.g. brittleness) of bone tissue and might also play an important role on the fracture mechanisms during screw insertion, hence on the amount of peri-implant damage. However, collagen cannot be assessed using µCT. Hence, for future studies, it would be interesting to use more sophisticated measurement techniques (e.g. 3D scanning SAXS [28]) to investigate the complex relationship between bone quality and peri-implant bone damage caused by screw insertion. Unfortunately, 3D scanning SAXS is an invasive technique and only a very limited number of individual trabeculae can be assessed per specimen due the complex methodology that requires vast computational resources. Further improvements in the measurement technique and computational performance are required to make this method applicable in a non-invasive fashion for larger volumes of interest as well as larger samples sizes.

The impaction of the bone during screw insertion can increase the implant-bone stability [29]. During this process, bony pieces can break off from the trabecular network and can serve as void filler which might enhance primary implant stability. An even higher stability would be expected if a perfectly intact peri-implant bone could be preserved during screw insertion. However, this is not the case. We recently conducted a computational study in which we found that despite the increased bone-screw interface surface of the bone-screw composite, its mechanical competence is decreased compared to models in which screws were placed digitally with perfectly intact peri-implant bone [30]. State-of-the-art computational models have demonstrated high over-predictions of the primary implant stability in screw-bone systems [31–33]. This is probably due to the fact that perfectly intact bone-screw interfaces were assumed. Hence, even though bone compaction can enhance primary implant stability in some cases [29], there is clear evidence, that local peri-implant bone damage occurs and hampers the mechanical performance of bone-implant systems when compared to idealized implant placement with perfectly preserved and intact peri-implant bone.

LTS screws induced more peri-implant damage than STS screws did. Based on these data we can conclude that the larger the outer diameter of a screw the more damage is induced in the peri-implant bone. However, corresponding in vitro mechanical tests (data not shown here) indicate no significant difference in bone-
3.1. Screw insertion in trabecular bone causes peri-implant bone damage

implant stiffness between STS and LTS screws. Furthermore, as osseointegration is known to be initiated by lesions of the pre-existing bone matrix [34], increased BDD could potentially correlate with improved secondary implant stability. Hence, further research is required to investigate the effect of BDD on the mechanical competence on primary and secondary implant stability. For this purpose, in vivo longitudinal studies in animals would be required as described here [35].

Employing μCT imaging, we used a non-invasive technique that captures peri-implant bone damage in three dimensions. This is a great advantage compared to histomorphometric analyses combined with fluorescent [1,23] and/or laser scanning microscopy [22] that has been used to investigate micro-damage near the implant site. Histomorphometric imaging techniques suffer from a limited field of view, imaging on discrete sections and are not able to capture peri-implant damage entirely in 3D. Furthermore, it is unclear to what extent the preparation of the histomorphometric slices induces further micro-damage.

Non-invasive 3D detection of micro-cracks in loaded cores of trabecular bone is possible using synchrotron light [36,37] or, alternatively μCT, but only when combined with a radio-opaque contrast agent such as Barium-Sulfate [38] or lead-uranyl acetate [39]. These radiographic techniques are capable of imaging micro-damage in peri-implant bone; however, they are limited in their field of view. Typically, bone regions within a single thread pitch only can be investigated in this way. Consequently, no information is obtained on how representative the investigated location is for the entire specimen. The strength of the present study is that a non-invasive μCT imaging technique was used with which the bone damage around the entire screw was visualized and quantified.

State-of-the-art patient-specific computational analyses are not able to accurately simulate the mechanical competence of orthopedic screws placed into human bone. Hence, the inclusion of a peri-implant bone damage region with reduced mechanical competence could potentially improve the accuracy of such in silico computational models. The knowledge gained from this study could be useful to improve the accuracy of patient-specific high-resolution μCT based finite element (μFE) analysis of implant-bone systems. While patient-specific finite element (FE) computer simulations of trabecular bone alone have shown to be in very good agreement with corresponding in vitro mechanical test [40–42], these in silico models tend to overestimate the mechanical response in implant-bone systems [33,43].

This study has several limitations: First, metal screws were used that create metal artifacts during μCT scanning. However, specific measures, such as high energy scans and titanium-aluminum alloy based screws were used to reduce the metal
artifact. Second, the current setup does not allow distinguishing the bone damage caused by the drilling procedure from the bone damage caused by screw insertion, as only two sets of scans per specimen were conducted (i.e. before guide hole drilling and after screw insertion). Nevertheless, the comparison of the two different screw types is valid because the exact same guide hole drilling procedure was used in both groups. Third, the method identifies only fragmentation of peri-implant bone trabeculae, not micro-damage within the trabeculae themselves. The current image resolution of 20 µm is not sufficient to assess peri-implant bone damage at the micro-scale (e.g. micro-cracks, cross-hatched damage or diffuse damage). This is due to the fact that micro-damage occurs at a length-scale that is at least one order of magnitude smaller. Fourth, depending on the trabecular dimensions and possible residual stresses in the trabecular network, elastic bending of trabeculae may be interpreted as damage by this registration method. However, structural changes captured at 20 µm can most likely be interpreted as bone damage considering the fact the micro-cracks already occur at dimensions of 1 to 2 µm.

In conclusion, this study is the first to localize and quantify peri-implant bone damage along the entire length of the screw; furthermore, this was done non-invasively and fully in 3D. We believe that this technique could be a promising method to investigate more systematically the effect of peri-implant bone damage on primary implant stability, such as caused by excessive loading and screw insertion. Furthermore, including peri-implant bone damage due to screw insertion into patient-specific in silico models of implant-bone systems could improve the accuracy of these models.

Funding

This study was funded in part by the Swiss Commission for Technology and Innovation (CTI) through grant KTI-Nr. 14067.1 PFLS-LS and by Synthes GmbH.

Conflicts of interest

None declared

Ethical approval

Bone cores were obtained from resected bones from orthopedic surgical interventions in collaboration with Schulthess Clinic (Zurich, Switzerland). The corresponding ethics committee approval (EK-29/2007) allows measurements by µCT as well as additional experimental experiments.
3.1. Screw insertion in trabecular bone causes peri-implant bone damage

References


Chapter 3. Assessing peri-implant bone damage


3.1. Screw insertion in trabecular bone causes peri-implant bone damage


3.1. Screw insertion in trabecular bone causes peri-implant bone damage


Chapter 4

Primary stability of single fracture fixation screws
4.1. A novel *in silico* method to quantify primary stability of screws in trabecular bone

Juri A. Steiner\(^1\), Patrik Christen\(^1\), Remo Affentranger\(^1\), Stephen J. Ferguson\(^1\) and G. Harry van Lenthe\(^1,2\)

\(^1\)Institute for Biomechanics, ETH Zurich, 8093 Zurich, Switzerland
\(^2\)Biomechanics Section, KU Leuven - University of Leuven, Celestijnenlaan 300, 3001 Leuven, Belgium

Submitted as:

Abstract:
Insufficient primary stability of screws in bone leads to screw loosening and failure. Unlike conventional continuum finite-element (FE) models, FE analysis based on high-resolution \(\mu\)CT images is capable of capturing the patient-specific bone micro-architecture, providing accurate and individual estimates of bone stiffness. However, such *in silico* models for screws in bone highly overestimate the apparent stiffness. We hypothesized that a more accurate prediction of primary implant stability of screws in bone is possible by (i) modeling interface detachment between the screw and bone and (ii) considering insertion-related bone damage.

Twenty trabecular bone specimens were extracted from the epiphyseal region of twelve cadaveric human femoral heads. In each specimen, a screw was inserted following the manufacturer’s guidelines. Two different screw types and loading scenarios were assessed (\(N=5\) for each case). Three different types of \(\mu\)FE models were tested: conventional \(\mu\)FE model; \(\mu\)FE model considering interface detachment and \(\mu\)FE model considering peri-implant bone damage in addition to interface detachment. In the third \(\mu\)FE model, specimen-specific Young’s moduli of the damaged peri-implant bone were defined such that the apparent stiffness of the *in silico* model matched each experimentally measured stiffness. Subsequently, a multi-linear regression analysis was conducted that related the bone morphometric parameters to the peri-implant bone tissue modulus. The robustness of the regression model was then assessed by performing a leave-1-out cross validation.
Chapter 4. Primary stability of single fracture fixation screws

The conventional μFE models overestimated the bone-implant stiffness by over 395%. In the second series of μFE models, interface detachment between screw and bone resulted in a minor (1-7%) reduction of bone-implant stiffness. In the third series of μFE models, consideration of insertion-related bone damage effectively corrected the over-prediction of bone-implant stiffness; the average absolute error was 11.4% for both loading scenarios and screw types. Cross-validation revealed an average prediction error of 14.2%.

We present a novel μFE modeling technique to quantify the apparent stiffness of screws in trabecular bone. As expected, the conventional μFE model highly overestimated the bone-implant stiffness. The incorporation of detachment between screw and bone contributed only little to a more accurate prediction in primary implant stability. However, the consideration of insertion-related bone damage was very effective. This approach provides an important step towards a better understanding of the detailed mechanisms of primary implant stability in human trabecular bone.

**Keywords:**
Finite Element Analysis, μCT, Implant stability

**Introduction**

Insufficient stability of screws used for fracture fixation in bone leads to screw loosening and is in most cases due to the low bone quality in which the screw is placed. In many cases where screw loosening occurs, revision surgery is required creating additional suffering for the patient as well as health care costs for the society. Hence, adequate primary stability of bone screws (i.e. initial stability of the implant in bone before bone ingrowth has taken place) is crucial for the successful outcome of instrumented fracture fixation systems. Especially in low-density bone, where the fixation of bone screws is reduced [1–3], accurate prediction of the mechanical performance is needed to improve fracture fixation techniques as well as surgical planning. The gold standard to quantify the performance of novel screws in bone is through experimental testing [2–4]. Typically, displacement driven loads are applied on single screws implanted in bone until failure occurs. From the resulting force-displacement curves, linear elastic behavior (i.e. bone-implant stiffness) and maximum force prior to failure (i.e. strength) are computed. Due to the high heterogeneity [5] and diversity inherent to bone micro-architecture, a large number of bone specimens is required to obtain clear outcomes with valid statistics using *in vitro* techniques.
4.1. A novel \textit{in silico} method to quantify primary stability of screws in trabecular bone

This is even more so as bone architecture does not only vary between patients \cite{6} but also within the same bone of a particular patient \cite{7,8}.

\textit{In silico} models capable of calculating the mechanical competence of bone-screw systems have been introduced as a potential alternative to \textit{in vitro} mechanical tests. Continuum finite element (FE) models have been proposed to quantify the mechanical competence of bone-implant systems, with a specific focus on the local behavior of the interface between the implant and bone. Continuum FE models offer a great variety of interface modeling options ranging from perfect bonding to the inclusion of friction, cohesive forces between materials, detachment at predetermined thresholds as well as other non-linear mechanical behaviors \cite{9–12}. However, in a typical continuum FE model, the trabecular bone microstructure is modeled as a continuous material without any local porous characteristics. Thus, by definition, these models do not have adequate resolution for an accurate and discrete representation of the highly diverse micro-architecture as well as of the mechanical behavior of the trabecular network. Attempts have been made to account for density variations in the bone by assuming a relationship between the local CT Hounsfield numbers and the local mechanical properties. This technique has been developed \cite{13–15} and validated \cite{16,17} on bone only and has been applied with moderate success in combination with implants \cite{18}.

Alternatively, in so-called \textit{µ}FE analysis, FE models are generated from high-resolution \textit{µ}CT images where image voxels are converted directly into hexahedron finite elements and are thus able to capture the micro-architectural variation in trabecular bone and have been put forward as a more advanced technique. Using this technique, it was possible to accurately represent the apparent mechanical behavior of bone \cite{19–21}. However, state-of-the-art \textit{µ}FE models of bone-screw systems overestimate the experimentally measured mechanical response \cite{22}.

We hypothesize that this overestimation may be related to (i) the assumption of bonded screw-bone interfaces, whereas by nature such bonding does not exist directly after screw insertion; and (ii) the assumption of intact peri-implant bone, whereas peri-implant damage has been demonstrated \cite{23–30}. Therefore, the goal of this study was to develop a \textit{µ}FE model that would represent in more detail the physical reality in order to accurately predict the primary stability of screws in trabecular bone by (i) modeling interface detachment between screw and bone and (ii) considering insertion-related bone damage.
Chapter 4. Primary stability of single fracture fixation screws

Methods

Samples  Twenty trabecular bone specimens (18 mm height; 16 mm diameter, bone volume fraction: 27.2% ± 4.1%) were extracted from the epiphyseal region of twelve cadaveric human femoral heads (age 66.5 ± 10.5 years). Two different screw designs were used. Both designs were 16 mm in length and had a core diameter of 2.1 mm. Their thread size was defined as 0.5 x (outer diameter - core diameter). The small thread size (STS) and large thread size (LTS) were 0.3 mm and 0.6 mm, respectively (Fig. 4.1). After predrilling, 10 screws for each screw design were placed into the bone in the center of randomly assigned specimens to an insertion depth of 11 mm, following the manufacturer’s guidelines (Fig. 4.1).

Bone imaging  Prior to mechanical testing, all specimens were scanned twice using micro-computed tomography (µCT 50, Scanco Medical AG, Brüttisellen, Switzerland; nominal isotropic resolution: 20 µm, energy: 90 kVp; integration time: 200 ms): once before (pre-insertion scan) and once after (post-insertion scan) screw placement. Bone morphometric parameters were determined for each bone sample at the screw insertion site. The cylindrical volume of interest (VOI; length 11 mm; diameter 2.7 and 3.3 mm corresponding to outer diameter of STS and LTS screw, respectively) was defined in the pre-insertion scan at the location where the screw

Figure 4.1.: In vitro mechanical tests were conducted with large threaded and small threaded screws (a) inserted in human trabecular bone cores from femoral heads (b). The bone-screw constructs were clamped tightly and loaded in compressive mode either in uniaxial direction of the screw (i.e. uniaxial loading) or 90° angulated to it (i.e. shear loading) (c).
4.1. A novel in silico method to quantify primary stability of screws in trabecular bone

would be inserted. Within this VOI, standard morphometric parameters [31,32] were quantified in the pre-insertion scan including bone volume fraction (BV/TV), bone surface over total volume (BS/TV), trabecular number (Tb.N), trabecular spacing (Tb.Sp), trabecular thickness (Tb.Th), and structural model index (SMI).

**Mechanical testing**  *In vitro* mechanical tests were performed on a mechanical testing machine (Zwick Roell Static Material Testing Machine 1456, Germany) using a custom-made fixation device (Fig. 4.1c). Two loading configurations were tested; the first represented a uniaxial compression (UC) test while the second represented a shear loading (SL) case. For each configuration, 5 STS and 5 LTS screws were used (Fig. 4.2). A preload of 1 N was applied. Five pre-conditioning cycles between 0 and 12 \( \mu m \) displacement were conducted. This was followed by a quasi-static loading ramp at 1 mm/min [33] until failure was reached. Apparent stiffness was calculated from the last loading ramp between 0 and 12 \( \mu m \) displacement.

Figure 4.2.: Two different screw designs were used. Both designs were 17.7 mm in length and had a core diameter of 2.1 mm. Their thread size was defined as 0.5 x (outer diameter - core diameter). The small thread size (STS) and large thread size (LTS) were 0.3 mm and 0.6 mm, respectively. Two loading configurations were tested; the first represented a uniaxial compression (UC) test while the second represented a shear loading (SL) case. For each loading configuration, 5 STS and 5 STL screws were used.

**Computational modeling**  For all twenty specimens, \( \mu FE \) models were created by a direct voxel-to-hexahedral element conversion [34]. In order to avoid metal artefacts that reduce the image quality of the bone surrounding the implant, \( \mu CT \) scans of the specimens prior to screw insertion were used for a digital screw placement. For this purpose, an image registration procedure was conducted as presented in
Chapter 4. Primary stability of single fracture fixation screws

A previous study [27]. In short, after image reconstruction, 3D rigid body image registration [35] was performed to align the two images, after which both images were segmented based on distinctive grey scale values for bone and screw (arbitrary units: 200 to 400 for bone and 800 and 1000 for the screw, respectively). Then, the segmented screw from the post-insertion scan was inserted digitally in the pre-insertion scan using an overlay procedure to obtain a bone-implant model without metal artefacts.

For each specimen, three \( \mu \)FE models were created. The first model was a two-component model consisting of a screw and bone. A quasi-static test was simulated mimicking the boundary conditions of the corresponding \textit{in vitro} tests. More specifically, displacements for the UC and SL case were applied on the flat top surface of the screw and within a small radius of 0.6 mm at the side of the round screw head, respectively. The radial boundaries and the bottom elements of the bone cores were fixed in all three directions. Bonded interfaces were assumed between the screw and the bone. The Young’s modulus of the titanium screw and the bone were 120 and 18 GPa [5], respectively. Stresses and strains in each element were calculated using the \( \mu \)FE solver ParOSol [36]. Apparent stiffness was defined as the sum of all reaction forces divided by the prescribed displacement.

The second model resembled the first one. After loading, volumetric strain was calculated and all bone elements in contact with the screw undergoing positive volumetric strain were removed from the model. Component labeling was applied to remove small disconnected bone particles before another simulation was run. Apparent stiffness was calculated as defined before.

In the third model, after modeling interface detachment, the bone elements in proximity to the screw were assigned a reduced Young’s modulus; the radial distance was 0.6 mm and 0.9 mm for the STS and LTS screw, respectively (Fig. 4.3). The sizes of these regions are in accordance with previous experimental findings on the extent of bone damage induced by screw insertion [27]. Next, a set of 10 quasi-static displacement tests was simulated for each specimen. In each simulation, a specific tissue Young’s modulus of the peri-implant bone damage region  \( E_{PIBD} \) was defined, ranging from 0.2 GPa to 2 GPa. B-spline interpolation was used to determine the specific bone tissue modulus such that the apparent stiffness of the model matched the experimentally measured stiffness.

\textit{Relating the peri-implant tissue modulus to bone morphometric parameters}

Multi-linear regression analyses were conducted relating the morphometric parameters to the specimen-specific peri-implant Young’s moduli. Akaike information
4.1. A novel in silico method to quantify primary stability of screws in trabecular bone

Figure 4.3.: The segmented image consists of three components: The screw (a), the bone (b) and the damaged peri-implant bone region around the screw (c).

a) Screw
b) Trabecular bone core
c) Damaged peri-implant bone
Chapter 4. Primary stability of single fracture fixation screws

criterion (AIC) [37, 38] was used to pick the most accurate regression model without over-fitting the data. Subsequently, the predicted $E_{PIBD}$ values were plugged back into the $\mu$FE model to compute the corresponding in silico stiffness values for each specimen. Subsequently, the same set of morphometric parameters were used to perform a 'leave-1-out' cross-validation procedure in which the regression model was built on 19 specimens to predict the one left out. This was repeated 19 times until every specimen was predicted using a regression model based on the 19 remaining specimens. Together with the standard coefficient of determination ($R^2$), mean average error (MAE) and mean average percentage errors (MAPE) were computed for the predicted stiffness values to assess the performance of all the linear regression models.

Results

The following in vitro stiffnesses were found for each configuration: STS-UC: $4'290 \pm 366$ N/mm; LTS-UC: $4'464 \pm 522$ N/mm; STS-SL: $994 \pm 180$ N/mm; STS-UC: $1'022 \pm 181$ N/mm. No significant differences were found regarding in vitro stiffness between the STS and LTS screws for the UC ($p > 0.60$) and SL ($p > 0.82$) loading cases.

A good correlation was found between the stiffness of the bone-screw system obtained from the conventional 2-component $\mu$FE model and the measured stiffness ($R^2=0.92$; Fig. 4.4a); however, the 2-component model highly overestimated the apparent stiffness; the slope of the regression was only 0.17. Furthermore, MAE and MAPE values were over 10’000 N/mm and 395 %, respectively (Fig. 4.4).

Interface element removal reduced the number of bone elements in contact with the implant by 28.10 % ($\pm 2.15$ %) and 46.98 % ($\pm 8.27$ %) for the UC and SL group, respectively, which in turn resulted in a reduction of apparent stiffness by 1.71 % ($\pm 0.69$ %) and 6.67 % ($\pm 4.61$ %).

For the 3-component $\mu$FE model, the best multiple regression analysis was obtained with the parameters $\frac{BS}{BV}$ ($p < 0.001$), Tb.N ($p < 0.02$) and Tb.Sp ($p < 0.031$): $E_{PIBD} \sim 3.88 + 0.09 \times \frac{BS}{BV} - 1.67 \times Tb.N - 4.30 \times Tb.Sp$ ($p < 0.002$). For this model, the scatter plot, containing the in silico bone-implant stiffness predicted by the $\mu$FE on the x-axis and the measured in vitro stiffness measured by the mechanical test on the y-axis, showed a good agreement with $R^2$ and slope close to 1 (Fig. 4.5). MAE and MAPE are 320 N/mm and 11.4%, respectively (Fig. 4.5b).

The 'leave-1-out' cross-validation method resulted in 375 N/mm and 14.2 % for MAE and MAPE, respectively. The Von Mises stress field in the bone around the implant revealed only very moderate changes due to interface element detachment.
4.1. A novel in silico method to quantify primary stability of screws in trabecular bone

Figure 4.4.: The standard linear μCT based finite-element model does not take into account any interface element detachment effects and does not consider any peri-implant bone damage. This results in a high overestimation of stiffness. Despite of the high correlation, the slope is far away from 1 (a) and the mean absolute error is over 300 % (b).

\[ R^2 = 0.923 \]
\[ S_{Exp} = 0.17 S_{FE} + 0.51 \]

MAE = 10066.2 N
MAPE = 332.82 %
Figure 4.5.: By taking into account the interface element detachment effect and the damaged peri-implant bone around the screw, the new three component µFE model is able to replicate the specimen specific in vitro fairly well. The stiffness prediction is based on a multi-linear regression analysis that links the bone morphometric parameters of each specimen to the corresponding Young’s modulus in the peri-implant bone. The bone parameters used in the multi-linear regression model are BS/BV (p < 0.001), Tb.N (d > 0.072), and Tb.Sp. (p < 0.031). The scatter plot shows an increased correlation and a slope close to 1 (a) as well as an improved mean absolute error of 11.4 % (b) when compared to the standard linear µCT model (Fig. 4.4). The scatter plot shows an improved mean absolute error of 11.4 % (b) when compared to the standard linear µCT model (Fig. 4.4). Please note the difference in scale in the scatter plots between Fig. 4.4 and 4.5.
4.1. A novel in silico method to quantify primary stability of screws in trabecular bone (Fig. 4.6a-4.6d). In contrast, the consideration of peri-implant bone damage due to screw insertion results in a substantial reduction of stress (Fig. 4.6e-4.6f).

Figure 4.6.: The Von Mises stress field in the bone around the implant revealed only very moderate changes due to interface element detachment (a-d). The consideration of peri-implant bone damage due to screw insertion results in a substantial reduction of stress (e-f).

Discussion

The main goal of this study was to test the hypotheses that a more accurate prediction of primary implant stability of screws in bone is possible by (i) modeling interface detachment between screw and bone and (ii) considering insertion-related bone damage. This goal has been achieved by assessing (i) the effect of interface element detachment during loading and (ii) peri-implant bone damage caused by
screw insertion. We found that interface element detachment played only a minor role, whereas the reduced mechanical competence of damaged peri-implant bone had a considerable effect on apparent stiffness in bone-screw systems. Our modeling approach is based on a statistical analysis that links the patient-specific bone morphometric parameters around the implant to the corresponding specimen-specific $E_{PIBD}$. We first showed by multiple regression analysis, and in combination with the Akaike Information Criterion, that BS/BV, Tb.N., and Tb.Sp are the most important factors to accurately predict $E_{PIBD}$ and corresponding stiffness for both screw designs and the two loading scenarios (MAPE = 11.4 %). Furthermore, we also assessed the robustness of the model by performing a leave-1-out cross validation in which the regression model was created on 19 specimens and then applied to predict $E_{PIBD}$ and bone-implant stiffness of the remaining one. This was repeated 19 times, and the mean average percentage error of the predicted bone-implant stiffness was calculated. The error was only slightly higher compared to the model containing all specimens (MAPE = 14.2 %). This indicates that the present model quantifies in an accurate and robust manner the stiffness of various screw types and loading angles in human trabecular bone.

We hypothesized that the overestimation of implant-bone stiffness may be related to (i) the assumption of bonded screw-bone interfaces; and (ii) the assumption of intact peri-implant bone. These are reasonable hypotheses since bone attachment is per se not present during primary implant stability and it has been shown that peri-implant damage occurs during screw insertion [23–30]. However, only a minor decrease in stiffness occurred (ranging from 1.7 % to 6.7 %) during element removal, whereas a substantial decrease (295 %) occurs when considering peri-implant bone damage. We showed that this damage is related to a large extent to the local microarchitecture of the bone at the insertion site of the intact bone. Interestingly, the mean of all $E_{PIBD}$ values computed by the linear regression model was 0.35 GPa (± 0.12 GPa). When, using $E_{PIBD}=0.35$ GPa for both screw types and loading cases, the predictive performance of stiffness decreased by a few percentage points only (MAE and MAPE are 419 N and 16.58 %, respectively). Hence, assuming an average $E_{PIBD}$ could be a valid and efficient alternative to the rather sophisticated specimen-specific approach that we have proposed in this study. The Von Mises stress field in the bone around the implant revealed only very moderate changes due to interface element detachment (Figure 6a-6d). In contrast, the consideration of peri-implant bone damage due to screw insertion results in a substantial reduction of stress (Fig 6e-6f). The remaining high stress underneath the screw (Fig 6e-6f) is due to the fact that peri-implant bone damage was detected only in radial direction of...
4.1. A novel in silico method to quantify primary stability of screws in trabecular bone

the screw and none underneath the screw [27]. Hence, as the mechanical competence of bone underneath the screw remains intact, the bone region underneath the screw produces higher stresses for the same deformation than the peri-implant bone region in radial distance to the screw.

The strength of the present study is that it is the first to relate the mechanical properties of peri-implant trabecular bone to the micro-architecture of the intact bone. The thickness of the damaged peri-implant bone has been determined in an earlier study in which we found that large threaded screws tend to induce more bone damage than small threaded screw with same core diameter [27]. The inclusion of a peri-implant region with reduced Young’s modulus has been already included in two earlier studies. In the first, a $\mu$FE model was developed that quantified the strains measured ex vivo around small implants inserted in 8 rat tibiae containing a damaged peri-implant cancellous bone region of 40-160 $\mu$m with an Young’s modulus of 0.1 GPa [39]. The predicted strain values correlated fairly well with the measured strain values ($R^2=0.90-0.95$). In the second, a continuum FE analysis study on a rabbit bone-implant system was conducted in which the reaction force during a non-destructive axial compression test on the fractured tibia fixed with a plate-screw system was predicted and compared to corresponding in vitro mechanical tests [10]. The FE model in this study contained a 0.6 mm thick damaged peri-implant bone region with a Young’s modulus of 5 GPa and was able to predict the axial stiffness with an error of 7.85 %. However, none of these studies had objective measures on how large the damaged peri-implant bone region should be nor how the reduced mechanical properties were related to the underlying microarchitecture of the intact bone prior to screw insertion. The differences in size and in mechanical properties of the damaged peri-implant bone might be due to several factors: e.g. different screw types, different species and different bone types (cortical vs. trabecular) and should therefore be evaluated in a small series of experiments, as in [27], prior to creating simulations of new screw types.

Our study has several limitations. First, titanium screws were used that create metal artifacts during $\mu$CT scanning. This can affect the segmentation quality close to the implant. However, specific measures were taken, including screw alignment at the center of rotation, high energy scans and titanium-aluminum alloy screws, to reduce the metal artifact to a minimum. Furthermore, the screws were inserted digitally, such that the trabecular bone was not affected by any sort of metal artefacts. Second, we have tested only two loading cases (uniaxial compression and shear loading). However, as the model showed to be robust for the two extreme loading cases, it is likely that it will also perform similarly for all other loading
cases within this range. Third, the validation has been carried out only within the linear range; yielding of bone was not simulated. Nevertheless, it is important to note that stiffness is a very important mechanical parameter for the assessment of primary implant stability of screws in osteoporotic bone. Considering bone only, stiffness does not only provide information about the compliance of the system but is also an excellent predictor for bone strength [40, 41]. In fact, our data shows that the same might be true for bone-implant system. *In silico* stiffness was not only a good predictor for *in vitro* stiffness ($R^2=0.93$) but also a good predictor for *in vitro* strength ($R^2=0.89$). Nevertheless, it would be useful to have *in silico* models that are validated also for non-linear mechanical behavior to shed more light on the potential relationship between stiffness and strength of bone-implant systems. The accurate predictions of stiffness, as achieved in this study, provide a solid and necessary base for the development of such models.

In conclusion, we confirmed the hypothesis that a more accurate prediction of primary implant stability of screws in bone is possible by (i) modeling interface detachment between screw and bone and (ii) considering insertion-related bone damage. However, modeling interface detachment between screw and bone seems to be less important than insertion-related bone damage. In the end, we have developed a patient-specific computational model that can quantify the apparent stiffness of screws in bone with an accuracy of 12%. The approach uses $\mu$CT based FE analysis in combination with a statistical modeling technique that links the tissue modulus of the damaged peri-implant bone to the native bone micro-architecture in a specimen-specific manner. Thus, we have brought further evidence that screw insertion causes peri-implant bone damage; a phenomenon that should be considered in the future for any computational analysis of primary implant stability of bone-implant systems. We believe that this novel technique provides an important step towards a better understanding of the detailed mechanisms of primary implant stability in human trabecular bone.

**Acknowledgements**

Bone cores were obtained from resected bones from orthopedic surgical interventions in collaboration with Schulthess Clinic (Zurich, Switzerland). The corresponding ethics committee approval (EK-29/2007) allows measurements by $\mu$CT as well as additional *in vitro* mechanical testing.
4.1. A novel in silico method to quantify primary stability of screws in trabecular bone

References


4.1. A novel in silico method to quantify primary stability of screws in trabecular bone


4.1. A novel in silico method to quantify primary stability of screws in trabecular bone

Chapter 5

Primary stability of a multi-screw fracture fixation system
5.1. Towards a clinically oriented patient-specific \textit{in silico} model to quantify primary implant stability in human osteoporotic bone - A proof of concept in the proximal humerus

Juri A. Steiner\textsuperscript{1}, Patrik Christen\textsuperscript{1}, Stephen J. Ferguson\textsuperscript{1} and G. Harry van Lenthe\textsuperscript{1,2}

\textsuperscript{1}Institute for Biomechanics, ETH Zurich, 8093 Zurich, Switzerland
\textsuperscript{2}Biomechanics Section, KU Leuven - University of Leuven, Celestijnenlaan 300, 3001 Leuven, Belgium

\textit{In preperation}

\textbf{Abstract:}
Due to the high variability in inter- and intra-patient bone quality, \textit{in vitro} mechanical testing of implants in bone is very material- and time-consuming. Recently, we demonstrated that \textmu CT based finite element (\textmu FE) models can predict well the apparent stiffness of single screws placed in human trabecular bone. The aims of the present study were (i) to establish a proof of concept for \textmu FE analyses of a clinically relevant multi-screw fracture fixation system and (ii) to develop and implement an experimental technique to validate these analyses. More specifically, a human cadaveric humerus was scanned twice using micro-computed tomography, once before (‘intact model’) and once after osteotomy and implant instrumentation (‘instrumented model’). Through image processing, two \textmu FE models were created: one representing the intact bone and one representing the instrumented bone. Between the two \textmu CT scans and after the implant insertion, \textit{in vitro} mechanical tests were conducted from which the stiffness of the intact and instrumented bone was measured, respectively. For the \textmu FE analyses of the intact model, the patient-specific bone tissue Young’s modulus was adapted, such that it matched the \textit{in vitro} apparent stiffness of the intact bone. The same bone tissue Young’s modulus was then used for the instrumented model. Additionally, in the instrumented model, a thin peri-implant damage region was added, represented by a Young’s modulus lower than that of intact bone. The displacements of 12 motion capture markers placed on various positions of the specimen (4 markers on the
humeral head, on the diaphysis and on the plate, respectively) were measured with a dual camera system and served as the ground truth for the computational analysis. In the \( \mu \)FE model, the displacement within the regions of the same 12 motion capture markers were computed. The comparison between \textit{in silico} and \textit{in vitro} experimental displacements showed a correlation of \( R^2 > 0.85 \) with a slope close to 1. This indicates that the \( \mu \)FE model is able to capture well the displacement pattern of the entire bone on the macro-level. In conclusion, this study presents a proof of concept for \( \mu \)FE analyses of a clinically relevant multi-screw fracture fixation as well as an experimental technique to validate these analyses. Based on the present approach, we plan to validate the predictive power of the proposed modeling technique with additional specimens.

**Keywords:**
Finite Element Analysis, \( \mu \)CT, fracture fixation, humerus, locking plate

**Introduction**

Although advances have been made in the diagnosis and the pharmacological treatment of osteoporosis [1–3], the prevalence of osteoporotic fractures is still increasing, because of the constantly growing proportion of the elderly [4,5]. In the year 2000, an estimated 9.0 million osteoporotic fractures occurred worldwide, of which 1.6 million (18.2\%) were at the hip, 1.7 million (18.5\%) at the forearm and 0.7 (7.9\%) million at the humerus [4]. Due to the aging population, the number of fractures will increase with up to 70-90\% in 2025 [5]. Total costs for the European healthcare system resulting from osteoporotic fractures have been estimated to reach approximately 50 billion Euros by 2020 [6]. Secure implant fixation is challenging, even more so when the underlying cause of a fracture is osteoporotic bone. Appropriate clinical treatment of osteoporotic fractures is challenging, because it is difficult to obtain a secure, mechanically stable implant fixation in low quality bone stock [7,8]. In order to improve fracture fixation in osteoporotic bone, new implant designs and novel approaches for non-invasive assessment of primary implant stability are required. However, mechanical testing of new fixation devices is challenging, because bone possesses a highly heterogeneous structure with anisotropic mechanical properties [9] that not only differ between individuals [10] but also among different sites of the same individual [10] and even within the same bone of a specific individual [11,12]. This makes \textit{in vitro} mechanical testing very material- and time-consuming.
5.1. Towards a clinically oriented patient-specific in silico model to quantify primary implant stability in human osteoporotic bone

As an alternative to in vitro studies, computer simulations (in silico experiments) could be very beneficial to accomplish parametrical investigations and thus to develop efficient optimization procedures regarding improved implant stability [13]. Thus far, most in silico studies of bone-screw systems have treated trabecular bone as a continuum material. In previous work, we demonstrated that the isotropic continuum assumption leads to fundamentally different bone stresses and strains close to the bone-implant interface [14] when compared to models that include the trabecular bone network. Hence, state-of-the-art continuum FE modeling cannot accurately replicate the mechanical behavior of implants in bone, because it does not take the anisotropic nature of bone into account.

Recently, we demonstrated that µFE models can accurately predict the apparent stiffness of single screws fixed in human trabecular bone when a thin peri-implant damage region was included in the model [15]. Our data showed that the mechanical properties of damaged peri-implant bone can be estimated well, and uniquely, based on the morphometric characteristics of the bone in which the screw had been placed, and that these estimates of the peri-implant bone properties are valid for multi-axial loading. Although we now have a refined µFE model at hand that provides accurate predictions of primary implant stability, this model has only been validated using single screws in human trabecular bone. Hence, in this project our aim was to establish a proof of concept for a patient-specific computational method to assess implant stability for a clinically relevant multi-screw implant system in human osteoporotic bone and to develop the methodology to validate these models.

Methods

**Specimen preparation** The tests were performed in accordance with pertinent laws regarding the use of human material. One fresh-frozen (-21 °C) human cadaveric humerus (female, age 89 years) was thawed overnight and then dissected to remove all soft tissue and articular cartilage. The specimen (Fig. 5.1a) was cut 120 mm from the most proximal part of the epiphysis and perpendicular to the axis of the bone. The distal end of the remaining diaphysis was fixed bi-cortically with two screws and embedded in polymethylmethacrylate (PMMA) up to 20 mm height proximally from the cut (Fig. 5.1b). A custom-made µCT sample holder, also made of PMMA, was used as an embedding mold (Fig. 5.1c).
Chapter 5. Primary stability of a multi-screw fracture fixation system

Figure 5.1.: One fresh-frozen (-21 °C) human cadaveric humerus (female, age 89 years) was thawed overnight and then dissected to remove all soft tissue and articular cartilage. The specimen (a) was cut 120 mm from the most proximal part of the epiphysis and perpendicular to the axis of the bone. The distal end of the remaining diaphysis was fixed bi-cortically with two screws and embedded in polymethylmethacrylate (PMMA) up to 20 mm height proximally from the cut (b). A custom-made µCT sample holder also made of PMMA was used as an embedding mold (c).

**Scanning and mechanical testing** The specimen was scanned using microcomputed tomography (µCT 100, Scanco Medical AG, Brüttisellen, Switzerland; nominal isotropic resolution: 40 µm, energy: 90 kVp; integration time: 300 ms). During scanning, the specimen was wrapped in a wet tissue that was soaked in phosphate buffered saline solution. Following scanning, a non-destructive biomechanical test was conducted to obtain the apparent stiffness of the intact bone using an electrodynamic testing machine (ElectroPuls E10000 Linear-Torsion, Germany) equipped with a 10kN load cell. Apparent stiffness was defined as the slope of the linear portion of the load-displacement curve. The specimen was fixed using a custom-made clamping system (Fig. 5.2) in a 30° lateral angulation, which is considered a physiologically relevant loading angle [16]. During pre-conditioning,
10 displacement-driven loading cycles up to 0.3 mm were applied to the specimen. This was immediately followed by a 0.3 mm loading ramp, within which the apparent stiffness was computed. The entire test was conducted at a speed of 0.06 mm/s.

Figure 5.2: *In vitro* mechanical tests were conducted at a speed of 0.06 mm/s, once before and once after plate instrumentation. In both cases, 10 displacement-driven pre-conditioning cycles going up 0.3 mm were applied. While in the intact case, the same displacement range as during pre-conditioning was applied during the loading ramp, in the instrumented case, a loading ramp until 10 mm (i.e. osteotomy gap size) was run. During the mechanical test of the instrumented case, motion capture markers (grey spheres on the specimen) recorded the displacement on the bone and the plate during loading.

After the non-destructive mechanical test, the intact specimen underwent implant instrumentation and osteotomy. Two parallel osteotomy cutting lines were marked on the bone surface going around the surgical neck region, with a separation of 10 mm, thus simulating a severe OTA type 11-A2 two-part fracture case [17]. A locking plate (PHILOS short 90 mm length; DePuys Synthes, Solothurn, Switzerland) was
fixed to the specimen using 4 proximal and 2 distal 3.5 mm locking screws. The plate was instrumented following the manufacturer’s guidelines using standard surgical tools provided by the company. An oscillating saw (Bosch PMF 180E) with a 0.7 mm thick blade was used to cut the bone. Twelve Aluminum plates (1 mm and 3 mm in thickness and diameter, respectively) were glued onto the instrumented bone as follows: 4 on the humeral head, 4 on the diaphysis and 4 on the fixation plate. A second µCT scan was made (‘instrumented’ scan) after which retroreflective motion capture MoCap markers (Vicon, prophysics, Switzerland) were glued on top of the 12 aluminum plates on the specimens. Then the specimen was biomechanically tested under the exact same conditions as in the intact case (Fig. 5.2); however, after the 10 pre-conditioning cycles loading was continuously increased until a displacement of 10 mm (i.e. size of osteotomy gap) was reached. Motion tracking measurements (CamBar B2, Axios3D, Germany) were conducted to capture the displacements of all MoCap markers on the specimen.

**Image processing** As mentioned in the previous section, the ‘intact model’ refers to the intact proximal humerus before instrumentation and the ‘instrumented model’ refers to proximal humerus after osteotomy and plate instrumentation. First, pre- and post-insertion images were segmented (arbitrary units: 100 to 300 for bone and 500 to 1000 for the plate and screws, respectively) and super-imposed on each other using the software Image Processing Language (IPL) by Scanco (Scanco Medical, Brütisellen, Switzerland). Second, a virtual osteotomy was conducted on the pre-insertion image by identifying in the superimposed image the defect between the epiphysis and diaphysis. Third, the thresholded implant from the post-insertion image was extracted and placed into the pre-insertion image now containing the osteotomy. In the end, two types of models were obtained: An intact model directly from the pre-insertion scan by simple thresholding (Fig. 5.3a and 5.3c), and an instrumented model (Fig. 5.3b and 5.3d) as a combination of the pre-insertion scan (i.e. bone) and post-insertion scan (i.e. implant).
5.1. Towards a clinically oriented patient-specific in silico model to quantify primary implant stability in human osteoporotic bone

<table>
<thead>
<tr>
<th>Intact</th>
<th>Instrumented</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Lateral view" /></td>
<td><img src="image2" alt="Lateral view" /></td>
</tr>
<tr>
<td><img src="image3" alt="Sagital view" /></td>
<td><img src="image4" alt="Sagital view" /></td>
</tr>
</tbody>
</table>

Figure 5.3.: Pre- and post-insertion images were segmented and super-imposed with each other. Next, virtual osteotomy was conducted on the pre-insertion image by identifying in the superimposed image the large defect in the surgical neck region. Then, the thresholded implant from the post-insertion image was extracted and placed into the pre-insertion image now containing the osteotomy. In the end, two types of models were obtained: An intact model directly from the pre-insertion scan (a and c), and an instrumented model (b and d) as a combination of the pre-insertion scan (i.e. bone) and post-insertion scan (i.e. implant).

**Computational modeling** For the intact and the instrumented case, $\mu$FE models were created by a direct voxel-to-hexahedral element conversion [18] [18]. In total, the intact and the instrumented model contained 266 Mio and 315 Mio elements,
Chapter 5. Primary stability of a multi-screw fracture fixation system

respectively. In order to account for the compliance at the embedding site of the specimen, a compliant zone at the distal end of the bone was defined with a Young’s modulus of 1 GPa (Fig. 5.3 bone region in transparent grey). At the very bottom of the model, all bone elements were displacement-constrained in all three directions (Fig. 5.3 bone surface in red). A set of 10 quasi-static displacement tests (0.3 mm unconstrained displacement on top of the humeral head) was simulated on the intact model. In each simulation, a specific bone tissue Young’s modulus \( E_{\text{Bone}} \) was defined, ranging from 7 GPa to 16 GPa. The models were solved at the Swiss National Supercomputing Centre (CSCS) in Lugano with the \( \mu \)FE solver ParOSol [19,20] using 960 24-core CPUs (Cray XC40) in parallel on the Dora cluster. B-spline interpolation was used to determine the specific \( E_{\text{Bone}} \) such that the apparent stiffness of the model matched the experimentally measured stiffness. For the instrumented case, the same boundary conditions as in the intact case were applied. The value of \( E_{\text{Bone}} \) determined for the intact case was used. Additionally, damaged peri-implant bone, as caused by screw insertion, was simulated. Bone elements in proximity to the screw were assigned a reduced Young’s modulus within a radial distance of 0.3 mm from the surface normal. The size of this region is in accordance with previous experimental findings on the extent of bone damage induced by screw insertion [15,21]. Another set of 10 quasi-static displacement tests were simulated on the instrumented model. In each simulation, a damaged peri-implant bone tissue Young’s modulus \( E_{\text{PIBD}} \) was defined, ranging from 0.1 GPa to 1 GPa. Again, b-spline interpolation was used to determine the specific \( E_{\text{PIBD}} \), such that the apparent stiffness of the model matched the experimentally measured stiffness. In the last step, displacements at the marker positions were read out, based on reference points marked with aluminum plates during scanning, and correlated to the displacements measured \textit{in vitro}.

Results

The mechanical test revealed an apparent stiffness of 566 N/mm and 257 N/mm for the intact and instrumented case, respectively. For the intact computational model, a bone tissue modulus \( E_{\text{Bone}} = 7.35 \) GPa provided a match in apparent stiffness between the \textit{in silico} and \textit{in vitro} mechanical test. For the instrumented model, and using \( E_{\text{Bone}} = 7.35 \) GPa, a peri-implant bone modulus of \( E_{\text{PIBD}} = 0.9 \) GPa gave a perfect match in apparent stiffness between the \textit{in silico} and \textit{in vitro} mechanical test. While in the intact model, most of the deformation occurred close to the loading and embedding site, most of the deformation in the instrumented model occurred in the cortical bone around the fixation screws (Fig. 5.4). The scatter plot shows a
5.1. Towards a clinically oriented patient-specific *in silico* model to quantify primary implant stability in human osteoporotic bone

correlation of $R^2=0.852$ and a slope of 0.96 with the *in silico* displacement on the x-axis and the *in vitro* displacement on the y-axis (Fig. 5.5).

Figure 5.4.: Effective strain is shown at the same force level for both models. While in the intact model, most of the deformation occurs at the load application site, the instrumented case shows more deformation at in the damaged peri-implant bone region.
Chapter 5. Primary stability of a multi-screw fracture fixation system

Figure 5.5.: The in silico computational model (x-axis) predicts the in vitro displacement (y-axis) on various locations of the specimen quite well. The Pearson’s correlation coefficient is $R^2=0.852$ and the slope is almost 1.

Discussion

The aim of this study was to establish a proof of concept for a patient-specific computational method to assess implant stability for a clinically relevant bone-implant system in human osteoporotic bone and to develop the methodology to validate these models. The goal has been achieved by taking into account the patient-specific bone tissue Young’s modulus (7.35 GPa) as well as the reduced mechanical competence of damaged peri-implant bone (0.9 GPa). Through image processing, the instrumented model (Fig. 5.4b and 5.4d) was created successfully as a combination of the pre-insertion scan (i.e. bone) and post-insertion scan (i.e. implant only). The usage of a reduced peri-implant bone Young’s modulus has been shown to be essential to capture the mechanical competence of bone-implant systems [15]. The peri-implant bone Young’s modulus found in this study (0.9 GPa) is considerably higher than the average value in the aforementioned study (0.35 GPa). A potential explanation for this difference could be the presence of cortical bone in the current study. The previous study did not include any cortical bone. Moreover, further investigation is required to explore to what extent the screw design could influence this result. The displacements of 12 motion capture markers placed on various positions of the
specimen showed a coefficient of determination of over 0.85 with a slope close to 1 when correlating the μFE data with the \textit{in vitro} biomechanical test.

The study has several limitations. First of all, only 1 specimen was used. Hence, further specimens are required to confirm the current findings and to further support the proposed methodology. Second, because metal artefacts affected the image quality in the peri-implant bone, digital implant insertion had to be conducted by applying image superimposition of the pre- and post-insertion scan. Third, retroreflective motion capture (MoCap) markers scanned with the specimen became unusable for MoCap measurement during mechanical testing due to residual fatty bone marrow disposing on the marker surface during scanning and thus damaging their retroreflective capacity. Instead, aluminum plates were used during the μCT scans to indicate the marker position in the computational model and to serve as a place holder for the MoCap markers used for the \textit{in vitro} mechanical test in the instrumented case. Even though great care has been taken to ensure a rigid fixation between the bone and the embedding material, our motion tracking systems measured residual compliance at the embedding site. In order to account for this compliance at the embedding site of the specimen, a compliant zone at the distal part of the bone was defined. Fourth, the marker data of the epiphysis and diaphysis show a discrepancy between the FE model and the experimental data. According to FE analysis, the 4 markers on the epiphysis move down as a rigid block, whereas the experimental data show rather large differences between the markers, indicating rotation of the humeral head. This is due to the fact that the current boundary conditions in the FE only allow unconstrained displacements within the plane perpendicular to the applied displacement, whereas during the \textit{in vitro} experiments the humeral head was free to rotate. This partially explains the artificial stiffening resulting in a low bone tissue Young’s modulus that is required to match the \textit{in vitro} experimental apparent stiffness. Furthermore, the FE displacements of the 2x4 markers on the diaphysis and plate indicate that the embedding site was modeled too stiff and the bone too soft (Fig. 5.5). This might also explain the slight offset in the correlation plot; although it is important to note that the offset is still within the resolution of the μFE model (i.e. 40 μm). Nevertheless, despite these discrepancies, the FE model is able to capture well the displacement pattern of the entire bone on the macro-level. Fifth, no validation has been performed on the local level. Alternatively, image guided failure assessment would be required to verify if the validation on the global level (e.g. apparent stiffness, macro-displacements) corroborates with the measures on the local level (e.g. strains and displacements on microstructural level). However, for this purpose, metal replicas, such as Polyetheretherketon (PEEK), would have
to be used instead to avoid metal artefacts during the strain measurements. Such studies have already been performed recently [22–24]. Even though one of these studies demonstrated good correlations for displacements between the in vitro and in silico measurements on the local level [22], the study did not report any validation on the global level (i.e. apparent stiffness and/or macro-displacements).

In conclusion, this study presents a proof of concept for μFE analyses of a clinically relevant multi-screw fracture fixation as well as an experimental technique to validate these analyses. Based on this, we plan to validate the predictive power of the proposed method with further specimens to obtain an organ level in silico model for the patient-specific quantification of primary implant stability in osteoporotic bone. Future studies in this direction could make a strong contribution, by considering the reduced mechanical performance of peri-implant bone during primary implant stability and by validating the mechanics of the computational models on the local and on the global level with carefully designed in vitro experiments.

Acknowledgements

We thank the company DePuy Synthes for providing the bone and implant material.

References


5.1. Towards a clinically oriented patient-specific in silico model to quantify primary implant stability in human osteoporotic bone

A journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 17(12):1726–33, dec 2006.


Chapter 5. Primary stability of a multi-screw fracture fixation system


Chapter 6

Synthesis

Osteoporosis is defined as a systemic bone disease causing decreased bone density and altered bone micro-architecture which inevitably leads to an increased risk of fractures [1]. Despite the advances made in the diagnosis and pharmacological treatment of osteoporosis [2–4] the prevalence of osteoporotic fractures is still increasing because the proportion of the elderly in our population is constantly growing [5,6]. Statistics in 2002 reported a total of 9.0 million osteoporotic fractures worldwide; 1.6 million (18.2 %) were at the hip, 1.7 million (18.5 %) at the forearm and 0.7 (7.9 %) million at the humerus [5]. In Switzerland, osteoporotic fractures have been found to result in more hospital bed days and therefore higher health care costs than myocardial infarction and stroke [7,8].

The primary goal of fracture fixation is to obtain secure primary implant stability, in order to provide the necessary condition for biological fracture healing (i.e. secondary implant stability) and thus to reduce the potential risk of fixation failure or non-union requiring revision surgery. Secure implant fixation is more challenging when osteoporosis is the underlying cause of a fracture. Numerous experimental [9–12] and clinical studies [13,14] have shown that osteoporosis not only increases the risk for fractures, it also increases the risk for non-union and consequent revision surgery. However, the detailed mechanisms behind decreased implant stability in osteoporotic bone are still not well understood. Consequently, the treatment of fractures and osteoporotic fractures in particular may be sub-optimal.

In order to improve the treatment of fractures in osteoporotic bone, more detailed and quantitative understanding on the role of peri-implant bone for implant stability is needed. However, systematic experimental testing on a wide variety of human bone specimens is very costly in terms of material and time due to three key factors: First, bone is a highly heterogeneous material resulting in anisotropic mechanical properties [15] that differ not only across patients [16] but even within the same bone of the same patient [17,18]. Second, implants are highly variable, in terms
of design and application, depending on their function and anatomical location. Third, systematic and independent parametric analyses based on different implants that could be tested in the same bone specimen at the exact same location are obviously not possible, because each mechanical test will influence the following one. In view of these limitations, a computational approach, more specifically finite element (FE) modeling, has been proposed as an alternative strategy. In most FE studies that investigate the mechanical competence of bone-screw composites, bone is treated as a continuum material with homogenous material properties while only a few actually considered the anisotropic micro-architecture of bone [19–22]. A high potential is seen in high-resolution micro-computed tomography (µCT) images; a technique that has been verified and validated on trabecular bone structures [23,24]. A remaining great challenge regarding in silico modeling of implant-bone constructs lies in the description of the implant-bone interface. Only a few µCT based FE studies are available in which the interface representation could account for such complex mechanical behavior [17,22]. Reported methods include removal of elements at specific sites [17] and decreasing Young’s moduli of bone elements close to the implant [22]. So far, no single computational study has been performed that fully takes both the bone micro-architecture and the complex mechanical properties of the bone-screw interface into account. The overall aim of this thesis was to create a patient-specific computational model to quantify the primary implant stability of fracture fixation devices in osteoporotic bone. More specifically, following aims were proposed:

**Aim 1**: Development of an imaging method that localizes and quantifies the presence of peri-implant bone damage due to screw insertion. We hypothesized that bone damage occurs close to the implant only, and that it is affected by the screw thread design.

**Aim 2**: Improve the quantification of the apparent stiffness of single screws in human trabecular bone under multi-directional loading using µCT based FE. We hypothesized that a more accurate prediction of primary implant stability of screws in bone would be possible (i) by modeling interface detachment between screw and bone and (ii) by considering insertion-related bone damage.

**Aim 3**: Establish a proof of concept towards a clinically oriented patient-specific in silico model to quantify primary implant stability in human osteoporotic bone and develop an experimental technique to validate these analyses. We hypothesized, that the consideration of peri-implant bone damage due to screw inser-
ion would improve the accuracy for the prediction of the apparent implant-bone stiffness.

### 6.1. Assessing peri-implant bone damage

The major achievement of the first study (chapter 3) is the development of a method to localize and quantify peri-implant bone damage along the entire length of the screw; and to do so non-invasively and fully in 3D. We could show that the trabecular bone structure is affected by screw insertion. Bone damage was found close to the implant only. We also showed that screws with large threads had a slightly larger impact on the peri-implant bone than screws with small threads. In the past, state-of-the-art computational models have demonstrated high over-predictions of the primary implant stability in screw-bone systems [22, 25, 26]. Even though bone compaction can enhance primary implant stability in some cases [27], there is clear evidence that local peri-implant bone damage occurs and hampers the mechanical performance of bone-implant systems when compared to idealized implant placement with perfectly preserved and intact peri-implant bone [28]. This was the first study to localize and quantify peri-implant bone damage caused by screw insertion based on a non-invasive, three-dimensional, \( \mu \text{CT} \) imaging technique. Peri-implant bone damage due to screw insertion should be taken into consideration to further improve primary implant stability, especially in low quality osteoporotic bone. We believe that this technique could be a promising method to assess more systematically the effect of peri-implant bone damage on primary implant stability.

### 6.2. Primary stability of single fracture fixation screws

The major achievement of the second study (chapter 4) is the development of a novel \textit{in silico} method to accurately quantify primary implant stability of screws in trabecular bone. We confirmed the hypothesis that a more accurate prediction of primary implant stability of screws in bone requires modeling two phenomenon: (i) interface detachment between screw and bone and (ii) insertion-related bone damage. We demonstrated that insertion-related bone damage had a greater effect on implant stability than interface detachment between screw and bone. In short, we have developed a patient-specific computational model that can quantify the apparent stiffness of screws in bone with an error of \( \leq 12 \% \). The approach uses \( \mu \text{CT} \) based FE analysis in combination with a statistical modeling technique that
Chapter 6. Synthesis

links the tissue modulus of the damaged peri-implant bone to the native bone micro-architecture in a specimen-specific manner. Thus, we have brought further evidence that screw insertion causes peri-implant bone damage, a phenomenon that should be considered in the future for any computational analysis of primary implant stability of bone-implant systems. The clear link between the properties of the damaged peri-implant bone and the micro-architecture of the bone opens the door for image-based predictive models for individual patients, at least in the peripheral limbs. We believe that this novel technique provides an important step towards a better understanding of the detailed mechanisms of primary implant stability in human trabecular bone.

6.3. Primary stability of a multi-screw fracture fixation system

The major achievement of the last study (chapter 5) is the proof of concept for a clinically oriented and patient-specific in silico model to quantify the primary stability of a fracture fixation device in human osteoporotic bone. Furthermore this study presents a methodology to validate such a patient-specific microstructural finite element model using in vitro biomechanical tests combined with a motion tracking system that measures displacements on various sites of the specimen. We confirmed the hypothesis that the consideration of peri-implant bone damage due to screw insertion improves the accuracy of the prediction of the apparent implant-bone stiffness. Based on this demonstration case, we plan to further refine the proposed modeling technique by including further specimens in the study in order to validate the predictive power of the proposed method.

6.4. Limitations and future research

In this thesis, several limitations should be mentioned. In chapter 3, metal screws were used that create image artifacts during μCT scanning. However, specific measures, such as high energy scans and titanium-aluminum alloy based screws were used to reduce the metal artifact. Next, the setup used in chapter 3 does not allow distinguishing the bone damage caused by the drilling procedure from the bone damage caused by screw insertion, because only two sets of scans per specimen were conducted (before guide hole drilling and after screw insertion). Nevertheless, with the current setup, the comparison of the two different screw types is valid because the exact same guide hole drilling procedure was used in both groups, and drilling is an integral part of screw placement for osteosynthesis. Last, the method in chapter
3 identifies only fragmentation of peri-implant bone trabeculae, not micro-damage within the trabeculae themselves. The current image resolution of 20 µm is not sufficient to assess peri-implant bone damage at the micro-scale (e.g. micro-cracks, cross-hatched damage or diffuse damage). This is due to the fact that micro-damage occurs at a length-scale that is at least one order of magnitude smaller [29,30]. Last, depending on the trabecular dimensions and possible residual stresses in the trabecular network, elastic bending of trabeculae may be interpreted as damage by this registration method. However, structural changes captured at 20 µm can most likely be interpreted as bone damage considering the fact the micro-cracks already occur at dimensions of 1 to 2 µm [30]. Future studies applying the method proposed here, should use implant replicas made of a material that shows only little (e.g. Aluminum) or no metal artefact (e.g. PEEK). Furthermore, combining such materials with metal coatings that mimic the surface properties of conventional implants would be useful to minimize metal artefacts and therefore to accurately assess the influence of clinically relevant surface properties on peri-implant bone damage caused by screw insertion. Potential follow-up studies could also assess the impact of screw drilling and screw insertion separately by running an additional scan between drilling and insertion. Further improvement with advancements of computational power could be realized with increased resolution allowing for a distinctive representation of micro-damage and deformation. In chapter 4, we have tested only two loading cases (uniaxial compression and shear loading). However, as the model showed to be robust for the two extreme loading cases, it is likely that it will also perform similarly well for other load cases. The validation has been carried out only within the linear range; yielding of bone was not simulated. Nevertheless, it is important to note that stiffness is a very important mechanical parameter for the assessment of primary implant stability of screws in osteoporotic bone. Considering bone only, stiffness does not only provide information about the compliance of the system but is also an excellent predictor for bone strength [31,32]. In fact, our data shows that the same might be true for bone-implant system. \textit{in silico} stiffness was not only a good predictor for \textit{in vitro} stiffness (R²=0.93) but also a good predictor for \textit{in vitro} strength (R²=0.89). Furthermore, the principal goal of osteosynthesis is to limit interfragmentary motion to a level promoting bone healing, therefore the stiffness of the implant-bone system is of paramount importance. Nevertheless, it would be useful to have \textit{in silico} models that are validated also for non-linear mechanical behavior to shed more light on the potential relationship between stiffness and strength of bone-implant systems. The accurate predictions of stiffness, as achieved in this study, provide a solid and necessary base for the development of such models. In
Chapter 5, only 1 specimen was used. Hence, further specimens are required to confirm the current findings and to further support the proposed methodology. Second, no validation has been performed on the local level. For this purpose, metal replicas, such as Polyetheretherketon (PEEK), would have to be used instead to avoid metal artefacts during the strain measurements. Image guided failure assessment (IGFA) studies have been performed recently [33–35] that can measure displacements and strains in the peri-implant region during loading. One of these studies demonstrated good correlations for displacements and only moderate correlations for strains between the in vitro and in silico measurements [33]. However, on the macro level, the study did not report any values on apparent stiffness and/or displacements on the macro-level. In the future, IGFA studies would be useful that validate computational models on the macro-level (e.g. apparent stiffness, displacements within 10 mm - 500 µm; see p.20) and on the micro-level (e.g. strains and displacements within 10 - 500 µm; see p.20).

6.5. Conclusion

Considering the high variability in bone microarchitecture across patients and even within the same bone of the same patient, more effective methods than the ones currently available are required to improve primary implant stability in osteoporotic bone. For that purpose, three important aims have been achieved in this thesis. First, we developed a method to localize and quantify peri-implant bone damage along the entire length of the screw; and to do so non-invasively and fully in 3D. We demonstrated that peri-implant bone damage already occurs during screw insertion. Second, we developed a novel in silico method to accurately quantify primary implant stability of screw in trabecular bone by taking into account the reduced mechanical properties within the damaged peri-implant bone. Third, we developed a methodology for a patient-specific in silico model to quantify the primary implant stability of a locking plate in the human proximal humerus. In conclusion, with this thesis we have improved the understanding of primary fixation of screws and multi-screw implants in bone. Specifically, we have improved our knowledge on the importance of the patient-specific bone microarchitecture and on the mechanical consequences of bone damage during screw insertion. Furthermore, we have developed and implemented a methodology to take these aspects into account in computational models. These models can now be used to improve fracture fixation devices, especially those used in low quality bone. This would be very useful to improve standards of care in osteoporotic patients suffering from a bone fracture.
6.4. Limitations and future research

References


journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 16 Suppl 2:S93–S102, mar 2005.


6.4. Limitations and future research


Chapter 6. Synthesis


Chapter A

Validation of an optical motion tracking method
A.1. An optical motion tracking method to measure displacements of bone fragments and implants during mechanical loading

A.1.1. Introduction

Recently, we demonstrated that $\mu$CT based finite element (FE) models can accurately predict the apparent stiffness of single screws fixed in human trabecular bone [1]. With this technique, we now have a refined $\mu$CT based FE model at hand that provides accurate predictions of primary implant stability; however, it has only been validated for single screws in human trabecular bone. The ultimate goal is to create models of complex multi-screw implant systems in human osteoporotic bone, for which we need to develop a methodology to validate them. Optical motion capture (MoCap) techniques can be used to quantify displacements at various locations of the specimens. The aim of this study was to assess whether the accuracy and precision of the proposed motion tracking method are sufficient to serve as the ground truth for validating displacements of organ scale $\mu$CT based FE models.

A.1.2. Methods

Static validation against xyz-table

In a first step, the accuracy and the precision of the motion tracking system (CamBar B2, Axios3D, Germany) was assessed by mounting two locators on a xyz-table that consisted of four planar arranged, evenly distributed retroreflective markers. One locator was moved 1.000 mm in three orthogonal directions and the accuracy and the precision was determined using markers with 9.40 mm and 6.35 mm diameter. Furthermore, the effect of no filtering, a moving average filter and a Savitzky-Golay filter on accuracy and precision was assessed.

Dynamic validation against mechanical testing machine

Specimen preparation The mechanical tests were performed in accordance with the pertinent laws regarding the use of human material. One fresh-frozen (-21° C) human cadaveric humerus (female, age 89 years) was thawed overnight and then dissected to remove all soft tissue and articular cartilage. The specimen (Fig. A.1) was cut 120 mm from the most proximal part of the epiphysis and perpendicular to the axis of the bone. The distal end of the remaining diaphysis was fixed bi-cortically with two screws and embedded in polymethylmethacrylate (PMMA) up to 20 mm.
Appendix A. Validation of an optical motion tracking method

proximal from the cut. A custom-made sample holder also made of PMMA was used as an embedding mold (Fig. A.1). The intact specimen underwent implant instrumentation and osteotomy. Two osteotomy cutting lines were marked on the bone surface going around the surgical neck region with a distance of 10 mm to each other thus simulating a severe OTA type 11-A2 two-part fracture case [2]. A locking plate (PHILOS, 90 mm length; DePuy Synthes, Solothurn, Switzerland) was fixed to the specimen using 4 proximal and 2 distal 3.5 mm locking screws. The plate was instrumented following the manufacturer’s guidelines using standard surgical tools provided by the same company. An oscillating saw (Bosch PMF 180E) with an 0.7 mm thick blade was used to create the osteotomy. Retroreflective markers with a diameter of 3 mm were glued onto various anatomical sites of the specimen (Fig. A.1) with an instant glue to track their displacements during mechanical testing.

Figure A.1.: One fresh-frozen (-21° C) human cadaveric humerus (female, age 89 years) was thawed overnight and then dissected to remove all soft tissue and articular cartilage. The specimen (a) was cut 120 mm from the most proximal part of the epiphysis and perpendicular to the axis of the bone. The distal end of the remaining diaphysis was fixed bi-cortically with two screws and embedded in polymethylmethacrylate (PMMA) up to 20 mm height proximally from the cut (b). A custom-made µCT sample holder also made of PMMA was used as an embedding mold (c). Optical retroreflective motion capture markers were placed on various locations of the specimen (d).
A.1. An optical motion tracking method to measure displacements of bone fragments and implants during mechanical loading

Biomechanical testing The specimen was fixed using a custom-made clamping system (Fig. A.2 and A.3) in a 30° lateral angulation, which is considered a physiologically relevant loading angle [3]. The specimen was loaded using an electrodynamic testing machine (ElectroPuls™ E10000 Linear-Torsion, High Wycombe, UK) equipped with a 10kN load cell. During pre-conditioning, 10 displacement-driven loading cycles up to 0.3 mm were applied on the specimen. This was immediately followed by a continuously increasing load until a displacement of 10 mm (i.e. size of osteotomy gap) was reached. The entire test was conducted at a speed of 0.06 mm/s.

Figure A.2.: A biomechanical test was conducted to obtain the apparent stiffness of the instrumented bone using an all-electric testing machine (ElectroPuls™ E10000 Linear-Torsion, Germany) mounted with a 10kN load cell. During pre-conditioning, 10 displacement-driven loading cycles up to 0.3 mm were applied on the specimen. This was immediately followed by a continuously increasing load until a displacement of 10 mm (i.e. size of osteotomy gap) was reached. The entire test was conducted at a speed of 0.06 mm/s.
Figure A.3.: Optical stereo motion tracking measurements (CamBar B2, Axios3D, Germany) were conducted during the mechanical test to capture the displacements of all retroreflective motion capture (MoCap) markers on the specimen. The software required the assembly of markers in groups of 4 that defined a locator. The displacements of the MoCap markers were recorded relative to a reference locator (L0). An additional locator was put on the Instron actuator (L1) in order to synchronize the force-displacement data from the Instron with the displacement data from the CamBar system. The remaining three locators L2, L3 and L4 were placed on the humeral head, diaphysis and on the plate, respectively.

**Motion tracking and signal processing** Optical stereo motion tracking measurements (CamBar B2, Axios3D, Germany) were conducted during the mechanical test to capture the displacements of all retroreflective MoCap markers on the specimen. As preliminary tests showed thermo-dependent signal drifts (data now shown here),
A.1. An optical motion tracking method to measure displacements of bone fragments and implants during mechanical loading

the camera system was started 4 h prior to testing to reach a constant operating temperature during measurement [4]. For validation, only the displacement in the loading direction was assessed. The software required the assembly of markers in groups of 4 that defined a locator. In total, 5 locators were used (Fig. A.3). The displacements of the MoCap markers were recorded relative to a reference locator (L0) that was aligned in the loading direction of the Instron actuator, remained stationary throughout the entire test and was not attached to the specimen fixation setup. The displacement output was decomposed in three orthogonal directions, of which one was aligned with the loading direction of the Instron actuator. An additional locator was put on the Instron actuator (L1) in order to synchronize the force-displacement data from the Instron with the displacement data from the CamBar system. For this purpose, before starting with the pre-conditioning cycles, the actuator first moved 0.3 mm upwards after which it returned to its initial position. The load-free peak served as a reference point to synchronize the two systems during post-processing. The remaining three locators L2, L3 and L4 were placed on the humeral head, diaphysis and on the fixation plate, respectively (Fig. A.3). Data processing was done using Matlab (MATLAB, R2014a). A moving average filter with a window span of 5 data points was applied on the entire dataset to smooth the signal. B-Spline interpolation was used to obtain data signals with a constant frame rate of f=50 Hz. The accuracy was assessed by (1) comparing the measured displacement signal of L0 on the stationary reference locator from the CamBar to zero displacement and by (2) comparing L1 on the Instron actuator from the CamBar to the displacement signal of the actuator measured by the Instron. For this purpose, mean absolute error (MAE) was calculated. The precision was assessed by computing the moving average standard deviation (SD) of L0 and all its markers. Following synchronization, the displacement in loading direction was computed and plotted (Fig. [A.4]).
Appendix A. Validation of an optical motion tracking method

Figure A.4.: Before synchronization, the displacement patterns of the actuator between the CamBar and Instron displacement data are off by a few seconds (a). After the synchronization via the load-free peak as a reference point, the displacement pattern of the actuator between the CamBar and Instron data matched very well (b). Based on this signal synchronization, all the remaining locators were synchronized accordingly (c-f).

A.1.3. Results

For the static validation against the xyz-table, highest accuracy and precision with the 9.4 mm and 6.35 mm diameter marker size was reached with the moving average filter including a window span of 5 resulting in $4.2 \pm 4.4 \mu m$ and $9.7 \pm 2.8 \mu m.$
A.1. An optical motion tracking method to measure displacements of bone fragments and implants during mechanical loading

respectively. For the dynamic test, the displacement patterns of the actuator from the CamBar and Instron displacement data before synchronization were off by a few seconds (Fig A.4a). After the synchronization, the displacement patterns of the actuator from the CamBar and Instron data matched very well. The MAE of the L1 displacement signal was 21.1 $\mu$m. Based on this signal synchronization, all the remaining locators were synchronized accordingly (Fig A.4c - A.4f). The MAE of the L0 displacement signal was 5.5 $\mu$m with a SD = 0.2 $\mu$m (Fig A.4c). A summary of MAEs from the individual markers of L0 and L1 is shown in table A.1.

Table A.1.: Accuracy, computed as mean absolute error (MAE), and precision, expressed as standard deviation (SD), are displayed. The second row indicates MAE and SD values of locators L0 and L1. The subsequent rows list the MAE and SD values of the markers belonging to the corresponding locator. SD values in L0 vary between 0.2 and 1.2 $\mu$m. MAE in L0 and L1 including all their markers vary between 4.5 - 8.7 $\mu$m and 21.1 - 40.7 $\mu$m, respectively.

<table>
<thead>
<tr>
<th>$\mu$m</th>
<th>L0:SD</th>
<th>L0: MAE</th>
<th>L1:MAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>0.2</td>
<td>5.5</td>
<td>21.1</td>
</tr>
<tr>
<td>M1</td>
<td>0.8</td>
<td>4.5</td>
<td>40.7</td>
</tr>
<tr>
<td>M2</td>
<td>1.2</td>
<td>5.3</td>
<td>43.5</td>
</tr>
<tr>
<td>M3</td>
<td>0.8</td>
<td>5.1</td>
<td>35.2</td>
</tr>
<tr>
<td>M4</td>
<td>1.1</td>
<td>8.7</td>
<td>38.4</td>
</tr>
</tbody>
</table>

A.1.4. Discussion

The aim of this study was to assess the accuracy and precision of an optical Mo-Cap system used for measuring the displacements, during mechanical testing, on various locations on bone specimens instrumented with a fracture fixation device. For this purpose, static and dynamic measurements were conducted. For the static measurements, a locator was moved 1 mm in three orthogonal directions using a xyz table and its displacement was measured relative to a second locator. Two different marker sizes were used: 9.4 and 6.35 mm diameter. Precision and accuracy of the two markers sizes were as low as 4.2 $\pm$ 4.4 $\mu$m and 9.7 $\pm$ 2.8 $\mu$m, respectively.

For the dynamic measurements, a human humerus was prepared and instrumented with an orthopedic fracture fixation locking plate. The precision of the stationary locator L0 and its markers was within a range of 0.2 and 1.2 $\mu$m. While the accuracy of the measured markers on a stationary reference locator varied between 4.5 and 8.7 $\mu$m, the accuracy of the tracked markers on the moving Instron actuator was between 35.2 and 40.7 $\mu$m. Hence, the results from the stationary locator L0 are in line with
the static measurements on the xyz-table. The results from the moving Instron actuator are by an order of magnitude larger than in the static measurements. However the accuracy and precision values obtained overall in this study should still be sufficient for the validation of whole organ (e.g. proximal human humeri) μCT based FE models that have shown to work best at a resolution of 40 μm to fulfill the requirements for a sufficiently accurate microstructural representation [5] without exceeding the limits of the currently available computational capacity.

A.1.5. Acknowledgements

Data acquisition and evaluation based on a xyz-table was largely carried out by Florian Bolliger within the scope of his Bachelor thesis; his efforts are greatly appreciated. We thank the company DePuy Synthes for providing the bone and implant material.

References


Curriculum Vitae

Juri Alexis Steiner

Born on the 18th of November 1983 in Aarau, Switzerland

Education

2011–present  Doctoral thesis at the Institute for Biomechanics, ETH Zurich under the supervision of Prof. Dr. Harry van Lenthe and Prof. Dr. Stephen Ferguson

2010 – 2011  Research assistant under the supervision of Prof. Dr. Harry van Lenthe and Prof. Dr. Ralph Müller

2008 – 2010  M.Sc. Biomechanics Human Movement Sciences, ETH Zurich

2007 – 2008  B.Sc. Human Movement Sciences, ETH Zurich

2006 – 2007  1ère année de Biologie, UNIL Lausanne

2005 – 2006  1ère année des Sciences du Sport, UNIL Lausanne

2004 – 2005  Swiss Army Service: Combat Medic


Publications


**Professional appointments**

2008–2010 Institute for Biomechanics, ETH Zurich, Switzerland, Teaching Assistance

2011–2015 Institute for Biomechanics, ETH Zurich, Switzerland, Graduate Research Assistance

**Awards and honors**

2014 European Society of Biomechanics (ESB) Travel Award for the work entitled: “Towards an accurate computational description of the bone-implant interface.” *Presented at the 7th World Congress of Biomechanics, Boston, USA*, July 6-11, 2014.

**Conference Proceedings and Abstracts**


